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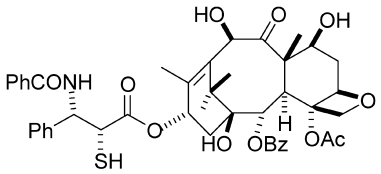

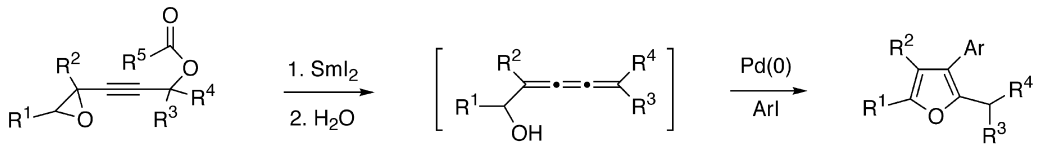

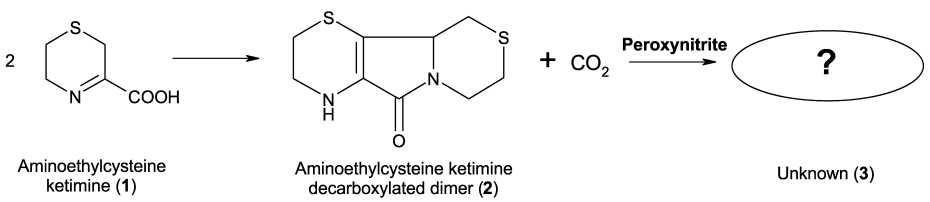

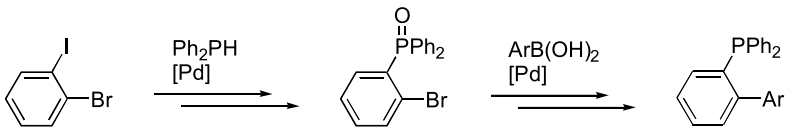

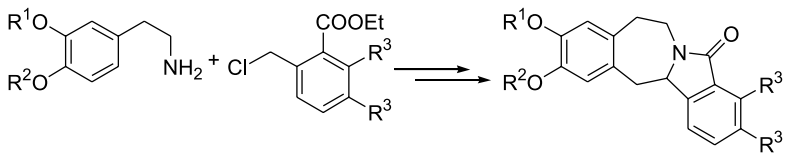

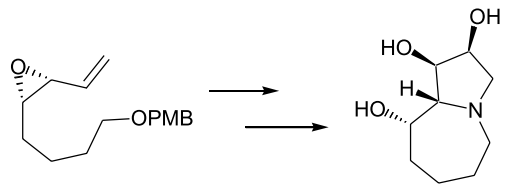

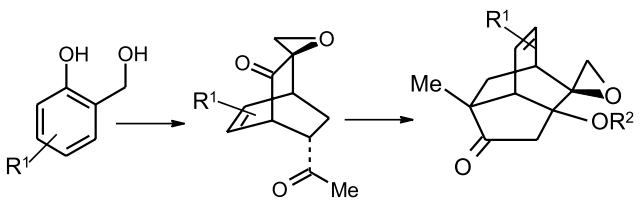

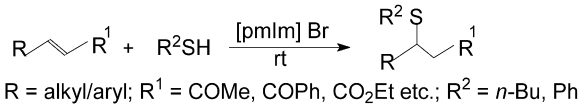

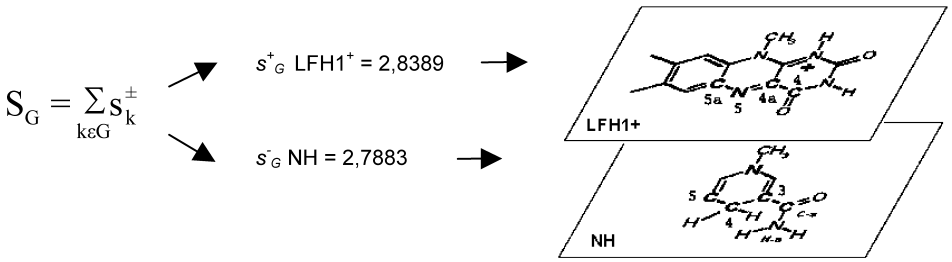

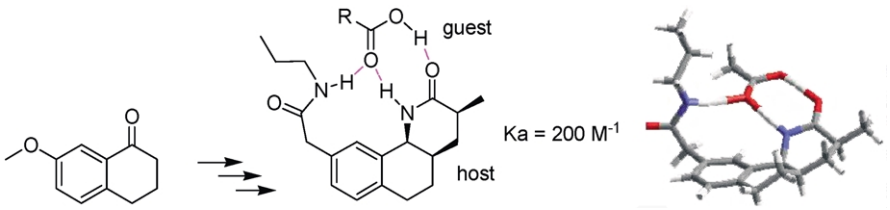

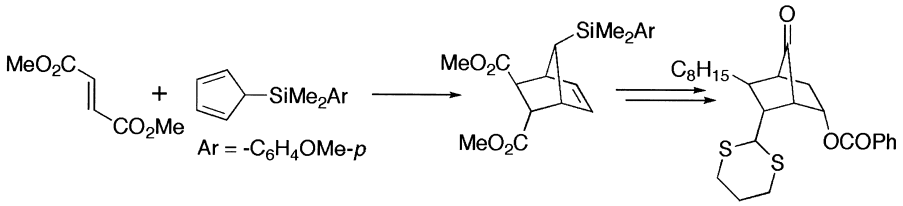

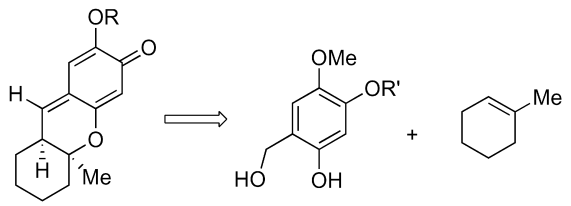

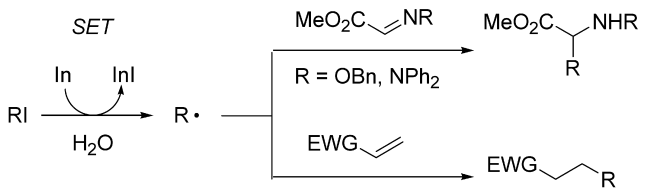

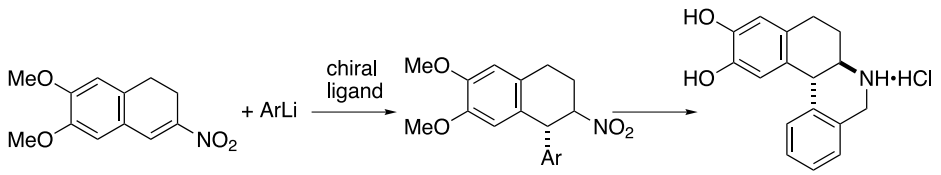

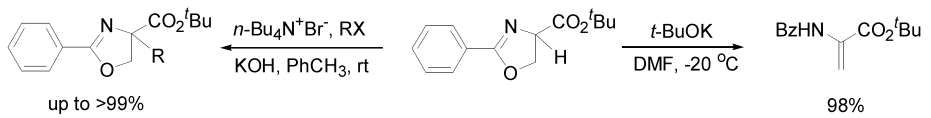

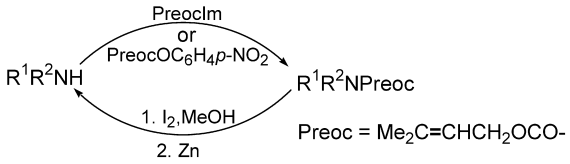

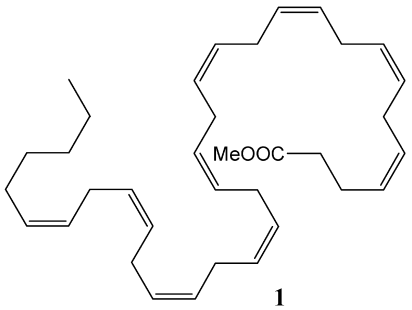

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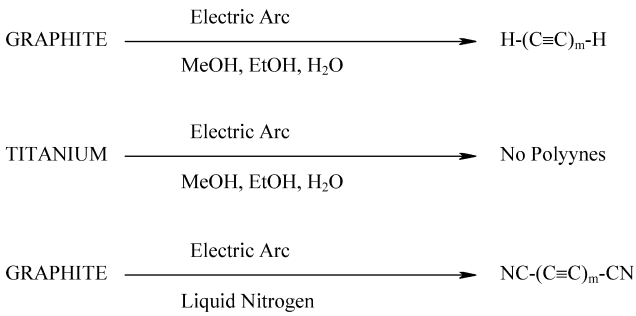
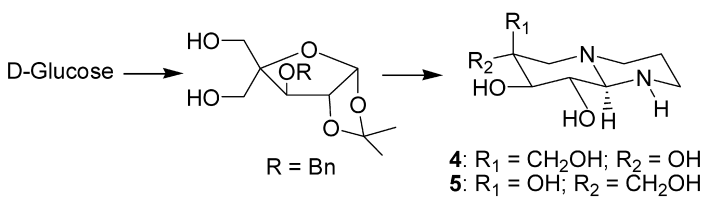
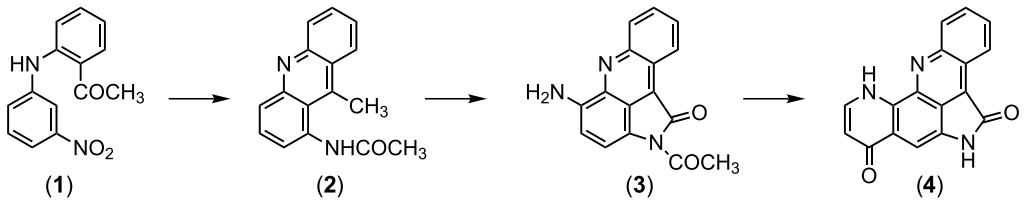
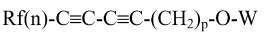


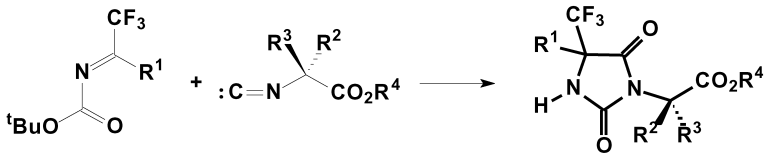




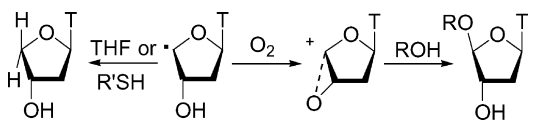
6,11-Dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline-5,8-dione (**4**) possessing a unique heterocyclic ring system was synthesized from 2-acetyl-3′-nitrodiphenylamine (**1**) in nine steps.

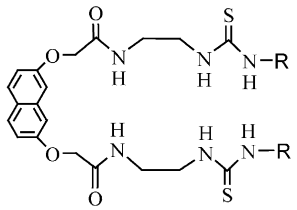


where *Rf(n)* is $F(CF_2)_n$, *n* is 4, 6 or 8, *p* is 1 or 2 and *W* is H, acrylate or methacrylate



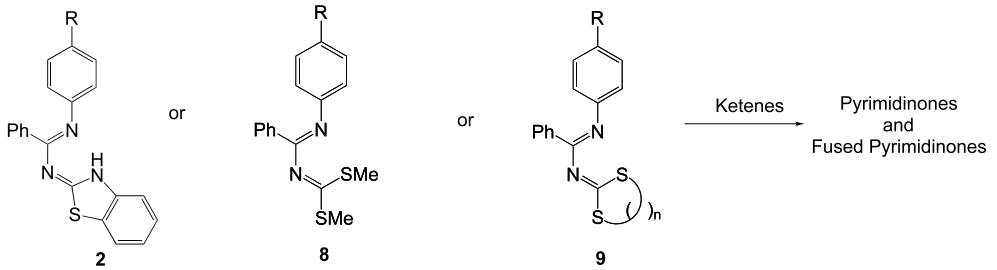
Simple, one-pot syntheses of trifluoromethyl-substituted hydantoins starting from Boc-protected imines of hexafluoroacetone and trifluoropyruvate are described. They represent valuable building blocks for the construction of constrained peptides or as scaffolds for the synthesis of highly potent VLA-4 antagonists.





1 R=*p*-nitrophenyl
2 R=1-naphthyl
3 R=*p*-tolyl

Three novel neutral anion receptors were synthesized and characterized. The recognition properties for α,ω-dicarboxylate were studied by UV–vis and fluorescence spectrometry.



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*Corresponding author
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Synthesis of novel thiol taxoids based on the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III: both the *syn* and *anti* 10-deacetyl-2′-deoxy-2′-mercaptopaclitaxels

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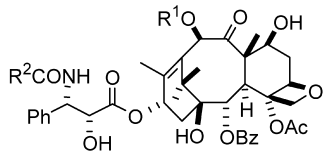
Abstract—Two new kinds of docetaxel compound, with a mercapto group instead of the hydroxyl on the C13 side chain (both *syn* and *anti*), via the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III route, were synthesized. The uses of *trans* and *cis* oxazoline compounds, and their stereoselective ring-opening reactions with thiolacetic acid, were proved to be key steps.

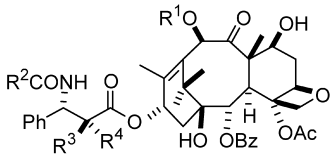
1. Introduction

The complex natural product paclitaxel (Taxol®) **1**, first isolated from *Taxus brevifolia*,[1] is a member of a large family of taxane diterpenoids.[2] Paclitaxel has excellent clinical activity against ovarian and breast cancers, and also shows promising results in the treatment of other cancers.[3] Extensive studies on the structure activity relationship (SAR) have been explored. It is already well known that a free hydroxyl group at the C-2′ position on the C-13 side chain is crucial for microtubule binding[4] and may play as a hydrogen bond donor.[5] In light of this hypothesis, the introduction of thiol functionality, which is more acidic instead of hydroxyl onto the C-13 side chain, would be of great interest for the study about the taxoid binding site on microtubules and for the development of new compounds bearing more desirable properties than paclitaxel. In our previous report,[6] the syntheses of new kinds of thiol surrogates of paclitaxel on the C-13 side chain instead of the C-2′ hydroxyl group **3a/3b** were demonstrated by means of 7-triethylsilyl baccatin III. Here, another kind of 2′ mercapto taxoids is reported, with a free hydroxyl on the C-10 position **4a/4b**, utilizing the 7,10-di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III (7,10-diTroc DAB) **5** approach. As a matter of fact, the 7,10-diTroc DAB proved to be another important synthetic intermediate for the semi-synthesis of many taxoids compounds,[7] as did the 7-TES-baccatin III. One example is the docetaxel **2**, a semisynthetic analog of paclitaxel. Meanwhile, simultaneous modification methods, on different positions in the taxoids structure, recently emerged[4a,8] and have begun to appear as an important tool in the search for new taxoid analogues bearing better physical, chemical and biological properties, especially when parallel[9] and



Paclitaxel **1** R^1= Ac R^2 = Ph

Docetaxel **2** R^1= H R^2 = ^{t}BuO



2′-Deoxy-2′-Mercaptopaclitaxel **3b** R^1= Ac R^2 = Ph R^3 = H, R^4 = SH
2′-Deoxy-2′-*epi*-Mercaptopaclitaxel **3** R^1= Ac R^2 = Ph R^3 = SH, R^4 = H
10-Deacetyl-2′-Deoxy-2′-Mercaptopaclitaxel **4a**
R^1= H R^2 = Ph R^3=H R^4=SH
10-Deacetyl-2′-deoxy-2′-*epi*-Mercaptopaclitaxel **4b**
R^1= H R^2 = Ph R^3=SH R^4=H

Keywords: Taxol; Oxazoline; Mercapto taxoid.
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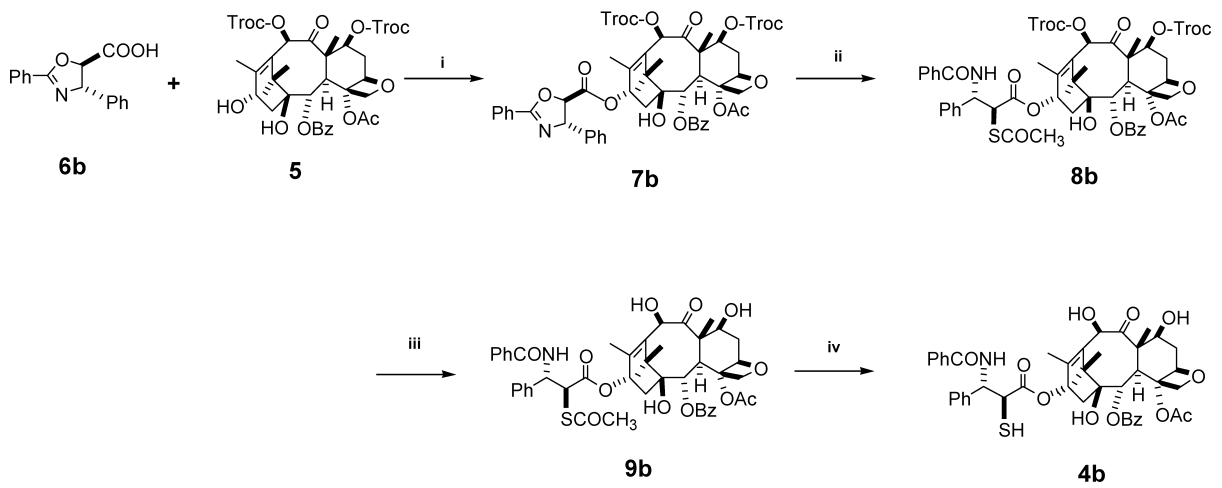


Scheme 1. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, 92%. (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 72%. (iii) Zn dust, MeOH/HAc (1:1), 60 °C, 2 h, 77%. (iv) LiOH, MeOH/H_2O, rt, 2 h, 68%.

combinatorial synthesis[10] were used for quick and convenient scans. In these cases, the thiol taxoid analogues, bearing two free hydroxyl groups at the 7 and 10 sites, would be interesting precursors for this kind of application, as the different reactivity of the two hydroxy groups are well known.

2. Results and discussion

The methodology applied to the synthesis of **4b** involved in a similar pathway, as described in our previous paper,[6a] with the *trans*-oxazoline carboxylic acids, **6b**, and 7,10-diTroc DAB, **5**,[7f] serving as starting materials, as shown in Scheme 1.

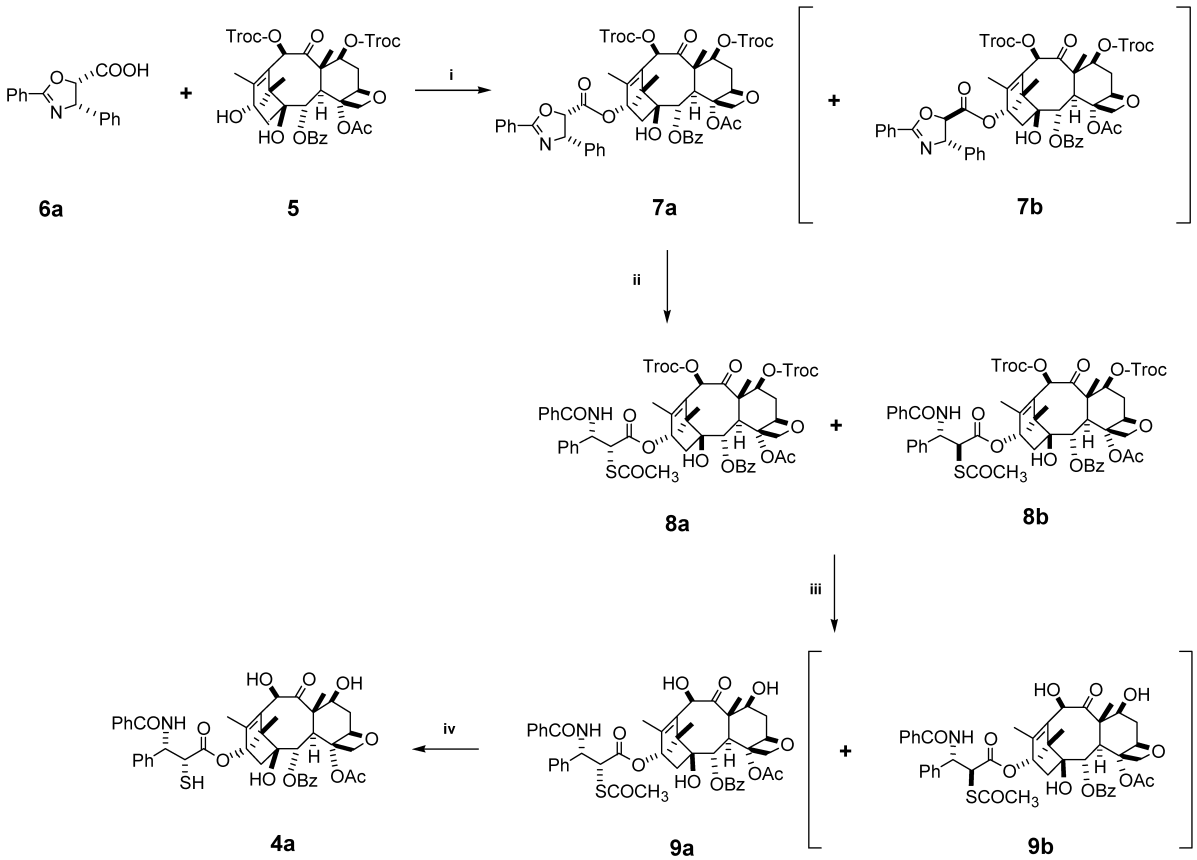
Thus, the excess (3.5 equiv.) *trans*- (4*S*, 5*R*)-2,4-diphenyl-oxazoline-5-carboxylic acid **6b**, which was generated by hydrolysis from the corresponding methyl ester,[11] was coupled with **5** in the presence of DCC and 4-pyrrolidino-pyridine to afford a new kind of oxazoline intermediate **7b**, which was fully characterized with a yield of 92%. First, the HRMS spectrum revealed a characteristic [M+H+4] molecular ion peak, showing the existence of six chlorine atoms. With the aid of 2D NMR experiments, the complete assignments of **7** could be made. First, the $^1H-^{13}C$ HMQC 2D NMR clearly showed the positions of the pairs of H20α,β, H6α,β and H14α,β, and the four alkyl methyl groups, at 1.20, 1.25, 1.85 and 2.02 ppm, respectively. Then, the two doublet peaks, at 4.94 and 5.60 ppm with a coupling constant of 7.0 Hz in ^1H NMR spectrum, were consistent with a *trans* oxazoline structure,[12] and correlated only with each other. As proved previously,[6a] the small amount of *cis* oxazoline ester mixed with the *trans* isomer did not affect the purity of the coupling product. The $^1H-^1H$ COSY 2D NMR revealed two correlated 7-Troc methylene protons, at 4.60 and 4.90 ppm, doublet (J=11.8 Hz) and the two correlated 10-Troc methylene protons, at 4.76 ppm, triplet (J=12.2 Hz). Other protons, such as H2 and H3 at 5.70 and 3.93 ppm, respectively, both doublet, J=7.0 Hz, correlated with each other, H7, at 5.58 ppm, multiplet, and correlated with the H6α and H6β, at 2.62 and 2.06 ppm, respectively and H5, at 4.93 ppm, multiplet, and correlated with the H6α only, were consistent with the desired structure.

A ring-opening reaction, with thiolacetic acid in a dilute 1,4-dioxane solution, was performed at 70 °C for 12 h to give the *anti* C-13 side chain product of **8b**. The disappearance of the two oxazoline ring proton peaks, and the appearance of the amide peak at 8.07 ppm (doublet, J=7.9 Hz), the H3′ at 5.71 ppm (doublet–doublet, J=4.07, 9.26 Hz), the H2′ at 4.82 ppm (doublet, J=4.10 Hz) and the C2′ thioacetyl group at 2.44 ppm, in the ^1H NMR spectrum demonstrated the formation of the *anti* C-13 side chain.

The two Troc groups, at the 7 and 10 positions, were then simultaneously removed by means of the zinc dust method in a mixture of methanol and acetic acid (1:1) at 60 °C to give **9b**.[7e] The ^1H NMR spectrum clearly showed the loss of the two Troc groups. Also, the H10 shifted from 6.07 ppm to, a relatively high field, 5.03 ppm due to the loss of the strong electron-withdrawing neighboring group, as did the H7 proton from 5.43 to 4.12 ppm. The HRMS spectrum further confirmed the removal of Troc groups as shown by a molecular ion peak of 870 ($[M+H]^+$).

Finally, the selective removal of the *S*-acetyl group from the side chain of **9b** was achieved under aqueous basic conditions. However, potassium bicarbonate, which was used in the paclitaxel case, was obviously not enough to completely cleave the *S*-acetyl group this time. Even with the excess amount of base used, there will always be some un-reacted starting material as with the use of potassium carbonate. Maybe the free C10 hydroxyl group accounted for the phenomenon of the increased acidity. Then, an equivalent amount of lithium hydroxide was used to afford **4b**. Surprisingly, no epimerization appeared to happen at the C2′ position, namely, no *syn* amide peak was found at around 7.0 ppm, which always accompanied the main product in the paclitaxel case.

Unlike the straightforward process for the *trans* isomer, with the synthesis of the *cis* oxazoline, **6a**, the problem of epimerization was again encountered, as in the case with 7-TES-baccatin III[6b] (Scheme 2). That is, when 3.5 equiv. of **6a** were coupled to **5**, only 38% of the *cis* oxazoline derivative **7a** was obtained, with more than half undergoing the C-5′ configuration inversion pathway to afford **7b**, with a



Scheme 2. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, **7a** (38%), **7b** (52%). (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 80 °C, 12 h, 95 °C, 12 h, **8a/8b**, 72%. (iii) Zn dust, MeOH/HAc (1:1), 60 °C, 2 h, **9a** (52.2%), **9b** (18%). (iv) LiOH, MeOH/H_2O, rt, 2 h, 58%.

yield of 52%, which was even worse than in the case employing 7-TES-baccatin III. Maybe this could be attributed to the more bulky Troc groups, which might further compress the space around the C-13 hydroxyl group. From a chemical point of view, the formation of an enol should be the intermediate process of the configuration inversion.[6b] However, the separation of **7a** and **7b** was easier than that of their TES counterparts, as the abundance of the *cis* derivative was clearly lower than that of **7b** on the TLC plate. The two peaks at 5.8 and 5.41 ppm, with a coupling constant of 10.6 Hz in the ^{1}H NMR spectrum of **7a** confirmed the *cis* structure,[12] while **7b** was identical in every respect with the *trans* sample. One of the obvious differences in the ^{1}H NMR spectrum of **7a** was that the H13 occurred at 5.56 ppm, compared to 6.24 ppm with **7b**, which proved by the correlation with the H14α and H14β in the ^{1}H–^{1}H COSY 2D NMR analysis. Another difference was the exchange of the chemical shifts between the protons on the C4 acetyl group (2.04–2.24 ppm) and the two C14 protons (2.25–2.42 to 1.92–2.02 ppm).

The ring-opening reaction with thiol acetic acid inherited the bad configuration inversion behavior of the *cis* oxazoline structure. Even though the temperature applied to the reaction vial was carefully controlled, the product was a mixture with the **8a**:**8b** ratio 3.2:1 (confirmed by ^{1}H NMR), while the amide peak at 6.87 ppm revealed the *syn* side chain. Again, the pressure from the two bulky Troc groups has caused greater instability of **8a** than in the TES counterpart (in which a *cis*/*trans* ratio of 35:1 was received), with another enolation process occurring in the reaction procedure. Therefore, it would be easier for the activated molecular species to carry sufficient energy to overcome the energy barrier to directly undergo the C5′ configuration inversion pathway.[6b] In that case, the temperature used for the 7-TES-baccatin model seemed to be not suitable for the di-Troc conditions. No further optimization of the process has been made in this paper.

The two isomers could be separated after removing of the Troc groups using zinc dust to obtain both **9a** and **9b**, which could be distinguished by the chemical shift features of the amides at 6.84 and 8.17 ppm for **9a** and **9b**, respectively. Removal of the *S*-acetyl group by an equivalent amount of lithium hydroxide in aqueous methanol solution of **9a** afforded **4a**, with the evidence of the disappearance of the doublet peak at 4.8 ppm on the ^{1}H NMR and HRMS. On this occasion, a small amount of **4b** accompanied the **4a**.

3. Conclusions

In conclusion, two new kinds of docetaxel compound with a mercapto group instead of a hydroxyl on the C13 side chain (both *syn* and *anti*), via the 7,10-di-(2,2,2-trichloroethyl-oxycarbonyl)-10-deacetylbaccatin III route, were synthesized. The uses of *trans* and *cis* oxazoline compounds, and their stereoselective ring-opening reactions with thiolacetic acid, were proved to be key steps. This kind of thiol taxoids, bearing two free hydroxyl functional groups,

will be useful in the search for new taxoid analogues, with better physical, chemical and biological properties, using combinatorial or parallel syntheses.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. (4*S*,5*R*) and (4*S*,5*S*) 2,4-diphenyloxazoline-5-carboxylic acids were synthesized by the literature procedure.[11] 7,10-Di-(2,2,2-trichloroethyloxycarbonyl)-10-deacetylbaccatin III **5** was prepared by the literature method from 10-deacetylbaccatin III.[7f] Toluene and dioxane were freshly distilled over sodium-benzophenone ketyl. Solvents for re-crystallization were purified by standard methods before use. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. Preparative TLC was performed with Merck 60 F_{254} plates with a 1 mm thickness.

Melting points were measured with Büchi 530 melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded using Bruker Avance 500 or 600 spectrometers with TMS as internal standard. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. ^{13}C NMR were recorded using Bruker Avance 300 or 600 spectrometers. Infrared spectra were recorded on JASCO FTIR-200 Spectrometer. Mass spectra were obtained using JEOL JMS AX505WA or JMS-600 Mstation spectrometers. Elemental analyses were performed using EA 1110 (CHNS-O) (Thermo Finnigan, Italy). Optical rotations were measured using JASCO 3100 polarimeter.

4.1.1. Compound 7b. A solution of DCC (130 mg, 0.63 mmol) in dry toluene (10 mL) was added to a suspension of 7,10-diTroc-10-deacetylbaccatin III **5** (187 mg, 0.21 mmol), *trans*-carboxylic acid **6b** (168 mg, 0.63 mmol) and catalytic amount of 4-pyrrolidinopyridine in 10 mL of dry toluene at 0 °C under N_2 while stirring. After 10 min at 0 °C, the reaction mixture was stirred for another 2 h at room temperature (the reaction was monitored by TLC, EtOAc/hexane=1:2), then passed through a short silica gel plug (~5 g) and further eluted with 50 mL of EtOAc. The combined eluent was concentrated to dry under reduced pressure. A mixture of EtOAc and hexane (20:20 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtration was concentrated again. Careful purification of the residue by flash chromatography twice (EtOAc/hexane, 1:3) afforded the desired product **7b** (220 mg, 0.19 mmol, 92%) as a white solid. An analytical sample was obtained by re-crystallization (EtOAc/hexane) as white fluffy needles: mp 214–6 °C (dec.); $[\alpha]_D^{10}=-41.1°$ (*c*=0.50, $CHCl_3$); IR (KBr) 3573, 3016, 2958, 1764, 1732, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.20 (s, 3H), 1.74 (s, 1H), 1.85 (s, 3H), 2.02–2.08 (m, 8H), 2.25–2.29 (m, 1H), 2.38–2.42 (m, 1H), 2.62–2.68 (m, 1H), 3.93 (d, *J*=7.0 Hz, 1H), 4.15 (d, *J*=8.5 Hz, 1H), 4.30 (d, *J*=8.6 Hz, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.76 (t, *J*=12.1 Hz, 2H), 4.86 (d, *J*=11.8 Hz, 1H), 4.94 (m, 2H), 5.56 (m, 2H), 5.60 (d, *J*=7.3 Hz, 1H), 5.69 (d, *J*=7.0 Hz,1H), 6.24–6.28 (m, 2H), 7.37–7.65(m, 11H), 8.06 (d, *J*=7.9 Hz, 2H), 8.18 (d, *J*=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 11.00, 14.94, 21.18, 21.84, 26.63, 33.47, 35.87, 43.35, 47.23, 56.46, 71.95, 74.54, 75.11, 76.50, 76.63, 77.38, 77.68, 79.25, 79.30, 80.82, 83.74, 83.94, 94.45, 126.66, 127.05, 128.59, 128.96, 129.07, 129.31, 130.33, 132.50, 132.57, 134.16, 141.04, 142.60, 153.38, 153.48, 164.00, 167.16, 170.24, 170.32, 200.87; HRMS (FAB) *m*/*z*=1144.1240 $[M+H+2]^+$, Calcd for $C_{51}H_{50}Cl_6NO_{16}$(1142.1244. Anal. Calcd for $C_{51}H_{49}Cl_6NO_{16}$: C, 53.51; H, 4.32; N, 1.22; Found: C, 53.59; H, 4.44; N, 1.20.

4.1.2. (2′*S*,3′*S*) 3′-*N*-Benzoylamino-2′-deoxy-2′-thioacetyl-7,10-di-(2,2,2-trichloroethyloxycarbonyl)paclitaxel 8b. Compound **7b** (100 mg, 0.087 mmol), thiolacetic acid (1.0 mL) and dioxane (3.0 mL) were added in an 8 mL pressure vial at room temperature. The vial was then closed tightly with a Teflon disk lid, and was heated at 70 °C for 12 h. After concentration under reduced pressure, the sticky yellowish oil was purified by flash chromatography (EtOAc/hexane, 1:3) to get **8b** (76.8 mg, 0.063 mmol, 72%) as a white solid. An analytical sample was obtained by re-crystallization (EtOAc/hexane) as white crystals: mp 173–5 °C; $[\alpha]_D^{16}=-71.2°$ (*c*=0.506, $CHCl_3$); IR (KBr) 3417, 3019, 2955, 1767, 1738, 1663, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.13 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 1.76 (s, 1H), 1.80 (s, 3H), 2.00–2.04 (m, 1H), 2.12–2.21 (m, 2H), 2.32 (s, 3H), 2.44 (s, 3H), 2.59–2.64 (m, 1H), 3.78 (d, *J*=7.0 Hz, 1H), 4.11 (d, *J*=8.6 Hz, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 4.59 (d, *J*=11.8 Hz, 1H), 4.75 (t, *J*=12.0 Hz, 2H), 4.82 (d, *J*=4.1 Hz, 1H), 4.88 (d, *J*=11.8 Hz, 1H), 4.93 (d, *J*=8.9 Hz, 1H), 5.43–5.46 (dd, *J*=7.2, 10.6 Hz, 1H), 5.62 (d, *J*=7.0 Hz, 1H), 5.71 (dd, *J*=4.1, 9.3 Hz, 1H), 6.07 (m, 2H), 7.36–7.63 (m, 11H), 7.89 (m, 2H), 8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.73, 13.59, 21.03, 21.93, 26.24, 30.40, 33.18, 35.08, 43.06, 50.04, 54.42, 56.09, 71.78, 74.25, 76.21, 76.25, 77.12, 77.38, 78.82, 78.94, 80.46, 83.69, 126.12, 127.12, 128.66, 128.70, 128.77, 128.95, 129.27, 130.15, 131.81, 131.97, 133.89, 137.78, 142.13, 153.00, 153.15, 166.90, 170.09, 171.21, 192.41, 200.62; HRMS (FAB) *m*/*z*=1220.1223 $[M+H+2]^+$, Calcd for $C_{53}H_{54}Cl_6NO_{17}S$=1218.1231. Anal. Calcd for $C_{53}H_{53}Cl_6NO_{17}S$: C, 52.14; H, 4.38; N, 1.15; S, 2.63; Found: C, 52.16; H, 4.46; N, 1.12; S, 2.42.

4.1.3. (2′*S*,3′*S*) 10-Deacetyl-2′-deoxy-2′-*epi*-acetylmercaptopaclitaxel 9b. Zinc dust (100 mg) was added in one portion to a vigorously stirred solution of **8b** (75 mg, 0.0615 mmol) in a mixture of 2 mL MeOH and 2 mL acetic acid at 60 °C under N_2. After 2 h, the reaction mixture was cooled down, then passed through a cotton plug and eluted with EtOAc (20 mL). The eluent was concentrated to dry and the residue was re-dissolved in a mixture of EtOAc and brine (45 mL:15 mL). The organic layer was then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by flash chromatography (EtOAc/hexane=1:1) to afford product **9b** (41 mg, 0.047 mmol, 77%) as a white solid: mp 164–6 °C; $[\alpha]_D^{11}=-85.1°$ (*c*=0.77, $CHCl_3$); IR (KBr) 3368, 2941,

2833, 1732, 1646, 1548 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.68 (s, 1H), 1.69 (s, 3H), 1.78–1.85 (m, 1H), 2.08–2.20 (m, 2H), 2.28 (s, 3H), 2.43 (s, 3H), 2.53–2.59 (m, 1H), 3.77 (d, J=7.1 Hz, 1H), 4.11–4.15 (m, 3H), 4.29 (d, J=8.5 Hz, 1H), 4.78 (d, J=4.0 Hz, 1H), 4.92 (d, J=8.2 Hz, 1H), 5.0 (s, 1H), 5.60 (d, J=7.1 Hz, 1H), 5.69 (dd, J=3.9, 9.3 Hz, 1H), 6.05 (t, J=8.6 Hz, 1H), 7.29–7.62 (m, 11H), 7.90 (d, J=7.4 Hz, 2H), 8.06 (d, J=7.5 Hz, 2H), 8.16 (d, J=9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.11, 13.57, 20.87, 22.23, 26.58, 30.67, 35.66, 37.13, 43.23, 46.65, 50.29, 54.80, 57.75, 72.11, 72.29, 74.62, 75.13, 76.77, 79.22, 81.02, 84.40, 126.46, 127.40, 128.75, 128.92, 129.03, 129.41, 129.44, 130.40, 132.21, 134.03, 134.05, 135.92, 138.16, 138.42, 167.23, 167.27, 170.16, 171.45, 192.73, 211.54; HRMS (FAB) m/z=870.3159 $[M+H]^+$, Calcd for $C_{47}H_{52}NO_{13}S$=870.3145.

4.1.4. (2′*S*,3′*S*) 10-Deacetyl-2′-deoxy-2′-*epi*-mercaptopaclitaxel 4b. A solution of $LiOH{\cdot}H_2O$ (1.56 mg, 0.037 mmol) in 0.2 mL water (degassed before used) was added dropwise to a stirred solution of **9b** (32 mg 0.037 mmol) in 2 mL MeOH at room temperature during 30 min under N_2. After addition, the reaction was continued for another 1.5 h. A mixture of $CHCl_3$ and water (15 mL:15 mL) was added. The mixture was acidified by 2 or 3 drops of 1 N HCl to pH 1–2. The aqueous layer was extracted with $CHCl_3$ (3×15 mL) and the combined organic layer was washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by preparative TLC ($CHCl_3$/MeOH=20:1) in dark place to afford final product **4b** (20.8 mg, 0.025 mmol, 68%) as a white solid: mp 206–8 °C (dec.); $[\alpha]_D^{13}$=+11.7° (c=0.40, MeOH); IR (KBr) 3465, 2986, 2927, 1726, 1663, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.08 (s, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 1.63 (s, 1H), 1.72 (s, 3H), 1.79–1.84 (m, 1H), 2.00–2.04 (m, 2H), 2.2–2.22 (m, 2H), 2.36 (s, 3H), 2.53–2.59 (m, 2H), 3.80 (d, J=8.3 Hz, 1H), 3.85 (dd, J=4.3, 13.1 Hz, 1H), 4.13–4.15 (m, 3H), 4.30 (d, J=10.1 Hz, 1H), 4.93 (d, J=7.1 Hz, 1H), 5.05 (s, 1H), 5.63 (d, J=8.5 Hz, 1H), 5.77 (dd, J=4.2, 11.3 Hz, 1H), 6.05 (m, 1H), 7.29–7.63 (m, 11H), 7.94 (d, J=8.8 Hz, 2H), 8.06 (d, J=8.8 Hz, 2H), 8.18 (d, J=11.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.17, 14.02, 14.51, 23.08, 23.21, 26.76, 29.63, 30.09, 35.72, 43.34, 45.06, 46.90, 57.99, 71.73, 72.39, 74.85, 75.08, 76.49, 76.98, 79.19, 81.37, 84.43, 126.52, 127.51, 128.88, 129.11, 129.21, 129.48, 129.56, 130.45, 132.45, 167.40, 170.02, 173.32, 211.61; HRMS (FAB) m/z=828.3065 $[M+H]^+$, Calcd for $C_{45}H_{50}NO_{12}S$=828.3196.

4.1.5. Compound 7a. A solution of DCC (464 mg, 2.25 mmol) in dry toluene (20 mL) was added to a suspension of 7,10-diTroc-10-deacetylbaccatin III **5** (570 mg, 0.636 mmol), *cis*-carboxylic acid **6a** (600 mg, 2.25 mmol) and catalytic amount of 4-pyrrolidinopyridine in 30 mL of dry toluene at 0 °C under N_2 while stirring. After 10 min at 0 °C, the reaction mixture was stirred for another 3 h at room temperature (the reaction was monitored by TLC, EtOAc/hexane=1:2), then passed through a short silica gel plug (~5 g) and further eluted with 50 mL of EtOAc. The combined eluent was concentrated to dry under reduced pressure. A 1:1 mixture of EtOAc and hexane (40 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtration was concentrated again. Careful purification of the residue by flash chromatography twice (EtOAc/hexane, 1:3) afforded **7b** (378 mg, 0.33 mmol, 52%) as a white solid (proved by ^{1}H NMR) and **7a** (276 mg, 0.24 mmol, 38%) as a white solid: mp 174–6 °C; $[\alpha]_D^{16}$=−53.4° (c=1.14, $CHCl_3$); IR (KBr) 3526, 3043, 2974, 1759, 1728, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.58 (s, 1H), 1.59 (s, 3H), 1.81 (s, 3H), 1.92 (m, 1H), 2.01 (m, 1H), 2.04 (m, 1H), 2.24 (s, 3H), 2.59–2.64 (m, 1H), 3.75 (d, J=6.9 Hz, 1H), 4.13 (d, J=8.5 Hz, 1H), 4.27 (d, J=8.5 Hz, 1H), 4.60 (d, J=11.8 Hz, 1H), 4.74–4.79 (dd, J=15.1, 11.8 Hz, 2H), 4.90 (d, J=11.8 Hz, 1H), 4.92–4.94 (m, 1H), 5.43 (d, J=10.5 Hz, 1H), 5.48–5.51 (dd, J=10.7, 7.2 Hz, 1H), 5.60 (t, J=8.1 Hz, 1H), 5.61 (d, J=7.0 Hz, 1H), 5.79 (d, J=10.5 Hz, 1H), 6.13 (s, 1H), 7.25–7.65 (m, 11H), 8.04 (d, J=7.3 Hz, 2H), 8.11 (d, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.95, 14.57, 21.23, 22.59, 26.51, 33.48, 36.12, 43.15, 47.07, 56.36, 71.86, 73.97, 74.40, 76.47, 76.60, 77.40, 77.68, 79.10, 79.29, 80.94, 81.62, 83.84, 94.46, 126.76, 128.46, 128.89, 128.95, 129.05, 129.13, 129.30, 130.30, 131.84, 132.53, 134.13, 136.59, 142.50, 153.40, 153.46, 164.78, 167.02, 168.25, 169.90, 200.87; HRMS (FAB) m/z=1144.1240 $[M+H+2]^+$, Calcd for $C_{51}H_{50}Cl_6NO_{16}$=1142.1244. Anal. Calcd for $C_{51}H_{49}Cl_6NO_{16}$: C, 53.51; H, 4.32; N, 1.22; Found: C, 53.93; H, 4.40; N, 1.02.

4.1.6. (2′*R*,3′*S*) 3′-*N*-Benzolamino-2′-deoxy-2′-thiolacetyl-7,10-di-(2,2,2-trichloroethyloxycarbonyl)paclitaxel 8a. Compound **7a** (270 mg, 0.236 mmol), thiolacetic acid (1.3 mL) and dioxane (4.0 mL) were added in an 8 mL pressure vial at room temperature. The vial was then closed tightly with a Teflon disk lid, and was heated stepwise at 70 °C for 12 h, 80 °C 12 h and 95 °C 12 h. After concentration under reduced pressure, the sticky oil was purified by flash chromatography (EtOAc/hexane, 1:3) to get **8a** (207 mg, 0.17 mmol, 72() as a white solid, which mixtured with *trans*- diastereoisomer **8b** (the ratio of *cis*/*trans* is 3.2:1 as shown by ^{1}H NMR): mp 181–3 °C; $[\alpha]_D^{16}$=+6.3° (c=1.77, $CHCl_3$); IR (KBr) 3415, 3010, 2953, 1768, 1732, 1679, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.14 (s, 3H), 1.18 (s, 3H), 1.58 (s, 1H), 1.80 (s, 3H), 1.89 (s, 3H), 2.00–2.06 (m, 1H), 2.13–2.44 (m, 2H), 2.31 (s, 3H), 2.46 (s, 3H), 2.59–2.62 (m, 1H), 3.82 (d, J=6.9 Hz, 1H), 4.12 (m, 1H), 4.28 (d, J=8.5 Hz, 1H), 4.57 (d, J=11.7 Hz, 1H), 4.74 (m, 3H), 4.89 (d, J=11.8 Hz, 1H), 4.93 (d, J=9.3 Hz, 1H), 5.52 (d, J=8.1 Hz, 1H), 5.60 (d, J=7.0 Hz, 1H), 5.72 (m, 1H), 6.05 (m, 1H), 6.20 (s, 1H), 6.87 (d, J=8.7 Hz, 1H), 7.31–8.10 (m, 15H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.68, 14.48, 20.84, 22.25, 26.23, 30.49, 33.13, 34.91, 42.97, 46.80, 49.04, 55.77, 56.10, 70.90, 74.10, 76.07, 77.21, 78.78, 78.87, 80.29, 83.66, 94.15, 126.50, 127.21, 128.63, 129.28, 130.04, 131.94, 132.08, 133.54, 134.84, 139.13, 142.04, 153.05, 166.46, 166.75, 168.40, 169.97, 195.50, 200.56; HRMS (FAB) m/z=1220.1223 $[M+H+2]^+$, Calcd for $C_{53}H_{54}Cl_6NO_{17}S$=1218.1231.

4.1.7. (2′*R*,3′*S*) 10-Deacetyl-2′-deoxy-2′-acetylmercaptopaclitaxel 9a. Zinc dust (250 mg) was added in one portion to a vigorously stirred solution of **8a/8b** (195 mg, 0.16 mmol) in a mixture of 3 mL MeOH and 3 mL acetic

acid at 62 °C under N_2. After 2 h, the reaction mixture was cooled down, then passed through a cotton plug and eluted with EtOAc (20 mL). The eluent was concentrated to dry and the residue was re-dissolved in a mixture of EtOAc and brine (60:15 mL). The organic layer was then dried over anhydrous sodium sulfate. After concentration in vacuo, the crude product was purified by preparative TLC (EtOAc/hexane=1:1) to afford *trans* product **9a** (24 mg, 0.028 mmol, 18%) and *cis*-product **9a** (73 mg, 0.084 mmol, 52.5%) as a white solid: mp 168–70 °C; $[\alpha]_D^{14}$=+9.62° (*c*=0.21, $CHCl_3$); IR (KBr) 3374, 2942, 2832, 1726, 1647, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.07 (s, 3H), 1.13 (s, 3H), 1.54 (br, 2H), 1.72 (s, 3H), 1.79 (s, 3H), 1.88–1.92 (m, 2H), 2.10–2.47 (m, 1H), 2.30 (s, 3H), 2.44 (s, 3H), 2.55 (m, 1H), 3.83 (d, *J*=7.1 Hz, 1H), 4.13 (s, 1H), 4.17 (d, *J*=8.5 Hz, 1H), 4.19 (br, 1H), 4.26 (d, *J*=8.5 Hz, 1H), 4.75 (d, *J*=10.5 Hz, 1H), 4.92 (d, *J*=8.2 Hz, 1H), 5.13 (s, 1H), 5.60 (d, *J*=7.1 Hz, 1H), 5.73 (t, *J*=9.7 Hz, 1H), 6.03 (t, *J*=8.8 Hz, 1H), 6.85 (t *J*=8.7 Hz, 1H), 7.33–7.72 (m, 11H), 7.72 (d, *J*=7.5 Hz, 2H), 8.02 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (DMSO, 150 MHz) δ 9.81, 13.56, 20.81, 22.37, 26.51, 30.20, 42.85, 45.91, 52.56, 70.73, 70.76, 73.57, 74.81, 75.34, 76.87, 80.15, 83.79, 127.45, 127.74, 128.09, 128.35, 128.50, 128.67, 129.47, 130.06, 131.54, 134.15, 135.57, 136.83, 139.27, 165.21, 166.23, 166.31, 169.49, 170.69, 192.56, 209.28; HRMS (FAB) *m*/*z*=870.3150 $[M+H]^+$, Calcd for $C_{47}H_{52}NO_{13}S$=870.3145. Anal. Calcd for $C_{47}H_{51}NO_{13}S$: C, 64.90; H, 5.91; N, 1.61; S, 3.68; Found: C, 64.60; H, 6.40; N, 1.46; S, 3.20.

4.1.8. (2′*R*,3′*S*) 10-Deacetyl-2′-deoxy-2′-mercapto-paclitaxel 4a. A solution of $LiOH{\cdot}H_2O$ (2.69 mg, 0.064 mmol) in 0.2 mL water (degassed before used) was added dropwise to a stirred solution of **9a** (55.6 mg 0.064 mmol) in 2 mL MeOH at room temperature under N_2. After addition, the reaction was continued for another 1.5 h. A mixture of $CHCl_3$ and water (15 mL:15 mL) was added. The mixture was acidified by 2 or 3 drops of 1 N HCl to pH 1–2. The aqueous layer was extracted with $CHCl_3$ (3×15 mL) and the combined organic layer was washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuum, the crude product was purified by preparative TLC ($CHCl_3$/MeOH=20:1) in dark place to afford final product **4a** (31 mg, 0.037 mmol, 57.8%) as a white solid: mp 198–200 °C; $[\alpha]_D^{12}$=−3.38° (*c*=0.308, MeOH); IR (KBr) 3417, 2947, 2854, 1731, 1633, 1528 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.08 (s, 3H), 1.14 (s, 3H), 1.24–1.31 (m, 2H), 1.52 (s, 3H), 1.70 (s, 1H), 1.73 (s, 3H), 1.82 (m, 1H), 2.04 (m, 1H), 2.21 (m, 1H), 2.27 (d, *J*=5.8 Hz, 1H), 2.56–2.60 (m, 1H), 3.86 (d, *J*=7.0 Hz, 1H), 4.02 (t, *J*=8.6 Hz, 1H), 4.16 (d, *J*=8.5 Hz, 1H), 4.20 (m, 2H), 4.29 (d, *J*=8.5 Hz, 1H), 4.95 (d, *J*=9.4 Hz, 1H), 5.19 (s, 1H), 5.64 (d, *J*=7.0 Hz, 1H), 5.66 (t, *J*=8.0 Hz, 1H), 6.04 (t, *J*=8.6 Hz, 1H), 7.05 (m, 1H), 7.28–7.62 (m, 11H), 7.80 (d, *J*=7.4 Hz, 2H), 8.06 (d, *J*=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.15, 14.71, 20.94, 22.80, 26.68, 29.46, 31.18, 36.00, 37.22, 43.24, 46.66, 47.28, 56.01, 57.82, 71.87, 72.22, 74.67, 75.08, 76.78, 79.21, 81.20, 84.34, 127.30, 127.40, 128.70, 128.93, 129.02, 129.22, 129.47, 130.36, 132.23, 124.02, 134.22, 136.01, 138.74, 138.95, 167.20, 167.41, 170.13, 171.10, 211.68; HRMS (FAB) *m*/*z*=828.3008 $[M+H]^+$, Calcd for $C_{45}H_{50}NO_{12}S$=828.3196.

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Synthesis of polysubstituted furans by palladium-catalyzed coupling of butatrienyl carbinols with aryl halides and triflates

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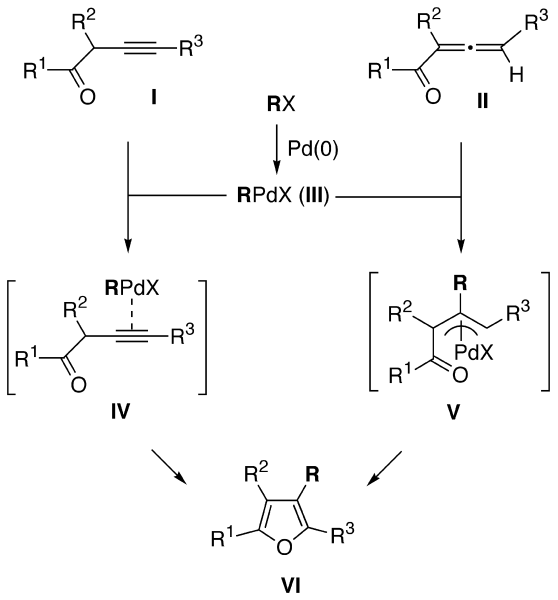
Abstract—An efficient one-pot two-step synthesis of polysubstituted furans is described using readily available 4,5-epoxy-2-alkynyl esters as starting materials. In the first step, reduction of these with SmI_2 affords buta-1,2,3-trienyl carbinol intermediates which, in the second step, participate in Pd(0)-catalyzed cyclization reactions with aryl halides and triflates by a mechanism probably involving oxidative addition, intramolecular oxypalladation and reductive elimination steps. In this manner, up to four carbon substituents are incorporated onto the furan ring, with the aryl group being introduced at the furan 3- or 4-positions. These features make the method particularly suitable for regioselective synthesis of tetrasubstituted furans.

1. Introduction

Alkyne- and allene substrates with an internal C-, O- or N-based nucleophile have been extensively used in palladium-catalyzed coupling reactions with aryl-, vinyl- or allyl halides and triflates (R-X) leading to the efficient preparation of a variety of substituted carbocyclic and heterocyclic structures incorporating the organic fragment (R).[1] When an oxygen nucleophile (carboxylic acid, alcohol or ketone) is appended to an alkynyl or allenyl moiety,[2,3] the application of this strategy results in the regioselective synthesis of substituted furans and related derivatives,[4] a topic of current interest due to the synthetic, biological and industrial importance of these compounds.[5] These reactions proceed through the intermediacy of RPdX complexes (**III**) formed by oxidative addition of R-X to Pd(0), that can promote the coupling process typically in two different ways. For alkyne substrates typified by **I**, the organopalladium **III** activates the unsaturated system of **I** towards intramolecular attack by the internal oxygen nucleophile. After cyclization, reductive elimination follows to give the product **VI**. Alternatively, the addition of RPdX across the allene π-system of substrates **II** results in formation of a new C–C bond at the central carbon of the diene, and a π-(allyl)palladium complex **V** which then suffers intramolecular nucleophilic attack to form the cyclic structure (Scheme 1).

In the context of regioselective furan synthesis from acyclic



Scheme 1.

precursors,[4] we have introduced the use of epoxyalkynyl esters **VII** as precursors of buta-1,2,3-trienyl carbinols **VIII**, that are substrates for a Pd(II)-promoted cycloisomerization leading to furans **X** (Scheme 2).[6] The overall transformation **VII→X** takes place in one pot and the presumed role of Pd(II) is to activate the central triene double bond of **VIII** to undergo nucleophilic attack by the internal hydroxyl group.

Conceivably, an analogous treatment of intermediates **VIII** with organopalladium complexes **III**, generated in situ from Pd(0) and R-X (where R=aryl or vinyl) could be expected to

Keywords: Furans; Palladium-catalyzed coupling; Intramolecular oxypalladation; [3]Cumulenes.
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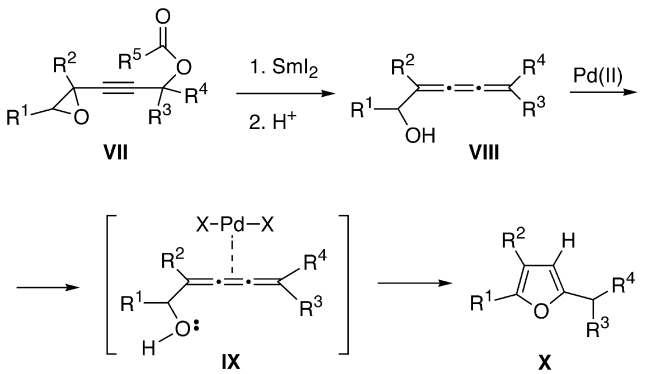
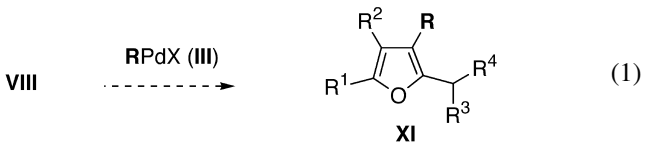


Scheme 2.

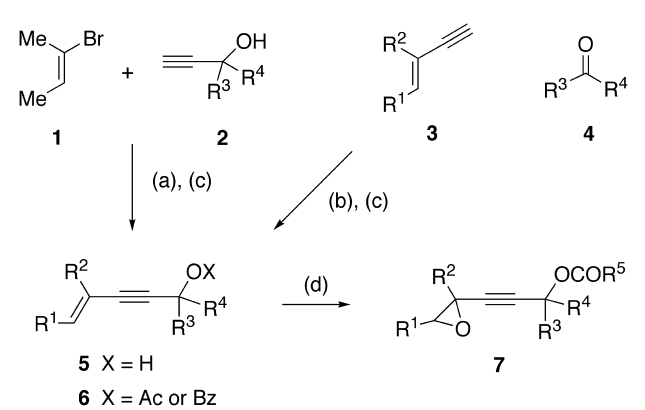
promote a similar cyclization with concomitant coupling between the furyl and R fragments, thus leading to a more highly substituted furan **XI** (Eq. (1)). While alcohols of type **VIII** have been involved in alternative previous syntheses of furans,[7] prior to this work their use in Pd-catalyzed couplings with organic halides was unprecedented.[8] In this paper we describe the results of a study on a new Pd-catalyzed cyclization involving buta-1,2,3-trienyl carbinols **VIII** and aryl halides or triflates. Overall, the regioselective synthesis of polysubstituted arylated furans **XI** (R=Ar) from esters **VII** is achieved in a one-pot two-step process.[9] This work expands the scope of our previously reported synthesis of 2,3,5-trisubstituted furans from **VII**[6] by extending it to include the 2,3,4-tri- and 2,3,4,5-tetrasubstituted patterns through the formation of a new C–C bond at the furan 3- or 4-positions.



(1)

2. Results and discussion

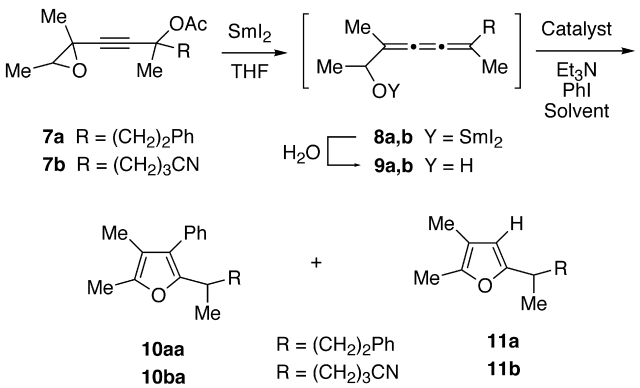
Representative substrates of type **7** were prepared either by Sonogashira coupling[10] between vinyl bromide (**1**) and propargyl alcohol (**2**) fragments, or by addition of alkynyllithium reagents, derived from suitable enynes **3**, to aldehydes or ketones **4**, followed in both cases by esterification and epoxidation (Scheme 3).



Scheme 3. (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, rt, to give **5**. (b) (i) *n*-BuLi, THF, −78→0 °C; (ii) **4**, THF, −78→rt; (iii) H_2O, to give **5**, or (iii) BzCl, 0 °C→rt, to give **6** (X=Bz). (c) From **5**; Ac_2O, DMAP, Et_3N, to give **6** (X=Ac). (d) MCPBA, CH_2Cl_2, rt.

Initial exploratory studies were conducted starting from epoxides **7a**,**b** and iodobenzene (Table 1). Treatment of **7a** with SmI_2 (2.1 equiv.) at −5 °C in THF afforded the presumed samarium alkoxide **8a**. Direct treatment of this with PhI and catalytic $Pd(PPh_3)_4$ at various temperatures led in all cases to degradation. In contrast, isolated alcohol **9a** (crude from **7a**, 92% yield), when treated with PhI (1 equiv.), $Pd(PPh_3)_4$ (5 mol%) and Et_3N (5 equiv.) in refluxing THF, afforded the expected arylated tetrasubstituted furan **10aa** in 36% yield (two steps from **7a**). A similar yield of **10aa** (33%) was obtained when isolation of intermediate **9a** was omitted and, instead, water (1 equiv.) was added to the alkoxide **8a** prior to treatment with $Pd(PPh_3)_4$/PhI/Et_3N (entry 1 of Table 1). An analogous treatment of alcohol **9b**, generated in situ from alkoxide **8b** with 1 equiv. of water, produced the corresponding furan **10ba** in 26% yield (entry 2). An important problem encountered in these preliminary experiments was the competing formation of the corresponding

Table 1. Study of reaction conditions for the pd(0)-catalyzed reaction of alcohols **9a**,**b** with PhI



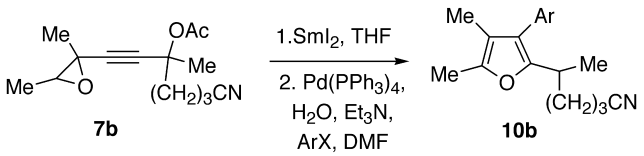
	7	Catalyst[a]	Solvent	T[b]	10[c]	11[c]
1	**7a**	$Pd(PPh_3)_4$	THF	70	**10aa** (33)	**11a** (12)
2	**7b**	$Pd(PPh_3)_4$	THF	70	**10ba** (26)	**11b** (16)
3	**7a**	$Pd_2dba_3{\cdot}CHCl_3$	THF	70	—	—
4	**7a**	$Pd(Oac)_2$/4$AsPh_3$	THF	70	**10aa**[d]	**11a**[d]
5	**7a**	$PdCl_2(MeCN)_2$	THF	70	—	**11a** (50)
6	**7b**	Pd_2dba_3/4TFP	THF	70	—	**11b** (47)
7	**7b**	$Pd(OAc)_2$/3PPh_3	THF	70	—	**11b** (25)
8	**7a**	$Pd(PPh_3)_4$	MeCN[e]	70	**10aa**[d]	**11a** (9)
9	**7b**	$Pd(PPh_3)_4$	DMF[e]	60	**10ba** (48)	**11b** (d)
10[f]	**7b**	$Pd(PPh_3)_4$	DMF[e]	80	—	—
11	**7b**	$Pd(OAc)_2$	DMF[e]	80	—	**11b** (50)
12	**7b**	$Pd(OAc)_2$/3PPh_3	DMF[e]	100	**10ba** (33)	**11b**[d]
13[g]	**7b**	$Pd(PPh_3)_4$	DMF[e]	70	**10ba** (53)	**11b**[d]
14[g]	**7b**	$Pd(PPh_3)_4$[h]	DMF[e]	70	**10ba** (56)	—
15[g,i]	**7b**	$Pd(PPh_3)_4$[h]	DMF[e]	70	**10ba** (28)	—

[a] Unless otherwise indicated, 5 mol% of the palladium complex was used. TFP=tri(2-furyl)phosphine.
[b] Bath temperature (°C) for the Pd-catalyzed step.
[c] Isolated yield (%) of pure product for two steps from epoxides **7a** or **7b**.
[d] Trace.
[e] After the reduction step, THF was evaporated and the resulting residue was dissolved in the appropriate solvent.
[f] K_2CO_3 (5 equiv.) was employed in place of Et_3N.
[g] Two equivalents of PhI were used.
[h] Reaction run with 10 mol% of $Pd(PPh_3)_4$.
[i] Water was omitted.

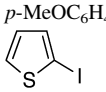
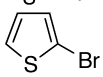
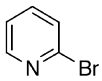
cycloisomerization products, the 2,3,5-trisubstituted furans **11a** and **11b**,[6] that were isolated in comparatively important amounts (10–16%). A survey of reaction conditions was then conducted to improve the efficiency of the reaction, proceeding in all cases without isolation of intermediate alcohols **9**. By using THF as solvent (entries 1–7), $Pd(PPh_3)_4$ was determined to be superior to other catalysts tested (entries 3–7), that either promoted the formation of trisubstituted furans **11** (entries 5–7) or led to considerable degradation (entries 3 and 4). Results improved considerably with a change of solvent from THF to DMF, which caused the yield of **10ba** to increase to 48%, while the amount of trisubstituted furan **11b** decreased substantially (entry 9). Further improvements were realized by doubling the amount of arylating agent (entry 13), particularly when the amount of catalyst was also increased (entry 14). Under this latest conditions formation of furan **11b** was not observed, and these were adopted as standard conditions for subsequent reactions. Further changes in base (entry 10) or catalyst (entries 11 and 12) were not effective. In sharp contrast with earlier results obtained in THF (vide supra), the direct treatment of samarium alkoxide **8b** with $Pd(PPh_3)_4$, PhI and Et_3N in DMF, without generation of alcohol **9b**, under otherwise standard conditions, also afforded the desired **10ba** (entry 15). However, even in this case, the yield of **10ba** was substantially lower (28%) than that obtained in the presence of water (entry 14) while the reaction time increased considerably (3 days in entry 15 vs 16 h in entry 14).

Using the conditions of entry 14, the method was applied to arylating agents other than PhI taking ester **7b** as model substrate. These results are collected in Table 2. A number of aryl- (entries 1–7) and heteroaryl (entries 8–11) coupling agents could be incorporated successfully into the sequence, and the corresponding arylated furans **10b** were obtained in moderate-to-good yields, usually without interference from formation of compounds of type **11**. Both electron-deficient and electron-rich aromatics have been employed successfully in this reaction. However, the use of 4-iodoanisole (**12g**, entry 7), with a strong electron-donating *p*-MeO group, was complicated by Ar–Ph exchange between Pd and the PPh_3 ligands at the level of a $ArPd(PPh_3)_2X$ intermediate (see **III**, R=Ar in Scheme 1).[2m,11–13] Thus, using the standard procedure, **12g** afforded a low yield (22%) of the expected product **10be**, the major product of this reaction being **10ba** (46%), the result of incorporation of a phenyl rather than a 4-methoxyphenyl group. The undesired formation of **10ba** was completely suppressed by carrying out the reaction from the isolated alcohol **9b**. In this manner the arylated furan **10be** was obtained in an improved 40% yield and no **10ba** was found.[14] When the arylating agent contained both C–I and C–Br bonds susceptible of oxidative addition, the reaction took place chemoselectively at the C–I bond (entry 4) and this made it possible to incorporate a bromoaryl group into the final product. Bromides were effective partners, however, in the heteroaromatic series as shown by entries 9–11. In a brief examination, the corresponding triflates were found to give mixed results. Thus, while phenyl triflate and phenyl iodide gave comparable results (entries 1 and 2), the triflate was substantially inferior to the iodide in the *p*-tolyl case (entries 5 and 6). Attempts to extend the reaction to cyclohexenyl triflate, 2-bromo-*trans*-2-butene and ethyl *cis*-3-iodoacrylate failed.

Table 2. Preparation of furans **10b** from epoxide **7b** and Ar-X

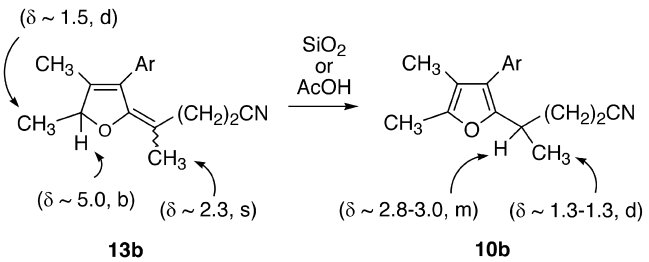


7b **10b**

	Ar-X	12	T (t)[a]	10b[b]
1	PhI	**12a**	70 (16)	**10ba** (56)
2	PhOTf	**12b**[c]	70 (24)	**10ba** (54)
3	*p*-$MeCOC_6H_4I$	**12c**	80 (24)	**10bb** (64)
4	*p*-BrC_6H_4I	**12d**	70 (48)	**10bc** (73)
5	*p*-MeC_6H_4I	**12e**	80 (18)	**10bd** (53)
6	*p*-MeC_6H_4OTf	**12f**	80 (82)	**10bd** (39)
7[d]	*p*-$MeOC_6H_4I$	**12g**	60 (13)	**10be** (40)
8		**12h**	70 (22)	**10bf** (46)
9		**12i**	70 (72)	**10bf** (53)
10		**12j**	70 (72)	**10bg** (52)[e]
11		**12k**	80 (72)	**10bh** (53)

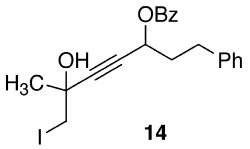
[a] Bath temperature (°C) for the Pd-catalyzed step. Within brackets, reaction time (h).
[b] Isolated yield (%) of pure product for two steps starting from epoxide **7b**.
[c] 5 mol% $Pd(PPh_3)_4$ was used.
[d] An aqueous work-up was performed after reduction with SmI_2 to isolate alcohol **9b** prior to cyclization.
[e] The 2,3,5-trisubstituted furan **11b** was also obtained (5%).

Interestingly, the ^1H NMR spectra of the crude products revealed that the expected furans **10b** were accompanied in most cases by variable amounts of dienes **13b**. This was deduced from the observation of a broad signal at $\delta\sim5.0$ assigned to the methine C*H*–O of **13b** and a singlet at $\delta\sim2.3$ corresponding to the side-chain methyl group. In comparison, the corresponding furans of type **10b** displayed a characteristic multiplet at $\delta\sim2.8–3.0$ corresponding to the side-chain methine proton, absent in **13b**, as well as a doublet at $\delta\sim1.2–1.3$ for the side-chain Me group. Upon stirring EtOAc solutions of the crude product mixtures with AcOH or SiO_2, or simply proceeding directly to the chromatographic purification in silica gel, dienes **13b** were completely converted into the corresponding furans **10b** (Eq. (2)).[15]



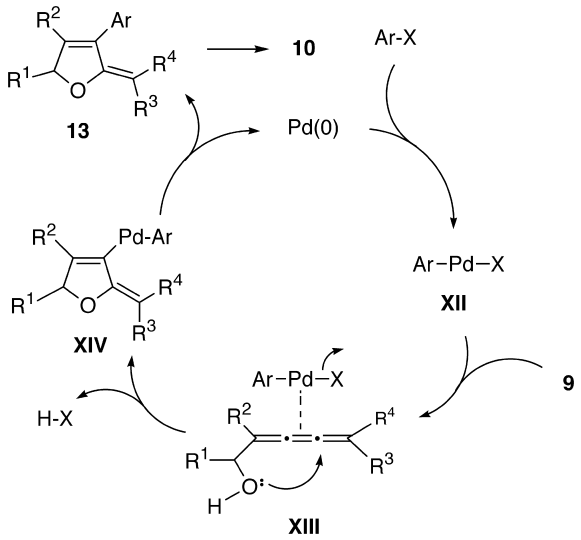
13b **10b** (2)

The method has also been applied successfully to other substrates **7** in combination with aryl halides **12**, and these results are collected in Table 3. Highly substituted furans containing in most cases carbon substituents at all ring positions were thus obtained efficiently from epoxides **7** in a one-pot two-step process. Therefore, the intramolecular oxypalladation/reductive elimination sequence appears to be particularly well suited to the synthesis of tetrasubstituted furans. This is a particularly interesting feature because the regioselective introduction of four different carbon substituents onto the furan ring is a difficult task and only a limited number of methods have been described in the literature that manage it efficiently.[2m,3a,15a,16] The formation of an arylated 2,3,5-trisubstituted furan **10e**, lacking the C-5 substituent, was also tested (entry 6) and this required a slight modification in the reduction step to avoid the competing formation of iodohydrin **14**, observed under the standard reduction conditions. Compound **14** is the result of iodide anion-promoted epoxide ring-opening, a process well documented in the literature,[17] which is facilitated in **7e**, relative to the other substrates, by the less hindered approach of the anion to the terminal epoxide. After a brief survey of reaction conditions, it was found that dropwise addition of the substrate to an excess SmI_2 (3.1 equiv.) at 10 °C suppressed completely the unwanted formation of **14** and the ensuing cyclization led to **10e** in a reasonable yield.



14

Table 3 also reveals good tolerance of the whole sequence for both acid- and base-sensitive functional groups, as shown by the presence of carbonyl, cyano and protected hydroxyl groups in the final products (entries 3, 5, 7 and 8). Branched substituents are readily accommodated at different ring positions (entries 1–3, 5 and 7), and the formation of bicyclic products is shown to be feasible (entries 10 and 11). A further point of interest is the additional flexibility that this strategy offers to the existing methodology in the creation of regiochemical patterns around the furan nucleus. Thus, the heterocyclic ring carbon framework and three ring substituents are provided by the simple vinyl halide, acetylene and aldehyde or ketone fragments used in the assembly of the starting material **7**, whereas the fourth substituent is incorporated from the aryl halide **12**.



Scheme 4.

A plausible mechanistic interpretation for the transformation of trienes **9** into arylated furans **10** is shown in Scheme 4. Thus, after activation of the central triene double bond with an arylpalladium(II) **XII**, generated from Ar-X and Pd(0), intramolecular oxypalladation would lead to a

Table 3. General preparation of furans **10** from epoxides **7** and Ar-X (**12**)

7 **10**

	7	R^1	R^2	R^3	R^4	12	T (t)[a]	10b[b]
1	**7a**[c]	CH_3	CH_3	$(CH_2)_2Ph$	CH_3	**12a**	80 (13)	**10aa** (56)
2	**7a**[c]					**12d**	70 (15)	**10ab** (62)
3	**7b**[c]	CH_3	CH_3	$(CH_2)_3CN$	CH_3	**12a**	70 (16)	**10ba** (56)
4	**7c**[c]	CH_3	CH_3	$(CH_2)_2Ph$	H	**12c**	70 (13)	**10c** (74)
5	**7d**[c]	*i*-Pr	*i*-Bu	$(CH_2)_2Ar$[d]	H	**12d**	60 (18)	**10d** (76)
6	**7e**[e]	H	CH_3	$(CH_2)_2Ph$	H	**12d**	60 (110)	**10e** (59)
7	**7f**[c]	CH_2OMOM	CH_3	$(CH_2)_3CN$	CH_3	**12c**	40 (72)	**10f** (63)
8	**7g**[c]	CH_2OMOM	CH_3	$(CH_2)_2Ph$	H	**12d**	100 (10)	**10ga** (65)
9	**7g**[c]					**12c**	100 (10)	**10gb** (60)
10	**7h**[e]	$(CH_2)_4$		$(CH_2)_2Ph$	H	**12a**	70 (9)	**10ha** (74)
11	**7h**[e]					**12c**	70 (9)	**10hb** (68)

[a] Bath temperature (°C) for the Pd-catalyzed step. Within brackets, reaction time (h).
[b] Isolated yield (%) of pure product for two steps from epoxides **7**.
[c] R^5=CH_3.
[d] Ar=3,4-dimethoxyphenyl.
[e] R^5=Ph.

new diorganopalladium complex **XIV**. Reductive elimination and aromatization, in this order, then affords furans **10**, through dienes **13**.[18] As mentioned earlier, these dienes have been observed in the crude products and they are seen to isomerize to the corresponding furans **10**. Therefore, it can be safely concluded that reductive elimination does indeed precede aromatization as described in Scheme 4.

3. Conclusions

Highly substituted furans are effectively prepared by Pd(0)-catalyzed coupling of penta-2,3,4-trien-1-ols **9** and aryl halides. The generation[19] and use of these compounds starting from epoxypropargyl esters **7** is convenient due to (i) easy assembly of the starting materials from readily available precursors, (ii) the possibility of incorporating useful functionality, (iii) mild reaction conditions, and (iv) the possibility of carrying out the transformations **7→9→10** in one-pot, without isolation of **9**.[20] This method should find particular application in the regioselective synthesis of tetrasubstituted furans.

4. Experimental

4.1. General

All reactions involving air- and moisture-sensitive materials were performed using standard bench-top techniques.[21] Acetic anhydride, 5-oxohexanenitrile, 4-phenylbutan-2-one, diiodomethane, iodobenzene, DMF, CH_2Cl_2, diethylamine and triethylamine were distilled from CaH_2 and purged with Ar. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. DMF and triethylamine were similarly deoxygenated for Pd-catalyzed reactions. Flash column chromatography[22] was performed on silica gel (230–400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 (7 μm, 25×2.5 cm) column using a refraction index detector. Routine ^1H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, using $CDCl_3$ as solvent and internal reference (δ 7.26 for ^1H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV. Solutions of SmI_2 in THF were prepared from Sm and diiodomethane using a literature procedure.[23] Palladium complexes and phosphines were purchased and used as received, with the exception of $Pd(PPh_3)_4$, that was prepared as reported.[24] Epoxides **7a**, **7b** and **7h** have been prepared as reported.[6]

4.2. Procedure for the preparation of alcohols 5 from vinyl bromide 1 and propargylic alcohols 2

In a typical experiment, a solution of a propargylic alcohol **2** (30.0 mmol) in Et_2NH (10 mL) was added to a solution of *trans*-2-bromobut-2-ene (**1**) (2.84 mL, 30.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.450 g, 0.640 mmol) and CuI (0.530 g, 2.81 mmol) in Et_2NH (120 mL) under Ar. The resulting solution was stirred for 15 h at rt. Then a solution of NH_4Cl (100 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography to yield enynols **5**.

4.3. Procedure for the preparation of alcohols 5 from enynes 3 and aldehydes or ketones 4

In a typical experiment, *n*-BuLi (1.24 M in hexanes, 11.3 mL, 14.0 mmol) was added dropwise to a solution of an enyne **3** (13.0 mmol) in THF (50 mL) at −78 °C under Ar. The resulting solution was allowed to reach 0 °C, kept at this temperature for 1 h and cooled again to −78 °C. A solution of an appropriate aldehyde or ketone (**4**, 11.0 mmol) in THF (10 mL) was added, and the reaction mixture was allowed to reach rt. After stirring the mixture 3 h at the same temperature, it was quenched with water (50 mL) and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). The crude products **5** were treated as indicated below for the individual cases.

4.4. Procedure for acetylation of alcohols 5

In a typical experiment, a mixture of **5** (8.43 mmol), DMAP (0.310 g, 2.53 mmol), Et_3N (3.52 mL, 30.0 mmol) and Ac_2O (1.81 mL, 20.0 mmol) was stirred for 3 h at rt. The mixture was diluted with EtOAc (10 mL) and poured over a mixture of H_2O/ice (~10 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The crude products **6** were treated as indicated below for the individual cases.

4.5. Procedure for epoxydation of esters 6

In a typical experiment, to a solution of the appropriate ester **6** (10.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added MCPBA (77%, 4.43 g, 20.0 mmol). The solution was stirred for 15 min, allowed to warm to rt and further stirred at the same temperature (total reaction time: 5 h). 1 M NaOH (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The residue after evaporation was purified as indicated below for the individual cases to yield epoxides **7**.

4.5.1. (*E*)-6-Methyl-1-phenyloct-6-en-4-yn-3-ol (5c). Prepared from 5-phenylpent-1-yn-3-ol[25] and **1**. Elution with 90:10 hexanes/EtOAc afforded **5c** (58%) as an oil: ^1H NMR δ 1.84 and 1.87 (2s, total 6H), 2.05–2.15 (m, 2H), 2.31 (br s, $W_{1/2}$=10 Hz, 1H), 2.86 (t, J=7.8 Hz, 2H), 4.57–4.59 (m, 1H), 5.75–5.82 (m, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR δ 16.2, 22.9, 31.4, 39.5, 62.2, 84.4, 93.6, 118.0, 125.9, 128.3, 128.4, 128.4, 132.8, 141.3; IR (neat) ν 3355 (O–H, s), 3060 (=C–H, w), 2214 (C≡C, w), 1050 (C–O, s) cm^{-1}; HRMS calcd for $C_{14}H_{15}O$ ($M-CH_3$) 199.1123, found 199.1126.

4.5.2. (4*S,5*S**)-4,5-Epoxy-4-methyl-1-(2-phenylethyl)-hex-2-ynyl acetate (7c).** Alcohol **5c** was acetylated and the crude acetate, without further purification, was subjected to the epoxidation conditions. The crude epoxide was purified by flash chromatography (90:10 hexanes/EtOAc) to

yield **7c** (94% for two steps) as an oil: ^{1}H NMR δ 1.42 and 1.43 (2 d, J=5.3 Hz, 3H), 1.53 (s, 3H), 2.05–2.11 (m, 5H, that includes 2s at 2.05 and 2.06), 2.76 (t, J=7.8 Hz, 2H), 2.94–3.00 (m, 1H), 5.39 (t, J=6.5 Hz, 1H), 7.16–7.31 (m, 5H); ^{13}C NMR δ 15.4, 20.8, 22.9, 31.1, 36.0, 36.0, 52.3, 60.7, 60.7, 63.2, 81.2, 83.4, 83.4, 126.0, 128.2, 128.3, 140.4, 169.6; IR (neat) ν 1741 (C=O, s) cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1405.

4.5.3. (*Z*)-1-(3,4-Dimethoxy)phenyl-6-isobutyl-8-methylnon-6-en-4-yn-3-ol (5d). Prepared from (*Z*)-3-isobutyl-5-methyhex-3-en-1-yne[26] and 3-(3,4-dimethoxyphenyl)propanal.[27] The crude product was purified by flash chromatography (80:20 hexanes/EtOAc) to yield **5d** (90%) as an oil: ^{1}H NMR δ 0.86–1.00 (m, 12H), 1.65–2.03 (m, 6H), 2.73–2.86 (m, 3H), 2.76 (t, J=7.9 Hz, included in m at 2.73–2.86), 3.86 and 3.87 (2s, 6H), 4.51–4.54 (m, 1H), 5.47 (d, J=9.3 Hz, 1H), 6.73–6.82 (m, 3H); ^{13}C NMR δ 21.9, 22.4, 26.7, 29.7, 31.0, 39.7, 46.2, 55.5, 55.7, 62.0, 83.6, 93.3, 111.0, 111.5, 118.9, 120.1, 133.9, 146.2, 147.0, 148.6; IR (neat) ν 3472 (O–H, s), 1602 (C=C, w) cm^{-1}; HRMS calcd for $C_{22}H_{32}O_3$ 344.2351, found 344.2348.

4.5.4. (4*S,5*R**)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-4,5-epoxy-4-isobutyl-6-methylhept-2-ynyl acetate (7d).** Alcohol **5d** was acetylated and the crude acetate, without further purification, was subjected to the epoxydation conditions. The crude epoxide was purified by flash chromatography (80:20 hexanes/EtOAc) to yield **7d** (83% for two steps) as an oil: ^{1}H NMR δ 0.94–1.11 (m, 12H), 1.25–1.41 (m, 1H), 1.61–1.78 (m, 2H), 1.96–2.07 (m, 6H), 2.07 (s, included in m at 1.61–2.07), 2.51 (d, J=9.1 Hz, 1H), 2.69 (t, J=7.8 Hz, 2H), 3.86 and 3.87 (2s, 6H), 5.35–5.40 (m, 1H), 6.68–6.81 (m, 3H); ^{13}C NMR δ 18.3, 19.7, 20.9, 22.4, 22.9, 25.9, 30.9, 36.4, 45.5, 55.4, 55.7, 55.9, 63.4, 70.0, 70.1, 82.0, 82.7, 111.2, 111.5, 120.1, 133.1, 147.3, 148.8, 169.7; IR (neat) ν 1743 (C=O, s) cm^{-1}; HRMS calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2401.

4.5.5. 4-Methyl-1-(2-phenylethyl)pent-4-en-2-ynyl benzoate (6e). The procedure for preparation of alcohols **5** was followed from 2-methylbut-1-en-3-yne and hydrocinnamaldehyde. After stirring the reaction mixture at rt for 1 h, it was cooled to 0 °C and neat benzoyl chloride (1.2 equiv.) was added in one portion. The mixture was stirred for 1 h at rt and quenched with sat NH_4Cl. The usual extractive work-up with EtOAc afforded a crude product that was purified by flash chromatography (95:5 hexanes/EtOAc) to yield **6e** (96%) as an oil: ^{1}H NMR δ 1.99 (s, 3H), 2.27–2.43 (m, 2H), 2.96 (t, J=7.7 Hz, 2H), 5.35 (d, J=1.6 Hz, 1H), 5.45 (s, 1H), 5.85 (t, J=6.4 Hz, 1H), 7.24–7.40 (m, 5H), 7.47–7.53 (m, 2H), 7.59–7.65 (m, 1H), 8.15 (d, J=7.7 Hz, 2H); ^{13}C NMR δ 23.2, 31.3, 36.4, 64.2, 85.2, 86.8, 122.8, 125.8, 126.0, 128.2, 128.3, 128.4, 128.4, 129.6, 129.7, 133.0, 140.6, 165.2; IR (neat) ν 2226 (C≡C, w), 1721 (C=O, s), 1604 (C=C, m) cm^{-1}; HRMS calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1466.

4.5.6. 4,5-Epoxy-4-methyl-1-(2-phenylethyl)pent-2-ynyl benzoate (7e). Prepared from **6e**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) to yield **7e** (89%) as an oil: ^{1}H NMR δ 1.58 and 1.59 (2s, 3H), 2.18–2.34 (m, 2H), 2.76 and 2.78 (2 d, J=5.5 Hz, 1H), 2.87 (t, J=7.7 Hz, 2H), 3.03 and 3.05 (2d, J=5.5 Hz, 1H), 5.66 (t, J=6.5 Hz, 1H), 7.22–7.35 (m, 5H), 7.46 (t, J=7.4 Hz, 2H), 7.59 (t, J=7.3 Hz, 1H), 8.06 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 22.7, 31.2, 36.1, 46.9, 55.2, 63.6, 79.2, 85.1, 126.1, 128.3, 128.4, 129.5, 129.7, 133.1, 140.1, 165.2; IR (neat) ν 1721 (C=O, s), 1600 (C=C, m), 1262 (C–O, s) cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1403.

4.5.7. (*E*)-5-Hydroxy-10-methoxymethoxy-5,8-dimethyldec-8-en-6-ynenitrile (5f). Prepared from (*E*)-3-methyl-5-methoxymethoxypent-3-en-1-yne[28] and 5-oxahexanenitrile. The crude product was purified by flash chromatography (60:40 hexanes/EtOAc) to yield **5f** (90%) as an oil: ^{1}H NMR δ 1.45 (s, 3H), 1.72–1.85 (m, 7H), 1.80 (s, included in m at 1.72–1.85), 2.34–2.37 (m, 2H), 3.30 (s, 3H), 3.43 (s, 1H), 4.14 (d, J=6.7 Hz, 2H), 4.55 (s, 2H), 5.74 (m, 1H); ^{13}C NMR δ 16.9, 20.8, 22.8, 30.0, 41.7, 54.9, 64.5, 67.2, 81.6, 94.7, 96.8, 119.4, 122.1, 132.4.

4.5.8. (*E*)-1-(3-Cyanopropyl)-6-methoxymethoxy-1,4-dimethylhex-4-en-2-ynyl acetate (6f). Prepared from **5f**. The crude product was purified by flash chromatography (65:35 hexanes/EtOAc) to afford **6f** (90%) as an oil: ^{1}H NMR δ 1.71 (s, 3H), 1.86–2.10 (m, 10H), 1.86 and 2.02 (2s, included in m at 1.86–2.10), 2.39–2.44 (m, 2H), 3.36 (s, 3H), 4.21 (d, J=6.7 Hz, 2H), 4.62 (s, 2H), 5.82 (t, J=6.7 Hz, 1H); ^{13}C NMR δ 16.6, 20.3, 21.4, 22.5, 26.2, 40.1, 54.8, 65.2, 74.1, 83.4, 92.7, 95.4, 119.0, 120.6, 133.4, 168.5; IR (neat) ν 2244 (C≡N, m), 1735 (C=O, s), 1684 (C=C, w) cm^{-1}; HRMS calcd for $C_{16}H_{23}NO_4$ 293.1627, found 293.1633.

4.5.9. (4*S,5*S**)-1-(3-Cyanopropyl)-4,5-epoxy-6-methoxymethoxy-1,4-dimethylhex-2-ynyl acetate (7f).** Prepared from **6f**. The crude product was purified by flash chromatography (65:35 hexanes/EtOAc) to yield **7f** (98%) as an oil. The characterized sample was additionally purified by HPLC (60:40 hexanes/EtOAc, 8 mL/min, t_R=27 min): ^{1}H NMR δ 1.47 (s, 3H), 1.59 (s, 3H), 1.64–2.27 (m, 6H), 1.93 (s, included in m at 1.64–2.27), 2.32–2.37 (m, 2H), 3.03 (t, J=5.3 Hz, 1H), 3.03 (s, 3H), 3.57–3.74 (m, 2H), 4.60 (s, 2H); ^{13}C NMR δ 16.8, 20.3, 21.5, 22.7, 26.1, 40.1, 51.1, 55.1, 62.3, 66.9, 67.0, 73.5, 82.6, 83.3, 83.4, 96.5, 119.1, 168.6; IR (neat) ν 2244 (C≡N, m), 1739 (C=O, s) cm^{-1}; HRMS calcd for $C_{13}H_{16}NO_3$ (M−OAc-CH_3) 234.1130, found 234.1121.

4.5.10. (4*S,5*S**)-4,5-Epoxy-6-methoxymethoxy-4-methyl-1-(2-phenylethyl)hex-2-ynyl acetate (7g).** The alkynylation, acetylation and epoxidation procedures described above were successively followed starting from (*E*)-3-methyl-5-methoxymethoxypent-3-en-1-yne[28] and hydrocinnamaldehyde, without purification of the intermediates. The crude epoxide product was purified by flash chromatography (80:20 hexanes/EtOAc) to yield **7g** (75%) as an oil: ^{1}H NMR δ 1.56 (s, 3H), 2.03 (s, included in m at 2.03–2.12), 2.03–2.12 (m, 5H), 2.74 (t, J=7.8 Hz, 2H), 3.08–3.13 (apparent t, 1H), 3.36 (s, 3H), 3.66–3.84 (m, 2H), 4.66 (s, 2H), 5.35 (t, J=6.5 Hz, 1H), 7.14–7.30 (m, 5H); ^{13}C NMR δ 20.6, 22.8, 31.0, 35.8, 35.8, 51.0, 55.0, 62.1, 62.2, 62.9, 67.0, 81.6, 82.5, 96.5, 125.9, 128.1, 128.2, 128.2, 128.3, 140.2, 169.4; IR (neat) ν 1751 (C=O, s), 1228

(C–O, s) cm^{-1}; HRMS calcd for $C_{19}H_{24}O_5$ 332.1624, found 332.1612.

4.5.11. 3,6-Dimethyl-8-phenylocta-3,4,5-trien-2-ol (9a). To a solution of SmI_2 (ca. 0.1 M in THF, 15.0 mL, 1.5 mmol) was added via cannula a solution of **7a** (0.18 g, 0.63 mmol) in THF (2 mL) at −5 °C under Ar, and the mixture was stirred at the same temperature for 2 h. Dry air was bubbled through the solution to destroy excess SmI_2, the reaction mixture was allowed to reach rt and a saturated K_2CO_3 solution (10 mL) was added. After separation, the aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo afforded triene **9a** (92% yield, diastereomeric mixture), that was used without further purification: ^{1}H NMR δ 1.34 (dd, J=9.5, 7.9 Hz, 3H), 1.92 (s, 3H), 1.95 (s, 3H), 2.47 (t, J=7.9 Hz, 2H), 2.82–2.89 (m, 2H), 4.27 (s, 1H), 7.17–7.32 (m, 5H).

4.5.12. 9-Hydroxy-5,8-dimethyldeca-5,6,7-trienenitrile (9b). The procedure described above for the preparation of **9a** was followed starting from **7b**. The crude product was purified by flash chromatography (65:33:2 hexanes/EtOAc/Et_3N), to yield **9b** (85% yield, diastereomeric mixture) as an oil: ^{1}H NMR δ 1.34 (d, J=6.3 Hz, 3H), 1.85–1.96 (m, 9H), 1.92 (s, included in m at 1.85–1.96), 2.27–2.34 (m, 2H), 2.35 (t, J=7.1 Hz, 2H), 4.27 (m, 1H); ^{13}C NMR δ 16.4, 18.5, 18.7, 21.7, 21.9, 22.6, 23.1, 23.2, 35.1, 35.4, 70.1, 70.4, 112.5, 112.6, 117.0, 117.3, 119.5, 119.6, 153.1, 153.3, 155.8; IR (neat) ν 3580–3250 (O–H, m), 2240 (C≡N, m) cm^{-1}; HRMS calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1302.

4.6. General procedure for preparation of furans 10 from epoxides 7

In a typical experiment, to a solution of SmI_2 (ca. 0.1 M in THF, 13 mL, 1.3 mmol) was added via cannula a solution of **7** (0.60 mmol) in THF (2 mL) at −5 °C under Ar, and the mixture was stirred at the same temperature for 1–5 h (TLC control). Dry air was bubbled through the solution to destroy excess SmI_2, the mixture was purged with Ar for 10 min, and then was allowed to reach rt. Removal of the solvent in vacuo afforded a residue that was dissolved in DMF (8.1 mL) containing H_2O (0.60 mmol). After addition of Et_3N (0.42 mL, 3.01 mmol), an aryl halide or triflate (1.20 mmol) and $Pd(PPh_3)_4$ (0.070 g, 0.06 mmol), the solution was purged with Ar for 10 min and stirred at the appropriate temperature until complete consumption of the trienol intermediate (reaction temperatures and times are given in Tables 2 and 3). The reaction mixture was allowed to reach room temperature, the solvent was removed at 0.5 mm Hg, and the resulting oil was partitioned between EtOAc (100 mL) and H_2O (100 mL). After separation, the aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The crude product obtained after solvent evaporation was purified as specified below for the individual cases.

4.6.1. 2,3-Dimethyl-5-(1-methyl-3-phenylpropyl)-4-phenylfuran (10aa). Prepared from **7a** and **12a**. The crude product was purified by flash chromatography (hexanes) and HPLC (hexanes, 9 mL/min, t_R=72 min): ^{1}H NMR δ 1.29 (d, J=6.7 Hz, 3H), 1.73–1.87 (m, 1H), 1.91 (s, 3H), 1.97–2.12 (m, 1H), 2.27 (s, 3H), 2.36–2.56 (m, 2H), 2.81–2.95 (m, 1H), 7.02–7.43 (m, 10H); ^{13}C NMR δ 9.0, 11.5, 20.5, 30.8, 33.8, 37.7, 113.6, 122.4, 125.5, 126.3, 128.1, 128.2, 1283, 129.5, 134.3, 142.4, 145.1, 152.4; IR (neat) ν 3080–3020 (=C–H, s), 2950 (C–H, s), 1270 (C–O–C, s) cm^{-1}; HRMS calcd for $C_{22}H_{24}O$ 304.1823, found 304.1827.

4.6.2. 3-(4-Bromophenyl)-4,5-dimethyl-2-(1-methyl-3-phenylpropyl)furan (10ab). Prepared from **7a** and **12d**. The crude product was purified by flash chromatography (hexanes) and HPLC (hexanes, 8 mL/min, t_R=17 min): ^{1}H NMR δ 1.32 (d, J=6.9 Hz, 3H), 1.79–1.92 (m, 4H), 1.92 (s, included in m at 1.79–1.92), 2.00–2.16 (m, 1H), 2.31 (s, 3H), 2.40–2.60 (m, 2H), 2.80–2.94 (m, 1H), 7.01–7.33 (m, 7H), 7.54 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 8.9, 11.5, 20.3, 30.7, 33.7, 37.5, 113.4, 120.3, 121.3, 125.5, 128.1, 128.2, 128.3, 131.1, 131.4, 133.3, 142.1, 145.4, 152.6; IR (neat) ν 3024 (=C–H, w), 2922 (C–H, s), 1602 (ArC–C, m), 1071 (C–O–C, m) cm^{-1}; HRMS calcd for $C_{22}H_{23}{}^{79}BrO$ 382.0932, found 382.0918; HRMS calcd for $C_{22}H_{23}{}^{81}BrO$ 384.0912, found 384.0909.

4.6.3. 5-(4,5-Dimethyl-3-phenylfuran-2-yl)hexanenitrile (10ba). Prepared from **7b** and **12a** or **12b**. The crude product was purified by flash chromatography (97:3 hexanes/EtOAc) and HPLC (97:3 hexanes/EtOAc, 8 mL/min, t_R=28 min): ^{1}H NMR δ 1.29 (d, J=6.9 Hz, 3H), 1.40–1.84 (m, 4H), 1.87 (s, 3H), 2.08–2.14 (m, 2H), 2.25 (s, 3H), 2.77–2.92 (m, 1H), 7.21–7.44 (m, 5H); ^{13}C NMR δ 8.8, 11.5, 16.6, 20.3, 23.4, 30.5, 34.5, 113.7, 119.6, 122.9, 126.5, 128.3, 129.3, 133.9, 145.3, 151.1; IR (neat) ν 3090–3010 (=C–H, w), 2990–2880 (C–H, m), 2220 (C≡N, m), 1610 (C=C, w) cm^{-1}; HRMS calcd for $C_{18}H_{21}NO$ 276.1623, found 276.1627.

4.6.4. 5-[3-(4-Acetylphenyl)-4,5-dimethylfuran-2-yl]-hexanenitrile (10bb). Prepared from **7b** and **12c**. The crude product was purified by flash chromatography (80:20 hexanes/EtOAc) and HPLC (80:20 hexanes/EtOAc, 8 mL/min, t_R=33 min): ^{1}H NMR δ 1.24 (d, J=6.9 Hz, 3H), 1.32–1.47 (m, 2H), 1.51–1.78 (m, 2H), 1.82 (s, 3H), 2.11 (t, J=7.0 Hz, 2H), 2.19 (s, 3H), 2.58 (s, 3H), 2.75–2.87 (m, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.96 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 8.7, 11.2, 16.6, 20.0, 23.2, 26.3, 30.6, 34.4, 113.2, 119.4, 121.9, 128.3, 129.2, 135.0, 139.1, 145.8, 151.7, 197.4; IR (neat) ν 2990–2860 (C–H, m), 2220 (C≡N, m), 1680 (C=O, s), 1610 (C=C, m), 1270 (C–O–C, s) cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1739.

4.6.5. 5-[3-(4-Bromophenyl)-4,5-dimethylfuran-2-yl]-hexanenitrile (10bc). Prepared from **7b** and **12d**. The crude product was purified by flash chromatography (92:8 hexanes/EtOAc): ^{1}H NMR δ 1.26 (d, J=6.9 Hz, 3H), 1.39–1.51 (m, 2H), 1.56–1.77 (m, 2H), 1.84 (s, 3H), 2.14 (t, J=7.1 Hz, 2H), 2.23 (s, 3H), 2.72–2.86 (m, 1H), 7.09 (d, J=8.3 Hz, 2H), 7.52 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 8.6, 11.3, 16.6, 20.1, 23.3, 30.5, 34.4, 113.3, 119.4, 120.4, 121.6, 130.9, 131.4, 132.8, 145.5, 151.2; IR (neat) ν 3020 (=C–H, w), 2980 (C–H, m), 2220 (C≡N, m) cm^{-1}; HRMS calcd

for $C_{18}H_{20}{}^{79}BrNO$ 345.0728, found 345.0725; HRMS calcd for $C_{18}H_{20}{}^{81}BrNO$ 347.0708, found 347.0719.

4.6.6. 5-(4,5-Dimethyl-3-*p*-tolylfuran-2-yl)hexanenitrile (10bd). Prepared from **7b** and **12e** or **12f**. The crude product was dissolved in EtOAc (25 mL/mmol, based on **7b**) and stirred with silica gel (1.25 g/mmol, based on **7b**) at rt for 15 min. After filtration and solvent evaporation, the residue was purified by flash chromatography (98:2 hexanes/Et_3N): ^1H NMR δ 1.28 (d, J=6.9 Hz, 3H), 1.38–1.81 (m, 4H), 1.86 (s, 3H), 2.12 (t, J=7.1 Hz, 2H), 2.24 (s, 3H), 2.40 (s, 3H), 2.76–2.90 (m, 1H), 7.11 (d, J=7.8 Hz, 2H), 7.22 (d, J=7.8 Hz, 2H); ^{13}C NMR δ 8.8, 11.5, 16.7, 20.3, 21.1, 23.4, 30.5, 34.5, 113.8, 119.7, 122.7, 129.1, 129.2, 130.9, 136.2, 145.2, 151.0; IR (neat) ν 3020 (=C–H, m), 2990–2880 (C–H, s), 2225 (C≡N, w), 1610 (C=C, w) cm^{-1}; HRMS calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1775.

4.6.7. 5-[3-(4-Methoxyphenyl)-4,5-dimethylfuran-2-yl]-hexanenitrile (10be). Prepared from **7b** and **12g** with the following modification. The reaction mixture after the SmI_2 treatment was worked-up to isolate alcohol **7b**, as described above. Crude **7b** was then reacted with **12g**, $Pd(PPh_3)_4$ and Et_3N according to the general procedure. The crude product was purified by flash chromatography (90:8:2 hexanes/EtOAc/Et_3N): ^1H NMR δ 1.25 (d, J=6.9 Hz, 3H), 1.41–1.82 (m, 7H, that includes s at 1.82), 2.11 (t, J=7.0 Hz, 2H), 2.22 (s, 3H), 2.72–2.83 (m, 1H), 3.84 (s, 3H), 6.93 (d, J=8.7 Hz, 2H), 7.12 (d, J=8.7 Hz, 2H); ^{13}C NMR δ 8.9, 11.5, 16.7, 20.4, 23.5, 30.5, 34.6, 55.2, 113.8, 114.0, 119.7, 126.2, 130.5, 145.2, 151.0, 158.3; IR (neat) ν 2940–2810 (C–H, m), 2210 (C≡N, w), 1570 (ArC–C, m), 1500 (ArC–H, s), 1270 and 1240 (C–O, m) cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1732.

4.6.8. 5-(4,5-Dimethyl-3-thiophen-2-ylfuran-2-yl)hexanenitrile (10bf). Prepared from **7b** and **12h** or **12i**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) and HPLC (95:5 hexanes/EtOAc, 8 mL/min, t_R=30 min): ^1H NMR δ 1.27 (d, J=6.9 Hz, 3H), 1.46–1.92 (m, 7H), 1.92 (s, included in m at 1.46–1.92), 2.16–2.22 (m, 5H), 2.99–3.08 (m, 1H), 6.89 (d, J=2.4 Hz, 1H), 7.06–7.09 (dd, J=5.0, 3.6 Hz, 1H), 7.29 (d, J=5.1 Hz, 1H); ^{13}C NMR δ 9.0, 11.4, 16.8, 20.1, 23.4, 30.8, 34.4, 114.1, 115.7, 119.6, 124.7, 125.9, 127.2, 134.8, 145.6, 152.5; IR (neat) ν 3106 (=C–H, m), 2925 (C–H, s), 2246 (C≡N, m), 1596 (ArC–C, m) cm^{-1}; HRMS calcd for $C_{16}H_{19}NOS$ 273.1187, found 273.1186.

4.6.9. 5-(4,5-Dimethyl-3-thiophen-3-ylfuran-2-yl)hexanenitrile (10bg). Prepared from **7b** and **12j**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) and HPLC (95:5 hexanes/EtOAc, 8 mL/min, t_R=30 min): ^1H NMR δ 1.26 (d, J=6.9 Hz, 3H), 1.41–1.83 (m, 4H), 1.88 (s, 3H), 2.14 (t, J=7.0 Hz, 2H), 2.22 (s, 3H), 2.82–2.96 (m, 1H), 7.00–7.07 (m, 2H), 7.35–7.38 (m, 1H); ^{13}C NMR δ 9.0, 11.5, 16.7, 20.2, 23.5, 30.8, 34.5, 113.8, 117.7, 119.7, 121.9, 125.3, 128.5, 133.9, 145.4, 151.5; IR (neat) ν 3105 (=C–H, m), 2925 (C–H, s), 2246 (C≡N, m), 1599 (ArC–C, w) cm^{-1}; HRMS calcd for $C_{16}H_{19}NOS$ 273.1187, found 273.1198.

4.6.10. 5-(4,5-Dimethyl-3-pyridin-3-ylfuran-2-yl)hexanenitrile (10bh). Prepared from **7b** and **12k**. The crude product was dissolved in EtOAc (25 mL/mmol, based on **7b**) and stirred with silica gel (1.25 g/mmol, based on **7b**) at rt for 15 min. After filtration and solvent evaporation, the residue was purified by flash chromatography (50:50 hexanes/Et_3N) and HPLC (58:42 hexanes/EtOAc, 8 mL/min, t_R=44 min): ^1H NMR δ 1.24 (d, J=6.9 Hz, 3H), 1.40–1.46 (m, 2H), 1.49–1.79 (m, 2H), 1.82 (s, 3H), 2.15 (t, J=7.0 Hz, 2H), 2.21 (s, 3H), 2.67–2.81 (m, 1H), 7.29–7.34 (m, 1H), 7.50–7.53 (m, 1H), 8.45 (s, 1H), 8.52 (d, J=3.6 Hz, 1H); ^{13}C NMR δ 8.7, 11.4, 16.5, 20.3, 23.4, 30.8, 34.5, 113.5, 119.48, 119.5, 123.3, 129.9, 136.6, 146.0, 147.7, 150.0, 152.1; IR (neat) ν 3015 (=C–H, w), 2985–2885 (C–H, m), 2250 (C≡N, w), 1616 and 1580 (ArC–C, w) cm^{-1}; HRMS calcd for $C_{17}H_{20}N_2O$ 268.1576, found 268.1571.

4.6.11. 3-(4-Acetylphenyl)-4,5-dimethyl-2-(3-phenylpropyl)furan (10c). Prepared from **7c** and **12c**. The crude product was purified by flash chromatography (hexanes) and HPLC (90:10 hexanes/EtOAc, 4 mL/min, t_R=55 min): ^1H NMR δ 1.92–2.00 (m, 5H), 1.92 (s, included in m at 1.92–2.00), 2.26 (s, 3H), 2.58–2.72 (m, 7H), 2.64 (s, included in m at 2.58–2.72), 7.11–7.33 (m, 7H), 7.99 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 9.1, 11.4, 25.9, 26.5, 30.2, 35.2, 113.4, 122.0, 125.7, 128.2, 128.4, 128.4, 129.2, 134.9, 139.5, 141.8, 145.8, 149.8, 197.7; IR (neat) ν 3026 (=C–H, w), 2923 (C–H, m), 1683 (C=O, s), 1606 (C=C, s), 1268 (C–O–C, s) cm^{-1}; HRMS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1771.

4.6.12. 3-(4-Bromophenyl)-2-[3-(3,4-dimethoxyphenyl)-propyl]-4-isobutyl-5-isopropylfuran (10d). Prepared from **7d** and **12d**. The crude product was purified by flash chromatography (98:2 hexanes/EtOAc): ^1H NMR δ 1.44 (d. J=6.5 Hz, 6H), 1.26–1.42 (m, 7H), 1.28 (d, J=6.9 Hz, included in m at 1.26–1.42), 1.83–1.95 (m, 2H), 2.21 (d, J=7.3 Hz, 2H), 2.48–2.60 (m, 4H), 2.99 (q, J=6.9 Hz, 1H), 3.86 (s, 6H), 6.61–6.77 (m, 3H), 7.09 (d, J=8.3 Hz, 2H), 7.48 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 21.7, 22.3, 25.6, 25.9, 28.6, 30.4, 32.5, 34.7, 55.7, 55.8, 110.9, 111.5, 115.6, 120.1, 120.2, 121.1, 131.1, 131.3, 133.9, 134.7, 146.9, 148.6, 149.0, 154.2; IR (neat) ν 2955 (C–H, s), 1515 (ArC–C, s), 1032 (C–O–C, m) cm^{-1}; HRMS calcd for $C_{28}H_{35}{}^{79}BrO_3$ 498.1770, found 498.1765; HRMS calcd for $C_{28}H_{35}{}^{81}BrO_3$ 500.1749, found 500.1764.

4.6.13. 3-(4-Bromophenyl)-4-methyl-2-(3-phenylpropyl)-furan (10e). Prepared from **7e** and **12d** with the following modification. The solution of **7e** in THF was added dropwise to SmI_2 (~0.1 M in THF, 3 equiv. with respect to **7e**) at 10 °C and the mixture was stirred for 20 min at the same temperature. It was then proceeded according to the general procedure. The crude product was purified by flash chromatography (hexanes) and HPLC (hexanes, 7 mL/min, t_R=31 min): ^1H NMR δ 1.88–2.05 (m, 5H), 1.95 (s, included in m at 1.88–2.05), 2.48–2.65 (m, 4H), 7.06–7.49 (m, 8H), 7.51 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 9.0, 25.9, 30.0, 35.1, 119.1, 120.5, 121.3, 125.8, 128.3, 128.4, 130.9, 131.5, 132.6, 137.6, 141.8, 152.2; IR (neat) ν 3027 (=C–H, w), 2931 (C–H, s), 1799 (s), 1760 (s), 1115 (C–O, m) cm^{-1}; HRMS calcd for $C_{20}H_{19}{}^{79}BrO$ 354.0619, found 354.0618; HRMS calcd for $C_{20}H_{19}{}^{81}BrO$ 356.0599, found 356.0596.

4.6.14. 4-Hydroxy-5-iodo-4-methyl-1-(2-phenylethyl)-pent-2-ynyl benzoate (14). Obtained from **7e** in 35% yield when the reduction step with SmI_2 was performed according to the unmodified general procedure: ^{1}H NMR δ 1.69 (s, 3H), 2.15–2.37 (m, 2H), 2.60 (s, 1H), 2.91 (t, J=7.1 Hz, 2H), 3.44 (d, J=10.1 Hz, 1H), 3.52 and 3.53 (2 d, J=10.1 Hz, 1H), 5.66 (t, J=6.5 Hz, 1H), 7.19–7.38 (m, 5H), 7.44–7.50 (m, 2H), 7.57–7.63 (m, 1H), 8.04–8.07 (m, 2H); ^{13}C NMR δ 20.3, 20.4, 27.8, 31.3, 36.2, 63.8, 66.5, 81.5, 87.1, 126.1, 128.4, 128.4, 128.5, 129.7, 129.8, 133.2, 140.6, 165.4; IR (neat) ν 3438 (O–H, m), 1721 (C=O, s), 1287 (C–O, m), 712 (C–I, m) cm^{-1}; HRMS calcd for $C_{21}H_{21}IO_3$ 448.0535, found 448.0533.

4.6.15. 5-[3-(4-Acetylphenyl)-5-methoxymethoxymethyl-4-methylfuran-2-yl]hexanenitrile (10f). Prepared from **7f** and **12c**. The crude product was dissolved in EtOAc (125 mL/mmol, based on **7f**) and AcOH was added until pH=5. The solution was washed with water and the aqueous layer was back-extracted with EtOAc. The residue after evaporation was purified by flash chromatography (70:30 hexanes/EtOAc): ^{1}H NMR δ 1.28 (d, J=6.9 Hz, 3H), 1.42–1.90 (m, 4H), 1.97 (s, 3H), 2.15 (t, J=7.1 Hz, 2H), 2.64 (s, 3H), 2.80–2.89 (m, 1H), 3.43 (s, 3H), 4.53 (s, 2H), 4.70 (s, 2H), 7.31 (d, J=7.9 Hz, 2H), 7.96 (d, J=7.0 Hz, 2H); ^{13}C NMR δ 8.8, 16.9, 20.0, 23.4, 26.6, 31.0, 34.5, 55.3, 58.9, 95.2, 119.0, 119.5, 122.4, 128.6, 129.6, 135.6, 138.6, 145.6, 154.3, 197.7; IR (neat) ν 2930 (C–H, s), 2100 (C≡N, m), 1681 (C=O, s), 1606 (C=C, m), 1034 (C–O, m) cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_4$ 369.1940, found 369.1936.

4.6.16. 3-(4-Bromophenyl)-5-methoxymethoxymethyl-4-methyl-2-(3-phenylpropyl)furan (10ga). Prepared from **7g** and **12d**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) and HPLC (86:14 hexanes/EtOAc, 7 mL/min, t_R=23 min): ^{1}H NMR δ 1.59–2.01 (m, 5H), 1.97 (s, included in m at 1.59–2.01), 2.54–2.65 (m, 4H), 3.43 (s, 3H), 4.53 (s, 2H), 4.71 (s, 2H), 7.05–7.49 (m, 7H), 7.51 (d, J=2.0 Hz, 2H); ^{13}C NMR δ 8.9, 25.8, 30.0, 35.2, 55.3, 58.9, 95.2, 119.1, 120.7, 122.0, 125.8, 128.2, 128.4, 131.0, 131.5, 132.5, 141.7, 145.1, 151.8; IR (neat) ν 3027 (=C–H, w), 2926 (C–H, s), 1602 (ArC–C, w), 1034 (C–O–C, m) cm^{-1}; HRMS calcd for $C_{23}H_{25}{}^{79}BrO_3$ 428.0987, found 428.0986; HRMS calcd for $C_{23}H_{25}{}^{81}BrO_3$ 430.0967, found 430.0976.

4.6.17. 4-(4-Acetylphenyl)-2-methoxymethoxymethyl-3-methyl-5-(3-phenylpropyl)furan (10gb). Prepared from **7g** and **12c**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) and HPLC (86:14 hexanes/EtOAc, 9 mL/min, t_R=60 min): ^{1}H NMR δ 1.91–2.03 (m, 5H), 2.01 (s, included in m at 1.91–2.03), 2.56–2.69 (m, 7H), 2.63 (s, included in m at 2.56–2.69), 3.43 (s, 3H), 4.54 (s, 2H), 4.71 (s, 2H), 7.08–7.32 (m, 7H), 7.97 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 9.0, 26.0, 26.6, 29.9, 35.2, 55.3, 58.8, 95.2, 119.0, 122.2, 125.7, 128.2, 128.4, 128.5, 129.4, 135.2, 138.8, 141.6, 145.3, 152.3, 197.7; IR (neat) ν 3026 (=C–H, w), 2928 (C–H, s), 1686 (C=O, s), 1607 (C=C, s), 1033 (C–O, m) cm^{-1}; HRMS calcd for $C_{25}H_{28}O_4$ 392.1988, found 392.1993.

4.6.18. 3-Phenyl-2-(3-phenylpropyl)-4,5,6,7-tetrahydrobenzofuran (10ha). Prepared from **7h** and **12a**. The crude product was purified by flash chromatography (hexanes) and HPLC (90:10 hexanes/EtOAc, 8 mL/min, t_R=35 min): ^{1}H NMR δ 1.84–2.19 (m, 6H), 2.54–2.56 (m, 2H), 2.73–2.88 (m, 6H), 7.23–7.51 (m, 10H); ^{13}C NMR δ 21.8, 23.0, 23.2, 26.0, 30.4, 35.3, 116.8, 121.0, 125.6, 126.1, 128.1, 128.3, 128.4, 128.7, 134.0, 142.0, 148.7, 149.4; IR (neat) ν 3026 (=C–H, m), 2932 (C–H, m), 1605 (ArC–C, s) cm^{-1}; HRMS calcd for $C_{23}H_{24}O$ 316.1827, found 316.1821. This product decomposes rapidly in the absence of solvent.

4.6.19. 3-(4-Acetylphenyl)-2-(3-phenylpropyl)-4,5,6,7-tetrahydrobenzofuran (10hb). Prepared from **7h** and **12c**. The crude product was purified by flash chromatography (95:5 hexanes/EtOAc) and HPLC (97:3 hexanes/EtOAc, 10 mL/min, t_R=60 min): ^{1}H NMR δ 1.73–2.09 (m, 6H), 2.44–2.46 (m, 2H), 2.64–2.77 (m, 9H), 2.64 (s, included in m at 2.64–2.77), 7.13–7.36 (m, 7H), 7.97 (d, J=8.5 Hz, 2H); ^{13}C NMR δ 21.8, 22.8, 23.1, 26.1, 30.2, 35.2, 116.5, 120.3, 125.7, 128.2, 128.4, 128.5, 128.5, 134.7, 139.3, 141.7, 149.2, 150.3, 197.6; IR (neat) ν 3026 (=C–H, w), 2931 (C–H, m), 1686 (C=O, s), 1605 and 1582 (ArC–H, s), 1266 (C–O–C, s) cm^{-1}; HRMS calcd for $C_{25}H_{26}O_2$ 358.1932, found 358.1922. This product decomposes rapidly in the absence of solvent.

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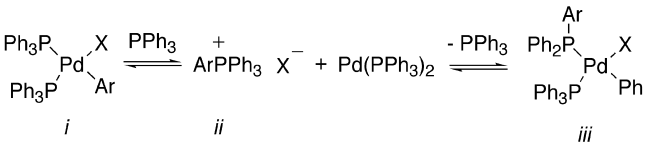

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Structural elucidation of the oxidation product of aminoethylcysteine ketimine decarboxylated dimer by peroxynitrite☆

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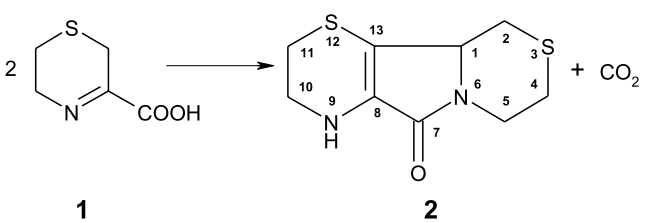
Abstract—Aminoethylcysteine ketimine decarboxylated dimer (**2**) is a natural sulfur compound with antioxidant properties. **2** Inhibits some reactions mediated by peroxynitrite, a strong oxidizing and nitrating agent that reacts with several biomolecules. This work aims to elucidate the structure of the product resulting from the interaction of **2** with peroxynitrite using 1D and 2D NMR experiments and ion trap mass spectrometry. This product is a dimerized form of **2** and is hereafter referred to as **3**. During the reactions leading to **2** and during the formation of **3**, no chiral selection is operated; all optical isomers are present in D_2O and have been evidenced by ^1H NMR methods in D_2O plus β- or γ-cyclodextrin.

1. Introduction

Aminoethylcysteine ketimine (2*H*-1,4-thiazine-5,6-dihydro-3-carboxylic acid) (**1**) is the product of enzymatic and non-enzymatic α-deamination and cyclization of the parent amino acid *S*-aminoethyl-L-cysteine.[1–3] **1** Is a component of a class of sulfur-containing ketimino acids whose occurrence in human biological liquids and mammalian brain, human included, has been previously demonstrated.[4,5] **1** Dimerizes spontaneously into a tricyclic product that loses a carboxyl group, yielding the aminoethylcysteine ketimine decarboxylated dimer (**2**) (Scheme 1).[6,7] **2** Has been detected in bovine cerebellum, normal human urine and human plasma, suggesting a possible biological relevance for this compound.[8–10] In vitro studies have indicated that **2** is an antioxidant agent able to protect mitochondrial membranes, microsomes, and LDL from lipid peroxidation induced by reactive oxygen species.[11–13] Recently, it has been found that **2**, at concentrations similar to those present in human plasma, efficiently protects cultured human monocytic cells U937 against *tert*-butyl hydroperoxide-induced oxidative challenge.[14] Moreover, it has been found that **2** is an efficient inhibitor of some reactions mediated by peroxynitrite ($ONOO^-$).[15] Reactive oxygen and nitrogen species are broadly recognized as major contributors to aging, neurodegenerative diseases and atherosclerosis. Among these species, peroxynitrite, which may be formed in vivo by the fast reaction between nitrogen monoxide ($NO^{\cdot}$) and the superoxide anion ($O_2^{\cdot-}$),[16] is an oxidizing and nitrating agent that reacts with a variety of biomolecules, such as lipids, thiols, amino acids, antioxidants, and nucleic acids.[17–22] Under physiological conditions, peroxynitrite predominantly reacts with carbon dioxide to give the nitrosoperoxycarboxylate anion ($ONOOCO_2^-$) that can



1 **2**

Scheme 1. Chemical structures of **1** and **2**.

☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2004.03.048

Keywords: ^1H NMR; ^{13}C NMR; Aminoethylcysteine ketimine; Peroxynitrite; Chirality; Cyclodextrin.

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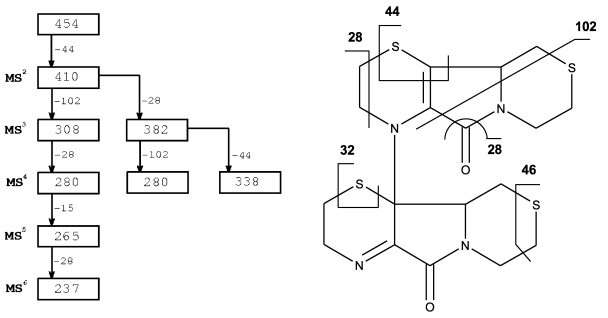


Figure 1. Fragmentation pattern of **3** obtained by a multiple stage mass analysis. The numbers indicated in the boxes are the observed molecular weights expressed in Da.

participate in the oxidation and nitration process.[23–26] In a previous paper, we have shown that **2** interacts with H_2O_2 yielding a sulfoxide derivative.[27] As a result of treatment with peroxynitrite, **2** undergoes an oxidative modification yielding a new derivative, hereafter referred to as **3**. This work aims to elucidate the structure of **3** using 1D and 2D NMR experiments and ion trap mass spectrometry.

2. Results and discussion

The HPLC analysis of the reaction mixture resulting from the addition of peroxynitrite to **2** shows the presence of two main peaks: one peak eluting with a retention time of 26 min due to unreacted **2** (about 25% of the initial concentration) and one peak with a retention time of 28 min due to **3**, produced in a yield of about 30% (data not shown). Addition of **2** to a solution of decomposed peroxynitrite does not result in a significant decrease in the concentration of **2** or in the formation of **3**. The UV spectra recorded at the top of the two peaks appear similar with an absorption maximum at 308 nm. It has been reported that the presence of the carbon dioxide/bicarbonate pair may modulate the oxidative chemistry of peroxynitrite.[23–26] Addition of 25 mM sodium bicarbonate to the reaction mixture does not alter the HPLC-profile of the oxidation products of **2**, which suggests that either peroxynitrite or the CO_2–peroxynitrite adduct have similar oxidation chemistry and reactivity with **2**. In order to establish the structure of **3**, this compound was isolated by preparative chromatography and submitted to mass spectrometry and NMR analysis.

2.1. Mass spectrometry analysis

Compound **3** was submitted to mass analysis on an ion-trap instrument. The full MS spectrum shows the molecular ion *m/z* 455, corresponding to MW 454 Da, and low amounts of the ion *m/z* 477, which is attributed to the monocharged Na^+ salt. The fragmentation pattern (Fig. 1) is in full agreement with the asymmetric structure suggested by the NMR analysis reported in Section 2.2. In particular, the presence of a signal at *m/z* 227, which does not correspond to the peak at *m/z* 229 of the parent molecule, may be due to the homolytic cleavage of the bond junction between the two molecular moieties evidenced by NMR (see Section 2.2).

2.2. NMR analysis

Spectral analysis of **2** has been previously reported at lower field.[27] In order to clarify the molecular structure of **3**, a complete assignment of the proton and carbon spectra of the precursor **2** was also performed using 1D and 2D NMR techniques.

2.2.1. Assignment of aminoethylcysteine ketimine decarboxylated dimer (2). Compound **2** is soluble both in water and in organic solvents such as CD_2Cl_2, $CDCl_3$ and DMSO-d_6. All the spectra in different solvents appear well resolved with no significant difference. The ^1H and ^{13}C assignments of **2** in CD_2Cl_2 as obtained by 2D experiments (COSY, TOCSY, HSQC and HMBC) are reported in Table 1. The structure of **2** presents one chiral carbon atom in position 1 that can be in a *R* or *S* configuration (Scheme 1). The presence of both chiral isomers in **2** was verified by performing a ^1H spectrum in an aqueous solution containing β cyclodextrin (12 mM).[28] Both optical isomers were present in equal amount indicating that **2** was a racemic mixture.

2.2.2. Assignment of the $ONOO^-$-oxidation derivative of 2 (3). Compound **3** is soluble in D_2O and in diverse organic solvents such as DMSO-d_6 and CD_2Cl_2. **3** Undergoes a slow

Table 1. ^1H (600 MHz) and ^{13}C (150 MHz) assignments of **2** in CD_2Cl_2 at 300 K

Type		δ ^{13}C CD_2Cl_2 (ppm)	δ ^1H CD_2Cl_2 (ppm)	m[a]	J_{H-H} (Hz)[b]
1	CH	60.66	3.994	dd	11.0, 3.3
2	CH_2	34.75	H_{eq} 2.856	dddd	13.1, 3.3, 2.0, 0.9
			H_{ax} 2.371	dd	13.1, 11.0
4	CH_2	26.62	H_{eq} 2.574	ddd	13.4, 3.5, 2.0
			H_{ax} 2.619	dddd	13.4, 12.0, 2.8, 0.9
5	CH_2	41.81	H_{eq} 4.479	ddd	13.3, 2.8, 2.0
			H_{ax} 3.114	ddd	13.3, 12.0, 3.5
7	CO	163.86	—	—	—
8	C	131.24	—	—	—
9	NH	—	4.39	bs[c]	—
10	CH_2	42.59	3.589	m	—
11	CH_2	26.53	3.036	m	—
13	C	115.84	—	—	—

[a] m=multiplicity.
[b] Scalar coupling constants, reported as absolute numbers, are given at ±0.1 Hz.
[c] bs=broad signal.

hydrolysis in D_2O and decomposes after a certain period of time in CD_2Cl_2, whereas it shows high stability in DMSO-d_6.

In order to obtain the full structural assignment of **3**, it was necessary to analyze the spectra of the compound in the different solvents, namely, CD_2Cl_2, DMSO and D_2O, and to fit together all the resulting information.

The ^1H spectra recorded in DMSO-d_6 and in D_2O appear much more complex and overlapped than the spectrum in CD_2Cl_2, which was the solvent chosen for identifying all different spin systems by means of 2D experiments.

In all solvents, the observed number of ^1H resonances reveals the presence of at least two structural isomers. These two main forms will be hereafter referred to as form I and form II. The ratio of these two forms varies from one solvent to another, being ≈1:1 in water and ≈3:2 in CD_2Cl_2.

Spectral integration performed on properly grouped resonances indicates the presence of 22 protons for each

Table 2. ^1H (600 MHz) and ^{13}C (150 MHz) assignments of **3** in CD_2Cl_2 and DMSO-d_6 at 300 K

Type		δ ^{13}C CD_2Cl_2 (ppm)	δ ^{13}C DMSO-d_6 (ppm)	δ ^1H CD_2Cl_2 (ppm)	δ ^1H DMSO-d_6 (ppm)	m[a]	J_{H-H} (Hz)[b]	Main HMBC connections[c]
1	CH	61.26	59.27 59.43	4.121	4.07	dd	11.2, 3.3	7, 8
2	CH_2	34.20	34.33 34.56	H_{eq} 2.85 H_{ax} 2.453	H_{eq} 2.90–2.93 H_{ax} 2.25–2.31	m dd	— −13.1, 11.2	4, 13
4	CH_2	29.52	28.91 28.93	H_{eq} 2.59 H_{ax} 2.67	H_{eq} 2.61–2.65 H_{ax} 2.46–2.53	m m	— —	
5	CH_2	42.08	41.22 41.26	H_{eq} 4.50 H_{ax} 3.16	H_{eq} 4.21–4.29 H_{ax} 2.96–3.03	m m	— —	7
7	CO	163.1[d]	163.96 164.10	—	—	—	—	
8	C	126.7[d]	129.48 129.88	—	—	—	—	
10	CH_2	42.30	46.87[e]	H_{eq} 3.64 H_{ax} 3.64	H_{eq} 3.43 H_{ax} 3.09	m	—	8, 13′
11	CH_2	25.96	27.00 27.16	H_{eq} 3.19 H_{ax} 3.19	H_{eq} 3.11 H_{ax} 2.96	m m	— —	13
13	C	129.0[d]	127.35 128.38	—	—	—	—	
Form I[f]								
1′	CH	61.75	69.91	4.314	4.43	d	11.2, 3.8	7′
2′	CH_2	27.93	31.04	H_{eq} 3.23 H_{ax} 2.85	H_{eq} 2.87 H_{ax} 2.38	m m	— —	4′, 13′
4′	CH_2	26.69	26.88	H_{eq} 2.55 H_{ax} 2.85	H_{eq} 2.54–2.58 H_{ax} 2.54–2.58	m m	— —	
5′	CH_2	42.64	43.42	H_{eq} 4.67 H_{ax} 3.13	H_{eq} 4.44–4.45 H_{ax} 3.07–3.14	m	— —	7′
7′	CO	162.60	161.89	—	—	—	—	
8′	C	161.42	160.87	—	—	—	—	
10′	CH_2	51.62	48.45	H_{eq} 4.08 H_{ax} 3.99	H_{eq} 3.95 H_{ax} 3.95	m m	— —	8′
11′	CH_2	33.43	23.28	H_{eq} 3.44 H_{ax} 3.49	H_{eq} 2.66 H_{ax} 2.66	m m	— —	13′
13′	C	66.58	64.46	—	—	—	—	
Form II[f]								
1′	CH	64.62	69.16	4.204	4.37	dd	11.5, 3.3	7′
2′	CH_2	30.27	30.63	H_{eq} 2.88 H_{ax} 2.46	H_{eq} 2.91 H_{ax} 2.77	m m	— —	4′, 13′
4′	CH_2	27.30	26.88	H_{eq} 2.54–2.58 H_{ax} 2.54–2.58	H_{eq} 2.61 H_{ax} 2.78	m m	— —	
5′	CH_2	42.88	43.61	H_{eq} 4.44–4.45 H_{ax} 3.07–3.14	H_{eq} 3.14 H_{ax} 4.58	m m	— —	7′
7′	CO	162.56	161.91	—	—	—	—	
8′	C	161.42	160.87	—	—	—	—	
10′	CH_2	52.28	47.94	H_{eq} 4.08 H_{ax} 3.99	H_{eq} 4.02 H_{ax} 3.66	m m	— —	8′
11′	CH_2	33.80	24.02	H_{eq} 3.44 H_{ax} 3.49	H_{eq} 2.83 H_{ax} 2.60	m m	— —	13′
13′	C	66.33	65.33	—	—	—	—	

[a] m=multiplicity.
[b] Scalar coupling constants, reported as absolute numbers, are given at ±0.1 Hz and are here reported only in the case of CD_2Cl_2 solutions for the sake of clarity.
[c] The most significant long range connections derived from the $^1H-^{13}C$ HMBC experiment, indicated as $^1H\rightarrow^{13}C$, are reported.
[d] These values of chemical shifts were determined from the HMBC experiment and are given with only one significant figure after the decimal point.
[e] Broad signal.
[f] Two structural forms, I and II, can be clearly detected for resonances of the M2 moiety of **3**.

structural isomer and hence suggests a dimeric structure. Moreover, in both organic solvents, no resonance due to exchangeable protons is observable; in particular, in CD_2Cl_2, the resonance at 4.39 ppm due to the proton attached to the nitrogen atom of **2** (H-9) is absent. The $\{^1H\}$ ^{13}C spectrum of **3** in a DMSO-d_6 solution shows for each structural form, a number of carbon signals higher than that expected for a simple symmetric dimer; some signals are clearly split whereas some other ones are just broadened. By summing together the split resonances in the $\{^1H\}$ ^{13}C spectrum, the number of carbon atoms for each structural form reduces to 18 and hence agrees with a dimeric structure. In particular, in the 160–165 ppm range, the $\{^1H\}$ ^{13}C spectrum shows the presence of five signals (two resonances clearly split and another one rather broadened), whereas four other signals (i.e., due to two split resonances) are observable in the 125–130 ppm range. All other signals are in the 20–70 ppm range.

The $^1H-^{13}C$ HSQC map and the DEPT-135 experiment reveal the presence of 10 CH_2 and two CH groups, and allow the quaternary carbons to be identified.

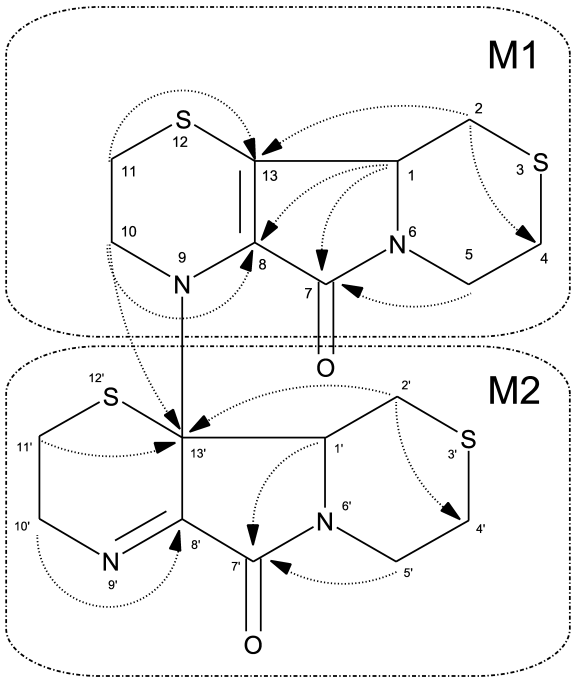
In particular, the absence of resonances at 64.46 and 65.33 ppm in the DEPT-135 spectrum confirms that these resonances are due to quaternary carbons.

Therefore, the analysis of the ^1H and ^{13}C spectra, even though complicated by the presence of at least two isomers, reveals that the molecular formula of **3** includes 18 carbon and 22 hydrogen atoms.

The COSY spectrum recorded in CD_2Cl_2 solutions allows the six spin systems to be identified; the full assignment in CD_2Cl_2 is reported in Table 2 together with the assignment of the strongly overlapped spectrum in DMSO-d_6. All these data and the comparison with the assignment of **2** allow one to sketch for **3** two possible monomeric units, M1 and M2 (Scheme 2).

The M1 unit agrees with the presence in the MS spectrum of **3** of a signal at *m/z* 227, which may be due to the homolytic cleavage of the bond junction between the two monomeric units.

In order to complete the spectral assignment, all resonances due to quaternary carbons have to be assigned, and the junction point between the two monomeric units has to be unequivocally determined. In order to assign the resonances due to quaternary carbon atoms and to establish the connectivity of the different spin systems, a $^1H-^{13}C$ HMBC experiment was performed. The connections between C-7′ with H-5′, and C-8′ with H-10′, allow the last two quaternary carbons of the second monomeric unit M2 to be assigned. The analysis of all cross-peaks allows the different spin systems to be linked through the quaternary carbons. Finally, the connection between carbon C-13′ of the M2 unit with proton H-10 of the M1 unit, indicates where the two monomeric units bound to each other and completes the structural elucidation of **3** (Scheme 2). The ion fragments (Fig. 1) are also in agreement with the structure obtained by NMR data.



Scheme 2. Chemical structure of **3**. The long range connections ($^1H\rightarrow^{13}C$) derived from the HMBC experiment are shown with arrows.

Although stable in the solid form, **3** undergoes slow hydrolysis in dilute aqueous solutions to yield **2** as the unique reaction product detectable under the adopted HPLC conditions. With this procedure, a ratio of 1 mol of **2** per mole of **3** is observed. The rate of hydrolysis increases with the decrease in pH; in particular, in 0.1 M HCl complete hydrolysis of **3** was observed after 2 min. This observation agrees with the presence at the C-13′ carbon atom of a thioaminal bond connecting the M1 and M2 moieties of **3**, which can regenerate a unit of **2** when left under mild hydrolytic conditions.[29]

The molecular structure of **3** (Scheme 2) shows the presence of three asymmetric carbons, namely C-1, C-1′ and C-13′, which can give rise to 2^3 optical isomers. However, the chirality in C-13′ is determined by the chirality in C-1′. In fact, due to the constrains imposed by the presence of the five-membered ring belonging to M2, the axial proton on C-1′ must be in a *trans* conformation with respect to the (C-13′)–(N-9) bond. Thus, if the chirality of C-1′ is *R*, the chirality of C-13′ is *S*. Therefore, the number of optical isomers of the compound **3** is only 4, and the stereochemistry will be discussed only in terms of two chiral centers, namely C-1 and C-1′.

In D_2O, all ^1H signals belonging to both the M1 and M2 moieties are clearly split revealing two forms, present in a 1:1 ratio; for instance, a splitting of 0.036 and 0.019 ppm is observed for H-1 and H-1′, respectively. Due to the presence of the two chiral centers C-1 and C-1′, the two observed forms are probably due to two pairs of diastereoisomers, *SS*/*RR* and *RS*/*SR*; however, we were unable to identify the respective signals for each pair of diastereoisomers. In addition, the spectrum of **3** in D_2O plus γ cyclodextrin shows a clear splitting of some resonances, such as those of H-1 and H-$2'_{eq}$ (Fig. 2). In particular, the splitting of each

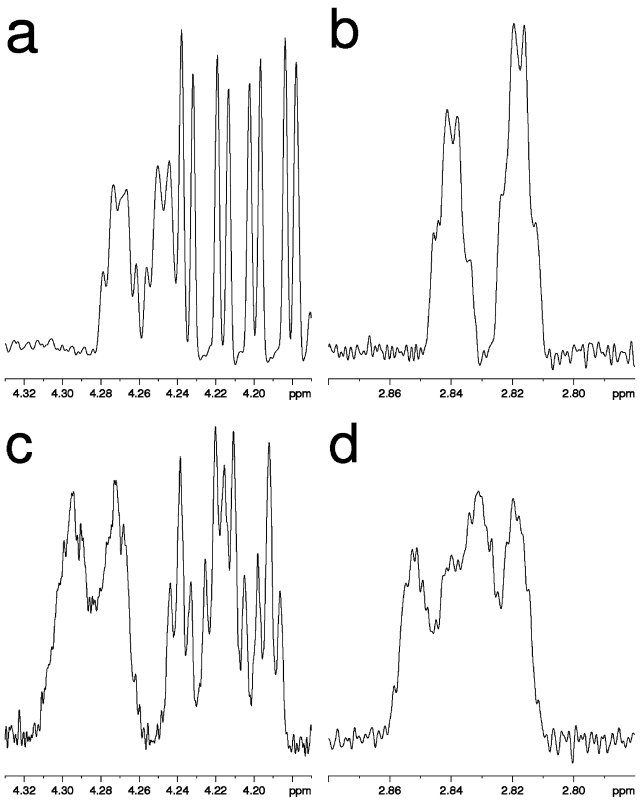


Figure 2. Expanded regions of the ^{1}H spectrum of **3** recorded in D_2O without (a) and (b) and with (c) and (d) γ-cyclodextrin at 25 mM. Spectral regions (a) and (c), and (b) and (d) refer to H-1 and H-$2'_{eq}$, respectively.

double doublet of H-1 into two double doublets confirms that four optical isomers are present.

In the low polarity solvent, CD_2Cl_2, only the resonances due to the M2 moiety are split revealing two forms, present in a ≈3:2 ratio. The presence of a 3:2 ratio between the two forms and the selective splitting regarding only the M2 moiety suggest that these forms are not due to the configurations of carbon atoms C-1 and C-1′. In fact, in that case, the two forms would have been present in a 1:1 ratio as observed in D_2O, and signals belonging to both moieties would have been split. Therefore, the presence of the two forms in CD_2Cl_2 seems due to something else.

A tentative explanation could lie in the presence of two rotational isomers, possibly due to a restricted rotation around the N-9–C-13 bond. In this case, the two rotational isomers are in a slow equilibrium with respect to the NMR time scale and this slow rotation hides completely the presence of the configurational isomers due to the asymmetric carbons. In addition, in a solvent such as DMSO-d_6 that has an intermediate polarity, the rate of the rotation between rotamers may become of the same order of magnitude as the NMR time scale, and the resulting spectra appear complex and reveal the simultaneous presence of both broad and sharp resonances.

However, to properly interpret the behavior of the compound in CD_2Cl_2 and DMSO-d_6, a study of the temperature dependence is required, which could not be undertaken due to the poor thermal stability of the compound.

Finally, on the basis of previous studies on the reaction mechanism of secondary amines with $ONOO^-$,[30] we propose a free radical mechanism, involving one-electron oxidation by $ONOO^-$ of the secondary amino group of **2** to form the amino radical at N-9 and its corresponding isomeric carbon-centered C-13 radical. Dimerization may proceed by combination of the two radical forms (Scheme 3).

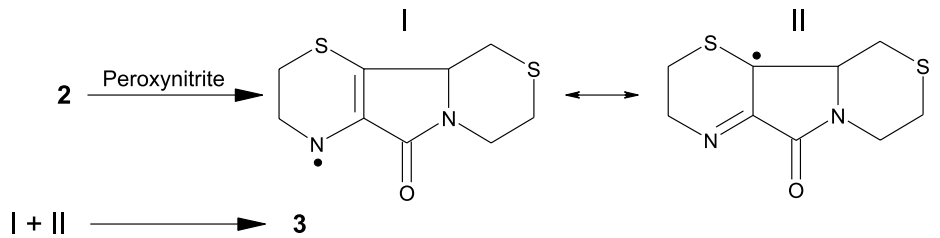
3. Conclusion

In this paper, we have shown that $ONOO^-$ reacts with aminoethylcysteine ketimine decarboxylated dimer (**2**) to yield a dimerized form of the parent compound (Scheme 2). Identification has been achieved by mass spectrometry and NMR analyses of the isolated product, and a full NMR characterization has been reported. A mechanism for the formation of the $ONOO^-$-oxidation derivative of **2** has been proposed, but remains to be proved and will be the object of further investigations.

4. Experimental

4.1. Chemicals

Compound **2** was prepared as reported by Pecci et al.[7] Peroxynitrite was synthesized essentially as described by Beckmann et al.[31] Five milliliters of an acidic solution (0.6 M HCl) of H_2O_2 (0.7 M) were mixed with 5 mL of KNO_2 (0.6 M) on ice for 1 s and the reaction quenched with 5 mL of ice-cold NaOH (1.2 M). Excess hydrogen peroxide was removed by passing the solution through a manganese dioxide column. The solution was then frozen overnight (−20 °C) and the yellow liquid layer on top of the ice crystals collected for the experiments. The concentration of $ONOO^-$ was determined spectrophotometrically at 302 nm using a molar absorption coefficient of 1670 $M^{-1}\,cm^{-1}$.



Scheme 3. Proposed mechanism for the formation of **3** through the radical dimerization of **2**.

According to the IUPAC nomenclature, the name of **3** is 2,2′,3,3′,7,7′,8,8′,10,10′,10a,10a′-dodecahydro-5*H*,5′*H*-4,10b′-i[1,4]thiazino[4′,3′:1,2]pyrrolo[3,4-*b*][1,4]thiazine-5,5′-dione.

4.2. Peroxynitrite reaction and HPLC analysis

0.5 mL of peroxynitrite (4 mM final concentration) were added at once to a 4.5 mL solution of compound **2** (4 mM) in K-phosphate buffer (0.5 M, pH 7.4) at 25 °C with stirring and incubated for 10 min. The reaction mixture was then analyzed by RP chromatography. HPLC analysis was carried out with a Waters chromatograph equipped with two model 501 pumps, a Model 680 gradient controller, a U6K sample injector, a 996 Photodiode Array Detector and a Millenium chromatography manager. The column was a 4.6×250 mm Waters Symmetry C18, 5 μm. The mobile phases were A: 50 mM ammonium acetate; B: acetonitrile: water (80:20, v/v). The column was preconditioned 15 min before sample loading, followed by linear gradient from A to 100% B over 30 min. Flow rate was 1 mL min^{-1}. For preparative HPLC, the column was a 7.8×300 mm Prep Nova-Pak HR C18, 6 μm. The mobile phases were: A: water; B: acetonitrile:water (80:20, v/v); linear gradient: from A to 100% B over 30 min and flow rate: 1 mL min^{-1}. The eluent was monitored at 308 nm and the fractions eluting between 28 and 30 min, corresponding to the main reaction product, were collected. The eluted fractions of 10 HPLC runs were pooled and lyophilized (freeze/dried) before submitting to mass spectrometry and NMR analysis.

4.3. Mass spectrometry

ESI (electrospray ionization) was used in conjunction with the MS^n (multiple stage mass analysis) capability of the ion trap. Mass spectra were acquired with a Finnigan LCQ ion trap mass spectrometer with standard electrospray source in positive ion mode. ESI source parameters optimization and all mass spectral characterization of the analyzed compounds were obtained by 5 μL min^{-1} sample infusion of pure compound or HPLC isolated fractions. Spray voltage was set to 4.5 kV, capillary temperature to 240 °C, sheath gas flow to 80 (arbitrary units), capillary voltage 34 V, octapole 1 and octapole 2 offset −3.75 and −5.5 V. The ion signal was optimized using the automatic tune function of the instrument on a sample of synthetic **2**. Nitrogen was used as sheath gas, helium as trap-collision gas. Multiple stage mass spectral analysis was performed manually, submitting each selected trapped ion to further fragmentation by choosing every time the more efficient collision energy; isolation width of the parent ion was set to three *m*/*z* units. The aqueous mobile phase creates sufficient ionization in the simple charged state. Thus, a fragmentation tree can be constructed. Full scan mass chromatograms of the singly charged compound were obtained by scanning the mass range 50–300 or 50–500 Da.

4.4. NMR analyses

Proton and carbon NMR spectra were run at 300 K on a Bruker AMX600 spectrometer operating at 600.13 and 150.93 MHz, respectively. **2** was analyzed in $CDCl_3$ (30 mM), CD_2Cl_2 (15 mM), DMSO-d_6 (30 mM) and D_2O (15 mM). **3** was dissolved in CD_2Cl_2 (15 mM), DMSO-d_6 (15 mM) and D_2O (15 mM). Literature pulse sequences[32] were used for 1D and 2D experiments. Chemical shifts (δ-scale) of proton and carbon spectra are reported with respect to the solvent residual signal except for the spectra recorded in D_2O for which 2,2-dimethyl-2-silapentane-5-sulfonate sodium salt (DSS) was used as an internal standard. For each experiment, the number of scans was adjusted to yield acceptable signal-to-noise ratios.

^1H spectra were recorded by using 32k data points and a recycle delay of 5 s. In the case of D_2O, a soft presaturation of the residual HOD signal was also applied. $\{^1H\}$ ^{13}C power-gated spectra were recorded by using the WALTZ-16 proton decoupling scheme, 64k data points, 16 dummy scans and a recycle delay of 4 s.

2D spectra in D_2O and CD_2Cl_2 were recorded with gradients selection of the coherence in order to decrease the experimental time and to avoid sample degradation during the analysis.

$^1H-^1H$ gradient-selected COSY-45 experiments were recorded in the magnitude mode with the following acquisition and processing parameters: a spectral width of 3 kHz in both dimensions, 1024 data points in f_2, 512 increments in f_1, a relaxation delay of 1 s, 16 dummy scans and eight scans; the data were processed in the magnitude mode with a sine bell window function and a 512×512 data matrix size.

The DEPT-135 experiment was performed with a selected heteronuclear coupling constant of $^1J_{C-H}$=140 Hz, 64k data points, a recycle delay of 2 s and a number of scans of 20,000 scans.

$^1H-^1H$ NOESY experiments were recorded in the phase sensitive mode (TPPI) with a mixing time of 400 ms and by using the following parameters: a spectral width of 3 kHz in both dimensions, 1024 data points in f_2, 512 increments in f_1, a recycle delay of 1 s, 16 dummy scans and 24 scans; the data were processed with an exponential window function and a 512×512 data matrix size.

$^1H-^1H$ TOCSY experiments were recorded in the phase sensitive mode (TPPI) with a mixing time of 80 ms and by using the following parameters: a spectral width of 3 kHz in both dimensions, 1024 data points in f_2, 512 increments in f_1, a recycle delay of 1 s, four dummy scans and 88 scans; the data were processed with a sine bell window function and a 512×512 data matrix size.

$^1H-^{13}C$ gradient-selected HSQC experiments, with ^{13}C GARP decoupling, were recorded in the echo–antiecho phase-sensitive mode by using a selected heteronuclear scalar coupling constant of $^1J_{C-H}$=150 Hz, and the following parameters: a spectral width of 3 kHz in f_2 and 20 kHz in f_1, 1024 data points in f_2, 512 increments in f_1, a recycle delay of 1 s, 32 dummy scans and 16 scans; the data were processed with a sine bell window function and a 512×512 data matrix size.

$^1H-^{13}C$ gradient-selected HMBC were recorded in the

magnitude mode with a low pass filter of 0.00357 s and a delay for evolution of 0.08 s. The following parameters were also used: a spectral width of 3 kHz in f_2 and 30 kHz in f_1, 1024 data points in f_2, 512 increments in f_1; a recycle delay of 1 s, 32 dummy scans and 74 scans; the data were processed with a sine bell window function and a 512×512 data matrix.

4.5. Supplementary information

The ^1H and ^{13}C assignments of **2** in $CDCl_3$, DMSO-d_6 and D_2O; the ^1H assignment of **2** in D_2O in the presence of β-cyclodextrin; and the ^1H assignment of **3** in D_2O are available as supplementary information.

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Palladium-catalysed synthesis of biaryl phosphines

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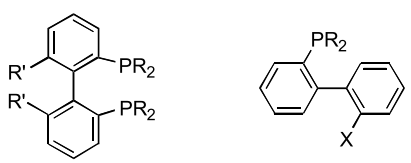
Abstract—Monodentate, biphenyl-type phosphines have emerged as a powerful class of ligands in homogeneous catalysis. Synthetic methods for these ligands are limited, however. We report that the palladium-catalysed Suzuki coupling of $OPR_2(o\text{-}C_6H_4X)$ (R=Ph, *t*-Bu; X=Br, I) with arylboronic acids affords a variety of biaryl phosphine oxides including those that contain heterocycles. The corresponding phosphines are readily obtained by treatment with $HSiCl_3$. The methodology provides an easy entry to monodentate biaryl and heterobiaryl P^X (X=N, O, S) phosphines with diverse steric and electronic properties.

1. Introduction

Phosphines play an extremely important role in homogeneous catalysis, with the choice of ligand often being the crucial factor in determining the success of a reaction.[1] In particular, those possessing novel electronic and steric properties and functional groups are of extra interest, as they can have beneficial effects for metal-catalysed reactions in a homogeneous or multi-phasic solution or on solid surfaces.[1] A class of ligand worthy of note is those containing *ortho*-substituted biphenyl backbones, which can be distinguished into two groups, mono- and bis-phosphines (Scheme 1). Of the latter, 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) and its derivatives are probably the best known, although their chemistry have not been extensively explored.[2] Hayashi has shown that BIPHEP is an excellent ligand for C–C and C–N bond formation.[2b,c] In an interesting development by Mikami, the dynamic axial chirality of BIPHEP ligands has been successfully exploited in asymmetric transformations through asymmetric activation.[2a,d] Several chiral derivatives of BIPHEP are known and have been used in a number of asymmetric reactions, including asymmetric hydrogenation.[2g]



Scheme 1.

The monodentate analogues of BIPHEP-type ligands have only recently emerged as powerful ligands. Although they have found success in metal-catalysed reactions such as hydroformylation[3] and asymmetric allylic alkylation,[4] they have shown to be most outstanding in palladium-catalysed C–X bond forming reactions, including Suzuki coupling, arylation of enolates, Hiyama reaction, aromatic amination, and etherisation.[5] These phosphines represent some of the most effective ligands identified so far for C–X bond formation.[6] The effectiveness of the ligands is attributed to two factors; they are electron-rich and sterically crowded. It is generally accepted that the former factor facilitates oxidative addition whilst the latter can be expected to enhance reductive elimination. *t*-Butyl and cyclohexyl spectator groups at phosphorus have been used to provide electron density, whilst both the spectator group and the biphenyl unit provide the steric bulk. However, the biphenyl group may be more significant in the effectiveness of these ligands than first realised and may provide the key to their success. They could shield and stabilise palladium from coordination to further ligands through steric as well as electronic interactions, thus providing a highly active monophosphine–palladium catalyst.[7] Very recently, an X-ray study of the structure of $[PdL_2]$ [L=2-(dicyclohexylphosphino)biphenyl] has indeed revealed an unusual η^1-coordination of one of the biphenyl rings to Pd(0).[7d] Additionally, when donor substituents are present, possible hemilabile coordination to palladium could provide further stabilisation in the catalyst resting state, thereby increasing catalyst lifetime.

The monodentate biphenyl phosphines are most often prepared using Grignard and lithium reagents.[3–5] More recently, Buchwald has developed an improved synthesis for alkylphosphinobiphenyl ligands, where aryl magnesium halides are reacted with benzyne, followed by addition of a

Keywords: Phosphines; Suzuki coupling; Palladium catalysis; Homogeneous catalysis.
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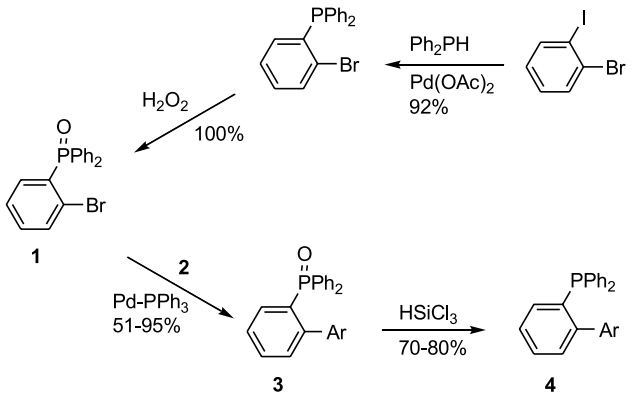
chlorodialkylphosphine.[8] Following an initial report,[9] we describe herein an alternative methodology for the synthesis of biphenyl-based phosphines, which utilises the palladium-catalysed Suzuki reaction. By constructing the biphenyl component in this manner, we could potentially generate ligands with varying steric and electronic properties due to the increased commercial availability of arylboronic acids and the increased functional group tolerance of the Suzuki reaction compared with more traditional methods. The methodology could also be easily extended to incorporate various biaryl groups, giving rise to novel hemilabile phosphine ligands P^X (X=N, O, S) that may find use in coordination chemistry and catalysis.[10] Suzuki coupling has been employed in phosphine synthesis in only a few instances.[11] Of relevance to this study is that of Buchwald, in which arylboronic acids are asymmetrically coupled with a bromonaphthylphosphonate in high yields and excellent ee values.[11b] To our knowledge, however, this simple method has not been applied to the synthesis of biaryl- or heterobiaryl-phosphines to be described herein.

2. Results and discussion

We have recently reported the catalytic synthesis of aryl-phosphines applicable to catalysis in solvents of widely differing solubility properties.[12] The approach utilised a common haloarylphosphine oxide $OPPh_{3-n}(p\text{-}C_6H_4Br)_n$ as a starting block. Using a similar approach but starting with the *ortho*-brominated $OPPh_2(o\text{-}C_6H_4Br)$ **1**, various biphenyl phosphines and related ligands could be easily envisioned through Suzuki coupling with aryl boronic acids **2** (Scheme 2).



Scheme 2.

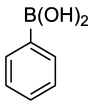
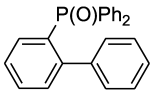
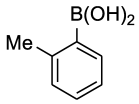
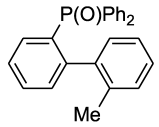
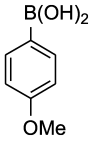
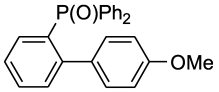
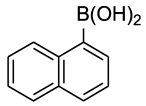
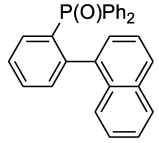
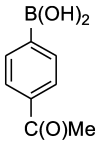
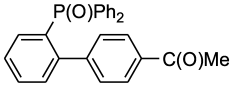
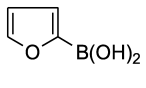
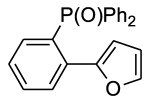
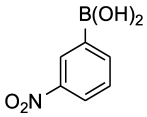
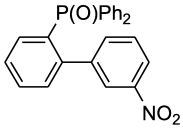
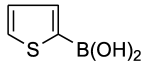
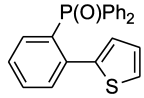
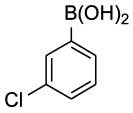
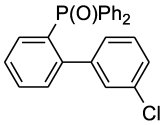
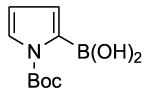
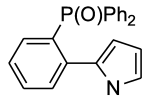
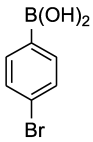
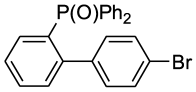
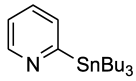
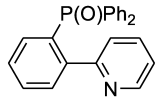
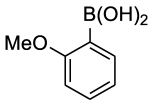
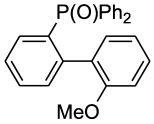
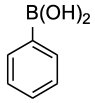
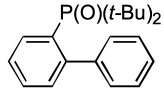
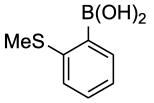
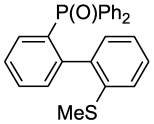
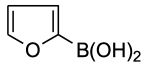
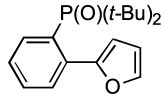
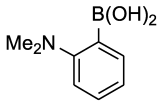
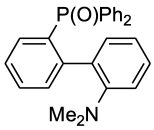
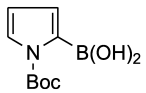
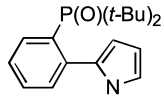
Our synthesis starts with the preparation of the bromophosphine oxide **1**. To enhance the catalytic nature of the overall methodology, the P–C coupling procedures developed by Stelzer were used, in which palladium is used to couple diphenylphosphine or diphenylphosphine oxide with various aryl halides.[13] Compound **1** could be obtained in 92% yield by coupling diphenylphosphine with 1,2-bromoiodobenzene with 1.1 equiv. of NaOAc in the presence of $Pd(OAc)_2$ in DMAc at 130 °C, followed by oxidation with H_2O_2. The starting block **1** was also obtained in 65% yield by the direct coupling of diphenylphosphine oxide with 1,2-bromoiodobenzene. The catalyst used was $Pd(dba)_2$, this time in the presence of 1,3-bis(diphenylphosphino)propane (DPPP) and using $(i\text{-Pr})_2NEt$ as base in toluene at 120 °C. This direct coupling results in a lower yield and requires longer reaction times; but the oxidation step is no longer necessary. The phosphine oxide starting material is a stable solid compared to the air- and moisture-sensitive free phosphine.

The coupling partners to **1** are the boronic acids **2a**–**n** (Table 1). All of these are commercially available, apart from 2-*N*,*N*-dimethylaminophenylboronic acid **2i**,[14] and 1-*t*-butoxycarbonylpyrrol-2-yl boronic acid **2n**,[15] which were synthesised according to literature procedures. Thus, dimethylaniline and pyrrole were *ortho*-lithiated, quenched with $B(OMe)_3$ and acidified, leading to **2i** and **2n** in ca. 50% isolated yield, respectively. In the case of pyrrole, *N*-Boc-protection was necessary first; but the Boc group would be removed after the Suzuki coupling step (vide infra). We were unsuccessful in synthesising 2-pyridinylboronic acid,[16a] required for the synthesis of **3o**. However, the corresponding stannane, 2-pyridinyltributyltin **2o**,[16b] could readily be accessed, which could yield **3o** via the Stille reaction.

The key to our methodology is the Suzuki cross coupling step. Generally, the coupling reaction was conducted using equimolar amounts of **1** and arylboronic acids **2** and 2 equiv. of a base (K_3PO_4) in dioxane at 105 °C. The palladium catalyst was formed in situ from $Pd(dba)_2$ and 4 equiv. of PPh_3. Table 1 illustrates the compounds obtained and their corresponding yields. The *ortho*-positioned $OPPh_2$ moiety in **1** represents a considerably more bulky substituent than those typically encountered in other Suzuki reactions. Consequently, it might be expected that a ligand such as PPh_3, chosen for its ease of handling and availability, would be inferior in comparison to PR_3 (R=Cy, *t*-Bu) or those based on biphenyls, which are considerably more electron-rich and bulky and have been shown to be highly effective towards Suzuki coupling involving considerable steric hindrance.[6] However, **1** couples readily under the aforementioned conditions with phenylboronic acid **2a** as well as *meta*- and *para*-substituted arylboronic acids **2b**–**d** to give the corresponding biaryls in good yields. The reactions preceded equally well with electron-rich and -deficient boronic acids, and they illustrated the expected tolerance of the Suzuki coupling step to various functionalities, including ether, nitro and carbonyl groups. However, some difficulty was experienced with the coupling of **1** with the halo-substituted arylboronic acids **2e** and **2f**, using the conditions described, in which the coupling partners were directly mixed; lower yields of **3e** and **3f** resulted, probably due to arylboronic acid homo-coupling. To obtain reasonable yields, slow introduction of the boronic acids via a dropping funnel during the course of the reaction was necessary; thereby good yields of coupling products were delivered. The presence of halogen functional groups makes phosphines derived from these oxides open to the possibility of accessing polymer or solid-bound biphenyl-based phosphines, analogues of which have been employed for the Suzuki coupling of aryl bromides and chlorides.[17]

As with other Suzuki reactions, the coupling of **1** was significantly more difficult with arylboronic acids containing *ortho*-substituents (**2g**–**j**) to give di-*ortho*-substituted

Table 1. Suzuki coupling of **2** with **1** and **5** leading to **3** and **6**

Boronic acid		Products **3a–i**	Yield (%)[a]	Boronic acid		Products **3j–6n**	Yield (%)
	**2a**		83		**2j**		74[b]
	**2b**		72		**2k**		71[b]
	**2c**		78		**2l**		90[b]
	**2d**		76		**2m**		81[b]
	**2e**		72		**2n**		83[b,c]
	**2f**		66		**2o**		51[b,d]
	**2g**		95[b]		**2a**		81[e]
	**2h**		75[b]		**2l**		84[e]
	**2i**		66[b]		**2n**		75[b,c,f]

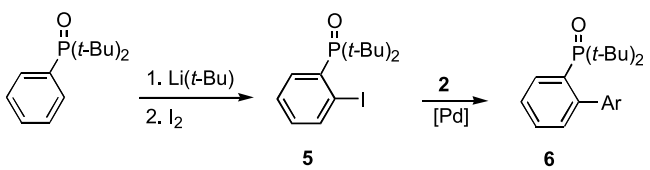
[a] Conditions: 1.0 equiv. **2**, 2.0 equiv. K_3PO_4, 3 mol% $Pd(dba)_2$, 12 mol% PPh_3, dioxane, 105 °C, 12 h.
[b] 2.0 equiv. **2**, reaction run for 48 h.
[c] 3.0 equiv. Na_2CO_3 used as base, DMF, 130 °C.
[d] 5 mol% $Pd(dba)_2$, 20 mol% PPh_3, 1.0 equiv. CuO, DMF, 100 °C.
[e] 1.5 equiv. **2**, 3.3 equiv. KF, 5 mol% $Pd(dba)_2$, 20 mol% PCy_3, dioxane, 105 °C, 24 h.
[f] 5 mol% $Pd(dba)_2$, 20 mol% PPh_3, DMF.

biaryls. Under the conditions outlined above, the reaction proceeded sluggishly, with very low yields of biaryls (**3g–j**) produced. With extra addition of boronic acid and a prolonged reaction time, however, good to excellent yields of products were obtained using the Pd/PPh_3 catalyst. P(*t*-Bu)$_3$ was also examined for the reaction of **1** with 2-methoxyphenylboronic acid **2g**, and 2-methylthiophenylboronic acid **2h**, as it had been reported to outperform PPh_3 in the cross-coupling of aryl chlorides and arylboronic acids, and to be tolerant of *ortho*-substitution in both substrates.[7a] However, the reported conditions, when applied to our reactions, gave lower yields (71% for **2g** and 54% for **2h**) than those obtained with PPh_3. This may be due to the fact that P(*t*-Bu)$_3$ is sterically too demanding for the phosphinyl group. Fu has observed that the sterically less hindered PCy_3 is more effective than P(*t*-Bu)$_3$ in the Suzuki coupling of aryl chlorides that lead to tri-*ortho*-substituted biaryls.[7a] It may also be partly due to

experimental factors. P(*t*-Bu)$_3$ is a viscous oil at room temperature, and transferring accurate catalytic amounts from storage vial to reaction vessel is problematic. As previously discussed, the metal/ligand ratio can have dramatic influence on such C–C coupling reactions;[7a] thus it is vital that the amount of ligand added to a reaction can be carefully controlled. In this context, the phosphonium salts derived from P(*t*-Bu)$_3$ and developed by Fu could be a good alternative.[18] In contrast, the naphthylboronic acid **2k** coupled readily with **1** under the standard conditions to give **3k** in good yield. However, a more bulky variant, 2-(1-methoxynaphthalene)boronic acid, failed to couple with **1** under various conditions, including replacing PPh_3 with P(*t*-Bu)$_3$ and using different bases. Use of DMF as solvent at higher temperatures also proved unsuccessful. A successful coupling of such sterically hindered substrates may demand the use of a new catalyst.[5c]

The last sub-category of biaryls synthesised according to Scheme 2 differs in that they incorporate the heterocycles furan, thiophene, pyrrole and pyridine. Few examples exist in the literature for the synthesis of heterocyclic biaryl compounds via the Suzuki or Stille reaction.[19] Using the same conditions used for **2a**–**d**, compound **1** readily underwent coupling with the heterocyclic boronic acids **2l** and **2m** to yield the expected phosphine oxides **3l** and **3m** in good yields, though these conditions were unsuccessful when **2n** was applied, in which case only starting material was recovered. However, the coupling of **2n** proceeded smoothly when a modified procedure for pyrrole and indole 2-boronic acids was adopted.[20] Thus, under Pd(0)–PPh_3 catalysis in aqueous DMF in the presence of Na_2CO_3 at 130 °C, the reaction went to completion, furnishing **3n** in 83% yield. Contrary to the literature example,[20] there is no need to remove the *N*-Boc-protecting group after the reaction, as it is displaced either during the reaction or in workup. To synthesise **3o**, a different strategy to the Suzuki reaction was applied, due to the unavailability of the necessary boronic acid. The corresponding stannane **2o** was utilised instead, and **3o** was accessed via the Stille reaction. The reaction was run at 100 °C for 24 h in DMF in the presence of Pd(dba)$_2$ and PPh_3. A higher yield of 51% was obtained when 1 equiv. of CuO was added compared to 35% without an additive. Previously, it has been reported that the Stille reaction of **2o** proceeds faster and with higher yields when cupric oxide is used as additive.[21]

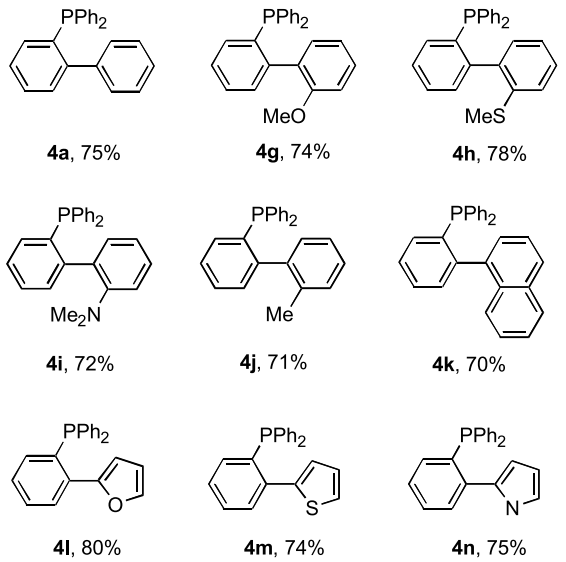
The methodology is also applicable to the synthesis of analogous dialkylphosphines. Scheme 3 shows the synthesis of biaryls containing a di-*t*-butylphosphinyl unit. The *ortho*-iodinated OP(*t*-Bu)$_2$(*o*-C_6H_4I) **5** coupled with **2a**, **2l** or **2n**, furnishing **6a**, **6l** and **6n** in good yields (Table 1). The coupling of **5** with **2a** and **2l** required the more bulky PCy_3 as ligand for palladium, probably due to the much increased steric hindrance of the transmetallation step. With PCy_3,



Scheme 3.

active Pd(0)–monophosphine species could be generated, which should be more easily accessible to the substrates than a Pd(0)L$_2$ species. Since a number of such dialkylphosphines have already been reported,[5h] only three examples are provided in Table 1. The starting iodophosphine oxide **5** can be easily accessed via the method developed by Snieckus.[22]

The free phosphines **4** can be easily obtained from the oxides **3** by reduction with trichlorosilane (Scheme 2). This standard method of phosphine reduction was carried out by simply heating a mixture of **3**, trichlorosilane and triethylamine in toluene at 120 °C overnight. Selected examples of reduction are seen in Scheme 4. In general, the phosphines **4** were obtained as white crystallised solids in good yields. The exception to this was **4l**, which was off-white in colour, and **4n**, which gradually turned pale orange. Compound **4m** could not readily be obtained as a solid. The crystallised form was obtained by cooling in a dry ice/acetone bath; but when allowed to warm to room temperature, an oil was formed.



Scheme 4.

3. Conclusions

We have previously shown that the Heck and related reactions can provide a powerful route to arylphosphines with special solubility properties.[12] The work presented here highlights a general programme based on the Suzuki and, to a limited degree, Stille coupling reactions, for the simple preparation of various biphenyl and hetero-biaryl phosphine ligands, P^X (X=C, N, O, S), in which their stereoelectronic properties can be varied in a systematic fashion, thus enabling rapid catalyst screening and mechanistic study. The elegant work of Buchwald demonstrates further the utility of the method by showing the feasibility of introducing axial chirality.[11b] The hemilabile P^X ligands are worthy of special note. Hemilabile ligands have been extensively studied in coordination chemistry, homogeneous catalysis and materials chemistry, and many examples of their successful applications in these areas exist in the literature.[10] However, few biphenyl and

hetero-biaryl hemilabile phosphines have been reported. The Suzuki coupling protocol now makes these ligands readily accessible, thus opening the door for their chemistry to be investigated.

4. Experimental

4.1. General considerations

All reactions were carried out under an argon atmosphere. Dioxane and THF were distilled under N_2 over sodium benzophenone ketyl, toluene, DMF and triethylamine distilled over CaH. Diphenylphosphine and arylboronic acids were purchased from Aldrich, unless otherwise stated. 2-*N*,*N*-Dimethylaminophenylboronic acid **2i**,[14] 1-*t*-butoxycarbonylpyrrol-2-yl boronic acid **2n**,[15] and 2-pyridinyltributyltin **2o**[16b] were prepared according to published procedures. Elemental analysis was performed by the Microanalysis Laboratory, Department of Chemistry, University of Liverpool.

4.1.1. 2-Diphenylphosphinylbromobenzene (1). *Method A*. An oven-dried, 100 mL Schlenk tube equipped with a magnetic stir bar, a rubber septum and a reflux condenser was charged with NaOAc (2.59 g, 31.6 mmol), $Pd(OAc)_2$ (35 mg, 0.14 mmol) and *N*,*N*-dimethylacetamide (65 mL). 1,2-Bromoiodobenzene **3** (3.7 mL, 29 mmol) and diphenylphosphine (5.0 mL, 29 mmol) were added via syringe and heated at 130 °C for 3 days. The reaction was cooled to room temperature, and the mixture diluted with water (50 mL) and extracted with $CHCl_3$. The combined organic extracts were concentrated in vacuo, and purified by flash chromatography (1:2 EtOAc/hexane) to yield 2-diphenylphosphinobromobenzene[13] as a white precipitate (9.00 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.57 (m, 1H), 7.38–7.32 (m, 6H), 7.30–7.25 (m, 4H), 7.21–7.16 (m, 2H), 6.77–6.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3 (d, J_{CP}=11.2 Hz), 136.2 (d, J_{CP}=10.4 Hz), 134.9, 134.4 (d, J_{CP}=20.0 Hz), 133.4 (d, J_{CP}=2.4 Hz), 130.6, 130.5 (d, J_{CP}=30.2), 129.4, 129.1 (d, J_{CP}=7.2 Hz), 127.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ −3.9. Anal. Calcd for $C_{18}H_{14}PBr$: C, 63.34; H, 4.10. Found: C, 63.16; H, 4.07.

To a solution of 2-diphenylphosphinobromobenzene (9.00 g, 26.4 mmol) in 50 mL MeOH, a couple of drops of 30% H_2O_2 were added at 0 °C and stirred for 1 h at room temperature. The product was partitioned between 100 mL $CHCl_3$ and 50 mL H_2O. The phases were separated and the organic layer was washed with brine (50 mL), dried over $MgSO_4$ and evaporated in vacuo to give **1** as a white precipitate, quantitatively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65 (m, 5H), 7.58–7.31 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (d, J_{CP}=10.4 Hz), 135.2 (d, J_{CP}=8.0 Hz), 133.7 (d, J_{CP}=2.4 Hz), 133.5 (d, J_{CP}=104.7 Hz), 132.5 (d, J_{CP}=9.6 Hz), 132.3 (d, J_{CP}=2.4 Hz), 132.2 (d, J_{CP}=107.9 Hz), 128.9 (d, J_{CP}=12.0 Hz), 127.3 (d, J_{CP}=11.2 Hz), 127.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.2. Anal. Calcd for $C_{18}H_{14}POBr$: C, 60.59; H, 3.93. Found: C, 60.54; H, 3.96.

Method B. An oven-dried, 100 mL Schlenk tube equipped with a magnetic stir bar, a rubber septum and a reflux condenser was charged with diphenylphosphine oxide (6.86 g, 34.0 mmol), $Pd(dba)_2$ (0.56 g, 1.2 mmol) and DPPP (0.42 g, 1.2 mmol) in 50 mL toluene. 1,2-Bromoiodobenzene (5.2 mL, 41 mmol), and (*i*-Pr)$_2$NEt (7.4 mL, 43 mmol) was added via syringe and the mixture refluxed at 120 °C for 4 days. After cooling to room temperature, the product was partitioned between 100 mL $CHCl_3$ and 50 mL H_2O. The phases were separated and the organic layer was washed with brine (50 mL), dried over $MgSO_4$ and evaporated in vacuo to give a pale orange precipitate. Purification by flash chromatography (2:1 EtOAc/hexane) gave the title compound **1** as a white solid (7.90 g, 65% yield).

4.2. General procedure for the Suzuki coupling of 1 with arylboronic acids 2

To a Schlenk tube were charged $OPPh_2$(*o*-C_6H_4Br) **1** (0.50 g, 1.4 mmol) and arylboronic acid (1.4 mmol) together with $Pd(dba)_2$ (24 mg, 0.04 mmol), PPh_3 (44 mg, 0.17 mmol) and K_3PO_4 (0.59 g, 2.8 mmol) in 5 mL of dioxane under an atmosphere of argon. The Schlenk tube was stirred at 105 °C for 12 h and cooled to room temperature. The mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography (2:1 EtOAc/hexane).

4.2.1. 2-Diphenylphosphinylbiphenyl (3a). The reaction was conducted according to the general procedure. Crystallisation from EtOAc/hexane yielded 0.42 g (83%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.52 (m, 5H), 7.45–7.18 (m, 11H), 7.08–7.01 (M, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (d, J_{CP}=4.0 Hz), 134.4 (d, J_{CP}=12.0 Hz), 133.5 (d, J_{CP}=103.8 Hz), 132.4, 132.3, 132.0 (d, J_{CP}=8.8 Hz), 132.0, 131.6, 131.5 (d, J_{CP}=3.2 Hz), 130.5, 128.4, 128.0 (d, J_{CP}=97.5 Hz), 127.5, 126.9 (d, J_{CP}=12.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. Anal. Calcd for $C_{24}H_{19}PO$: C, 81.33; H, 5.41. Found: C, 81.23; H, 5.39. This compound was previously obtained via a multi-lithiation procedure from $OPPh_3$.[23]

4.2.2. 2-Diphenylphosphinyl-4′-methoxybiphenyl (3b). The reaction was conducted according to the general procedure. Crystallisation from EtOAc/hexane yielded 0.39 g (72%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.27 (m, 14H), 7.14 (d, 2H, J=8.7 Hz), 6.57 (d, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9 (d, J_{CP}=8.0 Hz), 134.4 (d, J_{CP}=12.0 Hz), 133.7 (d, J_{CP}=103.9 Hz), 133.3 (d, J_{CP}=4.0 Hz), 133.1 (d, J_{CP}=115.8 Hz), 132.4 (d, J_{CP}=9.6 Hz), 132.1 (d, J_{CP}=2.4 Hz), 131.9, 131.9 (d, J_{CP}=9.6 Hz), 131.4 (d, J_{CP}=3.2 Hz), 128.9 (d, J_{CP}=12.8 Hz), 128.4 (d, J_{CP}=12.0 Hz), 126.7 (d, J_{CP}=12.0 Hz), 113.1, 55.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. Anal. Calcd for $C_{25}H_{21}PO_2$: C, 78.10; H, 5.52. Found: C, 77.80; H, 5.51.

4.2.3. 2-Diphenylphosphinyl-4′-acetylbiphenyl (3c). The reaction was conducted according to the general procedure. Crystallisation from EtOAc/hexane yielded 0.43 g (78%) of the title compound as white crystals. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.64 (d, 2H, J=8.3 Hz), 7.59–7.29 (m, 14H), 7.31 (d, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 146.9, 145.6, 136.1, 134.4 (d, J_{CP}=12.0 Hz), 133.3 (d, J_{CP}=104.7 Hz), 132.2 (d, J_{CP}=2.4 Hz), 132.1, 131.9 (d, J_{CP}=9.6 Hz), 131.7 (d, J_{CP}=2.4 Hz), 131.4 (d, J_{CP}=115.0 Hz), 128.9 (d, J_{CP}=12.0 Hz), 128.6 (d, J_{CP}=12.8 Hz), 127.5, 127.5 (d, J_{CP}=12.8 Hz), 26.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. Anal. Calcd for $C_{26}H_{21}PO_2$: C, 78.78; H, 5.34. Found: C, 78.39; H, 5.43.

4.2.4. 2-Diphenylphosphinyl-3′-nitrobiphenyl (3d). The reaction was conducted according to the general procedure. Crystallisation from EtOAc/hexane yielded 0.42 g (76%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.26 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.8 (d, J_{CP}=107.9 Hz), 135.7 (d, J_{CP}=105.5 Hz), 134.2 (d, J_{CP}=12.0 Hz), 133.8 (d, J_{CP}=2.4 Hz), 132.5 (d, J_{CP}=10.4 Hz), 132.4 (d, J_{CP}=3.2 Hz), 131.9 (d, J_{CP}=9.6 Hz), 128.9 (d, J_{CP}=12.0 Hz), 128.9, 128.8 (d, J_{CP}=12.0 Hz), 128.4, 127.9 (d, J_{CP}=12.0 Hz), 127.3 (d, J_{CP}=11.2 Hz), 125.1, 122.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.6. Anal. Calcd for $C_{24}H_{18}PO_3N$: C, 72.17; H, 4.55; N, 3.50. Found: C, 71.94; H, 4.59; N, 3.28.

4.2.5. 2-Diphenylphosphinyl-3′-chlorobiphenyl (3e). The reaction was conducted according to the general procedure, with the exception that the arylboronic acid **2e** was added slowly (over 6 h) during the course of the reaction via a dropping funnel in 5 mL dioxane. Crystallisation from EtOAc/hexane yielded 0.39 g (72%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 4H), 7.44–7.26 (m, 10H), 7.15–7.10 (m, 2H), 7.02–6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8 (d, J_{CP}=8.8 Hz), 139.1 (d, J_{CP}=4.0 Hz), 134.3 (d, J_{CP}=12.0 Hz), 133.7, 133.3 (d, J_{CP}=104.7 Hz), 133.1, 132.1 (d, J_{CP}=9.6 Hz), 132.1 (d, J_{CP}=2.4 Hz), 132.0 (d, J_{CP}=9.6 Hz), 131.9, 131.7 (d, J_{CP}=2.4 Hz), 131.5, 131.0, 128.5, 128.1 (d, J_{CP}=98.3 Hz), 127.2 (d, J_{CP}=12.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. Anal. Calcd for $C_{24}H_{18}POCl$: C, 74.12; H, 4.68. Found: C, 74.19; H, 4.69.

4.2.6. 2-Diphenylphosphinyl-4′-bromobiphenyl (3f). The reaction was conducted according to the general procedure, with the exception that the arylboronic acid **2f** was added slowly (over 6 h) during the course of the reaction via a dropping funnel in 5 mL dioxane. Crystallisation from EtOAc/hexane yielded 0.40 g (66%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (m, 5H), 7.44–7.25 (m, 9H), 7.17–7.14 (d, 2H, J=8.6 Hz), 7.07–7.04 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8 (d, J_{CP}=8.8 Hz), 139.5 (d, J_{CP}=4.0 Hz), 134.3 (d, J_{CP}=12.0 Hz), 133.3 (d, J_{CP}=104.7 Hz), 132.0 (d, J_{CP}=104.8 Hz), 132.2, 132.2 (d, J_{CP}=2.4 Hz), 132.0 (d, J_{CP}=9.6 Hz), 132.0 (d, J_{CP}=9.6 Hz), 131.7 (d, J_{CP}=3.2 Hz), 130.6, 128.5 (d, J_{CP}=12.0 Hz), 127.3 (d, J_{CP}=12.0 Hz), 122.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. Anal. Calcd for $C_{24}H_{18}POBr$: C, 66.59; H, 4.16. Found: C, 66.57; H, 4.17.

4.2.7. 2-Diphenylphosphinyl-2′-methoxybiphenyl (3g). The reaction was conducted according to the general procedure; with the exception that the reaction time was increased to 48 h, and an extra equivalent (1.40 mmol) of the arylboronic acid **2g** was added after 24 h. Crystallisation from EtOAc/hexane yielded 0.51 g (95%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.15 (m, 15H), 7.05 (ddd, 1H, J=8.0, 8.0, 1.8 Hz), 6.80 (ddd, 1H, J=7.3, 7.3, 0.8 Hz), 6.35 (d, 1H, J=8.1 Hz), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0 (d, J_{CP}=8.0 Hz), 134.4, 133.7 (d, J_{CP}=111.1 Hz), 133.5 (d, J_{CP}=104.7 Hz), 133.1, 132.5 (d, J_{CP}=8.8 Hz), 131.6 (d, J_{CP}=2.4 Hz), 131.3 (d, J_{CP}=9.6 Hz), 131.0 (d, J_{CP}=2.4 Hz), 129.5, 129.0 (d, J_{CP}=4.0 Hz), 128.5 (d, J_{CP}=12.0 Hz), 127.9 (d, J_{CP}=12.0 Hz), 126.9 (d, J_{CP}=12.0 Hz), 119.7, 109.6, 54.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2. Anal. Calcd for $C_{25}H_{21}PO_2$: C, 78.10; H, 5.52. Found: C, 77.89; H, 5.66.

4.2.8. 2-Diphenylphosphinyl-2′-methylthiobiphenyl (3h). The reaction was conducted according to the general procedure, with the exception that the reaction time was increased to 48 h, and an extra equivalent (1.40 mmol) of the arylboronic acid **2h** was added after 24 h. Crystallisation from EtOAc/hexane yielded 0.42 g (75%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.60–7.23 (m, 11H), 7.18–7.13 (m, 2H), 7.05–6.94 (m, 2H), 6.66 (dd, 1H, J=7.8, 0.9 Hz), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (d, J_{CP}=8.8 Hz), 138.0 (d, J_{CP}=4.0 Hz), 137.9, 135.8 (d, J_{CP}=108.7 Hz), 135.7 (d, J_{CP}=105.5 Hz), 134.6 (d, J_{CP}=12.0 Hz), 132.9 (d, J_{CP}=9.6 Hz), 132.5 (d, J_{CP}=8.8 Hz), 132.5 (d, J_{CP}=9.6 Hz), 132.1, 131.0 (d, J_{CP}=2.4 Hz), 128.9 (d, J_{CP}=12.0 Hz), 128.6, 128.5 (d, J_{CP}=12.0 Hz), 124.0, 123.7, 15.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.9. Anal. Calcd for $C_{25}H_{21}POS$: C, 74.97; H, 5.30. Found: C, 74.68; H, 5.25.

4.2.9. 2-Diphenylphosphinyl-2′-dimethylaminobiphenyl (3i). The reaction was conducted according to the general procedure with the exception that the reaction time was increased to 48 h, and an extra equivalent (1.40 mmol) of the arylboronic acid **2i** was added after 24 h. Crystallisation from EtOAc/hexane yielded 0.36 g (66%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.30 (m, 13H), 7.15–7.10 (m, 1H), 6.85–6.67 (m, 4H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0 (d, J_{CP}=12.0 Hz), 134.9 (d, J_{CP}=103.9 Hz), 133.1 (d, J_{CP}=10.4 Hz), 132.3 (d, J_{CP}=9.6 Hz), 132.1 (d, J_{CP}=10.4 Hz), 132.0, 131.8, 131.4, 130.6 (d, J_{CP}=101.5 Hz), 129.0, 128.9, 128.4 (d, J_{CP}=12.0 Hz), 128.3 (d, J_{CP}=12.0 Hz), 126.4 (d, J_{CP}=12.0 Hz), 120.9, 117.9, 43.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.4. Anal. Calcd for $C_{26}H_{24}PON$: C, 78.56; H, 6.10; N, 3.52. Found: C, 78.29; H, 6.05; N, 3.38.

4.2.10. 2-Diphenylphosphinyl-2′-methylbiphenyl (3j). The reaction was conducted according to the general procedure with the exception that the reaction time was increased to 48 h, and an extra equivalent (1.40 mmol) of the arylboronic acid **2j** was added after 24 h. Crystallisation from EtOAc/hexane yielded 0.38 g (74%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–6.92 (m, 18H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.2 (d, J_{CP}=12.0 Hz), 133.5 (d, J_{CP}=103.9 Hz), 133.3 (d, J_{CP}=103.9 Hz), 132.3 (d, J_{CP}=9.6 Hz), 131.9 (d, J_{CP}=3.2 Hz), 131.8 (d, J_{CP}=9.6 Hz), 131.5 (d, J_{CP}=3.2 Hz), 131.5 (d, J_{CP}=2.4 Hz), 131.1, 129.7, 128.4 (d, J_{CP}=12.0 Hz), 128.3 (d, J_{CP}=12.0 Hz), 127.9, 127.0 (d,

J_{CP}=12.8 Hz), 124.6, 20.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.7. Anal. Calcd for $C_{25}H_{21}PO$: C, 81.50; H, 5.76. Found: C, 81.33; H, 5.72.

4.2.11. 1-(2-Diphenylphosphinylphenyl)naphthalene (3k). The reaction was conducted according to the general procedure. Crystallisation from EtOAc/hexane yielded 0.40 g (71%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.67 (m, 1H), 7.63–7.17 (m, 17H), 6.97–6.92 (m, 1H), 6.87–6.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (d, J_{CP}=11.2 Hz), 133.4 (d, J_{CP}=11.2 Hz), 133.2, 132.3 (d, J_{CP}=8.8 Hz), 132.0, 131.6, 131.5 (d, J_{CP}=12.0 Hz), 131.5, 131.0 (d, J_{CP}=9.6 Hz), 130.5 (d, J_{CP}=3.2 Hz), 129.8, 128.6, 128.4, 128.3, 128.2, 127.7, 127.5 (d, J_{CP}=12.0 Hz), 127.0 (d, J_{CP}=108.6 Hz), 125.6, 125.2 (d, J_{CP}=98.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.8. Anal. Calcd for $C_{28}H_{21}PO$: C, 83.14; H, 5.24. Found: C, 82.97; H, 5.13.

4.2.12. 2-(2-Diphenylphosphinylphenyl)furan (3l). The reaction was conducted according to the general procedure, with the exception that a longer reaction time of 48 h was employed. Crystallisation from EtOAc/hexane yielded 0.43 g (90%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.72 (m, 14H), 7.16 (d, 1H, J=1.3 Hz), 7.03 (d, 1H, J=3.3 Hz), 6.16 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4 (d, J_{CP}=4.8 Hz), 142.9, 135.0 (d, J_{CP}=7.2 Hz), 135.3 (d, J_{CP}=12.0 Hz), 133.3 (d, J_{CP}=105.5 Hz), 132.4 (d, J_{CP}=2.4 Hz), 132.0 (d, J_{CP}=9.6 Hz), 131.8 (d, J_{CP}=3.2 Hz), 130.1 (d, J_{CP}=9.6 Hz), 130.0 (d, J_{CP}=101.5 Hz), 128.6 (d, J_{CP}=12.0 Hz), 127.6 (d, J_{CP}=12.0 Hz), 112.9, 111.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.9. Anal. Calcd for $C_{22}H_{17}PO_2$: C, 76.73; H, 4.99. Found: C, 76.85; H, 4.97.

4.2.13. 2-(2-Diphenylphosphinylphenyl)thiophene (3m). The reaction was conducted according to the general procedure, with the exception that a longer reaction time of 48 h was employed. Crystallisation from EtOAc/hexane yielded 0.41 g (81%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.29 (m, 15H), 7.03 (dd, 1H, J=5.1, 1.1 Hz), 6.74 (dd, 1H, J=5.1, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (d, J_{CP}=4.8 Hz), 139.8 (d, J_{CP}=8.0 Hz), 134.7 (d, J_{CP}=12.0 Hz), 132.8 (d, J_{CP}=105.5 Hz), 132.8 (d, J_{CP}=8.8 Hz), 132.8, 131.8, 131.6 (d, J_{CP}=9.6 Hz), 131.2 (d, J_{CP}=2.4 Hz), 131.2 (d, J_{CP}=114.2 Hz), 128.2 (d, J_{CP}=12.8 Hz), 127.1 (d, J_{CP}=12.0 Hz), 127.0, 126.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.9. Anal. Calcd for $C_{22}H_{17}POS$: C, 73.31; H, 4.77. Found: C, 73.43; H, 4.76.

4.2.14. 2-(2-Diphenylphosphinylphenyl)pyrrole (3n). The reaction was conducted according to the general procedure; with the exception that 3 equiv. of Na_2CO_3 was used as base, and the reaction was heated at 130 °C in DMF for 48 h. Crystallisation from EtOAc/hexane yielded 0.40 g (83%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.73–7.02 (m, 14H), 6.65 (m, 1H), 6.26 (m, 1H), 5.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3 (d, J_{CP}=8.0 Hz), 134.6 (d, J_{CP}=12.8 Hz), 132.9 (d, J_{CP}=2.4 Hz), 132.9 (d, J_{CP}=93.5 Hz), 132.3 (d, J_{CP}=3.2 Hz), 132.1 (d, J_{CP}=9.6 Hz), 131.6 (d, J_{CP}=4.8 Hz), 131.2, 130.7 (d, J_{CP}=9.6 Hz), 128.8 (d, J_{CP}=12.0 Hz), 127.6 (d, J_{CP}=100.7 Hz), 125.5 (d, J_{CP}=12.8 Hz), 120.1, 109.6 (d, J_{CP}=5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.1. Anal. Calcd for $C_{22}H_{18}PON$: C, 76.95; H, 5.29; N, 4.08. Found: C, 77.00; H, 5.50; N, 3.97.

4.2.15. 2-(2-Diphenylphosphinylphenyl)pyridine (3o). To a Schlenk tube were charged **1** (0.50 g, 1.4 mmol) and 2-pyridyltributyltin **2o** (1.03 g, 2.80 mmol) together with $Pd(dba)_2$ (40 mg, 0.07 mmol), PPh_3 (73 mg, 0.28 mmol) and CuO (0.11 g, 1.4 mmol) in 50 mL of DMF under an atmosphere of argon. The Schlenk tube was stirred at 100 °C for 48 h and cooled to room temperature. The mixture was diluted with water (25 mL) and extracted with $CHCl_3$ (3×50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography (EtOAc). Crystallisation from EtOAc/hexane yielded 0.25 g (51%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 1H, J=4.3 Hz), 7.80 (d, 1H, J=7.8 Hz), 7.64–7.56 (m, 6H), 7.48–7.28 (m, 9H), 6.94 (ddd, 1H, J=7.6, 4.8, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (d, J_{CP}=4.0 Hz), 149.1, 146.3 (d, J_{CP}=8.0 Hz), 135.8, 134.7 (d, J_{CP}=12.0 Hz), 133.7 (d, J_{CP}=104.5 Hz), 132.4 (d, J_{CP}=2.4 Hz), 132.0 (d, J_{CP}=8.8 Hz), 131.9 (d, J_{CP}=9.6 Hz), 131.6 (d, J_{CP}=101.5 Hz), 131.5 (d, J_{CP}=3.2 Hz), 128.5 (d, J_{CP}=12.0 Hz), 128.1 (d, J_{CP}=12.0 Hz), 126.1, 122.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3. Anal. Calcd for $C_{23}H_{18}PON$: C, 77.73; H, 5.12; N, 3.94. Found: C, 77.60; H, 5.24; N, 3.77.

4.3. General procedure for the Suzuki coupling of OP(*t*-Bu)$_2$(*o*-C$_6$H$_4$I) 5 with arylboronic acids 2

To a Schlenk tube were charged OP(*t*-Bu)$_2$(*o*-C$_6$H$_4$I) **5** (0.50 g, 1.4 mmol) and arylboronic acid **2** (2.1 mmol), $Pd(dba)_2$ (39 mg, 0.068 mmol), PCy_3 (77 mg, 0.27 mmol) and KF (0.26 g, 4.5 mmol) in 15 mL of dioxane under an atmosphere of argon. The reaction mixture was stirred for 24 h at 105 °C and cooled to room temperature. Dilution with water (25 mL) was followed by extraction with $CHCl_3$ (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (5:1 EtOAc/hexane) gave the coupled products **6** (Scheme 3).

4.3.1. 2-Di-*t*-butylphosphinylbiphenyl (6a). The reaction was conducted following the general procedure. Crystallisation from EtOAc/hexane yielded 0.35 g (81%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J=8.9, 8.9 Hz, 1H), 7.46 (dd, J=7.3, 7.3 Hz, 1H), 7.37 (dd, J=7.6, 7.6 Hz, 1H), 7.30–7.20 (m, 6H), 1.25 (d, J=13.4 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=4.0 Hz), 142.7 (d, J_{CP}=2.4 Hz), 133.6 (d, J_{CP}=8.8 Hz), 131.5 (d, J_{CP}=11.2 Hz), 130.3 (d, J_{CP}=2.4 Hz), 129.3, 129.1 (d, J_{CP}=75.9 Hz), 127.0, 126.7, 125.7 (d, J_{CP}=12.0 Hz), 37.4 (d, J_{CP}=58.3 Hz), 27.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 54.0. Anal. Calcd for $C_{20}H_{27}PO$: C, 76.39; H, 8.67. Found: 76.40; H, 8.73.

4.3.2. 2-(2-Di-*t*-butylphosphinylphenyl)furan (6l). The reaction was conducted following the general procedure. Crystallisation from EtOAc/hexane yielded 0.34 g (84%) of the title compound as white crystals. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.67 (dd, J=8.8, 8.8 Hz, 1H), 7.56 (m, 4H), 6.50–6.41 (m, 2H), 1.28 (d, J=13.4 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, J_{CP}=3.2 Hz), 141.7, 138.6 (d, J_{CP}=2.4 Hz), 133.6 (d, J_{CP}=8.0 Hz), 131.9 (d, J_{CP}=11.2 Hz), 131.2 (d, J_{CP}=74.3 Hz), 130.6 (d, J_{CP}=2.4 Hz), 126.9 (d, J_{CP}=10.4 Hz), 111.1, 109.1, 37.6 (d, J_{CP}=59.1 Hz), 27.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 54.0. Anal. Calcd for $C_{18}H_{17}PO_2$: C, 72.96; H, 5.79. Found: 72.81; H, 5.73.

4.3.3. 2-(2-Di-*t*-butylphosphinylphenyl)pyrrole (6n). The reaction was conducted following the general procedure; with the exception that PPh_3 (72 mg, 0.27 mmol) was used instead of PCy_3. The base used was aq. Na_2CO_3 (0.44 g, 4.1 mmol), and the solvent DMF. The reaction was performed at 130 °C, again for 24 h. Crystallisation from EtOAc/hexane yielded 0.31 g (75%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J=8.2, 4.3 Hz, 1H), 7.56 (dd, J=12.7, 7.9 Hz, 1H), 7.41 (dd, J=7.7, 7.7 Hz, 1H), 7.11 (dd, J=7.6, 7.6 Hz, 1H), 6.88 (m, 1H), 6.63 (m, 1H), 6.20 (m, 1H) 1.31 (d, J=13.7 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (d, J_{CP}=3.2 Hz), 132.8 (d, J_{CP}=12.8 Hz), 131.7 (d, J_{CP}=2.4 Hz), 130.5 (d, J_{CP}=8.8 Hz), 124.0 (d, J_{CP}=75.9 Hz), 123.0 (d, J_{CP}=12.8 Hz), 120.6, 110.3, 109.2, 108.4, 38.4 (d, J_{CP}=58.3 Hz), 28.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 64.0. Anal. Calcd for $C_{18}H_{26}PON$: C, 71.25; H, 8.65; N, 4.62. Found: 71.00; H, 8.55; N, 3.97.

4.4. General procedure for the reduction of oxides 3 to phosphines 4

A 10 mL toluene solution of **3** (1.00 mmol) was frozen in liquid nitrogen, to which trichlorosilane (5 equiv.) and triethylamine (5.5 equiv.) were added. The mixture was stirred at 120 °C under argon overnight. After cooling to room temperature, a saturated $NaHCO_3$ aqueous solution (1 mL) was added, and further stirred for 5 min. This was filtered through a pad of alumina and evaporated in vacuo to give a crude oily product. Purification by flash chromatography (9:1 hexane/EtOAc), and crystallisation in hexane gave the desired product as crystalline solids.

4.4.1. 2-Diphenylphosphinobiphenyl (4a). The general procedure on a 1.2 mmol scale gave 0.30 g (75% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.16 (m, 18H), 7.06 (ddd, 1H, J=7.6, 3.8, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 148.5, 142.1 (d, J_{CP}=6.4 Hz), 138.1 (d, J_{CP}=12.0 Hz), 136.3 (d, J_{CP}=13.6 Hz), 134.4, 134.3 (d, J_{CP}=20.0 Hz), 130.5 (d, J_{CP}=4.8 Hz), 130.1 (d, J_{CP}=4.0 Hz), 129.0, 128.8, 128.7 (d, J_{CP}=6.4 Hz), 127.9, 127.6 (d, J_{CP}=20.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.0. Anal. Calcd for $C_{24}H_{19}P$: C, 85.20; H, 5.62. Found: C, 84.83; H, 5.65.

4.4.2. 2-Diphenylphosphino-2′-methoxybiphenyl (4g). The general procedure on a 1.3 mmol scale gave 0.36 g (74% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, J=7.3, 7.3 Hz), 7.32–7.26 (m, 12H), 7.18–7.10 (m, 2H), 7.06 (dd, 1H, J=7.4, 1.6 Hz), 6.90 (dd, 1H, J=7.4, 7.4 Hz), 6.81 (d, 1H, J=8.4 Hz), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.6, 134.0 (d, J_{CP}=20.0 Hz), 131.7, 131.7, 130.8 (d, J_{CP}=24.0 Hz), 130.8, 129.4, 129.2 (d, J_{CP}=24.0 Hz), 128.6, 128.6, 128.5, 128.4 (d, J_{CP}=7.2 Hz), 127.7, 120.3, 110.6, 55.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ-11.7. Anal. Calcd for $C_{25}H_{21}PO$: C, 81.50; H, 5.76. Found: C, 81.80; H, 5.95.

4.4.3. 2-Diphenylphosphino-2′-methylthiobiphenyl (4h). The general procedure on a 1.1 mmol scale gave 0.30 g (78% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 1H), 7.34–7.16 (m, 14H), 7.13–7.10 (m, 1H), 6.98–6.94 (m, 1H), 6.81–6.79 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 138.0, 135.2, 134.4, 134.4, 134.2, 133.9 (d, J_{CP}=19.2 Hz), 130.8 (d, J_{CP}=3.2 Hz), 130.5 (d, J_{CP}=5.6 Hz), 129.2, 128.9, 128.7 (d, J_{CP}=7.2 Hz), 128.5 (d, J_{CP}=7.2 Hz), 128.4, 124.8, 124.1, 16.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.3. Anal. Calcd for $C_{25}H_{21}PS$: C, 78.09; H, 5.52. Found: C, 77.89; H, 5.50.

4.4.4. 2-Diphenylphosphino-2′-dimethylaminobiphenyl (4i). The general procedure on a 0.9 mmol scale gave 0.25 g (72% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.33–7.18 (m, 11H), 7.15–7.10 (m, 2H), 7.01–6.91 (m, 3H), 2.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (d, J_{CP}=12.8 Hz), 136.7 (d, J_{CP}=12.0 Hz), 136.3 (d, J_{CP}=3.2 Hz), 135.6 (d, J_{CP}=6.4 Hz), 133.6 (d, J_{CP}=20.0 Hz), 133.3 (d, J_{CP}=19.2 Hz), 132.2, 130.7 (d, J_{CP}=6.4 Hz), 129.6, 128.9, 128.4 (d, J_{CP}=12.0 Hz), 128.4, 128.1 (d, J_{CP}=16.0 Hz), 127.2, 121.7, 118.0, 43.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.6. Anal. Calcd for $C_{26}H_{24}PN$: C, 81.86; H, 6.35; N, 3.67. Found: C, 81.75; H, 6.36; N, 3.69.

4.4.5. 2-Diphenylphosphino-2′-methylbiphenyl (4j). The general procedure on a 1.0 mmol scale gave 0.26 g (71% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.01 (m, 18H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 137.1 (d, J_{CP}=11.2 Hz), 136.8 (d, J_{CP}=10.2 Hz), 136.7 (d, J_{CP}=11.2 Hz), 135.7, 133.8 (d, J_{CP}=19.3 Hz), 133.7 (d, J_{CP}=20.3 Hz), 130.3 (d, J_{CP}=3.1 Hz), 129.6 (d, J_{CP}=5.1 Hz), 128.6, 128.3 (d, J_{CP}=5.1 Hz), 128.3, 128.2, 127.4, 124.6, 123.2, 20.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −11.6 Anal. Calcd for $C_{25}H_{21}P$: C, 85.21; H, 6.00. Found: C, 85.33; H, 6.22.

4.4.6. 1-(2-Diphenylphosphinophenyl)naphthalene (4k). The general procedure on a 1.0 mmol scale gave 0.27 g (70% yield) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.79 (m, 2H), 7.46–7.27 (m, 10H), 7.21–7.15 (m, 6H), 7.12–7.05 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.5 (d, J_{CP}=6.4 Hz), 138.3 (d, J_{CP}=12.8 Hz), 138.0 (d, J_{CP}=12.0 Hz), 137.8 (d, J_{CP}=12.0 Hz), 134.2 (d, J_{CP}=4.0 Hz), 134.0 (d, J_{CP}=4.8 Hz), 133.7, 132.7, 131.3 (d, J_{CP}=5.6 Hz), 128.9, 128.7 (d, J_{CP}=6.4 Hz), 128.6 (d, J_{CP}=12.0 Hz), 128.6 (d, J_{CP}=20.8 Hz), 128.6, 128.4 (d, J_{CP}=3.2 Hz), 128.2 (d, J_{CP}=8.8 Hz), 126.7, 126.0 (d, J_{CP}=15.2 Hz), 125.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ −13.1. Anal. Calcd for $C_{28}H_{21}P$: C, 86.57; H, 5.46. Found: C, 86.10; H, 5.62.

4.4.7. 2-(2-Diphenylphosphinophenyl)furan (4l). The general procedure on a 1.2 mmol scale gave 0.32 g (80% yield) of the title compound as white crystals. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 1H), 7.41–7.16 (m, 13H), 6.96 (dd, 1H, J=7.7, 4.2 Hz), 6.50–6.49 (m, 1H), 6.37–6.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 142.5, 137.7 (d, J_{CP}=11.2 Hz), 136.6 (d, J_{CP}=26.4 Hz), 134.9, 134.8, 134.3 (d, J_{CP}=20.0 Hz), 129.1, 129.0, 128.9, 128.6 (d, J_{CP}=4.8 Hz), 127.9, 111.7, 111.0 (d, J_{CP}= 12.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −8.3. Anal. Calcd for $C_{22}H_{17}PO$: C, 80.47; H, 5.23. Found: C, 80.11; H, 5.2.

4.4.8. 2-(2-Diphenylphosphinophenyl)thiophene (4m). The general procedure on a 1.1 mmol scale gave 0.29 g (74% yield) of the title compound as an off-white oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 1H), 7.32–7.22 (m, 13H), 7.01 (dd, 1H, J=7.8, 3.7 Hz), 6.93 (m, 1H), 6.85 (dd, 1H, J=3.5, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (d, J_{CP}=6.4 Hz), 140.7 (d, J_{CP}=28.8 Hz), 138.1 (d, J_{CP}=12.0 Hz), 137.4 (d, J_{CP}=15.2 Hz), 134.7, 134.3 (d, J_{CP}=20.0 Hz), 131.6 (d, J_{CP}=4.8 Hz), 128.9 (d, J_{CP}= 5.6 Hz), 128.9, 128.9, 128.5 (d, J_{CP}=5.6 Hz), 128.3, 127.1, 126.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ −11.5.

4.4.9. 2-(2-Diphenylphosphinophenyl)pyrrole (4n). The general procedure on a 1.2 mmol scale gave 0.29 g (75% yield) of the title compound as white crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H) 7.58–7.25 (m, 12H), 7.14 (ddd, 1H, J=7.5, 7.5, 1.3 Hz), 6.96 (ddd, 1H, J=7.8, 4.4, 1.3 Hz), 6.73 (m, 1H), 6.24 (m, 1H), 6.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (d, J_{CP}=10.4 Hz), 134.9, 134.3 (d, J_{CP}=20.0 Hz), 132.1 (d, J_{CP}=9.6 Hz), 130.7 (d, J_{CP}=10.4 Hz), 129.7 (d, J_{CP}=5.6 Hz), 129.4, 129.2, 129.0 (d, J_{CP}=7.2 Hz), 128.8 (d, J_{CP}=9.6 Hz), 127.2, 118.8, 110.3 (d, J_{CP}=4.0 Hz), 109.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ −10.0. Anal. Calcd for $C_{22}H_{18}PN$: C, 80.71; H, 5.55; N, 4.28. Found: C, 80.48; H, 5.58; N, 4.23.

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A practical and highly efficient synthesis of lennoxamine and related isoindolobenzazepines

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Abstract—Lennoxamine and related isoindolobenzazepines were prepared in high yield by intramolecular condensation of aldehyde isoindolones under basic conditions followed by catalytic hydrogenation of the resulting dehydroisoindolobenzazepines.

1. Introduction

Lennoxamine (**1a**), an isoindolobenzazepine, was isolated from the Chilean plant *Berberis darwinii*.[1] Even though no important pharmacological activity of lennoxamine has been reported as normally found in the benzazepine derivatives,[2a–e] its unique structural features have captured the interest of many synthetic groups over the past 20 years.

The previous syntheses of lennoxamine and other isoindolobenzazepine derivatives could be classified into various approaches depending on the order of bond formation as shown in Figure 1.

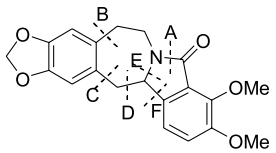
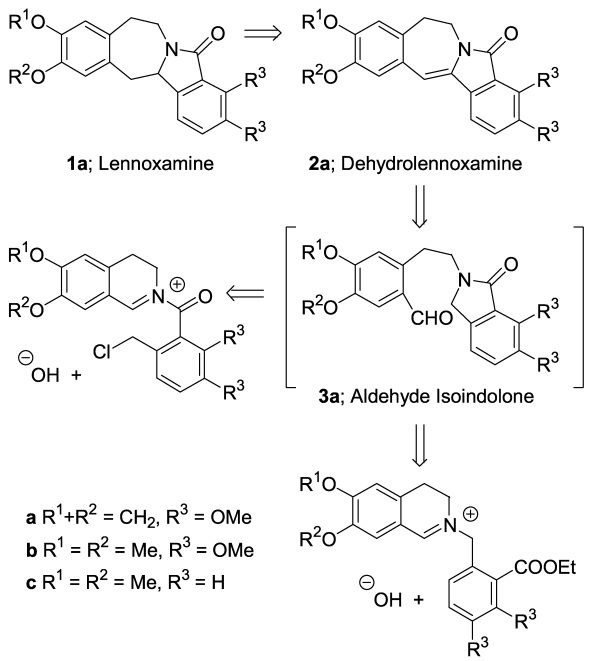


Figure 1.

The first approach involved prior construction of the benzazepine skeleton followed by isoindolone ring formaton via bond A[3a,b] or bond F.[4] The second approach concentrated on first the isoindolone ring formation which could then be manipulated to form the benzazepine ring via formation of bond B[5a–c] or bond C.[6a–c] Bond D formation of various phthalimide derivatives[7a–d] has been exploited in the third approach. The simultaneous formation of the isoindolone and the benzazepine skeleton was the focus of the fourth approach.[6c,8] The fifth approach utilized the rearrangement of various isoquinoline derivatives as a means to synthesize the isoindoloisoquinolines.[9a–e]

2. Results and discussion

In our previous synthetic routes (Scheme 1), the aldehyde isoindolone **3a** was the common unisolated intermediate which further cyclized smoothly to the dehydrolennoxamine



Scheme 1. Synthetic route.

Keywords: Lennoxamine; Isoindolobenzazepine alkaloids.
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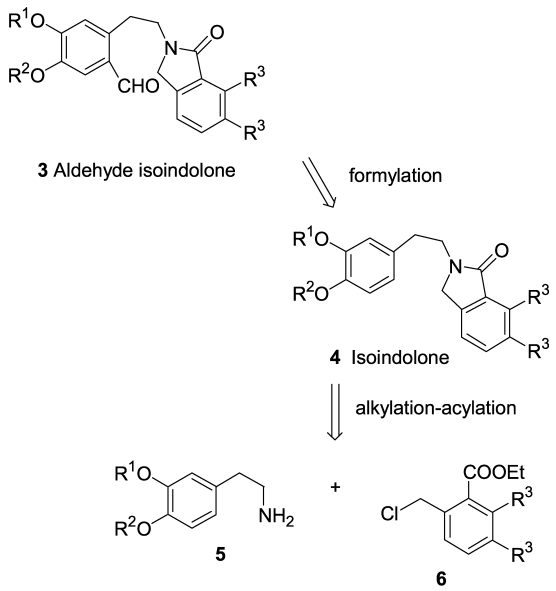
2a in high yield. The former pathway provided the desired isoindolone via hydroxide addition to the iminium salt to give the carbinolamine derivative which was opened to give the amide anion followed by intramolecular alkylation. The above pathway worked well only when the sixth position of the isoquinoline derivative was substituted with a methoxy group. The methoxy group apparently facilitated the breaking of the carbon–nitrogen bond to give the aldehyde and amide anion. Alternatively, in the other pathway, the methoxy group *ortho* to the carboethoxy group is required for the success of the synthesis. The methoxy group presumably activates the leaving group ability of the ester.[10] In this paper, we report a highly efficient, direct synthesis of aldehyde isoindolone which could be successfully cyclized to the isoindolobenzazepine derivatives irrespective of the oxygenation pattern on the aromatic ring.

The aldehyde isoindolone was synthesized by the route suggested by retrosynthetic analysis as shown in Scheme 2.



Scheme 2. Retrosynthetic analysis.

The aldehyde isoindolone **3** could be synthesized by formylation of the isoindolone precursor **4** which could conceivably be prepared by alkylation–acylation of the arylethylamine derivatives with ethyl 2-chloromethylbenzoates **6**.

To test the above idea, homoveratrylamine **5** was heated at reflux with ethyl 2-chloromethylbenzoate **6** in acetonitrile in the presence of triethylamine to give the expected isoindolone **4c** in 74% yield. Similarly, the other two isoindolones, **4a**, **4b** were obtained in 81 and 76% yields respectively from the reaction of the appropriate arylethylamines and ethyl 2,3-dimethoxy-6-chloromethylbenzoate.[11]

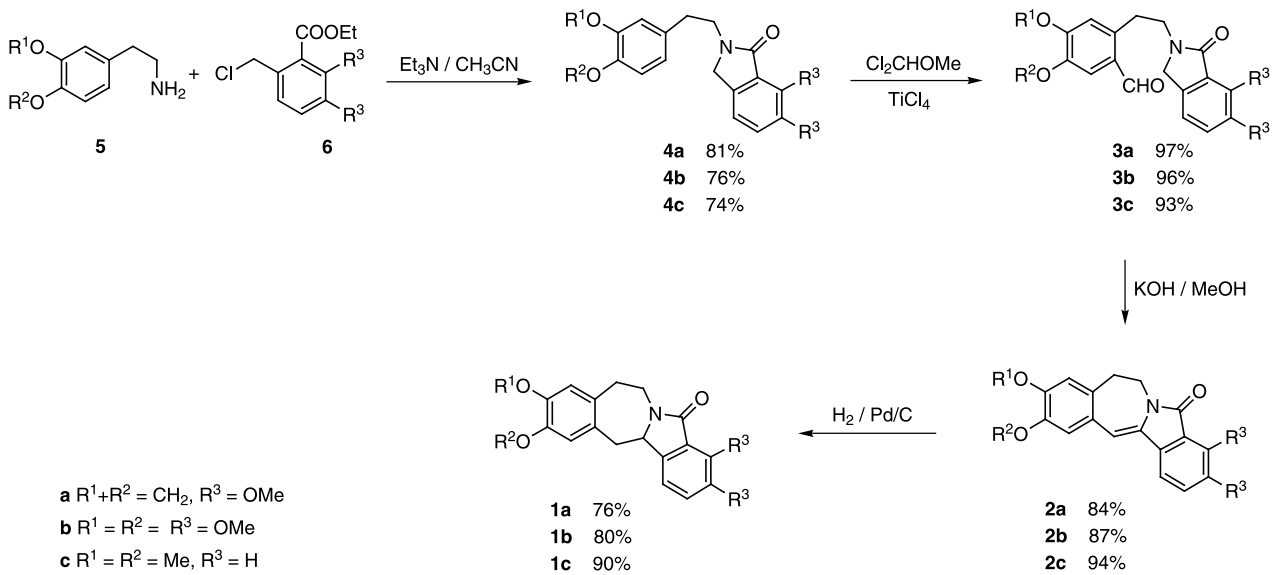
Formylation of the resulting isoindolones were carried out conveniently using dichloromethyl methyl ether and titanium tetrachloride in dichloromethane[12a–c] to give the aldehyde isoindolones, **3a**, **3b**, **3c** in excellent yields

The derived aldehyde isoindolones were cyclized smoothly in refluxing methanolic KOH to give the required dehydroisoindolobenzazepines, **2a**, **2b**, and **2c**, in excellent yields.

Lennoxamine, **1a** as well as other isoindolobenzazepines, **1b**, **1c**, could be readily obtained by catalytic hydrogenation of the dehydro intermediates **2a**, **2b**, and **2c** in 76, 80 and 90% yields, respectively (Scheme 3).

3. Conclusion

We have successfully developed a practical and highly efficient synthetic route for lennoxamine and other related isoindolobenzazepines. The route involved condensing of aldehyde isoindolones under basic conditions followed by catalytic hydrogenation of the resulting dehydroisoindolobenzazepines. The key aldehyde isoindolones were derived in two steps from alkylation–acylation of arylethylamines with ethyl 2-chloromethylbenzoate derivatives and insertion



Scheme 3. Preparation of lennoxamine and its derivatives.

of the C-1 aldehyde onto the aromatic ring using dichloromethyl methyl ether and $TiCl_4$.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz respectively using TMS as an internal standard. Mass spectra were determined at an ionizing voltage of 70 eV. Column chromatographic purifications were carried out using silica gel (70–230 mesh).

4.2. General procedure for the synthesis of isoindolones

A solution of arylethylamine derivatives (1 mmol), ethyl 2-chloromethylbenzoates (1 mmol) and triethylamine (1.2 mmol) in CH_3CN (5 mL) was heated under reflux for 3 h under nitrogen atmosphere. CH_3CN was removed and the crude product was extracted with CH_2Cl_2 and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness to give the crude amide as yellow solid, the product was further purified by column chromatography using 2% MeOH/CH_2Cl_2 as eluting solvent to give the isoindolones as pale yellow solid.

4.2.1. 2-(3,4-Methylenedioxyphenethyl)-6,7-dimethoxyphthalimidine (4a). Pale yellow crystals (81%), mp (EtOAc) 99–100 °C; IR (nujol) 1678 cm^{-1}; ^1H NMR δ 2.88 (t, 2H, J=7.5 Hz), 3.75 (t, 2H, J=7.5 Hz), 3.88 (s, 3H), 4.08 (s, 3H), 4.13 (s, 3H), 5.91 (s, 2H), 6.67 (dd, 1H, J=8.0, 1.6 Hz), 6.71 (d, 1H, J=8.0 Hz), 6.73 (d, 1H, J=1.6 Hz), 7.02, 7.06 (AB, 1H each, J=8.0 Hz). ^{13}C NMR δ 34.4, 44.3, 49.6, 56.7, 62.5, 100.8, 108.3, 109.0, 116.3, 117.6, 121.5, 125.0, 132.6, 134.5, 146.1, 147.1, 147.7, 152.2, 166.6. EIMS 341(M^+, 23), 206(96), 194(67), 193(16), 162(13), 149(16), 148(100), 135(13). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.90; H, 5.80; N, 3.92.

4.2.2. 2-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyphthalimidine (4b). Pale yellow crystals (76%), mp (EtOAc) 120–120.5 °C; IR (nujol) 1670 cm^{-1}; ^1H NMR δ 2.94 (t, 2H, J=7.5 Hz), 3.80 (t, 2H, J=7.5 Hz), 3.81 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.10 (s, 3H), 4.11 (s, 2H), 6.77 (d, 1H, J=8.5 Hz), 6.80 (dd, 1H, J=8.0, 0.4 Hz), 7.01, 7.07 (AB, 1H each, J=8.0 Hz). ^{13}C NMR δ 34.1, 44.2, 49.7, 55.72, 55.74, 55.81, 62.5, 111.3, 111.8, 116.3, 117.6, 120.5, 125.1, 131.4, 134.5, 147.1, 147.6, 148.9, 152.21, 166.6. EIMS 357(M^+, 13), 206(34), 165(14), 164(100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.83; H, 6.60; N, 3.82.

4.2.3. 2-(3,4-Dimethoxyphenylethyl)phthalimidine (4c). Pale yellow crystals (74%), mp (EtOAc–Hexane) 98–99 °C; IR (nujol) 1670 cm^{-1}; ^1H NMR δ 2.95 (t, 2H, J=7.0 Hz), 3.78 (s, 3H), 3.85 (s, 3H), 3.86 (t, 2H, J=7.0 Hz), 4.19 (s, 2H), 6.74 (s, 1H), 6.77 (d, 1H, J=8.0 Hz), 6.78 (d, 1H, J=8.0 Hz), 7.37 (d, 1H, J=7.0 Hz), 7.45 (t, 1H, J=7.0 Hz), 7.51 (td, 1H, J=7.0, 1.0 Hz), 7.85 (d, 1H, J=7.0 Hz). ^{13}C NMR δ 34.3, 44.2, 50.7, 55.74, 55.82, 111.3, 111.8, 120.5, 122.6, 123.5, 127.9, 131.11, 131.28, 132.8, 141.1, 147.6, 148.9, 168.4. EIMS 297(M^+, 13), 165(12), 164(100), 146(42), 91(15). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.28; N, 4.76.

4.3. General procedure for the synthesis of aldehyde isoindolones

A solution of isoindolones (2.18 mmol) in 25 mL of dry CH_2Cl_2 was cooled in an ice bath, and 0.3 mL of dichloromethyl methyl ether was added. While the solution was stirred and cooled, 1.2 mL (10.91 mmol) of $TiCl_4$ was added. After the addition was complete, the mixture was stirred for 5 min in an ice bath and for 3 h at room temperature. The reaction mixture was then poured into a flask containing crushed ice and was shaken thoroughly. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic solution was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the white solid so obtained was further purified by column chromatography using 2% MeOH/CH_2Cl_2 as eluting solvent to give the aldehyde isoindolones as white solid.

4.3.1. 2-(2-Formyl-4,5-methylenedioxyphenethyl)-6,7-dimethoxyphthalimidine (3a). White crystals (97%), mp (EtOH) 175.5–176.5 °C; IR (nujol) 1670 (broad), 1748 cm^{-1}; ^1H NMR δ 3.32 (t, 2H, J=7.0 Hz), 3.74 (t, 2H, J=7.0 Hz), 3.89 (s, 3H), 4.08 (s, 3H), 4.28 (s, 2H), 6.05 (s, 2H), 6.82 (s, 1H), 7.06, 7.09 (AB, 1H each, J=8.0 Hz), 7.27 (s, 1H), 10.09 (s, 1H). ^{13}C NMR δ 31.4, 44.4, 49.6, 56.7, 62.5, 102.0, 111.1, 111.3, 116.4, 117.7, 124.9, 128.4, 134.5, 138.5, 147.1, 152.25, 152.29, 166.8, 190.1. EIMS 369 (M^+, 27), 206(100), 194(8), 162(9), 148(9). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.11; H, 5.14; N, 3.79.

4.3.2. 2-(2-Formyl-4,5-dimethoxyphenylethyl)-6,7-dimethoxyphthalimidine (3b). White crystals (96%), mp (EtOH) 157–158 °C; IR (nujol) 1675 (broad), 1748 cm^{-1}; ^1H NMR δ 3.37 (t, 2H, J=7.0 Hz), 3.78 (t, 2H, J=7.0 Hz), 3.87 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.09 (s, 3H), 4.22 (s, 2H), 6.81 (s, 1H), 7.04, 7.08 (AB, 1H each, J=8.0 Hz), 7.33 (s, 1H), 10.15 (s, 1H). ^{13}C NMR δ 30.7, 44.2, 49.7, 56.0, 56.2, 56.8, 62.5, 113.6, 114.0, 116.3, 117.7, 124.9, 126.8, 134.5, 136.2, 147.1, 147.8, 152.2, 153.6, 166.8, 190.5. EIMS 385(M^+, 31), 207(13), 206(100), 193(14), 192(19), 164(31). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.31; H, 6.05; N, 3.80.

4.3.3. 2-(2-Formyl-4,5-dimethoxyphenylethyl)phthalimidine (3c). White crystals (93%), mp (EtOAc–hexane) 144–145 °C, lit.[9a] 148–150 °C; IR (nujol) 1680 (broad), 1748 cm^{-1}; ^1H NMR δ 3.39 (t, 2H, J=7.0 Hz), 3.84 (s, 3H), 3.85 (t, 2H, J=7.0 Hz), 3.94 (s, 3H), 4.32 (s, 2H), 6.80 (s, 1H), 7.32 (s, 1H), 7.41 (d, 1H, J=7.0 Hz), 7.46 (t, 1H, J=7.0 Hz), 7.52 (td, 1H, J=7.0, 1.0 Hz), 7.85 (d, 1H, J=7.0 Hz), 10.14 (s, 1H). ^{13}C NMR δ 30.9, 44.1, 50.6, 56.0, 56.2, 113.7, 114.3, 122.7, 123.5, 126.8, 128.0, 131.3, 132.7, 136.1, 141.2, 147.8, 153.7, 168.5, 190.7. EIMS 325(M^+, 10), 192(38), 191(48), 146(80), 105(100), 77(55), 51(20). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.81; H, 6.11; N, 4.31.

4.4. General procedure for the synthesis of dehydroisoindolobenzazepine derivatives

Aldehyde (1 mmol) was dissolved in a solution of KOH (500 mg) in MeOH (25 mL) and the mixture was heated at reflux for 1 h. MeOH was removed by evaporation and water was added. The aqueous mixture was extracted with CH_2Cl_2 and dried. The organic extracts were evaporated to dryness under reduced pressure. The crude product was recrystallized from MeOH to give the required dehydroisoindolobenzazepines.

4.4.1. 3,4-Dimethoxy-7,8-dihydro-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2a). Yellow crystals (84%), mp (MeOH) 208–209 °C, lit.[6b] 209–211 °C, lit.[9e] 213–214 °C. The spectroscopic data of compounds **2a**, **2b**, and **2c** are the same as those previously published.[9c]

4.4.2. 3,4-Dimethoxy-7,8-dihydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2b). Yellow crystals (87%), mp (MeOH) 185–189 °C, lit.[9c] 185–189 °C.

4.4.3. 7,8-Dihydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (2c). Yellow crystals (94%), mp (MeOH) 192–194 °C, lit.[6a] 195–196 °C, lit.[9a] 190–192 °C.

4.5. General procedure for the synthesis of isoindolobenzazepine derivatives

To a stirred solution of dehydroisoindolobenzazepines (250 mg) in EtOAc (15 mL), 10% Pd on carbon (51 mg) was slowly added. The mixture was hydrogenated (1 atm, balloon) and when the reaction was complete (TLC showed the absence of the highly fluorescent spot of the starting material), catalyst residue was removed by filtration, washed with EtOAc, and evaporated to dryness to give the required isoindolobenzazepines.

4.5.1. 3,4-Dimethoxy-13,13a-tetrahydro-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1a). White crystals (76%), mp (MeOH) 226–227 °C, lit.[1] 225 °C, lit.[3a] 228–229 °C. lit.[9e] 235–235.5 °C.

4.5.2. 3,4-Dimethoxy-13,13a-tetrahydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1b). White crystals (80%), mp (MeOH) 213–214 °C, lit.[9c] 213–214 °C.

4.5.3. 7,8,13,13a-Tetrahydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepine-5-one (1c). White crystals (90%), mp (EtOAc) 178–179 °C, lit.[5c] 178–179 °C, lit.[6c] 179 °C.

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Synthesis of (+)-(1*R*,2*S*,9*S*,9*aR*)-octahydro-1*H*-pyrrolo-[1,2-*a*]azepine-1,2,9-triol: a potential glycosidase inhibitor

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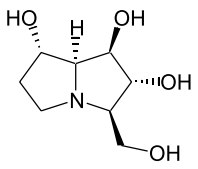
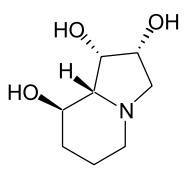
Abstract—The title compound was prepared as a potential glycosidase inhibitor. Key steps in the synthesis are vinyl epoxide aminolysis, ring-closing metathesis, *cis*-dihydroxylation and then ring closure.

1. Introduction

Polyhydroxylated pyrrolizidine [e.g., (+)-alexine (**1**)] and indolizidine [e.g., (−)-swainsonine (**2**)] alkaloids are potent glycosidase inhibitors,[1,2] making these compounds good lead compounds for the development of new drugs for the treatment of viral infections, cancer and diabetes.[3,4] Consequently a substantial volume of research has been conducted, aimed at the synthesis of these alkaloids and their analogues.[1,2,4,5] While compounds with the 5,5- and 5,6-heterocyclic ring system found in these natural products have been extensively studied, we were surprised to discover that analogues with the corresponding 5,7-heterocyclic ring system (i.e. 1*H*-pyrrolo[1,2-*a*]azepines) remain relatively unexplored. Recently we reported an asymmetric total synthesis of (−)-swainsonine (**2**) and two of its diastereomers, 1,2-*diepi*-swainsonine and 1,2,8a-*triepi*-swainsonine.[6] The non-chiral pool route used in that synthesis was very flexible, and we envisaged that it could be readily applied to polyhydroxylated systems of other ring size combinations, such as the 5,7-heterocyclic ring system of (+)-**11**, reported here (Scheme 1).



(+)-alexine (**1**)



(-)-swainsonine (**2**)

2. Results and discussion

The starting vinyl epoxide (−)-(2*S*,3*R*)-**3** was prepared from the corresponding Sharpless epoxy alcohol (92% ee) via Swern oxidation followed by a Wittig-olefination reaction.[6–9]

A solution of the vinyl epoxide (−)-**3** and allylamine (3 equiv.) in acetonitrile was heated at 120 °C in a closed teflon vessel in a microwave reactor (Milestone, ETHOS SEL), using LiOTf (1 equiv.) as a catalyst.[8] This gave only amino alcohol (−)-**4**[6,8] via an S_N2 ring opening, with no evidence of any other regio/stereoisomers. After protection of (−)-**4** as its *N*-Boc derivative, ring-closing metathesis using 5 mol% benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium (Grubbs' catalyst) in refluxing CH_2Cl_2 at high dilution (~4 mM)[6,8] for 20 h, gave the 2,5-dihydropyrrole (−)-**5** in excellent yield (85% overall for the 2 steps). Compound (−)-**5** was treated with 5 mol% $K_2OsO_4{\cdot}2H_2O$ and NMO (2.1 equiv.), to effect *cis*-dihydroxylation of the double bond, giving triol (−)-**6** also in excellent yield (96%). Only one diastereomeric product was isolated, which was expected to arise from delivery of the two hydroxyl groups to the least hindered face of the 3,4-double bond in (−)-**5**.[6] Triol (−)-**6** was then reacted with NaH and benzyl bromide, together with a catalytic amount of nBu$_4$NI.[10] This gave the desired tri-*O*-benzyl derivative (−)-**7** in 55% yield. The low yield was due primarily to the formation of an unwanted oxazolidinone (+)-**8**, which was isolated in 21% yield. No attempt was made to optimise the conditions of this reaction to lower the amount of (+)-**8** being formed, but it is likely that a higher concentration of *n*BuNI and/or benzyl bromide would improve the ratio of compounds (−)-**7** and (+)-**8** in the reaction. Compound (−)-**7** was then reacted with trifluoroacetic acid to accomplish N-deprotection. By using anisole as a cation trap, the *p*-methoxybenzyl (PMB) protecting

Keywords: 2,5-Dihydropyrroles; Vinyl epoxide; Aminolysis; Ring-closing metathesis; Dihydroxylation; Polyhydroxylated alkaloids; Azepine.
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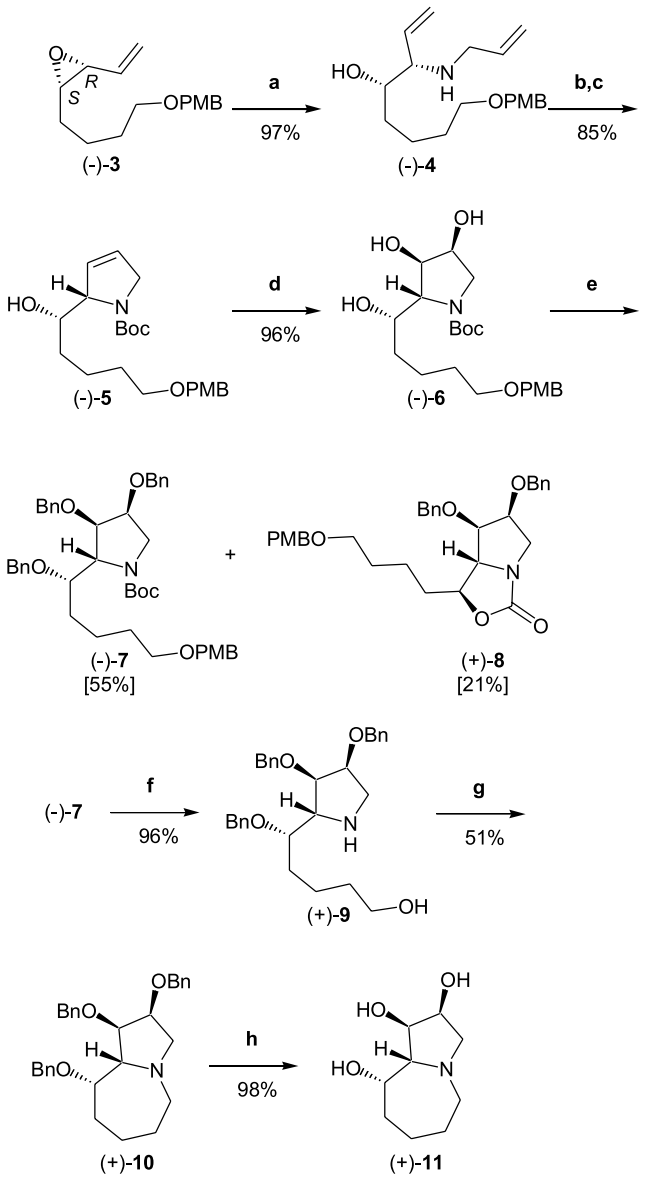

Scheme 1. Reagents and conditions: (a) allylamine (3 equiv.), LiOTf (1 equiv.), CH_3CN, 120 °C, microwave, 1 h; (b) $(Boc)_2O$ (2 equiv.), Et_3N (2 equiv.), Et_2O, rt, 18 h; (c) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2 reflux, 20 h; (d) $K_2OsO_4.2H_2O$ (5 mol%), NMO (2.2 equiv.), acetone, water, rt, 20 h; (e) NaH (6 equiv.), BnBr (5.5 equiv.), nBu$_4$NI (0.3 equiv.), THF, rt, 3 d; (f) TFA (10 equiv.), anisole (10 equiv.), CH_2Cl_2, rt, 2 h; (g) PPh_3 (2.5 equiv.), CBr_4 (2.5 equiv.), NEt_3 (40 equiv.) CH_2Cl_2 4 °C, 20 h; (h) $PdCl_2$ (0.9 equiv.), H_2 (1 atm), MeOH, rt, 1 h; ion-exchange.

group was also removed, resulting in the formation of amino alcohol (+)-**9** in high yield (96%).[6] Formation of the 7-membered azepine ring, was achieved by treating (+)-**9** with carbon tetrabromide and triphenylphosphine in the presence of triethylamine at 4 °C for 20 h. This gave a moderate yield (51%) of the protected bicyclic compound (+)-**10**, but it should be noted that this reaction was only performed once, and higher yields may be achieved with further optimisation (e.g., longer reaction time). Finally, *O*-benzyl removal by catalytic hydrogenolysis, using $PdCl_2$ under an atmosphere of H_2 (1 atm), gave (+)-**11**.HCl in excellent yield, which was purified by ion-exchange chromatography to give the free amine (+)-**11** as a white solid (mp 100–104 °C, $[\alpha]_D^{25}$=+60.3 (*c* 0.46, MeOH)) in 98% yield.

3. Conclusions

In summary, the synthesis of a potential glycosidase inhibitor, based on a novel 1*H*-pyrrolo[1,2-*a*]azepine structure has been achieved. We believe the method is flexible enough to allow the synthesis of many analogues, including those with different stereochemistries and/or larger ring systems simply by varying the vinyl epoxide stereochemistry, and/or epoxide side-chain length. Furthermore, this method could potentially be extended to the synthesis of the key 1*H*-pyrrolo[1,2-*a*]azepine core of the stemona alkaloids.[8]

4. Experimental

4.1. General

4.1.1. (3*S*,4*S*)-8-[(4-Methoxyphenyl)methoxy]-3-(2-propenylamino)-1-octen-4-ol (4). The vinyl epoxide **3**[6–9] (500 mg, 1.90 mmol) was dissolved in CH_3CN (3 mL) then allylamine (328 mg, 5.718 mmol) and LiOTf (297 mg, 1.90 mmol) were added. The mixture was placed in a teflon tube with a 100 bar pressure cap, then heated in a microwave reactor at 120 °C for 1 h. After cooling all volatiles were removed in vacuo to give an oil. Pure product was obtained by column chromatography on flash silica gel (increasing polarity from 5 to 15% MeOH in DCM as eluant), which gave the title compound (591 mg, 1.85 mmol, 97%) as a pale yellow oil.

$[\alpha]_D^{29}$=−7 (*c* 1.3, $CHCl_3$). MS (CI+) *m*/*z* 320 (100%) (M+1), HRMS (CI+) found 320.2238, Calcd for $C_{19}H_{30}NO_3$ 320.2226 (M+1). δ_H (300 MHz, $CDCl_3$): 1.20–1.70 (6H, m, H5, H6 and H7), 2.43 (2H, br.s, NH and OH), 2.77 (1H, t, *J*=8.7 Hz, H3), 3.07 (1H, ddt, *J*=13.8. 6.3, 1.2 Hz, H1′a), 3.20–3.50 (5H, m, H4, H8, H1′b), 3.80 (3H, s, OCH_3), 4.42 (2H, s, OCH_2Ar), 5.05–5.30 (4H, m, H1 and H3′), 5.49 (1H, ddd, *J*=16.8, 10.2, 8.4 Hz, H2), 5.87 (1H, m, H2′), 6.87 (2H, dt, *J*=9.0, 2.7 Hz, 2×ArCH), 7.25 (2H, dt, *J*=9.0, 2.7 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.3 (t, C6), 29.7, 33.4 (t, C5 and C7), 49.2 (t, C1′), 55.2 (q, OCH_3), 66.4 (d, C3), 70.0 (t, C8), 72.5 (t, OCH_2Ar), 72.6 (d, C4), 113.7 (d, 2×ArCH), 116.2, 118.5 (t, C1 and C3′), 129.2 (d, 2×ArCH), 130.6 (s, ArC), 136.4, 136.8 (d, C2 and C2′), 159.0 (s, ArC).

4.1.2. *N*-Boc derivative of 4 (1,1-dimethylethyl *N*-[(1*S*,2*S*)-1-ethenyl-2-hydroxy-6-[(4-methoxyphenyl)methoxy]-hexyl]-*N*-(2-propenyl)-carbamate. The amine **4** (110 mg, 0.344 mmol) was dissolved in Et_2O (10 mL), then triethylamine (75 mg, 0.776 mmol) and di-*tert*-butyldicarbonate (161 mg, 0.776 mmol) were added. The mixture was stirred at rt for under N_2 18 h then all volatiles were removed in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 25% to 50% EtOAc in petroleum spirit (pet. sp.) as eluant), which gave the title compound (135 mg, 0.322 mmol, 94%) as a clear oil. $[\alpha]_D^{29}$=−15 (*c* 1.0, $CHCl_3$). MS (CI+) *m*/*z* 420 (30%) (M+1), HRMS (CI+) found 420.2745, Calcd for $C_{24}H_{38}NO_5$ 420.2750 (M+1). δ_H (300 MHz, $CDCl_3$): 1.10–1.65 (7H, m, H3, H4, H5 and OH), 1.42 (9H, s, $(CH_3)_3C$), 3.41 (2H, br. t, *J*=6.0 Hz, H6), 3.77 (3H, s,

OCH_3), 3.60–3.84 (3H, m, H2 and H1″), 3.94 (1H, br. t, J=7.5 Hz, H1), 4.40 (2H, s, OCH_2Ar), 5.02–5.22 (4H, m, H2′ and H3″), 5.72–5.96 (2H, m, H1′ and H2″), 6.84 (2H, d, J=8.7 Hz, 2×ArCH), 7.23 (2H, d, J=8.7 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.4 (t, C4), 28.3 (q, (CH_3)$_3$C), 29.7, 34.2 (t, C3 and C5), 50.0 (br. t, C1″), 55.1 (q, OCH_3), 65.6 (d, C1), 69.9 (t, C6), 71.9 (br. d, C2), 72.4 (t, OCH_2Ar), 80.2 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 116.6, 117.8 (t, C2′ and C3″), 129.0 (d, 2×ArCH), 130.5 (s, ArCH), 134.2, 134.9 (d, C1′ and C2″), 158.0 (s, ArCH), 171.0 (br. s, CO).

4.1.3. 1,1-Dimethylethyl (2*S*)-2,5-dihydro-2-[(1*S*)-1-hydroxy-5-[(4-methoxyphenyl)methoxy]pentyl]-1*H*-pyrrole-1-carboxylate (5). The *N*-Boc derivative of **4** (500 mg, 1.193 mmol) was dissolved in dry DCM (300 mL) then benzylidene-bis-(tricyclohexlphosphine)dichlororuthenium (Grubbs' cat.) (50 mg, 0.061 mmol) was added. The mixture was heated at reflux under N_2 for 20 h, then cooled, before all solvent was removed in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 25 to 50% EtOAc in pet. sp. as eluant), which gave the title compound (426 mg, 1.088 mmol, 91.2%) as a clear oil. $[\alpha]_D^{29}$=−79 (*c* 0.9, $CHCl_3$). MS (CI+) *m*/*z* 392 (37%) (M+1), HRMS (CI+) found 392.2409, Calcd for $C_{22}H_{34}NO_5$ 392.2437 (M+1). δ_H (300 MHz, $CDCl_3$): 1.48 (9H, s, (CH_3)$_3$C), 1.20–1.73 (6H, m, H2′, H3′ and H4′), 3.44 (2H, t, J=6.3 Hz, H5′), 3.56–3.66 (1H, m, H2), 3.79 (3H, s, OCH_3), 3.99 (1H, br. d, J=15.7 Hz, H5a), 4.18 (1H, br. d, J=15.6 Hz, H5b), 4.41 (2H, s, OCH_2Ar), 4.54 (1H, m, H1′), 4.96 (1H, br. s, OH), 5.60–5.90 (2H, m, H3 and H4), 6.86 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH), 7.24 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 21.7 (t, C3′), 28.4 (q, (CH_3)$_3$C), 29.7, 33.3 (C2′ and C4′), 53.9 (t, C5), 55.2 (q, OCH_3), 70.0 (t, C5′), 70.0 (d, C2), 72.4 (t, OCH_2Ar), 75.4 (d, C1′), 80.4 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 126.4, 126.7 (d, C3 and C4), 129.0 (d, 2×ArCH), 130.5 (s, ArC), 156.6 (CO), 158.8 (s, ArC).

4.1.4. 1,1-Dimethylethyl (2*R*,3*R*,4*S*)-2-[(1*S*)-1-hydroxypentyl-5-[(4-methoxyphenyl)methoxy]]-3,4-dihydroxy-1-pyrrolidinecarboxylate (6). The 2,5-dihydropyrrole **5** (426 mg, 1.088 mmol) was dissolved in acetone (6 mL), then water (4 mL), *N*-methyl-morpholine-*N*-oxide (269 mg, 2.32 mmol) and $K_2OsO_4.2H_2O$ (20 mg, 0.0544 mmol) were added. The mixture was stirred at rt for 20 h, then all volatiles were removed in vacuo to give a brown oil. Pure product was obtained by column chromatography (increasing polarity from 2.5 to 10% MeOH in DCM as eluant), which gave the title compound (442 mg, 1.039 mmol, 95.5%) as a clear oil. $[\alpha]_D^{27}$=−28 (*c* 1.0, $CHCl_3$). MS (CI+) *m*/*z* 426 (100%) (M+1), HRMS (CI+) found 426.2482, Calcd for $C_{22}H_{36}NO_7$ 426.2492 (M+1). δ_H (300 MHz, $CDCl_3$): 1.40 (9H, s, (CH_3)$_3$C), 1.30–1.70 (8H, m, H2′, H3′, H4′ and 2×OH), 3.30–4.30 (9H, m, H2, H3, H4, H5, H1′, H5′ and OH), 3.78 (3H, s, OCH_3), 4.40 (2H, s, OCH_2Ar), 6.84 (2H, d, J=8.4 Hz, 2×ArCH), 7.23 (2H, d, J=8.4 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.0 (br. t, C3′), 28.1 (q, (CH_3)$_3$C), 29.2, 32.7 (t, C2′ and C4′), 51.3 (br. t, C5), 54.9 (q, OCH_3), 67.0 (br. d, C2), 69.5 (br. d, C4), 69.7 (t, C5′), 72.2 (t, OCH_2ArCH), 72.9 (br. d, C3), 76.4 (d, C1′), 80.3 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 129.0 (d, 2×ArCH), 130.1 (s, ArC), 156.8 (br. s, CO), 158.8 (s, ArC).

4.1.5. 1,1-Dimethylethyl (2*R*,3*R*,4*S*)-2-[(1*S*)-5-[(4-methoxyphenyl)methoxyoxy)]-1-(phenylmethoxy)pentyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinecarboxylate (7) and (1*S*,6*S*,7*R*,7*aR*)-tetrahydro-1-[4-[(4-methoxyphenyl)-methoxy]butyl]-6,7-bis(phenylmethoxy)-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one (8). The triol **6** (440 mg, 1.034 mmol) was dissolved in THF (60 mL) then NaH (302 mg, 6.024 mmol, 50% dispersion in wax), benzylbromide (0.64 mL, 5.50 mmol) and nBu$_4$NI (112 mg, 0.30 mmol) were added. The mixture was stirred at rt under N_2 for 3 d then poured into water (50 mL) and extracted with DCM (3×40 mL). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give an oil. Pure products were obtained by column chromatography (increasing polarity from 20 to 100% EtOAc in pet. sp. as eluant), which gave the title compound (396 mg, 0.569 mmol, 55%), and the oxazolidinone (116 mg, 0.218 mmol, 21%) as clear oils.

Compound **7**. $[\alpha]_D^{30}$=−29 (*c* 3.96, $CHCl_3$). MS (ES+) *m*/*z* 696.4 (100%) (M+1), HRMS (ES+) found 696.3895, Calcd for $C_{43}H_{54}NO_7$ 696.3900 (M+1). δ_H (300 MHz, $CDCl_3$): 1.45 (9H, s, (CH_3)$_3$C), 1.20–1.70 (6H, m, H2′, H3′ and H4′), 3.28–3.43 (3H, m, H5a and H5′), 3.52 (1H, br. d, J=6.3 Hz, H5b), 3.78 (3H, s, OCH_3), 3.75–3.87 (1H, m, H1′), 3.87–4.06 (2H, m, H3 and H4), 4.17–4.74 (7H, m, H2 and 3×OCH_2Ph), 4.40 (2H, s, OCH_2Ar), 6.86 (2H, d, J=9.0 Hz 2×ArCH), 7.21–7.36 (17H, m, 2×ArCH and 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): two rotamers were evident in equal intensity 22.9/23.2 (t, C3′), 28.4 (q, (CH_3)$_3$C), 29.6 (t, C4′), 30.0/30.4 (t, C2′), 48.8/49.5 (t, C5), 55.2 (q, OCH_3), 62.5/63.6 (d, C2), 69.9 (t, C5′), 71.2, 71.3/71.8, 72.4, 72.3/72.6 (t, OCH_2Ar and 3×OCH_2Ph), 75.3/76.3, 76.5/77.8, 78.4/78.6 (d, C3, C4 and C1′), 79.7/80.0 (s, (CH_3)$_3$$C$), 113.7 (d, ArCH), 127.6, 127.7, 127.7, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3 (d, 3×OCH$_2$*Ph*), 129.1 (d, 2×ArCH), 130.6 (s, ArCH), 137.6, 138.0, 138.4 (s, 3×OCH$_2$*Ph*), 159.0 (s, 2×ArCH), 164.0 (s, CO).

Compound **8**. $[\alpha]_D^{30}$=+28 (*c* 1.03, $CHCl_3$). MS (ES+) *m*/*z* 532.3 (47%) (M+1), HRMS (ES+) found 532.2698, Calcd for $C_{32}H_{37}NO_6$ 532.2699 (M+1). δ_H (300 MHz, $CDCl_3$): 1.40–1.86 (6H, m, H1′, H2′ and H3′), 3.37 (1H, dd, J=12.9, 1.5 Hz, H5a), 3.42 (2H, t, J=6.3 Hz, H4′), 3.53 (1H, dd, 9.0, 4.8 Hz, H7), 3.70–3.80 (2H, m, H5b and H7*a*), 3.77 (3H, s, OCH_3), 4.09 (1H, td, J=5.1, 1.5 Hz, H6), 4.22 (1H, ddd, J=7.2, 5.4, 3.6 Hz, H1), 4.39 (1H, d, J=12.0 Hz, OCH_2Ph), 4.41 (2H, s, OCH_2Ar), 4.59 (2H, AB system, J=12.0 Hz, OCH_2Ph), 4.65 (1H, d, J=12.0 Hz, OCH_2Ph), 6.86 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH), 7.22–7.38 (12H, m, 2×ArCH and 2×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.1 (t, C2′), 29.2 (C3′), 35.0 (t, C1′), 50.8 (t, C5), 55.1 (q, OCH_3), 65.0 (d, C7*a*), 69.4 (t, C4′), 71.9, 72.2, 72.4 (t, OCH_2Ar and 2×OCH_2Ph), 75.8, 79.0 (C6 and C7), 81.5 (d, C1), 113.6 (d, 2×ArCH), 127.7, 127.9, 127.9, 128.1, 128.4, 128.5 (d, 2×OCH$_2$*Ph*), 129.1 (d, 2×ArCH), 130.4 (s, ArC), 137.0, 137.2 (s, 2×OCH$_2$*Ph*), 159.0 (s, ArC), 160.9 (s, C3).

4.1.6. (1′*S*,2*R*,3*R*,4*S*)-1′,3,4-*tris*(Phenylmethoxy)-2-pyrrolidinepentanol (9). The carbamate **7** (396 mg, 0.569 mmol) was dissolved in DCM (5 mL), then TFA (5 mL) and anisole (0.60 mL, 5.44 mmol) were added. The mixture was stirred at rt for 2 h, then all volatiles were removed in vacuo.

The residue was dissolved in $CHCl_3$ then poured into sat. Na_2CO_3 solution (5 mL), and extracted with $CHCl_3$ (3×25 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 5 to 15% MeOH in DCM as eluant), which gave the title compound (260 mg, 0.547 mmol, 96%) as a clear oil. $[\alpha]_D^{26}$=+81 (*c* 2.60, $CHCl_3$). MS (ES+) *m/z* 476.7 (100%) (M+1), HRMS (ES+) found 476.2808, Calcd for $C_{30}H_{38}NO_4$ 476.2801 (M+1).

δ_H (300 MHz, $CDCl_3$): 1.26–1.90 (6H, m, H2′, H3′ and H4′), 2.96–3.15 (4H, m, H5, NH and OH), 3.31 (1H, dd, *J*=7.5, 2.4 Hz, H2), 3.50 (1H, td, *J*=7.2, 2.4 Hz, H5′), 3.58 (2H, t, *J*=6.3 Hz, H1′), 3.70 (1H, dd, *J*=7.5, 5.1 Hz, H3), 3.90 (1H, q, *J*=4.5 Hz, H4), 4.23 (1H, d, *J*=11.1 Hz OC*H*$_2$Ph), 4.32 (1H, d, *J*=11.7 Hz, OC*H*$_2$Ph), 4.50 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 4.55 (1H, d, *J*=11.4 Hz, OC*H*$_2$Ph), 4.60 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 4.62 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 7.15–7.40 (15H, m, 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.4 (t, C3′), 30.6, 32.5 (t, C2′ and C4′), 49.3 (t, C5), 61.6 (t, C1′), 63.0 (d, C2), 71.2, 71.9, 72.0 (t, 3×O*C*H$_2$Ph), 76.4, 77.5, 79.6 (C3, C4 and C5′), 127.5, 127.6, 127.6, 127.7, 127.9, 128.0, 128.2, 128.2, 128.2 (d, 3×OCH$_2$*Ph*), 137.9, 138.0, 138.3 (s, 3×OCH$_2$*Ph*).

4.1.7. (1*R*,2*S*,9*S*,9*aR*)-Octahydro-1,2,9-*tris*(phenylmethoxy)-1*H*-pyrrolo[1,2-*a*]azepine (10). The amino alcohol **9** (240 mg, 0.505 mmol) was dissolved in DCM (20 mL) then the solution was cooled to 0 °C. Carbontetrabromide (419 mg, 1.263 mmol), and triphenylphosphine (331 mg, 1.263 mmol) were added, then the mixture was stirred under N_2 for 5 min. Triethylamine (2.8 mL, 20.09 mmol) was added, then the mixture was stirred at 0 °C for 2 h, before being left to stand at 4 °C for 18 h. The mixture was poured into water (50 mL), then extracted with DCM (3×40 mL). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give a black semi solid. Pure product was obtained by column chromatography (increasing polarity from 1 to 5% MeOH in DCM as eluant), which gave the title compound (118 mg, 0.258 mmol, 51%) as a clear oil. $[\alpha]_D^{27}$=+64 (*c* 1.15, $CHCl_3$). MS (ES+) *m/z* 458.5 (100%) (M+1), HRMS (ES+) found 458.2694, Calcd for $C_{30}H_{36}NO_3$ 458.2695 (M+1). δ_H (300 MHz, $CDCl_3$): 1.30–1.46 (1H, m, H7a), 1.56–1.94 (5H, m, H6, H7b, H8), 2.51 (1H, ddd, *J*=11.7, 8.4, 4.8 Hz, H5a), 2.84 (1H, dd, *J*=9.3, 7.5 Hz, H3a), 2.90 (1H, dd, *J*=3.9, 2.4 Hz, H9*a*), 3.03 (1H, dt, *J*=11.7, 5.7 Hz, H5b), 3.22 (1H, dd, *J*=9.3, 5.1 Hz, H3b), 3.56 (1H, td, *J*=5.1, 2.4 Hz, H9), 3.85 (1H, t, *J*=4.5 Hz, H1), 4.02 (1H, dt, *J*=7.5, 5.1 Hz, H2), 4.22 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.35 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.53 (1H, d, *J*=12.3 Hz OC*H*$_2$Ph), 4.56 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.58 (1H, d, *J*=12.3 Hz OC*H*$_2$Ph), 4.59 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 7.17–7.42 (15H, m, 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.7 (t, C7), 30.0, 31.9 (t, C6 and C8), 56.5, 57.9 (t, C3 and C5), 70.5, 71.6, 72.3 (t, 3×O*C*H$_2$Ph), 72.3 (d, C9*a*), 75.9, 76.8 (d, C1 and C2), 80.4 (d, C9), 127.5, 127.5, 127.7, 127.9, 128.2, 128.2, 128.2, 128.3, 128.3 (d, 3×OCH$_2$*Ph*), 138.5, 138.5, 138.5 (s, 3×OCH$_2$*Ph*).

4.1.8. (1*R*,2*S*,9*S*,9*aR*)-Octahydro-1*H*-pyrrolo[1,2-*a*]azepine-1,2,9-triol (11). The tri-*O*-benzyl compound **10** (115 mg, 0.251 mmol) was dissolved in MeOH (4 mL) then $PdCl_2$ (40 mg, 0.226 mmol) was added and the flask flushed with H_2 (g). The mixture was stirred at rt under an atmosphere of H_2 for 1 h, then the flask was flushed with N_2, before the mixture was filtered through celite. The solids were washed with MeOH (2×10 mL), and the combined filtrates were evaporated in vacuo. The residue was dissolved in water (2 mL) and applied to Dowex-1 basic ion exchange resin (OH− form). Elution with water (50 mL), followed by evaporation of the eluant in vacuo gave the title compound (46 mg, 0.246 mmol, 97.9%) as a white solid. mp. 100–104 °C. $[\alpha]_D^{25}$=+60.3 (*c* 0.46, MeOH). MS (CI+) *m/z* 188 (100%) (M+1), HRMS (ES+) found 188.1301, Calcd for $C_9H_{18}NO_3$ 188.1287 (M+1). δ_H (300 MHz, D_2O): 1.22–1.38 (1H, m, H7a), 1.42–4.62 (4H, m, H6, H7b and H8a), 1.76–1.88 (1H, m, H8b), 2.34 (1H, dt, *J*=12.0, 6.3 Hz, H5a), 2.46 (1H, dd, *J*=10.2, 6.6 Hz, H3a), 2.63–2.70 (1H, m, H9*a*), 2.84 (1H, dt, *J*=11.7, 5.7 Hz, H5b), 3.00 (1H, dd, *J*=10.5, 5.4 Hz, H3b), 3.86–3.97 (3H, m, H1, H2 and H9). δ_C (75 MHz, D_2O ref CH_3CN): 21.4 (t, C7), 29.4, 36.1 (t, C6 and C8), 56.5, 59.7 (t, C3 and C5), 69.6 (d, C9*a*), 70.8 (d, C9), 73.6, 74.9 (d, C1 and C2).

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Cycloaddition between electron deficient partners: an efficient regio- and stereoselective synthesis of functionalised bicyclo[2.2.2]octenones. A tandem alkylation, stereochemical inversion and aldol condensation

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Abstract—A novel one step regio- and stereoselective synthesis of functionalised bicyclo[2.2.2]octenones from readily available aromatic precursors is described. The methodology involved in situ generation of reactive spiroepoxycyclohexadienones and $\pi^{4s}+\pi^{2s}$ cycloaddition with methyl vinyl ketone. Study on π-facial alkylation that led to the formation of homobrendane derivatives as a result of stereochemical inversion and aldol condensation in tandem, is also presented. The crystal structure of 6-acetyl-1-methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane and 3-methoxy-4,6,9-trimethyltricyclo[4.3.1.0^{3,7}]decan-8-en-5-one-spiro[2,2′]oxirane is also reported.

1. Introduction

Bridged bicyclo[2.2.2]octenones of type **1** are unique molecular systems since they offer a broad range of chemical reactivity by virtue of the rigid molecular framework, interactions among functional groups such as homoconjugation and electronic control and hence they have served as precursors for stereoselective synthesis of diverse molecular frameworks.[1–3] While simple bicyclo-[2.2.2]octenones are prepared in several steps via Diels–Alder reaction of cyclic 1,3-dienes and ketene equivalents followed by manipulation of the resulting adduct,[4] double Michael addition,[5a,c] Michael addition followed by reductive amination,[5b] homoallyl–homoallyl radical rearrangement[6] and cycloaddition of *o*-quinoneketals and related species[7] have been employed for the synthesis of complex bicyclo[2.2.2]octenones. However, these methods have several limitations with regard to introduction of functional groups and substituents on the bicyclo[2.2.2]octane frame and often give a mixture of regio-isomers. In view of the recent interest in the design of new methods that generate complex structures with atom economy and stereoselectivity,[8,9] we developed a method for generation of molecular complexity from simple aromatic precursors that involved cycloaddition of spiroepoxycyclohexa-2,4-dienones with electron rich π-partners[10a,b] and also reported the reaction of cyclohexadienones even with electron deficient π partners such as acrylates.[10c] We became interested in the synthesis of bicyclic diketo-epoxides of type **2** having an *endo* acetyl group, and explored the alkylative stereochemical inversion of acetyl group (*endo*→*exo*) especially since bicyclo[2.2.2]octanes of type **3** appeared to be potential precursors for the synthesis of AB ring system of taxanes.[2b] In order to extend the scope of the cycloaddition between cyclohexadienones with electron deficient π-systems and test the feasibility of alkylative stereochemical inversion, cycloaddition of spiroepoxycyclohexa-2,4-dienones of type **4** with methyl vinyl ketone was explored. We wish to report herein a facile one step synthesis of variously substituted and functionalised bicyclooctenones of type **2** having an *endo* acetyl group and also report the results of alkylation that led to stereochemical inversion of the acetyl group and aldol condensation in tandem (Fig. 1).

2. Results and discussion

Towards the synthesis of **2**, we attempted in situ generation of the spiroepoxycyclohexadienone by the periodate oxidation[11] of hydroxymethyl phenols and interception with methyl vinyl ketone. Thus, a solution of *o*-vanilyl alcohol and methyl vinyl ketone in acetonitrile was treated with aqueous sodium metaperiodate at ~5 °C, following a procedure developed in our laboratory.[11c] This gave the

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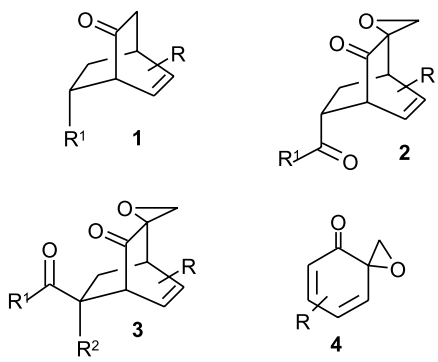
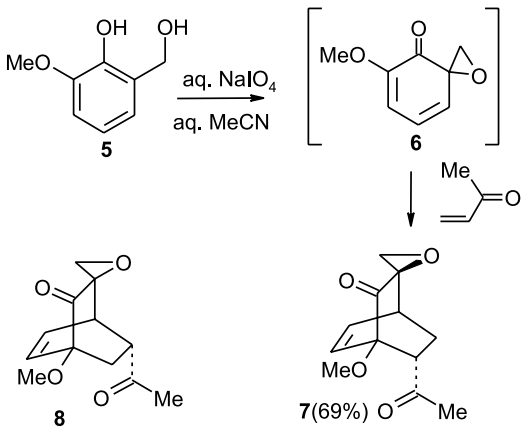


Figure 1.



Scheme 1.

adduct **7** in excellent yield (Scheme 1). The gross structure of the adduct was easily revealed from the following spectroscopic data. The IR spectrum showed absorption bands at 1745 and 1712 cm^{-1}, which suggested the presence of two carbonyl groups. The ^1H NMR (300 MHz) spectrum of the adduct exhibited characteristic signals at δ 6.56 (superimposed dd, $J_1=J_2=8.5$ Hz, 1H) and 6.25 (d, $J\sim8.5$ Hz, 1H) for the γ- and β- protons of β,γ-alkene moiety. It also showed a signal at δ 3.55 (s, 3H) due to –OMe and a highly characteristic AB pattern due to the methylene protons of an oxirane ring which appeared separately at δ 3.12 (part of AB system, $J_{AB}=6.3$ Hz, 1H) and 2.83 (part of AB system, $J_{AB}=6.3$ Hz, 1H). In addition, signals were observed at δ 3.27 (m, 1H), 2.59 (m, 1H), 2.25 (s overlapped with another signal, 4H, $COCH_3$+1H), 1.95 (m of d, $J=15$ Hz, 1H). The ^{13}C NMR spectrum also gave characteristic signals at δ 206.4 and 201.8 for the two carbonyl groups. The olefinic carbons were observed at δ 133.2 and 126.8. Other signals were observed at δ 87.03, 57.2, 54.5, 53.1, 49.3, 38.1, 32.7 and 27.3 for methine, methylene and quaternary carbons. These spectral features suggested the structure of the adduct but it was difficult to ascertain the stereochemical orientation of the oxirane ring, and distinguish between **7** and its regio-isomer **8** on the basis of spectral data alone. Hence, a single crystal structure determination was undertaken which confirmed structure **7** for the adduct (Fig. 2).

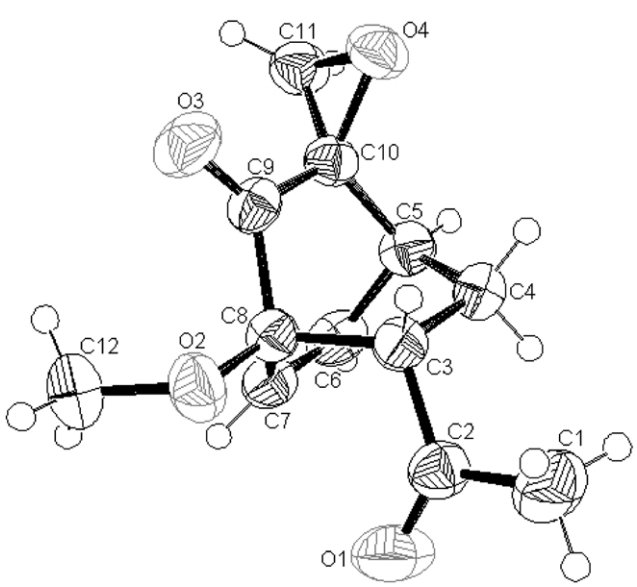
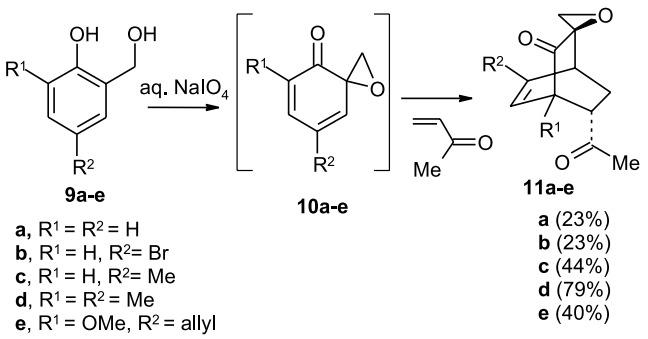


Figure 2. X-ray crystal structure of the adduct **7**.

In order to generalize the aforementioned cycloaddition, oxidation of various hydroxymethyl phenols to the corresponding spiroepoxycyclohexa-2,4-dienones and their interception with methyl vinyl ketone were examined (Scheme 2). All the hydroxymethyl phenols **9a–e** gave the corresponding adducts **11a–e** in moderate to excellent yields. The substituents on the aromatic ring (and hence in cyclohexa-2,4-dienones **10a–e**) appear to govern the efficiency of cycloaddition in a subtle manner. The methyl groups at C_2 and/or C_4 of the cyclohexadienones such as **10c**, **10d** enhance the efficiency of cycloaddition. Similarly, the presence of a methoxy group at C_2 (as in **6**) led to an excellent yield of the adduct but the cycloaddition of **10e** having a methoxy group at C_2 and allyl moiety at C_4 proceeds with moderate efficiency. Interestingly, the spiroepoxycyclohexadienone **10b** containing bromine at C_4 also underwent cycloaddition with reasonable efficiency to furnish the corresponding adduct. The structures of all adducts were deduced from their spectroscopic and analytical data, and comparison of their spectral features with those of **7**.



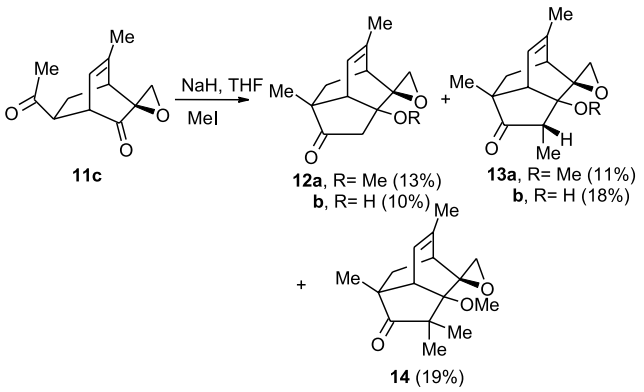
Scheme 2.

It may be mentioned that electron deficient systems such as cyclohexa-2,4-dienones and *o*-benzoquinone ketals generally react with electron rich π partners in inverse electron demand fashion.[10,12,13] Further, it is interesting to note the regio-selectivity in the above cycloaddition wherein the α-carbon of methyl vinyl ketone is bonded to C_2 of cyclohexa-2,4-dienones. Similar regioselectivity is also observed during cycloaddition of cyclohexa-2,4-dienones

even with electron rich dienophiles such as vinyl ethers wherein the carbon having polar electron donating group forms bond with C_2 carbon of cyclohexa-2,4-dienone.[12,13]

After having an efficient access to bicyclo[2.2.2]octenones, we explored the alkylative stereochemical inversion of acetyl group in **11c**. We considered it possible to selectively alkylate the methine carbon α to the carbonyl group of acetyl group. Further, it was thought that the electrophile might approach in a stereoselective manner from the *endo* face since the enolates derived from simple bicyclo[2.2.2]-octenones are known to undergo stereoselective alkylation from the π-face.[14]

Thus, the epoxyketone **11c** was treated with sodium hydride and methyl iodide at 80 °C. However, a very complex mixture of products was obtained. After considerable experimentation, it was observed that the treatment of **11c** with sodium hydride and methyl iodide at ~0 °C led to a reasonably clean reaction from which five closely related products **12**–**14** were isolated (Scheme 3). The structures of all the compounds were deduced from their spectroscopic



Scheme 3.

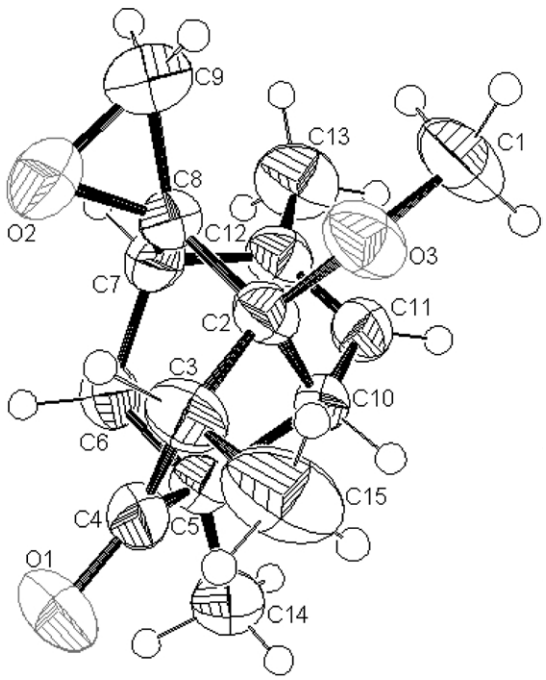


Figure 3. X-ray crystal structure of **13a**.

data. Though the gross structure of the compound **13a** was easily deduced from the spectroscopic data, the orientation of the methyl group present in the cyclopentanone ring was not easily discernible. Hence, X-ray single crystal structure determination of **13a** was undertaken which confirmed its formulation (Fig. 3).

The formation of **12**, **13** and **14** clearly indicated that the alkylation of **11c** had indeed occurred stereoselectively from the *endo* face so as to push the acetyl group to the *exo* orientation, as desired. However, multiple alkylation and aldol condensation also occurred to give the homobrendane derivatives **12**–**14**. Though the aforementioned reaction may not appear synthetically useful in this particular case, it provides an interesting class of compound not readily accessible otherwise, and importantly this observation suggests the possibility of generating stereochemical diversity from suitably designed *endo* Diels–Alder adducts.

3. Conclusion

In summary, a new one step method leading to complex bicyclo[2.2.2]octenones having an *endo* acetyl moiety, is described. The observations on alkylative stereochemical inversion provide further insight into the chemistry of such highly functionalised bicyclo[2.2.2]octenones and pave the way for the strategic design and synthesis of molecular systems that are not readily accessible otherwise.

4. Experimental

4.1. General

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. UV spectra were recorded on Shimadzu UV 160 or Shimadzu U 260 instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance-400 NMR spectrometer, Varian NMR and Varian VXR 300 instruments. Micro-analyses were done on a CEST 1106 instrument and HRMS on a Q-Tof micro (YA-105) Mass Spectrometer. Melting points were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored with thin layer chromatography silica gel and spots were visualized with iodine vapor. Column chromatography was performed using Acme/SRL silica gel (60–120 or 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixtures. The fractions eluted from column were concentrated at reduced pressure on a Buchi-RE 111 rotary evaporator.

4.1.1. 6-Acetyl-1-methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (7). To a solution of *o*-vanilyl alcohol (2 g, 12.98 mmol) in acetonitrile (50 mL) was added methyl vinyl ketone (5.4 mL, 64.94 mmol) and the reaction mixture was cooled in an ice bath (0–5 °C). A solution of $NaIO_4$ (5.6 g, 25.97 mmol) in water (50 mL) was then added dropwise to the reaction mixture over 30 min with stirring. After stirring for 1 h, it was brought to ambient temperature (~28 °C) and further stirred for 6 h. The reaction mixture was filtered and organic layer was separated and the

aqueous layer was extracted with ethyl acetate (3×50 mL). The organic extracts were combined, washed with brine (50 mL) and dried over anhydrous sodium sulfate. Removal of solvent under vacuum gave a residue, which was chromatographed on silica gel. Elution with pet-ether (60–80 °C)–ethyl acetate (84:16) gave the adduct **7** (1.9 g, 69%) as a colorless solid, mp 101–103 °C. IR (film) ν_{max}: 1712, 1745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.56 (superimposed dd, J_1=J_2=8.5 Hz, 1H, γ-H of β,γ-enone moiety), 6.25 (d, J~8.5 Hz, 1H, β-H of β,γ-enone moiety), 3.55 (s, 3H, –OMe), 3.12 (part of AB system, J_{AB}=6.3 Hz, 1H, CH_2– of oxirane ring), 2.83 (part of an AB system, J_{AB}=6.3 Hz, 1H, CH_2– of oxirane ring), 3.27 (m, 1H), 2.59 (m, 1H), 2.25 (s overlapped with another signal, 4H, $COCH_3$+1H), 1.95 (m of d, J=15 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 206.4, 201.8, 133.2, 126.8, 87.03, 57.2, 54.5, 53.1, 49.3, 38.1, 32.7 and 27.3 (12 Carbons). Analysis: Found C, 64.74; H, 6.43% Calc. C, 64.86; H, 6.31% for $C_{12}H_{14}O_4$. Mass (*m*/*z*): 222 (M^+).

Crystal data. $C_{12}H_{14}O_4$, M=222.23, monoclinic, $P21/a$, Z=4, λ=0.70930 Å, a=8.6630(18) Å, b=12.4770(17) Å, c=10.4920(18) Å, V=1098.1(3) $Å^3$, T=293(2) K, D_c=1.344 Mg/m^3, μ=0.101 mm^{-1}, F(000)=472, size=0.4×0.4×0.25 mm^3. Reflections collected/unique=1736/1736 [R(int)=0.0000], final R indices [$I>2\sigma(I)$]: R_1=0.0413, wR_2=0.1056, R indices (all data): R_1=0.0495, wR_2=0.1121. CCDC 231385. See: http://www.ccdc.cam.ac.uk/conts/retrieving.html (e-mail: deposit@ccdc.cam.ac.uk).

4.1.2. 6-Acetyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]-oxirane (11a). To a solution of salicyl alcohol **10a** (2 g, 16.13 mmol) in acetonitrile (50 mL) was added methyl vinyl ketone (6.6 mL, 80.6 mmol) and the reaction mixture was cooled in an ice bath (0–5 °C). A solution of $NaIO_4$ (6.9 g, 32.26 mmol) in water (60 mL) was then added dropwise to the reaction mixture over 45 min with stirring. After stirring for 1 h in ice bath, it was brought to ambient temperature (~28 °C) and further stirred. After completion of reaction (TLC, 5 h), the reaction mixture was filtered, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The organic extracts were combined and washed with brine (50 mL) and dried over anhydrous sodium sulfate. Solvent was removed under vacuum and the residue was chromatographed. Elution with petroleum ether (60–80 °C)–ethyl acetate (88:12) furnished the adduct **11a** (0.72 g, 23%) as a solid, mp 60–62 °C. IR (film) ν_{max}: 1738, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 6.49 (superimposed dd, J=7.2 Hz, 1H, γ-proton of the β,γ-enone group), 6.18 (superimposed dd, J=7.2 Hz, 1H, β-proton of the β,γ-enone moiety), 3.62 (d, J=4.8 Hz, 1H), 3.17 (m partly merged with another signal, 1H), 3.12 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 2.83 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 2.62–2.60 (m, 1H), 2.32–2.22 (m, 1H), 2.20 (s, 3H, $COCH_3$), 1.96–1.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 204.22, 203.01, 134.87, 127.24, 57.36, 52.97, 49.68, 47.74, 38.41, 28.37, 24.41. Mass (*m*/*z*): 192 (M^+); ES-MS: *m*/*z* calculated for $C_{11}H_{13}O_3$: 193.0865, $[M+H]^+$; found 193.0895.

4.1.3. 6-Acetyl-8-bromo-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (11b). To a solution of *p*-bromosalicyl alcohol **10b** (1 g, 4.926 mmol) in acetonitrile (20 mL) was added methyl vinyl ketone (2 mL, 24.63 mmol) and the reaction mixture was cooled in an ice bath (0–5 °C). A solution of $NaIO_4$ (2.11 g, 9.85 mmol) in water (25 mL) was then added dropwise to the reaction mixture over 30 min with stirring. After stirring for 1 h, it was brought to ambient temperature (~28 °C) and further stirred for 6 h. The reaction mixture was filtered and the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The organic extracts were combined, washed with brine (30 mL) and dried over anhydrous sodium sulfate. Removal of solvent under vacuum gave a residue, which was chromatographed on silica gel. Elution with petroleum ether (60–80 °C)–ethyl acetate (85:15) furnished the adduct **11b** (0.31g, 23.2%) as a solid, mp 112–114 °C. IR (film) ν_{max}: 1743, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 6.38 (dd, J_1=7 Hz, J_2=2 Hz, 1H), 3.70 (dd, J_1=7 Hz, J_2=2 Hz, 1H), 3.22 (part of an AB system, J_{AB}=6.5 Hz, 1H, OCH_2), 3.18- 3.13 (m, 1H), 3.06 (part of an AB system, J_{AB}=6.5 Hz, 1H, OCH_2), 2.78 (m, 1H), 2.42–2.33 (m, 1H), 2.2 (s partly merged with a m, 3H), 2.1–1.7 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 203.45, 201.05, 126.43, 123.47, 57.06, 52.34, 51.73, 49.05, 47.98, 28.33, 25.07. Mass (*m*/*z*): 272, 270 (M^+). Analysis: Found, C, 48.53; H, 4.29% requires C, 48.70, H, 4.05 for $C_{11}H_{11}O_3Br$.

4.1.4. 6-Acetyl-8-methyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (11c). A solution of 5-methylsalicyl alcohol **10c** (2 g, 14.5 mmol) and methyl vinyl ketone (6 mL, 72.46 mmol) in acetonitrile (50 mL) was cooled in an ice bath (0–5 °C) and a solution of $NaIO_4$ (6.2 g, 28.9 mmol) in water (60 mL) was added dropwise over 45 min with stirring. After stirring for 1 h, it was brought to ambient temperature (~28 °C) and further stirred for 6 h. Work-up as described above followed by removal of solvent gave a residue which after column chromatography [pet-ether–ethylacetate (82:18) furnished the adduct **11c** (1.3 g, 44%) as a solid, mp 96–98 °C. IR (film) ν_{max}: 1739, 1712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ, 5.73 (d, J=5.7 Hz, 1H), 3.53 (d, J=5.7 Hz, 1H), 3.14 (m merged with part of an AB system, J_{AB}=6 Hz, total 2H), 2.85 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 2.35 (br s, 1H), 2.19 (s merged with a m, total 4H), 2.03–1.98 (m, 1H), 1.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 204.39, 203.17, 145.1, 118.73, 57.24, 52.13, 49.68, 48.25, 43.74, 28.34, 23.57, 20.69. Analysis: Found, C, 69.53; H, 7.29% requires C, 69.9, H, 6.8% for $C_{12}H_{14}O_3$. Mass (*m*/*z*): 206 (M^+).

4.1.5. 6-Acetyl-1,8-dimethyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (11d). To a solution of 3,5-dimethyl salicyl alcohol **10d** (2 g, 13.16 mmol) and methyl vinyl ketone (5.3 mL, 65.79 mmol) in acetonitrile (50 mL) was added a solution of $NaIO_4$ (5.7 g, 26.31 mmol) in water (60 mL) dropwise at 0–5 °C. After stirring for 1 h the reaction mixture was brought to ambient temperature (~28 °C) and further stirred for 4 h. Work-up as described above followed by removal of solvent gave a residue which was chromatographed on silica gel. Elution with pet. ether–ethyl acetate (86:14) furnished the adduct (2.28 g, 78.65%) as a solid, mp 65–66 °C. IR (film) ν_{max}: 1735, 1714 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ, 5.51 (s, 1H), 3.11 (part of an AB system, J_{AB}=6 Hz, 1H), 2.97–2.95 (m, 1H), 2.85

(part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 2.42–2.35 (m, 2H), 2.15 (s, 3H), 1.93 (s, 3H), 1.71–1.70 (m, 1H), 1.26 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$+CCl_4): δ, 206.43, 203.52, 142.73, 124.98, 56.96, 52.16, 51.45, 51.04, 43.43, 31.43, 28.11, 20.53, 15.54. Analysis: Found, C, 70.56; H, 6.90% requires C, 70.90, H, 7.20 for $C_{13}H_{16}O_3$. Mass (*m*/*z*): 220 (M^+).

4.1.6. 6-Acetyl-8-allyl-1methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (11e). To a solution of 5-allyl-3-methoxy salicyl alcohol **10e** (2 g, 10.31 mmol) and methyl vinyl ketone (4.3 mL, 51.54 mmol) in acetonitrile (50 mL) was added a solution of $NaIO_4$ (4.4 g, 20.6 mmol) in water (45 mL) dropwise at 0–5 °C. After stirring for 1 h, the reaction mixture was brought to ambient temperature (~28 °C) and further stirred for 6 h. Work-up as described above followed by removal of solvent under vacuum gave a residue which was chromatographed on silica gel. Elution with pet-ether (60–80 °C)–ethyl acetate (90:10) gave the adduct **11e** as a colourless liquid (1.1 g, 40%). IR (film) ν_{max}: 1745, 1710 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.90 (br m, 1H), 5.84–5.70 (m, 1H), 5.21–5.15 (m, 2H), 3.54 (s, 3H), 3.28 (dd, J_1=10 Hz, J_2=6 Hz, 1H), 3.14 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 3.02 (m, 2H), 2.88 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2), 2.44 (m, 1H), 2.26 (s, 3H), 2.24–1.46 (m, 1H), 1.2 (dd of d, J_1=12 Hz, J_2=6 Hz, J_3=2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 206.54, 202.17, 145.15, 133.72, 119.08, 118.39, 87.18, 57.36, 54.46, 52.61, 50.20, 41.76, 39.30, 32.77, 26.89. Mass (*m*/*z*): 262 (M^+); ES-MS: *m*/*z* calculated for $C_{15}H_{19}O_4$: 263.1283, $[M+H]^+$; found 263.1292.

4.1.7. Alkylation of 6-acetyl-8-methyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2′]oxirane (11c): formation of 12–14. Sodium hydride [0.166–0.2 g (60%w/w), 2.91 mmol] was taken in a two necked flask fitted with a nitrogen inlet. It was washed with dry petroleum ether (3×5 mL) and dry THF (3 mL) was added. A solution of the compound **11c** (0.4 g, 1.94 mmol) in dry THF (10 mL) and MeI (2 mL) in dry THF (4 mL) was added to sodium hydride–THF at 0 °C. After completion of reaction (TLC, 3 h), the reaction mixture was poured into NH_4Cl solution, and diluted with ether. The organic layer was separated and the aqueous layer was extracted with ether (30 mL×4). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was removed under vacuum to give a residue, which was chromatographed on silica gel. Elution with pet-ether (60–80 °C)–ethyl acetate (92:8) gave a mixture of **13a** and **14**, which were separated by fractional recrystallization to give **13a** (0.050 g, 11%) and **14** (0.090 g, 18.9%) as colourless solids. Further elution with petroleum ether (60–80 °C)–ethyl acetate (89:11) gave compound **12a** (0.054 g, 12.7%) as a solid. Elution with pet-ether (60–80 °C)–ethyl acetate (82:18) gave compound **13b** (0.075 g, 17.6%) as a colourless solid. Elution with pet-ether (60–80 °C)–ethyl acetate (78:22) gave the compound **12b** (0.040 g, 10%) as a colourless solid.

Data for **12a**. Colourless solid, mp 95 °C, IR (film) ν_{max}: 1730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.82 (m of d, *J*=6 Hz, 1H), 3.10 (s, 3H), 2.97 (d, *J*=5.4 Hz, 1H), 2.77–2.70 (merged m, 3H), 2.28 (part of an AB system, J_{AB}=18 Hz, 1H), 1.98–1.83 (merged m, 5H), 1.05–0.99 (m, merged with a s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 215.24, 141.75, 120.77, 79.73, 64.55, 52.90, 52.29, 52.01, 49.17, 45.09, 43.90, 35.46, 20.40, 20.17. Mass (*m*/*z*): 234 (M^+); ES-MS: *m*/*z* calculated for $C_{14}H_{19}O_3$: 235.1334, $[M+H]^+$; found 235.1358.

Data for **12b**. Colourless solid, mp 90 °C. IR (film) ν_{max}: 1733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.86 (m of d, *J*=6 Hz, 1H), 3.12 (d, *J*=4.5 Hz, 1H), 2.58 (part of an AB system, J_{AB}=18 Hz, 1H), 2.72 (superimposed dd, *J*=6 Hz, 2H), 2.28 (part of an AB system, J_{AB}=18 Hz, 1H), 2.00–1.86 (m partly merged with d, 2H), 1.93 (d, *J*=1.5 Hz, 3H), 1.63 (s, 1H), 1.06 (m of d, *J*=15 Hz, 1H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 216.90, 144.40, 119.07, 75.10, 67.61, 54.04, 53.31, 51.72, 46.71, 45.30, 35.03, 20.38, 20.32. Mass (*m*/*z*): 220 (M^+). Analysis: Found C, 70.98; H, 7.17% Calc. C, 70.91; H, 7.27% for $C_{13}H_{16}O_3$.

Data for **13a**. Colourless solid, mp 100–101 °C. IR (film) ν_{max}: 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.89 (m, 1H, olefinic H), 3.15 (s, 3H, OCH_3), 2.94 (part of an AB system, J_{AB}=5.4 Hz, 1H, CH_2– of oxirane ring), 2.82 (part of an AB system overlapped with another signal, J_{AB}=5.4 Hz, 2H, 1H of CH_2– of oxirane ring+1H), 2.66 (d, *J*=6.23 Hz, 1H), 1.95–2 (s overlapped with another signal, 5H, olefinic –CH_3+2H), 1.1–1 (s overlapped with another signal, 7H, 2 -CH_3 signals+1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.3, 140.7, 121.5, 80.4, 64.0, 54.1, 52.6, 52.1, 47.9, 47.4, 44.9, 35.9, 20.4, 19.9 and 11.5 (15 Carbons). Analysis: Found C, 72.44; H, 8.25% Calc. C, 72.58; H, 8.06% for $C_{15}H_{20}O_3$. Mass (*m*/*z*): 248 (M^+).

Crystal data. The data given below is for two molecules in a unit cell parameter, both the molecules are Identical and for clarity purpose the ORTEP of only one molecule is shown in the paper. $C_{15}H_{20}O_3$, empirical formula $C_{30}H_{40}O_6$, formula weight 496.62, monoclinic, *P*21/*c*, *Z*=4, λ=0.70930 Å, *a*=11.602(2) Å, *b*=14.1010(8) Å, *c*=16.7290(10) Å, *V*=2735.6(6) Å^3, *T*=293(2) K, D_c=1.206 Mg/m^3, μ=0.083 mm^{-1}, *F*(000)=1072, size=0.40×0.25×0.15 mm^3. Reflections collected/unique=3643/3643 [*R*(int)=0.0000], Final *R* indices [$I>2\sigma(I)$]: R_1=0.0486, wR_2=0.1001, *R* indices (all data): R_1=0.0872, wR_2=0.1189. CCDC 231384. See: http://www.ccdc.cam.ac.uk/conts/retrieving.html (e-mail: deposit@ccdc.cam.ac.uk).

Data for **13b**. Colorless solid, mp 92–93 °C. IR (film) ν_{max}: 3470, 1738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.82 (m of d, *J*=4.8 Hz, 1H), 3.06 (d, *J*=5 Hz, 1H), 2.66 (m, 2H), 1.92–1.83 (s overlapped with a m, total 5H), 1.58 (s, 1H), 1.06–1.35 (d overlapped with m, *J*~7 Hz, total 4H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 219.83, 144.75, 119.84, 76.57, 68.81, 52.10, 51.78, 51.54, 46.86, 45.86, 35.73, 21.24, 20.74, 11.46. Mass (*m*/*z*): 234 (M^+); ES-MS: *m*/*z* calculated for $C_{14}H_{19}O_3$: 235.1334, $[M+H]^+$; found 235.1377.

Data for **14**. Colorless solid, mp 152 °C. IR (film) ν_{max}: 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.79 (m of d, *J*=5.4 Hz, 1H), 3.13 (s, 3H), 2.77 (d, *J*=6 Hz, 1H), 2.65 (part of an AB system, J_{AB}=6 Hz, 1H), 2.43 (part of an

AB system, J_{AB}=6 Hz, 1H), 2.0 (m of d, J=10.8 Hz, 1H), 1.88 (s, 3H), 1.74 (m, 1H), 1.25–1.20 (s, 3H), 1.08–1.01 (s overlapped with a m, total 7H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ, 221.56, 141.96, 121.15, 81.26, 63.81, 54.86, 53.74, 51.26, 48.79, 47.74, 46.27, 36.19, 24.25, 21.25, 20.33, 20.07. Mass (*m*/*z*): 262 (M^+); ES-MS: *m*/*z* calculated for $C_{16}H_{23}O_3$: 263.1647, $[M+H]^+$; found 263.1692.

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Catalysis by ionic liquid: a simple, green and efficient procedure for the Michael addition of thiols and thiophosphate to conjugated alkenes in ionic liquid, [pmIm]Br

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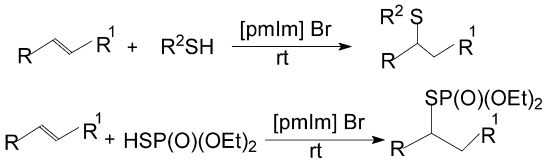
Abstract—A room temperature ionic liquid, 1-pentyl-3-methylimidazolium bromide, [pmIm]Br efficiently catalyzes Michael addition of thiols and diethyl dithiophosphate to a variety of conjugated alkenes such as α,β-unsaturated carbonyl compounds, carboxylic esters, nitriles and chalcones without requiring any other organic solvent and catalyst. The ionic liquid can be recycled for subsequent reactions without any appreciable loss of efficiency.

1. Introduction

Ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of non-volatility, non-flammability, recyclability and ability to dissolve a wide range of materials, among others.[1] During the past few years a variety of ionic liquids have been demonstrated as efficient and practical alternatives to organic solvents for many important organic transformations.[1,2] However, the ability of ionic liquids as a clean catalyst has not been explored to any great extent[3] although it is of much importance in the context of green synthesis. As a part of our drive[4] to avoid organic solvent and toxic catalysts in reactions we have initiated a program to explore the use of benign molten salts[4e–g] and room temperature ionic liquids as efficient catalysts as well as reaction media for useful organic transformations.

The Michael reaction, since its discovery in 1889[5] has been used as one of the most useful methods for effecting carbon–carbon bond formation and later has also been efficiently manipulated for carbon–sulfur and carbon–nitrogen bond forming processes.[6] This reaction is usually carried out under acid or base catalysis. However, to avoid side reactions occasionally encountered in presence of a strong acid or a base, several inorganic salts such as alumina,[7a] zeolite,[7b] bismuth nitrate[7c] among others have been introduced. Recently, conjugate addition of mercaptans to enones has attracted considerable interest[8] as it leads to the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[9] Thus, a number of procedures either based on the activation of thiol by a base or activation of the acceptor olefins with Lewis acids have been developed.[8,10] We report here the novel application of an inexpensive room temperature ionic liquid, 1-pentyl-3-methylimidazolium bromide,[11] [pmIm]Br as an efficient catalyst as well as reaction medium for the Michael addition of thiol and thiophosphate to conjugated alkenes without any conventional solvent and catalyst for the first time (Scheme 1).



R = alkyl/aryl; R^1 = COMe, COPh, CO_2Et etc.; R^2 = *n*-Bu, Ph

Scheme 1.

2. Results and discussion

The experimental procedure is very simple. A mixture of conjugated alkene, thiol (or dithiophosphate) and ionic liquid, [pmIm]Br was stirred at room temperature for a period of time. The reaction mixture was extracted with ether and the crude product was purified by column chromatography. The residual ionic liquid after being dried under vacuum was reused for subsequent reactions.

Keywords: Michael addition; Thiol; Thiophosphate; Ionic liquid; Green catalysis.
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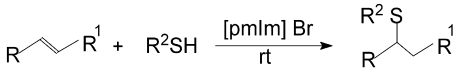
Table 1. Michael addition of thiols to conjugated alkenes



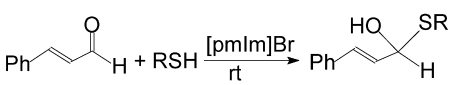
Entry	R	R^1	R^2	Time (h)	Yield (%)[a]	Reference
1	Me	COPh	*n*-Bu	1.25	85	
2	Me	COPh	Ph	0.75	88	10c
3	Me	COPh	(*p*-Cl)C_6H_4	0.75	83	
4	H	COMe	*n*-Bu	0.75	72	4g
5	H	COMe	Ph	0.75	75	4g
6	$(PhCH{=}CH)_2CO$		*n*-Bu	1.25	78[b]	8i
7	Cyclohexenone		Ph	0.5	90	4g
8	Cyclohexenone		*n*-Bu	0.75	91	7c
9	3-Methylcyclohexenone		Ph	No reaction		
10	Me	CHO	*n*-Bu	1.50	90	4g
11	Me	CHO	Ph	1.50	88	4g
12	H	CO_2Me	Ph	1.0[c]	89	4g
13	H	CO_2Me	*n*-Bu	2.0[c]	85	4g
14	CO_2Et	CO_2Et	Ph	0.75	91	4g
15	Ph	CO_2Et	Ph	No reaction		
16	H	CN	Ph	1.0[c]	90	4g
17	H	CN	*n*-Bu	1.50	88	4g
18	Ph	CN	Ph	No reaction		

[a] The yields refer to those of pure isolated products characterized by spectroscopic (IR, ^1H and ^{13}C NMR) data.
[b] The product corresponds to bis-addition.
[c] The reaction was carried out at 65 °C.

No loss of efficiency with regard to reaction time and yield was observed after three uses; however it can be mixed with fresh ionic liquid after three uses for comparable results in subsequent runs.

Both aliphatic and aromatic thiols react with a variety of acyclic and cyclic conjugated alkenes by this procedure to produce the corresponding adducts in high yields. The results are summarized in Table 1. As evident from the results, thiophenol and *n*-butanethiol underwent facile reactions with α,β-unsaturated ketones, aldehydes, esters and nitriles under this procedure. However, the reactions of α,β-unsaturated aldehydes are interesting. Crotonaldehyde undergoes the expected 1,4-addition with butanethiol (entry 10) and thiophenol (entry 11), whereas cinnamaldehyde does not combine with thiophenol even at elevated temperature. Interestingly, the reactions of butanethiol and ethanethiol proceed for 1,2-addition to the carbonyl functionality of cinnamaldehyde producing the corresponding allylic alcohols (Scheme 2) in high yields under identical reaction conditions. A diconjugated acyclic enone, 1,5-diphenylpent-1,4-dien-3-one (entry 8) undergoes bis-additions with two equivalent of thiols to provide the corresponding bis-adduct.

The conjugate addition of thiols to chalcones is considered



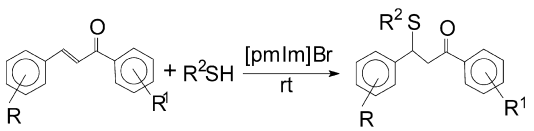
Entry	R	Time(h)	Yield(%)
1	*n*-Bu	2.5	93
2	Et	2.5	86

Scheme 2.

less facile compared to the addition to aliphatic acyclic enones and thus it is not always satisfactory with the reagents used for aliphatic enones. In our own experience, molten tetrabutylammonium bromide[4g] that efficiently catalyzes the addition of thiols to acyclic enones, esters and nitriles fails to effect reaction with chalcones. However, using the present procedure, the ionic liquid [pmIm]Br is successful for addition of aromatic as well as non-aromatic thiols to chalcones without any difficulty. The results are reported in Table 2. As evident from the results in Table 2, both electron withdrawing and electron donating substituents on aromatic ring of the chalcones are compatible with this procedure.

The addition of diethyl dithiophosphate to conjugated

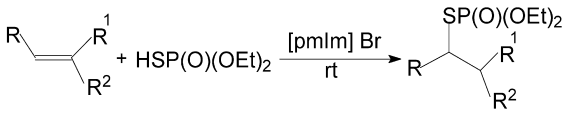
Table 2. Michael addition of thiols of chalcones



Entry	R	R^1	R^2	Time (h)	Yield (%)[a]	Reference
1	H	H	*n*-Bu	1.0	95	
2	H	H	Ph	0.5	94	8b
3	*p*-OMe	H	(*p*-Cl)C_6H_4	0.5	90	
4	*p*-OMe	H	*n*-Bu	1.75	86	
5	*p*-Cl	H	*n*-Bu	1.0	92	
6	*p*-Cl	H	(*p*-Cl)C_6H_4	0.5	90	
7	*p*-NO_2	H	*n*-Bu	1.5	93	
8	*p*-NO_2	H	(*p*-Cl)C_6H_4	0.75	87	
9	H	*p*-Me	Ph	0.5	91	13
10	H	*p*-Me	*n*-Bu	1.5	90	
11	*m*-OAc	H	*n*-Bu	1.5	82	
12	*m*-OAc	H	Ph	1.0	86	

[a] The Yields refer to those of pure isolated products characterized by spectroscopic (IR, ^1H and ^{13}C NMR) data.

Table 3. Michael addition of diethyl dithiophosphate to conjugated alkenes



Entry	R	R^1	R^2	Time (h)	Yield (%)[a]	Reference
1	H	COMe	H	0.05	88	
2	Me_2	COMe	H	0.75	89	12d
3	Cyclohexenone			0.75	71	
4	3-Methylcyclohexenone			No reaction		
5	Ph	COPh	H	0.75	93	12a
6	(*p*-Cl)C_6H_4	COPh	H	1	92	12a
7	(*p*-OMe)C_6H_4	COPh	H	1	90	12a
8	Ph	CO(*p*-Me)-C_6H_4	H	1	91	
9	Me	CHO	H	1.5	87	
10	Ph	CHO	H	No reaction		
11	H	CO_2Me	H	1	82	12b
12	H	CO_2Me	Me	1	89	
13	Me	CO_2Et	H	1	91	12c
14	Ph	CO_2Et	H	No reaction		
15	H	CN	H	0.75	86	
16	H	CN	Me	1	88	
17	Ph	CN	H	No reaction		

[a] The yields refer to those of pure isolated products characterized by spectroscopic (IR, ^1H and ^{13}C NMR) data.

carbonyl compounds, esters and nitriles is also found to proceed efficiently by the catalysis of this ionic liquid. The detailed results are presented in Table 3. The synthesis of these thiophosphate adducts are of considerable recent interest because of their various newer applications in industry and as useful synthetic intermediates in organic synthesis.[12]

These Michael additions are in general, very fast and clean. The crude products obtained are sufficiently pure, and purification by short column chromatography gave analytically pure samples. It has also been observed that these ionic liquid catalyzed additions are greatly influenced by the β-substitutions on the conjugated alkene. Thus, while cyclohex-2-en-1-one underwent facile addition, 3-methyl cyclohex-2-en-1-one remained inert (entry 9 in Table 1 and entry 4 in Table 3). Similarly phenyl substitutions at the β-positions of conjugated esters and nitriles made them inactive (entries 15, 18 in Table 1 and entries 14, 17 in Table 3). These inhibitions may be due to steric factors. The catalytic activity of [pmIm]Br for these Michael additions is established by the observation that no reaction was observed in the absence of ionic liquid. The optimum amount of ionic liquid has been determined to be the quantity required just to solubilize the reacting materials. Although the mechanism of action of this ionic liquid is yet to be established with further experiments it may be postulated that the bromide ion is hydrogen bonding to the thiol increasing the nucleophilicity of sulfur atom. This makes the thiolate anion a better nucleophile towards efficient addition to conjugated alkenes.

Very recently, a procedure using a [BmIm]PF_6/H_2O system has been reported for the conjugate addition of thiols to α,β-unsaturated ketones.[14] However, the present procedure using [pmIm]Br is a better alternative being more general in its application and requiring no water as an additive.

3. Conclusion

The present procedure catalyzed by a simple ionic liquid, [pmIm]Br provides an efficient and general methodology for Michael addition of thiols and diethyl thiophosphate to conjugated acyclic and cyclic enones, chalcones, aldehydes, esters and nitriles. The significant improvements offered by this procedure are: (a) fast reaction (0.5–2.0 h); (b) simple operation and mild conditions (room temperature), (c) high yields (72–95%); (d) cost efficiency providing recyclability of the catalyst, and (e) green aspects avoiding hazardous organic solvents, toxic catalysts and waste (atom efficiency). More significantly, this work clearly demonstrates the potential of a room temperature ionic liquid to act as an efficient and recyclable catalyst and shows much promise for further applications.

4. Experimental

4.1. General

The ionic liquid, [pmIm]Br was prepared following a reported procedure.[11] IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively.

4.1.1. General experimental procedure for Michael additions. Representative one (entry 1, Table 2). A mixture of chalcone (253 mg, 1 mmol), butanethiol (117 mg, 1.3 mmol) and [pmIm]Br (300 mg) was stirred at room temperature for a period of time as required to complete the reaction (TLC). The reaction mixture was washed with ether (3×10 mL) and the combined ether extract was evaporated to leave the crude product which was purified by column chromatography over silica gel (hexane/ether 96:4) to give pure adduct,

1,3-diphenyl-3-(thiobutyl)propan-1-one (315 mg, 92%) as a colorless oil; IR 3028, 2952, 1675, 1603 cm^{-1}; ^1H NMR δ 0.82 (t, J=7.2 Hz, 3H), 1.26–1.34 (m, 2H), 1.39–1.56 (m, 2H), 2.27–2.37 (m, 2H), 3.52 (d, J=7.0 Hz, 2H), 4.55 (t, J=7.0 Hz, 1H), 7.17–7.54 (m, 8H), 7.88–7.91 (m, 2H); ^{13}C NMR δ 14.0, 22.4, 31.5, 31.7, 44.7, 45.9, 127.6, 128.3 (2C), 128.5 (2C), 128.8 (2C), 128.9, 129.0, 133.6, 137.3, 142.7, 197.4. Anal. calcd for $C_{19}H_{22}OS$: C, 76.47; H, 7.43. Found: C, 76.31; H, 7.28.

The residual ionic liquid was further washed with ether and after being dried under vacuum was reused for subsequent reactions. This procedure was followed for all the conjugate additions listed in Tables 1–3. The known compounds were identified by comparison of their spectral data with those reported,[4g,7c,8b,i,10c,12a–d,13] and the new compounds were properly characterized by their IR, ^1H NMR and ^{13}C NMR spectroscopic data and elemental analyses. These data are presented below in order of their entries in the Tables 1–3.

4.1.2. 1-Phenyl-3-(thiobutyl)butan-1-one (entry 1, Table 1). Colorless oil; IR (neat) 3032, 2929, 1685, 1596 cm^{-1}; ^1H NMR δ 0.91 (t, J=7.4 Hz, 3H), 1.35 (d, J=6.7 Hz, 3H), 1.36–1.46 (m, 2H), 1.53–1.64 (m, 2H), 2.57 (t, J=7.3 Hz, 2H), 3.05–3.33 (m, 2H), 3.42–3.52 (m, 1H), 7.26–7.59 (m, 3H), 7.90–7.97 (m, 2H); ^{13}C NMR δ 14.1, 22.2, 22.5, 31.0, 32.2, 35.9, 46.6, 128.5 (2C), 129.1 (2C), 133.3, 137.4, 198.7. Anal. calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 70.96; H, 8.45.

4.1.3. 1-Phenyl-3-(4-chlorothiophenyl)butan-1-one (entry 3, Table 1). Colorless oil; IR (neat) 3062, 1681, 1475 cm^{-1}; ^1H NMR δ 1.37 (d, J=6.7 Hz, 3H), 3.07–3.31 (m, 2H), 3.85–3.92 (m, 1H), 7.20–7.57 (m, 7H), 7.89–7.91 (m, 2H); ^{13}C NMR δ 21.3, 39.5, 45.7, 128.2 (2C), 128.8 (2C), 129.3 (2C), 133.5, 133.8 (2C), 134.1, 137.8, 147.5, 198.2. Anal. calcd for $C_{16}H_{15}OSCl$: C, 66.08; H, 5.20. Found: C, 65.92; H, 5.03.

4.1.4. 3-(4-Chlorothiophenyl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (entry 3, Table 2). White crystal; mp 86–90 °C; IR (KBr) 2947, 1674, 1610 cm^{-1}; ^1H NMR δ 3.53–3.62 (m, 2H), 3.74 (s, 3H), 4.93 (dd, J_1=6.5 Hz, J_2=7.1 Hz, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.17–7.54 (m, 9H), 7.89 (d, J=7.3 Hz, 2H); ^{13}C NMR δ 45.1, 48.4, 55.6, 114.3 (2C), 128.5 (2C), 129.0 (2C), 129.3 (2C), 129.4 (2C), 133.4 (2C), 133.8, 134.1, 134.6 (2C), 137.1, 159.3, 197.3. Anal. calcd for $C_{22}H_{19}O_2SCl$: C, 69.01; H, 5.00. Found: C, 69.24; H, 5.22.

4.1.5. 3-(4-Methoxyphenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 4, Table 2). Colorless oil; IR (neat) 3057, 2835, 1683, 1608 cm^{-1}; ^1H NMR δ 0.84 (t, J=7.2 Hz, 3H), 1.26–1.35 (m, 2H), 1.43–1.54 (m, 2H), 2.24–2.38 (m, 2H), 3.50 (d, J=7.1 Hz, 2H), 3.77 (s, 3H), 4.52 (t, J=7.1 Hz, 1H), 6.84 (d, J=7.4 Hz, 2H), 7.26–7.56 (m, 5H), 7.90 (d, J=7.4 Hz, 2H); ^{13}C NMR δ 14.1, 22.4, 31.5, 31.7, 44.1, 45.9, 55.6, 114.2, 114.3, 128.5 (2C), 129.0 (2C), 129.2, 129.3, 133.6, 134.6, 137.2, 158.9, 197.6. Anal. calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36. Found: C, 73.01; H, 7.21.

4.1.6. 3-(4-Chlorophenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 5, Table 2). Colorless oil; IR (neat) 2956, 2869, 1687, 1596 cm^{-1}; ^1H NMR δ 0.84 (t, J=7.2 Hz, 3H), 1.20–1.57 (m, 4H), 2.26–2.40 (m, 2H), 3.49 (d, J=7.0 Hz, 2H), 4.52 (t, J=7.0 Hz, 1H), 7.24–7.57 (m, 7H), 7.89 (d, J=7.8 Hz, 2H); ^{13}C NMR δ 14.0, 22.3, 31.5, 31.6, 43.9, 45.7, 122.9 (2C), 128.9, 129.0, 129.1 (2C), 129.7 (2C), 133.8, 137.0, 141.3, 143.7, 197.1. Anal. calcd for $C_{19}H_{21}OSCl$: C, 68.55; H, 6.36. Found: C, 68.38; H, 6.30.

4.1.7. 3-(4-Chlorophenyl)-3-(4-chlorothiophenyl)-1-phenylpropan-1-one (entry 6, Table 2). White crystal; mp 84–86 °C; IR (KBr) 3061, 1685, 1473, 688 cm^{-1}; ^1H NMR δ 3.58 (d, J=7.1 Hz, 2H), 4.88 (t, J=7.1 Hz, 1H), 7.16–7.58 (m, 11H), 7.88 (d, J=7.8 Hz, 2H); ^{13}C NMR δ 44.8, 48.3, 128.4 (2C), 128.9 (2C), 129.0, 129.1 (2C), 129.4 (2C), 129.5 (2C), 130.8, 133.9, 134.5, 134.8 (2C), 137.5, 140.1, 196.8. Anal. calcd for $C_{21}H_{16}OSCl_2$: C, 65.12; H, 4.16. Found: C, 64.94; H, 4.04.

4.1.8. 3-(4-Nitrophenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 7, Table 2). Colorless oil; IR (neat) 2956, 2871, 1687, 1519, 1346 cm^{-1}; ^1H NMR δ 0.84 (t, J=7.2 Hz, 3H), 1.27–1.36 (m, 2H), 1.44–1.52 (m, 2H), 2.25–2.39 (m, 2H), 3.57 (d, J=7.1 Hz, 2H), 4.62 (t, J=7.1 Hz, 1H), 7.41–7.62 (m, 5H), 7.88–7.91 (m, 2H), 8.14–8.17 (m, 2H); ^{13}C NMR δ 13.9, 22.3, 31.5, 31.7, 44.1, 45.4, 123.9 (2C), 128.2 (2C), 129.1 (2C), 129.2 (2C), 133.9, 136.7, 147.3, 150.7, 196.6. Anal. calcd for $C_{19}H_{21}O_3SN$: C, 66.45; H, 6.16, N, 4.08. Found: C, 66.51; H, 6.03, N, 3.92.

4.1.9. 3-(4-Chlorothiophenyl)-3-(4-nitrophenyl)-1-phenylpropan-1-one (entry 8, Table 2). Yellow crystal; mp 95–97 °C; IR (KBr) 3058, 1681, 1519, 1346, 688 cm^{-1}; ^1H NMR δ 3.65 (d, J=7.1 Hz, 2H), 4.94 (t, J=7.1 Hz, 1H), 7.15–7.61 (m, 9H), 7.88–7.91 (m, 2H), 8.09–8.12 (m, 2H); ^{13}C NMR δ 44.3, 48.5, 124.2 (2C), 128.2 (2C), 128.4, 128.8 (2C), 128.9 (2C), 129.4 (2C), 131.6, 132.2, 134.1, 135.1 (2C), 136.6, 149.3, 196.2. Anal. calcd for $C_{21}H_{16}O_3SN$: C, 69.60; H, 4.45; N, 3.86. Found: C, 69.80; H, 4.26; N, 4.09.

4.1.10. 1-(4-Methylphenyl)-3-phenyl-3-thiobutylpropan-1-one (entry 10, Table 2). White crystal; mp 58 °C; IR (KBr) 3028, 2952, 1674, 1606 cm^{-1}; ^1H NMR δ 0.83 (t, J=7.3 Hz, 3H), 1.26–1.37 (m, 2H), 1.42–1.50 (m, 2H), 2.27–2.36 (m, 2H), 2.37 (s, 3H), 3.47 (d, J=7.1 Hz, 2H), 4.54 (t, J=7.1 Hz, 1H), 7.20–7.32 (m, 5H), 7.41 (d, J=8.2 Hz, 2H), 7.81 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 14.0, 22.0, 22.3, 31.6, 31.7, 44.8, 45.7, 127.5, 128.2 (2C), 128.6 (2C), 128.9 (2C), 129.7 (2C), 134.8, 142.8, 144.4, 197.0. Anal. calcd for $C_{20}H_{24}OS$: C, 76.88; H, 7.74. Found: C, 77.09; H, 7.69.

4.1.11. 3-(3-Acetoxyphenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 11, Table 2). Colorless oil; IR (neat) 3024, 2952, 1764, 1675, 1604 cm^{-1}; ^1H NMR δ 0.82 (t, J=7.2 Hz, 3H), 1.26–1.34 (m, 2H), 1.39–1.56 (m, 2H), 2.15 (s, 3H), 2.27–2.37 (m, 2H), 3.52 (d, J=7.0 Hz, 2H), 4.55 (t, J=7.0 Hz, 1H), 6.89–7.54 (m, 7H), 7.89 (d, J=8.3 Hz, 2H); ^{13}C NMR δ 14.0, 21.2, 22.4, 31.5, 31.7, 44.7, 45.9, 127.6, 128.3 (2C), 128.5, 128.8 (2C), 128.9, 129.0, 133.6, 137.3, 142.7, 157.3, 169.2, 197.4. Anal. calcd for $C_{21}H_{24}O_3S$: C, 70.76; H, 6.79. Found: C, 70.58; H, 6.89.

4.1.12. 3-(3-Acetoxyphenyl)-1-phenyl-3-thiophenylpropan-1-one (entry 12, Table 2). Gummy mass; IR (neat) 3026, 2948, 1762, 1681, 1610 cm^{-1}; ^1H NMR δ 2.15 (s, 3H), 3.56–3.75 (m, 2H), 4.98 (dd, J_1=6.2 Hz, J_2=8.0 Hz, 1H), 6.89 (m, 12H), 7.88–7.90 (m, 2H); ^{13}C NMR δ 21.2, 45.1, 48.6, 127.8 (2C), 127.9, 128.2 (3C), 128.3, 128.5, 129.1, 129.3, 133.2 (3C), 133.7, 134.7, 137.1, 141.6, 157.3, 169.2, 197.4. Anal. calcd for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35. Found: C, 73.21; H, 5.29.

4.1.13. *O,O*-Diethyl *S*-(3-oxobutyl)phosphorodithioate (entry 1, Table 3). Colorless oil; IR (neat): 2979, 2902, 1716, 1442, 1012, 960 cm^{-1}; ^1H NMR δ 1.33 (t, J=7.1 Hz, 6H), 2.14 (s, 3H), 2.81–2.86 (m, 2H), 2.98–3.08 (m, 2H), 4.05–4.24 (m, 4H); ^{13}C NMR δ 15.7 (d, J_{CP}=8.2 Hz) (2C), 26.8 (d, J_{CP}=3.5 Hz), 29.9, 43.8 (d, J_{CP}=3.8 Hz), 63.9 (d, J_{CP}=6.2 Hz) (2C), 205.7. Anal. calcd for $C_8H_{17}S_2O_3P$: C, 37.49; H, 6.69. Found: C, 37.33; H, 6.50.

4.1.14. *O,O*-Diethyl *S*-(3-oxocyclohexyl)phosphorodithioate (entry 3, Table 3). Colorless oil; IR (neat): 2981, 2868, 1716, 1012, 960 cm^{-1}; ^1H NMR δ 1.32 (t, J=7.1 Hz, 6H), 1.72–2.52 (m, 7H), 2.78 (dd, J_1=14.4 Hz, J_2=4.8 Hz, 1H), 3.50–3.64 (m, 1H), 4.05–4.23 (m, 4H); ^{13}C NMR δ 18.2 (d, J_{CP}=8.3 Hz) (2C), 26.4, 35.1 (d, J_{CP}=5.8 Hz), 43.0, 49.2 (d, J_{CP}=3.6 Hz), 51.4 (d, J_{CP}=5.3 Hz), 66.6 (d, J_{CP}=6.2 Hz) (2C), 209.9. Anal. calcd for $C_{10}H_{19}S_2O_3P$: C, 42.54; H, 6.78. Found: C, 42.36; H, 6.61.

4.1.15. *O,O*-Diethyl *S*-[3-(4-methylphenyl)-1-phenyl-3-oxopropyl]phosphorodithioate (entry 8, Table 3). Colorless oil; IR (neat): 2979, 2900, 1601, 1606, 1440, 1015, 962 cm^{-1}; ^1H NMR δ 1.08 (t, J=7.0 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H), 2.39 (s, 3H), 3.56–3.77 (m, 2H), 4.04–4.15 (m, 4H), 4.95–5.04 (m, 1H), 7.19–7.43 (m, 7H), 7.81 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 15.4 (d, J_{CP}=8.8 Hz), 15.7 (d, J_{CP}=8.8 Hz), 21.5, 46.0 (d, J_{CP}=7.1 Hz), 47.8 (d, J_{CP}=3.8 Hz), 63.6 (d, J_{CP}=5.4 Hz), 63.9 (d, J_{CP}=5.4 Hz), 127.5, 128.1 (2C), 128.3 (2C), 128.6 (2C), 129.3 (2C), 133.9, 141.6, 144.2, 195.4. Anal. calcd for $C_{20}H_{25}S_2O_3P$: C, 58.80; H, 6.17. Found: C, 58.59; H, 6.03.

4.1.16. *O,O*-Diethyl *S*-(1-methyl-3-oxopropyl)phosphorodithioate (entry 9, Table 3). Colorless oil; IR (neat): 2979, 2829, 1726, 1444, 1012, 960 cm^{-1}; ^1H NMR δ 1.35 (t, J=7.1 Hz, 6H), 1.46 (d, J=6.9 Hz, 3H), 2.69–2.77 (m, 1H), 2.83–2.92 (m, 1H), 3.69–3.85 (m, 1H), 4.08–4.22 (m, 4H), 9.74 (d, J=1.4 Hz, 1H); ^{13}C NMR δ 18.2 (d, J_{CP}=8.3 Hz) (2C), 25.3 (d, J_{CP}=5.8 Hz), 41.4 (d, J_{CP}=3.7 Hz), 53.5 (d, J_{CP}=5.7 Hz), 66.6 (d, J_{CP}=6.4 Hz) (2C), 201.9. Anal. calcd for $C_8H_{17}S_2O_3P$: C, 37.49; H, 6.69. Found: C, 37.32; H, 6.49.

4.1.17. *O,O*-Diethyl *S*-(2-carbomethoxypropyl)phosphorodithioate (entry 12, Table 3). Colorless oil; IR (neat): 2981, 2875, 1737, 1440, 1014, 960 cm^{-1}; ^1H NMR δ 1.23 (d, J=7.1 Hz, 3H), 1.33 (t, J=7.1 Hz, 6H), 2.76–2.97 (m, 2H), 3.05–3.15 (m, 1H), 3.68 (s, 3H), 4.08–4.18 (m, 4H); ^{13}C NMR δ 15.7 (d, J_{CP}=8.2 Hz) (2C), 16.8, 35.9 (d, J_{CP}=3.8 Hz), 40.4 (d, J_{CP}=4.2 Hz), 51.8, 63.9 (d, J_{CP}=6.0 Hz) (2C), 174.7. Anal. calcd for $C_9H_{19}O_4S_2P$: C, 37.75; H, 6.69. Found: C, 37.58; H, 6.52.

4.1.18. *O,O*-Diethyl *S*-(2-cyanoethyl)phosphorodithioate (entry 15, Table 3). Colorless oil; IR (neat): 2983, 2902, 2250, 1442, 1010, 962 cm^{-1}; ^1H NMR δ 1.33 (t, J=7.1 Hz, 6H), 2.73–2.78 (m, 2H), 3.02–3.13 (m, 2H), 4.06–4.24 (m, 4H); ^{13}C NMR δ 18.2 (d, J_{CP}=8.2 Hz) (2C), 21.7 (d, J_{CP}=3.1 Hz), 31.4 (d, J_{CP}=3.8 Hz), 66.9 (d, J_{CP}=6.8 Hz) (2C), 119.9. Anal. calcd for $C_7H_{14}NO_2S_2P$: C, 35.14; H, 5.90; N, 5.85. Found: C, 34.98; H, 5.75; N, 5.69.

4.1.19. *O,O*-Diethyl *S*-(2-cyanopropyl)phosphorodithioate (entry 16, Table 3). Colorless oil; IR (neat) 2983, 2902, 2250, 1454, 1010, 962 cm^{-1}; ^1H NMR δ 1.33–1.47 (m, 9H), 2.98–3.12 (m, 3H), 4.10–4.25 (m, 4H); ^{13}C NMR δ 15.7 (d, J_{CP}=8.2 Hz) (2C), 17.37, 27.2 (d, J_{CP}=3.5 Hz), 36.6 (d, J_{CP}=3.5 Hz), 64.4 (d, J_{CP}=6.8 Hz) (2C), 120.9. Anal. calcd for $C_8H_{16}O_2S_2P$: C, 37.93; H, 6.37; N, 5.53. Found: C, 37.76; H, 6.29; N, 5.40.

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Probing the hydride transfer process in the lumiflavine–1-methylnicotinamide model system using group softness

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Abstract—The hydride transfer process between the isoalloxazine moiety of flavins and the nicotinamide moiety of NAD(P)H has been explored by using density functional theory based reactivity index in the 1-methylnicotinamide–lumiflavine model system. Based on crystallographic data available, we have found that the group softness index helps to locate and orientate reactive regions in these interacting molecules while the electrophilicity index successfully describes the reactivity pattern of this system.

1. Introduction

Flavins (riboflavin, FMN, FAD) are cofactors of a widespread family of enzymes, the flavoenzymes, which are involved in a large number of biological functions. Dehydrogenation of a variety of substrates, mediation of one- and two-electron transfer, activation of molecular oxygen as well as photobiochemical processes are only a few examples of the versatility of flavoproteins.[1–4] A relevant aspect of the biological activity of these enzymes is that despite their versatility, their reactivity is restricted to the common structural feature of flavin cofactors, represented by the 7,8-dimethylisoalloxazine system (see **LF** in Fig. 1). The ribitol, pyrophosphate or ribose moieties of the different side chains attached at nitrogen 10 of the isoalloxazine ring are not directly involved in the catalytic process but in anchoring the cofactor to the protein, as it has been revealed by structural studies.[5–7] It is apparent that the reactivity of flavins might be modulated by the different oxidation and protonation states that the isoalloxazine moiety can undergo, and by the protein environment of the flavin-binding site.[4,8–10] Also, the use of artificial flavins as active site probes has provided important mechanistic information related to the tuning of the isoalloxazine reactivity by the apoprotein.[11–13]

Based on the experimental evidence available, Massey and Hemmerich[11] proposed that flavoproteins could be classified into five major divisions according to their reactivity. The regiospecificity and the spectral properties of two of these main groups suggest common structural features which could determine the type of reaction catalysed, providing some clues about flavoprotein catalysis. Enzymes

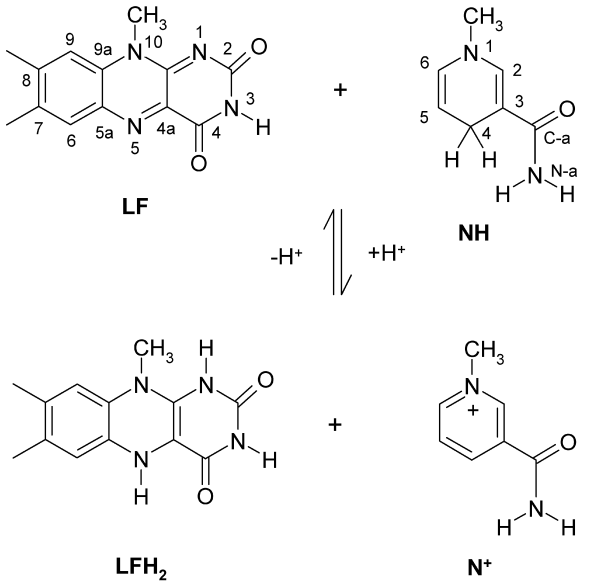

Figure 1. Hydride transfer reaction between lumiflavine (**LF**) and 1-methylnicotinamide (**NH**).

Keywords: Hydride transfer; Flavins; Density functional theory; Chemical softness; Electrophilicity.

Abbreviations: LF, oxidised lumiflavine; NH, reduced 1-methylnicotinamide; N^+, oxidised 1-methylnicotinamide; $LFH1^+$, oxidised lumiflavine protonated at N-1; $LFH5^+$, oxidised lumiflavine protonated at N-5; LFH_2, reduced lumiflavine; DFT, density functional theory; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; HSAB, hard–soft acid–base.

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of the dehydrogenases/oxidases class would be characterised by a 'red' semiquinone radical and hydrogen bonding to the apoprotein through the N-1 site of the isoalloxazine system, which leads to the activation of N-5 towards nucleophilic attack. The electron transferases class would be characterised by a 'blue' semiquinone radical, a planar structure for the reduced form, and hydrogen bonding to the apoprotein through N-5 of isoalloxazine, leading to the activation of C-4a towards nucleophilic attack (see Fig. 1). This general classification has received further support from experimental and theoretical studies.[14,15]

NAD(P)H and $NAD(P)^+$ are recurrent electron donors and acceptors, respectively, involved in two-electron transfer processes in flavoenzyme catalysis.[1,16] As in the case of isoalloxazine in flavins, reactivity in the NAD(P)H/$NAD(P)^+$ couples is restricted to the nicotinamide ring (see **NH** in Fig. 1). In these enzymes a direct transfer of a hydride equivalent takes place between the C-4 atom of nicotinamide and the N-5 position of isoalloxazine as shown diagrammatically in Figure 1. This overall mechanism is supported by crystallographic data, available for several enzymes, which show the nicotinamide ring stacked almost parallel to the central ring of the flavin, at a distance of approximately 3.5 Å as shown in Figure 2a.[5,6,17] This hydride transfer reaction can occur directly at the active site of an enzyme, as in flavin reductases,[18] or at an allosteric site where isoalloxazine, reduced or oxidised by the nicotinamide cofactor, is an intermediate of the catalysis.[1,11,19] Although the stereochemical course of the reaction is known, different electronic mechanisms have been proposed to account for the hydride transfer in the isoalloxazine–nicotinamide system, leading to controversy.[16,20,21] Besides, not only N-5 but also N-1 and C-4a of the isoalloxazine ring have been proposed as candidates for receiving the hydride ion from nicotinamide, the steric hindrance at these positions being the only argument exposed to explain the selectivity of this reaction.[7,14]

Semiempirical and ab initio theoretical studies on isoalloxazine have provided a good description of the geometry and the electronic properties of this molecule.[15,22–24] All these studies predict a planar structure for the oxidised form (**LF** in Fig. 1), either protonated or not, and a bent structure for the reduced heterocycle (**LFH_2** in Fig. 1). Theoretical transition-state studies on the hydride transfer in glutathione reductase, revealed an optimal arrangement for the frontier orbital interaction, with maximal overlap between the participating orbitals, where the largest contribution to the LUMO corresponds to the coefficients of N-5 of isoalloxazine.[25] Further investigations on the transition-state structures for hydride transfer in several enzymes have concluded that the frontier orbital interaction HOMO–LUMO controls the direct hydride transfer.[26–29] These studies on the structure of the transition state also suggest that a minimal molecular model can describe this chemical interconversion step in enzyme catalysis, and that the geometrical arrangement in the model complex is independent of the level of theory used to perform calculations.[21,26–32] Molecular orbital investigations at the extended Hückel level, carried out in order to explore the regional properties of the isoalloxazine–nicotinamide system, have shown that, during the hydride transfer, there is a region on the nicotinamide moiety from where electrons may be donated to another region able to accept them on the isoalloxazine ring. It has also been proposed that a charge transfer molecular complex is formed before hydride transfer occurs.[33]

The aim of this contribution is to provide new insights on the hydride transfer reaction occurring in the FAD/NAD(P) complex of flavoenzymes. In this work we explore the local

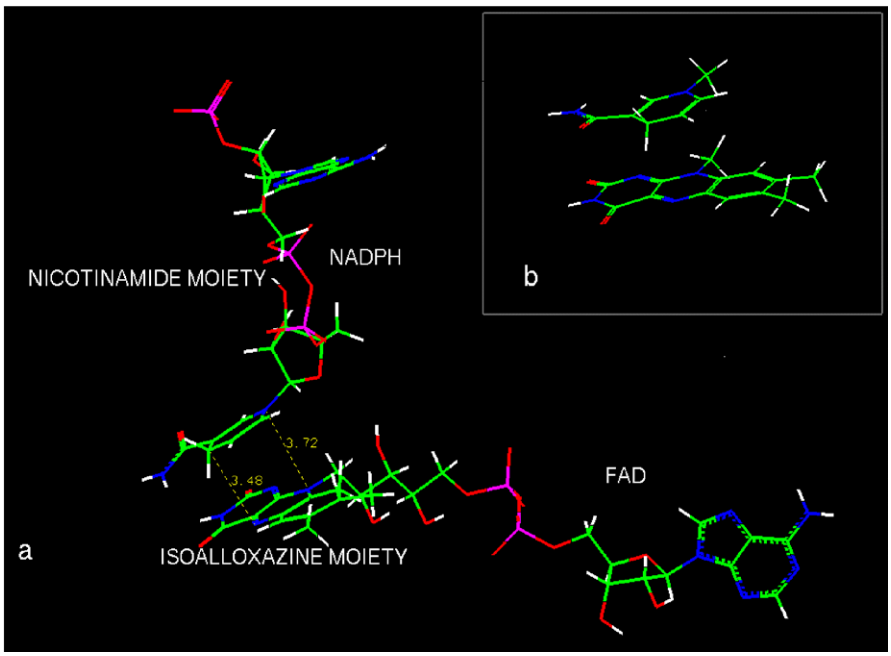

Figure 2. (a) Conformation of the FAD/NADP complex obtained from the crystal structure of glutathione reductase (1GET.pdb). For the sake of simplicity, the apoprotein is not shown. (b) Lumiflavine and 1-methylnicotinamide as a theoretical model used to represent the conformation of the FAD/NADP complex shown in (a).

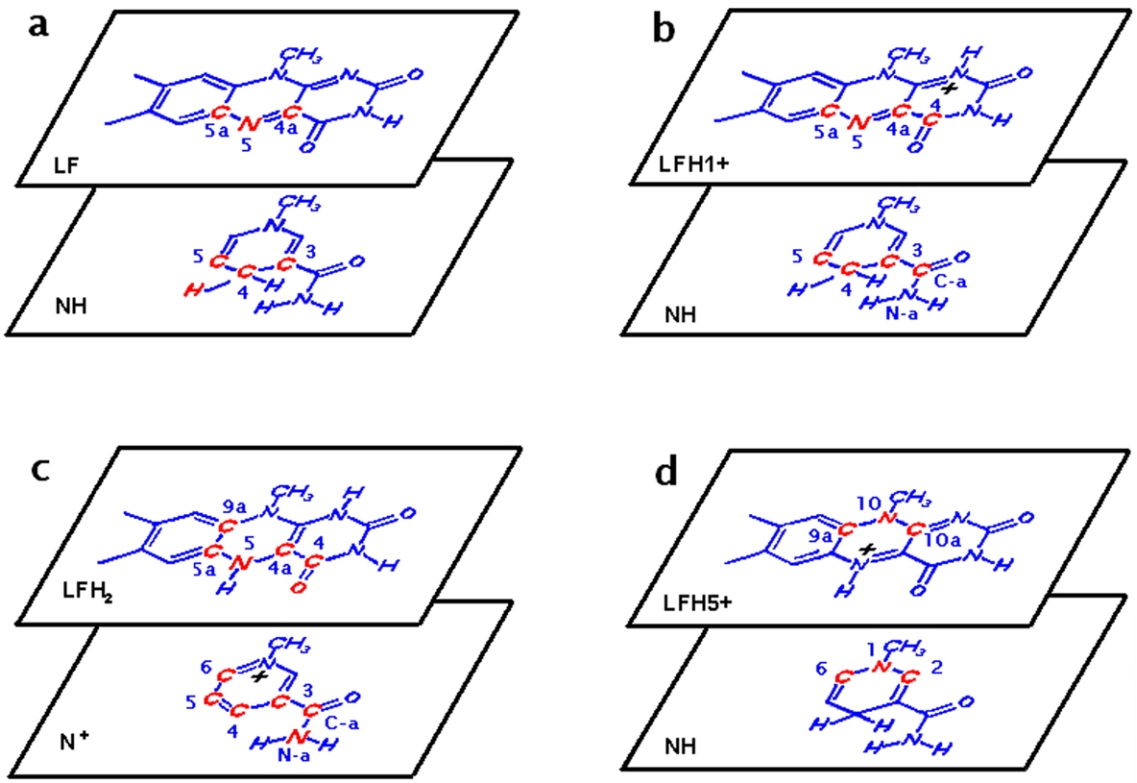

Figure 3. Molecular regions of lumiflavine and 1-methylnicotinamide with similar values of group softnesses. LF–NH system (a); $LFH1^{+}$–NH system (b); LFH_2–N^{+} system (c); $LFH5^{+}$–NH system (d).

and global reactivities of the isoalloxazine and nicotinamide moieties of FAD and NAD(P), by using the conceptual part of density functional theory (DFT)[34] which describes both reactivity and selectivity in terms of static response functions. The geometry of the FAD/NAD(P) complex was taken from the crystal structure of glutathione reductase (1GET.pdb)[6] as shown in Figure 2a. Lumiflavine (7,8,10-trimethylisoalloxazine, **LF**) and 1-methylnicotinamide (**NH**) were chosen as simplified models to represent the system under study (see Fig. 2b). The more likely protonated structures of oxidised lumiflavine, according to Massey and Hemmerich's proposal (at N-1 and at N-5), have also been considered (see Fig. 3b and d). The group softness, extended to more than one atom, s_G, was used to locate reactive regions in interacting molecules.[35]

1.1. The model

DFT provides a useful description of the ground states of molecular systems. Concepts like electronic chemical potential (μ), absolute hardness (η), chemical softness (S) and electrophilicity (ω) are well defined quantities that conveniently describe a complete picture of reactivity.[36–38] An excellent review describing the usefulness of DFT based reactivity indexes recently appeared.[39] The electronic chemical potential μ is the natural descriptor of the direction of charge transfer during a chemical interaction.[34] η has been associated with the resistance of the system to exchange electronic charge with the environment. A further approximation based on Koopmans theorem allows μ and η to be calculated in terms of the one electron energies of the frontier molecular orbitals HOMO and LUMO according to Eqs. 1 and 2:[34]

$$\mu \approx (\varepsilon_L + \varepsilon_H)/2 \quad (1)$$

$$\eta \approx \varepsilon_L - \varepsilon_H \quad (2)$$

where ε_L and ε_H are the energies of the LUMO and HOMO levels, respectively.

Another pertinent quantity is the chemical softness, S, related to the electronic polarizability of the system, whose operational expression using a finite difference approximation is:[34]

$$S \approx 1/(\varepsilon_L - \varepsilon_H) \quad (3)$$

Recently, it has been proposed that the global electrophilic power of a ligand may be described by the electrophilicity index, ω, a quantity measuring the stabilisation energy when the system acquires an amount of electronic charge from the environment. This index has been defined by the following quantitative relationship:[34]

$$\omega = \mu^2/2\eta \quad (4)$$

Besides the global reactivity indices, there is a set of local descriptors of reactivity that have been related to the selectivity of molecules towards specific reactions in some organic systems.[40,41] The Fukui function $f(\mathbf{r})$ is one of the most used descriptors of local reactivity.[34] A high value of this local index is associated with high reactivity at that point in the molecular region. Operational formulae to evaluate this index condensed to atoms have been presented.[42–44] Two regional reactivity indices, the regional softness s_k and the regional electrophilicity ω_k, condensed to

atom k, have been derived through the Fukui function:[34]

$$s_k^{\pm} = f_k^{\pm} S \tag{5}$$

$$\omega_k = f_k^{+} \omega \tag{6}$$

Where f_k is the Fukui function at site k in the direction of increasing (+) and decreasing (−) number of electrons. These indices are associated with nucleophilic and electrophilic attacks at site k, respectively. Note that according to Eqs. 5 and 6 the local softness and the local electrophilicity are distributed following the Fukui function.

Selectivity studies may be framed on a local HSAB principle,[35] stating that the favoured interactions will be those involving sites in the Lewis acid presenting softness values very close to those present in the Lewis base.[45] In the present study, we looked for active regions in lumiflavine and in 1-methylnicotinamide with similar softness values, which, when mimicking the crystallographic data available, are assumed to be in close contact when catalysis takes place (see Fig. 2b). We considered that these reactive regions should have similar shapes and sizes in each counterpart in order to allow the best possible interaction. Therefore, we focused on regions with the same number of atoms in each molecule, including the reactive sites N-5 and C-4a of isoalloxazine, and C-4 of nicotinamide. This present strategy is in agreement with previous studies on transition states structures in hydride transfer processes, where it was shown that the geometry of the transition-state complex is described by a minimal molecular model where the relative orientation imposed by the active site allows the polarization of the C4–H bond of nicotinamide.[21,26]

In order to characterise a more extended molecular region, including more than one atomic centre, we use the concept of group softness according to Eq. 7:[35]

$$s_G = \sum_{k \in G} s_k^{\pm} \tag{7}$$

with $s_k^{\pm}$ defined in Eq. 5. The concept of group softness has been introduced previously by Gazquez and Méndez[35] and others,[46] in a different context.

1.2. Computational details

All calculations were carried out using the Gaussian98 program package[47] at the B3LYP/6-31G level of theory. The geometry of the molecules under study was fully optimized. The minimised structures were in good agreement with earlier studies for oxidised and reduced forms of lumiflavine and 1-methylnicotinamide. The Fukui functions were obtained using an algorithm described elsewhere.[43,44]

2. Results and discussion

2.1. The regional picture

It has been suggested that short distance interactions of some molecules which display biological activity might proceed through regions within the molecules rather than through the whole molecular framework.[33,46] In fact, reactivity in flavoproteins seems to be mainly restricted to the region of the isoalloxazine ring system where N-5 and C-4a are located.[1–3,11] It has also been shown that Pearson's HSAB principle helps to determine the specificity and/or efficiency of enzymatic catalysis and drug–receptor interactions.[48,49] These findings led us to explore the regiospecific reactivity of lumiflavine and 1-methylnicotinamide, shown in Figure 2b, in the context of a local HSAB principle.

Table 1. Local reactivity indices of lumiflavine and 1-methylnicotinamide[a]

Molecule	Site (k)	f^+ (k)	f^- (k)	s^+ (k) (au)	s^- (k) (au)	$\omega(k)$ (eV)
NH	N-1	0.019	0.268		1.636	0.016
	C-2	0.304	0.037		0.226	0.251
	C-3	0.124	0.258		1.575	0.102
	C-4	0.000	0.013		0.079	0.000
	C-5	0.174	0.183		1.117	0.144
	C-6	0.103	0.042		0.256	0.085
	C-a	0.133	0.003		0.018	0.110
	H_t	0.000	0.042		0.256	0.000
N^+	C-3	0.075		0.484		0.711
	C-4	0.325		2.099		3.079
	C-5	0.006		0.039		0.057
	C-6	0.243		1.570		2.302
	C-a	0.009		0.058		0.085
	N-a	0.004		0.026		0.038
LF	N-1	0.026		0.212		0.087
	C-4a	0.142		1.159		0.475
	N-5	0.251		2.048		0.839
	C-5a	0.000		0.000		0.000
$LFH1^+$	C-4	0.023		0.170		0.251
	C-4a	0.075		0.555		0.820
	N-5	0.273		2.019		2.983
	C-5a	0.013		0.096		0.142
$LFH5^+$	C-4a	0.249		2.886		4.464
	N-5	0.197		2.283		3.531
	C-9a	0.062		0.719		1.111
	N-10	0.100		1.159		1.793
	C-10a	0.015		0.174		0.269
LFH_2	C-4	0.156	0.024		0.190	0.162
	C-4a	0.065	0.114		0.902	0.067
	N-5	0.000	0.257		2.033	0.000
	C-5a	0.049	0.042		0.332	0.051
	C-9a	0.057	0.070		0.554	0.059
	O-4	0.110	0.050		0.396	0.114

[a] All quantities evaluated at the fully optimised geometry at the B3LYP/6-31G level of theory.

Table 1 gathers the local properties for lumiflavine and 1-methylnicotinamide in their different oxidation and protonation states, obtained from Eqs. 5 and 6. The analysis of group softness s_G for the **LF**–**NH** pair (see Fig. 3a), calculated according to Eq. 7, shows that the regional softness of **LF** (the electrophile), considering atoms C-4a, N-5 and C-5a, and the corresponding s_G values in **NH** (the nucleophile), calculated considering the atoms C-3, H_t and C-5 of **NH**, display similar values. They are distributed as follows:

$$s_G^{+}\mathrm{LF} = s^{+}(\text{C-4a}) + s^{+}(\text{N-5}) + s^{+}(\text{C-5a})$$
$$= 1.159 + 2.048 + 0.000 = 3.207 \tag{8a}$$

$$s_G^{-}\mathrm{NH} = s^{-}(\text{C-3}) + s^{-}(\mathrm{H_t}) + s^{-}(\text{C-5})$$
$$= 1.575 + 0.256 + 1.117 = 2.948 \tag{8b}$$

The group softness values of the **LF** and **NH** units match to an extent of 91.9%. The orientation of these molecules is in agreement with the experimental model in Figure 2a. Inclusion of the local softness value at C-4 of **NH** (see Fig. 3a), which breaks the condition of an equal number of atoms in each subunit but does not greatly changes the size or the shape of the regions, increases the match to an extent of 94.4%. Other regions in the molecules make no significant contributions to the matching of the regional softness values, even when atoms located far from the active sites are considered.

For the **LFH1**$^+$–**NH** system shown in Figure 3b (oxidised lumiflavine protonated at N-1), we have found that the active regions comprising atoms C-4, C-4a, N-5 and C-5a of **LFH1**$^+$ (the electrophile), and C-a, C-3, C-4 and C-5 of **NH** (the nucleophile) concentrate the higher s_G values. Thus,

$$s_G^+\mathrm{LFH1}^+ = s^+(\text{C-4}) + s^+(\text{C-4a}) + s^+(\text{N-5}) + s^+(\text{C-5a}) = 0.170 + 0.555 + 2.019 + 0.096 = 2.840 \quad (9a)$$

$$s_G^-\mathrm{NH} = s^-(\text{C-a}) + s^-(\text{C-3}) + s^-(\text{C-4}) + s^-(\text{C-5}) = 0.018 + 1.575 + 0.079 + 1.117 = 2.789 \quad (9b)$$

For this system, the match in the group softnesses is about 98.2% (see Fig. 3b).

According to crystallographic data,[5] hydride transfer from **LFH$_2$** to **N**$^+$ should involve the same geometrical arrangement as the reverse reaction (see Fig. 1). In the **LFH$_2$**–**N**$^+$ system, shown in Figure 3c, atoms C-4, C-4a, N-5, C-5a, C-9a and O-4 (oxygen attached to C-4) of **LFH$_2$** (the nucleophile) are superimposed in space on atoms C-a, C-3, C-4, C-5, C-6 and N-a of **N**$^+$ (the electrophile). The group softness analysis predicts the following distribution:

$$s_G^-\mathrm{LFH}_2 = s^-(\text{C-4}) + s^-(\text{C-4a}) + s^-(\text{N-5}) + s^-(\text{C-5a}) + s^-(\text{C-9a}) + s^-(0\text{–}4) = 0.190 + 0.902 + 2.033 + 0.332 + 0.554 + 0.396 = 4.407 \quad (10a)$$

$$s_G^+\mathrm{LFH1}^+ = s^+(\text{C-a}) + s^+(\text{C-3}) + s^+(\text{C-4}) + s^+(\text{C-5}) + s^+(\text{C-6}) + s^+(\text{N-a}) = 0.058 + 0.484 + 2.099 + 0.039 + 1.570 + 0.026 = 4.276 \quad (10b)$$

giving a match of 97.0% between both subunits, in the orientation consistent with the crystallographic model (see Fig. 3c).

For the **LFH5**$^+$–**NH** system (see Fig. 3d), there is some controversy about the feasibility of the reaction between NAD(P)H and the oxidised flavin protonated at N-5. While NMR data have provided evidence that could support the existence of hydrogen bonding between the apoprotein and N-5 of the flavin in Old Yellow Enzyme, the pK_a value of the oxidised flavin counters this hypothesis.[50] The global softness match in this system, 52.7% (values taken from Table 2), is poor compared to the other systems under study. Group softness matches including the active sites (N-5, C-4a of **LFH5**$^+$ and C-4 of **NH**) are even poorer (see Table 1 and Fig. 3d). We could find similar values of s_G, which match to an extent of 96.8%, but located in regions of the molecules that do not include the active centers (atoms C-9a, N-10 and C-10a in the lumiflavine molecule, atoms N-1, C-2, and C-6 in the nicotinamide molecule). This result would suggest that more specific, local descriptors, such as local electrophilicity, might be important determinants of reactivity, as in the case of the **LF**–**NH**, **LFH1**$^+$–**NH** and **LFH$_2$**–**N**$^+$ systems, which we will discuss below.

Table 2. Global reactivity indices of lumiflavine and 1-methylnicotinamide[a]

Molecule	μ (eV)	η (eV)	S (au)	ω (eV)	ΔN (e)
N$^+$	−8.935	4.213	6.459	9.475	0.819[b]
NH	−2.712	4.458	6.105	0.825	
LFH5$^+$	−9.175	2.348	11.589	17.926	0.950[c]
LFH1$^+$	−8.968	3.680	7.395	10.927	0.769[c]
LF	−4.722	3.334	8.161	3.343	0.258[c]
LFH$_2$	−2.672	3.439	7.912	1.038	

[a] All quantities evaluated at the fully optimised geometry at the B3LYP/6-31G level of theory.
[b] Charge transfer from LFH$_2$ to N$^+$.
[c] Charge transfer from NH to neutral or protonated lumiflavine.

In summary, we have found in the lumiflavine (protonated or not) and in the 1-methylnicotinamide framework regions of atoms which display similar shapes, sizes and group softness values. According to the crystallographic data, the same active regions of FAD and NAD(P) are in close contact during the catalytic process. The above findings lead us to suggest that, when FAD and NAD(P) approach each other at short distances, an orientation of their active regions takes place to reach an optimal interaction, which might be achieved through the recognition of regions of the molecules with similar group softness values, in agreement with the HSAB principle.

2.2. Specific interactions

In the present approach, the comparison of regional softness based on the group softness s_G index, provides relevant clues about the orientation of the interacting partners. However, the complete reactivity picture may be conveniently complemented incorporating other local reactivity descriptors such as the local electrophilicity.

Table 2 summarises the global reactivity indices calculated for lumiflavine and 1-methylnicotinamide, in their oxidised and reduced states. The more likely protonated structures of oxidised lumiflavine (**LFH1**$^+$ and **LFH5**$^+$) have also been considered. The electronic chemical potential (μ) of the studied molecules correctly predicts that electron density flows from **NH** to **LF**, **LFH1**$^+$ or **LFH5**$^+$, and from **LFH$_2$**

to $\mathbf{N}^+$, depending on the direction of the enzyme catalysis. Electrophilicity values suggest the following order: $\mathbf{LFH5}^+ > \mathbf{LFH1}^+ > \mathbf{N}^+ > \mathbf{LF} > \mathbf{LFH_2} > \mathbf{NH}$. It can be seen that protonation of **LF** increases its electrophilicity, so it is possible that protonation at N-1 or N-5 may be the first step in some catalytic mechanisms where nucleophilic attack is determinant. If we consider that electrophilicity and nucleophilicity lie at opposite ends of a single scale, then the ω values properly indicate that **LF**, $\mathbf{LFH1}^+$ and $\mathbf{LFH5}^+$ behave as electrophiles with respect to **NH** (which in turn would behave as a nucleophile), whereas $\mathbf{N}^+$ behaves as an electrophile with respect to $\mathbf{LFH_2}$ (see Fig. 1). As stated in Eq. 6, the site of maximum electrophilicity will be the one exhibiting the highest value of the electrophilic Fukui function, that is, the active site of the electrophile.

As mentioned earlier, not only N-5, but also N-1 and C-4a are considered the most likely positions for receiving the hydride ion from nicotinamide in the **LF** molecule. Inspection of the local electrophilicity values in Table 1, shows that N-5 has the highest value (0.840 eV), followed by C-4a and N-1 (0.475 and 0.087 eV, respectively). Thus, our results indicate that N-5 would be the preferential site for nucleophilic attack, beyond the steric hindrance imposed by the enzyme environment, as has been proposed by some authors.[7] Note that in **NH** the local electrophilicity at C-4 vanishes and that of the H_t atom is very low (0.000), which is consistent with the nucleophilic behaviour of **NH** with respect to **LF**. Our results are also in good agreement with an enzymatic experiment in which 4-(^{3}H(NADH was used as the reducing substrate, and where hydride transfer to N-5 of isoalloxazine was detected.[51] When hydride transfer occurs between N-5 of $\mathbf{LFH_2}$ and C-4 of $\mathbf{N}^+$, the highest electrophilicity is found at C-4 of $\mathbf{N}^+$, in complete agreement with proposed mechanisms.[5] Note that the nucleophilic behavior of $\mathbf{N}^+$ with respect to $\mathbf{LFH_2}$, represented by low values of local electrophilicity, is also seen in this system. Local indices of $\mathbf{LFH1}^+$ indicate that protonation at N-1 increases the electrophilicity of N-5 almost fourfold with respect to **LF**, while that of C-4a is almost doubled. Protonation at N-5 dramatically increases the electrophilic power at C-4a (10 times) with respect to **LF**, while the same index for N-5 in $\mathbf{LFH5}^+$ is slightly higher than in $\mathbf{LFH1}^+$.

The global softnesses, calculated using Eq. 3, indicate that the S value of **NH** matches the global softnesses of **LF**, $\mathbf{LFH1}^+$ and $\mathbf{LFH5}^+$ to an extent of 74.8, 82.6 and 52.7%, respectively (values taken from Table 2). The S values for $\mathbf{LFH_2}$ and $\mathbf{N}^+$ match by 81.6%. Because in the hydride transfer reaction between oxidised flavins and NAD(P)H it is not clear whether the flavins are protonated or not at N-1 or N-5,[14,50] but in the reverse reaction—between reduced flavins and $NAD(P)^+$—protonation is irrelevant considering the overall mechanism, we could take the last value, 81.6% as a relative enzymatic reference for this reaction. In this context, the reaction between **NH** and $\mathbf{LFH1}^+$ should be favoured over **LF** or $\mathbf{LFH5}^+$, in accordance with Pearson's HSAB principle.[52] Global softness values calculated in this work clearly indicate that the reactivity in the lumiflavine–nicotinamide system is a consequence of a soft–soft interaction, where hydride transfer is the promoted covalent bonding characteristic of this type of interactions.[53]

Finally, a short discussion about the charge transfer pattern during the interaction between **LF** and **NH** is worth making. It has been reported that, at some stage of several catalytic mechanisms, flavins form charge transfer complexes with substrates such as NAD(P)H, or with residues of the active site of some enzymes.[1,19,54] It has also been proposed that hydride transfer can occur by three different mechanisms: (1) transfer of a hydride ion in a single step; (2) transfer of one electron followed by the transfer of a hydrogen atom or its reverse, and (3) transfer of two electrons and a proton in three steps.[21,55] An examination of charge transfer values ΔN, between molecules A and B, in Table 2, were evaluated from Pearson's equation $\Delta N=(\mu_A-\mu_B)/(\eta_A+\eta_B)$.[56] The results show that when hydride transfer occurs between $\mathbf{N}^+$ and $\mathbf{LFH_2}$, a relatively high value of ΔN (0.819 e) is obtained, thereby suggesting that the first or third mechanism might be operating, both of them involving a two-electron transfer, in agreement with the two electron acceptor nature of oxidised nicotinamide. Hydride transfer between **NH** and protonated lumiflavine also displays high ΔN values (0.769–0.950 e), likewise suggesting the presence of a two-electron transfer process. In contrast, a low value of ΔN for the hydride transfer from **NH** to **LF** (0.258 e) is observed. This result could be related to a one electron process in a first step (i.e. second mechanism), in complete agreement with theoretical transition state studies for the hydride transfer in several enzymes.[21] Previous theoretical work on transition state structure for the hydride transfer revealed that mechanisms (1) and (2) are prone to occur.[28,57] Note that if isoalloxazine is protonated mechanisms (1) and (3) are likely to occur, while if isoalloxazine is in its neutral state, then mechanism (2) could be operative. It is noteworthy that ΔN values can be related to the proposed mechanisms for this kind of reactions: small ΔN values may be related to radical mechanisms, while higher ΔN values may be related to two-electron transfer mechanisms. Moreover, it is also apparent that regardless of the direction of the catalysis or whether lumiflavine is protonated or not, there is always a charge transfer process coupled to the hydride transfer between lumiflavine and 1-methylnicotinamide.

Our results support the hypothesis of Massey and Hemmerich,[11] in terms that there are common structural features which determine the type of reaction catalysed. The regiospecific reactivity of the isoalloxazine system is such that protonation of N-1 of isoalloxazine leads to the activation of N-5 towards nucleophilic attack, while protonation of N-5 activates C-4a towards nucleophilic attack. However, Massey and Hemmerich restricted their proposal to enzymes that are able to stabilise the 'blue' or 'red' flavin radicals (electron transferases and dehydrogenases/oxidases, respectively). Our findings suggest that Massey and Hemmerich's proposal can be broadened to enzymes whose radical intermediates are very unstable or not formed at all, such as flavoproteins that catalyse transhydrogenation reactions, the first division of their flavoenzyme classification.[11] As already mentioned, among the several mechanisms proposed for transhydrogenation reactions of flavoenzymes, besides hydride transfer from different substrates, nucleophilic attack and radical intermediates have been considered.[3] In the light of our results it is possible to suggest that, when a dehydrogenation reaction

takes place through a nucleophilic attack, the hydrogen bonding of the oxidised isoalloxazine ring with the apoprotein determines the site of attack (N-5 or C-4a of isoalloxazine).

3. Conclusions

The hydride transfer reaction in the isoalloxazine–nicotinamide system can be understood as an interaction between soft species, controlled by frontier orbitals and nicely framed on the HSAB principle. The reactivity of the studied systems is well described by global descriptors derived from the conceptual part of DFT, such as the electronic chemical potential, electrophilicity and softness.

Regiospecificity of the hydride transfer reaction in the isoalloxazine–nicotinamide system seems to be modulated consistently by properties of extended molecular regions, including more than one atomic centre as proposed earlier.[33,35] We have found that reactive sites in interacting molecules are located in regions of the different molecular frameworks, with similar shapes and sizes, which display very similar group softnesses. This sort of regional shape similarities empirical rule at the active site would determine the final 3D form of the reactive species. These two factors would play important roles in both, drug and catalysts design.

The HSAB principle seems to be fundamental to understand enzymatic catalysis, not only at the global molecular level, but also when regiospecificity is considered. We have found that group softness, calculated through the Fukui functions, appears as a useful index for the identification of these active molecular regions, interacting at short distances, Nevertheless, other different condensed to atom properties, such as local electrophilicities, may also be determinants of the reactivity and might be complementary between the reacting molecules. The group softness index might be especially helpful to understand stacking interactions between macromolecules and chemical substrates, not only in enzymatic catalysis, but also in DNA intercalation and in drug–receptor interactions.

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Synthesis and study of a heterocyclic receptor designed for carboxylic acids

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Abstract—The synthesis of a tricyclic receptor having a bowl shape and three binding points for carboxylic acids has been achieved starting from readily available 1-tetralone derivatives according to two different methods. This host possesses a six-membered lactam moiety and a carboxamide at the end of a flexible arm. Association constant with benzoic acid and stoichiometry of the complex have been determined using ^{1}H NMR dilution experiments.

1. Introduction

In a previous paper,[1] we described the synthesis of a heterocyclic receptor for carboxylic acids. The design of this receptor is outlined in Figure 1. The three binding points are ensured by a five or a six-membered lactam and a remote carboxamide incorporated on the benzene ring of an heterocyclic structure having a bowl shape. In order to obtain this bowl shape, ring B must be saturated and a *cis*-fusion between rings B and C is required. In this preliminary communication, we gave only few details concerning the design and the synthetic pathway.

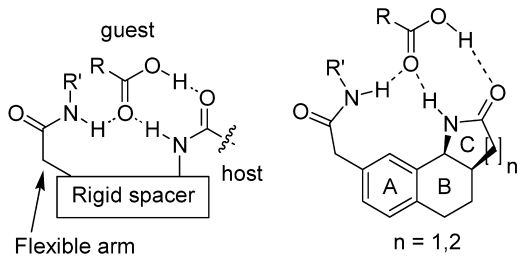

Figure 1. Cleft receptor design (left) and proposed receptor design (right).

The aim of this paper is to provide full details concerning both the design and the syntheses of this new kind of acids receptors.

2. Results and discussion

2.1. Design of the hosts

We performed first some molecular mechanic calculations (MM2 force field as implemented in PCMODEL® and CVFF force field as implemented in CERIUS[2]). We selected acetic acid as a model and tried the five and six-membered lactams **2a** and **2b** (Fig. 2).

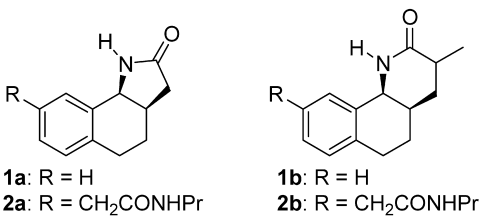

Figure 2. Selected five and six-membered lactams.

In these two cases, three hydrogen bonds can be obtained (structures depicted respectively in Figs. 3 and 4). We also performed some calculations at the PM3 level of theory on the six-membered lactam **2b**. Energy of the molecule was computed as a function of the dihedral angle θ between the benzene ring and the carboxamide group. As it can be seen in Figure 5, rotation about the flexible arm induces a maximum variation of 2 kcal mol^{-1}. As a consequence, it could be expected that the formation of a third hydrogen bond would be possible because the corresponding decreasing of the energy is larger than this variation.

In order to verify this hypothesis, it is necessary to compare the binding properties of receptors **1a**,**b** (two binding points)

Keywords: Molecular recognition; Carboxylic acids; Molecular modelling; Coupling reactions.
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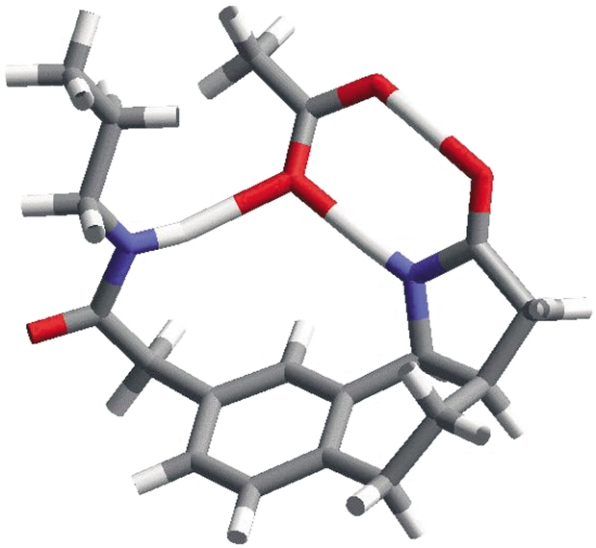


Figure 3. Molecular modelling of the five-membered lactam **2a** and its interactions with acetic acid.

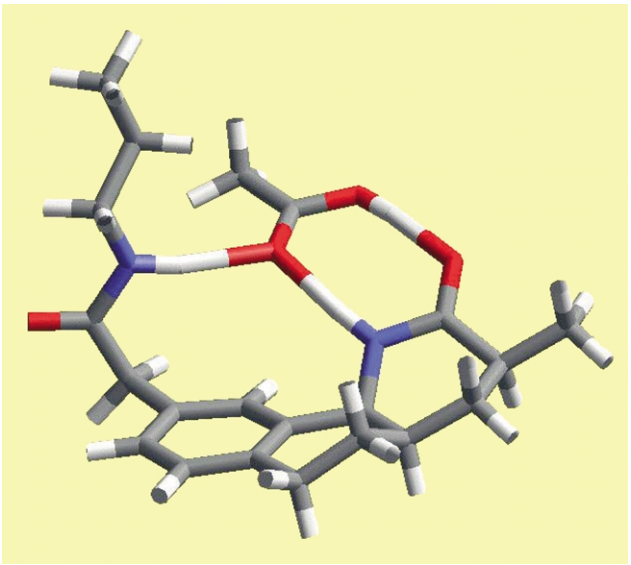


Figure 4. Molecular modelling of the six-membered lactam and its interactions with acetic acid.

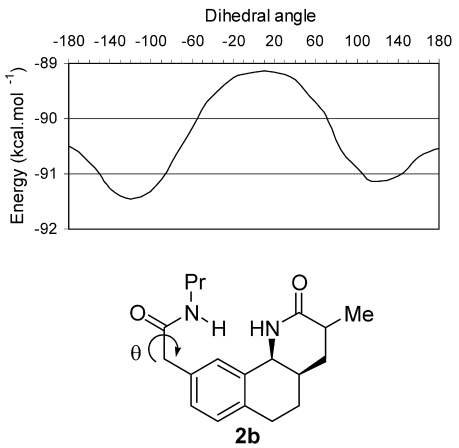


Figure 5. PM3 molecular modelling of host **2b** as a function of dihedral angle *θ*.

and receptors **2a**,**b** (three binding points). We decided first to synthesize the five-membered lactams.

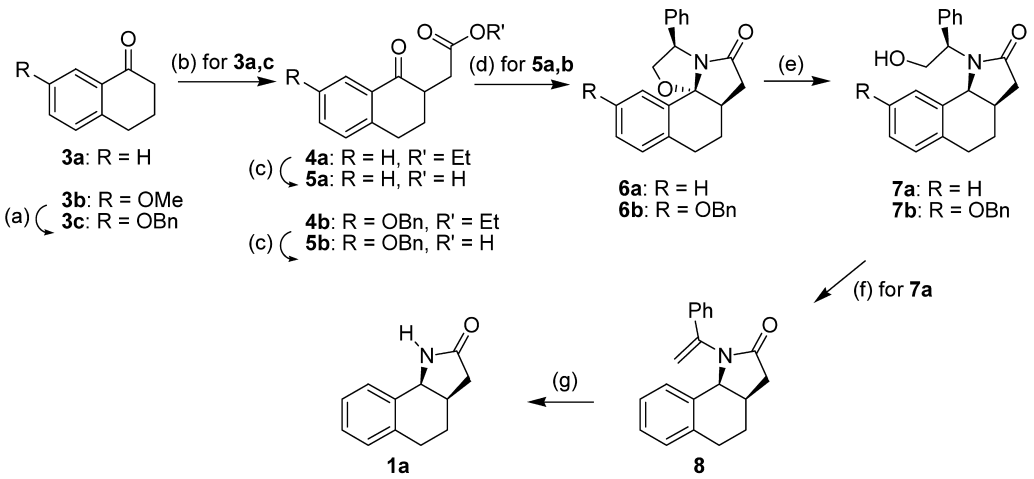
2.2. Towards the synthesis of the five-membered lactams

We selected the method used by Ennis et al.[2] in the β-tetralone series (Scheme 1). For this purpose, we needed an α-tetralone substituted at the 7-position by a group allowing further functional group interconversion leading to the carboxamide at the end of the flexible arm. The 7-benzyloxy-1-tetralone **3c** seemed to be a good choice since it could be obtained from the commercially available 7-methoxy-1-tetralone **3b**. Cleavage of the methoxy group of **3b** according to the procedure described by Chakrabotri et al.[3] and subsequent reaction with benzyl chloride under basic conditions afforded the required 7-substituted-1-tetralone **3c**. Tetralones **3a**,**c** where deprotonated with LDA and alkylated with ethyl bromoacetate in THF at −78 °C. While this work was in progress, Ennis and co-workers reported the same reaction on 1-tetralone **3a**.[4] The keto-esters **4a**,**b** thus obtained were then hydrolysed into the corresponding keto-acids **5a**,**b** and subsequent reaction with (*R*)-phenylglycinol led to the bis-lactams **6a**,**b**. As Ennis et al.[2] ring opening of bis-lactam **6a** proceeded smoothly but the same reaction on **6b** was more difficult and the yield was lower (67% for **6a** and 25% for **6b**). While dehydration of the alcohol **7a** led to the 7-unsubstituted lactam **8** in a 60% yield, only tarry material was obtained with the benzyloxy derivative. This first route being unsuccessful, we decided to focus our interest on the synthesis of the six-membered lactam.

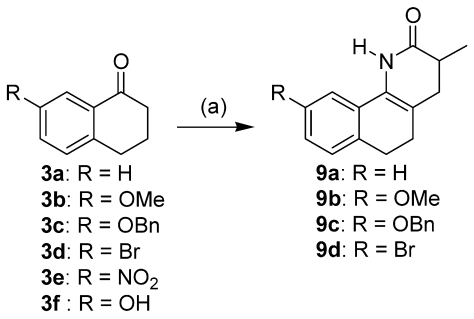
2.3. Synthesis of the six-membered lactam ring

The selected precursors were again 7-substituted-1-tetralones **3a**-**f**. They were reacted with methacrylamide under conditions published by Corriu's group[5] (Scheme 2). No reaction occurred with 7-nitro-1-tetralone **3e** and 7-hydroxy-1-tetralone **3f**, but benzo[*h*]quinolinones **9a**-**d** could be obtained in medium yields starting from tetralones **3a**-**d**. We tried to improve these yields by performing the reaction in various solvents but no significant improvement could be obtained. Having at hand the 7-substituted-1-tetralone **9d**, it was necessary to introduce the carboxamide group at the end of the flexible arm. We tried first the cuprous iodide catalysed reaction of the bromo derivative **9d** with diethyl malonate as described in our previous paper[1] (Scheme 3).

This method led to the targeted host **2b**. Careful examination of the ^{1}H NMR spectra of **2b** showed two signals corresponding to the N–H lactam and two signals for the methyl group at the 3-position. This fact could be explained by the epimerisation of the 3-position during the course of the synthesis. During the catalytic hydrogenation reaction of **13b** into **14**, the two hydrogen atoms attack the less hindered side of the molecule say *anti* to the methyl group leading to a racemic mixture of a single diastereoisomer. The ring junction is *cis* as showed by the small value of the coupling constant between the corresponding two hydrogen atoms (J=4 Hz). Moreover, a single signal is observed for the methyl group at the 3-position. However, epimerisation seems to occur during the decarboxylation



Scheme 1. Reagents, conditions and yields. (a) 1) PhSH, K_2CO_3, NMP, 30 min, 190 °C (80%). 2) K_2CO_3, Benzyl chloride, DMF, 4 h, 100 °C (90%); (b) 1) LDA, THF, 30 min, −78 °C. 2) Br–CH_2CO_2Et, 18 h, −78 °C→rt (40% for **4a**, 45% for **4b**); (c) KOH, EtOH, 2 h, reflux (85% for **5a** and **5b**); (d) (*R*)-phenylglycinol, toluene, 12 h, reflux (73% for **6a** and 72% for **6b**); (e) Et_3SiH, $TiCl_4$, CH_2Cl_2, 2 h, −78 °C (70% for **7a** and 25% for **7b**); (f) LiOH, H_2O, DMSO, 72 h, 100 °C (60%); (g) HCl, THF, H_2O, 8 h, reflux (40%).

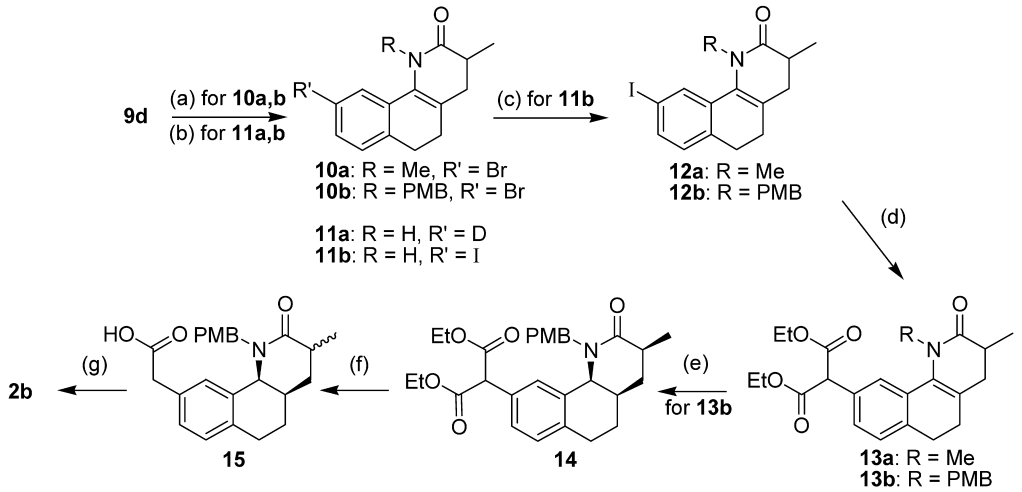


Scheme 2. Reagents, conditions and yields. (a) methacrylamide, $Si(OMe)_4$, CsF, 5 h, 80 °C (30–60%).

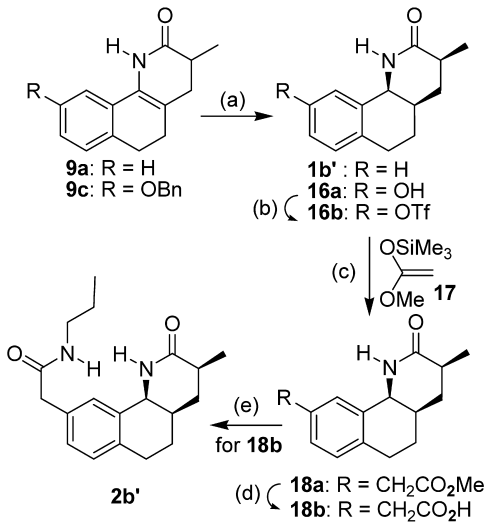
step which is carried out under basic conditions as shown by the duplication of the signal corresponding to the methyl group in the ^{1}H NMR spectrum of **15**. In order to avoid this troubleshooting decarboxylation step, we tried another synthesis involving the cross coupling reaction of the enoxysilane **17** with the triflate **16c** (Scheme 4). The required triflate **16b** was obtained within two steps starting from the benzyloxy derivative **9c**. Deprotection of the phenol and reduction of the C_{4a}–C_{10b} double bond of **9c** were achieved in the same pot via catalytic hydrogenation with 10% Pd–C and the phenol **16a** was converted into the triflate **16c** with ditriflimide under basic conditions. Cross coupling of the enoxysilane **17** with this triflate under conditions published by us[6] afforded ester **18a**. This ester was hydrolysed and the resulting intermediate carboxylic acid was converted into one of the stereoisomers **2b′** of the targeted host **2b**.

2.4. Binding properties of the hosts 1b′ and 2b′

We first performed some dilution experiments in order to study the self-association of the hosts **1b′** and **2b′**. They



Scheme 3. Reagents, conditions and yields. (a) CH_3I for **10a** and PMBCl for **10b**, KOH, DMSO, 30 min, rt (40% for **10a**, 60% for **10b**); (b) 1) *n*-BuLi, THF, 10 min, −78 °C. 2) *tert*-BuLi, 1 h, −78 °C. 3) MeOD for **11a** and I_2 for **11b**, 2 h, −78 °C (100% for **11a** by ^{1}H NMR, 70% for isolated **11b**); (c) same reagents and conditions as in a (40% for **12a** and 60% for **12b**); (d) EtOOC–CH_2–COOEt, NaH, CuI, dioxane, 5 h, reflux (40% for **13a**, 50% for **13b**); (e) H_2, Pd–C 10%, EtOH, 1 bar, 12 h, rt (45%); (f) 1) 3% NaOH, EtOH, 15 h, rt. 2) HCl, pH=2. 3) CuI, CH_3CN, 1 h, 60 °C (100% by ^{1}H NMR); (g) *n*-propylamine, EDCI, HOBt, MeCN, 72 h, rt (35%). 2) CAN, H_2O, MeCN, 5 h, rt (35%).



Scheme 4. Reagents, conditions and yields. (a) H_2, Pd–C 10%, EtOH, 1 bar, 12 h, rt (80% for **1b′** from **9a**, 85% for **16a** from **9c**); (b) Ditriflimide, DMF, NEt_3, 4 h 30, 0 °C→rt (40%); (c) $Pd(PPh_3)_4$, CH_3COOLi, THF, 21 h, reflux (40%); (d) 3% NaOH, EtOH, 15 h, rt (89%); (e) *n*-propylamine, EDCI, HOBt, MeCN, 72 h, rt (65%).

were dissolved in chloroform-*d* and on dilution, an upfield chemical shift of the lactam N–H proton could be observed. Classical Horman and Dreux[7] analysis of these shift values gave a Kd value (dimerisation constant) of about 20 M^{-1} for **2b′**. However, the method did not converge in the case of **1b′**. These two hosts were then titrated with benzoic acid. In order to specify the stoichiometry of the complexes formed, we first performed Job plots[8] (Fig. 6 for **1b′** and Fig. 8 for **2b′**). These plots clearly show the formation of 1/1 complexes (maximum value at x=0.5).

The association constants K_a were then determined assuming a 1/1 complexation process and neglecting the dimerisation process for **2b′**. K_a values of 80 and 200 M^{-1} were obtained for **1b′** and **2b′** respectively (Fig. 7 for **1b′** and Fig. 9 for **2b′**).

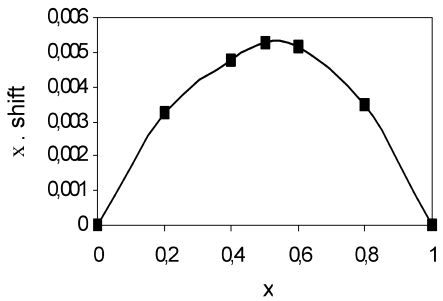


Figure 6. Job plot of host **1b′**. The sum of host and guest concentrations was constant (C_0=0.0135 mol L^{-1}, guest concentration=xC_0) and the chemical shift of the lactam proton was monitored.

3. Conclusion

Our initial goal was to design a new kind of host for carboxylic acids. We selected a tricyclic structure with a bowl shape and a carboxamide moiety at the end of a flexible arm. We first checked this design with molecular and quantum mechanics calculations. Calculations were in good agreement with this design and showed that both a five

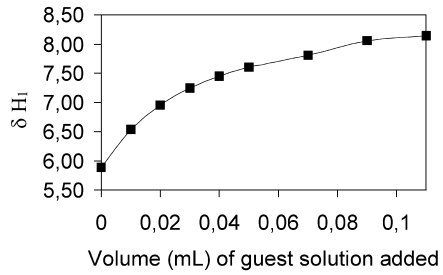


Figure 7. Titration of host **1b′** with benzoic acid. The initial guest concentration was 0.0204 mol L^{-1}. Aliquots of a guest solution (0.287 mol L^{-1}) were added and the chemical shift of the lactam proton was monitored.

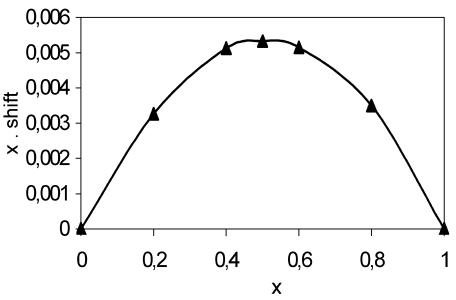


Figure 8. Job plot of host **2b′**. The sum of host and guest concentrations was constant (C_0=0.0135 mol L^{-1}, guest concentration=xC_0) and the chemical shift of the lactam proton was monitored.

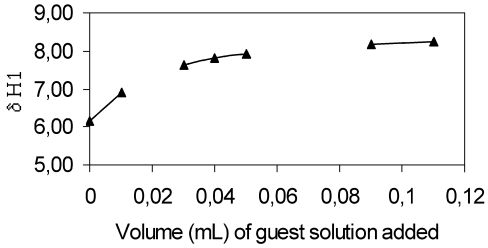


Figure 9. Titration of host **2b′** with benzoic acid. The initial guest concentration was 0.0193 mol L^{-1}. Aliquots of a guest solution (0.304 mol L^{-1}) were added and the chemical shift of the lactam proton was monitored. Owing to the complexity of spectra, some chemical shifts could not be measured.

or a six-membered lactam could be incorporated in the tricyclic part. Unfortunately the synthesis of the selected hosts was impossible in the case of a five membered lactam. However, it was possible to obtain the hosts **2b** and **2b′** with a six-membered lactam according to two different routes. A NMR study with monitoring of the lactam proton of **2b′** as a function of host and guest concentrations was then undertaken.

The lactam moiety of host **1b′** is able to bind with benzoic acid with an association constant of 80 M^{-1} in good agreement with a two binding points process. Addition of a third binding point (in **2b′**) ensures a significant increasing of the association constant and confirms that the flexible arm is really involved in the binding process.

We are now trying to incorporate an amine receptor in the flexible arm in order to obtain a receptor able to promote the

reaction between an acid and an amine via a supramolecular process.

4. Experimental

4.1. General details

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 300 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuteriodimethylsulfoxide (DMSO-d_6). Chemical shifts are given in ppm with TMS or HMDS as internal reference. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Flash chromatography was performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F254).

4.1.1. Ethyl (7-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (4b). To a cooled (−78 °C) solution of LDA (1.58 mmol, freshly prepared from diisopropylamine and *n*-butyllithium) in THF (1 mL), a solution of tetralone **3c** (400 mg, 1.58 mmol) in THF (1 mL) was slowly added. After 30 min stirring at −78 °C, a solution of ethyl bromoacetate (210 μL, 1.9 mmol) in THF (3.2 mL) was added. The resulting mixture was allowed to warm to rt and stirred for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was successively washed with water, an aqueous solution of sodium hydrogencarbonate (5%) and an aqueous solution of hydrochloric acid (5%). After drying on magnesium sulfate, the solvent was removed under reduced pressure. Flash chromatography on silica gel (cyclohexane/dichloromethane 8/2, R_f=0.3) afforded 241 mg (45%) of compound **4b** as a pale yellow oil. IR (KBr) 1682, 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, *J*=7.2 Hz), 1.92 (m, 1H), 2.18 (m, 1H), 2.34 (m, 1H), 2.99 (m, 4H), 4.11 (q, 2H, *J*=7.2 Hz), 5.02 (s, 2H), 7.09 (m, 2H), 7.22–7.39 (m, 5H), 7.51 (d, 1H, *J*=1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.7, 28.9, 29.9, 35.6, 45.1, 60.9, 70.5, 110.9, 122.8, 127.9, 128.4, 129.0, 130.4, 133.3, 137.0, 137.3, 151.9, 172.9, 198.7. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.41; H, 6.42.

4.1.2. 7-Benzyloxy-11-phenyl-2,2a,3,4,10,11-hexahydro-9-oxa-11a-aza-pentaleno[6a,1-a]naphthalen-1-one (6b). To a solution of ester **4b** (250 mg, 0.74 mmol) in ethanol (2.1 mL), potassium hydroxide (45.4 mg, 0.8 mmol) in ethanol (0.4 mL) was added and the resulting mixture was heated to reflux for 2 h. After cooling to rt, the solution was extracted with dichloromethane and the aqueous layer was acidified with diluted hydrochloric acid. Extraction with dichloromethane followed by drying on magnesium sulfate and removal of solvents under reduced pressure afforded 195 mg (85%) of crude (7-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)acetic acid **5b** as a white solid. IR (KBr) 1680, 1712, 3082 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (m, 1H), 2.18 (m, 1H), 2.34 (m, 1H), 2.99 (m, 4H), 5.02 (s, 2H), 7.09 (m, 2H), 7.22–7.39 (m, 5H), 7.51 (d, 1H, *J*=1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.9, 29.9, 35.5, 44.9, 70.5, 110.9, 123.0, 127.9, 128.5, 129.0, 130.5, 133.1, 137.0, 137.3, 157.9, 178.4, 198.8. A solution of the above ketoacid **5b** (200 mg, 0.64 mmol) and (*R*)-phenylglycinol (172 mg, 1.28 mmol) in toluene (3.2 mL) was heated to reflux for 12 h in a flask fitted with a Dean Stark trap. After cooling to rt, the toluene was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.4) to afford 190 mg (72%) of compound **6b** as a brown oil. IR (KBr) 1497, 1714 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (m, 1H), 2.25 (m, 1H), 2.41 (m, 1H), 2.70 (m, 3H), 2.70 (m, 1H), 3.89 (d, 1H, *J*=16.1 Hz), 4.10 (d, 1H, *J*=16.1 Hz), 4.08 (dd, 1H, *J*=8.7, 8.7 Hz), 4.59 (dd, 1H, *J*=8.7, 8.7 Hz), 5.25 (t, 1H, *J*=8.7 Hz), 6.42 (d, 1H, *J*=1.5 Hz), 6.75 (dd, 1H, *J*=6.5, 1.5 Hz), 6.98–7.36 (m, 11H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.5, 28.9, 41.2, 44.1, 58.8, 69.4, 71.5, 111.7, 117.4, 127.0, 127.8, 128.0, 128.2, 128.8, 129.3, 139.9, 179.6. Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 78.95; H, 6.2; N, 3.45.

4.1.3. 8-Benzyloxy-1-(3-hydroxy-1-phenylpropyl)-1,3,3a,4,5,9b-hexahydro-benz[*g*]indol-2-one (7b). To a cooled (−78 °C) solution of bis-lactam **6b** (194 mg, 0.47 mmol) in dichloromethane (2 mL), triethylsilane (335 μL, 2.07 mmol) was added. The mixture was stirred at −78 °C for 15 min and titanium tetrachloride (228 μL, 2.07 mmol) was slowly added. The solution was stirred −78 °C for 2 h, allowed to warm to rt and hydrolized with a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layer was washed with water, dried on magnesium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2/8, R_f=0.4) to afford 50 mg (25%) of compound **7b** as an amorphous solid. IR (KBr) 1659, 3266 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 2H), 2.30 (dd, 1H, *J*=18.0, 3.6 Hz), 2.49–2.82 (m, 3H), 2.85 (dd, 1H, *J*=18.0, 8.9 Hz), 3.75 (m, 2H), 4.10 (m, 1H), 4.52 (m, 1H), 4.31 (d, 1H, *J*=9.1 Hz), 5.05 (m, 2H), 6.40 (m, 1H), 6.61 (m, 1H), 6.92 (m, 2H), 7.11–7.25 (m, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.6, 29.9, 31.3, 60.9, 62.0, 62.5, 64.9, 116.0, 117.3, 127.3, 127.8, 128.1, 128.2, 129.1, 129.3, 130.1, 132.1, 133.4, 137.3, 154.9, 177.0. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.61; H, 6.44; N, 3.31.

4.2. General procedure for the Corriu's reaction of 1-tetralones with methacrylamide

Cesium fluoride must be dried on phosphoric anhydride, under vacuum at 100 °C. Under a stream of nitrogen, cesium fluoride, 7-substituted-1-tetralone, methacrylamide and tetramethoxysilane were introduced into a flask. The resulting mixture was heated at 80 °C for 5 h. The mixture was then cooled to rt, triturated with ethyl acetate and filtered on a celite pad. The solution was washed with water, dried on magnesium sulfate and the solvent was removed under reduced pressure. The final product was recrystallized or chromatographed on silica gel.

4.2.1. 3-Methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9a). According to the general procedure, 1-tetralone **3a** (3.2 g, 22 mmol), cesium fluoride (5.35 g, 35 mmol),

methacrylamide (1.9 g, 22 mmol) and tetramethoxysilane (5.15 mL, 35 mmol) afforded 1.8 g (40%) of **9a** after recrystallization from ethyl acetate. Mp 174 °C (lit.[5] 173 °C). IR (KBr) 1660, 3245 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, 3H, J=7.2 Hz), 2.15–2.61 (m, 5H), 2.69–2.77 (m, 2H), 7.02 (m, 4H), 7.39 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 27.0, 28.6, 34.6, 35.4, 114.4, 119.2, 127.1, 127.7, 128.4, 129.7, 136.1, 174.8. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.8; H, 7.1; N, 6.6.

4.2.2. 9-Methoxy-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9b). According to the general procedure, 7-methoxy-1-tetralone **3b** (0.39 g, 2.2 mmol), cesium fluoride (2.68 g, 17.5 mmol), methacrylamide (0.95 g, 2.2 mmol) and tetramethoxysilane (2.58 mL, 17.5 mmol) afforded 0.146 g (60%) of **9b** after recrystallization from ethyl acetate. Mp 114 °C. IR (KBr) 1672, 3220 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, 3H, J=7.5 Hz), 2.10–2.60 (m, 7H), 3.60 (s, 3H), 6.60 (d, 1H, J=1.5 Hz), 6.75 (dd, 1H, J=7.0, 1.5 Hz), 6.95 (d, 1H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.15, 29.62, 29.96, 36.96, 37.70, 58.18, 107.88, 114.98, 116.51, 129.10, 130.21, 131.47, 132.57, 160.95, 176.01. HRMS. Calcd for $C_{15}H_{17}NO_2$: 243.1259. Found: 243.1250.

4.2.3. 9-Benzyloxy-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9c). According to the general procedure, 7-benzyloxy-1-tetralone **3c** (0.555 g, 2.2 mmol), cesium fluoride (2.68 g, 17.5 mmol), methacrylamide (0.95 g, 2.2 mmol) and tetramethoxysilane (2.58 mL, 17.5 mmol) afforded 0.282 g (40%) of **9c** after flash chromatography on silica gel (cyclohexane/dichloromethane 3/7, R_f=0.4). Mp 159 °C (ethyl acetate). IR (KBr) 1660, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, 3H, J=7.4 Hz), 2.10–2.70 (m, 7H), 5.00 (s, 2H), 6.70 (m, 2H), 6.95 (d, 1H, J=8.1 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 27.3, 27.7, 34.6, 35.4, 70.6, 106.7, 113.5, 115.3, 127.8, 128.4, 128.9, 129.1, 130.8, 137.1, 137.3, 158.2, 174.8. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.05; H, 6.7; N, 4.3.

4.2.4. 9-Bromo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo-[*h*]quinolin-2-one (9d). According to the general procedure, 7-bromo-1-tetralone **3d** (5 g, 22 mmol), cesium fluoride (5.35 g, 35 mmol), methacrylamide (1.9 g, 22 mmol) and tetramethoxysilane (5.15 mL, 35 mmol) afforded 1.9 g (30%) of **9d** after recrystallization from ethyl acetate. Mp 212 °C. IR (KBr) 1670, 3230 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, 3H, J=7.4 Hz), 2.27–2.80 (m, 7H), 7.00 (d, 1H, J=8.1 Hz), 7.29 (d, 1H, J=8.1 Hz), 7.46 (s, 1H), 8.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 26.3, 27.4, 34.0, 34.7, 115.4, 120.2, 122.5, 127.5, 129.2, 129.7, 131.2, 134.3, 174.5. Anal. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.4; H, 4.9; N, 4.6.

4.3. General procedure for the halogen–lithium exchange reaction on 9-bromo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (9d)

In a flask flushed with nitrogen, the bromo derivative (0.292 g, 1 mmol) was dissolved in THF (6 mL) and the solution was cooled at −78 °C. Then, *n*-butyllithium (0.96 mL, 2.2 mmol) was added and the solution was stirred for 10 min at −78 °C. *tert*-Butyllithium (1 M solution, 3.4 mL, 3.4 mmol) was then added and the appropriate electrophile was added after 1 h stirring at −78 °C.

4.3.1. 9-Deutero-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (11a). The electrophile was methanol-*d* (1 mL, 2.4 mmol). After 2 h stirring at −78 °C, hydrolysis was carried out with a saturated aqueous solution of NH_4Cl. The solution was allowed to warm at rt and extracted with dichloromethane. The combined extracts were dried on magnesium sulfate and concentrated under reduced pressure to afford 0.214 mg of crude product **11a** which was not further purified. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (d, 3H, J=6.5 Hz), 2.4–2.8 (m, 7H), 7.30 (s, 3H), 7.90 (s, 1H).

4.3.2. 9-Iodo-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]-quinolin-2-one (11b). The electrophile was a solution of iodine (0.86 g, 3.4 mmol) in THF (8.6 mL). After 2 h stirring at −78 °C, hydrolysis was carried out with a saturated aqueous solution of sodium thiosulfate until disappearance of the red colour. The solution was allowed to warm at rt and extracted with dichloromethane. The combined extracts were dried on magnesium sulfate and concentrated under reduced pressure to afford 0.237 mg (70%) of **11b** after recrystallization from ethyl acetate. Mp 225 °C. IR (KBr) 1670, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (d, 3H, J=6.5 Hz), 2.35–2.80 (m, 7H), 6.92 (d, 1H, J=6.5 Hz), 7.47 (d, 1H, J=6.5 Hz), 7.52 (s, 1H), 7.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9, 26.8, 28.1, 34.6, 35.3, 91.9, 115.9, 127.7, 128.6, 130.0, 131.9, 135.5, 136.4, 174.8. Anal. Calcd for $C_{14}H_{14}INO$: C, 49.58; H, 4.16; N, 4.13. Found: C, 49.6; H, 4.2; N, 4.2.

4.4. General procedure for the protection of the N–H lactam

Potassium hydroxide (0.224 g, 4 mmol, previously dried under vacuum) was dissolved in freshly distilled DMSO (3 mL). The lactam and the alkylation reagent were then added. The mixture was stirred at rt for 30 min. Water was then added and the resulting solution was extracted with dichloromethane. The extracts were washed with water, dried and concentrated under reduced pressure.

4.4.1. 9-Bromo-1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (10a). According to the general procedure, compound **9d** (0.292 g, 1 mmol) and methyl iodide (0.25 mL, 4 mmol) afforded 0.123 g (40%) of N-protected compound **10a** as a yellow solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 7/3, R_f=0.3). Mp (ethyl acetate) 124 °C. IR (KBr) 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, 3H, J=7.4 Hz), 2.27–2.80 (m, 7H), 3.12 (s, 3H), 7.0 (d, 1H, J=8.1 Hz), 7.29 (d, 1H, J=8.1 Hz), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 26.3, 27.4, 34.0, 34.7, 36.1, 115.4, 120.2, 122.5, 127.5, 129.2, 129.7, 131.2, 134.3, 174.5. Anal. Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.9; H, 5.45; N, 4.6.

4.4.2. 9-Iodo-1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (12a). According to the general

procedure, compound **11b** (0.339 g, 1 mmol) and methyl iodide (0.25 mL, 4 mmol) afforded 0.142 g (40%) of N-protected compound **12a** as a pale yellow solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 7/3, R_f=0.3). Mp (ethyl acetate) 136 °C. IR (KBr) 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.2 Hz), 2.10–2.60 (m, 7H), 3.12 (s, 3H), 6.80 (d, 1H, J=7.0 Hz), 7.28 (d, 1H, J=1.5 Hz), 7.41 (dd, 1H, J=7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.4, 28.2, 28.3, 33.4, 34.5, 35.9, 91.5, 125.3, 129.8, 131.7, 132.9, 134.4, 135.7, 136.3, 175.7. Anal. Calcd for $C_{15}H_{16}INO$: C, 51.01; H, 4.57; N, 3.97. Found: C, 51.1; H, 4.7; N, 4.0.

4.4.3. 9-Iodo-1-(4-methoxybenzyl)-3-methyl-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one (12b). According to the general procedure, compound **11b** (0.339 g, 1 mmol) and 4-methoxybenzyl chloride (0.205 mL, 1.5 mmol) afforded 0.176 g (60%) of N-protected compound **12b** as a brown solid after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15, R_f=0.3). Mp (ethyl acetate) 102 °C. IR (KBr) 1667 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.1 Hz), 2.01–2.48 (m, 7H), 3.68 (s, 3H), 4.52 (d, 1H, J=11.8 Hz), 5.13 (d, 1H, J=11.8 Hz), 6.61 (m, 2H), 6.83 (m, 3H), 7.29 (d, 1H, J=1.5 Hz), 7.41 (dd, 1H, J=8.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3, 28.1, 28.3, 33.3, 36.4, 47.4, 55.6, 91.4, 113.9, 127.9, 129.7, 129.8, 130.5, 131.7, 133.0, 133.3, 135.7, 136.4, 159.0, 175.8. Anal. Calcd for $C_{22}H_{22}INO_2$: C, 57.53; H, 4.83; N, 3.05. Found: C, 57.40; H, 4.78. N, 2.99.

4.5. General procedure for the copper catalysed coupling reactions with diethyl malonate

To a suspension of sodium hydride (55% dispersion in mineral oil) in dry dioxane freshly distilled diethyl malonate was added under nitrogen. Cuprous iodide and the iodo derivative were then added and the mixture was heated to reflux for 5 h. After hydrolysis with a small amount of ice-water, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. After filtration, the organic extract was washed with a saturated aqueous solution of sodium thiosulfate. After drying on magnesium sulfate, the solvent was removed under reduced pressure.

4.5.1. 2-(1,3-Dimethyl-2-oxo-1,2,3,4,5,6-hexahydro-benzo[*h*]quinolin-9-yl)-malonic acid diethyl ester (13a). According to the general procedure, reaction of sodium hydride (0.088 g, 2 mmol) in dioxane (1.2 mL) with diethyl malonate (0.34 mL, 2 mmol), cuprous iodide (0.38 g, 2 mmol) and lactam **12a** (0.353 g, 1 mmol) afforded 0.154 g (40%) of **13a** as a brown oil after flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.3). IR (KBr) 1674, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (m, 9H), 2.15–2.61 (m, 7H), 3.06 (s, 3H), 4.13 (m, 4H), 4.53 (s, 1H), 6.85 (d, 1H, J=6.5 Hz), 7.30 (s, 1H), 7.40 (d, 1H, J=6.5 Hz). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.45; H, 6.99; N, 3.70.

4.5.2. 2-[1-(4-Methoxybenzyl)-3-methyl-2-oxo-1,2,3,4,5,6-hexahydrobenzo[*h*]quinolin-9-yl]malonic acid diethyl ester (13b). According to the general procedure, reaction of sodium hydride (0.088 g, 2 mmol) in dioxane (1.2 mL) with diethyl malonate (0.34 mL, 2 mmol), cuprous iodide (0.38 g, 2 mmol) and lactam **12b** (0.46 g, 1 mmol) afforded 0.246 g (50%) of **13b** as a pale brown oil after flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2, R_f=0.3). IR (KBr) 1674, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.0 Hz), 1.24 (m, 6H), 2.02–2.55 (m, 7H), 3.65 (s, 3H), 4.15 (m, 4H), 4.46 (s, 1H), 4.57 (d, 1H, J=16.0 Hz), 5.20 (d, 1H, J=16.0 Hz), 6.63 (d, 2H, J=11.0 Hz), 6.83 (d, 2H, J=11.0 Hz), 7.18 (m, 3H). Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.95; H, 6.8; N, 2.9.

4.6. General procedure for the catalytic hydrogenation reaction of benzo[*h*]quinolin-2-ones

The compound to reduce was dissolved in ethanol in a pressure vessel and palladium on carbon (10%) was added under nitrogen. The vessel was flushed with hydrogen and the mixture was stirred for 12 h at 1 bar. The mixture was filtered on a celite pad and the solvent was removed under reduced pressure.

4.6.1. 2-[1-(4-Methoxybenzyl)-3-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-benzo[*h*] quinolin-9-yl]-malonic acid diethyl ester (14). According to the general procedure, compound **13b** (0.49 g, 1 mmol) in ethanol (50 mL) containing 10% Pd–C (0.245 g) afforded 0.22 g (45%) of crude **14** as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (m, 9H), 1.26 (m, 1H), 1.65 (m, 1H), 1.85 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.6–2.8 (m, 2H), 3.65 (s, 3H), 4.11 (m, 4H), 4.21 (m, 1H), 4.45 (s, 1H), 5.65 (m, 2H), 6.68 (m, 2H), 7.05 (m, 5H).

4.6.2. 3-Methyl-3,4,4a,5,6,10b-hexahydro-1*H*-benzo[*h*]-quinolin-2-one (1b′). According to the general procedure, compound **9a** (0.64 g, 3 mmol) in ethanol (65 mL) containing 10% Pd–C (0.48 g) afforded 0.52 g (80%) of **1b′** as a yellow solid after recrystallization from ethyl acetate. Mp 122 °C. IR (KBr) 1670, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (d, 3H, J=5.0 Hz), 1.26 (m, 1H), 1.65 (m, 1H), 1.85 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.6–2.8 (m, 2H), 4.45 (dd, 1H, J=5.2, 3.2 Hz), 6.45 (m, 1H), 7.05–7.23 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.7, 27.1, 27.6, 32.9, 33.6, 35.6, 53.0, 126.9, 127.8, 128.3, 129.2, 136.3, 136.9, 176.2. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.0; H, 8.0; N, 6.55.

4.6.3. 9-Hydroxy-3methyl-3,4,4a,5,6,10b-hexahydro-1*H*-benzo[*h*]quinolin-2-one (16a). According to the general procedure, compound **9c** (0.16 g, 0.5 mmol) in ethanol (10 mL) containing 10% Pd–C (0.08 g) afforded 0.098 g (85%) of crude **16a** as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.02 (d, 3H, J=7.2 Hz), 1.18 (m, 1H), 1.61 (m, 1H), 1.84 (m, 1H), 1.96 (m, 1H), 2.29 (m, 1H), 2.52 (m, 1H), 2.65 (m, 2H), 4.35 (d, 1H, J=3.2 Hz), 6.51–6.68 (m, 2H), 6.82 (d, 1H, J=8.7 Hz).

4.6.4. Trifluoromethanesulfonic acid 3-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-benzo[*h*]quinolin-9-yl ester (16b). To a cooled solution (0 °C) of the crude phenol **16a** (0.76 g, 3.28 mmol) in freshly distilled DMF (22 mL)

containing triethylamine (1.15 mL, 8.2 mmol), ditriflimide (2.6 g, 7.22 mmol) was added. The mixture was stirred at 0 °C for 30 min and then at rt for 4 h. The solvent was removed under reduced pressure (1 mm Hg) and the residue was dissolved in diethyl ether. The solution was washed with water and the organic layer was dried on magnesium sulfate. The solvent was removed and the excess of ditriflimide was removed by recrystallization in cyclohexane. The ditriflimide was carefully washed with cyclohexane and the resulting organic layer was washed with water and dried on magnesium sulfate. After removing of the solvent, the residue was recystallized in cyclohexane to afford 0.48 g (40%) of triflate **16b** as a white solid. Mp 171 °C. IR (KBr) 1418, 1443, 1668, 3074, 3226 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (d, 3H, J=7.4 Hz), 1.22 (m, 1H), 1.69 (m, 1H), 1.89 (m, 1H), 1.91 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 2.61–2.88 (m, 2H), 4.47 (d, 1H, J=3.2 Hz), 6.61 (s, 1H), 7.19 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.8, 26.7, 26.8, 32.4, 33.1, 35.9, 53.0, 120.7, 120.9, 130.9, 133.6, 137.3, 139.2, 148.5, 176.1. ^{19}F ($CDCl_3$, 282.4 MHz) δ 73.3. Anal. Calcd for $C_{15}H_{16}F_3NO_4S$: C, 49.58; H, 4.44; N, 3.85. Found: C, 49.65; H, 4.51; N, 3.78.

4.6.5. (3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl)-acetic acid methyl ester (18a). Enoxysilane **17**[6] (0.366 g, 2.5 mmol corresponding to the *O*-silylated product) was added to a solution of triflate **16c** (0.363 g, 1 mmol), lithium acetate (0.2 g, 3 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.15 mmol) in THF (20 mL) under a nitrogen atmosphere. The mixture was heated to reflux for 16 h. After cooling at rt, an other amount of catalyst was added (0.023 g, 0.02 mmol) and the mixture was heated to reflux for 5 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate, R_f=0.3). After removal of the eluent, the residue was dissolved in dichloromethane, washed with water, dried on magnesium sulfate. Removal of the solvent followed by recrystallization in ethyl acetate afforded 0.115 g (40%) of compound **18a** as a white solid. Mp 114 °C. IR (KBr) 1652, 1742, 3190 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, 3H, J=5.0 Hz), 1.22 (m, 1H), 1.63 (m, 1H), 1.82 (m, 1H), 1.99 (m, 1H), 2.30 (m, 1H), 2.43 (m, 1H), 2.59–2.81 (m, 2H), 3.53 (s, 2H), 3.62 (s, 3H), 4.42 (m, 1H), 6.04 (m, 1H), 7.00–7.11 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.6, 27.1, 27.4, 32.9, 33.7, 35.5, 41.1, 52.5, 52.9, 128.9, 129.2, 129.6, 132.7, 135.9, 136.3, 172.4, 176.0. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.1; H, 7.4; N, 4.7.

4.6.6. 3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl acetic acid (18b). To a solution of ester **18a** (93 mg, 0.32 mmol) in ethanol (1 mL), sodium hydroxide (38.8 mg, 0.97 mmol) in ethanol (0.25 mL) was added and the resulting mixture was stirred at rt for 15 h. The solution was acidified to pH=2 with diluted hydrochloric acid and ethanol was evaporated. The solution was filtered and the solid was collected to afford 79 mg (89%) of crude **18b** as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (d, 3H, J=6.8 Hz), 1.18 (m, 1H), 1.37 (m, 1H), 1.65–1.73 (m, 2H), 1.91 (m, 1H), 2.30–2.43 (m, 2H), 2.53–2.72 (m, 2H), 3.52 (d, 1H, J=16.0 Hz), 3.63 (d, 1H, J=16.0 Hz), 4.47 (m, 1H), 6.97 (s, 2H), 7.36 (s, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.9, 25.7, 27.1, 31.5, 32.2, 36.0, 41.4, 53.4, 128.9, 129.0, 129.2, 133.1, 134.5, 136.7, 176.9, 178.3.

4.6.7. 2-(3-Methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinolin-9-yl)-*N*-propyl-acetamide (2b′). A solution of acid **18b** (0.039 g, 0.14 mmol), *n*-propylamine (0.012 mL, 0.14 mmol), HOBT (0.019 g, 0.14 mmol) and EDCI (0.027 g, 0.14 mmol) in acetonitrile (5 mL) was stirred at rt for 72 h. The mixture was diluted with ethyl acetate, washed with a 2M aqueous solution of HCl and then with a 2M aqueous solution of NaOH. After drying on magnesium sulfate, the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (ethyl acetate/methanol 9/1, R_f=0.5) to afford 0.029 g (65%) of compound **2b′** as a pale yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, J=7.3 Hz), 1.09 (d, 3H, J=7.2 Hz), 1.18–1.28 (m, 1H), 1.37 (qt, 2H, J=7.3, 6.9 Hz), 1.60–171 (m, 1H), 1.76–1.95 (m, 2H), 2.10 (s, 1H), 2.25–2.46 (m, 1H), 2.56–2.79 (m, 2H), 3,07 (t, 2H, J=6.9 Hz), 3.42 (s, 2H), 4.44 (m, 1H), 5.71 (m, 1H), 6.80 (m, 1H), 7.03 (m, 2H), 7.17 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.7, 16.8, 23.1, 27.0, 27.1, 32.7, 33.2, 35.7, 41.7, 43.9, 53.0, 128.7, 129.3, 129.8, 133.9, 135.6, 136.9, 171.3, 176.2. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.7, H, 8.45; N, 8.95.

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[2.2.1]-Bicyclic systems relevant to synthetic studies on CP-225,917—use of a new silylated cyclopentadiene

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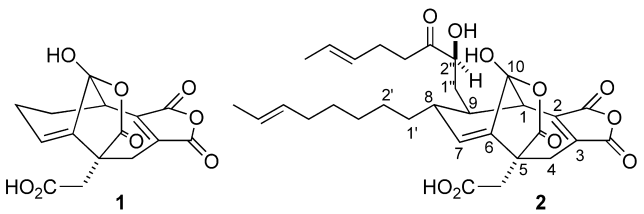
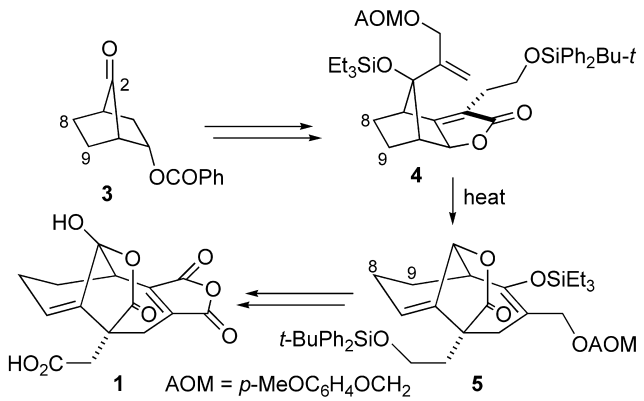
Abstract—The [2.2.1]-bicyclic ketone **6**, a potential synthetic precursor to CP-225,917, was prepared by a sequence beginning with Diels–Alder reaction between dimethyl fumarate and the silylated cyclopentadiene **38**. The adduct **40** was subjected to Tamao–Fleming oxidation, which converted it into alcohol **21**. During the oxidation $BF_3{\cdot}Et_2O$–AcOH was used instead of the more expensive $BF_3{\cdot}2AcOH$ complex. Alcohol **21** was elaborated into **6**, which carries one of the sidechains of CP-225,917, as well as other substituents that are appropriate for further elaboration.

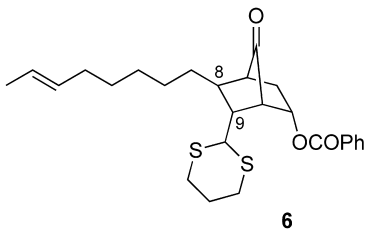
1. Introduction and discussion

Publications[1,2] from this laboratory have described two routes leading to the crystalline compound **1**, which represents the core structure of CP-225,917 (**2**), a fungal metabolite[3,4] that has attracted considerable attention from synthetic chemists[5] because of the challenge it poses, and the fact that it has potentially important biochemical properties related to the design of drugs for treatment of cancer and hypercholersterolemia.[3] One of our routes[1] involves the strain-assisted oxy-Cope rearrangement **4**→**5**, as summarized in Scheme 1. In order to explore further the use of this approach to CP-225,917 we needed to prepare a [2.2.1]-bicyclic system analogous to **3**, but with suitable substituents at C(8) and C(9).[4] In this paper we deal with the construction of **6**, a [2.2.1]-bicycle with the required substituent at C(8), a truncated substituent at C(9), and functional groups that should allow further elaboration along lines we have studied[1] with model compounds.





Scheme 1.



2. First route

Our initial approaches to **6** were based on two Diels–Alder sequences: (i) the known[6] cycloaddition of **7** and **8** to generate **9**, followed by conversion into **11** (Scheme 2), and (ii) the sequence[6,7] of Scheme 3. Esters **11**[6] and **14**[8] were then elaborated into several compounds of type **15**. However, attempts to displace the TsO group using I^- or

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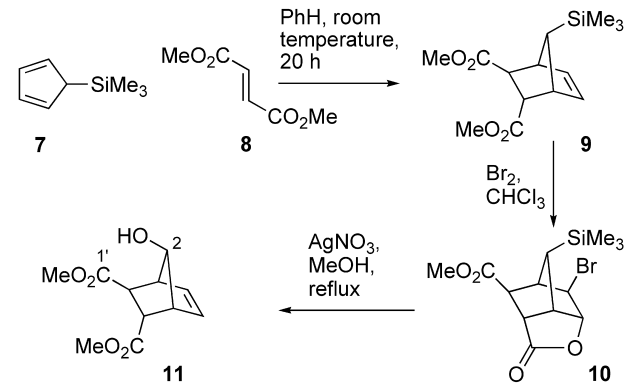
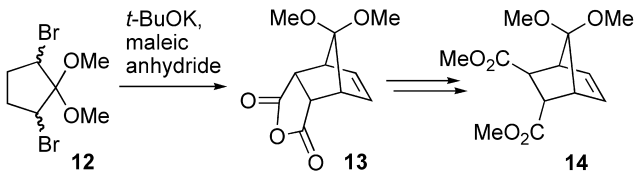


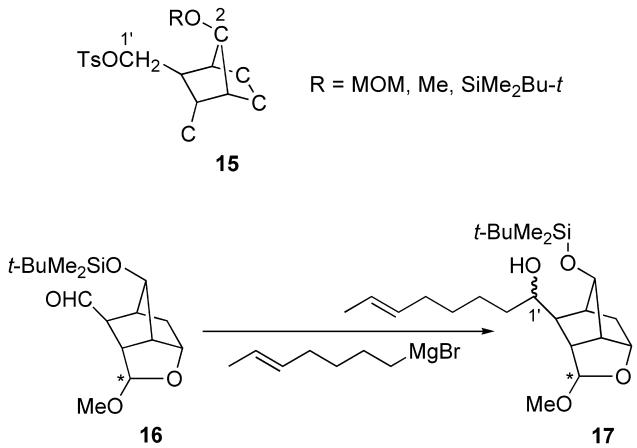
Scheme 2.



Scheme 3.

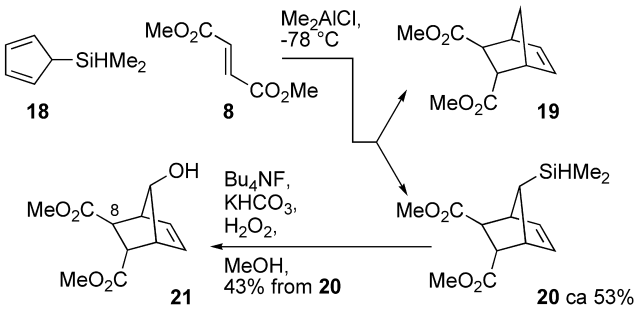
Bu_2CuLi—the latter serving as a simple model cuprate[9]—were unsuccessful or gave poor yields.

In one series of experiments, aldehyde **16** (stereochemistry at starred atom not established) was treated with the Grignard reagent derived from (*E*)-7-bromo-2-heptene[10,14] to generate the expected alcohols **17** (Scheme 4). The yield in this process was high (96%) when Rieke magnesium was used to generate the reagent. Unfortunately, deoxygenation of the resulting alcohols proved troublesome. Tosylation was unsuccessful, and sequential treatment with MsCl and $LiAlH_4$ gave a complex mixture, as did attempts to convert the alcohols into the corresponding bromides. The derived methyl xanthate and *p*-fluorophenylthionocarbonate could be formed (ca. 90% yield), but deoxygenation with Bu_3SnH caused some (ca. 30% in the case of the thionocarbonate) *E*→*Z* isomerization of the sidechain double bond.



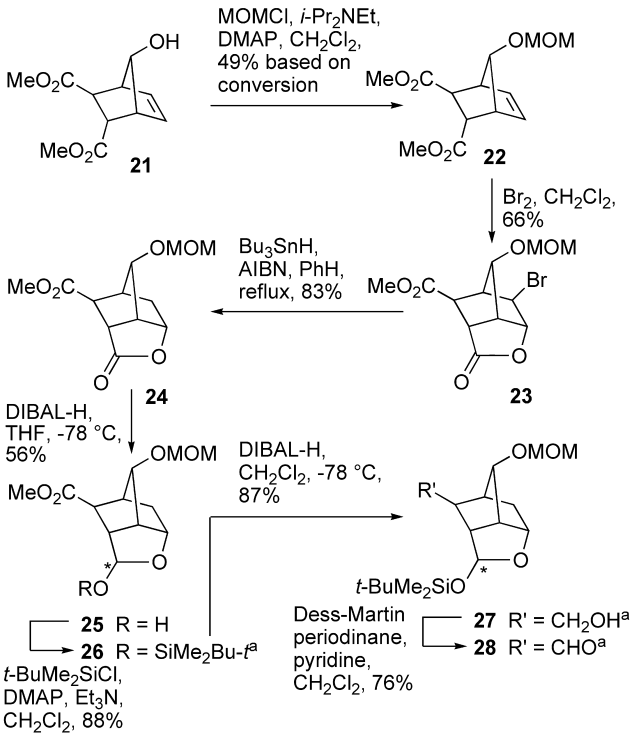
Scheme 4.

By this stage, our observations had made it clear that steric factors were responsible for the problems met in the reactions at C(1′) of the [2.2.1]-bicyclic substrates (see **15** for numbering). We assumed these problems would not arise if the C(2) oxygen function were *anti* to C(1′) and, in the event, this was indeed the case. Attempts to invert the C(2) stereochemistry (see **15** for numbering) of several of our [2.2.1]-bicycles were unsuccessful, and so we decided to modify the synthesis in such a way that the desired *anti* stereochemistry would be an intrinsic outcome of the route. In this regard, we were guided by the method we had used to make **11**. The structure of the precursor **9** suggested that an appropriate choice of silyl group would allow use of the Tamao–Fleming oxidation[15] to replace the silyl group by an hydroxyl with retention of stereochemistry. For this purpose, the silicon atom must carry certain substituents,[15] and the corresponding silylated cyclopentadiene (cf. **7**) should be available. A suitable cyclopentadiene[16] (**18**) had indeed been subjected to sequential Diels–Alder reaction and Tamao–Fleming oxidation,[17] and so we examined the Diels–Alder reaction between **18**[16] and dimethyl fumarate (Scheme 5). A stoichiometric amount of Me_2AlCl was required at −78 °C and, under these conditions, the desired product (**20**) was obtained in ca. 53% yield, as well as the corresponding desilylated material (**19**). We assume that the latter is formed by desilylation of **18** before it undergoes the cycloaddition. Tamao–Fleming oxidation then afforded the desired alcohol **21** in 43% yield from **20**. X-ray analysis[18] of the 3,5-dinitrobenzoate derivative of **21** confirmed the indicated stereochemistry. Although the Diels–Alder-oxidation sequence in its present form was not satisfactory (23% overall from **18**), we used our supply of **21** to develop a method for introducing the C(8) sidechain, as described below. Later, however, we found a better silylated diene, and we also modified our approach for elaborating the C(8) sidechain.

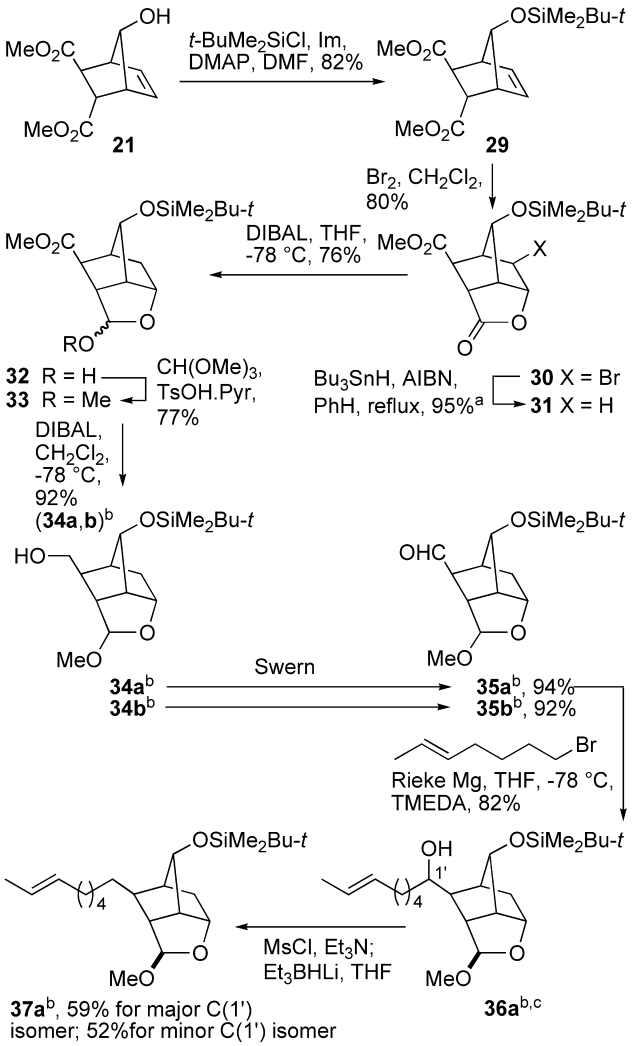


Scheme 5.

Alcohol **21** was protected as its MOM ether and subjected to bromolactonization (Scheme 6, **21**→**22**→**23**). Debromination with Bu_3SnH (**23**→**24**), and selective reduction of the lactone carbonyl to the corresponding lactols (**24**→**25**), followed by treatment with *t*-$BuMe_2SiCl$, took the route as far as the lactol ether **26** [a single isomer of unestablished stereochemistry at the starred carbon (Scheme 6)]. The remaining ester carbonyl was converted by reduction and oxidation into an aldehyde (**26**→**27**→**28**). Reaction of **28** with (*E*)-5-heptenylmagnesium bromide (generated using Rieke magnesium[19]) gave a complex mixture, and we suspected that the silyl-protected lactol unit was unstable in the presence of the Grignard reagent. Accordingly, we modified our selection of protecting groups, as summarized in Scheme 7, choosing a lactol methyl ether because our earlier experiments (see Scheme 4, **16**→**17**) had shown that



Scheme 6. [a]Single stereoisomer at starred atom.



Scheme 7. [a]76% by catalytic method. [b]The '**a**' series refers to *exo* OMe, '**b**' series refers to *endo* OMe. [c]Single isomer at C(1′) if no TMEDA is used.

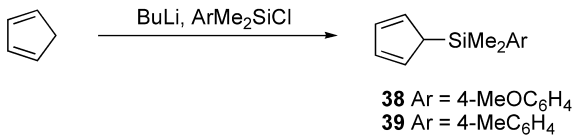
this mode of protection was compatible with the Grignard reagent.

Following standard procedures, alcohol **21** was silylated (**21→29**), subjected to bromolactonization (**29→30**), and then to tin hydride reduction (**30→31**). The dehalogenation was done with a stoichiometric amount of stannane, but could also be accomplished with a catalytic amount of Bu_3SnCl and a stoichiometric amount of $NaCNBH_3$ in refluxing *t*-BuOH. The catalytic procedure allowed us to generate lactone **31** in 76% yield from **30**; in the stoichiometric reaction the yield was 95%. The lactone carbonyl was then reduced selectively (76%) with DIBAL-H at −78 °C, and treatment of the resulting lactols **32** with $HC(OMe)_3$ in the presence of TsOH·pyridine gave the desired lactol methyl ethers **33** (77%) as a mixture of two isomers. The ester group was then reduced with DIBAL-H at −78 °C to room temperature; the two isomeric products (**34a** and **34b**) were separable and could be isolated in 79 and 14% yield (from a small scale experiment), respectively. X-ray analysis[18] of the minor isomer (**34b**) showed that the methoxy group was *endo*, a conclusion also reached by NOE measurements on **34a** and **34b**. Dess–Martin oxidation of the major (*exo*) isomer (**34a**), afforded the required aldehyde (**35a**, 80%), but Swern oxidation gave a higher yield (94%), and the Swern method was applied to the minor isomer **34b** (92%). Aldehyde **35a** reacted with (*E*)-5-heptenylmagnesium bromide, again generated with Rieke magnesium, to give a single alcohol (**36a**) in 60% yield. The stereochemistry at C(1′) was not established. When reaction of aldehyde **35a** with (*E*)-5-heptenylmagnesium bromide (from Rieke Mg) was done in the presence of 35 equiv. TMEDA per equiv aldehyde, alcohol **36a** was obtained as a 1:1.64 mixture of C(1′) isomers in 82% yield. Mesylation of the major isomer of **36a** (which corresponds to the single product obtained in the absence of TMEDA), and reduction with Et_3BHLi (**36a→37a**) completed elaboration of the C(8) sidechain (59% from **36a**). Similar treatment of the minor C(1′) isomer of **36a** (mesylation, 96%; reduction 52%) also gave **37a**, as expected. We did not subject **35b** to the same sequence of reactions but, as described below, we later elaborated both the major (**35a**) and minor (**35b**) isomers in a different way.

3. Second route

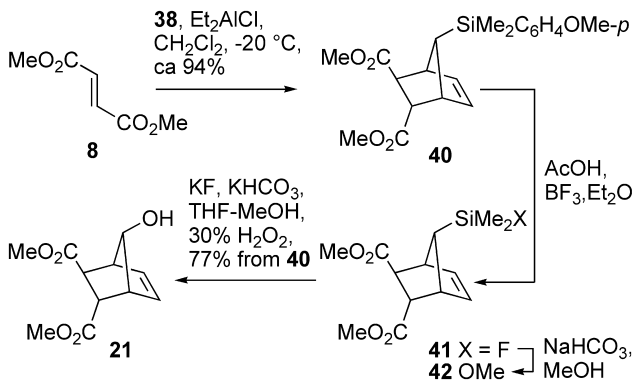
While the above work was in progress, we considered alternatives to the silylated cyclopentadiene **18**;[20] this was not a stable compound, and appeared to be subject to extensive desilylation under conditions of the Diels–Alder reaction. Among the silicon groups that permit Tamao–Fleming oxidation, we decided to examine an $ArMe_2Si$ group, in which the aromatic unit carries an electron-donating substituent, whose presence was expected to facilitate the Si→O exchange.[21] We prepared the two compounds **38** and **39**, in each case by treatment of lithium cyclopentadienide with the appropriate silane,

chlorodimethyltolylsilane[22] or chloro(4-methoxyphenyl)-dimethylsilane.[23] Diene **38** gave a cleaner product in its reaction with dimethyl fumarate, and was therefore used in subsequent work. The material, which was used crude, could be stored at room temperature without change (^{1}H NMR) for at least two weeks; in contrast, **18** has to be kept at a low temperature (i.e. below 10 °C), and even then did not survive for more than a few days. Attempts to purify[24] **38** did not effect much improvement, but the crude material was suitable for direct use in the next step (Scheme 8).



Scheme 8.

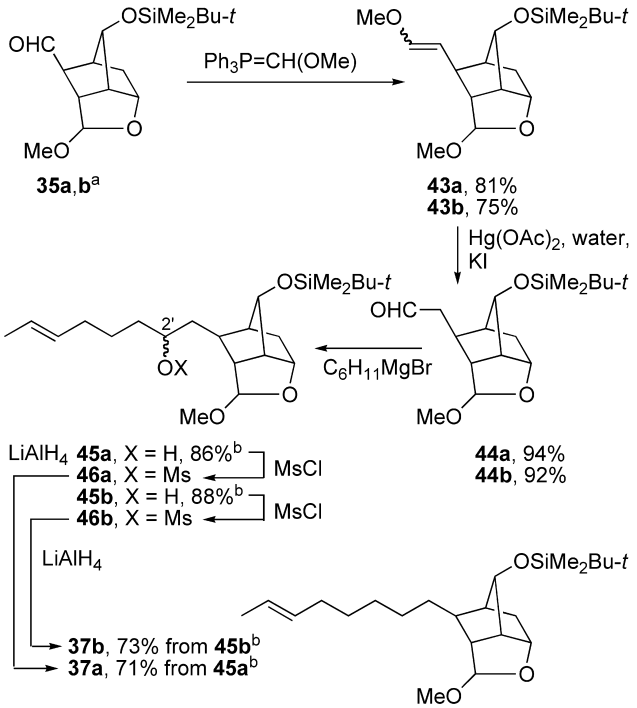
Reaction of an excess of **38** with dimethyl fumarate (**8**) at 0 °C in the presence of a stoichiometric amount of Et_2AlCl for 24 h gave **40** in ca. 94% yield (Scheme 9), but contaminated by ca. 7% (^{1}H NMR) of another substance which we speculate may be the *syn* isomer or the result of Diels–Alder reaction of a double bond isomer of the original cyclopentadiene. The impurity was not separable by chromatography. Replacement of the silyl unit by hydroxyl required some optimization, but we eventually found that this could be achieved by modification of a published procedure.[25] Treatment with 2 equiv. AcOH and 1 equiv. $BF_3{\cdot}Et_2O$ served to generate the fluorosilane **41**. The AcOH–$BF_3{\cdot}Et_2O$ mixture is less expensive than the $BF_3{\cdot}$2AcOH complex originally used,[25] and appears to work just as well. The crude fluorosilane was then treated with anhydrous MeOH in the presence of $NaHCO_3$, to afford the methoxysilane **42**. Finally, treatment of **42** in situ with 30% H_2O_2, KF, and $KHCO_3$ in 1:1 THF–MeOH gave the desired alcohol **21** in 77% overall yield from **40** (starting with 10 g of **40**). On a smaller scale (500 mg of **40**) the yield was 95%. Alcohol **21** was obtained pure, but its immediate precursors **41** and **42** were not characterized.



Scheme 9.

Although we had already generated the C_8-sidechain (see Scheme 7), we decided to examine a modified route, which is shown in Scheme 10.

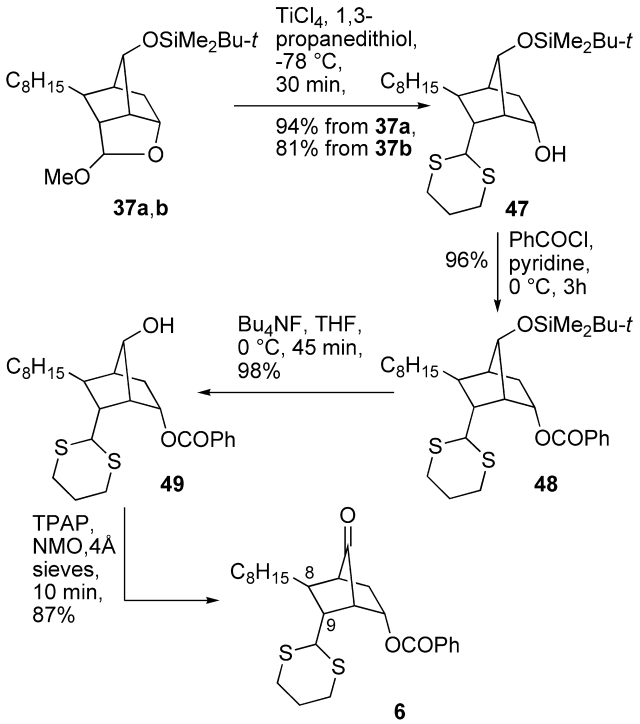
Aldehyde **35a** reacted smoothly with (methoxymethyl)-triphenylphosphorane, giving the enol ethers **43a** (81%), which were converted into the corresponding aldehyde **44a**



Scheme 10. [a]'**a**' series refers to *exo* OMe, '**b**' series refers to *endo* OMe. [b]Both isomers at C(2′).

by treatment with $Hg(OAc)_2$ in aqueous THF[26] (94%). Reaction with the appropriate Grignard reagent—in this case (*E*)-4-hexenylmagnesium bromide,[27] generated using Rieke magnesium—gave alcohols **45a** as a mixture of C(2′) isomers in 86% yield. We initially used TMEDA as an additive in the Grignard reaction, but later found that the yield was the same in its absence. The hydroxyl group of **45a** is less sterically hindered than that of **36a**, and mesylation (**45a→46a**) and reduction with $LiAlH_4$ gave **37a** (71% for the two steps). Aldehyde **35b** was converted in the same way and in comparable yield into **37b**. In both cases the reduction with $LiAlH_4$ went to completion, unlike the previous experiments with Et_3BHLi (see Scheme 7), and we regard the longer route of Scheme 10 as experimentally more convenient. In repeating this route we used a mixture of **35a** and **35b** for Wittig homologation, and obtained the desired enol ethers in 90% yield on a scale that affords 5 g of a mixture of **43a** and **43b**. On a similar scale, with this isomer mixture, the yield for the hydrolysis (**43a**,**b→44a**,**b**) was 94%, for the Grignard reaction 95%, and for the mesylation–reduction sequence (**46a**,**b→47a**,**b**) 90% (Scheme 11).

Demethylation of both **37a** and **37b** was initially troublesome, but we eventually found that treatment of **37a** with $BCl_3{\cdot}SMe_2$ in Et_2O gave the expected lactol (as a single isomer) in 74% yield; the minor isomer **37b** gave the same product in 73% yield. However, the lactol was too sensitive for further work and behaved in uncharacteristic ways.[28] Fortunately, a way around these difficulties was quickly found. Treatment of **37a** with propanedithiol in the presence of $TiCl_4$ at −78 °C gave the desired dithioketal **47** in 94% yield. Likewise, the minor isomer **37b** gave the same compound in 81% yield. When using a mixture of **37a** and **37b**, the yield was 84–98%. The secondary hydroxyl was



Scheme 11.

readily benzoylated (**47→48**, 96%), and then the silyl group was removed in the standard way (Bu_4NF, 98%) and the liberated hydroxyl was oxidized with TPAP to form the target ketone **6** (87%).

4. Conclusion

The silylated diene **38** has proven to be a convenient component in Diels–Alder reaction with dimethyl fumarate, and the silicon unit can be replaced by an hydroxyl in good yield and with retention of configuration. $BF_3{\cdot}OEt_2$ in the presence of AcOH, instead of the conventional reagent $BF_3{\cdot}2AcOH$, can be used for conversion of **40** to **41**, and is a considerably cheaper alternative. The sequence **38→40→21→44→6** constitutes a practical route to bicyclic ketones which have the functionality appropriate for further elaboration along lines already studied with model compounds in this laboratory.

5. Experimental

5.1. General

The general procedures used previously[29] in this laboratory were followed. The symbols s, d, t, and q used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. Unless indicated to the contrary, all new compounds were pure as judged by thin layer chromatography, and ^1H NMR and ^{13}C NMR spectra.

5.1.1. (2-*endo*,3-*exo*,7-*anti*)-7-(Dimethylsilanyl)bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (20) and (2-*endo*,3-*exo*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (19). Me_2AlCl (1 M in hexanes, 9.80 mL, 9.80 mmol) was added dropwise by syringe over 5 min to a stirred and cooled (−78 °C) solution of dimethyl fumarate (1.452 g, 9.780 mmol). Stirring was continued for 10 min, and a solution of 5-dimethylsilylcyclopentadiene[16] (ca. 26.52 g, ca. 27.4 mmol) in hexanes (37 mL) was added dropwise by cannula. Stirring was continued for 5 h at −78 °C and the mixture was quenched by addition of 10% aqueous $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (100 mL), and the organic extract was washed with brine (2×100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×20 cm), using 1:10 EtOAc–hexanes, gave a mixture (2.11 g) of **19** and **20** (ca. 1:1.7, yield of **20** by calculation is ca. 53%). The material was used directly without characterization.

5.1.2. (2-*endo*,3-*exo*,7-*anti*)-7-Hydroxybicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic acid dimethyl ester (21) and (2-*endo*,3-*exo*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (19). Bu_4NF (1 M in THF, 3.60 mL, 3.60 mmol), $KHCO_3$ (128 mg, 1.28 mmol) and H_2O_2 (30 w/w%, 1.0 mL, 9.7 mmol) were added in that order to a stirred solution of a mixture of **19** (ca. 80.3 mg, ca. 0.382 mmol) and **20** (ca. 163 mg, 0.598 mmol) in MeOH (1.5 mL) and THF (1.5 mL). Stirring was continued overnight. The mixture was diluted with brine (10 mL) and extracted with Et_2O (3×25 mL). The aqueous phase was saved for acidification at a later stage, and the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (25 mL), 10% aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×20 cm), using 1:10 EtOAc–hexanes, gave **19** (80.3 mg) and **21** (47.1 mg) as oils.

The aqueous phase that had been saved was acidified to pH 2 with 2 N hydrochloric acid, and extracted with Et_2O (3×25 mL). The combined organic extracts were washed with brine (2×30 mL) and dried ($MgSO_4$). Evaporation of the solvent gave an oil (160 mg). This material (160 mg) was dissolved in acetone (3.0 mL), and K_2CO_3 (447 mg, 3.24 mmol) and Me_2SO_4 (0.30 mL, 3.2 mmol) were added. The mixture was stirred overnight, diluted with EtOAc (25 mL), washed with brine (2×20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5×10 cm), using 1:3 to 3:1 EtOAc–hexanes, gave **21** (11.0 mg), bringing the total yield of **21** to 43%. The above procedure was used because some ester hydrolysis occurred in the oxidation step.

Compound **19**. FTIR (CH_2Cl_2 cast) 1731 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.27 (d, J=8.5 Hz, 1H), 1.58 (d, J=8.5 Hz, 1H), 2.84–2.89 (m, 1H), 2.96–2.99 (m, 1H), 3.09–3.13 (m, 1H), 3.26 (s, 3H), 3.33 (s, 3H), 3.46–3.51 (m, 1H), 5.96–6.02 (m, 2H); ^{13}C NMR (C_6D_6, 125 MHz) δ 46.0 (d), 47.5 (t), 47.6 (d), 48.1 (d), 48.4 (d), 51.4 (q), 51.7 (q), 135.4 (d), 137.6 (d), 173.0 (s), 174.4 (s); exact mass m/z calcd for $C_{11}H_{14}NaO_4$ 233.0790, found 233.0788.

Compound **21**. FTIR (CH_2Cl_2 cast) 3436, 1731 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 2.58–2.77 (broad peak, –OH), 2.75 (d, J=5.2 Hz, 1H), 2.89–2.96 (m, 1H), 2.97–3.04 (m, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 4.12–4.17 (m, 1H),

5.73–5.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 44.6 (d), 45.4 (d), 50.5 (d), 52.1 (d or q), 52.2 (d or q), 52.3 (d or q), 84.9 (d), 131.9 (d), 133.9 (d), 172.6 (s), 173.6 (s); exact mass *m/z* calcd for $C_{11}H_{14}NaO_5$ 249.0739, found 249.0735.

5.1.3. (2-*endo*,3-*exo*,7-*anti*)-7-(3,5-Dinitrobenzoyloxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester. A solution of pyridine (0.8 mL, 10 mmol) in CH_2Cl_2 (10 mL) was prepared. An aliquot of this solution (1 mL, 0.9 mmol) was added to a stirred solution of 3,5-dinitrobenzoyl chloride (143 mg, 0.600 mmol) in CH_2Cl_2 (2 mL). After 10 min a solution of alcohol **21** (70 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and stirring was continued overnight. The mixture was poured into dilute hydrochloric acid (2 N, 10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$) and evaporated. Crystallization of the residue from premixed 1:9 MeOH–hexane gave the derived dinitrobenzoate (60 mg, 46%). FTIR (Et_2O cast) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (d, *J*=4.8 Hz, 1H), 3.43–3.44 (m, 1H), 3.51 (dd, *J*=4.8, 4.0 Hz, 1H), 3.61–3.62 (m, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 5.11–5.12 (m, 1H), 6.08 (dd, *J*=5.6, 2.8 Hz, 1H), 6.31 (dd, *J*=5.6, 2.8 Hz, 1H), 9.02 (d, *J*=2.4 Hz, 2H), 9.18 (t, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.3 (d), 44.8 (d), 47.6 (d), 49.3 (d), 52.3 (q), 52.6 (q), 87.4 (d), 122.4 (d), 129.4 (d), 131.2 (d), 133.59 (s), 133.64 (d), 148.6 (s), 162.3 (s), 171.9 (s), 173.4 (s); exact mass *m/z* calcd for $C_{18}H_{16}N_2NaO_{10}$ 433.0697, found 443.0699. Single crystal X-ray analysis[18] confirmed the stereochemistry shown.

5.1.4. (2-*endo*,3-*exo*,7-*anti*)-7-(Methoxymethoxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (22). $MeOCH_2Cl$ (1.73 mL, 22.8 mmol) was added to a stirred and cooled (0 °C) solution of **21** (1.51 g, 6.53 mmol) and *i*-Pr_2NEt (4.60 mL, 26.5 mmol) in CH_2Cl_2 (22 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. At this point, examination by TLC (silica, 1:3 EtOAc–hexane) suggested that ca. 50% conversion had occurred. *i*-Pr_2NEt (4.80 mL, 22.6 mmol), DMAP (16 mg, 0.13 mmol) and $MeOCH_2Cl$ (1.50 mL, 19.7 mmol) were added to the solution at 0 °C. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction was quenched with 5% hydrochloric acid (25 mL), and the organic phase was washed with brine (2×40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×15 cm), using 1:3 to 3:1 EtOAc–hexanes, gave **21** (272 mg) and **22** (731 mg, 49% based on conversion). Compound **22**. FTIR (CH_2Cl_2 cast) 1733 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.86 (d, *J*=5.1 Hz, 1H), 3.04 (s, 3H), 3.18–3.25 (m, 4H), 3.27 (s, 3H), 3.33–3.37 (m, 1H), 3.39–3.44 (m, 1H), 4.03–4.07 (m, 1H), 4.33 (s, 2H), 5.94–6.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.4 (d), 44.9 (d), 48.5 (d), 50.2 (d or q), 51.9 (d or q), 52.2 (d or q), 55.4 (d or q), 90.3 (d), 95.9 (t), 130.8 (d), 133.6 (d), 172.6 (s), 173.8 (s) [seven d and three q in all]; exact mass *m/z* calcd for $C_{13}H_{18}NaO_6$ 293.1001, found 293.1005.

5.1.5. (2*R* *,8*R* *,9*R* *)-2-Bromo-8-(methoxymethoxy)-5-oxo-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (23). Br_2 (0.15 mL, 2.9 mmol) was added to a stirred and cooled (0 °C) solution of **22** (706 mg, 2.61 mmol) in CH_2Cl_2 (20 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL), and the organic phase was washed with brine (2×30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×13 cm), using 1:10 to 1:3 EtOAc–hexanes, gave **23** (578 mg, 66%). FTIR (CH_2Cl_2 cast) 1796, 1734 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 2.07–2.09 (m, 1H), 2.40–2.43 (m, 1H), 2.70–2.77 (m, 2H), 3.04 (s, 3H), 3.16 (s, 3H), 3.31 (s, 1H), 4.06–4.09 (m, 1H), 4.26 (d, *J*=9.4 Hz, 1H), 4.33 (d, *J*=9.4 Hz, 1H), 4.88–4.93 (m 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 39.2 (d), 47.7 (d), 48.8 (d), 49.0 (d), 49.1 (d), 52.3 (q), 55.8 (q), 82.2 (d), 88.6 (d), 95.9 (t), 170.1 (s), 175.4 (s); exact mass *m/z* calcd for $C_{12}H_{15}{}^{79}BrNaO_6$ 356.9950, found 356.9944.

5.1.6. (8*R* *,9*R* *)-8-(Methoxymethoxy)-5-oxo-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (24). A solution of **23** (578 mg, 1.73 mmol), AIBN (42.9 mg, 0.262 mmol) and Bu_3SnH (0.52 mL, 1.9 mmol) in PhH (10 mL) was refluxed for 3.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5×15 cm), using 1:10 to 1:2 EtOAc–hexanes, gave **24** (365 mg, 83%). FTIR (CH_2Cl_2 cast) 1783, 1733 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 1.08 (d, *J*=14.0 Hz, 1H), 1.93–1.98 (m, 1H), 2.35–2.39 (m, 2H), 2.43–2.47 (m, 1H), 2.85–2.87 (m, 1H), 2.91 (s, 3H), 3.17 (s, 3H), 3.98 (s, 1H), 4.14 (s, 2H), 4.49–4.52 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 34.7 (t), 40.7 (d), 43.2 (d), 47.6 (d), 48.2 (d), 52.0 (q), 55.4 (q), 79.9 (d), 83.3 (d), 96.2 (t), 171.9 (s), 177.0 (s); exact mass *m/z* calcd for $C_{12}H_{16}NaO_6$ 279.0845, found 279.0849.

5.1.7. (8*R* *,9*R* *)-5-Hydroxy-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (25). DIBAL-H (1 M in THF, 1.40 mL, 1.40 mmol) was added to a stirred and cooled (−78 °C) solution of **24** (145 mg, 0.566 mmol) in THF (5.0 mL). Stirring at −78 °C was continued for 4 h, and the mixture was quenched by addition of MeOH (3 mL). The mixture was taken up in EtOAc (75 mL), washed with 5% hydrochloric acid (5 mL), 10% aqueous $NaHCO_3$ (10 mL) and brine (2×10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×10 cm), using 1:2 to 1:1 EtOAc–hexanes, gave **25** (82 mg, 56%) as an oily mixture of two isomers (ca. 10:1). FTIR (CH_2Cl_2 cast) 3412, 1732 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) (major isomer) δ 1.18 (d, *J*=12.5 Hz, 1H), 2.01–2.06 (m, 1H), 2.11–2.16 (m, 1H), 2.37–2.42 (m, 1H), 2.40–2.48 (m, 1H), 2.69–2.75 (m, 1H), 2.97–3.02 (m, 4H), 3.26 (s, 3H), 4.27–4.33 (m, 3H), 4.70–4.72 (m, 1H), 4.99–5.04 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) (major isomer) δ 37.1 (t), 42.0 (d), 47.2 (d), 47.35 (d), 47.39 (d), 51.6 (q), 55.3 (q), 80.1 (d), 84.0 (d), 96.3 (t), 102.5 (d), 173.5 (s); exact mass *m/z* calcd for $C_{12}H_{18}NaO_6$ 281.1001, found 281.1004.

5.1.8. (8*R* *,9*R* *)-5-(*tert*-Butyldimethylsilanyloxy)-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (26). Et_3N (0.36 mL, 2.6 mmol), DMAP (one grain) and *t*-$BuMe_2SiCl$ (250 mg,

1.66 mmol) were added to a stirred solution of **25** (200 mg, 0.776 mmol) in CH_2Cl_2 (5.5 mL). Stirring was continued for 13 h, and then additional portions of Et_3N (0.40 mL, 2.9 mmol), DMAP (26.1 mg, 0.214 mmol) and *t*-$BuMe_2$-SiCl (240 mg, 1.59 mmol) were added. Stirring was continued for another 20 h. The mixture was diluted with EtOAc (20 mL), washed with brine (2×20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3×10 cm), using 1:20 to 7:10 EtOAc–hexanes, gave **26** (253.2 mg, 88%) as a single isomer (of unestablished stereochemistry), which was an oil. FTIR ($CHCl_3$ cast) 1737 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.15 (s, 3H), 0.17 (s, 3H), 0.97 (s, 9H), 1.20 (d, J=12.5 Hz, 1H), 2.08–2.09 (m, 1H), 2.11–2.16 (m, 1H), 2.49–2.53 (m, 1H), 2.72–2.77 (m, 1H), 3.02–3.08 (m, 4H), 3.25 (s, 3H), 4.30–4.38 (m, 3H), 4.66–4.72 (m, 1H), 5.22 (s, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −4.6 (q), −4.0 (q), 18.2 (s), 26.1 (q), 37.1 (t), 42.0 (d), 47.0 (d), 47.3 (d), 48.7 (d), 51.5 (q), 55.2 (q), 80.0 (d), 83.9 (d), 96.2 (t), 103.0 (d), 173.7 (s); exact mass m/z calcd for $C_{18}H_{32}NaO_6Si$ 395.1866, found 395.1869.

5.1.9. [(8*R,9*R**)-5-(*tert*-Butyldimethylsilanyloxy)-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.$0^{6,7}$]non-9-yl]methanol (27).** DIBAL-H (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **26** (251 mg, 0.674 mmol) in CH_2Cl_2 (8.0 mL). Stirring at −78 °C was continued for 7 h and then overnight at room temperature. The mixture was quenched by addition of MeOH (2.0 mL) and diluted with EtOAc (25 mL). Saturated aqueous potassium sodium tartrate (25 mL) was added and the mixture was stirred for 1 h. The organic phase was separated and washed with brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×9.5 cm), using 1:10 to 1:1 EtOAc–hexanes, gave **27** (203.2 mg, 87%) as a solid: mp 85–87 °C. FTIR ($CHCl_3$ cast) 3445 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.19 (s, 6H), 1.00 (s, 9H), 1.34 (d, J=12.5 Hz, 1H), 1.38–1.42 (m, 1H), 1.64–1.69 (m, 1H), 1.87–1.93 (m, 1H), 2.09 (s, 1H), 2.13–2.22 (m, 1H), 2.98–3.02 (m, 1H), 3.07–3.17 (m, 5H), 4.06 (s, 1H), 4.37 (s, 2H), 4.72–4.77 (m, 1H), 5.24 (s, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −4.6 (q), −3.9 (q), 18.2 (s), 26.1 (q), 37.9 (t), 40.2 (d), 46.0 (d), 47.5 (d), 48.2 (d), 55.1 (q), 64.5 (t), 80.3 (d), 83.5 (d), 96.0 (t), 103.4 (d); exact mass m/z calcd for $C_{17}H_{32}NaO_5Si$ 367.1917, found 367.1914.

5.1.10. (8*R,9*R**)-5-(*tert*-Butyldimethylsilanyloxy)-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.$0^{6,7}$]nonane-9-carbaldehyde (28).** Dess–Martin periodinane (218 mg, 0.514 mmol) was added to a stirred solution of **27** (80.0 mg, 0.232 mmol) and pyridine (0.40 mL, 4.9 mmol) in CH_2Cl_2 (10 mL). Stirring was continued overnight, CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were washed with brine (2×20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5×13 cm), using 1:10 EtOAc–hexanes, gave **28** (60.1 mg, 76%) as an oil. FTIR ($CHCl_3$ cast) 1726 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.17 (s, 6H), 0.99 (s, 9H), 1.13 (d, J=12.5 Hz, 1H), 1.56–1.59 (m, 1H), 2.07–2.12 (m, 1H), 2.23 (s, 1H), 2.63–2.65 (m, 1H), 2.94–2.96 (m, 1H), 3.00 (s, 3H), 3.75 (s, 1H), 4.25 (s, 2H), 4.64–4.67 (m, 1H), 5.05 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −4.7 (q), −3.9 (q), 18.2 (s), 26.1 (q), 37.0 (q), 39.1 (d), 44.7 (d), 47.4 (d), 54.6 (d or q), 55.2 (d or q), 80.1 (d), 83.1 (d), 96.1 (t), 102.9 (d), 199.2 (d); exact mass m/z calcd for $C_{17}H_{30}NaO_5Si$ 365.1760, found 365.1765.

5.1.11. (2-*endo*,3-*exo*,7-*anti*)-7-(*tert*-Butyldimethylsilanyloxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (29). Imidazole (10.1 g, 148 mmol) and DMAP (1.04 g, 8.50 mmol) were tipped into a stirred and cooled (ice-bath) solution of **21** (19.1 g, 84.5 mmol) in dry DMF (170 mL). *t*-$BuMe_2SiCl$ (19.11 g, 126.8 mmol) was then tipped in. The cold bath was removed and stirring was continued for 24 h. The mixture was poured into ice-cold water (500 mL) and extracted with Et_2O (4×100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated (water pump). Flash chromatography of the residue over silica gel (6.5×30 cm), using 3:7 EtOAc–hexane, gave **29** (27.0 g, 94%) as a viscous oil. FTIR ($CHCl_3$ cast) 1735 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.00 (s, 6H), 0.89 (s, 9H), 2.86 (d, J=5.1 Hz, 1H), 3.01–3.06 (m, 1H), 3.15–3.18 (m, 1H), 3.24 (s, 3H), 3.30 (s, 3H), 3.38–3.41 (m, 1H), 4.32–4.35 (m, 1H), 5.93–5.97 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.79 (q), −4.77 (q), 18.3 (s), 25.9 (q), 45.1 (d), 45.4 (d), 51.0 (d or q), 51.4 (d or q), 51.6 (d or q), 52.7 (d or q), 86.1 (d), 131.0 (d), 133.4 (d), 172.4 (s), 174.2 (s); exact mass m/z calcd for $C_{17}H_{28}NaO_5Si$ 363.1604, found 363.1607.

5.1.12. (2*R,8*R**,9*R**)-2-Bromo-8-(*tert*-butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.$0^{6,7}$]nonane-9-carboxylic acid methyl ester (30).** Br_2 (0.78 mL, 15 mmol) was added dropwise by syringe to a stirred and cooled (0 °C) solution of **29** (4.110 g, 12.07 mmol) in CH_2Cl_2 (60 mL). The cold bath was removed and stirring was continued overnight and the mixture was quenched by addition of saturated aqueous $NaHCO_3$. The organic phase was washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×20 cm), using 1:10 EtOAc–hexanes, gave **30** as solid (3.9112 g, 80%): mp 110–111 °C. FTIR ($CHCl_3$ cast) 1800, 1738 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ −0.03 (s, 3H), 0.01 (s, 3H), 0.90 (s, 9H), 2.06 (s, 1H), 2.23–2.26 (m, 1H), 2.54 (s, 1H), 2.63–2.66 (m, 1H), 3.19 (s, 3H), 3.35 (s, 1H), 4.28 (s, 1H), 4.89–4.91 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −5.1 (q), −4.9 (q), 18.3 (s), 26.0 (q), 39.3 (d), 47.4 (d), 48.9 (d), 50.8 (d or q), 51.0 (d or q), 52.1 (d or q), 79.1 (d), 89.0 (d), 170.6 (s), 175.7 (s); exact mass m/z calcd for $C_{16}H_{25}{}^{79}BrNaO_5Si$ 427.0552, found 427.0553. In some experiments run on a larger scale (e.g. 27 g of **29**), some desilylation occurs, but the resulting alcohol can be resilylated to afford **30** in the same overall yield.

5.1.13. (8*R,9*R**)-8-(*tert*-Butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.$0^{6,7}$]nonane-9-carboxylic acid methyl ester (31).** A solution of Bu_3SnH (3.10 mL, 11.5 mmol) and AIBN (234 mg, 1.43 mmol) was added to a solution of **30** (3.89 g, 9.59 mmol) in PhH (80 mL). The mixture was refluxed for 4 h, and the solvent was then concentrated to ca. 30 mL. Flash chromatography of the residue (the solution was applied directly to the column)

over silica gel (3.5×20 cm), using 1:5 EtOAc–hexanes, gave **31** as a solid (2.967 g, 95%): mp 79–80 °C. FTIR ($CHCl_3$ cast) 1785, 1736 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ −0.11 (s, 6H), 0.82 (s, 9H), 1.05–1.10 (m, 1H), 1.99–2.06 (m, 1H), 2.14–2.22 (m, 1H), 2.18–2.27 (m, 1H), 2.37 (s, 1H), 2.780 (d, J=5.2 Hz, 1H), 3.20 (s, 3H), 4.22 (s, 1H), 4.51 (t, J=6.2 Hz, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −5.10 (q), −5.07 (q), 18.1 (s), 25.8 (q), 34.3 (t), 40.8 (d), 44.8 (d), 46.9 (d), 50.0 (d), 51.8 (q), 78.6 (d), 80.3 (d), 172.3 (s), 177.3 (s); exact mass m/z calcd for $C_{16}H_{26}NaO_5Si$ 349.1447, found 349.1447.

5.1.14. (8*R* *,9*R* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (32). DIBAL-H (1 M in CH_2Cl_2, 3.0 mL, 3.0 mmol) was added dropwise over 5 min to a stirred and cooled (−78 °C) solution of **31** (456 mg, 1.39 mmol) in THF (15 mL). Stirring at −78 °C was continued for 5.75 h and then MeOH (2 mL) was added dropwise. The cooling bath was removed and, after 15 min, the mixture was diluted with EtOAc (15 mL). Saturated sodium potassium tartrate (1 mL) was added and stirring was continued for 15 min. The solution was dried ($MgSO_4$) and filtered through a sintered disk. The solid was washed with EtOAc (3×10 mL). The combined organic extracts were evaporated and flash chromatography of the residue over silica gel (1.5×22 cm), using first 1:19 EtOAc–hexane (50 mL), and then 3:7 EtOAc–hexane gave **32** (350 mg, 76%) as a colorless oil which solidified after standing overnight: mp 60–65 °C. FTIR ($CHCl_3$ cast) 3400, 1736 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) (major isomer signals) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.17 (d, J=13.0 Hz, 1H), 2.04–2.09 (m, 1H), 2.18–2.26 (m, 1H), 2.27–2.32 (m, 1H), 2.72–2.76 (m, 1H), 2.87–2.93 (m, 1H), 3.29 (s, 3H), 3.33–3.38 (m, 1H), 4.48–4.56 (m, 1H), 4.70–4.78 (m, 1H), 5.12–5.18 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ −4.92 (q), −4.88 (q), 18.2 (s), 25.9 (q), 36.6 (t), 43.7 (d), 47.2 (d), 47.3 (d), 49.1 (d), 51.5 (q), 79.2 (d), 80.5 (d), 102.8 (d), 174.0 (s); exact mass m/z calcd for $C_{16}H_{28}NaO_5Si$ 351.1604, found 351.1604.

5.1.15. (8*R* *,9*R* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carboxylic acid methyl ester (33). Lactols **32** (1.93 g, 5.87 mmol) and pyridinium *p*-toluenesulfonate (23.0 mg, 0.0915 mmol) were dissolved in $HC(OMe)_3$ (10 mL). The solution was stirred overnight, diluted with EtOAc (60 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (60 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5×18.5 cm), using 1:5 to 1:3 EtOAc–hexanes, gave **33** (1.551 g, 77%) as two oily fractions, one being largely the major isomer and the other being largely the minor isomer: FTIR on mixture of isomers ($CHCl_3$ cast) 1736 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) (major isomer signals) δ −0.02 (s, 3H), −0.01 (s, 3H), 0.86 (s, 9H), 1.24 (d, J=12.8 Hz, 1H), 2.08–2.13 (m, 1H), 2.22–2.30 (m, 1H), 2.31–2.36 (m, 1H), 2.77–2.82 (m, 1H), 2.86–2.89 (m, 1H), 3.19 (s, 3H), 3.28 (s, 3H), 4.52–4.56 (m, 1H), 4.59 (s, 1H), 4.68–4.74 (m, 1H); ^1H NMR (C_6D_6, 400 MHz) (minor isomer signals) δ −0.01 (s, 6H), 0.86 (s, 9H), 1.43 (d, J=13.6 Hz, 1H), 2.22–2.28 (m, 1H), 2.38–2.39 (m, 1H), 2.41–2.44 (m, 1H), 2.83–2.86 (m, 1H), 3.27 (s, 3H), 3.30 (s, 3H), 3.33–3.34 (m, 1H), 4.42 (s, 1H), 4.59–4.62 (m, 1H), 4.86–4.87 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) (major isomer signals) δ −4.98 (q), −4.95 (q), 18.1 (s), 25.9 (q), 36.8 (t), 43.7 (d), 46.4 (d), 47.2 (d), 49.5 (d), 51.4 (q), 54.3 (q), 79.1 (d), 80.4 (d), 108.9 (d), 173.9 (s); ^{13}C NMR (C_6D_6, 100 MHz) (minor isomer signals) δ −4.96 (q), −4.94 (q), 18.1 (s), 25.9 (q), 35.9 (t), 42.8 (d), 43.1 (d), 43.4 (d), 51.3 (d or q), 51.8 (d or q), 56.3 (q), 78.8 (d), 80.1 (d), 106.5 (d), 174.8 (s); exact mass (mixture of the isomers) m/z calcd for $C_{17}H_{30}NaO_5Si$ 365.1760, found 365.1759.

5.1.16. [(5*R* *,8*S* *,9*S* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]methanol (34a) and (5*R* *,8*R* *,9*R* *)-[8-(*tert*-butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]methanol (34b). The 'a' series refers to major isomer at acetal carbon, 'b' series is minor isomer at acetal carbon.

DIBAL-H (1 M in CH_2Cl_2, 53 mL, 53 mmol) was added dropwise over 20 min to a stirred and cooled (−78 °C) solution of **33** (5.65 g, 16.6 mmol) in THF (80 mL). The cooling bath was removed and stirring was continued overnight. The mixture was cooled (−78 °C) and precooled (−78 °C) MeOH (50 mL) was added dropwise by cannula. Stirring was continued for 15 min, and saturated aqueous sodium potassium tartrate (50 mL) was added. The cooling bath was removed, the mixture was diluted with EtOAc (50 mL), and stirring was continued for 1 h. The mixture was filtered through a pad of Celite (0.5×8 cm) using EtOAc (3×100 mL) as a rinse. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5×28.5 cm), using 1:1 EtOAc–hexane, gave three fractions: minor isomer **34b** (0.63 g), major isomer **34a** (2.48 g), and a mixed fraction of both isomers (1.69 g), the total yield being 4.8 g (92%). The minor isomer (**34b**) had: mp 67–69 °C. FTIR (CH_2Cl_2 cast) 3435 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 1.44 (d, J=12.4 Hz, 1H), 1.77–1.91 (m, 2H), 1.98 (s, 1H), 2.30 (ddd, J=12.6, 7.5, 3.9 Hz, 1H), 2.35–2.48 (m, 2H), 3.23–3.41 (m, 5H), 4.28 (s, 1H), 4.63 (dd, J=7.5, 5.1 Hz, 1H), 4.86 (d, J=4.2 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.6 (q), 18.3 (s), 26.1 (q), 37.4 (t), 41.7 (d), 41.8 (d), 43.3 (d), 52.0 (d), 56.6 (q), 65.1 (t), 78.5 (d), 80.3 (d), 107.3 (d); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.1811, found 337.1813. A TROESY experiment showed an NOE effect between C(5)*H* and C(7)*H*.

The major isomer (**34a**) was an oil. FTIR ($CHCl_3$ cast) 3440 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ −0.02 (s, 3H), −0.01 (s, 3H), 0.88 (s, 9H), 0.90–0.99 (m, 1H), 1.30 (d, J=12.3 Hz, 1H), 1.39 (td, J=7.5, 2.7 Hz, 1H), 1.90 (s, 1H), 1.98–2.05 (m, 1H), 2.30 (ddd, J=12.6, 7.2, 3.9 Hz, 1H), 2.90–2.95 (m, 1H), 3.00–3.20 (m, 2H), 3.26 (s, 3H), 4.26 (s, 1H), 4.65 (s, 1H), 4.71–4.80 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.7 (q), −4.6 (q), 18.3 (s), 26.1 (q), 38.0 (t), 42.7 (d), 46.0 (d), 46.5 (d), 50.0 (d), 54.4 (q), 64.8 (t), 78.9 (d), 80.8 (d), 109.5 (d); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.1811, found 337.1811. A TROESY experiment showed an NOE effect between C(1)*H* and C(5)*H*.

The structure of the minor isomer was established by single crystal X-ray analysis.[18]

5.1.17. (5*R* *,8*S* *,9*S* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carbaldehyde (35a). *Use of the Dess–Martin reagent*. Dess–Martin periodinane (1.80 g, 4.20 mmol) was added to a stirred solution of **34a** (548 mg, 1.75 mmol) and pyridine (4.0 mL, 50 mmol) in CH_2Cl_2 (23 mL), and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and then washed with a mixture of saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_3$ (25 mL). The organic phase was washed with brine (40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography (it is important to remove all Et_3N under oil pump vacuum before loading the material onto a flash chromatography column) of the residue over silica gel (4×19 cm), using 1:20 to 1:10 EtOAc–hexanes, gave **35a** (434.5 mg, 80%) as a solid: mp 32–34 °C. FTIR ($CHCl_3$ cast) 1723 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ −0.10 (s, 3H), −0.09 (s, 3H), 0.84 (s, 9H), 1.17 (d, *J*=13.0 Hz, 1H), 1.64 (d, *J*=3.0 Hz, 1H), 2.06–2.12 (m, 1H), 2.18–2.26 (m, 1H), 2.70–2.74 (m, 1H), 2.78–2.84 (m, 1H), 3.21 (s, 3H), 3.98 (s, 1H), 4.41 (s, 1H), 4.66–4.69 (m, 1H), 9.12 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.09 (q), −5.04 (q), 18.0 (s), 25.8 (q), 36.7 (t), 40.9 (d), 42.3 (d), 49.6 (d), 54.3 (d or q), 54.9 (d or q), 78.3 (d), 80.5 (d), 108.8 (d), 199.3 (d); exact mass *m*/*z* calcd for $C_{16}H_{28}NaO_4Si$ 335.1655, found 335.1658.

Use of Swern oxidation. Dry DMSO (1.23 mL, 17.5 mmol) was added dropwise from a syringe over 15 min to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.76 mL, 8.7 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred for 20 min and then **34a** (i.e. major isomer) (1.80 g, 5.81 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min, and stirring was continued for 30 min at −78 °C. Dry Et_3N (3.04 mL, 21.8 mmol) was added dropwise over 5 min. The cold bath was left in place, but not recharged, and stirring was continued for 2 h, by which time the temperature was ca. −50 °C. The cold bath was removed, and stirring was continued for 40 min, by which time the mixture had attained room temperature. Cold water (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×23 cm), using 1:4 EtOAc–hexane, gave **35a** (1.77 g, 98%). On a 2-g scale the yield was 98%.

5.1.18. (5*R* *,8*R* *,9*R* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]nonane-9-carbaldehyde (35b). A solution of DMSO (0.25 mL, 3.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise from a syringe to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.15 mL, 1.8 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 20 min and then **34b** (377 mg, 1.21 mmol) in CH_2Cl_2 (5 mL plus 2 mL as a rinse) was added dropwise, and stirring was continued for 40 min at −78 °C. Dry Et_3N (0.63 mL, 4.6 mmol) was added dropwise. The cold bath was left in place, but not recharged, and stirring was continued for 3 h, by which time the temperature was ca. −50 °C. The cold bath was removed, and stirring was continued for 40 min, by which time the mixture had attained room temperature. Cold water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×20 cm), using 1:4 EtOAc–hexane, gave **35b** (346.1 mg, 92%). FTIR (Et_2O cast) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.01 (s, 6H), 0.82 (s, 9H), 1.36 (d, *J*=13.2 Hz, 1H), 2.27 (ddd, *J*=13.2, 8.0, 4.4 Hz, 1H), 2.37 (br s, 1H), 2.56 (t, *J*=4.6 Hz, 1H), 2.6 (dd, *J*=7.2, 4.4 Hz, 1H), 3.04 (d, *J*=2.4 Hz, 1H), 3.38 (s, 3H), 3.89 (br s, 1H), 4.49 (dd, *J*=7.6, 5.2 Hz, 1H), 5.01 (d, *J*=4.4 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0 (q), 17.8 (s), 25.6 (q), 35.5 (t), 39.2 (d), 39.7 (d), 50.8 (d), 51.3 (d), 56.4 (q), 77.7 (d), 80.1 (d), 106.2 (d), 201.7 (d); exact mass *m*/*z* calcd for $C_{16}H_{28}NaO_4Si$ 335.1649, found 335.1652.

5.1.19. 1-[(5*R* *,8*S* *,9*S* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]-(*E*)-oct-6-en-1-ol (36a). *Procedure in absence of TMEDA*. K (118.7 mg, 3.035 mmol) cut into two pieces under hexane contained in a mortar was added to a suspension of $MgCl_2$ (159 mg, 1.63 mmol) in THF (10 mL) and the mixture was stirred and refluxed for 2 h (the metal pieces were removed with tweezers from the hexane, shaken free of solvent and added to the reaction mixture). The resulting dark gray suspension was cooled to room temperature (this took ca. 0.5 h), and a solution of (*E*)-7-bromo-2-heptene[10] (142.6 mg, 0.805 mmol) in THF (5 mL) was added dropwise over 3 min with stirring at 0 °C. Stirring at 0 °C was continued for 1 h, and a portion (10 mL, ca. 0.55 mmol) was transferred by syringe to a 50 mL flask cooled to −78 °C. A solution of **35a** (50.1 mg, 0.160 mmol) in THF (5.0 mL) was added dropwise with stirring to the above solution. Stirring at −78 °C was continued for 5 h, and then saturated aqueous NH_4Cl was added until pH=5 (pH paper). The mixture was filtered through a pad of Celite (5×1 cm) and the pad was washed with EtOAc (40 mL). The organic filtrate was washed with brine (45 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×19 cm), using 1:20 to 1:10 EtOAc–hexanes, gave **36a** as a single isomer (39.4 mg, 60%) as an oil. FTIR ($CHCl_3$ cast) 3454 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 0.02 (s, 6H), 0.88 (s, 9H), 1.02–1.38 (m, 9H), 1.58–1.67 (m, 3H), 1.83–1.89 (m, 1H), 1.93–2.04 (m, 2H), 2.31–2.39 (m, 1H), 2.47–2.53 (m, 1H), 2.90–2.97 (m, 1H), 3.13–3.23 (m, 1H), 3.31 (s, 3H), 4.50 (s, 1H), 4.74 (s, 1H), 4.79–4.75 (m, 1H), 5.40–5.48 (m, 2H); ^{13}C NMR (C_6D_6, 125 MHz) δ −4.9 (q), −4.7 (q), 18.1 (s), 18.2 (t), 25.3 (t), 26.0 (q), 29.8 (t), 32.9 (t), 36.3 (t), 38.1 (t), 44.1 (d), 45.4 (d), 50.0 (d), 52.2 (d), 54.3 (q), 73.1 (d), 79.0 (d), 80.7 (d), 109.8 (d), 125.1 (d), 131.6 (d); exact mass *m*/*z* calcd for $C_{23}H_{42}NaO_4Si$ 433.2750, found 433.2751.

Procedure in presence of TMEDA. K (1.278 g, 32.69 mmol) cut into small cubes (ca. 2×2×2 mm) under hexane in a mortar was added to a stirred suspension of anhydrous $MgCl_2$ (1.674 g, 17.40 mmol) in THF (30 mL) (the metal pieces were removed with tweezers from the hexane, shaken free of solvent and added to the reaction mixture). The mixture was refluxed for 2 h, cooled first to room temperature, and then to 0 °C. A solution of (*E*)-7-bromo-2-heptene[10] (1.038 g, 5.862 mmol) and $BrCH_2CH_2Br$ (2 drops) in THF (10 mL) was added dropwise from a syringe over ca. 10 min. The mixture was stirred at 0 °C for 1 h. At this stage no bromide was detected by TLC (silica, 1:19 EtOAc–hexane). The ice-bath was removed and replaced

by a dry ice-acetone bath. Dry TMEDA (7.5 mL, 50 mmol) was added to the stirred and cooled (−78 °C) Grignard solution, and a solution of **35a** (450 mg, 1.44 mmol) in THF (10 mL plus 2 mL as a rinse) was added dropwise by syringe. Stirring at −78 °C was continued for 1 h, and the reaction flask was transferred to a cooling bath (Haake immersion cooler, model EK 51-1) set at 0 °C, and stirring was continued for 20 h. MeOH (5 mL) was added at 0 °C, and the mixture was stirred for 15 min. Saturated aqueous NH_4Cl (20 mL) was added. The flask was removed from the cold bath and stirring was continued for 30 min, by which time the mixture had attained room temperature. The mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite (6.5×2 cm) supported on a sintered disc. The pad was washed with EtOAc (3×25 mL). The filtrate separated into two layers, and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×25.5 cm), using 7:13 EtOAc–hexane, gave a major isomer (300 mg) and a mixed fraction. The latter was rechromatographed over silica gel (3.5×25.5 cm), using first 1:9 EtOAc–hexane (200 mL), then 1:4 EtOAc–hexane (200 mL) and then 1:3 EtOAc–hexane (200 mL), to obtain the minor isomer (**36a** minor isomer at CHOH) (186.1 mg) and the major isomer (**36a** major isomer at CHOH; this corresponds to the single product obtained in the absence of TMEDA) (305.3 mg), total yield 491.4 mg (82%). The minor isomer of **36a**: FTIR (Et_2O cast) 3463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.11 (d, J=12.8 Hz, 1H), 1.21–1.60 (m, 11H), 1.86 (t, J=3.6 Hz, 1H), 1.92–1.95 (m, 2H), 2.14–2.22 (m, 2H), 2.64 (t, J=4.6 Hz, 1H), 3.24 (s, 3H), 3.27–3.35 (m, 1H), 4.31 (br s, 1H), 4.55–4.58 (m, 2H), 5.35–5.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0 (q), −4.9 (q), 17.86 (s), 17.93 (t), 25.3 (t), 25.7 (q), 29.5 (t), 32.5 (t), 35.0 (t), 37.3 (t), 41.0 (d), 45.9 (d), 49.5 (d), 50.2 (d), 54.4 (q), 72.9 (d), 78.0 (d), 80.7 (d), 109.0 (d), 124.9 (d), 131.1 (d); exact mass m/z calcd for $C_{23}H_{42}NaO_4Si$ 433.2745, found 433.2747.

5.1.20. *tert*-Butyl[(5*R,8*S**,9*S**)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (37a).** A solution of MsCl (0.101 mmol) in CH_2Cl_2 (0.7 mL) was added to a stirred and cooled (0 °C) solution of **36a** (the single isomer obtained without TMEDA) (22.9 mg, 0.0559 mmol) and Et_3N (0.10 mL, 0.72 mmol) in CH_2Cl_2 (3.0 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was diluted with EtOAc (30 mL), washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5×13.5 cm), using 1:20 to 1:4 EtOAc–hexanes, gave the desired mesylate as an oil, which was used without characterization.

The mesylate was dissolved in THF (4 mL) and Et_3BHLi (1 M in THF, 0.60 mL, 0.60 mmol) was added with stirring. The resulting solution was refluxed for 1.5 h. Examination by TLC (silica, 1:3 EtOAc–hexane) suggested that ca. 50% conversion had occurred. Refluxing was continued for another 8 h and Et_3BHLi (1 M in THF, ca. 0.30 mL, ca. 0.30 mmol) was added at the beginning of this period and after 2, 4, and 6 h. The mixture was then cooled to room temperature and water (0.5 mL) was added, followed by 3 N NaOH (0.8 mL) and 30% H_2O_2 (1.0 mL). The solution was stirred for 5 min and then diluted with EtOAc (25 mL). The organic phase was washed with brine (20 mL), dried $MgSO_4$ and evaporated. Flash chromatography of the residue over silica gel (2.5×17 cm), using 1:20 to 1:4 EtOAc–hexanes, gave **37a** (12.9 mg, 59%) as an oil. Compound **37a**: ^1H NMR (C_6D_6, 400 MHz) δ −0.02 (s, 6H), 0.87 (s, 9H), 1.03–1.39 (m, 10H), 1.58–1.64 (m, 3H), 1.75–1.79 (m, 1H), 1.92–2.02 (m, 3H), 2.26–2.33 (m, 1H), 2.83–2.92 (m, 1H), 3.27 (s, 3H), 4.29 (s, 1H), 4.67 (s, 1H), 4.75–4.81 (m, 1H), 5.36–5.45 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.9 (q), −4.8 (q), 18.1 (q), 18.2 (s), 25.9 (q), 27.9 (t), 29.5 (t), 29.8 (t), 33.0 (t), 35.2 (t), 38.1 (t), 44.0 (d), 45.4 (d), 49.5 (d), 50.1 (d), 54.2 (q), 79.1 (d), 80.6 (d), 109.5 (d), 125.0 (d), 131.8 (d); exact mass m/z calcd for $C_{23}H_{42}NaO_3Si$ 417.2801, found 417.2800.

5.1.21. *tert*-Butyl[(5*R,8*S**,9*S**)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (37a).** Et_3N (0.2 mL) was added to CH_2Cl_2 (9.8 mL). An aliquot (1.0 mL, 0.14 mmol) was added to a stirred solution of **36a** (minor isomer at CHOH) (48 mg, 0.12 mmol) in CH_2Cl_2 (2 mL). The solution was cooled to 0 °C and an aliquot (1.0 mL, 0.14 mmol) of a solution of MsCl (0.1 mL) in CH_2Cl_2 (9.9 mL) was injected. The cold bath was removed and stirring was continued for 5 h. Examination by TLC (silica, 1:4 EtOAc–hexane) showed the presence of some **36a** (minor isomer at CHOH). More Et_3N (0.2 mL stock solution) was added, followed by MsCl (0.1 mL stock solution) and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1×10 cm), using 35% EtOAc–hexane containing Et_3N (1%), gave the mesylate (55 mg, 96%) as an oil, which was used without characterization.

Et_3BHLi (1 M, THF, 1.12 mL) was added dropwise to a stirred solution of the mesylate (minor isomer at CHOMs) (55.0 mg, 0.112 mmol) in THF (5 mL), and stirring was continued for 23 h. More Et_3BHLi (1 M, THF, 1.12 mL) was added dropwise and the mixture was refluxed for 4 h. Another portion of Et_3BHLi (1 M, THF, 1.12 mL) was added dropwise and the mixture was refluxed for 5 h. No further change was observed by TLC (silica, 3:7 EtOAc–hexane). The mixture was cooled to 0 °C and water (1 mL), followed by aqueous NaOH (4 N, 2 mL) and H_2O_2 (30%, 1 mL) were added. The mixture was stirred for 15 min and then diluted with EtOAc (10 mL) and filtered. The solid was washed with EtOAc (3×5 mL). Evaporation of the filtrate and flash chromatography over silica gel (1×20 cm), using 1:3 EtOAc–hexane, gave **37a** (24 mg, 52%).

5.1.22. Cyclopenta-2,4-dienyl(4-methoxyphenyl)dimethylsilane (38). Cyclopentadiene dimer was cracked by heating (oil bath at 180 °C) in a simple distillation unit with a receiver cooled to −78 °C and protected from moisture. BuLi (1.6 M in hexanes, 78.0 mL, 125 mmol) was added dropwise over 45 min to a stirred and cooled (−78 °C) solution of freshly generated cyclopentadiene [9.9 mL (taken up into a syringe), 125 mmol] in dry THF (250 mL). After the addition the cold bath was replaced by an ice-water bath and stirring was continued for 30 min. The lithiated cyclopentadiene was added via cannula at

−78 °C over 90 min to a solution of chloro(4-methoxyphenyl)dimethylsilane[23a] (25.02 g, 125.1 mmol) in THF (250 mL) [a slight vacuum was applied to the silane-containing flask, and N_2 was admitted to the flask containing the lithiated cyclopentadiene]. The cooling bath was removed and the mixture was stirred overnight. Most (ca. 90%) of the THF was removed (rotary evaporator, water pump) and cold water (ca. 200 mL) was added to the residue, which was extracted with Et_2O (4×200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brownish, oily liquid (26 g, 90%), which is suitable for the next step. FTIR ($CDCl_3$ cast) 1593, 1502, 1278, 1247, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (The integration of the ^1H NMR spectrum is poor, the main signals being) δ 0.20 (s, 6H), 3.56–3.64 (m, 1H), 3.84 (s, 3H), 6.40–6.70 (m, 4H), 6.90–7.00 (m, 2H), 7.44–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1 (q), 54.9 (d or q), 55.0 (d or q), 113.52 (d), 113.54 (d), 129.0 (s), 134.9 (d), 135.0 (d), 160.6 (s); exact mass *m/z* calcd for $C_{14}H_{18}OSi$ 230.1127, found 230.1126.

5.1.23. (2-*endo*,3-*exo*,7-*anti*)-7-[(4-Methoxyphenyl)dimethylsilanyl]bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (40). Et_2AlCl (90.3 mL, 1 M in hexanes, 90.3 mmol) was added dropwise over 45 min to a stirred and cooled (−78 °C; dry ice-acetone) suspension of dimethyl fumarate (13.0 g, 90.3 mmol) in dry CH_2Cl_2 (90 mL). After 10 min, the cyclopentadienylsilane **38** (26.0 g, 113 mmol) was added dropwise by syringe over 60 min to the stirred mixture. The nitrogen inlet was removed and the reaction vessel was transferred to a preprepared bath set at −20 °C. Stirring at −20 °C was continued for 24 h (TLC control, silica, 1:9 EtOAc–hexane), by which time no dimethyl fumarate was present. The mixture was poured into saturated aqueous potassium sodium tartrate (200 mL) and the resulting thin emulsion was filtered through a pad of Celite (1×10 cm), using CH_2Cl_2 as a rinse. The aqueous phase of the filtrate was extracted with CH_2Cl_2 (4×200 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and a portion of the residue was purified by flash chromatography over silica gel (250 g silica gel for 10 g of the crude product, 5.5×22 cm), using first 1:9 EtOAc–hexane. After the excess of cyclopentadienylsilane had been eluted, the solvent was changed to 3:17 EtOAc–hexane. Another three batches of the crude Diels–Alder adduct were chromatographed on the same column, the 3:17 EtOAc–hexane solvent being expelled from the column before adding 1:9 EtOAc–hexane and applying the next batch. The Diels–Alder adduct was obtained as a colorless liquid (31.7 g, 94% based dimethyl fumarate as the limiting reagent). FTIR ($CHCl_3$ cast) 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 6H), 0.36–0.44 (m, 1H), 2.73 (d, J=4.5 Hz, 1H), 3.16–3.20 (m, 1H), 3.28–3.33 (m, 1H), 3.35–3.38 (m, 1H), 3.61 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 5.95 (dd, J=5.4, 2.7 Hz, 1H), 6.16 (dd, J=5.7, 3.0 Hz, 1H), 6.87–6.90 (m, 1H), 7.33–7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.4 (q), −1.3 (q), 14.0 (d), 22.6 (t), 31.5 (t), 48.6 (d), 48.8 (d), 49.1 (d), 50.1 (d), 50.7 (d), 51.5 (d), 51.8 (d), 54.7 (q), 113.4 (d), 129.7 (s), 134.7 (d), 134.9 (d), 137.1 (d), 160.3 (s), 173.1 (s), 174.6 (s); exact mass *m/z* calcd for $C_{20}H_{26}NaO_5Si$ 397.1447, found 397.1442.

5.1.24. (2-*endo*,3-*exo*,7-*anti*)-7-(Fluorodimethylsilanyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (41). AcOH (13.6 mL, 238 mmol) was added dropwise to a stirred and cooled (ice bath) solution of **40** (16.8 g, 44.9 mmol) in CH_2Cl_2 (170 mL) over 10 min. $BF_3{\cdot}OEt_2$ (13.6 mL, 107 mmol) was added dropwise over 10 min with stirring. The cooling bath was removed and stirring was continued for 1 h. The mixture was poured into ice-water (100 mL) with swirling, and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent (rotary evaporator) at room temperature gave the crude product (which contains anisole). The material was used immediately for the next step.

5.1.25. (2-*endo*,3-*exo*,7-*anti*)-7-(Methoxydimethylsilanyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dimethyl ester (42). $NaHCO_3$ (8.4 g. 100 mmol) was tipped into a stirred and cooled (ice bath) solution of the above crude product (18.32 g) in dry THF (84 mL). Dry MeOH (84 mL) was then added dropwise over 10 min from a syringe. The cold bath was removed and stirring was continued for 24 h. Evaporation of the solvents (rotary evaporator) at room temperature gave a semisolid. This was diluted with CH_2Cl_2 (200 mL) and the mixture was filtered through a sintered disc, the solids being washed with CH_2Cl_2. The solvent was evaporated (rotary evaporator) at room temperature to afford the crude product as an oil, which was used directly in the next step.

5.1.26. (2-*endo*,3-*exo*,7-*anti*)-7-Hydroxybicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic acid dimethyl ester (21). Powdered KF (14 g, 0.24 mol) and $KHCO_3$ (already in powder form, 24 g, 0.24 mol) were tipped into a stirred and cooled (ice bath) solution of the above methoxysilane (theoretical amount would be 13.34 g, 44.92 mmol) in 1:1 THF–MeOH (150 mL). Then H_2O_2 (30%, 134 mL, 1.18 mol) was added over 30 min from a syringe. The cooling bath was removed and stirring was continued overnight. The mixture was concentrated using a rotary evaporator at room temperature until 200 mL of solvent had been collected (the evaporator was equipped with a dry ice cold finger condenser). The residual mixture was filtered through a sintered disc and the solid was washed with CH_2Cl_2. The filtrate separated into two layers and the aqueous phase was extracted with CH_2Cl_2 (4×100 mL). *CAUTION*. The discarded aqueous phase should then be diluted with an equal volume of water, otherwise it becomes warm. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (1×100 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5×21 cm), using 1:1 EtOAc–hexane, gave pure **21** (6.46 g, 64% over three steps).

On a larger scale (15.7 g of the methoxysilane) the yield was 53%.

5.1.27. (2-*endo*,3-*exo*,7-*anti*)-7-Hydroxybicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic acid dimethyl ester (21). *Preparation without isolation of the methoxysilane intermediate* AcOH (8.23 mL, 144 mmol) was added dropwise

over 10 min to a stirred and cooled (ice bath) solution of **40** (10.15 g, 27.13 mmol) in CH_2Cl_2 (150 mL). $BF_3{\cdot}OEt_2$ (8.25 mL, 65.1 mmol) was then added dropwise over 10 min. The cooling bath was removed and stirring was continued for 1 h. The mixture was poured into ice-water (100 mL) with swirling, and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent (rotary evaporator) at room temperature gave the crude fluorosilane **41** (which contains anisole) (10.0 g). This material was used immediately for the next step.

$KHCO_3$ (16.31 g, 162.8 mmol) was added over 15 min in three equal portions to a stirred and cooled (ice bath) solution of the above crude product (**41**) (10.0 g) in a mixture of dry THF (75 mL) and dry MeOH (75 mL). The cold bath was removed and stirring continued for 8 h. [A very small amount of **41** was still present, as judged by TLC (silica, 1:9 EtOAc–hexane)]. The mixture was cooled in an ice bath and KF (7.88 g, 136 mmol) was tipped in, and then H_2O_2 (30%, 77.0 mL, 678 mmol) was added over 20 min. The ice bath was removed and stirring was continued for 8 h. The mixture was concentrated on a rotary evaporator at room temperature until 100 mL of solvent had been collected, the evaporator being equipped with a solid CO_2 cold finger condenser. The residual mixture was cooled to −15 °C (ice-salt bath) and ice-cold water (100 mL) and then EtOAc (100 mL) were added slowly. Saturated aqueous $Na_2S_2O_3$ (100 mL) was then added over 30 min with vigorous stirring. *CAUTION*. If the $Na_2S_2O_3$ solution is added at a faster rate, an exothermic reaction occurs and the contents of the flask are ejected. The mixture was allowed to come to room temperature over a period of 1 h by maintaining the mixture in an ice bath for 30 min and then in a cold water bath (25 °C) for 30 min. Stirring was then continued for 4 h. The mixture was filtered through a sintered disc and the solids were washed with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (4×100 mL) and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (4×20 cm), using 1:1 EtOAc–hexane, gave pure alcohol **21** (4.74 g, 77% overall from **40**).

5.1.28. *tert*-Butyl[(5*R* *,8*S* *,9*S* *)-5-Methoxy-9-(2-methoxyvinyl)-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (43a). A solution of *t*-BuOK (1.1734 g, 10.456 mmol) in THF (20 mL) was added dropwise to a stirred and cooled (0 °C) suspension of Ph_3PCH_2OMeCl (dried for 2 h at 80 °C under oil pump vacuum, 3.9430 g, 11.502 mmol) in THF (30 mL plus 5 mL as a rinse). Stirring was continued for 5 min and then a solution of the **35a** (1.1828 g, 3.834 mmol) in THF (20 mL plus 5 mL as a rinse) was added over 10 min by syringe to the ruby-red solution. Stirring at 0 °C was continued for 4 h, and the mixture was quenched at 0 °C with saturated aqueous $NaHCO_3$ solution (20 mL). The cold bath was removed and stirring was continued for 30 min. The mixture was filtered through a sintered disc and the solids were washed with hexane (3×25 mL). The organic filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography over silica gel (3.5×29 cm), using 1:9 EtOAc–hexane, gave **43a** (1.0607 g, 81%) as a 2.6:1 mixture of *Z*,*E* isomers. FTIR (Et_2O cast) unexceptional; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 0.9H, minor isomer) 0.02 (s, 2.1H, major isomer), 0.03 (s, 0.9H, minor isomer), 0.04 (s, 2.1H, major isomer), 0.83 (s, 9H), 1.18–1.22 (m, 1H), 1.77–1.83 (m, 1H), 1.88–1.91 (m, 1H), 1.96–1.97 (m, 1H), 2.13–2.18 (m, 1H), 2.67–2.69 (m, 1H), 3.27 (s, 3H), 3.49 (s, 2.1H for major isomer), 3.56 (s, 0.9H for minor isomer), 4.29–4.33 (m, 1H), 4.57–4.60 (m, 1H), 4.65 (s, 1H), 4.70–4.75 (m, 1H), 5.78 (d, *J*=8.0 Hz, 0.3H, minor isomer), 6.26 (d, *J*=12.0 Hz, 0.7H, major isomer); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.98 (q), −4.90 (q), 17.9 (s), 25.7 (q), 36.9 (t), 37.1 (t), 38.3 (d), 41.9 (d), 46.2 (d), 46.7 (d), 49.3 (d), 49.5 (d), 50.1 (d or q), 50.6 (d or q), 54.48 (d or q), 54.51 (d or q), 56.19 (d or q), 56.22 (d or q), 59.60 (d or q), 59.62 (d or q), 78.3 (d), 78.7 (d), 80.39 (d), 80.45 (d), 106.35 (d), 106.38 (d), 109.0 (d), 109.3 (d), 110.1 (d), 145.6 (d), 147.1 (d); exact mass *m*/*z* calcd for $C_{18}H_{32}NaO_4Si$ 363.1962, found 363.1961.

Later experiments were done using a mixture of **35a** and **35b**; these experiments gave a mixture of **43a** and **43b** in 90% yield (starting with 4.5 g of aldehyde).

5.1.29. *tert*-Butyl[(5*R* *,8*R* *,9*R* *)-5-methoxy-9-(2-methoxyvinyl)-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (43b). A solution of *t*-BuOK (321 mg, 2.85 mmol) in THF (10 mL) was added at a fast dropwise rate to a stirred and cooled (0 °C) suspension of Ph_3PCH_2-OMeCl (dried for 2 h at 80 °C under oil pump vacuum, 1.0747 g, 3.1351 mmol) in THF (15 mL). Stirring was continued for 10 min and then a solution of the **35b** (322.4 mg, 1.045 mmol) in THF (5 mL plus 5 mL as a rinse) was added by syringe to the ruby-red solution. Stirring at 0 °C was continued for 4 h, and the mixture was quenched at 0 °C with saturated aqueous $NaHCO_3$ solution (25 mL) and stirred for 10 min. The aqueous phase was extracted with Et_2O (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4×20 cm), using first 1:19 EtOAc–hexane (500 mL) to elute nonpolar material, and then 1:9 EtOAc–hexane, gave **43b** (266.7 mg, 75%) as a 2:1 mixture of *Z*,*E* isomers. FTIR (Et_2O cast) unexceptional; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 0.9H), 0.01 (s, 2.1H), 0.02 (s, 0.9H), 0.03 (s, 2.1H), 0.80 (s, 9H), 1.23–1.32 (m, 1H), 1.78 (br s, 0.7H), 1.88 (br s, 0.3H for minor isomer), 2.06–2.18 (m, 2H), 2.51–2.55 (m, 1H), 2.69 (d, *J*=8.0 Hz, 0.7H), 3.07 (d, *J*=8.4 Hz, 0.3H), 3.36 (s, 3H), 3.50 (s, 2.1H), 3.56 (s, 0.9H), 4.24–4.30 (m, 1H), 4.44 (dd, *J*=7.2, 5.2 Hz, 1H), 4.73 (dd, *J*=12.4, 8.8 Hz, 1H), 4.94 (dd, *J*=4.0, 1.2 Hz, 1H), 5.76 (d, *J*=8.0 Hz, 0.3H), 6.30 (d, *J*=12.0 Hz, 0.7H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ −5.0 (q), −4.9 (q), 18.0 (s), 25.7 (q), 33.2 (d), 36.1 (t), 36.3 (d), 36.4 (t), 45.6 (d), 45.8 (d), 47.4 (d), 51.83 (d or q), 51.9 (d or q), 56.2 (d or q), 56.4 (d or q), 56.5 (d or q), 59.7 (d or q), 78.0 (d), 78.5 (d), 79.97 (d), 80.02 (d), 106.8 (d), 107.29 (d), 107.32 (d), 110.2 (d), 145.5 (d), 147.4 (d); exact mass *m*/*z* calcd for $C_{18}H_{32}NaO_4Si$ 363.1962, found 363.1963.

Later experiments were done using a mixture of **35a** and **35b**; these experiments gave a mixture of **43a** and **43b** in 90% yield (starting with 4.5 g of aldehyde).

5.1.30. [(5*R* *,8*S* *,9*S* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]acetaldehyde (44a). $Hg(OAc)_2$ (2.60 g, 8.13 mmol) was added in

one portion to a stirred and cooled (0 °C) solution of enol ethers **43a** (921 mg, 2.70 mmol) in THF (70 mL) and water (7 mL). The cooling bath was removed and stirring was continued for 3 h. The mixture was recooled to 0 °C, diluted with Et_2O (100 mL) and quenched by dropwise addition (over 10 min) of freshly prepared saturated aqueous KI solution (50 mL). The ice bath was removed and stirring was continued for 15 min. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with saturated aqueous KI (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×29 cm), using 7:13 EtOAc–hexane, gave **44a** (829.3 mg, 94%). FTIR ($CDCl_3$ cast): 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.04 (s, 3H), −0.02 (s, 3H), 0.78 (s, 9H), 1.19 (d, J=12.0 Hz, 1H), 1.71 (br s, 1H), 1.78 (br s, 1H), 1.83 (t, J=7.4 Hz, 1H), 2.09–2.14 (m, 1H), 2.47 (d, J=8.0 Hz, 2H), 2.63 (br s, 1H), 3.21 (s, 3H), 4.21 (br s, 1H), 4.52 (t, J=6.0 Hz, 1H), 4.69 (br s, 1H), 9.67 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1 (q), −5.0 (q), 17.9 (s), 25.6 (q), 36.5 (d), 37.3 (t), 44.5 (d), 48.9 (d), 49.1 (t), 49.6 (d), 54.4 (q), 78.1 (d), 80.0 (d), 108.8 (d), 200.4 (d); exact mass m/z calcd for $C_{17}H_{31}O_4Si$ 327.1986, found 327.1989.

Later experiments were done using a mixture of **43a** and **43b**; these experiments gave a mixture of **44a** and **44b** in 94% yield (starting with 7.9 g of enol ethers).

5.1.31. [(5*R* *,8*R* *,9*R* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]acetaldehyde (44b). $Hg(OAc)_2$ (674 mg, 2.11 mmol) was added in one portion to a stirred and cooled (0 °C) solution of enol ethers **43b** (238.7 mg, 0.7009 mmol) in THF (18 mL) and water (1.8 mL). The cooling bath was removed and stirring was continued for 3 h. The mixture was cooled (0 °C) and quenched by slow addition (over 10 min) of freshly prepared saturated aqueous KI solution (20 mL). Stirring was continued for 10 min, the cold bath was removed, and the aqueous phase was extracted with Et_2O (3×25 mL). The combined organic extracts were washed with saturated aqueous KI (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5×27 cm), using first 1:9 EtOAc–hexane (500 mL) and then 7:13 EtOAc–hexane, gave **44b** (210.8 mg, 92%). FTIR (Et_2O cast): 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.00 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 1.31 (d, J=12.8 Hz, 1H), 1.80 (br s, 1H), 1.97 (dd, J=6.4, 4.4 Hz, 1H), 2.19 (ddd, J=13.2, 7.6, 4.0 Hz, 1H), 2.30 (ddd, J=15.6, 8.0, 2.4 Hz, 1H), 2.42 (ddd, J=15.6, 8.0, 2.4 Hz, 1H), 2.54–2.58 (m, 1H), 2.67 (dt, J=8.0, 2.0 Hz, 1H), 3.38 (s, 3H), 4.24 (br s, 1H), 4.44 (dd, J=12.4, 4.8 Hz, 1H), 4.91 (d, J=4.0 Hz), 9.64 (t, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ −4.99 (q), 4.95 (q), 17.9 (s), 25.6 (q), 32.0 (d), 36.7 (t), 43.6 (d), 45.9 (d), 48.5 (t), 51.8 (d or q), 56.7 (d or q), 77.7 (d), 79.7 (d), 106.9 (d), 202.0 (d); exact mass m/z calcd for $C_{17}H_{30}NaO_4Si$ 349.1806, found 349.1808.

Later experiments were done using a mixture of **43a** and **43b**; these experiments gave a mixture of **44a** and **44b** in 94% yield (starting with 7.9 g of enol ethers).

5.1.32. 1-[(5*R* *,8*S* *,9*S* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]-(*E*)-oct-6-en-2-ol (45a). *Use of TMEDA*. K (2.235 g, 57.33 mmol) cut into small cubes (ca. 2×2×2 mm) under hexane in a mortar was added to a stirred suspension of anhydrous $MgCl_2$ (2.898 g, 30.51 mmol) in THF (60 mL) (the metal pieces were removed with tweezers from the hexane, shaken free of solvent and added to the reaction mixture). The mixture was refluxed for 2 h, cooled first to room temperature, and then to 0 °C. A solution of (*E*)-6-bromo-2-hexene[27] (1.38 mL, 10.2 mmol) and $BrCH_2CH_2Br$ (2 drops) in THF (15 mL) was added dropwise from a syringe. The mixture was stirred at 0 °C for 4 h. At this stage no bromide was detected by TLC (silica, 1:19 EtOAc–hexane). The ice-bath was removed and replaced by a dry ice-acetone bath. Dry TMEDA (15.0 mL, 99.4 mmol) was added to the stirred and cooled (−78 °C) Grignard solution, and a solution of **44a** (829 mg, 2.54 mmol) in THF (15 mL plus 5 mL as a rinse) was added dropwise by syringe. The reaction flask was transferred to a cooling bath (Haake immersion cooler, model EK 51-1) set at 0 °C, and stirring was continued overnight. MeOH (10 mL) was added at 0 °C, and the mixture was stirred for 15 min and diluted with Et_2O. The mixture was filtered through a sintered disk, and the residue was washed with Et_2O. Saturated aqueous NH_4Cl (20 mL) was added to the filtrate, and the mixture was filtered, using Et_2O to wash the solid. The organic filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5×29 cm), using 3:17 EtOAc–hexane (500 mL) and then 1:3 EtOAc–hexane (200 mL), and then 7:13 EtOAc–hexane (200 mL), gave (**45a**, major isomer at CHOH) (374.5 mg) and a mixed fraction of major and minor isomers (**45a**, major isomer at CHOH and minor isomer at CHOH) (519.6 mg), total yield 894.1 mg (86%). Compound **45a** (major isomer at CHOH). FTIR ($CDCl_3$ cast): 3461 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.01 (s, 3H), 0.01 (s, 3H), 0.81 (s, 9H), 1.17 (d, J=12.4 Hz, 1H), 1.26–1.60 (m, 11H), 1.70–1.75 (m, 1H), 1.80–1.90 (m, 1H), 1.90–2.00 (m, 2H), 2.10–2.15 (m, 1H), 2.60–2.65 (m, 1H), 3.25 (s, 3H), 3.55–3.65 (m, 1H), 4.26 (br s, 1H), 4.53 (t, J=6.8 Hz, 1H), 4.62 (br s, 1H), 5.36–5.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.99 (q), −4.90 (q), 17.8 (q), 17.9 (s), 25.4 (t), 25.7 (q), 32.4 (t), 37.4 (t), 37.6 (t), 39.6 (d), 42.4 (t), 45.4 (d), 48.5 (d), 49.6 (d), 54.4 (q), 69.4 (d), 78.5 (d), 80.5 (d), 109.1 (d), 125.2 (d), 130.9 (d); exact mass m/z calcd for $C_{23}H_{42}NaO_4Si$ 433.2745, found 433.2748.

The minor sidechain alcohol isomer (which was obtained pure from another experiment done in the same way, but on a smaller scale): FTIR ($CDCl_3$ cast): 3434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.18 (d, J=12.8 Hz, 1H), 1.30–1.60 (m, 8H), 1.61–1.65 (m, 3H), 1.78–1.84 (m, 1H), 1.90–2.02 (m, 3H), 2.10–2.20 (m, 1H), 2.62–2.70 (m, 1H), 3.28 (s, 3H), 3.56–3.65 (m, 1H), 4.276 (br s, 1H), 4.58 (dd, J=7.2, 5.2 Hz, 1H), 4.64 (br s, 1H), 5.36–5.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.99 (q), −4.89 (q), 17.8 (q), 17.9 (s), 25.4 (t), 25.7 (q), 32.4 (t), 37.3 (t), 37.4 (t), 39.9 (d), 42.7 (d), 44.4 (d), 49.42 (d), 49.44 (d), 54.5 (q), 70.4 (d), 78.4 (d), 80.4 (d), 109.2 (d), 125.2 (d), 130.9 (d); exact mass m/z calcd for $C_{23}H_{42}NaO_4Si$ 433.2745, found 433.2745.

Experiment in absence of TMEDA. K (3.81 g, 97.4 mmol) cut into small cubes (ca. 2×2×2 mm) under hexane in a

mortar was added to a stirred suspension of anhydrous $MgCl_2$ (4.88 g, 51.4 mmol) in THF (100 mL). (The metal pieces were removed with tweezers from the hexane, shaken free of solvent and added to the reaction mixture.) The mixture was refluxed for 2 h, and then cooled first to room temperature, and then to 0 °C. A solution of (*E*)-6-bromo-2-hexene[27] (3.49 mL, 4.29 g, 25.7 mmol) and $BrCH_2CH_2Br$ (4 drops) in THF (25 mL) was added dropwise from a syringe. The mixture was stirred at 0 °C for 4 h. At this stage no bromide was detected by TLC (silica, 1:19 EtOAc–hexane). The ice-bath was removed and replaced by a dry ice-acetone bath. A solution of **44a** (2.10 g, 6.43 mmol) in THF (20 mL plus 5 mL as a rinse) was added dropwise by syringe. The reaction flask was transferred to a cooling bath (Haake immersion cooler, model EK 51-1) set at 0 °C, and stirring was continued overnight. MeOH (25 mL) was added at 0 °C, and the mixture was stirred for 15 min and diluted with Et_2O (50 mL). The mixture was filtered through a sintered disk, and the residue was washed with Et_2O (3×25 mL). Saturated aqueous NH_4Cl (25 mL) was added to the filtrate, and the mixture was filtered, using Et_2O (3×25 mL) to wash the solid. The organic filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5×26 cm), using 1:4 EtOAc–hexane, gave **45a** (2.33 g, 89%) as a mixture of isomers (isomeric at CHOH).

Later experiments were done using a mixture of **44a** and **44b**; these experiments gave a mixture of **45a** and **45b** in 95% yield (starting with 5.1 g of aldehydes).

5.1.33. 1-[(5*R* *,8*R* *,9*R* *)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{6,7}]non-9-yl]-(*E*)-oct-6-en-2-ol (45b). K (539 mg, 13.8 mmol) cut into small cubes (ca. 2×2×2 mm) under hexane in a mortar was added to a stirred suspension of anhydrous $MgCl_2$ (698 mg, 7.34 mmol) in THF (15 mL). (The metal pieces were removed with tweezers from the hexane, shaken free of solvent and added to the reaction mixture.) The mixture was refluxed for 2 h, and then cooled first to room temperature, and then to 0 °C. A solution of (*E*)-6-bromo-2-hexene[27] (0.33 mL, 2.5 mmol) and $BrCH_2CH_2Br$ (2 drops) in THF (5 mL) was added dropwise from a syringe over 5 min, using THF (5 mL) as a rinse. The mixture was stirred at 0 °C for 3.5 h. At this stage no bromide was detected by TLC (silica, 1:19 EtOAc–hexane). The ice-bath was removed and replaced by a dry ice-acetone bath. Dry TMEDA (5.0 mL, 33 mmol) was added to the stirred and cooled (−78 °C) Grignard solution, and a solution of **44b** (186 mg, 0.569 mmol) in THF (5 mL plus 2 mL as a rinse) was added dropwise by syringe. The reaction flask was transferred to a cooling bath (Haake immersion cooler, model EK 51-1) set at 0 °C, and stirring was continued for 20 h. MeOH (10 mL) was added over 10 min at 0 °C, and the mixture was stirred for 15 min. Et_2O (25 mL) was added, and the mixture was filtered through a sintered disc. The filtrate was quenched with saturated aqueous NH_4Cl (8 mL), and the mixture was filtered through a sintered disc, and the filtrate was dried ($MgSO_4$) and evaporated. The residue was kept overnight under good oil pump vacuum (0.001 mm Hg) to remove the hexenol formed in the reaction. Flash chromatography of the residue over silica gel (2×24 cm), using 1:3 EtOAc–hexane, gave **45b** (206.6 mg, 88%) as a mixture of isomers, which was used as such for the mesylation step. FTIR (Et_2O cast): 3508 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 6H), 0.82 (s, 9H), 1.20–1.52 (m, 7H), 1.60–1.65 (m, 3H), 1.70–1.75 (m, 1H), 1.90–2.25 (m, 5H), 2.50–2.55 (m, 1H), 2.76 (br s, 0.5H), 3.03 (br s, 0.5H), 3.45 (s, 3H), 3.55–3.70 (m, 1H), 4.25 (d, J=10.4 Hz, 1H), 4.43 (ddd, J=11.6, 7.2, 5.2 Hz, 71H), 4.91 (dd, J=7.6, 3.6 Hz, 1H), 5.38–5.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.95 (q), −4.93 (q), 17.87 (q), 17.96 (s), 25.62 (t), 25.68 (d), 25.89 (t), 32.51 (t), 32.60 (t), 34.4 (d), 36.4 (t), 36.55 (d), 36.64 (t), 37.2 (t), 37.5 (t), 40.8 (t), 43.1 (t), 43.9 (d), 44.3 (d), 45.7 (d), 47.7 (d), 51.5 (d), 51.7 (d), 56.97 (q), 56.99 (q), 67.6 (d), 72.8 (d), 78.07 (d), 78.15 (d), 79.9 (d), 80.2 (d), 106.9 (d), 107.1 (d), 124.83 (d), 124.85 (d), 131.26 (d), 131.29 (d); exact mass *m*/*z* calcd for $C_{23}H_{42}NaO_4Si$ 433.2745, found 433.2740.

Later experiments were done using a mixture of **44a** and **44b**; these experiments gave a mixture of **45a** and **45b** in 95% yield (starting with 5.1 g of aldehydes).

5.1.34. Methanesulfonic acid 1-[(5*R* *,8*S* *,9*S* *)-8-(*tert*-butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo-[4.2.1.0^{6,7}]non-9-ylmethyl]-(*E*)-hept-5-en-yl ester (46a). $MeSO_2Cl$ (0.25 mL, 3.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **45a** (mixture of both alcohol isomers) (865 mg, 2.11 mmol) and Et_3N (0.58 mL, 4.2 mmol) in dry CH_2Cl_2 (10 mL). The cold bath was removed and stirring was continued for 5 h. The mixture was diluted with Et_2O (25 mL) and quenched with water (25 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude mesylates **46a** (1.032 g, ca. 100%), which were used directly in the next step without characterization.

Later experiments were done using a mixture of **45a** and **45b**; these experiments also appeared to be quantitative (starting with 6.1 g of the alcohols).

5.1.35. Methanesulfonic acid 1-[(5*R* *,8*R* *,9*R* *)-8-(*tert*-butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo-[4.2.1.0^{6,7}]non-9-ylmethyl]-(*E*)-hept-5-en-yl ester (46b). A stock solution of $MeSO_2Cl$ (0.6 mL) in CH_2Cl_2 (9.4 mL) was prepared. An aliquot (1.0 mL, 0.78 mmol) of the stock solution was added dropwise to a stirred and cooled (0 °C) solution of **45b** (mixture of both isomers at CHOH) (200 mg, 0.487 mmol) and Et_3N (0.13 mL, 0.93 mmol) in dry CH_2Cl_2 (5 mL). The cold bath was left in place, but was not recharged, and stirring was continued overnight. The mixture was quenched with water (10 mL) and diluted with CH_2Cl_2 (25 mL). The organic phase was dried ($MgSO_4$) and evaporated to give crude mesylates **46b** (238 mg, 100%), which were used directly in the next step without characterization.

Later experiments were done using a mixture of **45a** and **45b**; these experiments also appeared to be quantitative (starting with 6.1 g of the alcohols).

5.1.36. *tert*-Butyl[(5*R* *,8*S* *,9*S* *)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (37a). A solution of **46a** (mixture of isomers at *C*HOMs) (1.03 g, 2.11 mmol) in THF (10 mL) was injected

dropwise over 10 min to a stirred slurry of $LiAlH_4$ (240 mg, 6.33 mmol) in THF (10 mL). An additional portion of THF (10 mL) was used as a rinse. The mixture was refluxed for 8 h, and then cooled to 0 °C. MeOH (5 mL) was added dropwise with stirring, and stirring was continued for 15 min. Saturated aqueous Na_2SO_4 (10 mL) was added, the ice bath was removed, and stirring was continued for 30 min, by which time the mixture had attained room temperature. The mixture was diluted with Et_2O (25 mL) and filtered through a sintered funnel. The solids were washed with Et_2O (3×25 mL) and the organic filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5×29 cm), using 1:9 EtOAc–hexane, gave **37a** (593.4 mg, 71% over two steps).

Later experiments were done using a mixture of **46a** and **46b**; these experiments gave a mixture of **37a** and **37b** in 90% yield from the parent alcohols (starting with 6.1 g of **45a** and **45b**).

5.1.37. *tert*-Butyl[(5*R,8*R**,9*R**)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{6,7}]non-8-yloxy]dimethylsilane (37b).** A solution of **46b** (mixture of isomers at C*H*OMs) (238 mg, 0.49 mmol) in THF (5 mL) was injected dropwise over 5 min to a stirred slurry of $LiAlH_4$ (55.8 mg, 1.46 mmol) in THF (8 mL). An additional portion of THF (2 mL) was used as a rinse. The mixture was refluxed for 6 h, and then cooled to 0 °C. EtOAc (2 mL) was added with stirring and stirring was continued for 10 min. The mixture was diluted with Et_2O (10 mL), and aqueous saturated Na_2SO_4 (3 mL) was added. The ice bath was removed, and stirring was continued for 15 min. The mixture was filtered through a sintered funnel, and the solids were washed with Et_2O (2×5 mL). The organic filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5×22 cm), using 1:9 EtOAc–hexane, gave **37b** (141.5 mg, 73% over two steps). FTIR (Et_2O cast): unexceptional; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 6H), 0.82 (s, 9H), 1.15–1.35 (m, 9H), 1.60–1.65 (m, 3H), 1.75–1.80 (m, 1H), 1.87–2.02 (m, 4H), 2.14 (ddd, J=12.8, 7.6, 4.0 Hz, 1H), 2.45–2.55 (m, 1H), 3.37 (s, 3H), 4.25 (br s, 1H), 4.41 (dd, J=7.2, 4.4 Hz, 1H), 4.90 (d, J=4.4 Hz, 1H), 5.35–5.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9 (q), 17.8 (q), 17.9 (s), 25.7 (q), 27.4 (t), 29.5 (t), 32.5 (t), 34.8 (t), 36.8 (t), 38.1 (d), 43.5 (d), 46.4 (d), 51.6 (d), 56.6 (q), 78.1 (d), 79.8 (d), 107.5 (d), 124.5 (d), 131.5 (d); exact mass m/z calcd for $C_{23}H_{42}NaO_3Si$ 417.2795, found 417.2801.

5.1.38. (2-*endo*,5-*exo*,6-*endo*,7-*syn*)-7-(*tert*-Butyldimethylsilanyloxy)-6-[1,3]dithian-2-yl-5-[(*E*)-oct-6-enyl]bicyclo[2.2.1]heptan-2-ol (47). *From* **37a**. $TiCl_4$ (1.0 M in CH_2Cl_2, 4.2 mL, 4.2 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **37a** (562.0 mg, 1.424 mmol) and 1,3-propanedithiol (0.56 mL, 5.6 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred for 30 min at −78 °C. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the cooling bath was removed. The mixture was diluted with Et_2O (50 mL) and filtered through a pad of Celite (4×3 cm), using Et_2O (50 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.6×30 cm), using 1:12 EtOAc–hexane, gave **47** (627 mg, 94%) as a colorless oil. FTIR (Et_2O cast) 3471 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.025 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.06–2.40 (m, 21H), 2.44 (ddd, J=12.6, 10.2, 5.1 Hz, 1H), 2.72–2.92 (m, 4H), 3.99 (s, 1H), 4.70 (d, J=11.8 Hz, 1H), 4.71–4.77 (m, 1H), 5.35–5.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.03 (q), −4.99 (q), 17.89 (q), 17.94 (s), 25.7 (q), 26.0 (t), 28.6 (t), 29.2 (t), 29.5 (t), 30.2 (t), 30.3 (t), 32.5 (t), 37.3 (t), 37.4 (t), 45.1 (d), 47.9 (d), 48.3 (d), 49.2 (d), 52.7 (d), 73.6 (d), 79.8 (d), 124.6 (d), 131.6 (d); exact mass (electrospray) m/z calcd for $C_{25}H_{46}NaO_2S_2Si$ 493.2601, found 493.2606.

From **37b**. $TiCl_4$ (1.0 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **37b** (47.4 mg, 0.120 mmol) and 1,3-propanedithiol (36.2 mL, 0.36 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 30 min at −78 °C. Saturated aqueous $NaHCO_3$ (2 drops) was added and stirring was continued for 5 min. The cooling bath was removed, the mixture was diluted with Et_2O (5 mL), and stirring was continued for 15 min, by which time the mixture had attained room temperature. The solution was dried (Mg_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1×18 cm), using 3:17 EtOAc–hexane, gave **47** (45.6 mg, 81%) as a colorless oil, spectroscopically identical with material made from **37a**.

5.1.39. Benzoic acid (2-*endo*,5-*exo*,6-*endo*,7-*syn*)-7-(*tert*-butyldimethylsilanyloxy)-6-[1,3]dithian-2-yl-5-[(*E*)-oct-6-enyl]bicyclo[2.2.1]hept-2-yl ester (48). PhCOCl (0.90 mL, 7.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **47** (612 mg, 1.30 mmol) in pyridine (20.0 mL, 247 mmol). The ice bath was removed and stirring was continued for 3 h. The mixture was diluted with Et_2O (150 mL), and washed successively with water, saturated aqueous $CuSO_4$ (twice) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.6×28 cm), using 1:20 EtOAc–hexane, gave **48** (716 mg, 96%) as a white solid: mp 60–62 °C. FTIR (CH_2Cl_2 cast) 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.14–2.08 (m, 20H), 2.26–2.38 (m, 1H), 2.54–2.76 (m, 4H), 4.08 (s, 1H), 4.44 (d, J=12.2 Hz, 1H), 5.35–5.49 (m, 2H), 5.78 (dt, J=10.6, 3.9 Hz, 1H), 7.43–7.59 (m, 3H), 8.06–8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0 (q), −4.9 (q), 17.9 (q), 18.0 (s), 25.72 (q), 25.74 (t), 28.6 (t), 29.1 (t), 29.2 (t), 29.5 (t), 29.9 (t), 32.5 (t), 35.0 (t), 37.3 (t), 44.9 (d), 46.3 (d), 47.1 (d), 49.2 (d), 50.9 (d), 76.5 (d), 79.3 (d), 124.6 (d), 128.3 (d), 129.5 (d), 131.1 (s), 131.6 (d), 132.6 (d), 166.4 (s); exact mass (electrospray) m/z calcd for $C_{32}H_{50}O_3NaS_2Si$ 597.2863, found 597.2860.

5.1.40. Benzoic acid (2-*endo*,5-*exo*,6-*endo*,7-*syn*)-6-[1,3]dithian-2-yl-7-hydroxy-5-[(*E*)-oct-6-enyl]bicyclo-[2.2.1]hept-2-yl ester (49). Bu_4NF (1.0 M in THF, 1.05 mL, 1.05 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **48** (202 mg, 0.351 mmol) in THF (20 mL). Stirring was continued for 45 min at 0 °C, and saturated aqueous NH_4Cl (10 mL) was added. The mixture was diluted with Et_2O (120 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.2×35 cm), using 1:3 EtOAc–hexane, gave **49** (158 mg,

98%) as a white solid: mp 100–101 °C. FTIR (CH_2Cl_2 cast) 3429, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17–2.89 (m, 26H), 4.24 (s, 1H), 4.46 (d, J=12.2 Hz, 1H), 5.35–5.48 (m, 2H), 5.84 (dt, J=10.6, 4.0 Hz, 1H), 7.44–7.61 (m, 3H), 8.09–8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9 (q), 25.7 (t), 28.7 (t), 29.15 (t), 29.2 (t), 29.6 (t), 29.9 (t), 32.5 (t), 34.7 (t), 37.2 (t), 44.0 (d), 46.2 (d), 47.7 (d), 49.5 (d), 50.8 (d), 76.0 (d), 79.1 (d), 124.6 (d), 128.4 (d), 129.5 (d), 131.0 (s), 131.6 (d), 132.7 (d), 166.5 (s); exact mass (electrospray) m/z calcd for $C_{26}H_{37}O_3S_2$ 461.2179, found 461.2182.

5.1.41. Benzoic acid (2-*endo*,5-*exo*,6-*endo*)-6-[1,3]dithian-2-yl-5-[(*E*)-oct-6-enyl]-7-oxobicyclo[2.2.1]-hept-2-yl ester (6). NMO (62.0 mg, 0.529 mmol) and TPAP (9.5 mg, 0.027 mmol) were added successively to a stirred solution of **49** (121.0 mg, 0.2626 mmol) and 4 Å molecular sieves (350 mg) in CH_2Cl_2 (4.0 mL). Stirring was continued for 10 min. The mixture was diluted with Et_2O (10 mL), filtered through a pad of silica gel (1.5×1.2 cm), using Et_2O (30 mL) as a rinse, and evaporated. Flash chromatography of the residue over silica gel (1.1×30 cm), using 1:6 EtOAc–hexane, gave **6** (105 mg, 87%) as a colorless oil. FTIR ($CDCl_3$, cast) 1777, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.10–2.11 (m, 19H), 2.21 (d, J=5.1 Hz, 1H), 2.36–2.45 (m, 1H), 2.59–2.83 (m, 3H), 2.91 (t, J=4.0 Hz, 1H), 4.48 (d, J=12.2 Hz, 1H), 5.34–5.47 (m, 2H), 5.57 (dt, J=10.8, 4.4 Hz, 1H), 7.46–7.54 (m, 2H), 7.56–7.63 (m, 1H), 8.05–8.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9 (q), 25.5 (t), 27.8 (t), 28.6 (t), 28.9 (t), 29.2 (t), 29.4 (t), 32.5 (t), 34.0 (t), 36.7 (t), 45.5 (d), 45.6 (d), 46.3 (d), 47.8 (d), 50.5 (d), 69.3 (d), 124.7 (d), 128.5 (d), 129.5 (d), 130.2 (s), 131.4 (d), 133.2 (d), 165.9 (s), 208.3 (s); exact mass (electrospray) m/z calcd for $C_{26}H_{34}NaO_3S_2$ 481.1842, found 481.1843.

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28. For example, treatment with $NaBH_4$ resulted in replacement of the OH by H, rather than in formation of a diol. The lactol decomposed on removal of solvent from its solutions. Also, reaction with $MeOCH{=}PPh_3$ proceeded in poor yield (ca. 45%).
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Synthesis and antitubercular activity of tricyclic analogs of puupehenone

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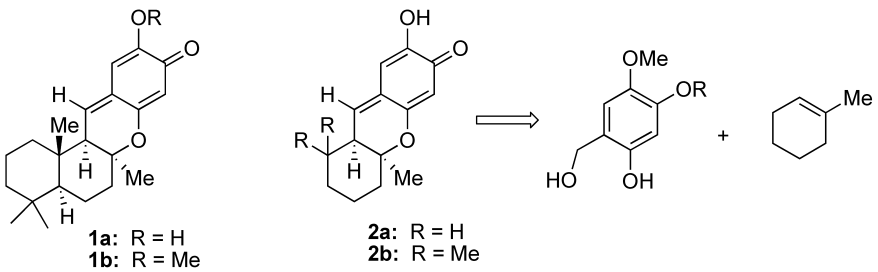
Abstract—Tricyclic analogs **2a** and **8** were prepared by four-step routes. The key step was an intermolecular hetero Diels–Alder reaction involving a quinone methide.

Puupehenone (**1a**), a tetracyclic terpene bearing a quinone methide subunit, was isolated from a deep water marine sponge, *Strongylophora hartmani*.[1] It exhibits 99% inhibition of *M. tuberculosis* $H_{37}Rv$ at 12.5 μg/ml.[2] Recently, *O*-methyl puupehenone (**1b**) was isolated and found to inhibit lipoxygenase activity at the sub micromolar level.[3] As part of a program to identify useful antitubercular agents for animal and human use,[4] we decided to synthesize and evaluate **2a**, a tricyclic analog of **1a**. Recently, a tricyclic *ortho*-quinone related to **2b** was synthesized by a route very different from our pathway and was a more active antitumor agent than **1a** (Scheme 1).[5]

We envisioned the synthesis of **2a** via a hetero-Diels–Alder reaction involving a quinone methide. Quinone methides were initially employed by Buchi in his elegant synthesis of gymnitrol.[6] The intramolecular version was used by Tius in his innovative synthesis of canniboid natural products.[7] Recently, Pettus and co-workers reported an interesting alkylative variant.[8] Quinone methides have been used in the synthesis of a number of compounds.[9]

Our route began with commercially available 3,4-dimethoxyphenol (**3**). Hydroxymethylation of phenols under basic conditions provides 2-hydroxymethylphenols.[10] When 3,4-dimethoxyphenol was treated with formalin and aqueous calcium oxide, the desired alcohol **4** was produced. Alcohol **4** was unstable to silica gel chromatography and decomposed in hours at ambient temperature. In practice, freshly prepared **4** was added to 1-methylcyclohexene and treated with trifluoroacetic acid using the protocol of Pettus[8] to afford the tricyclic benzopyran **5** in 45% yield over two steps from 3,4-dimethoxyphenol. Compound **5** was produced as a single regioisomer. The [4+2] cycloaddition generated both the carbon–carbon and carbon–oxygen bonds with a *cis* ring juncture, as determined by a NOESY experiment. The demethylation of **5** with boron tribromide afforded a catechol in 60% yield. Previous syntheses of puupehenone utilized a variety of oxidants to generate the quinone methide moiety. The reaction of PDC afforded an inseparable mixture of the desired quinone methide **2a** plus some of the *ortho*-quinone.



Scheme 1.

Keywords: Tricyclic analogs; Puupehenone; *Strongylophora hartmani*.
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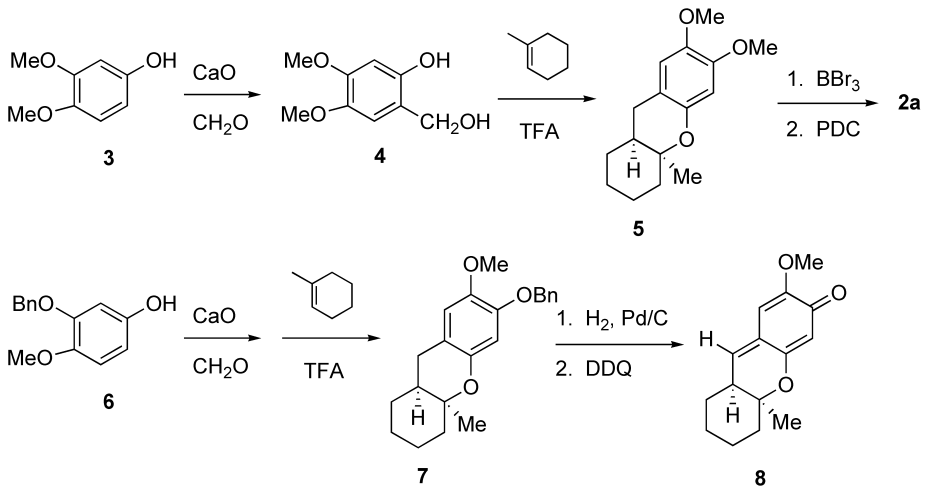

Scheme 2.

The synthesis of the *O*-methyl analog was also achieved. This synthesis began with the benzylation of isovanillin followed by oxidation of the aldehyde to a formate and hydrolysis of the formate with aqueous sodium hydroxide, to produce the known phenol **6** in 80% yield.[11] Hydroxymethylation of **6** with formalin and calcium oxide followed by a hetero-Diels–Alder reaction afforded benzopyran **7** in 40% yield over two steps. Catalytic hydrogenation[12] of compound **7** followed by treatment with DDQ, afforded product **8** in 95% isolated yield. The structure of **8** was confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and UV spectrometry (Scheme 2).

The combination of regioselective hydroxymethylation with the hetero-Diels–Alder reaction provides a convenient synthesis of tricyclic skeletons common to bioactive terpenes. This pathway should be compatible with considerable structural variation on both the phenol and alkene units.

Compound **8** and the aminoglycoside antibiotic gentamycin were tested in broth cultures of *Mycobacterium avium* subspecies *paratuberculosis* (*M. a. ptb*). Broth were sampled weekly and number of colony forming units were determined for each time point. Values are expressed as the percentage of the control treatment (bacteria in media alone). Preliminary results indicated that with a concentration of **8** at 0.625 μg/ml, after one week 43% of the bacteria remained, compared to 0.1% remaining with gentamycin.

1. Experimental

1.1. General

1.1.1. 2-Hydroxymethyl-4,5-dimethoxy-phenol (4). To 3,4-dimethoxyphenol (1.00 g, 6.5 mmol) in 20 mL of water at rt, was added 37% formalin (1.4 mL, 13.4 mmol) and followed by calcium oxide (0.18 g, 3.3 mmol). After one h, saturated aqueous ammonium chloride was added and the organic layer was extracted with ether, dried, concentrated and used immediately without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.51 (s, 1H), 4.80 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR 159.9, 149.5, 142.3, 116.7, 112.5, 101.4, 62.8, 56.8, 55.9. TLC (2:1 hexanes/ethyl acetate) R_f=0.23.

1.1.2. 6,7-Dimethoxy-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (5). To compound **4** (0.6 g, 3.26 mmol) in 40 mL of $CHCl_3$ at 0 °C, was added 1-methylcyclohexene (0.47 g, 4.9 mmol) followed by dropwise addition of trifluoroacetic acid (0.45 g, 3.91 mmol). The mixture was boiled for 3 h. After cooling to rt, the solution was diluted with water and extracted with CH_2Cl_2, dried, concentrated and purified by sgc using 4:1 hexanes/ethyl acetate to afford benzopyran **5** in 45% yield from 3,4-dimethoxyphenol. The *cis*-ring juncture was assigned by NOESY spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.38 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.03 (dd, J=12, 6 Hz, 1H), 2.25 (d, J=18 Hz, 1H), 1.94–1.90 (m, 1H), 1.67–1.24 (m, 8H), 1.19 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.4, 146.9, 142.8, 112.8, 110.31 101.3, 74.9, 56.6, 56.0, 38.7, 37.2, 29.2, 28.7, 25.8, 25.6, 21.9. HRMS (EI) calcd, for 262.1569, found 262.1572. TLC (2:1 hexanes/ethyl acetate) R_f=0.72.

1.1.3. 2-Hydroxy-10a-methyl-5,6,7,8,8a,10a-hexahydroxanthen-3-one (2a). To compound **5** (0.05 g, 0.19 mmol) in 5 mL of CH_2Cl_2 at −78 °C, was added slowly 1.0 M boron tribromide (0.57 mL, 0.57 mmol). After 30 min at −78 °C, the mixture was warmed to rt and stirred for 4 h. The solution was diluted with CH_2Cl_2 and water was added slowly. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$, brine, dried, concentrated and purified by sgc using 2:1 hexanes/ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.37 (s, 1H), 3.00 (dd, J=15, 6 Hz, 1H), 2.21 (d, J=18 Hz, 1H), 1.91–1.10 (m, 9H), 1.21 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.2, 142.9, 137.0, 116.2, 111.9, 104.3, 74.9, 38.7, 37.1, 29.1, 28.6, 25.8, 25.6, 21.9; HRMS (EI) m/z calcd for 234.1256, found 234.1259. TLC (2:1 hexanes/ethyl acetate) R_f=0.37.

To the catechol (0.020 g, 0.085 mmol) in 2 mL of CH_2Cl_2 at rt was added PDC (0.05 g, 0.13 mmol). After 4 h, the mixture was filtered through Celite and concentrated to afford **2a** and the *ortho*-quinone.

Spectra for *ortho*-quinone. ^{1}H NMR (300 MHz) 6.17(dd, J=2.1, 0.9 Hz, 1H), 5.84(s, 1H), 3.09–3.16(m, 1H), 2.43(d, J=13.8 Hz, 1H), 1.96–2.04 (m, 1H), 1.43–1.89 (m, 1H), 1.40 (s, 3H).

Spectra for **2a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J=1.5 Hz, 1H), 6.35 (s, 1H), 5.95 (d, J=3 Hz, 1H), 2.18–2.10 (m, 1H), 1.98–1.21 (m, 8H), 1.19 (s, 3H); HRMS (EI) m/z calcd for 232.1010, found 232.1102. TLC (2:1 hexanes/ethyl acetate) R_f=0.22.

1.1.4. 6-Benzyloxy-7-methoxy-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (7). To compound **6** (0.8 g, 3.5 mmol) in 20 mL of water at rt was added 37% formalin (0.77 g, 7.35 mmol) followed by calcium oxide (0.098 g, 1.75 mmol). After an hour, saturated aqueous ammonium chloride was added and the organic layer was extracted with ether, dried, concentrated and used immediately without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 6.56 (s, 1H), 6.51 (s, 1H), 5.10 (s, 2H), 4.76 (s, 2H), 3.82 (s, 3H); ^{13}C NMR 149.2, 148.9, 142.9, 136.9, 128.8, 128.2, 127.7, 117.3, 113.4, 103.7, 71.1, 66.2, 57.1. TLC (2:1 hexanes/ethyl acetate) R_f=0.13.

To the crude benzyl alcohol (0.4 g, 1.53 mmol) in 20 mL of $CHCl_3$ at 0 °C, was added 1-methylcyclohexene (0.22 g, 2.3 mmol) followed by dropwise addition of trifluoroacetic acid (0.035 g, 1.84 mmol). The mixture was boiled for 3 h. After cooling to rt, the solution was diluted with water and extracted with CH_2Cl_2, dried, concentrated and purified by sgc using 4:1 hexanes/ethyl acetate to afford benzopyran **7** in 40% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.28 (m, 5H), 6.57 (s, 1H), 6.43 (s, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.04 (dd, J=15, 6 Hz, 1H), 2.26 (d, J=15 Hz, 1H), 1.98–1.25 (m, 9H), 1.19 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.0, 147.1, 143.5, 137.5, 128.7, 127.9, 127.6, 113.9, 111.2, 103.5, 74.9, 71.1, 57.1, 38.7, 37.2, 29.2, 28.7, 25.8, 25.6, 21.9. HRMS (EI) m/z calcd for 338.1882, found 338.1887. TLC (2:1 hexanes/ethyl acetate) R_f=0.83.

1.1.5. 2-Methoxy-10a-methyl-5,6,7,8,8a,10a-hexahydro-xanthen-3-one (8). To compound **7** (0.1 g, 0.3 mmol) in 5 mL of THF at rt was added Pd/C (0.032 g, 0.03 mmol). The flask was flushed with hydrogen gas for 5 min and capped with a large balloon. After 1 h, the mixture was filtered through Celite, concentrated and purified by sgc using 4:1 hexanes/ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.41 (s, 1H), 3.81 (s, 3H), 3.03 (dd, J=15, 6 Hz, 1H), 2.24 (d, J=18 Hz, 1H), 1.94–1.25 (m, 9H), 1.20 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.5, 145.0, 140.8, 112.1, 110.4, 103.8, 74.8, 56.7, 38. 7, 37.2, 29.3, 28.6, 25.8, 25.5, 21. 9; HRMS (EI) m/z calcd for 248.1412, found 232.1418. TLC (2:1 hexanes/ethyl acetate) R_f=0.56.

To the phenol (0.02 g, 0.08 mmol), in 5 mL of dioxane at rt was added DDQ (0.022 g, 0.096 mmol). After 2 h, the mixture was filtered through Celite, concentrated and purified by sgc using 4:1 hexanes/ethyl acetate to afford **8** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (bs, 1H), 6.46 (s, 1H), 6.18 (s, 1H), 3.89 (s, 3H), 2.22 (dd, J=12, 3 Hz, 1H), 2.05–2.00 (m, 1H), 1.75–1.30 (m, 8H), 1.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.6, 156.4, 153.6, 142.0, 111.5, 106.8, 103.7, 79.8, 56.5, 52.5, 37.1, 26.9, 24.8, 24.2, 21.7. UV (CH_2Cl_2) λmax 240, 272, 335 nm; HRMS (EI) m/z calcd for 246.1256, found 232.1258. TLC (2:1 hexanes/ethyl acetate) R_f=0.43.

Acknowledgements

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Indium as a radical initiator in aqueous media: intermolecular alkyl radical addition to C=N and C=C bond

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Abstract—The carbon–carbon bond-forming method in aqueous media was investigated by using indium as a single-electron transfer radical initiator. The indium-mediated intermolecular alkyl radical addition to imine derivatives and electron-deficient C=C bond proceeded effectively.

1. Introduction

The use of water as a solvent has generated considerable interest from both economical and environmental points of view.[1] Particularly, the carbon–carbon bond-formation in aqueous media is a challenging problem.[2] Therefore, the indium-mediated carbon–carbon bond-forming reactions in aqueous media have been of great importance.[3] Recently, numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported.[3] In contrast, the corresponding reaction of water-sensitive imine derivatives has not been widely studied; therefore, the development of indium-mediated reactions of imines in aqueous media has been a subject of current interest. Chan's group reported the first studies on the indium-mediated allylation of *N*-sulfonylimines in aqueous media.[4] These allylation reactions would proceed through an allylindium (I) intermediate which reacts with the *N*-sulfonylimines, thus, simple alkylation reactions are not investigated. As a part of our program directed toward the development of reactions of imines in aqueous media,[5] we report here in detail the aqueous-medium alkylation reactions of imine derivatives based on the alkyl radical addition to carbon–nitrogen double bond.[6a] This reaction is the first example of carbon–carbon bond-forming radical reaction using indium as a radical initiator in aqueous media.[7] As shown below, we also report the indium-mediated radical addition to electron-deficient carbon–carbon double bond in aqueous media.

Keywords: Indium; Radical; Water; Imine; Oxime ether; Hydrazone.
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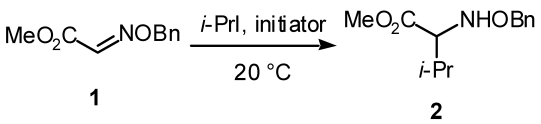
2. Results and discussion

2.1. Indium-mediated intermolecular carbon radical addition to glyoxylic imine derivatives

Among the different types of radical acceptors, the carbon–nitrogen double bond of imine derivatives has emerged as an excellent radical acceptor toward alkyl radicals, and thus numerous, powerful synthetic methods for the intramolecular carbon–carbon bond construction have been reported.[8] Recently, the several intermolecular radical reactions of imines were investigated in organic solvents mainly by the groups of Kim,[9] Bertrand,[10] Friestad,[11] as well as ourselves.[5,12] Our recent studies show that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using triethylborane as a radical initiator.[5a]

On the basis of these results, we newly investigated the intermolecular radical addition to imine derivatives by using indium as a new radical initiator.[13] As a preliminary experiment, the substrate of choice was the glyoxylic oxime ether **1** since it has shown an excellent reactivity toward nucleophilic carbon radicals in our previous work on triethylborane-induced radical reactions.[12a,e] Additionally, we also expected that the direct comparison of indium-mediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding indium as a single-electron transfer radical initiator.

In order to test the viability of indium as a radical initiator, the reaction of glyoxylic oxime ether **1** was investigated under the several reaction conditions (Scheme 1). To a



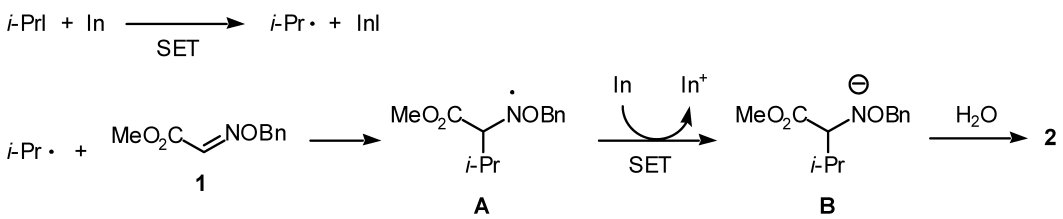
Scheme 1.

contrast, the indium-mediated alkyl radical addition to **3** gave selectively the desired *C*-monoalkylated products **4a**-**d** with no detection of *C*- and *N*-dialkylated products; thus, the indium was found to be a highly promising radical initiator for the radical reaction of hydrazones in aqueous media. The reaction of **3** with *i*-PrI proceeded smoothly to give 98% yield of the isopropylated product **4a** after being stirred for 1 h (Table 2, entry 1). In contrast, the reaction with *i*-PrBr did not take place because of the increase in bond

Table 1. Reaction of glyoxylic oxime ether **1**

Entry	Initiator	Solvent	Time (h)	Additive	Yield (%)
1[a]	In	H_2O:CH_2Cl_2 (4:1)	22	None	76
2[a]	In	CH_2Cl_2	24	None	No reaction
3[b]	In	H_2O:MeOH (2:1)	0.5	None	74
4[b]	In	H_2O:MeOH (2:1)	0.5	Galvinoxyl free radical	No reaction
5[c]	InI	H_2O:MeOH (2:1)	20	None	No reaction

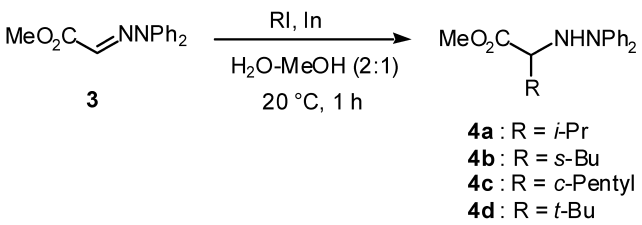
[a] Reactions were carried out with *i*-PrI (5 equiv.) and indium (7 equiv.).
[b] Reactions were carried out with *i*-PrI (4 equiv.×2) and indium (7 equiv.).
[c] Reaction was carried out with *i*-PrI (4 equiv.×2) and indium iodide (7 equiv.).



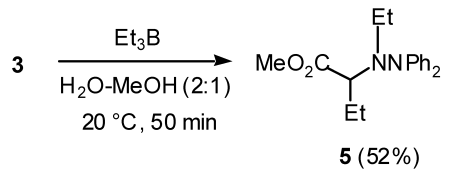
Scheme 2.

biphasic solution of **1** and *i*-PrI (5 equiv.) in H_2O–CH_2Cl_2 (4:1, v/v) was added indium (7 equiv.), and then the reaction mixture was stirred at 20 °C for 22 h. As expected, glyoxylic oxime ether **1** exhibits a good reactivity to give the desired isopropylated product **2** in 76% yield without formation of significant by-products such as a reduced product (Table 1, entry 1). When 1 equiv. of indium was used, **2** was obtained in only 8% yield and 72% yield of starting material **1** was recovered. In our recent studies, the triethylborane-induced reaction of **1** was usually run by using a large amount of alkyl iodides (more than 30 equiv.) to suppress the competitive reaction with ethyl radical generated from triethylborane.[12d,e] It is important to note that practically no reaction of **1** occurred in the absence of water (entry 2). These results suggest that water would be important for the activation of indium and for the proton-donor to the resulting amide anion (Scheme 2). In the case of monophasic reaction in H_2O–MeOH, the formation of isopropylated product **2** was observed after being stirred for only 0.5 h (entry 3). In the presence of galvinoxyl free radical as a radical scavenger, the reaction did not proceed effectively (entry 4). These results indicate that indium can serve as an initiator in aqueous media as well as triethylborane and thus, the reaction would proceed via the radical mechanism based on the single-electron transfer (SET) process from indium (Scheme 2). However, the reaction using indium (I) iodide instead of indium did not take place under similar reaction conditions (entry 5).

We next investigated the indium-mediated alkyl radical addition to glyoxylic hydrazone **3** (Scheme 3). In the case of the aqueous-medium reaction of **3** using triethylborane, the undesired *C*- and *N*-dialkylated product **5** was only obtained as a result of the additional *N*-alkylation (Scheme 4).[5a] In



Scheme 3.

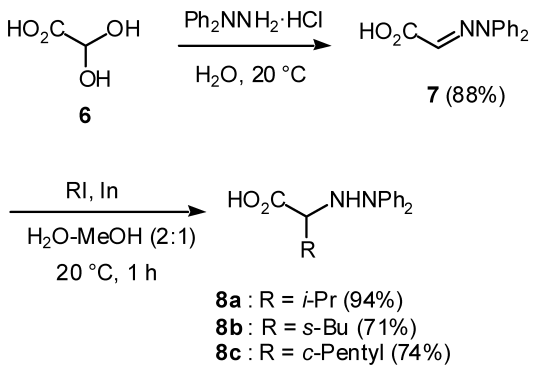


Scheme 4.

Table 2. Alkyl radical addition to glyoxylic hydrazone **3**[a]

Entry	RX	RX bond dissociation energy (kcal/mol)	Product	Yield (%)
1	*i*-PrI	53	**4a**	98
2	*i*-PrBr	68		No reaction
3	*s*-BuI		**4b**	90
4	*c*-Pentyl I		**4c**	79
5	*t*-BuI	49.5	**4d**	48
6	EtI	53.5		No reaction

[a] Reactions were carried out with RX (5 equiv.×2), indium (7 equiv.), and H_2O in MeOH at 20 °C for 1 h.

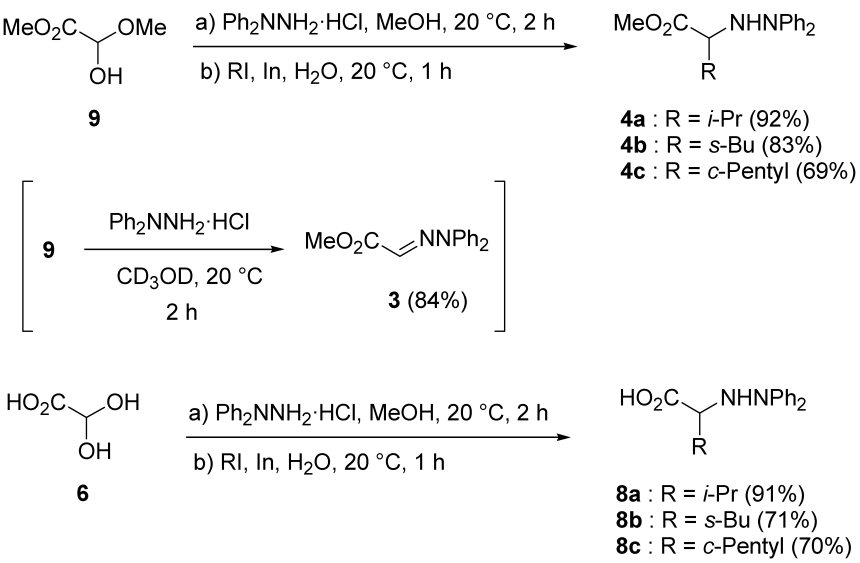


Scheme 5.

being stirred at 20 °C for 2 h. Subsequently, alkyl iodide, In, and H_2O were added to the reaction vessel to afford good yields of α-amino acid derivatives **4a-c** after the purification. The formation of hydrazone **3** was also confirmed in CD_3OD by ^1H NMR studies. The one-pot synthesis of α-amino acid derivatives using glyoxylic acid **6** was also studied. As expected, one-pot reaction proceeded effectively to give **8a-c** without interference of a free carboxyl group.

2.2. Indium-mediated intermolecular carbon radical addition to aldimine derivatives

To survey the scope and limitations of the present method, the alkylation reaction of aldimines was studied (Scheme 7).

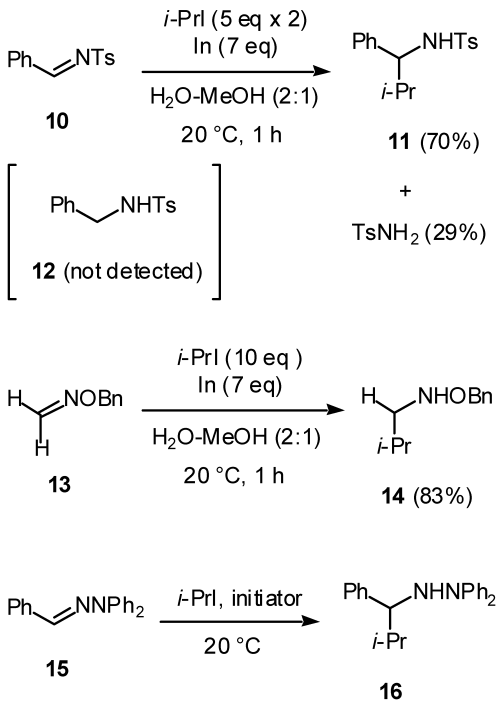


Scheme 6.

dissociation energy of *i*-PrBr (entry 2). Not only a secondary alkyl radicals but also the *tert*-butyl radical worked well to give **4b-d** in good yields after being stirred for 1 h (entries 3–5). However, primary ethyl iodide did not work because primary alkyl radicals are unstable and less nucleophilic radicals (entry 6). These results indicate that indium works as an effective radical initiator for generation of secondary and tertiary alkyl radicals from alkyl iodides.

We next investigated the reaction of hydrazone **7** having a free carboxyl group (Scheme 5). The glyoxylic hydrazone **7** was prepared from glyoxylic acid **6** and *N*,*N*-diphenylhydrazine hydrochloride in 88% yield. The indium-mediated reaction of **7** also proceeded in H_2O–MeOH without any problem to afford the good yields of products **8a-c**.

Integration of multi-step chemical reactions into one-pot reactions has attracted significant attention as an environmentally benign method.[14] The tolerance of the imine derivatives to the aqueous media prompted us to examine a one-pot reaction for the synthesis of α-amino acid derivatives in aqueous media (Scheme 6). Condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **9** with *N*,*N*-diphenylhydrazine hydrochloride proceeded smoothly without any additive in MeOH to give hydrazone **3** after



Scheme 7.

At first, we investigated the indium-mediated radical addition to *N*-sulfonylimine **10** prepared from benzaldehyde. The monophasic reaction of *N*-sulfonylimine **10** in H_2O–MeOH (2:1, v/v) proceeded effectively to give the desired isopropylated product **11** in 70% yield, accompanied with 29% of $TsNH_2$ as a hydrolysis product after being stirred for only 1 h. In our recent studies on zinc-mediated radical reaction of *N*-sulfonylimines, the competitive reduction of *N*-sulfonylimine giving **12** was observed as a significant side reaction.[5d] Therefore, it should be note that the indium-mediated radical reaction did not give the reduced product **12**. The indium-mediated radical addition to sterically less hindered formaldoxine ether **13** proceeded smoothly to give product **14** in 83% yield. In contrast, the reactivity of hydrazone **15**, prepared from benzaldehyde, is not high (Table 3). We have recently reported that the triethylborane-induced radical addition to aldoxime ethers proceeded effectively in the presence of $BF_3{\cdot}OEt_2$. Thus, the triethylborane-induced radical addition to **15** was also investigated under general reaction conditions which have been already established in the reaction of aldoxime ethers (entries 1 and 2). However, the triethylborane-induced radical addition to **15** did not take place probably due to basic diphenylamino group. In the case of indium-mediated reactions, the monophasic reaction of **15** in 1 M HCl–MeOH (2:1, v/v) gave the desired product **16**, accompanied with starting material **15** (entries 3 and 4). The biphasic reaction of **15** in H_2O–CH_2Cl_2 (4:1, v/v) proceeded slowly to give **16** in 54% yield after being stirred for 2 days (entry 5).

Table 3. Reaction of hydrazone **15**

Entry	Initiator	Solvent	Time (h)	Yield (%)
1[a]	Et_3B	CH_2Cl_2	0.5	No reaction
2[b]	Et_3B	CH_2Cl_2	0.5	No reaction
3[c]	In	1 M HCl:MeOH (2:1)	1	34 (59)[d]
4[c]	In	1 M HCl:MeOH (2:1)	7	38 (54)[d]
5[e]	In	H_2O: CH_2Cl_2 (4:1)	48	54

[a] Reaction was carried out with *i*-PrI (30 equiv.) and Et_3B (5 equiv.).
[b] Reaction was carried out with *i*-PrI (30 equiv.) and Et_3B (5 equiv.) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv.).
[c] Reactions were carried out with *i*-PrI (5 equiv.×2) and indium (7 equiv.).
[d] Yields in parentheses are for starting material **15**.
[e] Reaction was carried out with *i*-PrI (5 equiv.) and indium (7 equiv.).

2.3. Indium-mediated intermolecular carbon radical addition to electron-deficient C=C bond

To test the utility of indium as a single-electron transfer radical initiator, we next investigated the indium-mediated alkyl radical addition to compounds **17**-**20** having electron-deficient C=C bond (Fig. 1). Compounds **18** and **19** were readily prepared as shown in Scheme 8. The reaction of **21** with acryloyl chloride gave the **18** in 88% yield. Compound **19** was prepared by the reaction of **22** with acryloyl chloride followed by *N*-crotylation.

Reactions of **17**-**19** with *i*-PrI and indium were carried out in H_2O–MeOH at 20 °C (Scheme 9). In the case of substrate **17a**, the product **24a** was obtained only in 20% yield, probably due to the competitive polymerization of **17a**. In contrast, the radical addition to substrate **17b** having a

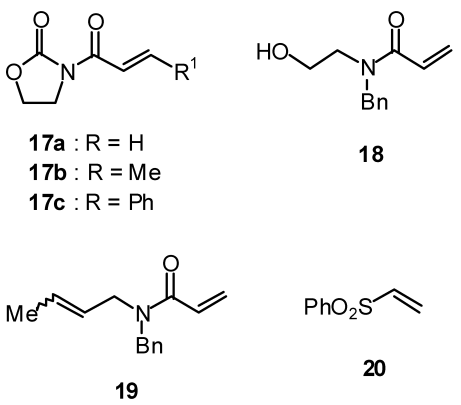
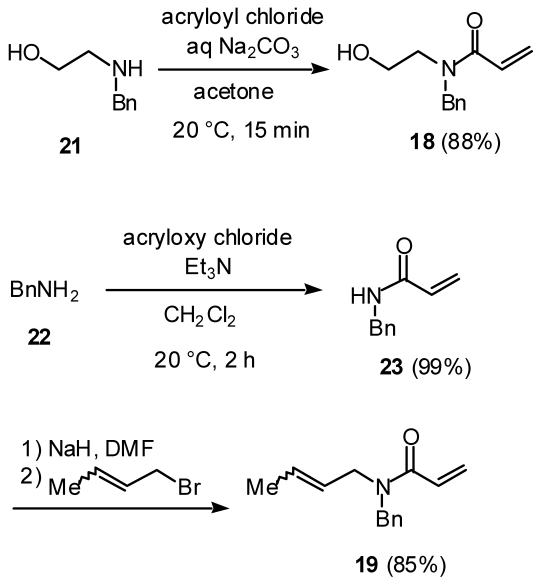
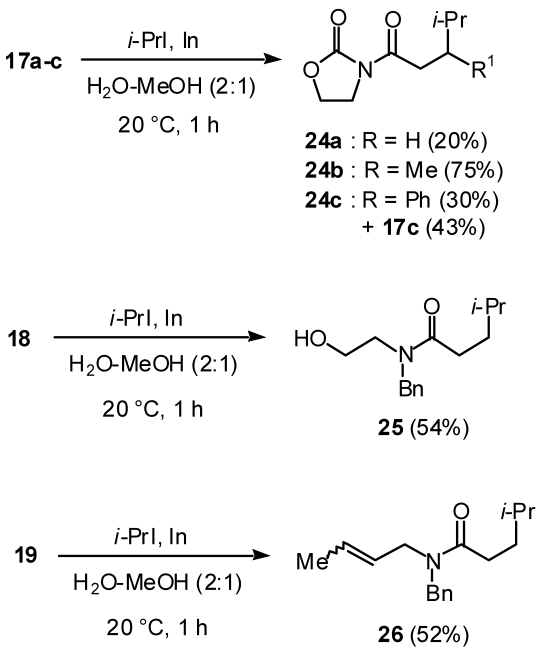


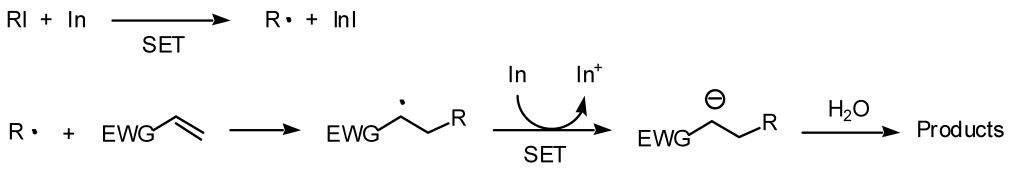
Figure 1.



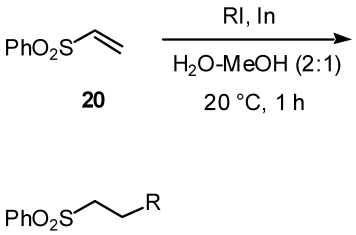
Scheme 8.



Scheme 9.



Scheme 10.



27a : R = *i*-Pr (86%)
27b : R = *s*-Bu (81%)
27c : R = *c*-Pentyl (80%)
27d : R = *t*-Bu (61%)

Scheme 11.

methyl group gave the desired product **24b** in 75% yield. In the case of substrate **17c** having a phenyl group, the radical reaction proceeded slowly to give 30% yield of the desired product **24c**, accompanied with 43% yield of starting material **17c**, after being stirred for 1 h. The reactions of **18** having a hydroxyl group and **19** having an additional olefin moiety also produced the isopropylated products **25** and **26** respectively. These reactions would proceed via the single-electron transfer process from indium as shown in Scheme 10.

We finally studied the radical addition to phenyl vinyl sulfone **20** (Scheme 11). To a solution of phenyl vinyl sulfone **20** and RI (5 equiv.) in MeOH were added indium (7 equiv.) and H_2O, and then the reaction mixture was stirred at 20 °C for 30 min. As expected, phenyl vinyl sulfone **20** exhibits a good reactivity to give the desired alkylated products **27a**-**d** in good yields with no detection of by-products such as a reduced product.

In general, free radical synthetic methods largely relied on toxic organotin chemistry; therefore, the development of tin-free reactions including SET processes from indium has been of great importance in radical chemistry.

3. Conclusion

We have demonstrated that indium has the potential to induce the radical reaction in aqueous media. The reaction of imine derivatives proceeded effectively, providing the one-pot synthesis of α-amino acids. Since the known examples of indium-mediated carbon–carbon bond-forming reactions in aqueous media are mainly limited to allylation reactions, it is noteworthy that newly-found reaction involves the alkylation of imine derivatives and electron-deficient olefins.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. Mass spectra were obtained by EI or CI methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$).

4.2. Indium-mediated reaction of glyoxylic oxime ether 1 in $H_2O-CH_2Cl_2$

To a micro tube containing **1**[12e] (50 mg, 0.259 mmol), *i*-PrI (0.13 mL, 1.30 mmol), indium (257 mg, 1.813 mmol), and CH_2Cl_2 (0.1 mL) was added dropwise H_2O (0.4 mL) at 20 °C. After being stirred at the same temperature for 22 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **2**[12e] (46.6 mg, 76%) as a colorless oil.

4.3. Indium-mediated reaction of glyoxylic oxime ether 1 in $H_2O-MeOH$

To a micro tube containing **1** (50 mg, 0.259 mmol), *i*-PrI (0.10 mL, 1.036 mmol), indium (257 mg, 1.813 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 15 min, *i*-PrI (0.10 mL, 1.036 mmol) was added to the reaction mixture. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **2** (45.1 mg, 74%) as a colorless oil.

4.3.1. (*E*)-(*N*,*N*-Diphenylhydrazono)acetic acid (7). To a solution of glyoxylic acid monohydrate **6** (1 g, 10.8 mmol) in H_2O (100 mL) was added *N*,*N*-diphenylhydrazine hydrochloride (2.4 g, 10.8 mmol) at 20 °C. After being stirred at the same temperature for 30 min, the product was crystallized out from the reaction mixture. Crystals were filtered and washed with H_2O. Purification of crystals by flash chromatography ($CHCl_3$/MeOH 30:1) afforded **7** (2.3 g, 88%). Colorless crystals. Mp 209–210 °C (AcOEt). IR ($CHCl_3$) 3022, 1741, 1592, 1547, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.49–6.16 (10H, m), 6.49 (1H, s). ^{13}C NMR ($CDCl_3$) δ 166.2, 141.7, 130.1, 126.7, 123.2. HRMS Calcd for $C_{14}H_{12}N_2O_2$ (M^+) 240.0898, found 240.0887. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.04; H, 5.13; N, 11.68.

4.4. General procedure for alkyl radical addition to glyoxylic hydrazones 3 and 7

To a micro tube containing **3**[5a] or **7** (0.197 mmol), RX (0.985 mmol), indium (196 mg, 1.38 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, RX (0.985 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1 or hexane/AcOEt 30:1 2-fold development) afforded **4a-c** and **4d**.

4.4.1. Methyl 2-(*N*,*N*-diphenylhydrazino)-3-methylbutanoate (4a). Colorless crystals. Mp 43–43.5 °C (hexane). IR ($CHCl_3$) 3012, 1731, 1589, 1489 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.98 (10H, m), 4.40 (1H, br s), 3.45 (3H, s), 3.41 (1H, d, J=6.3 Hz), 2.03–1.96 (1H, m), 1.07 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 173.8, 148.0, 129.0, 122.7, 120.9, 67.7, 51.2, 30.5, 19.2, 18.8. HRMS Calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1680, found 298.1696. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.70; H, 7.44; N, 9.28.

4.4.2. Methyl 2-(*N*,*N*-diphenylhydrazino)-3-methylpentanoate (4b). 1:1 Mixture of diastereomers with regard the *sec*-butyl group. A colorless oil. IR ($CHCl_3$) 3029, 3010, 2965, 1730, 1589 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.98 (10H, m), 4.41 (1H, br s), 3.53–3.50 (1H, br m), 3.47 (3H, s), 1.84–1.72 (1H, m), 1.66–1.52 (1H, m), 1.38–1.16 (1H, m), 1.04–0.87 (6H, m). ^{13}C NMR ($CDCl_3$) δ 174.1, 169.9, 148.2, 148.1, 129.0, 122.7, 121.0, 66.1, 66.0, 51.3, 51.2, 37.4, 37.0, 26.0, 25.9, 15.5, 15.3, 11.7, 11.4. HRMS Calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1836, found 312.1847.

4.4.3. Methyl 2-(*N*,*N*-diphenylhydrazino)-2-cyclopentylethanoate (4c). Colorless crystals. Mp 52.5–53 °C (AcOEt/hexane). IR ($CHCl_3$) 2953, 1732, 1589, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–7.00 (10H, m), 4.28 (1H, br s), 3.42 (3H, s), 3.42 (1H, br m), 2.13–2.02 (1H, m), 1.98–1.88 (1H, m), 1.66–1.28 (7H, m). ^{13}C NMR ($CDCl_3$) δ 174.3, 148.0, 129.0, 122.7, 120.9, 66.9, 51.3, 41.6, 30.0, 29.0, 25.1, 24.9. HRMS Calcd for $C_{20}H_{24}N_2O_2$ (M^+) 324.1836, found 324.1836. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.05; H, 7.45; N, 8.62.

4.4.4. Methyl 2-(*N*,*N*-diphenylhydrazino)-3,3-dimethylbutanoate (4d). A white solid. IR ($CHCl_3$) 2955, 1729, 1589, 1498 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.32–6.98 (10H, m), 4.35 (1H, br s), 3.36 (3H, s), 3.36 (1H, br d), 1.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 148.5, 129.1, 122.9, 121.3, 71.4, 51.0, 34.2, 27.0; HRMS Calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1836, found 312.1840.

4.4.5. 2-(*N*,*N*-Diphenylhydrazino)-3-methylbutanoic acid (8a). Colorless crystals. Mp 111–113 °C (AcOEt/hexane). IR ($CHCl_3$) 2968, 1711, 1590, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30–6.99 (10H, m), 3.04 (1H, d, J=5.4 Hz), 2.09–2.03 (1H, m), 1.07 (3H, d, J=6.9 Hz), 1.03 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 178.4, 148.1, 129.2, 123.2, 121.2, 67.0, 30.3, 19.0, 18.8. HRMS Calcd for $C_{17}H_{20}N_2O_2$ (M^+) 284.1523, found 284.1529. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.73; H, 7.01; N, 9.86.

4.4.6. 2-(*N*,*N*-Diphenylhydrazino)-3-methylpentanoic acid (8b). 1:1 Mixture of diastereomers with regard the *sec*-butyl group. Colorless crystals. Mp 112–114 °C (AcOEt/hexane). IR ($CHCl_3$) 2967, 1710, 1590, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.99 (10H, m), 3.57 (1/2H, d, J=4.5 Hz), 3.55 (1/2H, d, J=4.5 Hz), 1.86–1.81 (1H, m), 1.59–1.54 (1H, m), 1.38–1.26 (1H, m), 1.05–0.87 (6H, m). ^{13}C NMR ($CDCl_3$) δ 177.2, 148.2, 148.1, 129.3, 123.4, 121.2, 121.1, 65.3, 65.1, 37.1, 36.8, 26.0, 25.9, 15.4, 11.8, 11.6. HRMS Calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1680, found 298.1660. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.53; H, 7.42; N, 9.39.

4.4.7. 2-(*N*,*N*-Diphenylhydrazino)-2-cyclopentylethanoic acid (8c). A white solid. IR ($CHCl_3$) 3009, 2959, 1714, 1590, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30–6.98 (10H, m), 3.44 (1H, d, J=8.1 Hz), 2.16–2.04 (1H, m), 1.94–1.23 (8H, m). ^{13}C NMR ($CDCl_3$) δ 178.2, 129.2, 122.3, 121.2, 117.8, 66.2, 41.3, 29.8, 29.1, 25.1, 25.0. HRMS s for $C_{19}H_{22}N_2O_2$ (M^+) 310.1180, found 310.1167.

4.5. General procedure for the one-pot synthesis of α-amino acid derivatives

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **9** or glyoxylic acid monohydrate **6** (0.25 mmol) in MeOH (0.3 mL) was added *N,N*-diphenylhydrazine hydrochloride (55 mg, 0.25 mmol) at 20 °C. After being stirred at the same temperature for 2 h, RI (1.25 mmol) and indium (1.75 mmol) were added to the reaction mixture, and then H_2O (0.3 mL) was added dropwise to the reaction mixture at 20 °C over 5 min. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **4a-c** and **8a-c**.

4.5.1. 4-Methyl-*N*-(2-methyl-1-phenylpropyl)benzenesulfonamide (11). To a micro tube containing **10** (50 mg, 0.193 mmol), *i*-PrI (0.096 mL, 0.965 mmol), indium (191 mg, 1.35 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.40 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, *i*-PrI (0.096 mL, 0.965 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1, 2-fold development) afforded **10** (41 mg, 70%). Colorless crystals. Mp 136.5–138 °C (AcOEt/hexane). IR ($CHCl_3$) 3030, 1495, 1327, 1159 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.52–6.95 (9H m), 5.66 (1H, br s), 4.04–3.99 (1H, m), 2.31 (3H, s), 1.95–1.88 (1H, m), 0.95 (3H, d, J=6.6 Hz), 0.72 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 142.5, 139.8, 137.5, 128.9, 127.8, 126.9, 126.8, 126.7, 64.1, 34.2, 21.2, 19.2, 18.7.

HRMS Calcd for $C_{17}H_{20}NO_2S$ ([M−H]$^+$) 302.1214, found 302.1218. Anal. Calcd for $C_{17}H_{21}NO_2S{\cdot}1/2H_2O$: C, 66.50; H, 7.03; N, 4.56; S, 10.44. Found: C, 66.37; H, 6.94; N, 4.50; S, 10.74.

4.5.2. 2-Methyl-*N*-(phenylmethoxy)-1-propanamine (14). To a micro tube containing **13** (50 mg, 0.37 mmol), *i*-PrI (3.7 mL, 3.7 mmol), indium (366 mg, 2.59 mmol), and MeOH (0.4 mL) was added dropwise H_2O (0.80 mL) at 20 °C over 5 min. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **14** (55 mg, 83%). A colorless oil. IR ($CHCl_3$) 3011, 2959, 1496, 1469, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.38–7.25 (5H, m), 4.70 (2H, s), 2.74 (2H, d, J=6.8 Hz), 1.88 (1H, m), 0.91 (6H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 137.9, 128.3, 127.6, 75.9, 59.8, 25.8, 20.5. HRMS Calcd for $C_{11}H_{17}NO$ (M$^+$) 179.1309, found 179.1328.

4.5.3. 2-(2-Methyl-1-phenylpropyl)-1,1-diphenylhydrazine (16). To a micro tube containing hydrazone **15** (50 mg, 0.183 mmol) in CH_2Cl_2 (0.1 mL) were added *i*-PrI (0.182 mL, 1.83 mmol), indium (182 mg, 1.28 mmol) and H_2O (0.4 mL) at 20 °C. After being stirred at the same temperature for 2 days, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane 7-fold development) afforded **16** (31.0 mg, 54%). A colorless oil. IR ($CHCl_3$) 3018, 2963, 1590, 1494 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.23–6.87 (15H, m), 3.64 (1H, d, J=5.4 Hz), 2.14–1.98 (1H, m), 1.18–1.15 (1H, br m), 0.83 (3H, d, J=7.0 Hz), 0.69 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 148.2, 140.2, 129.0, 128.7, 127.7, 127.1, 122.3, 120.7, 67.6, 31.1, 19.9, 18.4. HRMS Calcd for $C_{22}H_{24}N_2$ (M$^+$) 316.1938, found 316.1944.

4.5.4. *N*-(2-Hydroxyethyl)-*N*-(phenylmethyl)propenoylamide (18). To a solution of *N*-benzylethanolamine **21** (1.0 g, 6.6 mmol) in acetone (30 mL) were added a solution of Na_2CO_3 (1.4 g, 13.2 mmol) in H_2O (2 mL) and acryloyl chloride (0.80 mL, 9.9 mmol) at 0 °C. After being stirred at 20 °C for 15 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 1:5) afforded **18** (1.18 g, 88%). After characterization by ^{1}H NMR and HRMS, unstable **18** was immediately subjected to radical reaction. The presence of rotamers (8:5) precluded a comprehensive assignment of all proton resonances. A colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37–7.17 (5H, m), 6.83–6.36 (2H, m), 5.72 (1H, dd, J=9.6, 2.4 Hz), 4.71 (10/13H, s), 4.68 (16/13H, s), 3.78–3.60 (4H, m). HRMS Calcd for $C_{12}H_{15}NO_2$ (M$^+$) 205.1102, found 205.1101.

4.5.5. *N*-(Phenylmethyl)propenoylamide (23). To a solution of benzylamine (300 mg, 2.8 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.39 mL, 2.8 mmol) and acryloyl chloride (0.27 mL, 3.36 mmol) at 0 °C. After being stirred at 20 °C for 2 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 2:1) afforded **23** (447 mg, 99%). A white solid. IR ($CHCl_3$) 3441, 1671 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.34–7.26 (5H, m), 6.33 (1H, dd, J=16, 1.8 Hz), 6.11 (1H, dd, J=16, 10 Hz), 5.68 (1H, dd, J=10, 1.8 Hz), 4.52 (2H, d, J=5.8 Hz). ^{13}C NMR ($CDCl_3$) δ 165.4, 138.0, 130.6, 128.7, 127.8, 127.5, 126.7, 43.6. HRMS Calcd for $C_{10}H_{11}NO$ (M$^+$) 161.0840, found 161.0843.

4.5.6. *N*-2-Butenyl-*N*-(phenylmethyl)-2-propenoylamide (19). To a solution of amide **23** (50 mg, 0.31 mmol) in DMF (1.5 mL) was added NaH (60% oil suspension, 75 mg, 1.86 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at 0 °C for 30 min, crotyl bromide (0.064 mL, 0.62 mmol) was added to the reaction mixture at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with Et_2O. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 3:1) afforded **19** (57 mg, 85%). The presence of rotamers (2:3 (*Z*-isomer), 5:7 (*E*-isomer)) precluded a comprehensive assignment of ^{1}H and ^{13}C NMR. A colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (5H, m), 6.63–6.39 (2H, m), 5.74–5.33 (3H, m), 4.63 (10/17H (*Z*)+10/17H (*E*), br s), 4.56 (14/17H (*E*), br s), 4.11 (4/17H (*Z*), br d, J=6.6 Hz), 3.99 (10/17H (*E*), br d, J=5.7 Hz), 3.92 (6/17H (*Z*), br d, J=6.3 Hz), 3.81 (14/17H (*E*), br d, J=4.5 Hz), 1.71–1.59 (3H, m). ^{13}C NMR ($CDCl_3$) δ 166.2, 137.2, 136.6, 129.0, 128.5, 128.2, 127.9, 127.5, 127.3, 127.2, 127.0, 126.1, 125.5, 125.3, 125.2, 124.9, 49.8, 49.5, 48.3, 48.2, 48.1, 47.3, 43.5, 41.7, 17.3 (2C), 12.6, 12.5. HRMS Calcd for $C_{14}H_{17}NO$ (M$^+$) 215.1310, found 215.1319.

4.6. General procedure for the radical addition to 17-19

To a micro tube containing **17**-**19** (0.20 mmol), *i*-PrI (0.10 mL, 1.0 mmol), indium (199 mg, 1.4 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, *i*-PrI (0.10 mL, 1.0 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2:1) afforded **24a**-**c**, and purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **25** and **26**.

4.6.1. 3-(4-Methylpentanoyl)-2-oxazolidine (24a). A colorless oil. IR ($CHCl_3$) 3027, 2960, 1783, 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.41 (2H, t, J=8.4 Hz), 4.01 (2H, t, J=8.4 Hz), 2.92 (2H, t, J=7.7 Hz), 1.63–1.50 (3H, m), 0.92 (6H, d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 173.8, 153.5, 61.9, 42.5, 33.2, 33.1, 27.6, 22.3. HRMS Calcd for $C_9H_{15}NO_3$ (M$^+$) 185.1051, found 185.1060.

4.6.2. 3-(3,4-Dimethylpentanoyl)-2-oxazolidine (24b). A

colorless oil. IR ($CHCl_3$) 2963, 1781, 1697 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.41 (2H, t, J=8.3 Hz), 4.02 (2H, t, J=8.3 Hz), 2.95 (1H, dd, J=16.2, 5.1 Hz), 2.74 (1H, dd, J=16.2, 9.3 Hz), 2.04–1.94 (1H, m), 1.69–1.58 (1H, m), 0.91 (3H, d, J=6.6 Hz), 0.87 (3H, d, J=6.6 Hz) 0.89 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 173.4, 153.4, 61.8, 42.5, 39.4, 35.0, 32.1, 19.9, 18.1, 15.6. HRMS Calcd for $C_{10}H_{17}NO_3$ (M^+) 199.1207, found 199.1203.

4.6.3. 3-[(4-Methyl-3-phenyl)pentanoyl]-2-oxazolidine (24c). A colorless oil. IR ($CHCl_3$) 3028, 2963, 2927, 1780, 1701, 1494, 1481 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31–7.14 (5H, m), 4.37–4.15 (2H, m), 3.91–3.73 (2H, m), 3.53 (1H, dd, J=16.5, 10.2 Hz), 3.21 (1H, dd, J=16.5, 4.8 Hz), 2.98 (1H, ddd, J=10.2, 8.2, 4.8 Hz), 1.96–1.85 (1H, m), 0.99 (3H, d, J=6.6 Hz), 0.75 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 172.6, 153.5, 143.0, 128.4, 128.0, 126.3, 61.9, 48.5, 42.5, 38.6, 33.2, 20.7, 20.5. HRMS Calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1363, found 261.1368.

4.6.4. *N*-(2-Hydroxyethyl)-4-methyl-*N*-(phenylmethyl)-pentanoylamide (25). The presence of rotamers (3:1) precluded a comprehensive assignment of all proton resonances. A colorless oil. IR ($CHCl_3$) 3393, 3008, 2960, 1626, 1469 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.17 (5H, m), 4.67 (2/4H, s), 4.61 (6/4H, s), 3.75–3.69 (2H, m), 3.56 (6/4H, t, J=4.5 Hz), 3.42 (2/4H, t, J=4.5 Hz), 2.59 (1H, br s), 2.48 (2/4H, t, J=7.5 Hz), 2.38 (6/4H, t, J=7.5 Hz), 1.62–1.53 (3H, m), 0.98 (3H, d, J=6.3 Hz), 0.86 (3H, d, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ 176.3, 174.3, 137.9, 136.4, 129.0, 128.6, 127.9, 127.8, 127.3, 126.3, 62.3, 60.1, 52.7, 50.0, 49.0, 48.5, 34.3, 34.1, 31.3, 27.9, 27.8, 22.4, 22.3. HRMS Calcd for $C_{15}H_{23}NO_2$ (M^+) 249.1727, found 249.1725.

4.6.5. *N*-(2-Butenyl)-4-methyl-*N*-phenylmethylpentanoylamide (26). The presence of rotamers (1:1 (*Z*-isomer), 2:3 (*E*-isomer)) precluded a comprehensive assignment of ^1H and ^{13}C NMR. A colorless oil. IR ($CHCl_3$) 3019, 2960, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.15 (5H, m), 5.65–5.31 (2H, m), 4.57 (4/7H (*Z*)+4/7H (*E*), br s), 4.49 (6/7H (*E*), br s), 4.05 (2/7H (*Z*), br d, J=7.2 Hz), 3.93 (4/7H (*E*), br d, J=5.7 Hz), 3.85 (2/7H (*Z*), br d, J=6.6 Hz), 3.74 (6/7H (*E*), br d, J=5.1 Hz), 2.40–2.30 (2H, m), 1.72–1.54 (6H, m), 0.92 (24/7H, d, J=5.7 Hz), 0.85 (18/7H, d, J=5.7 Hz). ^{13}C NMR ($CDCl_3$) δ 173.6, 137.9, 137.1, 129.0, 128.8, 128.5, 128.2, 127.6, 127.4, 127.1, 126.4, 126.3, 125.9, 125.6, 50.2, 49.9, 48.5, 48.1, 47.8, 47.2, 43.8, 41.6, 34.3, 31.3, 31.2, 29.7, 27.9, 27.8, 22.4, 22.3, 17.7, 17.6, 12.9. HRMS Calcd for $C_{17}H_{25}NO$ (M^+) 259.1935, found 259.1937.

4.7. General procedure for the radical addition to 20

To a micro tube containing **20** (95% of purity, 50 mg, 0.282 mmol), RI (1.41 mmol), indium (280 mg, 1.97 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.8 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **27a-d**.

4.7.1. 3-Methylbutyl phenyl sulfone (27a). A white solid. IR ($CHCl_3$) 2961 1469, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.11–3.06 (2H, m), 1.63–1.58 (3H, m), 0.87 (6H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 139.1, 133.5, 129.2, 127.9, 54.6, 30.9, 27.1, 21.9. HRMS Calcd for $C_{11}H_{16}O_2S$ (M^+) 212.0870, found 212.0879.

4.7.2. 3-Methylpentyl phenyl sulfone (27b). A colorless oil. IR ($CHCl_3$) 3028, 2964, 1587, 1464, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.17–3.00 (2H, m), 1.79–1.07 (5H, m), 0.85–0.80 (6H, m). ^{13}C NMR ($CDCl_3$) δ 139.1, 133.5, 129.2, 128.0, 54.4, 33.4, 28.8, 28.7, 18.6, 11.0. HRMS Calcd for $C_{12}H_{18}O_2S$ (M^+) 226.1026, found 226.1027.

4.7.3. 2-Cyclopentylethyl phenyl sulfone (27c). Colorless crystals. Mp 68–69 °C (AcOEt/hexane). IR ($CHCl_3$) 3028, 2954, 1587, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.13–3.07 (2H, m), 1.74–1.69 (5H, m), 1.58–1.50 (4H, m), 1.08–1.02 (2H, m). ^{13}C NMR ($CDCl_3$) δ 139.2, 133.6, 129.2, 128.0, 55.7, 38.7, 32.2, 28.5, 25.0. HRMS Calcd for $C_{13}H_{18}O_2S$ (M^+) 238.1026, found 238.1024. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.43; H, 7.47; S, 13.73.

4.7.4. 3,3-Dimethylbutyl phenyl sulfone (27d). Colorless crystals. Mp 60–60.5 °C (AcOEt/hexane). IR ($CHCl_3$) 3027, 2962, 1587, 1476, 1448, 1303, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.56 (5H, m), 3.09–3.04 (2H, m), 1.63–1.57 (2H, m), 0.87 (9H, s). ^{13}C NMR ($CDCl_3$) δ 139.2, 133.6, 129.2, 128.0, 52.9, 35.6, 30.0, 28.9. HRMS Calcd for $C_{12}H_{18}O_2S$ (M^+) 226.1026, found 226.1011. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.17. Found: C, 63.64; H, 7.86; S, 13.93.

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Improved asymmetric synthesis of dopamine D1 full agonist, dihydrexidine, employing chiral ligand-controlled asymmetric conjugate addition of aryllithium to a nitroalkene

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Abstract—Asymmetric conjugate addition of 2-trityloxymethylpheyllithium to a nitroalkene was mediated by a chiral ligand to give the key intermediate for dopamine D1 full agonist dihydrexidine **1**. The shortcut of both Curtius rearrangement and Pictet–Spengler type cyclization, which were the drawback of the previously reported synthesis involving asymmetric conjugate addition of phenyllithium to an enoate, was realized by the newly developed asymmetric reaction. Short and efficient synthetic way gave optically pure dihydrexidine in 45% overall yield via eight steps. Improved synthesis of the best chiral ligand **13** was realized under the Buchwald conditions.

1. Introduction

Nitrogen-containing heterocyclic compounds are abundant in nature. Among them chiral arene-fused-piperidine is one of the representative structural motifs often observed in biologically active phenanthridine and isoquinoline alkaloids[1,2] as well as artificial pharmaceuticals.[3] We have previously reported the asymmetric synthesis of a phenanthridine class of compounds, dihydrexidine **1**[4] being characterized by dopamine D1 full agonist activity.[5] The synthesis is featured by a chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a BHA enoate **4** as a key step (Fig. 1). However, the drawbacks of this synthesis are the Curtius rearrangement of a carboxylic acid moiety of **3** to an amine functionality of **2** and the following Pictet–Spengler type cyclization of inactivated phenyl group for the construction of a requisite arene-fused-piperidine motif. The shortcut of the Curtius reaction relies on the conjugate addition of phenyllithium to a nitroalkene **6** instead of an enoate **4** (Fig. 2). Further shortcut is possible by the conjugate addition of ortho-substituted phenyllithium to **6** giving **8** and reduction of a nitro group to an amine **7** that avoids tedious procedure for the Pictet–Spengler type cyclization (Fig. 2). We have already succeeded in the development of the chiral ligand-controlled asymmetric *ortho*-substituted aryllithium addition to **6** and further

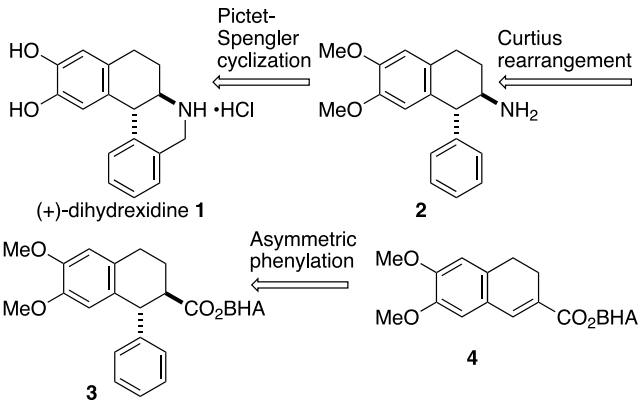

Figure 1. Asymmetric phenylation of **4**, Curtius rearrangement, and Pictet–Spengler cyclization for the synthesis of (+)-dihydrexidine **1**.

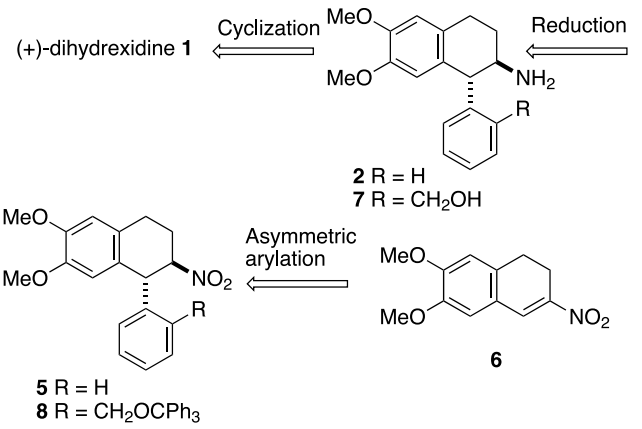

Figure 2. Asymmetric arylation of **6**, reduction to an amine, and Pictet–Spengler reaction or alkylation for the short synthesis of **1**.

Keywords: Asymmetric synthesis; Alkaloid; Piperidine; Agonist; Dopamine.
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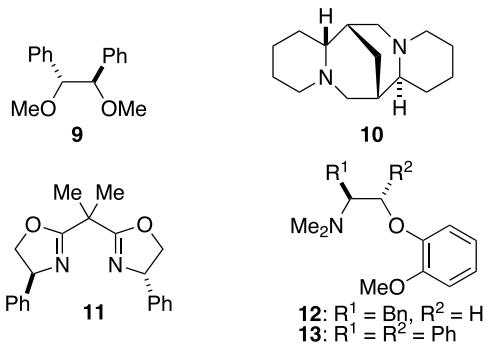


Figure 3. The bidentate and tridentate chiral ligands **9**-**13**.

construction of an arene-fused piperidine motif.[6] We describe herein full detail for the approach toward the improved synthesis of dihydrexidine **1**.

2. Results and discussion

2.1. Chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a nitroalkene

The first chiral ligand-mediated asymmetric alkyllithium addition to nitroalkenes was developed by Seebach, giving the corresponding substituted nitroalkanes in moderate enantioselectivity.[7] The impressive recent successes were the catalytic asymmetric addition of dialkylzinc[8] and arylboronic acid.[9] The sparteine-mediated conjugate addition of the lithiated *N*-Boc allylic and benzylic amines to nitroalkenes was also a great success, which provided an efficient way to the synthesis of simple piperidines in high enantioselectivities.[10] As a challenge to this end,[11,12] we began our study with examination of a chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a cyclic nitroalkene **6**.[13]

The reaction of phenyllithium with **6**[14] in toluene was examined in the presence of a chiral diether ligand **9** that gave a nice stereoselection in the reaction of an enoate **4** (Fig. 3). However, the reaction was not smooth at −20 °C for 0.5 h to give *ent*-**5** as a *trans*/*cis* mixture in 33% yield (Table 1, entry 1). The enantioselectivity was determined to be 22% ee by a chiral stationary phase HPLC. *ortho*-TMS-Substituted phenyllithium, prepared from (2-bromophenyl)-trimethylsilane,[15] was not a good nucleophile, giving the product **5a** (R=TMS) in low chemical yield (entry 2). The bidentate Box ligand **11** mediated the reaction at −78 °C for 0.5 h to give **5** in 68% yield. However, enantioselectivity was only 14% ee (entry 4). A tridentate aminodiether ligand **12** was also not a good mediator, giving **5** in 19% ee and 58% yield (entry 5). Fortunately, (−)-sparteine **10** was found to be the best ligand, at −78 °C for 1 h affording *ent*-**5** in 88% yield and 44% ee (entry 3).

Epimerization of the *cis*-**5** to the requisite *trans*-**5** was easily carried out by treating a *trans*:*cis* 62:38-mixture of *ent*-**5** (entry 3) with triethylamine in acetonitrile at room temperature for 18 h, giving the *trans*:*cis* 86:14-mixture in 98% yield (Fig. 4). Recrystallization of the mixture three times from methanol gave optically and diastereomerically pure nitro compound *ent*-**5** in 27% recovery yield. The following treatment with zinc in 6 N HCl and ethanol at room temperature for 2.5 h gave the amine *ent*-**2** in 86% yield. The spectroscopic and analytical data excepting the sign of specific rotation were identical with those of **2** prepared previously. Thus, the asymmetric synthesis of (−)-dihydrexidine **1** is possible in 11% overall yield from **6**.

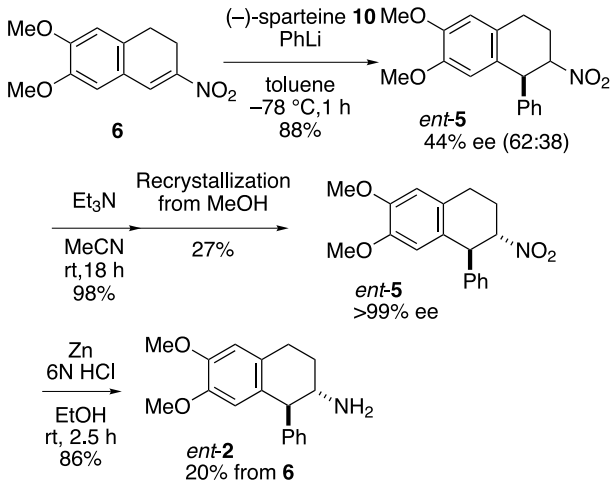
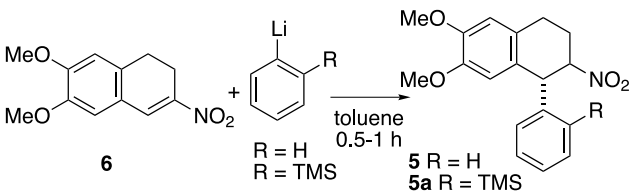


Figure 4. Synthesis of the key intermediate *ent*-**2**.

Table 1. Chiral ligand-mediated asymmetric reaction of a nitroalkene **6** with aryllithium



Entry	Chiral ligand	R	Temperature (°C)	Product **5**	Yield (%)	*trans*/*cis*	ee (%)
1	**9**	H	−20	*ent*-**5**	33	52:48	22
2	**9**	TMS	−78	**5a**	10	49:51	27
3	**10**	H	−78	*ent*-**5**	88	62:38	44
4	**11**	H	−78	**5**	68	41:59	14
5	**12**	H	−78	**5**	58	71:29	19

The chiral ligand of 1.4–2.0 equiv./ArLi was used. ee of *trans*-**5**. ee of *cis* isomer is nearly same with that of *trans*-**5**.

2.2. 2-Trityloxymethylphenyllithium as the key nucleophile for the efficient asymmetric synthesis of (+) dihydrexidine (1)

A straightforward synthetic way toward **1** is the conjugate addition of 2-hydroxymethylphenyllithium to nitroalkene **6** and subsequent reduction of the nitro group of **8** to an amino group of **7** and cyclization to construct piperidine motif **1** (Fig. 2). The chiral ligand **12** controlled the asymmetric addition of 2-trityloxymethylphenyllithium[16] to **6** at −95 °C for 1 h to afford the adduct **8** as a *trans*/*cis* mixture in 86% ee. Subsequent treatment with sodium bicarbonate in refluxing ethanol for 4 h and following detritylation with conc. HCl in THF-methanol at room temperature for 18 h gave **8a** (R=CH_2OH) of 86% ee in 86% yield (Fig. 5).

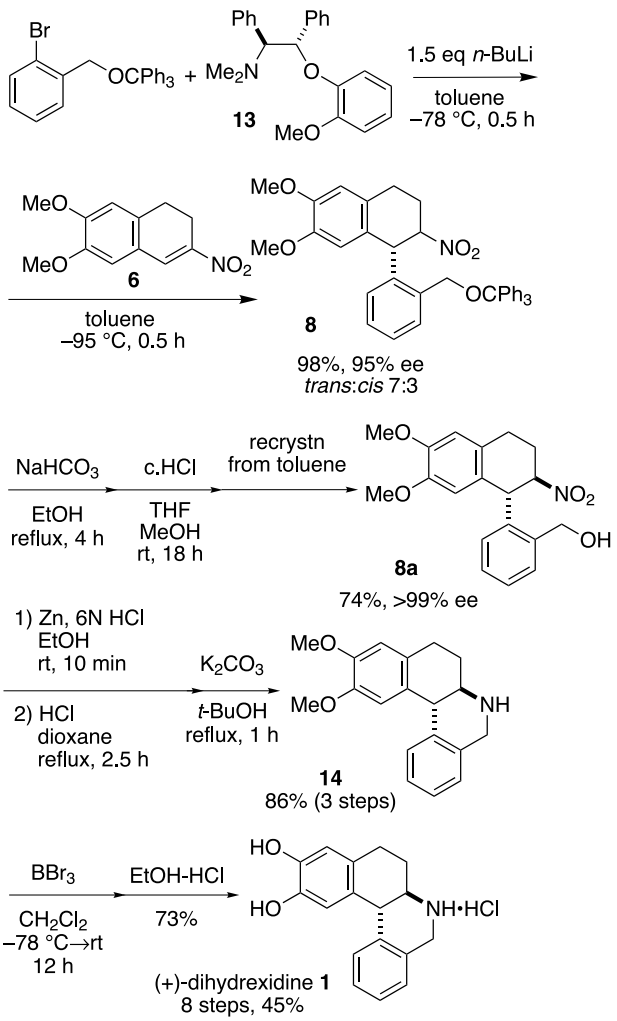


Figure 5. Efficient asymmetric total synthesis of **1**.

Much more improvement was possible by the mediation of a chiral ligand **13** to afford, after epimerization and detritylation, **8a** (R=CH_2OH) of 95% ee in 83% overall yield (Fig. 5).[6] Recrystallization from toluene gave back optically pure **8a** (R=CH_2OH) in 87% yield.

The zinc reduction of a nitro group of **8a** in a mixture of conc. HCl and ethanol at room temperature for 10 min, chlorination of the resulting alcohol with HCl in refluxing dioxane for 2.5 h, and then cyclization with potassium carbonate in refluxing *tert*-butanol for 1 h provided a fused piperidine **14** in 86% three step overall yield. Further demethylation with boron tribromide and hydrochloride formation completed the total synthesis of (+)-dihydrexidine **1** in 45% overall yield via 8 steps from a nitroalkene **6**.

2.3. Improved synthesis of a chiral tridentate aminodiether ligand (13)

The chiral ligand **13** was prepared in much more sophisticated way than the previous synthesis[12e] (Fig. 6). Treatment of a chiral amino alcohol with 2-iodoanisole under the Buchwald's conditions,[17] copper(I) iodide, cesium carbonate in butyronitrile at 125 °C for 1 day, gave **13** in 82% yield. Production of **13** over 10 g was possible under the conditions. It is also important to note that both enantiomers of **13** are available from the corresponding chiral amino alcohols.

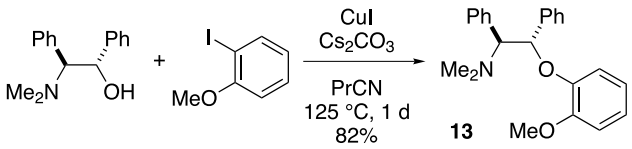


Figure 6. One step synthesis of **13**.

3. Conclusion

Improvement of the previously reported synthetic route to dihydrexidine **1** was realized by employing chiral ligand-mediated asymmetric conjugate addition of aryllithium to a nitroalkene **6**. Shortcut of both Curtius rearrangement and Pictet–Spengler type cyclization enabled an efficient and short step synthesis of optically pure target. The asymmetric reaction to a nitroalkene becomes the fundamental for the synthesis of the related candidates of pharmaceuticals.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were taken in $CDC1_3$ unless otherwise noted. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR was expressed in cm^{-1}. The extract was dried over Na_2SO_4 unless otherwise noted. Purification was carried out using silica gel column chromatography. All reactions were carried out under an argon atmosphere unless otherwise stated.

4.1.1. (1*S*,2*S*)-6,7-Dimethoxy-2-nitro-1-phenyl-1,2,3,4-tetrahydronaphthalene (*ent*-5) (Table 1, entry 3). To a solution of (−)-sparteine **10** (984 mg, 4.2 mmol) in toluene (25 mL) was added phenyllithium (1.7 mL, 1.8 M in cyclohexane-ether, 3.0 mmol) at −78 °C over 1 min. After 0.5 h stirring, nitroalkene **6**[14] (235 mg, 1.0 mmol) in toluene (5.0 mL) was added over 2 min, and the mixture was stirred for additional 1 h. The mixture was quenched with MeOH (2.0 mL) and then satd NH_4Cl (30 mL), and extracted with AcOEt. The extract was washed with 10% HCl, satd

$NaHCO_3$, and brine, and then dried. Concentration and chromatography (hexane/AcOEt=10/1) gave a mixture of 62/38 *trans*- and *cis*-*ent*-**5** (277 mg, 88% yield) as pale yellow amorphous of $[\alpha]_D^{25}=+75.3$ (*c* 1.0, $CHCl_3$). The ratio of the stereoisomers was determined to be (1*S*,2*S*)/(1*R*,2*R*)=72:28 and (1*S*,2*R*)/(1*R*,2*S*)=71:29 by a chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH=9/1, 1.0 mL/min, 254 nm, 14.5 min for (1*S*,2*S*), 18.6 min for (1*R*,2*R*), 25.2 min for (1*R*,2*S*), and 30.1 min for (1*S*,2*R*)). ^{1}H NMR: 2.17–2.21 (0.38H, m, *cis*), 2.29–2.49 (1.62H, m, *trans* and *cis*), 2.90–3.11 (2H, m, *trans* and *cis*), 3.61 (1.86H, s, *trans*), 3.71 (1.14H, s, *cis*), 3.87 (1.86H, s, *trans*), 3.89 (1.14H, s, *cis*), 4.72 (0.62H, d, *J*=7.9 Hz, *trans*), 4.82 (0.38H, d, *J*=5.8 Hz, *cis*), 4.85–4.88 (0.62H, m, *trans*), 4.98–5.02 (0.38H, m, *cis*), 6.24 (0.62H, s, *trans*), 6.40 (0.38H, s, *cis*), 6.62 (0.62H, s, *trans*), 6.66 (0.38H, s, *cis*), 6.93 (0.76H, dd, *J*=3.7, 7.1 Hz, *cis*), 7.12 (1.24H, d, *J*=7.7 Hz, *trans*), 7.23–7.33 (3H, m, *trans* and *cis*).

A solution of the above mixture of *ent*-**5** (230 mg, 0.74 mmol) and Et_3N (0.10 mL, 0.74 mmol) in MeCN (3.0 mL) was stirred for 18 h at rt. The mixture was concentrated, and the resulting residue was dissolved in AcOEt. The solution was washed with 10% HCl, satd $NaHCO_3$, and brine, and then dried. Concentration gave a 86:14 *trans*/*cis* mixture of *ent*-**5** (226 mg, 98% yield), whose recrystallization 3 times from methanol afforded the enantiomerically and diastereomerically pure *trans*-*ent*-**5** (77 mg, 27% yield) as colorless needles of mp 139.5–140.5 °C and $[\alpha]_D^{25}=+93.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: 2.37–2.49 (2H, m), 2.92–3.05 (2H, m), 3.61 (3H, s), 3.87 (3H, s), 4.72 (1H, d, *J*=8.3 Hz), 4.84–4.88 (1H, m), 6.24 (1H, s), 6.62 (1H, s), 7.11 (2H, d, *J*=7.7 Hz), 7.26–7.33 (3H, m). ^{13}C NMR: 26.7, 26.9, 48.8, 55.8, 55.9, 89.8, 110.7, 112.4, 126.7, 127.3, 127.6, 128.9, 129.0, 141.4, 147.8, 148.0. IR (KBr): 1554, 1512. EIMS *m*/*z*: 313 (M^+), 280, 265, 235, 176, 165, 91. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.91; H, 6.03; N, 4.21.

4.1.2. (1*S*,2*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-amine (*ent*-2). To a solution of *ent*-**5** (31 mg, 0.10 mmol) in EtOH (1.0 mL) and 6 N HCl (0.3 mL, 1.8 mmol) was added Zn (65 mg, 1.0 mmol). After stirred for 2.5 h at rt the mixture was filtered, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$, and the solution was washed with satd $NaHCO_3$ and brine, and then dried. Concentration and recrystallization from AcOEt gave *ent*-**2** (24 mg, 86% yield) as colorless needles of mp 101.0–102.5 °C and $[\alpha]_D^{25}=-20.6$ (*c* 1.3, $CHCl_3$). ^{1}H NMR: 1.27 (2H, s), 1.73 (1H, m), 2.04 (1H, m), 2.87 (1H, ddd, *J*=4.3, 4.9, 16.5 Hz), 2.97 (1H, ddd, *J*=4.9, 5.5, 6.1 Hz), 3.18 (1H, m), 3.58 (3H, s), 3.68 (1H, d, *J*=7.9 Hz), 3.86 (3H, s), 6.18 (1H, s), 6.62 (1H, s), 7.16–7.33 (5H, m). ^{13}C NMR: 27.7, 30.7, 54.5, 55.5, 55.7, 55.8, 110.9, 113.0, 126.6, 128.4, 129.9, 128.5, 130.3, 144.5, 147.2,147.4. IR (KBr): 3400, 3100, 1610, 1510. EIMS *m*/*z*: 283 (M^+), 266, 251. Anal. Calcd for $C_{18}H_{21}NO_2\cdot 1/10H_2O$: C, 75.81; H, 7.49; N, 4.91. Found: C, 75.79; H, 7.43; N, 4.68.

4.1.3. (1*S*,2*S*)- and (1*S*,2*R*)-6,7-Dimethoxy-2-nitro-1-(2-trityloxymethylphenyl)-1,2,3,4-tetrahydronaphthalene (*cis*- and *trans*-8). The title compound was prepared in 98% yield as a 70/30 *trans*/*cis* mixture of pale yellow needles of mp 71–74 °C by using a chiral ligand **13**.[6]

4.1.4. {2-[(1*S*,2*R*)-6,7-Dimethoxy-2-nitro-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}methanol (8a). A mixture of above **8** (289 mg, 0.49 mmol) and $NaHCO_3$ (414 mg, 4.9 mmol) in EtOH (5.0 mL) was heated under reflux for 4 h. The mixture was filtered and the filtrate was concentrated to give a 98:2 *trans*/*cis* mixture. The solution of the residue in MeOH (1.9 mL), THF (1.9 mL), and 12 N HCl (0.6 mL, 7.4 mmol) was stirred at rt for 18 h, and then diluted with AcOEt. The organic layer was washed with satd $NaHCO_3$ and brine, and then dried. Concentration and chromatography (hexane/AcOEt=4:1) gave **8a** (109 mg, 85% yield) as colorless prisms of mp 47–49 °C and $[\alpha]_D^{25}=-147$ (*c* 0.90, $CHCl_3$) for 95% ee (HPLC: Daicel Chiralpak AD; hexane/*i*-PrOH=4:1, 1.0 mL/min; 254 nm, major 12.8 min and minor 16.7 min). ^{1}H NMR: 1.89 (1H, brs), 2.41–2.51 (2H, m), 2.94–3.06 (2H, m), 3.58 (3H, s), 3.86 (3H, s), 4.77 (1H, s), 5.08–5.10 (1H, m), 6.20 (1H, s), 6.62 (1H, s), 6.96 (1H, d, *J*=6.1 Hz), 7.23–7.40 (2H, m), 7.42 (1H, d, *J*=7.4 Hz). ^{13}C NMR: 26.3, 26.5, 44.6, 55.8, 63.3, 88.5, 110.8, 112.3, 126.7, 127.6, 127.7, 128.6, 129.6, 129.9, 138.8, 140.0, 147.9, 148.0. IR (neat): 3487, 1547, 1516, 1462, 1404, 1369, 1254. EIMS *m*/*z*: 343 (M^+), 326, 296, 278, 265. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.16; H, 6.17; N, 3.93.

Recrystallization from toluene afforded the enantiomerically and diastereomerically pure **8a** (77 mg, 87% yield) as colorless prisms of mp 52–53 °C and $[\alpha]_D^{25}=-154$ (*c* 0.81, $CHCl_3$) for >99% ee.

4.1.5. (6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (14). A suspension of the above **8a** (31 mg, 0.09 mmol) and Zn (59 mg, 0.90 mmol) in EtOH (3.0 mL) and 6 N HCl (0.5 mL, 3.0 mmol) was stirred for 10 min at rt. The mixture was filtered, and the filtrate was concentrated. A solution of the resulting amine in 1,4-dioxane (1.3 mL) and 12 N HCl (0.8 mL) was heated under reflux for 2.5 h. Concentration gave the intermediate chloride, which was immediately dissolved in *t*-BuOH (2.5 mL). To the solution was added K_2CO_3 (500 mg, 3.6 mmol), and the mixture was heated under reflux for 1 h. The mixture was cooled to rt, poured into water, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over K_2CO_3. Concentration and chromatography (AcOEt/MeOH=9:1) gave **14** (23 mg, 86% yield) as colorless prisms of mp 155–156 °C (>99% ee) and $[\alpha]_D^{25}=-222$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: 1.69–1.75 (2H, m), 2.14–2.21 (1H, m), 2.71 (1H, ddd, *J*=6.7, 10.7, 10.7 Hz), 2.78–2.84 (1H, m), 2.90–2.95 (1H, m), 3.77 (3H, s), 3.83 (1H, d, *J*=10.7 Hz), 3.88 (3H, s), 4.03 (1H, d, *J*=15.6 Hz), 4.11 (1H, d, *J*=15.6 Hz), 6.74 (1H, s), 6.91 (1H, s), 7.16 (1H, d, *J*=7.4 Hz), 7.21–7.29 (2H, m), 7.47 (1H, d, *J*=7.4 Hz). ^{13}C NMR: 27.4, 28.9, 44.6, 49.1, 56.0, 56.1, 58.8, 110.0, 111.9, 126.0, 126.1, 126.8, 128.5, 130.7, 130.9, 136.1, 137.7, 146.6, 147.1. IR (KBr): 3294, 1504. EIMS *m*/*z*: 295 (M^+), 278, 263, 165. The hydrochloride: colorless needles of mp >236 °C (dec) (>99% ee). $[\alpha]_D^{25}=+123$ (*c* 0.75, EtOH). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.53; H, 6.69; N, 4.16.

The absolute configuration was determined to be (6a*R*,12b*S*) by comparison of the specific rotation with that reported ($[\alpha]_D^{25}$=+106 (*c* 0.75, EtOH) for >99% ee).[18]

4.1.6. (6a*R*,12b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (1). To a solution of **14** (20 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was added BBr_3 (0.3 mL, 1.0 M in hexane, 0.3 mmol) over 10 min at −78 °C, and the mixture was stirred at rt for 12 h. The mixture was quenched with MeOH (3.0 mL), stirred for 0.5 h, and then concentrated. The residue was dissolved in water, and the pH was adjusted to 9–10 with $NaHCO_3$ under Ar atmosphere. The mixture was extracted with $CHCl_3$, and the combined organic layers were dried and concentrated to give 20 mg of a pale yellow powder. A solution of the powder in EtOH (1 mL) and EtOH–HCl (3 mL) was stirrer at rt for 0.5 h and concentrated. The residue was azeotoropically dried with benzene (3 mL) and recrystallized from AcOEt/isopropanol to give **1** (15 mg, 73% yield) as pale yellow powder of mp >122 °C (dec) and $[\alpha]_D^{25}$=+85.5 (*c* 0.24, EtOH). ^{1}H NMR (DMSO): 1.98 (1H, m), 2.23 (1H, m), 2.70–2.85 (2H, m), 3.00 (1H, m), 4.22 (1H, d, *J*=11.0 Hz), 4.41 (1H, d, *J*=15.8 Hz), 4.44 (1H, d, *J*=15.8 Hz), 6.68 (1H, s), 6.78 (1H, s), 7.35–7.50 (4H, m), 8.93 (1H, m), 8.95 (1H, m), 9.67 (1H, s), 9.95 (1H, s). ^{13}C NMR (DMSO): 25.3, 26.3, 40.3, 43.9, 56.6, 114.6, 115.9, 124.3, 126.3, 126.8, 127.5, 127.7, 127.8, 130.5, 143.2, 144.0. IR (nujol): 3000–3700, 1610, 1510. CIMS *m*/*z*: 268 (M^++1). HRMS-CI (*m*/*z*): $[M+H]^+$ Calcd for $[C_{17}H_{19}NO_2]^+$, 268.1337. Found, 268.1135.

4.1.7. (1*S*,2*S*)-1-Dimethylamino-2-(2-methoxyphenoxy)-1,2-diphenylethane (13). A mixture of CuI (7.80 g, 33.3 mmol, 67 mol %), cesium carbonate (41.5 g, 133 mmol), (1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethanol[19] (12.1 g, 50 mmol), and 2-iodoanisole (23.5 g, 100 mmol) in butyronitrile (60 mL) was stirred at 125 °C for 1 day.[17] The reaction mixture was cooled to rt and filtered, and the filter cake was washed well with AcOEt. The combined filtrate and the washings were extracted with 10% HCl (3×100 mL) and the acid extracts were cooled at 0 °C for 1 h. The resulting precipitates were filtered and washed with AcOEt. The collected precipitates were dissolved in 5 M NaOH (200 mL), and the solution was extracted with Et_2O several times. The extracts were washed with brine and dried over K_2CO_3. Concentration and recrystallization from hexane gave **13** (14.3 g, 82% yield) as colorless needles of mp 72–73 °C.[12e]

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An unusual base-dependent α-alkylation and β-elimination of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate: practical synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate

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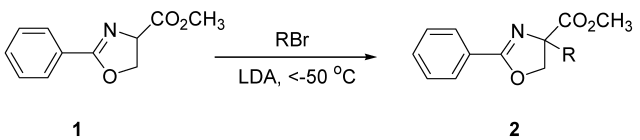
Abstract—Practical synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate from *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate (**6**) were developed. The α-alkylation and β-elimination of **6** are dramatically dependent upon base conditions. The phase-transfer catalytic condition bearing solid KOH in toluene gives α-alkylation (up to >99%), and *t*-BuOK in DMF gives β-elimination (98%).

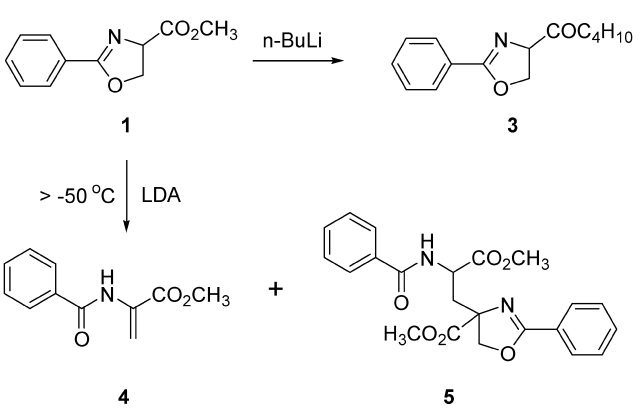
1. Introduction

α-Alkylserines have been extensively studied, due to their important roles in the fields of synthetic and biological chemistry.[1] As their quaternary carbon centers induce preferable conformations in peptide backbones,[2] α-alkylserine moieties have been employed in the design of biologically active peptidomimetics.[3] In addition, α-alkylserines are frequently found in several biologically active natural products, such as mycestericins,[4] (+)-lactacystin,[5] and (+)-conagenin,[6] and α-alkylserines themselves are useful synthetic building blocks via chemical transformations.[1] A number of synthetic methods[7] have been reported for α-alkylserines. Among them, the alkylation of phenyloxazoline derivatives of serine esters is the most practical (Scheme 1).[7l]



Scheme 1.

The oxazoline moiety can not only provides sufficient acidity to the α-hydrogen of the ester group, but also acts as an excellent protecting group for both the amino and hydroxyl groups in the serine ester. The following hydrolysis under acidic conditions can provide α-alkylserines. However, it usually requires a strong base (LDA) and low temperature conditions below −50 °C for alkylation, otherwise β-elimination (**4**) and the following Michael addition (**5**) are predominant.[7l] In the case of *n*-BuLi at −100 °C, only the corresponding *n*-butyl ketone can be prepared by substitution (Scheme 2).[8] Herein, we report the unusual base dependent α-alkylation and β-elimination in the oxazoline ester and the practical reaction conditions for the selective synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate.



Scheme 2.

2. Results and discussion

As part of our program for the conformational studies of the peptidomimetics bearing α-alkylserines, we needed

Keywords: α-Alkylserines; Benzamidoacrylate; Phase-transfer catalytic alkylation.
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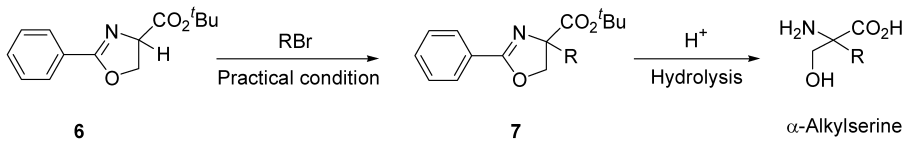


6 7

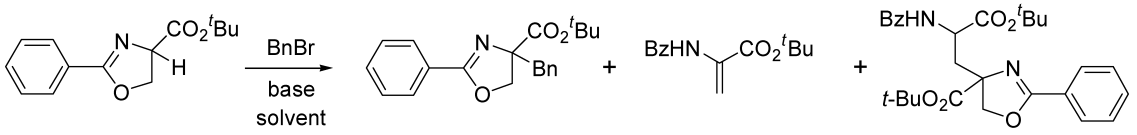
Scheme 3.

practical synthetic methods for the various α-alkylserines. So we adapted the α-alkylation of 2-phenyl-2-oxazoline-4-carboxylic ester and investigated the practical reaction conditions. As shown in Scheme 3, we chose the *tert*-butyl ester **6** as the substrate, which might reduce the ester hydrolysis in the practical base conditions, such as mild alkali bases at 0 °C or room temperature.

Substrate **6** is easily prepared by coupling ethyl benzimidate and serine *tert*-butyl ester in 98% yield.[9] To determine the optimal alkylation conditions, the benzylation was performed using *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate **6** along with benzyl bromide (5 equiv.), and various bases (5 equiv.) in tetrahydrofuran at 0 °C. K_2CO_3[10] (entry 1) and DBU[11] (entry 2), which have been applied in the α-epimerization of oxazoline esters, unexpectedly gave no α-alkylation and β-elimination product. Interestingly, in the series of *tert*-butoxide bases, the relative ratio of **7f** (α-alkylation) to **8** and **9** (β-elimination) depended on the cation, as shown in Table 1. The α-benzylation increased as follows: $Li^+ > Na^+ > K^+$ (entries 3–5). We assume that the enhanced covalent bond character of the enolate intermediate might contribute to the increase in α-alkylation. In the case of solid alkali hydroxides, although they are weak bases as compared to alkali *tert*-butoxides, they delivered **7f** in modest chemical yields (83%–85%), except for LiOH (entries 6–8). Notably, 40% aq. tetrabutylammonium hydroxide gave only **7f** without any β-elimination products, although the chemical yield was low because of partial hydrolysis (entry 9). These results finally prompted us to employ a phase-transfer catalytic reaction. Surprisingly, solid KOH in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB, 5 mol%) in toluene afforded **7f** in a very high chemical yield (99%), without any β-elimination (entry 10). The high chemical yield could be produced even at room temperature (98%, entry 11). The replacement of solid KOH with 50% aq. KOH reduced the chemical yield, due to low reaction rate (entry 12). The hydrolysis of **7f** with 6 N-HCl, followed by the purification using ion-exchange resin afforded (±)-α-benzylserine in 98% yield.[4m,12] Further investigations of the phase-transfer catalytic alkylation with various alkyl halides, using the above optimal reaction conditions,[13] were performed. As shown in Table 2, all the active alkyl halides (entry c–m) performed α-alkylation in very high yield, but aliphatic halides (entry a and b) provided relatively lower chemical yield, which might be due to the low reactivity. The high chemical yields indicate that phase-transfer catalytic condition is very efficient for the synthesis of (±)-α-alkylserines.

After the optimization of the selective α-alkylation, we focused our attention toward optimizing the β-elimination condition for *tert*-butyl benzamidoacrylate **8**, which is one of the versatile synthetic intermediates. There have been a few synthetic methods for benzamidoacrylates, but generally they need several steps or gave relatively low chemical yields.[14] In Table 1 (entry 3), *tert*-BuOK showed the most promising possibility for the selective β-elimination, but there was still some amount of dimeric side product **9** via

Table 1. Optimal conditions for the alkylation of **6**[a]

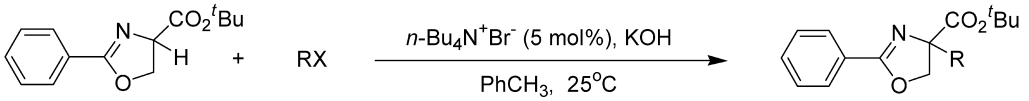


6 7f 8 9

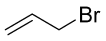
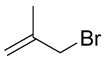
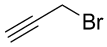
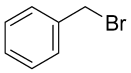
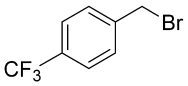
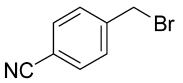
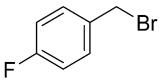
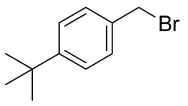
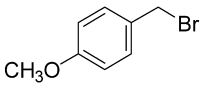
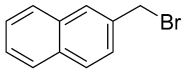
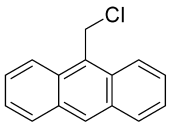
No	Base	Solvent	Temperature (°C)	Time	**7f** Yield[b] (%)	**8** Yield[b] (%)	**9** Yield[b] (%)
1	K_2CO_3[c]	DMF/*t*-BuOH	rt	12 h	0	0	0
2	DBU[c]	CH_2Cl_2	rt	12 h	0	0	0
3	*t*-BuOK	THF	0	2 min	0	83	5
4	*t*-BuONa	THF	0	2 min	18	43	9
5	*t*-BuOL	THF	0	2 min	57	18	10
6	KOH	THF	0	0.75 h	83	0	3
7	NaOH	THF	0	1.25 h	85	0	3
8	LiOH	THF	rt	5 day	25	0	0
9	40% aq. n-Bu_4NOH	THF	0	10 min	38	0	0
10	KOH/TBAB[d]	$PhCH_3$	0	3 h	99	0	0
11	KOH/TBAB[d]	$PhCH_3$	rt	2 h	98	0	0
12	50% aq. KOH/TBAB[d]	$PhCH_3$	0	2 day	32	0	0

[a] The reaction was carried out with 5.0 equiv. of benzyl bromide and 5.0 equiv. of base in tetrahydrofuran or toluene under the given conditions.
[b] Isolated yields.
[c] **6** was recovered.
[d] 5 mol% of tetra-*n*-butylammonium bromide (TBAB) was used.

Table 2. Phase-transfer catalytic alkylation[a]



6 **7**

Entry	RX	Time (h)	Yield[b] (%)
a	CH_3I	2.5	65
b	CH_3CH_2I	1.0	52
c		0.4	>99
d		0.4	>99
e		0.4	>99
f		2.0	98
g		2.5	>99
h		3.5	99
i		3.0	98
j		1.0	92
k		0.2	80
l		1.0	96
m		0.5	95

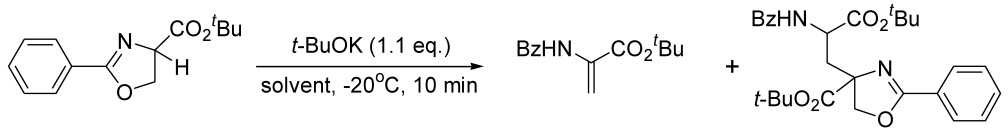
[a] The reaction was carried out with 5.0 equiv. of alkylating agent and 5.0 equiv. of solid KOH in toluene under the given conditions.
[b] Isolated yields.

1,4-addition. To increase the selectivity for β-elimination, various solvents were employed at the lower reaction temperature (−20 °C). As shown in Table 3, generally the more polar aprotic solvent gave the higher selectivity for β-elimination, which might be due to the stabilization of the enolate intermediate by the solvation. Among the solvents, DMF showed the best result in both the selectivity and the chemical yield (98%), but no reaction was detected in case of *t*-BuOH.

3. Conclusions

We founded the unusual base dependent α-alkylation and β-elimination of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate (**6**). The α-alkylation and β-elimination are dramatically dependent upon base conditions. The phase-transfer catalytic condition in the presence of alkyl halides could selectively give the corresponding α-alkylated products in high yield. In case of *t*-BuOK, *tert*-butyl

Table 3. β-Elimination for benzamidoacrylate[a]



6 **8** **9**

No	Solvent	**8** Yield[b] (%)	**9** Yield[b] (%)
1	THF	91	2
2	*n*-Hexane	50	8
3	DMF	98	0
4	*t*-BuOH[c]	0	0

[a] The reaction was carried out with 1.1 equiv. of base in the corresponding solvent at −20 °C for 10 min.
[b] Isolated yields.
[c] **6** was recovered.

benzamidoacrylate could be obtained in high yield by the selective β-elimination. The easy preparation of substrate **6**, the high chemical yields, and the very mild reaction conditions could make these methods very practical for the synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate, which are very useful synthetic intermediates.

4. Experimental

4.1. General

Infrared spectra were taken on a Perkin–Elmer 1710 FT-IR spectrometer. Mass spectra were obtained on a VG Trios-2 GC-MS and JEOL JMS-700 instrument. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300 and a JEOL JNM-GCX 400 spectrometers using TMS as the internal standard. Most reagents were obtained from commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone, and methylenechloride from CaH_2.

4.1.1. 2-Phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (6). To a methylenechloride solution (60 mL) of ethyl benzimidate hydrochloride (3.71 g, 20.0 mmol) and L-serine *tert*-butyl ester hydrochloride (3.52 g, 20.0 mmol) in methylenechloride was added triethylamine (5.58 mL, 40.0 mmol). The reaction mixture was refluxed for 2 h and stirred for 10 h at room temperature. The reaction mixture was diluted with methylenechloride (200 mL), washed with sat. aq. $NaHCO_3$ soln. (2×50 mL) and water (2×50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to afford **6** (5.16 g, 98% yield) as a white solid; mp: 42–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J=7.1 Hz, 2H), 7.53–7.36 (m, 3H), 4.84 (dd, J=8.0, 10.5 Hz, 1H), 4.62–4.53 (m, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 165.9, 131.6, 128.5, 128.1, 127.0, 82.0, 69.7, 69.3, 27.9 ppm; IR (KBr) 2979, 1734, 1644, 1453, 1364, 1298, 1222, 1156, 1089, 1026, 967, 846, 777, 696 cm^{-1}; MS (FAB) *m*/*z* 248 [M+H]$^+$; HRMS calculated for $C_{14}H_{17}NO_3$: 247.1208. Found: 248.1285 [M+H]$^+$.

4.2. General procedure for the phase-transfer catalytic alkylations (7a-7m)

To a toluene solution (0.80 mL) of 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **6** (50.0 mg, 0.200 mmol), tetrabutylammonium bromide (3.2 mg, 0.01 mmol) and KOH (56.1 mg, 1.00 mmol) was added the corresponding alkyl halide (1.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (2×5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=20:1) to afford the compounds **7a**-**7m**.

4.2.1. 4-Methyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7a). A pale yellow oil (34 mg, 65% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=7.3 Hz, 2H), 7.59–7.38 (m, 3H), 4.46 (d, J=8.8 Hz, 1H), 4.11 (d, J=8.8 Hz, 1H), 2.30 (s, 3H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 164.7, 131.8, 128.7, 128.3, 127.0, 82.0, 76.2, 74.5, 27.9, 24.8 ppm; IR (KBr) 2978, 1729, 1645, 1452, 1287 cm^{-1}; MS (FAB) *m*/*z* 262 [M+H]$^+$; HRMS calculated for $C_{15}H_{19}NO_3$: 261.3163. Found: 262.1443 [M+H]$^+$.

4.2.2. 4-Ethyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7b). A pale yellow oil (29 mg, 52% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J=8.3 Hz, 2H), 7.51–7.37 (m, 3H), 4.71 (d, J=8.9 Hz, 1H), 4.21 (d, J=8.9 Hz, 1H), 1.95 (qd, J=1.4, 7.5 Hz, 2H), 1.50 (s, 9H), 0.94 (t, J=7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 164.1, 131.5, 128.5, 128.2, 127.4, 81.7, 78.9, 73.4, 31.0, 27.9, 8.0 ppm; IR (KBr): 2973, 2926, 1726, 1646, 1455, 1364, 1252, 1146, 1067, 1026, 971, 845, 778, 694 cm^{-1}; MS (ESI) *m*/*z* 276 [M+H]$^+$, 298 [M+Na]$^+$; HRMS calculated for $C_{16}H_{21}NO_3$: 275.1521. Found: 276.1600 [M+H]$^+$.

4.2.3. 4-Allyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7c). A pale yellow oil (59 mg, >99% yield); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.98 (d, J=6.8 Hz, 2H), 7.52–7.38 (m, 3H), 5.80–5.66 (m, 1H), 5.20–5.13 (m, 2H), 4.70 (d, J=8.8 Hz, 1H), 4.27 (d, J=8.8 Hz, 1H), 2.76–2.60 (m, 2H), 1.50 (s, 9H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 171.3, 164.6, 131.9, 131.6, 128.6, 128.3, 127.2, 119.5, 82.0, 77.8, 73.1, 42.1, 27.9 ppm; IR (KBr) 2979, 1728, 1644, 1452, 1365, 1275, 1147, 1089, 1027, 978, 922, 846, 777, 696 cm^{-1}; MS (FAB) *m/z* 288 $[M+H]^+$; HRMS calculated for $C_{17}H_{21}NO_3$: 287.1521. Found: 288.1601 $[M+H]^+$.

4.2.4. 4-(2-Methyl-allyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7d). A yellow oil (61 mg, >99% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.0 Hz, 2H), 7.45–7.34 (m, 3H), 4.85 (s, 1H), 4.82 (d, *J*=8.8 Hz, 1 H), 4.68 (s, 1H), 4.29 (d, *J*=8.8 Hz, 1 H), 2.83 (d, *J*=14.6 Hz, 1H), 2.53 (d, *J*=14.6 Hz, 1H), 1.74 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 164.2, 140.9, 131.5, 128.5, 128.2, 127.3, 114.3, 81.9, 77.9, 73.3, 45.5, 27.8, 23.9 ppm; IR (KBr) 2976, 2926, 1727, 1644, 1453, 1365, 1286, 1160, 1102, 978, 898, 846, 776, 695 cm^{-1}; MS (ESI) *m/z* 302 $[M+H]^+$, 324 $[M+Na]^+$; HRMS calculated for $C_{18}H_{23}NO_3$: 301.1678. Found: 302.1755 $[M+H]^+$.

4.2.5. 4-Prop-2-ynyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7e). A pale yellow caramel (58 mg, >99% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J*=6.8 Hz, 2H), 7.51–7.36 (m, 3H), 4.85 (d, *J*=8.8 Hz, 1H), 4.47 (d, *J*=8.8 Hz, 1H) 2.95 (dd, *J*=2.7, 16.7 Hz, 1H), 2.69 (dd, *J*=2.7, 16.7 Hz, 1H), 1.95 (t, *J*=2.7 Hz, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 165.5, 131.8, 128.6, 128.2, 126.9, 82.5, 78.7, 77.4, 73.5, 71.0, 27.9, 27.8 ppm; IR (KBr): 2979, 1731, 1641, 1453, 1366, 1279, 1161, 1101, 978, 845, 695 cm^{-1}; MS (FAB) *m/z* 286 $[M+H]^+$; HRMS calculated for $C_{17}H_{19}NO_3$: 285.1365. Found: 286.1442 $[M+H]^+$.

4.2.6. 4-Benzyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7f). A pale yellow caramel (67 mg, 98% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.1 Hz, 2H), 7.50–7.15 (m, 8H), 4.66 (d, *J*=8.8 Hz, 1H), 4.31 (d, *J*=8.8 Hz, 1H), 3.25 (dd, *J*=13.8, 46.7 Hz, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.6, 135.6, 131.5, 130.3, 128.5, 128.1, 128.0, 127.2, 126.8, 82.1, 78.7, 72.8, 43.1, 27.8 ppm; IR (KBr) 2978, 1726, 1644, 1453, 1366, 1280, 1160, 1095, 978, 847, 697 cm^{-1}; MS (FAB) *m/z* 338 $[M+H]^+$; HRMS calculated for $C_{21}H_{23}NO_3$: 337.1678. Found: 338.1750 $[M+H]^+$.

4.2.7. 4-(4-Trifluoromethylbenzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7g). A white solid (82 mg, >99% yield); mp: 61–63 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.1 Hz, 2H), 7.51–7.38 (m, 7H), 4.66 (d, *J*=8.9 Hz, 1H), 4.26 (d, *J*=8.9 Hz, 1H), 3.29 (dd, *J*=13.8, 25.1 Hz, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.0, 140.0, 131.8, 130.7, 129.3, 128.9, 128.5, 128.3, 127.0, 125.0, 82.5, 78.5, 73.2, 42.9, 27.8 ppm; IR (KBr) 2979, 1728, 1645, 1452, 1366, 1327, 1281, 1163, 1121, 1066, 1023, 980, 849, 695 cm^{-1}; MS (FAB) *m/z* 406 $[M+H]^+$; HRMS calculated for $C_{22}H_{22}F_3NO_3$: 405.1552. Found: 406.1634 $[M+H]^+$.

4.2.8. 4-(4-Cyano-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7h). A pale yellow needle (73 mg, 99% yield); mp: 66–68 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58–7.37 (m, 7H), 4.63 (d, *J*=9.1 Hz, 1H), 4.23 (d, *J*=9.1 Hz, 1H), 3.35 (d, *J*=13.8 Hz, 1H), 3.18 (d, *J*=13.8 Hz, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.0, 141.4, 131.8, 131.7, 131.1, 128.4, 128.2, 126.8, 118.7, 110.7, 82.5, 78.2, 73.3, 43.2, 27.8 ppm; IR (KBr) 2978, 2228, 1728, 1644, 1452, 1366, 1281, 1159, 1092, 979, 847, 759, 697 cm^{-1}; MS (FAB) *m/z* 363 $[M+H]^+$; HRMS calculated for $C_{22}H_{22}N_2O_3$: 362.1630. Found: 363.1696 $[M+H]^+$.

4.2.9. 4-(4-Fluoro-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7i). A yellow caramel (71 mg, 98% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J*=7.1 Hz, 2H), 7.51–7.37 (m, 3H), 7.26–7.21 (m, 2H), 6.96–6.88 (m, 2H), 4.63 (d, *J*=8.8 Hz, 1H), 4.27 (d, *J*=8.8 Hz, 1H) 3.20 (dd, *J*=13.9, 21.2 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.7, 164.1 160.7, 131.9, 131.8, 131.6, 131.3, 128.5, 128.2, 127.1, 115.0, 114.8, 82.2, 78.6, 72.9, 42.3, 27.9 ppm; IR (KBr) 2978, 1726, 1644, 1510, 1366, 1279, 1224, 1160, 1101, 979, 846, 695 cm^{-1}; MS (FAB) *m/z* 356 $[M+H]^+$; HRMS calculated for $C_{21}H_{22}FNO_3$: 355.1584. Found: 356.1666 $[M+H]^+$.

4.2.10. 4-(4-*tert*-Butyl-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7j). A pale yellow caramel (73 mg, 92% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J*=7.1 Hz, 2H), 7.51–7.36 (m, 3H), 7.26–7.16 (m, 4H), 4.67 (d, *J*=8.9 Hz, 1H), 4.31 (d, *J*=8.9 Hz, 1H), 3.22 (dd, *J*=13.8, 38.6 Hz, 2H), 1.46 (s, 9H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.5, 149.5, 132.5, 131.5, 129.9, 128.5, 128.1, 127.3, 125.0, 82.0, 78.9, 73.0, 42.8, 34.3, 31.2, 27.9 ppm; IR (KBr) 2964, 1723, 1644, 1454, 1365, 1278, 1161, 1091, 1025, 978, 847, 695 cm^{-1}; MS (FAB) *m/z* 394 $[M+H]^+$; HRMS calculated for $C_{25}H_{31}NO_3$: 393.2304. Found: 394.2381 $[M+H]^+$.

4.2.11. 4-(4-Methoxy-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7k). A yellow oil (60 mg, 80% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.3 Hz, 2H), 7.50–7.36 (m, 3H), 7.17 (d, *J*=8.5 Hz, 2H), 6.75 (d, *J*=8.5 Hz, 2H), 4.65 (d, *J*=8.8 Hz, 1H), 4.30 (d, *J*=8.8 Hz, 1H), 3.72 (s, 3H), 3.19 (dd, *J*=13.9, 17.8 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 164.5, 158.4, 131.5, 131.3, 128.6, 128.5, 128.2, 127.5, 113.5, 82.1, 78.9, 72.7, 55.1, 42.2, 27.9 ppm; IR (KBr) 2929, 1726, 1643, 1513, 1455, 1365, 1252, 1160, 1091, 1033, 978, 846, 695 cm^{-1}; MS (FAB) *m/z* 368 $[M+H]^+$; HRMS calculated for $C_{22}H_{25}NO_4$: 367.1784. Found: 368.1856 $[M+H]^+$.

4.2.12. 4-(Naphthalene-2-ylmethyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7l). A pale yellow solid (75 mg, 96% yield); mp: 82–84 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.3 Hz, 2H), 7.76–7.67 (m, 4H), 7.50–7.35 (m, 6H), 4.70 (d, *J*=8.9 Hz, 1H), 4.38 (d, *J*=8.9 Hz, 1H), 3.43 (s, 2H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.7, 133.3, 133.2, 132.3, 131.5, 129.0, 128.6, 128.5, 128.2, 127.6, 127.5, 127.4, 127.2, 125.8, 125.5, 82.2, 78.9, 72.8, 43.2, 27.9 ppm; IR (KBr) 2977, 1726, 1643, 1452, 1365, 1280, 1159, 1092, 978, 846, 752, 696 cm^{-1}; MS (FAB) *m/z* 388 $[M+H]^+$; HRMS calculated for $C_{25}H_{25}NO_3$: 387.1834. Found: 388.1910 $[M+H]^+$.

4.2.13. 4-(Anthracenyl-9-ylmethyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7m). A yellow solid (84 mg, 95% yield); mp: 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51–8.37 (m, 3H), 7.94–7.92 (m, 4H), 7.54–7.33 (m, 7H), 4.63–4.08 (m, 4H), 1.60 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.1, 131.5, 131.3, 131.2, 128.8, 128.3, 128.0, 127.8, 127.4, 127.0, 126.2, 125.5, 124.7, 82.3, 79.69, 72.0, 33.4, 27.9 ppm; IR (KBr) 2977, 1723, 1645, 1451, 1230 cm^{-1}; MS (FAB) *m/z* 438 $[M+H]^+$; HRMS calculated for $C_{29}H_{27}NO_3$: 437.1991. Found: 438.2070 $[M+H]^+$.

4.3. Dimeric Michael adduct: 4-(2-benzoylamino-2-*tert*-butoxycarbonyl-ethyl)-2-phenyl-4,5-dihydro-oxazole-4-carboxylic acid *tert*-butyl ester (9)

A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.26 (m, 10H), 4.73 (d, J=9.2 Hz, 1H), 4.61–4.54 (m, 1H), 4.27 (d, J=9.2 Hz, 1H), 2.62–2.25 (m, 2H), 1.42 (s, 9H), 1.35 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 167.2, 165.3, 134.2, 133.7, 132.1, 131.4, 128.6, 128.2, 127.4, 126.9, 82.8, 81.6, 76.0, 74.4, 52.1, 39.1, 27.9, 27.8 ppm; IR (KBr) 2978, 1732, 1647, 1529, 1487, 1367, 1289, 1154 cm^{-1}; MS (FAB) *m/z* 495 $[M+H]^+$; HRMS calculated for $C_{28}H_{34}N_2O_6$: 494.2417. Found: 495.2498 $[M+H]^+$.

4.4. (±)-α-Benzylserine

To an ethanol solution (1.5 mL) of 4-benzyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **7f** (500 mg, 1.48 mmol) was added 6 N-HCl (1.5 mL) and the reaction mixture was refluxed for 24 h. After the solvent was removed in vacuo, the residue was purified by column chromatography (5% aq. NH_4OH) using ion-exchange resin (Dowex® 50WX8-100) to give (±)-α-benzylserine as a white solid (365 mg, 98%). Physical and spectral properties were consistent with the literature values.[4m,12]

4.5. *tert*-Butyl benzamidoacrylate (8)

To a dimethylformamide solution (1.5 mL) of 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **6** (50.0 mg, 0.200 mmol) was added a dimethylformamide solution (0.5 mL) of *tert*-BuOK (25 mg, 0.22 mmol) by dropwise at −20 °C. The reaction mixture was stirred at −20 °C for 10 min. After completion of the reaction, the excess *tert*-BuOK was quenched with a few drops of sat. aq. NH_4Cl. After removal of the solvent in vacuo, the residue was diluted with ethyl acetate (50 mL), washed with water (3×5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=5:1) to afford **8** (49 mg, 98% yield) as a yellow needle; mp: 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (br, 1H), 7.83–7.80 (m, 2H), 7.53–7.40 (m, 3H), 6.69 (s, 1H), 5.88 (s, 1H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.3, 134.4, 131.9, 128.7, 126.9, 107.8, 83.1, 60.4, 27.7 ppm; IR (KBr) 3418, 2976, 1677, 1519, 1370, 1338, 1159 cm^{-1}; MS (FAB) *m/z* 248 $[M+H]^+$; HRMS calculated for $C_{14}H_{17}NO_3$: 247.1208. Found: 248.1290 $[M+H]^+$.

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Prenyl carbamates: preparation and deprotection

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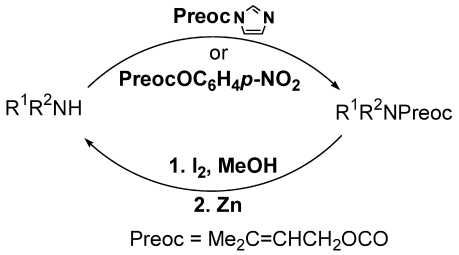
Abstract—Prenyloxycarbonylimidazole (PreocIm) and prenyl *p*-nitrophenyl carbonate (PreocOC_6H_4*p*-NO_2), two substitutes for the unstable prenyl chloroformate, allowed an efficient introduction of the prenyloxycarbonyl group to a variety of primary and secondary amines. Deprotection of prenyl carbamates was readily achieved by, first their conversion to 2-iodo-3-methoxy-3-methylbutyl carbamates with iodine in methanol followed by reductive β-elimination with zinc powder. These reaction conditions are compatible with the presence of a number of functional groups such as Boc and Cbz carbamates, sulfides, double bonds, indoles and aromatic ethers.

1. Introduction

The principle of using carboxyl-protecting groups for the blocking of amines through the conversion of the latter into urethanes (carbamates) was the most successful innovation in peptide synthesis. Since the invention by Bergmann and Zervas in 1932 of the benzyloxycarbonyl group (Cbz group),[1] the first easily and selectively removable carbamate protecting group, an impressive arsenal of amino-protecting groups has been developed.[2] However, because of the increasing complexity of the molecules synthesized, which contain a multiplicity of functional groups, there is a constant need for new protecting groups to overcome the difficulties encountered in the experimental realization of the synthetic plan of these molecules.

In the course of a study devoted to the search of new protecting groups for alcohols and amines,[3] we have recently reported in a preliminary account a mild and chemoselective method for the cleavage of prenyl carbamates.[4]

We now report, in full details, studies of this method of deprotection of prenyl carbamates as well as their efficient preparation using two new and readily available reagents (Scheme 1).



Scheme 1.

2. Results and discussion

2.1. Introduction of the prenyloxycarbonyl amino-protecting group

A survey of the literature revealed that there are only few examples of synthesis of prenyl carbamates.[5] In all cases, prenyl chloroformate was used as a reagent, generated either by reaction of 3-methyl-2-buten-1-ol (prenol) with phosgene[5a] or triphosgene ($Cl_3COCOOCl_3$).[5d]

After several experiments, treatment of 2-phenylethylamine (**3b**), used as a model compound, with 2 equiv. of prenyl chloroformate, made in situ by reaction of commercial phosgene in toluene, in the presence of triethylamine, gave the carbamate **4b** in only 30% yield, after purification on silica gel. An attempt to purify prenyl chloroformate by vacuum distillation (15 mm Hg) in a Kugelrohr apparatus afforded a fraction boiling between 50 and 60 °C containing, except the chloroformate, prenyl chloride and isoprene. Other related substituted allyl chloroformates are known to decompose easily even at room temperature.[6]

Keywords: Amines; Carbamates; Iodine; Prenylation; Protecting groups.
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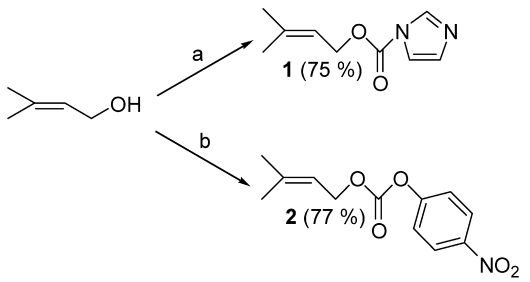
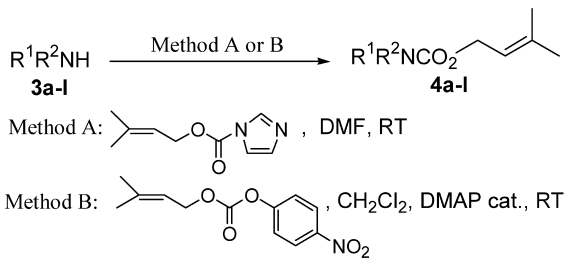
Then, looking for a more efficient and safer method for the synthesis of prenyl carbamates, we turned our attention to an other class of N-alkoxycarbonylation agent: imidazole carboxylic esters.[6b,7] Advantages of imidazolides over chloroformates are their greater stability which allows their purification on silica gel[8] and the use of commercially available *N*,*N*′-carbonyldiimidazole (CDI) for their preparation, a much safer reagent than phosgene. However, imidazolides are less reactive toward amines than chloroformates.

Prenyloxycarbonylimidazole (**1**) was readily prepared in 75% yield by reaction of prenol with CDI in CH_2Cl_2 at room temperature (Scheme 2). Treatment of 2-phenylethylamine (**3b**), a test substrate, with imidazolide **1**, in CH_2Cl_2 at room temperature for 24 h, afforded the corresponding carbamate **4b** in 75% yield. The employment of DMF as solvent instead of CH_2Cl_2 decreased dramatically the reaction time (5 h vs 24 h) and improved the yield (85%).



Scheme 2. Reagents and conditions: (a) CDI, CH_2Cl_2, 4 h, room temperature; (b)*p*-$NO_2C_6H_4OCOCl$, pyridine, 24 h, room temperature.

This mild method for prenyl carbamate formation (Scheme 3) was tested on a number of diversely functionalized amines and the results of this study are shown in Table 1. First, the reaction time of the carbamate formation was very depending on the substrate varying from 4 to 120 h. With most substrates, the *N*-prenyloxycarbonylation proceeded smoothly and in good yields (51–97%). However, with methionine, tryptophan and glucosamine derivatives (entries 15, 17, 21), the reaction was sluggish, providing the corresponding carbamate in low yields (0–33%).[9]



Scheme 3.

Frustrated by the low yielding introduction of the Preoc group to these important natural products, we looked for an other reagent able to form prenyl carbamates under mild conditions and in good yields whatever the amine used. We focused our attention to mixed carbonates activated by a *p*-nitrophenyl moiety, an interesting class of compounds used for the preparation of a large range of carbamates.[10]

Prenyl *p*-nitrophenyl carbonate (**2**), a crystalline solid, was easily made by reaction of prenol, in the presence of pyridine, with commercially available *p*-nitrophenyl chloroformate in CH_2Cl_2 at room temperature for 24 h (Scheme 2).

To evaluate the reactivity of amines toward the mixed carbonate **2**, a 1:1 mixture of L-methionine methyl ester (**3h**) and **2** was dissolved in CH_2Cl_2. Disappointingly, the reaction proceeded quite slowly at room temperature since 48 h were necessary for the reaction to attain completion. Gratifyingly, in the presence of a catalytic amount of DMAP (10 mol%), *N*-prenyloxycarbonyl-L-methionine methyl ester (**4h**) was isolated in 91% yield after stirring for 9 h at room temperature. As seen in Table 1, the mixed carbonate **2**, in the presence of DMAP, is a quite an efficient agent for the introduction of the Preoc group to amines (81–97% yield) except for the glucosamine derivative **3k** (entry 22) which reacted very sluggishly. Furthermore, during workup, *p*-nitrophenol formed during the reaction can be removed from the organic solution by a basic washing (Na_2CO_3) leaving the carbamate pratically pure. As seen in entry 20, the ε-amino group of L-lysine methyl ester derivative **3j** was regioselectively protected by reagent **2** in good yield (81%). Not much reagents are able to accomplish this transformation and anyhow with somewhat inferior yields.[11]

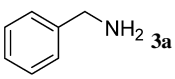
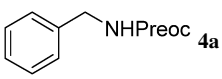
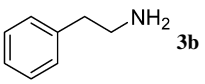
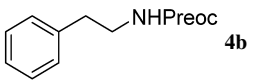
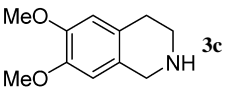
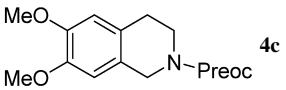
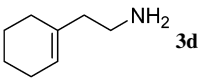
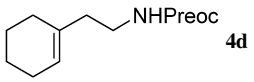
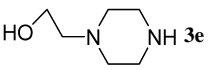
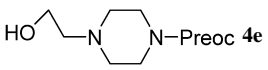
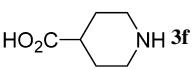
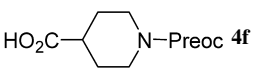
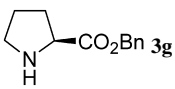
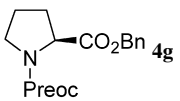
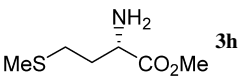
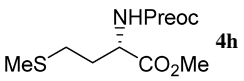
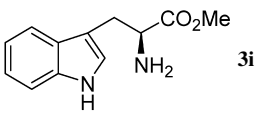
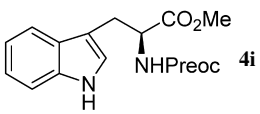
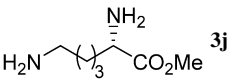
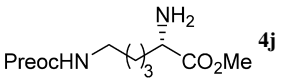
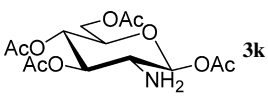
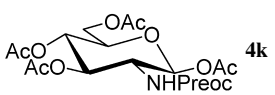
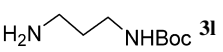
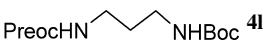
2.2. Cleavage of the *N*-prenyloxycarbonyl protecting group

There is only one method describing in the literature the deprotection of prenyl carbamates, using palladium technology, tested only on two substrates.[5b–c] Convinced that the prenyl moiety should be useful in the protection of functional groups such as acids, alcohols and amines, we first searched for mild method for the deprotection of prenyl ethers. We found that iodine in dichloromethane and dichlorodicyanoquinone in dichloromethane–water could chemoselectively cleave prenyl ethers in good yields.[3a–c] Encouraged by this success in the chemistry of prenyl group, we decided to apply these two techniques of prenyl group removal to amines. In both cases, cleavage of the prenyl carbamate derived from 2-phenylethylamine, compound **4b**, failed, leading to the recovery of the starting material, even after 24 h at room temperature.

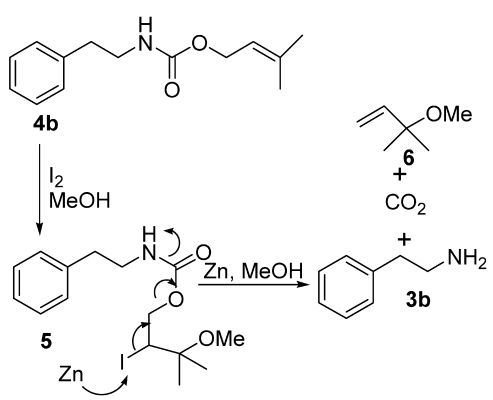
On the other hand, iodine in methanol reacted smoothly with **4b** to afford the 2-iodo-3-methoxy-3-methylbutyl carbamate **5** in 76% yield (Scheme 4). Compounds bearing a 2-haloalkoxycarbonyl system such as **5** are known to fragment in the presence of a metal.[12] Indeed, treatment of **5** with 2 equiv. of zinc in methanol, a good and commonly used electron donor, furnished 2-phenylethylamine (**3b**) in 70% yield (not optimized) (Scheme 4). We did not tried to detect the presence of 3-methoxy-3-methyl-1-butene (**6**), produced during the fragmentation, because of its low boiling point (80 °C).[13]

In order to simplify the process and to improve the overall yield, zinc was directly added to the reaction mixture containing the 2-iodo-3-methoxy-3-methylbutyl carbamate **5** and the excess of iodine. This addition was accompanied

Table 1. Synthesis of Preoc-N-protected amines using *N*-prenyloxycarbonylimidazole or prenyl *p*-nitrophenyl carbonate (**2**) as reagents

Entry	Substrate	Method[a]	Product	Time (h)	Yield (%)
1	 **3a**	A	 **4a**	4	88
2		B		1.5	98
3	 **3b**	A	 **4b**	5	85
4		B		3	97
5	 **3c**	A	 **4c**	48	51
6		B		2	94
7	 **3d**	A	 **4d**	4	97
8		B		3	93
9	 **3e**	A	 **4e**	4	93
10		B		1.5	95
11	 **3f**	A[b]	 **4f**	4	68
12		B[b]		1	91
13	 **3g**	A	 **4g**	120	52
14		B		3	90
15	 **3h**	A	 **4h**	120	33
16		B		9	91
17	 **3i**	A	 **4i**	120	201
18		B		24	85
19	 **3j**	A	 **4j**	24	51
20		B		1.5	81
21	 **3k**	A	 **4k**	48	0
22		B		120	39
23	 **3l**		 **4l**	3	80
24				2	97

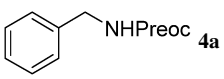
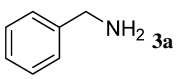
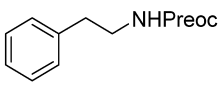
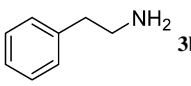
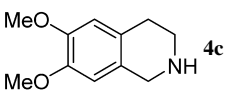
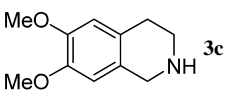
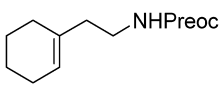
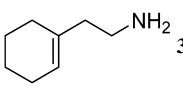
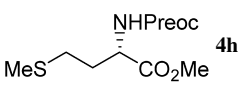
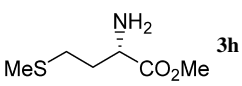
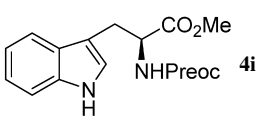
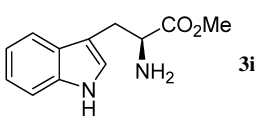
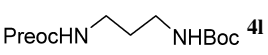
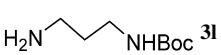
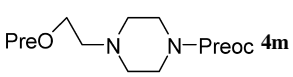
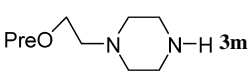
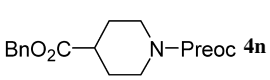
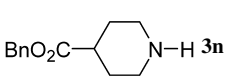
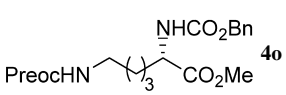
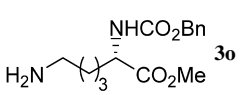
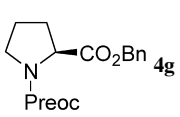
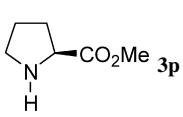
[a] Method A: $(CH_3)_2C{=}CHCH_2OCOlm$, DMF, room temperature. Method B: $(CH_3)_2C{=}CHCH_2OCO_2C_6H_4p\text{-}NO_2$ DMAP cat., CH_2Cl_2, room temperature.
[b] In the case of this amino acid, a 2:1 mixture of dioxane and water was used as solvents.



Scheme 4.

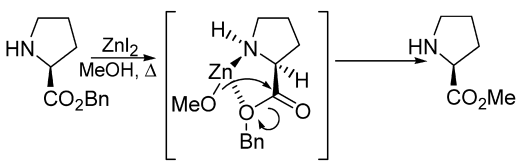
by the discoloration of the solution (ZnI_2 formation), concomitant effervescence as CO_2 liberated and heat formation. 2-Phenylethylamine (**3b**) was obtained in 85% yield which is superior to the 53% yield obtained via the two-step sequence. The reasons for the acceleration of the release of amine **3b** when zinc was added to the reaction mixture are uncertain. Iodine in excess may transform zinc into an active species, as it does with magnesium (Gilman catalyst),[14] achieving its fast oxidative insertion to the C–I bond.[15] An other explanation of the acceleration rate of the deprotection of the carbamate **4b**, under the conditions above, is that zinc iodide, obtained by reaction of zinc with iodine in excess, initiates the formation of the organozinc intermediate as do magnesium halides for Grignard reagents.[16]

Table 2. One-step deprotection of prenyl carbamates with I_2 in MeOH followed by Zn[a]

Entry	Substrate	Product	Yield (%)
1	 **4a**	 **3a**	83
2	 **4b**	 **3b**	85
3	 **4c**	 **3c**	78
4	 **4d**	 **3d**	88
5	 **4h**	 **3h**	83
6	 **4i**	 **3i**	53
7	 **4l**	 **3l**	82
8	 **4m**	 **3m**	63
9	 **4n**	 **3n**	75
10	 **4o**	 **3o**	85
11	 **4g**	 **3p**	70

[a] Reaction conditions: I_2 (2 equiv.), 7 h, room temperature then Zn (4 equiv.), 30 min; entries 4 and 8: I_2 (4 equiv.), Zn (8 equiv.); entry 6: I_2 (2 equiv.), 24 h, room temperature (without Zn).

The applicability of the method for the deprotection of prenyl carbamates was tested on diversely functionalized substrates and the results of this study are presented in Table 2. As depicted in the table, amines **3a**–**p** were obtained in acceptable to excellent yields (53–88%). Commonly used amino protecting groups such as Boc and Cbz groups were found stable under our conditions of Preoc deprotection (entries 7 and 10). In the presence of a double bond, the *N*-Preoc group has been deprotected in an excellent yield (88%) using 4 equiv. of iodine and 8 equiv. of zinc (entry 4). Interestingly, the prenyl carbamate of compound **3m** has been cleaved chemoselectively in the presence of a prenyl ether in an acceptable yield (63%, entry 8). The release of the tetrahydroisoquinoline alkaloid **3c** occurred in good yield (78%) without affecting the two methoxy groups (entry 3). Surprisingly, in the presence of methanol, the liberation of the amine of *N*-Preoc-L-tryptophan methyl ester **4i** happened without the need of adding zinc (entry 6). In the case of this substrate, the 2-iodo-3-methoxy-3-methylbutyl carbamate intermediate was not observed by TLC. We have no rationale to explain this result. Removal of the carbamate of *N*-Preoc proline benzyl ester **4g** occurred with complete transesterification by methanol (entry 11). As no transesterification of the benzyl ester of isonipecotic derivative **3n** was observed, under the same reaction conditions, we assume that the formation of the methyl ester **3p** is very likely the result of an intramolecular delivery of the methoxide anion to the carbonyl site of the ester by zinc, coordinated to the nitrogen of the pyrrolidine ring of the proline derivative (Scheme 5).



Scheme 5.

In order to test this hypothesis, L-proline benzyl ester (**3g**) was treated with 2 equiv. of zinc iodide in refluxing methanol for 30 min (Scheme 5). After a basic workup to extract zinc salts from the organic phase and purification of the residue on silica gel, L-proline methyl ester was obtained in 75% yield, thus confirming our assumption on the mechanism of the transesterification. Unfortunately, *N*-Preoc derivative of 1,3,4,6-tetra-*O*-acetyl-D-glucosamine, compound **4k**, under the conditions of *N*-Preoc deprotection, gave an untractable mixture of compounds.

3. Conclusion

In summary, we have introduced *N*-prenyloxycarbonylimidazole and prenyl *p*-nitrophenyl carbonate as two reagents for a facile installation of the prenyloxycarbonyl group. Both reagents are easily prepared in good yields from commercially available products, much safer and easier to handle than phosgene. If the applicability of the imidazolide is restricted to the protection of reactive primary and secondary amines, that of the mixed carbonate is more general and included amino acids. Another advantage of the carbonate is its high crystallinity which allows its purification by simple crystallization and therefore its preparation on a large scale. Having on hands a variety of prenyl carbamates diversely functionalized, we developed a simple one-pot two-step procedure for the chemoselective unmasking of amino groups. Furthermore, iodine and zinc, involved in this amino deprotection reaction, are cheap and non-toxic reagents. Because of its chemoselectivity and efficiency, this method of cleavage of *N*-prenyloxycarbonyl group should extent the use of prenyl carbamates for the protection of amine compounds.

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded in $CDCl_3$ (δ_H=7.25) at ambient probe temperature on a Bruker AC 200 (200 MHz) spectrometer. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS}=0), multiplicity (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperature on a Bruker AC 200 (50.3 MHz) in $CDCl_3$ used as reference (δC=77.0). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at the sodium D line (598 nm). Melting points were determined on a Büchi 530 apparatus and are uncorrected. Combustion analyses were performed by 'Service de Microanalyse', CNRS, Solaize. Reagents and solvents were purified by standard means. Ether and dioxane were distilled from sodium wire/benzophenone and stored under a nitrogen atmosphere. Acetonitrile, dichloromethane, dimethylformamide, pyridine and triethylamine were distilled from calcium hydride. Methanol was distilled from magnesium metal. Zinc dust $<10\mu$m (Aldrich) was used for reductive elimination reactions. All other chemicals were used as received.

4.1.1. (3-Methyl-2-butenyl)oxycarbonylimidazole (1). To a suspension of carbonyldiimidazole (3 g, 18.5 mmol) in CH_2Cl_2 (20 mL), cooled to 0 °C, was added dropwise a solution of 3-methyl-2-buten-1-ol (1.85 mL, 1 equiv.) in CH_2Cl_2 (20 mL). The mixture was allowed to warm up to room temperature and stirred for 4 h. After evaporation of the solution to dryness, the residue was purified by chromatography on silica gel (ether–petroleum ether, 1.5:1) to give the imidazolide **1** as an oil (2.51 g, 75%). IR (film): 1760 cm^{-1}.^{1}H NMR: 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 4.88 (d, 2H, J=7.43 Hz, CH_2–CH=CMe_2), 5.44 (brt, 1H, J=7.42 Hz, CH=CMe_2), 7.05 (s, 1H), 7.41 (s, 1H), 8.12 (s, 1H). ^{13}C NMR: 18.0, 25.7, 64.8, 117.0, 117.1, 130.4, 137.0, 141.6, 148.7. Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99, H, 6.71, N, 15.55, O, 17.76. Found: C, 59.80, H, 6.88, N, 15.37, O, 17.95.

4.1.2. (3-Methyl-2-butenyl) 4-nitrophenyl carbonate (2). To a solution of 4-nitrophenyl chloroformate (3.9 g, 19 mmol) in CH_2Cl_2 (28 mL), cooled to 0 °C, was added dropwise a mixture of 3-methyl-2-buten-1-ol (1.93 mL, 1 equiv.) and pyridine (1.63 mL, 1.05 equiv.) in 12 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 16 h, diluted with ether, washed once with Na_2CO_3 saturated solution, twice with water. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized in heptane to afford the carbonate **2** as a crystalline solid (3.75 g, 77%). Mp 72–74 °C. IR (KBr): 1760, 1680 cm^{-1}. ^{1}H NMR: 1.78 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 4.78 (d, 2H, J=7.42 Hz, CH_2–CH=CMe_2), 5.44 (brt, 1H, J=7.43 Hz, CH=CMe_2), 7.38 (d, 2H, J=9.2 Hz, Ar), 8.27 (d, 2H, J=9.2 Hz, Ar). ^{13}C NMR: 18.2, 25.9, 66.1, 117.1, 121.8 (2C), 125.3 (2C), 141.7, 145.3, 152.6, 155.7. Anal. calcd for $C_{12}H_{13}NO_5$: C, 57.37, H, 5.22, N, 5.58, O, 31.84. Found: C, 57.55, H, 5.29, N, 5.35, O, 31.80.

4.2. General procedures for the preparation of prenyl carbamates

Method A. Using N-prenyloxycarbonylimidazole (**1**) *as reagent*. To 1 mmol of the amine dissolved in DMF (2 mL) was added at room temperature the imidazolide **1** (0.2 g, 1.1 equiv.) in DMF (2 mL). Reaction progress was monitored by TLC (ether–petroleum ether, 2:1). After disappearance of the imidazolide, the mixture was diluted with ether, washed twice with water. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography on silica gel. When the hydrochloride salt was used as a starting material, one or two (for the lysine derivative) equivalents of Et_3N were added, prior to the addition of the imidazolide, and the mixture was stirred for 15 min.

Method B. Using prenyl p-nitrophenyl carbonate (**2**) *as a reagent*. To a stirred solution of 1 mmol of the amine dissolved in CH_2Cl_2 (3 mL) were successively added the carbonate **2** (0.276 g, 1.1 equiv.) and DMAP (12 mg, 0.1 equiv.). The solution became quickly yellow due to the formation of *p*-nitrophenol. The reaction mixture was stirred at room temperature until the blue spot of the carbonate observed on TLC (ether–petroleum ether, 1:1, R_f=0.7) became very weak. The reaction mixture was

diluted with ether, washed once with Na_2CO_3 saturated solution, twice with water. The aqueous layer was back extracted once with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography on silica gel. All compounds prepared by this method have spectroscopic and physical data identical with those a sample synthesized by Method A.

4.2.1. *N*-(3-Methyl-2-butenyl)oxycarbonylbenzylamine (4a). *Method A*. Ether–petroleum ether (1:2), 88% yield, oil. IR (film): 1695, 1530 cm^{-1}. ^1H NMR: 1.72 (s, 3H, Me), 1.77 (s, 3H, Me), 4.36 (d, 2H, J=5.93 Hz, CH_2Ph), 4.60 (d, 2H, J=7.15 Hz, CH_2–CH=CMe$_2$), 5.13 (brs, 2H, NH), 5.36 (brt, 1H, J=7.17 Hz, CH=CMe$_2$), 7.31 (brs, 5H, Ph). ^{13}C NMR: 18.0, 25.8, 45.1, 61.9, 119.2, 127.4, 127.5 (2C), 128.7 (2C), 138.7 (2C), 156.8. Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21, H, 7.81, N, 6.39, O, 14.49. Found: C, 70.84, H, 7.95, N, 6.41, O, 14.79.

Method B. 98% yield.

4.2.2. *N*-(3-Methyl-2-butenyl)oxycarbonyl-2-phenylethylamine (4b). *Method A*. Ether–petroleum ether (1:1), 85% yield, oil. IR (film): 1690, 1530 cm^{-1}. ^1H NMR: 1.72 (s, 3H, Me), 1.77 (s, 3H, Me), 2.82 (t, 2H, J=7 Hz, CH_2Ph), 3.45 (q, 2H, J=6.8 Hz, CH_2CH$_2$Ph), 4.56 (d, 2H, J=7.17 Hz, CH_2–CH=CMe$_2$), 4.74 (s, 1H, NH), 5.34 (brt, 1H, J=7.16 Hz, CH=CMe$_2$), 7.18–7.36 (m, 5H, Ph). ^{13}C NMR: 18.0, 25.8, 36.2, 42.2, 61.7, 119.3, 126.5, 128.6 (2C), 128.8 (2C), 138.7, 138.8, 156.7. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07, H, 8.21, N, 6.0, O, 13.72. Found: C, 72.05, H, 8.37, N, 6.07, O, 13.65.

Method B. 97%.

4.2.3. [*N*-(3-Methyl-2-butenyl)oxycarbonyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4c). *Method A*. Ether–petroleum ether (3:2), 51% yield, solid, mp 74–75 °C (petroleum ether). IR (KBr): 1700, 1610, 1520 cm^{-1}. ^1H NMR: 1.72 (s, 3H, Me), 1.76 (s, 3H, Me), 2.76 (t, 2H, J=5.71 Hz, ArCH_2CH$_2$), 3.70 (brt, 2H, J=5.5 Hz, ArCH$_2$CH_2), 3.84 (s, 3H, Me), 3.85 (s, 3H, Me), 4.54 (s, 2H, ArCH_2N), 4.62 (d, 2H, J=7.07 Hz, CH_2–CH=CMe$_2$), 5.37 (brt, 1H, J=7.07 Hz, CH=CMe$_2$), 6.59 (s, 1H, Ar), 6.61 (s, 1H, Ar). ^{13}C NMR: 18.1, 25.8, 28.4, 41.5, 45.4, 56.0 (2C), 62.4, 109.2, 111.6, 119.6, 125.1, 126.4, 138.2, 147.7 (2C), 155.9. Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86, H, 7.59, N, 4.59, O, 20.96. Found: C, 66.68, H, 7.75, N, 4.62, O, 20.93.

Method B. 94% yield.

4.2.4. *N*-(3-Methyl-2-butenyl)oxycarbonyl-2-(1-cyclohexenyl)ethylamine (4d). *Method A*. Ether–petroleum ether (1:2), 97% yield, oil. IR (film): 1705, 1525 cm^{-1}. ^1H NMR: 1.50–1.69 (m, 4H), 1.72 (s, 3H, Me), 1.76 (s, 3H, Me), 1.83–2.07 (m, 4H), 2.12 (t, 2H, J=6.8 Hz, CH_2CH$_2$N), 3.25 (q, 2H, J=6.5 Hz, CH_2N), 4.46 (d, 2H, J=7.2 Hz, CH_2–CH=CMe$_2$), 4.64 (brs, 1H, NH), 5.35 (brt, 1H, J=7.78 Hz, CH=CMe$_2$), 5.46 (brs, 1H, CH=C). ^{13}C NMR: 18.0, 22.4, 22.8, 25.2, 25.8, 27.9, 38.1, 38.7, 61.6, 119.3, 123.6, 134.4, 138.6, 156.6. Anal. calcd for $C_{14}H_{23}NO_2$: C, 70.75, H, 9.77, N, 5.90, O, 13.48. Found: C, 70.45, H, 9.89, N, 5.97, O, 13.76.

Method B. 93% yield.

4.2.5. 4-(3-Methyl-2-butenyl)oxycarbonyl-1-(2-hydroxyethyl)piperazine (4e). *Method A*. Ether–MeOH (9:1), 93% yield, oil. IR (film): 3440, 1700 cm^{-1}. ^1H NMR: 1.72 (s, 3H, Me), 1.77 (s, 3H, Me), 2.49 (t, 4H, J=4.9 Hz, 2CH_2N), 2.57 (t, 2H, J=5.34 Hz, CH_2CH$_2$OH), 3.51 (t, 4H, J=4.94 Hz, CH_2N), 3.67 (t, 2H, J=5.44 Hz, CH_2OH), 4.50 (d, 2H, J=7.07 Hz, CH_2CH=CMe$_2$), 5.36 (brt, 1H, J=7.1 Hz, CH=CMe$_2$),. ^{13}C NMR: 18.0, 25.7, 43.7, 52.7 (3C), 58.0, 59.7, 62.3, 119.3, 138.1, 155.5. Its spectroscopic data were in perfect agreement with those described in the literature.[5c]

Method B. 95% yield.

4.2.6. *N*-(3-Methyl-2-butenyl)oxycarbonyl isonipecotic acid (4f). *Method A*. In the case of this substrate, the reaction was effected in a mixture dioxane–water (2:1) in the presence of 1 equiv. of triethylamine. After stirring for 4 h at room temperature, the reaction mixture was acidified with 1N HCl solution, extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel, eluent: ether–petroleum ether (2:1) then CH_2Cl_2–MeOH (9:1) to give **4f** (68% yield) as a crystalline solid, mp 80 °C (isopropyl ether). IR (KBr): 3180, 1730, 1670 cm^{-1}. ^1H NMR: 1.61 (qd, 2H, J=2.5, 13 Hz, H-3a and H-5a), 1 67 (s, 3H, Me), 1.72 (s, 3H, Me), 1.90 (brd, 2H, J=13.3 Hz, H-3e and H-5e), 2.47 (m, 1H, CHCO$_2$H), 2.89 (td, 2H, J=2.7, 12.5 Hz, H-2a and H-6a), 4.03 (brd, 2H, J=13.2 Hz, H-2e and H-6e), 4.55 (d, 2H, J=7.07 Hz, CH_2-CH=CMe$_2$), 5.31 (brt, 1H, J=7.1 Hz, CH=CMe$_2$), 11.0 (brs, CO$_2$$H$). ^{13}C NMR: 18.0, 25.8, 27.7, 30.3, 40.7, 43.1 (2C), 62.5, 119.3, 138.3, 155.7, 179.7. Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73, H, 7.94, N, 5.81, O, 26.52. Found: C, 59.72, H, 8.10, N, 5.76, O, 26.41.

Method B. 91% yield.

4.2.7. *N*-(3-Methyl-2-butenyl)oxycarbonyl-L-proline benzyl ester (4g). *Method A*. AcOEt–petroleum ether (1:3), 52% yield, oil, $[\alpha]_D^{20}=-53.3$ (c 0.5, CHCl$_3$). IR (film): 1475, 1705 cm^{-1}. ^1H NMR (2 rotamers): 1.66 (s, 3H, Me), 1.70 (s, 6H, 2Me), 1.75 (s, 3H, Me), 1.91 (m, 6H), 2.22 (m, 2H), 3.58 (m, 4H, 2CH_2N), 4.34 (dd, 1H, J=3.8, 8.5 Hz, CHCO$_2$Bn), 4.42 (dd, 1H, J=3.7, 8.4 Hz, CHCO$_2$Bn), 4.6 (m, 4H, 2 CH_2-CH=CMe$_2$), 5.16 (m, 5H, 2CH_2Ph, CH=CMe$_2$), 5.36 (brt, 1H, J=7 Hz, CH=CMe$_2$), 7.34 (brs, 10H, Ph). ^{13}C NMR (2 rotamers): 18.1 (2C), 23.6, 24.4, 25.75, 26.0, 29.9, 30.9, 46.4, 46.8, 59.0, 59.3, 62.2, 62.3, 66.6, 66.7, 119.4, 119.5, 128.0 (4C), 128.2, 128.3, 128.6 (4C), 135.8 (2C), 137.97, 138.07, 154.7, 155.3, 172.6, 172.8. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12, H, 7.30, N, 4.41, O, 20.16. Found: C, 67.91, H, 7.44, N, 4.48, O, 20.15.

Method B. 90% yield.

4.2.8. *N*-(3-Methyl-2-butenyl)oxycarbonyl-L-methionine methyl ester (4h). *Method A*. Ether–petroleum ether (1:1), 33% yield, crystalline solid, mp 34–35 °C, $[\alpha]_D^{20}=+23.15$ (c 1.7, CHCl$_3$). IR (film): 3340, 1740, 1700, 1530 cm^{-1}. ^1H

NMR: 1.68 (s, 3H, Me), 1.73 (s, 3H, Me), 1.95 (m, 1H, C*H*CH_2S), 2.06 (s, 3H, Me), 2.11 (m, 1H, C*H*CH_2S), 2.51(t, 2H, *J*=7.5 Hz, CH_2S), 3.73 (s, 3H, Me), 4.45 (q, 1H, *J*=7.6, 13 Hz, C*H*CO_2Me), 4.55 (d, 2H, *J*=7.18 Hz, CH_2-CH=CMe_2), 5.31 (brt, 1H, *J*=7.15 Hz, C*H*=CMe_2), 5.40 (brs, 1H, NH). ^{13}C NMR: 15.4, 18.0, 25.7, 29.9, 32.1, 52.5, 53.1, 62.1, 118.9, 138.9, 156.1, 172.6. Anal. calcd for $C_{12}H_{21}NO_4S$: C, 52.34, H, 7.69, N, 5.09, O, 23.24, S, 11.64. Found: C, 52.28, H, 7.80, N, 5.09, O, 23.16, S, 11.67.

Method B. 91% yield.

4.2.9. *N*-(3-Methyl-2-butenyl)oxycarbonyl-L-tryptophan methyl ester (4i). *Method A*. Ether–petroleum ether (2:1), 20% yield, crystalline solid, mp 102–104 °C, $[\alpha]_D^{20}$=+51.2 (*c* 0.5, $CHCl_3$). IR (KBr) 3370, 3340, 1735, 1700, 1620, 1540 cm^{-1}. ^{1}H NMR: 1.71 (s, 3H, Me), 1.76 (s, 3H, Me), 3.31 (d, 2H, *J*=5.2 Hz, CH_2-CHCO_2Me), 3.68 (s, 3H, Me), 4.57 (d, 2H, *J*=7.04 Hz, CH_2–CH=CMe_2), 4.72 (q, 1H, *J*=5.5, 13.4 Hz, C*H*CO_2Me), 5.3 (m, 2H, NH and C*H*=CMe_2), 7.0 (d, 1H, *J*=2 Hz, NC*H*=), 7.12 (t, 1H, *J*=6.9 Hz, Ar), 7.21(t, 1H, *J*=6.7 Hz, Ar), 7.34 (d, 1H, *J*=7.5 Hz, Ar), (7.56 (d, 1H, *J*=7.4 Hz, Ar), 8.4 (brs, 1H, NH). ^{13}C NMR: 18.1, 25.8, 28.0, 52.4, 54.6, 62.2, 109.8, 111.4, 118.6, 118.9, 119.6, 122.2, 123.0, 127.6, 136.3, 138.9, 156.2, 172.7. Anal. calcd for $C_{18}H_{22}N_2O_4$: C, 65.44, H, 6.71, N, 8.48, O, 19.37. Found: C, 65.23, H, 6.92, N, 8.44, O, 19.47.

Method B. 85% yield.

4.2.10. N^{ε}-(3-Methyl-2-butenyl)oxycarbonyl-L-lysine methyl ester (4j). *Method A*. In the case of this substrate, 1 mmol of lysine methyl ester·2HCl was dissolved in dioxane–H_2O (1:1). The reaction mixture was diluted with water and extracted three times with CH_2Cl_2. Chromatography on silica gel of the residue (CH_2Cl_2–MeOH, 92:8) gave the N-monoprotected lysine derivative **4j**, obtained as an oil (51% yield). ^{1}H NMR: 1.40 (m, 6H, 3CH_2), 1.51 (brs, 2H, NH_2), 3.1 (dd, 2H, *J*=6.3, 12.6 Hz, CH_2N), 3.36 (t, 1H, *J*=7.1 Hz, C*H*CO_2Me), 3.64 (s, 3H, Me), 4.46 (d, 2H, *J*=7.12 Hz, CH_2-CH=CMe_2), 4.96 (brs, 1H, NH), 5.24 (brs, 1H, *J*=7.1 Hz, C*H*=CMe_2). Compound **4j** was characterized as its hydrochloride salt. To 1 mmol of **4j** dissolved in 5 mL of dry ether, cooled to 0 °C, was added 4 N HCl in dioxane (0.35 mL, 1.5 equiv.). After stirring the reaction mixture for 30 min, the precipitate was filtered and washed with dry ether to give the hydrochloride salt (0.363 g, 90% yield). Mp 98–99 °C, $[\alpha]_D^{20}$=+14.6 (*c* 1.2, H_2O). IR (KBr): 3360, 1745, 1690, 1600, 1525 cm^{-1}. ^{1}H NMR (D_2O):1.53 (m, 4H), 1.74 (s, 3H, Me), 1.79 (s, 3H, Me), 2.0 (m, 2H), 3.15 (t, 2H, *J*=6.3 Hz, CH_2N), 3.88 (s, 3H, Me), 4.19 (t, 1H, *J*=7.1 Hz, C*H*–CO_2Me), 4.57 (d, 2H, *J*=7.02 Hz, CH_2–CH=CMe_2), 5.38 (brt, 1H, *J*=7.05 Hz, C*H*=CMe_2). ^{13}C NMR: 19.9, 24.0, 27.6, 31.0, 32.0, 42.5, 55.4, 56.1, 64.8, 120.7, 143.5, 151.2, 173.3. Anal. calcd for $C_{13}H_{25}ClN_2O_4$: C, 50.56, H, 8.16, Cl, 11.48, N, 9.07. Found: C, 50.87, H, 8.38, Cl, 11.50, N, 9.02.

Method B. 81% yield.

4.2.11. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(3-methyl-2-butenyl)oxycarbonylamino-β-D-glucopyranose (4k). *Method A*. 0% yield; several products were observed by TLC (ether).

Method B. The reaction was effected in DMF. After a usual workup, the solid residue was purified by flash chromatography on silica gel (ether–petroleum ether, 4:1) to give the N-protected sugar **4k** in 39% yield obtained as a white crystalline solid, mp 121–124 °C, $[\alpha]_D^{20}$=+17.7 (*c* 1.2, $CHCl_3$). IR (KBr): 3350, 1745, 1705, 1530 cm^{-1}. ^{1}H NMR: 1.66 (s, 3H, Me), 1.70 (s, 3H, Me), 2.0 (s, 6H, 2OAc), 2.04 (s, 3H, OAc), 2.07 (s, 3H, OAc), 3.80 (m, 1H, H-5), 3.93 (m, 1H, H-2), 4.08 (brd, 1H, *J*=12.4 Hz, H-6), 4.27 (dd, 1H, *J*=4.3, 12.4 Hz, H-6), 4.51 (d, 1H, *J*=6.7 Hz, C*H*–CH=CMe_2), 5.05 (t, 1H, *J*=9.5 Hz, H-3 or H-4), 5.12–5.4 (m, 3H, H-3 or H-4, N*H*, C*H*=CMe_2), 5.65 (d, 1H, *J*=8.5 Hz, H-1). ^{13}C NMR: 18.0, 20.6 (2C), 20.7, 20.8, 25.7, 54.8, 61.8, 62.2, 68.2, 72.5, 72.7, 92.6, 118.9, 138.8, 156.2, 169.5(2C), 170.7, 170.8. Anal. calcd for $C_{20}H_{29}NO_{11}$: C, 52.28, H, 6.36, N, 3.05, O, 38.31. Found: C, 52.54, H, 6.60, N, 3.01, O, 37.84.

4.2.12. 1-*N*-tert-Butoxycarbonyl-3-*N*-(methyl-2-butenyl)oxycarbonyl-1,3-diaminopropane (4l). *Method A*. Ether–petroleum ether (1.5:1), 80% yield, crystalline solid, mp 47–48 °C. ^{1}H NMR: 1.42 (s, 9H, C$(CH_3)_3$), 1.61 (q, 2H, *J*=6.3 Hz, CH_2), 1.70 (s, 3H, Me), 1.74 (s, 3H, Me), 3.18 (m, 4H, 2 CH_2N), 4.54 (d, 2H, *J*=7.12 Hz, CH_2–CH=CMe_2), 4.90 (brs, 1H, NH), 5.18 (brs, 1H, NH), 5.32 (brt, 1H, *J*=7.11 Hz, C*H*=CMe_2). ^{13}C NMR: 18.0, 25.8, 28.4 (3C), 30.6, 37.2, 37.7, 61.7, 79.3, 119.3, 138.5, 156.4, 157.1. Anal. calcd for $C_{14}H_{26}N_2O_4$: C, 58.72, H, 9.15, N, 9.78, O, 22.35. Found: C, 58.50, H, 9.38, N, 9.67, O, 22.37.

Method B. 97% yield.

4.2.13. 1-[2-(3-Methyl-2-butenyl)oxyethyl]-4-(3-methyl-2-butenyl)oxycarbonylpiperazine (4m). To a solution of the alcohol **4e** (0.52 g, 2.1 mmol) in DMF (5 mL), cooled to −50 °C, were successively added NaH (60% dispersion in mineral oil, 0.104 g, 1.2 equiv) and prenyl bromide (0.29 mL, 1.5 equiv.). The reaction mixture was allowed to warm up to 0 °C (90 min), diluted with ether, washed with water. The aqueous phase was extracted once with ether. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (ether) to give **4m** (0.492 g, 74% yield) obtained as a yellow oil. IR (film): 1700 cm^{-1}.^{1}H NMR: 1.67 (s, 3H, Me), 1.71 (s, 3H, Me), 1.75 (s, 6H, 2Me), 2.45 (t, 4H, *J*=5.1 Hz, 2 CH_2N), 2.59 (t, 2H, *J*=5.8 Hz, CH_2–CH_2OPre), 3.49 (t, 4H, *J*=5.2 Hz, 2CH_2N), 3.54 (t, 2H, *J*=5.8 Hz, CH_2OPre), 3.97 (d, 2H, *J*=6.91 Hz, OCH_2–CH=CMe_2), 4.57 (d, 2H, *J*=7.05 Hz, NCO_2CH_2-CH=CMe_2), 5.34 (m, 2H, 2C*H*=CMe_2). ^{13}C NMR: 18.0 (2C), 25.7, 25.8, 43.6, 53.3 (3C), 58.0, 62.3, 67.3, 67.5, 119.5, 121.1, 136.9, 138.0, 155.6. Anal. calcd for $C_{17}H_{30}N_2O_3$: C, 65.77, H, 9.74, N, 9.02, O, 15.46. Found: C, 65.77, H, 9.90, N, 8.76, O, 15.50.

4.2.14. 1-(3-Methyl-2-butenyl)-4-(benzyloxycarbonyl)-piperidine (4n). To a solution of the acid **4f** (0.3 g, 1.2 mmol) in acetonitrile (3 mL), cooled to 0 °C, was added DBU (0.21 mL, 1.16 equiv.). After stirring for 15 min at

0 °C, benzyl bromide (0.18 mL, 1.25 equiv.) was added. The reaction mixture was stirred for 2 h at room temperature, diluted with ether, washed once with water. The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by chromatography on silica gel (ether–petroleum ether, 1:2) to afford the benzyl ester **4n** as an oil (0.367 g, 89% yield). IR (film): 1730, 1695 cm^{-1}.^{1}H NMR: 1.64 (m, 2H, H-3a and H-5a), 1.71 (s, 3H, Me), 1.76 (s, 3H, Me), 1.93 (brd, 2H, J=13.1 Hz, H-3e and H-5e), 2.52 (m, 1H, C*H*–CO_2H), 2.89 (td, 2H, J=2.3, 12.3 Hz, H-2a and H-6a), 4.07 (brd, 2H, J=12.4 Hz, H-2e and H-6e), 4.58 (d, 2H, J=6.8 Hz, CH_2-CH=CMe_2), 5.13 (s, 2H, CH_2Ph), 5.35 (brt, 1H, J=7.20 Hz, C*H*=CMe_2), 7.35 (s, 5H, Ar). ^{13}C NMR: 18.1, 25.8, 27.9 (2C), 41.1, 43.2 (2C), 62.3; 66.3, 119.5, 128.1 (2C), 128.3, 128.6 (2C), 136.0, 138.1, 155.5, 174.2. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86, H, 7.60, N, 4.23, O, 19.31. Found: C, 68.81, H, 7.88, N, 4.21, O, 19.57.

4.2.15. N^{α}-Benzyloxycarbonyl-N^{ε}-(3-methyl-2-butenyl)oxycarbonyl-L- lysine methyl ester (4o). To a solution of the N^{ε}-protected lysine derivative **4j** (0.5 g, 1.8 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C, were successively added triethylamine (0.4 mL, 1.5 equiv.) and benzyl chloroformate (0.38 mL, 1.5 equiv.). The reaction mixture was stirred for 2 h at room temperature, diluted with ether, washed twice with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (ether–petroleum ether, 2:1) to furnish the di-N protected lysine **4o** (0.51 g, 69% yield) as a colorless oil. IR (film): 3330, 1740, 1700, 1530 cm^{-1}.^{1}H NMR: 1.38 (m, 4H), 1.64 (s, 3H, Me), 1.69 (s, 3H, Me), 3.09 (dd, 2H, J=6.5, 12 Hz, CH_2N), 3.67 (s, 3H, OMe), 4.3 (dd, 1H, J=5.7, 12 Hz, C*H*CO_2Me), 4.49 (d, 2H, J=6.92 Hz, CH_2–CH=CMe_2), 5.01 (brs, 1H, N*H*), 5.05 (s, 2H, CH_2Ph), 5.27 (brt, 1H, J=7.20 Hz, C*H*=CMe_2), 5.68 (d, 1H, J=7.9 Hz, N*H*), 7.28 (brs, 5H, Ph). ^{13}C NMR: 18.0, 22.4, 25.7, 29.4, 32.0, 40.4, 52.3, 53.8, 61.6, 66.9, 119.3, 128.0 (2C), 128.1, 128.5 (2C), 136.3, 138.3, 156.1, 156.9, 173.0. Anal. calcd for $C_{21}H_{30}N_2O_6$: C, 62.05, H, 7.44, N, 6.89, O, 23.62. Found: C, 61.87, H, 7.57, N, 6.98, O, 24.07.

4.3. General procedure for the deprotection of prenyl carbamates

To a well-stirred solution of 1 mmol of the prenyl carbamate in methanol (6 mL) was added, at room temperature, iodine (0.508 g, 2 equiv.). The reaction progress was monitored by TLC. In most cases, the spot of the 2-iodo-3-methoxy-3-methylbutyl carbamate was slightly more polar than that of the starting material and was well UV-absorbing (254 nm). After disappearance of the starting material, zinc (0.26 g, 4 equiv.) was added and the stirring was continued for 30 min. After concentration, CH_2Cl_2 and saturated Na_2CO_3 solution were added and the formed precipitate and zinc in excess were filtered on a funnel. The aqueous layer was extracted once with CH_2Cl_2. The combined organic phases were washed once with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel. Most amines were characterized as their hydrochloride salts, prepared by dissolving 0.5 mmol of the amine in dry ether (4 mL), cooling the solution to 0 °C, and adding 4 N HCl solution in dioxane (0.25 mL, 2 equiv.). The precipitate was filtered and washed with dry ether, dried.

4.3.1. Benzylamine (3a). Reaction time: 5 h; CH_2Cl_2–MeOH–Et_3N (85:10:5), 83% yield, liquid. ^{1}H NMR: 1.82 (brs, 2H, NH_2), 3.83 (s, 2H, PhCH_2), 7.30 (m, 5H, Ar). ^{13}C NMR: 46.4, 126.9, 127.2 (2C), 128.6 (2C), 143.1. Its spectroscopic data are in agreement with those of an authentic sample.

4.3.2. 2-Phenylethylamine (3b). Reaction time: 5 h; CH_2Cl_2–MeOH–Et_3N (85:10:5), 85% yield, liquid. ^{1}H NMR: 1.27 (s, 2H, NH_2), 2.75 (t, 2H, J=6.6 Hz, PhCH_2), 2.97 (t, 2H, J=6.7 Hz, C$H_2$$NH_2$), 7.18–7.34 (m, 5H, Ph). ^{13}C NMR: 40.2, 43.6, 126.2, 128.5 (2C), 128.9 (2C), 139.9. Its spectroscopic data were in accordance with those of an authentic sample.

4.3.3. 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (3c). Reaction time: 6 h, CH_2Cl_2–MeOH–Et_3N (86:10:4), 78% yield. It was characterized as its hydrochloride salt: mp 258–260 °C. ^{1}H NMR (D_2O): 3.04 (t, 2H, J=6.2 Hz, ArC$H_2$$CH_2$$NH_2^+$), 3.49 (t, 2H, J=6.3 Hz, ArCH_2C$H_2$$NH_2^+$), 3.81 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.28 (s, 2H, ArC$H_2$$NH_2^+$), 6.81 (s, 1H, Ar), 6.87 (s, 1H, Ar).^{13}C NMR (D_2O): 24.5, 42.1, 44.5, 55.9, 56.0, 109.7, 111.9, 120.0, 124.2, 147.4, 148.1. Its spectroscopic data were agreement with those of a commercial sample.

4.3.4. 2-(1-Cyclohexenyl)ethylamine (3d). Reaction time: 7 h, CH_2Cl_2–MeOH–Et_3N (85:10:5), 88% yield, liquid. ^{1}H NMR: 1.49–1.66 (m, 4H, 2CH_2), 1.85–2.0 (m, 4H, 2CH_2), 2.06 (t, 2H, J=6.8 Hz, C$H_2$$CH_2$N), 2.09 (s, 2H, N$H_2$), 2.74 (t, 2H, J=6.7 Hz, C$H_2$$NH_2$), 5.43 (brs, 1H, C*H*=C). ^{13}C NMR: 22.5, 22.9, 25.3, 28.1, 39.7, 41.7, 123.2, 134.9. Its spectroscopic data were in accordance with those of an authentic sample.

4.3.5. L-Methionine methyl ester (3h). Reaction time: 7 h, CH_2Cl_2–MeOH (95:5), oil, 83% yield. It was characterized as its hydrochloride salt: mp 145–149 °C, $[\alpha]_D^{20}$=+23.4 (*c* 1.2, H_2O) [Lit.[17] $[\alpha]_D^{20}$=+25.2 (*c* 5.1, H_2O), mp 147–150 °C]. ^{1}H NMR: 2.14 (s, 3H, Me), 2.29 (sextuplet, 2H, J=6.3, 7.2 Hz, SCH_2CH_2), 2.72 (t, 2H, J=7.2 Hz, SCH_2), 3.88 (s, 3H, OMe), 4.34 (t, 1H, J=6.3 Hz, C*H*CO_2Me). ^{13}C NMR: 14.4, 28.9, 29.2, 52.2, 54.1, 171.0. These NMR data were in agreement with those of a commercial sample.

4.3.6. L-Tryptophan methyl ester (3i). For this substrate, after stirring for 24 h, at room temperature, the prenyl carbamate of tryptophan methyl ester **4i** in methanol (6 mL), in the presence of two equivalents of iodine (0.508 g), the mixture was concentrated. The residue was diluted with CH_2Cl_2, washed with saturated sodium thiosulfate solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed once with brine, dried (Na_2SO_4), evaporated to dryness. The residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to give compound **3i** as a yellow oil (0.115 g, 53% yield). It was characterized as its hydrochloride salt: mp 215–216 °C, $[\alpha]_D^{20}$=+17.1 (*c* 0.5, MeOH) [Lit.[18] mp 213–214 °C, $[\alpha]_D$=+17 (*c* 2, MeOH)]. ^{1}H NMR: 3.36 (d, 2H, J=5.65 Hz, CH_2CHCO_2Me), 3.77 (s,

3H, OMe), 4.35 (t, 2H, J=6.1 Hz, C*H*CO_2Me), 7.21 (t, 1H, J=6.8 Hz, Ar), 7.24 (t, 1H, J=7 Hz, Ar), 7.25 (brs, 1H, NCH=), 7.50 (d, 1H, J=7.1 Hz, Ar), 7.55 (d, 1H, J=6.9 Hz, Ar). ^{13}C NMR: 26.1, 53.8, 54.1, 106.4, 112.6, 118.5, 120.1, 122.7, 125.9, 126.9, 136.8, 170.9. These spectroscopic data were in accordance with those of a commercial sample.

4.3.7. 1-*tert*-Butoxycarbonyl-1,3-diaminopropane (3l). Reaction time: 4 h, CH_2Cl_2–MeOH–Et_3N (85:10:5), oil, 82% yield.^{1}H NMR: 1.39 (s, 9H, C(CH_3)$_3$), 1.57 (quintuplet, 2H, J=6.7 Hz, $CH_2CH_2CH_2$), 2.74 (t, 2H, J=6.7 Hz, CH_2NH_2), 2.87 (s, 2H, NH_2), 3.16 (q, 2H, J=6.4 Hz, CH_2NHBoc), 5.1 (brs, 1H, NH). ^{13}C NMR: 28.4 (3C), 33.5, 38.4, 39.7, 79.0, 156.2. Spectroscopic data were in accordance with those of an authentic sample.

4.3.8. 1-[2-(3-Methyl-2-butenyl)oxyethyl]piperazine (3m). In the case of this substrate, 4 equiv. of iodine and 8 equiv. of zinc were added. Reaction time: 7 h, CH_2Cl_2–MeOH–Et_3N (85:10:5), 63% yield, oil. It was characterized as its dihydrochloride salt: mp 160–162 °C (dec.). ^{1}H NMR (D_2O): 1.72 (s, 3H, Me), 1.78 (s, 3H, Me), 3.55 (t, 2H, J=6 Hz, NCH_2CH_2O), 3.7 (m, 8H, 4 CH_2), 3.87 (t, 2H, J=6 Hz, NCH_2CH_2O), 4.11 (d, 2H, J=7.2 Hz, CH_2-CH=CMe_2), 5.40 (t, 1H, J=7.1 Hz, C*H*=CMe_2). ^{13}C NMR (D_2O): 17.8, 25.4, 41.0 (2C), 49.1 (2C), 56.9, 62.6, 67.6, 119.2, 141.4. Anal. calcd for $C_{11}H_{22}N_2O$·2HCl: C, 48.71, H, 8.92, Cl, 26.14, N, 10.33, O, 5.90. Found: C, 48.84; H, 9.02, Cl, 25.84, N, 10.10, O, 6.2.

4.3.9. 4-(Benzyloxycarbonyl)piperidine (3n). Reaction time: 5 h, CH_2Cl_2–MeOH–Et_3N (86:10:4), 77% yield, oil. Characterized as its hydrochloride salt. Mp 145–147 °C (dec.). ^{1}H NMR (D_2O): 1.86 (m, 2H, H-3a and H-5a), 2.16 (dd, 2H, J=3.3, 13.5 Hz, H-3e and H-5e), 2.76 (m, 1H, C*H*CO_2Bn), 3.06 (td, 2H, J=2.7, 12.5 Hz, H-2a and H-6a), 3.43 (dt, 2H, J=3.5, 12 Hz, H-2e and H-6e), 5.16 (s, 2H, CH_2Ph), 7.43 (s, 5H, Ph). ^{13}C NMR (D_2O): 24.8 (2C), 38.6, 43.4 (2C), 67.7, 128.7 (2C), 129.2, 129.4 (2C), 136.0, 175.7. Anal. calcd for $C_{13}H_{18}ClNO_2$: C, 61.05, H, 7.09, Cl, 13.86, N, 5.48, O, 12.51. Found: C, 61.24, H, 7.45, Cl, 14.1, N, 5.35, O, 12.24.

4.3.10. N^{α}-Benzyloxycarbonyl-L-lysine methyl ester (3o). Reaction time: 5 h, CH_2Cl_2–MeOH–Et_3N (85:10:5), oil, 85% yield. This compound was characterized as its N^{ε}-Boc derivative (Boc_2O, Et_3N, CH_2Cl_2, 2 h, room temperature), 74% yield, oil, $[\alpha]_D^{20}$=+4.2 (*c* 0.15, $CHCl_3$), $[\alpha]_D^{20}$=−9.2 (*c* 0.34, acetone). [Lit.[19,20] $[\alpha]_D^{20}$=+3.8 (*c* 2, $CHCl_3$), $[\alpha]_D^{28}$=−10 (*c* 1, acetone)]. ^{1}H NMR: 1.3–1.55 (m, 13H, $2CH_2$ and C(CH_3)$_3$), 1.6–1.85 (m, 2H, CH_2), 3.08 (m, 2H, CH_2NBoc), 3.73 (s, 3H, OMe), 4.35 (q, 1H, J=6.8, 12.8 Hz, C*H*CO_2Me), 4.61 (brs, 1H, N*H*Boc), 5.1 (s, 2H, CH_2Ph), 5.46 (d, 1H, J=7.5 Hz, N*H*Z), 7.34 (s, 5H, Ph). ^{13}C NMR: 24.4, 28.4 (3C), 29.6, 32.2, 40.1, 52.4, 53.8, 79.2, 128.2, 128.5 (4C), 136.3, 156.1, 172.9. ^{13}C NMR data were identical with those described in the literature.[20]

4.3.11. L-Proline methyl ester (3p). Reaction time: 5 h, CH_2Cl_2–MeOH–Et_3N (85:15), oil, 70% yield. Characterized as its hydrochloride salt. Mp 67–69 °C (ether), $[\alpha]_D^{20}$=−31.6 (*c* 1.6, H_2O) [lit.[21] mp 71 °C, $[\alpha]_D^{20}$=−32.6 (*c* 2.1, MeOH). ^{1}H NMR (D_2O): 2.03–2.3 (m, 3H), 2.51 (m, 1H), 3.46 (m, 2H, CH_2N), 3.88 (s, 3H, OMe), 4.54 (dd, 1H, J=7, 8.5 Hz, C*H*CO_2Me). ^{13}C NMR (D_2O): 23.8, 28.6, 46.8, 54.3, 60.0, 170.9. Its spectroscopic data were consistent with those of a commercial sample.

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Tetratriacontanonaenoic acid, first natural acid with nine double bonds isolated from a crustacean *Bathynella natans*

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Abstract—The very-long-chain polyunsaturated fatty acid—all*Z*-4,7,10,13,16,19,22,25,28-tetratriacontanonaenoic acid was determined and identified in the freshwater crustacean species *Bathynella natans* living in caves of central Europe by means of liquid chromatography—mass spectrometry with atmospheric pressure chemical ionization. The full structure was elucidated by using extensive spectroscopic analysis (^{1}H and ^{13}C NMR, MS, IR and UV) including a chemical method. This acid was described in nature for the first time. A hypothesis is suggested for its origin and biosynthesis.

1. Introduction

As part of our scientific program, whose main goal is to discover new and unusual compounds from the flora and fauna worldwide, we have screened a number of animals collected from caves. Among these, *Bathynella natans* was chosen for detailed chemical investigation,[1,2] due to its previously discovered content of very long chain polyunsaturated fatty acids (VLCPUFA). This species belongs to the family Bathynellacea, which contains about 70 genera distributed through all geographic regions. The crustacean species belonging to the Syncacarides are characterized by a primitive organization and ancient origin. They live in alpine lakes, rivers and groundwater, i.e. in the depths of limestone caves. In 1886, the Vejdovsky discovered,[3] the first Bathynellacea, *B. natans*, in Prague. In the dry summer of 2003, when even groundwater level decreased deep below its normal level, we obtained more individuals of *B. natans*, which were then used for analyses.

VLCPUFA were recently characterized in different plants and/or animals, mainly in aquatic, e.g. Baltic herring[4] or dinoflagellates.[5] In this study, we continue our reinvestigation of the fatty acid composition of freshwater crustaceans collected in the caves near Prague.

2. Results and discussion

The total lipid fraction of *B. natans* was analyzed by two-dimensional TLC in order to determine its lipid components. One unidentified lipid, designated X, was detected. Lipid X gave a positive reaction (blue spot) with molybdate-based Zinzade's reagent and Dragendorff stain gave a dark orange spot. On the basis of this coloring, we assumed that lipid X was diacyl phosphatidyl choline (PC). This assumption was confirmed by further analysis. The APCI mass spectrum gave a pseudomolecular ion $[M+H]^+$ at *m/z* 994 as the major peak, and minor fragments at *m/z* 968, 996 and 966 components. Fragment ions derived from the peak at *m/z* 994 appeared at *m/z* 549, 729 and 812, corresponding to $[M+H-R_1CO]^+$, $[M+H-R_2CO]^+$ and $[M+H-\text{choline}]^+$. A further ion at *m/z* 184 (choline+H) confirmed the structure of lipid X as tetratriacontanonaenoyl-oleoyl phosphatidyl choline. The minor molecular species showing peaks at *m/z* 968, 996 and 966 were found to be phosphatidyl choline with acyls 16:0 or 18:0 or 16:1 and tetratriacontanonaenoyl. Lipid X was then transesterified and five FAMEs (fatty acid methyl esters) were obtained.

The FAMEs were separated according to the degree of unsaturation on plates impregnated with $AgNO_3$. The lowest spot was extracted and the mass spectrum was measured by the APCI technique, see Figure 1. The APCI mass spectrum of VLCPUFA had characteristic ions consistent with 34:9 FAME. In contrast to previously published spectra,[6,7] this spectrum exhibited a peculiar feature. The pseudomolecular ion $[M+42]^+$ is conventionally taken to be mainly characteristic for PUFA, but in fact it

Keywords: *Bathynella natans*; Freshwater crustacean; LC-MS/APCI; Tetratriacontanonaenoic acid.
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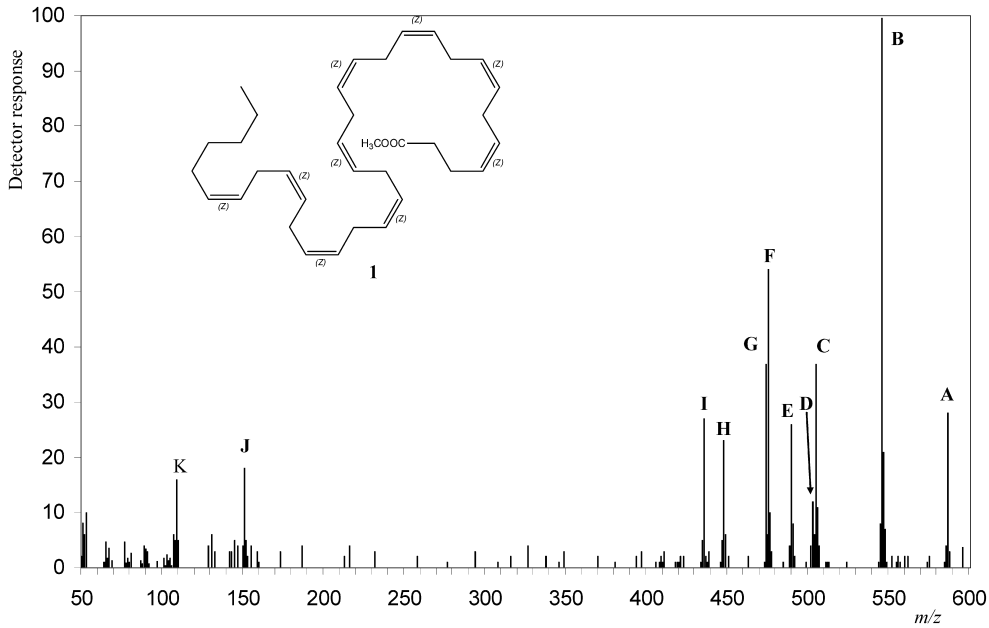

Figure 1. LC–MS/APCI of 34:9ω6 FAME from *Bathynella natans*. Ions (abundance): (A) $[M+H+2\times CH_3CN]^+$, *m/z* 587 (28); (B) $[M+H+CH_3CN]^+$, *m/z* 546 (100); (C) $[M+H]^+$, *m/z* 505 (37); (D) $[M-H[^+$, *m/z* 503 (12); (E) $[M+H-CH_3]^+$, *m/z* 490 (26); (F) $[M+H-C_2H_5]^+$, *m/z* 476 (54); (G) $[M+H-CH_3O]^+$, *m/z* 474 (37); (H) $[M+H-C_4H_9]^+$, *m/z* 448 (23); (I) $[M+H-C_5H_9]^+$, *m/z* 436 (27); (J) *m/z* 151 (18) (diagnostic ion, see text); (K) *m/z* 109 (16) (diagnostic ion, see text).

also arises by the addition of acetonitrile from the mobile phase. We were able for the first time to identify a pseudomolecular ion arising by the double addition of acetonitrile on polyenoic fatty acid. This effect is probably due to the unusual numbers of methylene-interrupted double bonds.

However, the determination of position of double bonds was unsuccessful on the basis of the cleavage of nitrogen derivatives (i.e., 4,4-dimethyloxazoline and/or picolinyl ester; data not shown). Nevertheless, this method was described as successful either for substances with equal-length chain, but having only one double bond,[6] or for shorter-chain compounds having a maximum of eight double bonds and only 28 carbon atoms.[5] In our case, this technique failed, or its results were ambiguous. Therefore, we used the method[5,6,8] based on the ratios of ions at *m/z* 109 and 151. The *m/z* 109/151 ratio is near unity and hence the presumed structure is ω-6.

We used the following methods for the full confirmation of the above structure, in particular for double bond location. After hydrogenation of the compound from the lowest spot, only one peak was seen in the gas chromatogram with an ECL value of 34:0, indicating a chain length of 34 carbon atoms without branching. The EI mass spectrum of this peak contained fragment ions characteristic for saturated FAME, i.e. *m/z* 74, 87 and weak ions at *m/z* 522 $[M]^+$, together with diagnostic ions at *m/z* 491 (M−MeO) and *m/z* 479 ($M-C_3H_7$). Further, the PUFA was not conjugated, as shown by the UV spectra (see Section 3). The double-bond stereochemistry was established by FTIR. All double bonds were *Z* because the IR spectrum of the PUFA exhibited absorption at 723 cm^{-1} and no absorption in the 960–980 cm^{-1} region.[9] This stereochemistry was further confirmed by ^{13}C NMR, since the allylic carbons (C-6, C-9, C-12, C-15, C-18, C-21, C-24 and C-27), resonated[10] between 26 and 27 ppm. All our spectral data point to all*Z*-4,7,10,13,16,19,22,25,28-tetratriacontanonaenoic acid (**1**) as the unknown acid.

The toxicity of compound **1** was tested in the *Artemia salina* shrimp bioassay (see Table 1). Table 1 also indicates that compound **1** was active only against Gram-positive bacteria but not against Gram-negative bacteria and yeast. This compound is now studied in view of its further potential by high physiological activity.

Table 1. Bioactivities of fatty acid (**1**)

Test organism	**1**[a]
Staphylococcus aureus[b]	78.1±2.00
Bacillus subtilis[b]	95.6±2.81
Escherichia coli[b]	0.0±0.00
Saccharomyces cerevisiae[b]	0.1±0.02
Artemia salina[c,d]	1.4±0.08

[a] Presented as mean±SE (*n*=10).
[b] Sample (10 μg) was applied on 6.3 mm paper disks; values are diameters (mm) of inhibitory zones.
[c] In μg/ml (minimum lethal doses).
[d] The details are in Section 3.

The origin of **1** is most likely bacterial or algal (the diets of the crustacean) and gives rise to interesting biosynthetic considerations, in particular with regard to the order of double-bond introduction, relative to other lower organisms.[5]

Conventional theory suggests successive chain elongation and desaturation of 22:5(ω-6) as a possible mechanism for the biosynthesis of this VLCPUFA. Alternatively, 34:9(ω-6) could be formed by a different mechanism but no information is available in this respect. Further research of the pathways of polyunsaturated fatty acid biosynthesis in marine organisms is needed.

In summary, a new metabolite has been isolated from *B. natans*. The main novelty of this compound is the presence of nine non-methylene interrupted double bonds in its molecule. To our knowledge, this is the first time that a fatty acid with nine double bonds, e.g. tetratriacontanonaenoic acid, is reported as a natural or synthetic product.

3. Experimental

3.1. General

UV spectra were measured by a Cary 118 (Varian) apparatus in MeOH in the range 200–350 nm. A Perkin–Elmer Model 1310 (Perkin–Elmer, Norwalk, CT) infrared spectrophotometer was used for scanning infrared spectroscopy of methyl esters as neat film. NMR spectra were recorded on a Bruker AMX 500 spectrometer (Bruker Analytik, Karlsruhe, Germany) at 500.1 MHz (^{1}H) and 125.7 MHz (^{13}C). The positive-ion MS/ESI spectrum was recorded on a VG 7070E-HF spectrometer (Micromass, Manchester, UK). The stearic, oleic, palmitic, palmitoleic, cerotic, montanic and melissic acids were purchased from Sigma-Aldrich (Prague, Czech Republic).

The LC–MS/APCI was realized as mentioned previously,[6] briefly: the HP 1090 series (HP 1090 series, Hewlett Packard, USA) was used with two columns (HIRPB-250AM 250×2.1 mm ID, 5 μm phase particle). A quadruple mass spectrometer system Navigator (Finnigan MAT, San Jose, CA, USA) was used: vaporizer temperature 400 °C, capillary heater temperature 220 °C, corona current 5 μA, sheath gas high-purity nitrogen, pressure ca. 380 kPa, and auxiliary gas (also nitrogen) flow rate 1500 ml/min. Ions with *m/z* 50–1500 were scanned with a scan time of 0.5 s, flow 0.37 ml/min. FAMEs were separated using a gradient solvent program with acetonitrile–dichloromethane (90:10) and linear from 10 to 40 min acetonitrile–dichloromethane (70:30).

GC–MS of a FAME mixture was done on a Finnigan 1020 B in EI mode. Splitless injection was 100 °C, and a fused-silica capillary column (Supelcowax 10; 60 m×0.25 mm i.d., 0.25 μm film thickness; Supelco, Prague) was used. The temperature program was as follows: 100 °C for 1 min, subsequently increasing at 20 °C/min to 180 °C and at 2 °C/min to 280 °C, which was maintained for 1 min. The carrier gas was helium at a linear velocity of 60 cm/s. All spectra were scanned within the range *m/z* 70–650.

3.2. Biological material

The specimens of *B. natans*were collected in September 2003, in caves near Srbsko near Prague at a depth of between 5 and 8 m. The crustaceans were carefully cleaned and lyophilized. A voucher specimen (TR-130903/11) is available from the first author.

3.3. Extraction and isolation

The specimens of *B. natans* (250 g), extracted with 2×150 ml of $CHCl_3$–MeOH (1:1), yielded total lipids (1630 mg). These were fractionated by preparative TLC (20 cm×20 cm) using Si gel 60, and developed by two-dimensional chromatography with chloroform–methanol–formic acid–water (65:25:9:1, v/v) and chloroform–methanol–ammonia–water (50:40:3:7, v/v). Zinzade's reagent was used to specifically identify all phospholipids, while Dragendorff's reagent was used to visualize PC. For preparative purposes, the spots were visualized by spraying with fluorescein, scraped off the silica gel plate, and extracted with chloroform–methanol (1:1). The yield of lipid X was 10.2 mg.

The fatty acyl components of the unknown PC were obtained as their methyl esters by reaction of the PC with methanolic HCl followed by column chromatography including elution with *n*-hexane–diethyl ether (9:1).

Glass plates (20×20 cm) were impregnated by silver nitrate and developed[11,12] by $CHCl_3$–MeOH (100:1) in the first, and hexane–acetone (100:3) in the second dimension. The spots were sprayed with fluorescein and detected under UV light. The appropriate spots were scraped off, and compounds **1**, **2**–**3** and **4**–**5** were extracted from the silica gel by diethyl ether. Compounds **2**–**5** were identified by GC–MS as methyl esters of 16:0, 18:0, 16:1 and 18:1 acids.

Hydrogenation of compound **1** was carried out in 1 ml of methanol with catalytic amounts of PtO_2. FAME was extracted with *n*-hexane and subjected to gas chromatography.

3.3.1. Compound 1. Methyl all*Z*-4,7,10,13,16,19,22,25,28-tetratriacontanonaenoate (**1**): Colorless oil, 4.1 mg; UV λ_{max} (MeOH) (log ε) 209 (3.36) (nm); IR (neat) ν_{max} 3500 (OH), 3010 (=CH), 2950, 2930, 2870, 1710 (C=O), 1460, 1435, 1410, 1380, 1370, 1240, 940, 720 (HC=CH, *Z*) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 5.35–5.41 (m, 18H, =C–*H*), 2.70–2.75 (m, 16H, =CH–C*H*$_2$–HC=), 2.35–2.39 (m, A_2B_2, 4H, –C*H*$_2$–C*H*$_2$–COOH), 2.00 (m, 2H, –C*H*$_2$–HC=), 1.36–1.41 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 0.89 (t, 3H, C*H*$_3$–); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 179.6 (s, C-1, *C*OOH), 131.9 (d, C-29), 126.9–128.7 (d, 16×C), 129.1 (d, C-5), 33.5 (t, C-2), 31.6 (C-32), 29.4 (t, C-31), 27.3 (t, C-30), 26.6 (t, C-4), 25.4–25.8 (t, 8× =CH–C*H*$_2$–CH=), 24.6 (t, C-3), 22.6 (t, C-33), 14.2 (q, C-34); HR-MS/ESI calcd for $C_{35}H_{52}O_2Na$, 527.3870, found *m/z* 527.3865 $[M+Na]^+$.

Methyl tetratriacontanoate: GC–MS/EI (70 eV) *m/z* $[M]^+$ 522 (38), 493 (M−C_2H_5; 14), 491 (M−MeO; 13), 479 (M−C_3H_7; 18), 199 (9), 143 (50), 87 (73), 74 (100), 69 (31), 67 (28), 55 (46).

3.4. Assay for biological activity

The sample (~0.05 mg) was dissolved in 50 μl of DMSO and added to a vial of artificial seawater (3.0 ml). Approximately 20 brine shrimp, *Artemia salina*, were added to the vial and then observed periodically over a 24 h period. A positive assay was the death of all brine shrimp. The test organisms were from the Czechoslovak Collection of Microorganisms, Brno. Antibacterial assays were carried out according to the literature.[11] The amount of the compound was 10 μg per test disk (see Table 1).

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Polyynes and cyanopolyynes synthesis from the submerged electric arc: about the role played by the electrodes and solvents in polyynes formation

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Abstract—The products of the electric arc between graphite electrodes have been investigated by high performance liquid chromatography-diode-array detector (HPLC-DAD) analysis in various media: distilled water, liquid nitrogen, methanol, ethanol, *n*-hexane and benzene. In distilled water, hydrogen capped polyynes H–(C≡C)$_n$–H were the unique products demonstrating that carbon is supplied by the graphite electrodes while hydrogen is supplied by the solvent plasmalysis (in this case water plasmalysis). Arcing graphite electrodes in liquid nitrogen produces cyanopolyynes: N≡C–(C≡C)$_n$–C≡N demonstrating that in this case the end groups of the polyyne chains are supplied by molecular nitrogen plasmalysis caused by the electric arc. Graphite arcing in methanol and ethanol produces very clean solutions (by-products negligible or absent) of hydrogen-capped polyynes with C_8H_2 as the main product accounting for more than 70 mol percent of the total polyyne concentration. By replacing graphite electrodes with titanium electrodes in methanol or in ethanol, polyynes are not formed at all; only trace amounts of polycyclic aromatic hydrocarbons (PAHs) were detected. When arcing with graphite electrodes is conducted in *n*-hexane or in benzene, polyyne formation is accompanied by a significant production of PAH, especially in benzene. These results have been rationalized in terms of carbonization or coking tendency of a given solvent. The effect of using titanium electrodes in place of graphite electrodes has been investigated also in *n*-hexane and in benzene as well as the effects of very high electric current intensity employed to ignite and sustain the submerged electric arc.

1. Introduction

In a series of papers[1–5] we have reported the discovery that polyynes having the general formula H–(C≡C)$_n$–H are easily formed when graphite electrodes are arced into certain solvents. Furthermore, we have also started the investigation of the chemistry of polyynes[3,6,7] which, for the first time, are easily available in solution, thus permitting this new exploration.

There are still many questions concerning the easy formation of polyynes from the electric arc in solution. The key question that this work intends to answer is the following: are the polyynes produced by the carbon vaporization from the graphite electrodes or instead they are produced by the plasmalysis of the solvent caused by the extremely high temperature of the electric arc? To produce an unequivocal answer, we have designed a series of key experiments ranging from replacing the organic solvent with liquid nitrogen to exclude the interference of the solvents and by replacing graphite with titanium electrodes in the arc.

Furthermore, we intend to analyze the work and the results of Beck and co-workers[8–10] who have used electric arc and other electric discharge systems in toluene in order to produce fullerenes and instead obtained and identified a plethora of polycyclic aromatic hydrocarbons (PAH). Sometimes fullerenes were present but they failed to find polyynes.[8–10]

2. Results and discussion

2.1. Polyynes synthesis by arcing graphite electrodes in water

The electric arc between graphite electrodes in certain solvents like methanol, acetonitrile, *n*-hexane and decahydronaphthalene produces in a few minutes polyyne solutions at a concentration of 10^{-3}–10^{-4} M without any concentration operation.[1–5] This synthesis represents a new advantageous and one-shot route to polyynes as an alternative to the classic step-synthesis proposed about 30 years ago.[11] The basic mechanism proposed, involves

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carbon vaporization from the graphite electrodes under the extremely high temperature produced by the electric arc (estimated to be above 4000 °C), above the vaporization point of elemental carbon.[1–5] Elemental carbon is vaporized from the electrodes and oligomerizes to form polyyne chains and then is quenched into the solvent surrounding the plasma ball of the arc. The same mechanism was proposed by Tsuji and co-workers for polyyne formation under laser ablation of graphite particles suspended in a solvent.[12]

Usually the polyynes are detected as hydrogen-terminated chains although in certain special cases[2–5] (acetonitrile), we have also found other end groups derived from the solvent. In general, it is reasonable to think that the hydrogen end capping is derived from the solvent plasmalysis caused by the electric arc. In fact, the solvent plasmalysis caused by the electric arc generates atomic hydrogen, which then reacts with the diradicalic carbon chains produced by carbon vaporization from the electrodes.

To test this hypothesis, we have also studied the submerged electric arc between graphite electrodes in distilled water. Since we have a carbon source form the graphite electrodes and an hydrogen source from the plasmalysis of water we expected to produce hydrogen-capped polyynes. This was indeed the case as discussed in Section 4.1. The electronic spectrum of the crude polyyne mixture (Section 4.1) matches satisfactorily the pattern of analogous mixtures obtained by arcing graphite in other solvents.[1–5] Furthermore, as shown in Figure 1, the HPLC analysis of the polyyne mixture formed in water reveals the presence of polyynes C_8H_2 and $C_{10}H_2$ as the major arcing products; the former polyyne was detected at an approximate concentration of 5×10^{-6} M while the latter at only 1×10^{-7} M.

Thus, it appears clear that the hydrogen atoms present as end groups in the polyyne chains in this specific case are derived from water dissociation at the high temperature of the arc, while elemental carbon is supplied by the graphite electrodes.

2.2. Formation of polyynes by arcing graphite electrodes in liquid nitrogen

Once it was clarified that the polyyne chains are produced with hydrogen end groups in water, it does not appear surprising that the polyynes produced between graphite electrodes submerged in liquid nitrogen are also hydrogen-terminated (see Section 4.2). In fact, in our electric arc in liquid nitrogen, we have excluded the presence of any organic solvent but not the presence of humidity. Therefore, the arc between graphite electrodes in liquid nitrogen necessarily involves the plasmalysis of small amounts of water, which supplies the hydrogen necessary for end-capping the polyyne chain.

As expected, the graphite arc in liquid nitrogen produces cyanopolyynes as main products, while the hydrogen-capped polyynes are only minor products. This is shown in Figure 2 and implies that the nitrogen molecules are activated by the electric arc and plasmalyzed to atomic nitrogen. The carbon vapour reacts with atomic nitrogen forming cyanopolyynes; the formation of cyanopolyynes (and polyynes) in the electric arc in liquid nitrogen represents a clear indication that the elemental carbon for the polyyne chains is supplied exclusively from the graphite electrodes and not from the solvent. This conclusion was quite expected since we know that the electric arc in vacuum conditions between graphite electrodes produces polyyne ions.[13,14] Instead, when the electric arc between graphite electrodes is struck under a low pressure of cyanogen gas (N≡C–C≡N) under Kraetschmer–Huffmann conditions,[15] cyanopolyynes belonging to the general formula: N≡C–$(C\equiv C)_n$–C≡N were obtained.[16]

When the graphite electrodes were arced in liquid nitrogen

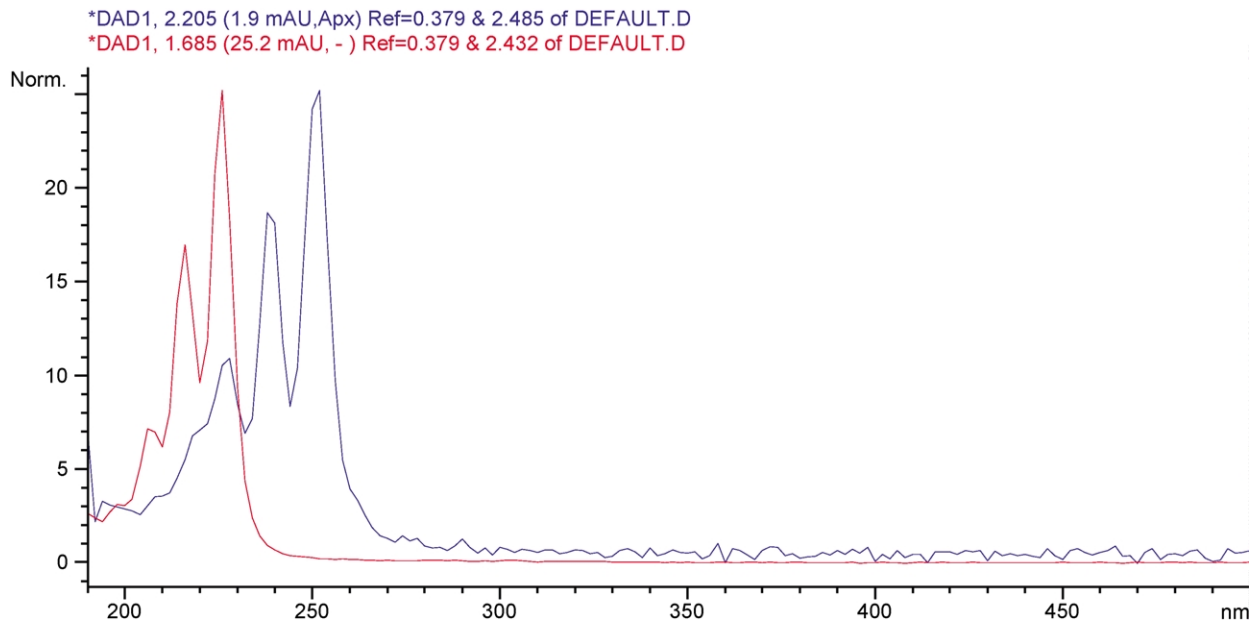

Figure 1. Electronic absorption spectra of polyynes C_8H_2 and $C_{10}H_2$ produced by arcing graphite electrodes in distilled water and detected by HPLC-DAD analysis. The first absorption spectrum in the left is due to C_8H_2 which has a retention time of 1.685 min and the other spectrum is due to $C_{10}H_2$ with a retention time of 2.205 min. The absorbance scale in the ordinate is normalized and is in mAU units.

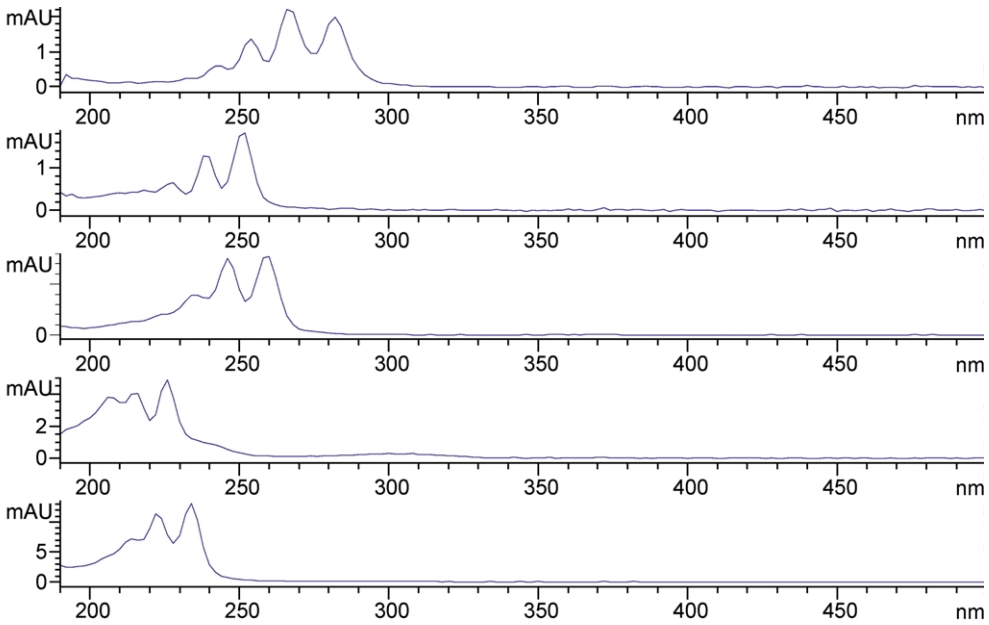

Figure 2. Individual electronic absorption spectra of each molecular species separated by the liquid chromatographic analysis. From bottom to top of Figure 2 it is possible to distinguish the spectrum of C_6N_2 with t_R=1.55, then C_8H_2 with t_R=1.64 followed by C_8N_2 (t_R=1.87), $C_{10}H_2$ (t_R=2.11) and $C_{10}N_2$ (t_R=2.39).

the cyanopolyynes (and polyynes) formed were quenched into the very cold reservoir of the liquid nitrogen surrounding the plasma ball. When liquid nitrogen vaporizes, it drags the cyanopolyynes and polyynes, which presumably are insoluble but are embedded in liquid nitrogen, outside the reactor into the gas washing bottle filled with a solvent like *n*-octane. When nitrogen bubbles into the bottle, it releases the polyynes into the octane solvent, which acts as a trap. The HPLC separation of the cyanopolyynes and polyynes trapped in the octane solvent was made using a C8 column and each molecular specie eluted was detected with a diode-array detector (DAD) detector. Figure 2 reports the spectra of each specie eluted. From bottom to top of Figure 2 it is possible to observe the detection of $N{\equiv}C{-}(C{\equiv}C)_2{-}C{\equiv}N$ followed by $H{-}(C{\equiv}C)_4{-}H$. Then the spectra of $N{\equiv}C{-}(C{\equiv}C)_3{-}C{\equiv}N$ followed by $H{-}(C{\equiv}C)_5{-}H$ are observed and finally $N{\equiv}C{-}(C{\equiv}C)_4{-}C{\equiv}N$ was also detected. Elsewhere we

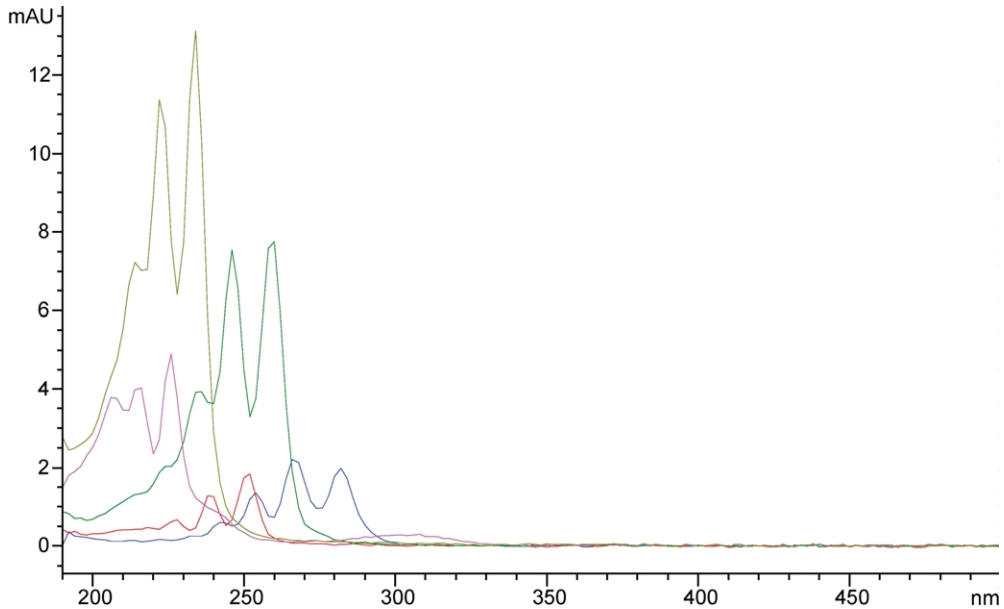

Figure 3. Electronic absorption spectra of the polyynes formed from graphite arcing in liquid nitrogen. In this figure the products are shown at their real absorption intensity in mAU scale. The liquid chromatographic analysis (HPLC) was able to separate the mixture into its components. The electronic spectrum of each component eluted was recorded by the diode-array detector (DAD). The three main components are easily and definitively identified from their electronic absorption spectra and are, respectively, C_6N_2 (light green line), C_8N_2 (dark green line) and $C_{10}N_2$ (blue line). The spectra of these three dicyanopolyynes in this figure are easily identifiable from the longest wavelength absorption band lying at 233, 260 and 283 nm, respectively. There are also two other minor components in Figure 3: the hydrogen-terminated polyynes C_8H_2 (pink line), $C_{10}H_2$ (red line). Furthermore, $C_{12}H_2$ has also been identified although at very low concentration (not shown in Figure 3).

Table 1. Synopsis of products formed by arcing graphite or titanium in selected solvents

Solvent Electrodes	Hexane Graphite (% mol)	Hexane Titanium (% mol)	Benzene Graphite (% mol)	Benzene Titanium (% mol)	Methanol Graphite (% mol)	Methanol Titanium (% mol)	Ethanol Graphite (% mol)	Ethanol Titanium (% mol)
Polyyne C6	20.3	23.9	13.8	Detected	7.2	n.d.	8.9	n.d.
Polyyne C8	61.2	72.7	68.3	83	77.8	n.d.	73.5	n.d.
Polyyne C10	14.8	3.4	12.6	17	12.8	n.d.	12.3	n.d.
Polyyne C12	2.9	n.d.	3.2	Traces	2.2	n.d.	3.7	n.d.
Polyyne C14	0.63	n.d.	2.1	Traces	Detected	n.d.	1.5	n.d.
Polyyne C16	0.17	n.d.	Traces	n.d.	n.d.	n.d.	0.1	n.d.
Polyyne C18	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Benzene	n.d.	Traces?			n.d.	Traces	n.d.	Traces
Indene	n.d.	Traces	n.d.	n.d.	n.d.	n.d.	n.d.	n.d
Naphthalene	Traces	Traces	Detected	Detected	Traces	Traces	Traces	Traces
Acenaphthene	Traces	n.d.	Detected	n.d.	n.d.	Traces	n.d.	Traces
Acenaphtylene	Traces	Traces	Detected	Detected	n.d.	n.d.	n.d.	n.d.
Biphenyl	n.d.	n.d.	Detected	Detected	n.d.	Traces	n.d.	n.d.
Phenanthrene	n.d.	n.d.	Detected	Detected	n.d.	Traces	n.d.	n.d.
Anthracene	n.d.	n.d.	Detected	Detected	n.d.	Traces	n.d.	n.d.
Perylene	n.d.	n.d.	Detected	Detected	Traces	Traces	n.d.	n.d.
Pyrene	Traces	n.d.	Detected	n.d.	n.d.	n.d.	n.d.	n.d.
Crysene	Traces	n.d.	Detected	n.d.	n.d.	n.d.	n.d.	n.d.
Fluoranthene	n.d.	n.d.	Detected	Detected	n.d.	Traces	n.d.	n.d.
Benzo[*b*]fluoranthene	Traces	Traces?	Detected	Detected	Traces	n.d.	n.d.	n.d.
Benzo[*b*]naphto[2,1-cd]thiophene	n.d.	n.d.	Traces	Traces	n.d.	n.d.	n.d.	n.d.
Total polyyne conc. (mol/l)	4×10^{-4}	2×10^{-6}	5×10^{-4}	2×10^{-5}	5×10^{-4}	None	3×10^{-4}	None
Carbon black formation	Yes	Yes	Abundant	Abundant	Small	Small	Small	Small

n.d.=not detected.

have discussed both the spectra and the assignments of the molecular species just reported.[17] Figure 3 shows that the cyanopolyynes were the dominant species in the synthesis from the graphite arc in liquid nitrogen while the normal polyynes are only present as a minority and can be considered by-products derived from the humidity as discussed previously.

2.3. About the role played by organic solvents when the submerged arcing is made between graphite electrodes

The discussion about the formation of cyanopolyynes and polyynes in liquid nitrogen and in water, respectively, underlines the key role played by the electrodes during graphite arcing and suggests a minor to negligible contribution from the solvent as elemental carbon source. Instead the solvent clearly supplies the end groups of the polyynes chains.

When the graphite electrodes are arced into a solvent like *n*-hexane, as described in Section 4, although by far the main reaction product consists of a mixture of polyynes, it is possible to detect other by-products by HPLC-DAD analysis. These by-products are not found when graphite electrodes are arced in liquid nitrogen or are present in extremely small trace amounts when the arc is made in certain solvents like methanol, ethanol or water (see Table 1).

To elucidate the nature of these by-products, as described in Section 4.3, we precipitated all the hydrogen-terminated polyynes present in an *n*-hexane solution as acetylides by treatment with a Cu(I) reagent.[1–5] After this treatment, it was possible to observe a profound alteration of the electronic absorption spectrum of the hexane solution (see Fig. 4). Before the precipitation, the electronic absorption spectrum of the graphite arced hexane solution (Fig. 4A) was dominated by the absorption bands due to the polyynes,[1–5] but after their precipitation as Cu(I) acetylides it was possible to observe the spectrum (Fig. 4B) of the non-precipitable by-products. Of course, if the unique result of arcing between graphite electrodes in hexane would have been the polyynes, after their precipitation the hexane solution should have appeared completely clean and free from absorption bands. This is not the case, because the HPLC-DAD analysis of such a solution freed from polyynes reveals a plethora of products but no trace at all of the polyynes. This is shown in Figure 5A and B. In Figure 5A the polyynes are clearly distinguishable as a sharp and intense peak in the chromatogram but they are completely absent from Figure 5B after their complete separation as acetylides. The molecular species of Figure 5B are a mixture of polycyclic aromatic hydrocarbons (PAHs). This

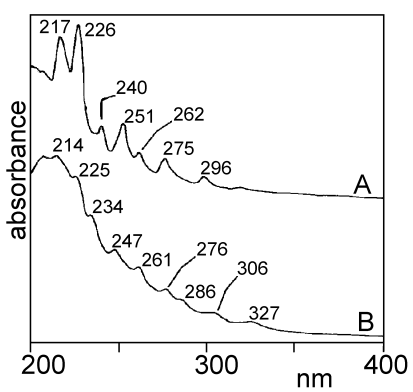

Figure 4. (A) Electronic absorption spectrum of polyynes obtained in *n*-hexane after arcing with graphite electrodes. (B) Spectrum after polyyne precipitation from solution as acetylides. The residual absorption bands are due to PAHs formed as secondary products during arcing. The two spectra have been shifted for clarity. The absorbance units in the ordinate are in arbitrary scale.

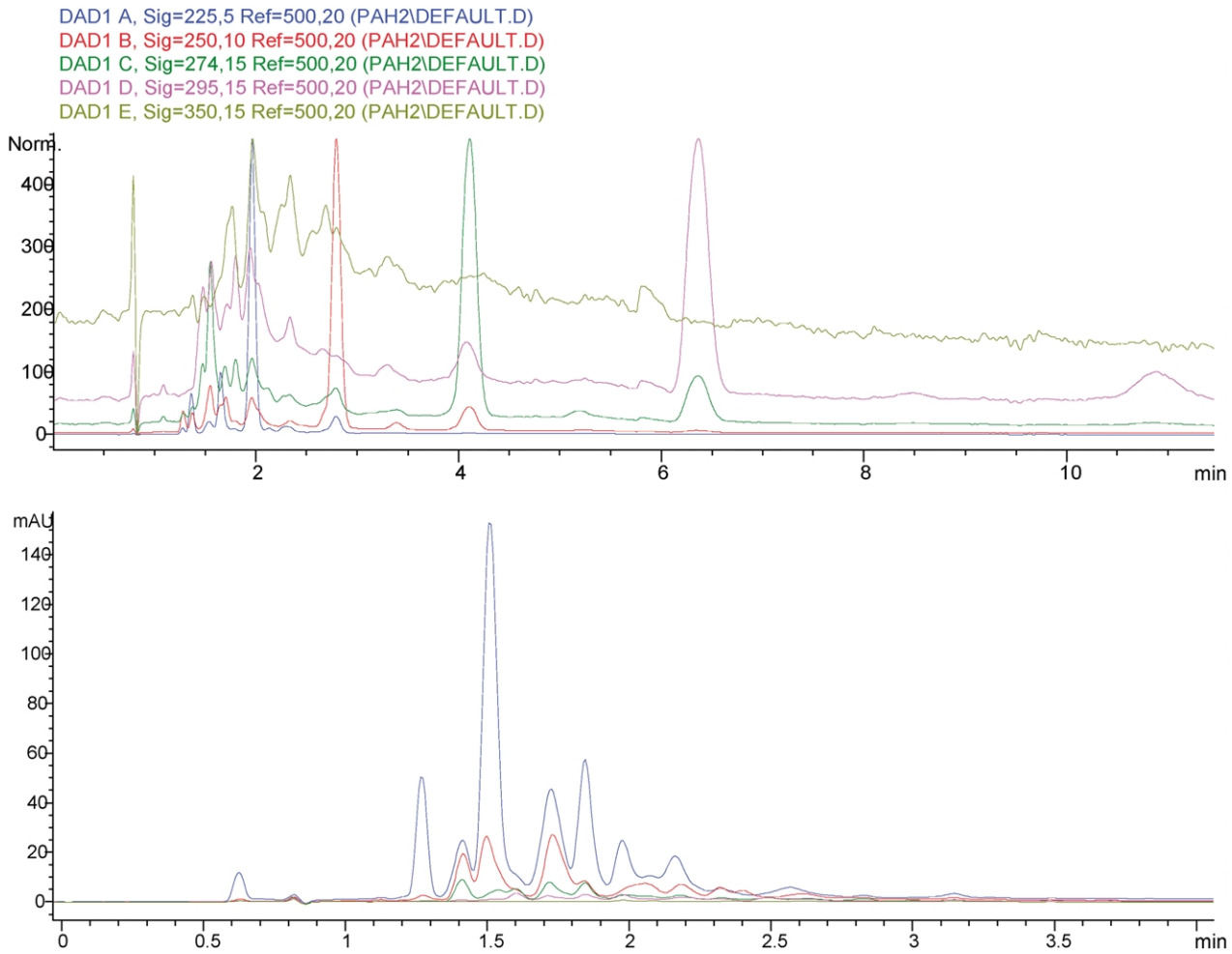

Figure 5. (A) Normalized HPLC Chromatogram showing the polyynes formed in *n*-hexane in standard conditions at 10 A. Each sharp peak is a polyyne. The polyynes detected at C_8H_2, $C_{10}H_2$, $C_{12}H_2$, $C_{14}H_2$ and even $C_{16}H_2$ as the broad peak after 10 min of retention time. The abscissa is reporting the elution time in minutes, the ordinate reports the DAD response in milli-absorption units (normalized). The blue line was detected at the fixed wavelength of 225 nm, the red line at 250 nm, the green line at 274 nm, the pink line at 295 nm and the grey line at 350 nm. (B) HPLC chromatogram of molecular species non-precipitable as acetylides, identified as PAHs on the basis of their electronic spectra. Note the absence of the C_8H_2, $C_{10}H_2$, $C_{12}H_2$ polyynes which appear at about 2, 2.7 and 4 min in the Figure 5A. The abscissa is reporting the elution time in minute, the ordinate reports the DAD response in milli-absorption units. The blue line was detected at the fixed wavelength of 225 nm, the red line at 250 nm.

has been established on the basis of their retention time in the chromatogram and on the basis of their electronic absorption spectra in comparison to the spectra of our standards or of Agilent PAHs library spectra. For instance, we unequivocally identified the presence of naphthalene, acenaphthalene, benzo[*b*]fluoranthene, pyrene and crysene of a total of 17 different compounds eluted, all with spectra suggesting a PAH nature, although in some case some cyclic polyynes and ene–ynes cannot be excluded, because of the lack of standard and reference spectra.

The presence of PAH in solvents subjected to the electric arc is not a surprise or a novelty. For instance Beck and colleagues[8–10] have already investigated the effect of electric discharges in toluene with the aim of producing C_{60} fullerene. Instead they found in all cases the formation of mixtures of PAH, and in some cases fullerenes were present but only in trace amounts. The mentioned authors[8–10] have explored different conditions of electric discharges in hydrocarbon solvents ranging from arc between graphite electrodes to scintillysis, from radio-frequency plasma to silent electric discharges, conditions which are completely different from those used in our previous works[1–5] and in the present work. Only in one case have Beck et al. adopted the electric arc in conditions very close to ours[8] using an electric arc at 10–15 A, but also in that case they failed to detect polyynes and obtained instead a complex mixture of PAH. The reason for this failure may be attributed to the workup used for product isolation and analysis: the toluene solution after two-hour arcing was distilled under reduced pressure to dryness after the addition of dichloromethane. The residue after solvent evaporation was used for the GC–MS analysis.[8] However, we know from our studies[1–7] that polyynes are only stable in solution. When solvent is distilled off the polyynes decompose into other products. This justifies completely the failure to detect linear polyynes by Beck et al.[8] Since, we have used HPLC techniques coupled with a diode array detector for the analysis of the products of the arc, we have not caused any alteration of the components of the crude mixture of products which was injected as it was produced after a simple filtration. Furthermore, as shown in Figure 6, when arcing in hexane is conducted at 20 A, the polyynes are still present and detectable but the fraction of other products

(PAH) increases significantly. Under these conditions PAH may become the dominant products.

Beck and co-workers[10] also made an interesting comparative study between the products formed by solvent thermal pyrolysis above 1000 °C and the products formed by electric discharges in organic solvents like scintillysis,[9] radio-frequency plasma treatment and silent electric discharges. In all cases examined, more or less the same PAH mixtures are produced, together with the formation of thermal carbon black or, which is the same, pyrocarbon. Thus, it appears clear that electric discharge in solvents causes their carbonization. The PAHs detected are the by-products and the intermediates which lead to the formation of carbon black,[18–21] but also polyynes are considered the key intermediates which lead both to PAH and soot formation.[18,19]

Based on the preceding discussion, it appears clear that the PAH observed by arcing graphite electrodes in hexane are derived from the solvent pyrolysis in the plasma ball of the arc while the polyynes are released by the graphite electrodes. Since polyynes are also considered the precursors of PAH and soot formation[18,19] it cannot be excluded that a fraction of them, once formed are converted into PAH and soot during the arcing operation. This may explain why the concentration of polyynes grows proportionally to the arcing time in the early stages of arcing but after a certain concentration is reached, say 10^{-3}–10^{-4} M, it is impossible to further increase their concentration. Probably an equilibrium is reached at that point between the concentration of the polyynes and their transformation into other products by incorporation into the PAH and pyrocarbon or by consumption by the pyrolysis/plasmalysis and/or by the photolysis, since we have demonstrated that the polyynes are photolyzed by the action of the UV light.[6] Thus, the light emitted by the arc may be one of the contributory factors which limits their maximum concentration in a given solution.

2.4. About the role played by the electrodes: results obtained by arcing with titanium electrodes in place of graphite electrodes

Once the role of the graphite electrodes in the production of the polyynes had been clarified, a couple of crucial tests were made by replacing the graphite electrodes with titanium electrodes.

The first study was conducted in *n*-hexane arcing with titanium electrodes. Surprisingly, and contrarily to all the partial conclusions of the preceding sections, C_6H_2, C_8H_2 and $C_{10}H_2$ polyynes where found in the hexane solution arced between titanium electrodes (Table 1). Five other products were found in comparable concentrations to the two polyynes mentioned. All were PAH and three of them were identified as naphthalene, acenaphthalene and indene while the remaining two presumable PAH have received only a tentative assignment (see Table 1). The formation of polyynes observed by arcing hexane with titanium electrodes seems to contradict many conclusions of the preceding sections. However, it must be noticed that the arcing in hexane produced a significant amount of carbon black. Since no carbon electrodes were used, it appears clear that all the carbon black formed derived from the pyrolysis and carbonization of *n*-hexane. To explain the polyyne formation, it is possible to think that the pyrocarbon particles formed from hexane plasmalysis entered into the plasma ball of the arc or coated the surface of the titanium electrodes as a thin layer. Under these conditions, the pyrocarbon acted as a source of carbon vapour in the plasma phase for the production of the polyynes.

As shown in Table 1, although the relative concentration of the polyynes detected in *n*-hexane arced with Ti electrodes appears comparable to the distribution of polyynes in *n*-hexane prepared with graphite electrodes, the overall polyyne concentration in the solution prepared with graphite electrodes exceeds by two order of magnitudes

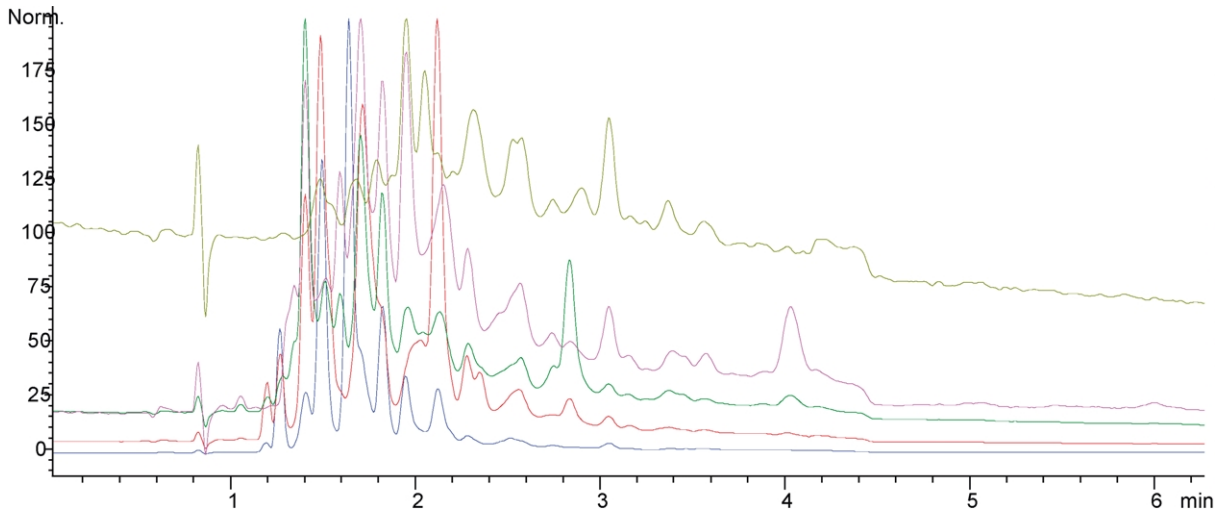

Figure 6. HPLC chromatogram obtained by arcing at 20 A instead of the usual 10 A in *n*-hexane. The polyynes are still produced but with significant amounts of PAHs. Compare this figure with Figure 5A. The abscissa is reporting the elution time in minutes, the ordinate reports the DAD response in milli-absorption units (normalized). The blue line was detected at the fixed wavelength of 225 nm, the red line at 250 nm, the green line at 274 nm, the pink line at 295 nm and the grey line at 350 nm.

the total concentration of the polyynes in *n*-hexane prepared with Ti electrodes under similar conditions (same current intensity and arcing time). Thus, the fundamental contribution from the graphite electrodes in supplying elemental carbon for the polyynes production is clear. Furthermore, it is remarkable that with graphite electrodes long chain polyynes $C_{12}H_2$, $C_{14}H_2$ and $C_{16}H_2$ were also formed and detected in appreciable amounts, while with Ti electrodes the longest detectable chain was $C_{10}H_2$ (see Table 1).

Approximately similar results were observed when *n*-hexane was replaced with benzene (Table 1): graphite electrodes produced a higher concentration of polyynes with a wider distribution of detectable chains in comparison to titanium electrodes. A striking peculiarity of benzene is the formation of a plethora of HPLC-DAD detectable PAHs as reported in Table 1 (plus others separated by HPLC but not identified on the basis of the electronic absorption spectra), the distribution of the PAHs was richer and more complete with graphite electrodes rather than with Ti electrodes. In this case, the contribution of the solvent to PAHs and pyrocarbon formation appears quite evident.

Completely opposite results to those discussed in the case of *n*-hexane and benzene have been observed in the case of alcohols like methanol and ethanol (Table 1).

When methanol or ethanol was used as solvent for arcing with Ti electrodes, the formation of carbon black derived from solvent carbonization was reduced to a minimum. Simultaneously, the HPLC-DAD analysis revealed the complete absence of any polyynes in these oxygenated solvents. Instead, only PAHs were detected but in trace amount (Table 1). Among the PAHs detected in methanol, biphenyl, naphthalene, acenaphthalene, phenanthrene, anthracene were easily identified based both on their retention times and on their peculiar UV spectral pattern in comparison with the spectral pattern of authentic reference compounds. Perylene and fluoranthene were also reasonably identified based on the retention time and on the reasonable match of reference UV spectra. In any case, the PAHs formed under these conditions were present in at least two orders of magnitude lower concentration than the polyynes formed by arcing the graphite electrodes in methanol. Moreover, PAH formation in methanol was considerably lower than the trace amounts produced in *n*-hexane.

Arcing of graphite electrodes in methanol or even better in ethanol, produces the cleanest polyyne solution with extremely small to negligible amounts of PAHs (Table 1). Thus, these alcohols appear to date the best solvents for the cleanest synthesis of polyynes with the electric arc technique. As already reported for other solvents, also in methanol and ethanol the dominant polyyne is C_8H_2, accounting for more than 70 mol percent of the total polyyne mixture. The yield of longer polyynes decreases as the chain length grows (Table 1). Polyynes $C_{10}H_2$ and $C_{12}H_2$ were formed in appreciable amounts together with the C_6H_2. In ethanol also $C_{14}H_2$ and $C_{16}H_2$ were detected.

To explain the various results in different solvents as reported in Table 1, it is useful to recall a petrochemical process known as 'coking' which involves the thermal carbonization of an hydrocarbon[22,23] (or hydrocarbon mixture). The coke produced can be considered equivalent to the pyrocarbon mentioned above. The coking tendency of an hydrocarbon under pyrolytic conditions depends on its C/H ratio and the presence of oxygen in the molecule but essentially it depends from its enthalpy of formation.[22,23] Thus, the energy necessary to produce 1 kg of carbon is +2325 kJ/kg in the case of *n*-hexane and becomes +9787 kJ/kg in the case of ethanol but reaches the very high value of +16770 kJ/kg in the case of methanol. In the case of aromatic hydrocarbons, coking is an exothermic process and occurs with the evolution of considerable amount of heat. For instance, in the case of benzene, the heat evolved in the process is −1150 kJ/kg, for naphthalene −1270 kJ/kg. The maximum value of heat emission in the coking process is offered by acetylene: −9450 kJ/kg.[22] In these last three cases the coking process is spontaneous due to the exothermicity of the process. Therefore, when arcing is conducted with aromatic hydrocarbons like benzene (or toluene[8–10]), because of their spontaneous tendency to carbonization, the formation of PAH mixtures in relatively large quantity can be observed together with pyrocarbon or coke. Instead the amount of PAHs and coke decreases significantly when *n*-hexane is arced and decreases further when methanol is used in place of *n*-hexane for arcing. This because of the unfavourable thermodynamics in the carbonization process. As shown above the carbonization thermodynamics of alcohols are extremely unfavourable also because these molecules contain oxygen. Thus, in the case of alcohols, PAH formation is extremely low to negligible and similarly can be concluded for pyrocarbon formation in these media.

3. Summary and conclusions

With a series of experiments, we have thrown more light on the understanding of the process of polyyne formation by the submerged electric arc between graphite electrodes.

Arcing graphite electrodes in distilled water produces hydrogen-terminated polyyne chains $H-(C{\equiv}C)_n-H$, and this demonstrates that the hydrogen is coming from water plasmalysis at the arc temperature while carbon is vaporized from the graphite electrodes.

Arcing graphite electrodes in liquid nitrogen with our simple apparatus permits trapping of the polyynes formed which consist essentially of cyanopolyynes $N{\equiv}C-(C{\equiv}C)_n-C{\equiv}N$. Under the high arc temperature molecular nitrogen is divided into atomic nitrogen, which terminates the ends of the polyyne chains formed by the association of elemental carbon vapour released by the graphite electrodes. Together with the cyanopolyynes, normal hydrogen-terminated polyynes have also been detected in the mixture produced by arcing in liquid nitrogen. The formation of the hydrogen-capped polyynes can be explained because of the presence of humidity and traces of water in the liquid nitrogen and in the reactor.

The key role of the graphite electrodes in polyyne formation is underlined by the fact that when arcing in methanol and in ethanol is conducted with titanium electrodes no trace of polyynes could be detected by the HPLC-DAD analysis. Instead, with graphite electrodes, very clean solutions of polyynes can be produced up to 10^{-3} M concentration in alcohols. The cleaning of the alcohol solutions refers to the negligible presence of by-products like PAHs. Only polyynes are present and C_8H_2 is by far the dominant specie in these solutions accounting for more than 70 mol percent of the total polyyne concentration.

Arcing with graphite electrodes in *n*-hexane and in benzene produces a plethora of PAHs as secondary products together with polyynes, which remain the dominant products by two orders of magnitude in comparison to the total concentration of PAHs. Arcing *n*-hexane with very high electric current density increases the PAH concentration.

PAHs are formed essentially by solvent pyrolysis or plasmalysis. Depending on the type of solvent and its tendency to carbonize, PAH production can be very high as in the case of benzene or negligible as in the case of alcohols.

When graphite electrodes are replaced with titanium electrodes, polyynes are formed as well in *n*-hexane and in benzene and this is in contrast with the results in methanol and ethanol. However, in the case of Ti electrodes in *n*-hexane and in benzene the polyynes concentration is about two orders of magnitude lower than that achieved with graphite electrodes. The formation of polyynes in these solvents is connected with their tendency to form PAHs and pyrocarbon.

4. Experimental

Graphite rods (99.999% purity, 6 mm diameter × 150 mm length) used as electrodes were obtained from Aldrich. All solvents used were HPLC grades from Fluka or Riedel de Haen. Titanium rods used as electrodes were from Aldrich. The titanium used as electrode had 99.7% purity. Each electrode had a length of 8.5 cm and a diameter of 0.65 cm. Liquid nitrogen was purchased from SIAD gas tecnici.

The electric arc was produced using a DC power supply Cosmo 2000 from K.E.R.T. (Italy). An electric current of 10 A was used with tension in the range of 10–30 V as already discussed previously.[2–5] To work with 20 A, two power supply Cosmo 2000 were used conned in parallel to ignite and sustain the arc in the various liquids studied. As usual[1–5] the electric arc was ignited and sustained by putting in contact the two electrodes and moving them up and down.

Before HPLC analysis or spectroscopy, the solutions were filtered to remove the carbon black particles formed during arcing. Fitration was made on Acrodisc 13LC syringe filters made in PVDF, 13 mm diam. Pore size 0.2 μm.

The electronic absorption spectra were recorded on a Shimadzu UV160A spectrophotometer on filtered solutions in organic solvents.

The high performance liquid chromatographic (HPLC) analysis of the filtered solutions was conducted on a Agilent Technologies System Model 1100 equipped with a DAD and a C-8 column Zorbax. A mixture of CH_3CN/water 80/20 v/v was used as mobile phase and pumped at a rate of 1.5 ml/min into the HPLC column. The concentration of polyynes produced was calculated on the basis of the absorption intensity of each polyyne eluted by the column using the molar extinction coefficients reported in literature.[11]

The PAH were identified on the basis of a standard PAH library supplied by Agilent Technology together with the analytical instrument and software. An additional PAH library was constructed internally using PAH standard solutions obtained from Fluka.

4.1. The electric arc between graphite electrodes submerged in water

The arc was conducted between graphite electrodes submerged in distilled water at 10 A as detailed previously.[1–5] The electronic absorption spectrum of the crude aqueous solution of polyynes and other products showed the following absorption bands: 200, 215 and 226 nm as the most intense. Other weaker bands were observed at 238, 246, 250, 259, 274, 284, 300 and 323 nm.

The HPLC-DAD analysis revealed the presence of the following polyynes: C_6, C_8 and C_{10}. Polyyne C_8 was by far the most abundant product.

4.2. The electric arc in liquid nitrogen between graphite electrodes

A three-necked round bottomed Duran flask of 100 ml equipped with two graphite electrodes arranged in a 'V' geometry was filled with liquid nitrogen and immersed in liquid nitrogen in a Dewar flask. The third neck of the flask was fitted with a valve connected with a Drechsel tube (a gas washing bottle) containing 50 ml of *n*-octane.

The electric arc was ignited and sustained at 9.5 A and 15–30 V (DC current) by putting in contact and by moving slightly up and down the two graphite electrodes submerged into liquid nitrogen into the three-necked flask. The bright light of the arc can be easily observed, and the heat generated by the arc caused the partial vaporization of the liquid nitrogen, which was forced to bubble into the gas-washing bottle attached to the reaction flask. The products formed in the electric arc were hence forced to pass into the octane solvent trap outside the reactor into the Drechsel tube. Periodically samples of the *n*-octane solution were collected and analyzed by electronic absorption spectroscopy and by HPLC-DAD analysis. The following polyynes and cyanopolyynes were identified based on the retention time and the electronic spectra: C_6N_2, C_8H_2, C_8N_2, $C_{10}H_2$, $C_{10}N_2$.

4.3. The electric arc between graphite electrodes in *n*-hexane: evidences of solvent pyrolysis with formation of PAH

The electric arc between graphite electrodes has been conducted in the three-necked round bottomed flask at about 10 A and 15–30 V as detailed elsewhere.[1–5] The flask was filled with *n*-hexane (70 ml) and was externally cooled with a water/ice bath.

The polyyne solution in hexane obtained after 15 min arcing was filtered, poured into 100 ml of an aqueous solution of ammonia (26%), Cu(I)Cl (2.5 g) and hydroxylamine hydrochloride (1.5 g). The organic solution was vigorously shaken with the aqueous solution for a long time and then it was left settling. All polyynes were precipitated as copper salts (acetylides) and could be observed as copper-colored precipitates. The hexane solution still showed absorption bands in the UV spectrum. The non-precipitable polyynes (non-hydrogen capped polyynes) and other species were present in the solvent. The HPLC analysis of the solution revealed the presence of PAH. About 15 components were separated by the C-8 column. One third of them show electronic spectra of ene–ynes or cyclic polyynes. The remaining two thirds of components eluted were identified as PAHs on the basis of their UV spectra. Among the PAHs, naphthalene, acenaphthalene, benzo[*b*]fluoranthene, pyrene and crysene were unequivocally identified.

4.4. The electric arc between graphite electrodes at very high current density

The electric arc between graphite electrodes in hexane was repeated as detailed in the preceding Section 2.3. Instead of using 10 A, by connecting in parallel two power supply, it was possible to work with 20 A at about 32 V. Enhanced formation of carbon black was observed. The filtered hexane solution was analyzed by HPLC-DAD. The polyynes C_6H_2, C_8H_2, $C_{10}H_2$ and $C_{12}H_2$ were clearly identified. Possibly $C_{14}H_2$ was also present. C_8H_2 was dominant in the usual conditions of arcing at 10 A. In these conditions both C_6H_2 and $C_{10}H_2$ appear to have a concentration comparable to that of C_8H_2. The concentration of the PAHs now appears dominant in comparison to the polyyne concentration, exactly the opposite conditions occurred at low current density where the polyynes are the dominant species. About 17 PAHs and other components were eluted by the C-8 column. Among them naphthalene, acenaphthalene and pyrene have been firmly identified. Some ene–yne or cyclic polyyne was present as well.

4.5. Electric arc between titanium electrodes in *n*-hexane

The electric arc between two titanium electrodes submerged in *n*-hexane was conducted in the usual manner (three-necked flask of 100 ml charged with 70 ml of *n*-hexane externally cooled by a water/ice bath; current 10 A, electrodes in contact moved up and down). The electric arc in this specific case appeared much less intense and less bright than in the case of carbon arc made by graphite electrodes under similar conditions. A gradual darkening of the solvent was noticed by progressing with the arcing time. The titanium electrodes were slightly consumed and a depot of carbon black can be observed at the bottom of the flask; its amount increased by the progress of the arcing. The analysis of the filtered solution was made as usual by HPLC-DAD. The following polyynes were clearly identified C_6H_2, C_8H_2, $C_{10}H_2$ with the second being largely dominant. The polyynes are accompanied by PAHs and other by-products. Indene, naphthalene and acenaphthylene were identified among the PAHs.

4.6. The electric arc between titanium electrodes in methanol; a comparison with carbon arc

The electric arc between titanium electrodes submerged in methanol (60 ml) was conducted in the three-necked round bottomed flask of 100 ml, cooled externally with a water/ice bath. The titanium electrodes were arranged in the usual 'V' geometry. The arc was ignited and sustained at 10 A by moving slowly up and down the titanium electrodes kept in contact. After 10 min arcing the polyyne solution obtained was filtered and injected into the HPLC-DAD for analysis. The formation of carbon derived from the carbonization of the solvent was much less significant than in the previous experiment made in *n*-hexane. In this case, no polyynes were detected even in trace amounts by HPLC analysis. Only a mixture of about 12 PAHs was obtained. Among them biphenyl, naphthalene, acenaphthalene, phenanthrene, anthracene, perylene and fluoranthene were identified.

For comparison the titanium electrodes were replaced with graphite electrodes and the above experiment repeated under the same conditions with fresh and pure methanol in the three necked flask. After arcing for 10 min and after filtration the solution obtained was analyzed by HPLC-DAD. The polyyne C_8H_2 was by far the most abundant molecular specie detected followed by $C_{10}H_2$ and C_6H_2. The polyyne $C_{12}H_2$ was present in detectable amounts. The other by-products essentially made by PAHs were present in trace amount relative to C_8H_2. Naphthalene and acenaphthalene were identified.

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Selective sulfonylation of 4-*C*-hydroxymethyl-β-L-threo-pento-1,4-furanose: synthesis of bicyclic diazasugars

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Dedicated to Professor N. S. Narasimhan on the occasion of his 75th birthday

Abstract—Hydroxymethylation of α-D-xylo-pentodialdose **6** using excess formaldehyde and sodium hydroxide in THF–water (one pot aldol and crossed Cannizzaro reactions) followed by hydrogenolysis of C3-*O*-benzyl group afforded triol **8**. The regio-selective α- and β-sulfonylation of hydroxymethyl groups in **8** afforded **9a** (α-sulfonylation) and **14** (β-sulfonylation) in good yield. The cleavage of the 1,2-acetonide functionality, individually in **9a** and **14**, followed by reaction with 1,3-diaminopropane gave in situ formation of sugar aminals, that undergo concomitant nucleophilic displacement of the sulfonyloxy group by amino functionality to give hitherto unknown bicyclic diazasugars **4** and **5**, respectively, with a hydroxymethyl substituent at C-7.

1. Introduction

Azasugars, also known as iminosugars, demonstrate significant glycosidase inhibitory activity[1] and are therefore promising substrates in investigating structure-activity relationship of glycoproteins that play an important role in many biochemical processes including carbohydrate metabolic disorders,[2] viral infection,[3] cancer metastasis,[4] and immune response.[5] The search for new natural and unnatural azasugars thus opened a dynamic research field at the interface between glycobiology and synthetic organic chemistry. This resulted in the development of a new class of azasugars namely bicyclic diazasugrs **1** (Fig. 1). In general, the sugar analogues in which both the ring and glycosidic oxygen atoms have been replaced by nitrogen atoms, in a bicyclic system, are known as bicyclic diazasugars. Naturally occurring kifunensine **2**[6] and nagstatin **3**[7] are the bicyclic diazasugars which showed selectivity in enzyme inhibition,[8] enabling us to understand the processes of the intractable diseases such as nephritis, cancer and immune disorders.

In recent years, improved glycosidase inhibition is being examined for each hydroxyl substituent in azasugars and

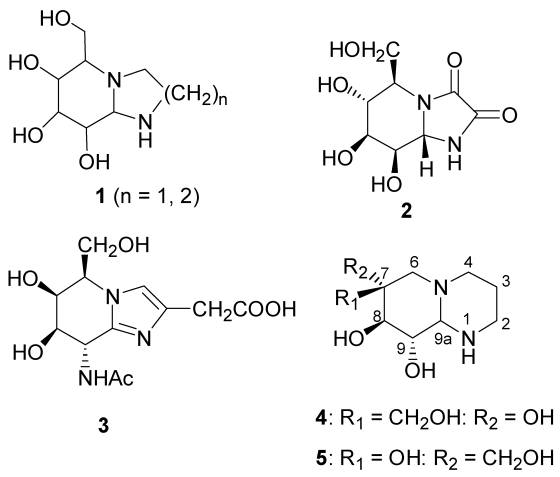

Figure 1. Bicyclic diazasugars.

systematic data of the inhibition of β-glucosidases is documented in the literature.[2,4,9] In this respect, Berges and co-workers have reported a number of new analogues of bicyclic diazasugars with different stereochemical orientation of the –OH functionality at C-6/C-7/C-8/C-9, as well as presence or absence of hydroxymethyl substituent at C-6 and observed that the presence of the hydroxymethyl substituent at C-6 of diazasugars had a significant effect on enzyme substrate activity.[10] Inspired by this observation and as a part of our continuing interest in the synthesis and evaluation of glycosidase inhibitory activities of

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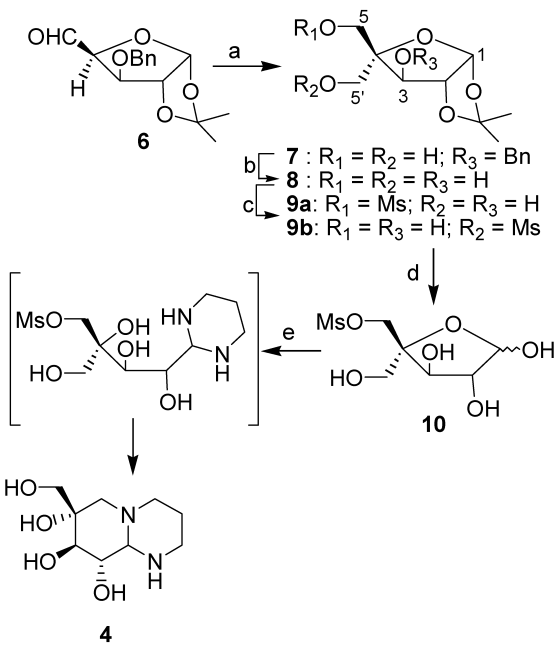
azasugars;[11] we are now reporting an efficient route for the synthesis of hitherto unknown hydroxymethyl bicyclic diazasugars **4** and **5** with both hydroxyl and hydroxymethyl substituents at C-7 (Fig. 1).

2. Results and discussion

2.1. Synthesis of bicyclic diazasugar 4

The aldol-crossed Cannizzaro reactions of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo-petodialdo-1,4-furanose (**6**)[12] with excess formaldehyde and sodium hydroxide in THF–water afforded diol **7** and triol **8** in the ratio 2:1 (Scheme 1). Selective sulfonylation of α- or β-hydroxymethyl group in **7** using either methane- or *p*-toluenesulfonyl chloride, under variety of reaction conditions, and also by use of dibutyltin oxide[13] afforded inseparable mixture in poor selectivity. In an attempt to achieve the selective α- or β-sulfonylation, we performed the reactions with triol **8** in which the bulky –OBn group at C3 is replaced by an –OH group. The formation of **8** (C-3 debenzylated product), as a minor product, under aldol-crossed Cannizzaro reactions in the basic medium is uncommon. We believe that the initially formed aldol-adduct **A** undergoes intra-molecular hydride delivery, assisted by the lone pair of electrons on the benzyloxy oxygen via a six membered transition state, to give intermediate ion pair **B**. Hydration of **B** followed by the loss of benzaldehyde, as shown in Figure 2, affords triol **8**.

The triol **8** in high yield, however, was obtained by hydrogenolysis of **7** with 10% Pd/C in methanol. Treatment of **8** with methanesulfonyl chloride (0.95 equiv.) in pyridine at −10 °C gave a mixture of mono-mesylated products **9a** and **9b** in the 3:1 ratio (Scheme 1). The major product **9a**



Scheme 1. Reagents and conditions: (a) HCHO, NaOH, THF–H_2O, rt, 10 h, (**7**, 41%), (**8**, 21%); (b) 10% Pd/C, MeOH, H_2, rt, 24 h, 93%; (c) MsCl, pyridine, −10 °C, 4 h, (**9a**, 44%); (d) TFA–H_2O, 0 °C to rt, 3 h, 93%; (e) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 81%.

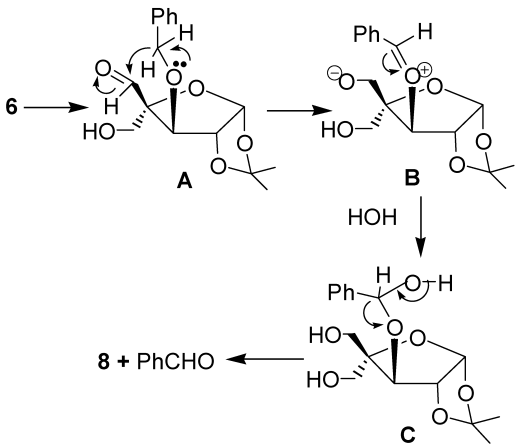


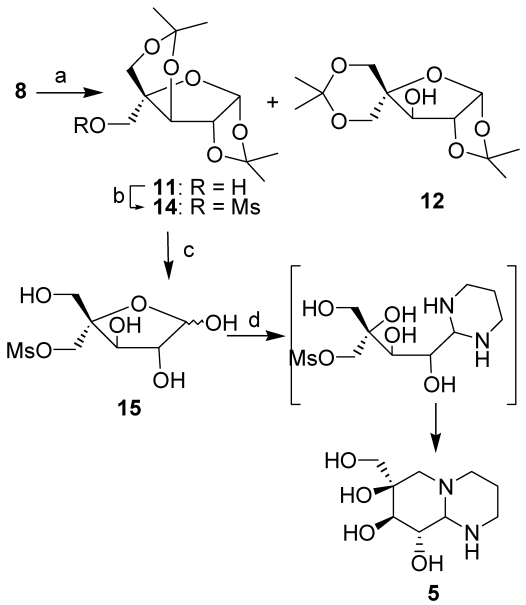
Figure 2. Mechanism for the formation of **8**.

was crystallized out from the binary solvent system (chloroform/hexane=1/1) on keeping the solution at 0 °C for 24 h.[14] The formation of the mono-mesylated product **9a** was evident from the ^{1}H NMR spectrum wherein one of the methylene protons, appeared at δ 4.33 as a AB quartet,[15] were assigned to the $-CH_2OMs$ group while; the other methylene protons, appeared at δ 3.59 as a singlet, were assigned to the $-CH_2OH$ functionality. The assignment of α or β-mesylated product was established by 1D-NOESY experiments. Thus, in compound **9a**, irradiation of a signal at δ 3.59 ($-CH_2OH$) showed NOE for the methylene protons at δ 4.33 ($-CH_2OMs$) and for a singlet at δ 4.19 corresponding to C-3 Hα. This indicated that the mesylation had occurred at the β-CH_2OH group resulting in (4*R*) absolute configuration at C-4. The good selectivity in the favor of **9a** could be attributed to the presence of α-oriented 1,2-acetonide functionality that hindered the mesylation of α-CH_2OH group. In the subsequent steps, the de-protection of the 1,2-acetonide functionality in **9a** (TFA/water=3/2) followed by reaction with 1,3-diaminopropane (1 equiv.) in methanol–water for 12 h afforded diazasugar **4** as a hygroscopic semi-solid in good yield.

2.2. Synthesis of bicyclic diazasugar 5

For the synthesis of C-7 epimeric diazasugar **5**, it was necessary to have α-sulfonyloxy methylene group at C-4 of **8**. This was visualized by prior protection of C3-βOH and C4 β-CH_2OH groups in **8** as an acetonide group.

Therefore, the regio-selective acetonide formation of triol **8** under various reaction conditions (e.g. change of catalyst and solvent) was studied (Scheme 2). As shown in Table 1, the reaction of acetone (as a reagent and solvent) in the presence of *p*-TSA afforded two products **11** and **12** in the ratio 15:85 in 78% yield (entry 1).[16] The use of CSA as a catalyst led to the poor selectivity (entry 2); while the copper sulphate afforded exclusive formation of undesired acetonide **12** albeit in low yield (entry 3). Alternatively, the reaction of triol **8** using 2,2-dimethoxypropane as a reagent was studied. The reaction of triol **8** with 2,2-dimethoxypropane (1 equiv.) in acetone using *p*-TSA as a catalyst, afforded two products **11** and **12** in the ratio 68:32 in 87% yield (entry 4).[17] Again, the use of CSA had no effect on regio-selectivity (entry 5), and in copper sulphate the



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxypropane, MeOH, *p*-TSA, 25 °C, 5 min, 97%; (b) MsCl, pyridine, 0 °C, 4 h, 92%; (c) TFA–H_2O, 0 °C to rt, 3 h, 97%; (d) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 79%.

reaction of **14** with TFA–water (3:2) furnished a hemiacetal, that on reaction with 1,3-diaminopropane in methanol–water gave the bicyclic diazasugar **5** as a semi-solid.

2.3. Conformational assignment

The bicyclic diazasugars are known to exist in $^4C_1$ and $^1C_4$ conformations (Fig. 3).[10] The presence of $-CH_2OH$ and $-OH$ groups on the same carbon atom (C-7), in compounds **4** and **5**, decides their conformation and configuration at C-7. Therefore, three structures **A**, **B** and **C** and **A′**, **B′**, and **C′** for compounds **4** and **5**, respectively, were considered. The coupling constant information, determined from the ^1H NMR spectra and decoupling experiments in D_2O, was used to assign the conformations for compounds **4** and **5** (Table 2). In case of **4**, appearance of a doublet of doublet at δ 3.49 and a doublet at δ 3.40 ($J_{9,9a}$=8.9 Hz; $J_{9,8}$=9.6 Hz) for H-9 and H-8, respectively, clearly indicated the *trans*-diaxial relationship between the H-8, H-9 and H-9a and thus ruled out the possibility of structure **C** with $^1C_4$ conformation. The coupling constant $J_{9,9a}$ was informative for the determination of the configuration at C-9a and the appearance of a doublet at δ 2.95, corresponding to H-9a,

Table 1. Selective acetonide formation in **8**

Entry	Reagent (equiv.)	Solvent	Catalyst	Reaction conditions		Product	Yield[a] (%)	Ratio[b] (**11**:**12**)
				Temperature (°C)	Time			
1	Acetone (30)		*p*-TSA	25	30 min	**11**, **12**	78	15:85
2	Acetone (30)		CSA	25	1.5 h	**11**, **12**	79	42:58
3	Acetone (30)		$CuSO_4$	30	2 days	**12**	19[c]	
4	2,2-Dimethoxy propane (1.1)	Acetone	*p*-TSA	20	5 min	**11**, **12**	87	68:32
5	2,2-Dimethoxy propane (1.1)	Acetone	CSA	25	40 min	**11**, **12**	78	10:90
6	2,2-Dimethoxy propane (1.1)	Acetone	$CuSO_4$	30	15 h	**11**, **12**	55[c]	55:45[17]
7	2,2-Dimethoxy propane (1.1)	DMF	*p*-TSA	25	5 min	**11**, **12**	89	39:61
8	2,2-Dimethoxy propane (1.1)	Methanol	*p*-TSA	25	5 min	**11**	89	100:00

[a] Yields refer to the isolated combined yields after chromatography.
[b] Ratio has been determined by ^1H NMR of the crude mixture.
[c] Starting recovered 40~50%.

reaction was found to be sluggish with poor regio-selectivity (entry 6). The change of solvent to DMF in the presence of *p*-TSA decreased the selectivity (entry 7). However, the use of methanol in the presence of *p*-TSA afforded **11** exclusively in a short reaction time and high yield (entry 8). We believe that a protic solvent like methanol increases the acidity of the *p*-TSA catalyst due to intermolecular hydrogen bonding. Under these conditions the initially formed spirocyclic acetonide **12** is likely to be unstable and the more stable bicyclic acetonide, derived from primary and secondary hydroxyl, affords acetonide **11** as the only isolable product.[18] This fact was confirmed by recording the ^1H NMR of **12** in methanol-d_4 before and after addition of catalytic amount of *p*-TSA wherein compound **12** was found to be completely converted to **11** within 5 min.

In the subsequent steps, the mesylation of the α-CH_2OH in 1,2:3,5-bis-acetonide **11** afforded the mesylate **14** in good yield (Scheme 2). The α-mesylated product **14** was confirmed by 1D-NOESY spectra wherein irradiation of signal at δ 4.17 for C3-Hα showed NOE for the methylene protons at δ 4.39 and 4.53 (C4-α-CH_2OMs). In the next step,

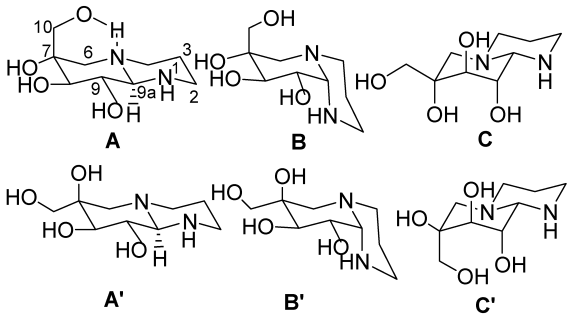


Figure 3. Conformational structures of **4** and **5**.

Table 2.

Compound	*J* (Hz)					
	$J_{2a,2e}$	$J_{4a,4e}$	$J_{6a,6e}$	$J_{8,9}$	$J_{9,9a}$	$J_{10a,10b}$
4	12.3	11.4	13.2	9.6	8.9	9.7
5	11.4	12.3	13.0	9.6	8.8	

with large coupling constant for ($J_{9,9a}$=8.9 Hz) indicated the structure **A** with $^4C_1$ conformation. The initial geometry in the precursor **9a** ensures that in the product **4** the −OH substituents at C-9, C-8 and C-8, C-7 should be *trans* and therefore the $-CH_2OH$ substituent was assigned the axial orientation with (7*S*) absolute configuration. Furthermore, we believe that the intra-molecular hydrogen bonding between $-CH_2OH$ and a lone pair of electrons on a fused ring nitrogen atom, in a six-membered transition state, stabilize the conformation **A**.

Since the ^{1}H NMR spectrum of **5** is different from **4**, it was thought that **5** could exist in different conformation. However, the appearance of one doublet of doublet at δ 3.59 ($J_{9,9a}$=8.9 Hz and $J_{9,8}$=9.8 Hz) and a doublet at δ 3.42 ($J_{8,9}$=9.6 Hz) for H-9 and H-8, respectively, indicated the *trans*-diaxial relationship of H-8, H-9 and H-9a. In addition, the appearance of a doublet at δ 3.21 for H-9a with large coupling constant ($J_{9a,9}$=8.9 Hz) indicated the $^4C_1$ conformation as shown in structure **A′**. Since the relative stereochemistry of substituents at C-9, C-8 and C-7 in precursor **15** is retained in the product formation, the $-CH_2OH$ substituent was assigned the equatorial orientation with (7*R*) absolute configuration.

2.4. Conclusion

In conclusion, we have demonstrated the utility of the aldol-crossed Cannizzaro reactions of α-D-xylo-pentodialdose **6** for the synthesis of hitherto unknown diazasugars **4** and **5** with hydroxymethylene substituents. In addition, a convenient method for the selective acetonide formation between the primary and secondary hydroxyl functionalities, in the presence of two primary hydroxymethylene groups, was developed using 2,2-dimethoxypropane and *p*-TSA in the presence of methanol as a solvent. A study of orientation of the hydroxymethylene group at C-7, in **4** and **5**, on the glycosidase inhibitory activity is in progress.

3. Experimental

3.1. General

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR as a thin film or in nujol mull or using KBr pellets and are expressed in cm^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in Hz. The assignments of the signals were confirmed by decoupling, DEPT and ^{1}H–^{1}H COSY experiments. Elemental analyses were carried out with C,H-analyzer. Optical rotations were measured using a Bellingham Stanley-ADP digital polarimeter using sodium light (D line 589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh) and in some cases with ammonia solution. Amberlite A-21 anion exchange resin (OH^- form, weak base) was used for neutralization. The reactions were carried out in oven-dried glassware under dry N_2. Methanol, pyridine, THF, were purified and dried before use. Petroleum ether (PE) that was used is a distillation fraction between 40–60 °C. 1,3-Diaminopropane and 10% Pd/C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves-washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure. The suitably protected α-D-xylopentodialdose **6** was prepared as per the reported procedure.[12]

3.1.1. 1,2-*O*-Isopropylidene-3-*O*-benzyl-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (7) and 1,2-*O*-isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (8). To a solution of the aldehyde **6** (1.0 g, 3.60 mmol) in THF–water (30 mL, 2:1) was added sodium hydroxide (0.288 g, 7.20 mmol) in water (10 mL), formaldehyde solution (37–41% w/v, Merck) (0.238 g, 7.925 mmol), respectively and the reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was neutralized with formic acid (0.5 mL) and evaporated to dryness. The residue thus obtained was extracted with ethyl acetate (3×30 mL), dried ($MgSO_4$) and concentrated. Purification of syrupy residue by column chromatography (20% ethyl acetate/PE) gave diol **7** (0.456 g, 41%) as a pale yellow solid, mp 70–71 °C; [Found: C, 62.08; H, 7.31. $C_{16}H_{22}O_6$ requires C, 61.92; H, 7.14%]; R_f (60% ethyl acetate/*n*-hexane) 0.34; $[\alpha]_D$=−42.5 (*c* 0.8, $CHCl_3$); ν_{max} (KBr) 3400–3250 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (3H, s, *Me*), 1.54 (3H, s, *Me*), 2.35–2.60 (2H, br s, O*H*, exchange with D_2O), 3.57–3.77 (4H, m, 2×CH_2OH), 4.10 (1H, d, *J*=1.6 Hz, *H*3), 4.54 (1H, d, *J*=11.8 Hz, *O*-CH_2Ph), 4.74 (1H, d, *J*=11.8 Hz, *O*-CH_2Ph), 4.76 (1H, dd, *J*=1.6, 4.4 Hz, *H*2), 6.00 (1H, d, *J*=4.4 Hz, *H*1), 7.26–7.39 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.8, 27.3, 63.1, 63.4, 72.5, 84.7, 85.7, 89.8, 104.8, 113.0, 127.5, 128.1, 128.5, 136.7.

Further elution with 60% ethyl acetate/PE gave **8** (0.166 g, 21%) as white solid, mp 98–99 °C (lit.[19a] mp 98–100 °C).

3.1.2. 1,2-*O*-Isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (8). Diol **7** (1.0 g, 3.22 mmol) and 10% Pd/C (0.22 g) in dry methanol was hydrogenolyzed under hydrogen (at 78 psi) at 25 °C for 24 h. The reaction mixture was filtered through celite, washed with methanol, concentrated and purified by chromatography (60% ethyl acetate/PE) to give triol **8** (0.652 g, 93%) as a white solid, mp 98–99 °C (lit.[19a] mp 98–100 °C); [Found: C, 49.19; H, 7.48. $C_9H_{16}O_6$ requires C, 49.08; H, 7.32]; R_f (60% ethyl acetate/*n*-hexane) 0.15; $[\alpha]_D$=−5.71 (*c* 0.35, MeOH) (lit.[19b] $[\alpha]_D$=−7.5, *c* 4, ethanol); ν_{max}(KBr) 3480–3300 (br band) cm^{-1}; δ_H (300 MHz, D_2O) 1.22 (3H, s, *Me*), 1.42 (3H, s, *Me*), 3.42–3.70 (4H, m, 2×CH_2OH), 4.11 (1H, br s, *H*3), 4.64 (1H, obscure with D_2O signal, *H*2) (confirmed by ^{1}H–^{1}H COSY experiments), 5.89 (1H, d, *J*=4.4 Hz, *H*1); δ_C (75 MHz, D_2O) 25.6, 26.1, 60.6, 61.2, 76.0, 87.5, 90.7, 104.5, 113.5.

3.1.3. 1,2-*O*-Isopropylidene-4-(*R*)-*C*-(hydroxymethyl)-5-*O*-methanesulfonyl-β-L-threo-pento-1,4-furanose (9a). To a cooled solution of triol **8** (1.0 g, 4.54 mmol) at −10 °C in dry pyridine (1.5 mL) was added methanesulfonyl chloride (0.49 g, 4.27 mmol) and stirring was

continued at −10 °C for 4 h. The reaction was decomposed by addition of ice water. Pyridine was co evaporated with toluene (2×3 mL). Chromatographic purification (10% ethyl acetate/PE) gave a mixture of monomesyl derivatives **9a** and **9b** (1.10 g, 81%). The isomeric mixture was dissolved in chloroform–hexane (30 mL, 1:1) and refrigerated at 0 °C for 24 h to afford **9a** (0.594 g, 44%) as a white solid, mp 139–140 °C; [Found: C, 40.19; H, 6.33. $C_{10}H_{18}SO_8$ requires C, 40.26; H, 6.08]; R_f (60% ethyl acetate/*n*-hexane) 0.22; $[\alpha]_D$=−53.3 (*c* 0.15, MeOH); ν_{max} (nujol) 3460–3200 (br), 1356 cm^{-1}; δ_H (300 MHz, D_2O) 1.23 (3H, s, *Me*), 1.46 (3H, s, *Me*), 3.12 (3H, s, *Me*), 3.59 (2H, s, C*H*$_2$OH), 4.19 (1H, br s, *H*3), 4.33 (2H, AB quartet, *J*=10.5 Hz, C*H*$_2$OMs), 4.68 (1H, obscure with D_2O signal, *H*2) (confirmed by $^1H-^1H$ COSY experiments), 5.94 (1H, d, *J*=4.1 Hz, *H*1); δ_C (75 MHz, D_2O) 24.8, 25.4, 36.5, 59.4, 67.8, 75.0, 86.7, 88.5, 104.9, 113.4. [For NOE experiment, 0.011 g of **9a** was dissolved in 0.8 mL of D_2O and the solution was purged with N_2 for 15 min].

3.1.4. (7*S*,8*R*,9*S*,9a*R*)-Octahydro-7-hydroxymethyl-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]pyrimidine (4). A solution of **9a** (0.5 g, 1.67 mmol) in TFA–H_2O (6 mL, 3:2) was stirred at 25 °C for 3 h. TFA was evaporated in vacuo and co evaporated with water (2×2 mL). The hemiacetal **10** thus obtained (0.398 g, 93%) was dissolved in water (6 mL) and 1,3-diaminopropane (0.057 g, 0.769 mmol; 0.5 equiv.) was added carefully with stirring. After 30 min a second lot of 1,3-diaminopropane (0.057 g, 0.5 equiv.) in MeOH (10 mL) was added dropwise at room temperature. After 12 h amberlite A-21 anion exchange resin (OH^- form, weak base) was added to neutralize methanesulfonic acid. The solution was filtered and the solvent was evaporated to give a gum that was dissolved in ethanol (1 mL) and precipitated with diethyl ether (15 mL). The precipitate thus obtained was filtered, washed with diethyl ether and dried. Chromatographic purification of the residue with chloroform/methanol/ammonia (80/19/1) afforded **4** (0.272 g, 81%) as a hygroscopic semi-solid mass; [Found: C, 35.25; H, 9.01. $C_9H_{18}N_2O_4{\cdot}5H_2O$ requires C, 35.06; H, 9.15]; R_f (66% methanol/chloroform) 0.14; $[\alpha]_D$=−4.0 (*c* 0.5, MeOH); ν_{max} (nujol) 3460–3150 (br), 2858 and 2735 cm^{-1}; δ_H (300 MHz, D_2O) 1.62–1.78 (2H, m, *H*3), 2.24 (1H, ddd, *J*=11.4, 10.5, 4.1 Hz, *H*2a), 2.32 (1H, d, *J*=3.2 Hz, *H*6a), 2.67 (1H, ddd, *J*=12.3, 10.5, 4.3 Hz, *H*4a), 2.71 (1H, d, *J*=13.2 Hz, *H*6e), 2.88 (1H, ddd, *J*=11.4, 3.8, 3.0 Hz, *H*2e), 2.95 (1H, d, *J*=8.9 Hz, *H*9a), 3.17 (1H, br d, *J*=12.3 Hz, *H*4e), 3.40 (1H, d, *J*=9.6 Hz, *H*8), 3.46 (2H, s, C*H*$_2$OH), 3.49 (1H, dd, *J*=9.8, 8.9 Hz, *H*9); δ_C (75 MHz, D_2O) 23.0, 42.9, 52.3, 57.6, 63.8, 71.0, 72.3, 72.4, 77.4.

3.1.5. 1,2:3,5-Di-*O*-isopropylidene-4-(*R*)-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (11). To a suspension of triol **8** (0.5 g, 2.27 mmol) in methanol (10 mL) was added 2,2-dimethoxypropane (0.380 g, 2.49 mmol) followed by *p*-toluenesulfonic acid (0.01 g, cat.) at 20 °C. The mixture became homogeneous after 5 min and tlc analysis indicated that the reaction was complete. The solution was concentrated, diluted with DCM (20 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4) and concentrated. Chromatography with 5% ethyl acetate/PE gave **11** (0.524 g, 89%) as colourless needles, mp 94–95 °C; [Found: C, 55.58; H, 7.92. $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.74]; R_f (33% ethyl acetate/*n*-hexane) 0.40; $[\alpha]_D$=+32.0 (*c* 0.25, $CHCl_3$); ν_{max}(KBr) 3500–3410 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.34 (3H, s, *Me*), 1.39 (3H, s, *Me*), 1.41 (3H, s, *Me*), 1.58 (3H, s, *Me*), 3.68 (1H, d, *J*=12.1 Hz, OC*H*$_2$), 3.70 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.86 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.93 (1H, d, *J*=12.1 Hz, OC*H*$_2$), 4.14 (1H, s, *H*3), 4.64 (1H, d, *J*=4.1 Hz, *H*2), 6.06 (1H, d, *J*=4.1 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 21.5, 25.5, 26.1, 26.3, 63.0, 63.8, 74.7, 85.4, 85.7, 99.1, 105.8, 112.2.

3.1.6. 1,2:5,5′-Di-*O*-isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (12). *p*-Toluenesulfonic acid (0.01 g, cat.) was added to a suspension of triol **8** (0.4 g, 1.82 mmol) and 2,2-dimethoxypropane (0.208 g, 1.99 mmol) in acetone (5 mL) at 20 °C. The mixture became homogeneous after 5 min and tlc analysis indicated that the reaction was complete. The solution was concentrated, diluted with DCM (20 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4) and concentrated. The crude product on chromatography with 5% ethyl acetate/PE gave **11** (0.279 g, 59%). Further elution with 10% ethyl acetate/PE gave **12** (0.132 g, 28%) as a clear syrup; [Found: C, 55.66; H, 7.86. $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.74]; R_f (33% ethyl acetate/*n*-hexane) 0.39; $[\alpha]_D$=−10.7 (*c* 1.5, $CHCl_3$); ν_{max} (nujol) 3418 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (3H, s, *Me*), 1.40 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.51 (3H, s, *Me*), 3.30–3.51 (1H, br s, exchange with D_2O, O*H*), 3.74 (1H, d, *J*=12.0 Hz, OC*H*$_2$), 3.91 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.99 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 4.03 (1H, d, *J*=12.0 Hz, OC*H*$_2$), 4.52 (1H, s, *H*3), 4.60 (1H, d, *J*=4.0 Hz, *H*2), 5.89 (1H, d, *J*=4.0 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 19.3, 25.5, 26.4, 27.5, 61.7, 65.7, 75.3, 82.0, 86.7, 98.2, 105.0, 111.9.

3.1.7. 1,2:3,5-Di-*O*-isopropylidene-4-(*S*)-*C*-(methanesulfonyloxymethyl)-β-L-threo-pento-1,4-furanose (14). To a solution of **11** (0.2 g, 0.77 mmol) in anhydrous pyridine (0.5 mL) was added methanesulfonyl chloride (0.106 g, 0.93 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Usual work-up and chromatography (10% ethyl acetate/PE) provided monomesylate **14** (0.24 g, 92%) as a white solid, mp 99–100 °C; [Found: C, 46.23; H, 6.57. $C_{13}H_{22}SO_8$ requires C, 46.14; H, 6.55]; R_f (25% ethyl acetate/*n*-hexane) 0.38; $[\alpha]_D$=+10.0 (*c* 0.2, $CHCl_3$); ν_{max}(KBr) 1352 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 ((3H, s, *Me*), 1.40 (3H, s, *Me*), 1.42 (3H, s, *Me*), 1.64 (3H, s, *Me*), 3.17 (3H, s, *Me*), 3.72 (1H, d, *J*=12.6 Hz, OC*H*$_2$), 3.98 (1H, d, *J*=12.6 Hz, OC*H*$_2$), 4.17 (1H, s, *H*3), 4.39 (1H, d, *J*=11.1 Hz, C*H*$_2$OMs), 4.53 (1H, d, *J*=11.1 Hz, C*H*$_2$OMs), 4.64 (1H, d, *J*=3.8 Hz, *H*2), 6.09 (1H, d, *J*=3.8 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 21.0, 25.3, 26.0, 26.2, 38.1, 62.1, 69.7, 74.4, 82.9, 84.8, 99.0, 106.5, 112.5.

3.1.8. (7*R*,8*R*,9*S*,9a*R*)-Octahydro-7-hydroxymethyl-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]pyrimidine (5). A solution of **14** (0.135 g, 0.326 mmol) in TFA-H_2O (4 mL, 3:2) was stirred for 3 h. TFA was evaporated under vacuum and co evaporated with water (3×2 mL) to leave a hemiacetal **15** (0.106 g, 97%). The hemiacetal **15** (0.105 g, 0.314 mmol) was dissolved in water (3 mL) and 1,3-diaminopropane (0.012 g, 0.161 mmol) (0.5 equiv.) was

added carefully with stirring. After 0.5 h extra 0.5 equiv. of 1,3-diaminopropane (0.012 g, 0.161 mmol) in MeOH (7 mL) was added dropwise at room temperature. Stirring was continued for 12 h and the solution was treated with amberlite A-21 anion exchange resin (OH^- form, weak base) to remove sulfonic acid. The solvent was filtered and evaporated to give a gum that was dissolved in ethanol (1 mL) and then ether was added with shaking. The precipitate thus obtained again washed with ether and dried. Column chromatographic purification of the residue with chloroform/methanol/ammonia (Merck, 25% solution)=70/29/1 afforded **5** (0.054 g, 79%) as a hygroscopic semi-solid mass; [Found: C, 37.71;H, 9.53. $C_9H_{18}N_2O_4{\cdot}4H_2O$ requires C, 37.23; H, 9.02%]; R_f (66% methanol/chloroform) 0.10; $[\alpha]_D$=+26.7 (*c* 0.15, MeOH); ν_{max} (nujol) 3500–3220 (br), 2832 and 2737 cm^{-1}; δ_H (300 MHz, D_2O) 1.72–1.87 (2H, m, *H*3), 2.34 (1H, ddd, *J*=11.4, 10.5, 4.1 Hz, *H*2a), 2.43 (1H, d, *J*=13.2 Hz, *H*6a), 2.80 (1H, d, *J*=13.2 Hz, *H*6e), 2.80–3.02 (2H, m, *H*2e and *H*4a), 3.21 (1H, d, *J*=8.9 Hz, *H*9a), 3.33 (1H, br d, *J*=12.3 Hz, *H*4e), 3.42 (1H, d, *J*=9.6 Hz, *H*8), 3.46 (2H, s, C*H*$_2$OH), 3.59 (1H, dd, *J*=9.8, 8.9 Hz, *H*9); δ_C (75 MHz, D_2O) 21.6, 42.7, 51.4, 57.4, 63.5, 70.1, 71.9, 72.4, 76.7.

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14. The mother liquor was found to be a mixture of **9a** and **9b**. Attempts to separate the mixture by flash chromatography were unsuccessful.
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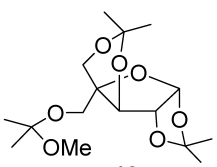
16. The structure of compounds **11** and **12** were confirmed by their conversion to monotosylate derivatives and NMR studies. In the tosylate derivative of **12** H-3 showed considerable downfield shift.



13

17. In the reactions of 2,2-dimethoxypropane (entry 4) we isolated ~10% of **13** as a white solid, mp 72–73 °C; [Found: C, 58.03; H, 8.31. $C_{16}H_{28}O_7$ requires C, 57.81;H, 8.49%]; R_f (33% ethyl acetate/*n*-hexane) 0.75; $[\alpha]_D=-13.3$ (*c* 0.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3+D_2O$) 1.28 (3H, s, *Me*), 1.32 (3H, s, *Me*), 1.33 (3H, s, *Me*), 1.35 (3H, s, *Me*), 1.42 (3H, s, *Me*), 1.56 (3H, s, *Me*), 3.20 (3H, s, O*Me*), 3.31 (1H, d, *J*=12.2 Hz, CH_2), 3.66 (1H, d, *J*=11.5 Hz, CH_2), 3.70 (1H, d, *J*=11.5 Hz, CH_2), 4.12 (1H, d, *J*=12.2 Hz, CH_2), 4.39 (1H, s, *H*3), 4.56 (1H, d, *J*=4.0 Hz, *H*2), 5.99 (1H, d, *J*=4.0 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 19.8, 24.3 (strong), 25.3, 26.0, 27.6, 48.8, 61.1, 62.7, 74.2, 82.2, 85.7, 97.6, 100.0, 105.5, 111.7. This **13** on treatment with *p*-TSA in methanol gave **11** only.
18. The formation of acetonide between α-CH_2OH and βC3-OH (*trans* fusion) is less favored than between β-CH_2OH and βC3-OH (*cis* fusion) and also hindered due to the 1,2-*O*-isopropylidene functionality.
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Synthetic studies of benzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline

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Abstract—6,11-Dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline-5,8-dione (**6**), which possesses a unique heterocyclic ring system similar to that in plakinidines A–D (**1**–**4**), was synthesized from 2-acetyl-3′-nitrodiphenylamine (**16**) in nine steps.

1. Introduction

A series of structurally unique pentacyclic aromatic alkaloids have been obtained from marine organisms. In 1990, the isolation and structure elucidation of new cytotoxic alkaloids, plakinidines A (**1**), B (**2**) and C (**3**), from a *Plakortis* sponge were reported.[1] ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallographic analysis revealed that the structure of **1** is 9,10-dihydro-7-(methylamino)-benzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthrolin-8(11*H*)-one. Plakinidines B (**2**) and C (**3**) are the *N*-methyl and 9,10-didehydro derivatives of **1**, respectively. Furthermore, plakinidine D (**4**) was isolated from the ascidian *Didemnum rubeum*.[2] Those alkaloids possess a unique heterocyclic parent ring system, benzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline (**5**). In this report, we describe the synthesis of 6,11-dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline-5,8-dione (**6**) (Fig. 1).

2. Results and discussion

First, we attempted to prepare **6** via benzo[*b*][1,10]phenanthroline (**12**) (Scheme 1). 2-Acetyl-2′-nitrodiphenylamine[3] (**7**) was heated in sulfuric acid–acetic acid to give 9-methyl-4-nitroacridine (**8**). 4-Amino-9-methylacridine (**9**), which was obtained by the catalytic reduction of **8**, was treated with 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione[4] to give Meldrum's acid derivative (**10**).

Nitration of **10** with fuming nitric acid in acetic acid at rt gave the desired nitro compound (**11**) in only 36% yield. Treatment of **10** with copper(II) nitrate[5] in acetic anhydride in the presence of ascorbic acid at 70 °C gave **11** in 79% yield. The structure of **11** was confirmed by ^{1}H NMR measurements. No nuclear Overhauser effect (NOE) was observed between the protons at 2.95 ppm (C_9–CH_3) and all other protons except that at 8.34 ppm (C_8–H).

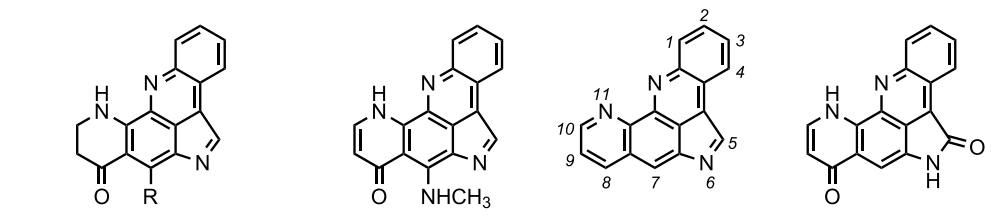

Figure 1.

Keywords: Acridine; Phenanthroline; Nitration; Cyclization.
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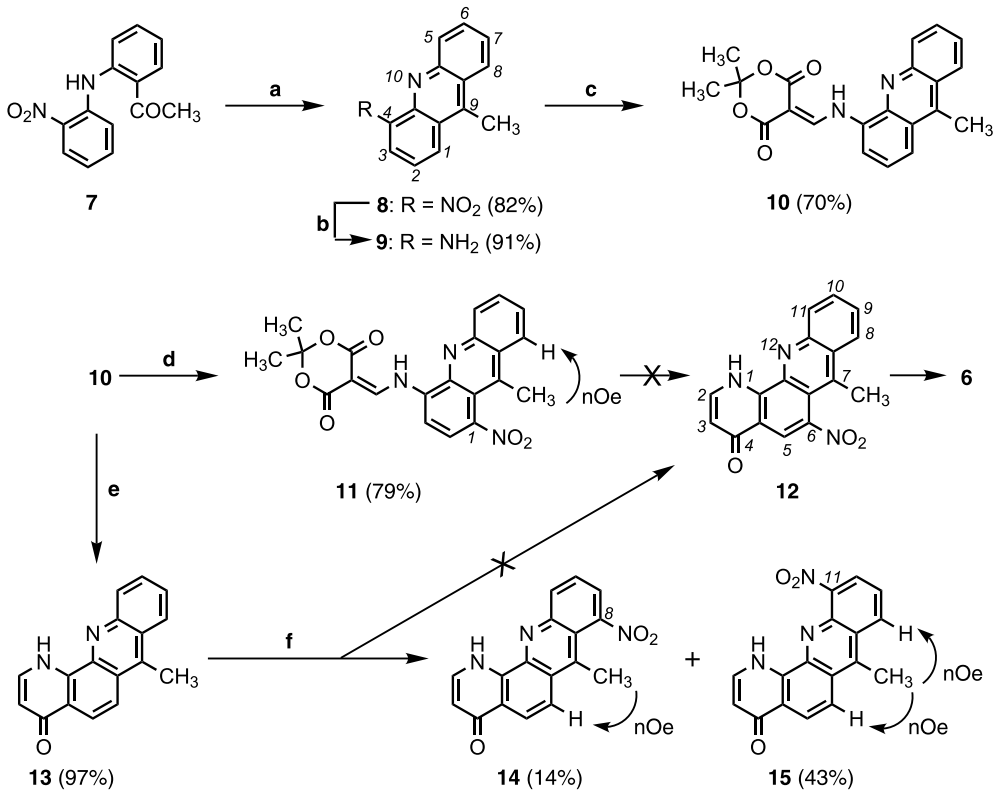


Scheme 1. (a) H_2SO_4, CH_3CO_2H, 95–105 °C, 30 min; (b) H_2, 10% Pd–C, $CH_3CO_2C_2H_5$, 20 min; (c) (i) Meldrum's acid, $CH(OCH_3)_3$, reflux, 1 h, (ii) **9**, $CH(OCH_3)_3$, reflux, 20 min; (d) $Cu(NO_3)_2{\cdot}3H_2O$, $(CH_3CO)_2O$, ascorbic acid, 70 °C, 9 h; (e) $(C_6H_5)_2O$, reflux, 15 min; (f) KNO_3, H_2SO_4–fum. H_2SO_4 (4:1), CH_3NO_2, −25 °C, 39 h.

All attempts at the thermal cyclization of **11** to **12** in diphenyl ether[4] at various temperatures met with failure (e.g., 250–260 °C: a complex mixture; 200–210 °C: no reaction).

On the other hand, treatment of **10** at 250–260 °C for 15 min gave the cyclized product (**13**) in quantitative yield. Nitration of **13** with copper(II) nitrate in acetic anhydride in the presence of ascorbic acid at 70 °C gave a complex mixture. Treatment of **13** with potassium nitrate in sulfuric acid–oleum at −25 °C gave 8-nitro- (**14**) and 11-nitrobenzo[*b*][1,10]phenanthrolinone (**15**) in 14 and 43% yields, respectively, but no 6-nitrobenzo[*b*][1,10]-phenanthrolinone (**12**). The structures of **14** and **15** were confirmed by ^{1}H NMR measurements. No NOE was observed between the protons at 2.95 ppm (C_7–CH_3) and all other protons except that at 8.08 ppm (C_6–H) for **14**. In contrast, NOE was observed between (a) the protons at 3.25 ppm (C_7–CH_3) and 8.11 ppm (C_6–H) and (b) the protons at 3.25 ppm (C_7–CH_3) and 8.60 ppm (C_8–H) for **15**.

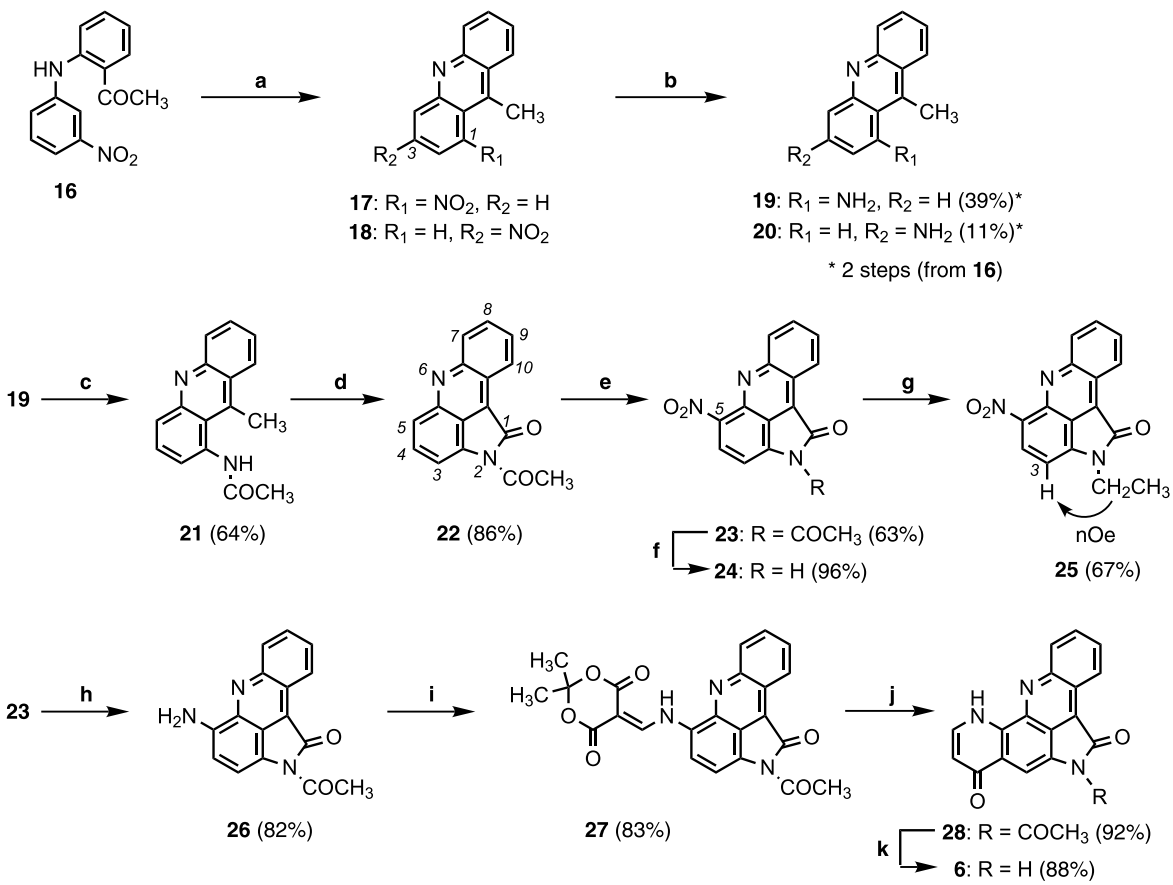
The results demonstrated that it is difficult to prepare **6** via benzo[*b*][1,10]phenanthrolinone (**12**). Thus, we examined another route to **6**, as shown in Scheme 2.

2-Acetyl-3′-nitrodiphenylamine[6] (**16**) was heated in sulfuric acid–acetic acid to afford 9-methyl-1-nitroacridine (**17**) and 9-methyl-3-nitroacridine (**18**). As the separation of the isomeric mixture (**17** and **18**, approximately 2:1 ratio) was difficult (it was possible only by column chromatography using a large amount of silica gel), the mixture was reduced with tin(II) chloride in hydrochloric acid to give 1-aminoacridine (**19**) and 3-aminoacridine (**20**) in 39 and 11% yields from **16**, respectively.

Oxidation of **21**, which was obtained by acetylation of **19**, with selenium dioxide[7] gave a cyclized product, pyrrolo[2,3,4-*kl*]acridine (**22**) in 86% yield. Nitration of **22** with potassium nitrate in sulfuric acid at 0–5 °C afforded 5-nitropyrrolo[2,3,4-*kl*]acridine (**23**), the structure of which was confirmed by ^{1}H NMR measurement of the *N*-ethyl compound (**25**) that was obtained from **23** in two steps. NOE was observed between the protons at 4.07 ppm (CH_2CH_3) and 6.93 ppm (C_3–H).

Amine **26**, which was obtained by reducing **23** with sodium hydrosulfite in aqueous tetrahydrofuran, was treated with 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione to give Meldrum's acid derivative (**27**). Thermal cyclization of **27** in diphenyl ether followed by deacetylation with aqueous sulfuric acid furnished 6,11-dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline-5,8-dione (**6**) in 81% yield (from **27**).

Thus, the compound (**6**) possessing a unique pentacyclic ring system was synthesized from 2-acetyl-3′-nitrodiphenylamine (**16**) in nine steps. The synthetic studies of plakinidine C (**3**) are in progress.



Scheme 2. (a) H_2SO_4, CH_3CO_2H, 110–120 °C, 20 min; (b) $SnCl_2{\cdot}2H_2O$, HCl, 70–80 °C, 3 h; (c) $(CH_3CO)_2O$, rt, 14 h; (d) SeO_2, dioxane, 70–75 °C, 1 h; (e) KNO_3, H_2SO_4, 0–5 °C, 1 h; (f) 10% H_2SO_4, dioxane, 80 °C, 30 min; (g) C_2H_5I, K_2CO_3, acetone, reflux, 1 h; (h) $Na_2S_2O_4$, THF–H_2O, rt, 1 h; (i) (i) Meldrum's acid, $CH(OCH_3)_3$, reflux, 1 h, (ii) **26**, $CH(OCH_3)_3$, reflux, 30 min; (j) $(C_6H_5)_2O$, reflux, 10 min; (k) 20% H_2SO_4, dioxane, 90 °C, 20 min.

3. Experimental

3.1. General

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ (unless otherwise specified) at 270.05 MHz with a JEOL JNM-EX 270 spectrometer and chemical shifts were recorded in δ values relative to an internal standard, tetramethylsilane. Mass spectra were recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were carried out on a Perkin–Elmer Model 240B elemental analyzer. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed initially with a rotary evaporator and finally under high vacuum. Column (or flash) chromatography was performed with E. Merck silica gel 60 (230–400 mesh).

3.1.1. 9-Methyl-4-nitroacridine (8). A solution of 2-acetyl-2′-nitrodiphenylamine (**7**, 0.152 g, 0.59 mmol) and sulfuric acid (0.6 mL) in acetic acid (7.5 mL) was heated at 95–105 °C for 30 min. After cooling, the reaction mixture was diluted with water (30 mL) and basified with aqueous ammonia. The precipitated yellow crystals were collected by filtration, dried, and chromatographed (ethyl acetate–hexane 1:4–1:2) to give **8** (0.116 g, 82%) as a yellow solid. Mp 154–156 °C (ethyl acetate–hexane). MS *m*/*z* (%): 238 (M^+, 100), 192 (39), 180 (24). High-resolution MS Calcd for $C_{14}H_{10}N_2O_2$: 238.0742. Found: 238.0741. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.75; H, 4.28; N, 11.51. ^{1}H NMR δ: 3.19 (3H, s, CH_3), 7.59 (1H, dd, J=8.9, 7.3 Hz, C_2–H), 7.63–7.88 (2H, m, C_6–H, C_7–H), 8.05 (1H, dd, J=7.3, 1.3 Hz, C_3–H), 8.22–8.32 (2H, m, C_5–H, C_8–H), 8.48 (1H, dd, J=8.9, 1.3 Hz, C_1–H).

3.1.2. 4-Amino-9-methylacridine (9). Nitroacridine **8** (126 mg, 0.53 mmol) in ethyl acetate (40 mL) containing 10% palladium on carbon (70 mg) was catalytically hydrogenated at 1 atm for 20 min. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed (ethyl acetate–hexane, 1:1) to give **9** (100 mg, 91%) as an orange solid. Mp 92–94 °C (hexane). MS *m*/*z* (%): 208 (M^+, 100). High-resolution MS Calcd for $C_{14}H_{12}N_2$: 208.1000. Found: 208.0996. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 81.07; H, 5.95; N, 13.43. ^{1}H NMR δ: 3.08 (3H, s, CH_3), 5.1–5.5 (2H, br, NH_2), 6.94 (1H, dd, J=7.3, 1.0 Hz, C_3–H), 7.36 (1H, dd, J=8.9, 7.3 Hz, C_2–H), 7.53 (1H, ddd, J=7.6, 6.6, 1.3 Hz, C_6–H or C_7–H), 7.57 (1H, dd, J=8.9, 1.0 Hz, C_1–H), 7.71 (1H, ddd, J=8.6, 6.6, 1.3 Hz, C_7–H or C_6–H), 8.15–8.25 (2H, m, C_5–H, C_8–H).

3.1.3. 5-[[(9-Methylacridin-4-yl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (10). After Meldrum's acid (64 mg, 0.44 mmol) in trimethyl orthoformate (7 mL) was refluxed for 1 h, a solution of **9** (50 mg, 0.24 mmol) in trimethyl orthoformate (4 mL) was added. The resulting

solution was refluxed for 20 min and then evaporated. The residue was chromatographed ($CHCl_3$–hexane, 1:5) to give **10** (61 mg, 70%) as a yellow solid. Mp 240–242 °C (CH_2Cl_2–ether). MS *m/z* (%): 362 (M^+, 27), 304 (94), 276 (59), 232 (100), 231 (65). High-resolution MS Calcd for $C_{21}H_{18}N_2O_4$: 362.1266. Found: 362.1263. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.29; H, 5.10; N, 7.59. ^{1}H NMR δ: 1.81 (6H, s, $C(CH_3)_2$), 3.15 (3H, s, C_9–CH_3), 7.58 (1H, dd, *J*=8.9, 7.3 Hz, C_2–H), 7.63 (1H, ddd, *J*=7.9, 6.6, 1.3 Hz, C_7–H), 7.71 (1H, dd, *J*=7.3, 1.0 Hz, C_3–H), 7.82 (1H, ddd, *J*=8.6, 6.6, 1.3 Hz, C_6–H), 8.11 (1H, dd, *J*=8.9, 1.0 Hz, C_1–H), 8.27 (1H, d, *J*=7.9 Hz, C_8–H), 8.36 (1H, d, *J*=8.6 Hz, C_5–H), 8.98 (1H, d, *J*=14.9 Hz, CH=), 13.30 (1H, d, *J*=14.9 Hz, NH).

3.1.4. 5-[[(9-Methyl-1-nitroacridin-4-yl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (11). (a) Fuming nitric acid (2.5 mL) was added dropwise to **10** (30 mg, 0.083 mmol) in acetic acid (7.5 mL). The resulting mixture was stirred for 5 h, diluted with water (75 mL), and extracted with $CHCl_3$ (3×40 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$) to give **11** (12 mg, 36%) as a yellow solid. Mp >250 °C. MS *m/z* (%): 407 (M^+, 17), 349 (100), 304 (90), 276 (35), 232 (72), 231 (49). High-resolution MS Calcd for $C_{21}H_{17}N_3O_6$: 407.1117. Found: 407.1113. ^{1}H NMR δ: 1.82 (6H, s, $C(CH_3)_2$), 2.95 (3H, s, CH_3), 7.59 (1H, d, *J*=8.3 Hz, C_3–H), 7.74 (1H, ddd, *J*=8.6, 7.9, 1.3 Hz, C_6–H), 7.92 (1H, dd, *J*=8.6, 7.9, 1.3 Hz, C_7–H), 8.01 (1H, d, *J*=8.3 Hz, C_2–H), 8.34 (1H, d, *J*=8.6 Hz, C_8–H), 8.40 (1H, d, *J*=8.6 Hz, C_5–H), 8.96 (1H, d, *J*=14.5 Hz, CH=), 13.38 (1H, d, *J*=14.5 Hz, NH).

(b) Copper(II) nitrate trihydrate (406 mg, 1.7 mmol) was added in portions over 7 h to a heated (70 °C) solution of **10** (300 mg, 0.83 mmol) in acetic anhydride (20 mL) containing ascorbic acid (42 mg) under argon atmosphere. The reaction mixture was heated at 70 °C for 2 h under argon atmosphere, cooled, diluted with water (200 mL), stirred at 25 °C for 30 min, and extracted with ethyl acetate (3×150 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$–hexane 1:5) to give **11** (266 mg, 79%).

3.1.5. 7-Methylbenzo[*b*][1,10]phenanthrolin-4(1*H*)-one (13). A mixture of **10** (30 mg, 0.083 mmol) and diphenyl ether (20 mL) was refluxed for 15 min under argon atmosphere. The mixture was cooled and diluted with petroleum ether (40 mL). After 16 h, the precipitated yellow crystals of **13** were collected by filtration and washed with petroleum ether. Yield 21 mg (97%). Mp 285–288 °C ($CHCl_3$–ether). MS *m/z* (%): 260 (M^+, 100), 232 (63). High-resolution MS Calcd for $C_{17}H_{12}N_2O$: 260.0950. Found: 260.0954. ^{1}H NMR δ: 3.03 (3H, s, CH_3), 6.63 (1H, d, *J*=7.3 Hz, C_3–H), 7.67 (1H, ddd, *J*=8.6, 7.3, 1.3 Hz, C_9–H), 7.84 (1H, ddd, *J*=8.6, 7.3, 1.3 Hz, C_{10}–H), 7.88 (1H, d, *J*=9.6 Hz, C_6–H), 7.92 (1H, d, *J*=7.3 Hz, C_2–H), 8.17 (1H, d, *J*=9.6 Hz, C_5–H), 8.20 (1H, d, *J*=8.6 Hz, C_{11}–H), 8.26 (1H, d, *J*=8.6 Hz, C_8–H), 10.80 (1H, brs, NH).

3.1.6. Nitration of 13. A suspension of **13** (131 mg, 0.50 mmol) in nitromethane (3 mL) was added in portions over 15 min to a cooled (−25 °C) solution of potassium nitrate (43.8 mg, 0.43 mmol) and sulfuric acid–oleum (4:1, 2.5 mL) in nitromethane (2 mL). The reaction mixture was stirred at −25 °C for 35 h. Potassium nitrate (43.8 mg, 0.43 mmol) was added and the entire mixture was stirred at −25 °C for 4 h. The reaction mixture was poured into ice water, basified with aqueous NaOH solution, and extracted with $CHCl_3$ containing 10% methanol (3×100 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$–methanol 100:1–50:1) to give 7-methyl-8-nitrobenzo[*b*][1,10]phenanthrolin-4(1*H*)-one (**14**, 21 mg, 14%) and 7-methyl-11-nitrobenzo[*b*][1,10]phenanthrolin-4(1*H*)-one (**15**, 66 mg, 43%) as a yellow solid.

Compound **14**. Mp 245–250 °C ($CHCl_3$–ether). MS *m/z* (%): 305 (M^+, 100), 288 (66), 259 (33), 231 (24). High-resolution MS Calcd for $C_{17}H_{11}N_3O_3$: 305.0800. Found: 305.0806. ^{1}H NMR ($CDCl_3$–CD_3OD) δ: 2.95 (3H, s, CH_3), 6.76 (1H, d, *J*=7.3 Hz, C_3–H), 7.86 (1H, dd, *J*=8.6, 7.3 Hz, C_{10}–H), 8.01 (1H, dd, *J*=7.3, 1.3 Hz, C_9–H), 8.08 (1H, d, *J*=9.6 Hz, C_6–H), 8.11 (1H, d, *J*=7.3 Hz, C_2–H), 8.34 (1H, d, *J*=9.6 Hz, C_5–H), 8.51 (1H, dd, *J*=8.6, 1.3 Hz, C_{11}–H).

Compound **15**. Mp >250 °C ($CHCl_3$–ether). MS *m/z* (%): 305 (M^+, 100), 277 (19), 259 (27). High-resolution MS Calcd for $C_{17}H_{11}N_3O_3$: 305.0800. Found: 305.0793. ^{1}H NMR ($CDCl_3$–CD_3OD) δ: 3.25 (3H, s, CH_3), 6.84 (1H, d, *J*=7.3 Hz, C_3–H), 7.79 (1H, dd, *J*=8.9, 7.3 Hz, C_9–H), 8.10 (1H, d, *J*=7.3 Hz, C_2–H), 8.11 (1H, d, *J*=9.6 Hz, C_6–H), 8.22 (1H, dd, *J*=7.3, 1.3 Hz, C_{10}–H), 8.37 (1H, d, *J*=9.6 Hz, C_5–H), 8.60 (1H, dd, *J*=8.9, 1.3 Hz, C_8–H).

3.1.7. 9-Methyl-1-nitroacridine (17) and 9-methyl-3-nitroacridine (18). A solution of 2-acetyl-3′-nitrodiphenylamine (**16**, 2.00 g, 7.80 mmol) and sulfuric acid (1.2 mL) in acetic acid (12.0 mL) was heated at 110–120 °C for 20 min. After cooling, the reaction mixture was diluted with water (80 mL), basified with 25–28% aqueous ammonia solution, and extracted with $CHCl_3$ (3×80 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$) to give an isomeric mixture of **17** and **18** (1.48 g, 80%) as a yellow solid, which was used in the next step. A part of the mixture (0.37 g) was chromatographed (benzene) using a large amount (400 g) of silica gel to give **17** (0.24 g) and **18** (0.11 g).

Compound **17**. Mp 174–176 °C ($CHCl_3$–hexane) [lit.[6] mp 175–176 °C]. ^{1}H NMR δ: 2.93 (3H, s, CH_3), 7.66 (1H, ddd, *J*=8.6, 6.6, 1.3 Hz), 7.72 (1H, dd, *J*=8.6, 7.3 Hz), 7.80–7.90 (2H, m), 8.23 (1H, d, *J*=8.9 Hz), 8.30 (1H, d, *J*=8.9 Hz), 8.39 (1H, dd, *J*=8.6, 1.3 Hz).

Compound **18**. Mp 198–201 °C ($CHCl_3$–hexane) [lit.[6] mp 198–200 °C]. ^{1}H NMR δ: 3.20 (3H, s, CH_3), 7.68 (1H, ddd, *J*=8.6, 6.6, 1.3 Hz), 7.87 (1H, ddd, *J*=8.6, 6.6, 1.3 Hz), 8.25–8.35 (3H, m), 8.42 (1H, d, *J*=8.9 Hz, C_1–H), 9.16 (1H, d, *J*=2.0 Hz, C_4–H).

3.1.8. 1-Amino-9-methylacridine (19) and 3-amino-9-methylacridine (20). An isomeric mixture of nitroacridines (**17** and **18**, 400 mg, 1.68 mmol), hydrochloric acid (8 mL), tin(II) chloride dihydrate (800 mg, 3.54 mmol) was heated

at 70–80 °C for 3 h. After cooling, the reaction mixture was basified with 5% aqueous NaOH solution and extracted with $CHCl_3$ (6×40 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed; elution with ethyl acetate–$CHCl_3$ (1:9–1:4) gave **19** (172 mg, 49%) and further elution with $CHCl_3$–methanol (9:1–4:1) gave **20** (48 mg, 14%) as a solid with a low melting point, respectively.

Compound **19**. ^{1}H NMR δ: 3.42 (3H, s, CH_3), 4.39 (2H, br, NH_2), 6.72 (1H, d, J=7.3 Hz), 7.4–7.6 (2H, m), 7.66 (1H, d, J=8.6 Hz), 7.73 (1H, dd, J=8.6, 7.6 Hz), 8.13 (1H, d, J=8.6 Hz), 8.22 (1H, dd, J=8.6 Hz).

Compound **20**. ^{1}H NMR δ: 3.05 (3H, s, CH_3), 4.29 (2H, br, NH_2), 7.05 (1H, dd, J=9.2, 2.3 Hz, C_2–H), 7.29 (1H, d, J=2.3 Hz, C_4–H), 7.4–7.7 (2H, m), 8.09 (1H, d, J=9.2 Hz, C_1–H), 8.12 (1H, d, J=8.6 Hz), 8.17 (1H, d, J=8.6 Hz).

3.1.9. 1-Acetylamino-9-methylacridine (21). A solution of **19** (140 mg, 0.67 mmol) in acetic anhydride (2.0 mL) was stirred for 14 h. The reaction mixture was diluted with ice water (20 mL), basified with 10% KOH solution, and extracted with $CHCl_3$ (3×20 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$–methanol 97:3) to give **21** (108 mg, 64%) as a yellow solid. Mp 218–220 °C ($CHCl_3$–ether). MS *m*/*z* (%): 250 (M^+, 65), 208 (100). High-resolution MS Calcd for $C_{16}H_{14}N_2O$: 250.1106. Found: 250.1106. ^{1}H NMR δ: 2.33 (3H, s, $COCH_3$), 3.27 (3H, s, C_9–CH_3), 7.5–7.9 (4H, m), 8.0–8.4 (3H, m).

3.1.10. 2-Acetylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (22). A suspension of **21** (100 mg, 0.40 mmol) and SeO_2 (100 mg, 0.90 mmol) in dioxane (20 mL) was heated at 70–75 °C for 1 h. The reaction mixture was evaporated and the residue was chromatographed ($CHCl_3$) to give **22** (90 mg, 86%) as an orange solid. Mp 226–227 °C ($CHCl_3$–ether). MS *m*/*z* (%): 262 (M^+, 24), 220 (100). High-resolution MS Calcd for $C_{16}H_{10}N_2O_2$: 262.0742. Found: 262.0736. Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: 73.18; H, 4.19; N, 10.33. ^{1}H NMR δ: 2.88 (3H, s, CH_3), 7.84 (1H, dd, J=8.9, 6.9 Hz, C_4–H), 7.86 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_9–H), 7.96 (1H, ddd, J=8.6, 6.9, 1.6 Hz, C_8–H), 8.03 (1H, d, J=8.9 Hz, C_5–H), 8.16 (1H, d, J=6.9 Hz, C_3–H), 8.46 (1H, dd, J=8.6, 1.3 Hz, C_7–H), 8.90 (1H, dd, J=8.3, 1.6 Hz, C_{10}–H).

3.1.11. 2-Acetyl-5-nitropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (23). Potassium nitrate (20.2 mg, 0.20 mmol) was added to an ice-cooled solution of **22** (26.2 mg, 0.10 mmol) in sulfuric acid (2.0 mL). The reaction mixture was stirred at 0–5 °C for 1 h, diluted with ice water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (3×20 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed ($CHCl_3$) to give **23** (19.3 mg, 63%) as a yellow solid. Mp 237–239 °C (ethyl acetate–hexane). MS *m*/*z* (%): 307 (M^+, 54), 265 (100), 235 (31). High-resolution MS Calcd for $C_{16}H_9N_3O_4$: 307.0593. Found: 307.0596. ^{1}H NMR δ: 2.90 (3H, s, CH_3), 7.96 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_9–H), 8.06 (1H, ddd, J=8.9, 6.9, 1.3 Hz, C_8–H), 8.25 (1H, d, J=7.9 Hz, C_3–H), 8.60 (1H, dd, J=8.9, 1.3 Hz, C_7–H), 8.65 (1H, d, J=7.9 Hz, C_4–H), 8.93 (1H, dd, J=8.3, 1.3 Hz, C_{10}–H).

3.1.12. 5-Nitropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (24). A solution of **23** (15.4 mg, 0.05 mmol) and 10% H_2SO_4 (0.5 mL) in dioxane (2.5 mL) was heated at 80 °C for 30 min. After cooling, the reaction mixture was diluted with water (15 mL) and neutralized with $NaHCO_3$. The precipitated orange crystals of **24** were collected by filtration and washed with water. Yield 12.7 mg (96%). Mp >250 °C. MS *m*/*z* (%): 265 (M^+, 100), 235 (33). High-resolution MS Calcd for $C_{14}H_7N_3O_3$: 265.0487. Found: 265.0486. ^{1}H NMR ($CDCl_3$–CD_3OD) δ: 6.98 (1H, d, J=7.6 Hz, C_3–H), 7.87 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_9–H), 8.00 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_8–H), 8.58 (1H, ddd, J=8.3, 1.3, 0.7 Hz, C_7–H), 8.63 (1H, d, J=7.6 Hz, C_4–H), 8.86 (1H, ddd, J=8.3, 1.3, 0.7 Hz, C_{10}–H).

3.1.13. 2-Ethyl-5-nitropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (25). A mixture of **24** (10.6 mg, 0.04 mmol), potassium carbonate (11.1 mg, 0.08 mmol), and ethyl iodide (63 mg, 0.4 mmol) in dry acetone (5 mL) was refluxed for 1 h. The reaction mixture was cooled and filtered. The filtrate was evaporated and the residue was chromatographed ($CHCl_3$) to give **25** (7.9 mg, 67%) as a yellow solid. Mp 253–257 °C (ethyl acetate–ether). MS *m*/*z* (%): 293 (M^+, 100), 278 (29), 263 (40). High-resolution MS Calcd for $C_{16}H_{11}N_3O_3$: 293.0800. Found: 293.0794. ^{1}H NMR δ: 1.46 (3H, t, J=7.3 Hz, CH_2CH_3), 4.07 (2H, q, J=7 Hz, CH_2CH_3), 6.93 (1H, d, J=7.6 Hz, C_3–H), 7.87 (1H, ddd, J=7.9, 6.9, 1.3 Hz, C_9–H), 7.99 (1H, ddd, J=8.6, 6.9, 1.3 Hz, C_8–H), 8.55 (1H, dd, J=8.6, 1.3 Hz, C_7–H), 8.65 (1H, d, J=7.6 Hz, C_4–H), 8.86 (1H, dd, J=7.9, 1.3 Hz, C_{10}–H).

3.1.14. 2-Acetyl-5-aminopyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (26). A mixture of **23** (30.7 mg, 0.10 mmol) in THF (15 mL) and sodium hydrosulfite (122 mg, 0.70 mmol) in water (3.0 mL) was stirred for 1 h. After evaporation of THF, the reaction mixture was diluted with water and extracted with $CHCl_3$ (3×20 mL). The extract was washed with water, dried, and evaporated to give **26** (22.6 mg, 82%) as a pale purple solid. MS *m*/*z* (%): 277 (M^+, 40), 235 (100). High-resolution MS Calcd for $C_{16}H_{11}N_3O_2$: 277.0851. Found: 277.0851. ^{1}H NMR δ: 1.55 (2H, br, NH_2), 2.85 (3H, s, CH_3), 6.82 (1H, d, J=7.6 Hz, C_4–H), 7.86 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_9–H), 7.93 (1H, ddd, J=8.6, 6.9, 1.3 Hz, C_8–H), 7.96 (1H, d, J=7.6 Hz, C_3–H), 8.53 (1H, ddd, J=8.6, 1.3, 0.7 Hz, C_7–H), 8.92 (1H, ddd, J=8.3, 1.3, 0.7 Hz, C_{10}–H).

3.1.15. 5-[[(2-Acetyl-1-oxo-1,2-dihydropyrrolo[2,3,4-*kl*]acridin-5-yl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (27). After Meldrum's acid (23.1 mg, 0.16 mmol) in trimethyl orthoformate (4 mL) was refluxed for 1 h, a solution of **26** (22.4 mg, 0.08 mmol) in trimethyl orthoformate (2 mL) was added. The resulting solution was refluxed for 30 min and then evaporated. The residue was washed with ether (20 mL) to give **27** (29.0 mg, 83%) as a red solid. Mp 213–215 °C (decomp.) (ethyl acetate–ether). MS *m*/*z* (%): 431 (M^+, 29), 373 (23), 329 (53), 301 (78), 287 (62), 259 (100). High-resolution MS Calcd for $C_{23}H_{17}N_3O_6$: 431.1117. Found: 431.1115. Anal. Calcd for $C_{23}H_{17}N_3O_6$: C, 64.04; H, 3.97; N, 9.74. Found: 63.78; H, 3.91; N, 9.65.

^{1}H NMR δ: 1.82 (6H, s, $C(CH_3)_2$), 2.88 (3H, s, $COCH_3$), 7.65 (1H, d, J=7.9 Hz, C_4–H), 7.93 (1H, ddd, J=8.6, 6.9, 1.7 Hz, C_9–H), 8.02 (1H, ddd, J=8.6, 6.9, 1.7 Hz, C_8–H), 8.16 (1H, d, J=7.9 Hz, C_3–H), 8.59 (1H, dd, J=8.6, 1.7 Hz, C_7–H), 8.92 (1H, dd, J=8.6, 1.7 Hz, C_{10}–H), 9.16 (1H, d, J=14.5 Hz, CH═), 12.57 (1H, d, J=14.5 Hz, NH).

3.1.16. 6-Acetyl-6,11-dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]phenanthroline-5,8-dione (28). A mixture of **27** (25.9 mg, 0.06 mmol) and diphenyl ether (3 mL) was refluxed for 10 min under argon atmosphere. The reaction mixture was cooled and diluted with ether (10 mL). After 1 h, the precipitated yellow crystals of **28** were collected by filtration and washed with ether. Yield 18.1 mg (92%). Mp >250 °C. MS *m*/*z* (%): 329 (M^+, 43), 287 (100), 259 (29). High-resolution MS Calcd for $C_{19}H_{11}N_3O_3$: 329.0800. Found: 329.0800. ^{1}H NMR ($CDCl_3$–CF_3CO_2D) δ: 2.99 (3H, s, $COCH_3$), 7.78 (1H, d, J=6.6 Hz, C_9–H), 8.1–8.3 (2H, m, C_2–H, C_3–H), 8.60 (1H, dd, J=7.6, 1.7 Hz, C_1–H or C_4–H), 8.79 (1H, s, C_7–H), 8.85 (1H, d, J=6.6 Hz, C_{10}–H), 9.03 (1H, dd, J=7.9, 1.7 Hz, C_4–H or C_1–H).

3.1.17. 6,11-Dihydrobenzo[*b*]pyrrolo[4,3,2-*de*][1,10]-phenanthroline-5,8-dione (6). A mixture of **28** (16.5 mg, 0.05 mmol) and 20% H_2SO_4 (0.2 mL) in dioxane (7.5 mL) was heated at 90 °C for 20 min. After cooling, the reaction mixture was diluted with water (20 mL) and neutralized with $NaHCO_3$. The precipitated crystals of **6** were collected by filtration, washed with water and ether, and dried. Yield 12.7 mg (88%). Mp >250 °C. MS *m*/*z* (%): 287 (M^+, 100), 259 (46). High-resolution MS Calcd for $C_{17}H_9N_3O_2$: 287.0695. Found: 287.0696. ^{1}H NMR (DMSO-d_6) δ: 6.40 (1H, d, J=7.3 Hz, C_9–H), 7.50 (1H, s, C_7–H), 7.93 (1H, dd, J=7.3, 6.9 Hz, C_{10}–H), 8.02 (1H, ddd, J=7.9, 6.9, 1.3 Hz, C_3–H), 8.12 (1H, ddd, J=8.3, 6.9, 1.3 Hz, C_2–H), 8.56 (1H, dd, J=8.3, 1.3 Hz, C_1–H), 8.83 (1H, dd, J=7.9, 1.3 Hz, C_4–H), 11.24 (1H, s, N_6–H), 12.82 (1H, d, J=6.9 Hz, N_{11}–H).

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Synthesis of two new families of fluorinated compounds: 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols and 1H,1H-perfluoro-2,4-alkyldiynols and their acrylates and methacrylates

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Abstract—The synthesis of two new families of compounds, 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols and 1H,1H-perfluoro-2,4-alkyldiynols, and their acrylates and methacrylates, precursors of polymeric systems with important physical properties, is described.

1. Introduction

Conjugated diynes and polyynes[1] are relatively abundant in naturally-occurring substances with diverse biological activity, and are also of interest as synthetic precursors of molecules with very high carbon content. Von Baeyer[2] performed the first investigations on polyynes and demonstrated that the synthesised molecules were highly unstable. As a result, chemists avoided this type of compounds, as indicated by the absence of publications on the topic until 50 years later, when Wegner[3] described the solid-state reactivity of these compounds in terms of a polymerization reaction. Since then, polydiacetylene chemistry has become an integral part of modern organic materials science, essentially due to its interesting, inter alia, non-linear optical properties.[4]

The synthesis of asymmetric disubstituted conjugated diacetylenes, the precursors of polydiacetylenes, has been widely studied but never with molecules that contain a perfluoroalkyl chain directly bonded to an *sp* carbon atom. Due to the important known physico-chemical properties of this chain, for example, its high electron-attracting character, chemical inertness, thermal stability and hydro- and lipophobicity, and in the context of our research into new organic materials with properties of technological interest, we have studied the preparation of a new class of diacetylene compounds of the general formula

$$Rf(n)-C\equiv C-C\equiv C-(CH_2)_p-OW$$

where Rf(n) is $F(CF_2)_n$; n is 4, 6, 8, p is 1, 2 and W is H, acrylate or methacrylate. The purpose of the hydroxyl group is to form the corresponding acrylates or methacrylates by reaction with acryloyl or methacryloyl chloride. These compounds have been polymerised in radical conditions and the formation, reactivity and structure of these new polymers has been reported.[5] These new pre-ordered polymers are the starting materials for a second polymerization of the diacetylene moiety under thermal conditions.[6]

To date there have been no reports in the literature of the molecular systems described in this paper. The only similar molecules that have been recently reported[7] are $Rf(n)-(CH_2)_j-C\equiv C-C\equiv C-(CH_2)_p-OH$, with n=6, 8; j>3 and p=3. Notably, the author comments that all attempts to prepare fluorinated diacetylenes with j<3 were unsuccessful. In other words, the author was unable to link the perfluorinated radical directly to the diacetylenic system as described here.

2. Results and discussion

2.1. Synthesis of 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols

The best-known reaction used in the formation of asymmetric acetylenes is the Cadiot–Chodkiewicz coupling[8] from a 1-haloalkyne and a terminal alkyne, using a Cu(I) catalyst in ethylamine and hydroxylamine hydrochloride. The synthesis of perfluorodiacetylenic alcohols was first attempted from $Rf(n)-C\equiv C-H$ and $X-C\equiv C-(CH_2)_2OH$. The perfluorinated terminal acetylene was obtained

Keywords: Synthesis; Perfluoroalkynediynes; 1H,1H,2H,2H-Perfluoro-3,5-alkyldiynols and 1H,1H-perfluoro-2,4-alkyldiynols; Acrylates and methacrylates; Alkyne coupling reactions.
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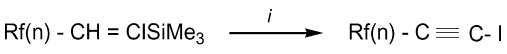


Scheme 1. *i*: (a) ^{t}BuOK (7.9 equiv.), THF. (b) I_2 (2.9 equiv.); n=4, 6, 8.

according to the method described by Huang,[9] that is, addition of perfluoroalkyl iodide to trimethylsilylacetylene, followed by elimination of HI with ^{t}BuOK, and the 1-bromo- and 1-iodo acetylenic alcohols were obtained by the Strauss method and via acetylenic Grignard reagents, respectively.[10]

The coupling reaction took place accordingly and yielded the desired product but only with a 19% yield.[11] It is noteworthy that 14.4 equiv. of the hydroxylamine hydrochloride were employed as described in the literature for the coupling of other ordinary acetylenes.[8a]A similar problem was encountered when the reaction was then attempted with only the stoichiometric amount of hydroxylamine hydrochloride as described by Galluci et al.[12]

A modification of the Shonogashira reaction[13] was then tried between 1H-2-perfluoroalkyl-1-alkyne and 4-bromo-3-butyn-1-ol, in the presence of $PdCl_2(PPh_3)_2$, CuI and Et_3N in THF affording the desired 1H,1H,2H,2H-perfluoro-3,5-alkyldiynol. However, some byproducts were again isolated in substantial amount from the reaction mixture and were identified as *N*,*N*-diethyl-1H,2H-perfluoro-1-hexenylamine, $Rf(4)-HC{=}CH-N(CH_2CH_3)_2$ similar to the case described by Yoneda.[14] When this author attempted to synthesise ethynylarenes, for example, 3,3,3-trifluoropropyne, by reaction with iodobenzene in the presence of Pd catalyst and Et_3N he obtained *N*,*N*-diethyl-3,3,3-trifluoro-1-propenylamine as the unique product.

Due to the problems described above and the low yields of the target products, the possibility of performing the coupling with a pair of reagents with the opposite functionalisation, that is $Rf(n)-C{\equiv}C-X$ and $H-C{\equiv}C-(CH_2)_2OH$, was considered. This process benefits from the additional advantage that the 3-butyn-1-ol is commercially available.

The synthesis of 1-iodo-2-perfluoroalkylalkynes has been described previously in a two-step procedure from the alkyne.[15] However, in our work this product was prepared via a new one-pot method by reaction from 2H-perfluoro-1-iodo-1-trimethylsilyl-1-octene, prepared as explained earlier, by reaction first with ^{t}BuOK, to yield 2H-perfluoro-1-trimethylsilyl-1-octyne and then with iodine without isolation of the alkyne (Scheme 1) with a higher yield (45% in all cases) than that described previously and greater ease of manipulation.

The next step was the coupling of 1-iodo-2-perfluoroalkylalkynes with 3-butyn-1-ol. Of the currently described methods relevant to this study, that described by Alami,[16] also based on Cu(I) catalysis, seemed the most appropriate. According to the described procedure, the reaction between 1-iodo-1-perfluorohexyne and 3-butyn-1-ol was carried out at room temperature in pyrrolidine, with CuI as catalyst. However, once again we obtained the product derived from nucleophilic attack of pyrrolidine to the perfluoroacetylene.

To avoid nucleophilic attack, both bulky and non-nucleophilic bases were assayed, and finally the desired coupling product was obtained using $^{i}Pr_2NH$ in the presence of CuI as catalyst (Scheme 2).

A yield of 40% was achieved by using 10% molar CuI and 2 equiv. of 3-butyn-1-ol.

2.2. Synthesis of 1H,1H-perfluoro-2,4-alkyldiynols

In contrast to the synthesis of 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols, in the case of 1H,1H-perfluoro-2,4-alkyldiynols, the only useful pair of reagents are $Rf(n)-C{\equiv}C-I$ and propargyl alcohol, $H-C{\equiv}C-CH_2OH$, since that $I-C{\equiv}C-CH_2OH$ is highly unstable and decomposes at low temperature.[17] Another difference was that the process that allowed us to prepare 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols might be modified because propargyl alcohol can only be satisfactorily coupled when the amine is bidentate;[18] whilst with monodentate amines the copper(I) derivative is quantitatively precipitated from the solution.

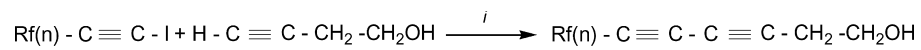
Thus, 1H,1H-perfluorohexyl-2,4-pentyldiynol was obtained by coupling the 1-iodo-1-perfluorooctyne with propargyl alcohol in the presence of TMEDA, (Scheme 3) with a yield of 60%.

2.3. Formation of acrylates and methacrylates

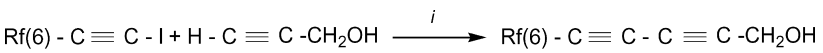
Following the preparation of 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols and 1H,1H-perfluoro-2,4-alkyldiynols, their acrylates and methacrylates were synthesised according to standard methods,[19] by reaction with acryloyl and methacryloyl chloride, respectively.

3. Conclusions

Here, we have described the synthesis of a new family of fluorinated compounds, not previously described in the literature, of general formula $Rf(n)-C{\equiv}C-C{\equiv}C-(CH_2)_p-OH$, where n is 4, 6, 8 and p is 1, 2. These products contain four functional groups: (a) a conjugated diacetylene,



Scheme 2. *i*: CuI (5% molar), $^{i}Pr_2NH$ (2 equiv.), r.t., 3 h.



Scheme 3. *i*: CuI, TMEDA, acetone, r.t., 2.5 h.

able to polymerize under different reaction conditions; (b) a perfluorinated chain of different lengths, useful for its known properties of hydro- and lipophobicity, thermal stability and chemical inertness; (c) one or two methylene groups which act as spacers and give the molecule different degrees of flexibility; and (d) a hydroxyl group able to form the corresponding acrylates or methacrylates, also described, which can polymerise in the presence of a radical initiator.[5]

4. Experimental

4.1. General methods

IR spectra were registered using a Perkin–Elmer Spectrum-one instrument. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Varian Unity-300 spectrometer with TMS (^{1}H) and $CFCl_3$ (^{19}F) as internal standards. The MS were determined by electronic impact (ei, 70 eV) in a Hewlett Packard 5973 mass spectrometer coupled to an HP 6890 Series gas chromatograph. The reactions were followed by GC–MS using an HP 19091J-433, HP-5, 5% phenyl methyl siloxane (0.25 μm) column.

4.2. General procedure for preparation of 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols

$NaHCO_3$ (1.00 g, 12 mmol) and $Na_2S_2O_3$ (2.08 g, 12 mmol) were added to a stirred solution of perfluoroalkyl iodide (10 mmol) and 1-trimethylsilylacetylene (10 mmol) in a mixture of MeCN (15 mL) and water (10 mL). Stirring was continued at 10–15 °C for 30 min. The resulting mixture was diluted with water (20 mL) and extracted with diethyl ether (30 mL×3). The combined organic layer was washed with NaCl solution (20 mL×2), dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure to yield the crude adduct. The adduct, diluted in anhydrous diethyl ether (20 mL), was added to a stirred suspension of ^{t}BuOK (25 mmol) in anhydrous diethyl ether (10 mL) at −20 °C. The mixture was stirred at −20 °C for 1 h and at 0 °C for a further 4 h. After this time, the mixture was brought to room temperature and iodine (10 mmol) was added for 1 h. The resulting mixture was diluted with water (20 mL) and extracted with diethyl ether (30 mL×3). The combined organic layer was washed with $Na_2S_2O_3$ solution (20 mL×2), dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure to yield the crude adduct contaminated with siloxanes.

3-Butyn-1-ol (20 mmol) in Pr^i_2NH (10 mmol) and CuI (1 mmol, 190 mg) were added to a stirred solution of crude 1-iodo-2-perfluoroalkylalkyne (10 mmol) in ethyl ether (15 mL). After stirring at room temperature for 4 h under nitrogen atmosphere, the mixture was filtered and extracted with diethyl ether. The organic extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Filtration through silica gel (elution solvent: hexane–ethyl acetate, 8.5:1.5) yielded pure diyne.

4.2.1. 1H,1H,2H,2H-Perfluoro-3,5-decadiynol. ^{19}F NMR (300 MHz, $CFCl_3$): δ=83.62 (m, CF_3–, 3F); 99.57 (m, –CF_2–C≡C–, 2F); 125.59 (m, $CF_3CF_2CF_2$–, 2F); 128.04 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=3.82 (t, –CH_2OH, J=6.0 Hz, 2H); 2.64 (t, –C$H_2$$CH_2$OH, J=6.0 Hz, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ=118.00–105.00 (m, –$C$$F_2$– and $C$$F_3$–); 85.01 (–C≡C–C≡$C$–$CH_2$–); 74.95 (–C≡C–$C$≡C–$CH_2$–); 65.92 (–C≡$C$–C≡C–$CH_2$–); 61.00 (t, –$C$≡C–C≡C–$CH_2$–, J_{C-F}=141.9 Hz); 60.09 (–CH_2–$C$$H_2$OH); 23.63 (–$C$$H_2$$CH_2$OH); MS (ei): 312 (M)$^{\cdot+}$; 282 (M−$CH_2$OH)$^{\cdot+}$; 69 $(CF_3)^+$ ppm; IR (film): ν=3367 (st OH); 2962, 2928 (st Csp^3–H); 2266; 2175 (st C≡C); 1238; 1209; 1138 (st C–F) cm^{-1}; yellow oil; yield: 34%.

4.2.2. 1H,1H,2H,2H-Perfluoro-3,5-dodecadiynol. ^{19}F NMR (300 MHz, $CFCl_3$): δ=83.11 (m, CF_3–, 3F); 99.02 (m, –CF_2–C≡C–, 2F); 123.61 (m, –CF_2–CF_2–C≡C–, 2F); 124.44 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 125.13 (m, CF_3–CF_2–CF_2–, 2F); 128.42 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=3.83 (m, C≡C-CH_2–CH_2OH, 2H); 2.65 (m, –C≡C–CH_2–CH_2OH, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ=120.00–105.00 (m, –$C$$F_2$– and $C$$F_3$–); 84.88 (–$CF_2$–C≡C–C≡$C$–$CH_2$); 76.20 (–$CF_2$–C≡C–$C$≡C–$CH_2$–); 63.90 (–$CF_2$–C≡$C$–C≡C–$CH_2$–); 60.10 (t, –$CF_2$–$C$≡C–C≡C–$CH_2$–, J_{C-F}=141.5 Hz); 60.01 (–C≡C–CH_2–$C$$H_2$OH), 23.55 (–C≡C–$C$$H_2$–$CH_2$OH); MS (ei): 412 (M)$^{\cdot+}$; 382 (M−$CH_2$OH)$^{\cdot+}$; 69 $(CF_3)^+$ ppm; IR (film): ν=3347 (st OH); 2267; 2176 (st C≡C); 1248; 1203; 1147 (st C–F) cm^{-1}; white solid, mp 47–9 °C (uncorrected); yield: 38%.

4.2.3. 1H,1H,2H,2H-Perfluoro-3,5-tetradecadiynol. ^{19}F NMR (400 MHz, $CFCl_3$): δ=83.23 (m, CF_3–, 3F); 99.15 (m, –CF_2–C≡C–, 2F); 123.51 (m, –CF_2–CF_2–C≡C–, 2F); 124.33 (m, –CF_2–CF_2–CF_2–CF_2–C≡C–, 4F); 124.53 (m, CF_3–CF_2–CF_2–CF_2–, 2F); 125.17 (m, CF_3–CF_2–CF_2–, 2F); 128.58 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=3.83 (t, –C≡C–CH_2–CH_2–OH, J=6.0 Hz, 2H); 2.65 (m, –C≡C–CH_2–CH_2–OH, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ=119.09–104.68 (m, –$C$$F_2$– and $C$$F_3$–); 85.18 (–$CF_2$–C≡C–C≡$C$–$CH_2$–); 76.65 (–$CF_2$–C≡C–$C$≡C–$CH_2$–); 64.21 (t, –$CF_2$–C≡$C$–C≡C–$CH_2$–, J_{C-F}= 21.2 Hz); 60.34 (t, –CF_2–C≡C–C≡C–CH_2–, J_{C-F}= 143.2 Hz); 60.30 (–C≡C–CH_2–$C$$H_2$–OH); 23.83 (–C≡C–$C$$H_2$–$CH_2$–OH); MS (ei): 512 (M)$^{\cdot+}$; 482 (M−$CH_2$OH)$^{\cdot+}$ 69 $(CF_3)^+$ ppm; IR (film): ν=3378 (st OH); 2921; 2851 (st Csp^3–H); 2267; 2176 (st C≡C); 1248; 1212; 1151 (st C–F) cm^{-1}; viscous yellow oil; yield: 35%.

4.3. Procedure for preparation of 1H,1H-perfluoro-2,4-tridecadiynol

(a) Preparation of Hay catalyst. Cuprous chloride (2.02 mmol, 200 mg) was added to a stirred solution of tetramethylene diamine (100 μL) in acetone (2.5 mL). The resulting blue-green suspension of CuCl.TMEDA complex was separated from the excess of CuCl.

(b) Propargyl alcohol (0.175 mmol, 10 μL) and Hay catalyst (172 μL) was added to a solution of 1-iodo-1-perfluorodecyne (0.175 mmol, 100 mg) diluted with anhydrous acetone (1 mL). The mixture was stirred at room temperature under nitrogen atmosphere for 2.5 h. Then the reaction mixture was poured into dilute HCl and extracted with diethyl ether

(3×25 mL). The organic layer was washed with water (3×25 mL), dried (anh. Na_2SO_4), filtered and the solvent was removed under reduced pressure. Filtration through silica gel (elution solvent: hexane–ethyl acetate, 8.5:1.5) yielded (0.114 mmol, 57 mg, 65%) of pure diyne as a yellowish oil. ^{19}F NMR (400 MHz, $CFCl_3$): δ=83.33 (m, CF_3–, 3F); 99.96 (m, –CF_2–C≡C–, 2F); 123.61 (m, –CF_2–CF_2–C≡C–, 2F); 124.42 (m, –CF_2–CF_2–CF_2–CF_2–C≡C–, 4F); 124.64 (m, CF_3–CF_2–CF_2–CF_2–, 2F); 125.26 (m, CF_3–CF_2–CF_2–, 2F); 128.66 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=4.41 (s, –C≡C–CH_2–OH, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ=120.00–105.00 (m, –CF_2– and CF_3–); 83.57 (–CF_2–C≡C–C≡C–CH_2OH); 74.71 (–CF_2–C≡C–C≡C–CH_2OH); 67.02 (–CF_2–C≡C–C≡C–CH_2OH); 62.95 (t, –CF_2–C≡C–C≡C–CH_2OH, J_{C-F}=142.0 Hz); 50.98 (–C≡C–CH_2–O–); MS (ei): 498 $(M)^{\cdot+}$; 481 $(M-OH)^+$; 69 $(CF_3)^+$ ppm; IR (film): ν=3318 (st OH); 2972 (st Csp^3–H); 2266; 2174 (st C≡C); 1243; 1203; 1151 (st C–F) cm^{-1}.

4.4. General procedure for preparation of 1H,1H,2H,2H-perfluoro-3,5-alkyldiynols acrylates and 1H,1H-perfluoro-2,4-alkyldiynols acrylates

Acryloyl chloride (15.4 mmol, 1.25 mL) in anhydrous CH_2Cl_2 (25 mL) was added to a stirred solution of the perfluoroalkyldiynol (12.4 mmol) in anhydrous Et_3N (18 mmol, 2.5 mL) and anhydrous CH_2Cl_2 (100 mL) at 0 °C under nitrogen atmosphere. Subsequently, stirring was continued at room temperature for 3 h. The resulting mixture was diluted with water (3×120 mL), extracted with diethyl ether (3×50 mL), dried (anh. Na_2SO_4), filtered and the solvent removed under reduced pressure. Filtration through silica gel (eluent hexane–ethyl acetate, 9.5:0.5) yielded the desired ester.

4.4.1. 1H,1H,2H,2H-Perfluoro-3,5-decadiynyl acrylate. ^{19}F NMR (300 MHz, $CFCl_3$): δ=83.41 (m, CF_3–, 3F); 99.48 (m, –CF_2–C≡C–, 2F); 125.38 (m, CF_3–CF_2–CF_2–, 2F); 127.82 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=6.50 (dd, –OCO–CH=$CH_{cis}H_{trans}$, J_{gem}=1.5 Hz, J_{trans}=17.4 Hz, 1H); 6.18 (dd, –OCO–CH=$CH_{cis}H_{trans}$, J_{cis}=10.2 Hz, J_{trans}=17.4 Hz, 1H); 5.93 (dd, –OCO–CH=C$H_{cis}H_{trans}$, J_{gem}=1.5 Hz, J_{cis}=10.2 Hz, 1H); 4.34 (t, –C≡C–CH_2–CH_2–O–, J=6.6 Hz, 2H); 2.80 (m, –C≡C–CH_2–CH_2–O–, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ=165.95 (CO ester); 131.70 (–OCO–CH=CH_2); 127.74 (–OCO–CH=CH_2); 119.50–104.60 (m, –CF_2– and CF_3–); 83.54 (–CF_2–C≡C–C≡C–CH_2O–); 74.84 (–CF_2–C≡C–C≡C–CH_2O–); 63.98 (–CF_2–C≡C–C≡C–CH_2O–); 59.79 (t, –CF_2–C≡C–C≡C–CH_2O–, J_{C-F}=141.5 Hz); 60.85 (–CH_2–CH_2O–); 19.95 (–CH_2–CH_2O–) ppm; MS (ei): 366 $(M)^+$; 294 $(M-HOCOCH{=}CH_2)^+$; 55 $(COCH{=}CH_2)^+$; HRMS (ei): 366.0299, $C_{13}H_7F_9O_2$ requires 366.0302; IR (film): ν=2966 (st Csp^3–H); 2269; 2176 (st C≡C); 1733 (st CO ester); 1638 (st C=C); 1239; 1186, 1139 (st C–F) cm^{-1}; reddish viscous oil, yield: 70%.

4.4.2. 1H,1H,2H,2H-Perfluoro-3,5-dodecadiynyl acrylate. ^{19}F NMR (300 MHz, $CFCl_3$): δ=83.43 (m, CF_3–, 3F); 99.44 (m, –CF_2–C≡C–, 2F); 123.89 (m, –CF_2–CF_2–C≡C–, 2F); 124.71 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 125.40 (m, CF_3–CF_2–CF_2–, 2F); 128.73 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=6.49 (dd, –OCOCH=$CH_{cis}H_{trans}$, J_{trans}=17.1 Hz, J_{gem}=1.2 Hz, 1H); 6.18 (dd, –OCOCH=$CH_{cis}H_{trans}$, J_{cis}=10.5 Hz, J_{trans}=17.1 Hz, 1H); 5.92 (dd, –OCOCH=C$H_{cis}H_{trans}$, J_{cis}=10.5 Hz, J_{gem}=1.2 Hz, 1H); 4.34 (t, –C≡C–CH_2–CH_2–O–, J=6.6 Hz, 2H); 2.80 (m, –C≡C–CH_2–CH_2–O–, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ=165.67 (CO ester); 131.70 (–OCOCH=CH_2); 127.76 (–OCOCH=CH_2); 120.00–100.00 (m, –CF_2– and CF_3–); 83.55 (–CF_2–C≡C–C≡C–CH_2–); 75.90 (–CF_2–C≡C–C≡C–CH_2–); 64.01 (–CF_2–C≡C–C≡C–CH_2–); 60.88 (–C≡C–CH_2–CH_2–O–); 60.40 (t, –CF_2–C≡C–C≡C–CH_2–, J_{C-F}=144.3 Hz); 19.98 (–C≡C–CH_2–CH_2–O–) ppm; MS (ei): 466 $(M)^{\cdot+}$; 394 $(M-CH_2{=}CHCOOH)^{\cdot+}$; 55 $(COCH{=}CH_2)^+$; HRMS (ei): 466.0230, $C_{15}H_7F_{13}O_2$ requires 466.0238; IR (film): ν=2965, 2929 (st Csp^3–H); 2267; 2177 (st C≡C); 1734 (st CO); 1637 (st C=C); 1241; 1199; 1148 (st C–F) cm^{-1}; reddish oil, yield: 73%.

4.4.3. 1H,1H,2H,2H-Perfluoro-3,5-tetradecadiynyl acrylate. ^{19}F NMR (400 MHz, $CFCl_3$): δ=83.20 (m, CF_3–, 3F); 99.26 (m, –CF_2–C≡C–, 2F); 123.50 (m, –CF_2–CF_2–C≡C–, 2F); 124.31 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 124.50 (m, –CF_2–CF_2–CF_2–CF_2–C≡C–, 2F); 125.15 (m, CF_3–CF_2–CF_2–CF_2–, 4F); 128.54 (CF_3–CF_2–, 2F) ppm; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=6.46 (dd, –COOCH=$CH_{cis}H_{trans}$, J_{trans}=17.6 Hz, J_{gem}=1.2 Hz, 1H); 6.15 (dd, –COOCH=$CH_{cis}H_{trans}$, J_{cis}=10.4 Hz, J_{trans}=17.6 Hz, 1H); 5.89 (dd, –COOCH=$H_{cis}H_{trans}$, J_{cis}=10.4 Hz, J_{gem}=1.2 Hz, 1H); 4.31 (t, –C≡C–CH_2–CH_2–O–, J=6.4 Hz, 2H); 2.77 (m, –C≡C–CH_2–CH_2–O–, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ=165.88 (CO ester); 131.94 (–COOCH=CH_2); 127.95 (–COOCH=CH_2); 119.31–104.65 (m, –CF_2– and CF_3–); 83.73 (–CF_2–C≡C–C≡C–CH_2–); 76.78 (–CF_2–C≡C–C≡C–CH_2–); 64.20 (–CF_2–C≡C–C≡C–CH_2–); 61.07 (–C≡C–CH_2–CH_2–O–); 60.56 (t, –CF_2–C≡C–C≡C–CH_2–, J=142.8 Hz); 20.17 (–C≡C–CH_2–CH_2–O–) ppm; MS (ei): 566 $(M)^{\cdot+}$; 494 $(M-CH_2{=}CHCOOH)^{\cdot+}$; 55 $(COCH{=}CH_2)^+$; HRMS (ei): 566.0157, $C_{17}H_7F_{17}O_2$ requires 566.0174; IR (film): ν=2967 (st Csp^3–H); 2267; 2176 (st C≡C); 1734 (st CO); 1638 (st C=C); 1244; 1199; 1152 (st C–F) cm^{-1}; reddish viscous oil, yield: 76%.

4.4.4. 1H,1H-Perfluoro-2,4-tridecadiynyl acrylate. ^{19}F NMR (400 MHz, $CFCl_3$): δ=83.18 (m, CF_3–, 3F); 99.98 (m, –CF_2–C≡C–, 2F); 123.47 (m, –CF_2–CF_2–C≡C–, 2F); 124.28 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 124.45 (m, –CF_2–CF_2–CF_2–CF_2–C≡C–, 2F); 125.12 (m, CF_3–CF_2–CF_2–CF_2–, 4F); 128.52 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=6.51 (dd, –OCO–CH=$CH_{cis}H_{trans}$, J_{gem}=1.2 Hz, J_{trans}=16.0 Hz, 1H); 6.18 (dd, –OCO–CH=$H_{cis}H_{trans}$, J_{cis}=10.4 Hz, J_{trans}=16.0 Hz, 1H); 5.82 (dd, –OCO–CH=C$H_{cis}H_{trans}$, J_{gem}=1.2 Hz, J_{cis}=10.4 Hz, 1H); 4.8 (m, –C≡C–CH_2–O–, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ=164.92 (CO ester); 132.93 (–CH=CH_2); 127.10 (–CH=CH_2); 119.33–104.48 (m, –CF_2– and CF_3–); 87.09 (–CF_2–C≡C–C≡C–CH_2O–); 72.71 (t, –CF_2–C≡C–C≡C–CH_2O–, J_{C-F}=146.4 Hz); 51.02 (–C≡C–CH_2–O–); MS (ei): 552 $(M)^+$; 533

(M−F·$^+$); 481 (M−HOOCCH=CH_2)$^+$; 55 (COCH=CH_2)$^+$ ppm; HRMS (ei): 552.0021, $C_{16}H_5F_{17}O_2$ requires 552.0018; IR (film): ν=2964 (st Csp^3–H); 2271; 2180 (st C≡C); 1741 (st CO); 1635 (st C=C); 1244; 1203; 1153 (st C–F) cm^{-1}; reddish viscous oil, yield: 69%.

4.5. General procedure for preparation of 1H,1H,2H,2H-perfluoro-3,5-alkadiynols methacrylates

Preparation of methacrylates was as described for the general procedure of preparation of acrylates except that methacryloyl chloride was used instead of the acryloyl chloride.

4.5.1. 1H,1H,2H,2H-Perfluoro-3,5-dodecadiynyl methacrylate. ^{19}F NMR (300 MHz, $CFCl_3$): δ=83.18 (m, CF_3–, 3F); 99.21 (m, –CF_2–C≡C–, 2F); 123.65 (m, –CF_2–CF_2–C≡C–, 2F); 124.51 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 125.17 (m, CF_3–CF_2–CF_2–, 2F); 128.48 (m, CF_3–CF_2–, 2F) ppm; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=6.15 (s, –OCOC(CH_3)=$CH_{cis}H_{trans}$, 1H); 5.62 (s, –OCOC(CH_3)=C$H_{cis}H_{trans}$, 1H); 4.30 (t, –C≡C–CH_2–CH_2–O–, J=6.6 Hz, 2H); 2.77 (m, –C≡C–CH_2–CH_2–O–, 2H); 1.96 (s, –OCOC(CH_3)=CH_2, 3H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ=166.82 (*C*O ester); 135.67 (–OCO*C*(CH_3)=CH_2); 126.24 (–OCOC(CH_3)=*C*H_2); 120.00–100.00 (m, –*C*F_2– and *C*F_3–); 83.58 (–CF_2–C≡C–C≡*C*–CH_2–); 77.12 (–CF_2–C≡C–*C*≡C–CH_2–); 63.85 (–CF_2–C≡*C*–C≡C–CH_2–); 60.89 (–C≡C–CH_2–*C*H_2–O–); 60.23 (t, –CF_2–*C*≡C–C≡C–CH_2–, J_{C-F}=145.5 Hz); 19.98 (–C≡C–*C*H_2–CH_2–O–); 18.05 (–OCOC(*C*H_3)=CH_2) ppm; MS (ei): 480 (M)·$^+$; 394 (M−HOCOC(CH_3)=CH_2)·$^+$; 69 (COC(CH_3)=CH_2 and CF_3)$^+$; HRMS (ei): 480.0381, $C_{16}H_9F_{13}O_2$ requires 480.0395; IR (film): ν=2966 (st Csp^3–H); 2266; 2177 (st C≡C); 1725 (st CO); 1639 (st C=C); 1241; 1204; 1148 (st C–F) cm^{-1}; reddish viscous oil, yield: 79%.

4.5.2. 1H,1H,2H,2H-Perfluoro-3,5-tetradecadiynyl methacrylate. ^{19}F NMR (400 MHz, $CFCl_3$): δ=83.20 (m, CF_3–, 3F); 99.26 (m, –CF_2–C≡C–, 2F); 123.50 (m, –CF_2–CF_2–C≡C–, 2F); 124.31 (m, –CF_2–CF_2–CF_2–C≡C–, 2F); 124.50 (m, –CF_2–CF_2–CF_2–CF_2–C≡C–, 2F); 125.15 (m, CF_3–CF_2–CF_2–CF_2–, 4F); 128.54 (CF_3–CF_2–, 2F) ppm; ^{1}H NMR (400 Mhz, $CDCl_3$, TMS_{int}): δ=6.46 (dd, –COOCH=$CH_{cis}H_{trans}$, J_{trans}=17.6 Hz, J_{gem}=1.2 Hz, 1H); 6.15 (dd, –COOC*H*=$CH_{cis}H_{trans}$, J_{cis}=10.4 Hz, J_{trans}=17.6 Hz, 1H); 5.89 (dd, –COOCH=C$H_{cis}H_{trans}$, J_{cis}=10.4 Hz, J_{gem}=1.2 Hz, 1H); 4.31 (t, –C≡C–CH_2–CH_2–O–, J=6.4 Hz, 2H); 2.77 (m, –C≡C–CH_2–CH_2–O–, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ=165.88 (*C*O ester); 131.94 (–COOCH=*C*H_2); 127.95 (–COO*C*H=CH_2); 119.31–104.65 (m, –*C*F_2– and *C*F_3–); 83.73 (–CF_2–C≡C–C≡*C*–CH_2–); 76.78 (–CF_2–C≡C–*C*≡C–CH_2–); 64.20 (–CF_2–C≡*C*–C≡C–CH_2–); 61.07 (–C≡C–CH_2–*C*H_2–O–); 60.56 (t, –CF_2–*C*≡C–C≡C–CH_2–, J=142.8 Hz); 20.17 (–C≡C–*C*H_2–CH_2–O–) ppm; MS (ei): 580 (M)·$^+$; 494 (M−HOCOC(CH_3)=CH_2)·$^+$; 69 (COC(CH_3)=CH_2 and CF_3)$^+$; HRMS (ei): 580.0347, $C_{18}H_9F_{17}O_2$ requires 580.0331; IR (film): ν=2967 (st Csp^3–H); 2267; 2176 (st C≡C); 1734 (st CO); 1638 (st C=C); 1244; 1199; 1152 (st C–F) cm^{-1}; reddish viscous oil, yield; 72%.

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Trifluoromethyl-substituted hydantoins, versatile building blocks for rational drug design

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Dedicated to Professor W. Steglich on the occasion of his 70th birthday

Abstract—Preparatively simple, one-pot syntheses of trifluoromethyl-substituted hydantoins starting from Boc-protected imines of hexafluoroacetone and trifluoropyruvate are described. They represent valuable building blocks for the construction of constrained peptides or as scaffolds for the synthesis of highly potent VLA-4 antagonists.

1. Introduction

A major drawback of peptide drugs is their rapid degradation by proteases, their low lipophilicity and the lack of transport systems to direct peptides into cells. Therefore, cell membranes generally resist passage of most peptides. Consequently, they are rapidly excreted via liver and kidney. The high conformational flexibility of peptides creates another problem: bioactive peptides often bind to different receptor sites causing undesired side effects.[1,2]

Incorporation of α,α-disubstituted α-amino acids into key positions of peptides is an efficient strategy to retard proteolytic degradation and to stabilize secondary structure motifs.[3] Due to the unique properties of the trifluoromethyl group, including high electronegativity, high lipophilicity and high sterical demand, α-trifluoromethyl α-amino acids [α-TfmAAs] are a special subclass of α,α-disubstituted α-amino acids, which may improve the profile of bioactive compounds considerably,[4] by enhancing absorption and transport rates as well as permeability through certain body barriers. An advantage of applying fluoromodification to stabilize peptides and proteins is, that this strategy is complementary to other existing stabilization methods.[5] Another attractive feature of most trifluoromethyl-substituted compounds is their relatively low toxicity and high stability compared to monofluoromethyl and difluoromethyl analogues.[6] Finally, ^{19}F NMR spectroscopy provides a highly efficient method for conformational studies of fluorine-containing peptides as well as for elucidating metabolic processes. Consequently, rational design of mechanism-based fluorinated biologically active compounds is a powerful tool for an efficient drug research.[7,8]

In this context, the development of methodology for incorporation of fluoromodified amino acids into key positions of drug candidates via heterocyclic building blocks, e.g. hydantoins, to improve their therapeutic profile is of current interest.[9] On the other hand, a wide range of therapeutic properties has been reported for hydantions and thiohydantions, including antiviral, antibacterial, antifungal, herbicidal, anticonvulsant, antidiabetic, anti-inflammatory, antiulcer and antiarythmic activities.[10,11] Therefore, the development of new strategies for the synthesis of hydantions, combined with fluoromodification continues to attract the attention of medicinal chemists.[12]

Herein we disclose an efficient, one-pot synthesis of trifluoromethyl- and bis(trifluoromethyl)-substituted hydantoin derivatives which can be used as 'Aib surrogates' starting from Boc-protected imines of 3,3,3-trifluoropyruvates and hexafluoroacetone (Scheme 1).

2. Results an discussion

The highly electrophilic acylimines of hexafluoroacetone[13]

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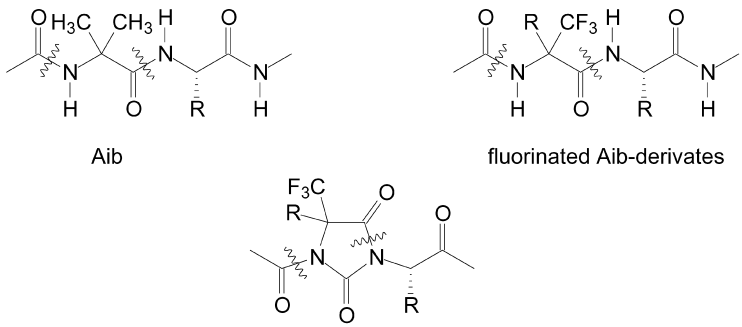


Scheme 1.

and 3,3,3-trifluoropyruvates[14] are excellent traps for isonitriles[15] to give [4+1] cycloadducts,[16,17] which can be readily transformed into dipeptide esters with up to three trifluoromethyl groups[18] on treatment with methanol/1 N HCl. These dipeptide fragments represent interesting lipophilic building blocks for the construction of sterically crowded peptidomimetics.

Surprisingly, when Boc-protected imines derived from methyl 3,3,3-trifluoropyruvate **1a** and hexafluoroacetone **1b** were reacted with isonitriles **2** (substituent pattern see Table 1) in dry benzene at 60 °C for 6–8 h, elemental analyses and mass spectra data reveal that the expected [1:1] adducts are unstable. Under the reaction conditions applied, elimination of $(CH_3)_2C{=}CH_2$ takes place. An analogous isobutene elimination, occurring at rt, was observed on activation of Boc-protected α-TFM amino acids with DCC. At 0 °C oxazolones are formed quantitatively within 20–30 min. The oxazolones turned out to be stable below −30 °C on exclusion of moisture. But on rising the temperature above 0 °C a retro ene reaction starts to convert the oxazolones into Leuchs anhydrides (Scheme 2).[19]

Table 1. Syntheses of hydantoins **5** from Boc-imines **1** and isonitriles **2**

Imine	Isonitrile	Product	R^1	R^2	R^3	R^4
1a	**2a**	**5a**	CO_2Me	H	H	Me
1a	**2b**	**5b**	CO_2Me	CF_3	CH_2Ph	Me
1a	**2c**	**5c**	CO_2Me	CF_3	Ph	Me
1b	**2d**	**5d**	CF_3	H	CH_2CHMe_2	*t*-Bu
1b	**2e**	**5e**	CF_3	H	CH_2-cyclopropyl	*t*-Bu

In analogy, we postulate that in the case of [4+1] cycloadducts **3** a retro ene reaction is the reason for the readily occurring isobutene elimination. Originally, the products isolated we ascribed the structure of 5-imino-1,3-oxazolidin-2-ones **4**.[20] But when we found that these

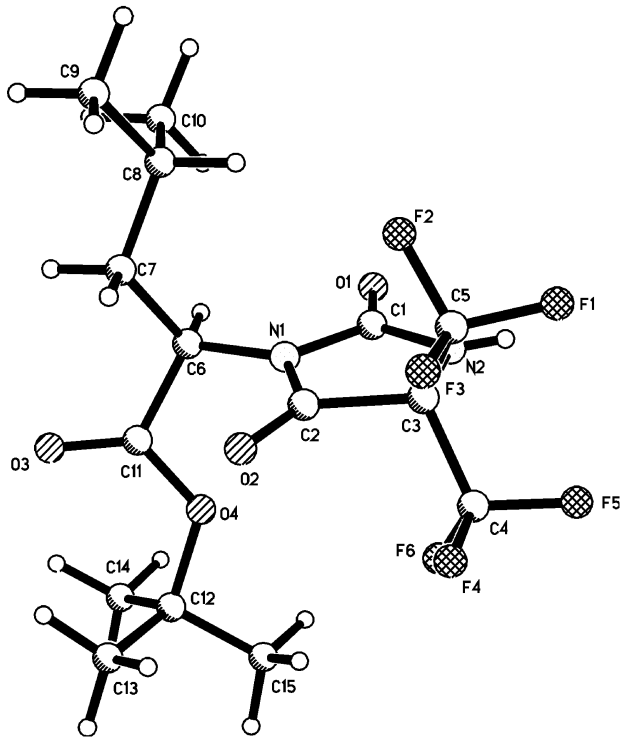
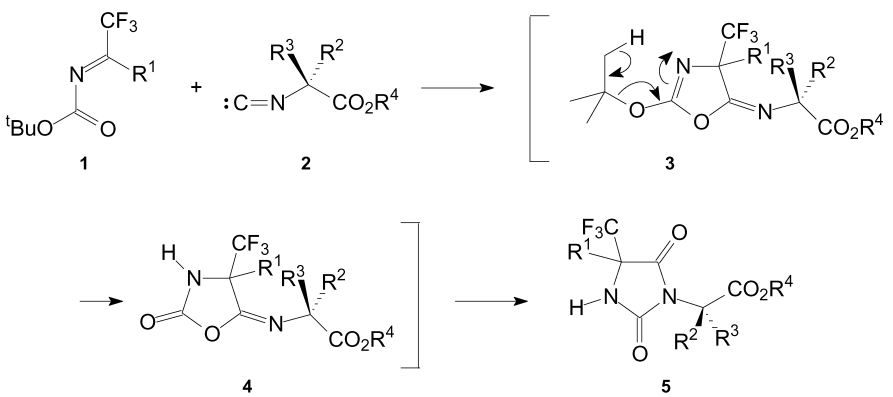
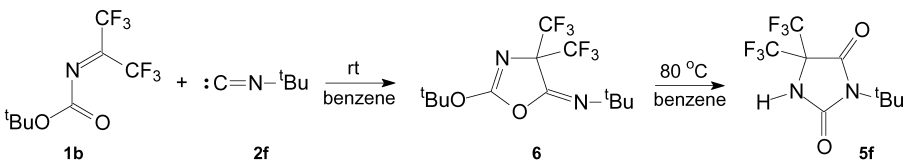


Figure 1. X-ray structure of **5d**.



Scheme 2.



Scheme 3.

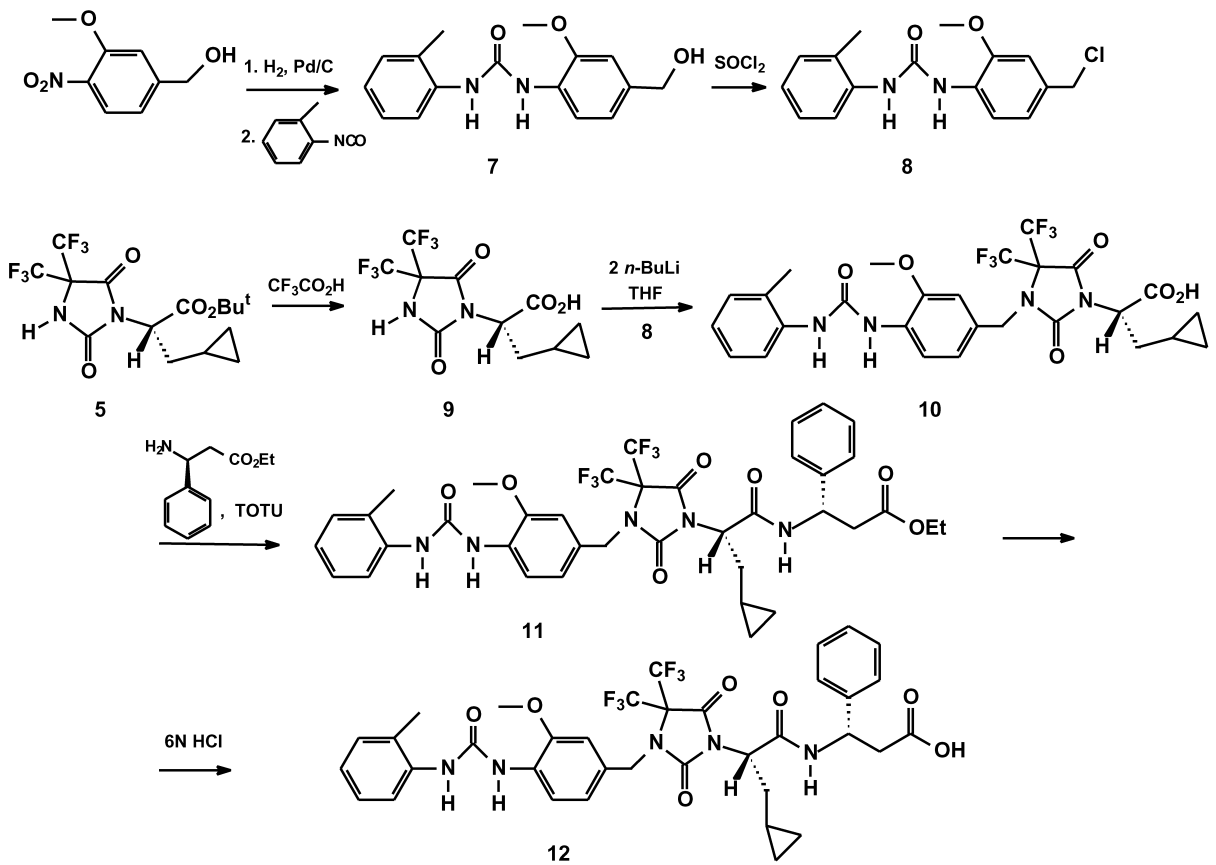
products remained unchanged on treatment with HCl at rt, we reexamined the structural assignment. We found that the [4+1] cycloadducts formed first, undergo a retro ene reaction (**3→4**). However, under the reaction conditions applied the newly formed compounds **4** are unstable too. In a consecutive rearrangement they are converted into hydantoins **5**. A resonance line in the region of δ=154–156 ppm can be assigned to an urea function incorporated into a five-membered ring system.[21]

An X-ray structure analysis[22] (Fig. 1) unequivocally proved that 4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolidine **5d** is formed in a three step sequence (**1→3→4→5**). When imine **1b** and isonitriles derived from chiral (*S*)-leucine and (*S*)-cyclopropylalanine are used, 5,5-bis(trifluoromethyl)hydantoin-modified dipeptides **5d**,**e** are obtained in very good yields.

To confirm the mechanism for the reaction of imines with isonitriles we investigated a series of similar transformations. We found that imine **1b** and *tert*-butyl isonitrile **2f** afforded a stable [1:1] adduct **6** on reaction at rt in benzene (Scheme 3). **6** was isolated and purified by low temperature crystallization. The rearrangement **6→5f** was achieved on heating under reflux in dry benzene for 16 h.

Structural variability can be generated by chain elongation in N- and C-terminal position. A typical example for a drug candidate is the VLA-4 receptor antagonist **12**[23] (Scheme 3). VLA-4 (=very late antigen 4), a member of the integrin receptor family, is expressed on activated leukocytes, which use the VLA-4 receptors for the adhesion to endothelium cells during inflammatory processes. Blocking of this receptor might be an interesting option to treat inflammatory diseases like asthma, rheumatoid arthritis and multiple sclerosis. The IC_{50} of **12** in a cell attachment assay using VLA-4 expressing U937 cells and its natural ligand VCAM-1 (=vascular cell adhesion molecule 1) was determined to 5.55 nM.

Compound **12** was prepared as shown in Scheme 4. The bis(trifluoromethyl)hydantoin **5e** was deprotected to give acid **9**, which was alkylated using 4-(3-(2-methylphenyl)-ureido-3-methoxybenzyl chloride **8** in the presence of 2 equiv. of *n*-BuLi in THF. **8** was prepared in three steps starting from 3-methoxy-4-nitrobenzyl alcohol, reduction of



Scheme 4.

the nitro group, addition to 2-methylphenyl-isocyanate and transformation of the resulting benzyl alcohol **7** to the corresponding chloride using $SOCl_2$. The VLA-4 antagonist **12** was prepared by coupling of (*S*)-3-amino-3-phenyl-propionic acid ethyl ester to the hydantoin **10** in the presence of TOTU followed by cleavage of the ester group with 6 N HCl (Scheme 4).

3. Conclusion

We developed a highly efficient synthesis for 4-trifluoromethyl- **5a–c** and 4,4-bis(trifluoromethyl)-substituted hydantoins **5d**,**e** which can be used as lipophilic, rigid building blocks for peptide modification. The three step synthesis can be performed as one-pot procedure and represents an impressive example for the high efficiency and elegance of domino reactions.[24,25] **5e** was used as the central scaffold in the synthesis of the highly potent VLA-4 antagonist **12**.

4. Experimental

4.1. General

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ=0 ppm); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F spectra were recorded at 188 and 282 MHz with trifluoroacetic acid (TFA, δ=0 ppm) as external standard. Optical rotations $[\alpha]_D$ were measured using a Polartronic polarimeter (Schmidt and Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-Rapid Elemental Analyzer (Hereaus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI=70 eV). For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in text. Organic solvents were dried and distilled prior to use.

2-(*N*-Benzoyl)imino- and 2-*N*-(*tert*-butoxycarbonyl)imino-1,1,1,3,3,3-hexafluoropropane were prepared according to the method given in lit.[13b] Methyl 2-[*N*-(benzyloxycarbonyl)imino]- and methyl 2-[*N*-(*tert*-butoxycarbonyl)-imino]-3,3,3-trifluoropropionate were prepared according to the protocol described in lit.[14b] and lit.,[26] respectively. Isonitriles **2a–c** were prepared according to the method given in lit.[17] Isonitriles **2d**,**e** were prepared from *tert*-butyl *N*-formyl-(*S*)-leucinate and *tert*-butyl *N*-formyl-(*S*)-cycloalaninate, respectively, using diphosgene and were taken into reaction with imine **1b** without isolation (see below).

4.2. Trifluoromethyl-substituted hydantoins. General procedure

Equimolar amounts (5 mmol) of an acylimine **1** and an isonitrile **2** were stirred in dry benzene (25 mL) at 60 °C for 6–8 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes).

4.2.1. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-acetate 5a. Yield: 1.12 g (75%) **5a**; oil. IR (KBr): ν=3360, 3290, 1810, 1780, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=3.78 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 7.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=40.09, 53.01, 54.92, 68.56 (q, *J*=31.4 Hz), 120.78 (q, *J*=284.9 Hz), 155.38, 161.25, 161.86, 166.60. ^{19}F NMR ($CDCl_3$): δ=4.07 (s, 3F, CF_3). Anal. calcd for $C_9H_9F_3N_2O_6$ (298.16): C, 36.25; H, 3.04; N 9.39. Found: C, 36.40; H 3.19; N, 9.35.

4.2.2. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-2-benzyl-3,3,3-trifluoro-propionate 5b. Yield: 2.00 g (88%) **5b**. *Diastereomer 1*: R_f=0.31 (ethyl acetate/hexanes=1:2); mp 116–119 °C. ^{1}H NMR ($CDCl_3$): δ=3.64 (s, 3H, OCH_3), 3.73 (d, 1H, *J*=14.4 Hz, CH_2), 3.90 (s, 3H, OMe), 4.20 (d, 1H, *J*=14.4 Hz, CH_2), 7.17 (m, 2H, H_{arom}), 7.26 (m, 3H, H_{arom}), 7.40 (m, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=35.86, 53.11, 55.00, 67.52 (q, *J*=31.4 Hz), 120.59 (q, *J*=285.0 Hz), 123.46 (q, *J*=287.4 Hz), 128.08, 128.38, 130.92, 132.13, 154.39, 160.89, 161.60, 163.15. ^{19}F NMR ($CDCl_3$): δ=3.80 (s, 3F, CF_3), 7.46 (3, 3F, CF_3).

Diastereomer 2: R_f=0.26 (ethyl acetate/hexanes=1:2); oil. ^{1}H NMR ($CDCl_3$): δ=3.64 (s, 3H, OCH_3), 3.76 (d, 1H, *J*=14.3 Hz, CH_2), 3.90 (s, 3H, OCH_3), 4.19 (d, 1H, *J*=14.3 Hz, CH_2), 7.15 (m, 2H, H_{arom}), 7.27 (m, 3H, H_{arom}), 7.49 (m, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=35.79, 53.10, 55.01, 67.50 (q, *J*=31.5 Hz), 69.02 (q, *J*=28.4 Hz), 120.60 (q, *J*=285.3 Hz), 123.50 (q, *J*=287.2 Hz), 128.10, 128.40, 130.90, 132.17, 154.43, 160.92, 161.57, 163.26. ^{19}F NMR ($CDCl_3$): δ=3.63 (s, 3F, CF_3), 7.30 (s, 3F, CF_3). Anal. calcd for $C_{17}H_{14}F_6N_2O_6$ (456.28): C, 44.75; H, 3.09; N, 6.14. Found: C, 44.59; H, 3.31; N, 6.17.

4.2.3. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-2-phenyl-3,3,3-trifluoro-propionate 5c. Yield: 1.33 g (60%) **5c**; oil (mixture of diastereomers, ratio 1:1). *Diastereomer 1*: R_f=0.33 (ethyl acetate/hexanes=1:2). ^{1}H NMR ($CDCl_3$): δ=3.80 (s, 3H, OMe), 3.87 (s, 3H, OCH_3), 7.37 (m, 4H, H_{arom}, NH), 7.57 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=54.12, 54.93, 67.70 (q, *J*=31.3 Hz), 69.58 (q, *J*=29.5 Hz), 120.65 (q, *J*=284.8 Hz), 123.37 (q, *J*=287.9 Hz), 127.30 (q, *J*=1.9 Hz), 128.01, 128.66, 129.80, 154.04, 160.62, 161.05, 163.23. ^{19}F NMR ($CDCl_3$): δ=3.95 (s, 3F, CF_3), 11.53 (s, 3F, CF_3).

Diastereomer 2: R_f=0.26 (ethyl acetate/hexanes=1:2). ^{1}H NMR ($CDCl_3$): δ=3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.23 (s, 1H, NH), 7.39 (m, 3H, H_{arom}), 7.58 (s, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=53.99, 54.86, 67.46 (q, *J*=31.5 Hz), 69.40 (q, *J*=29.5 Hz), 120.49 (q, *J*=284.9 Hz), 123.24 (q, *J*=288.1 Hz), 127.18 (q, *J*=1.8 Hz), 127.93, 128.52, 129.67, 153.61, 160.70, 160.99, 163.08. ^{19}F NMR ($CDCl_3$): δ=3.73 (s, 3F, CF_3), 11.42 (s, 3F, CF_3). Anal. calcd for $C_{16}H_{12}F_6N_2O_6$ (442.25): C, 43.45; H, 2.73; N, 6.33. Found: C, 43.85; H, 2.94; N, 6.21.

4.2.4. *tert*-Butyl *N*-formyl-(*S*)-leucinate.[27] A solution of 4.04 g (40 mmol) of triethylamine in 10 mL of dichloromethane was added to a solution of 8.94 g (40 mmol) of *S*-leucine *tert*-butyl ester hydrochloride and 3.40 g (40 mmol) of cyanomethyl formate[27] in 60 mL of dichloromethane at 0 °C. The reaction solution was allowed to warm up to rt overnight. It was washed twice with brine. The organic phase was dried over $MgSO_4$, filtrated and evaporated. Distillation of the residue under reduced pressure gave *tert*-butyl (*S*)-3-*N*-formyl-3-leucinate (7.5 g, 87%) as an oil; bp 118 °C/0.02 Torr. ^{1}H NMR ($CDCl_3$): δ=0.84 (d, 3H, *J*=5.0 Hz, CH_3), 0.87 (d, 3H, *J*=5.0 Hz, CH_3), 1.36 (s, 9H, $(CH_3)_3$), 1.49 (m, 3H, CH, CH_2), 4.51 (m, 1H, N–CH), 6.75 (br.s, 1H, NH), 8.10 (s, 1H, CH═O).

4.2.5. *tert*-Butyl (*S*)-2-[4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(methyl-propyl)acetate 5d. Diphosgene (2.4 g, 12.1 mmol) was added to a solution of *N*-formyl-(*S*)-leucine *tert*-butyl ester (2.5 g, 11.6 mmol) and triethylamine (2.5 g, 24.7 mmol) in dry dichloromethane (100 mL) at −30 °C. The reaction mixture was allowed to warm up to −10 °C during 1 h and was stirred further at this temperature until the reaction was complete (TLC-control). The reaction solution was washed at rt twice with 7% aqueous $NaHCO_3$ solution. The organic phase was separated and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was taken up in dry benzene (70 mL). Boc-imine of hexafluoroacetone **1b** (3.0 g, 11.3 mmol) in dry benzene (10 mL) was added dropwise to this solution at rt. The reaction mixture was heated to 60 °C overnight, then benzene was removed in vacuo. Column chromatography of the residue over silica gel (eluent: petroleum ether/ethyl acetate=10/1) gave 3.70 g (80%) of **5d** as white crystals; mp 105–106 °C; $[\alpha]^{20}$=−24° (*c*=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.88 (d, 3H, *J*=5.2 Hz, CH_3), 0.92 (d, 3H, *J*=5.2 Hz, CH_3), 1.32 (m, 1H, CH), 1.41 (s, 9H, $(CH_3)_3$), 1.83 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 4.64 (dd, 1H, N–CH, *J*=4.4, 11.7 Hz), 7.93 (br.s, 1H, NH). ^{19}F NMR ($CDCl_3$): δ=4.8 (m, 6F, 2×CF_3). ^{13}C NMR ($CDCl_3$): δ=20.95, 23.41, 25.20, 27.99, 36.68, 53.35, 66.39 sept. (C–CF_3, *J*=32.0 Hz), 83.97, 120.49 q (CF_3, *J*=286.5 Hz), 156.18, 160.54, 167.52. Anal. calcd for $C_{15}H_{20}F_6N_2O_4$ (406.3): C, 44.34; H, 4.96; N, 6.89. Found: C, 44.60; H, 5.28; N 7.02.

4.2.6. *tert*-Butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate. (*S*)-3-Cyclopropylalanine (3.5 g, 27.1 mmol) was added at rt to a mixture of dioxane (50 mL) and conc. sulfuric acid (5 mL), prepared by cautious dropwise addition of the acid to dioxane at 5 °C. The solution was transferred together with isobutylene (40 mL) in a sealed tube at −78 °C. The sealed tube was shaken at rt for 24 h. The sealed tube was carefully opened (under cooling) and the reaction mixture was cautiously poured into a stirred mixture of triethylamine (30 mL) and water (50 mL), cooled to 5 °C. After removal of the excess of isobutylene, the product was extracted with diethyl ether (2×50 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue-a pale yellow oil (4.2 g, 84%) was used for the following reaction without further purification. ^{1}H NMR ($CDCl_3$): δ=0.10 (m, 2H, CH_2), 0.49 (m, 2H, CH_2), 0.81 (m, 1H, CH), 1.25 (br. m, 2H, NH_2), 1.50 (s, 9H, $C(CH_3)_3$), 1.61 (m, 2H, CH_2), 3.41 (dd, 1H, *J*=1.5, 10.1 Hz, N–CH).

A mixture of (*S*)-cyclopropyl-alanine *tert*-butyl ester (10.0 g, 54 mmol) and cyanomethyl formiate (4.7 g, 55.2 mmol) in dichloromethane (100 mL) was stirred at rt overnight. The solvent was removed in vacuo. Distillation of the residue under reduced pressure gave *tert*-butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate (8.8 g, 76%) as an oil; bp 120 °C/0.3 Torr. ^{1}H NMR ($CDCl_3$): δ=0.09 (m, 2H, CH_2), 0.48 (m, 2H, CH_2), 0.65 (m, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$), 1.69 (m, 2H, CH_2), 4.63 (m, 1H, N-CH), 6.31 (1H, NH), 8.20 (s, 1H, CH═O).

4.2.7. *tert*-Butyl (*S*)-2-[4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(cyclopropylmethyl)acetate 5e. Diphosgene (2.4 g, 12.1 mmol) was added to a solution of *tert*-butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate (2.5 g, 11.7 mmol) and triethylamine (2.5 g, 24.7 mmol) in dry dichloromethane (100 mL) at −30 °C. The reaction solution was allowed to warm up to −15 °C during 1 h and was stirred further at this temperature until the reaction was complete (TLC-control). The organic phase was washed twice with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was dissolved in benzene (70 mL). Boc-imine of hexafluoroacetone **1b** (3.05 g, 11.5 mmol) in benzene (10 mL) was added dropwise at rt to this solution. The mixture was heated at 60 °C (bath temperature) overnight, then benzene was removed in vacuo. Column chromatography of the residue over silica gel (eluent: hexanes/ethyl acetate=8/1) gave 3.70 g (78%) **5e** as white crystals; mp 76–77 °C; $[\alpha]^{20}$=−28° (*c*=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.08 (m, 2H, CH_2), 0.42 (m, 2H, CH_2), 0.50 (m, 1H, CH), 1.40 (s, 9H, $(CH_3)_3$), 2.02 (m, 2H, CH_2), 4.67 (dd, 1H, N–CH, *J*=4.4, 11.7 Hz), 7.73 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=3.46, 5.21. 7.76, 27.99, 32.96, 55.41, 66.48 (sept., C-CF_3, *J*=32.0 Hz), 83.94, 120.49 (q, CF_3, *J*=286.5 Hz), 156.19, 160.55, 166.96. ^{19}F NMR ($CDCl_3$): δ=4.89 (m, 6F, 2×CF_3). Anal. calcd for $C_{15}H_{18}F_6N_2O_4$ (404): C, 44.55; H, 4.45; N, 6.93. Found: C, 44.60; H, 4.76; N, 6.72.

4.2.8. 2-*tert*-Butyloxy-4,4-bis(trifluoromethyl)-5-*tert*-butylimino-4*H*-oxazol 6. A mixture of imine **1b** (1.5 g, 5.7 mmol) and *tert*-butylisonitrile (0.47 g, 5.7 mmol) in dry benzene (50 mL) was stirred at rt for 48 h. The solvent was removed under reduced pressure, the remaining solid was recrystallized from hexanes at 0 °C to give 1.7 g (86.3%) **6** as white crystals; mp 73 °C. ^{1}H NMR ($CDCl_3$): δ=1.30 (s, 9H, $NCMe_3$), 1.62 (s, 9H, $OCMe_3$). ^{13}C NMR ($CDCl_3$): δ=29.25, 31.28, 58.39, 78.33 (sept., C-CF_3, *J*=32.0 Hz), 90.62, 123.09 (q, CF_3, *J*=287.5 Hz), 141.19, 164.45. ^{19}F NMR ($CDCl_3$): δ=3.36 (s, 6F, 2×CF_3). Anal. calcd for $C_{13}H_{18}F_6N_2O_2$ (348.3): C, 44.83; H, 5.21; N, 8.04. Found: C, 44.80; H, 5.59; N, 8.32.

4.2.9. 1-*tert*-Butyl-4,4-bis(trifluoromethyl)-2,5-dioxo-imidazolidin 5f. A solution of **6** (1.3 g, 3.7 mmol) in 30 mL benzene was heated at 80 °C for 16 h. After removing of solvent the remaining solid was recrystallized from hexanes to give 0.99 g (90.8%) of **5f** as white crystals; mp 114–115 °C. ^{1}H NMR ($CDCl_3$): δ=1.59 (s, 9H, $NCMe_3$), 7.56 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=29.25, 61.08, 65.73 (sept., C–CF_3, *J*=32.0 Hz), 120.92 (q, CF_3, *J*=287.5 Hz), 159.97, 161.96. ^{19}F NMR ($CDCl_3$):

δ=4.10 (s, 6F, 2×CF_3). Anal. calcd for $C_9H_{10}F_6N_2O_2$ (292.19): C, 37.00; H, 3.45; N, 9.59. Found: C, 37.00; H, 3.39; N, 9.56.

4.3. (*S*)-3-((*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido-3-methoxy-benzyl)-2,5-dioxo-imidazolin-1-yl)-2-cyclopropylmethyl)acetylamino)-3-phenylpropionic acid 12

4.3.1. 4-[3-(2-Methylphenyl)ureido]-methoxybenzyl alcohol 7. 3-Methoxy-4-nitrobenzyl alcohol (15.0 g, 81.8 mmol) was hydrogenated in methyl *tert*-butyl ether (500 mL) in the presence of a palladium/carbon catalyst while cooling with ice. After the hydrogen uptake ceased, the catalyst was filtered off, and 2-methylphenyl isocyanate (10.14 g, 81.8 mmol) was added to the stirred filtrate within 30 min. The reaction mixture was stirred overnight, and the precipitate was filtered off and washed with methyl *tert*-butyl ether. Yield: 20.5 g (88%) **7**.

^{1}H NMR (DMSO-d_6): δ=2.22 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.43 (d, 2H, *J*=6.0 Hz, CH_2), 5.07 (t, 1H, *J*=6.0 Hz, OH), 6.83 (d, 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.80 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.05 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.45 (s, 1H, NH), 8.56 (s, 1H, NH). MS (ESI): 287.2 $[M+H]^+$.

4.3.2. 4-[3-(2-Methylphenyl)ureido]-3-methoxybenzyl chloride 8. Thionyl chloride (7.65 mL, 104.8 mmol) was added dropwise to a suspension of **7** (15.0 g, 53.4 mmol) in methylene chloride (300 mL) while cooling with ice. The reaction mixture was stirred at rt for 3 h. After standing overnight the mixture was poured into heptane (1000 mL). The heptane was decanted off from the oil, which had separated. The oil was again suspended in heptane, and the heptane was decanted off. This procedure was repeated two times. Then the residue was dissolved in methylene chloride and poured into ice-cold diisopropyl ether (800 mL). The mixture was stirred for 2 h while cooling with ice. The precipitate was filtered off, washed with diisopropyl ether and dried over phosphorus pentoxide to give 12.0 g (75%) of **8**.

^{1}H NMR (DMSO-d_6): δ=2.23 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.73 (m, 2H, CH_2), 6.96 (m, 2H, H_{arom}), 7.15 (m, 3H, H_{arom}), 7.78 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.12 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.55 (s, 1H, NH), 8.70 (s, 1H, NH).

4.3.3. (*S*)-2-[4,4-Bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(cyclopropylmethyl)-acetic acid 9. Was obtained from compound **5e** on stirring in a solution of trifluoroacetic acid in dichloromethane (3/7). The solvent and trifluoroacetic acid were removed under reduced pressure. The residue was purified by freeze drying. The crude product **9** was used for the next reaction step.

4.3.4. (*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)-2-(cyclopropylmethyl)acetic acid 10. A *n*-BuLi solution (3.2 mL. 2.5 M in hexane) was added to a solution of **9** (1.39 g, 4.0 mmol) in dry THF (40 mL) under argon at −40 °C. The reaction mixture was allowed to warm up to 0 °C while stirring, a solution of 4-(3-(2-methylphenyl)-ureido)-3-methoxybenzyl chloride **8** (2.43 g, 8.0 mmol) in dry THF (20 mL) was added, and the reaction mixture was stirred at rt for 3 h. Then 1 N HCl (20 mL) was added and THF removed in vacuo. The aqueous phase was extracted twice with methyl *tert*-butyl ether. The combined organic phase was dried with $NaSO_4$, and after filtration, concentrated in vacuo. The residue was purified by preparative HPLC. Concentration of the product fractions and freeze drying gave 1.41 g (57%) **10**.

^{1}H NMR (DMSO-d_6): δ=0.00 (m, 1H, CH), 0.13 (m, 1H, CH), 0.36 (m, 2H, CH_2), 0.50 (m, 1H, CH), 2.00 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.73 (d, 1H, *J*=15.8 Hz, CH_2), 4.84 (d, 1H, *J*=15.8 Hz, CH_2), 4.94 (dd, 1H, *J*=4.5, 11.3 Hz, CH), 6.82 ('d', 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.77 (d, 1H, *J*=7.1 Hz, H_{arom}), 8.08 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.63 (s, 1H, NH), 13.58 (bs, 1H, COOH). MS (ESI): 617.1 $[M+H]^+$.

4.3.5. Ethyl (*S*)-3-(*S*)-2-(4,4-bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxo-imidazolidin-1-yl)-2-(cyclopropylmethyl)acetylamino-3-phenylpropionate 11. TOTU (728 mg, 2.28 mmol) (*O*-((cyano(ethoxycarbonyl)-methylene)amino-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate) and *N*,*N*-diisopropylamine (368 μL) were added to a solution of **10** (1.41 g, 2.28 mmol) and of ethyl-(*S*)-3-amino-3-phenylpropionate (442 mg, 2.28 mmol) in dry DMF (20 mL) at 0 °C. After stirring at rt for 1 h, the DMF was removed in vacuo, the residue was dissolved in ethyl acetate, and the organic phase was washed successively with aqueous $KHSO_4/K_2SO_4$ solution, saturated $NaHCO_3$ solution and water. The organic phase was dried over $NaSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography over silica gel, eluent: heptane/ethyl acetate (3:2). After removal of the solvent was obtained 1.48 g (82%) **11**.

^{1}H NMR (DMSO-d_6): δ=0.07 (m, 1H, CH), 0.18 (m, 1H, CH), 0.40 (m, 2H, CH_2), 0.56 (m, 1H, CH), 1.10 (t, 3H, *J*=6.8 Hz, CH_3), 1.97 (m, 1H, CH), 2.22 (m, 1H, CH), 2.23 (s, 3H, CH_3), 2.78 (d, 2H, *J*=7.5 Hz, CH_2), 3.82 (s, 3H, OCH_3), 4.00 (m, 2H, OCH_2), 4.70 (d, 1H, *J*=15.8 Hz, CH_2), 4.75 (m, 1H, CH), 4.80 (d, 1H, *J*=15.8 Hz, CH_2), 5.24 ('q', 1H, *J*=7.5 Hz, CH), 6.80 ('d', 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.30 (m, 5H, H_{arom}), 7.75 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.06 (d, 1H, *J*=7,5 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.62 (s, 1H, NH), 8.63 (d, 1H, *J*=7.5 Hz, NH). MS (ESI): 792.2 $[M+H]^+$.

4.3.6. (*S*)-3-((*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)-2-(cyclopropylmethyl)-acetylamino)-3-phenylpropionic acid 12. A solution of **11** (1.46 g, 1.84 mmol) in *N*-methyl-2-pyrrolidone (40 mL) was heated with 6N HCl (20 mL) at 60 °C for 6 h. After cooling to rt, the reaction mixture was poured into water (300 mL), and the precipitate was filtered off, washed with water and dried over phosphorus pentoxide. The crude product was subjected twice to column chromatography over silica gel (eluent: dichloromethane/methanol/acetic acid/water=94/5/0.5/0.5). After removal of the solvents, the residue was dissolved in dichloromethane, washed with water and dried

over $NaSO_4$. After removal of the solvent and lypophilization were obtained 1.19 g (85%) **12**.

^{1}H NMR (DMSO-d_6): δ=0.06 (m, 1H, CH), 0.18 (m, 1H, CH), 0.40 (m, 2H, CH_2), 0.55 (m, 1H, CH), 1.97 (m, 1H, CH), 2.22 (m, 1H, CH), 2.23 (s, 3H, CH_3), 2.7 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.68 (d, 1H, J=15.8 Hz, CH_2), 4.77 (m, 1H, CH), 4.82 (d, 1H, J=15.8 Hz, CH_2), 5.18 ('q', 1H, J=7.5 Hz, CH), 6.80 ('d', 1H, J=8.2 Hz, H arom.), 6.95 (m, 2H, H $_{arom}$), 7.15 (m, 2H, H_{arom}), 7.30 (m, 5H, H_{arom}), 7.77 (d, 1H, J=8.2 Hz, H_{arom}), 8.05 (d, 1H, J=7,5 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.56 (d, 1H, J=7.5 Hz, NH), 8.61 (s, 1H, NH), 12.32 (bs, 1H, COOH). MS (ESI): 764.2 $[M+H]^+$.

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Thermal decomposition of the *tert*-butyl perester of thymidine-5′-carboxylic acid. Formation and fate of the pseudo-C4′ radical

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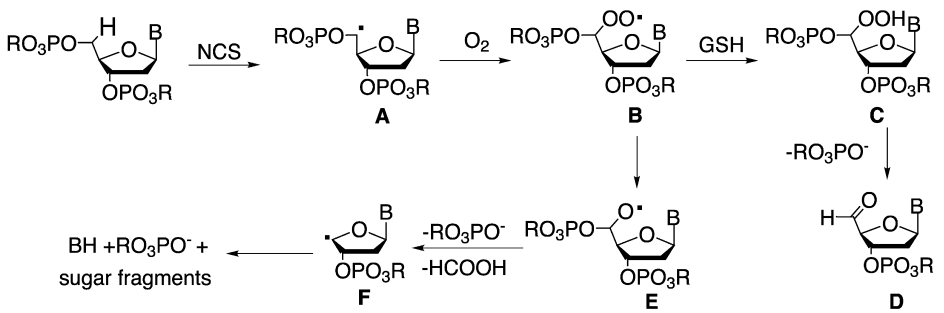
Abstract—Thermal decomposition of the *tert*-butyl perester of thymidine-5′-carboxylic acid **1** carried out at 85 °C in different solvents affords the *tert*-butylacetal **4a**, deriving from in cage decomposition, and pseudo C4′ radicals **2**. Radicals **2** can be reduced to **5** by hydrogen atom abstraction from thiol (thiophenol or glutathione) or THF, or can be oxidized to cations **8** by dioxygen or perester **1** itself. Cations **8** are stereoselectively trapped by the nucleophilic solvent (*tert*-butanol, methanol, water) to give acetals **4a**-**c**.

1. Introduction

Damage of the sugar unit of DNA is mainly determined by formation of free radicals through hydrogen atom abstraction from one of the five available positions. The free radical can repair itself by hydrogen atom abstraction from glutathione (GSH), or can lead to modifications of the sugar unit (DNA-damage), or can lead to the strand-breakage.[1–3]

The main nucleolytic agents include hydroxyl radicals, ionizing radiations and enediynes, a family of anticancer antibiotics (neocarcinostatin, NCS). For steric reasons, the preference for the H-abstraction is H5′>H4′>H3′>H2′>H1′.[4] Many of the proposed mechanisms for the strand-breakage of DNA include the initial formation of C5′ radicals. Most of the studies carried out on the fate of the C5′ radical came from rationalisation of products deriving from degradation of DNA induced by NCS in the presence of GSH under aerobic conditions.[3,4] It is worth noting that the strand-breakage is base-selective, preferentially occurring (75%) on the thymidine unit.[5] The several proposed mechanisms can be described as depicted in Scheme 1. Trapping of the C5′ radical **A** by molecular oxygen leads to the peroxyl radical **B**, which can evolve in two different ways: (i) hydrogen abstraction from GSH leading to the hydroperoxide **C**, and then to the aldehyde **D** by loss of the phosphate unit (80%); (ii) formation of the oxy radical **E** (in an unclear way!), and then of the pseudo C-4′ radical **F** by β-fragmentation. The pseudo C-4′ radical **F** should be responsible for the observed fragmentation products, that is, BH, RO_3PO^-, and unidentified sugar fragments.[6,7]



Scheme 1. Proposed mechanism for the fate of C5′ radical under aerobic conditions.

Keywords: DNA damage; Radical decomposition; Cage decomposition; Nucleoside; Thymidine; Thymidine-5′-carboxylic acid *tert*-butyl perester.
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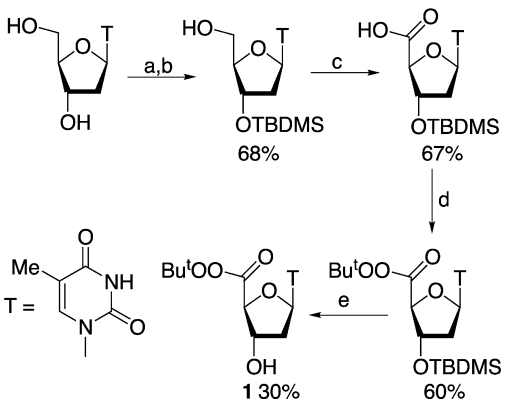
Model studies on the fate of the postulated pseudo C-4′ radical intermediate **F** are lacking. At the present, we are interested in radical-based damage associated with the C-5′ position. As a part of this work we have undertaken model studies on the fate of the pseudo C-4′ radical **2**.

2. Results and discussion

We have chosen the *tert*-butyl perester of thymidine-5′-carboxylic acid **1** as a possible precursor of the pseudo C-4′ radical **2**. Perester **1** has been obtained in 30% overall yield through the multi-step synthesis depicted in Scheme 2.



Scheme 2. Reagents and conditions: (a) THF/DMF, TBDMS-Cl, Imidazole, $AgNO_3$, 98%; (b) MeOH, PPTS, 69%; (c) MeCN/H_2O, TEMPO, BAIB, 98%; (d) THF, CDI, *t*-BuOOH, 90%; (e) THF, TBAF, 50%.

The decomposition of **1** was performed at 85 °C in several solvents (THF, *t*-BuOH, MeOH, H_2O/*t*-BuOH) in the absence and in the presence of thiol (thiophenol, PhSH, or glutathione, GSH) in order to discover both the capability of **1** of behaving as radical **2** precursor and to investigate the fate of radical **2** under different reaction conditions. In all cases complete disappearance of **1** was monitored within 1 h.[8]

The decomposition of **1** in THF gave thymine **3** (46%) and the *tert*-butyl acetal **4a** (25%) as major products together with minor amounts (14%) of the reduced product **5** (Table 1, entry 1). The acetal **4a** was separated as (4′*S*) diasteroisomer. The (4′*S*) configuration was supported by the ^{1}H NMR spectrum through analysis of coupling constants in addition to NOE experiments. In particular, in $CDCl_3$ solution we found $J_{3'-4'}$=0, indicating a dihedral angle of near 90°. Moreover, irradiation on the C3′–OH proton caused a nuclear Overhauser enhancement of H4′ and H3′ protons, and minor enhancements of *tert*-butyl and H1′ protons.

Unfortunately, no evidence of any sugar fragments, expected to accompany the formation of thymine, could be obtained both by GC–MS and HPLC analysis of the reaction mixture. In addition, the reaction mixture was reacted with TMS-Cl following the procedure of Corey.[9] Also in this case subsequent GC–MS analysis did not show the presence of any possible sugar fragment.

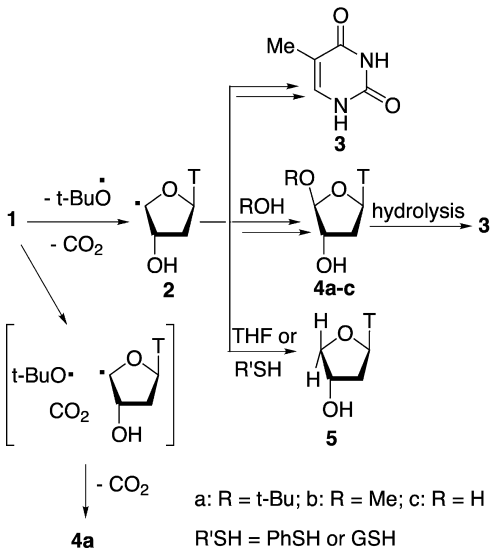
Compound **5** was that expected from the pseudo C-4′ radical **2** through hydrogen atom abstraction reaction and it can be confidently assumed to be a radical probe. The hydrogen abstraction reaction by **2** occurred from the THF solvent, as proved by the high deuterium isotope effect (k_H/k_D=7) observed when the decomposition of **1** was carried out in THF-d8. In this deuterated solvent the yield of **5** faded from 14 to 2%, as evidenced by HPLC analysis of the reaction mixture. This hydrogen atom abstraction reaction is an example of an 'identity reaction',[10] since both the abstracting radical **2** and the resulting radical (THF) are tetrahydrofuran-2-yl radicals.

When the decomposition of **1** was performed in THF in the presence of a 5-fold excess of thiophenol (a strong hydrogen donor) the yield of **5** increased from 14 to 58% at the expense of thymine **3**, whereas the yield of the acetal **4a** remained unchanged (Table 1, entry 2). These findings clearly indicate that the thermal decomposition of perester **1** in THF can lead to radicals **2**, which are responsible for both thymine **3** and the reduction product **5**. On the contrary, the acetal **4a** was not derived from diffusible radicals **2**. It was most likely derived from thermal decomposition of **1** with loss of carbon dioxide and in cage coupling of the resulting radicals (Scheme 3). The in cage decomposition of *tert*-butyl peresters is well documented.[11]

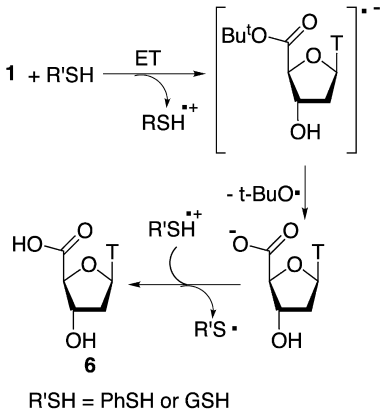
Small amounts of the thymidinoic acid **6** were also detected in the reaction carried out in the presence of PhSH. The acid **6** was probably formed by a SET process between perester **1** and PhSH, leading to a perester radical anion $\mathbf{1}^{\bullet-}$, from which **6** eventually arose by loss of *tert*-butoxy radicals (Scheme 4). Similar SET processes between peresters and the sulfur atom of sulfides[12] and thiols[13] have been already reported.

Table 1. Products (%) from thermal decomposition of 1.5 mM solutions of perester 1

Conditions	Thymine **3** (%)	Acetal **4a** (%)	Product **5** (%)	Others (%)
THF, air	46	25	14	None
THF, air, PhSH (5 mol equiv.)	7	24	58	**6** (7)
t-BuOH, air	12	73	n.d.	None
t-BuOH, air, PhSH (5 mol equiv.)	15	33	35	**6** (8)
MeOH, air	7	12	n.d.	**6** (10), 1:3 mixture of **4b**+**7** (42)
MeOH, air, PhSH (5 mol equiv.)	5	10	10	**6** (20), **7** (30)
H_2O/*t*-BuOH, air	87	n.d.	n.d.	None
H_2O/*t*-BuOH, air, GSH (1 mol quiv.)	46	n.d.	27	**6** (4)
H_2O/*t*-BuOH, air, GSH (5 mol equiv.)	40	n.d.	23	**6** (13)
H_2O/*t*-BuOH, argon	60	n.d.	n.d.	**6** (10)
H_2O/*t*-BuOH, argon, GSH (5 mol equiv.)	45	n.d.	28	**6** (12)



Scheme 3.



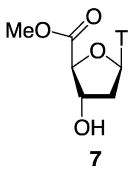
Scheme 4.

The decomposition of **1** carried out in *tert*-butanol in the presence of a 5-fold excess of PhSH similarly gave the radical product **5** and the in cage product **4a** together with minor amounts of thymine **3** and acid **6** (Table 1, entry 4). The decomposition repeated in the absence of the thiol hydrogen donor led to suppression of the radical product in favour of the acetal **4a** (Table 1, entry 3). In both cases the acetal **4a** was separated as (4′*S*) diasteroisomer.

On these bases we can infer that, similar to the reaction carried out in THF, the decomposition of **1** in *tert*-butanol furnishes both the in cage product **4a** and radicals **2**. In both solvents, and in the presence of thiol radicals, **2** afford the reduction product **5**. But, different from THF, in *tert*-butanol and in the absence of thiol radicals, **2** mainly give the acetal **4a** instead of thymine **3**.

The formation of the acetal **4a** as deriving from reaction of radical **2** with *tert*-butanol is an amazing result. In fact, no reaction was expected between a radical species and a nucleophilic solvent. This finding was supported by results obtained from the decomposition of **1** carried out in methanol, which led to the formation of both *tert*-butylacetal **4a** and methylacetal **4b**, the former deriving from the in cage decomposition, the latter from radical **2** (Table 1, entry 5). As a matter of fact, the reduction product **5** was formed at the expense of the acetal **4b**, but not of the acetal **4a**, when the reaction was carried out in the presence of PhSH (Table 1, entry 6).

However, in both reactions the major product was the methyl ester **7**. This product was formed even by standing at room temperature a methanol solution of **1** (50% conversion after ca. 2 h) and it probably derives through a trans-esterification reaction. Unfortunately, the acetal **4b** and the ester **7** formed an inseparable mixture both by HPLC and column chromatography. As a consequence, the methyl acetal **4b** was not obtained as a pure product. Its identification arose by ^{1}H NMR spectral comparison of the above (**4b**+**7**) mixture with a pure sample of **7**. Moreover, negative-ions ES-MS spectrum showed both peaks at *m*/*z* 241 and 269, ascribable to ($M^{-}-1$) of **4b** and **7**, respectively, whereas positive-ions ES-MS spetrum showed peaks at *m*/*z* 265 and 293, ascribable to ($M^{+}+23$) of **4b** and **7**, respectively.



In addition to the above products, the acid **6** was found both in the absence and, to a major extent, in the presence of PhSH. The formation of acid **6** in the absence of reductant species, such as thiols, is still unclear.

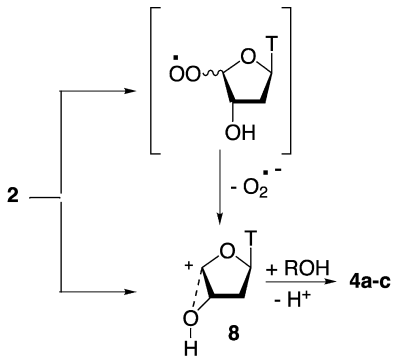
In order to investigate the effect of water on the behaviour of perester **1** (and radical **2**), the decomposition of **1** was carried out in a 3:1 water/*tert*-butanol mixture as solvent. The presence of *tert*-butanol as a co-solvent was necessary owing to the low solubility of **1** in water.

TLC analysis showed that complete disappearance of **1** occurred within 1 h with concomitant formation of thymine **3** and acetal **4a** as the only detectable reaction products in a time-dependent ratio. After prolonged heating of the reaction mixture (ca. 3 h) thymine **3** was found as the only product in 87% yield (Table 1, entry 7). On the other hand, independent experiments showed that the acetal **4a** underwent complete hydrolysis to **3** by heating in 3:1 water/*tert*-butanol.

Thermal decomposition of **1** was repeated in the presence of glutathione (GSH) as hydrogen donor. After 1 h heating, TLC analysis showed the presence of products **3** and **4a** together with the reduction product **5** and small amounts of the acid **6**. After prolonged heating (3 h), HPLC analysis showed the disappearance of the acetal **4a**; thymine **3** and compound **5** were the major products, together with minor amounts of acid **6** (Table 1, entries 8, 9). The latter was most probably derived from **1** through SET reduction by GSH;[13] as expected, the yield of acid **6** increased with increasing the GSH concentration.

These findings can be easily rationalized by assuming that the chemical behavior of perester **1** (and radical **2**) in water/*tert*-butanol is strictly related to that exhibited in neat *tert*-butanol and methanol. That is, perester **1** can undergo both the in cage decomposition leading to acetal **4a** and thermal fragmentation leading to radicals **2**, which can be reduced to **5** through hydrogen atom abstraction from GSH. In the absence of the thiol hydrogen donor radicals **2** could be trapped by the nucleophilic solvent (*tert*-butanol and water) to give acetals **4a** and **4c**, from which thymine **3** eventually arises by hydrolysis (Scheme 3). In addition, perester **1** could be reduced by thiol (thiophenol or GSH) to acid **6** (Scheme 4).

For the formation of acetals **4** from radicals **2**, we can infer that, under the reaction conditions employed and in the absence of any thiol, radicals **2** could undergo dioxygen oxidation to cations **8**, probably through the intermediacy of a peroxyl radical followed by loss of superoxide radical anion, $O_2^{\cdot -}$.[14] Cations **8** can probably afford acetals **4a-c** through nucleophilic attack by the solvent. The stereoselective formation of (4′*S*)-**4a** indicates that the nucleophilic attack occurs from the side opposite to the C3′–OH group. This finding might suggest that cation **8** can be stabilized through an oxiranium structure (Scheme 5).



Scheme 5.

To obtain evidence on the role played by dioxygen we performed reactions in water/*tert*-butanol in the absence of air under an argon atmosphere. In the absence of GSH thymine **3** was formed in only 60% yield together with acid **6** (10%) (Table 1, entry 10), whereas, as already mentioned, only thymine **3** (87%) was found in the presence of air (Table 1, entry 7). We suggest that, in the absence of dioxygen, radical **2** can be oxidized by perester **1** itself, with eventual formation of acid **6**. On the contrary, no effect of the presence of oxygen was found in reactions carried out in the presence of GSH, as expected, since the oxidation of radical **2** is prevented by the hydrogen atom abstraction from the thiol H-donor (Table 1, entry 11).

3. Conclusion

In conclusion, we showed that perester **1** undergoes thermal decomposition leading to both the in cage product **4a** and free radicals **2**. These latter can be reduced to **5** by hydrogen atom abstraction from thiol, if present, or can be oxidized to cation **8** by dioxygen or, in the absence, by perester **1** itself. In turn, cation **8** can be stereoselectively trapped by the nucleophilic solvent to give acetals **4a-c**. Acetals **4a**,**c** are in turn hydrolysed by water to thymine **3**. The oxidation of **2** by perester **1** eventually gives acid **6** by initial SET reaction; acid **6** was also formed through analogous SET reaction between **1** and the thiol, PhSH or GSH.

In THF and in the absence of thiol, radical **2** undergoes both identity hydrogen atom abstraction from the solvent and thermal fragmentation to thymine **3**. This reaction occurs through a still obscure mechanism, since our attempts to obtain evidence of the nature of the sugar fragments failed.

4. Experimental

4.1. General

NMR spectra were recorded with a Varian Gemini 400 instrument using Me_4Si as an internal standard. HPLC analyses were performed with a Waters 600E instrument equipped with a XTerra C-18 MS column and a diode array detector. Mass spectra were recorded with a VG 7070E instrument using electron spray ionisation both in positive (ES+) and negative (ES-) ionization.

Thymidine and thymine were commercially available. Thymidine-5′-carboxylic acid **6**[15] and the reduced product **5**[16] were identified by comparison with spectral data reported in the literature. The *tert*-butylacetal **4a** and the perester **1** were characterized by NMR and MS spectral analysis. Elemental analysis was not performed for perester **1** owing to the impossibility of obtaining a satisfactory analytical sample. The methylacetal **4b** was not separated as a pure compound; its characterization came from ^{1}H NMR and MS spectral analysis of a mixture of **4b** and **7**.

4.2. 3′,5′-*O*-(*tert*-Butyldimethylsilyl)thymidine[17]

Following the procedure of Ogilvie,[18] thymidine (1.00 g, 4.10 mmol) was dissolved in a 1:1 mixture of dry THF/DMF (15 mL), then imidazole (1.10 g, 16.50 mmol), $AgNO_3$ (1.55 g, 9.10 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.40 g, 9.10 mmol) were added, in this order, under a nitrogen atmosphere and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, diluted with ethyl acetate (20 mL), washed with several portions of water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column by gradual elution with ethyl acetate/hexane mixture (up to 20% ethyl acetate). 3′,5′-*O*-(*tert*-butyldimethylsilyl)thymidine was obtained as a white solid (1.90 g, 4.05 mmol).

4.3. 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine[19]

Following the procedure of white[20] pyridinium *p*-toluenesulphonate (PPTS; 4.10 g, 16.20 mmol) was added to a solution of 3′,5′-*O*-(*tert*-butyldimethylsilyl)thymidine (1.90 g, 4.05 mmol) in methanol (30 mL). The resulting mixture was stirred at room temperature until TLC showed disappearance of starting material (16–20 h), then the solvent was evaporated under reduced pressure. The residue

was dissolved in ethyl acetate (10 mL), washed with several portions of water, dried over $MgSO_4$ and concentrated under reduced pressure. Crude 3′-*O*-(*tert*-butyldimethylsilyl)thymidine was obtained as a white solid (1.00 g, 2.80 mmol) and reacted without further purification.

4.4. 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine-5′-carboxylic acid[21]

Following the procedure of Piancatelli et al.[22] tetramethylpiperidinium-*N*-oxide (TEMPO; 0.10 g, 0.60 mmol) and bis-acetoxyiodobenzene (BAIB; 2.15 g, 6.70 mmol) were added to a solution of 3′-*O*-(*tert*-butyldimethylsilyl)thymidine (1.00 g, 2.80 mmol) in 1:1 MeCN/H_2O (20 mL). After stirring at room temperature for 2 h, the reaction mixture was diluted with ethyl acetate (10 mL), washed with several portions of water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column by gradual elution with ethyl acetate/hexane mixture (up to 40% ethyl acetate). 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine-5′-carboxylic acid was obtained as a white solid (1.00 g, 2.75 mmol).

4.4.1. 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine-5′-carboxylic acid *tert*-butyl perester. Carbonyl diimidazole (CDI; 0.45 g, 2.75 mmol) was added to a solution of 3′-*O*-(*tert*-butyldimethylsilyl) thymidine-5′-carboxylic acid (1.00 g, 2.75 mmol) in dry THF (20 mL). The solution was stirred at room temperature for 1 h under nitrogen atmosphere, then cooled at 0–5 °C (ice bath) and *tert*-butyl hydroperoxide (*t*-BuOOH; 5 M solution in decane; 1.20 mL, 6.05 mmol) was added dropwise. The reaction mixture was stirred for 20 min, then diluted with diethyl ether (20 mL), washed with several portions of cold brine, dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was chromatographed on florisil column by gradient elution with diethyl ether/hexane mixture (up to 70% ether). The title product was obtained as a white solid (1.10 g, 2.50 mmol) [δ_H ($CDCl_3$) 9.2 (1H, br s, disappeared on D_2O shake; NH), 8.0 (1H, s, H6), 6.57 (1H, dd, J_1=9.5 Hz, J_2=4.8 Hz, H1′), 4.54 (1H, d, J=4.0 Hz, H3′), 4.43 (1H, s, H4′), 2.29 (1H, A part of an ABX system, J_{AB}=13.0 Hz, J_{AX}=4.8 Hz, H2″), 2.04 (1H, B part of an ABXY system, J_{AB}=13.0 Hz, J_{BX}=9.5 Hz, J_{BY}=4.0 Hz, H2′), 1.93 (3H, s, CH_3), 1.35 (9H, s, *t*-BuO), 0.9 (9H, s, *t*-BuSi), 0.12 (3H, s, CH_3Si), 0.11 (3H, s, CH_3Si); δ_C ($CDCl_3$) 0.00 (CH_3Si), 0.03 (CH_3Si), 17.57 (CH_3), 22.96 (q), 30.60 (CH_3), 31.03 (CH_3), 44.40 (CH_2), 80.84 (CH), 87.93 (CH), 89.63 (q), 91.33 (CH), 116.63 (q), 140.86 (CH), 115.87 (q), 168.83 (q), 174.02 (q); MS (ES^-) *m*/*z* 441 $(M-1)^-$, MS(ES^+) *m*/*z* 465 $(M+Na)^+$].

4.4.2. Thymidine-5′-carboxylic acid *tert*-butyl perester (1). To a solution of 3′-*O*-(*tert*-butyldimethylsilyl)thymidine-5′-carboxylic acid *tert*-butyl perester (1.10 g, 2.50 mmol) in dry THF (10 mL) tetrabutylammonium fluoride (TBAF; 1 M solution in THF, 2.75 mL, 2.75 mmol) was added dropwise at 0–5 °C (ice bath) under nitrogen atmosphere. The reaction mixture was stirred for 30 min, then cold brine (5 mL) was added. The resulting mixture was extracted with diethyl ether (5×10 mL), the organic phase washed with cold brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the *tert*-butyl perester of thymidine-5′-carboxylic acid as a white solid (0.40 g, 1.25 mmol) [mp 85–86 °C; δ_H ($CDCl_3$) 9.1 (1H, br s, NH), 8.0 (1H, s, H6), 6.6 (1H, dd, J_1=8.5 Hz, J_2=4.5 Hz, H1′), 4.65 (1H, d, J=4.0 Hz, H3′), 4.6 (1H, s, H4′), 2.5 (1H, A part of an ABX system, J_{AB}=13.0 Hz, J_{AX}=4.5 Hz, H2″), 2.1 (1H, B part of an ABXY system, J_{AB}=13.0 Hz, J_{BX}=8.5 Hz, J_{BY}=4.0 Hz, H2′), 1.95 (3H, s, CH_3), 1.4 (9H, s, *t*-Bu); δ_C (DMSO) 15.57 (CH_3), 28.90 (CH_3), 53.16 (CH_2), 68.94 (q), 74.34 (CH), 84.76 (CH), 86.09 (CH), 110.47 (q), 136.51 (CH), 151.21 (q), 164.30 (q), 169.39 (q); MS(ES^-) *m*/*z* 327 $(M-1)^-$; UV λ_{max}=266 nm]. The title perester was found to be stable for several days at −14 °C in the solid state, whereas it underwent smooth decomposition in solution [$t_{1/2}$ (*t*-BuOH, 20 °C)=11 h; $t_{1/2}$(MeOH, 20 °C)=2 h] or by column chromatography.

4.5. Thermal decomposition of thymidine-5′-carboxylic acid *tert*-butyl perester (1)

General procedure. A 1.5 mM solution of perester **1** (5 mL) in the appropriate solvent (THF, methanol, *tert*-butanol, 3:1 water/*tert*-butanol) in a sealed tube was bubbled with the appropriate gas (air or argon), then kept in a thermostatic bath a 85 °C for 1 h, unless otherwise stated. In all cases qualitative and quantitative analyses of reaction mixtures were performed by HPLC. When appropriate, reactions were repeated on 50 mL scale, the solvent eliminated under reduced pressure and the residue chromatographed on silica gel column by gradient elution with ethyl acetate/*n*-hexane.

4.5.1. Thermal decomposition of *tert*-butyl perester 1 in THF. The reaction was carried out on analytical scale both in the absence and in the presence of thiophenol (4 μL, 5 mol equiv.). Yields of reaction products, determined by HPLC analysis, are given in Table 1, entries 1 and 2, respectively. Attempts to analyse reaction mixtures by GC/MS were unsuccessful: no peaks were detected.

The reaction in the presence of thiophenol was carried out on preparative scale. Column chromatography separated pure samples of the reduced product **5**, the acid **6**, and [(*S*)-4-hydroxy-(*S*)-5-*tert*-butoxytetrahydrofuran-(*R*)-2-yl]-thymine **4a** as a white solid [δ_H ($CDCl_3$) 9.0 (1H, br s, NH), 7.7 (1H, s, H6), 6.65 (1H, t, J=7.0 Hz, H1′), 5.3 (1H, s, H4′), 4.2 (1H, d, J=4.0 Hz, H3′), 2.4 (1H, A part of an ABX system, J_{AB}=14.0 Hz, J_{AX}=7.0 Hz, H2″), 2.1 (1H, B part of an ABXY system, J_{AB}=14.0 Hz, J_{BX}=7.0 Hz, J_{BY}=4.0 Hz, H2′), 2.0 (3H, s, CH_3), 1.3 (9H, s, *t*-Bu); δ_H (DMSO) 11.2 (1H, br s, NH), 7.6 (1H, s, H6), 6.35 (1H, t, J=8.0 Hz, H1′), 5.35 (1H, d, J=4 Hz; collapsing to s upon irradiation at δ 4.0; H4′), 5.15 (1H, s; disappeared on D_2O shake; C3′−OH), 4.0 (1H, t, J=4.0 Hz, H3′), 2.1 (1H, A part of an ABX system, J_{AB}=13.5 Hz, J_{AX}=8.0 Hz; collapsing to A part of an AB system, J=13.5 Hz, upon irradiation at δ 6.35; H2″), 2.0 (1H, B part of an ABXY system, J_{AB}=13.5 Hz, J_{BX}=8.0 Hz, J_{BY}=4.0 Hz; collapsing to B part of an ABX system upon irradiation at δ 6.35; H2′), 1.8 (3H, s, CH_3), 1.2 (9H, s, *t*-Bu); δ_C (DMSO) 13.05 (CH_3), 29.07 (CH_3), 37.85 (CH_2), 75.59 (q), 75,91 (CH), 85.46 (CH), 103.92 (CH), 110,26 (q), 137.02 (CH), 151.33 (q), 164.34 (q); MS(ES^+) *m*/*z* 307 $(M+Na)^+$; MS(ES^-) *m*/*z* 283 $(M-1)^-$; UV λ_{max}=266 nm. Calcd for $C_{13}H_{20}N_2O_5$: C. 54,92; H. 7,09; N. 9,85; O. 28,14. Found: C. 55,20; H. 7,13; N. 9,80%].

The reaction in the absence of thiophenol was repeated on analytical scale in deuterated THF-d8. HPLC analysis showed a peak with the same retention time of **5**, which was identified as the deuterated **5**-d. Compounds **5**-d and **4a** were present in 2 and 14% yield, respectively.

4.5.2. Thermal decomposition of *tert*-butyl perester (1) in *tert*-butanol. The reaction was carried out on analytical scale both in the absence and in the presence of thiophenol (4 μL, 5 mol equiv.). Yields of reaction products are given in Table 1, entries 3 and 4, respectively. The reaction in the absence of thiophenol was carried out on preparative scale. Column chromatography separated the (4′*S*)-acetal **4a** as the main reaction product together with minor amounts of thymine **3**.

4.5.3. Thermal decomposition of *tert*-butyl perester (1) in methanol. The reaction was carried out on analytical scale both in the absence and in the presence of thiophenol (4 μL, 5 mol equiv.). In both cases HPLC analysis (Table 1, entries 5, 6) showed peaks due to thymine **3**, *tert*-butylacetal **4a**, the reduced product **5**, and acid **6**, in addition to an unknown peak **X**. Both reactions were repeated on preparative scale both in the absence and in the presence of thiophenol. Column chromatography separated the product responsible for the peak **X**. In the reaction carried out in the presence of thiophenol the product **X** was identified as pure thymidine-5′-carboxylic acid methyl ester **7**[23] [δ_H (DMSO) 11.2 (1H, br s, NH), 7.95 (1H, s, H6), 6.34 (1H, dd, J_1=9.2 Hz, J_2=5.2 Hz, H1′), 5.85 (1H, d, J=3.2 Hz, H4′), 4.45 (1H, broad signal; collapsing to doublet, J=5.0 Hz, upon irradiation at δ 5.85, H3′), 3.75 (3H, s, OMe), 2.10 (1H, A part of an ABX system, J_{AB}=13.0 Hz, J_{AX}=5.2 Hz, H2″), 2.0 (1H, B part of an ABXY system, J_{AB}=13.0 Hz, J_{BX}=9.2 Hz, J_{BY}=5.0 Hz, H2′), 1.77 (3H, s, CH_3); δ_C (DMSO) 13.12 (CH_3), 38.61 (CH_3), 52.98 (CH_2), 74.32 (CH), 84.99 (CH), 86.17 (CH), 110.26 (q), 136.78 (CH), 151.21 (q), 164.34 (q), 172.21 (q); MS(ES$^-$) *m/z* 269 $(M-1)^-$; MS(ES$^+$) *m/z* 293 $(M+Na)^+$].

An independent experiment showed that perester **1** decomposed in methanol solution at room temperature to give the methyl ester **7** as the exclusive reaction product. In the reaction carried out in the absence of thiophenol the product **X** was found to be a 3:1 mixture of the methyl ester **7** and the methyl acetal **4b**, as indicated by ^{1}H NMR and MS spectral analysis [(4-hydroxy-5-methoxytetrahydrofuran-2-yl]thymine **4b**: δ_H (DMSO) 11.2 (1H, br s, NH), 7.22 (1H, s, H6), 6.45 (1H, t, J=7.5 Hz, H1′), 5.44 (1H, d, J=3.2 Hz, H4′), 4.38 (3H, s, OMe), 4.12 (1H, broad signal; collapsing to doublet, upon irradiation at δ 5.44, H3′), 2. 0–2.15 (2H, multiplet, H2′), 1.77 (3H, s, CH_3); δ_C (DMSO) 13.15 (CH_3), 37.36 (CH_3), 55.07 (CH_2), 74.58 (CH), 85.63 (CH), 110.10 (CH), 110.97 (q), 136.22 (CH), 151.40 (q), 164.20 (q); MS(ES$^-$) *m/z* 241 $(M-1)^-$; MS(ES$^+$) *m/z* 242 $(M)^+$, 265 $(M+Na)^+$].

4.5.4. Thermal decomposition of *tert*-butyl perester (1) in 3:1 water/*tert*-butanol. The reaction was carried out on analytical scale both in the absence and in the presence of glutathione (2 or 5 mol equiv.) with different oxygen concentrations. Yields of reaction products are given in Table 1, entries 7–13.

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Synthesis of the anionic fluororeceptors based on thiourea and amide groups and recognition property for α,ω-dicarboxylate

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Abstract—Three new neutral receptors (**1**, **2** and **3**) containing thiourea and amide groups were synthesized by simple steps in good yields. The binding properties for anions of **1**, **2** and **3** were examined by UV−vis, fluorescence, and ^{1}H NMR spectroscopy. Receptors **1**, **2** and **3** all had a better adipate anion selectivity by comparison with other dicarboxylate anions. The association constants of **1**, **2** and **3** with adipate were higher as compared to other anions (malonate, succinate, glutarate). In particular, a distinct color change was observed from light yellow to orange-red upon addition of adipate to the solution of **1** in DMSO. The UV−vis and fluorescence data indicate that a 1:1 stoichiometry complex is formed between compound **1**, **2** or **3** and dicarboxylate anions through hydrogen bonding interactions.

1. Introduction

Anions, especially dicarboxylates, play an important role in chemical and biological processes,[1] dicarboxylates are critical components of numerous metabolic processes including, for instance, the citric acid and glyoxylate cycles.[1g] They also play an important role in the generation of high-energy phosphate bonds and in the biosynthesis of important intermediates.[1h] The development of artificial receptors for on-line and real time detection of biologically important anions and for environmental monitoring of harmful anion pollutants has attracted considerable attention in the field of supramolecular chemistry.[1] To date, several receptors containing different functional groups for selective binding of dicarboxylate anions have been reported.[2,3] However, the sensors based on the fluorescence emission for dicarboxylate anions are still rare.[3] A system of fluorescence receptor generally consists of two parts. One part is an anion-binding site which can be mainly divided into two categories: neutral and positive-charge units. Neutral binding units employ hydrogen bonding NH-based donors such as pyrroles, amides, urea/thiourea or Lewis acids.[4] Positively charged binding units use ammonium derivatives or guanidinium centers for binding negatively charged anions.[5] The other is the fluorophore part which converts the binding process or recognition phenomena to optical signals. In numerous possible hydrogen bonding donor groups, thiourea and amide moieties have become the focus of the development of neutral anion receptors, because the hydrogen bonding of these functional groups is directional in character resulting in relatively strong complexes with various specific chain length dicarboxylate anions.[3]

To our best knowledge, although some neutral anion receptors containing amide or thiourea units have been reported in the last decades,[4b−d,6] the neutral receptors for dicarboxylate anions containing simultaneously both binding units of thiourea and amide in a molecule have seldom been reported. The cooperative act of two functional groups for anion could enhance effectively selectivity in the recognition and the stability of the resultant complex. In this paper, we report the synthesis and binding properties of three new neutral anion receptors (**1**, **2** and **3**) containing both thiourea and amide functionalities. The anionic recognition of receptors has been investigated by UV−vis absorption and fluorescence emission spectrometry.

2. Results and discussion

The structures of receptors **1**−**3** are shown in Scheme 1. They were synthesized by the reaction of *p*-nitrophenylisothiocyanate or *p*-tolylisothiocyanate or 1-naphthylisothiocyanate and 2,7-bis(aminoethylenecarbamoylmethoxy) naphthalene (**4**) in high yields. All of these compounds were characterized by IR, ^{1}H NMR, MS and elemental analysis.

2.1. Fluorescence and absorption spectra

The fluorescence and absorption spectra were recorded from a solution of these compounds in the absence or presence of

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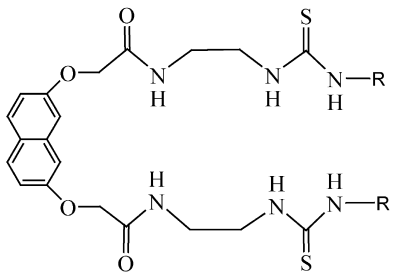


1 R=*p*-nitrophenyl
2 R=1-naphthyl
3 R=*p*-tolyl

Scheme 1. The structure of compounds of **1**, **2**, **3**.

dicarboxylate anions [$^{-}O_2C(CH_2)_nCO_2^{-}$] such as malonate, succinate, glutarate, adipate (n=1,2,3,4). In each case the counter cation was tetrabutylammonium.

Figure 1(a) showed that the fluorescence spectra of a mixture of receptor **1** (5×10^{-5} M) with different concentrations of adipate in DMSO. The emission at 334 nm is from the naphthalene moiety, and the emission at 436 nm may be due to the conjugative system of *p*-nitrophenylthiourea. Upon gradual increase of the concentration of adipate, the fluorescence intensities of **1** at 334 and 436 nm were gradually enhanced, which can be explained by expansion of the conjugative system as a result of an intermolecular charge transfer process. Two discernible isoemissive points (364 and 419 nm) were observed. These results demonstrates that **1** with adipate formed 1:1 complex.[7] As shown in the inset of Figure 1(a), the satisfactory non-linear fitting curve further illuminated the formation of 1:1 complex between **1** and adipate. In comparison with adipate, other dicarboxylate anions showed similar phenomena of fluorescence changes, but the variation was considerably smaller in each case.

It was particularly noteworthy that an obvious color change occurred while adipate was added into receptor **1** in DMSO. Upon gradual increase of the concentration of adipate, the color of solution of receptor **1** was changed from light yellow to orange-red, which could be easily observed by the naked-eyes. As shown in Figure 1(b), on gradual increase of the concentration of adipate, the intensity of absorption band at 290 nm was decreased gradually, a bathochromic shift occurred from 362 to 374 nm, and a new absorption band appeared with a maximum absorption at 478 nm, which demonstrated further that **1** formed complex with adipate. The color change can be attributed to the appearance of a new long wavelength peak. Similarly, a color change can be observed while adding other dicarboxylate anions into the solution of **1** in DMSO, but the changes were indistinct. The selectivity of **1** for recognition of different dicarboxylates depends on the chain length of the anionic species. However, there was no new peak in the visible range and no color change upon adding dicarboxylate anions into receptors **2** and **3**. The origin of color in host solution might be ascribed to the charge-transfer interactions between the electron-rich donor nitrogen of the thiourea units and the electron-deficient *p*-nitrophenyl moieties. While the receptor bound anions, hydrogen bonds were constructed to form stable complexes, and the electron density in the supramolecular system was increased very much to enhance the charge-transfer interactions between the electron-rich and electron-deficient moieties, which resulted in a visible color change.[7a,8]

The occurrence of dual fluorescence is commonly due to either intramolecular charge transfer (ICT)[9a–c] or the formation of excimer.[9d,c] Figure 2(a) shows that the dual fluorescence of interaction of **2** and adipate was observed, which may arise from the locally excited (LE) state at 393 nm and charge transfer (CT) state or the formation of naphthalene excimer at 485 nm in equilibrium, respectively. As shown in Figure 2(a), the introduction of adipate resulted in quenching of the short wavelength LE emission while enhancing of the emission at 485 nm, which can be due to the formation of a new conjugative system. A noticeable isoemissive point at 436 nm was observed. The complexation between **2** and adipate by multi-hydrogen bonding was an important reason resulted in these variations. As shown in the inset of Figure 2(a), the satisfactory non-linear fitting curve further verified the formation of 1:1 complex between **2** and adipate. Figure 2(b) shows the absorption spectra of **2** with added adipate. Isobestic points at 278 and 316 nm

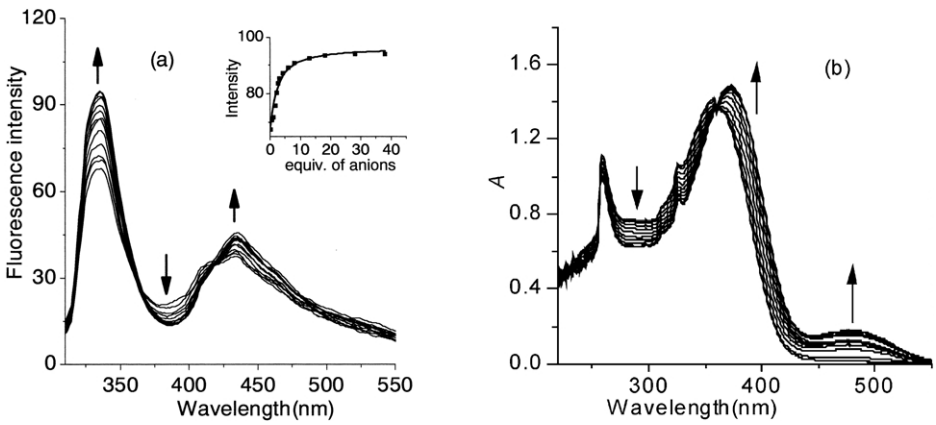


Figure 1. (a) Fluorescence spectra of **1** (5×10^{-5} mol/L, DMSO) upon the addition of various amounts of adipate in DMSO, λ_{ex}=291 nm, equivalent of Bu_4N^+(adipate): 0⟶38. The non-linear fitting curve of change in fluorescence intensity at 334 nm with respect to amount of Bu_4N^+ (adipate) was shown in the inset. (b) UV–vis absorption spectra of **1** (5×10^{-5} mol/L) upon the addition of various amounts of adipate in DMSO. Equivalent of Bu_4N^+ (adipate): 0⟶35.

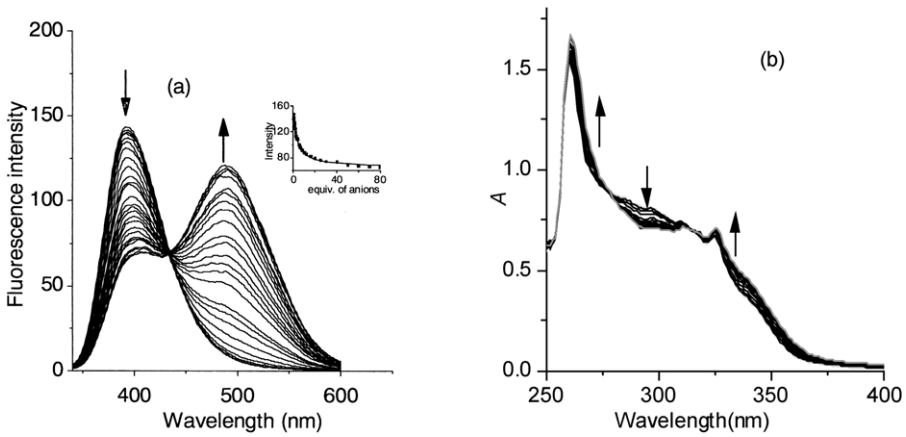


Figure 2. (a) Fluorescence spectra of **2** (5×10^{-5} mol/L, DMSO) upon the addition of various amounts of adipate in DMSO, λ_{ex}=330 nm, equivalent of Bu_4N^+ (adipate): 0⟶80. The non-linear fitting curve of change in fluorescence intensity at 393 nm with respect to amount of Bu_4N^+ (adipate) was shown in the inset. (b) UV–vis absorption spectra of **2** (5×10^{-5} mol/L) upon the addition of various amounts of adipate in DMSO. Equivalent of Bu_4N^+ (adipate): 0⟶26.

were observed. These observations clearly showed the formation of 1:1 hydrogen bonding complex.[7] Similar but smaller variations in the fluorescence and absorption spectra were obtained while adding other dicarboxylate anions into the solution of **2**. Receptor **2** has also a preferential selectivity for adipate in contrast to the other dicarboxylates examined by us.

Figure 3(a) shows the emission spectra of receptor **3** (2.5×10^{-5}) in the presence of excess adipate in DMSO. The addition of adipate as a recognized response-induced anion was found to dramatically enhance the fluorescent intensity.[10] A remarkable intensity increase is up to ca. 200%. The adipate-induced signal effect is well interpreted by efficient emission retrieval upon a hydrogen bonding interaction between the adipate and the thiourea and amide units of **3**. Figure 3(b) shows the absorption spectra of **3** with added adipate. Isobestic points at 283 and 315 nm were observed. These observations clearly showed the formation of a 1:1 hydrogen-bonding complex.[7] Similarly, receptor **3** also has a preferential selectivity for adipate anion in comparison with the other smaller dicarboxylate ions.

2.2. ^{1}H NMR study

^{1}H NMR spectroscopy is of immense value in the understanding of receptor–substrate interaction and is capable of providing a revealing picture of the detail of the interaction between receptor and dicarboxylate anions. Addition of 1 equiv. of the tetrabutylammonium salts of adipate to **1**, **2** or **3** in DMSO-d_6 caused remarkable downfield shifts of the NH resonances in the ^{1}H NMR. In the case of **3** with adipate, the proton chemical shifts of amide (H_a) and thiourea (H_b, H_c) changed from 8.27 to 9.81 ($\Delta\delta$=1.54 ppm), 9.47 to 12.05 ($\Delta\delta$=2.58 ppm), 7.66 to 8.88 ($\Delta\delta$=1.22 ppm), respectively. The larger downfield shift for H_b ($\Delta\delta$=2.58 ppm) may be due to the formation of two hydrogen bondings between H_b with adipate. A probable structure for the complex of **3** with dicarboxylate anions is shown in Scheme 2. These results show that receptor **3** and adipate form a 1:1 stoichiometry complex via

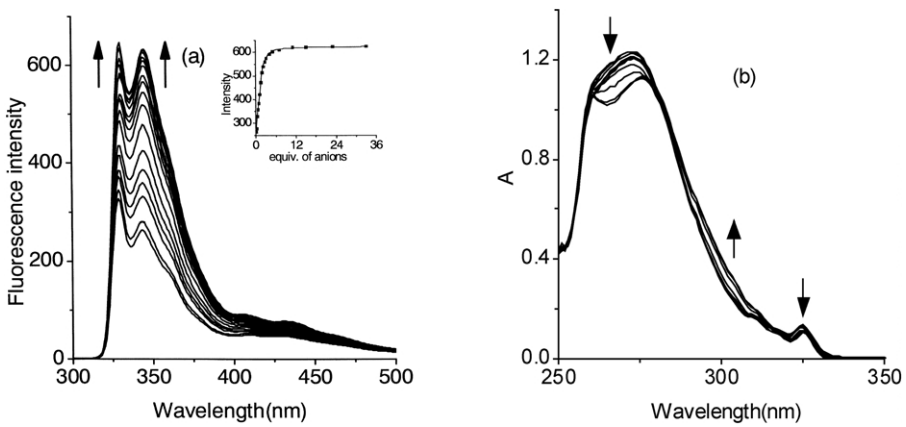
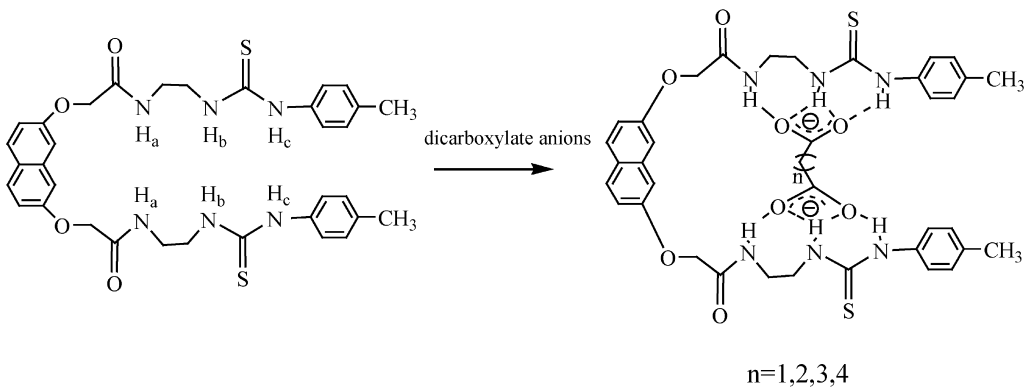


Figure 3. (a) Fluorescence spectra of **3** (2.5×10^{-5} mol/L, DMSO) upon addition of various amounts of adipate in DMSO, λ_{ex}=296 nm, equivalent of Bu_4N^+ (adipate): 0⟶33. The non-linear fitting curve of change in fluorescence intensity at 326 nm with respect to amount of Bu_4N^+ (adipate) added was shown in the inset. (b) UV–vis absorption spectra of **3** (5×10^{-5} mol/L) upon the addition of various amounts of adipate in DMSO. Equivalent of Bu_4N^+ (adipate): 0⟶19.



Scheme 2. Possible binding model of **3** with dicarboxylate anions.

hydrogen-bonding interaction between the amide and thiourea with the carboxyl groups.

2.3. Determination of the association constants (K_{ass}) of the complexes

For the complex of 1:1 stoichiometry, according to the following relation:[12]

$$X = X_0 + (X_{lim} - X_0)/2c_0\{c_H + c_G + 1/K_{ass} - [(c_H + c_G + 1/K_{ass})^2 - 4c_Hc_G]^{1/2}\}$$

Where X represented the fluorescence intensity, and c_H and c_G represented the corresponding concentration of host and anion guest. The association constants obtained by a non-linear least-squares analysis of X vs. c_H and c_G are listed in Table 1. The data showed that all receptor **1**, **2**, and **3** have an excellent selectivity for adipate over other dicarboxylate anions. All correlation coefficients (R) obtained are larger than 0.99, which illustrated also the formation of 1:1 stoichiometry complex between receptor **1** or **2** or **3** and dicarboxylate anions.[7] The association constants of receptor **1**, **2**, **3** for dicarboxylate anions are larger than those of neutral receptors only containing thiourea groups reported previously,[2f,3] which supported the notion that the cooperative act of thiourea and amide groups in binding for anion by multiple hydrogen bonding interactions played an important role.

2.4. Conclusion

The neutral anion receptors **1**, **2** and **3** were synthesized easily in high yields. Receptor **1**, **2** and **3** can form 1:1 complex with dicarboxylate anions containing three to six carbons by multiple hydrogen bonding interactions. All receptors have a high selectivity for the adipate which has the longest carbon chain of the series of dicarboxylate ions examined, and there is an observable color change by the naked-eyes for **1** with dicarboxylate anions, which holds promise to be used as optical chemosensors for dicarboxylate anions. Receptor **3** has an excellent ability to for complex with adipate in comparison with **1**, **2**, which indicates that receptor **3** could be used as a fluorescent chemosensor to recognize adipate.

3. Experimental

3.1. Materials and methods

Ethanol and $CHCl_3$ were dried and distilled before using according to standard practice. All other commercially available reagents were used without further purification. The tetrabutylammonium salts were used as anionic substrates. Melting points were measured on a Reichert 7905 melting-point apparatus (uncorrected). The infrared spectra were performed on a Nicolet 670 FT-IR spectrophotometer. The mass spectra were recorded on a ZAB-HF-3F spectrometer. Elemental analyses were determined by a Perkin–Elmer 204B elemental autoanalyzer. ^{1}H NMR spectra were recorded on a Varian Mercury VX-300 MHz spectrometer. UV–vis spectra were taken on a TU-1901 spectrometer. Fluorescence spectra were obtained on a Schimadzu RF-5301 spectrometer.

3.2. Syntheses

3.2.1. 2,7-Bis(ethoxycarbonylmethoxy) naphthalene.[11] A mixture of 2,7-naphthalenediol (4.0 g, 25 mmol), K_2CO_3

Table 1. Association constants K_{ass} $(mol/L)^{-1}$ of receptors **1**, **2** and **3** with guest anions

Anion	Receptor **1** K_{ass} $(M^{-1})^a$	R[b]	Receptor **2** K_{ass} $(M^{-1})^a$	R	Receptor **3** K_{ass} $(M^{-1})^a$	R
Malonate[c]	$(2.3\pm0.2^d)\times10^3$	0.9912	$(2.3\pm0.3^d)\times10^3$	0.9936	$(3.2\pm0.1^d)\times10^3$	0.9901
Succinate[c]	$(4.2\pm0.4^d)\times10^3$	0.9900	$(3.0\pm0.3^d)\times10^3$	0.9904	$(4.8\pm0.1^d)\times10^3$	0.9906
Glutarate[c]	$(3.8\pm0.2^d)\times10^3$	0.9977	$(4.0\pm0.2^d)\times10^3$	0.9982	$(1.4\pm0.1^d)\times10^4$	0.9915
Adipate[c]	$(1.0\pm0.1^d)\times10^4$	0.9917	$(6.0\pm0.3^d)\times10^3$	0.9974	$(3.2\pm0.5^d)\times10^4$	0.9990

[a] The data were calculated from fluorescence titration in DMSO.
[b] The values of R were obtained by the results of non-linear curve fitting.
[c] The anions were used as their tetrabutylammonium salts.
[d] All error values.

(7.2 g, 52 mmol), and ethyl bromoacetate (5.4 mL, 50 mmol) in acetone (200 mL) was refluxed overnight under N_2. The reaction mixture was evaporated to dryness, dissolved in water, and extracted with CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4. After filtration and evaporation, the crude product was recrystallized from a mixture of CH_2Cl_2/petroleum ether (30–60 °C) to give 2,7-bis(ethoxycarbonylmethyloxy) naphthalene as white crystals: 6.5 g, 78% yield. Mp 117–119 °C. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J=8.7 Hz, 2H, naph-4, 5H), 7.01 (d, J=8.7 Hz, 2H, naph-3, 6H), 6.88 (s, 2H, naph-1, 8H), 4.64 (s, 4H, OCH_2), 4.22 (q, J=7 Hz, 4H, CH_2C), 1.24 (t, J=7 Hz, 6H, CH_3).

3.2.2. 2,7-Bis(aminoethylenecarbamoylmethoxy) naphthalene (4). A mixture of the above mentioned diester (1.66 g, 5 mmol), excess ethylenediamine (2.5 mL) in dry $CHCl_3$ (20 mL) and anhydrous EtOH (20 mL) was stirred for 2 h at room temperature. After evaporation of the solvent and the residual ethylenediamine under reduced pressure, a light yellow powder (1.74 g, 97%) was obtained. Mp 139–140 °C. IR (KBr): 3369 (s), 3303 (m), 2948 (w), 2854 (m), 1658 (s), 1631 (w), 1595 (w), 1539 (s), 1515 (m), 1253 (m), 1209 (s), 1198 (m), 1062 (m), 842 (m), 604 (w), 513 (w) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.11 (s, br, 2H, HNCO), 7.75 (d, J=8.7 Hz, 2H, naph-4, 5H), 7.15 (s, 2H, naph-1, 8H), 7.08 (d, J=8.7 Hz, 2H, naph-3, 6H), 4.56 (s, 4H, OCH_2), 3.15 (q, J=12 Hz, 4H, CH_2NH), 2.61 (q, J=12 Hz, 4H, CH_2NH_2). FAB-MS m/z (%): 361 (M^++1, 38), 331 (M^+-29, 8), 192 (M^+-168, 14). Elemental analysis: calcd for $C_{18}H_{24}N_4O_4$: C 59.99%, H 6.71%, N 15.55%. Found: C 59.95%, H 6.70%, N 15.58%.

3.2.3. 2,7-Bis(*p*-nitrophenylthioureylene-ethenecarbamoyl-methoxy)naphthalene (1). To a solution of *p*-nitrophenylisothiocyanate (0.36 g, 2 mmol) in dry $CHCl_3$ (5 mL), **5** (0.36 g, 1 mmol) in dry $CHCl_3$ (5 mL) was added slowly at room temperature. After stirring for 6 h, the precipitate was filtered off, and dried in vacuum to give **1** (0.68 g) as a yellow powder in 94% yield. Mp 138–140 °C. IR (KBr): 3381 (m), 3333 (m), 3067 (w), 2926 (w), 1659 (m), 1632 (m), 1597 (m), 1531 (m), 1513 (m), 1329 (s), 1304 (m), 1212 (m), 839 (w), 690 (w), 592 (w), 470 (w) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.26 (s, br, 2H, NHAr), 8.34 (s, br, 2H, NHCS), 8.32 (s, br, 2H, NHCO), 8.13 (d, J=8.7 Hz, 2H, naph-4, 5H), 7.76–7.73 (m, 8H, ArH), 7.18 (s, 2H, naph-1, 8H), 7.10 (d, J=8.7 Hz, 2H, naph-3, 6H), 4.58 (s, 4H, CH_2O), 3.65 (s, br, 4H, CH_2NCO), 3.42 (s, br, 4H, CH_2NCS). FAB-MS m/z (%): 721 (M^++1, 15), 583 (M^+-137, 6). Elemental analysis: calcd for $C_{32}H_{32}N_8O_8S_2$: C 53.32%, H 4.47%, N 15.55%. Found: C 53.30%, H 4.45%, N 15.58%.

3.2.4. 2,7-Bis(1-naphthylthioureylene-ethenecarbamoyl-methyloxy)naphthalene (2). To a solution of 1-naphthylisothiocyanate (0.37 g, 2 mmol) in dry $CHCl_3$ (5 mL), **5** (0.36 g, 1 mmol) in dry $CHCl_3$ (5 mL) was added slowly at room temperature. After stirring for 6 h, the precipitate was filtered off, and dried in vacuum to give **2** (0.69 g) as pale powder in 95% yield. Mp 136–138 °C. IR (KBr): 3533 (w), 3444 (w), 3281 (m), 3064 (w), 2930 (w), 1651 (m), 1633 (m), 1542 (s), 1515 (m), 1477 (m), 1436 (m), 1251 (m), 1211 (s), 1059 (m), 840 (m), 781 (m), 607 (w), 470 (w) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.72 (s, br, 2H, NH-naph), 8.21 (s, br, 2H, NHCO), 7.76 (d, J=9.0 Hz, 2H, naph-4, 5H), 7.56 (s, br, 2H, NHCS), 7.92–7.42 (m, 14H, naph-H), 7.17 (s, 2H, naph-1, 8H), 7.09 (d, J=9.0 Hz, 2H, naph-3, 6H), 4.50 (s, 4H, CH_2O), 3.58 (s, br, 4H, CH_2NCO), 3.41 (s, br, 4H, CH_2NCS). FAB-MS m/z (%): 731 (M^++1, 18), 588 (M^+-142, 7). Elemental analysis: calcd for $C_{40}H_{38}N_6O_4S_2$: C 65.73%, H 5.24%, N 11.50%. Found: C 65.54%, H 5.24%, N 11.52%.

3.2.5. 2,7-Bis(*p*-tolylthioureylene-ethenecarbamoyl-methyloxy)naphthalene (3). To a solution of *p*-tolyll-isothiocyanate (0.30 g, 2 mmol) in dry $CHCl_3$ (5 mL), **5** (0.36 g, 1 mmol) in dry $CHCl_3$ (5 mL) was added slowly at room temperature. After stirring for 6 h, the precipitate was filtered off, and dried in vacuum to give **3** (0.59 g) as white powder in 89% yield. Mp 200–202 °C. IR (KBr): 3324 (s), 3289 (s), 3068 (m), 3022 (w), 2940 (m), 1683 (s), 1650 (s), 1633 (m), 1537 (s), 1514 (s), 1437 (m), 1389 (m), 1253 (m), 1216 (s), 1056 (m), 834 (m), 762 (w), 571 (m) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.47 (s, br, 2H, NHCS), 8.27 (s, br, 2H, NHCO), 7.76 (d, J=9.0 Hz, 2H, naph-4, 5H), 7.66 (s, br, 2H, NHAr), 7.19–7.06 (m, 12H, naph-1, 8H, naph-3, 6H, ArH), 4.56 (s, 4H, CH_2O), 3.61 (s, br, 4H, CH_2NCO), 3.33 (s, br, 4H, CH_2NCS), 2.24 (s, 6H, $ArCH_3$). FAB-MS m/z (%): 659 (M^++1, 28), 552 (M^+-106, 10). Elemental analysis: calcd for $C_{34}H_{38}N_6O_4S_2$: C 61.98%, H 5.81%, N 12.76%. Found: C 62.03%, H 5.74%, N 12.79%.

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Synthesis of novel heterocyclic fused 1,3-diazabuta-1,3-dienes and accompanying rearrangements in their cycloaddition reactions with ketenes: synthesis of heterocyclic fused pyrimidinone derivatives

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Abstract—The reactions of 1,3-diazabuta-1,3-dienes **1** with 2-aminothiophenol have been shown to result in excellent yields of *N*-benzothiazol-2-yl-*N'*-aryl benzamidines **2**. Their regioselective [4+2] cycloadditions with various ketenes are shown to yield novel benzothiazolo pyrimidinones **4**. A similar and convenient protocol for the synthesis of bisthiosubstituted 1,3-diazabuta-1,3-dienes **8** and **9** and interesting rearrangements accompanying their [4+2] cycloadditions with a number of ketenes are described.

1. Introduction

Nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules. The synthesis of nitrogen-containing heterocycles has attracted considerable attention due largely to their importance as building blocks for many therapeutically useful materials and the wide range of potential biological activity of both synthetic and naturally occurring derivatives. The hetero-Diels–Alder methodology employing azadienes represents a straightforward and an efficient approach to nitrogen-containing six membered heterocycles. Extensive studies have been carried out on this [4+2] cycloaddition process and the rapid and rigorous development in this area has led to several reviews highlighting the utility of azadienes as readily available templates in the synthesis of novel heterocycles and complex natural products.[1] Dienes containing two nitrogen atoms have attracted attention of chemists in recent years because of their importance in natural product synthesis.[1] In the last decade there have been numerous reports concerning the participation of 1,3-diazabuta-1,3-dienes as 4π components in cycloaddition reactions with isocyanides,[2] oxazolines,[3] enamines,[4] alkynes[5] etc. On the other hand the reactions of ketenes with 1,3-diaza-1,3-butadienes are reported to undergo [4+2] as well [2+2] cycloadditions. A vast prevalence of such reported cycloadditions correspond to [4+2] cycloaddition type in which 1,3-diazabuta-1,3-dienes add as 4π components across C=C bond of the ketenes.[6] Over the years, we have been actively involved in the synthesis and cycloaddition reactions of various functionalized 1,3-diazabuta-1,3-dienes and have developed a simple protocol for the synthesis of stable acyclic 1,3-diazadienes.[7] It is noticed that rearrangements accompany the [4+2] cycloaddition reactions of 4-tertiaryamino-4-methylthio-1,3-diazabuta-1,3-dienes, 4-(*N*-arylamino)-4-methylthio-1,3-diazabuta-1,3-dienes and 4-(*N*-arylamino)-4-tertiaryamino-1,3-diazabuta-1,3-dienes with various ketenes.[8] In view of these observations and our interest in the synthesis of new diazadienes, it was considered worthwhile to synthesise and examine the reactions of heterocyclic fused 1,3-diazabuta-1,3-dienes with various ketenes.

2. Results and discussion

Thus, the treatment of 4-tertiaryamino-4-methylthio-1,3-diazabuta-1,3-dienes **1** with 2-aminothiophenol, in refluxing toluene resulted in good yields of the desired benzothiazolo fused 1,3-diazabuta-1,3-dienes **2**. The structural assignments to the diazadienes **2** were based on spectral and analytical evidence. The detailed spectral features of the 1,3-dienes **2** are described in the experimental section, however; only the salient features are mentioned here. The 1,3-diene **2b**, for example, characterized as *N*-benzothiazol-2-yl-*N'*-*p*-tolyl-benzamidine, was analysed for $C_{21}H_{17}N_3S$ and showed a molecular ion peak at *m*/*z* 343. Its ^{1}H NMR spectrum showed the absence of the protons corresponding

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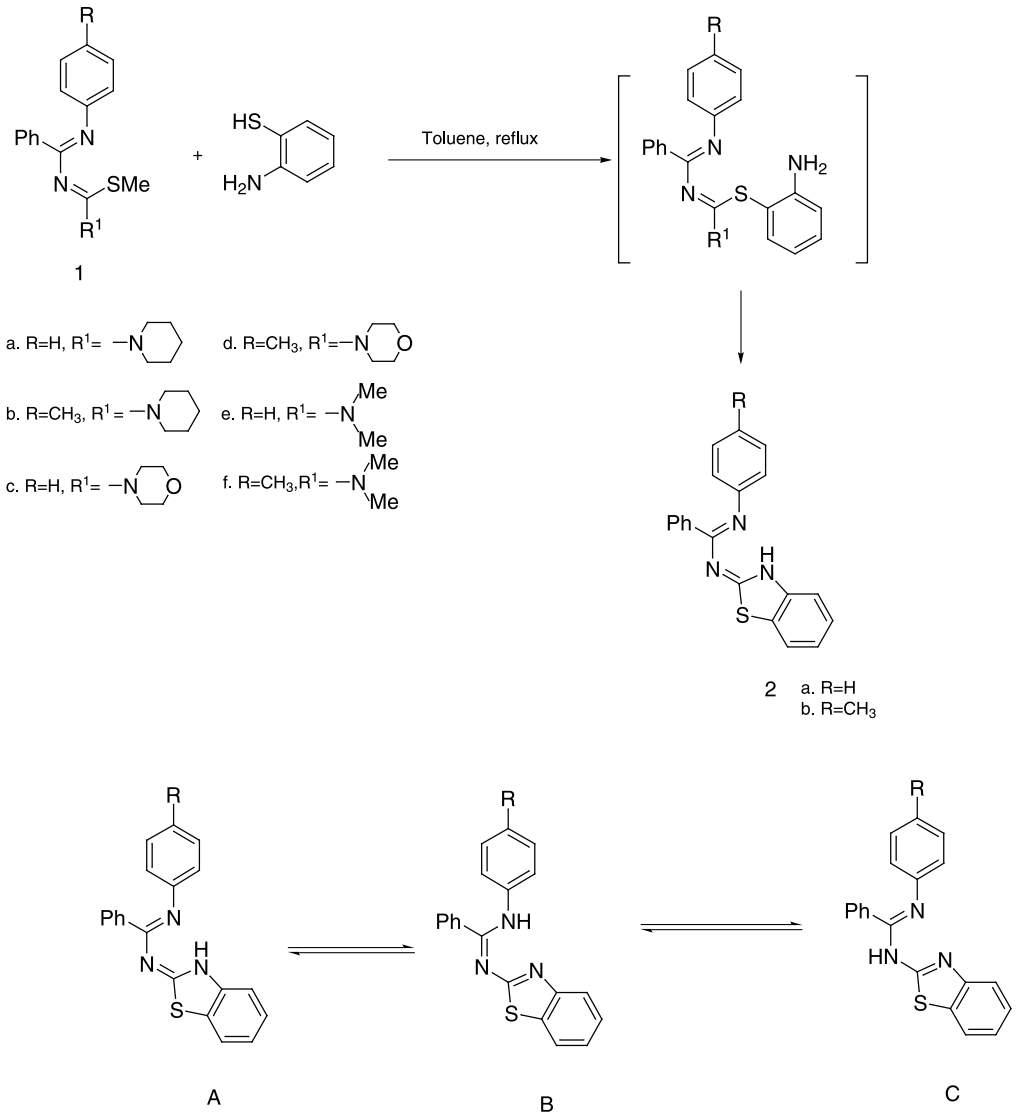
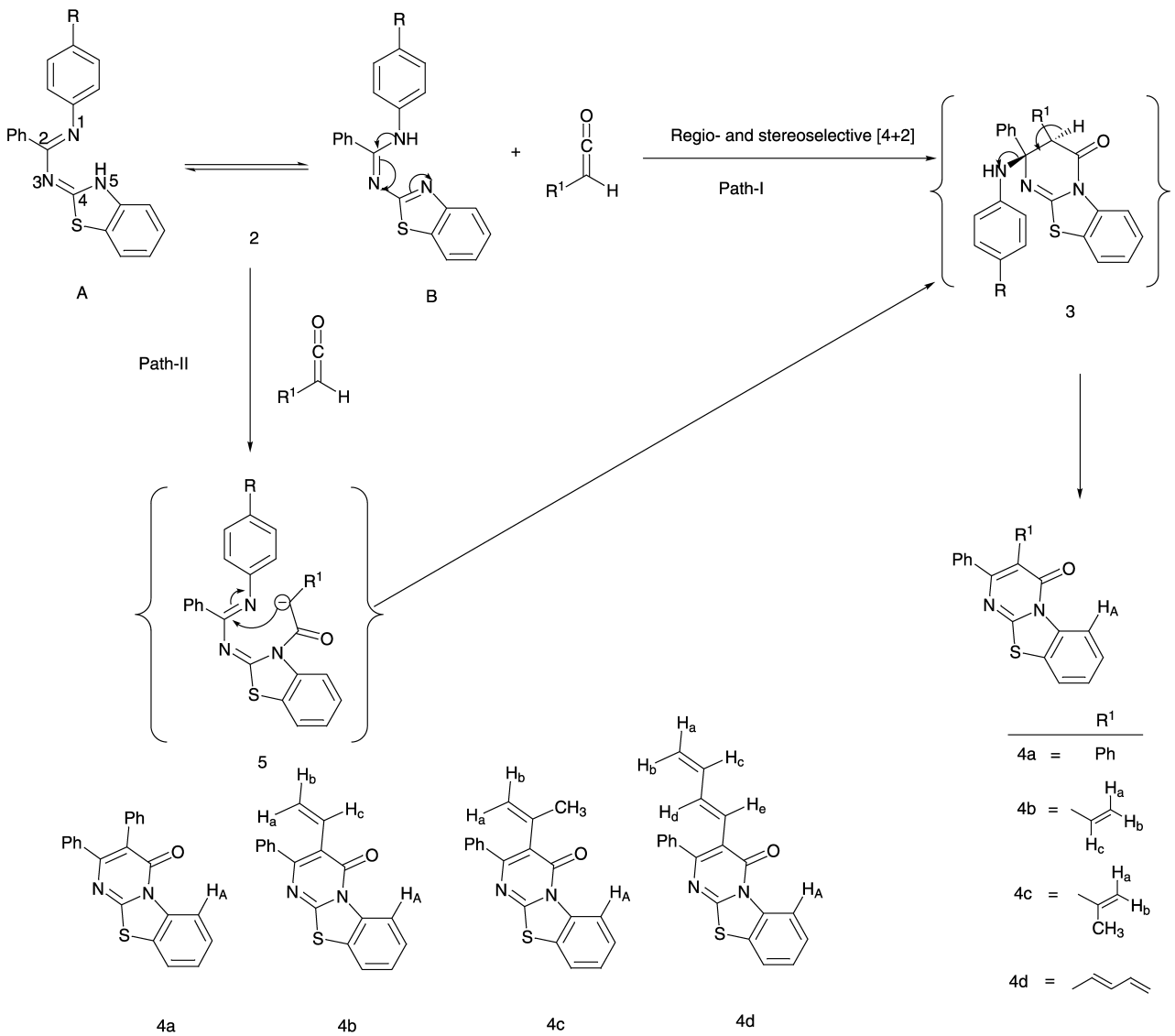
to the secondary amine and the methylthio functions and the presence of a singlet at δ 2.29 for a methyl group attached to an aromatic ring and a broad singlet appeared at δ 12.62 for an exchangeable N–H proton. The signals in its ^{13}C NMR spectrum are also in agreement with the assigned structure. The formation of *N*-aryl-*N*′-(2-benzothiazolyl)-benzamidines **2** in these reactions may be explained by the initial displacement of methylmercaptan, by attack of the sulphur of aminothiophenol on C-4 of 1,3-diazabutadiene, followed by the displacement of secondary amine by the nitrogen of aromatic amine group via an addition–elimination mechanism (Scheme 1).

1,3-Diazabutadienes **2** probably exist in a number of tautomeric forms (**A**, **B** and **C**). In order to have an idea about the predominant tautomeric form in this mixture and to examine the regiochemical aspects of their cycloadditions, we have examined their reactions with ketenes. Thus, the reactions of 1,3-diazabutadienes **2** with monophenyl, vinyl-, and isopropenyl ketenes, generated in situ from phenylacetyl chloride, crotonyl chloride, and 3,3-dimethylacryloyl chloride, respectively, in the presence of triethylamine in methylene chloride, resulted in good yields of the products which were characterized as novel benzothiazolo fused pyrimidinones **4**. The detailed spectral features of these pyrimidinones are discussed in the experimental section while the salient features are mentioned here. For example, pyrimidinone **4b**, analyzed for $C_{18}H_{12}N_2OS$ showed a molecular ion peak at *m*/*z* 304 in its mass spectrum. ^{1}H NMR spectrum attests to the presence of vinylic protons and loss of the aryl amine attached to the phenyl-bearing carbon. The aromatic proton H_A in pyrimidinones **4** appeared unexpectedly downfield, around δ 9.12–9.15 as doublet of a doublet, probably due to the deshielding effect of the carbonyl group. The signals in the ^{13}C NMR spectrum were also in agreement with the assigned structure. The probable mechanisms for the formation of pyrimidinones **4** are depicted in Scheme 2. It is assumed that the stereoselective [4+2] cycloaddition of tautomer **2B** with ketene forms an intermediate **3**, which on elimination of the aromatic amine leads to the desired benzothiazolopyrimidinone **4** (Path I). The formation of **4** may also be explained by an initial nucleophilic attack of the N-5 of **2A** on ketene carbonyl to form an intermediate **5**, its



Scheme 1.



Scheme 2.

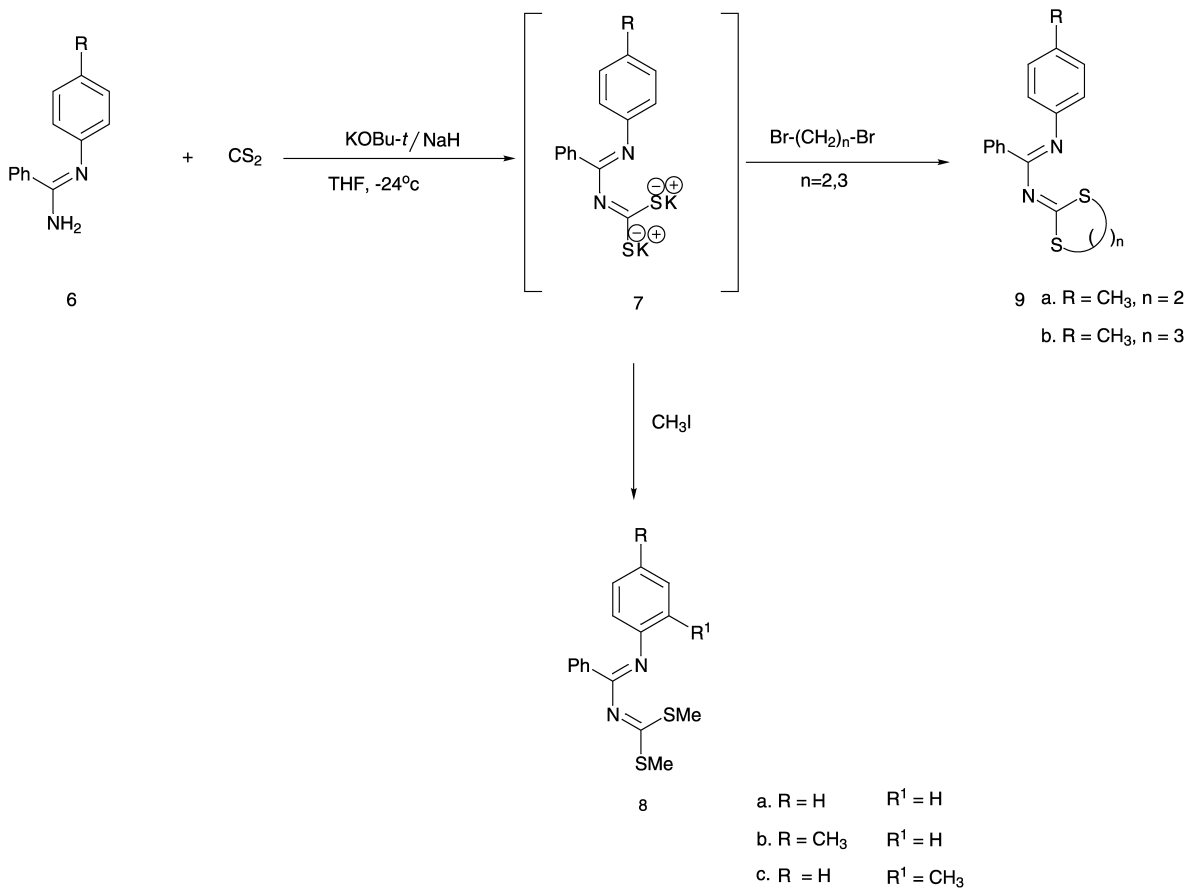
cyclisation to **3** and usual elimination of aromatic amine (Path II). The tautomeric form **2B** appears to be more stable and hence preferred over the form **2A** due to the higher stabilization imparted by its aromatic benzothiazole component. Thus, the regioselective and stereoselective [4+2] cycloaddition (Path I) similar to one reported earlier,[8e] appears to be a preferred route for the formation of fused pyrimidinones **4** (Scheme 2).

Recent disclosure from our laboratory has shown remarkable substituent dependent tandem [1,5]H, [1,3]NHPh and [1,5]NHPh sigmatropic shifts accompanying [4+2] cycloaddition reactions of 4-N-arylamino substituted 1,3-diazabuta-1,3-dienes with butadienylketene.[9] In continuation of these studies, we have examined the reactions of benzothiazole-incorporated 1,3-diazabuta-1,3-dienes **2** with butadienylketene. The treatment of benzothiazolyl incorporated 1,3-diazabuta-1,3-dienes **2** with butadienylketene, generated in situ, was found to result in the exclusive formation of 5-butadienyl pyrimidinone **4d**, while no product corresponding to the rearrangement observed earlier could be isolated. The pyrimidinone **4d** was characterized on the basis of analytical data and spectral evidence. It appears that the more stable tautomeric form **2B** of 1,3-diazabuta-1,3-dienes **2**, undergoes regio/stereoselective [4+2] cycloaddition reaction with butadienylketene to form an intermediate **3** which on elimination of aromatic amine results in the formation of pyrimidinone **4d**. The alternative mechanistic possibility (Path II) involving initial nucleophilic attack, followed by cyclisation and elimination of aromatic amine, is less likely as this would have resulted in rearranged pyrimidinone derivatives as observed in reactions of *N*-arylamino-1,3-diazabuta-1,3-diene with butadienylketene.[9b] A simpler and more acceptable explanation for the exclusive formation of pyrimidinones **4d** in these reactions assumes an additional nucleophilic push from sulfur in intermediate **3**, which shortens its life time and favours the elimination of arylamine over rearrangement involving [1,5]H sigmatropic shift followed by a [1,5]NH-Ph shift.

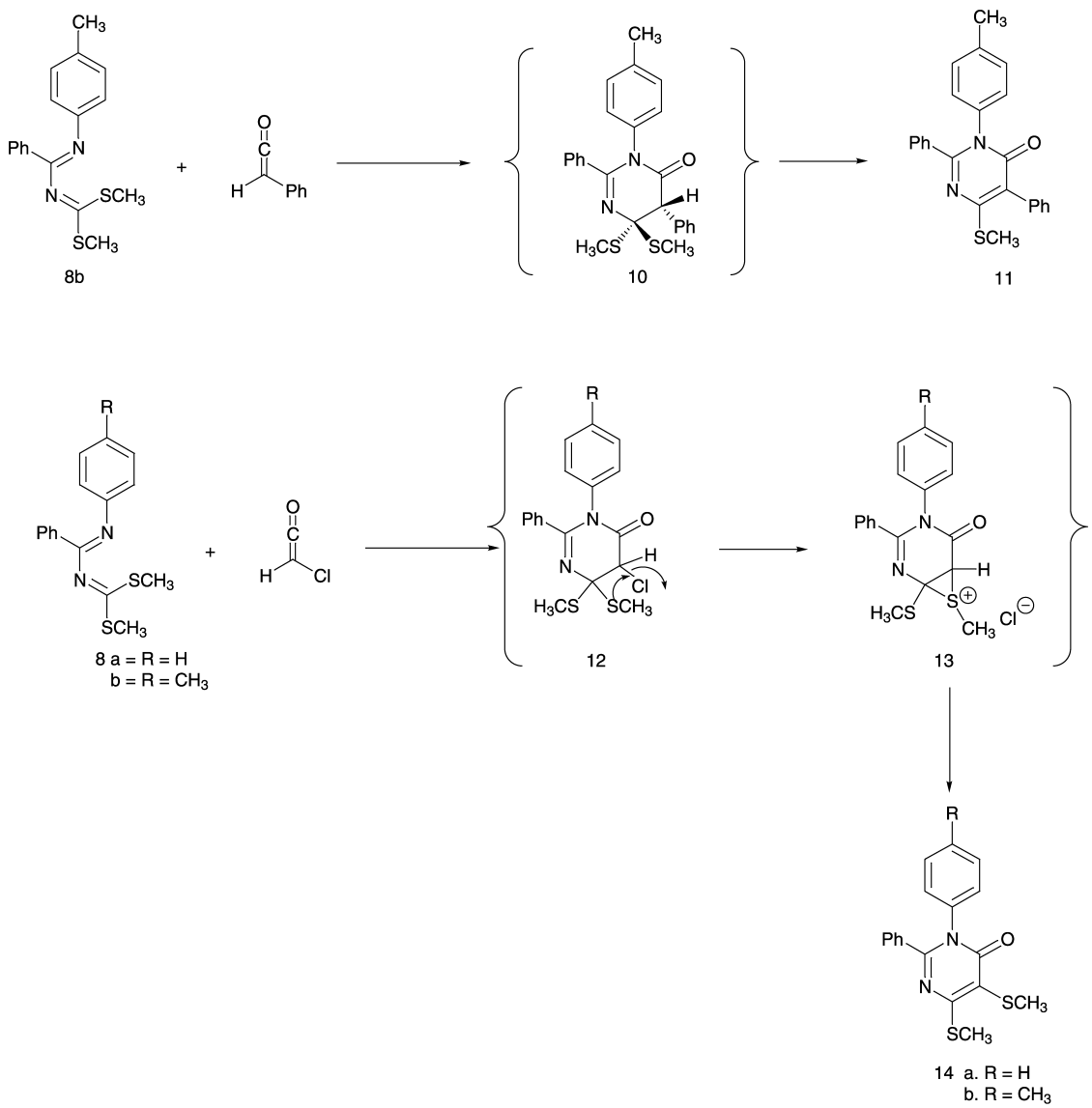
Inspired by the highly stereo- and regioselective cycloadditions observed in these reactions, it was considered worthwhile to extend these studies to other similar

heterocyclic fused 1,3-diazabuta-1,3-dienes. Thus, simple and elegant protocols for the synthesis of 4,4-bisthioalkyl substituted 1,3-diazabuta-1,3-dienes have been developed (Scheme 3). The treatment of benzamidines **6** with carbon disulfide in the presence of potassium-*tert*-butoxide/sodium hydride and subsequent treatment of resulting intermediate **7** with methyl iodide, 1,3-dibromopropane and 1,2-dibromoethane resulted in good yields of 4,4-bismethylthio-1,3-diazabuta-1,3-dienes **8a**–**c**, 1-aryl-2-phenyl-4[2-(1,3-dithiolanyl)]-1,3-diazabuta-1,3-diene **9a** and 1-aryl-2-phenyl-4[2-(1,3-dithianyl)]-1,3-diazabuta-1,3-diene **9b** derivatives, respectively. The structural assignments to the product **8** and **9** were based on analytical data and spectral evidences. The compound **9b**, for example, exhibited a molecular ion peak at *m*/*z* 326. Its ^{1}H NMR spectrum exhibited a multiplet at δ 2.03 (2H) for $-CH_2-$ group, a singlet at δ 2.31 for $-CH_3$ and a multiplet at δ 2.91 for four methylene protons attached to sulfur, in addition to the aromatic protons. The assigned structure was further corroborated by its ^{13}C spectrum which showed a peak at δ 20.8 for $-CH_2-$, a peak at δ 21.6 for $-CH_3$ and a peak at δ 29.7 corresponding to two $-SCH_2$ carbons.

The 1,3-diazabuta-1,3-dienes, **8**, **9a** and **9b** (Schemes 4 and 5) obtained were treated with various ketenes, generated in situ from the corresponding acid chlorides. The treatment of **8b** with phenylacetyl chloride in presence of dry triethylamine resulted in the isolation of 2,5-diphenyl-6-methylthio-3-(*p*-tolyl)-pyrimidin-4(3*H*)-one **11** presumably via the initial formation of pyrimidinone **10** as an intermediate. However, [1,2]-methylthio shift, similar to the one reported earlier,[8c] have been shown to accompany the [4+2] cycloadditions in reactions of **8** with chloroketene. These reactions resulted in the formation of 2-phenyl-3-aryl-5,6-bismethylthio-pyrimidin-4(3*H*)-one **14** and probably involve an initial formation of an intermediate **12**, its subsequent transformation to episulfonium intermediate **13** before rearrangement to **14** (Scheme 4). On the other hand, the reactions of 1,3-diazabuta-1,3-dienes **9** with chloroketene resulted in a mixture (≈1:1) of pyrimidinones **19** and **20** (Scheme 5). The separation of this mixture of **19** and **20** with very close R_f values was accomplished by careful silica gel column chromatography with natural loss of yields. The pyrimidinones **19** and **20** were characterized on the basis of their analytical and spectral data. Compound **19b** (Scheme 5), for example, analyzed for $C_{22}H_{20}N_2S_2O_2Cl_2$ exhibited in its mass spectrum a molecular ion peak at *m*/*z* 479 (M^+). Its IR spectrum showed a sharp peak at 1678 cm^{-1}, assigned to the α,β-unsaturated carbonyl group. Its ^{1}H NMR spectrum exhibited a multiplet at δ 2.07 (2H) for the $-CH_2-$ group, singlet at δ 2.31 (3H) for the aromatic substituted methyl group, a triplet (J=7.0 Hz) at δ 3.06 for the methylene protons attached to sulfur, a triplet (J=7.0 Hz) at δ 3.26 for methylene attached to another sulfur and a singlet at δ 4.12 for the methylene attached to chlorine, in addition to the aromatic protons. Its ^{13}C NMR spectrum was also in agreement with the assigned structure. The pyrimidinone **20b** on the other hand was analyzed for $C_{20}H_{18}N_2OS_2$ and exhibited in its mass spectrum a molecular ion peak at *m*/*z* 366 (M^+). Its IR spectrum



Scheme 3.

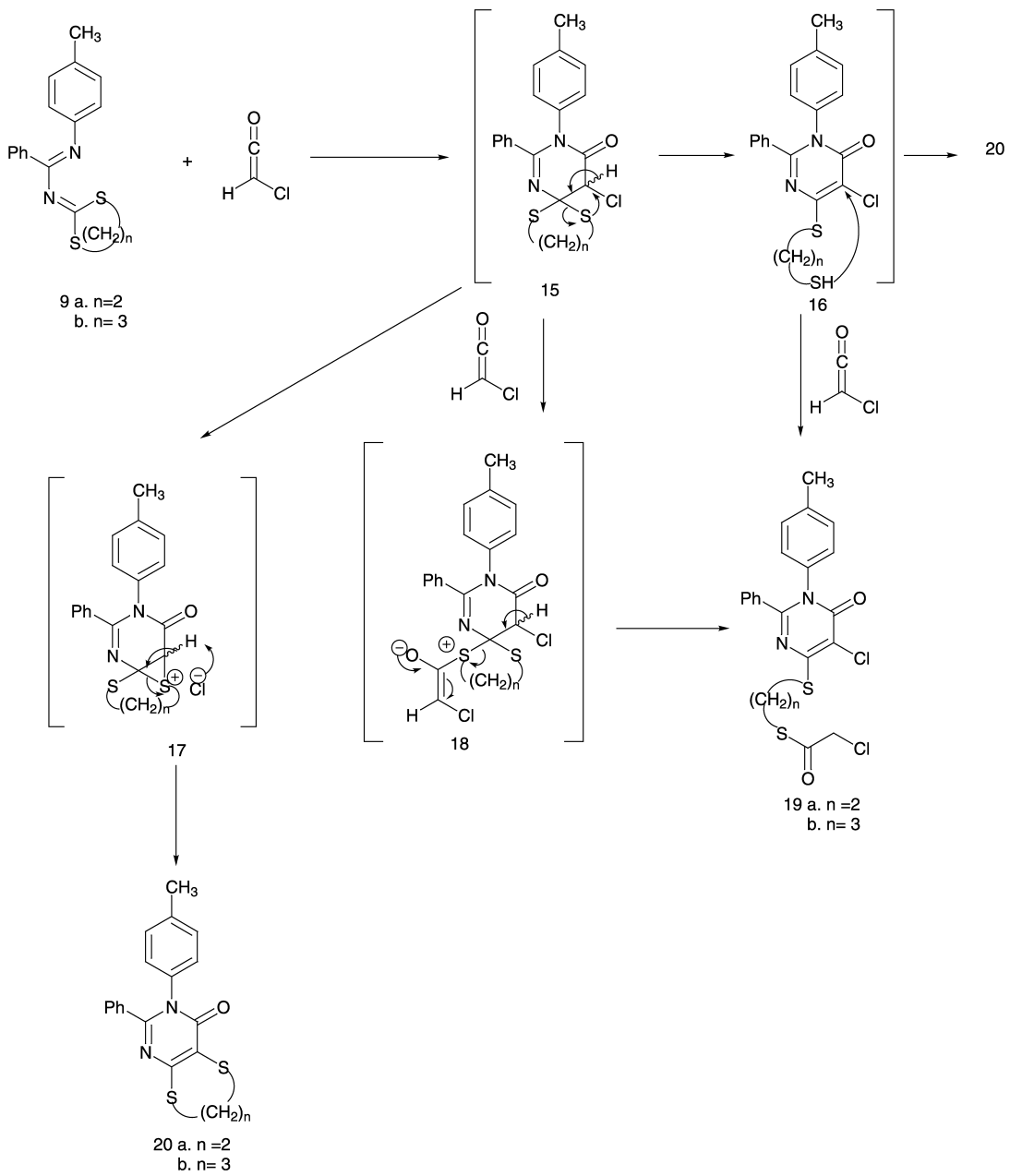


Scheme 4.

showed intense absorption at 1672 cm^{-1} due to the α,β-unsaturated carbonyl group. Its ^1H NMR spectrum exhibited a multiplet at δ 2.14–2.22 (2H) corresponding to the methylene, a singlet at δ 2.28 (3H) corresponding to the aromatic substituted $-CH_3$ group, a triplet (J=6.0 Hz) at δ 3.59 for the methylene attached to sulfur, another triplet (J=6.0 Hz) at δ 3.69 for the for the second $-S-CH_2-$ group, in addition to the aromatic protons. The assigned structure was further corroborated by signals present in its ^{13}C NMR spectrum which showed a signal at δ 159.7 indicating the presence of a carbonyl carbon and two signals at δ 27.6 and 30.1 corresponding to two methylene carbons.

The plausible mechanism for the formation of pyrimidinones **19** and **20** is depicted in Scheme 5. In this scheme it is believed that 1,3-diazabuta-1,3-diene **9** undergoes [4+2] cycloaddition reaction with chloroketene resulting in initial formation of intermediate **15** which leads to intermediate **16**. The nucleophilic reaction of the thiol of intermediate **16** with either chloroketene or chloroaceteyl chloride results in the formation of pyrimidinones **19**. The pyrimidinones **19** may also be the result of proton assisted sulfur ring opening of intermediate **18**, which in turn is obtained by the reaction of the second molecule of ketene at the sulfur of intermediate **15**. The formation of pyrimidinones **20** from intermediate **15** probably proceeds through a rearrangement involving an episulfonium intermediate **17**, wherein dehydrohalogenation is accompanied by a 1,2-alkylthio shift. The formation of pyrimidinones **20** by dehydrohalogenation of intermediate **16** may be ruled out on the basis of arguments eluded to, earlier reported similar reactions.[8c]

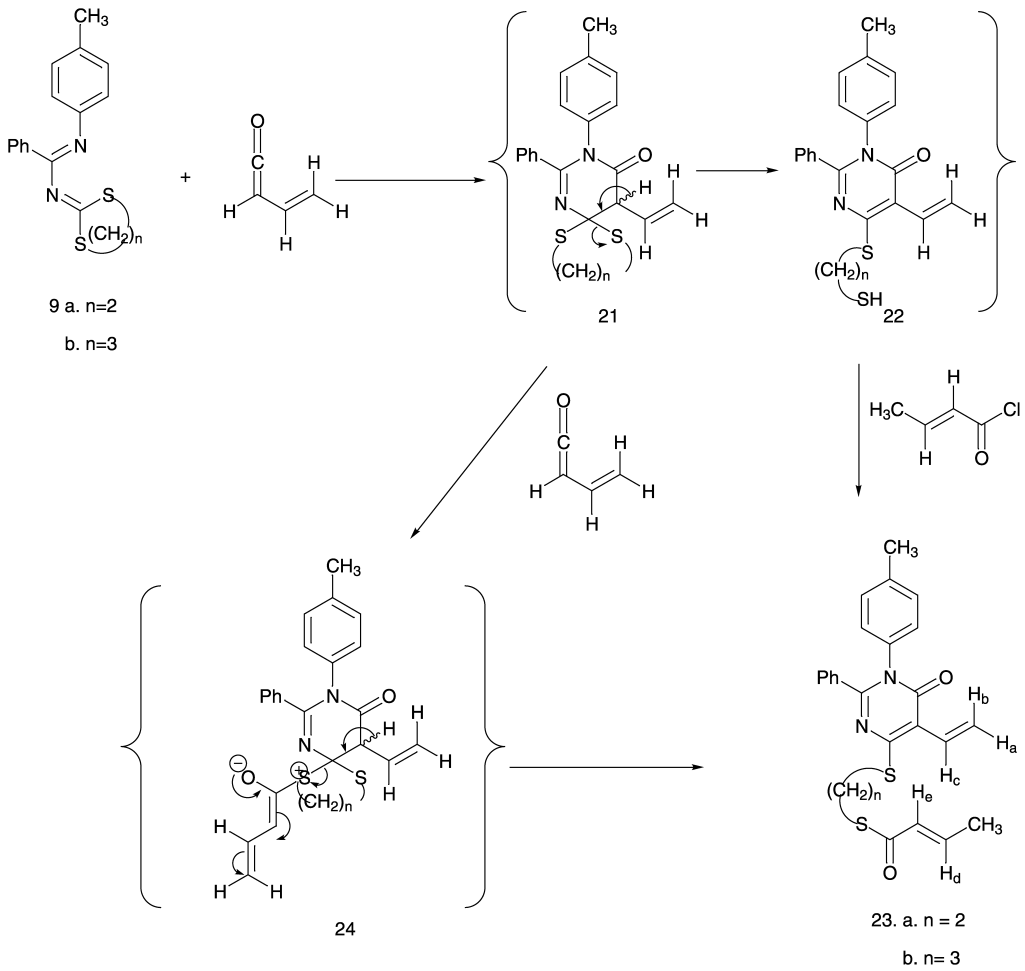
Similarly, the reactions of 1-(*p*-tolyl)-2-phenyl-4-[2-(1,3-dithiolanyl)]-1,3-diazabuta-1,3-diene **9a** and 1-(*p*-tolyl)-2-phenyl-4-[2-(1,3-dithianyl)]-1,3-diazabuta-1,3-diene **9b** with vinyl ketene, generated in situ from crotonyl chloride and triethylamine in dry methylene chloride, resulted in the isolation of products which were characterized as pyrimidinones **23** on the basis of analytical data and spectral evidence. For example, 2-phenyl-3-(*p*-tolyl)-5-vinyl-6-{8-[(*E*)-5,8-dithiaoct-2-ene-4-one]}-pyrimidin-4(3*H*)-one **23a** (Scheme 6) analyzed for $C_{25}H_{24}N_2O_2S_2$ showed by EIMS a



Scheme 5.

molecular ion peak at *m/z* 448. Its IR spectrum showed a strong absorption at 1669 cm^{-1} due to α,β-unsaturated carbonyl group. Its ^1H NMR spectrum showed a doublet of doublet (J=6.8, 1.6 Hz) at δ 1.68 for the isopropenyl $-CH_3$ group, a singlet at δ 2.30 for the aromatic substituted $-CH_3$ group, two multiplets at δ 3.26–3.34 (2H) and δ 3.40–3.47 (2H) for the protons of two methylene groups attached to sulfur, a doublet of doublet (J=11.4, 2.6 Hz) at δ 5.56 (H_a), a doublet of a doublet with fine splitting (J=15.3, 1.6 Hz) at δ 6.12 (H_e), a doublet of a doublet (J=17.6, 2.6 Hz) at δ 6.54 (H_b), a doublet of doublet (J=17.6, 11.4 Hz) at δ 6.73 (H_c), a doublet of a quartet (J=15.4, 6.9 Hz) at δ 6.90 (H_d) in addition to the aromatic protons. The assigned structure was further corroborated by its ^{13}C NMR spectrum. The plausible mechanism for the formation of pyrimidinones **23** is depicted in Scheme 6 and is similar to the one proposed for the formation of pyrimidinones **19**. It is believed that 1,3-diazabuta-1,3-diene **9** undergoes an initial [4+2] cycloaddition reaction with vinyl ketene leading to the formation of an intermediate **21**, which isomerises to pyrimidinones **22** and its reactions with crotonyl chloride results in the formation of desired pyrimidinones **23**. It is also possible that the sulfur of intermediate **21** attacks the carbonyl carbon of another molecule of ketene to form an intermediate **24** which undergoes proton assisted ring opening to form the pyrimidinones **23** (Scheme 6).

Thus, a conceptually attractive strategy has been developed for the synthesis of novel heterocyclic fused 1,3-diazabuta-1,3-dienes, which have been shown to undergo interesting cycloaddition with various ketenes. Additionally, bisthio substituted 1,3-diazabuta-1,3-dienes have also been formed. Depending on the ketene used, this class of dienes leads to a series of structurally distinct



Scheme 6.

pyrimidinones, some of which are the result of an interesting rearrangement.

3. Experimental

3.1. General

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) and AC-E 300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) or Bruker AC-300E (75.0 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120) mesh or Harrison Research Chromatotron using 2 mm plates (Silica gel 60 PF_{254}). THF/Diethyl ether were dried over sodium benzophenone ketyl and distilled under nitrogen. Dichloromethane dried over di-phosphorous pentoxide and stored over molecular sieves (4A).

3.2. Starting materials

Benzamidines,[10] 1-aryl-2-phenyl-4-thiomethyl-4-tertiary-amino-1,3-diazabuta-1,3-dienes **1**[7] were prepared by reported methods. Phenyl-, propenyl-, crotonoyl-, 3,3-dimethylacryl-, chlorides and sorbyl chloride[11] where prepared from the corresponding acid and thionyl chloride.

3.3. General method for the preparation of *N*-aryl-*N*′-(2-benzothiazol)-benzamidine 2

A solution of 1-aryl-2-phenyl-4-thiomethyl-4-tertiary amino-1,3-diazabuta-1,3-diene **1** (10 mmol) and 2-amino-thiophenol (12 mmol) in dry toluene (30 mL) was refluxed for a period of 6–7 h. After the completion of reaction (tlc), solvent was removed under reduced pressure and the crude product was purified through silica gel column chromatography and recrystallized using hexane–chloroform mixture (5:1).

3.3.1. *N*-Benzothiazol-2-yl-*N*′-phenyl-benzamidine 2a. Yellow crystalline solid, yield: 82%; mp 134–135 °C. Anal. Calcd for $C_{20}H_{15}N_3S$: C, 79.92; H, 4.59; N, 12.76.

Found: C, 80.05; H, 4.57; N, 12.80%. IR (KBr) ν_{max}: 1651, 1589 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 6.96 (d, J=7.7 Hz, 2H, ArH); 7.05–7.42 (m, 8H, ArH); 7.58 (d, J=7.9 Hz, 2H, ArH); 7.76 (dd, J=7.9, 3.7 Hz, 2H, ArH); 12.87 (s, 1H, NH, D_2O exchangeable). δ_C (50.4 MHz, $CDCl_3$): 121.0, 121.2, 123.8, 124.2, 125.2, 125.8, 128.2, 129.0, 129.7, 130.3, 132.7, 134.8, 139.2, 151.0, 159.8, 173.2. m/z: 329 (M^+).

3.3.2. *N*-Benzothiazol-2-yl-*N'*-*p*-tolyl-benzamidine 2b. Pale yellow crystalline solid, yield: 79%; mp 97–98 °C. Anal. Calcd for $C_{21}H_{17}N_3S$: C, 73.44; H, 4.99; N, 12.23. Found: C, 73.45; H, 4.97; N, 12.20%. IR (KBr) ν_{max}: 1652, 1589, 1437, 1385 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.29 (s, 3H, $-CH_3$); 6.84 (d, J=8.1 Hz, 2H, ArH); 7.00 (d, J=8.1 Hz, 2H, ArH); 7.23–7.33 (m, 5H, ArH); 7.55 (dd, J=7.5, 1.4 Hz, 2H, ArH); 7.71–7.76 (m, 2H, ArH); 12.62 (br, 1H, NH, D_2O exchangeable). δ_C (50.4 MHz, $CDCl_3$): 20.9 ($-CH_3$) 121.0, 121.1, 123.7, 124.1, 125.7, 128.1, 129.5, 129.6, 130.1, 132.8, 134.8, 137.0, 151.0, 159.8, 173.2. m/z: 343 (M^+).

3.4. Reactions of 1,3-diazabutadienes 2 with phenyl-/vinyl-/isopropenyl-/butadienyl-ketenes

General procedure. To a well stirred solution of 1,3-diazabuta-1,3-diene **2** (10 mmol) and triethylamine (40 mmol) in dry methylene chloride (30 mL) was added dropwise a solution of phenylacetyl chloride/crotonyl chloride/3,3-dimethylacryloyl chloride/sorbyl chloride (20 mmol) in dry methylene chloride (30 mL) over a period of 1 h at 0 °C. After completion of the reaction (tlc), the reaction mixture was first washed with saturated sodium bicarbonate solution (2×25 mL) and water (5×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane (1:10, V/V).

3.4.1. 2,3-Diphenyl-9-thia-1,4a-diaza-fluoren-4-one 4a. White crystalline solid, yield: 73%; mp 132–133 °C. Anal. Calcd for $C_{22}H_{14}N_2OS$: C, 74.51; H, 3.91; N, 7.91. Found: C, 74.45; H, 3.91; N, 7.90%. IR (KBr) ν_{max}: 1662, 1526, 1454, 1861 cm^{-1}. δ_H (300 MHz): 7.19–7.41 (m, 8H, ArH); 7.48–7.56 (m, 2H, ArH); 7.70–7.73 (m, 3H, ArH); 9.12–9.15 (dd, J=9.2, 1.8 Hz, 1H, H_A). δ_C (50.4 MHz, $CDCl_3$): 119.5, 120.2, 121.9, 124.7, 127.0, 127.1, 127.6, 127.9, 128.3, 129.0, 129.7, 131.3, 133.7, 136.4, 137.9, 156.3, 159.6, 161.6. m/z: 354 (M^+).

3.4.2. 2-Phenyl-3-vinyl-9-thia-1,4a-diaza-fluoren-4-one 4b. Colourless solid, yield: 78%; mp 141–142 °C. Anal. Calcd for $C_{18}H_{12}N_2OS$: C, 71.12; H, 3.94; N, 9.21. Found: C, 71.10; H, 3.95; N, 9.17%. IR (KBr) ν_{max}: 1679, 1549, 1504 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 5.48 (dd, J=11.0, 4.4 Hz, 1H, H_b); 6.52 (dd. J=18.0, 4.4 Hz, 1H, H_a); 6.59 (dd, J=18.0, 11.0 Hz, 1H, H_c); 7.45–7.70 (m, 8H, ArH); 9.12–9.15 (dd, J=8.2, 1.2 Hz, 1H, H_A). δ_C (50.4 MHz, $CDCl_3$): 114.2, 120.1, 121.7, 124.5, 126.8, 126.9, 127.0, 129.3, 129.4, 129.5, 136.1, 137.6, 159.4, 160.4. m/z: 304 (M^+).

3.4.3. 3-Isopropenyl-2-phenyl-9-thia-1,4a-diaza-fluoren-4-one 4c. Colourless solid, yield: 72%; mp 132–133 °C. Anal. Calcd for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43; N, 8.80. Found: C, 71.68; H, 4.45; N, 8.81%; IR (KBr) ν_{max}: 1662, 1526, 1454, 1861 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.04 (s, 3H, $-CH_3$); 4.96 (s, 1H, H_a); 5.30 (s, 1H, H_b); 7.38–7.71 (m, 8H, ArH); 9.12–9.15 (dd, J=9.2, 1.8 Hz, 1H, H_A). δ_C (50 MHz): 119.5, 120.2, 121.9, 124.7, 127.0, 127.1, 127.6, 127.9, 128.3, 129.0, 129.7, 131.3, 133.7, 136.4, 137.9, 156.3, 159.6, 161.6. m/z=318 (M^+).

3.4.4. 3-Buta-1,3-dienyl-2-phenyl-9-thia-1,4a-diaza-fluoren-4-one 4d. White crystalline solid, yield: 62%; mp 174–175 °C. Anal. Calcd for $C_{20}H_{14}N_2SO$: C, 72.70; H, 4.27; N, 8.48. Found: C, 72.68; H, 4.27; N, 8.50%. IR (KBr) ν_{max}: 1682, 1662, 1552 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 5.15 (d, J=10.2 Hz, 1H, H_a); 5.38 (d, J=16.8 Hz, 1H, H_b); 6.35 (ddd, J=10.2, 10.2, 16.9 Hz, 1H, H_c); 6.47 (d, J=15.5 Hz, 1H, H_e); 7.46–7.77 (m, 8H, ArH and H_d); 9.18–9.20 (dd, J=9.1, 1.8 Hz, 1H, H_A). δ_C (50 MHz, $CDCl_3$): 114.4, 116.1, 120.2, 121.7, 124.7, 125.9, 127.0, 127.1, 128.4, 129.4, 129.6, 135.0, 136.2, 137.3, 138.7, 159.6 and 161.6. m/z: 330 (M^+).

3.5. General method for the preparation of 1-aryl-2-phenyl-4,4-bismethylthio-1,3-diazabuta-1,3-dienes 8, 1-(*p*-tolyl)-2-phenyl-4[2-(1,3-dithianyl)]-1,3-diazabuta-1,3-diene 9a and 1-(*p*-tolyl)-2-phenyl-4[2-(1,3-dithiolanyl)]-1,3-diazabuta-1,3-dienes 9

To a well stirred suspension of potassium *t*-butoxide/sodium hydride (22 mmol) in dry THF (30 mL) was added a solution of benzamidine (20 mmol) in dry THF at −20 °C under an atmosphere of nitrogen and stirring continued for about 5–10 min. To this a solution of carbon disulphide (22 mmol) in dry THF (10 mL) was added and the reaction mixture allowed to stir for further 10–15 min and added a solution of 1,3-dibromopropane/1,2-dibromoethane (22 mmol) or methyl iodide (45 mmol) in dry THF (10 mL). The reaction mixture was further stirred for a period of 2–3 h. After the completion of the reaction (tlc), solvent was evaporated under reduced pressure, the crude product was washed with water (2×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane (1:10,V/V).

3.5.1. 1,2-Diphenyl-4,4-bis(thiomethyl)-1,3-diazabuta-1,3-diene 8a. Pale yellow crystalline solid, yield: 72%; mp 93–94 °C. Anal. Calcd for $C_{16}H_{16}N_2S_2$: C, 63.96; H, 5.37; N, 9.32; Found: C, 63.98; H, 5.36; N, 9.34%. IR (KBr) ν_{max}: 1609, 1579, 1503 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.40 (s, 6H, 2×$-SCH_3$); 6.95–6.99 (m, 3H, ArH); 7.21–7.26 (m, 2H, ArH); 7.39–7.46 (m, 3H, ArH); 7.86–7.91 (m, 2H, ArH). δ_C (50.4 MHz, $CDCl_3$): 15.0 (2×$-SCH_3$), 121.2, 123.2, 127.9, 128.2, 128.2, 128.8, 130.7, 134.3, 149.3, 159.0, 163.1. m/z: 300 (M^+, 5%), 287 (15%), 286 (20%).

3.5.2. 1-(*p*-Tolyl)-2-phenyl-4,4-bis(thiomethyl)-1,3-diazabuta-1,3-diene 8b. Yellow crystalline solid, yield: 78%; mp 98–100 °C. Anal. Calcd for $C_{17}H_{18}N_2S_2$: C, 64.93; H, 5.77; N, 8.9; Found: C, 64.94; H, 5.79; N, 9.0%. IR (KBr) ν_{max}: 1609, 1579, 1503 cm^{-1}, δ_H (200 MHz, $CDCl_3$): 2.33 (s, 3H, $-CH_3$); 2.40 (s, 6H, 2×$-SCH_3$); 6.90

(d, J=8.2 Hz, 2H, ArH); 7.05 (d, J=8.2 Hz, 2H, ArH); 7.40–7.43 (m, 3H, ArH); 7.85–7.89 (m, 2H, ArH). δ_C (50.4 MHz, $CDCl_3$): 15.0 (2×$-SCH_3$), 21.1 (q, $-CH_3$), 121.4 (d), 127.9 (d), 128.2 (d), 128.9 (d), 130.5 (d), 132.2 (s), 134.8 (s), 148.8 (s), 158.1 (s), 162.5 (s). m/z: 315 (M^++1, 5%), 314 (M^+, 6%), 300 (16%), 299 (80%).

3.5.3. 1-(*o*-Tolyl)-2-phenyl-4,4-bis(thiomethyl)-1,3-diazabuta-1,3-diene 8c. Yield: 69%; viscous oil. Anal. Calcd for $C_{17}H_{18}N_2S_2$: C, 64.93; H, 5.77; N, 8.9; Found: C, 64.92; H, 5.76; N, 9.1%. IR (KBr) ν_{max}: 1609, 1579, 1503 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.14 (s, 3H, $-CH_3$); 2.37 (s, 6H, 2×$-SCH_3$); 6.86 (d, J=7.8 Hz, 1H, ArH); 6.90 (dd, J=7.2, 7.4 Hz, 1H, ArH); 7.06 (dd, J=7.2, 7.4 Hz, 1H, ArH); 7.12 (d, J=7.8 Hz, 1H, ArH); 7.38–7.47 (m, 3H, ArH); 7.90–7.94 (m, 2H, ArH). m/z: 314 (M^+).

3.5.4. *N*-[1,3]Dithian-2-ylidene-*N'*-*p*-tolyl-benzamidine 9a. Yellow crystalline solid, yield: 61%; mp 130–132 °C. Anal. Calcd for $C_{17}H_{16}N_2S_2$: C, 65.35; H, 5.16; N, 8.97. Found: C, 65.37; H, 5.14; N, 8.99%. IR (KBr) ν_{max}: 1609, 1579, 1503 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.32 (s, 3H, $-CH_3$); 3.44 (m, 4H, 2×$-CH_2-$); 6.68 (d, J=7.9 Hz, 2H, ArH); 6.99 (d, J=8.3 Hz, 2H, ArH); 7.38–7.46 (m, 3H, ArH); 7.92–7.94 (m, 2H, ArH). m/z: 312 (M^+).

3.5.5. *N*-[1,3]Dithiolan-2-ylidene-*N'*-*p*-tolyl-benzamidine 9b. Colourless crystalline solid, yield: 58%; mp 90–91 °C. Anal. Calcd for $C_{18}H_{18}N_2S_2$: C, 66.22; H, 5.56; N, 8.58. Found: C, 66.26; H, 5.58; N, 8.56%. IR (KBr) ν_{max}: 1609, 1579, 1503 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.03 (m, 2H, $-CH_2-$); 2.31 (s, 3H, $-CH_3$); 2.91 (m, 4H, 2×$-SCH_2-$); 6.97 (d, J=8.0 Hz, 2H, ArH); 7.09 (d, J=7.9 Hz, 2H, ArH); 7.38–7.46 (m, 3H, ArH); 7.90 (m, 2H, ArH). δ_C (75 MHz, $CDCl_3$): 20.8 ($-CH_2-$), 21.6 ($-CH_3$), 29.7 (2×$-SCH_2$), 121.4, 127.6, 128.8, 129.1, 130.5, 132.5, 134.4, 146.0, 150.9, 165.3. m/z: 328 (M^++2), 327 (M^++1), 326 (M^+).

3.6. General procedure for the reactions of 1,3-diazabutadienes 8 with phenyl-/chloroketenes

To a well stirred solution of 1,3-diazabuta-1,3-diene **8** (10 mmol) and triethylamine (40 mmol) in dry methylene chloride (30 mL) was added dropwise a solution of phenylacetyl chloride/chloroacetyl chloride (20 mmol) in dry methylene chloride (30 mL) over a period of 1 h at 0 °C. After completion of the reaction (tlc), the reaction mixture was first washed with saturated sodium bicarbonate solution (2×25 mL) and water (5×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane mixture (1:10, V/V).

3.6.1. 2,5-Diphenyl-3-(*p*-tolyl)-6-methylthio-pyrimidine-4(3*H*)-one 11. White crystalline solid, yield: 82%; mp 185–186 °C. Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 75.00; H, 5.21; N, 7.29. Found: C, 74.75; H, 5.34; N, 6.99%. IR (KBr) ν_{max}: 1671 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.32 (s, 3H, $-CH_3$); 2.49 (s, 3H, $-SCH_3$); 6.98–7.41 (m, 14H, ArH). δ_C (50.4 MHz, $CDCl_3$): 15.0 ($-SCH_3$), 21.0 ($-CH_3$), 121.3, 127.9, 128.1, 128.6, 130.5, 132.2, 134.6, 146.6, 158.1, 162.5. m/z: 384 (M^+).

3.6.2. 2,3-Diphenyl-5,6-bis(methylthio)-pyrimidine-4(3*H*)-one 14a. White crystalline solid, yield: 71%; mp 221–222 °C. Anal. Calcd for $C_{18}H_{16}N_2OS_2$. C, 63.50; H, 4.74; N, 8.23. Found: C, 63.52; H, 4.75; N, 8.25%. IR (KBr) ν_{max}: 1668, 1550 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.58 (s, 6H, 2×$-SCH_3$); 7.06–7.32 (m, 10H, ArH). m/z: 340 (M^+).

3.6.3. 2-Phenyl-3-(*p*-tolyl)-5,6-bis(methylthio)-pyrimidine-4(3*H*)-one 14b. Colourless solid, yield: 67%; mp 190–192 °C. Anal. Calcd for $C_{19}H_{18}N_2OS_2$. C, 64.40; H, 5.08; N, 7.91. Found: C, 64.53; H, 4.98; N, 8.08%. IR (KBr) ν_{max}: 1669, 1548 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.31 (s, 3H, $-CH_3$); 2.47 (s, 3H, $-SCH_3$); 2.59 (s, 3H, $-SCH_3$); 6.98 (d, J=8.2 Hz, 2H, ArH); 7.11 (d, J=8.2 Hz, 2H, ArH); 7.18–7.32 (m, 5H, ArH). m/z: 354 (M^+).

3.7. General procedure for the reactions of 1,3-diazabutadienes 9 with vinyl-/chloro ketene

To a well stirred solution of 1,3-diazabuta-1,3-diene **9** (10 mmol) and triethylamine (40 mmol) in dry methylene chloride (30 mL) was added dropwise a solution of crotonylchloride/chloroacetyl chloride (25 mmol) in dry methylene chloride (30 mL) over a period of one hour at 0 °C After completion of the reaction (tlc), the reaction mixture was first washed with saturated sodium bicarbonate solution (2×25 mL) and water (5×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane (1:10,V/V).

3.7.1. 2-Phenyl-3-(*p*-tolyl)-5-chloro-6-{6-[3,6-dithiahex-1-chloro-2-one]}-pyrimidine-4(3*H*)-one 19a. Pale white solid, yield: 37%; mp 140–142 °C. Anal. Calcd for $C_{21}H_{18}N_2O_2S_2Cl_2$: C, 54.19; H, 3.87; N, 6.02. Found: C, 53.94; H, 4.02; N, 5.88%. IR (KBr) ν_{max}: 1672 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.31 (s, 3H, $-CH_3$); 3.29–3.35 (m, 2H, $-CH_2-$); 3.39–3.45 (m, 2H, $-CH_2-$); 4.14 (s, 2H, $-CH_2-$); 6.99 (d, J=8.2 Hz, 2H, ArH); 7.11 (d, J=8.2 Hz, 2H, ArH); 7.19–7.31 (m, 5H, ArH). δ_C (75 MHz, $CDCl_3$): 21.1 ($-CH_3$), 29.6 ($-CH_2-$), 29.9 ($-CH_2-$), 47.8 ($-CH_2-$), 114.7, 127.8, 128.1, 129.1, 129.6, 129.9, 133.8, 134.1, 138.8, 156.2, 156.9, 160.8, 193.3. m/z: 465 (M^+).

3.7.2. 2-Phenyl-3-(*p*-tolyl)-5-chloro-6-{7-[3,7-dithiahept-1-chloro-2-one]}-pyrimidine-4(3*H*)-one 19b. Colourless crystalline solid, yield: 33%; mp 94–95 °C. Anal. Calcd for $C_{22}H_{20}N_2O_2S_2Cl_2$: C, 55.11; H, 4.17; N, 5.84 Found: C, 54.90; H, 3.86; N, 5.56%. IR (KBr) ν_{max}: 1678 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.07 (m, 2H, $-CH_2-$); 2.31(s, 3H, $-CH_3$); 3.06 (t, J=7.0 Hz, 2H, $-S-CH_2-$); 3.26 (t, J=7.0 Hz, 2H, $-S-CH_2-$); 4.12 (s, 2H, $-CH_2-$); 6.99 (d, J=8.2 Hz, 2H, ArH); 7.11 (d, J=8.2 Hz, 2H, ArH); 7.20–7.33 (m, 5H, ArH). δ_C (50.4 MHz, $CDCl_3$): 21.1 ($-CH_3$), 28.2 ($-CH_2-$), 29.0 ($-CH_2-$), 29.6 ($-CH_2-$), 47.8 ($-CH_2-$), 114.7, 127.9, 128.1, 129.1, 129.6, 129.8, 134.1, 134.2, 138.9, 156.0, 157.1, 161.5 (C-4), 193.7 (C=O). m/z: 479 (M^+).

3.7.3. 2-Phenyl-(*p*-tolyl)-3,6,7-trihydro-pyrimidino-[4,5,*b*]-dithiane-4-one 20a. White crystalline solid, yield: 36%; mp 158–160 °C. Anal. Calcd for $C_{19}H_{16}N_2OS_2$: C,

64.77; H, 4.54; N, 7.95. Found: C, 63.97; H, 4.32; N, 7.74%. IR (KBr) ν_{max}: 1682 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.23 (s, 3H, $-CH_3$); 3.42–3.48 (m, 2H, $-CH_2-$); 3.64–3.66 (m, 2H, $-CH_2-$); 7.00 (d, J=8.3 Hz, 2H, ArH); 7.26 ((d, J=8.3 Hz, 2H, ArH); 7.24–7.51 (m, 5H, ArH). δ_C (50.4 MHz, $CDCl_3$): 20.9 ($-CH_3$), 34.1 ($-CH_2-$), 40.4 ($-CH_2-$), 118.1, 128.2, 129.0, 129.2, 129.4, 133.6, 134.5, 160.2. *m/z*: 352 (M^+).

3.7.4. 2-Phenyl-3-(*p*-tolyl)-3,6,7,8-tetrahydro-pyrimido-[4,5,*b*]-1,4-dithiapene-4-one 20b. White crystalline solid, yield: 36%; mp 273–274 °C. Anal. Calcd for $C_{20}H_{18}N_2OS_2$ C, 65.57; H, 4.91; N, 7.65. Found: C, 64.64; H, 5.53; N, 7.54%. IR (KBr) ν_{max}: 1672 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.14–2.22 (m, 2H, $-CH_2-$); 2.28 (s, 3H, $-CH_3$); 3.59 (t, J=6 Hz, 2H, $-S-CH_2-$); 3.69 (t, J=6 Hz, 2H, $-S-CH_2-$); 6.96 (d, J=8.3 Hz, 2H, ArH); 7. 08 (d, J=8.3 Hz, 2H, ArH); 7.13–7.26 (m, 5H, ArH). δ_C (50.4 MHz, $CDCl_3$): 21.1 ($-CH_3$), 27.6 ($-CH_2-$), 30.1 ($-CH_2-$), 30.6 ($-CH_2-$), 119.7, 127.8, 128.2, 129.1, 129.5, 133.8, 134.1, 136.5, 153.6, 159.7. *m/z*: 366 (M^+).

3.7.5. 2-Phenyl-3-(*p*-tolyl)-5-vinyl-6-{8-[(*E*)-5,8-dithiaoct-2-ene-4-one]}-pyrimidine-4(3*H*)-one 23a. Colourless crystalline solid, yield: 69%; mp 157–158 °C. Anal. Calcd for $C_{25}H_{24}N_2O_2S_2$: C, 66.93; H, 5.39; N, 6.24. Found: C, 66.95; H, 5.38; N, 6.26%. IR (KBr) ν_{max}: 1669 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.68 (dd, J=6.8, 1.6 Hz, 3H, $-CH_3$); 2.30 (s, 3H, $-CH_3$); 3.26–3.34 (m, 2H, $-S-CH_2-$); 3.40–3.47 (m, 2H, $-S-CH_2-$); 5.56 (dd, J=11.4, 2.6 Hz, 1H, H_a); 6.12 (dd, J=15.3, 1.6 Hz, 1H, H_e); 6.54 (dd, J=17.6, 2.6 Hz, 1H, H_b); 6.73 (dd, J=17.6, 11.4 Hz, 1H, H_c); 6.90 (dq, J=15.4, 6.9 Hz, 1H, H_d); 6.99 (d, J=8.2 Hz, 2H, ArH); 7.12 (d, J=8.2 Hz, 2H, ArH); 7.16–7.32 (m, 5H, ArH). δ_C (50.4 MHz, $CDCl_3$): 18.0 ($-CH_3$), 21.1 ($-CH_3$), 29.3 ($-CH_2-$), 30.2 ($-CH_2-$), 116.0, 121.0, 127.0, 127.4, 127.8, 128.4, 129.3, 129.6, 129.7, 129.9, 134.5. 134.6, 141.3, 142.1, 155.4, 159.5, 116.1 (C-4), 189.0 (C=O). *m/z*: 448 (M^+).

3.7.6. 2-Phenyl-3-(*p*-tolyl)-5-vinyl-6-{9-[(*E*)-5,9-dithianon-2-ene-4-one]}-pyrimidine-4(3*H*)-one 23b. White crystalline solid, yield: 72%; mp 98–100 °C. Anal. Calcd for $C_{26}H_{26}N_2O_2S_2$: C, 67.53; H, 5.62; N, 6.06. Found: C, 67.28; H, 5.86; N, 5.93%. IR (KBr) ν_{max}: 1672 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.88 (dd, J=7.1, 1.5 Hz, 3H, $-CH_3$); 2.00–2.12 (m, 2H, $-CH_2-$); 2.31 (s, 3H, $-CH_3$); 3.05 (t, J=7.1 Hz, 2H, $-S-CH_2-$); 3.29 (t, J=7.1 Hz, 2H, $-S-CH_2-$); 5.56 (dd, J=11.7, 2.2 Hz, 1H, H_a); 6.11 (dd, J=15.4, 1.8 Hz, 1H, H_e); 6.54 (dd, J=17.1, 2.2 Hz, 1H, H_b); 6.75 (dd, J=17.1, 11.7 Hz, 1H, H_c); 6.90 (dq, J=15.4, 7.1 Hz, 1H, H_d); 7.00 (d, J=8.3 Hz, 2H, ArH); 7.12 (d, J=8.3 Hz, 2H, ArH); 7.18–7.32 (m, 5H, ArH). δ_C (75 MHz, $CDCl_3$): 17.9 ($-CH_3$), 21.1 ($-CH_3$), 27.4 ($-CH_2-$), 29.2 ($-CH_2-$), 30.2 ($-CH_2-$), 115.8, 120.8, 127.5, 127.8, 128.5, 129.3, 129.6, 130.1, 134.6. 138.5, 140.8, 155.2, 159.5, 161.7 (C-4), 189.4 (C=O). *m/z*: 462 (M^+).

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