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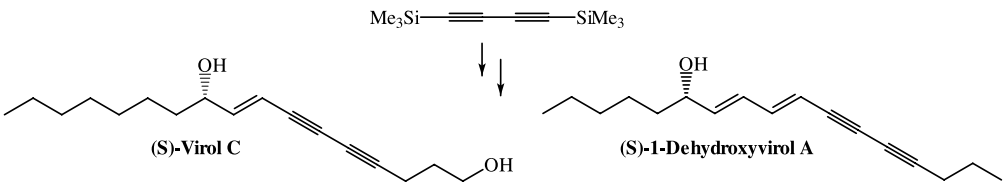
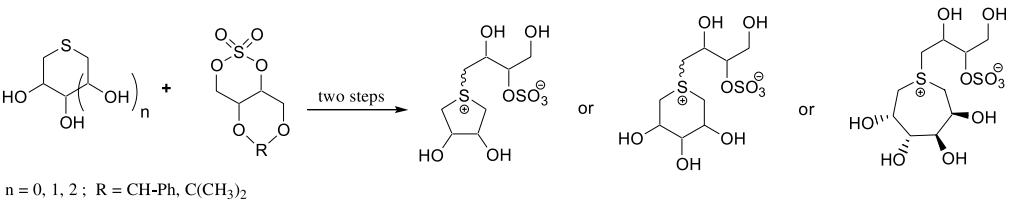
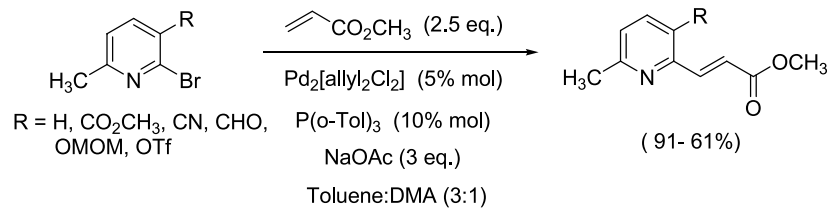
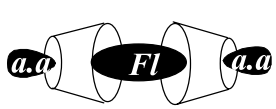


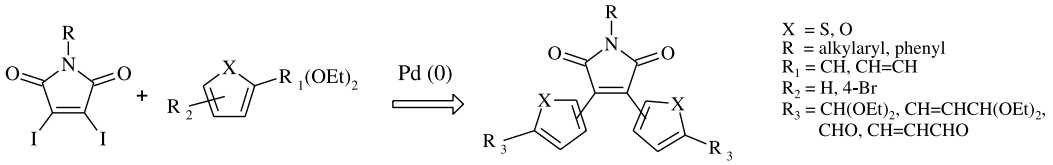
(*S*)-Virol C and (*S*)-1-dehydroxyvirol A have been synthesized starting from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.

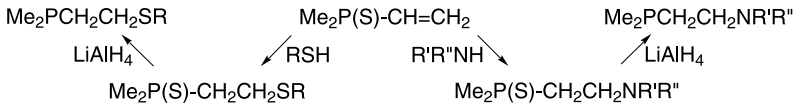


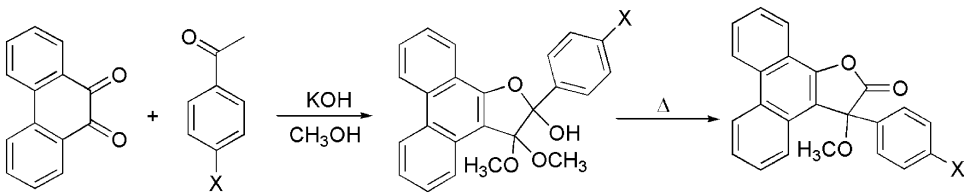


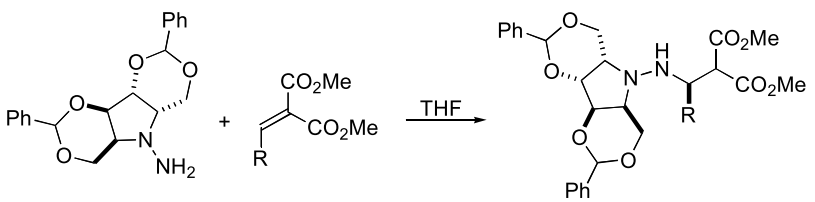


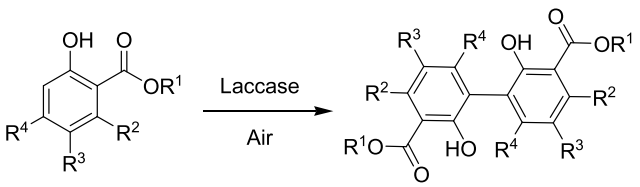
Fl: Pyrene, Xanthone, Anthraquinone
a.a.: Phenylalanine, Methionine, Histidine

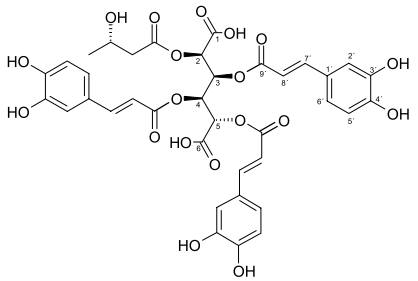


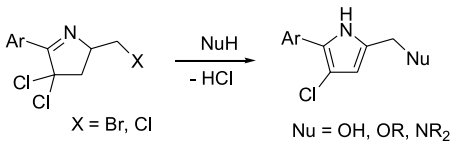


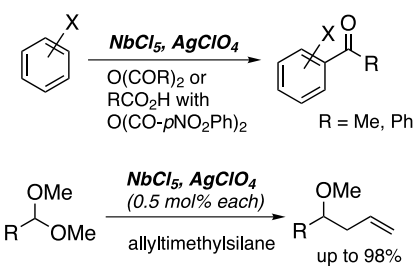


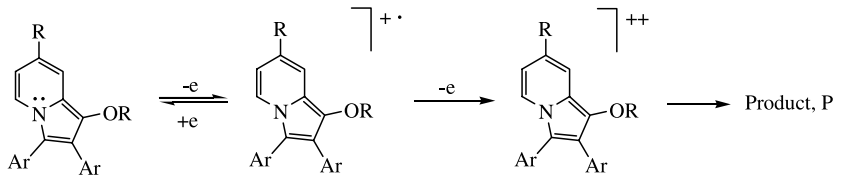


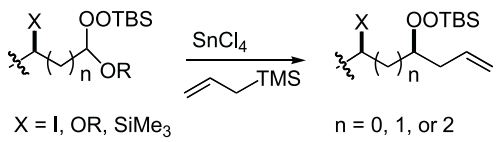


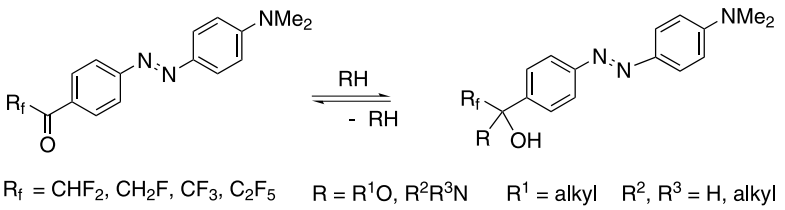


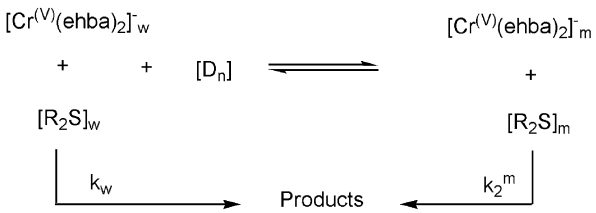












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Publisher's note

Message from the Chairman of the Executive Board of Editors: Tetrahedron Young Investigator Awards

It is an honor and a privilege to succeed Professor Léon Ghosez as Chairman of the Executive Board of Editors for Tetrahedron Publications. The five journals that our editorial board oversees have long been committed to publishing important new work in all aspects of organic chemistry as well as at the interface of chemistry and biology. Besides renewing and reinvigorating that commitment, one of my goals as Chairman is to explore new ways that Tetrahedron journals can provide better, faster service to authors, reviewers, and readers. Recent major changes in the way scientific findings are published and disseminated have created important new opportunities for enhancing and accelerating both processes. I intend to explore these opportunities with all members of our community, and would welcome any input from you.

It gives me great pleasure on this particular occasion to announce the winners of the Tetrahedron Young Investigator Awards. These two new awards are given to individuals who have exhibited 'exceptional creativity and dedication' in the field of Organic Synthesis as well as in the field of Bioorganic and Medicinal Chemistry.

The inaugural recipients of the two Young Investigator Awards, respectively, are Professor David W. MacMillan of the California Institute of Technology and Professor Laura L. Kiessling of the University of Wisconsin at Madison. I'm delighted to announce that both Professor MacMillan and Professor Kiessling will present award lectures at the upcoming Tetrahedron Symposium in Bordeaux, France on 29th June–1st July 2005 (for details of this conference, please see www.tetrahedron-symposium.elsevier.com). Furthermore, two Symposium-in-Print will be compiled and published in their honor.

David W. MacMillan,
California Institute of Technology

Laura L. Kiessling,
University of Wisconsin at Madison

On behalf of my fellow editors at Tetrahedron Publications, I congratulate these two fine chemists for the significant achievements that they have already made in their still-young careers.

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Silicon–mercury derivatives in organic synthesis

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Contents

1. Introduction

Compounds containing Hg–C bonds are known to be the oldest, most common, stable and best investigated organometallic derivatives. Although they differ widely in their stability, all of them are unreactive towards oxygen and oxidizing agents, water and at least weak acids, possess low reactivity towards many organic electrophiles and tolerate the presence of a broad range of functional groups.[1] Nothing like this is true for compounds having Hg–Si bonds. In general, silylmercurials are extremely sensitive to oxygen and moisture, enjoy poor stability towards light, and react readily with many electrophilic substrates. A systematic study of silicon–mercury compounds has only been started since the middle of the 1960s and the first planned synthesis of these species was reported in 1963.[2] Since then, more than 30 compounds having an Hg–Si bond have been described, mainly during the period between 1963 and 1975. After 1980, progress became focused on the use of silylmercurials as unique substrates in transmetalation reactions, efficient silylating and dehalogenating agents, and as a source of silyl radicals. Due to its prominent place

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Table 1. Preparation of silylmercurials from metal amalgams and halosilanes

Entry	Silylmercurial	Reagents	Conditions	Yield (%)	Ref.
1	$Hg(SiMe_3)_2$	Li/Hg, Me_3SiCl, NaCl, KI	Et_2O, rt, 3 days	50–70	14,17
2	$Hg(SiMe_3)_2$	Al/Hg, Me_3SiCl	THF, reflux, 5 h	—	18
3	$Hg(SiMe_3)_2$	Na/Hg, Me_3SiI	Et_2O, rt, 2 days	73	19
4	$Hg(SiMe_3)_2$	Na/Hg, Me_3SiBr	rt, 3–4 days	80	20

in the arsenal of the organic chemist, bis(trimethylsilyl)-mercury has been promoted to the status of reagent.[3]

Mercury is a relatively electronegative metal, the Pauling electronegativity value for this element (1.9) being greater than those of the alkali and alkaline earth metals (0.8–1.5). The electronegativity value for silicon is 1.8, which is roughly 0.7 units lower than that for carbon, and Hg–Si bonds should, therefore, have a lower polarity than Hg–C bonds. The covalent radius of silicon (1.17 Å), however, is greater than that of carbon (0.77 Å). Consequently, bonds between Hg and Si are long (2.47–2.51 Å) and easily polarizable.[4] In fact, silylmercurials show little ionization in solution and most are soluble in alkanes. On the other hand, the highly polarizable nature of 'soft' Hg–Si bonds makes silicon–mercury species relatively good nucleophiles. This is probably the reason why, at least in some cases, the pattern of reactivity of covalent silylmercurials resembles that of the more ionic silicon–alkali metal derivatives. Long Hg–Si bonds are also associated with low bond dissociation energies (ca. 48 kcal/mol), which facilitate homolytic reactions.[5,6] Essentially, all silylmercurials exist as linear or nearly linear species in which the mercury atom utilizes the sp-hybridized orbitals for bonding. This tendency to form linear molecules is so strong that the formation of common five to six-membered rings involving the Si–Hg–Si fragment is quite unfavorable.

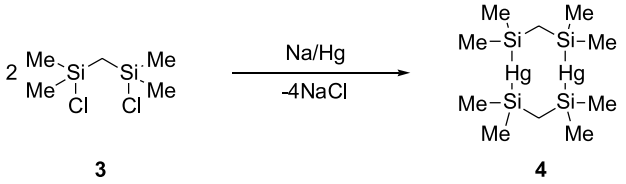
A large part of this review will be devoted to the demonstration of the synthetic utility of silylmercurials. We have attempted to make a computerized search of the literature through to the end of 2003. Since the early chemistry of silicon–mercury compounds has been partially reviewed,[7–9] publications, which have appeared prior to 1980, are only mentioned when necessary for the context. Readers are referred to various publications[4,10–13] for a more thorough treatment of the structure and bonding aspects of silicon–mercury chemistry. It is also important to note that, since all mercury derivatives are highly toxic, the use of silicon–mercury reagents can only be recommended when they provide special capabilities beyond the scope of other types of metal–silicon bonded compounds, in particular, derivatives of the Group 1 metals.

2. Preparation of silylmercurials

Silicon–mercury reagents can be prepared in a number of different ways depending on the substituents at the silicon atom. The most common methods are: (i) direct synthesis from alkali metal amalgams and halosilanes, (ii) reactions of diorganomercury compounds with hydrosilanes, and (iii) reactions of silylmetallic derivatives with mercury halides. All other methods are of relatively minor importance and are used only in special cases.

2.1. From alkali metal amalgams and halosilanes

The first synthesis and adequate characterization of bis(trimethylsilyl)mercury, $Hg(SiMe_3)_2$ (**1**), the most popular and most extensively investigated species among the silylmercurials, were reported by Wiberg et al.[2] The original process involves shaking sodium amalgam with Me_3SiBr for prolonged periods in the absence of air. Since then, several other improved procedures have been described (Table 1). Diethyl ether is the solvent of choice in these reactions. Other solvents such as THF, DME, and hydrocarbons have also been studied, but they generally give poorer yields. The best results were obtained if the lithium amalgam was stirred with Me_3SiI, generated in situ from Me_3SiCl and KI, in ether at room temperature.[14] The purity and yield of **1** are excellent, but, if required, the resulting product can be readily purified further by sublimation at 60 °C in vacuo (ca. 10^{-2} Torr). Conspicuously enough, bis(triethylsilyl)mercury, $Hg(SiEt_3)_2$ (**2**), another synthetically important silicon–mercury derivative, has never been prepared by this route. Attempts to make the silylmercury compound $Hg(SiPh_3)_2$ from Ph_3SiBr by the sodium amalgam method gave a mixture of bis(triphenylsilyl)-mercury and hexaphenyldisilane which could not easily be separated.[15] Nevertheless, the preparative potential of the method can be demonstrated by the synthesis of the cyclic disilylmercurial **4**. Sodium amalgam and the 2,4-dichloro-2,4-disilapentane **3** react slowly in pentane at room temperature to give **4** in 56% yield (Scheme 1).[16]

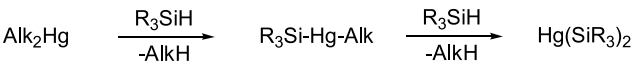


3 **4**

Scheme 1.

2.2. From hydrosilanes and diorganomercury compounds

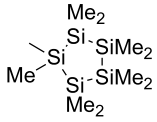
These reactions appear to be well adapted for the synthesis of silylmercurials, because they trade the weaker Si–H bond for the stronger C–H bond (Scheme 2). Although silicon generally forms stronger bonds than carbon to electronegative elements such as oxygen and halogens, the reverse is true for the bond to hydrogen. The saturated carbon–hydrogen bond dissociation energy generally exceeds the silicon–hydrogen energy by ca. 10 kcal mol^{-1}. The first direct evidence that silyl radicals are involved as



Scheme 2.

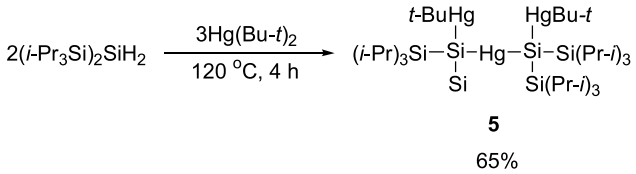
Table 2. Preparation of disilylmercurials from hydrosilanes and diorganomercury compounds

Entry	Disilylmercurial	Reagents	Conditions	Yield (%)	Ref.
1	$Hg(SiMe_3)_2$	$HgEt_2$, Me_3SiH	140–160 °C, UV	60	24
2	$Hg(SiEt_3)_2$	Hg(Bu-*t*)$_2$, Et_3SiH	140 °C	50	22
3	$Hg(SiEt_3)_2$	$HgEt_2$, Et_3SiH	145–150 °C, UV	13	25
4	$Hg[Si(Bu\text{-}t)_3]_2$	Hg(Bu-*t*)$_2$, (Bu-*t*)$_3$SiH	85 °C, 24 h	—	26
5[a]	$Hg(SiMePhR)_2$	Hg(Bu-*t*)$_2$, (+)-RPhMeSiH	100 °C, 9 h	95	27
6[a]	$Hg(SiMePhR)_2$	Hg(Bu-*t*)$_2$, (−)-RPhMeSiH	135 °C, 8 h	—	28
7	$Hg(SiMe_2Ph)_2$	Hg(Bu-*t*)$_2$, Me_2PhSiH	100–195 °C, 12 h	45	29
8	$Hg(SiPh_3)_2$	$Hg(CH_2Ph)_2$, Ph_3SiH	125–130 °C, 6 h	35–45	15
9	$Hg(SiPh_3)_2$	$HgEt_2$, Ph_3SiH	160–170 °C, 45 h	12	30
10	$Hg[Si(C_6F_5)_3]_2$	$Hg[N(SiMe_3)_2]_2$, $(C_6F_5)_3SiH$	165–170 °C, 15 h	57	31
11	$Hg(SiMe_2Cl)_2$	Hg(Bu-*t*)$_2$, Me_2SiClH	85 °C, 2 days	35	32
12[a]	$Hg[Si(R)Cl_2]_2$	Hg(Bu-*t*)$_2$, $RSiCl_2H$	Heptane, reflux, 12 h	—	33
13	$Hg(SiCl_3)_2$	$Hg(CH_2SiMe_3)_2$, Cl_3SiH	20 °C, UV	100	34
14	$Hg(SiCl_3)_2$	$Hg(Et)SiCl_3$, Cl_3SiH	30 °C, 2.5 h, UV	72	35
15	$Hg(Si_2Cl_5)_2$	Hg(Bu-*t*)$_2$, Cl_5Si_2H	—	—	36
16	$Hg(SiMe_2SiMe_3)_2$	Hg(Bu-*t*)$_2$, Me_3SiMe_2SiH	Heptane, 85 °C, 4 h	79	37
17	$Hg[(SiMe_2)_2SiMe_3]_2$	Hg(Bu-*t*)$_2$, $Me_3Si(Me_2Si)_2H$	Heptane, 85 °C, 4 h	78	37
18[b]	$Hg(SiR_2Me)_2$	Hg(Bu-*t*)$_2$, MeR_2SiH	Heptane, 85 °C, 4 h	88	37
19[c]	$Hg[Si(HgBu\text{-}t)R_2]_2$	Hg(Bu-*t*)$_2$, R_2SiH_2	120 °C, 4 h	65	23
20	$Hg[Si(SiMe_3)_2Me]_2$	Hg(Bu-*t*)$_2$, $Me(Me_3Si)_2SiH$	Heptane, 85 °C, 4 h	88	37
21	$Hg[Si(SiMe_3)_2Ph]_2$	Hg(Bu-*t*)$_2$, $Ph(Me_3Si)_2SiH$	Heptane, 85 °C, 4 h	82	37
22	$Hg[Si(SiMe_2Ph)_2Me]_2$	Hg(Bu-*t*)$_2$, $Me(Me_2PhSi)_2SiH$	Heptane, 85 °C, 4 h	95	37
23	$Hg[Si(SiMe_2Ph)_2Me]_2$	Hg(Bu-*t*)$_2$, $Me(Me_2PhSi)_2SiH$	85 °C, 86 h	89	38
24	$Hg(SiEt_2SiEt_3)_2$	Hg(Bu-*t*)$_2$, Et_3SiEt_2SiH	160 °C, 19 h	8	39
25[d]	$Hg(SiMe_2R)_2$	Hg(Bu-*t*)$_2$, RMe_2SiH	Cyclohexane, reflux	49	40
26	$Hg[Si(SiMe_3)_3]_2$	Hg(Bu-*t*)$_2$, $(Me_3Si)_3SiH$	Heptane, 85 °C, 4 h	82	37
27	$Hg[Si(SiMe_3)_3]_2$	Hg(Bu-*t*)$_2$, $(Me_3Si)_3SiH$	Pentane, rt, 24 h	87	41
28	$Hg[Si(SiCl_3)_3]_2$	Hg(Bu-*t*)$_2$, $(Cl_3Si)_3SiH$	Heptane, 70 °C, 2 h	48	42
29	$Hg[Si(Si(OMe)_3)_3]_2$	Hg(Bu-*t*)$_2$, $[(MeO)_3Si]_3SiH$	Heptane, 80 °C, 1 h	80	42
30	$Hg[Si(GeMe_2Ph)_2Me]_2$	Hg(Bu-*t*)$_2$, $Me(Me_2PhGe)_2SiH$	Heptane, 85 °C, 4 h	87	37

[a] R = 1-Naphthyl.
[b] R = $PhMe_2SiMe_2Si$.
[c] R = *i*-Pr_3Si.
[d] R = 

intermediates in these reactions was recently presented by Apeloig et al.[21] In passing, we note that bis(germyl)- and bis(stannyl)mercurials can also be prepared from hydrogermanes or hydrostannanes and dialkylmercurials.[22]

The diverse diorganomercury compounds including $HgEt_2$, $Hg(CH_2SiMe_3)_2$ and $Hg(CH_2Ph)_2$ are able to undergo organyl/silyl exchange, although Hg(Bu-*t*)$_2$ is the reagent of choice for performing such reactions. The latter are usually carried out at elevated temperatures ranging from 80 to 160 °C or under UV irradiation at room temperature (Table 2). The synthetic scope of the method is mainly limited by the availability of the requisite hydrosilane reagent. By the use of chloro- and alkoxy-bearing hydrosilanes a variety of functional disilylmercury derivatives have been prepared (Table 2; entries 11–15, 28 and 29). Thus, when $Hg(CH_2SiMe_3)_2$ is irradiated in the presence of trichlorosilane, $Hg(SiCl_3)_2$ is formed in almost quantitative yield. This compound is stable for a long period if stored in the dark at room temperature. In similar reactions with dichloromethylsilane and dichloro(1-naphthyl)silane, $Hg(SiCl_2Me)_2$ and $Hg[SiCl_2(1\text{-Nph})]_2$ are formed, respectively. The silylmercurial $Hg(SiClMe_2)_2$ was found to be more sensitive to light than other similar compounds, decomposing under UV-irradiation. The thermal reaction of $HSiClMe_2$ with Hg(Bu-*t*)$_2$, however, gave the corresponding disilylmercurial in 35% yield. With oligosilanes as reactants, similar reactions produce the corresponding bis(oligosilyl)mercurials (Table 2; entries 16–29). The involvement of dihydrosilanes in the synthesis has also been studied. Thus, bis(tri-isopropylsilyl)dihydrosilane has been transformed efficiently into the trimercury compound **5** by treatment with di-*t*-butylmercury (Scheme 3).[23]



Scheme 3.

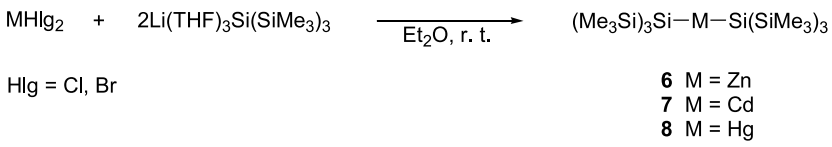
The synthesis of $Hg[Si(C_6F_5)_3]_2$ illustrates the use of the hydrosilane methodology to obtain a silylmercury derivative starting from $Hg[N(SiMe_3)_2]_2$ instead of the dialkylmercurial (Table 2; entry 10).

2.3. From silylmetallic derivatives and mercury salts

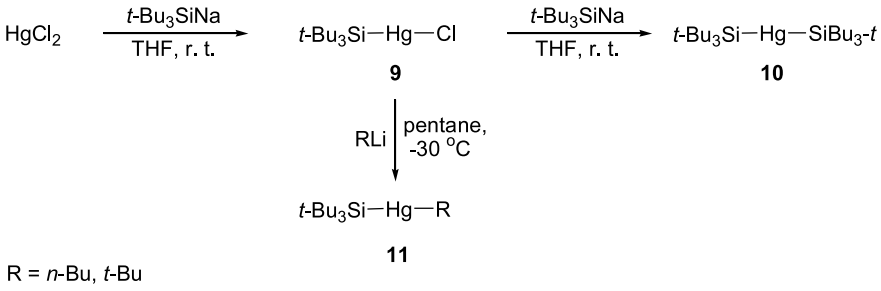
In this method, based on metathesis reactions, steric bulkiness around silicon is essential for the formation of the Hg–Si bond, otherwise decomposition reactions

Table 3. Preparation of silylmercurials from silylmetallic derivatives and mercury salts

Entry	Silylmercurial	Reagents	Conditions	Yield (%)	Ref.
1	Hg(Cl)Si(Bu-*t*)$_3$	$HgCl_2$, (*t*-Bu)$_3$SiNa	THF, rt	91	45
2	Hg[Si(Bu-*t*)$_3$]$_2$	$HgCl_2$, (*t*-Bu)$_3$SiNa	THF, rt	86	45
3	Hg[SiH(Si(Bu-*t*)$_3$)$_2$]$_2$	$HgCl_2$, [(*t*-Bu)$_3$Si]$_2$Si(H)Na	THF/benzene/pentane	82	46
4	Hg(SiPh$_3$)$_2$	Hg(OAc)$_2$, (Ph$_3$Si)$_2$AlEt	Toluene, 80 °C	40–70	43
5	Hg[Si(SiMe$_3$)$_3$]$_2$	$HgBr_2$, (Me$_3$Si)$_3$SiLi	Et_2O, rt	56	44



Scheme 4.

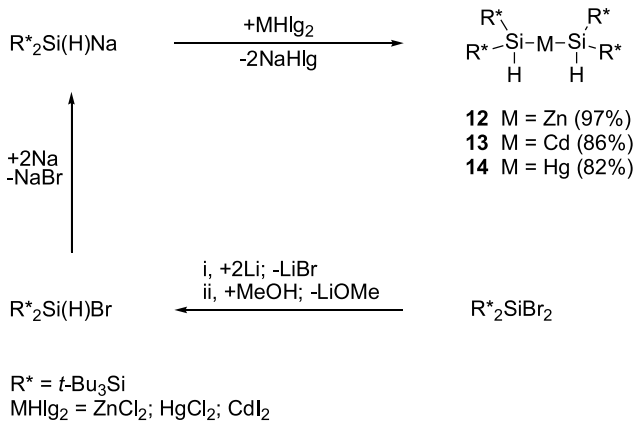


Scheme 5.

resulting from the reduction of a metal salt are observed. The very first synthesis of this type was accomplished in 1973 using the reaction of (Ph$_3$Si)$_2$AlEt(THF)$_2$ with Hg(OAc)$_2$.[43] The preparation of silylmercurials using alkali metal derivatives of silicon has become synthetically important only relatively recently, particularly with the widespread use of the highly hindered Ph$_3$Si, (Me$_3$Si)$_3$Si ('hypersilyl') and *t*-Bu$_3$Si ('supersilyl') groups (Table 3), for example, the bis(hypersilyl)metals **6**–**8** were isolated in 56–81% yield from the reaction of the metal dihalides with the hypersilyllithium. After several weeks under nitrogen, the cadmium derivative **7** shows signs of decomposition. In contrast, the compounds **6** and **8** are stable indefinitely in the solid state (Scheme 4).[44]

The reaction in Scheme 5 constitutes a more recent example from literature which illustrates the synthetic potential of the method. The supersilylmercurials **9** and **10** are prepared in THF by the action of *t*-Bu$_3$SiNa on $HgCl_2$ in a molar ratio of 1:1 and 2:1, respectively. These compounds are thermally stable up to 200 °C and are comparatively inert to water and oxygen. Treatment of **9** with organolithium compounds produced the silyl(alkyl)mercurials **11** (Scheme 5).[45]

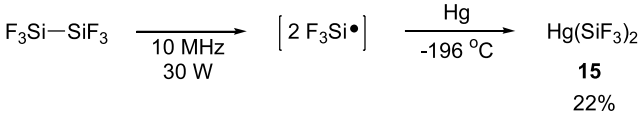
The bis[(disupersilyl)silyl]metals **12**–**14** were obtained in THF/benzene/pentane by the reaction of R*$_2$SiHNa (R*= *t*-Bu$_3$Si) with $ZnCl_2$, CdI_2 and $HgCl_2$ in a molar ratio of 2:1 (Scheme 6). These compounds form colorless, not hydrolysis- and not air-sensitive, crystals, the stabilities of which for thermolysis and photolysis decrease for the Zn > Hg > Cd species. According to the X-ray structure analysis, the compounds **12**–**14** are monomeric with a non-linear framework Si–M–Si (angle SiMSi for M=Zn/Cd/Hg 170.7/174.2/174.4°).[46]



Scheme 6.

2.4. Miscellaneous reactions

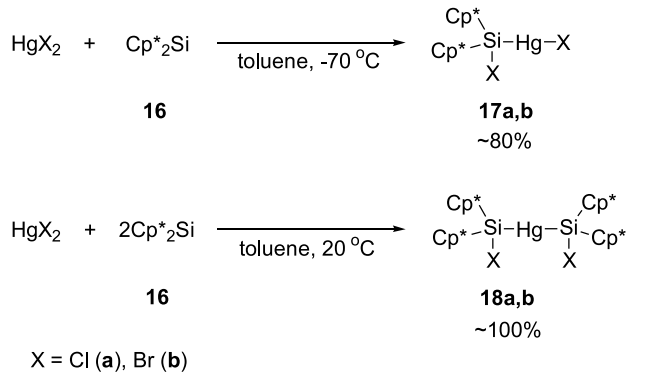
Lagow and co-workers have reported the synthesis of trifluorosilylmercury derivatives by using a novel approach.[47,48] Thus, the disilylmercurial **15** was prepared in 22% yield by co-condensation of mercury vapor with trifluorosilyl radicals generated from hexafluorodisilane in a low-temperature glow discharge (Scheme 7). Hexafluorodisilane is an excellent precursor for the synthesis of



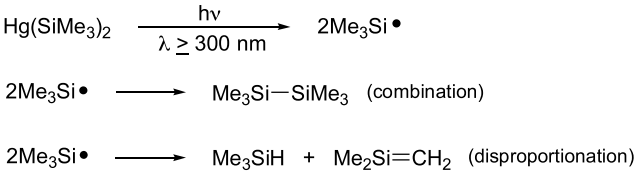
Scheme 7.

trifluorosilyl radicals, because the silicon–silicon bond energy of 50 kcal mol^{-1} is considerably lower than the silicon–fluorine bond energy of about 140 kcal mol^{-1}. The compound **15** is a colorless, crystalline solid, soluble in most common organic solvents. The apparent experimental difficulties, however, do not permit the routine use of this method.

The reaction of decamethylsilicocene **16** with $HgCl_2$ or $HgBr_2$ in toluene at −70 °C in a 1:1 molar ratio led to the formation of the monosilylmercury compounds **17**, which were obtained in about 80% yield as air- and moisture-sensitive yellow powders (Scheme 8). Both compounds are soluble in common organic solvents and can be stored in solution (−30 °C) without decomposition for a few days. In the solid state, they decompose, even at low temperature, within hours. The reaction of 2 equiv of decamethylsilicocene **16** with mercury halides at room temperature, in toluene, led to the formation of the disilylmercury derivatives **18**, which were isolated in almost quantitative yields (Scheme 8). These compounds decompose in solution within days at room temperature and, in the solid state, they can be stored at −30 °C for a few days without decomposition.[49]



Scheme 8.



Scheme 9.

3. Application of silylmercurials in organic synthesis

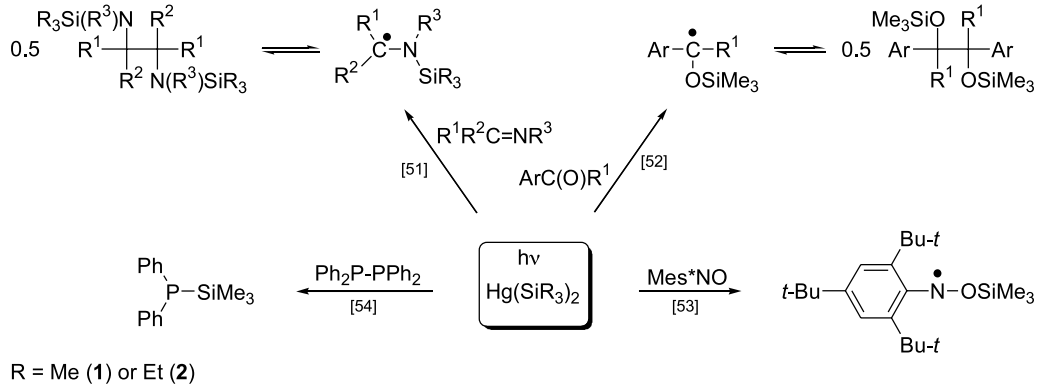
At the present time, there are five major uses of silylmercurials in organic synthesis: (i) generation of free silyl radicals, (ii) transmetalation reactions producing more reactive organometallics, (iii) silylation reactions, (iv) Wurtz-type coupling and dehalogenation reactions, and (v) formation of metal–mercury bonds. Since the mechanistic aspects of these transformations are little studied, in the following discussion the reactions will be mainly treated in terms of the resulting products and not in terms of the reaction mechanisms.

3.1. Generation of silyl radicals

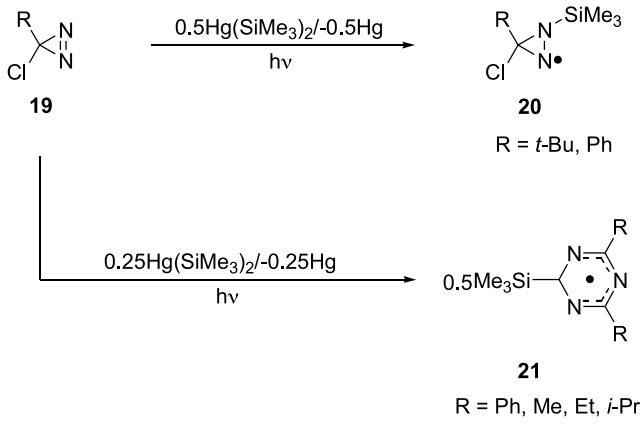
The ability to dissociate readily with the formation of silyl radicals is one of the most significant properties of compounds containing the Hg–Si bond. Historically, much of the important pioneering work on the radical chemistry of silylmercurials was carried out by Eaborn and co-workers and by Vyazankin and co-workers in the 1960s.[7] Trialkylsilyl radicals can be generated by the room-temperature photolysis of bis(trialkylsilyl)mercury vapor (~0.1 Torr) using Pyrex-filtered radiation from a medium-pressure mercury lamp ($\lambda \geq 300$ nm). When the photolysis of $Hg(SiMe_3)_2$ was carried out in the absence of a trapping agent, a mixture of disproportionation and combination products in a 5:100 molar ratio was obtained (Scheme 9).[50]

Trialkylsilyl radicals can be selectively trapped with a variety of reagents. Some examples of such reactions taken mainly from the early chemistry of disilylmercurials are given in Scheme 10. For further details, interested readers are referred to the original papers.[51–54]

The thermal or photochemical reaction of 3-chlorodiazirines **19** with $Hg(SiMe_3)_2$ in a molar ratio of 2:1 leads to the formation of N^1-silylated diaziridinyl radicals **20**. Use of a 4-fold molar excess of 3-chlorodiaziridine gives rise to N^2-silylated 1,2,3,5-tetrazinyl radicals **21**, most likely via the diaziridinyl radicals **20** (Scheme 11). The tetrazinyl



Scheme 10.

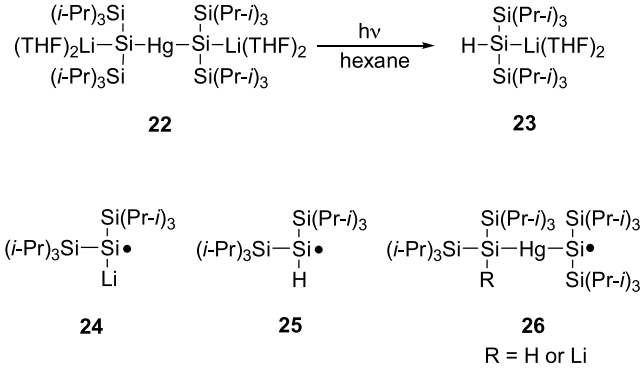


Scheme 11.

radicals **21** are in equilibrium with the corresponding dimers and are thermolabile.[55]

Introduction of sterically demanding groups in the disilylmercurials increases the kinetic stability of the forming silyl radicals. Thus, it has recently been demonstrated that the compounds $Hg[Si(SiMe_3)_3]_2$, $Hg[Si(Bu\text{-}t)_3]_2$, $Hg[SiH(Si(Bu\text{-}t)_3)_2]_2$, and the related highly sterically hindered disilylmercurials are excellent precursors for generation of the persistent silyl radicals.[21,45,46]

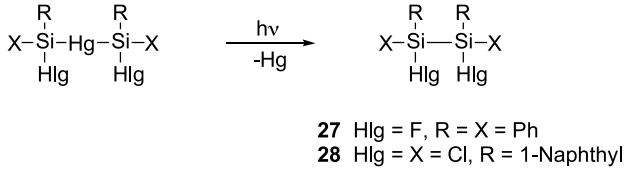
Irradiation of the geminal dimetallic compound **22** in hexane yields **23** as the major product. The EPR spectrum observed during the irradiation can be interpreted as a superposition of the signals of three radicals: the silyl radical with an α-Si–Li bond **24**, the silyl radical **25**, and the Hg-substituted radical **26** (Scheme 12). The structure of **24** is confirmed by the presence of a quartet centered at $g=2.0073$ resulting from the interaction of the unpaired electron with a ^{7}Li nuclei ($I=3/2$) and two quartets of satellites resulting from the interaction of the unpaired



Scheme 12.

electron with the α- and β-^{29}Si nuclei $a\{^7Li\}=1.25$ G. The hyperfine coupling constant (hfc) value $a\{^{29}Si(\alpha)\}=32.0$ G. These data indicate that the Si–Li bond in **24** does not dissociate in solution. Quantum-mechanical calculations are consistent with the observed hfc in **24**. Thus, for the model radical, $[(Me_3Si)_2Li]Si^{\cdot}$, which has a planar geometry around the central Si atom, the calculations predict $a\{^{29}Si(\alpha)\}=30.2$ G and $a\{^7Li\}=1.0$ G, in good agreement with the experimental values of **24**.[23]

The route employing the photolysis of disilylmercury compounds appeared to be a very helpful method for the formation of Si–Si bonds. Although the simple disilanes are easily available via halosilane/alkali metal coupling reactions, the disilylmercurial approach allows the preparation of halide-free solutions. Moreover, the photochemical route tolerates functional groups on the silicon atom (Table 4). Examples of this are the syntheses of the disilanes **27** and **28** (Scheme 13).[33,55,56] The related disilanes $n\text{-}Si_4Cl_{10}$ and $[(X_3Si)_3Si]_2$ (X=Cl, AlkO) were prepared in a similar manner.[36,42]



Scheme 13.

The method is very suitable for preparing dendritic polysilanes. Thus, when heated without protection from light, the disilylmercurial **29** decomposed to form the dimer **30**, which is a double-cored dendritic polysilane with the longest chain containing only six silicon atoms (Scheme 14). The structure of **30** was solved by X-ray crystallography.[57]

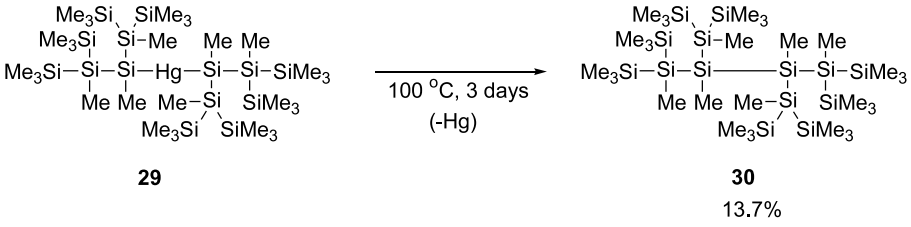
3.2. Transmetalation reactions producing more reactive organometallics

The initial reports of the synthesis of Me_3SiLi and Et_3SiLi using transmetalation of the corresponding disilylmercurials by lithium and the demonstration of the validity of the method for the synthesis of $Mg(SiMe_3)_2$ and $Al(SiMe_3)_3$ have given rise to a multitude of applications. The most commonly employed solvents in these reactions are toluene, pentane and tetrahydrofuran. Toluene and pentane give better yields than tetrahydrofuran, although the reaction rate is higher in tetrahydrofuran than in hydrocarbons. There are a number of other methods that have been used to prepare specific silylmetallic reagents, especially silyllithium species.[58–60] The mercury/metal exchange is the only

Table 4. Formation of Si–Si bonds by photochemical reactions of functionalized silylmercurials

Entry	Silylmercurial	Product	Conditions	Yield (%)	Ref.
1	$Hg(SiPh_2F)_2$	$FPh_2Si\text{-}SiPh_2F$	Heptane, rt, UV	70	56
2[a]	$Hg(SiRCl_2)_2$	$Cl_2RSi\text{-}SiRCl_2$	Heptane, rt, UV	—	33
3	$Hg(SiCl_2SiCl_3)_2$	$Cl_3SiCl_2Si\text{-}SiCl_2SiCl_3$	Heptane, rt, UV	36	36
4	$Hg[Si(SiCl_3)_3]_2$	$(Cl_3Si)_3Si\text{-}Si(SiCl_3)_3$	Hexane, 50 °C, UV	83	42
5	$Hg[Si(Si(OMe)_3)_3]_2$	$[(MeO)_3Si]_3Si\text{-}Si[Si(OMe)_3]_3$	Hexane, 50 °C, UV	86	42

[a] R=1-Naphthyl.



29 **30** 13.7%

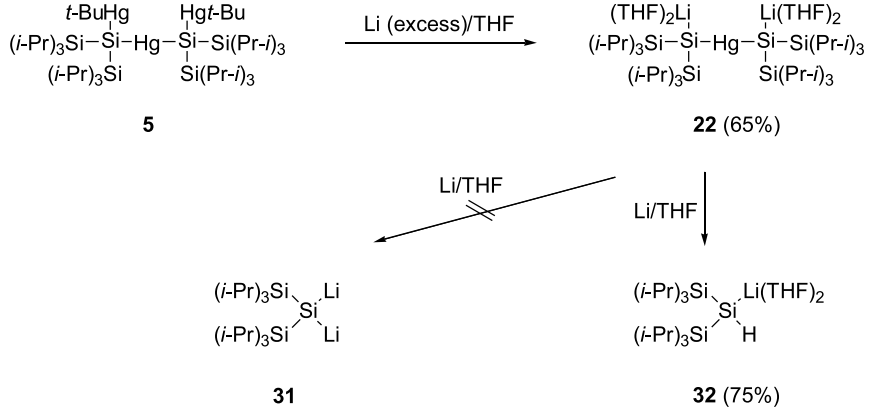
Scheme 14.

Table 5. Metal–mercury exchange reactions

Entry	Product	Silylmercurial	Metal	Conditions	Yield (%)	Ref.
1	$LiSiMe_3$	$Hg(SiMe_3)_2$	Li	Toluene, rt, 12 h	—	37
2	$LiSiMe_3$	$Hg(SiMe_3)_2$	Li	Hexane, rt	—	20
3[a]	$LiSiMe_3(THF)_2$	$Hg(SiMe_3)_2$	Li	THF, 0 °C, 24 h	—	37
4	$LiSiEt_3$	$Hg(SiEt_3)Et$	Li	THF, rt, 48 h	—	73
5	$LiSi(SiMe_2Ph)_2Me$	$Hg[Si(SiMe_2Ph)_2Me]_2$	Li	Toluene, rt, 18 h	80	38
6	$LiSiMe_2SiMe_3$	$Hg(SiMe_2SiMe_3)_2$	Li	Toluene, rt, 12 h	—	37,62
7	$LiSiMe_2SiMe_3(THF)_n$	$Hg(SiMe_2SiMe_3)_2$	Li	THF, rt, 6 h	—	37
8	$Li(SiMe_2)_2SiMe_3$	$Hg[(SiMe_2)_2SiMe_3]_2$	Li	Toluene, rt, 12 h	—	37,62
9	$Li(SiMe_2)_2SiMe_3(THF)_n$	$Hg[(SiMe_2)_2SiMe_3]_2$	Li	THF, rt, 6 h	—	37,62
10	$LiSi(SiMe_3)_2Me$	$Hg[Si(SiMe_3)_2Me]_2$	Li	Toluene, rt, 12 h	—	37
11	$LiSi(SiMe_3)_2Me(THF)_n$	$Hg[Si(SiMe_3)_2Me]_2$	Li	THF, rt, 6 h	—	37
12[b]	$LiSi(SiMe_2Ph)_2Me$	$Hg[Si(SiMe_2Ph)_2Me]_2$	Li	Toluene, rt, 12 h	71	37
13	$LiSi(SiMe_2Ph)_2Me\ (Et_2O)_n$	$Hg[Si(SiMe_2Ph)_2Me]_2$	Li	Et_2O, 0 °C, 24 h	—	37
14[b]	$LiSi(SiMe_3)_2Ph$	$Hg[Si(SiMe_3)_2Ph]_2$	Li	Toluene, rt, 12 h	—	37,62
15	$LiSi(SiMe_3)_2Ph\ (Et_2O)_n$	$Hg[Si(SiMe_3)_2Ph]_2$	Li	Et_2O, 0 °C, 24 h	—	37
16[c]	$LiSiR_2Me\ (Et_2O)_2$	$Hg(SiR_2Me)_2$	Li	Et_2O, 0 °C, 24 h	—	37
17[b]	$LiSi(SiMe_3)_3$	$Hg[Si(SiMe_3)_2]_2$	Li	Toluene, rt, 12 h	—	37
18	$LiSi(SiMe_3)_3(THF)_n$	$Hg[Si(SiMe_3)_2]_2$	Li	THF, rt, 6 h	—	37
19	$LiSi(GeMe_2Ph)_2Me$	$Hg[Si(GeMe_2Ph)_2Me]_2$	Li	Et_2O, 0 °C, 24 h	—	37
20	$KSi(SiMe_3)_3$	$Hg[Si(SiMe_3)_3]_2$	K	Pentane/toluene, rt	90	61
21	KSi_6Me_{11}-*cyclo*	$Hg(Si_6Me_{11}$-*cyclo*$)_2$	Na/K	THF, rt	—	66
22	$RbSi(SiMe_3)_3$	$Hg[Si(SiMe_3)_3]_2$	Rb	Pentane/toluene, rt	94	61
23	$CsSi(SiMe_3)_3$	$Hg[Si(SiMe_3)_3]_2$	Cs	Pentane/toluene, rt	92	61
24	$Mg(SiMe_3)_2$	$Hg(SiMe_3)_2$	Mg	DME, rt, 8 days	25	68
25	$Mg(SiMe_3)_2$ (DME)	$Hg(SiMe_3)_2$	Mg	DME, ultrasonic bath	80	69
26[d]	$Mg(SiMe_3)_2$ L	$Hg(SiMe_3)_2$	Mg	Et_2O, L	85	70
27	$Al(SiMe_3)_3$ THF	$Hg(SiMe_3)_2$	Al	THF/pentane	90	74
28	$Al(SiMe_3)_3\ P(SiMe_3)_3$	$Hg(SiMe_3)_2$	Al	THF/pentane, $P(SiMe_3)_2$	88	74
29	$NaAl(SiMe_3)_4$	$Hg(SiMe_3)_2$	Na	Et_2O/pentane, $Al(SiMe_3)_3$	85	71
30	$KAl(SiMe_3)_4$	$Hg(SiMe_3)_2$	K	Et_2O/pentane, $Al(SiMe_3)_3$	48	71

[a] The solvated $LiSiMe_3(THF)_3$ could be recrystallized from pentane at 0 °C and the molecular structure in the solid state was elucidated by X-ray diffraction.
[b] The unsolvated compound exists as dimer in the solid state as determined by X-ray diffraction.
[c] R = $SiMe_2SiMe_2Ph$.
[d] L = $Me_2N(CH_2)_3NMe_2$.

currently available route, however, to the simple silyllithium derivatives free from additives such as HMPA and halide salts. Furthermore, it is an important means of obtaining organometallic reagents $MSi(SiMe_3)_3$ (M = K, Rb, Cs) inaccessible in other ways (Table 5).[61] Finally, silylmercurials are valuable precursors of functionally substituted silyllithium species, for example, a mercury–lithium exchange reaction of **5** yields the silyllithium



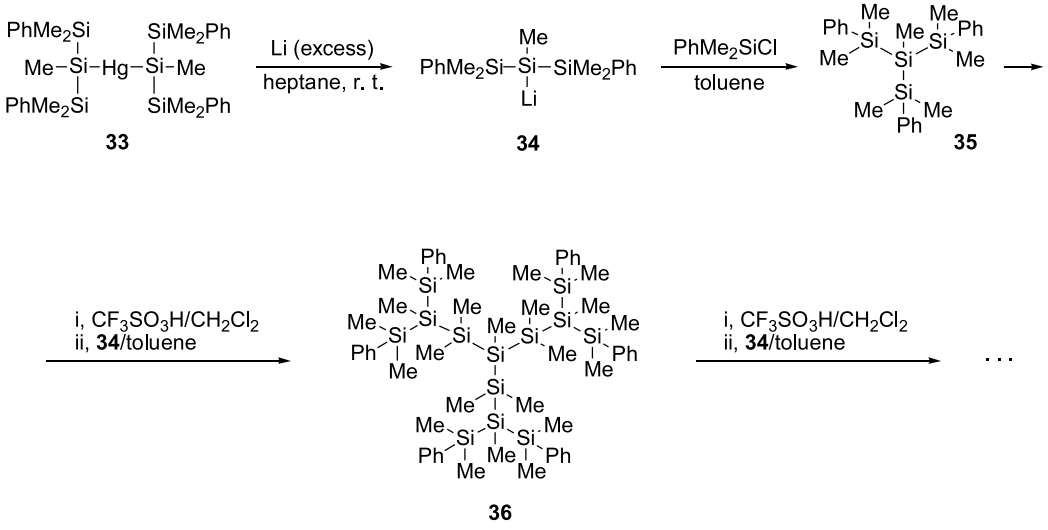
5 **22** (65%) **31** **32** (75%)

Scheme 15.

derivative **22** which exhibits unique properties as the Si–Li bond provides a nucleophilic silicon site while the Si–Hg bond can be photolytically cleaved to produce a silyl radical site. Treatment of **22** with an excess of lithium in THF, however, did not lead to the expected 1,1-dilithiosilane **31**. Instead, a new silyllithium species **32** was obtained as the major product (Scheme 15).[23]

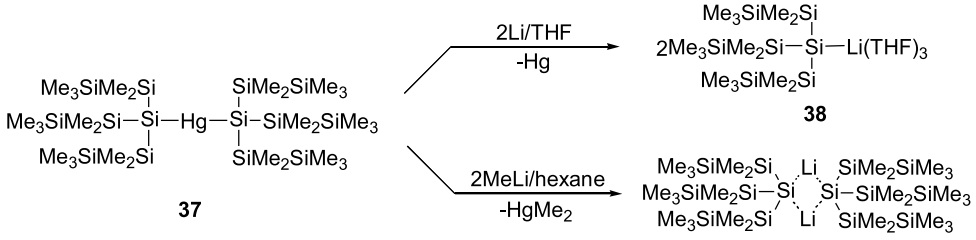
In a series of papers, Sekigushi and co-workers adapted the mercury approach for the production of polysilane dendrimers[37,38,62–65] and Scheme 16 illustrates this methodology. The silyllithium reagent **34** was prepared and isolated as highly inflammable yellow crystals by the reaction of bis(1,3-diphenylpentamethyltrisilanyl)mercury **33** and lithium in 80% yield. $PhMe_2SiCl$ was then reacted with the silyllithium **34** in toluene to give quantitatively colorless crystals of **35** possessing a core and three branching points for a dendrimer. Finally, the resulting **35** was treated with 3 equiv of CF_3SO_3H in dichloromethane followed by reaction with **34** in toluene to yield the first generation **36** in 43% yield.[38]

The use of the mercury/alkali metal exchange reaction to prepare a branched silyllithium reagent has been applied to



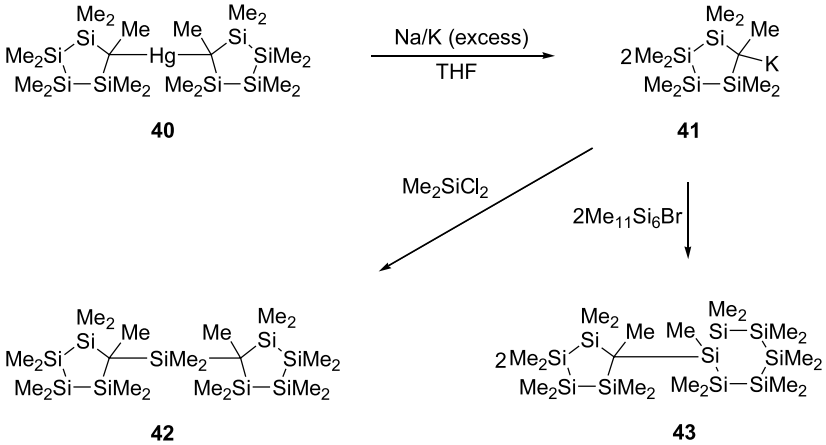
33 **34** **35** **36**

Scheme 16.



37 **38** **39**

Scheme 17.



40 **41** **42** **43**

Scheme 18.

the synthesis of the lithioheptasilane **38** and its dimer **39** from **37** (Scheme 17).[60]

The reaction of $Hg(SiEt_3)_2$ with potassium in benzene gives no Et_3SiK, but, instead, Et_3SiPh in quantitative yield. It is hypothesized that the initially formed Et_3SiK abstracts a proton from benzene to yield Et_3SiH and PhK, which couple with each other to give Et_3SiPh. The interaction between the silylmercurial $Hg(Si_6Me_{11}$-*cyclo*$)_2$ and sodium–potassium alloy was, however, successfully used to prepare *cyclo*-$Si_6Me_{11}K$.[66] Nonamethylcyclopentasilanyl potassium **41** has also been prepared via a mercury/potassium exchange reaction from bis(cyclopentasilanyl)mercury **40**. This potassium reagent offers a new route to permethylated polycyclic polysilanes such as **42** and **43** (Scheme 18).[67]

The transmetalation reaction of $Hg(SiMe_3)_2$ with Mg provides a route to the silylmagnesium derivatives and the reaction conditions for this synthesis were found to be critical. Stirring magnesium powder with $Hg(SiMe_3)_2$ in DME for 8 days affords $Mg(SiMe_3)_2(DME)$ in 25% yield. The reaction in THF using magnesium turnings gave the compound $Mg(SiMe_3)_2(THF)_2$ after 4–5 weeks.[68] More recently, the synthesis of $Mg(SiMe_3)_2(DME)$ has been improved by carrying out the reaction in an ultrasonic bath. Thus, the latter compound may be obtained in 80% yield in 4 days at 30 °C using a 14-fold excess of magnesium over $Hg(SiMe_3)_2$.[69] A slow, low-yielding reaction occurs in the direct synthesis of $Mg(SiMe_3)_2(TMDAP)$ (TMDAP= $Me_2N(CH_2)_3NMe_2$) using magnesium powder and Me_3SiCl in TMDAP with mercury present as a catalyst. If the TMDAP-Et_2O solution of $Hg(SiMe_3)_2$ is treated with excess Mg, the product is obtained in 85% yield.[70]

Sodium and potassium tetrakis(trimethylsilyl)aluminate **44** and **45** are synthesized by the reaction of sodium and potassium with bis(trimethylsilyl)mercury and tris(trimethylsilyl)aluminium (Scheme 19).[71]

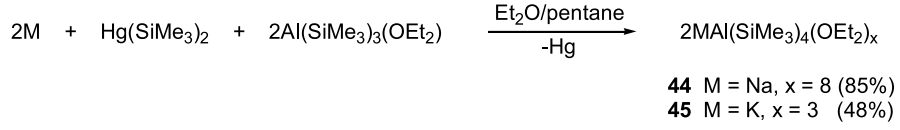
Lithium tetrakis(trimethylsilyl)aluminate, $LiAl(SiMe_3)_4(DME)_2$, prepared by the reaction of Me_3SiCl with lithium and aluminium in the presence of mercury, reacts with $Zn(OAc)_2$ and $CdCl_2$ to give the corresponding silylmetal derivatives, $Zn(SiMe_3)_2$ and $Cd(SiMe_3)_2$.[71,72] The silylzinc compound is less stable than the mercury analog; it can be stored for about 3 weeks at −20 °C, but decomposes slowly, with separation of the metal, at room temperature. The silylcadmium compound is even less stable than the silylzinc and decomposes within 2 days at room temperature.

The various metal–mercury exchange reactions are summarized in Table 5.

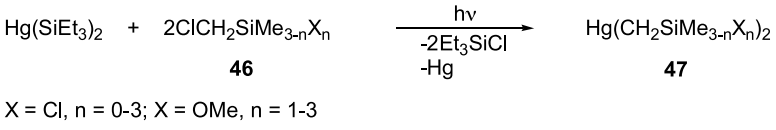
3.3. Carbomercuration reactions

As early as 1975 Werner, Neumann and Becker have reported that primary alkyl halides AlkX (X=Cl, Br) react rapidly with $Hg(SiMe_3)_2$ in daylight, forming Me_3SiX and $AlkHgSiMe_3$.[75] Aryl bromides behave quite similarly, but continue the reaction to Ar_2Hg. These transformations exhibit the characteristic of a radical-chain process with an S_H2 mechanism. More recent work by Vyazankin and co-workers has shown that organomercury species **47** containing reactive Si–Cl or Si–OMe groupings may be isolated in 79–91% yields from the photochemical reaction of chloromethylsilanes **46** with $Hg(SiMe_3)_2$ (Scheme 20).[76,77]

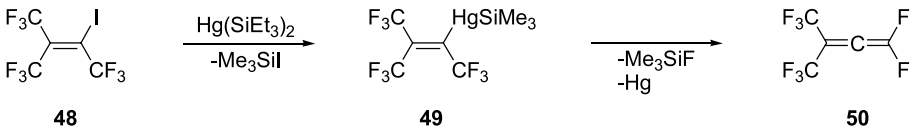
In the dark, $Hg(SiMe_3)_2$ reacts more readily with iodobenzene than with bromobenzene, and is almost completely consumed after 16 h at 20 °C. The products are Ph_2Hg (75%), Me_3SiI (82%), Me_3SiPh (9%), Hg (18%), and PhHgI (6%). Considering the negligible yields of Me_3SiH and aromatic hydrocarbons, the bimolecular concerted mechanism was suggested.[19] The basic product from the reaction of $Hg(SiMe_3)_2$ with bromopentafluorobenzene (7 days, 20 °C, in the dark) was $C_6F_5SiMe_3$ (67%). The reaction proceeds through the isolable intermediate $C_6F_5HgSiMe_3$, which undergoes decomposition to $C_6F_5SiMe_3$ and Hg(0) under the same conditions. Similarly, the intermediate silylmercurial $F_2C{=}CF{-}Hg{-}SiMe_3$ obtained after treatment of $F_2C{=}CFBr$ with $Hg(SiMe_3)_2$ can be converted into $F_2C{=}CFSiMe_3$ (3 days, 60 °C) in good overall yield.[78]



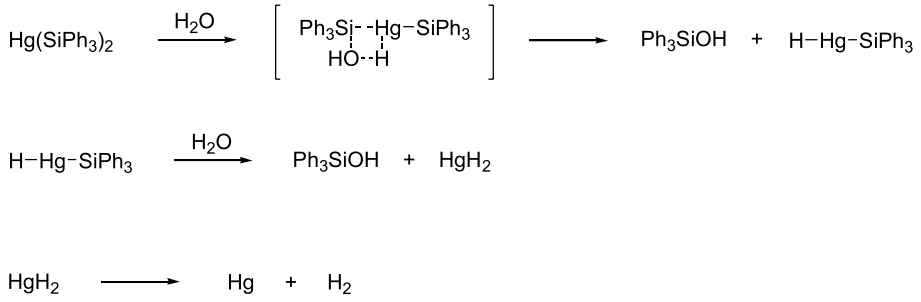
Scheme 19.



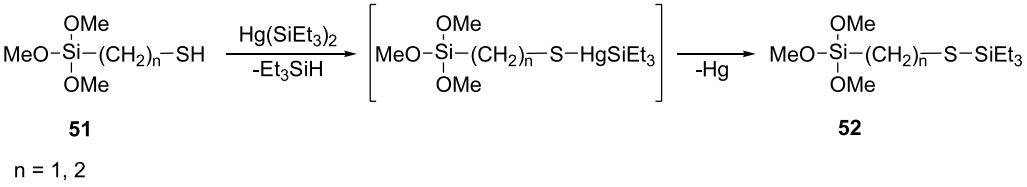
Scheme 20.



Scheme 21.



Scheme 22.



Scheme 23.

Bis(trimethylsilyl)mercury reacts at 0 °C in the dark with 2-iodoperfluoro-3-methylbut-2-ene **48** forming the silylmercury derivative **49**. β-Elimination of mercury and trifluromethylsilane from **49** then gave compound **50** in good yield (Scheme 21).[79]

3.4. Silylation of organic and organoelement compounds

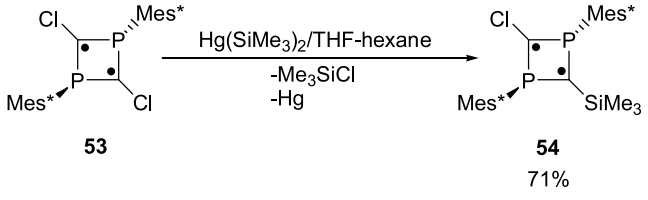
3.4.1. Proton-donor nucleophilic substrates. The interaction of solid $Hg(SiPh_3)_2$ with water is likewise very slow, but, in benzene saturated with water, it decomposes rapidly to give mercury, triphenylsilanol, and hydrogen as the major products, along with lesser amounts of Ph_3SiH, hexaphenyldisiloxane, and hexaphenyldisilane. The reactions presented in Scheme 22 are likely to be responsible for the formation of the major products; other reactions of the postulated $HHgSiPh_3$ intermediate may be responsible for the production of Ph_3SiH and $(Ph_3Si)_2O$.[15]

Alkanethiols **51** are silylated at 50 °C in benzene with an equimolar amount of $Hg(SiEt_3)_2$ to give the corresponding S-silylated derivatives **52**. While the mechanism of this transformation is not known, it is speculated that at least two steps are involved, viz. heteromercuration of the thiol forming a silyl(alkylthio)mercurial, followed by a demercuration reaction (Scheme 23).[80]

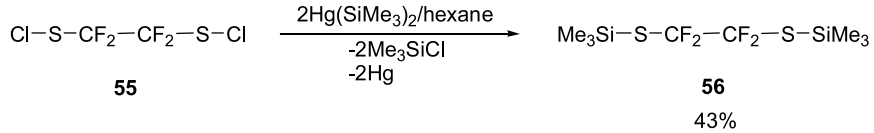
3.4.2. Organic and organoelement halides. Especially interesting for synthetic applications are the polar reactions of silylmercurials with organic and organoelement halides, leading to the corresponding silyl derivatives. The observed results are generally far superior to those observed in other conventional silylation reactions that use more ionic silylmetallic derivatives, such as lithiosilanes. Thus, the silylmercurial route permits the conversion of metalloid or metal halides into silyl derivatives in salt-free non-polar media. Besides, the silylmercurial reagents are milder and more selective reagents than the silyl-alkali metal derivatives. In one example, a recently described selective monosilylation of the 2,4-dichloro-1,3-diphosphacyclobutane-2,4-diyl **53** using $Hg(SiMe_3)_2$ allowed the conversion of this compound into the 2-chloro-4-trimethylsilyl derivative **54** in 71% yield (Scheme 24).[81]

The silylmercurial method has also allowed the preparation of the disilyl derivative **56** starting from 1,1,2,2-tetrafluoroethane-1,2-bis-sulfenyl chloride **55** (Scheme 25).[82]

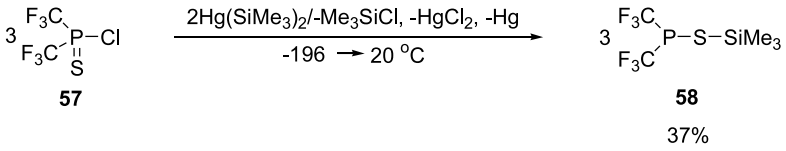
Rheingold and co-workers have successfully silylated bis(cyclopentadienyl)dichloroniobium using bis(trimethylsilyl)mercury. Attempts to synthesize niobium-silyl species from Cp_2NbCl_2 and the silylating reagents $LiSiMe_3$, $Al(SiMe_3)_3(OEt_2)$ and $LiSi(SiMe_3)_3(THF)_3$ failed. The reaction between Cp_2NbCl_2 and $Hg(SiMe_3)_2$, however, gave $Cp_2Nb(SiMe_3)Cl$ in good yield.[83] A somewhat similar chemistry was performed with zirconium derivatives.[84] The reaction of $Hg(SiMe_3)_2$ with Cp_2ZrCl_2 in a 3:1 molar ratio leads to the monosilylated species $Cp_2Zr(SiMe_3)Cl$ in 33%



Scheme 24.



Scheme 25.



57 **58**

37%

Scheme 26.

yield. When the reagents were allowed to react for 15 days in refluxing benzene, a second, more volatile zirconium compound $Cp_2Zr(SiMe_3)_2$ formed.

It should be noted that, in some special cases, the interaction of silylmercurials with organoelement halides can be complicated by reduction and other side reactions, for example, $Hg(SiMe_3)_2$ exhibits a different reactivity towards MCl_4 (M=Si, Ge, Sn). While the reaction with $SiCl_4$ gives $Me_3SiSiCl_3$, in the case of $GeCl_4$ and $SnCl_4$ the products are Ge_2Cl_6, Me_6Si_2 and $Me_3SiGeCl_3$, and $SnCl_2$, respectively.[85] Caution should be also exercised with this technique when $R_nCl_{4-n}Ti$ (n=0–3) and related species are used because of the oxidizing ability of Ti^{4+}.[86]

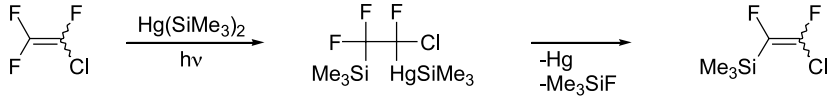
The phosphinous ester **58** is formed in moderate yield by the rapid reaction of **57** with $Hg(SiMe_3)_2$ (Scheme 26). The analogous reaction of $(F_3C)_2P(O)Cl$ gave none of the expected phosphinous ester $(F_3C)_2POSiMe_3$, but, instead, the phosphonate ester $(F_3C)_2P(O)OSiMe_3$ was isolated in 38% yield.[87]

3.4.3. Unsaturated systems. As already mentioned in Section 3.3 in connection with the carbomercuration reactions, bis(trimethylsilyl)mercury reacts with electron-deficient fluoroolefins under UV irradiation via insertion of the olefin into the Si–Hg bond of the silylmercurial to give an unstable addition product, which may occasionally be isolated, but which easily decomposes to give an olefin in which a vinylic fluorine has been replaced by a trimethylsilyl group.[88,89] For example, the reaction of chlorotrifluoroethylene **59** with $Hg(SiMe_3)_2$ initially affords the mercurated alkane **60**, which loses Hg and Me_3SiF to give a mixture of *cis*- and *trans*-2-chloro-1,2-difluorovinyltrimethylsilanes **61** (Scheme 27).[88]

Irradiation of *cis*-1,2-difluoroethylene and $Hg(SiMe_3)_2$ afforded a mixture of *cis*- and *trans*-2-fluorovinyltrimethylsilanes. Hexafluoropropene **62** gave a mixture of the *cis*- and *trans*-isomers of trimethyl-1,2,3,3,3-pentafluoropropenylsilane **63** and **64** and, by their further reaction with $Hg(SiMe_3)_2$, two bis(trimethylsilyl)tetrafluoropropenes **65** and **66**. The stereochemistry of **65** and **66** could not be established, but small-scale experiments suggested that **65** was formed exclusively from **63**, and **66** from **64** (Scheme 28).[90]

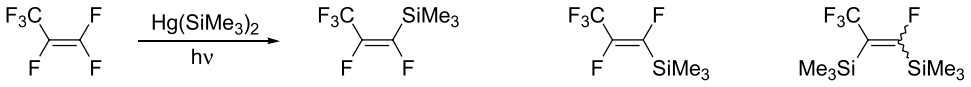
With octafluorobut-2-ene **67**, a mixture of geometric isomers **68** was formed. The *cis*:*trans* ratio (45:55) was the same whether *cis*- or *trans*-octafluorobutene was used. Unless the olefin was present in a large excess, further reaction of **68** with $Hg(SiMe_3)_2$ gave the compound **69** in high yield (Scheme 29).[79]

Hexafluorocyclobutene **70** upon photochemical reaction with $Hg(SiMe_3)_2$ gave a mixture of 1-trimethylsilylpentafluoro- and 1,2-bis(trimethylsilyl)tetrafluoro-cyclobutenes **71** and **72** in yields of 59 and 31%, respectively (Scheme 30).[90] Perfluorocyclopentene and perfluorocyclohexene formed the corresponding 1-trimethylsilylperfluorocycloalkenes in ca. 75% yield.[79] The reaction of $Hg(SiMe_3)_2$ with hexafluorobenzene was rapid under irradiation and the products from an approximately equimolar mixture of reagents were trimethyl(pentafluorophenyl)silane (61% yield), and 1,3- and 1,4-bis(trimethylsilyl)perfluorobenzenes (7 and 25% yield, respectively).



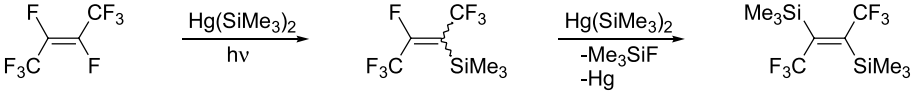
59 **60** **61**

Scheme 27.



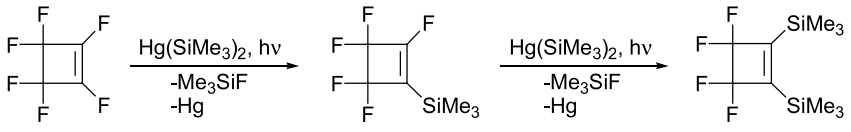
62 **63** (8%) **64** (25%) **65** (6%) **66** (22%)

Scheme 28.



67 **68** **69**

Scheme 29.

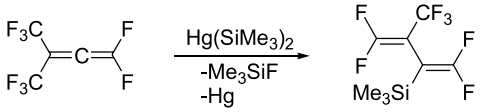


70 **71** 59% **72** 31%

Scheme 30.

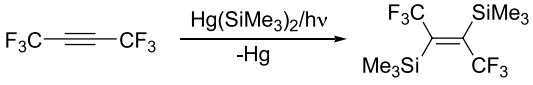
Use of a three- to four-fold excess of hexafluorobenzene gave 91% yield of trimethyl(pentafluorophenyl)silane.[90,91]

Perfluoro-3-methylbuta-1,2-diene **50** reacts in the dark with $Hg(SiMe_3)_2$ to give 1,1,4,4-tetrafluoro-2-trifluoromethyl-3-trimethylsilabuta-1,3-diene **73** (Scheme 31).[79]



50 **73**

Scheme 31.

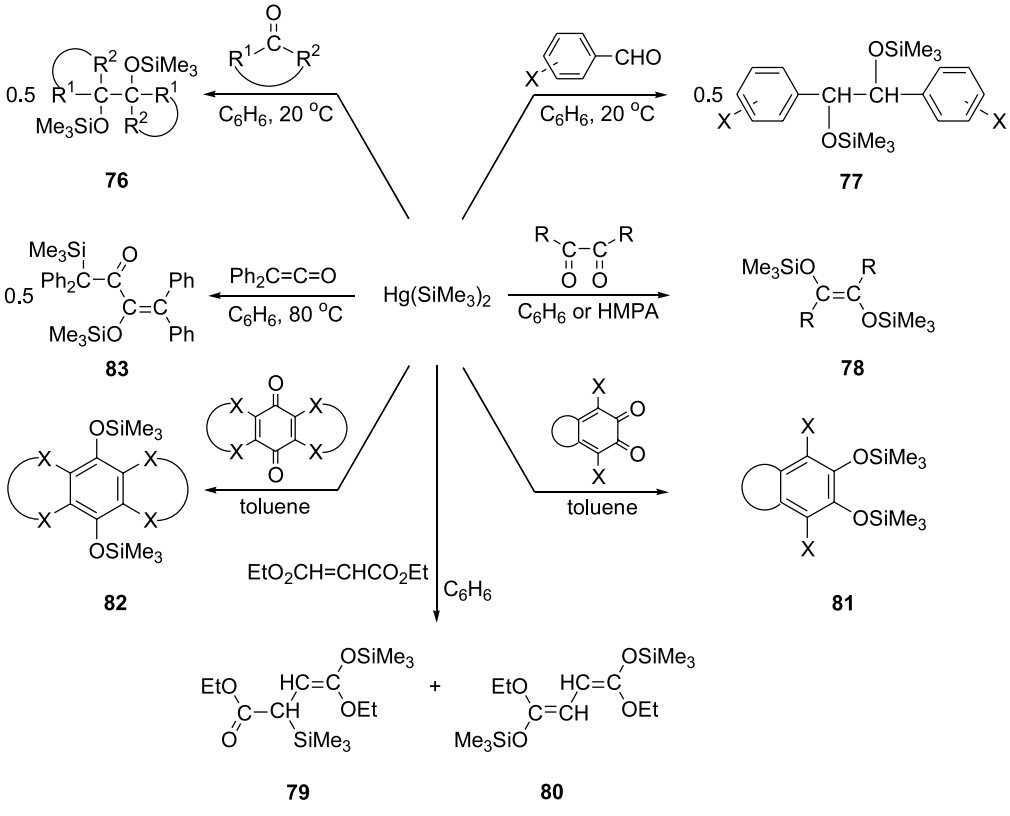


74 **75**

Scheme 32.

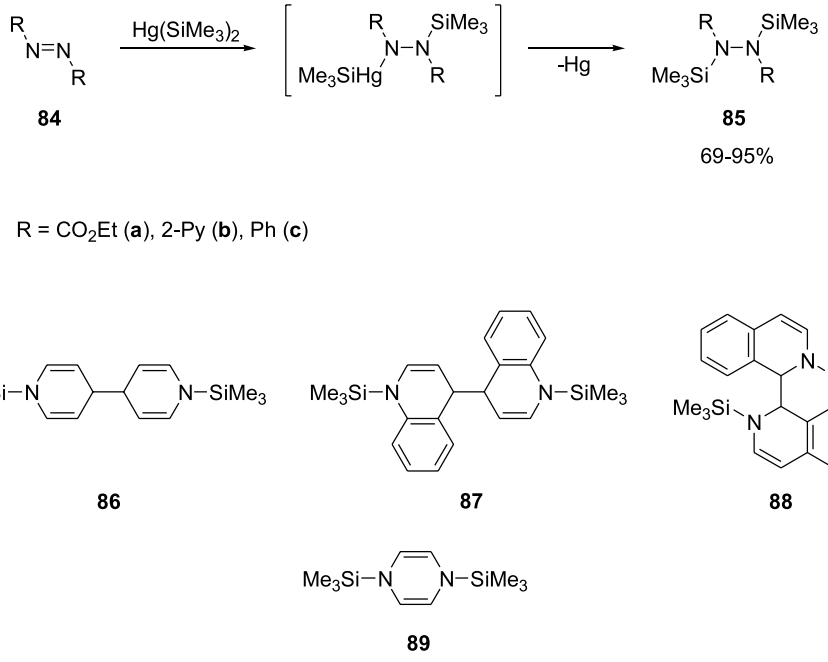
Irradiation of the disilylmercurial **1** in a Pyrex vessel with perfluorobut-2-yne **74** gives mercury and hexafluoro-*trans*-2,3-bis(trimethylsilyl)but-2-ene **75** almost quantitatively (Scheme 32).[90]

Ketones are reductively dimerized by $Hg(SiMe_3)_2$, yielding 1,2-bis(trimethylsilyloxy)ethanes **76**. The ESR and NMR spectra showed the intermediate formation of ketyl radicals.[53,92,93] An analogous reaction with aromatic aldehydes leads to the bis(*O*-silyl)hydrobenzoin derivatives **77**.[94] 1,2-Diketones undergo 1,4-addition to give bis(*O*-silyl)enediols **78**, while esters of conjugated dicarboxylic acids give *O*-silyl ketene acetals: maleic diester yields mainly the *C*,*O*-bis-silyl derivative **79** (1,4-addition), whereas fumaric diester yields mainly the *O*,*O*-bis-silyl product **80** (1,6-addition).[94] In addition 1,2- and 1,4-quinones are readily transformed by $Hg(SiMe_3)_2$ to the corresponding bis(*O*-silyl)benzenoid systems **81** or **82**.[53,94,95] Diphenyl ketene is dimerized to the *C*,*O*-bis-silyl derivative of the 1,1,4,4-tetraphenyl-2,3-butanedione **83** (Scheme 33).[96] All these reactions proceed much faster in HMPA as the solvent than in benzene, but they are especially accelerated up by UV irradiation.



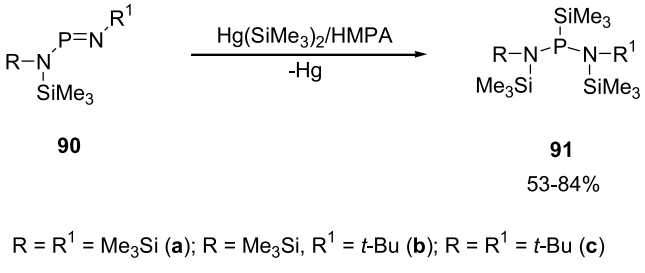
76 **77** **83** **78** **82** **81** **79** **80**

Scheme 33.



Scheme 34.

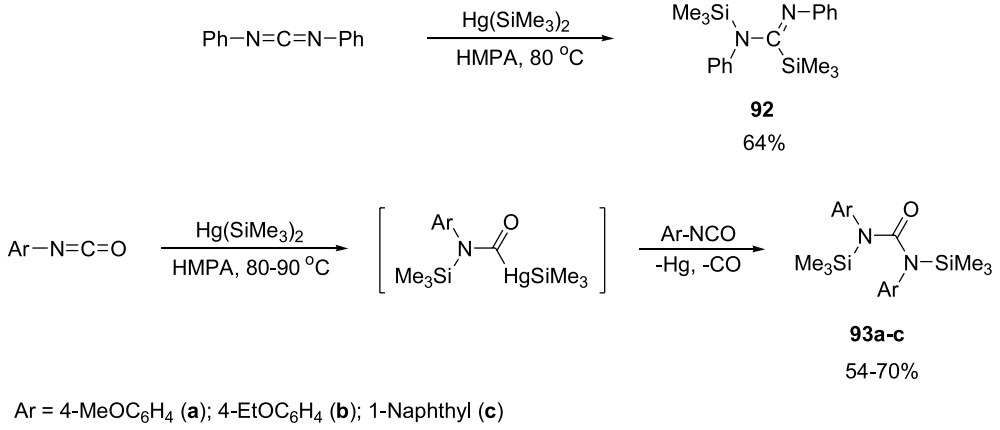
The reactions of $Hg(SiMe_3)_2$ with azodiethylcarboxylate, 2,2′-azodipyridine and azobenzene (**84a–c**) are known to produce the saturated *N*,*N*′-bis-silylated derivatives **85** (Scheme 34).[97] Aromatic nitrogen heterocycles are also reductively silylated. The reactions where molar ratios of 1:2 are taken lead, in the case of pyridine, quinoline and isoquinoline, to the compounds **86–88**. The 1:1 molar reaction with pyrimidine affords *N*,*N*′-bis-silyl-1,4-dihydropyrazine **89**. In all cases, $Hg(SiMe_3)_2$ apparently behaves as a nucleophile; the mercurated intermediates are thermally unstable and form (in part after symmetrization) the final product mentioned and the yields are high.[97]



Scheme 35.

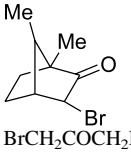
Another important preparative reaction of $Hg(SiMe_3)_2$ is the facile reductive disilylation of amino(imino)phosphanes **90** in HMPA to give the compounds **91**, which are difficult to obtain by other routes (Scheme 35).[98,99] With **90a**, the reaction is completed in 1 h at 40 °C, whereas the reaction with the sterically more crowded **90b,c** requires more vigorous conditions (ca. 90 °C, 10 h). Besides, the rate of the reaction decreases drastically if the solvent is changed from HMPA to THF.

Finally, the reactivity of $Hg(SiMe_3)_2$ towards compounds with cumulated double bonds has been studied (Scheme 36). With diphenyl carbodiimide, *C*,*N*-bis-silylformamidine **92** is formed. Aryl isocyanates react with $Hg(SiMe_3)_2$ yielding mainly *N*,*N*′-bis-silylurea derivatives **93**.[96]



Scheme 36.

Table 6. Preparation of silyl ethers of enols from α-bromo-substituted carbonyl compounds[100,101]

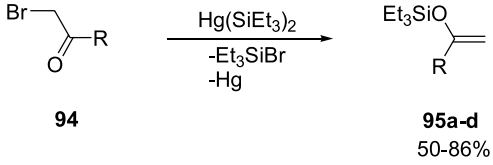
Entry	Carbonyl compound	Product	Conditions	Yield (%)
1	$BrCH_2COBu$-*t*	**95a**	Hexane, UV	—
2	$BrCH_2COPh$	**95b**	Hexane, 67 °C	83
3	$BrCH_2COC_6H_4Br$-4	**95c**	Hexane, 20 °C	50
4	$BrCH_2COC_6F_5$	**95d**	Hexane, −30 °C	86
5	$BrC(CH_3)_2C(O)H$	**96**	Benzene, 20 °C	95
6	$BrCH(Ph)COCH_3$	**97**	Benzene, 20 °C	78
7		**98**	Benzene, 100 °C	96
8	$BrCH_2COCH_2Br$	**99**	Benzene, 20 °C	69

Only one double bond of CO_2 and CS_2 reacts with $Hg(SiMe_3)_2$, forming the silyl esters of silyl formic acid, $Me_3SiC(O)OSiMe_3$, or silyl thioformic acid, $Me_3SiC(S)SSiMe_3$, respectively, whereas SO_2 forms bis-silyl sulfoxylate, $(Me_3SiO)_2S$. For most of these reactions, HMPA is recommended as the solvent.[96]

3.4.4. α-Halogen-substituted carbonyl compounds. Carbonyl compounds functionalized at the α-carbon with chlorine or bromine react with $Hg(SiR_3)_2$, providing the silyl ethers of enols (Table 6), for example, α-brominated methyl ketones **94** react with $Hg(SiEt_3)_2$ to form the *O*-silylated keto enols **95** (Scheme 37).[93,100] By this route, substituted α-bromoketones or their cyclic equivalents interact with $Hg(SiEt_3)_2$ to give a wide spectrum of silylated enols such as **96–99**.[101] The most likely mechanism for all these reactions is an SET route including the generation of ion-radicals.[102] In accordance with this assumption, the reactions are speeded up by electron-withdrawing substituents in the benzene ring of aryl ketones as well as UV irradiation.

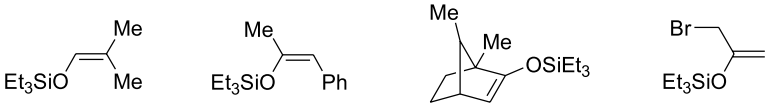
The reaction of $Hg(SiMe_3)_2$ with Cl_3CCHO at 0 °C in benzene gives rise to the silyl enol $Cl_2C{=}CH{-}OSiMe_3$ in 70% yield.[94] The method is also applicable to the preparation of *O*-silylated ketene acetals **101** starting from the α-bromocarboxylic acid esters **100** (Scheme 38).[103]

The action of $Hg(SiEt_3)_2$ on ethyl bromocyanoacetate **102** leads to the silyl enol derivative **103** (Scheme 39)[104] and treatment of the α,α-dibromomethyl ketone **104** with $Hg(SiEt_3)_2$ offers a new route to the silyl ether of enol **105** with an α-bromine atom in the enol fragment. The reaction is stereoselective and leads exclusively to the *E*-isomer (Scheme 40).[105]



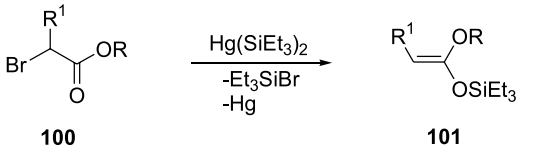
94 **95a-d** 50-86%

R = *t*-Bu (**a**); Ph (**b**); 4-BrC_6H_4 (**c**); C_6F_5 (**d**)



96 **97** **98** **99**

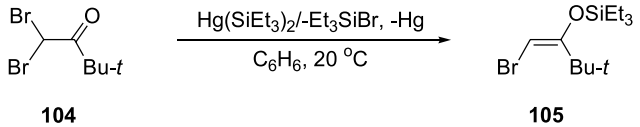
Scheme 37.



100 **101** 69-83%

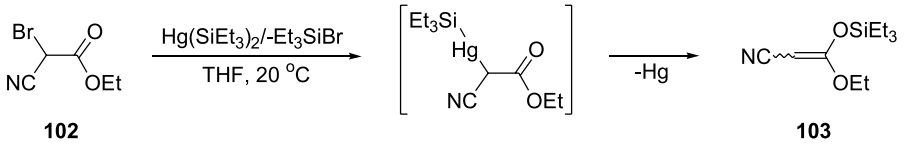
R = Et, R^1 = H (**a**); R = Et, R^1 = Me (**b**); R = Me, R^1 = Et (**c**)

Scheme 38.



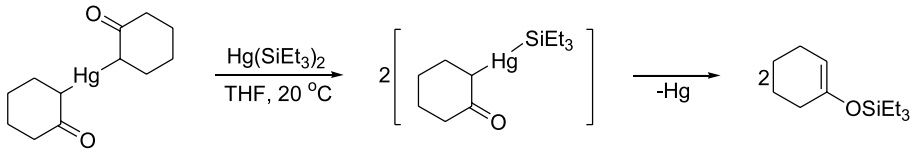
104 **105** 84%

Scheme 40.



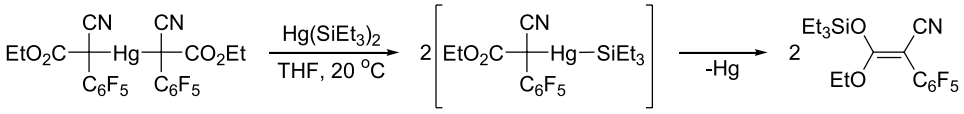
102 **103** 57%

Scheme 39.



106 **107** 74%

Scheme 41.



108 **109** 75%

Scheme 42.

3.4.5. Functionalized diorganomercurials. Treatment of some functionalized diorganomercury compounds with bis(trialkylsilyl)mercurials gives rise to the formation of the mixed organo(silyl)mercury derivatives, which in turn undergo demercuration reaction to give the silylated products. The substrate is frequently a mercury derivative of a CH-acidic compound, for example, the silyl ether of enol **107** has been prepared from **106** in 74% yield according to Scheme 41.[106]

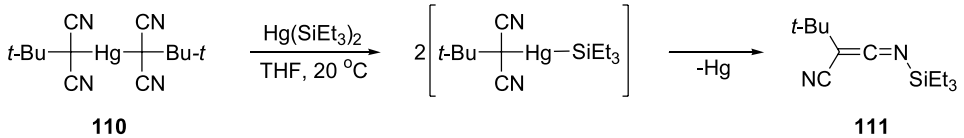
As a preparative method to be used in the synthesis of simple silylated enols, this technique does not provide advantages over the conventional methods. It shows a high degree of promise, however, as a method for the silylation of polyfunctionalized species. An illustrative example is described by Scheme 42, which demonstrates the use of a metathesis reaction for the regioselective silylation of a CO function in the presence of a CN group in **108** to form **109**.[107] Note that the mercurated *t*-butylmalononitrile **110** reacts cleanly with $Hg(SiEt_3)_2$ to give the *N*-silylated ketenimine **111** (Scheme 43).[108]

The ligand exchange between **112** and $Hg(SiEt_3)_2$ also took place easily, giving the corresponding silylated enol **113** (Scheme 44).[107]

The interaction of mercurated diazoacetone **114** and $Hg(SiEt_3)_2$ offers an attractive possibility of synthesizing the silyldiazoacetone **115** in almost quantitative yield (Scheme 45).[109]

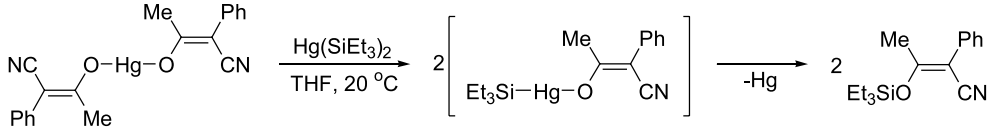
3.5. Dehalogenation and Wurtz-type coupling reactions

A number of reactions between disilylmercurials and



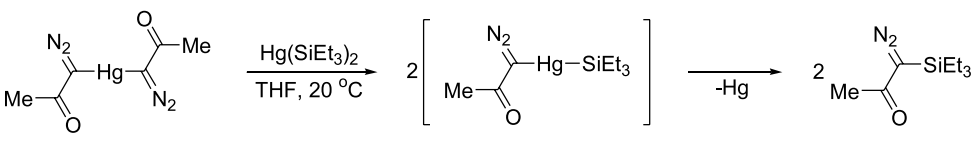
110 **111** 90%

Scheme 43.



112 **113** 72%

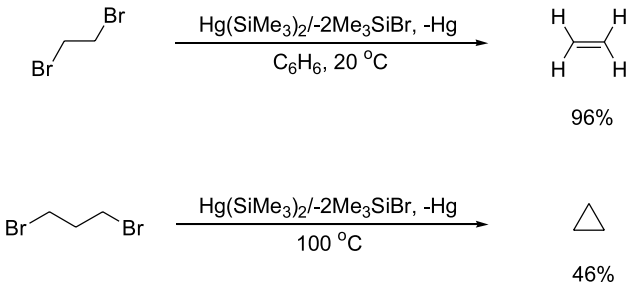
Scheme 44.



114 **115**

Scheme 45.

organic or organoelement halides result in reductive coupling or, in the case of the dihalides, vicinal or geminal dehalogenation. A free radical mechanism for these transformations appears unlikely, since they occur in the dark, and they are clean, giving no indication of the formation of dimerization or disproportionation products of possible radical intermediates. Typical examples are the reactions of bis(trimethylsilyl)mercury with 1,2-dibromoethane and 1,3-dibromopropane, affording ethene and cyclopropane, respectively (Scheme 46).[110,111]



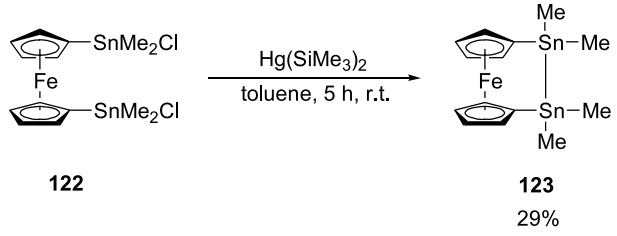
Scheme 46.

Bis(trimethylgermyl)mercury, $Hg(GeMe_3)_2$, the pattern of reactivity of which closely resembles that of the silicon analogue, reacts with *erythro*-2,3-dibromo-4-methylpentane **116** to produce 98% of the *cis*-olefin **117**; the *threo* isomer correspondingly produces 96% of the *trans*-olefin, demonstrating the *cis*-nature of the elimination (Scheme 47).[112]

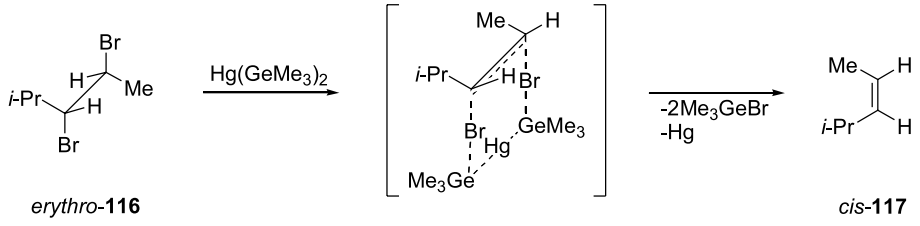
1,2-Dibromoadamantane **118** was debrominated with $Hg(SiMe_3)_2$ in the presence of 2,5-dimethylfuran as the trapping agent to give the compound **119**. In the absence of the dienic trap, 1,2-dibromoadamantane **118** gave the hydrocarbon **120** in low yield (Scheme 48).[112]

Addition of 2 M equiv of the α-bromomethyl ketones **94** to benzene solution of $Hg(SiEt_3)_2$ results in the formation of the γ-diketones **121**. These reactions proceed through the formation of the silyl enol derivatives **95**, which are then converted into the diketones (Scheme 49).[102]

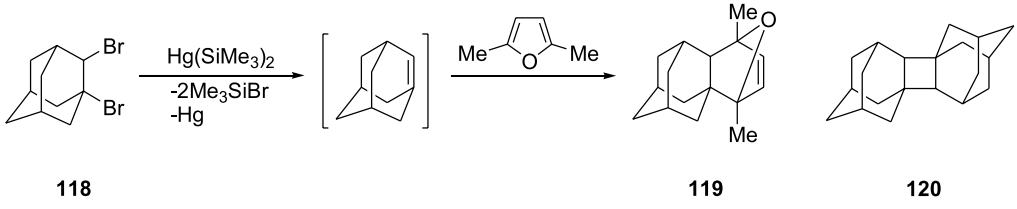
With trialkyltins R_3SnX (X=Cl, MeO, EtO, Me_3SiO, $MeCO_2$, R_3SnO), bis(trimethylsilyl)mercury reacts in a 2:1 molar ratio to form the distannanes R_6Sn_2 (R=Me, Et, Bu and Ph) in 65–98% yields.[113] When the reaction was applied to 1,1′-bis(chlorodimethylstannyl)ferrocene **122**, 1,2-distanna[2]ferrocenophane **123** was conveniently produced (Scheme 50).[114]



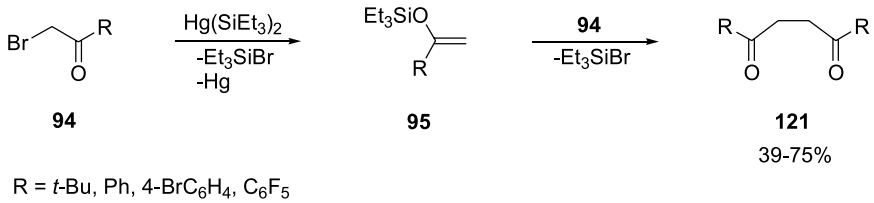
Scheme 50.



Scheme 47.

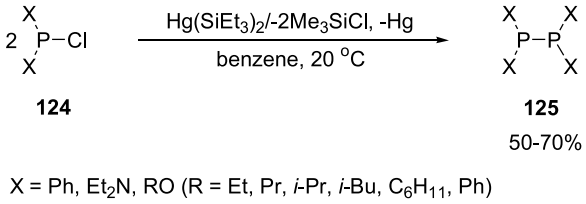


Scheme 48.



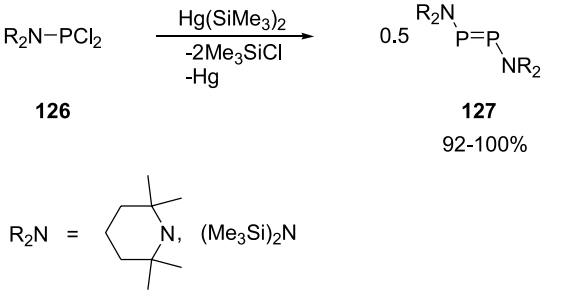
Scheme 49.

A P–P bond is easily formed by the reaction of **124**, for example, Ph_2PCl, and $Hg(SiMe_3)_2$ to give **125**. Dialkylchlorophosphites and diamidochlorophosphites behave similarly (Scheme 51).[115]

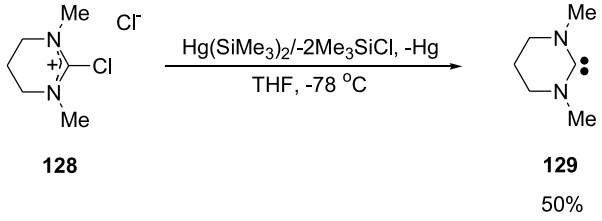


Scheme 51.

The interaction of compounds $RECl_2$ (E=P, As) containing highly polarized E–Cl bonds with disilylmercurials is a conceptually simple method of reductive geminal dehalogenation.[113,116] This method does indeed work well, although the mechanistic aspects of the reactions remain unclear, for example, the geminal dechlorination of the sterically crowded dichlorophosphines **126** is of great importance for the synthesis of the diphosphenes **127** (Scheme 52).[117,118] The intermediate formation of the diphosphine, RP(Cl)-P(X)R, followed by 1,2-elimination of ClX (X=Cl or Me_3Si), is the most likely, although the reaction mechanism can also be discussed in terms of the possible intermediate formation of phosphinidene, [RP]. Interestingly, whereas the treatment of Et_2NPCl_2 with $Hg(SiMe_3)_2$ affords the cyclotetraphosphine $(Et_2N)_4P_4$ as a



Scheme 52.



Scheme 53.

major product, a similar reaction with magnesium in THF leads to redistribution of the diethylamino group, giving $(Et_2N)_2P\text{-}P(NEt_2)_2$ and $(Et_2N)_3P$.[119]

In recent years, several new examples of geminal dehalogenation have been quoted, for example, bis(trimethylsilyl)mercury reacting with chloro-iminium and -amidinium salts to give the stable aminocarbenes.[120] A major advantage of this method in comparison with the deprotonation of formamidinium salts by alkali metal amides is that the reaction allows the preparation of metal-free dicoordinate carbon species. The reaction in Scheme 53 demonstrates the utility of this route in preparing the stable 1,3-dimethyltetrahydropyrimid-2-ylidene **129** starting from the chloroiminium salt **128**.[120]

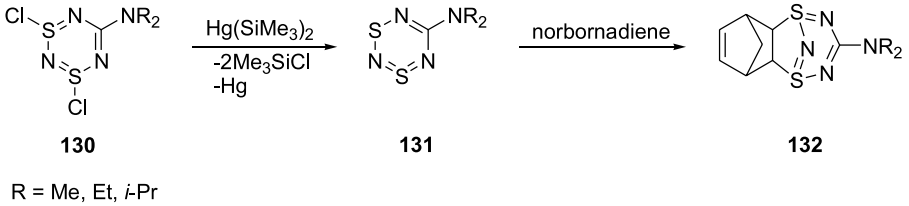
The dechlorination of cyclothiazyl chlorides **130** with $Hg(SiMe_3)_2$ in diethyl ether at −78 °C produced the thermally unstable compounds formulated as $R_2NCNS_2N_3$. The existence of the π-electron-rich S–N heterocycles **131** in the dechlorinated products is indicated by the presence of $R_2NCS_2N_3^+$ as the ion with the highest *m/e* in the mass spectra, and the formation of the adducts **132** with norbornadiene (Scheme 54).[121]

3.6. Formation of metal–mercury bonds

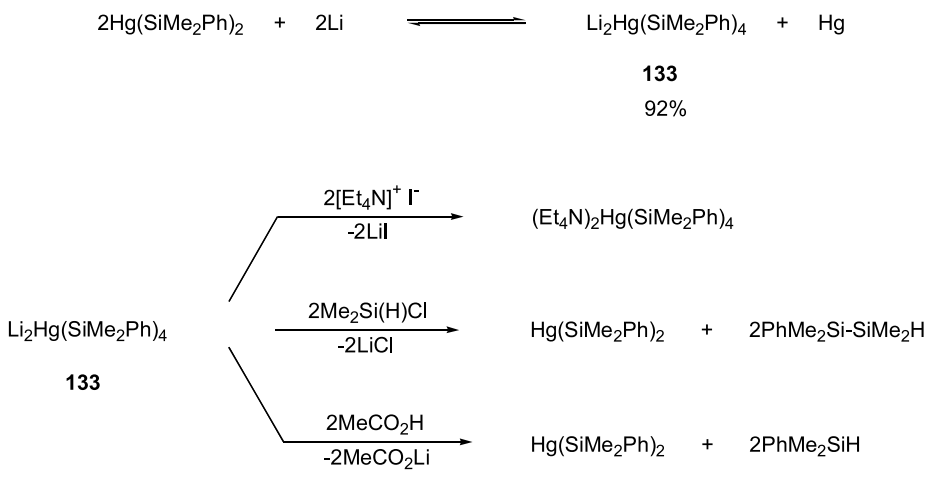
The most important application of silylmercurials in coordination chemistry is the synthesis of metal–silicon and metal–mercury bonded complexes. The organosilylmetallic compounds $LiHg(SiMe_3)_3$ and $M_2Hg(SiMe_3)_4$ (M=Li, Na, K) were prepared by the reaction of $LiSiMe_3$ or Na(K) with $Hg(SiMe_3)_2$.[122] Subsequently, this method was extended to the reactions of $Hg(SiMe_2Ph)_2$ with Li and K by Gladyshev et al.[123] These authors noted that $Li_2Hg(SiMe_2Ph)_4$ **133** is reversibly reduced with a large excess of mercury metal to form $Hg(SiMe_2Ph)_2$. Scheme 55 illustrates the preparation and some typical reactions of the complex **133** in which it acts as a salt-like species and as a source of the Me_3Si^- anion.

X-ray crystallographic studies have been performed on $Li_2Hg(SiMe_3)_4$ and $Li_2Hg(SiMe_2Ph)_4$.[124] Interestingly, the decrease in the ^{199}Hg–^1H coupling constants in the NMR spectra from the bis- to the tetrakis-(trimethylsilyl)mercury derivatives is similar to that observed for increasing alkyl substitution in other organometallic compounds. If a Fermi constant is a predominant term in this coupling, the decrease is consistent with the hybridization being sp in $Hg(SiMe_3)_2$, sp^2 in $LiHg(SiMe_3)_3$, and sp^3 in $Li_2Hg(SiMe_3)_4$.[122]

The use of disilylmercurials in transferring an Me_3Si group to a metal substrate was described in Section 3.4.2. In

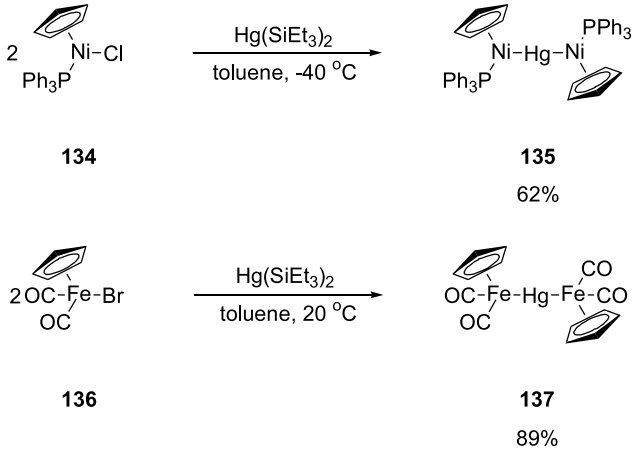


Scheme 54.



Scheme 55.

contrast to the reactions of $Hg(SiMe_3)_2$ with Cp_2ZrCl_2 and Cp_2NbCl_2, however, the interaction of $Hg(SiEt_3)_2$ with 2 equiv of the nickel chloride complex **134** gives the complex **135** as a major product.[125] In a further example, treatment of **136** with $Hg(SiEt_3)_2$ yields the complex **137** (Scheme 56).[126] The mechanism of these reactions has not been investigated, but was proposed to include the initial formation of an M–Hg–Si intermediate (M=Ni or Fe), which may then react with $Hg(SiEt_3)_2$ to form the organobimetallic compounds.



Scheme 56.

Several products have been isolated from the reaction of silylmercurials with transition metal carbonyl complexes. The complexes *cis*-$(OC)_4Fe(SiMe_3)_2$ and $Hg[Fe(CO)_4SiMe_3]_2$ are prepared from the photochemical reaction of $Hg(SiMe_3)_2$ with $Fe(CO)_5$.[127] The interaction of $Hg(SiEt_3)_2$ with $Co_2(CO)_8$ in a molar ratio of 1:2 gave the mercurial complex $Hg[Co(CO)_4]_2$, along with the cobalt–silyl complex $Et_3SiCo(CO)_4$.[24] The reaction between $Hg(SiMe_3)_2$ and $Os(H)Cl(CO)(PPh_3)_2$ produces a mixture of osmium–silicon bonded products.[128]

4. Concluding remarks

The most important applications of silylmercurials to organic synthesis are their use as substrates in transmetalation reactions, as effective silylating and dehalogenating agents, and as a source of silyl radicals. The mechanistic details of these reactions seem to vary considerably and can be far more complex than might be indicated by the reaction schemes. In particular, it is not entirely appropriate to say that these organometallic species are acting as nucleophiles, in as much as their role as electrophiles is of comparable significance. On the other hand, recent studies indicate that a growing number of reactions, such as the interaction with α-halogen-substituted carbonyl compounds, which were thought to proceed by two-electron processes, in many cases proceed by one-electron processes. It appears almost certain that many additional details concerning the reactivity of silylmercurials await future exploration.

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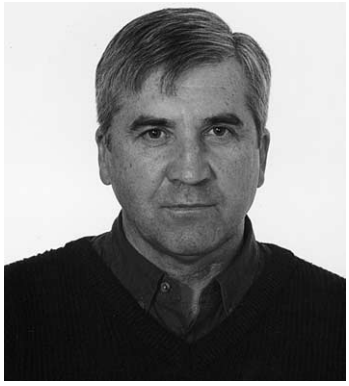
Biographical sketch



Vadim D. Romanenko was born in Alchevsk, Ukraine, in 1946. He studied at the Institute of Chemical Technology (Dnepropetrovsk) and received his PhD degree there under direction of Professor S. I. Burmistrov. Since 1975 he has been working at the National Academy of Sciences of Ukraine from which he earned his Doctor of Chemistry degree in 1988. He became a full professor in 1991. He has been a visiting scientist at the Centre of Molecular and Macromolecular Studies in Lodz (Poland), the Shanghai Institute of Organic Chemistry (China), the University of Pau and des Pays de l'Adour (France), the University Paul Sabatier (France), the University California Riverside (USA). His research interests include a wide range of topics at the border between organic and inorganic chemistry, in particular the chemistry of multiply bonded heavy main group elements. He is the author of approximately 270 papers on organoelement chemistry. He is also author of numerous reviews and two monographs on low-co-ordinated phosphorus compounds.

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Novel cytotoxic kaurane-type diterpenoids from the New Zealand Liverwort *Jungermannia* species

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Abstract—Novel cytotoxic rearranged kaurene- and *ent*-kaurene-type diterpenoids against HL-60 cells have been isolated from the unidentified New Zealand liverwort *Jungermannia* species together with previously known *ent*-kaurane-type diterpenoids. Their structures were determined by extensive NMR techniques, chemical degradation and X-ray crystallographic analysis.

1. Introduction

Liverworts have much amount of terpenoids and aromatic compounds containing the cellular oil bodies.[1,2] Some compounds possess novel carbon skeletons and shows interesting biological properties.[3] Southern hemisphere has more numerous endemic liverwort species than northern hemisphere including Japan. Therefore, we focused on the chemical constituents of New Zealand and Argentinean liverworts and reported the isolation of a number of new terpenoids and phenolics.[4a–4d] The genus *Jungermannia* L. belonging to the Jungermanniaceae (Jungermanniales) contain various sesqui- and diterpenoids.[5] *Jungermannia* species are not only morphologically but also chemically interesting because they are generally polymorphic and their chemical constituents depend on the collection site.[5] Recently, we reported the isolation and structural characterization of new *ent*-kaurane-type, *ent*-1β-hydroxy-9(11),16-kauradien-15-one (**1**) and *ent*-9(11),16-kauradiene-12,15-dione (**2**), and rearranged kaurane-type diterpenoid, jungermannenone A (**3**), from the unidentified New Zealand *Jungermannia* species together with known *ent*-kaurane-type diterpenoids, *ent*-11α-hydroxy-16-kauren-15-one (**4**) and (16*R*)-*ent*-11α-hydroxykauran-15-one (**5**).[6] Additionally, compounds **1–4** exhibited cytotoxicity against human leukemia cell line (HL-60 cells).[6–9] Further fractionation of the ether extract of this species resulted in the isolation of four rearranged kaurane- **6–9** and eight *ent*-kaurane-type diterpenoids **10–17**, along with four known *ent*-kauranes **18–21**. Here, we report on their isolation and structural characterization and cytotoxic as well as apoptotic properties.

2. Results and discussion

Four new rearranged kaurane- **6–9** and eight new *ent*-kaurane-type diterpenoids **10–17** have been isolated from the ether extract of the unidentified *Jungermannia* species by the column chromatography on silica gel, Sephadex® LH-20, Lobar® and preparative HPLC, together with four known *ent*-kaurane-type diterpenoids, *ent*-6β-hydroxy-16-kauren-15-one (**18**),[10] *ent*-16-kauren-15-one (**19**),[11] *ent*-11α,15α-dihydroxy-16-kaurene (**20**)[12] and *ent*-11α-acetoxy-7β-hydroxy-16-kauren-15-one (**21**).[13] Their structures were elucidated by a combination of extensive NMR techniques, chemical degradation and X-ray crystallographic analysis.

The structure of jungermannenone A (**3**) has been reported in the previous paper, however, the absolute configuration remained to be clarified.[6] Therefore, the diol **22**[6] prepared from **3** by $LiAlH_4$ reduction was esterified with (1*S*)-(−)-camphanic chloride to give (1*S*)-(−)-camphanic ester **23** as single crystals. X-ray crystallographic analysis of **23** was carried out and gave the ORTEP drawing as shown in Figure 1. Thus, the absolute configuration of **3** was established to be rearranged *ent*-kaurane-type as shown in Figure 1.

Keywords: *Jungermannia*; Liverwort; Kaurane-type diterpenoid; Cytotoxic.
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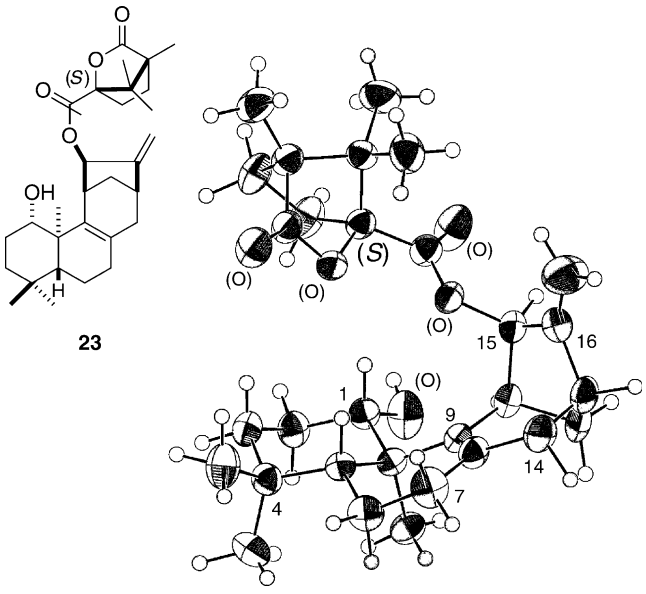


Figure 1. ORTEP drawing of **23**. Anisotropic ellipsoids are represented by a 50% probability level.

The EIMS spectrum of jungermannenone B (**6**) showed the molecular ion peak at *m/z* 284 and IR spectrum confirmed the presence of a carbonyl group (1729 cm^{-1}). The ^1H NMR spectrum (Table 1) of **6** was similar to those of compounds **1–4**, suggesting that **6** is a kaurane-type diterpenoid. The ^{13}C NMR (Table 2) and DEPT spectra displayed a carbonyl carbon (δ 201.9), an *exo*-methylene (δ 115.1 t, 151.1 s) and two olefinic quaternary carbons (δ 127.4, 139.1), as well as three methyls, seven methylenes, three methines and two quaternary carbons. Furthermore, the analysis of ^1H–^1H COSY (Fig. 2) and HMQC spectra of **6** led to the same skeleton as jungermannenone A (**3**). This presumption was clarified by HMBC analysis of **6** as shown in Figure 2. Its stereochemistry was exhibited by NOESY spectrum in which showed the NOEs, (i) H-19 and H-20, H-6α, H-3α, (ii) H-18 and H-6β, H-5, H-3α, H-3β, (iii) H-5 and H-18, H-6β, H-1β, (iv) H-20 and H-19, H-11, H-6α, and (v) H-12α and H-14α, as shown in Figure 3. Thus, the stereostructure of **6** was decided as shown in Figure 3.

The IR spectrum of jungermannenone C (**7**), which had the molecular ion peak at *m/z* 300, showed the presence of a hydroxyl (3441 cm^{-1}) and a ketone carbonyl (1735 cm^{-1}) group. The acetylation of **7** gave a monoacetate **24** that showed the presence of an acetoxyl group (δ_H 2.00 s, δ_C 21.2 q, 170.6 s) in ^1H and ^{13}C NMR (Table 3) spectra. In addition ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **7** were similar to those of **3** and **6**. The analyses of ^1H–^1H COSY and HMBC spectra of **7** as shown in Figure 4 clarified the structure to be a rearranged kaurane-type with the hydroxy group at C-12. The stereochemistry of the hydroxyl group was elucidated to be β configuration by the measurement of NOESY spectrum in which the NOE was observed between H-12 and H-20, H-14α as shown in Figure 5. Accordingly, the stereostructure of **7** was clarified as shown in Figure 5.

Table 1. ^1H NMR data of **6–10** ($CDCl_3$, 600 MHz)

H	6	7	8	9	10
1	1.88–1.93 m α 1.24 ddd (12.6, 12.6, 4.7)[a] β	1.84–1.90 m α 1.23 ddd (13.5, 13.5, 5.2) β	3.48 ddd (11.5, 6.3, 4.4)	1.92 m 1.19 m	3.44 ddd (11.8, 6.0, 4.4)
2	1.52–1.60 2H m	1.56 m α 1.58 m β	1.79 m α 1.59 m β	1.68 dddd (13.7, 13.7, 13.7, 3.6) α 1.58 m β	1.78 dddd (13.5, 13.5, 11.8, 4.1) α 1.56–1.60 m β
3	1.37 m α 1.13 ddd (12.6, 12.6, 4.9) β	1.37 m α 1.13 ddd (13.5, 13.5, 5.8) β	1.41 dt (13.7, 3.8) α 1.24 ddd (13.7, 13.7, 4.4) β	1.37 br d (13.5) α 1.15 ddd (14.0, 14.0, 4.7) β	1.42 ddd (13.5, 4.1, 3.0) α 1.27 ddd (13.5, 13.5, 4.4) β
5	1.11 dd (12.6, 1.9)	1.10 dd (12.6, 1.9)	0.95 d (12.1)	1.18 s	0.92 dd (12.9, 1.6)
6	1.41 m α 1.66 m β	1.40 m α 1.66 like dd (13.2, 6.9) β	1.36 dddd (12.1, 12.1, 12.1, 6.0) α 1.61 m β	4.47 d (4.9)	1.35 dddd (12.9, 12.9, 12.9, 5.8) α 1.56–1.60 m β
7	1.88–1.93 2H m	1.92 ddd (11.0, 11.0, 6.9) α 1.84–1.90 m β	1.90 m α 1.87 m β	1.95 m α 2.28 dd (18.4, 5.2) β	1.83–1.88 m α 1.90 m β
11	3.06 d (4.7)	3.09 s	4.07 s	3.12 d (4.4)	3.85 d (4.7)
12	1.62 d (11.0) α 1.88–1.93 m β	4.01 s	3.99 s	1.74 d (11.0) α 1.94 m β	1.62 d (11.3) α 1.83–1.88 m β
13	3.03 br s	2.98 m	3.02 br s	3.07 br s	2.48 like br s
14	2.45 dd (17.3, 4.9) α 1.88–1.93 m β	2.53 dd (17.0, 4.9) α 2.05 like d (17.0) β	2.55 dd (17.3, 4.9) α 2.12 d (17.3) β	2.52 dd (17.0, 4.9) α 1.91 m β	2.18 dd (18.1, 4.7) α 2.04 d (18.1) β
16					2.32 quint.d (7.4, 1.4)
17	5.40 s 5.90 s	5.51 s 6.06 s	5.63 s 6.17 s	5.42 s 5.91 s	1.12 d (7.4)
18	0.85 s	0.85 s	0.834 s	0.95 s	0.85 s
19	0.82 s	0.82 s	0.827 s	1.21 s	0.83 s
20	1.00 s	0.99 s	1.14 s	1.39 s	1.08 s
OH		2.21 br s	3.34 br s 4.99 d (6.3)		4.85 d (6.0)

[a] *J* values in Hz (in the parenthesis).

Table 2. ^{13}C NMR data of **6–18** ($CDCl_3$, 100 MHz)

C	6	7	8	9	10	11	12	13	14	15	16[a]	17	18
1	34.9	34.9	76.1	37.9	76.1	42.9	41.8	41.5	39.6	40.3	37.2	42.4	42.2
2	18.62[b]	18.54[b]	28.3	18.8	28.5	18.8	18.5	18.4	19.3	19.2	19.1	18.7	18.5
3	41.6	41.5	40.1	43.2	40.4	44.02	44.0	43.7	42.3	42.1	41.8	43.8	43.9
4	33.3	33.2	32.96	34.1	33.1	34.2	34.1	34.1	33.9	33.6	33.4	34.2	34.1
5	51.7	51.5	51.5	53.9	52.1	56.1	56.2	56.0	44.4	43.4	51.7	55.9	56.2
6	18.58[b]	18.51[b]	18.5	65.7	18.6	68.4	67.4	67.0	18.3	17.5	18.9	68.2	67.2
7	31.8	31.3	32.4	41.9	32.9	46.4	42.1	42.4	29.5	23.9	32.6	46.6	41.7
8	127.4	127.9	131.3	123.5	130.5	44.0	50.9	49.2	45.4	49.8	125.2	42.8	50.8
9	139.1	135.7	134.3	138.8	137.5	46.7	52.7	63.9	154.0	151.1	137.8	54.7	52.9
10	39.1	38.8	44.57	38.8	45.1	38.8	39.6	38.2	38.2	39.0	37.5	37.4	39.9
11	44.9	53.4	54.5	44.9	45.6	18.2	18.1	65.1	115.9	117.4	21.9	66.9	18.3
12	32.6	74.8	74.1	32.5	33.4	33.2	24.7	33.0	39.2	36.3	27.9	43.2	32.3
13	37.7	45.3	44.64	37.8	34.1	40.6	35.5	35.2	38.5	36.6	36.1	39.4	38.6
14	40.4	40.5	40.4	40.5	32.8	37.7	38.9	38.7	40.8	39.7	36.4	37.0	38.1
15	201.9	200.5	203.9	201.9	219.8	83.0	225.2	223.2	87.3	203.6	65.3	83.0	211.0
16	151.1	148.5	148.7	151.0	47.1	157.8	47.2	49.0	162.5	151.8	153.0	157.9	149.1
17	115.1	118.2	119.5	115.3	11.8	104.7	10.1	11.1	107.6	115.4	108.1	105.8	114.5
18	33.1	33.0	33.02	33.4	33.2	33.8	33.6	33.5	32.7	32.6	33.2	33.7	33.7
19	21.6	21.5	21.6	23.9	21.7	24.1	23.9	23.8	21.3	21.9	21.7	24.0	24.0
20	20.1	20.1	15.2	21.2	14.9	19.2	18.9	18.8	25.4	24.6	20.0	19.0	19.0

[a] Measured by 150 MHz.
[b] Interchangeable signals in the vertical column.

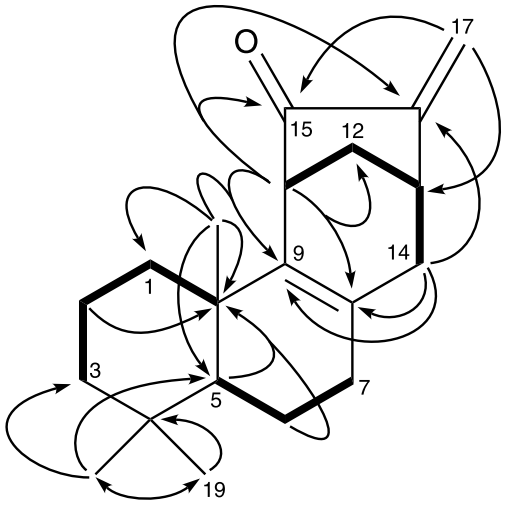


Figure 2. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **6**.

The HREIMS and IR spectra of jungermannenone D (**8**) showed the molecular formula as $C_{20}H_{28}O_3$ (anal. *m/z* 316.2015) and the presence of a hydroxyl (3539, 3304 cm^{-1}) and a carbonyl group (1702 cm^{-1}), respectively. The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) resembled those of **7** except for the presence of methine (δ_H 3.48 ddd; δ_C 76.1) bearing oxygen atom. The acetylation of **8** gave a monoacetate **25** (δ_H 2.00 s; δ_C 21.2 q, 170.4 s). However, the IR and ^{13}C NMR (Table 3) spectra of **25** showed the presence of an additional secondary hydroxyl group (3472 cm^{-1}; δ_C 75.6 d), which might possess the hydrogen bonding with a carbonyl group (C-15). The structure of **8** was revealed to be a rearranged kaurane-type diterpenoid with two hydroxy groups at C-1 and C-12 by the detailed analyses of ^{1}H–^{1}H COSY, HMQC and HMBC spectra. It was clarified that the stereochemistry of each hydroxyl

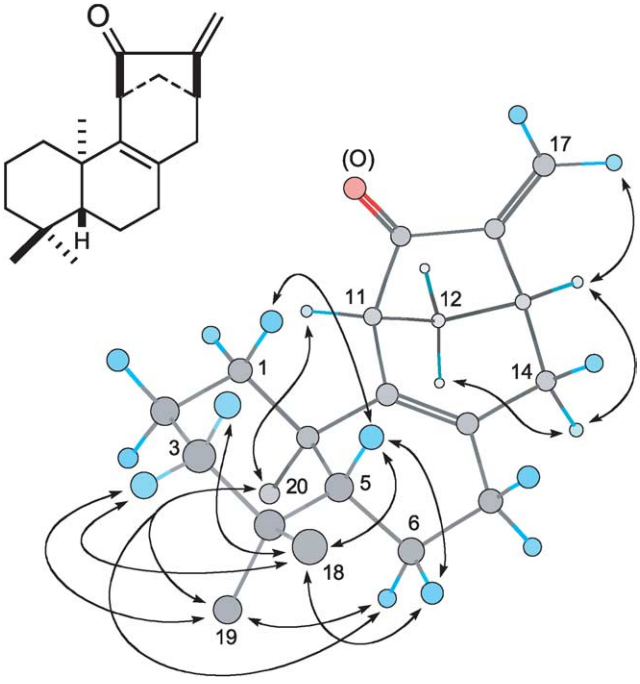


Figure 3. The NOE correlations of **6**.

Table 3. ^{13}C NMR data of **24**, **25**, **29** and **31** ($CDCl_3$, 100 MHz)

C	24	25	29	31
1	34.8	75.6	39.5	44.1
2	18.51[a]	28.6	19.3	18.6
3	41.5	40.3	42.6	43.7
4	33.3	33.0	33.8	34.0
5	51.5	51.6	44.4	56.3
6	18.48[a]	18.4	17.9	67.7
7	31.2	32.3	29.0	42.6
8	128.1	131.1	44.0	43.6
9	135.9	135.0	153.9	51.9
10	39.0	45.0	38.1	36.5
11	50.3	51.0	115.4	76.9
12	77.4	77.0	39.0	38.4
13	42.8	42.7	38.6	42.4
14	40.7	40.9	41.6	39.1
15	199.3	202.3	86.9	82.0
16	148.1	147.8	156.4	83.6
17	117.8	119.2	107.9	20.3
18	33.1	33.1	32.9	34.2
19	21.5	21.6	21.1	24.3
20	20.1	15.1	25.6	21.6
$OCOCH_3$	21.2	21.2	21.8	
$OCOCH_3$	170.6	170.4	170.9	

[a] Interchangeable signals in the vertical column.

group at C-1 and C-12 was α and β configuration, respectively by NOESY spectrum (Figure 6) of **8**. Thus, the relative stereostructure of **8** was shown in Figure 6.

The ^1H and ^{13}C NMR spectra (Tables 1 and 2) of jungermannenone E (**9**) (obsd *m/z* 300.2093 $[M]^+$, $C_{20}H_{28}O_2$) closely resembled those of **6**–**8**. Its IR spectrum showed the presence of a hydroxyl (3492 cm^{-1}) and a carbonyl (1719 cm^{-1}) group. The ^{13}C NMR confirmed the presence of an *exo*-methylene (δ 115.3 t, 151.0 s), a ketone carbonyl (δ 201.9), two quaternary olefinic carbons (δ 123.5, 138.8) and a methine (δ 65.7) bearing a hydroxyl group, together with three methyls, six methylenes, three methines and two quaternary carbons. The analyses of ^1H–^1H COSY, HMQC and HMBC spectra decided the structure of **9** as a rearranged kaurane-type with a hydroxy group at C-6. The stereochemistry was exhibited by NOESY spectrum in which the NOEs were observed between

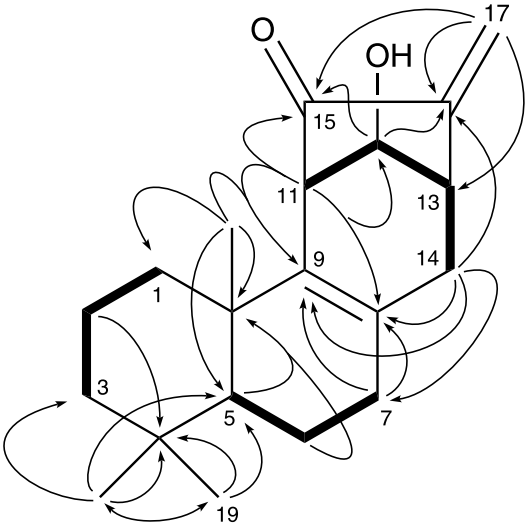


Figure 4. The ^1H–^1H (bold lines) and ^1H–^{13}C long-range (arrows) correlations by ^1H–^1H COSY and HMBC spectra of **7**.

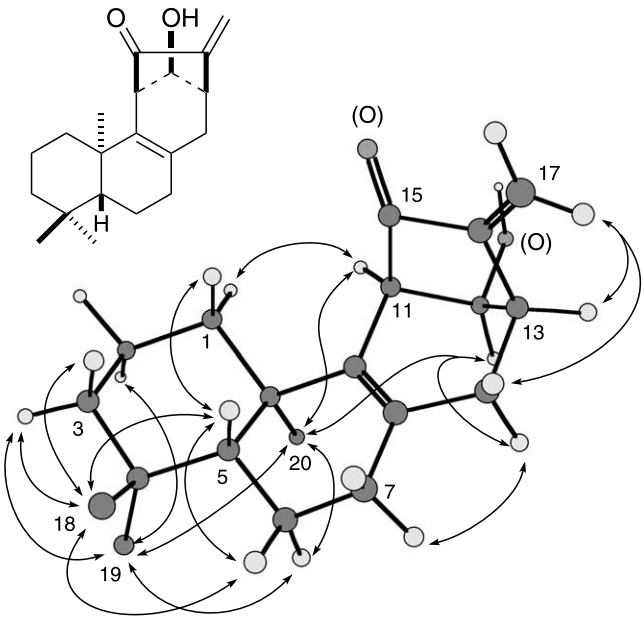


Figure 5. The NOE correlations of **7**.

(i) H-19 and H-20, H-3α, H-2α, (ii) H-20 and H-19, H-11, H-2α, (iii) H-18 and H-5, H-6β, (iv) H-5 and H-18, H-7β, H-6β, and (v) H-6β and H-18, H-5, H-7α, H-7β. Thus, the stereostructure of **9** was decided as shown in drawing.

The absolute configuration of **6**–**9** was elucidated by comparison of CD spectra with that of **3**. The CD spectra of **6**–**9** were demonstrated to have each first negative (**6**; λ_{max} 350 nm, **7**; λ_{max} 346 nm, **8**; λ_{max} 338 nm, **9**; λ_{max} 349 nm) and second positive (**6**; λ_{max} 274 nm, **7**; λ_{max}

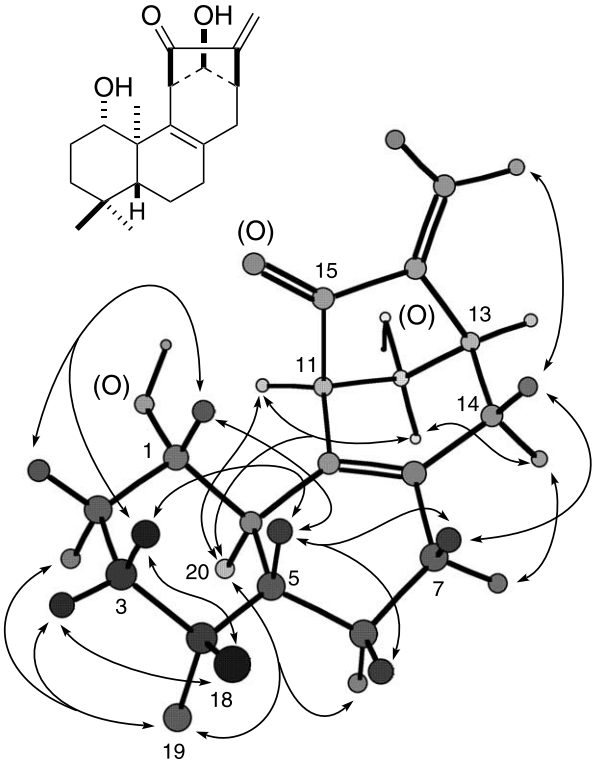


Figure 6. The NOE correlations of **8**.

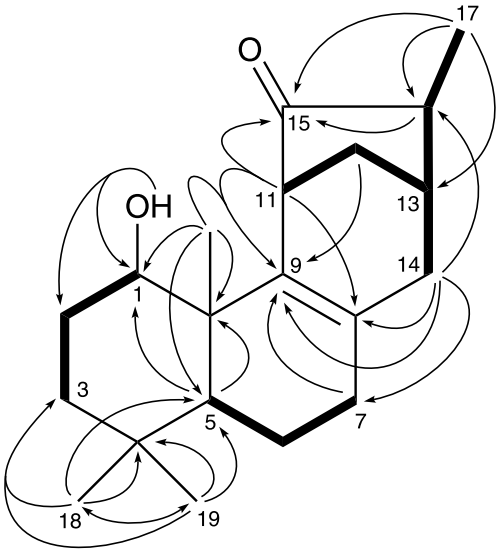


Figure 7. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **10**.

269 nm, **8**; λ_{max} 273 nm, **9**; λ_{max} 274 nm) Cotton effects as shown in **3** (λ_{max} 344 nm for the first negative, λ_{max} 275 nm for the second positive).[6] Thus, it was established that jungermannenones B–E (**6**–**9**) possess the same absolute configuration as jungermannenone A (**3**) with the rearranged *ent*-kaurane-type diterpenoid.

The IR and ^{13}C NMR (Table 2) spectra of **10** (obsd *m/z* 302.2242 $[M]^{+}$, $C_{20}H_{30}O_2$) showed the presence of a secondary hydroxyl (3456 cm^{-1}, δ_C 76.1 d) and a ketone carbonyl (1716 cm^{-1}, δ_C 219.8 d) group. The ^{1}H NMR spectrum (Table 1) confirmed the presence of three tertiary methyls (δ 0.85, 0.83, 1.08), a secondary methyl (δ 1.12) and a methine proton (δ 3.44) connecting a hydroxy group. The ^{1}H and ^{13}C NMR spectra were similar to those of **3** and **6**–**9**, indicating the presence of a rearranged kaurane-type diterpenoid. The ^{1}H–^{1}H COSY of **10** confirmed the presence of three partial segments, (i) –CH(OH)–CH_2–CH_2–, (ii) –CH–CH_2–CH_2–, and (iii) –CH–CH_2–CH(CH_2)–CH_3. The connectivity of each partial segment and analysis of HMBC spectrum as shown in Figure 7 led to the structure of **10** to be 16,17-dihydroxyjungermannnenone A. The NOEs of **10** was observed between (i) H-18 and H-5, H-3α, H-3β, (ii) H-19 and H-20, H-6α, H-2α, (iii) H-20 and H-19, H-11, H-6α, (iv) H-5 and H-18, H-7β, H-6β, H-1, (v) H-1 and H-5, H-2β, H-3β, (vi) H-16 and H-13, H-12β, (vii) H-17 and H-14β, and (viii) H-14α and H-12α. Therefore, the stereochemistry of the hydroxyl group at C-1 and the secondary methyl at C-17 were elucidated to be each α and β configuration. It was assumed that the 16α,17-dihydrojungermannenone A (**10**) possesses the same absolute configuration as **3** and **6**–**9** to take into consideration of the CD spectrum of **10** which observed first negative (λ_{max} 296 nm) and second positive (λ_{max} 236 nm) Cotton effect.[14]

The IR and EIMS spectra of **11** showed the presence of a hydroxy group (3480 cm^{-1}) and the molecular ion at *m/z* 304. Its molecular formula was found to be $C_{20}H_{32}O_2$ by HREIMS. The ^{1}H NMR spectrum (Table 4) exhibited two methine protons (δ 3.74, 4.51), an *exo*-methylene proton (δ 4.99, 5.11) and three tertiary methyl protons. Furthermore,

Table 4. ^{1}H NMR data of **11**–**15** ($CDCl_3$, 600 MHz)

H	11	12	13	14	15
1	1.82 br d (13.2)[a] α	1.71 m α	1.83 br d (13.7) α	1.86–1.92 m α	1.87 dsext. (12.9, 1.6) α
	0.84 ddd (13.2, 13.2, 3.3) β	0.74 ddd (12.4, 12.4, 3.6) β	0.94–1.00 m β	1.15 ddd (12.9, 12.9, 4.1) β	1.14 ddd (12.9, 12.9, 4.1) β
2	1.70 m α	1.63–1.68 m	1.70 ddddd (13.7, 13.7, 13.7, 3.6, 3.6) α	1.45–1.51 m	1.48–1.56 m α
	1.42–1.47 m β	1.41 m	1.45 m β	1.52–1.63 m	1.42 dquint. (17.3, 3.6) β
3	1.37 br d (13.2) α	1.36 like quint.d (12.9, 1.6) α	1.38 m	1.37 dsext. (13.5, 1.6) α	1.34 dsext. (12.9, 1.9) α
	1.13–1.19 m β	1.17 m β	1.18 m	1.10 ddd (13.5, 13.5, 3.8) β	1.09 m β
5	0.89 s	0.95 s	0.94–1.00 m	1.76 dd (11.0, 8.0)	1.48–1.56 m
6	4.51 s	4.53 br s	4.53 br s	1.86–1.92 m	1.48–1.56 m α
				1.45–1.51 m	2.21 m β
7	1.42–1.47 m α	1.40 dd (14.3, 3.0) α	2.11 dd (14.6, 3.0) α	1.95 m α	1.76 m α
	1.90 dd (14.3, 3.3) β	2.07 dd (14.3, 3.3) β	1.44 dd (14.6, 3.3) β	1.52–1.63 m β	1.79 m β
9	1.39 d (8.2)	1.15 br d (9.1)	1.17 br s		
11	1.60–1.67 2H m	1.22 m	3.98 d (5.2)	5.37 t (3.6)	5.42 t (3.6)
		1.63–1.68 m			
12	1.72 m α	1.76 dddd (6.3, 6.3, 6.3, 3.0) α	1.92 ddd (15.1, 5.2, 3.8) α	2.45 ddd (17.0, 4.4, 3.0) α	2.60 ddd (17.6, 4.7, 2.7) α
	1.48 m β	1.63–1.68 m β	1.97 br d (15.1) β	2.03 like br d (17.0) β	2.13 br d (17.6) β
13	2.69 br s	2.44 br s	2.44 m	2.71 br s	2.96 br s
14	2.37 d (12.1) α	2.81 dd (12.4, 1.1) α	2.73 d (12.4) α	1.44 d (11.0) α	1.58 d (11.0) α
	1.13–1.19 m β	1.48 like br d (12.4) β	1.50 like d (12.4) β	1.52–1.63 m β	1.68 dd (11.0, 4.9) β
15	3.74 br s			4.08 dt (11.5, 2.5)	
16		2.19 quint. (6.9)	2.23 quint. (7.1)		
17	5.11 s	1.12 d (6.9)	1.27 d (7.1)	5.04 s	5.40 t (1.1)
	4.99 d (3.0)			5.11 s	5.89 t (1.1)
18	0.97 s	0.97 s	0.98 s	0.83 s	0.90 s
19	1.21 s	1.20 s	1.19 s	0.89 s	0.90 s
20	1.41 s	1.45 s	1.37 s	1.07 s	1.10 s

[a] *J* values in Hz (in the parenthesis).

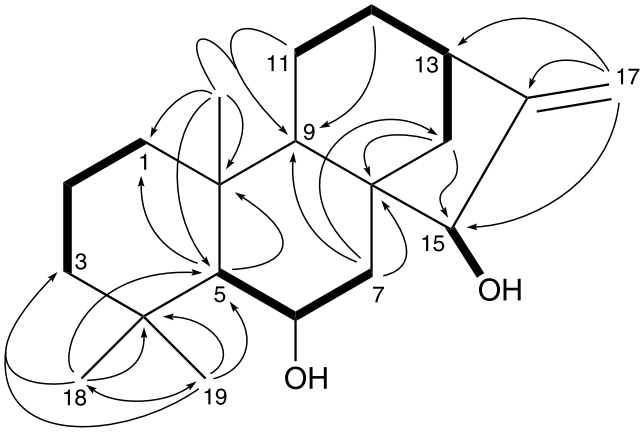


Figure 8. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **11**.

the ^{13}C NMR (Table 2) and DEPT spectra displayed two methines (δ 68.4, 83.0) bearing a hydroxyl group, an *exo*-methylene carbon (δ 104.7 t, 157.8 s), along with three methyls, seven methylenes, three methines and three quaternary carbons. Since the above spectral evidence was similar to those of compounds **18**–**20**, the structure of **11** was supported to be kaurane-type diterpenoid. Successively, the analysis of ^{1}H–^{1}H COSY and HMBC spectra as shown in Figure 8 led to the structure of **11** as 16-kaurene-6,15-diol. This assumption was further confirmed by the formation of **11** from known compound **18**[10] by $LiAlH_4$ reduction. The stereochemistry of the hydroxyl group at C-6 and C-15 was clarified to be each α and β configuration by the NOESY spectrum as shown in Figure 9.

The absolute configuration of **11** was attempted to compare with the diol derived from **18**. However, since the absolute configuration of **18** have not been mentioned in the reference,[10] its CD spectrum was measured and showed the first negative and second negative Cotton effects. The first negative (λ_{max} 350 nm) Cotton effect of **18** corresponding to an enone system was the same as that of *ent*-kaurenes, **21** (λ_{max} 347 nm) and **26**[15] (λ_{max} 350 nm). Accordingly, the absolute configuration of **18** was confirmed to be *ent*-6β-hydroxy-16-kauren-15-one. And then, the spectral data of **11** was identical with those of the diol derived from **18**. Inevitably, the absolute structure of **11** was established to be *ent*-16-kaurene-6β,15α-diol.

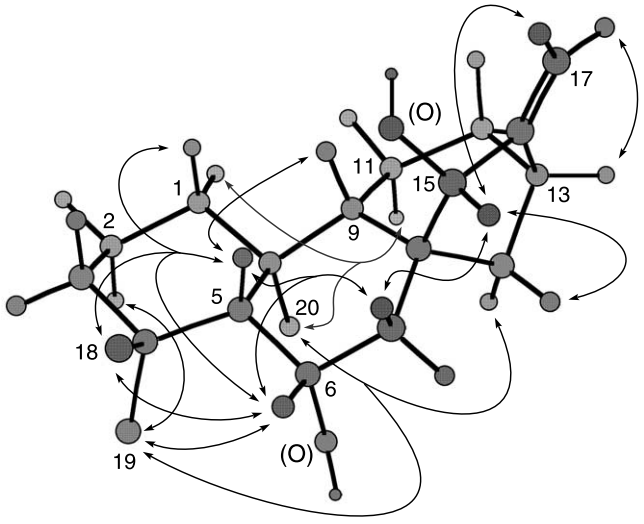


Figure 9. The NOE correlations of **11**.

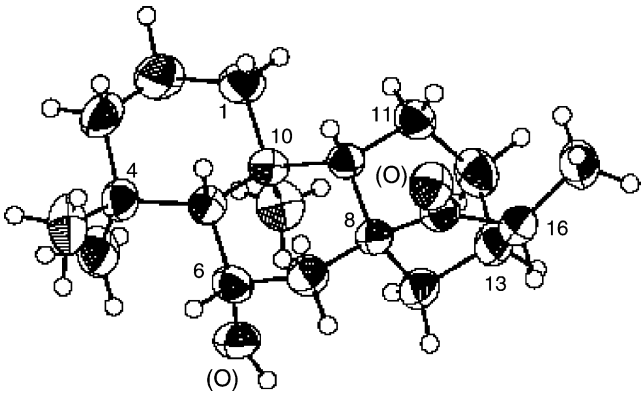


Figure 10. ORTEP drawing of **12**. Anisotropic ellipsoids are represented by a 50% probability level.

As the ^{1}H and ^{13}C NMR (Tables 4 and 2) of **12** (obsd *m*/*z* 304.2393 $[M]^{+}$, $C_{20}H_{32}O_2$) resembled those of **5**, **18** and **19**, the structure of **12** was presumed to be a kaurane-type diterpenoid. The IR and ^{13}C NMR spectra showed the presence of a hydroxyl (3558 cm^{-1}) and a carbonyl (1713 cm^{-1}, δ_C 225.2) group. The ^{1}H NMR displayed three tertiary methyls, one secondary methyl and a methine proton bearing a hydroxyl group. Further analyses of the ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY spectra clarified that the structure of **12** is the same *ent*-kaurane-type diterpenoid as **18** except for the presence of a secondary methyl at C-17β in place of the *exo*-methylene. Moreover, the X-ray crystallographic analysis showed the ORTEP drawing as shown in Figure 10. Thus the stereostructure of **12** was established to be 6α-hydroxy-kauran-15-one.

The HREIMS spectrum of **13** exhibited to have the molecular formula as $C_{20}H_{32}O_3$ (obsd *m*/*z* 320.2350 $[M]^{+}$). The IR spectrum showed the presence of a carbonyl (1726 cm^{-1}) and a hydroxyl (3480 cm^{-1}) group. The ^{1}H and ^{13}C NMR spectra (Tables 4 and 2) displayed two methine protons connecting the hydroxyl group (δ_H 3.98 d, 4.53 br s; δ_C 65.1, 67.0) and a ketone carbonyl carbon (δ_C 223.2), as well as three tertiary methyls, a secondary methyl, six methylenes, four methines and three quaternary carbons. These spectral data resembled those of **5** and **12**, indicating that **13** is *ent*-kaurane-type diterpenoid with a secondary methyl at C-17 and two hydroxy groups. The determination of the structure of **13** was carried out by the analysis of ^{1}H–^{1}H COSY and HMBC spectra as shown in Figure 11. Successively, the NOESY spectrum as shown in Figure 12 established that the stereostructure of **13** was 6α,11β-dihydroxykauran-15-one.

The absolute configuration of **12** and **13** was determined by the CD spectra that indicated the first negative (λ_{max} 308 nm in **12**, λ_{max} 307 nm in **13**) and second positive (λ_{max} 272 nm in **12**, λ_{max} 273 nm in **13**) Cotton effects. The negative Cotton effect of **12** and **13** with the saturated ketone system was the same that of (16*R*)-*ent*-kauran-15-one (**27**) (λ_{max}

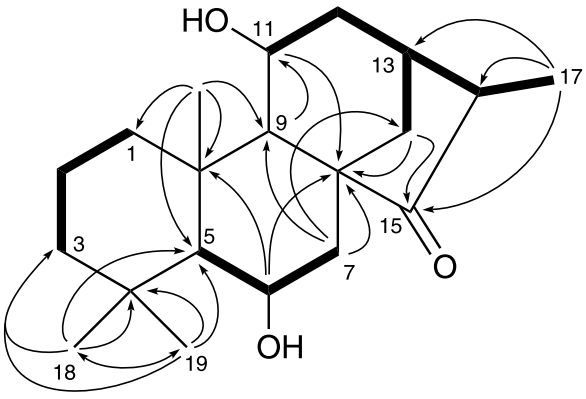


Figure 11. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **13**.

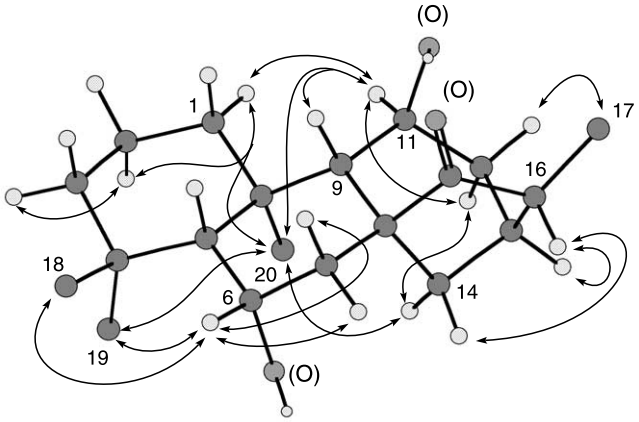


Figure 12. The NOE correlations of **13**.

314 nm) and (16*R*)- *ent*-16-methoxymethylkauran-15-one (**28**) (λ_{max} 307 nm).[16] Thus, the absolute configuration of **12** and **13** was established to be (16*R*)-*ent*-6β-hydorxykauran-15-one and (16*R*)-*ent*-6β,11α-dihydroxykauran-15-one, respectively.

The IR and EIMS spectra of **14** showed the presence of a hydroxyl group (3574 cm^{-1}) and the molecular ion peak at *m/z* 286. The similarity of the ^{1}H and ^{13}C NMR spectra (Tables 4 and 2) to those of **1** and **2** presumed that the structure of **14** might be an *ent*-kaurene-type diterpenoid with $\Delta_{9,11}$ and $\Delta_{16,17}$ double bonds. The DEPT spectra displayed a trisubstituted double bond (δ 115.9 d, 154.0 s), an *exo*-methylene (δ 107.6 t, 162.5 s) and a methine (δ 87.3) connecting the hydroxy group, as well as three methyls, seven methylenes, two methines and three quaternary carbons. Furthermore, the acetylation of **14** gave a monoacetate **29** in which an acetoxyl group (δ_H 2.16; δ_C 21.8 q, 170.9 s) was observed in the ^{1}H and ^{13}C NMR (Table 3) spectra. Further analyses of ^{1}H–^{1}H COSY and HMBC spectra of **14** as shown in Figure 13 clarified the structure as 9(11),16-kauradien-15-ol. The stereochemistry was confirmed NOEs by NOESY spectrum as shown in Figure 14. Accordingly, the structure of **14** was decided to be 9(11),16-kauradien-15β-ol.

The ^{1}H and ^{13}C NMR spectra (Tables 4 and 2) of **15** (obsd *m/z* 284.2132 $[M]^{+}$, $C_{20}H_{28}O$) also resembled those of **14**

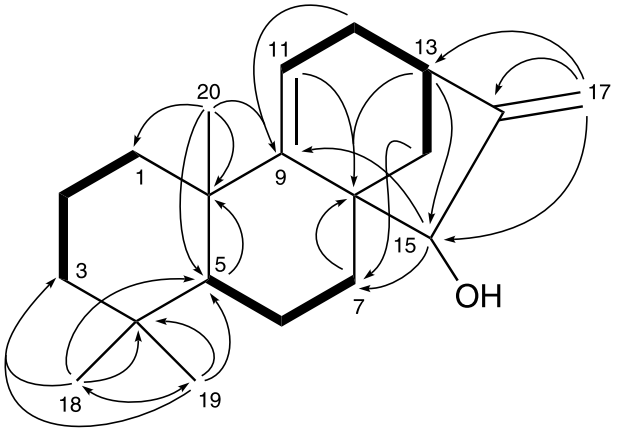


Figure 13. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **14**.

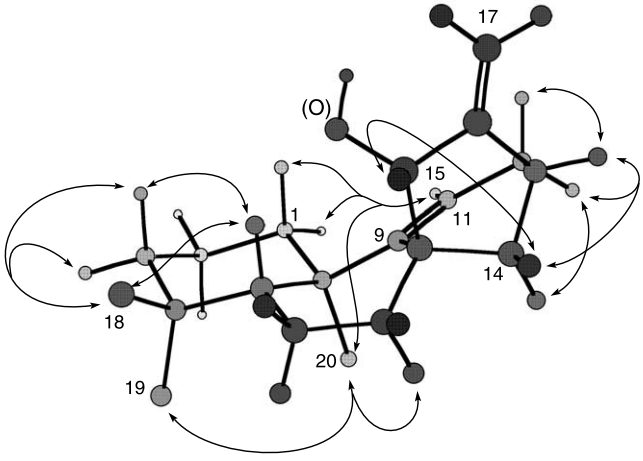


Figure 14. The NOE correlations of **14**.

except for the presence of a ketone that observed by the IR and ^{13}C NMR spectra (1728 cm^{-1}, δ_C 203.6). The analyses of ^{1}H–^{1}H COSY, HMBC and NOESY spectra led to the structure as 9(11),16-kauradien-15-one. The CD spectrum of **15** showed the same first positive (λ_{max} 351 nm) and second negative (λ_{max} 266 nm) Cotton effects as those of **1**

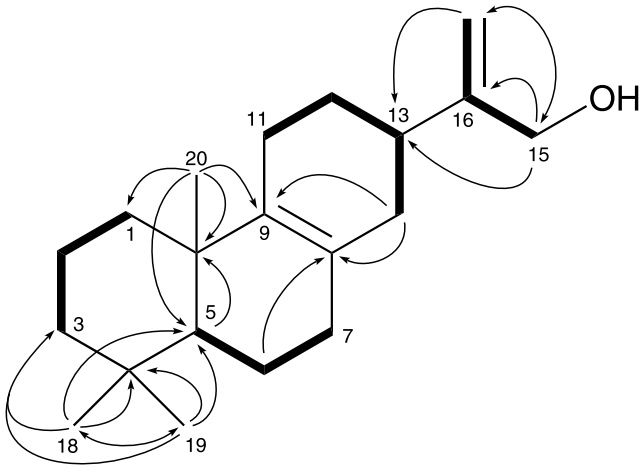


Figure 15. The ^{1}H–^{1}H (bold lines) and ^{1}H–^{13}C long-range (arrows) correlations by ^{1}H–^{1}H COSY and HMBC spectra of **16**.

Table 5. ^{1}H NMR data of **16**, **17** and **31** ($CDCl_3$, 600 MHz)

H	**16**	**17**[a]	**31**
1	1.73 m α	1.87 br d (13.2)	1.73 like br d (12.9) α
	1.04 ddd (12.9, 12.9, 3.8)[b] β	1.09 ddd (13.2, 13.2, 3.7)	1.09 ddd (12.9, 12.9, 3.6) β
2	1.59 dddd (13.7, 12.9, 3.6, 3.6) α	1.45 m	1.65 ddddd (13.8, 13.8, 12.9, 3.3, 3.3) α
	1.45 m β	1.67 m	1.44 m β
3	1.39 like br d (13.2) α	1.15–1.23 m	1.40 like br d (15.4) α
	1.15 ddd (14.3, 14.3, 4.1) β	1.38 br d (9.9)	1.20 ddd (13.2, 13.2, 3.8) β
5	1.14 dd (12.9, 2.5)	0.97 s	0.89 s
6	1.47 m α	4.51 br s	4.47 br s
	1.67 br dd (13.2, 7.7) β		
7	1.87–1.92 m α	1.50 dd (14.3, 2.9)	1.30 dd (14.6, 3.3) α
	2.02 m β	1.99 dd (14.3, 3.3)	1.83 dd (14.3, 3.3) β
9		1.60 br s	1.52 br s
11	1.94 m α	4.06 d (4.8)	4.32 like t (3.6)
	2.06 m β		
12	1.75 m α	2.11 ddd (14.3, 4.8, 2.9)	2.11 d (11.3) α
	1.49 m β	1.74 like br d (16.1)	1.90 m β
13	2.27 m	2.65 like br s	2.24 t (6.3)
14	1.99 m α	2.36 d (12.4) α	2.34 d (12.6) α
	1.87–1.92 m β	1.15–1.23 m β	1.23 m β
15	4.13 2H s	3.74 s	2.88 br s
17	4.86 quint. (1.1)	5.03 s	1.32 s
	5.05 q (1.4)	5.12 s	
18	0.88 s	0.97 s	0.95 s
19	0.85 s	1.19 s	1.21 s
20	0.97 s	1.32 s	1.43 s
OH			2.61 br s

[a] Measured by 400 MHz.
[b] *J* values in Hz (in the parenthesis).

(the first at λ_{max} 352 nm, the second at λ_{max} 268 nm)[6] and exsertifolin G (**30**) (the first at λ_{max} 348 nm, the second at λ_{max} 265 nm).[17]

Additionally, the spectral data of the diol formed from **15** by reduction with $LiAlH_4$ were identical with those of **14**. Thus, the absolute configuration of **14** and **15** were established to be *ent*-9(11),16-kauradien-15α-ol and *ent*-9(11),16-kauradien-15-one, respectively.

The EIMS of **16** showed the molecular ion at *m/z* 288 and its HREIMS displayed the molecular formula as $C_{20}H_{32}O$, indicating five degrees of unsaturation. The IR spectrum confirmed the presence of a hydroxyl group (3313 cm^{-1}). The ^{1}H and ^{13}C NMR spectra (Tables 5 and 2) exhibited the methylene (δ_H 4.13 s; δ_C 65.3) connecting the hydroxy group, an *exo*-methylene group (δ_H 4.86 quit., 5.05 q; δ_C 108.1 t, 153.0 s) and two olefinic quaternary carbons (δ_C 125.2, 137.8) as well as three tertiary methyls, eight methylenes, two methines and two quaternary carbons. These spectral data supported that **16** might be tricyclic diterpenoid with a primary hydroxyl group. The analysis of 2D COSY as shown in Figure 15 led to the cloven structure of the five-member ring of a kaurene skeleton. The NOEs were observed between (i) H-18 and H-5, H-3α, H-3β, H-6β, (ii) H-19 and H-20, H-3α, H-2α, (iii) H-20 and H-19, H-2α, H-1α, and (iv) H-13 and H-14α, H-14β, H-12α. Thus, the structure of **16** was established to be 8,15-*seco*-8,16-kauradien-15-ol.

Compound **17** was converted to **31** while the measurements of NMR. Therefore, the other spectroscopic data of **17** could not obtain completely. The ^{1}H and ^{13}C NMR spectra (Tables 5 and 2) of **17** showed the presence of three methines (δ_H 3.74 s, 4.06 d, 4.51 br s; δ_C 66.9, 68.2, 83.0) and an *exo*-methylene (δ_H 5.03, 5.12 each s; δ_C 105.8 t, 157.9 s), as well as three tertiary methyls, six methylenes, three methines and three quaternary carbons. As these spectral data resembled those of **11** and **20**, the structure of **17** was supported to be *ent*-kaurene-type diterpenoid with three hydroxyl groups. The detailed analysis of 2D NMR assumed the structure to be 16-kaurene-6,11,15-triol.

The IR spectrum of **31** showed the presence of a hydroxyl group (3461 cm^{-1}) and its HREIMS displayed the molecular formula as $C_{20}H_{32}O_3$ (obsd *m/z* 320.2357 $[M]^+$). In the ^{1}H NMR (Table 5) of **31**, a secondary methyl signal was newly observed in place of an *exo*-methylene of **17**. Additionally, the ^{13}C NMR (Table 3) and DEPT spectra exhibited the presence of three methines (δ 67.7, 76.9, 82.0) and quaternary carbons (δ 83.6) bearing an oxygen atom, four methyls, six methylenes, three methines and three

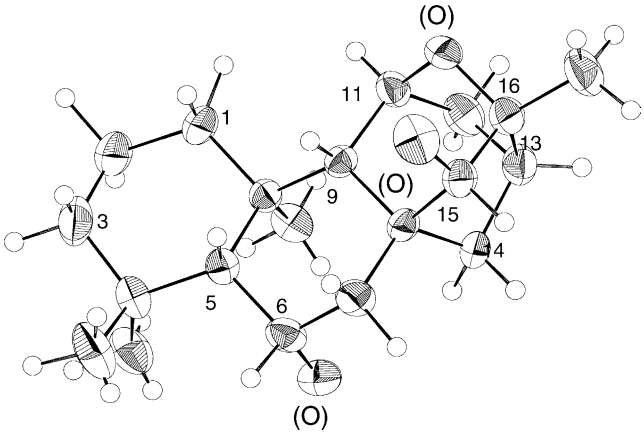


Figure 16. ORTEP drawing of **31**. Anisotropic ellipsoids are represented by a 50% probability level.

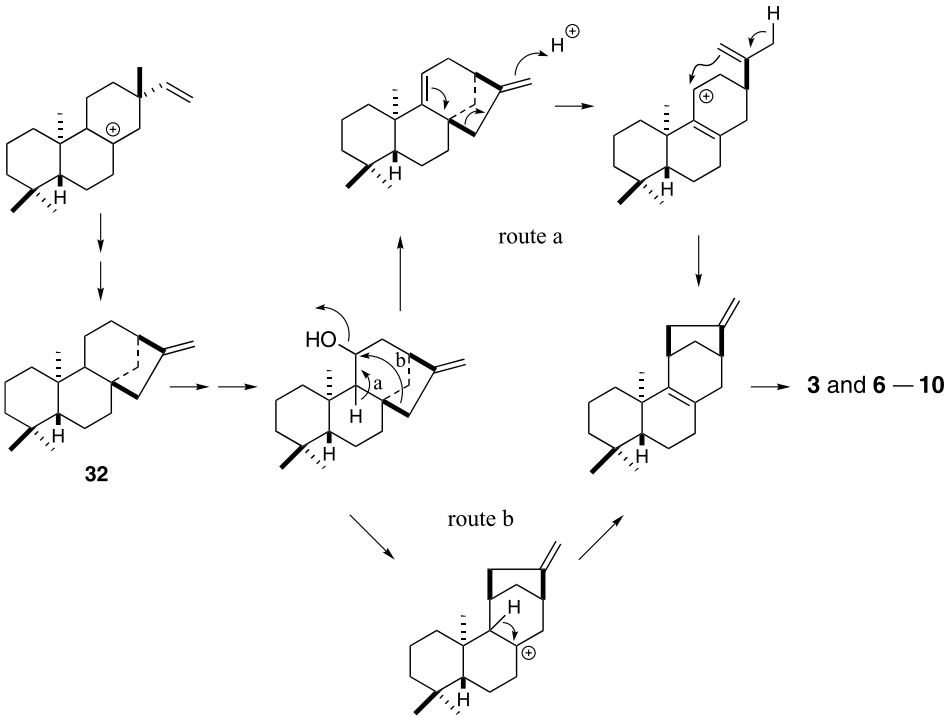


Figure 17. Proposed biogenetic pathway of **3** and **6–10**.

quaternary carbons. These spectral data supported that compound **31** possessed two secondary hydroxyl group and an ether linkage in the molecular. The confirmation of the structure was clarified by the analyses of ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY spectra of **31**. X-ray crystallographic analysis of **31**, which gave as single crystals, was carried out and the ORTEP drawing was obtained as shown in Figure 16. Thus, the structure of **31** was established to be 11β,16β-epoxykaurane-6α,15β-diol. Consequently, the stereostructure of **17** was suggested to be 16-kaurene-6α,11β,15β-triol. The formation of **31** from **17** has been recognized to form via protonation of the double bond and neutralization of the cation formed at C-16 by the hydroxyl group at C-11β.[18]

Although the absolute configuration of **16**, **17** and **31** has not been confirmed yet, these compounds are presumed to be *ent*-kaurane-type diterpenoids by consideration of the presence of *ent*-kaurane-type as main components in the present species. Therefore, compounds **16**, **17** and **31** were concluded as 8,15-*seco*-8,16-*ent*-kauradien-15-ol, *ent*-16-kaurene-6β,11α,15α-triol and *ent*-11α,16α-epoxykaurane-6β,15α-diol, respectively.

The species belonging to the genus *Jungermannia* L. contain much kind of diterpenoids, such as clerodane-, *ent*-kaurane-, pimarane-, and labdane-type. The present unidentified *Jungermannia* species, which dose not found in Japan, contained much amount of kaurane-type diterpenoids. Moreover, as we are aware, the isolation of rearranged kaurane-type diterpenoids **3** and **6–10** are the first report from the liverworts. Compounds **3** and **6–10** might be biosynthetically formed from an *ent*-kaurene **32** via *ent*-9(11)-kaurene-type, followed by cleavage of five-member ring and recyclization (route a), or from the elimination of the hydroxy group at C-11 and 1,3-rearrangment (route b) as shown in Figure 17.

Some *ent*-kaurane-type diterpenoids have been reported to possess antitumor activity.[19] Apoptosis-inducing compounds are promising candidates for cancer chemotherapy. We have reported the cytotoxicity against HL-60 cells of compounds **1–4**.[6–9] It was found that treatment with *ent*-11α-hydroxy-16-kauren-15-one (**4**) in HL-60 cells induced apoptosis and the enone group played a pivotal role in the ability of **4** to induce apoptosis.[20,21] Therefore we next investigated the cytotoxicity of compounds **5–8** and **18**

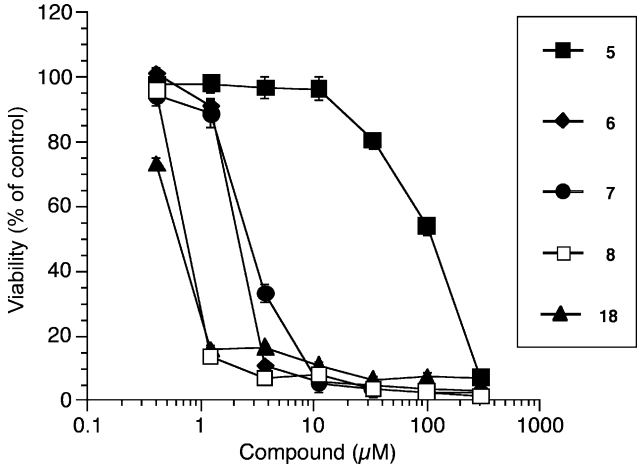


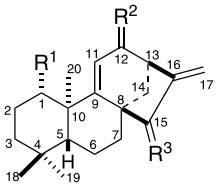
Figure 18. Cytotoxicity of **5–8** and **18** in HL-60 cells. HL-60 cells were treated with the indicated compound at the indicated concentration for 24 h. Then, the viability was determined using a cell counting kit. Data were mean ± SD ($n=4$).

against HL-60 cells by colorimetric 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium monosodium salt (WST-8) assay. As shown in Figure 18, each compound exhibited the cytotoxicity against HL-60 cells in a dose-dependent manner. The cytotoxicity was different among the compounds. IC_{50} values of compounds **5**, **6**, **7**, **8**, and **18** were >100, 1.21, 1.28, 0.78 and 0.40 μM, respectively. Furthermore, treatment with all of the compounds caused proteolysis of poly(ADP-ribose) polymerase, a sign of activation of apoptotic machinery, whereas the feature of cell death induced by treatment with **6–8** was apoptosis (data not shown).

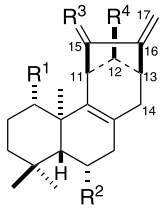
3. Experimental

3.1. General

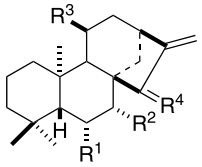
Melting points are uncorrected. The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer by the diffuse reflectance method. The ^1H and ^{13}C NMR spectra were recorded on a JEOL Eclipse 400 (400 MHz) or a Varian Unity 600 (600 MHz) spectrometer in $CDCl_3$ as the solvent with TMS (^1H NMR) and δ 73.03 ($CHCl_3$, ^{13}C NMR) as internal references. The mass spectra including high-resolution mass spectra were recorded on a JEOL JMS



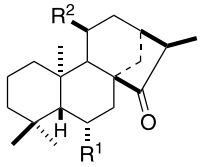
1 R^1=OH, R^2=H, H, R^3=O
2 R^1=H, R^2=R^3=O
14 R^1=H, R^2=H, H, R^3=βOH, αH
15 R^1=H, R^2=H, H, R^3=O
29 R^1=H, R^2=H, H, R^3=βOAc, αH



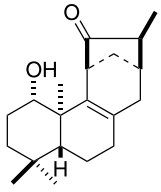
3 R^1=OH, R^2=R^4=H, R^3=O
6 R^1=R^2=R^4=H, R^3=O
7 R^1=R^2=H, R^3=O, R^4=OH
8 R^1=R^4=OH, R^2=H, R^3=O
9 R^1=R^4=H, R^2=OH, R^3=O
22 R^1=OH, R^2=R^4=H, R^3=βOH, αH
24 R^1=R^2=H, R^3=O, R^4=OAc
25 R^1=OH, R^2=H, R^3=O, R^4=OAc



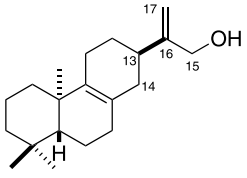
4 R^1=R^2=H, R^3=OH, R^4=O
11 R^1=OH, R^2=R^3=H, R^4=βOH, αH
17 R^1=OH, R^2=H, R^3=OH, R^4=βOH, αH
18 R^1=OH, R^2=R^3=H, R^4=O
19 R^1=R^2=R^3=H, R^4=O
20 R^1=R^2=H, R^3=OH, R^4=βOH, αH
21 R^1=H, R^2=OH, R^3=OAc, R^4=O



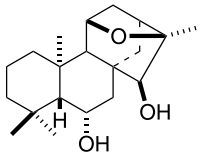
5 R^1=H, R^2=OH
12 R^1=OH, R^2=H
13 R^1=R^2=OH



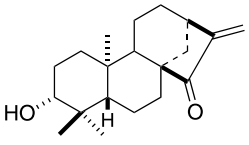
10



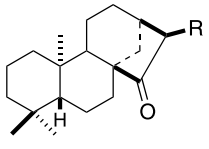
16



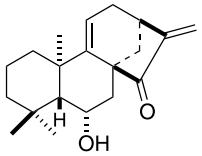
31



26



27 R=CH_3
28 R=CH_2OMe



30

AX-500 spectrometer. The UV spectra were obtained on a HITACHI U-3000.The CD spectra were recorded on a JASCO J-725 spectrometer. The specific rotations were measured by a JASCO DIP-1000 polarimeter with $CHCl_3$ as a solvent. X-ray reflection data were collected with a Mac Science MXC18 diffractometer using MoKα radiation (λ= 0.71073 Å). Preparative HPLC was performed by JASCO pump system. Column chromatography (CC) was carried out on silica gel 60 (0.2–0.5 mm, 0.04–0.063 mm, Merck), cosmosil 75C_{18}-OPN (Nakarai Tesque) and Sephadex® LH-20 (Pharmacia). TLC and preparative TLC were carried out on silica gel 60 F254 plate (Merck) and visualized by spraying Godin reagent[22] followed by heating at 120 °C.

3.2. Plant material

An unidentified *Jungermannia* species (NZ-49) was collected in Jackson River, New Zealand, 2000 and identified by J. E. B., and a voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Tokushima Bunri University.

3.3. Extraction and isolation

The ether extract (8.6 g) of *Jungermannia* species was divided into nine fractions by column chromatography (CC) on silica gel (35–70 mesh) using an *n*-hexane–EtOAc gradient solvent system. Fraction 3 was chromatographed on Sephadex® LH-20 and silica gel to give Jungermannenone B (**6**, 43.8 mg) and diterpene mixture. The mixture was rechromatographed on reverse phase silica gel and preparative HPLC (Chemcosorb 5Si-U, 5% Et_2O/*n*-hexane, 5% EtOAc/*n*-hexane; Nucleosil 50–5, 10% EtOAc/*n*-hexane) to yield *ent*-9(11),16-kauradien-15α-ol (**14**, 24.7 mg), *ent*-9(11),16-kauradien-15-one (**15**, 71.1 mg) and *ent*-16-kauren-15-one (**19**, 74.3 mg). *Ent*-6β-hydroxy-16-kauren-15-one (**18**, 19.7 mg) was isolated from fraction 4 by CC on Sephadex® LH-20, silica gel, and Lobar® (LiChroprep® Si-60, 10% Et_2O/*n*-hexane).

CC on Sephadex® LH-20, silica gel and Lobar® (LiChroprep® Si-60, 1% Et_2O/CH_2Cl_2) of fraction 5 divided into six subfractions. Jungermannenone E (**9**, 3.8 mg) and (16*R*)-*ent*-6β-hydroxykaur-15-one (**12**, 5.5 mg) was isolated by CC on silica gel and preparative HPLC (Chemcosorb 5ODS-H, MeOH) of fraction 5-2. Fraction 5-3 was chromatographed on silica gel, Lobar® (LiChroprep® Si-60, 20% Et_2O/*n*-hexane) and preparative HPLC (Chemcosorb 5Si-U, 10% EtOAc/*n*-hexane or 15% Et_2O/*n*-hexane) to give *ent*-16-kaurene-6β,15α-diol (**11**, 1.1 mg) and 8,15-*seco*-8,16-*ent*-kauradien-15-ol (**16**, 1.8 mg). 16α,17-Dihydrojungermannenone A (**10**, 4.8 mg) was purified by preparative HPLC (Chemcosorb 5Si-U, 15% EtOAc/*n*-hexane) of fraction 5-5. Fraction 5-6 was chromatographed on Sephadex® LH-20 and reverse phase silica gel to yield *ent*-11α,15α-dihydroxy-16-kaurene (**20**, 89.6 mg).

Fraction 6 was chromatographed on Sephadex® LH-20 and silica gel to divide seven subfractions. Jungermannenone C (**7**, 118.1 mg) and *ent*-11α-acetoxy-7β-hydroxy-16-kauren-15-one (**21**, 6.5 mg) were isolated by CC on silica gel and preparative HPLC (Chemcosorb 5ODS-H, CH_3CN; Chemcosorb 5Si-U, 30% EtOAc/*n*-hexane) of fraction 6-4. (16*R*)-*Ent*-6β,11α-dihydroxykaur-15-one (**13**, 25.6 mg) and *ent*-16-kaurene-6β,11α,15α-triol (**17**, 17.5 mg) were purified by CC on silica gel and preparative HPLC (Chemcosorb 5ODS-H, CH_3CN; Chemcosorb 5Si-U, 20% EtOAc/*n*-hexane) of fraction 6-5. Fraction 6-7 was repeatedly chromatographed on silica gel to give Jungermannenone D (**8**, 116.3 mg).

3.3.1. Jungermannenone B (6). Oil; $[\alpha]_D^{18}$ −323.3° (*c* 1.17); FTIR ν_{max} 1729 cm^{-1}; HREIMS obsd *m/z* 284.2138 $C_{20}H_{28}O$ requires 284.2140; UV λ_{max} (log ε) 349 nm (2.62), 268 nm (3.08), 229 nm (3.91) (*c* 1.94×10^{-4}, EtOH); CD $\Delta\varepsilon_{350\ nm}$ −4.23, $\Delta\varepsilon_{274\ nm}$ +4.07 (*c* 1.94×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 1 and 2; EIMS *m/z* (int.) 284 $[M]^+$ (84), 269 (86), 227 (7), 213 (16), 201 (18), 189 (99), 173 (100), 162 (15), 157 (14), 145 (25), 131 (23), 129 (30), 117 (32), 105 (26), 91 (39), 79 (14), 69 (21), 55 (17), 41 (19).

3.3.2. Jungermannenone C (7). Crystal; mp 72–74 °C (from *n*-hexane); $[\alpha]_D^{17}$ −262.2° (*c* 5.41); FTIR ν_{max} 3441, 1735, 1648 cm^{-1}; HREIMS obsd *m/z* 300.2077 $C_{20}H_{28}O_2$ requires 300.2089; UV λ_{max} (log ε) 345 nm (2.85), 264 nm (3.32), 226 nm (4.18) (*c* 1.04×10^{-4}, EtOH); CD $\Delta\varepsilon_{346\ nm}$ −8.78, $\Delta\varepsilon_{269\ nm}$ +7.01 (*c* 1.04×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 1 and 2; EIMS *m/z* (int.) 300 $[M]^+$ (100), 285 (74), 267 (9), 257 (9), 239 (9), 229 (9), 215 (25), 203 (13), 190 (16), 176 (30), 162 (19), 158 (14), 143 (18), 131 (33), 117 (22), 105 (17), 91 (25), 69 (25), 55 (14), 44 (19).

3.3.3. Jungermannenone D (8). Crystal; mp 166–167 °C (from *n*-hexane); $[\alpha]_D^{18}$ −242.4° (*c* 1.31); FTIR ν_{max} 3539, 3304, 1702, 1641 cm^{-1}; HREIMS obsd *m/z* 316.2015 $C_{20}H_{28}O_3$ requires 316.2038; UV λ_{max} (log ε) 339 nm (2.95), 266 nm (3.35), 230 nm (4.11) (*c* 1.04×10^{-4}, EtOH); CD $\Delta\varepsilon_{338\ nm}$ −8.05, $\Delta\varepsilon_{273\ nm}$ +4.59 (*c* 1.04×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 1 and 2; EIMS *m/z* (int.) 316 $[M]^+$ (29), 298 (100), 283 (44), 257 (47), 241 (44), 227 (61), 215 (25), 199 (36), 188 (58), 171 (30), 161 (24), 155 (25), 145 (40), 143 (33), 131 (27), 129 (31), 117 (25), 109 (19), 105 (27), 91 (33), 81 (26), 69 (14), 55 (19), 44 (24).

3.3.4. Jungermannenone E (9). Oil; $[\alpha]_D^{19}$ −328.6° (*c* 1.28); FTIR ν_{max} 3492, 1719, 1647 cm^{-1}; HREIMS obsd *m/z* 300.2093 $C_{20}H_{28}O_2$ requires 300.2089; UV λ_{max} (log ε) 349 nm (0.61), 275 nm (3.30), 229 nm (4.09) (*c* 1.23×10^{-4}, MeOH); CD $\Delta\varepsilon_{349\ nm}$ −5.15, $\Delta\varepsilon_{274\ nm}$ +4.92 (*c* 1.23×10^{-4}, MeOH); ^1H and ^{13}C NMR: Tables 1 and 2; EIMS *m/z* (int.) 300 $[M]^+$ (48), 285 (17), 267 (100), 226 (32), 211 (15), 204 (16), 197 (28), 187 (97), 173 (14), 162 (7), 155 (7), 145 (12), 131 (12), 129 (12), 117 (10), 105 (11), 91 (16), 69 (21), 55 (14), 41 (11).

3.3.5. 16α,17-Dihydrojungermannenone A (10). Crystal; mp 84–85 °C (from Et_2O); $[\alpha]_D^{19}$ −18.7° (*c* 0.62); FTIR ν_{max} 3456, 1716 cm^{-1}; HREIMS obsd *m/z* 302.2242 $C_{20}H_{30}O_2$ requires 302.2246; CD $\Delta\varepsilon_{296\ nm}$ −20.7, $\Delta\varepsilon_{236\ nm}$ +13.0 (*c* 6.82×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 1 and 2; EIMS *m/z* (int.) 302 $[M]^+$ (100), 287 (4), 274 (8), 269 (16), 243 (88), 227 (5), 215 (16), 203 (23), 201 (25), 199 (5), 189 (9), 185 (10), 177 (12), 175 (21), 157 (8), 145 (24), 131 (12),

119 (11), 105 (14), 91 (16), 85 (17), 70 (9), 61 (12), 55 (9), 43 (63).

3.3.6. *Ent*-16-kaurene-6β,15α-diol (11). Oil; $[\alpha]_D^{20}$ −62.8° (*c* 0.64); IR ν_{max} 3480 cm^{-1}; HREIMS: obsd *m/z* 304.2404 $C_{20}H_{32}O_2$ requires 304.2402; ^1H and ^{13}C NMR: Tables 4 and 2. EIMS *m/z* (int.) 304 $[M]^+$ (78), 286 (100), 271 (96), 253 (41), 246 (34), 243 (30), 228 (26), 217 (18), 203 (30), 201 (18), 189 (16), 176 (16), 163 (17), 153 (22), 147 (24), 137 (27), 125 (27), 119 (25), 109 (49), 91 (50), 84 (58), 79 (37), 69 (72), 55 (48), 41 (55).

3.3.7. (16*R*)-*Ent*-6β-hydroxykaur-15-one (12). Crystal; mp 198–200 °C (from *n*-hexane); $[\alpha]_D^{26}$ −86.8° (*c* 1.56); FTIR ν_{max} 3558, 1713 cm^{-1}; HREIMS obsd *m/z* 304.2393 $[M]^+$ $C_{20}H_{32}O_2$ requires 304.2402; CD $\Delta\varepsilon_{308\ nm}$ −1.0, $\Delta\varepsilon_{272\ nm}$ +0.1 (*c* 2.27×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 4 and 2; EIMS *m/z* (int.) 304 $[M]^+$ (100), 286 (41), 271 (29), 257 (17), 246 (55), 243 (30), 228 (16), 213 (17), 189 (9), 173 (9), 161 (7), 153 (48), 152 (18), 145 (5), 135 (13), 123 (18), 109 (36), 93 (18), 81 (28), 69 (28), 55 (20), 43 (24); Elementary analysis: calcd for $C_{20}H_{32}O_2$ (Mr 304.48), C 78.90, H 10.59, Found C 78.82, H 11.24. Crystal data. Recrystallized from *n*-hexane; Orthorhombic, space group $P2_12_12_1$, a=6.227 (3) Å, b=13.792 (8) Å, c=19.857 (2) Å, α=90.0°, β=90.0°, γ=90.0°, V=1705.4(2) $Å^3$, Z=4; D_x=1.186 mg m^{-3}, Data collection: DIP image plate, Cell refinement: Scalepack (HKL), Data reduction: maXus, Program used to refine structure: maXus, Refinement on F^2, fullmatrix least squares refinement, R(gt)=0.054, wR(gt)=0.110, S(gt)=0.739.

3.3.8. (16*R*)-*Ent*-6β,11α-dihydroxykaur-15-one (13). Crystal; mp 168–169 °C (from *n*-hexane); $[\alpha]_D^{19}$ −73.3° (*c* 2.58); FTIR ν_{max} 3480, 1726 cm^{-1}; HREIMS obsd *m/z* 320.2350 $[M]^+$ $C_{20}H_{32}O_3$ requires 320.2351; CD $\Delta\varepsilon_{307\ nm}$ −0.93, $\Delta\varepsilon_{273\ nm}$ +0.12 (*c* 1.47×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 4 and 2; EIMS *m/z* (int.) 320 $[M]^+$ (19), 302 (23), 287 (48), 269 (12), 241 (22), 233 (15), 229 (17), 211 (70), 196 (32), 178 (53), 167 (24), 159 (26), 153 (68), 150 (76), 139 (45), 123 (60), 121 (50), 109 (73), 105 (78), 93 (77), 91 (70), 81 (54), 79 (57), 74 (80), 69 (100), 55 (80), 43 (42), 41 (76); Elementary analysis: calcd for $C_{20}H_{32}O_3$ (M_r 320.48), C 74.95, H 10.06, Found C 74.94, H 10.35.

3.3.9. *Ent*-9(11),16-kauradien-15α-ol (14). Crystal; mp 52–54 °C (from Et_2O); $[\alpha]_D^{18}$ +74.2° (*c* 1.04); FTIR ν_{max} 3574 cm^{-1}; HREIMS obsd *m/z* 286.2299 $[M]^+$ $C_{20}H_{30}O$ requires 286.2297; ^1H and ^{13}C NMR: Tables 4 and 2; EIMS *m/z* (int.) 286 $[M]^+$ (86), 271 (100), 253 (38), 229 (5), 201 (24), 196 (11), 183 (11), 175 (21), 162 (10), 157 (17), 145 (20), 131 (22), 128 (15), 119 (18), 117 (22), 105 (30), 91 (43), 79 (21), 69 (21), 55 (21), 41 (21).

3.3.10. *Ent*-9(11),16-kauradien-15-one (15). Crystal; mp 53 °C (from Et_2O); $[\alpha]_D^{17}$ +235.8° (*c* 1.49); FTIR ν_{max} 1728, 1646 cm^{-1}; HREIMS obsd *m/z* 284.2132 $[M]^+$ $C_{20}H_{28}O$ requires 284.2140; UV λ_{max} (log ε) 350 nm (2.61), 263 nm (3.15), 232 nm (4.08) (*c* 3.17×10^{-4}, EtOH); CD $\Delta\varepsilon_{351\ nm}$ +5.23, $\Delta\varepsilon_{266\ nm}$ −5.82 (*c* 3.17×10^{-4}, EtOH); ^1H and ^{13}C NMR: Tables 4 and 2; EIMS *m/z* (int.) 284 $[M]^+$ (60), 269 (79), 227 (7), 213 (15), 201 (17), 189 (100), 173 (93), 162 (15), 157 (11), 145 (22), 131 (19), 129 (22), 117 (25), 105 (21), 91 (32), 79 (13), 69 (24), 55 (18), 41 (17).

3.3.11. 8,15-*Seco*-8,16-*ent*-kauradien-15-ol (16). $[\alpha]_D^{20}$ −33.1° (*c* 1.28); FTIR ν_{max} 3313 cm^{-1}; HREIMS obsd *m/z* 288.2442 $[M]^+$ $C_{20}H_{32}O$ requires 288.2453; ^1H and ^{13}C NMR: Tables 5 and 2; EIMS *m/z* (int.) 288 $[M]^+$ (57), 273 (100), 255 (55), 230 (34), 215 (18), 203 (18), 199 (10), 185 (19), 173 (17), 159 (32), 147 (26), 131 (30), 123 (19), 119 (26), 109 (26), 105 (36), 91 (34), 81 (24), 69 (31), 55 (19), 41 (18).

3.3.12. *Ent*-16-kaurene-6β,11α,15α-triol (17). Physical and spectroscopic data cloud not measure; ^1H and ^{13}C NMR: Tables 5 and 2.

3.3.13. *Ent*-11α,16α-epoxykaurane-6β,15α-diol (31). Amorphous; $[\alpha]_D^{22}$ −36.2° (*c* 2.02); FTIR ν_{max} 3461 cm^{-1}; HREIMS obsd *m/z* 320.2357 $[M]^+$ $C_{20}H_{32}O_3$ requires 320.2352; ^1H and ^{13}C NMR: Tables 5 and 3; EIMS *m/z* (int.) 320 $[M]^+$ (80), 302 (8), 287 (10), 246 (17), 239 (9), 228 (12), 213 (8), 190 (9), 175 (7), 161 (7), 151 (14), 145 (11), 137 (15), 122 (21), 109 (27), 105 (33), 91 (40), 79 (36), 69 (45), 55 (56), 43 (100). Crystal data. Orthorhombic, space group $P2_12_12_1$, a=8.132 (4) Å, b=9.855 (7) Å, c=22.109 (2) Å, α=90.0°, β=90.0°, γ=90.0°, V=1771.8(2) $Å^3$, Z=4; D_x=1.201 mg m^{-3}, Data collection: DIP image plate, Cell refinement: Scalepack (HKL), Data reduction: maXus, Program used to refine structure: SHELXL-97, Refinement on F^2, fullmatrix least squares refinement, R(gt)=0.0605, wR(gt)=0.1633, S(ref)=1.146.

3.3.14. Esterification of 22. To a solution of compound **22** (11.3 mg) in CH_2Cl_2 (5 ml) and dry pyridine (0.5 ml), (1*S*)-(−)-camphanic chloride (31.5 mg) and 4-dimethylaminopyridine (DMAP, 46.0 mg) were added and stirred at room temperature for 4 days, then purified by CC on Sephadex® LH-20 to afford (1*S*)-(−)-camphanic ester **23** (16.1 mg): crystal; mp 249 °C; $[\alpha]_D^{19}$ −69.4° (*c* 0.57); FTIR ν_{max} 3498, 1770, 1724 cm^{-1}; HREIMS obsd *m/z* 482.3028 $C_{30}H_{42}O_5$ requires 482.3033; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81, 0.88, 0.995, 1.002, 1.06, 1.12 (each 3H, s), 1.23 (1H, dd, J=12.1, 1.8 Hz), 1.35 (1H, dt, J=13.5, 3.8 Hz), 1.88–2.04 (4H, m), 1.74–1.80 (2H, m), 1.41–1.71 (8H, m), 2.34 (1H, dd, J=16.5, 4.8 Hz), 2.52 (1H, ddd, J=15.0, 10.6, 4.4 Hz), 2.74 (1H, br s), 3.78 (1H, t, J=5.1 Hz), 3.93 (1H, dd, J=11.0, 4.8 Hz), 4.90 (1H, s), 5.07 (1H, s), 5.84 (1H, dt, J=6.2, 2.2 Hz); EIMS *m/z* (int.) 482 $[M]^+$ (7), 464 (7), 423 (8), 381 (4), 284 (15), 266 (8), 251 (7), 225 (16), 197 (11), 183 (100), 157 (11), 143 (16), 131 (10), 109 (12), 99 (24), 83 (32), 81 (21), 55 (29), 41 (10); Elementary analysis: calcd for $C_{30}H_{42}O_5$ $0.1H_2O$ (M_r 484.44), C 74.38, H 8.74, Found C 74.11, H 8.46. Crystal data. Recrystallization from *n*-hexane–MeOH–EtOAc, Orthorhombic, space group $P2_12_12_1$, a=7.126 (2) Å, b=16.430 (6) Å, c=22.632 (11) Å, α=90.0°, β=90.0°, γ=90.0°, V=2649.8(2) $Å^3$, Z=4; D_x=1.210 mg m^{-3}, Data collection: DIP image plate, Cell refinement: Scalepack (HKL), Data reduction: maXus, Program used to refine structure: SHELXL-97, Refinement on F^2, fullmatrix least squares refinement, R(gt)=0.0542, wR(gt)=0.1409, S(ref)=1.168.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the

Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 265117 ((16*R*)-*ent*-6β-hydroxykaur-15-one), 265118 (jungermannenone A (1*S*)-(−)-camphanic ester) and 265119 (*ent*-11α,16α-epoxykaurane-6β,15α-diol). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.3.15. Acetylation of 7. Compound **7** (17.3 mg) was added to pyridine (1 ml) and Ac_2O (1 ml), and kept at room temperature overnight, and then worked up as usual to give a monoacetate **24** (16.1 mg): oil; $[\alpha]_D^{18}$ −250.0° (*c* 1.52); FTIR ν_{max} 1739, 1648, 1229, 1045 cm^{-1}; HREIMS obsd *m/z* 342.2193 $C_{22}H_{30}O_3$ requires 342.2195; UV λ_{max} (log ε) 346 nm (2.38), 264 nm (2.84), 227 nm (3.71) (*c* 2.68×10^{-4}, EtOH); CD $\Delta\varepsilon_{345\ nm}$ −2.75, $\Delta\varepsilon_{267\ nm}$ +2.46, $\Delta\varepsilon_{237\ nm}$ +2.22 (*c* 2.68×10^{-4}, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (1H, ddd, *J*=12.4, 12.4, 5.5 Hz, H-1), 1.86 (1H, m, H-1), 1.43 (1H, m, H-2), 1.67 (1H, dd, *J*=13.2, 6.2 Hz, H-2), 1.13 (1H, m, H-3), 1.39 (1H, m, H-3), 1.10 (1H, dd, *J*=12.4, 1.5 Hz, H-5), 1.53–1.61 (2H, m, H-6), 1.87–1.96 (2H, m, H-7), 3.18 (1H, s, H-11), 4.88 (1H, s, H-12), 3.10 (1H, br s, H-13), 2.07 (1H, d, *J*=16.8 Hz, H-14), 2.63 (1H, dd, *J*=16.8, 4.8 Hz, H-14), 5.50 (1H, s, H-17), 6.05 (1H, s, H-17), 0.85 (3H, s, H-18), 0.82 (3H, s, H-19), 1.01 (3H, s, H-20), 2.00 (3H, s, -OCO*CH*$_3$); ^{13}C NMR: Table 3; EIMS *m/z* (int.) 342 $[M]^+$ (18), 324 (3), 300 (24), 282 (41), 267 (30), 254 (100), 239 (13), 228 (16), 213 (25), 197 (14), 187 (21), 171 (23), 161 (40), 157 (23), 155 (21), 143 (32), 131 (36), 124 (23), 117 (32), 105 (26), 95 (15), 91 (43), 81 (20), 77 (17), 69 (64) 55 (36), 43 (100).

3.3.16. Acetylation of 8. Compound **8** (18.1 mg) was treated in the same manner as described above to give a monoacetate **25** (13.6 mg): crystal; mp 122–124 °C; $[\alpha]_D^{18}$ −167.5° (*c* 1.36); FTIR ν_{max} 3472, 1741, 1710, 1647, 1231 cm^{-1}; HREIMS obsd *m/z* 358.2147 $C_{22}H_{30}O_4$ requires 358.2144; UV λ_{max} (log ε) 339 nm (2.60), 267 nm (3.04), 230 nm (3.82) (*c* 2.35×10^{-4}, EtOH); CD $\Delta\varepsilon_{342\ nm}$ −3.56, $\Delta\varepsilon_{271\ nm}$ +2.52, $\Delta\varepsilon_{241\ nm}$ +2.00 (*c* 2.35×10^{-4}, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (1H, ddd, *J*=10.6, 6.2, 6.2 Hz, H-1), 1.57–1.64 (2H, m, H-2, H-6), 1.80 (1H, m, H-2), 1.25 (1H, ddd, *J*=13.9, 13.9, 4.4 Hz, H-3), 1.41 (1H, m, H-3), 0.95 (1H, dd, *J*=12.1, 1.5 Hz, H-5), 1.37 (1H, m, H-6), 1.87–1.95 (2H, m, H-7), 4.13 (1H, s, H-11), 4.87 (1H, s, H-12), 3.12 (1H, br s, H-13), 2.14 (1H, d, *J*=17.7 Hz, H-14), 2.65 (1H, dd, *J*=17.7, 5.1 Hz, H-14), 5.61 (1H, s, H-17), 6.15 (1H, s, H-17), 0.84 (3H, s, H-18), 0.83 (3H, s, H-19), 1.13 (3H, s, H-20), 2.00 (3H, s, –OCO*CH*$_3$), 4.51 (1H, d, *J*=6.2 Hz, –O*H*); ^{13}C NMR: Table 3; EIMS *m/z* (int.) 358 $[M]^+$ (24), 325 (3), 298 (31), 280 (11), 270 (20), 258 (8), 252 (16), 239 (25), 227 (11), 211 (10), 199 (87), 198 (29), 185 (15), 181 (24), 171 (27), 169 (22), 157 (16), 155 (22), 143 (46), 135 (18), 129 (33), 117 (22), 105 (39), 99 (31), 91 (37) 81 (43), 77 (23), 69 (44), 67 (33), 55 (44), 43 (100).

3.3.17. Acetylation of 14. Compound **14** (9.8 mg) was treated in the same manner as described above to give *ent*-15α-acetoxy-9(11),16-kauradiene (**29**) (10.4 mg): oil; $[\alpha]_D^{17}$ −8.0° (*c* 0.84); FTIR ν_{max} 1740, 1238, 1044 cm^{-1}; HREIMS obsd *m/z* 328.2407 $C_{22}H_{32}O_2$ requires 328.2403; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.91 (1H, m, H-1α), 1.29 (1H, ddd, *J*=12.9, 12.9, 3.3 Hz, H-1β), 1.43–1.50 (4H, m, H-2, H-5, H-6, H-14α), 1.59 (1H, m, H-2), 1.41 (1H, dsext., *J*=13.5, 1.6 Hz, H-3α), 1.09 (1H, ddd, *J*=13.5, 13.5, 3.8 Hz, H-3β), 1.61–1.68 (2H, m, H-6, H-7), 1.93 (1H, m, H-7), 5.37 (1H, t, *J*=3.3 Hz, H-11), 2.48 (1H, ddd, *J*=17.3, 4.7, 3.3 Hz, H-12α), 2.13 (1H, like br d, *J*=16.5 Hz, H-12β), 2.76 (1H, br s, H-13), 1.74 (1H, dd, *J*=11.0, 5.2 Hz, H-14β), 5.49 (1H, t, *J*=2.5 Hz, H-15), 4.84 (1H, t, *J*=1.9 Hz, H-17), 5.03 (1H, dd, *J*=2.7, 1.1 Hz, H-17), 0.79 (3H, s, H-18), 0.88 (3H, s, H-19), 1.07 (3H, s, H-20), 2.16 (3H, s, –OCO*CH*$_3$); ^{13}C NMR: Table 3; EIMS *m/z* (int.) 328 $[M]^+$ (37), 313 (58), 286 (24), 268 (56), 253 (100), 243 (8), 225 (6), 199 (12), 189 (27), 183 (16), 171 (14), 163 (13), 157 (21), 145 (26), 131 (25), 129 (24), 117 (22), 105 (30), 91 (40), 81 (21), 69 (37), 55 (24), 43 (55).

3.3.18. Reduction of 15. To a suspension of $LiAlH_4$ (12 mg) in dry Et_2O (4 ml) was added the compound **15** (10.4 mg) in dry Et_2O and stirred for 1 h at room temperature. Work-up as usual gave the resulting mixture which was chromatographed on silica gel (10% EtOAc/*n*-hexane) to give a monoalcohol (8.4 mg), the spectral data of which were completely identical with those of **14**.

3.3.19. Reduction of 18. To a suspension of $LiAlH_4$ (8 mg) in dry Et_2O (4 ml) was added the mixture of **18** (8.7 mg) in dry Et_2O and stirred for 1 h at room temperature. Work-up as usual gave the resulting mixture, which was purified by prep. HPLC (Chemcosorb 5 Si–U, 15% EtOAc/*n*-hexane) to yield a diol (1 mg), the spectral data of which were identical with those of **11**.

3.4. Biological assay

3.4.1. Cell culture. Human myeloid leukemia HL-60 cells were cultured to the exponential growth phase in RPMI 1640 supplemented with 10% (v/v) fetal calf serum in a humidified atmosphere containing 5% CO_2.

3.4.2. Cell viability assay. Cytotoxicity against HL-60 cells was assessed as follows: 4×10^4 cells seeded onto 96-well plates were incubated with compounds at the indicated concentrations at 37 °C for 24 h. Cell viability was determined using the colorimetric 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt (WST-8) method using cell counting kit-8 according to the manufacturer's instructions (Wako Pure Chemicals, Ltd., Osaka, Japan).

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Anthracene derivatives bearing two urea groups as fluorescent receptors for anions

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Abstract—For the recognition and sensing of anionic analytes, comparative studies were carried out on the anion bindings of pyrophosphate, $H_2PO_4^-$, and dicarboxylates to the anthracene derivatives bearing two urea groups on the 1,8 and 9,10-positions as fluorescent chemosensors for anions. Their binding properties were compared using fluorescence and ^1H NMR, and the results were rationalized with an ab initio study.

1. Introduction

Using supramolecular chemistry, the recognition and sensing of anionic analytes has recently emerged as a key research field.[1] Fluorescence is an important detection method owing to its simplicity and high detection limit.[2] Indeed, during the recent decade, there have been many reports regarding anion selective receptors using the fluorescent changes as a means of detection.[1a,3]

Recently, an 1,8-bisurea anthracene derivative was reported to be a selective fluorescent chemosensor for fluoride ion.[3i] In a while, Gunnlaugsson et al. reported 9,10-bisthiourea anthracene derivatives as fluorescent PET chemosensors for dicarboxylates and pyrophosphate.[3j] In general, for most anion binding studies, only few similar anions have been used, which could result in inconclusive anion selectivity in consideration of diverse anions. Therefore, in order to establish proper anion selectivity of a particular receptor, it is very important to consider a wide range of structurally different anions. Thus, in continuation of our work, this article reports the syntheses and binding properties of anthracene derivatives bearing two urea or thiourea groups as fluorescent chemosensors for anions including $H_2PO_4^-$, pyrophosphate, and dicarboxylates. The binding properties of the 1,8- and 9,10-isomers for $H_2PO_4^-$ and pyrophosphate are compared using ^1H NMR, fluorescence, and ab initio calculations. Here, we confirm a unique 1:2 binding of host **1** with $H_2PO_4^-$ from the ^1H NMR and theoretical investigations. We further investigate the main factors determining the binding features. Indeed, we find that though both of these 1,8- and 9,10-bisurea receptors are highly selective for adiapte, only the 1,8-bisurea receptor is highly selective for $H_2PO_4^-$.

2. Results and discussion

1,8-Anthracenedimethanol was used as the starting material for the synthesis procedure. Following the published procedures,[4] 1,8-anthracenedimethanamine **8** was obtained in a 55% yield (Scheme 1). Treating 8 with phenyl isothiocyanate and 4-(trifluoromethyl)-phenyl isothiocyanate in CH_2Cl_2 afforded compounds **2** and **3** in 70 and 80% yields, respectively (Scheme 1). 9,10-Anthracenedimethanamine 9 was prepared following the published procedure.[3j] The 9,10-bisurea anthracenes **4** and **5** were synthesized from 9 giving 65 and 75% yields, respectively. Bisamide anthracene **6** was also obtained in a 85% yield from the reaction of compound **8** with phenylacetyl chloride in CH_2Cl_2. The 1,8-bisurea anthracene **1** was synthesized following the published procedures.[3i]

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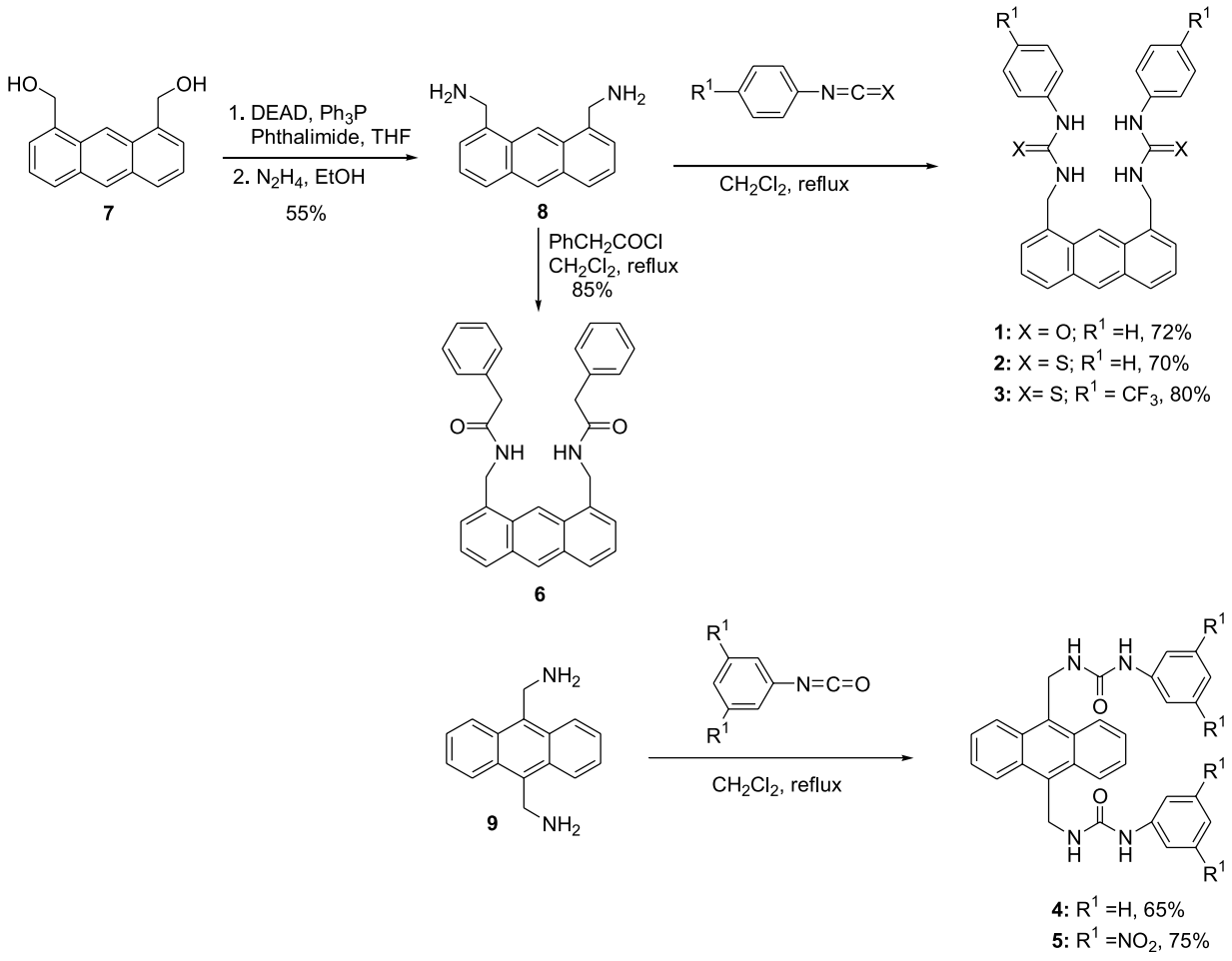

Scheme 1. Synthesis of bisurea derivatives (**1**–**6**).

Gunnlaugsson et al. reported[3j] that the 9,10-thiourea anthracene derivatives effectively recognized pyrophosphate, glutarate and malonate with 1:1 binding. In the case of $H_2PO_4^-$, we find that it involves with 1:2 binding based on the NMR experiments. Similar results were also observed for receptors **4** and **5** upon the addition of pyrophosphate and $H_2PO_4^-$. Based on the NMR titration experiments (Fig. 1) as well as the Job plots, 1:1 binding with pyrophosphate and 1:2 binding with **5** were confirmed. At a glance, it was expected that the 1,8-anthracene derivatives would form 1:1 bindings with $H_2PO_4^-$ as well as with pyrophosphate unlike the case of 9,10-anthracene derivative. However, the NMR titration experiments (Fig. 1) and Job plot (see Supporting Information) using fluorescence indicated that **1** also recognized pyrophosphate with 1:1 binding and $H_2PO_4^-$ with 1:2 binding. With $H_2PO_4^-$, the urea resonances were gradually shifted downfield by >1.2 ppm in DMSO-d_6, confirming the formation of an anion–receptor complex. In the case of pyrophosphate, the peak for the amide protons in the urea group severely broadens, therefore, the chemical shift changes in the 9-H of the anthracene moiety were examined instead of those in the amide protons.

The calculated structures of host **1** with dihydrogen phosphate, pyrophosphate and dicarboxylate anions demonstrate interesting binding features. As shown in Figure 2, the

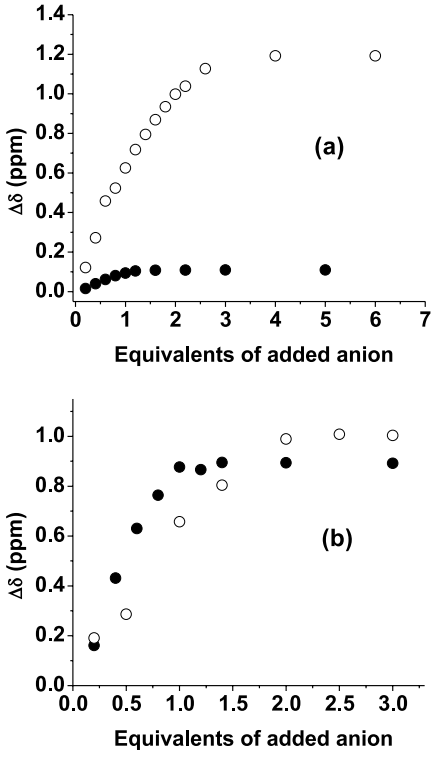

Figure 1. ^{1}H NMR titration of **1** (a) and **5** (b) with phosphate (○) and pyrophosphate (●) in DMSO-d_6.

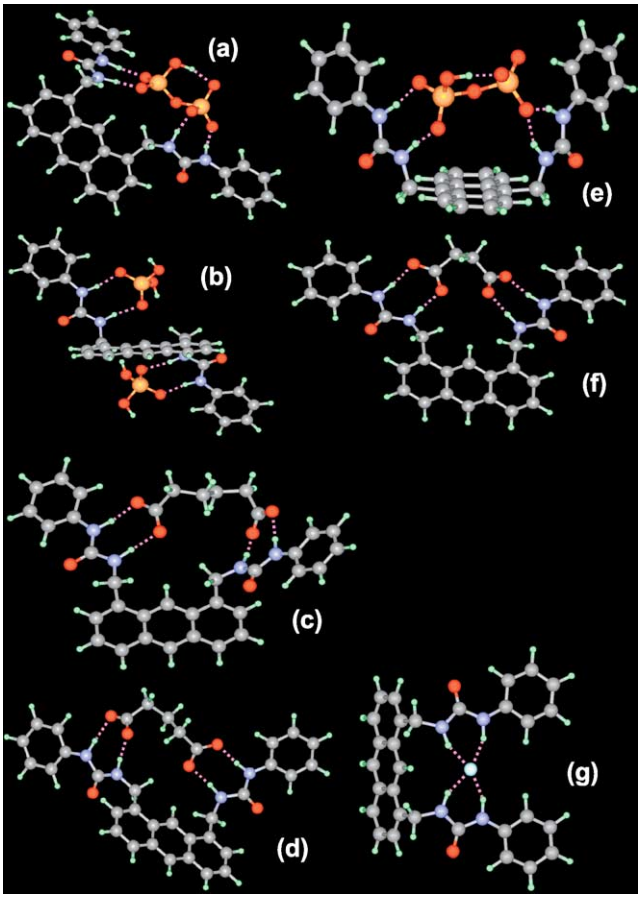

Figure 2. Calculated structures of **1**-pyrophosphate (a), **1**-2 $H_2PO_4^-$ (b), **1**-adipate (c), **1**-glutarate (d), **4**-pyrophosphate (e), **1**-succinate (f) and **1**-F^- (g).

unique tweezer-like binding modes of **1** with dihydrogen phosphate, pyrophosphate and dicarboxylates were observed. The two amide protons in each urea or thiourea group in **1** could make hydrogen bonds with the two negatively charged oxygens of $H_2PO_4^-$. As shown in Figure 2, the tweezer-like binding mode can provide two independent binding sites for $H_2PO_4^-$, which explains the 1:2 binding of **1** with $H_2PO_4^-$.

Since **1**, **2**, **3**, **4** and **6** are fluorescent, the binding affinities of these hosts for various anions (tetrabutylammonium salts of pyrophosphate, $H_2PO_4^-$, adipate, glutarate, succinate, malonate, $CH_3CO_2^-$, HSO_4^-, F^-, Cl^-, Br^- and I^-) were further examined using the fluorescence changes in acetonitrile–DMSO (9:1, v/v). **1** and **4** (6 μM) displayed large CHEQ (chelation enhanced quenching) effects with pyrophosphate, adipate, glutarate, succinate, malonate, $H_2PO_4^-$, $CH_3CO_2^-$ and F^-. From the fluorescence titration experiments of **1** (6 μM) with pyrophosphate (Fig. 3), adipate (Fig. 4), glutarate, succinate, malonate, F^-, Cl^-, Br^- and I^-, the association constants were calculated to be 101,300, 103,600, 23,400, 7780, 4880, 71,300, 610, 120 and 30 M^{-1} (errors $<10\%$), respectively (Table 1).[5] Therefore, pyrophosphate and adipate showed almost equal binding strengths toward **1** in acetonitrile–DMSO (9:1, v/v). The Job plot (see Supporting Information) using fluorescence indicated that **1** recognized adipate, glutarate, succinate, malonate and F^- with 1:1 binding. The association

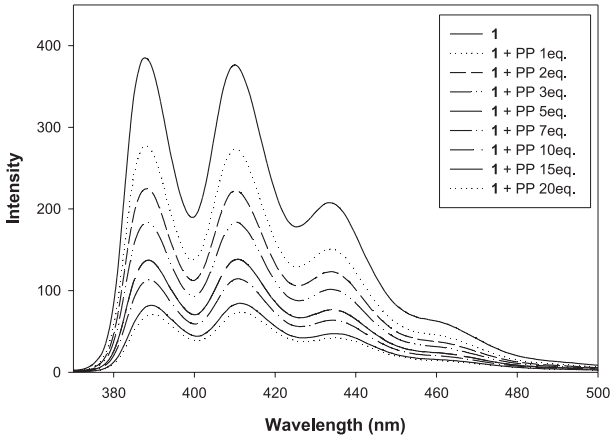

Figure 3. Fluorescent titrations of **1** (6 μM) with tris(tetrabutylammonium) hydrogenpyrophosphate in acetonitrile–DMSO (9:1, v/v) (excitation at 367 nm).

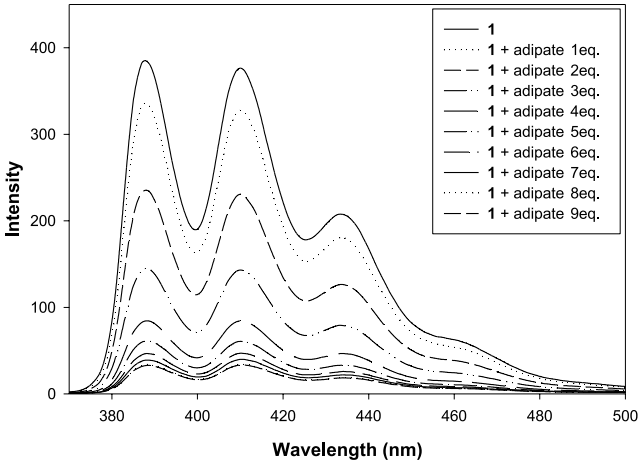

Figure 4. Fluorescent titrations of **1** (6 μM) upon the addition of di(tetrabutylammonium) adipate in acetonitrile–DMSO (9:1, v/v).

constants of **4** with pyrophosphate, adipate (Fig. 5), glutarate, succinate and malonate were calculated to be 12,400, 91,380, 20,960, 6900 and 3080 M^{-1} (errors $<10\%$), respectively (Table 1).[5] Even with this tweezer-like binding mode, the receptor **1** provides a relatively rigid and pre-organized binding site compared with that of **4**. Indeed, the association constant of **1** with pyrophosphate is approximately nine times larger than that of **4**.

Based on the fluorescent titration experiments the association constants of **2** and **3** with pyrophosphate were calculated to be 12,800 and 23,400, respectively. As expected, the electron withdrawing groups on the phenyl ring increases the binding affinities approximately twice.

On the other hand, host **6** did not show any fluorescent change after adding 100 equiv of anions, which means that urea or thiourea groups are certainly needed for the recognition of the anion.

Table 1 shows the ab initio calculation results[6] for **1**-anion and **4**-anion complexes. The calculated binding energies of **1** with $H_2PO_4^-$ in the gas phase showed that the 1:1 complex

Table 1. Experimental free energy changes and calculated interaction energy changes for **1**-anion complexes and **4**-anion complexes in kcal/mol

	Host	K_a (M^{-1})[a]	ΔG^{flou}_{expt}	$-\Delta E^{gas}_{calc}$	$-\Delta E^{MeCN}_{calc}$	$-\Delta G^{scaled}$
$HP_2O_7^{-3}$	**1**	101300	6.83	169.52	15.38	6.92
	4	12400	5.58	159.50	9.11	4.10
Adipate	**1**	103570	6.84	102.07	15.83	7.12
	4	91380	6.76	—	—	—
Glutarate	**1**	23400	5.96	111.23	12.13	5.46
	4	20960	5.89	—	—	—
Succinate	**1**	7780	5.31	112.57	11.78	5.30
	4	6900	5.23	—	—	—
Malonate	**1**	4880	5.03	126.82	9.81	4.41
	4	3080	4.76	—	—	—
$H_2PO_4^-$	**1**	—	—	61.62 (54.31)[b]	7.47 (14.53)	—
	4	—	—	36.21 (58.13)	−3.79 (6.78)	—
F^-	**1**	71300	6.62	78.95	12.69	5.71

[a] The association constants K_a (M^{-1}) were measured using Flourescence titration (25 °C). Anions used in this assay were in the form of their tetrabutylammonium salts. ΔG^{Flou}_{expt} is the change in Gibbs free energy as obtained from Fluorescence titrations. ΔE^{gas}_{calc} is the interaction energy in the gas phase by B3LYP/6-31(+)G* calculations. $\Delta E^{sol}_{calc}=\Delta E^{sol}_{1\text{-anion}}-\Delta E^{sol}_{sol-anion}-\Delta E^{sol}_{TBA-anion}$, where $\Delta E^{sol}_{1\text{-anion}}$ is the interaction energy of the **1**-anion complex in acetonitrile solution based on Isodensity surface polarized continuum model (IPCM), $\Delta E^{sol}_{sol-anion}$ is the interaction energy of the anion with solvent molecules in the first solvation shell of an anion, and $\Delta E^{sol}_{TBA-anion}$ (sol=MeCN) is the interaction energy of tetrabutylammonium with the anion in acetonitrile. The countercation correction (sutraction of $\Delta E^{sol}_{TBA-anion}$) is applied only to the F^- as this effect is almost negligible for other anions.[7] The free energy change was approximately obtained by scaling the internal energy change. To obtain realistic values in acetonitrile, ΔG^{scaled} was evaluated by scaling with 45 percent of the ΔE^{sol}_{calc}.

[b] Values in parantheses correspond to 1:2 complex.

was 7.3 kcal/mol more stable than the 1:2 complex, while in acetonitrile the 1:2 complex was 6.8 kcal/mol more stable than the 1:1 complex. It was also observed that **4** prefers 1:2 complexation with $H_2PO_4^-$. Among the pyrophosphate and dicarboxylates, glutarate is calculated to bind better to **1** in the gas phase. In acetonitrile, the binding energy gains of **1** with adipate over pyrophosphate, glutarate, succinate, and malonate were 0.45, 3.71, 4.05 and 6.02 kcal/mol, respectively. The free energy gain of the **1**-anion complexation in acetonitrile for adipate over pyrophosphate, glutarate, succinate, and malonate was 0.20, 1.66, 1.82 and 2.71 kcal/mol, respectively (which are in reasonable agreement with the corresponding experimental values: 0.01, 0.88, 1.53 and 1.81 kcal/mol, respectively). The calculations were carried out for the binding of **4** with $H_2PO_4^-$ and pyrophosphate. In acetonitrile the free energy change for the binding of **4** with pyrophosphate was predicted to be 4.10 kcal/mol, somewhat smaller than the experimental value (5.58 kcal/mol). Figure 2 shows the optimized

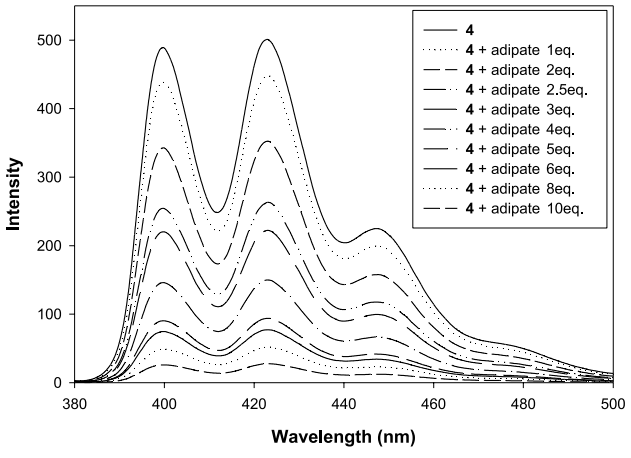

Figure 5. Fluorescent titrations of **4** (6 μM) upon the addition of di(tetrabutylammonium) adipate in acetonitrile–DMSO (9:1, v/v).

structures of **1** complexed with pyrophosphate, adipate and two $H_2PO_4^-$ molecules. On the other hand, among the dicarboxylates, considering the electron withdrawing nature of the aliphatic chains, the negative partial charge distribution at the carboxylate oxygen atoms will be the lowest in the case of adipate, and the highest in the case of malonate. For example, the average partial charges of the carboxylate oxygen atoms were −0.629, −0.635, −0.647 and −0.655 for adipate, glutarate, succinate,and malonate, respectively. Therefore, malonate would maximally bind to **1**. However, in this case the head to head H-bonding between the two oxygen atoms in each of the carboxyl groups with the two hydrogen atoms in each of the urea receptor arms is unfavorable due to the repulsion between the two negatively charged heads. Therefore, one of the carboxyl groups needs to be twisted at the cost of one head-to-head H-bond with the hydrogen atoms of one of the urea arm. In fact, the optimized geometry of the **1**-malonate shows that one carboxyl group forms head-to-head H-bonding while another carboxyl group does not (Fig. 2f). This decreases the binding with **1** with malonate. In the case of glutarate and succinate, the formation of head-to-head H-bonding with the hydrogen atoms of the urea arms creates strain on the connecting chain between the two carboxylic groups, thereby weakening the H-bonds. Even though the partial charge distribution on the carboxyl oxygen atoms of the adipate is the lowest among the dicarboxylates, there is the least strain on the aliphatic chain and the formation of H-bonding with the hydrogen atoms of both urea arms is much more favorable. On the other hand, the interaction between the malonate and the solvent molecules will be the largest among the above dicarboxylates. Therefore, upon considering above factors, the binding of different dicarboxylates with the anthracene-based bisurea receptors will be a compromise between the H-bonding, the strain on the connecting chain of the two carboxyl groups, and the ionic solvation energies of the anions in the solvent. Therefore, even though adipate has least partial negative charges on the carboxyl oxygen atoms, it binds most strongly with **1** among

the dicarboxylates because of the less strain on the connecting aliphatic chain and less interaction with the solvent molecules around it.

3. Conclusion

This study examined the binding properties of new anthracene derivatives for various anions using fluorescence, ^{1}H NMR, and ab initio calculations. The 1,8-bisurea anthracene derivative (**1**) showed a slightly better binding for dicarboxylates with 1:1 complexation than the 9,10-bisurea anthracene derivative (**4**). Among the dicarboxylates, both the 1,8 and 9,10 derivatives showed particularly strong bindings to the adipate. On the other hand, for pyrophosphate, only the 1,8-bisurea receptor was found to be particularly highly selective (i.e. 10 times more selective than the 9,10-bisurea receptor). Both of the derivatives were confirmed to form a 1:2 complexation with $H_2PO_4^-$, based on ^{1}H NMR and theoretical investigations. It was also demonstrated that the H-bonding, the strain on the connecting chain of the two carboxyl groups, and the ionic solvation energies of the anions in the solvent were three main factors determining the binding of the different dicarboxylates with the anthracene-based bisurea receptors.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. 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 thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with a thickness of 1 mm.

Melting points were measured using a Büchi 530 melting point apparatus, and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 9503 DPX 250 MHz. Chemical shifts were given in ppm and coupling constants (J) in Hz. Mass spectra were obtained using a JMS-HX 110A/110A Tandem Mass Spectrometer (JEOL).

4.1.1. 1,8-[Bis(phenylthiourea)methyl]anthracene 2. *Procedure A*. 1,8-Anthracenedimethanamine 8 was obtained in 53% yield from 1,8-anthracenedimethanol following the published procedure.[4] A solution of 1,8-anthracenedimethanamine **8** (60 mg, 0.254 mmol) and phenyl thioisocyanate (207 mg, 1.02 mmol) in dry CH_2Cl_2 (25 mL) was refluxed for 2 h. After cooling down to room temperature, the solid was filtered and washed with $CHCl_3$ followed by ethyl acetate. Analytically pure 2 was obtained in 70% yield (90 mg): mp 254 °C, dec; ^{1}H NMR (DMSO-d_6) δ 9.64 (brs, 2H), 8.89 (s, 1H), 8.68 (s, 1H), 8.24 (brs, 2H), 8.05 (d, 2H, J=7.5 Hz), 7.42–7.58 (m, 8H), 7.26–7.34 (m, 4H), 7.11 (t, 2H, J=7.5 Hz), 5.42 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 181.6, 139.9, 135.2, 131.9, 129.9, 129.3, 128.5, 128.3, 125.9, 125.7, 125.0, 124.2, 118.6, 46.4; HRMS (FAB) m/z=507.1678 $(M+H)^+$, calcd for $C_{30}H_{27}N_4S_2$=507.1677. Anal. Calcd for $C_{30}H_{26}N_4S_2$: C, 71.11; H, 5.17; N, 11.06. Found: C, 70.98; H, 5.08; N, 11.23.

4.1.2. 1,8-[Bis(4-trifluoromethylphenylthiourea)methyl] anthracene 3. Application of procedure A to 60 mg of 1,8-anthracenedimethanamine 8 (0.254 mmol) and 207 mg of 4-trifluoromethylphenyl thioisocyanate (1.02 mmol) in dry CH_2Cl_2 (25 mL) gave 130 mg of **3** (80% yield): mp 248 °C, dec; ^{1}H NMR (DMSO-d_6) δ 9.97 (brs, 2H), 8.89 (s, 1H), 8.70 (s, 1H), 8.54 (brs, 2H), 8.07 (t, 2H, J=5.8 Hz), 7.78 (d, 4H, J=8.6 Hz), 7.63 (d, 4H, J=8.6 Hz), 7.51–7.57 (m, 4H), 5.43 (d, 4H, J=4.3 Hz); ^{13}C NMR (DMSO-d_6) δ 189.8, 144.2, 134.9, 132.1, 130.1, 128.7, 127.4, 126.4, 126.1, 124.0, 123.1, 118.8, 117.9, 55.7, 46.6; HRMS (FAB) m/z=643.1431 $(M+H)^+$, calc. for $C_{32}H_{25}F_6N_4S_2$=643.1425. Anal. Calcd for $C_{32}H_{24}F_6N_4S_2$: C, 59.80; H, 3.76; N, 8.72. Found: C, 59.58; H, 3.54; N, 8.98.

4.1.3. 9,10-[Bis(phenylurea)methyl]anthracene 4. Application of procedure A to 60 mg of 9,10-anthracenedimethanamine (0.254 mmol) and 142 mg of phenyl isocyanate (1.02 mmol) in dry CH_2Cl_2 (25 mL) gave 78 mg of **4** (65% yield): mp 248 °C, dec; ^{1}H NMR (DMSO-d_6) δ 8.61 (s, 2H), 8.53 (m, 4H), 7.63 (m, 4H), 7.39 (d, 4H, J=8.9 Hz), 7.20 (d, 4H, J=7.4 Hz), 6.88 (m, 4H), 5.32 (d, 4H, J=4.8 Hz); ^{13}C NMR (DMSO-d_6) δ 155.8, 141.3, 132.2, 130.5, 129.4, 126.8, 125.9, 121.8, 118.4, 36.2; HRMS (FAB) m/z=475.2133 $(M+H)^+$, calcd for $C_{30}H_{27}N_4O_2$=475.2137.

4.1.4. 9,10-[Bis(3,5-dinitrophenylurea)methyl]anthracene 5. Application of procedure A to 60 mg of 9,10-anthracenedimethanamine (0.254 mmol) and 250 mg of 3,5-dinitrophenyl isocyanate (1.02 mmol) in dry CH_2Cl_2 (25 mL) gave 125 mg of **5** (75% yield): mp 297 °C, dec; ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 2H), 8.66 (brs, 4H), 8.59 (m, 4H), 8.35 (brs, 2H), 7.67 (m, 4H), 7.16 (brs, 2H), 5.41 (d, 4H, J=4.7 Hz); ^{13}C NMR (DMSO-d_6) δ 155.1, 148.9, 143.4, 131.7, 130.4, 126.8, 125.8, 117.7, 110.7, 36.3; FAB MS m/z=655.2 $(M+H)^+$, calc. for $C_{30}H_{23}N_8O_{10}$=655.2. Anal. Calcd for $C_{30}H_{22}N_8O_{10}$: C, 55.05; H, 3.39; N, 17.12. Found: C, 55.35; H, 3.42; N, 17.12.

4.1.5. *N*,*N*′-[1,8-Anthrylbis(methylene)]bis-benzeneacetamide 6. Application of procedure A to 60 mg of 1,8-anthracenedimethanamine (0.254 mmol) and 157 mg of 3,5-dinitrophenyl isocyanate (1.02 mmol) in dry CH_2Cl_2 (25 mL) gave 102 mg of **6** (85% yield): mp 256 °C, dec; ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.63 (m, 3H), 8.01 (d, 2H, J=4.3 Hz), 7.47 (t, 2H, J=3.3 Hz), 7.41 (d, 2H, J=3.5 Hz), 7.29 (t, 4H, J=3.8 Hz), 7.25 (d, 4H, J=3.8 Hz), 7.20 (t, 2H, J=3.5 Hz), 4.85 (d, 4H, J=3.0 Hz), 3.54 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 172.1, 137.1, 135.9, 132.0, 129.9, 129.7, 128.9, 128.3, 128.1, 127.1, 125.9, 125.3, 118.8, 43.2, 41.3; HRMS (FAB) m/z=473.2224 $(M+H)^+$, calcd for $C_{32}H_{29}N_2O_2$=473.2229. Anal. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.05; H, 6.00; N, 6.08.

4.2. Preparation of fluorometric anion titration solutions

Stock solutions (1 mM) of the tetrabutylammonium salts of

$H_2PO_4^-$, HSO_4^-, $CH_3CO_2^-$, F^-, Cl^-, Br^-, I^-, pyrophosphate, adipate, glutarate, succinate and malonate in CH_3CN were prepared. Stock solutions of hosts (0.1 mM) were prepared in DMSO. Test solutions were prepared by placing 4–40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with CH_3CN–DMSO.

For all measurements, excitation was at 367 nm; emission was measured at 420 nm. Both excitation and emission slit widths were 3 nm.

4.3. NMR experiments

All NMR experiments were performed on a Bruker 9503 DPX (250 MHz). A solution (6 mM) of hosts in DMSO-d_6 was titrated with an aliquot of a stock solution (10 mM) of guests as tetrabutylammonium salts in the same solvent. 1,8-Bis(aminomethyl)anthracene **2**[6] was synthesized following the published procedure.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.009

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Stereoselective total synthesis of (*S*)-Virol C and (*S*)-1-dehydroxyvirol A

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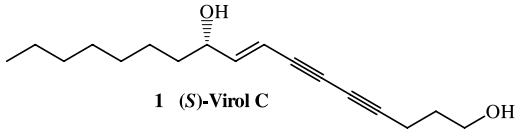
Abstract—A stereoselective total synthesis of (*S*)-Virol C and (*S*)-1-dehydroxyvirol A has been developed, based upon the selective and sequential substitution of the two trimethylsilyl groups of readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.

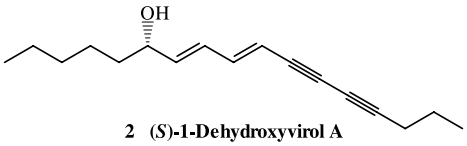
1. Introduction

Water hemlock, *Cicuta virosa* (*Umbelliferae*), is a well-known toxic plant widely distributed in temperate regions. The main toxic component of the plant is cicutoxin,[1] a chemical belonging to the class of conjugated polyacetylenes, which was shown to induce tonic and clonic convulsion and respiratory paralysis by acting directly on the central nervous system. Recently, cicutoxin and related polyacetylenic alcohols, congeners of cicutoxin, such as isocicutoxin, Virol A and Virol C have been isolated from *C. virosa* and their stereostructures elucidated on the basis of spectroscopic analysis.[2] Some of these cicutoxin analogues have been synthesized by stereoselective routes[3–6] to confirm their stereochemistry and to obtain supply of these compounds for pharmacological study.

We have recently reported a straightforward and general route to a variety of unsymmetrical conjugated diynes, based upon the selective and sequential substitution of the trimethylsilyl groups of the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne with alkyl, aryl and vinyl groups.[7] We have successfully applied the above methodology to the synthesis of polyacetylenic compounds, such as dihydroxerulin and xerulin, potent inhibitors of the biosynthesis of cholesterol,[8] and of Montiporic acids A and B, bioactive metabolites from *Montipora digitata*, possessing antibacterial and cytotoxic properties.[9] In connection with our ongoing work, we report here the total synthesis of (*S*)-Virol C[3,5,6] **1** and (*S*)-1-dehydroxyvirol A **2**, a Virol A derivative.[4]



1 (*S*)-Virol C



2 (*S*)-1-Dehydroxyvirol A

2. Results and discussion

Our overall retrosynthesis is summarized in Schemes 1 and 2. In the case of (*S*)-Virol C the stereogenic center can be obtained by enantioselective chemical reduction of the carbonyl group of the polyunsaturated compound **3**. The double disconnection of the C_3–C_4 and C_7–C_8 bonds of compound **3** affords the conjugated diyne **4**, which, after appropriate desilylation reactions, can be subjected to coupling reactions involving, respectively, an alkylation reaction with the halide **6**, followed by a coupling reaction with the keto vinyl derivative **5**.

In a similar manner, in the case of (*S*)-1-dehydroxyvirol A, the stereogenic center can be obtained by enantioselective chemical reduction of the carbonyl group of the polyunsaturated compound **7**. The double disconnection of the

Keywords: Silicon and compounds; Polyacetylenes; Coupling reactions; Enantioselective reductions.
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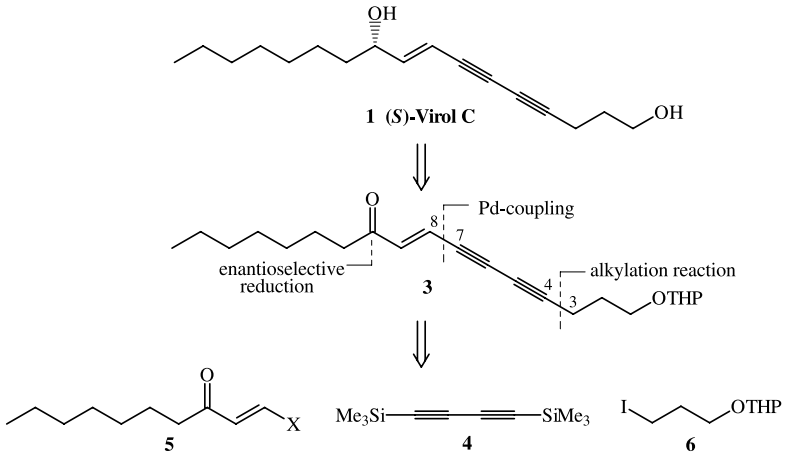
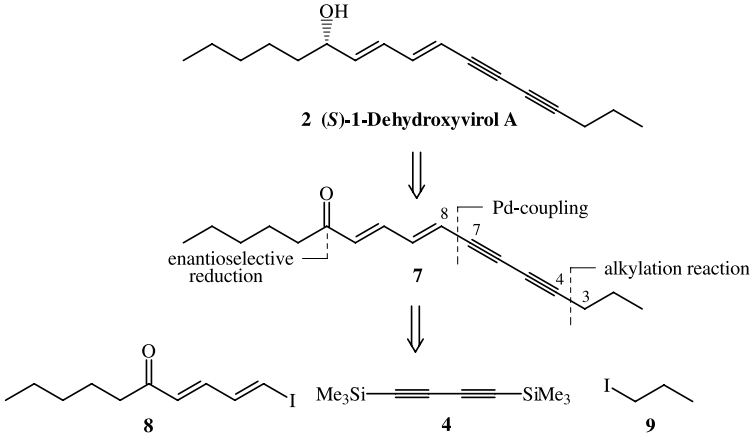
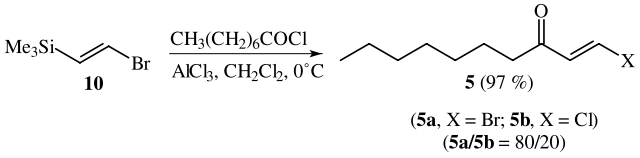


Scheme 1.



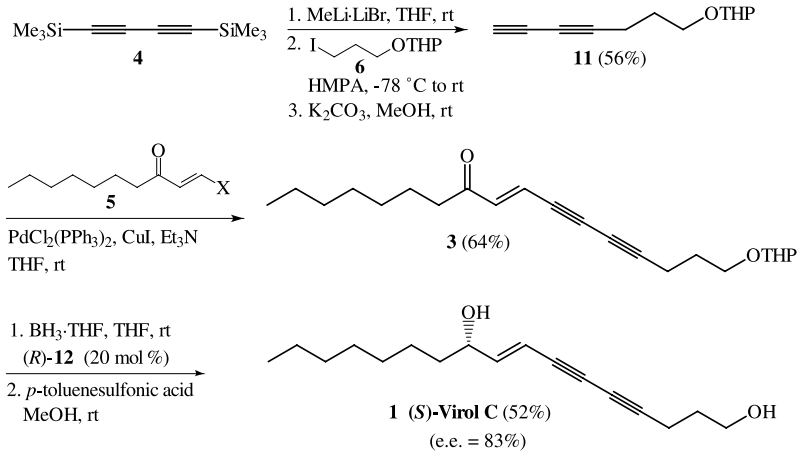
Scheme 2.



Scheme 3.

C_3–C_4 and C_7–C_8 bonds of compound **7** can lead to the same conjugated diyne **4**, which can be subjected to an alkylation reaction with the halide **9**, followed by a coupling reaction with the keto dienyl derivative **8**.

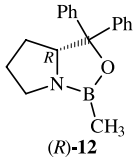
Accordingly, the synthesis of (*S*)-Virol C started with the preparation of the basic fragment **5**. This compound was obtained in 97% yield by a simple acylation reaction[10] of



Scheme 4.

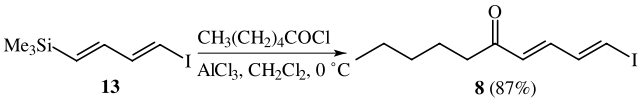
(*E*)-1-bromo-2-trimethylsilylethene **10** with the octanoyl chloride–$AlCl_3$ complex, as a mixture of compound **5a** (the (*E*)-bromovinylketone) and compound **5b** (the (*E*)-chlorovinylketone) (Scheme 3).

Then, the total synthesis of (*S*)-Virol C was performed as depicted in Scheme 4. To obtain compound **11**,[3] the diyne **4** was selectively desilylated with MeLi–LiBr complex affording the lithium salt of the mono-silylated terminal diyne[11] which was alkylated with 3-iodo-1-propanol tetrahydropyranyl ether **6**. Subsequent desilylation reaction with K_2CO_3 in MeOH led to terminal diyne **11**[3] (56% yield) which was subjected to a Pd(II)-catalyzed cross-coupling reaction[12] with the halovinylketone **5** to give the conjugated enediyne **3** in 64% yield. The CBS (Corey, Bakshi, Shibata) enantioselective reduction of the carbonyl group of compound **3** with borane catalyzed by (*R*)-2-methyloxazaborolidine **12**,[13] followed by the deprotection reaction with *p*-toluenesulfonic acid completed the sequence leading to (*S*)-Virol C **1** (52% yield, 83% ee).



(*R*)-**12**

The synthesis of (*S*)-1-dehydroxyvirol A **2** was realized employing the same synthetic approach. Thus, the basic fragment **8** was synthesized in 87% yield and with a high stereoselectivity (≥97%) by a simple acylation reaction of (1*E*,3*E*)-1-iodo-4-trimethylsilylbuta-1,3-diene **13**[14] with the hexanoyl chloride–$AlCl_3$ complex (Scheme 5).



13 **8** (87%)

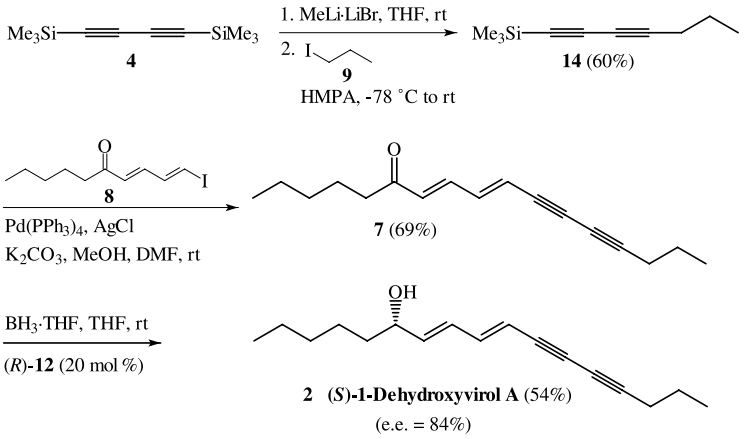
Scheme 5.

The total synthesis of (*S*)-1-dehydroxyvirol A was performed as depicted in Scheme 6. Compound **14** was obtained in 60% yield according to our reported procedure,[8] then coupled directly with the iododerivative **8** in the presence of a K_2CO_3/MeOH and a catalytic amount of AgCl and $Pd(PPh_3)_4$[7,15] affording the polyunsaturated ketone **7** in 69% yield. Finally, the enantioselective reduction of the carbonyl group of compound **7** with borane catalyzed by (*R*)-**12** completed the sequence leading to (*S*)-1-dehydroxyvirol A **2** in 54% yield (84% ee). It is noteworthy that as a chiral reagent for the enantioselective reduction was selected as catalyst the oxazaborolidine that afforded the higher enantiomeric enrichments. Indeed, several attempts were performed with the (*S*)-BINAL-H[16] reagent, obtaining higher yields (in the range 76–97%), but lower ee (in the range 38–70%) for compounds **1** and **2**.

In conclusion, we believe that our synthetic approach to both compounds **1** and **2** compares favorably with other synthetic procedures as far as number of steps and chemical yields. A special advantage of our strategy is represented by the possibility of starting from a common intermediate and of employing the same reaction sequence. Moreover, in principle, both stereogenic centers can be obtained by the same chiral reagent used in both opposite configurations. Taking also into account the ready availability of the starting materials, the mild reaction conditions and the experimental simplicity of the operations involved we believe that our approach is very useful.

3. Experimental

Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a J & W capillary column (DB-1301, 30 m×0.25 mm id). GC/mass-spectrometry analysis was performed on a Shimadzu GCMS-QP5000 gas chromatograph-mass spectrometer equipped with a Zebron capillary column (methyl polysiloxane, 30 m×0.25 mm id). ^{1}H-NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer. ^{13}C NMR spectra were recorded in deuterochloroform or acetone-d_6 on a Bruker AM 500 spectrometer. IR spectra were recorded on a Perkin–Elmer FT-IR 1710 spectrometer. Elemental analyses were recorded on a Carlo Erba EA 1108 elemental analyzer. Optical rotations were measured at 589 nm with a Perkin–Elmer 343 polarimeter. Enantiomeric excesses were



4 **9** **14** (60%) **8** **7** (69%) **2** (*S*)-**1-Dehydroxyvirol A** (54%) (e.e. = 84%)

Scheme 6.

evaluated using HPLC with a Chiralcel OD-H column (Daicel) on an Agilent 1100 instrument. Melting points (uncorrected) were determined on a Reichert Microscope. Solvents were dried before use as follows: methylene chloride was distilled over phosphorus pentoxide, *N*,*N*-dimethylformamide was distilled over molecular sieves and tetrahydrofuran was distilled from sodium. (*R*)-2-Methyl-CBS-oxazaborolidine **12** and 1,4-bis(trimethylsilyl)-1,3-butadiyne **4**[7] were purchased from Aldrich.

3.1. Synthesis of (*S*)-Virol C

3.1.1. 2-(Hepta-4,6-diynyloxy)-tetrahydro-2*H*-pyran (11).[3] MeLi–LiBr complex (1.5 M) in ether (6.83 mL, 10.24 mmol) was added, under nitrogen, to a THF solution (18 mL) of 1,4-bis(trimethylsilyl)-1,3-butadiyne **4** (1.80 g, 9.3 mmol) at room temperature. After complete desilylation (5 h), the reaction mixture was cooled to −80 °C and HMPA (3.24 mL, 18.60 mmol) was added. A solution of **6** (2.51 g, 9.3 mmol) in THF (18 mL) was slowly dropped at the same temperature, then the mixture was slowly brought to room temperature. After reaction completion (18 h), the mixture was quenched with a saturated aqueous solution of NaCl (100 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. After percolation on florisil column (20% ethyl acetate/petroleum ether) the residue was dissolved in methanol (18 mL) and K_2CO_3 (1.54 g, 11.15 mmol) was added at room temperature. The reaction mixture was stirred for 1.5 h, then concentrated under vacuum. A saturated aqueous solution of NaCl (100 mL) was added, then the reaction mixture extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (10% ethyl acetate/petroleum ether) leading to the title compound **11** as a pale yellow oil (1.0 g, 56% yield).

The spectral data of compound **11** are in accordance with the literature.[3]

3.1.2. (1*E*)-1-Bromodec-1-en-3-one (5a) and (1*E*)-1-chlorodec-1-en-3-one (5b). A CH_2Cl_2 solution (10 mL) of freshly distilled octanoyl chloride (1.09 g, 6.7 mmol) was added, under nitrogen, to a cold (0 °C) suspension of anhydrous $AlCl_3$ (0.89 g, 6.7 mmol) in 10 mL of CH_2Cl_2. The resulting mixture was stirred for 10 min at 0 °C, then a solution of (*E*)-1-bromo-2-trimethylsilylethene **10** (1.0 g, 5.58 mmol) in 10 mL of CH_2Cl_2 was added dropwise. After complete addition, the reaction mixture was stirred at 0 °C for 1 h, quenched with a saturated aqueous solution of NH_4Cl (50 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (5% ethyl acetate/petroleum ether) leading to a 80:20 mixture of (1*E*)-1-bromodec-1-en-3-one **5a** and (1*E*)-1-chlorodec-1-en-3-one **5b** (1.21 g, 97% yield) as a colorless oil. The mixture of **5a** and **5b** was employed for the preparation of compound **3**.

5a)+(**5b**. δ_H (500 MHz, $CDCl_3$) 7.47 (d, J=14.0 Hz, vinylic H of **5a**), 7.24 (d, J=13.5 Hz, vinylic H of **5b**), 6.74 (d, J=14.0 Hz, vinylic H of **5a**), 6.47 (d, J=13.5 Hz, vinylic H of **5b**), 2.46 (t, J=7.4 Hz, 2H), 1.58–1.50 (m, 2H), 1.27–1.16 (m, 8H), 0.82 (t, J=6.9 Hz, 3H).

5a. MS *m*/*z* 153 (23), 150 (56), 148 (60), 135 (65), 133 (62), 107 (15), 105 (14), 83 (14), 69 (23), 57 (31), 55 (46), 43 (53), 42 (27), 41 (100%).

5b. MS *m*/*z* 153 (17), 106 (24), 104 (76), 91 (32), 89 (100), 69 (15), 61 (19), 57 (15), 55 (25), 53 (11), 43 (44), 42 (22), 41 (84%).

3.1.3. (9*E*)-17-(Tetrahydropyranyl-2-oxy)-eptadec-9-en-11,13-diyn-8-one (3). A solution of diyne **11** (0.774 g, 4.03 mmol) in THF (20 mL) was added at room temperature, under nitrogen, to a stirred mixture of **5** (0.90 g, 4.03 mmol), $PdCl_2(PPh_3)_2$ (0.060 g, 0.08 mmol), CuI (0.031 g, 0.16 mmol) and Et_3N (0.84 mL, 6.05 mmol) in THF (20 mL). After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NaCl (50 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (10% ethyl acetate/petroleum ether) leading to compound **3** as a pale yellow oil (0.887 g, 64% yield). [Found: C, 76.75; H, 9.43. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36%]; ν_{max} (neat) 2929, 2856, 2229, 1692, 1589, 1465, 1455, 1440, 1383, 1368, 1354, 1201, 1136, 1122, 1076, 1035, 958 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.55 (d, J=16.0 Hz, 1H), 6.49 (d, J=16.0 Hz, 1H), 4.52–4.49 (m, 1H), 3.80–3.69 (m, 2H), 3.45–3.35 (m, 2H), 2.44 (t, J=7.4 Hz, 2H), 2.42 (t, J=7.0 Hz, 2H), 1.82–1.69 (m, 3H), 1.66–1.58 (m, 1H), 1.56–1.40 (m, 6H), 1.25–1.13 (m, 8H), 0.79 (t, J=7.0 Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 198.6, 139.0, 121.7, 98.6, 88.4, 83.5, 72.0, 65.4, 65.0, 62.0, 41.1, 31.5, 30.4, 29.0, 28.9, 28.1, 25.3, 23.8, 22.4, 19.3, 16.5, 13.9; MS *m*/*z* 259 (8), 217 (7), 203 (5), 189 (26), 176 (18), 161 (9), 147 (7), 145 (7), 143 (6), 131 (9), 129 (9), 115 (19), 85 (100), 77 (11), 67 (30), 57 (60), 55 (49), 43 (82), 41 (88%).

3.1.4. (10*S*)-(8*E*)-Heptadec-8-en-4,6-diyn-1,10-diol (Virol C) 1.[3,5] 0.61 mL (0.61 mmol) of a 1.0 M THF solution of BH_3THF were added at room temperature, under nitrogen, to 0.10 mL (0.10 mmol) of a 1.0 M solution of (*R*)-2-methyl-CBS-oxazaborolidine in toluene and stirred for 5 min. A solution of 0.175 g of ketone **3** (0.51 mmol) in 2.5 mL of THF was dropped, then the reaction mixture was stirred for 1 h. After addition of 20 mL of water, the mixture was extracted with ethyl acetate (3×20 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by percolation on florisil column (10% ethyl acetate/petroleum ether), dissolved in CH_3OH (2 mL), then *p*-toluenesulfonic acid monohydrate (0.019 g, 0.1 mmol) was added at room temperature. After reaction completion (1 h), the mixture was quenched with water (20 mL), and extracted with ethyl acetate (3×20 mL). The organic extracts dried over Na_2SO_4 and concentrated under vacuum. The residue was percolated on florisil (50% ethyl acetate/petroleum ether) affording 0.070 g of Virol C (52% yield, 83% ee determined by

HPLC, hexane/2-propanol 90/10, 0.5 mL/min), $[\alpha]_D = +6.4$ ($c=0.81$, CH_3OH), lit.[2] $[\alpha]_D = +6.4$ ($c=0.82$, CH_3OH). After crystallization from diethyl ether/hexane, Virol C **1** was obtained as a white solid (mp 56–58 °C). [Found: C, 77.79; H, 9.95. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99%]; ν_{max} (KBr) 3318, 3235, 2954, 2931, 2853, 2237, 1622, 1463, 1423, 1133, 1061, 1037, 1017, 961, 725 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.24 (dd, $J=15.9$, 5.8 Hz, 1H), 5.69 (dd, $J=15.9$, 1.4 Hz, 1H), 4.13 (dq, $J=1.4$, 5.8 Hz, 1H), 3.71 (t, $J=6.5$ Hz, 2H), 2.43 (t, $J=6.5$ Hz, 2H), 1.87 (br s, 2H), 1.76 (quintet, $J=6.5$ Hz, 2H), 1.53–1.45 (m, 2H), 1.37–1.18 (m, 10H), 0.85 (t, $J=6.9$ Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 148.9, 108.5, 83.5, 74.7, 73.3, 72.1, 65.5, 61.3, 36.9, 31.8, 30.9, 29.4, 29.2, 25.2, 22.6, 16.1, 14.1; MS *m/z* 217 (1), 191 (1), 177 (2), 163 (6), 145 (2), 135 (8), 127 (10), 115 (9), 107 (8), 91 (15), 77 (13), 57 (100), 55 (21), 43 (45), 41 (32%).

3.2. Synthesis of 1-dehydroxyvirol A

3.2.1. 1-Trimethylsilyl-1,3-heptadiyne (14). This compound was prepared in 60% yield (yellow oil) according to our reported procedure.[8] [Found: C, 73.00; H, 9.88. $C_{10}H_{16}Si$ requires C, 73.10; H, 9.81%]; ν_{max} (neat) 2964, 2937, 2902, 2875, 2227, 2109, 1460, 1251, 1181, 846, 761, 630 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.23 (2H, t, $J=7.2$ Hz), 1.53 (2H, sextet like $J=7.2$ Hz) 0.97 (3H, t, $J=7.2$ Hz), 0.16 (9H, s); δ_C (125.7 MHz, $CDCl_3$) 88.4, 83.0, 80.1, 65.5, 21.6, 21.2, 13.5, −0.3; MS *m/z* 164 (M^+, 7), 150 (15), 149 (100), 121 (6), 120 (7), 107 (7), 105 (7), 93 (5), 91 (7), 83 (11), 79 (9), 77 (6), 73 (3), 69 (4), 67 (7), 53 (10), 43 (25%).

3.2.2. (1*E*,3*E*)-1-Iodo-deca-1,3-dien-5-one (8). A CH_2Cl_2 solution (10 mL) of freshly distilled hexanoyl chloride (0.894 g, 6.64 mmol) was added, under nitrogen, to a cold (0 °C) suspension of anhydrous $AlCl_3$ (0.885 g, 6.64 mmol) in 10 mL of CH_2Cl_2. The resulting mixture was stirred for 10 min at 0 °C, then a solution of (1*E*,3*E*)-1-iodo-4-trimethylsilylbutadiene **13** (1.395 g, 5.53 mmol) in 14 mL of CH_2Cl_2 was added dropwise. After complete addition, the reaction mixture was stirred at 0 °C for 2 h, quenched with 0.1 N HCl (50 mL), and extracted with ethyl acetate (3× 50 mL). The organic extracts were washed with water (3× 50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by percolation on florisil column (10% ethyl acetate/petroleum ether) affording 1.343 g of compound **8** (87% yield), which was immediately employed for the preparation of compound **7**. δ_H (500 MHz, $CDCl_3$) 7.11 (dd, $J=14.4$, 11.2 Hz, 1H), 6.95 (dd, $J=15.4$, 11.2 Hz, 1H), 6.93 (d, $J=14.4$ Hz, 1H), 6.12 (d, $J=15.4$ Hz, 1H), 2.47 (t, $J=7.4$ Hz, 2H), 1.55 (quintet, $J=7.4$ Hz, 2H), 1.30–1.17 (m, 4H), 0.83 (t, $J=7.0$ Hz, 3H).

3.2.3. (7*E*,9*E*)-Heptadeca-7,9-dien-11,13-diyn-6-one (7). To a solution of iodide **8** (1.343 g, 4.83 mmol) in anhydrous DMF (12 mL) at room temperature, under nitrogen, were successively added $Pd(PPh_3)_4$ (0.278 g, 0.24 mmol), AgCl (0.138 g, 0.96 mmol) and K_2CO_3 (5.332 g, 38.64 mmol). The resulting mixture was stirred for 5 min, then MeOH (1.236 g, 38.64 mmol), was added followed by a solution of the diyne **14** (0.792 g, 4.82 mmol) in anhydrous DMF (12 mL). The reaction mixture was warmed to 40 °C and stirred at the same temperature. After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (10% ethyl acetate/petroleum ether) leading to 0.807 g of compound **7** (69% yield). After crystallization from hexane, the title compound was obtained as a white solid (mp 65–67 °C). [Found: C, 84.35; H, 9.20. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%]; ν_{max} (KBr) 3041, 2960, 2932, 2871, 2219, 1682, 1593, 1575, 1460, 1335, 1126, 1072, 1005 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.07 (dd, $J=15.3$, 11.3 Hz, 1H), 6.68 (dd, $J=15.3$, 11.3 Hz, 1H),), 6.18 (d, $J=15.3$ Hz, 1H), 5.96 (d, $J=15.3$ Hz, 1H), 2.49 (t, $J=7.5$ Hz, 2H), 2.28 (t, $J=6.9$ Hz, 2H), 1.60–1.49 (m, 4H), 1.31–1.18 (m, 4H), 0.95 (t, $J=7.4$ Hz, 3H), 0.83 (t, $J=7.0$ Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 200.2, 141.6, 140.0, 131.3, 118.8, 88.0, 81.1, 73.4, 65.2, 40.9, 31.3, 23.8, 22.3, 21.6, 13.8, 13.3; MS *m/z* 242 (M^+, 4), 213 (4), 185 (11), 171 (9), 157 (7), 152 (9), 143 (7), 128 (26), 115 (18), 95 (8), 91 (7), 77 (8), 71 (12), 65 (7), 63 (8), 55 (14), 51 (9), 43 (100), 41 (34%).

3.2.4. (6*S*)-(7*E*,9*E*)-Heptadeca-7,9-dien-11,13-diyn-6-ol (1-dehydroxyvirol A) 2.[4] 0.50 mL (0.50 mmol) of a THF solution (1.0 M) of BH_3. THF were added at room temperature, under nitrogen, to 0.083 mL (0.083 mmol) of a toluene solution (1.0 M) of (*R*)-2-methyl-CBS-oxazaborolidine and stirred for 5 min. A solution of 0.10 g of ketone **7** (0.413 mmol) in 2 mL of THF was dropped, then the reaction mixture was stirred for 1 h. After addition of 20 mL of water, the mixture was extracted with ethyl acetate (3×20 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (10% ethyl acetate/petroleum ether) leading to 0.055 g (54% yield) of dehydroxyvirol A **2** as a pale yellow oil (84% ee determined by HPLC, hexane/2-propanol 97/3, 0.5 mL/min). $[\alpha]_D = +16.5$ ($c=0.60$, CH_3OH), lit.[4] $[\alpha]_D = +15.4$ ($c=0.67$, CH_3OH). [Found: C, 83.59; H, 9.85. $C_{17}H_{24}O$ requires C, 83.55; H, 9.90%]; ν_{max} (neat) 3366, 3024, 2959, 2931, 2864, 2228, 2136, 1636, 1588, 1459, 1383, 985 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.63 (dd, $J=15.6$, 10.9 Hz, 1H), 6.22 (dd, $J=15.3$, 10.9 Hz, 1H), 5.80 (dd, $J=15.3$, 6.4 Hz, 1H), 5.57 (d, $J=15.6$ Hz, 1H), 4.14 (q, $J=6.4$ Hz, 1H), 2.27 (t, $J=7.0$ Hz, 2H), 1.79 (br s, 1H), 1.59–1.44 (m, 4H), 1.35–1.20 (m, 6H), 0.96 (t, $J=7.4$ Hz, 3H), 0.85 (t, $J=6.9$ Hz, 3H); δ_C (125.7 MHz, acetone-d_6) 145.7, 143.3, 128.7, 109.7, 86.1, 77.3, 75.4, 71.9, 66.3, 38.3, 32.7, 26.0, 23.5, 22.6, 21.9, 14.5, 13.8; MS *m/z* 215 (3), 202 (2), 201 (2), 187 (2), 173 (8), 145 (9), 131 (85), 129 (6), 128 (8), 117 (9), 115 (15), 105 (6), 99 (7), 95 (9), 91 (13), 77 (11), 71 (22), 55 (12), 43 (100), 41 (29%).

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Short synthesis of new salacinol analogues and their evaluation as glycosidase inhibitors

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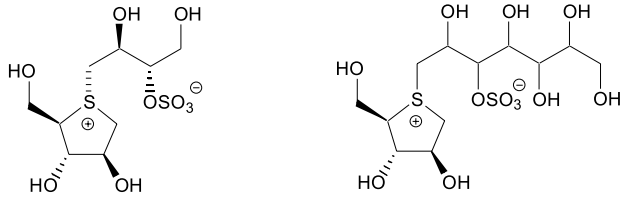
Abstract—Versatile synthesis of some analogues of the naturally-occurring α-glucosidase inhibitor salacinol (**1**), involving thioanhydro alditol moieties with *erythro*, D,L-*threo*, *xylo*, *ribo*, D-*arabino* and D-*manno* configurations is described. Nucleophilic attack at the least-hindered carbon atom of an L- or D-protected erythritol cyclic sulfate by the thioanhydro alditol sulfur atom yielded the desired zwitterionic compounds. In addition, the preparation of the cyclic sulfates of 2,4-*O*-benzylidene-D-erythritol and 2,4-*O*-isopropylidene-L-erythritol was improved. Enzyme inhibition tests showed that most of the new compounds were weak but specific inhibitors, while good inhibitory activity was found for a six-membered ring analogue (β-glucosidase: $K_i = 16$ μM).

1. Introduction

Salacinol **1** and kotalanol **2** are α-glucosidase inhibitors isolated from the Hippocrateaceae plant *Salacia reticulata* WIGHT, a large woody climbing plant widespread in Sri Lanka and South India (Fig. 1). Extracts of this plant have been traditionally used in the Ayurvedic system of Indian medicine as a treatment for non-insulin-dependent diabetes.[1] The methanol extract from the roots and stems of *S. reticulata* is reported to show inhibitory activity against the increase in serum glucose levels after the administration of sucrose or maltose in rats.[1b] It was demonstrated that **1** and **2** were responsible for this inhibitory activity.[1a,c] These novel glycosidase inhibitors have unique zwitterionic structures in which the sulfonium cation is stabilized by the sulfate anion. It is assumed that the sulfonium center permanently mimics the incremental positive charge that forms at both the ring oxygen and the anomeric carbon of the glycoside during hydrolysis in the active site of a glycosidase. Variation of the chiral centers and/or ring sizes would be expected to modulate the binding interactions and consequently modulate the specificity towards the glycosidases.[2,3] In view of both its very high glycosidase inhibitory activity and its novel structure, chemists have conducted much research on the total synthesis of **1** and its analogues. As the absolute configurations of the kotalanol **2** side chain have not yet been established, all the work has focused on salacinol.[3–7] Nitrogen and selenium analogues have also been described.[3,6,8–10]



salacinol **1** kotalanol **2**

Figure 1.

All the strategies described in the literature to obtain the zwitterionic moiety are based on the same reaction: the nucleophilic attack of the heteroatom of a protected or unprotected polyhydroxylated heterocycle at the least-hindered carbon atom of an L- or D-protected erythritol cyclic sulfate (Scheme 1). L-protected erythritol provides the side chain of salacinol and D-protected erythritol its enantiomer.

In 2000, Yuasa et al. were the first to present the synthesis of salacinol **1** and its diastereoisomer **3** (Fig. 2).[4] Later,

Keywords: Salacinol; Glycosidsase inhibitors; Cyclic sulfate; Thia-anhydroalditol; Zwitterion; Sulfonium sulfate inner salt.
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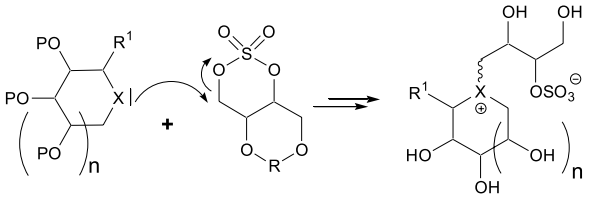


n = 0, 1, 2 ; R = CH-Ph, $C(CH_3)_2$
R^1= H, CH_2OP X = S, NH, Se; P = protecting group or H

Scheme 1. General strategy.

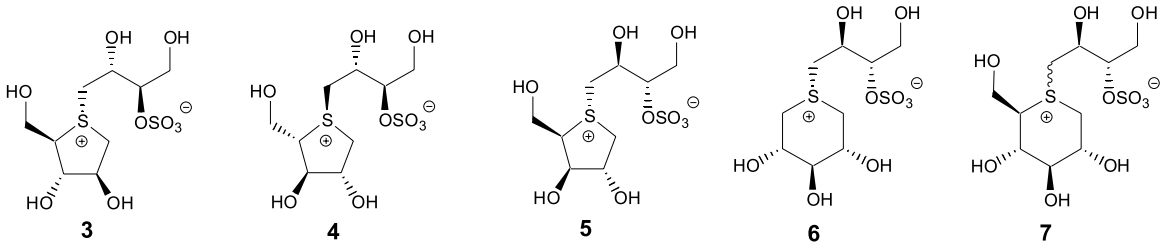


Figure 2. Salacinol stereoisomers and six-membered ring analogues.

Ghavami et al. reported their own synthesis of **1**, its enantiomer **4** and the diastereoisomers **3** and **5** (Fig. 2).[5–7] More recently the same group extended this method to prepare other sulfonium analogues with two different six-membered rings,[3] one of them obtained from alditols using the procedure described by Benazza et al.[11] Never observed with the five-membered ring, the coupling reaction with a six-membered ring resulted in the formation of two configurations at the sulfur atom. In the series with no hydroxymethyl group, the epimers were separated and four diastereoisomers were obtained (**6** is given as an example, Fig. 2). When the hydroxymethyl group was present, the separation was not possible and mixtures of epimers (e.g., **7**) were obtained (Fig. 2).[3]

To add to this new class of glycosidase inhibitors, we undertook the synthesis of several salacinol analogues obtained with the same general strategy (Scheme 1). For further structure–function studies, we modulated the ring size and its stereocenters, and kept the same L-erythritol sulfated side chain as salacinol and its enantiomer derived from the D-erythritol. Inhibition activities towards six commercial glycosidases are presented for all the compounds synthesized.

2. Results and discussion

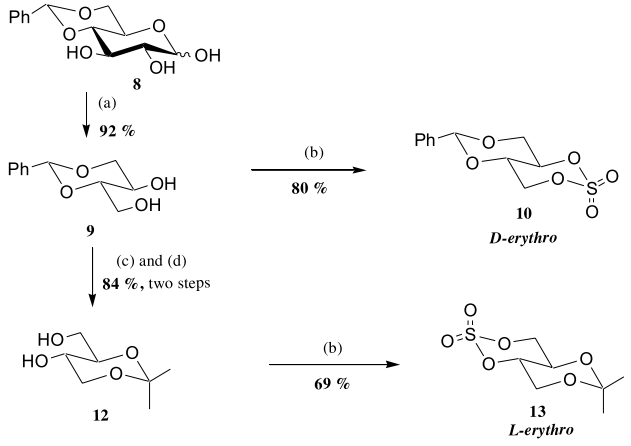
We synthesized the protected D- and L-erythritol cyclic sulfates from 4,6-*O*-benzylidene-D-glucose[12] by a modified procedure previously reported with no experimental section or description of compounds by Muraoka et al. (Scheme 2).[9] The L stereoisomer synthesis has also been described from L-glucose as starting material.[4,5] To obtain large quantities of both **10** and **13**, the following reactions were performed at a scale of several grams.

In the standard protocol, the aldehyde obtained from $NaIO_4$ oxidation of the 4,6-*O*-benzylidene-D-glucose is usually isolated. To shorten this part of the synthesis, we performed the periodidate oxidation and the reduction with $NaBH_4$ in one pot. Iodine was also formed but could easily be reduced by treatment with sodium thiosulfate. The diol **9** was thereby isolated in very high yield (92%).

Preparations of the corresponding cyclic sulfite with good yields have been described (82%,[5] >95%[9]), but we failed to reproduce these results even after numerous attempts. Our yields were around 55 to 60%; two syntheses of such cyclic sulfite/sulfate are reported with 60% yield[13] and 62% yield.[4]

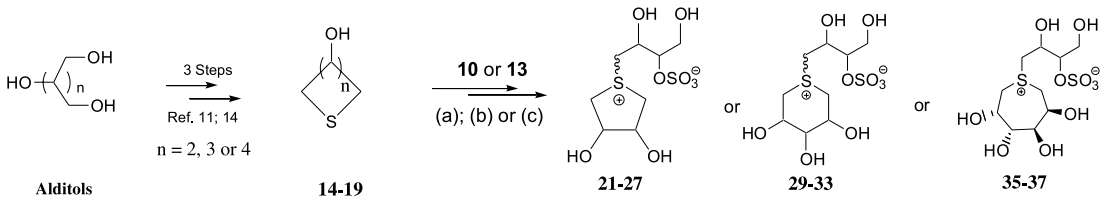
We observed that this cyclic sulfite was partially unstable in workup conditions and purification steps. Hydrolysis of the sulfite occurred easily and starting diol was isolated, although it was not present at the end of the reaction (from TLC). To prevent this side reaction, and as the reaction with $SOCl_2$ was total, we oxidized the sulfite to the sulfate **10** after a simple evaporation of the crude reaction mixture under vacuum. The non-isolated sulfite was converted into sulfate **10** with 80% overall yield.

The diol **9** also afforded the L-erythritol series when correctly protected by acetonide and then subjected to hydrogenolysis over Pd/C. The diol **12** was isolated in 84% yield from **9**.



Scheme 2. Reagents and conditions: (a) $NaIO_4$, $NaHCO_3$, H_2O, rt then $NaBH_4$, H_2O/EtOH, rt; (b) $SOCl_2$, anh. NEt_3, CH_2Cl_2, 0 °C then $RuCl_3$, $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$, rt; (c) $CH_3(OCH_3)C{=}CH_2$, TsOH, DMF, 0 °C; (d) **11**, H_2, Pd/C, EtOH, rt.

Instability of the corresponding cyclic sulfite was also observed, and was even more marked. This problem was also solved by applying our one-pot method. The crude cyclic sulfite obtained after concentration under vacuum



Scheme 3. Reagents and conditions: (a) HFIP, Na_2CO_3, reflux; (b) H_2O, H^+ (Dowex 50 W×8), rt; (c) H_2, Pd/C, $AcOH/H_2O$, rt.

was oxidized to give **13** in 69% yield. With these three one-pot operations, we shortened the total synthesis of the desired sulfates and notably increased the yields for their preparation.

The polyhydroxylated thiaheterocycles **14** to **19** (Table 1, Scheme 3) used in these experiments were prepared by Benazza et al. They were obtained from expeditious reactions of acetylated α,ω-dibromoalditols with sodium sulfide.[11,14] With tetritols as substrates the bis-cyclic sulfates[15a] or the more recently described bis-cyclic thionocarbonates[15b] were also used as bis-electrophilic intermediates.

The coupling reactions (Scheme 3) were all performed in hexafluoroisopropanol (HFIP) as Ghavami et al. had demonstrated its efficiency in such reactions.[7] Addition of sodium carbonate increases the stability of the sulfate under reflux.[5,16] The results are presented in Table 1. In some cases (entries 1, 2, 6, 8, 10), an *R*/*S* stereocenter was created on the sulfur atom and our mixtures were not separable. The compounds are all characterized as mixtures of the two configurations. In other cases (entries 3, 4, 11 and 12), the sulfur atom is not stereogenic, correlated to the C2 axis of the starting thiaheterocycles. As compound **15** is racemic, two diastereoisomers were obtained after coupling reactions corresponding to the structures **24a** and **24b**, and **26a** and **26b** (entries 3 and 4). These mixtures were also not separable. As compound **19** is optically pure, only one diastereoisomer was isolated with **10** (compound **36**) and with **13** (compound **34**) (entries 11 and 12).

Based on the wide differences in yields obtained, the thiaheterocycle reactivities seemed to depend on the ring size and configurations of asymmetric carbon atoms. Thus with the five-membered ring (entries 1 to 4) the yields for zwitterionic compounds were good to excellent (from 62 to 95%). In contrast, the three six-membered rings tested reacted poorly (entries 5 to 10). The coupling reaction did not take place with the L-erythritol cyclic sulfate **13** (entries 5, 7 and 9) or with the compound **10** (entries 6, 8 and 10), the yields were modest (except with **17**: 60%, entry 7). The sulfur atom of the seven-membered ring **19** (entries 11 and 12) did not react as well as the five-membered one but the two cyclic sulfates could even so be coupled to give the desired zwitterionic molecules. As for the six-membered ring, the reaction was much more efficient with the benzylidene protected cyclic sulfate than with acetonide protected compound **13**.

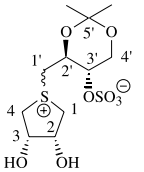
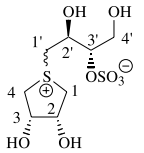
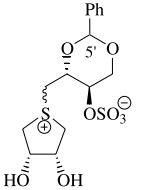
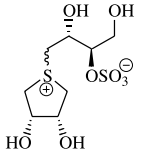
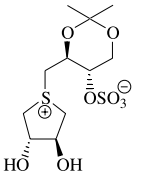
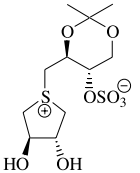
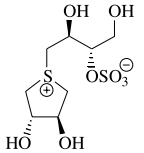
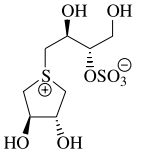
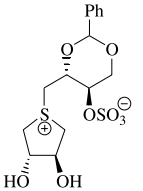
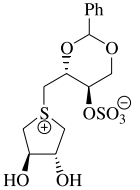
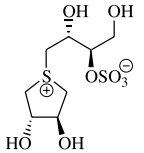
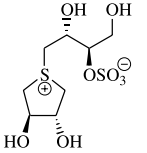
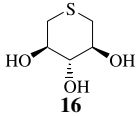
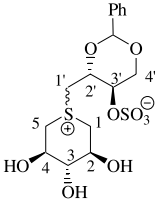
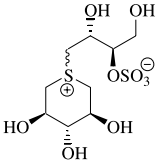
We suggest that this effect may be attributed to the size and shape of the thiaheterocycle ring, resulting in nucleophilicity variation of the sulfur atom. In addition, the steric hindrance was greater for the methyl in the equatorial position than for the phenyl. Thus the accessibility of the nucleophile at the least-hindered carbon atom of the cyclic sulfate was reduced.

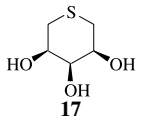
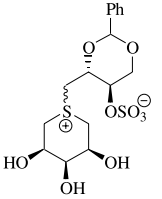
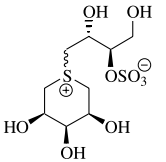
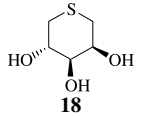
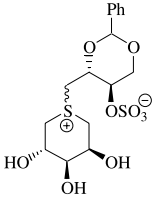
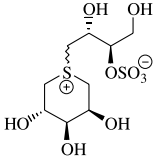
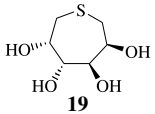
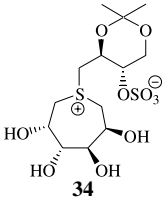
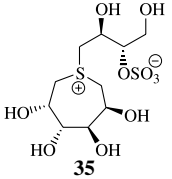
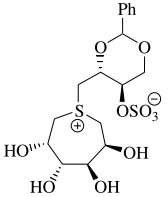
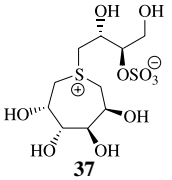
The last step was the diol deprotection. Two methods were used: hydrolysis under acidic conditions, and benzylidene hydrogenolysis over Pd/C. All the reactions were long, several days at room temperature. For the acid hydrolysis, we found it more convenient to use a Dowex resin as this can be easily removed by filtration (entries 1, 3, 6, 8, 10–12). With the hydrogenolysis over Pd/C, after 48 h the reaction mixture had to be filtered to eliminate Pd/C and fresh catalyst was added (entries 2 and 4). Probably, traces of sulfur compounds or other impurities had poisoned the catalyst. Given this difficulty and the longer reaction time, the benzylidene acidic cleavage was preferred (entries 6, 10 and 12). All the yields obtained (from 23 to 82%) are comparable to those in the literature[3,5] and were not optimized. Except for compounds **29**,[3] all the compounds synthesized are new salacinol analogues and were fully characterized.

3. Inhibition studies

The new salacinol analogues and the thiosugars were screened against six commercial glycosidases. The results for the zwitterions are given in Table 2 and are compared with the reported activity of salacinol **1**.[17] This compound presents a specificity among the glycosidase inhibitors. It is very active against disaccharidases such as α-glucosidase from rice and inactive against other glucosidases or mannosidase. All the thiosugars tested are inactive. The compounds **21** to **27**, which contain the five-membered ring, are inactive against the α-glucosidase from rice. As salacinol is a good inhibitor of this enzyme ($IC_{50}=1.1\times 10^{-3}$ mM), the hydroxymethyl group is essential to a good inhibition in this case. Except for compound **35**, which was never active, all the compounds inhibited at least one enzyme. They were moderately selective but the activities found were weak, around 1 to 3 mM except for compounds **29a** and **29b**, which exhibited a very high activity towards β-glucosidase. In the literature, these two compounds were reported to be inactive towards an α-glucoamylase.[3] All the compounds tested were inactive against α-glucosidase from baker's yeast and α-galactosidase from green coffee beans. Finally, we have shown that salacinol analogues can be not only α-glucosidase inhibitors but can also be active toward β-glucosidases.

Table 1. Coupling reactions of thiaheterocycles **14**–**19** with **10** or **13** and deprotection reactions

Entry	Heterocycle	Cyclic sulfate	Time (a)	Yield %	Isolated protected zwitterion (*R*/*S* diastereoisomer ratio: 50/50 unless specified otherwise)		Time (b) or (c)	Yield %	Isolated deprotected zwitterion	
1	 **14**	**13**	21 h	64	 **20a**+**20b**	83/17	4 d (b)	82	 **21a**+**21b**	83/17
2		**10**	40 h	62	 **22a**+**22b**	83/17	8 d (c)	32	 **23a**+**23b**	86/14
3	 (±)-**15**	**13**	22 h	97	 **24a**	 **24b**	4 d (b)	51	 **25a**	 **25b**
4		**10**	26 h	75	 **26b**	 **26b**	9 d (c)	38	 **27a**	 **27b**
5	 **16**	**13**			No reaction					
6		**10**	7 d	38	 **28a**+**28b**	70/30	7 d (b)	50	 **29a**+**29b**	77/23

7	 **17**	**13**			No reaction				
8		**10**	7 d	60	 **30a**+**30b**	67/33	8 d (b)	64	 **31a**+**31b**	80/20
9	 **18**	**13**			No reaction				
10		**10**	9 d	41	 **32a**+**32b**		4 d (b)	61	 **33a**+**33b**	
11	 **19**	**13**	5 d	21	 **34**		3 d (b)	76	 **35**	
12		**10**	8 d	63	 **36**		4 d (b)	23	 **37**	

(a); (b); (c): see Scheme 3.

4. Conclusion

We have prepared several new salacinol analogues in good overall yields using free heterocycles in coupling reactions. Furthermore, we have improved, in terms of step number and yields on a scale of several grams, the synthesis of the two key cyclic sulfate intermediates. The cyclic sulfates **10** and **13** were obtained efficiently and easily from inexpensive D-glucose in three and five steps, respectively. As the thiosugars are inactive against all the glycosidases tested, the zwitterionic structure is responsible for the detected inhibition. Following the results of inhibition activities shown in Table 2, the presence of the hydroxymethyl group in the D-arabinothiolane moiety of salacinol seems important for the effectiveness of the inhibition. The ring size also seems to play a role, as a six-membered ring was found to be very active towards β-glucosidase, compared with the five or seven-membered rings. This is probably due to both the presence of more than two hydroxyl groups and to the conformation change. Finally, in agreement with the reported literature results[3,5,6] the alditol ring stereochemistry obviously plays an important part since among the three configurations tested for the six-membered ring analogues, only one was active.

5. Experimental

All the reactions were monitored by TLC with Merck 60F-254 precoated silica (0.2 mm) on aluminium. Flash chromatography was performed with Merck Kieselgel 60 (40–63 μm); the solvent systems are given v/v. NEt_3 was distilled over CaH_2. Melting points were measured with a Reichert microscope and are uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 in $CDCl_3$, CD_3OD or D_2O (see indication). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. IR spectra were recorded on a Perkin–Elmer FT-IR Paragon 500. Optical rotations were measured on a JASCO DIP-370 polarimeter with a sodium (589 nm) lamp at 25 °C. High resolution mass spectra (HRMS) were recorded by the Centre Régional de Mesures Physiques de l'Ouest, Rennes.

5.1. Synthesis of cyclic sulfates 10 and 13

5.1.1. 2,4-*O*-Benzylidene-D-erythritol 9. To a solution of 4,6-*O*-benzylidene-D-glucose[12] **8** (10.0 g, 37.4 mmol) in 70 mL of water was added a solution of $NaIO_4$ (16.1 g, 75.4 mmol) and $NaHCO_3$ (3.17 g, 37.7 mmol) in 130 mL of water at 0 °C. The pH was maintained to 6–7 by adding few drops of a saturated $NaHCO_3$ solution. The mixture was stirred at room temperature for 5 h. A solution of $NaBH_4$ (2.00 g, 52.9 mmol) in 20 mL of water was added dropwise at 0 °C. The mixture was stirred at rt for 30 min, and neutralized with acetic acid. The precipitate formed was filtered, and rinsed with ethyl acetate. The filtrate was extracted with ethyl acetate (3×50 mL), the organic phases were washed with 1 N $Na_2S_2O_3$ (75 mL) and with brine (75 mL) and dried over $MgSO_4$. The diol **9** was concentrated under vacuum and purified by flash chromatography (cyclohexane/AcOEt: 3/7). A white solid (7.24 g) was isolated in 92% yield. The spectral data agreed with those already described.[5]

5.1.2. 2,4-*O*-Benzylidene-1,3-*O*-sulfonyl-D-erythritol 10. To a solution of diol **9** (3.00 g, 14.3 mmol) and anhydrous NEt_3 (5.4 mL, 38.6 mmol) in 50 mL of anhydrous DCM at 0 °C under Ar, was added dropwise a solution of freshly distilled $SOCl_2$ (1.4 mL, 18.6 mmol) in 50 mL of anhydrous DCM. After complete addition (1 h), the mixture was concentrated under vacuum to give a brown solid. To a solution of this solid (14.3 mmol) in 100 mL of DCM/CH_3CN (5/5) containing $RuCl_3$ (59.3 mg, 0.28 mmol) was added a solution of $NaIO_4$ (9.17 g, 42.9 mmol) in 50 mL of water. The mixture was stirred for 3 h and then diluted with 200 mL of DCM. The aqueous phase was extracted with 50 mL of DCM. The organic phases were washed with brine (200 mL), and dried over $MgSO_4$. The sulfate **10** was concentrated under vacuum and purified by flash chromatography (cyclohexane/AcOEt: 9/1+0.1% NEt_3). A white solid (3.11 g) was isolated in 80% yield. R_f 0.17 (cyclohexane/AcOEt 9/1+0.1% NEt_3).

The spectral data agreed with those already described.[5]

5.1.3. 1,3-*O*-Benzylidene-2,4-*O*-isopropylidene-L-erythritol 11. A solution of diol **9** (4.37 g, 20.8 mmol), distilled 2-methoxypropene (6.0 mL, 62.9 mmol) and TsOH (67.4 mg, 0.35 mmol) in non-anhydrous DMF was vigorously stirred at 0 °C for 24 h. The mixture was neutralized with 1.03 g of Na_2CO_3. The precipitate was filtered, and washed with cyclohexane. To the filtrate was added 400 mL of water, and the aqueous phase was extracted with 200 mL of cyclohexane. The organic phases were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (cyclohexane/AcOEt: 9/1+0.1% NEt_3) to give **11** in 96% yield as a white solid (4.99 g). R_f 0.39 (cyclohexane/AcOEt 9/1+0.1% NEt_3). $[\alpha]_D=+2$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.80–7.47 (m, 2H, H_{arom}); 7.38–7.35 (m, 3H, H_{arom}); 5.62 (s, 1H, H_5); 4.23 (dd, 1H, H_{4a}, $J=4.0$, 10.3 Hz); 4.01–3.95 (m, 2H, H_{1a} and H_{1b}); 3.93–3.88 (m, 1H, H_3); 3.80–3.73 (m, 2H, H_{4b} and H_2); 1.57 (s, 3H, CH_3); 1.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 137.2 (C_{arom}); 129.2–128.3–126.1 (C_{arom}); 102.0 (C_5); 100.0 (C_6); 75.0 (C_2); 69.6 (C_4); 66.6 (C_3); 62.3 (C_1); 29.1 (CH_3); 19.3 (CH_3). HRMS (ESI+) calcd for $[M+Na]^+$ 273.1103. Found 273.1113.

5.1.4. 2,4-*O*-Isopropylidene-L-erythritol 12. To a solution of **11** (4.86 g, 19.4 mmol) in 160 mL of ethanol, was added 2.46 g of 10% Pd/C. The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 days. The catalyst was filtered on membrane and rinsed with methanol. The filtrate was concentrated under vacuum and ethanol (160 mL) and fresh 10% Pd/C (2.02 g) were added. The mixture was stirred at rt for 5 days under an atmosphere of H_2. The catalyst was filtered on membrane and rinsed with methanol. The filtrate was concentrated under vacuum and the crude product was purified by flash chromatography (cyclohexane/AcOEt: 4/6). A colorless oil was obtained in 88% yield (2.78 g). R_f 0.26 (cyclohexane/AcOEt 4/6). $[\alpha]_D=+45$ (*c* 1.1, MeOH). ^1H NMR (CD_3OD) δ 3.82–3.76 (m, 2H, H_{1a} and H_{4a}); 3.69–3.57 (m, 3H, H_3, H_{1b} and H_{4b}); 3.48 (td, 1H, H_2, $J=5.6$, 9.2, 9.2 Hz); 1.48 (s, 3H,

Table 2. Evaluation of the inhibition properties

Glycosidase	IC_{50} mM[17], Salacinol **1**	K_i in mM									
		21	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**
α-Glucosidase from rice	(0.0011)	NI	NI	NI	NI	1.41[a]	NI	1.32[a]	NI	NI
α-Glucosidase from baker's yeast	(NI)	NI	NI	NI	NI	NI	NI	NI	NI	nd
β-Glucosidase from almond	(NI)	NI	2.47[a]	1.87[a]	NI	0.016±0.001[b]	NI	NI	NI	NI
α-Galactosidase from green coffee beans	Nd	NI	NI	NI	NI	NI	nd	NI	NI	nd
β-Galactosidase from *A. oryzae*	Nd	0.853±0.074[b]	0.716±0.140[b]	NI	1.29[a]	NI	0.85[a]	NI	NI	NI
α-Mannosidase from jack beans	(2.1)[c]	NI	NI	NI	NI	0.467±0.097[b]	1.34[a]	3.59[a]	NI	1.83[a]

[a] Preliminary determined with K_M and one K'_M.
[b] Competitive inhibitor, Hanes–Woolf method.
[c] From almond; NI: no inhibition detected; nd: not determined.

CH_3); 1.35 (s, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 99.9 (C_5); 76.5 (C_3); 65.5 (C_1); 64.0 (C_2); 63.3 (C_4); 28.9 (CH_3); 19.7 (CH_3). HRMS (ESI+) calcd for $[M+Na]^+$ 185.0790. Found 185.0786.

5.1.5. 2,4-*O*-Isopropylidene-1,3-*O*-sulfonyl-L-erythritol 13. To a solution of diol **12** (1.08 g, 6.66 mmol) and anhydrous NEt_3 (2.8 mL, 20.1 mmol) in 28 mL of anhydrous DCM at 0 °C under Ar, was added dropwise a solution of freshly distilled $SOCl_2$ (680 μL, 9.37 mmol) in 28 mL of anhydrous DCM. After complete addition (45 min), the mixture was concentrated under vacuum to give a brown solid. To a solution of this solid (6.6 mmol) in 50 mL of DCM/CH_3CN (5/5) containing $RuCl_3$ (33.5 mg, 0.16 mmol) was added a solution of $NaIO_4$ (4.64 g, 21.7 mmol) in 25 mL of water. The mixture was stirred for 24 h and then diluted with 100 mL of DCM and 100 mL of water. The aqueous phase was extracted twice with 100 mL of DCM. The organic phases were washed with brine (2×100 mL), and dried over $MgSO_4$. The sulfate **13** was concentrated under vacuum and purified by flash chromatography (pentane/ether 9/1). A white solid (1.03 g) was isolated in 69% yield. R_f 0.16 (pentane/ether 9/1). $[\alpha]_D=-4$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 4.66 (td, 1H, H_2, $J_{2-1a}=5.4$ Hz, $J_{2-1b}=J_{2-3}=10.3$ Hz); 4.61 (dd, 1H, H_{4a}, $J_{4a-3}=J_{4a-4b}=10.3$ Hz); 4.46 (dd, 1H, H_{4b}, $J_{4b-3}=4.8$ Hz, $J_{4b-4a}=10.3$ Hz); 4.22 (td, 1H, H_3, $J_{3-4b}=4.8$ Hz, $J_{3-4a}=J_{3-2}=10.3$ Hz); 4.03 (dd, 1H, H_{1a}, $J_{1a-2}=5.4$ Hz, $J_{1a-1b}=10.3$ Hz); 3.92 (dd, 1H, H_{1b}, $J_{1b-2}=J_{1b-1a}=10.3$ Hz); 1.55 (s, 3H, CH_3); 1.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 101.1 (C_5); 76.6 (C_2); 73.3 (C_4); 64.7 (C_3); 60.8 (C_1); 28.5 (CH_3); 18.9 (CH_3). HRMS (ESI+) calcd for $[M+Na]^+$ 247.0252. Found 247.0264.

5.2. General procedure for the coupling reactions

The thiaheterocycle (1 mmol) and cyclic sulfate **10** or **13** (1.2 mmol) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol HFIP (3 mL) under argon in the presence of anhydrous Na_2CO_3 (0.24 mmol). The mixture was refluxed for the time indicated in Table 1, concentrated under vacuum and purified by flash chromatography (mixture of DCM/MeOH, see R_f details for each compound).

5.2.1. 1-[(1,4-Anhydro-1-thioerythritol)-1-ium]-1,3-dideoxy-2,4-*O*-isopropylidene-L-erythritol-3-sulfate 20. 43 mg as a white solid, mixture of non-separable diastereoisomers **20a/20b** (83/17). R_f 0.11 (DCM/MeOH, 85/15).

Major isomer. ^1H NMR (CD_3OD) δ 4.48–4.45 (m, 2H, H_2 and H_3); 4.37–4.23 (m, 2H, $H_{2'}$ and $H_{3'}$); 4.16 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.4$ Hz, $J_{1'a-1'b}=13.6$ Hz); 4.07 (dd, 1H, $H_{4'a}$, $J_{4'a-3'}=5.3$ Hz, $J_{4'a-4'b}=11.5$ Hz), 3.99 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=4.6$ Hz, $J_{1'b-1'a}=13.6$ Hz), 3.85 (dd, 1H, $H_{4'b}$, $J_{4'b-3'}=9.0$ Hz, $J_{4'b-4'a}=11.5$ Hz), 3.75 (dd, 2H, H_{1a} and H_{4a}, $J=5.0$, 12.9 Hz), 3.41–3.36 (m, 2H, H_{1b} and H_{4b}), 1.53 (s, 3H, CH_3), 1.41 (s, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 101.2 ($C_{5'}$); 75.6 (C_2 or C_3); 75.1 (C_2 or C_3); 70.9 ($C_{2'}$ or $C_{3'}$); 70.4 ($C_{2'}$ or $C_{3'}$); 63.2 ($C_{4'}$); 50.7 ($C_{1'}$); 46.1 (C_1 or C_4); 45.6 (C_1 or C_4); 28.5 (CH_3); 19.6 (CH_3).

Minor isomer. ^1H NMR (CD_3OD) δ 4.62–4.57 (m, 2H, H_2

and H_3); 4.37–4.23 (m, 2H, $H_{2'}$ and $H_{3'}$); 4.08 (dd, 1H, $H_{1'a}$, $J=5.3$, 11.5 Hz); 3.92 (dd, 1H, $H_{4'a}$, $J=3.5$, 13.4 Hz); 3.87–3.81 (m, 2H, $H_{4'b}$ and $H_{1'b}$); 3.66–3.55 (m, 4H, $2H_1$ and $2H_4$); 1.53 (s, 3H, CH_3); 1.41 (s, 3H, CH_3). ^{13}C RMN (CD_3OD) δ 74.7 (C_2 or C_3); 74.5 (C_2 or C_3); 70.6 ($C_{2'}$ or $C_{3'}$); 47.9 (C_1 or C_4); 45.8 (C_1 or C_4); 28.4 (CH_3); 19.7 (CH_3).

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.2.2. 1-[(1,4-Anhydro-1-thioerythritol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 22. 148 mg as white solid, mixture of non-separable diastereoisomers **22a/22b** (83/17). R_f 0.22 (DCM/MeOH, 80/20); mp 135 °C; $[\alpha]_D=-45$ (*c* 0.91, MeOH). IR KBr cm^{-1} 3403; 1403; 1264; 1233; 1094; 1013.

Major isomer. ^1H NMR (CD_3OD) δ 7.49–7.45 (m, 2H, H_{arom}); 7.40–7.36 (m, 3H, H_{arom}); 5.68 (s, 1H, $H_{5'}$); 4.52–4.47 (m, 1H, $H_{4'a}$); 4.45–4.40 (m, 3H, $H_{3'}$, H_2 and H_3); 4.39–4.34 (m, 1H, $H_{2'}$); 4.29 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.4$ Hz, $J_{1'a-1'b}=13.9$ Hz); 4.10 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=5.1$ Hz, $J_{1'b-1'a}=13.9$ Hz); 3.83 (dd, 1H, $H_{4'b}$, $J=9.6$, 9.6 Hz); 3.71 (dd, 1H, H_{4a} or H_{1a}, $J=5.1$, 11.6 Hz); 3.69 (dd, 1H, H_{1a} or H_{4a}, $J=5.6$, 10.9 Hz); 3.40 (dd, 1H, H_{4b} or H_{1b}, $J=5.1$, 13.4 Hz); 3.35 (dd, 1H, H_{1b} or H_{4b}, $J=5.6$, 13.4 Hz). ^{13}C NMR (CD_3OD) δ 138.4 (C_{arom}); 130.3–129.3–127.3 (C_{arom}); 102.7 ($C_{5'}$); 77.4 ($C_{2'}$); 75.7 (C_2 or C_3); 75.2 (C_2 or C_3); 69.9 ($C_{4'}$); 69.0 ($C_{3'}$); 50.2 ($C_{1'}$); 46.0 (C_1 or C_4); 45.8 (C_1 or C_4).

Minor isomer. ^1H NMR (CD_3OD) δ 7.49–7.45 (m, 2H, H_{arom}); 7.40–7.36 (m, 3H, H_{arom}); 5.68 (s, 1H, $H_{5'}$); 4.55–4.60 (m, 2H, H_2 and H_3); 4.52–4.47 (m, 2H, $H_{4a'}$ and $H_{3'}$); 4.39–4.34 (m, 1H, $H_{2'}$); 4.04 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.2$ Hz, $J_{1'a-1'b}=13.5$ Hz); 3.94 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=5.9$ Hz, $J_{1'b-1'a}=13.5$ Hz); 3.87–3.79 (m, 1H, $H_{4'b}$); 3.65–3.51 (m, 4H, $2H_1$ and $2H_4$). ^{13}C NMR (CD_3OD) δ 77.2 ($C_{2'}$); 74.7 (C_2 or C_3); 74.5 (C_2 or C_3); 69.4 ($C_{3'}$); 47.3 (C_1 or C_4); 45.9 (C_1 or C_4).

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.2.3. 1-[(1,4-Anhydro-1-thiothreitol)-1-ium]-1,3-dideoxy-2,4-*O*-isopropylidene-L-erythritol-3-sulfate 24. 259 mg as white solid, mixture of non-separable diastereoisomers **24a/24b** (50/50). R_f 0.31 (DCM/MeOH, 80/20); $[\alpha]_D=+43$ (*c* 1.06, MeOH). IR KBr cm^{-1} 3404; 1385; 1268; 1228; 1050; 1013. For the mixture ^1H NMR (CD_3OD) δ 4.65 (br s, 2H, H_2 and H_3); 4.61 (br s, 2H, H_2 and H_3); 4.36–4.25 (m, 4H, $2H_{3'}$ and $2H_{2'}$); 4.10 (dd, 1H, $H_{4'a}$, $J=3.7$, 5.2 Hz); 4.08–4.02 (m, 2H, $H_{4'a}$ and $H_{1'a}$); 3.96 (br d, 2H, $2H_{1'}$, $J=4.0$ Hz); 3.90–3.72 (m, 9H, $2H_1$, $2H_4$. H_{1a}, H_{4a}, $H_{1'b}$ and $2H_{4'b}$); 3.51 (br d, 1H, H_{4b} or H_{1b}, $J=4.5$ Hz); 3.48 (br d, 1H, H_{1b} or H_{4b}, $J=4.8$ Hz); 1.54 (s, 3H, CH_3); 1.53 (s, 3H, CH_3); 1.42 (s, 6H, CH_3). ^{13}C NMR (CD_3OD) δ 79.0 (C_2 or C_3); 78.9 (C_2 or C_3); 78.7 (C_2 or C_3); 78.6 (C_2 or C_3); 70.9 ($C_{2'}$ or $C_{3'}$); 70.7 ($C_{2'}$ or $C_{3'}$); 70.6 ($C_{2'}$ or $C_{3'}$); 63.3 ($C_{4'}$); 53.4 (C_1 or C_4); 52.5 (C_1 or C_4); 50.2 ($C_{1'}$); 49.4 ($C_{1'}$); 49.2 (C_1 and C_4); 28.5 (CH_3); 19.6 (CH_3).

Remarks. Absent δ for some carbons means that the signals are not detected.

5.2.4. 1-[(1,4-Anhydro-1-thiothreitol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 26. 243 mg as white solid, mixture of non-separable diastereoisomers **26a/26b** (50/50). R_f 0.20 (DCM/MeOH, 85/15); mp 143 °C; $[\alpha]_D=-42$ (*c* 1.27, MeOH). IR KBr cm^{-1} 3397; 1402; 1263; 1229; 1091; 1053; 1013. For the mixture ^1H NMR (CD_3OD) δ 7.51–7.47 (m, 4H, H_{arom}); 7.42–7.33 (m, 6H, H_{arom}); 5.68 (s, 2H, $2H_{5'}$); 4.63 (br s, 2H, H_2 and H_3); 4.59 (br s, 2H, H_2 and H_3); 4.53–4.47 (m, 2H, $2H_{4'a}$); 4.47–4.40 (m, 2H, $2H_{3'}$); 4.38–4.34 (m, 2H, $2H_{2'}$); 4.18 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.3$ Hz, $J_{1'a-1'b}=13.6$ Hz); 4.03–4.12 (m, 2H, $2H_{1'}$); 3.98 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=5.6$ Hz, $J_{1'b-1'a}=13.6$ Hz); 3.86–3.76 (m, 6H, $2H_4$. H_{1a}, H_{4a} and $2H_{4'b}$); 3.74–3.70 (m, 2H, $2H_1$); 3.51 (br d, 1H, H_{4b} or H_{1b}, $J=13.9$ Hz); 3.47 (br d, 1H, H_{1b} or H_{4b}, $J=13.9$ Hz). ^{13}C NMR.(CD_3OD) δ 138.4 (C_{arom}) 130.3–129.4–127.3 (C_{arom}); 102.8 ($C_{5'}$); 102.7 ($C_{5'}$); 79.0 (C_2 or C_3); 78.9 (C_2 or C_3); 78.8 (C_2 or C_3); 78.6 (C_2 or C_3); 77.5 ($C_{2'}$); 77.3 ($C_{2'}$); 69.9 ($C_{4'}$); 69.1 ($C_{3'}$); 53.4 (C_1 or C_4); 52.8 (C_1 or C_4); 49.6 ($C_{1'}$); 49.4 (C_1, C_4 or $C_{1'}$); 49.3 (C_1, C_4 or $C_{1'}$); 49.1 (C_1, C_4 or $C_{1'}$).

Remarks. Absent δ for some carbons means that the signals are not detected.

5.2.5. 1-[(1,5-Anhydro-1-thioxylitol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 28. 65 mg as a white solid, mixture of non-separable diastereoisomers **28a/28b** (70/30). R_f 0.18 (DCM/MeOH, 85/15); mp 142 °C; $[\alpha]_D=-46$ (*c* 1.02, MeOH). IR KBr cm^{-1} 3406; 1403; 1260; 1225; 1094; 1068; 1013.

Major isomer. ^1H NMR (CD_3OD) δ 7.50–7.45 (m, 2H, H_{arom}); 7.41–7.34 (m, 3H, H_{arom}); 5.69 (s, 1H, $H_{5'}$); 4.51–4.38 (m, 3H, $H_{2'}$, $H_{3'}$ and $H_{4'a}$); 4.21–4.16 (m, 2H, H_2 and H_4); 4.01 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.2$ Hz, $J_{1'a-1'b}=13.9$ Hz); 3.91 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=4.9$ Hz, $J_{1'b-1'a}=13.9$ Hz); 3.88–3.79 (m, 1H, $H_{4'b}$); 3.75 (dd, 1H, H_3, $J=5.1$, 5.1 Hz); 3.70 (dd, 1H, H_{5a} or H_{1a}, $J=2.3$, 13.1 Hz); 3.67 (dd, 1H, H_{1a} or H_{5a}, $J=2.5$, 13.1 Hz); 3.52–3.47 (m, 2H, H_{1b} and H_{5b}). ^{13}C NMR δ (CD_3OD) δ 138.3 (C_{arom}); 130.4–129.4–127.3 (C_{arom}); 102.8 ($C_{5'}$); 77.0 ($C_{2'}$); 69.9 (C_3); 69.8 ($C_{4'}$); 69.2 ($C_{3'}$); 68.7 (C_2 and C_4); 43.8 ($C_{1'}$); 42.5 (C_1 or C_5); 41.7 (C_1 or C_5).

Minor isomer. ^1H NMR (CD_3OD) δ 7.50–7.45 (m, 2H, H_{arom}); 7.41–7.34 (m, 3H, H_{arom}); 5.69 (s, 1H, $H_{5'}$); 4.51–4.38 (m, 3H, $H_{2'}$, $H_{3'}$ and $H_{4'a}$); 4.12–4.04 (m, 2H, $2H_{1'}$); 3.98–3.89 (m, 2H, H_2 and H_4); 3.88–3.79 (m, 1H, $H_{4'b}$); 3.62–3.56 (m, 3H, H_{1a}, H_{5a} and H_3); 3.40–3.28 (m, 2H, H_{1b} and H_{5b}). ^{13}C NMR δ (CD_3OD) δ 77.1 ($C_{2'}$); 68.9 (C_2 or C_4); 68.5 (C_2 or C_4); 45.8 ($C_{1'}$); 40.3 (C_1 or C_5)); 39.7 (C_1 or C_5).

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.2.6. 1-[(1,5-Anhydro-1-thioribitol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 30. Flash chromatography eluent (DCM/MeOH, 85/15), 63 mg as a white solid, mixture of non-separable diastereoisomers

30a/30b (67/33). R_f 0.15 (DCM/MeOH, 80/20); mp decomp.; $[\alpha]_D = -38$ (*c* 0.25, NaOH 0.01 N). IR KBr cm^{-1} 3450; 3388; 1407; 1250; 1231; 1098; 1014.

Major isomer. ^1H NMR (CD_3OD) δ 7.50–7.45 (m, 2H, H_{arom}); 7.41–7.36 (m, 3H, H_{arom}); 5.69 (s, 1H, $H_{5'}$); 4.51–4.38 (m, 3H, $H_{2'}$, $H_{3'}$ and $H_{4'a}$); 4.27–4.19 (m, 2H, H_2 and H_4); 4.08–3.96 (m, 2H, H_3 and $H_{1'a}$); 3.88–3.81 (m, 2H, $H_{1'b}$ and $H_{4'b}$); 3.49–3.32 (m, 2H, H_{1a} and H_{5a}); 3.31–3.28 (m, 1H, H_{5b} or H_{1b}); 3.23 (dd, 1H, H_{1b} or H_{5b}, $J=2.7$, 13.7 Hz). ^{13}C NMR (CD_3OD) δ 138.3 (C_{arom}); 130.4–129.4–127.3 (C_{arom}); 102.8 ($C_{5'}$); 77.1 ($C_{2'}$); 71.8 (C_3); 69.9 ($C_{4'}$); 69.0 ($C_{3'}$); 66.9 (C_2 or C_4); 66.7 (C_2 or C_4); 40.4 ($C_{1'}$); 35.5 (C_1 and C_5).

Minor isomer. ^1H NMR (CD_3OD) δ 7.50–7.45 (m, 2H, H_{arom}); 7.41–7.36 (m, 3H, H_{arom}); 5.69 (s, 1H, $H_{5'}$); 4.51–4.38 (m, 3H, $H_{2'}$, $H_{3'}$ and $H_{4'a}$); 4.15 (dd, 1H, $H_{1'a}$, $J=3.2$, 13.9 Hz); 4.08–3.96 (m, 4H, H_2, H_3, H_4 and $H_{1'b}$); 3.88–3.81 (m, 1H, $H_{4'b}$); 3.49–3.32 (m, 4H, $2H_1$ and $2H_5$). ^{13}C NMR (CD_3OD) δ 77.0 ($C_{2'}$); 71.9 (C_3); 69.1 ($C_{3'}$); 67.6 (C_2 or C_4); 67.5 (C_2 or C_4); 46.8 ($C_{1'}$); 38.3 (C_1 or C_5);. 36.9 (C_1 or C_5).

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.2.7. 1-[(1,5-Anhydro-1-deoxy-1-thio-D-arabinitol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 32. 58 mg as a white solid, mixture of non-separable diastereoisomers **32a/32b** (50/50). R_f 0.19 (DCM/MeOH, 85/15); mp 141 °C; $[\alpha]_D = -48$ (*c* 0.44. MeOH). IR KBr cm^{-1} 3404; 1402; 1263; 1227; 1091; 1013. For the mixture ^1H NMR (CD_3OD) δ 7.50–7.47 (m, 4H, H_{arom}); 7.42–7.37 (m, 6H, H_{arom}); 5.68 (s, 1H, $H_{5'}$); 5.67 (s, 1H, $H_{5'}$); 4.52–4.36 (m, 7H, $2H_{2'}$, H_4 or H_2, $2H_{4'a}$ and $2H_{3'}$); 4.34–4.24 (m, 3H, H_2, H_4, H_2 or H_4); 4.18 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.6$ Hz, $J_{1'a-1'b}=14.4$ Hz); 4.09 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=3.9$ Hz, $J_{1'b-1'a}=14.4$ Hz); 4.04 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.3$ Hz, $J_{1'a-1'b}=14.1$ Hz); 3.97 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=4.6$ Hz, $J_{1'b-1'a}=14.1$ Hz); 3.88–3.78 (m, 4H, $2H_3$ and $2H_{4'b}$); 3.62–3.52 (m, 3H, H_{5a}, H_{1a}, H_{5a} or H_{1a}); 3.47–3.36 (m, 3H, H_{1b}, H_{5b}, H_{1a} or H_{5a}); 3.30–3.25 (m, 1H, H_{5b} or H_{1b}); 3.23 (dd, 1H, H_{1b} or H_{5b}, $J=5.4$, 13.4 Hz). ^{13}C RMN (CD_3OD) δ 138.3 (C_{arom}); 130.4–130.3–129.4–127.3 (C_{arom}); 102.8 ($C_{5'}$); 102.7 ($C_{5'}$); 77.3 ($C_{2'}$); 77.0 ($C_{2'}$); 71.7 (C_3); 70.6 (C_3); 69.8 ($C_{4'}$); 69.4 (C_2, C_4 or $C_{3'}$); 69.1 (C_2, C_4 or $C_{3'}$); 68.7 (C_2, C_4 or $C_{3'}$); 68.2 (C_2, C_4 or $C_{3'}$); 65.1 (C_4 or C_2); 63.2 (C_4 or C_2); 45.6 ($C_{1'}$); 43.4 ($C_{1'}$); 42.2 (C_1 or C_5); 37.8 (C_1 or C_5); 37.2 (C_1 or C_5).

Remarks. Absent δ for some carbons means that the signals are not detected.

5.2.8. 1-[(1,6-Anhydro-1-thio-D-mannitol)-1-ium]-1,3-dideoxy-2,4-*O*-isopropylidene-L-erythritol-3-sulfate 34. Flash chromatography eluent (DCM/MeOH, 85/15), 23 mg as a white solid. R_f 0.17 (DCM/MeOH, 80/20); mp 168 °C; $[\alpha]_D = -9$ (*c* 1.08, H_2O). IR KBr cm^{-1} 3388; 3349; 1390; 1276; 1225; 1091; 1059; 1012. ^1H NMR (D_2O) δ 4.69–4.67 (m, 1H, H_2 or H_5); 4.60–4.57 (m, 1H, H_5 or H_2); 4.40 (ddd, 1H, $H_{2'}$, $J_{2'-1'a}=3.1$ Hz, $J_{2'-1'b}=6.4$ Hz, $J_{2'-3'}=9.1$ Hz); 4.37 (td, 1H, $H_{3'}$, $J_{3'-4'a}=5.6$ Hz, $J_{3'-4'b}=J_{3'-2'}=9.1$ Hz); 4.11 (dd, 1H, $H_{4'a}$, $J_{4'a-3'}=5.6$ Hz, $J_{4'a-4'b}=11.9$ Hz); 4.08 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.1$ Hz, $J_{1'a-1'b}=14.1$ Hz); 4.09–4.03 (m, 1H, H_{6a} or H_{1a}); 3.97 (dd, 1H, $H_{4'b}$, $J_{4'b-3'}=9.1$ Hz, $J_{4'b-4'a}=11.9$ Hz); 3.90–3.73 (m, 5H, H_{1a} or H_{6a}, H_3, $H_{1'b}$, H_4 and H_{6b} or H_{1b}); 3.66–3.62 (m, 1H, H_{1b} or H_{6b}); 1.58 (s, 3H, CH_3); 1.46 (s, 3H, CH_3). ^{13}C NMR (D_2O) δ 100.8 ($C_{5'}$); 74.3 (C_4 or C_3); 74.2 (C_4 or C_3); 70.4 ($C_{3'}$); 70.0 (C_2 or C_5); 68.8 ($C_{2'}$); 66.9 (C_5 or C_2); 61.6 ($C_{4'}$); 44.8 ($C_{1'}$); 43.7 (C_6 or C_1); 39.7 (C_1 or C_6); 26.8 (CH_3); 18.8 (CH_3).

5.2.9. 1-[(1,6-Anhydro-1-thio-D-mannitol)-1-ium]-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol-3-sulfate 36. Flash chromatography eluent (DCM/MeOH, 85/15), 84 mg as a white solid. R_f 0.20 (DCM/MeOH, 80/20). Mp 160 °C. $[\alpha]_D = -63$ (*c* 0.92, MeOH). IR KBr cm^{-1} 3387; 1414; 1258; 1219; 1096; 1060; 1013. ^1H NMR δ; (CD_3OD) δ 7.46–7.50 (m, 2H, H_{arom}); 7.34–7.41 (m, 3H, H_{arom}); 5.67 (s, 1H, $H_{5'}$); 4.52–4.58 (m, 1H, H_2 or H_5); 4.42–4.50 (m, 2H, $H_{3'}$ and $H_{4'a}$); 4.40 (td, 1H, H_5 or H_2, $J=1.5$, 1.5, 8.6 Hz); 4.33–4.37 (m, 1H, $H_{2'}$); 4.11 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}=3.5$ Hz, $J_{1'a-1'b}=14.1$ Hz); 3.98 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}=4.8$ Hz, $J_{1'b-1'a}=14.1$ Hz); 3.96 (dd, 1H, H_{6a} or H_{1a}, $J=8.5$, 13.1 Hz); 3.79–3.86 (m, 1H, $H_{4'b}$); 3.69–3.76 (m, 3H, H_3, H_4 and H_{6b} or H_{1b}); 3.66 (dd, 1H, H_{1a} or H_{6a}, $J=8.0$, 14.4 Hz); 3.54 (dd, 1H, H_{1b} or H_{6b}, $J=1.2$, 14.4 Hz). ^{13}C NMR (CD_3OD) δ 138.4 (C_{arom}); 130.3–129.4–127.3 (C_{arom}); 102.8 ($C_{5'}$); 77.3 ($C_{2'}$); 76.1 (C_4 or C_3); 75.8 (C_4 or C_3); 71.2 (C_2 or C_5); 69.9 ($C_{4'}$); 69.0 (C_2, C_5 or $C_{3'}$); 68.3 (C_2, C_5 or $C_{3'}$); 47.4 ($C_{1'}$); 46.6 (C_6 or C_1); 42.0 (C_1 or C_6).

5.3. General procedure for isopropylidene and benzylidene protecting groups removal

Method A. (Conditions (b)). The protected zwitterion (0.224 mmol) and 151 mg of Dowex 50WX8 (16–40 mesh, H^+ form) in 7 mL of distilled water were stirred at rt for the time indicated in Table 1. The mixture was filtered, and the resin washed with water. The water was removed under vacuum and the residue was purified by flash chromatography (mixture of DCM/MeOH/H_2O, see R_f details for each compound).

Method B. (Conditions (c)). The benzylidene protected zwitterion (0.237 mmol) and 10% Pd/C (80 mg) in 4.5 mL of AcOH/H_2O (4/1) were stirred under an atmosphere of H_2 (balloon) at rt for several days. As the reaction slowed down, the catalyst was removed by filtration over a membrane and washed with MeOH and distilled water. The filtrate was concentrated under vacuum, and 4.5 mL of AcOH/H_2O (4/1) and 76 mg of 10% Pd/C were added. The reaction was stirred under an atmosphere of H_2 at rt for the total time indicated in Table 1. The catalyst was removed by filtration over a membrane and washed with distilled water. The mixture was concentrated under vacuum and purified by flash chromatography (mixture of DCM/MeOH/H_2O, see R_f details for each compound).

5.3.1. 1-[(1,4-Anhydro-1-thioerythritol)-1-ium]-1,3-dideoxy-L-erythritol-3-sulfate 21. *Method A*. 56 mg as a colorless oil, mixture of non-separable diastereoisomers **21a/21b** (83/17). R_f 0.26 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D = +22$ (*c* 1.06, H_2O). IR KBr cm^{-1} 3398; 1253; 1234; 1096; 1057; 1013; 920.

Major isomer. ^{1}H NMR (D_2O) δ 4.62–4.57 (m, 2H, H_2 and H_3); 4.30–4.40 (m, 2H, $H_{3'}$ and $H_{2'}$); 4.07 (dd, 1H, $H_{1'a}$, J= 3.4, 13.6 Hz); 3.95 (dd, 1H, $H_{4'a}$, J=3.1, 9.7 Hz); 3.93–3.89 (m, 1H, $H_{1'b}$); 3.87–3.80 (m, 3H, H_{1a}, H_{4a} and $H_{4'b}$); 3.47 (td, 2H, H_{1b} and H_{4b}, J=5.4, 13.2, 13.2 Hz). ^{13}C NMR (D_2O) δ 79.7 ($C_{3'}$); 73.4 (C_2 or C_3); 73.3 (C_2 or C_3); 65.6 ($C_{2'}$); 59.5 ($C_{4'}$); 51.1 ($C_{1'}$); 44.2 (C_1 or C_4); 43.8 (C_1 or C_4).

Minor isomer. ^{1}H NMR (D_2O) δ 4.75–4.70 (m, 2H, H_2 and H_3); 4.40–4.30 (m, 2H, $H_{2'}$ and $H_{3'}$); 3.89–3.93 (m, 1H, $H_{1'a}$); 3.80–3.87 (m, 2H, $H_{1'b}$ and $H_{4'a}$); 3.63–3.77 (m, 5H, $2H_1$, $2H_4$ and $H_{4'b}$). ^{13}C NMR (D_2O) δ 79.9 ($C_{3'}$); 72.8 (C_2 or C_3); 72.7 (C_2 or C_3); 65.4 ($C_{2'}$); 48.4 ($C_{1'}$); 44.3 (C_1 or C_4); 43.5 (C_1 or C_4). HRMS (ESI+) calcd for $[M+Na]^+$ 327.0184. Found 327.0186.

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.3.2. 1-[(1,4-Anhydro-1-thioerythritol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 23. *Method B*. 23 mg as a colorless oil, mixture of non-separable diastereoisomers **23a/23b** (86/14). R_f 0.25 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D=-22$ (c 1.05, H_2O); IR KBr cm^{-1} 3396; 1405; 1253; 1231; 1095; 1013.

Major isomer. ^{1}H NMR (D_2O) δ 4.65–4.60 (m, 2H, H_2 and H_3); 4.40 (ddd, 1H, $H_{2'}$, $J_{2'-1'a}$=3.5 Hz, $J_{2'-1'b}$= 7.5 Hz, $J_{2'-3'}$=14.8 Hz); 4.38–4.35 (m, 1H, $H_{3'}$); 4.10 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}$=3.5 Hz, $J_{1'a-1'b}$=13.6 Hz); 3.99 (dd, 1H, $H_{4'a}$, J=3.3, 12.8 Hz); 3.96 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}$=7.5 Hz, $J_{1'b-1'a}$=13.6 Hz); 3.97–3.83 (m, 3H, H_{1a}, H_{4a}, $H_{4'b}$); 3.51 (2dd, 2H, H_{1b} and H_{4b}, J=5.4, 13.3 Hz). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 73.5 (C_2 or C_3); 73.4 (C_2 or C_3); 65.7 ($C_{2'}$); 59.6 ($C_{4'}$); 51.1 ($C_{1'}$); 44.2 (C_1 or C_4); 43.9 (C_1 or C_4).

Minor isomer. ^{1}H NMR (D_2O) δ 4.77–4.73 (m, 2H, H_2 and H_3); 4.43–4.38 (m, 2H, $H_{2'}$ and $H_{3'}$); 3.97–3.83 (m, 3H, $H_{4'a}$ and $2H_{1'}$); 3.82–3.66 (m, 5H, $2H_1$, $2H_4$ and $H_{4'b}$). ^{13}C NMR (D_2O) δ 72.9 (C_2 or C_3); 44.4 (C_1 or C_4); 43.6 (C_1 or C_4). HRMS (ESI+) calcd for $[M+Na]^+$ 327.0184. Found 327.0182.

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.3.3. 1-[(1,4-Anhydro-1-thiothreitol)-1-ium]-1,3-dideoxy-L-erythritol-3-sulfate 25. *Method A*. 72 mg as a colorless oil, mixture of non-separable diastereoisomers **25a/25b** (50/50). R_f 0.52 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D=+23$ (c 1.01, H_2O). IR KBr cm^{-1} 3394; 1404; 1254; 1229; 1053; 1011. ^{1}H NMR (D_2O) δ 4.85 (br s, 2H, H_2 and H_3;); 4.80 (br s, 2H, H_2 and H_3); 4.45–4.35 (m, 4H, $2H_{3'}$ and $2H_{2'}$); 4.06–3.80 (m, 14H, $4H_{4'}$, $4H_{1'}$, H_{1a}, H_{4a}, $2H_1$ and $2H_4$); 3.68 (br d, 1H, H_{4b} or H_{1b}, J=15.4 Hz); 3.65 (br d, 1H, H_{1b} or H_{4b}, J=14.6 Hz). ^{13}C NMR (D_2O) δ 79.9 ($C_{3'}$); 79.7 ($C_{3'}$); 77.2 (C_2 or C_3); 77.2 (C_2 or C_3); 77.1 (C_2 or C_3); 77.0 (C_2 or C_3); 65.9 ($C_{2'}$); 65.6 ($C_{2'}$); 59.6 ($C_{4'}$); 51.1 (C_1, C_4 or $C_{1'}$); 50.5 (C_1, C_4 or $C_{1'}$); 50.4 (C_1, C_4 or $C_{1'}$); 50.2 (C_1, C_4 or $C_{1'}$); 47.6 (C_1 or C_4); 47.3 (C_1 or C_4). HRMS (ESI+) calcd for $[M+Na]^+$ 327.0184. Found 327.0188.

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.3.4. 1-[(1,4-Anhydro-1-thiothreitol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 27. *Method B*. 52 mg as a colorless oil, mixture of non-separable diastereoisomers **27a/27b** (50/50). R_f 0.54 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D=-24$ (c 1.04. H_2O). IR KBr cm^{-1} 3395; 1404; 1254; 1233; 1051; 1009. ^{1}H NMR (D_2O) δ 4.82–4.80 (m, 2H, H_2 and H_3); 4.77–4.75 (m, 2H, H_2 and H_3); 4.41–4.31 (m, 4H, $2H_{2'}$ and $2H_{3'}$); 4.02–3.77 (m, 14H, $4H_{4'}$, $4H_{1'}$, H_{1a}, H_{4a}, $2H_1$ and $2H_4$); 3.65 (br d, 1H, H_{4b} or H_{1b}, J=14.9 Hz); 3.61 (br d, 1H, H_{1b} or H_{4b}, J=14.7 Hz). ^{13}C NMR (D_2O) δ 79.9 ($C_{3'}$); 79.7 ($C_{3'}$); 77.2 (C_2 or C_3); 77.1 (C_2 or C_3); 77.1 (C_2 or C_3); 77.0 (C_2 or C_3); 65.9 ($C_{2'}$); 65.5 ($C_{2'}$); 59.5 ($C_{4'}$); 51.1 (C_1, C_4 or $C_{1'}$); 50.5 (C_1, C_4 or $C_{1'}$); 50.4 (C_1, C_4 or $C_{1'}$); 50.2 (C_1, C_4 or $C_{1'}$); 47.5 (C_1 or C_4); 47.3 (C_1 or C_4). HRMS (ESI+) calcd for $[M+Na]^+$ 327.0184. Found 327.0179.

5.3.5. 1-[(1,5-Anhydro-1-thioxylitol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 29. *Method A*. 24 mg as a colorless oil, mixture of non-separable diastereoisomers **29a/29b** (77/23). R_f 0.37 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D=-14$ (c 1.06, H_2O). IR KBr cm^{-1} 3397; 1403; 1250; 1063; 1009.

Major isomer. ^{1}H NMR (D_2O) δ 4.53–4.43 (m, 1H, $H_{2'}$); 4.42–4.36 (m, 1H, $H_{3'}$); 4.32–4.27 (m, 2H, H_4 and H_2); 4.06–3.95 (m, 1H, $H_{4'a}$); 3.92–3.86 (m, 2H, $H_{1'a}$ and $H_{4'b}$); 3.85–3.70 (m, 4H, H_{1a}, H_{5a}, $H_{1'b}$ and H_3); 3.61–3.50 (m, 2H, H_{1b} and H_{5b}). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 71.5 (C_3); 66.6 (C_4 and C_2); 65.5 ($C_{2'}$); 59.5 ($C_{4'}$); 42.9 ($C_{1'}$); 38.7 (C_1 or C_5); 38.5 (C_1 or C_5).

Minor isomer. ^{1}H NMR (D_2O) δ 4.53–4.43 (m, 1H, $H_{3'}$); 4.42–4.36 (m, 1H, $H_{2'}$); 4.06–3.95 (m, 4H, $H_{1'a}$, $H_{4'a}$, H_2 and H_4); 3.92–3.86 (m, 2H, $H_{1'b}$ and $H_{4'b}$); 3.85–3.70 (m, 2H, H_{1a} and H_{5a}); 3.61–3.50 (m, 1H, H_3); 3.42 (br d, 1H, H_{5b} or H_{1b}, J=11.7 Hz); 3.39 (br d, 1H, H_{1b} or H_{5b}, J=11.7 Hz). ^{13}C NMR (D_2O) δ 75.6 (C_3); 67.3 (C_4 or C_2); 65.2 ($C_{2'}$); 47.9 ($C_{1'}$); 40.7 (C_1 or C_5); 40.6 (C_1 or C_5). HRMS (ESI+) calcd for [M+Na]+357.0290. Found 357.0293.

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.3.6. 1-[(1,5-Anhydro-1-thioribitol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 31. *Method A*. 24 mg as a colorless oil, mixture of non-separable diastereoisomers **31a/31b** (80/20). R_f 0.16 (DCM/MeOH/H_2O, 55/40/5). $[\alpha]_D=-19$ (c 0.51, H_2O). IR KBr cm^{-1} 3403; 1403; 1254; 1231; 1089; 1016.

Major isomer. ^{1}H NMR (D_2O) δ 4.50–4.34 (m, 4H, $H_{3'}$, H_4, H_2 and $H_{2'}$); 4.10–4.08 (m, 1H, H_3); 4.00 (dd, 1H, $H_{4'a}$, $J_{4'a-3'}$=3.3 Hz, $J_{4'a-4'b}$=12.8 Hz); 3.89 (dd, 1H, $H_{4'b}$, $J_{4'b-3'}$=2.9 Hz, $J_{4'b-4'a}$=12.8 Hz); 3.83 (dd, 1H, $H_{1'a}$, $J_{1'a-2'}$=3.4 Hz, $J_{1'a-1'b}$=13.8 Hz); 3.70 (dd, 1H, $H_{1'b}$, $J_{1'b-2'}$=7.7 Hz, $J_{1'b-1'a}$=13.8 Hz); 3.61–3.52 (m, 2H, H_{1a} and H_{5a}); 3.49–3.40 (m, 2H, H_{1b} and H_{5b}). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 69.6 (C_3); 65.5 (C_4, C_2 or $C_{2'}$); 65.2 (C_4, C_2, or $C_{2'}$); 59.5 ($C_{4'}$); 41.7 ($C_{1'}$); 35.6 (C_1 or C_5); 35.5 (C_1 or C_5).

Minor isomer. ^{1}H NMR (D_2O) δ 4.50–4.34 (m, 2H, $H_{3'}$ and $H_{2'}$); 4.20–4.14 (m, 3H, H_2, H_3 and H_4); 4.01–3.96 (m, 2H, $H_{1'a}$ and $H_{4'a}$); 3.90–3.86 (m, 2H, $H_{1'b}$ and $H_{4'b}$); 3.61–3.52 (m, 2H, H_{1a} and H_{5a}); 3.49–3.40 (m, 2H, H_{1b} and H_{5b}). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 70.1 (C_3); 65.8 (C_4 and C_2); 47.8 ($C_{1'}$); 35.2 (C_1 or C_5); 34.9 (C_1 or C_5). HRMS (ESI+) calcd for $[M+Na]^+$ 357.0290. Found 357.0289.

Remarks for the minor isomer. Absent δ for some carbons means that the signals are not detected.

5.3.7. 1-[(1,5-Anhydro-1-thio-D-arabinitol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 33. *Method A*. 25 mg as a colorless oil, mixture of non-separable diastereoisomers **33a/33b** (50/50). R_f 0.40 (DCM/MeOH /H_2O, 55/40/5). $[\alpha]_D=-44$ (*c* 0.99, H_2O). IR (KBr) cm^{-1} 3400, 1251; 1069; 1014. ^{1}H NMR (D_2O) δ 4.58 (td, 1H, H_4 or H_2, $J=$ 2.4, 2.4, 6.8 Hz); 4.50 (td, 1H, H_4 or H_2, $J=2.1$, 6.0, 6.0 Hz); 4.47–4.30 (m, 6H, 2(H_2 or H_4), 2$H_{3'}$ and 2$H_{2'}$); 4.01–3.86 (m, 9H, 4$H_{1'}$, 4$H_{4'}$ and H_3); 3.82–3.73 (m, 3H, H_{1a}, H_3 and H_{5a}); 3.67 (dd, 1H, H_{5a} or H_{1a}, $J=2.3$, 13.3 Hz); 3.60–3.53 (m, 3H, 2(H_{5b} or H_{1b}) and H_{1a} or H_{5a}); 3.51 (dd, 1H, H_{1b} or H_{5b}, $J=9.7$, 12.4 Hz); 3.32 (dd, 1H, H_{1b} or H_{5b}, $J=9.1$, 12.9 Hz). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 79.8 ($C_{3'}$); 71.6 (C_3); 69.2 (C_3); 66.0 (C_4 or C_2); 65.8 (C_4 or C_2); 65.3 ($C_{2'}$); 64.9 (C_4 or C_2); 64.6 (C_4 or C_2); 59.5 ($C_{4'}$); 46.0 ($C_{1'}$); 45.7 ($C_{1'}$); 40.7 (C_1 or C_5); 38.9 (C_1 or C_5); 38.8 (C_1 or C_5); 36.8 (C_1 or C_5). HRMS (ESI+) calcd for $[M+Na]^+$ 357.0290. Found 357.0290.

5.3.8. 1-[(1,6-Anhydro-1-thio-D-mannitol)-1-ium]-1,3-dideoxy-L-erythritol-3-sulfate 35. *Method A*. 14 mg as a colorless oil. R_f 0.34 (DCM/MeOH/H_2O, 55/40/5); $[\alpha]_D=-29$ (*c* 1.19, H_2O). IR (KBr) cm^{-1} 3397, 1248, 1103; 1056; 1019. ^{1}H NMR (D_2O) δ 4.70–4.68 (m,1H, H_2 or H_5); 4.61–4.58 (m, 1H, $H_{2'}$); 4.42 (td, 1H, H_5 or H_2, $J=3.3$, 7.9, 7.9 Hz); 4.39–4.33 (m, 1H, $H_{3'}$); 4.15 (dd, 1H, $H_{1'a}$, $J=$ 8.8, 13.2 Hz); 4.02 (dd, 1H, H_{6a} or H_{1a}, $J=3.4$, 10.0 Hz); 3.99 (dd, 1H, $H_{4'b}$, $J=3.1$, 8.6 Hz); 3.91–3.85 (m, 3H, H_4 or H_3, $H_{1'b}$ and $H_{4'b}$); 3.80 (dd, 1H, H_3 or H_4. $J=1.8$, 8.8 Hz); 3.78–3.70 (m, 2H, H_{1a} or H_{6a} and H_{6b} or H_{1b}); 3.65–3.60 (m, 1H, H_{1b} or H_{6b}). ^{13}C NMR (D_2O) δ 79.9 ($C_{3'}$); 74.3 (C_4 or C_3); 74.1 (C_4 or C_3); 69.9 (C_2 or C_5); 66.9 ($C_{2'}$); 65.5 (C_5 or C_2); 59.5 ($C_{4'}$); 47.4 (C_6 or C_1); 43.7 ($C_{1'}$); 39.1 (C_1 or C_6). HRMS (ESI+) calcd for $[M+Na]^+$ 387.0396. Found 387.0396.

5.3.9. 1-[(1,6-Anhydro-1-thio-D-mannitol)-1-ium]-1,3-dideoxy-D-erythritol-3-sulfate 37. *Method A*. 11 mg as a colorless oil. R_f 0.36 (DCM/MeOH/H_2O, 55/40/5). $[\alpha]_D=-70$ (*c* 0.83, H_2O). IR (KBr) cm^{-1} 3404; 1405; 1249; 1102; 1054; 1013. ^{1}H NMR (D_2O) δ 4.69–4.67 (m,1H, H_2 or H_5); 4.61–4.58 (m, 1H, $H_{2'}$); 4.40–4.33 (m, 2H, $H_{3'}$ and H_5 or H_2); 4.13 (dd, 1H, $H_{1'a}$, $J=8.6$, 13.0 Hz); 4.02–3.97 (m, 1H, H_{6a} or H_{1a}); 3.98 (dd, 1H, $H_{4'a}$, $J=2.7$, 12.7 Hz); 3.89–3.75 (m, 5H, H_3, H_4, H_{6b} or H_{1b}, $H_{1'b}$ and $H_{4'b}$); 3.72 (dd, 1H, H_{1a} or H_{6a}, $J=7.6$, 14.9 Hz); 3.65–3.61 (m, 1H, H_{1b} or H_{6b}). ^{13}C NMR (D_2O) δ 79.8 ($C_{3'}$); 74.3 (C_4 or C_3); 74.1 (C_4 or C_3); 69.9 (C_2 or C_5); 66.8 ($C_{2'}$); 65.4 (C_5 or C_2); 59.5 ($C_{4'}$); 47.5 (C_6 or C_1); 43.1 ($C_{1'}$); 39.4 (C_1 or C_6). HRMS (ESI+) calcd for $[M+Na]^+$ 387.0396. Found 387.0391.

5.4. Inhibition studies

α-glucosidase from rice, α-glucosidase from baker's yeast, β-glucosidase from almond, α-galactosidase from green coffee beans, β-galactosidase from *Aspergillus oryzae*, α-mannosidase from jack beans and all substrates (4- or 2-nitrophenyl α or β-glycopyranosides) were purchased from Sigma. Assays were run at 25 °C in a phosphate buffer (25 mM) at pH 6.8 using the corresponding 4-nitrophenyl-glycoside in a total volume of 1 mL. The potential inhibitors were tested at a final concentration of 1 mM and the amount of enzyme of each assay was adjusted so that the system would give the initial rate. After two incubation times (5 and 30 min) of the enzyme in the presence of the tested molecule, the substrate was added and the optical absorbance was followed at 400 nm. The initial rate was determined, compared with that obtained without the test compound, and the percentage inhibition was calculated. When the percentage inhibition was higher than 33%, the K_i was determined by the Hanes–Woolf method. Four substrate concentrations (0.04 to 2.5 mM) and four inhibitor concentrations (0.005 to 0.8 mM) were chosen. The K_i was then calculated from the Michaelis–Menten (K_M and four K'_M) constants obtained in the presence or absence of inhibitor. When the percentage of inhibition was between 33 and 10%, the K_i was determined with the equation $K_i=[I]/(K'_M/K_M-1)$, using only one K'_M value.

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Efficient and fast Heck vinylation of 2-bromo-6-methyl pyridines with methylacrylate. Application to the synthesis of 6-methyl cyclopenta[*b*]pyridinone

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Abstract—Heck vinylation of 2-bromo-6-methyl-3-substituted pyridines using η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ complex/toluene and dimethylacetamide (DMA) as co-solvent with methyl acrylate is reported. Electronic and steric effects were investigated engaging diversely 2-bromo-3,6-disubstituted pyridines. As application, a new synthesis of the 6-methyl cyclopenta[*b*]pyridinone building-block connecting Heck vinylation, alkene reduction and Dieckmann condensation is described.

1. Introduction

The Heck palladium-catalyzed vinylation reaction is one of the most attractive tools for the C–C bond formation in organic synthesis.[1] In contrast to Kumada, Suzuki, Stille and others cross-coupling reactions using vinylmetal compounds, the Heck-type olefination is a more functional group tolerant and low cost reaction. Among numerous examples of Heck reactions of halopyridines we counted only, to the best of our knowledge, 11 Heck vinylation reactions of 2-halopyridines with acrylate derivatives allowing good to moderate yields.[2] Nitrogen-based heteroaryls such as pyridines represent highly efficient ligands in-themselves.[3] Thus 2-halopyridines revealed as bad substrates for Heck vinylation probably due to the formation after oxidation step of a pyridyl-bridge palladium dimer preventing further coupling reaction steps.[4,5] Recently we focused our research program on an efficient preparation of numerous 3-substituted-6-methyl-pyridine acrylates **I** applied to a straightforward route to new annulated-cycloalkylpyridines **II**. This framework is present in numerous biologically active compounds[6,2i] such as novel 8-azasteroïd analogues[6a,e] **III** and natural product such as cananodine[7] **IV** (Fig. 1).

Herein, we report a new quantitative and fast kinetic Heck vinylation of a panel of 3-substituted-2-bromo-6-methyl-pyridines using η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ complex/toluene and dimethylacetamide (DMA) as co-solvent. As direct application the 6-methyl cyclopenta[*b*]pyridinone **1** as precursor of novel 8-azasteroïd analogues[6e] was ready prepared via a reduction/Dieckmann condensation sequence.

2. Results and discussion

2.1. Synthesis of 2-bromo-6-methylpyridines

Treatment of 2-hydroxy-6-methylnicotinic acid **2** with $POBr_3$ in refluxed chlorobenzene followed by cold methanol treatment directly provided 2-bromo-6-methyl-nicotinate **3** (Scheme 1). DIBAL reduction of 2-bromo-6-methyl 3-cyanopyridine **4** afforded 2-bromo-3-formyl-6-methyl pyridine **5**. The protected 2-bromo-3-hydroxy-6-methylpyridines **8**, **9** were synthesized in a two steps procedure, bromination of 6-methyl-3-hydroxypyridine **6** affording 2-bromo-3-hydroxy-6-methylpyridine **7** followed by methoxymethyl (MOM) or triflate (OTf) protection of the hydroxyl group (Scheme 1).

2.2. Heck vinylation reaction of 2-bromopyridines with methyl acrylate

We were first interested on the Heck coupling reaction of

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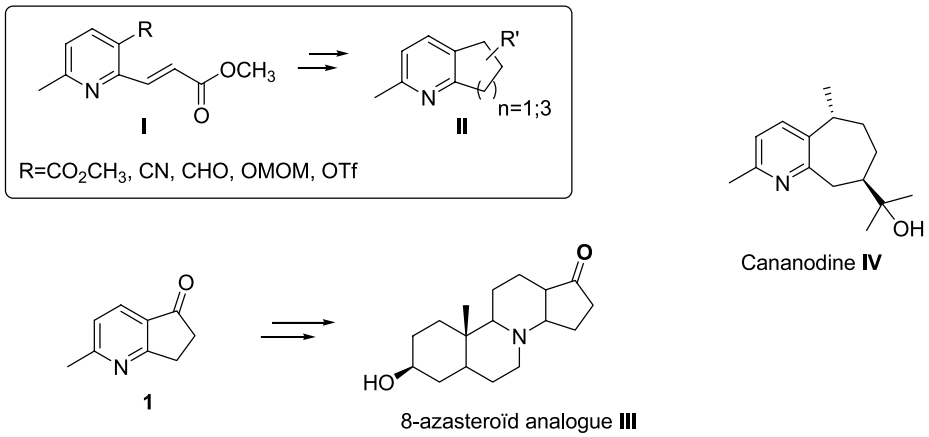
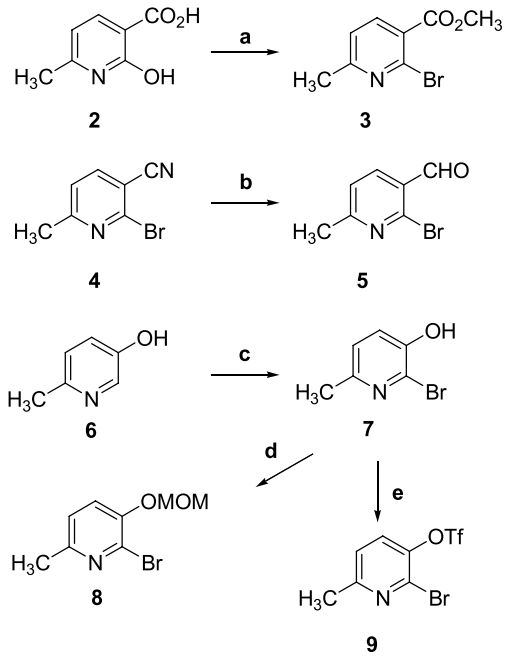


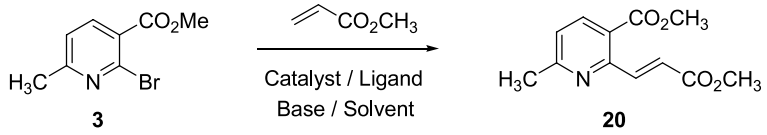
Figure 1.



Scheme 1. (a) $POBr_3$, chlorobenzene, Py then MeOH, O °C, 70% (b) DIBAL-H, toluene, −78 °C, 93% (c) Br_2, Py, 69% (d) MOMCl, DIPEA, CH_2Cl_2, 76% (e) Tf_2O, Py, CH_2Cl_2, 95%.

2-bromo-6-methylnicotinate **3** with methyl acrylate in order to prepare the cyclopenta[c]pyridinone **1**. The initial different assays were summarized in Table 1. Standard Heck conditions for heteroaromatic system [$Pd(OAc)_2$/P(o-tol)$_3$ (1:2), DMF, 130 °C, 24 h][8] were completely inefficient with our substrates (entry 1). Following the Jeffery's conditions[9a,b] using tetrabutylammonium salts[9c] as phase-transfer catalyst and a more polar solvent such as dimethylacetamide (DMA), the 2-pyridyl acrylate compound **20** was obtained only in poor 10% yield (entry 2). Note that any improvement was observed by replacing NaOAc by K_2CO_3 and Cs_2CO_3 bases or over a 48 h refluxing period. We thus decided to use the recent Little and Fu conditions [$Pd_2(dba)_3$/P(^{t}Bu)$_3$ (1:4), Dioxane, reflux, 24 h][10] affording a modest 56% yield of 2-pyridyl acrylate **20** (entry 3). A survey of the literature revealed that Reider and co-workers[2f] carried out the Heck coupling reaction of 6-butyl-2-bromo-3-formyl pyridine with *ter*-butyl acrylate in 85% yield using allylpalladium chloride dimer catalyst, tri-*o*-tolylphosphine and sodium acetate in toluene during a 20 h refluxing period. Using the same conditions the 2-pyridyl acrylate **20** was obtained in 45% yield (entry 4). It should be easily improved using a more polar co-solvent, dimethylacetamide (DMA). Surprisingly complete conversion was obtained in only 5 h (GC-MS monitoring) leading to 84% of pure product (entry 5). Longer refluxing period decreases the yield and higher temperature reaction led to rapid decomposition of the catalyst as black palladium mirror.

Table 1. Heck vinylation of 2-bromo-6-methyl nicotinate with methyl acrylate

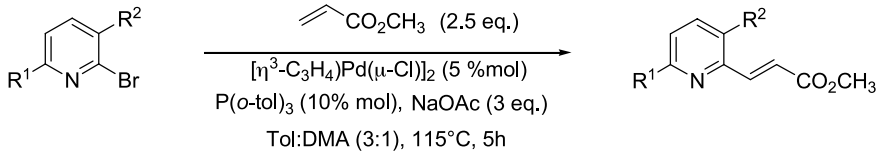


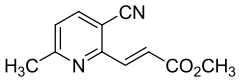
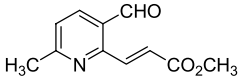
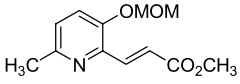
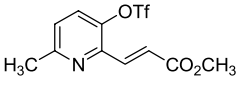
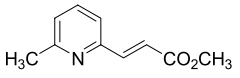
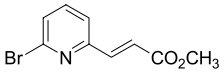
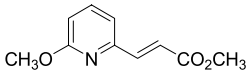
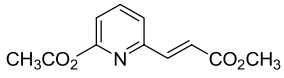
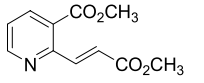
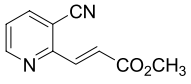
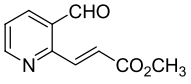
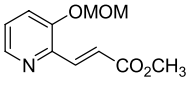
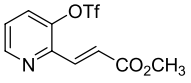
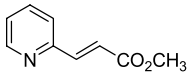
Entry	Catalyst/ligand	Base	Solvent/temperature (°C)	Time (h)	Yield[a]
1	$Pd(OAc)_2$, P(o-tol)$_3$ (1:2)	Et_3N	DMF, 130	24	—
2	$Pd(OAc)_2$, P(o-tol)$_3$ (1:2) Bu_4NHSO_4 (1eq.)	NaOAc	DMA, 100	48	10
3	$Pd_2(dba)_3$, P(^{t}Bu)$_3$ (1:4)	Cs_2CO_3	Dioxane, 85	24	56
4	[(η^3-(C_3H_4)Pd(μ-Cl)]$_2$, (*o*-Tol)$_3$P (1:2)	NaOAc	Toluene, 100	20	45
5	[(η^3-(C_3H_4)Pd(μ-Cl)]$_2$, (*o*-Tol)$_3$P (1:2)	NaOAc	Toluene/DMA (3:1), 100	5	84

[a] Isolated yields, average two runs. DMF: dimethylformamide; DMA: *N*,*N*-dimethylacetamide.

The efficiency of this new Heck vinylation procedure was then tested with a large panel of 3-substituted 2-bromo-6-methyl pyridines substrates (Table 2, entries 1–4). Heck vinylations of 3-carboxy 6-methyl pyridine derivatives **4**, **5** gave excellent 81 and 91% yields (entries 1–2). The same reaction carried out without DMA failed. It should be noted that the original Heck condition [$Pd(OAc)_2$/P(*o*-tol)$_3$ (1:4), DMF, 130 °C, 24 h][8] failed with 3-cyano compound **4** and gave only 8% of 2-pyridyl acrylate **22** starting with the 3-formyl-6-methyl pyridine **5**. In a similar way Little and Fu's conditions [$Pd_2(dba)_3$/P(^{t}Bu)$_3$ (1:4), $CsCO_3$ (1.1 equiv), Dioxane, reflux, 24 h][10] was surprisingly inefficient with the 3-carboxy-6-methyl pyridine substrates **4**, **5**. Protected 3-hydroxy-6-methyl pyridine derivatives **8**–**9** could be easily coupled with methyl acrylate using the new procedure (entries 3,4). Moreover, Heck coupling reaction

Table 2. Heck vinylation of 2-bromopyridine derivatives with methylacrylate



Entry	R^1	R^2		Product		Yield[a]
1	CH_3	CN	**4**		**21**	81
2	CH_3	CHO	**5**		**22**	91
3	CH_3	OMOM	**8**		**23**	82
4	CH_3	OTf	**9**		**24**	61
5	CH_3	H	**10**		**25**	65
6	Br	H	**11**		**26**	92
7	OCH_3	H	**12**		**27**	98
8	CO_2CH_3	H	**13**		**28**	99
10	H	CO_2CH_3	**14**		**29**	36
11	H	CN	**15**		**30**	35
12	H	CHO	**16**		**31**	42
13	H	OMOM	**17**		**32**	27
14	H	OTf	**18**		**33**	9
15	H	H	**19**		**34**	None

[a] Isolated yields, average of two runs.

of the 3-pyridyl triflate **9** with methyl acrylate occurred selectively at the C-2 position. We further extended our procedure to 3 or 6-substituted 2-bromopyridines (entries 5–8, 10–14, Table 2) in order to study the influence of steric and electronic effects. We first observed that the Heck vinylation with methyl acrylate of diversely 2-bromopyridines **11**–**13** substituted at the C-6 position as well as with electron donor and withdrawing electron groups successfully gave good to excellent yields of 2-pyridylacrylates **26**–**28** (entries 5–8, Table 2).

Note that Pd-olefination of 6-methyl-2-bromopyridine **10**, the less hindrered model at C-6 position, occurred in a more modest 65% yield. These results suggest that steric hindrance at C-6 position is the main factor of a successful Heck vinylation probably by preventing the coordination of the nitrogen atom of the pyridine with the catalyst likely avoiding the formation of the unreactive pyridyl-bridge palladium dimer after the oxidation step.[3,4]

Heck vinylation of 2-bromopyridines **14**–**16** only substituted at C-3 position afforded 2-pyridylacrylates **29**–**31** in 36–42% modest yields (entries 10–12). We noticed that a 20 h refluxing period or the use of 20 mol% catalyst do not improve the yield and surprisingly more than 50% of starting material was already recovered. Further assays with protected 3-hydroxy pyridine **17** and 3-pyridyl triflate **18** provided the corresponding 2-pyridyl acrylates **32**, **33** with poor 27 and 9% yields, respectively (entries 13,14). Furthermore, the Heck vinylation of the naked 2-bromopyridine **19** failed under new conditions (entries 15). The results clearly show that the yield of Heck vinylation depend on the chelating power of the group at C-3 position ($CHO > CO_2CH_3 \sim CN > OMOM \sim OTf$) which competes with the nitrogen atom of the pyridine as potential ligand and should prevent partially the formation of the unreactive dimer.[3,4]

2.3. Application to the synthesis of 6-methyl-cyclopenta[*b*]pyridinone

We applied our new procedure to propose the synthesis of the 6-methyl-cyclopenta[*b*]pyridinone **1** which has been only once reported but in a poor 5.5% global yield over four steps from cyclopenta-1,3-dione.[11] A two-steps sequence was thus envisioned from β-2-pyridyl acrylate **20**. Hydrogenation of the double-bond under soft condition provided the diester compound **35** followed by a Dieckmann condensation-decarboxylation[12] sequence to give the 6-methyl-cyclopenta[*b*]pyridinone **1** in a 81% overall yield (Scheme 2).

3. Conclusion

The use of η^3-allylpalladium chloride dimer/P(*o*-Tol)$_3$ in the presence of toluene associated to dimethylacetamide (DMA) as a co-solvent provided a convenient catalyst system for fast Heck vinylation 2-bromo-3,6-disubstituted pyridines and 2-bromo-6-disubstituted pyridines. The efficiency of the catalyst system with 2-bromo-3-substituted pyridines is however lower. Application to the synthesis of the potential starting material for the synthesis of 8-azasteroïd analogue[6e] 6-methyl-cyclopenta[*b*]pyridinone **1** was achieved via a reduction/Dieckmann condensation sequence in 57% yield over three steps starting from commercially available 2-hydroxy-3-carboxy-6-methyl pyridine **2**. Moreover, Heck vinylation of the 2-bromo-3-triflyl-6-methyl pyridine **9** with methyl acrylate provides selectively the (3-triflyl-6-methyl 2-pyridyl) acrylate **24** which could be a good candidate for the synthesis of cananodine.[7]

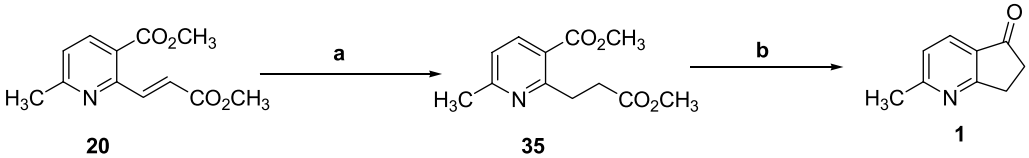
4. Experimental

4.1. General

Tetrahydrofuran (THF), ether (Et_2O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Methanol and ethanol were distilled from magnesium turning. dimethylacetamide was distilled under 4 Å molecular sieves. For flash chromatography, Merck silica gel (70–230 mesh) was used. The melting points were measured on a Kofler melting points apparatus and were not corrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance-300 spectrometer operating at 300 MHz. Commercially available starting materials were used without further purification. Infrared spectra were recorded on a Perkin-Elmer IRTF 1650 spectrophotometer. Elemental analysis of compounds was carried out on a Carlo Erba 1160. Mass spectrum was recorded on a JEOL JMS AX-500 spectrometer, in electronic impact (EI). The starting compounds **4**, **10**–**13**, **15**, **16**, **19** are commercially available. The compounds **14**,[13] **18**[14] are prepared according to the procedures described in literature.

4.2. Synthesis of 2-bromo pyridines substrates

4.2.1. Methyl 2-bromo-6-methylpyridine-3-carboxylate (3). Phosphoryl tribromide (6.14 g, 21.4 mmol) was added by small portion to a solution of nicotonic acid **2** (1.43 g, 9.3 mmol), pyridine (251 μl) and chlorobenzene (30 ml) at



Scheme 2. (a) H_2 (1 atm), Pd/C (10 mol%), MeOH, rt, 94% (b) MeONa (1.5 equiv), THF, refux, 2 h then HCl (4.5 M), reflux 86%.

room temperature under N_2. The mixture was refluxed for 1 h and concentrated under vacuum before treating with an excess of cold methanol (4 ml). The solution was stirred for an additional 1 h and again concentrated under vacuum. The residue was dissolved in (15 ml) and freeze water was added (10 ml). The pH was adjusted to 8 by adding K_2CO_3 before extraction of the product with CH_2Cl_2. The organic layer was washed with 10% aq Na_2CO_3 (10 ml), satd aq. NH_4Cl (10 ml) and dried ($MgSO_4$). After evaporation of the solvent the crude oil was chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to give **3** as a colourless oil (1.50 g, 70%); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 7.02 (d, 1H, $J=7.8$ Hz, H_{5pyr}), 7.80 (d, 1H, $J=7.8$ Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 24.0, 52.4,121.7, 125.8, 139.6, 162.3, 165.0; IR (KBr) ν 2953, 1732 (C=O ester), 1589, 1493, 1345, 1275–1249, 1145, 1051. Anal. Calcd for $C_8H_8BrNO_2$ (230.08): C, 41.77; H, 3.51; N, 6.09. Found: C, 41.73; H, 3.42; N, 6.24%.

4.2.2. 2-bromo-6-methylpyridine-3-carbaldehyde (5). A solution of 2-bromo-6-methylpyridine-3-carbonitrile **4** (1 g, 5.1 mmol) in toluene (15 ml) was cooled at −60 °C. Diisobutylaluminium hydride (3.4 ml of 1.5 M solution in toluene, 5.12 mmol) was added dropwise over a 45 min period while the temperature was maintained under −50 °C. The solution was stirred for 2.5 h at −50 °C and then carefully quenched by the dropwise addition of a mixture of 2 M sulfuric acid (10 ml), toluene (6 ml), and THF (3 ml). The resulted mixture was stirred for 16 h at room temperature and water (15 ml) was added. The organic layer was separated, washed with water (10 ml), brine and concentrated in vacuo to afford **5** as a yellow solid (929 mg, 93%) which was used without further purification; mp 66 °C; ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H, CH_3), 7.27 (d, 1H, $J=7.6$ Hz, H_{5pyr}), 8.07 (d, 1H, $J=7.6$ Hz, H_{4pyr}), 10.30 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 25.1, 123.5, 128.5, 138.4, 145.2, 166.1, 191.4; IR (KBr) ν 3346, 2886, 1979, 1690(C=O ester), 1584, 1341, 1058, *m/z* (EI) 200.0; Anal. Calcd for C_7H_6BrNO (199.98): C, 42.03; H, 3.02; N, 7.00. Found: C, 42.36; H, 2.85; N, 7.21%.

4.2.3. 2-bromo-6-methylpyridin-3-ol (7). A solution of bromide (1.14 ml, 22.2 mmol) in pyridine (20 ml) was slowly added over a 10 min period to a solution of 6-methylpyridin-3-ol **6** (2.2 g, 20.2 mmol) in pyridine (40 ml) at room temperature. The reaction mixture was stirred for an additional 1.5 h and concentrated under vacuum. Water was added (15 ml) until complete precipitation. The beige solid obtained corresponding to **7** was filtered, washed by cool water and dry under reduced pressure (2.6 g, 69%); mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 6.98 (d, 1H, $J=8.0$ Hz, H_{5pyr}), 7.12 (d, 1H, $J=8.0$ Hz, H_{4pyr}), 10.25 (1H, OH); ^{13}C NMR ($CDCl_3$) δ 22.6, 123.6, 124.1, 129.3, 148.8, 149.0; IR (KBr) ν 2923–2431, 1560, 1494, 1293, 1218, 1083; *m/z* (EI) 187.0(98%), 189(100%); Anal. Calcd for C_6H_6BrNO (188.02): C, 38.33; H, 3.22; N, 7.45. Found: C, 38.15; H, 3.14; N, 7.53%.

4.2.4. 2-bromo-3-(methoxymethoxy)-6-methylpyridine (8). Diisopropylethylenediamine DIPEA (2 ml, 11.1 mmol) and chloro(methoxy)methane (565 µl, 7.5 mmol) was added to a solution of 2-bromo-6-methylpyridin-3-ol **7** (700 mg, 3.7 mmol) in dry CH_2Cl_2 (45 ml) at 0 °C under N_2. The solution was stirred for 1 h at 0 °C and for 12 h at room temperature and then quenched with water (10 ml). Extraction with CH_2Cl_2 (2×15 ml), washing with brine, drying with $MgSO_4$ and concentration in vacuo afford **8** a colorless oil (660 mg, 76%) which was used without further purification; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.40 (s, 3H, CH_2OCH_3), 5.12 (s, 2H, OCH_2O), 6.92 (d, 1H, $J=8.3$ Hz, H_5), 7.22 (d, 1H, $J=8.3$ Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 23.4, 56.7, 95.5, 123.2, 124.2, 132.5, 148.8, 152.3; IR (KBr) ν 2958–2926, 1557, 1455, 1269, 1156, 1062, 972; *m/z* (EI) 231.0(98%), 233.0(100%); Anal. Calcd for $C_8H_{10}BrNO_2$ (232.11): C, 41.40; H, 4.34; N, 6.04. Found: C, 41.48; H, 4.21; N, 6.37%.

4.2.5. 2-bromo-6-methylpyridin-3-yl trifluoromethanesulfonate (9). A solution of 2-bromo-6-methylpyridin-3-ol **7** (1 g, 5.3 mmol) and pyridine (800 µl, 10.6 mmol) in CH_2Cl_2 (30 ml) was cooled to 0 °C before adding slowly triflic anhydride (1.08 ml, 6.4 mmol). The mixture was stirred for 1 h at 0 °C and for 12 h at room temperature and quenched by addition of water (10 ml). The pH of the aqueous phase was adjusted to 9 by adding K_2CO_3 before extraction with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$). After evaporation of the solvent, the crude product was chromatographed on silica gel using AcOEt/Petrol (20:80) as eluent to give of **9** as a yellow oil (1.62 g, 95%); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 7.02 (d, 1H, $J=8.3$ Hz, H_5), 7.33 (d, 1H, $J=8.3$ Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 23.9, 1186.7, 123.9, 131.1, 134.7, 142.9, 159.9; IR (KBr) ν 1584–1565, 1431, 1217, 1139, 1052; *m/z* (EI) 319(98%), 321(100%); Anal. Calcd for $C_7H_5BrF_3NO_3S$ (320.09): C, 26.27; H, 1.57; N, 4.38. Found: C, 26.27; H, 1.69; N, 4.49%.

4.2.6. 2-bromo-3-(methoxymethoxy)pyridine (17). The procedure described above, using 2-bromopyridin-3-ol (647 mg, 3.72 mmol) instead of 2-bromo-6-methylpyridin-3-ol, gave **17** (527 mg, 65%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H, CH_2OCH_3), 5.22 (s, 2H, OCH_2O), 7.15 (dd, 1H, $J=8.1$, 4.5 Hz, H_5), 7.36 (dd, 1H, $J=1.1$, 8.1 Hz, H_4), 7.97 (dd, 1H, $J=4.5$, 1.1 Hz, H_3); ^{13}C NMR ($CDCl_3$) δ 56.9, 95.3, 123.5, 123.8, 133.7, 142.9, 151.1; IR (KBr) ν 2959–2933, 1560, 1452, 1414, 1270, 1156, 1092–1053, 971; *m/z* (EI) 217(98%), 219(100%); Anal. Calcd for $C_7H_8BrNO_2$ (218.07): C, 38.56; H, 3.70; N, 6.42. Found: C, 38.59; H, 3.98; N, 6.88%.

4.3. Synthesis of pyridine acrylates (20–34)

4.3.1. Methyl 2-((*E*)-2-(methoxycarbonyl)vinyl)-6-methylpyridine-3-carboxylate (20). A degassed mixture of methyl 2-bromo-6-methylpyridine-3-carboxylate **3** (0.30 g, 1.3 mmol), methyl acrylate (293 µl, 3.3 mmol), allylpalladium chloride dimer $Pd_2(allyl_2Cl_2)$ (24 mg, 0.065 mmol), P(*o*-Tol)$_3$ (40 mg, 0.13 mmol), Na_2CO_3 (320 mg, 3.9 mmol), toluene (2.53 ml) and dimethyacetamide DMA (0.84 ml) was heated in a sealed tube at 115 °C for 5 h. The reaction mixture was filtrated though Celite, washed with AcOEt and concentrated in vacuo. The residue was chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to afford **20** (256 mg, 84%) as a white solid; mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, CH_3), 3.82(s, 3H, CO_2CH_{3pyr}), 3.94 (s, 3H, CO_2CH_{3acry}), 7.09 (d,

1H, $J=15.4$ Hz, H), 7.19 (d, 1H, $J=8.1$ Hz, H_5), 8.11 (d, 1H, $J=8.1$ Hz, H_4), 8.51 (D, 1H, $J=15.4$ Hz, H), ^{13}C NMR ($CDCl_3$) δ 25.2, 52.2, 53.0, 123.6, 123.8, 125.1, 139.2, 141.28, 152.2, 162.3, 166.7, 167.6; IR (KBr) ν 2933–2953, 1714 (C=O ester); 1588, 1466–1438, 1319–1170, 1077 (C–O); *m/z* (EI) 235.0; Anal. Calcd for $C_{12}H_{13}NO_4$ (235.09): C, 61.28; H, 5.56; N, 5.95. Found: C, 61.34; H, 5.39; N, 6.08%.

4.3.2. (*E*)-Methyl 3-(3-cyano-6-methylpyridin-2-yl)acrylate (21). The procedure described above, using 2-bromo-6-methylpyridine-3-carbonitrile **4**, gave **21** (213 mg, 81%) as a yellow solid; mp 138 °C; ^1H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3), 3.86 (s, 3H, CO_2CH_3), 7.25 (d, 1H, $J=8.1$ Hz, H_5), 7.26 (d, 1H, $J=15.2$ Hz, H_{acry}), 7.85 (d, 1H, $J=8.1$ Hz, H_4), 7.97 (d, 1H, $J=15.2$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 25.1, 52.1, 106.8, 116.1, 123.6, 126.4, 137.9, 140.3, 154.1, 163.1, 166.4; IR (KBr) ν 3071–2963, 2225 (C≡N), 1721 (C=O ester), 1583, 1457, 1179; *m/z* (EI) 202.0; Anal. Calcd for $C_{11}H_{10}N_2O_2$ (202.19): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.24; H, 4.34; N, 13.22%.

4.3.3. (*E*)-Methyl 3-(3-formyl-6-methylpyridin-2-yl)-acrylate (22). The procedure described above, using 2-bromo-6-methylpyridine-3-carbaldehyde **5**, gave **22** (243 mg, 91%) as a yellow solid; mp 110 °C; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H, CH_3), 3.85 (s, 3H, CO_2CH_3), 7.20 (d, 1H, $J=15.2$ Hz, H_{acry}), 7.32 (d, 1H, $J=8.0$ Hz, H_5), 8.07 (d, 1H, $J=8.0$ Hz, H_4), 8.47 (d, 1H, $J=15.2$ Hz, H_{acry}), 10.40 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 25.1, 51.9, 124.3, 126.3, 127.0, 137.9, 138.4, 152.7, 163.8, 164.8, 190.0; IR (KBr) ν 2962, 1725, 1699, 1562, 1452, 1300, 1200, 1181; *m/z* (EI) 205.0; Anal. Calcd for $C_{11}H_{11}NO_3$ (205.25): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.22; H, 5.46; N, 6.52%.

4.3.4. (*E*)-Methyl 3-(3-(methoxymethoxy)-6-methylpyridin-2-yl)acrylate (23). The procedure described above, using 2-bromo-3-(methoxymethoxy)-6-methylpyridine **8**, gave **23** (253 mg, 82%): colourless oil; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.44 (s, 3H, CH_2OCH_3), 3.78 (s, 3H, CO_2CH3), 5.19 (s, 2H, OCH2O), 7.00 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.05 (d, 1H, $J=8.7$ Hz, H_5), 7.34 (d, 1H, $J=8.7$ Hz, H_4), 8.05 (d, 1H, $J=15.8$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.0, 52.1, 56.7, 95.0, 121.8, 123.2, 125.4, 138.5, 144.9, 150.7, 151.8, 168.1; IR (KBr) ν 2955–2842, 1717, 1637, 1740–1436, 1320, 1250, 1167; *m/z* (EI) 237.0; Anal. Calcd for $C_{12}H_{15}NO_4$ (237.30): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.64; H, 6.24; N, 5.86%.

4.3.5. 2-((*E*)-2-(Methoxycarbonyl)vinyl)-6-methylpyridin-3-yl trifluoromethanesulfonate (24). The procedure described above, using 2-bromo-6-methylpyridin-3-yl trifluoromethanesulfonate **9**, gave **24** (258 mg, 61%) as a yellow oil; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H, CH_3), 3.82 (s, 3H, CO_2CH_3), 7.15 (d, 1H, $J=15.4$ Hz, H_{acry}), 7.22 (d, 1H, $J=8.6$ Hz, H_5), 7.53 (d, 1H, $J=8.6$ Hz, H_4), 7.83 (d, 1H, $J=15.4$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.5, 52.3, 116.7, 121.0, 125.8, 125.9, 130.3, 134.8, 143.6, 144.6, 159.2, 166.9; IR (KBr) ν 3248, 3079–2850, 1727, 1454–1428, 1216, 1136; *m/z* (EI) 325.0; Anal. Calcd for $C_{11}H_{10}F_3NO_5S$ (325.29): C, 40.62; H, 3.10; N, 4.31; S,9.86. Found: C, 40.63; H, 2.97; N, 4.31; S, 9.74%.

4.3.6. (*E*)-Methyl 3-(6-methylpyridin-2-yl)acrylate (25). The procedure described above, using 2-bromo-6-methylpyridine **10**, gave **25** (150 mg, 65%) as a beige solid; mp 72 °C; ^1H NMR ($CDCl_3$) δ 2.92 (s, 3H, CH_3), 3.75 (s, 3H), 6.87 (d, 1H, $J=15.8$ Hz, H_{acry}); 7.06 (d, 1H, $J=7.5$ Hz, H_5), 7.16 (d, 1H, $J=7.5$ Hz, H_3), 7.52 (d, 1H, $J=7.5$ Hz, H_4), 7.61 (d, 1H, $J=15.8$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 24.5, 51.7, 121.2, 121.5, 124.0, 136.8, 143.9, 152.1, 158.9, 167.3; IR (KBr) ν 3407, 3026–2960, 1723, 1591–1577, 1473, 1344, 1202; *m/z* (EI) 177.0 Anal. Calcd for $C_{10}H_{11}NO_2$ (177.21): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.78; H, 6.21; N, 7.87%.

4.3.7. (*E*)-Methyl 3-(6-bromopyridin-2-yl)acrylate (26). The procedure described above, using 2,6-dibromopyridine **11**, gave **26** (290 mg, 92%): white powder; mp 138 °C; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H, CO_2CH_3), 6.96 (s, 1H, $J=15.6$ Hz, H_{acry}), 7.33 (d, 1H, $J=7.5$ Hz), 7.42 (d, 1H, $J=7.5$ Hz), 7.55 (d, 1H, $J=7.5$ Hz), 7.56 (d, 1H, $J=15.6$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 52.0, 123.0, 123.4, 128.7, 139.0, 141.6, 142.6, 154.0, 166.9; IR (KBr) ν 2924, 1727, 1646, 1571–1549, 1437, 1320–1300, 1209–1121, 973; *m/z* (EI) 241(100%), 243(98%); Anal. Calcd for $C_9H_8BrNO_2$ (242.11): C, 44.66; H, 3.33; N, 5.79. Found: C, 44.49; H, 3.62; N, 5.72%.

4.3.8. (*E*)-Methyl 3-(6-methoxypyridin-2-yl)acrylate (27). The procedure described above, using 2-bromo-6-methoxypyridine **12**, gave **27** (246 mg, 98%): colourless oil; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H, CO_2CH_3), 3.91 (s, 3H, OMe), 6.89 (d, 1H, $J=8.3$ Hz, H_5), 6.90 (d, 1H, $J=8.3$ Hz, H_3), 6.93 (d, 1H, $J=15.4$ Hz, H_{acry}), 7.51 (d, 1H, $J=8.3$ Hz, H_4), 7.54 (d, 1H, $J=15.4$ Hz, H_{acry}); ^{13}C NMR ($CDCl_3$) δ 51.7, 53.2, 112.8, 118.4, 121.2, 138.9, 143.2, 150.0, 163.6, 167.4; IR (KBr) ν 3407, 3026–2960, 1723, 1591–1577, 1473, 1344, 1202; *m/z* (EI) 193.0; Anal. Calcd for $C_{10}H_{11}NO_3$ (193.23): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.73; N, 7.07%.

4.3.9. Methyl 6-((*E*)-2-(methoxycarbonyl)vinyl)pyridine-2-carboxylate (28). The procedure described above, using methyl 6-bromopyridine-2-carboxylate **13**, gave **28** (285 mg, 99%): beige powder; mp 112 °C; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, CO_2CH_3), 3.99 (s, 3H, CO_2CH_3), 6.95 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.61 (d, 1H, $J=7.9$ Hz), 7.75 (d, 1H, $J=15.8$ Hz, H_{acry}), 7.85 (d, 1H, $J=7.9$ Hz, H_4), 8.06 (d, 1H, $J=7.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 52.3, 53.4, 123.8, 125.7, 126.7, 138.2, 143.1, 148.7, 153.6, 165.8, 167.1; IR (KBr) ν 2964–2852, 1725, 1458, 1438, 1316–1301, 1245, 1155, 977; *m/z* (EI) 221.0 Anal. Calcd for $C_{11}H_{11}NO_4$ (221.22): C, 59.73; H, 5.01; N, 6.33. Found: C, 59.81; H, 5.14; N, 6.13%.

4.3.10. Methyl 2-((*E*)-2-(methoxycarbonyl)vinyl)pyridine-3-carboxylate (29). The procedure described above, using methyl 2-bromopyridine-3-carboxylate **14**, gave **29** (110 mg, 36%): yellow oil; ^1H NMR ($CDCl_3$) δ 3.81(s, 3H, CO_2CH_3), 3.95 (s, 3H, CO_2CH_3), 7.10 (d, 1H, $J=15.1$ Hz, H_{acry}), 7.34 (dd, 1H, $J=7.9$, 4.9 Hz, H_5), 8.22 (dd, 1H, $J=1.9$, 8.1 Hz, H_4), 8.48 (d, 1H, $J=15.4$ Hz, H_{acry}), 8.73 (dd, 1H, $J=1.9$, 4.9 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.2, 53.1, 123.9, 125.4, 125.9, 138.9, 140.9, 152.7, 152.9, 166.4,

167.5; IR (KBr) ν 3046–2854, 1717 (C=O ester); 1588, 1630, 1560, 1421, 1284–1258, 1083 (C–O); *m/z* (EI) 221.0.

4.3.11. (*E*)-Methyl 3-(3-cyanopyridin-2-yl)acrylate (30). The procedure described above, using 2-bromopyridine-3-carbonitrile **15**, gave **30** (86 mg, 35%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H, CO_2CH_3), 7.23 (d, 1H, J=15.4 Hz, H_{acry}), 7.40 (dd, 1H, J=4.5, 7.9 Hz, H_5), 7.98 (d, 1H, J=15.4 Hz, H_{acry}), 7.97 (dd, 1H, J=1.5, 7.9 Hz, H_4), 8.17 (dd, 1H, J=1.5, 4.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.5, 110.1, 116.0, 122.2, 127.0, 138.1, 140.8, 153.3, 155.1, 166.6; IR (KBr) ν 3077, 2947–2853, 2229, 1724, 1557, 1437, 1312, 1245–1172, 977; *m/z* (EI) 188.0.

4.3.12. (*E*)-Methyl 3-(3-formylpyridin-2-yl)acrylate (31). The procedure described above, using 2-bromopyridine-3-carbaldehyde **16**, gave **31** (104 mg, 42%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, CO_2CH_3), 7.18 (d, 1H, J=15.4 Hz, H_{acry}), 7.46 (dd, 1H, J=7.9, 4.5 Hz, H_5), 8.17 (dd, 1H, J=7.9, 1.5 Hz, H_4), 8.47 (d, 1H, J=15.4 Hz, H_{acry}), 8.80 (dd, 1H, J=4.5, 1.5 Hz, H_6), 10.43 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 52.5, 124.8, 126.9, 129.7, 138.1, 138.8, 153.6, 154.1, 167.2, 190.6, IR (KBr) ν 2957, 1724–1702, 1560, 1438, 1308, 1189,–1170; *m/z* (EI) 191.0; Anal. Calcd for $C_{10}H_9NO_3$ (191.19): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.78; N, 6.64%.

4.3.13. (*E*)-Methyl 3-(3-(methoxymethoxy)pyridin-2-yl)acrylate (32). The procedure described above, using 2-bromo-3-(methoxymethoxy)pyridine **17**, gave **32** (78 mg, 27%): colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_2OCH_3), 3.74 (s, 3H, CO_2CH_3), 5.19 (s, 2H, OCH_2O), 6.95 (d, 1H, J=15.8 Hz, H_{acry}), 7.17 (dd, 1H, J=4.1, 8.6 Hz, H_5), 7.41 (dd, 1H, J=8.6, 1.1 Hz, H_4), 8.05 (d, 1H, J=15.8 Hz, H_{acry}), 8.20 (dd, 1H, J=1.1, 4.1 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.1, 56.8, 94.8, 122.1, 122.5, 125.6, 138.2, 143.1, 143.2, 152.7, 168.0; IR (KBr) ν 3360, 2953–2925, 1714, 1575, 1442, 1309, 1201–1165, 983; *m/z* (EI) 223.0; Anal. Calcd for $C_{11}H_{13}NO_4$ (223.28): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.26; H, 6.43; N, 6.41%.

4.3.14. (*E*)-Methyl 3-(3-(trifluoromethylsulfonyl)pyridin-2-yl)acrylate (33). The procedure described above, using 2-bromopyridin-3-yl trifluoromethanesulfonate **18**, gave **33** (36 mg, 9%): yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, CO_2CH_3), 7.10 (d, 1H, J=15.4 Hz, H_{acry}), 7.34 (dd, 1H, J=8.3, 4.5 Hz, H_5), 7.65 (d, 1H, J=8.3, 1.5 Hz, H_4), 7.82 (d, 1H, J=15.4 Hz, H_{acry}), 8.57 (dd, 1H, J=1.5, 4.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 52.5, 114.4, 125.9, 126.2, 130.3, 134.5, 145.3, 145.9, 149.7, 166.8; IR (KBr) ν 2955, 2926, 2854, 1727, 1428, 1308, 1217, 1138, 1075; *m/z* (EI) 311.0.

4.3.15. Methyl 2-(2-(methoxycarbonyl)ethyl)-6-methylpyridine-3-carboxylate (35). A degassed suspension of 10% Pd on charcoal (1.37 g, 1.3 mmol) in a solution of methyl propenoate **20** (3.04 g, 12.92 mmol) in MeOH (120 ml) was vigorously stirred for 3 h at room temperature under H_2. The reaction mixture was filtered though Celite, washed with AcOEt (50 ml) and concentrated in vacuo. The residue was then chromatographied on silica gel using AcOEt/Petrol (30:70) as eluent to afford **35** (2.87 g, 94%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H, CH_3), 2.78 (t, 2H, J=7.5 Hz, $CH_2CO_2CH_3$), 3.47 (t, 2H, J=7.5 Hz, $CH_2CH_2CO_2CH_3$), 3.619 (s, 3H, CO_2CH_3), 3.89 (s, 3H, CO_2CH_3), 7.04 (d, 1H, J=7.9 Hz, H_{5pyr}), 8.05 (d, 1H, J=7.9 Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 24.9, 31.9, 33.1, 51.8, 52.5, 121.1, 122.6, 139.3, 160.8, 161.6, 167.1 ($CO_2CH_{3\text{-pyr}}$), 174.2 ($CO_2CH_{3\text{-aliph}}$); IR (KBr) ν 2995–2953, 1727, 1592, 1436, 1369, 1279–1257, 1196–1141, 1081; *m/z* (EI) 237.0; Anal. Calcd for $C_{12}H_{15}NO_4$ (237.21): C, 60.76; H, 6.37; N, 5.90. Found: C, 60.75; H, 6.38; N, 5.86%.

4.3.16. 6,7-Dihydro-2-methylcyclopenta[*b*]pyridin-5-one (1). Sodium methoxide (68 mg, 1.26 mmol) was added to a solution of diester **35** (200 mg, 0.84 mmol) in THF (6 ml) under N_2. The mixture was warmed to reflux during 2 h. The solvent was removed under vacuo and 2 ml of HCl 4.5 M was added. The mixture was stirred 2 h at reflux. The pH was then adjusted to 8 by adding K_2CO_3 before extraction with CH_2Cl_2 The organic layer was washed with 10% aq Na_2CO_3 (5 ml), satd aq. NH_4Cl (5 ml) and dried ($MgSO_4$). After evaporation of the solvent the crude oil was chromatographied on silica gel using AcOEt as eluent to give **3** as a beige oil (107 mg, 86%); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, CH_3), 2.76 (t, 2H, J=6.0 Hz, CH_2CH_2-C=O), 3.22 (t, 2H, J=6.0 Hz, CH_2–C=O), 7.17 (d, 1H, J=7.9 Hz, H_{5pyr}), 7.90 (d, 1H, J=7.9 Hz, H_{4pyr}); ^{13}C NMR ($CDCl_3$) δ 25.7, 29.1, 36.2, 122.8, 128.4, 132.4, 166.5, 174.9, 205.1 (C=O); IR (KBr) 2925–2854, 1723 (C=O), 1590, 1307, 1107, 1031; *m/z* (EI) 147.0; Anal. Calcd for C_9H_9NO (147.16): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.33; N, 9.23%.

References and notes

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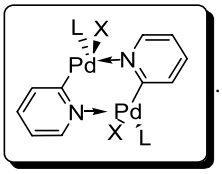

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A spectrofluorimetric study of binary fluorophore–cyclodextrin complexes used as chiral selectors

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Abstract—Six binary complexes between three fluorophores (pyrene, xanthone and anthraquinone) and β-cyclodextrin (β-CD) or heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin (am-β-CD) were tested at two pH values (8.0 and 9.0) as chiral selectors for three α-amino acids chosen as model. The conditional constant (β_{2T}) values for ternary complexes (fluorophore-CD-amino acid), determined by means of fluorescence spectroscopy, showed that the binary complexes are suitable receptors for chiral recognition. The effect of α-amino acids on stability and stoichiometric ratio of the binary complexes has also been studied. The binary complexes were in most cases stabilized by adding the ternary agent. The trend of stoichiometric ratios found is supported by variations in fluorescence spectra. Those relative to pyrene (**Py**) show little changes going from binary to ternary complexes, while those recorded in the presence of xanthone (**Xan**) give the most significant variations underlining a deep reorganization of guest. Anthraquinone (**Aq**) shows an intermediate behavior.

1. Introduction

Chiral recognition is one of the most fundamental aims in stereochemistry. Many authors, such as Ogston,[1] Cramer,[2] and more recently Davankov,[3] have tried to understand the nature of interactions that are needed for a chiral selector to recognize enantiomers. The importance of this topic is also due to the fact that the activity of most biological molecules, indeed in protein recognition phenomena, seems to be due to ability of receptors to interact with amino acid residues in order to give inclusion complexes or supramolecular species.[4] As amino acids are the main constituents of proteins and, as they show a marked trend to form complexes with a wide variety of molecules, in the last three decades many researchers have attempted to find artificial receptors for these chiral molecules. In fact a better understanding of interactions working in chiral recognition processes can be useful, not only because most therapeutic drugs are developed from chiral amino acid intermediates and are required in an enantiomerically pure form, but also because it can allow the development of new methods of asymmetric synthesis and chromatographic resolution of enantiomers.

Several papers have been published on the synthesis of chiral macrocyclic compounds and their ability to recognize enantiomers.[5] On this subject Cram et al. have reported the synthesis of macrocycles having binaphthyl units, which are able to selectively interact with enantiomers of amino acids.[6] More recently Escuder et al.[7] have reported the synthesis of molecular receptors able to selectively interact with enantiomers of tyrosine, phenylalanine and tryptophan.

Among semi-natural receptors, cyclodextrins are very important. Thanks to their intrinsically chiral cavity, cyclodextrins have been used in chiral recognition of both L/D amino acids[8] and small peptide segments.[9] Very often the chiral recognition of α-amino acids results from a ternary complex, formed between a functionalised cyclodextrin, a metal ion and the chiral molecule;[10] in other cases, as recently reported by Liu et al.,[11] the high L-enantioselectivity for leucine is due to the presence of a functional group on the primary rim of cyclodextrin that changes its ability towards molecular and chiral recognition.

Among enantioselective sensors, fluorescent ones are particularly interesting, due to the high sensitivity and selectivity of the detection method.[12] Until now, little attention has been addressed to the possibility of using fluorescent binary host/guest complexes, formed by cyclodextrin, in studying chiral recognition processes. On this subject, some years ago, Yang and Bohne[13] reported results concerning the interaction of the complex pyrene/β-cyclodextrin with the enantiomers of tryptophan. The

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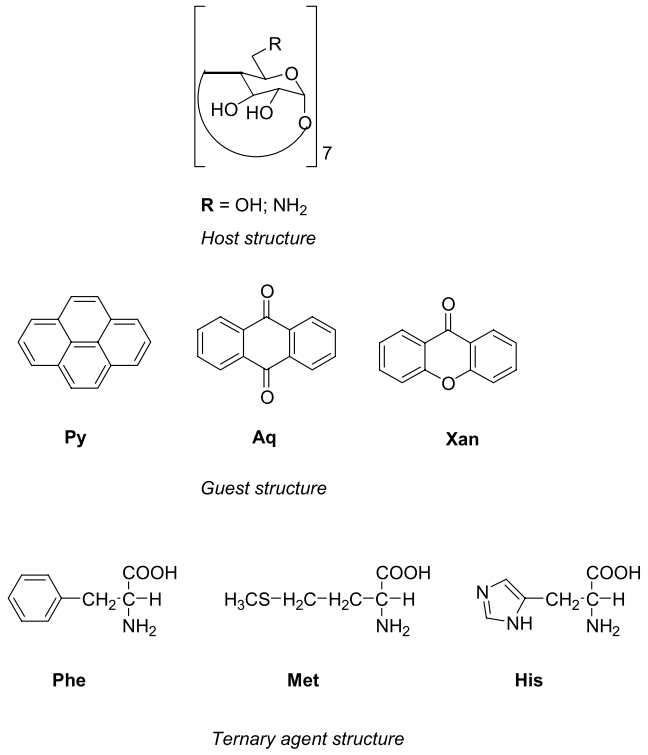

Figure 1.

authors found an enantioselectivity ratio of 3.6 for the D-enantiomer. However, they underlined that this high ratio was registered only in the presence of *t*-BuOH (20 mM).

More recently we have reported results concerning the study of stability and chiral recognition ability of the binary complex pyrene/heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin (**Py**/am-β-CD)[14] and, on that occasion, we pointed out the good chiral recognition ability of the system studied versus some α-amino acids. This ability, in our opinion, was due to the extension of the empty volume of macrocycle cavity that, after inclusion of the fluorescent guest, could be differently occupied by enantiomers of the same amino acid. Recently, in order to identify new fluorescent chiral sensors, we have reported preliminary data concerning the study of stability and stoichiometric ratio of complexes formed by some fluorescent molecules in the presence of β-cyclodextrin (β-CD) and am-β-CD.[15]

In the present work we have tested the binary complexes formed by pyrene (**Py**), xanthone (**Xan**) and anthraquinone (**Aq**) in the presence of am-β-CD and β-CD, in order to investigate how the symmetry and volume of the cavity of the binary complex influence the chiral recognition. This and the effect of the structure of the ternary agent on the stability of binary complexes were investigated using three different α-amino acids: phenylalanine (**Phe**), methionine (**Met**) and histidine (**His**). The study was carried out by spectrofluorimetric titration, in borate buffer at pH = 8.0 and 9.0 in order to investigate how the charge of the binary complex influences the interaction with ternary agent. Host, guest and ternary agent structures are depicted in Figure 1.

2. Results and discussion

In Tables 1 and 2 the values of stability constants, as a function of pH value, and stoichiometric ratios for the studied complexes, are reported.

In any case the stoichiometric ratio was determined by Job plot analysis.[16] Furthermore, in the above Tables the ratios β_{2T}/β_2 are also reported, where β_2 is the stability constant of binary complexes and β_{2T} is the overall association constant determined in the presence of the ternary agent. These ratios allow the evaluation of the effect due to the ternary agent on the stability of the binary complex.

Table 1. Stability constants and stoichiometric ratios (s.r.) of ternary complexes formed in the presence of β-CD

Guest	S.r. (Fl/CD)	S.r. (Fl/CD/aa)	Ternary agent	$\beta_{2T}/10^6$ (M^{-2}),[a] pH = 8.0	β_{2T}/β_2, pH = 8.0	$\beta_{2T}/10^6$ (M^{-2}),[a] pH = 9.0	β_{2T}/β_2, pH = 9.0
Py	(1:2)	(1:2:2)		7.5[b]		12.0[b]	
			L-**Phe**	0.9	0.1	7.4	0.6
			D-**Phe**	3.3	0.4	7.1	0.6
			L-**Met**	1.8	0.2	1.2	0.1
			D-**Met**	6.7	0.9	3.7	0.3
			L-**His**	3.1	0.4	4.1	0.3
			D-**His**	1.2	0.2	10.7	0.9
Xan	(1:1)	(1:2:1)		420[b,c]		1100[b,c]	
			L-**Phe**	5.0		6.1	
			D-**Phe**	5.4		5.4	
			L-**Met**	6.2		4.7	
			D-**Met**	6.6		1.9	
			L-**His**	7.3		5.4	
			D-**His**	9.8		6.8	
Aq	(1:2)	(1:2:1)		2.4[b]		10.8[b]	
			L-**Phe**	2.7	1.1	5.8	0.5
			D-**Phe**	1.8	0.7	2.1	0.2
			L-**Met**	1.1	0.4	6.9	0.6
			D-**Met**	6.2	2.6	3.8	0.3
			L-**His**	11.1	4.6	1.3	0.1
			D-**His**	5.2	2.2	3.1	0.3

[a] Stability constant values are reproducible within 10%.
[b] See Ref. 15.
[c] As a consequence of the stoichiometric ratio of the binary complex, this value is a K (M^{-1}).

Table 2. Stability constants and stoichiometric ratios (s.r.) of ternary complexes formed in the presence of am-β-CD

Guest	S.r. (Fl/CD)	S.r. (Fl/CD/aa)	Ternary agent	$\beta_{2T}/10^6$ (M^{-2}),[a] pH=8.0	β_{2T}/β_2, pH=8.0	$\beta_{2T}/10^6$ (M^{-2}),[a] pH=9.0	β_{2T}/β_2, pH=9.0
Py	(1:2)	(1:2:2)		1.7[b]		4.8[b]	
			L-**Phe**	8.9[c]	5.2	5.2[c]	1.1
			D-**Phe**	1.2[c]	0.7	7.6[c]	1.6
			L-**Met**	13.4[c]	7.9	8.8[c]	1.8
			D-**Met**	2.2[c]	1.3	1.5[c]	0.3
			L-**His**	7.9[c]	4.6	6.2[c]	1.3
			D-**His**	6.5[c]	3.8	3.5[c]	0.7
Xan	(1:2)	(1:2:1)		3.7[b]		4.5[b]	
			L-**Phe**	7.1	1.9	8.9	2.0
			D-**Phe**	7.0	1.9	7.1	1.6
			L-**Met**	6.8	1.8	4.9	1.1
			D-**Met**	2.7	0.7	2.4	0.5
			L-**His**	6.1	1.6	10.9	2.4
			D-**His**	2.4	0.6	4.5	1.0
Aq	(1:2)			1.4[b]		2.3[b]	
			L-**Phe**	1.8	1.3	2.4	1.0
			D-**Phe**	1.4	1.0	1.5	0.6
			L-**Met**	1.5	1.1	1.5	0.6
			D-**Met**	1.3	0.9	1.8	0.8
			L-**His**	2.1	1.5	1.2	0.5
			D-**His**	1.8	1.3	1.6	0.7

[a] Stability constant values are reproducible within 10%.
[b] See Ref. 15.
[c] See Ref. 14.

As can be seen from the Tables, in all cases, the complexation of fluorophore to β-CD or am-β-CD can be described by sequential complexation of cyclodextrin molecules (Eqs. 1 and 2):[17]

$$S + CD \overset{K_1}{\rightleftharpoons} SCD \tag{1}$$

$$SCD + CD \overset{K_2}{\rightleftharpoons} S(CD)_2 \tag{2}$$

In the presence of a ternary agent, K_1 and K_2 are conditional equilibrium constants since they include a term related to the ternary agent concentration. The overall association constant will be given by Eq. 3:

$$\beta_{2T} = K_1 K_2 = [S(CD)_2]/([S][CD]^2) \tag{3}$$

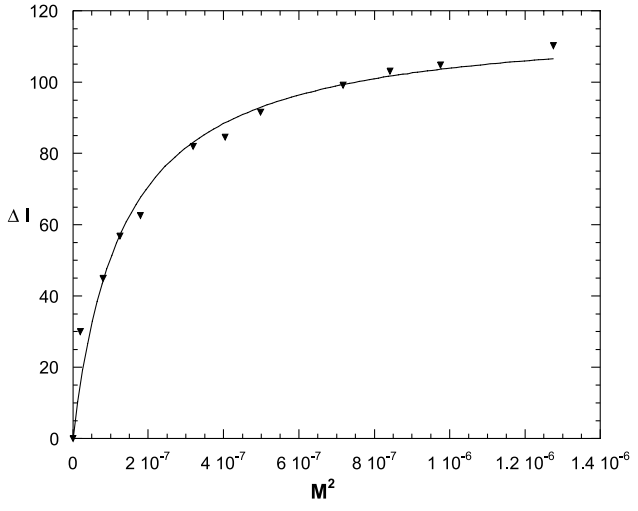

Figure 2. Curve fitting analysis of fluorescence spectral titration of **Xan** with β-CD, in the presence of L-**Met**, in borate buffer solution at pH=8.0.

If [CD]≫[S] the change in the fluorescence intensity as function of CD concentration will be given by Eq. 4:

$$\Delta I = (\Delta\alpha\beta_{2T}S_t[CD_0]^2)/(1 + \beta_{2T}[CD_0]^2) \tag{4}$$

where $\Delta\alpha$ is the difference of emission quantum yields of free and complexed substrate, S_t and $[CD_0]$ are the total concentration of substrate and cyclodextrin, respectively.

All guests used in this work have shown a good sensitivity to microenvironmental changes. In fact, in all cases considered, we detected significant changes of fluorescent intensity (ΔI ranging from −110 up to 80 a.u.) when the CD concentration increased and these changes were higher in the presence of ternary agent (Fig. 2). In particular **Py** and **Aq** showed a higher fluorescent intensity when they were included in CD cavity, than **Xan**. This latter result perfectly agrees with the reported dependence on medium polarity of emission spectrum of **Xan**.[18] Indeed, a decrease in the fluorescence intensity was observed by addition of a solvent less polar than water, such as 1,4-dioxane, to an aqueous solution of **Xan**.

The analyzed properties of ternary complexes are obviously influenced by the structure of the three partners, that is, fluorophore, cyclodextrin, amino acid. For example, the pH differently affects the two cyclodextrins according to the behavior of hydroxyl or amino groups as a function of the medium acidity. Consequently, the pH variation can be important in determining stability, stoichiometric ratio and chiral recognition ability of the complex.

2.1. Stoichiometric ratio

The symmetry and size of the fluorophore used plays an important role in determining the binary complex stoichiometric ratio. In fact, the most symmetric guests, **Py** and **Aq**, form binary complexes having a (1:2) (fluorophore/CD)

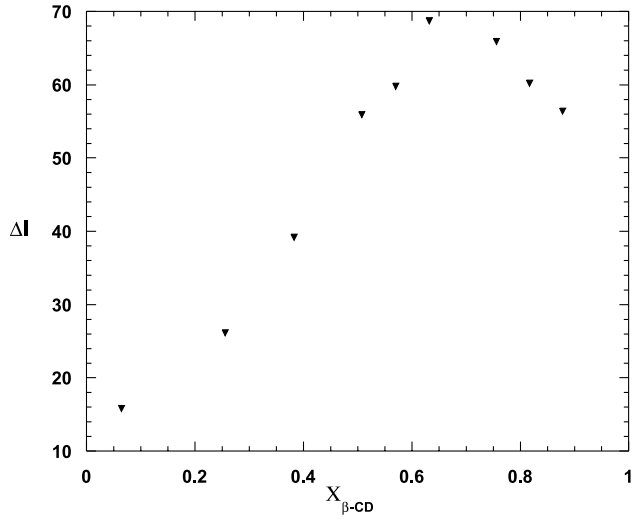

Figure 3. Job plot of the ternary complex **Xan**/β-CD/L-**Phe** in borate buffer solution at pH = 8.0.

stoichiometric ratio, whereas **Xan** forms (1:1) and (1:2) (fluorophore/CD) binary complexes with β-CD and am-β-CD, respectively. As can be seen from Tables 1 and 2 the addition of ternary agent does not change the binary complex stoichiometric ratio, only in the case of **Xan**/β-CD was a change in the stoichiometric ratio observed (Fig. 3).

However, data obtained from Job plot analysis show that the six binary complexes have different properties of inclusion towards the amino acids. Thus, **Py** forms a ternary complex having a (1:2:2) (**Py**/CD/amino acid) stoichiometric ratio, where each cyclodextrin cavity is equally occupied by a chiral molecule. The **Aq** guest, smaller than **Py**, probably gives a more flexible binary complex. As a consequence of this, the ternary agent partially displaces **Aq**, so, in the presence of β-CD, a ternary complex having a (1:2:1) (**Aq**/β-CD/amino acid) stoichiometric ratio was observed. In this complex, the chiral molecule can occupy only the cavity having a major empty volume. A particular behavior has been found in the presence of the **Aq**/am-β-CD complex; in fact, in this case, the Job plot analysis did not give a curvilinear plot. Probably, more ternary complexes, having different stoichiometric ratios [(1:2:1) and (1:2:2) (fluorophore/am-β-CD/amino acid)] were present.

Some different results were found for **Xan**. The asymmetric arrangement of the guest molecule with respect to cyclodextrin cavity[15] seems to be responsible for the lower ternary complex symmetry. It is noteworthy that in the presence of the binary complex **Xan**/β-CD the addition of the amino acid leads to a reorganization in the host–guest interactions and a change in the guest/host stoichiometric ratio [from (1:1) in the binary complex to (1:2) in the ternary complex]. Probably, in the presence of the amino acid, the guest molecule is partially moved out of the β-CD cavity and interacts much more with solvent molecules. Thus in order to reduce such an unfavorable interaction, a second β-CD molecule encloses the protruding part of the guest. This result is different from that previously reported by Bohne et al.[20] They found no change in stoichiometric ratio of the binary complex **Xan**/β-CD on the addition of aliphatic alcohols.

The trend of stoichiometric ratios found is supported by variations in fluorescence spectra. Those relative to **Py** show little change going from binary to ternary complexes, while those recorded in the presence of **Xan** give the most significant variations underlining a deep reorganization of the guest. **Aq** shows an intermediate behavior.

2.2. Host structure

Data reported in Tables 1 and 2 show that host structure is one among the factors that affect the ternary complexes stability. In fact, it often has a scarce relevance in determining the difference in stability between two complexes. In some cases (six), the complexes formed by am-β-CD are more stable (from 10 up to 2 times) than complexes formed by β-CD, and in some other cases (twelve) the former are less stable (from 11 up to 2 times). Finally, for eighteen ternary complexes a scarce influence of host structure was observed. However, in order to evaluate the effect of the ternary agent on the stability of binary complexes, it is suitable to consider the β_{2T}/β_2 ratio rather than the β_{2T} values.

As can be seen from the Tables, in the presence of am-β-CD, in most cases, the addition of a ternary agent stabilizes the binary complex. In general this stabilization is higher at pH = 8.0 than at pH = 9.0. In order to explain these data, it is possible to consider the different charge of the host, when the pH increases, or, alternatively, the different interactions between ternary agent and primary rim of the host at two different pH values.

At pH = 8.0, the am-β-CD is in its charged form; it interacts better with water molecules and consequently, the effect of addition of the amino acid is greater, as water molecules are displaced from the empty volume of the cyclodextrin cavity. On the other hand, as previously reported,[14] data obtained seem to indicate that electrostatic interactions present, at pH = 8.0, between the ammonium groups of am-β-CD and the carboxylate group of the amino acid, are more efficient than the hydrogen bonds that stabilize the system at pH = 9.0.

A more diversified behavior was registered in the presence of β-CD. In particular for **Aq**/β-CD, in most cases, the binary complex was stabilized by adding the ternary agent and the degree of stabilization is higher at pH = 8.0 than at pH = 9.0. This result, apparently anomalous, can be explained considering the effect of base concentration. In fact, as previously reported,[15] a higher base concentration, on going from pH = 8.0 to pH = 9.0, could break the network of hydrogen bonds on the secondary rim, allowing the best substrate–cyclodextrin complex fit; as a consequence, the more stable complex will be less affected by adding the ternary agent. For **Py**/β-CD complex, a destabilization of the binary complex was always observed. The lack of β_{2T}/β_2 ratio values for **Xan**/β-CD complex does not allow a comparison between the two **Xan**/CD systems.

2.3. Guest structure

The studied guests have different polarity and hydrophobicity. In particular **Py** is hydrophobic and apolar, while **Aq** and **Xan** are moderately hydrophilic but apolar and polar, respectively.

Data reported in Table 2 seem to indicate that, in the presence of am-β-CD, the degree of stabilization is determined by guest hydrophobicity. In fact, β_{2T}/β_2 ratios are higher in the presence of the **Py**/am-β-CD complex, while less significant differences were obtained between **Aq**/am-β-CD and **Xan**/am-β-CD complexes, underlining that guest symmetry plays a secondary role.

Instead, in the presence of β-CD (Table 1), it is not easy to identify the guest parameter responsible for β_{2T} values.

2.4. Ternary agent structure

The ternary agents studied have different side chains: apolar for **Phe**, polarizable for **Met**, polar and negatively (at pH values investigated) charged for **His**. However, data reported in the Tables show that, in the presence of both am-β-CD and β-CD and apart from the guest used, there is not a simple correlation between complex stability and side chain structure of the ternary agent. Despite this, and in order to evaluate how the ternary agent nature affects the ternary complex stability, it could be interesting to compare these data with those previously reported for similar systems.

Previously, Bohne et al.[20] found that the **Xan**/β-CD complex, having a (1:1) stoichiometric ratio, was destabilized by adding the structural isomers of butanol. Differently in the present work, the addition of amino acid molecules induces a variation in the stoichiometric ratio [from (1:1) to (1:2)] of **Xan**/β-CD complex. For **Xan**/am-β-CD complex the inclusion of amino acids molecules does not change the stoichiometric ratio. Furthermore, in most cases, there is a stabilization of the binary complex and also when the ternary complex is less stable than the binary complex (D-**Met** at pH=8.0 and 9.0, D-**His** at pH=8.0), the entity of destabilization is lower than that recorded in the presence of alcohols. Probably this is a consequence of the different nature of ternary agents used. In fact, the charged amino acid molecules are more solvated and less deeply included, reducing their destabilizing effect.

The stability of ternary complexes formed by the **Py**/β-CD complex, in the presence of alcohols[21] and amino acids[19] has been previously reported. Data obtained in the present work, in buffer solution, show that the stability of the complexes is higher than that previously reported, underlining the importance of the solvent medium. Probably, in our case, the higher ion concentration induces the apolar **Py** to interact more strongly with the cyclodextrin cavity and, consequently, to feel more strong by the effect of ternary agent presence.

It is noteworthy that the stabilities of complexes, determined by us, are comparable with those previously reported in the presence of alcohols that had been considered more efficient ternary agents than amino acids.[19] Furthermore, differently from that previously reported by Bohne et al.,[19] also **His**, having a charged side chain, is able to interact with the binary complex giving rise, in most cases, to its stabilization.

2.5. Chiral discrimination

In Table 3 the enantioselectivity ratios for the different binary complexes as a function of pH values are reported.

As can be seen from the Table, the binary complexes are able to differentiate amino acids not only for their different size and shape, but also for their chirality. The highest L-enantioselectivity is 7.4, for **Phe** with **Py**/am-β-CD, while the highest D-enantioselectivity is 5.6, for **Met** with **Aq**/β-CD.

Some interesting observations can be inferred from data in Table 3. The binary complexes fluorophore/am-β-CD generally show L-enantioselectivity, the D-enantioselectivity of **Aq**/am-β-CD complex at pH=9.0 could be a consequence of the fact that for this complex at least two different ternary complexes are present. The behavior of binary complexes of β-CD is more variegated. In fact, for **Py**/β-CD and **Xan**/β-CD the D-enantioselectivity prevails, while **Aq**/β-CD shows L-enantioselectivity.

Looking at guest structure, in the presence of both β-CD and am-β-CD, enantioselectivity ratios decrease going from **Py**

Table 3. Enantioselectivity ratios (E.r.) determined in the presence of β-CD and am-β-CD

Guest	Ternary agent	E.r. (β-CD), pH=8.0	E.r. (β-CD), pH=9.0	E.r. (am-β-CD), pH=8.0	E.r. (am-β-CD), pH=9.0
Py					
	Phe	3.7 (D>L)	1.0	7.4 (L>D)[a]	1.5 (D>L)[a]
	Met	3.7 (D>L)	3.1 (D>L)	6.1 (L>D)[a]	5.9 (L>D)[a]
	His	2.6 (L>D)	2.6 (D>L)	1.2 (L>D)[a]	1.8 (L>D)[a]
Xan					
	Phe	1.1 (D>L)	1.1 (L>D)	1.0	1.3 (L>D)
	Met	1.1 (D>L)	2.5 (L>D)	2.5 (L>D)	2.0 (L>D)
	His	1.3 (D>L)	1.3 (D>L)	2.5 (L>D)	2.4 (L>D)
Aq					
	Phe	1.5 (L>D)	2.8 (L>D)	1.3 (L>D)	1.6 (L>D)
	Met	5.6 (D>L)	1.8 (L>D)	1.2 (L>D)	1.2 (D>L)
	His	2.1 (L>D)	2.4 (D>L)	1.2 (L>D)	1.3 (D>L)

[a] See Ref. 14.

Table 4. Experimental conditions

Guest	C_{guest} (M)	λ_{ex} (nm)	$\Delta\lambda_{em}$ (nm)[a]	Solvent[a]	Ex. slit (nm)	Em. slit (nm)
Py	2×10^{-7}	337	360:450	MeOH	1.5	1.5
Aq[b]	2×10^{-6}	310	320:450	Diox	5	5
Aq[c]	2×10^{-6}	310	320:450	Diox	3	5
Xan	4×10^{-6}	348	360:450	MeOH	1.5	3

[a] See Section 3.2.
[b] In the presence of β-CD.
[c] In the presence of am-β-CD.

to **Xan** (**Py** > **Aq** > **Xan**), underlining that the best chiral selector is the complex having the most hydrophobic guest. This result perfectly agrees with Alexander et al.[22] who observed that chiral recognition ability of cyclic receptors depends on the number of included water molecules that had been excluded by the chiral molecule.

Chiral recognition ability is also influenced by the binary complex symmetry. In fact, the complexes formed by **Py** and **Aq** show higher enantioselectivity than those formed by **Xan** as a consequence of their symmetry. This seems to confirm that, in the presence of binary complex, the ability to interact with a chiral molecule depends on the extension of the empty volume of the cyclodextrin cavity. This result agrees with Buvári-Bacza et al.[23] who determined that cyclodextrins having a different number of substituents and, consequently, different size cavities have different chiral discrimination ability.

Chiral recognition ability is not dependent on the effect (stabilization or destabilization) of ternary agent addition, as can be seen from data relative to **Py**/β-CD/**Phe** and **Py**/am-β-CD/**Met** at pH = 8.0. Differently from that previously reported by Inoue et al.[24] who observed a loss of chiral recognition with the enhancement in complex stability. In our opinion, the disagreement comes from the difference in substrate-CD interaction and substrate–binary complex interaction. Indeed, the former leads to the best host–guest fit, whereas the latter should consist of an optimal arrangement of components of ternary complex.

In conclusion the binary complexes studied seem to be promising chiral selectors able to discriminate very dilute solution of enantiomers. In many cases, the enantioselectivity ratios, determined by us, are comparable or higher than those previously reported using other molecular receptors for amino acids. On this subject Escuder et al.,[7] studying the chiral recognition ability of some amino acid appended diphenylglycoluril based receptors, found a L-enantioselectivity, in the presence of **Phe**, equal to 2.2. Furthermore, considering binary complexes formed by functionalized β-cyclodextrins, in the presence of Cu^{2+}, Corradini et al.[10e] reported L-enantioselectivity, in the presence of **Phe**, that ranged from 1.12 up to 5.26. In our case, the L-enantioselectivity for **Phe** ranges from 1.0 up to 7.4.

3. Experimental

3.1. Materials

The heptakis-(6-amino-6-deoxy)-β-cyclodextrin was synthesized and purified according to the procedure described in the literature.[25] The product was dried for 24 h in a dryer under vacuum over phosphorous pentoxide at 60 °C and then was stored in the same apparatus at 40 °C.

Py, **Aq** and **Xan** (spectrofluorimetric grade) were purchased from Fluka and used without further purification.

All amino acids were purchased from Aldrich and used without further purification.

Borate buffer solutions (0.05 M) were prepared according to standard procedure, using freshly double-distilled decarbonised water. The actual pH of the solutions was recorded using a PH M82 Radiometer equipped with a GK2401C combined electrode.

3.2. Spectrometric measurements

The solution of β-CD or am-β-CD in borate buffer (1.4×10^{-3} M) was filtered before use by a Millipore 0.45 μm filter. Guests solutions were prepared by injecting a guest solution (MeOH or 1,4-dioxane) ($\sim10^{-3}$ M) into a buffer solution. Measurement solutions were prepared by adding increasing volumes of the CD to 1 mL of the guest and ternary agent solution into a volumetric flask. In these solutions, the concentrations of the guest and the ternary agent were constant. The concentration of ternary agent was equal to 1×10^{-3} M, while the concentration of CD increased from 1.4×10^{-4} M to 1.3×10^{-3} M. All measurement solutions were deareated, before use, by Ar for 12 min. The concentration of guests and the experimental condition are reported in Table 4.

Steady-state fluorescence spectra were acquired with a JASCO FP-777W spectrofluorimeter. Excitation, emission slits, excitation wavelength (λ_{ex}) and emission interval ($\Delta\lambda_{em}$) are reported in Table 4.

Every spectrum was averaged over 50 scans. A suitable wavelength was chosen after recording a difference spectrum by comparison to a sample without cyclodextrin and one with the highest cyclodextrin concentration.

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Synthesis of substituted bis(heteroaryl)maleimides

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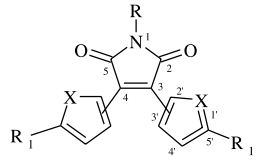
Abstract—Substituted bis(fur-2-yl), bis(fur-3-yl) and bis(thien-2-yl) maleimides with potential antidiabetic properties are described. Their synthesis involves, as a key step, a Suzuki cross-coupling between various boron derivatives and the diiodomaleimides. Therefore, a wide range of substituted symmetric and non-symmetric maleimide derivatives can be prepared.

1. Introduction

Protein tyrosine phosphatases (PTPases) are key signal transduction enzymes which regulate the level of tyrosine phosphorylation of proteins in coordination with the competing action of protein tyrosine kinases (PTKs). PTPases are responsible for phosphotyrosine residue dephosphorylation whereas PTKs catalyse tyrosine phosphorylation. Defect in PTPases activity has been associated with a number of human diseases such as diabetes, obesity and cancer.[1] In particular, protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of the insulin-signaling cascade, and recent knock-out studies in mice[2] demonstrated that this enzyme is an attractive therapeutic target for the treatment of Type II diabetes.[3]

To achieve selectivity over most of the hundred of human PTPases, bidentate (binding with both the active site and an adjacent site) PTP1B inhibitors have been developed.[4] Substituted maleimides are well known for their biological activity. As a result, in our search of new PTP1B inhibitors, we have synthesized bis(heteroaryl)maleimides (Fig. 1), for this scaffold should allow the development of bidentate inhibitors. Substituents have been introduced on the free imide nitrogen, for, some *N*-substituted bis(aryl)imidazoles



X = S, O
R_1 = $CH(OEt)_2$, $(CH)_2CH(OEt)_2$, CHO, $(CH)_2CHO$
R = arylalkyl, phenyl

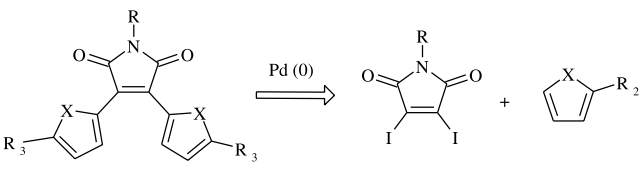
Figure 1.

PTPases inhibitors showed greater potency than non-substituted ones.[5]

As far as we know, photoinduced synthesis of non-substituted bisfurylmaleimides and bisthienylmaleimides alone, has already been reported.[6] Actually, bisindolylmaleimides, bisazaindolylmaleimides and mixed indolylazaindolylmaleimides along with carbazoles, are, because of their pharmaceutical interests, the most widely described maleimides. They are prepared from their heteroaryl and dihalogenomaleimide precursors, using Grignard reagent (also LiHMDS) and a palladium catalysis (Stille, Suzuki).[7] Other methods use the reaction between a glyoxalate and an arylacetamide or, an homocoupling reaction of 3-arylacetic acid followed by an amidification.[8]

In this publication, we report the first synthesis of substituted bis(fur-2-yl) and bis(thien-2-yl)maleimides via a one-pot Pd/C catalysed Suzuki cross-coupling, between the diiodomaleimides and the [(2-diethoxyalkyl)heteroaryl] boronic acids (Scheme 1).

Substituted bis(fur-3-yl)maleimide synthesis could not be carried out according to the same conditions, but rather, required a modified Suzuki coupling, between the diiodomaleimide and the [(2-diethoxyalkyl)-4-heteroaryl] boronate using PdCl2(dppf) as the catalyst. Finally, a new synthetic route to non-symmetric bis(heteroaryl) maleimides has been developed.



Scheme 1.

Keywords: Bis(heteroaryl)maleimides; Suzuki cross-coupling.
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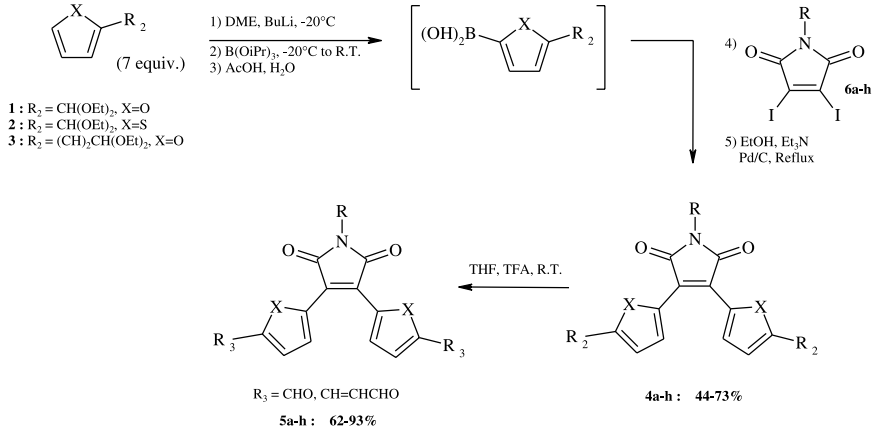
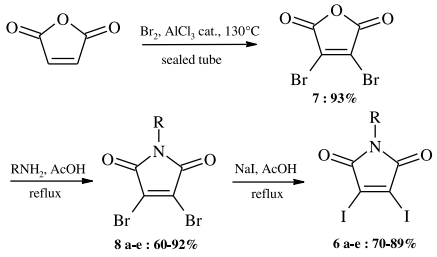


Scheme 2.

2. Discussion and results

2.1. Synthesis of bis[(5-formyl)heteroar-2-yl] maleimides

The desired intermediates [(2-diethoxyalkyl)heteroaryl] boronic acids were prepared according to McClure and *coll*.[9] (Scheme 2). As mentioned by the authors, those were not isolated to avoid any loss of material. Instead, the crude solution was successfully used in the subsequent Suzuki cross-coupling. 0.3 equiv of Pd/C (10 wt %) were used each time as a catalyst. As for the yields of the isolated diacetals **4a–h**, they were satisfactory as shown in Table 1. The desired bis[(5-formyl)heteroar-2-yl] maleimides **5a–h** were obtained by acidic hydrolysis using trifluoroacetic acid. The recovery yields were good though, some degradation of the product was observed (Table 1). The diiodomaleimides **6a–d** were prepared in three steps from maleic anhydride (Scheme 3).[10] The first step involved bromination in a sealed tube with bromine in the presence of aluminium chloride (catalytic amount) to provide **7** (93% yield). This dibromo derivative was then treated with different substituted anilines in acetic acid to give the corresponding dibromomaleimides **8a–d** with moderate yields. Finally, treatment of **8a–d** with sodium iodide in acetic acid led to products **6a–d** which were used in the Suzuki coupling described above. When instead, the dibromomaleimides **8a–d** were used, an average 15% yield decrease was observed. Monosubstitution was not observed whatever the diiodomaleimide/furaldehyde acetal ratio used. 3,4-Diiodo-



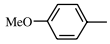
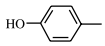
Scheme 3.

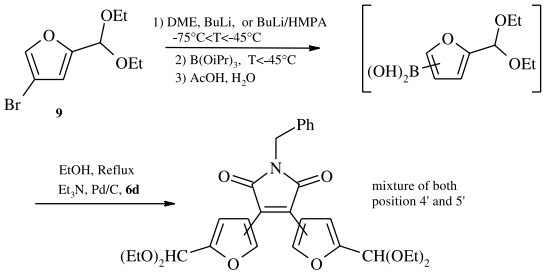
2,5-dihydro-[1-(4-hydroxy benzyl)]-1*H*-pyrrol-2,5-dione **6e** was obtained by demethylation of the methoxy derivative **6d**, in standard conditions by treatment with boron tribromide.

2.2. Synthesis of bis[(5-alkyl)fur-3-yl]maleimides

We first thought to prepare such derivatives via a classical Suzuki cross-coupling too (Scheme 4), which required 2-diethoxymethyl-4-furanboronic acid. This latter was potentially available from the 2-diethoxymethyl-4-bromofuraldehyde[11] **9** via an halogen/metal exchange to form the lithiated furaldehyde acetal. It should have then be trapped by trisopropylborate in order to give the intermediate borane. Nevertheless, triisopropylborate was not electrophilic enough to trap all the 4-lithiofuran at such temperatures ($T < -45$ °C). Despite long reaction times,

Table 1. Synthesized bis[(5-diethoxy)heteroar-2-yl] and [(5-formyl)heteroar-2-yl] maleimides

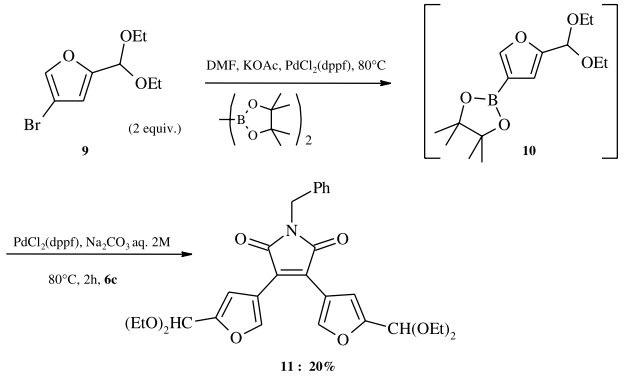
R	X	R_2	Compound (yield)	R_3	Compound (yield)
H	O	$CH(OEt)_2$	**4a** (64%)	CHO	**5a** (86%)
	O	$CH(OEt)_2$	**4b** (44%)	CHO	**5b** (87%)
	O	$CH{=}CHCH(OEt)_2$	**4c** (59%)	CH=CH–CHO	**5c** (62%)
	O	$CH(OEt)_2$	**4d** (73%)	CHO	**d** (89%)
	S	$CH(OEt)_2$	**4e** (65%)	CHO	**5e** (77%)
	O	$CH(OEt)_2$	**4f** (60%)	CHO	**5f** (89%)
	O	$CH(OEt)_2$	**4g** (58%)	CHO	**5g** (85%)
	O	$CH(OEt)_2$	**4h** (62%)	CHO	**5h** (93%)



Scheme 4.

only a mixture of both bis(fur-2-yl) and bis(fur-3-yl)maleimides could be isolated (Scheme 4).[12]

So we used a palladium catalysed reaction to force the formation of the borane in position 4. Bis(pinacolato)diborane (Scheme 5) is thermally stable, easy to handle in the air and known to be a useful boron nucleophile for cross or homocoupling reaction with arylhalides.[13] Borane **10** was generated in situ and coupled to diiodobenzylmaleimide **6c** to give **11**.



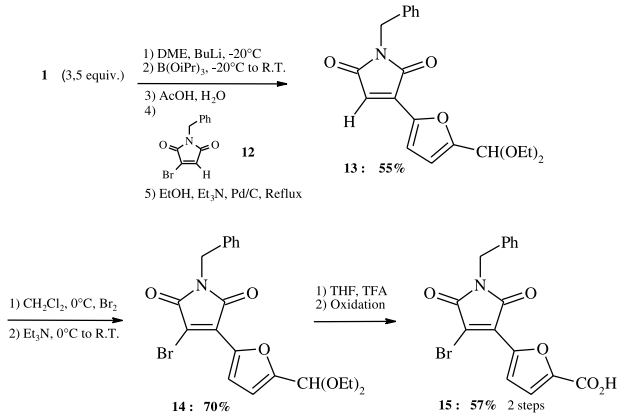
Scheme 5.

The poor stability of the various maleimide species would be accountable for the low yield observed. Indeed, maleimides are generally unstable in aqueous basic mixtures and, as for monofurylmaleimides, they were found to be highly unstable. When anhydrous conditions were used (dry Na_2CO_3, K_3PO_4 or Et_3N), no product was formed. The reaction at room temperature for 24 h resulted in a 4% yield increase while no starting material was recovered. So far, none of the experimental conditions used has resulted into a significant yield improvement.

2.3. Synthesis of non-symmetric maleimides

Since a monooxidation of bis[(5-formyl)heteroar-2-yl] maleimides would give a mixture of di, mono and non-oxidized maleimides, this series of compound has rather been prepared from 3-bromobenzylmaleimide **12** via a Suzuki cross-coupling-bromination-Suzuki coupling sequence. Thereof a wider range of compounds is accessible than with the commonly used methods.[7]

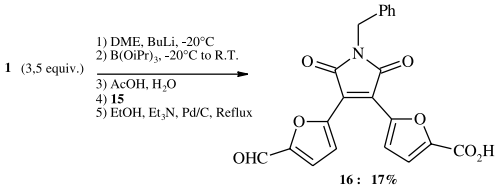
Firstly, compound **12** was isolated as a byproduct of 3,4-dibromobenzylmaleimide **8c** synthesis from benzylmaleimide. It was then coupled to 2-furaldehyde diethyl acetal



Scheme 6.

1 using the Suzuki coupling conditions described in Section 2.1 (Scheme 6). One will notice, as mentioned in the previous paragraph, that compound **13** was rapidly degradated when heated for too long a time. Nevertheless, its bromination by successive treatment with bromine and triethylamine[14] afforded product **14** in a good yield.

Then, 4-bromo-3-[(5-carboxyl)fur-2-yl]-2,5-dihydro-1-(benzyl)-1*H*-pyrrol-2,5-dione **15** was prepared from **14** by acetal acidic hydrolysis and subsequent mild oxidation[15] using sodium hypochloride as the oxidant. Using the previously described Suzuki cross-coupling (cf Section 2.1), the non-symmetric maleimide **16** was finally prepared in a 17% yield from acetal **1** and compound **15** (Scheme 7).



Scheme 7.

Material losses (water solubility) during the purification steps are responsible for the low yield observed which is not representative of the great effectiveness of this reaction.

3. Conclusion

In conclusion, we have developed new efficient methods, based on Suzuki cross-coupling reactions, to synthesize various symmetric and non-symmetric heteroarylmaleimides. The biological evaluation of these new compounds is now under investigation.

4. Experimental

4.1. General

Melting points were determined using Büchi Melting Point B-540 and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 WB (300 MHz). The coupling constants are recorded in Hz and the chemical

shifts are reported in ppm (δ, ppm) downfield from TMS which was used as the internal standard. IR spectra were obtained with a Perkin–Elmer FT Paragon 1000 PC. MS spectra were registered on a Perkin–Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230–400 mesh). Analytical TLC was carried out on silica gel F_{254} plates. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred via syringe.

4.1.1. 2-Furaldehyde diethyl acetal (1). To a solution of 2-furaldehyde (10.00 g, 104 mmol) and ammonium chloride (2.90 g) in ethanol (18.20 mL, 312 mmol) was added triethyl orthoformate (15.20 mL, 115 mmol). The mixture was refluxed during 16 h. After cooling the solution to room temperature, the solvent was removed under reduced pressure and the residue diluted with ethyl acetate. The organic layer was washed with a saturated sodium hydrogenocarbonate solution and dried over anhydrous $MgSO_4$. After solvent removal, the crude was purified by chromatography on silica gel (eluent: light petroleum–ethyl acetate: 99/1) to afford **1** (17.70 g, 99%) as a yellow oil.[16]

4.1.2. 2-Thiophenecarboxaldehyde diethyl acetal (2). To a solution of 2-thiophenecarboxaldehyde (1.67 mL, 17.83 mmol) and ammonium chloride (446 mg) in ethanol (3.2 mL, 53.46 mmol) was added triethyl orthoformate (3.26 mL, 19.62 mmol). The mixture was refluxed during 16 h. After cooling the solution to room temperature, the solvent was removed under reduced pressure and the residue diluted with ethyl acetate. The organic layer was washed with a saturated sodium hydrogenocarbonate solution and dried over anhydrous $MgSO_4$. After solvent removal, the crude was purified by chromatography on silica gel (eluent: light petroleum–ethyl acetate: 99/1) to afford **2** (17.70 g, 99%) as a yellow oil.[16]

4.1.3. 2-(3,3-Diethoxypropenyl)furan (3). To a solution of *trans*-3-(2-furyl)acrolein (3.50 g, 28.42 mmol) and ammonium chloride (770 mg) in ethanol (5 mL) was added triethyl orthoformate (5.20 mL, 31.26 mmol). The mixture was stirred at room temperature during 4 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate. The organic layer was washed with a saturated sodium hydrogenocarbonate solution and dried over anhydrous $MgSO_4$. After solvent removal, the crude residue was purified by chromatography on silica gel (eluent: light petroleum–ethyl acetate: 99/1) to afford **3** (5.11 g, 99%) as a brown oil; ν_{max} (film)/cm^{-1} 3054, 2979, 1675, 1629, 1473, 1387, 1121, 1019, 965; δ_H (200 MHz, $CDCl_3$) 7.34 (1H, d, $J=1.8$ Hz, $H_{furan.}$), 6.53 (1H, dd, $J=16.0$, 1.0 Hz, $H_{vinyl.}$), 6.35 (1H, dd, $J=3.3$, 1.8 Hz, $H_{furan.}$), 6.27 (1H, d, $J=3.3$ Hz, $H_{furan.}$), 6.11 (1H, dd, $J=16.0$, 4.7 Hz, $H_{vinyl.}$), 5.05 (1H, dd, $J=4.7$, 1.0 Hz, C*H*(OEt)$_2$), 3.72–3.48 (4H, m, 2C*H*$_2$CH$_3$), 1.26–1.18 (6H, m, 2CH$_2$C*H*$_3$); δ_C (200 MHz, $CDCl_3$) 152.0 (*C*), 142.3 (*C*H$_{furan.}$), 125.2 (*C*H$_{vinyl.}$), 121.0 (*C*H$_{vinyl.}$), 111.3 (*C*H$_{furan.}$), 108.9 (*C*H$_{furan.}$), 100.7 (*C*H), 60.8 (2*C*H$_2$), 15.2 (2*C*H$_3$); *m*/*z* 197 (M+1); (Anal. Calcd for $C_{11}H_{16}NO_3$: C, 67.32; N, 8.22; H, 24.46. Found: C, 67.51; N, 8.26; H, 24.36).

4.2. 3,4-Bis[(5-diethoxymethyl)heteroar-2-yl]-2,5-dihydro-1-(*substituted*)-pyrrol-2,5-dione (4a–h). General procedure

Under an inert atmosphere, *n*-butyllithium (50.57 mmol, 2.5 M in hexane) was added dropwise to a solution of diethyl acetal derivatives (**1**–**3**) (42.13 mmol) in ethylene glycol dimethyl ether at −20 °C. The mixture was stirred an additional time (3 h) with continuous cooling. Then triisopropylborate (50.57 mmol) was then added dropwise at −20 °C afterwards the mixture was allowed to rise to room temperature under continuous stirring (~2 h). The reaction was quenched with the addition of 3.13 mL of acetic acid (54.78 mmol) and 3.79 mL of water (210.70 mmol). Then, **6a**–**h** (6.02 mmol), ethanol (23.00 mL), triethylamine (3.35 mL, 24.08 mmol) and palladium on activated carbon (10 wt % Pd/C, 1.9 g, 1.80 mmol) were added and the mixture was refluxed under stirring during 24 h. The solution was cooled to room temperature and the catalyst was filtered on Celite, washed with ethyl acetate and the filtrate concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water and dried over anhydrous $MgSO_4$. After solvent removal, the crude residue was purified by column chromatography (eluent: light petroleum–ethyl acetate) to give the desired compounds **4a**–**h**.

4.2.1. 3,4-Bis[5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1*H*-pyrrol-2,5-dione (4a). Yellow solid (64%), mp 98–99 °C; ν_{max} (KBr)/cm^{-1} 3055, 2982, 1771, 1727, 1528, 1443, 1348, 1100, 1054; δ_H (200 MHz, $CDCl_3$) 8.59 (1H, br s, N*H*), 7.52 (2H, d, $J=3.5$ Hz, $H_{furan.}$), 6.64 (2H, d, $J=3.5$ Hz, $H_{furan.}$), 5.69 (2H, s, 2C*H*(OEt)$_2$), 3.65 (8H, dq, $J=1.6$, 7.1 Hz, 4C*H*$_2$CH$_3$), 1.26 (12H, t, $J=7.1$ Hz, 4CH$_2$CH$_3$); δ_C (200 MHz, $CDCl_3$) 169.4 (2*C*=O), 155.5 (2*C*), 144.9 (2*C*), 119.3 (2*C*), 118.8 (2*C*H$_{furan.}$), 110.9 (2*C*H$_{furan.}$), 96.0 (2*C*H(OEt)$_2$), 61.3 (4*C*H$_2$), 15.0 (4*C*H$_3$); *m*/*z* 451 (M+18), 456 (M+23); (Anal. Calcd for $C_{22}H_{27}NO_8$: C, 60.96; N, 3.23; H, 6.28. Found: C, 60.85; N, 3.29; H, 6.39).

4.2.2. 3,4-Bis[5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-phenyl-1*H*-pyrrol-2,5-dione (4b). Red solid (44%), mp 80–81 °C; ν_{max} (KBr)/cm^{-1} 3124, 3054, 2980, 1713, 1683, 1664, 1503, 1393, 1169, 1113, 1058, 818; δ_H (200 MHz, $CDCl_3$) 7.58 (2H, d, $J=3.6$ Hz, $H_{furan.}$), 7.48–7.35 (5H, m, $H_{arom.}$), 6.66 (2H, d, $J=3.6$ Hz, $H_{furan.}$), 5.69 (2H, s, 2C*H*(OEt)$_2$), 3.65 (8H, dq $J=7.1$, 1.9 Hz, 4C*H*$_2$CH$_3$), 1.24 (12H, t, $J=7.1$ Hz, 4C*H*$_2$CH$_3$); δ_C (200 MHz, $CDCl_3$) 168.2 (2*C*=O), 155.8 (2*C*), 144.9 (2*C*), 131.5 (*C*), 129.0 (2*C*H$_{arom.}$), 127.9 (*C*H$_{arom.}$), 126.4 (2*C*H$_{arom.}$), 119.2 (2*C*H$_{furan.}$), 118.6 (2*C*), 111.1 (2*C*H$_{furan.}$), 96.1 (2*C*H(OEt)$_2$), 61.4 (4*C*H$_2$), 15.2 (4*C*H$_3$); *m*/*z* 527 (M+18), 532 (M+23); (Anal. Calcd for $C_{28}H_{31}NO_8$: C, 66.00; N, 2.75; H, 6.13. Found: C, 65.89; N, 2.73; H, 5.92).

4.2.3. 1-Benzyl-3,4-bis{[5-(3,3-diethoxy)propenyl]fur-2-yl}pyrrol-2,5-dione (4c). Violet coloured oil (59%); ν_{max} (film)/cm^{-1} 3054, 2986, 1676, 1630, 1422, 1121, 896; δ_H (200 MHz, $CDCl_3$) 7.48 (2H, d, $J=3.7$ Hz, $H_{furan.}$), 7.42–7.26 (5H, m, $H_{arom.}$), 6.59 (1H, dd, $J=16.0$, 1.0 Hz, $H_{vinyl.}$), 6.52 (2H, d, $J=3.7$ Hz, $H_{furan.}$), 6.37 (1H, dd, $J=16.0$, 4.1 Hz, $H_{vinyl.}$), 5.06 (2H, dd, $J=4.1$, 1.0 Hz, 2C*H*(OEt)$_2$),

4.75 (2H, s, N–CH_2), 3.79–3.41 (8H, m, 4CH_2CH$_3$), 1.22 (12H, t, J=7.0 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 169.1 (2C=O), 155.3 (2C), 145.5 (2C), 136.3 (C), 128.6 (2CH$_{arom.}$), 128.4 (2CH$_{arom.}$), 128.4 (2CH$_{vinyl.}$), 127.7 (CH$_{arom.}$), 120.3 (2CH$_{vinyl.}$), 119.9 (2CH$_{furan.}$), 117.9 (2C), 112.1 (2CH$_{furan.}$), 100.0 (2CH(OEt)$_2$), 60.9 (4CH$_2$), 41.8 (N–CH_2), 15.2 (4CH$_3$); m/z 576 (M+1), 598 (M+23); (Anal. Calcd for $C_{33}H_{37}NO_8$: C, 68.85; N, 2.43; H, 6.48. Found: C, 68.79; N, 2.41; H, 6.39).

4.2.4. 3,4-Bis[(5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (4d). Red solid (73%), mp 107–109 °C; ν_{max} (KBr)/cm^{-1} 3054, 2979, 2932, 1769, 1706, 1679, 1434, 1401, 1114, 1057, 1018; δ_H (200 MHz, $CDCl_3$) 7.54 (2H, d, J=3.5 Hz, $H_{furan.}$), 7.41–7.21 (5H, m, $H_{arom.}$), 6.65 (2H, d, J=3.5 Hz, $H_{furan.}$), 5.68 (2H, s, 2CH(OEt)$_2$), 4.75 (2H, s, N–CH_2), 3.64 (8H, dq, J=1.6, 7.0 Hz, 4CH_2CH$_3$), 1.24 (12H, t, J=7.0 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 168.9 (2C=O), 155.4 (2C), 144.9 (2C), 136.1 (C), 128.5 (2CH$_{arom.}$), 128.3 (2CH$_{arom.}$), 127.6 (CH$_{arom.}$), 118.7 (2CH$_{furan.}$), 118.4 (2C), 110.9 (2CH$_{furan.}$), 95.9 (2CH(OEt)$_2$), 61.2 (4CH$_2$), 41.6 (N–CH_2), 15.0 (4CH_3); m/z 524 (M+1), 541 (M+18), 546 (M+23); (Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; N, 2.68; H, 6.35. Found: C, 66.63; N, 2.61; H, 6.29).

4.2.5. 3,4-Bis[(5-diethoxymethyl)thien-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (4e). Red oil (65%); ν_{max}(film)/cm^{-1} 1741, 1699, 1284; δ_H (200 MHz, $CDCl_3$) 7.75 (2H, d, J=3.9 Hz, $H_{thiophen.}$), 7.27–7.44 (5H, m, $H_{arom.}$), 7.08 (2H, d, J=3.9 Hz, $H_{thiophen}$), 5.76 (2H, s, 2CH(OEt)$_2$), 4.75 (2H, s, N–CH_2), 3.64 (8H, q, J=7.1 Hz, 4CH_2CH$_3$), 1.25 (12H, t, J=7.1 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 169.5 (2C=O), 148.5 (2C), 136.0 (2C), 131.1 (C), 129.5 (2CH$_{arom.}$), 128.5 (2CH$_{arom.}$), 128.4 (CH$_{arom.}$), 127.6 (2CH$_{thiopen.}$), 126.9 (2C), 125.3 (2CH$_{thiophen.}$), 97.9 (2CH(OEt)$_2$), 60.8 (4CH$_2$), 41.9 (N–CH_2), 14.9 (4CH_3); m/z 556 (M+1), 578 (M+23); (Anal. Calcd for $C_{29}H_{33}NO_6S_2$: C, 62.68; N, 2.52; H, 5.99. Found: C, 62.55; N, 2.55; H, 6.07).

4.2.6. 3,4-Bis[(5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-(phenylethyl)-1*H*-pyrrol-2,5-dione (4f). Red solid (60%), mp 45–46 °C; ν_{max}(KBr)/cm^{-1} 2976, 2931, 1764, 1705, 1618, 1583, 1527, 1438, 1362, 1115, 1017; δ_H (200 MHz, $CDCl_3$) 7.51 (2H, d, J=3.5 Hz, $H_{furan.}$), 7.34–7.21 (5H, m, $H_{arom.}$), 6.63 (2H, d, J=3.5 Hz, $H_{furan.}$), 5.67 (2H, s, 2CH(OEt)$_2$), 3.82 (2H, t, J=7.3 Hz, CH_2), 3.65 (8H, dq, J=1.9, 7.0 Hz, 4CH_2CH$_3$), 2.94 (2H, t, J=7.3 Hz, CH_2), 1.24 (12H, t, J=7.0 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 169.1 (2C=O), 155.5 (2C), 145.1 (2C), 138.0 (C), 128.8 (2CH$_{arom.}$), 128.5 (2CH$_{arom.}$), 126.5 (CH$_{arom.}$), 118.7 (2CH$_{furan.}$), 118.4 (2C), 110.9 (2CH$_{furan.}$), 96.1 (2CH(OEt)$_2$), 61.4 (4CH$_2$), 39.5 (N–CH_2), 34.5 (CH$_2$), 15.1 (4CH$_3$); m/z 555 (M+18), 560 (M+23); (Anal. Calcd for $C_{30}H_{35}NO_8$: C, 66.53; N, 2.68; H, 6.35. Found: C, 66.69; N, 2.75; H, 6.46).

4.2.7. 3,4-Bis[(5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-(4-methoxybenzyl)-1*H*-pyrrol-2,5-dione (4g). Red solid (58%), mp 58–59 °C; ν_{max}(KBr)/cm^{-1} 3164, 3054, 2986, 1708, 1683, 1662, 1514, 1430, 1399, 1032; δ_H (200 MHz, $CDCl_3$) 7.51 (2H, d, J=3.5 Hz, $H_{furan.}$), 7.33 (2H, d, J=8.7 Hz, $H_{arom.}$), 6.83 (2H, d, J=8.7 Hz, $H_{arom.}$), 6.61 (2H, d, J=3.5 Hz, $H_{furan.}$), 5.65 (2H, s, 2CH(OEt)$_2$), 4.68 (2H, s, N–CH_2), 3.76 (3H, s, O–CH_3), 3.64 (8H, dq, J=7.1, 1.5 Hz, 4CH_2CH$_3$), 1.22 (12H, t, J=7.1 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 168.7 (2C=O), 158.7 (C–O), 155.0 (2C), 144.6 (2C), 129.5 (2CH$_{arom.}$), 128.1 (C), 118.3 (2CH$_{furan.}$), 118.2 (2C), 113.5 (2CH$_{arom.}$), 110.5 (2CH$_{furan.}$), 95.6 (2CH(OEt)$_2$), 60.9 (4CH$_2$), 54.8 (N–CH_2), 40.8 (CH$_2$), 14.7 (4CH$_3$); m/z 508 (M−[OEt]), 571 (M+18), 576 (M+23); (Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.09; N, 2.53; H, 6.37. Found: C, 65.01; N, 2.49; H, 6.44).

4.2.8. 3,4-Bis[(5-diethoxymethyl)furan-2-yl]-2,5-dihydro-1-(4-hydroxybenzyl)-1*H*-pyrrol-2,5-dione (4h). Red oil (62%); ν_{max}(film)/cm^{-1} 3054, 2986, 1708, 1680, 1614, 1517, 1422, 1156, 1053; δ_H (200 MHz, $CDCl_3$) 7.51 (2H, d, J=3.5 Hz, $H_{furan.}$), 7.21 (2H, d, J=8.4 Hz, $H_{arom.}$), 6.73 (2H, d, J=8.4 Hz, $H_{arom.}$), 6.61 (2H, d, J=3.5 Hz, $H_{furan.}$), 5.65 (2H, s, 2CH(OEt)$_2$), 4.63 (2H, s, N–CH_2), 3.62 (8H, dq, J=1.5, 7.1 Hz, 4CH_2CH$_3$), 1.21 (12H, t, J=7.1 Hz, 4CH_2CH$_3$); δ_C (200 MHz, $CDCl_3$) 169.2 (2C=O), 155.9 (C–O), 155.4 (2C), 145.1 (2C), 130.0 (2CH$_{arom.}$), 127.9 (C), 118.8 (2CH$_{furan.}$), 118.7 (2C), 115.5 (2CH$_{arom.}$), 111.0 (2CH$_{furan.}$), 96.1 (2CH(OEt)$_2$), 61.5 (4CH$_2$), 41.4 (N–CH_2), 15.1 (4CH$_3$); m/z 540 (M+1), 562 (M+23); (Anal. Calcd for $C_{29}H_{33}NO_9$: C, 64.55; N, 2.60; H, 6.16. Found: C, 64.32; N, 2.49; H, 6.05).

4.3. 4-Bis[(5-formyl)heteroar-2-yl]-2,5-dihydro-1-(substituted)-1*H*-pyrrol-2,5-dione (5a–h). General procedure

A solution of **4a–h** (1.59 mmol) and trifluoroacetic acid (1.21 mL, 15.90 mmol) in THF (15 mL) was stirred at room temperature during 2 h. Then, the mixture was taken up in pentane (30 mL), filtered and the precipitate was washed with pentane to give the title compounds **5a–h**.

4.3.1. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1*H*-pyrrol-2,5-dione (5a). Red solid (86%), mp 249 °C; ν_{max}(KBr)/cm^{-1} 3055, 2987, 1738, 1681, 1653, 1551, 1436, 1345, 1185, 1032, 814; δ_H (200 MHz, $CDCl_3$) 9.92 (2H, s, CHO), 7.78 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.55 (1H, br s, NH), 7.4 (2H, d, J=3.8 Hz, $H_{furan.}$); δ_C (200 MHz, $CDCl_3$) 179.6 (2CHO), 169.2 (2C=O), 153.4 (2C), 148.3 (2C), 122.1 (2CH$_{furan.}$), 121.6 (2C), 120.0 (2CH$_{furan.}$); m/z 286 (M+1), 308 (M+23), 318 (M+33); (Anal. Calcd for $C_{14}H_7NO_6$: C, 58.96; N, 4.91; H, 2.47. Found: C, 58.93; N, 4.71; H, 2.49).

4.3.2. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1-phenyl-1*H*-pyrrol-2,5-dione (5b). Red solid (87%), mp 257 °C; ν_{max}(KBr)/cm^{-1} 3055, 2987, 1713, 1675, 1600, 1549, 1404, 1339, 1166, 1028, 828; δ_H (200 MHz, $CDCl_3$) 9.94 (2H, s, CHO), 7.85 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.54–7.25 (7H, m, $H_{furan.}$, $H_{arom.}$); δ_C (200 MHz, $CDCl_3$) 178.8 (2CHO), 167.4 (2C=O), 153.9 (2C), 148.5 (2C), 131.8 (C), 129.4 (2CH$_{arom.}$), 128.8 (CH$_{arom.}$), 127.6 (2CH$_{arom.}$), 122.6 (2CH$_{furan.}$), 121.5 (2C), 120.7 (2CH$_{furan.}$); m/z 362 (M+1), 379 (M+18); (Anal. Calcd for $C_{20}H_{11}NO_6$: C, 66.49; N, 3.88; H, 3.07. Found: C, 65.21; N, 4.10; H, 3.00).

4.3.3. 3-(5-{1-Benzyl-2,5-dioxo-4-[5-(3-oxopropenyl) fur-2-yl]-2,5-dihydro-1*H*-pyrrol-3-yl}fur-2-yl)-propenal

(5c). Violet coloured solid (62%), mp 163 °C; ν_{max}(KBr)/cm^{-1} 3055, 2987, 1708, 1670, 1620, 1428, 1120, 1031, 892; δ_H (200 MHz, $CDCl_3$) 9.56 (2H, d, J=7.8 Hz, C*H*O), 7.60 (2H, d, J=3.7 Hz, $H_{furan.}$), 7.52–7.26 (5H, m, $H_{arom.}$), 7.18 (2H, d, J=15.8 Hz, $H_{vinyl.}$), 6.93 (2H, d, J=3.7 Hz, $H_{furan.}$), 6.87 (1H, dd, J=15.8, 7.8 Hz, $H_{vinyl.}$), 4.77 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 192.1 (2*C*HO), 168.3 (2*C*=O), 153.6 (2*C*), 148.0 (2*C*), 135.8 (2*C*$H_{vinyl.}$), 135.7 (*C*), 128.8 (2*C*$H_{arom.}$), 128.5 (2*C*$H_{arom.}$), 128.1 (*C*$H_{arom.}$), 127.7 (2*C*$H_{vinyl.}$), 121.3 (2*C*$H_{furan.}$), 119.2 (2*C*), 119.0 (2*C*$H_{furan.}$), 42.1 (N–CH_2); *m*/*z* 428 (M+1), 445 (M+18), 450 (M+23); (Anal. Calcd for $C_{25}H_{17}NO_6$: C, 70.25; N, 3.28; H, 4.01. Found: C, 70.27; N, 3.30; H, 3.98).

4.3.4. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (5d). Red solid (89%), mp 174 °C; ν_{max}(KBr)/cm^{-1} 3055, 2987, 1708, 1683, 1662, 1432, 1400, 1031, 981; δ_H (200 MHz, $CDCl_3$) 9.92 (2H, s, C*H*O), 7.81 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.47–7.27 (7H, m, $H_{furan.}$, $H_{arom.}$), 4.82 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 178.8 (2*C*HO), 167.9 (2*C*=O), 154.1 (2*C*), 148.6 (2*C*), 135.5 (*C*), 128.8 (2*C*$H_{arom.}$), 128.6 (2*C*$H_{arom.}$), 128.2 (*C*$H_{arom.}$), 120.9 (2*C*$H_{arom.}$), 120.6 (2*C*$H_{arom.}$), 120.4 (2*C*), 42.3 (N–CH_2); *m*/*z* 376 (M+1), 398 (M+23); (Anal. Calcd for $C_{21}H_{13}NO_6$: C, 67.20; N, 3.49; H, 3.73. Found: C, 66.90; N, 3.45; H, 3.70).

4.3.5. 3,4-Bis[(5-formyl)thien-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (5e). Orange solid (77%), mp 166–168 °C; ν_{max}(KBr)/cm^{-1} 1716, 1694, 1390; δ_H (200 MHz, $CDCl_3$) 9.96 (2H, s, 2*C*HO), 7.87 (2H, d, J=4.1 Hz, $H_{thiophen.}$), 7.77 (2H, d, J=4.1 Hz, $H_{thiophen.}$), 7.31–7.47 (5H, m, $H_{arom.}$), 4.81 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 182.7 (2*C*HO), 168.3 (2*C*=O), 147.2 (2*C*), 136.9 (2*C*), 135.4 (1 C and 2*C*$H_{arom.}$), 132.5 (2*C*$H_{arom.}$), 129.0 (2*C*), 128.8 (*C*$H_{arom.}$), 128.7 (2*C*$H_{thiophen.}$), 128.1 (2*C*$H_{thiophen.}$), 42.5 (*C*H_2); *m*/*z* 408 (M+1), 430 (M+23); (Anal. Calcd for $C_{21}H_{13}NO_4S_2$: C, 61.90; N, 3.44; H, 3.22. Found: C, 61.88; N, 3.39; H, 3.17).

4.3.6. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1-(phenylethyl)-1*H*-pyrrol-2,5-dione (5f). Orange solid (89%), mp 155 °C; ν_{max}(KBr)/cm^{-1} 3055, 2986, 1711, 1681, 1440, 1364, 1027, 982, 816; δ_H (200 MHz, $CDCl_3$) 9.91 (2H, s, 2C*H*O), 7.75 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.38 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.34–7.23 (5H, m, $H_{arom.}$), 3.88 (2H, t, J=7.4 Hz, CH_2), 2.97 (2H, t, J=7.4 Hz, CH_2); δ_C (200 MHz, $CDCl_3$) 178.9 (2*C*HO), 168.0 (2*C*=O), 154.0 (2*C*), 148.6 (2*C*), 137.5 (*C*), 128.8 (2*C*$H_{arom.}$), 128.7 (2*C*$H_{arom.}$), 126.8 (*C*$H_{arom.}$), 120.8 (2*C*$H_{furan.}$), 120.7 (2*C*$H_{furan.}$), 120.2 (2*C*), 40.0 (*C*H_2), 34.3 (*C*H_2); *m*/*z* 390 (M+1), 412 (M+23); (Anal. Calcd for $C_{22}H_{15}NO_6$: C, 67.87; N, 3.60; H, 3.88. Found: C, 67.94; N, 3.94; H, 3.60).

4.3.7. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1-(4-methoxybenzyl)-1*H*-pyrrol-2,5-dione (5g). Red solid (85%), mp 208–209 °C; ν_{max}(KBr)/cm^{-1} 3054, 2986, 1707, 1684, 1662, 1515, 1430, 1334, 1032, 813; δ_H (200 MHz, $CDCl_3$) 9.91 (2H, s, C*H*O), 7.79 (2H, d, J=4.0 Hz, $H_{furan.}$), 7.38 (2H, d, J=4.0 Hz, $H_{furan.}$), 7.36 (2H, d, J=8.6 Hz, $H_{arom.}$), 6.86 (2H, d, J=8.6 Hz, $H_{arom.}$), 4.74 (2H, s, N–CH_2), 3.78 (3H, s, O–CH_3); δ_C (200 MHz, $CDCl_3$) 178.8 (2*C*HO), 167.9 (2*C*=O), 159.5 (*C*–O), 154.1 (2*C*), 148.6 (2*C*), 130.1 (2*C*$H_{arom.}$), 127.8 (*C*), 120.8 (2*C*$H_{furan.}$), 120.5 (2*C*$H_{furan.}$), 120.4 (2*C*), 114.1 (2*C*$H_{arom.}$), 55.2 (O–CH_3), 41.8 (N–CH_2); *m*/*z* 406 (M+1), 423 (M+18), 428 (M+23); (Anal. Calcd for $C_{22}H_{15}NO_7$: C, 65.19; N, 3.46; H, 3.73. Found: C, 65.30; N, 3.77; H, 3.49).

4.3.8. 3,4-Bis[(5-formyl)fur-2-yl]-2,5-dihydro-1-(4-hydroxybenzyl)-1*H*-pyrrol-2,5-dione (5h). Red solid (93%), mp 223 °C; ν_{max}(KBr)/cm^{-1} 3056, 2986, 1707, 1672, 1517, 1435, 1400, 1027, 811; δ_H (200 MHz, $CDCl_3$) 9.89 (2H, s, C*H*O), 7.79 (2H, d, J=3.9 Hz, $H_{furan.}$), 7.38 (2H, d, J=3.9 Hz, $H_{furan.}$), 7.31 (2H, d, J=8.5 Hz, $H_{arom.}$), 6.79 (2H, d, J=8.5 Hz, $H_{arom.}$), 4.73 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 178.9 (2*C*HO), 167.4 (2*C*=O), 155.4 (*C*–O), 153.4 (2*C*), 148.5 (2*C*), 129.7 (2*C*$H_{arom.}$), 127.0 (*C*), 121.2 (2*C*$H_{furan.}$), 120.5 (2*C*$H_{furan.}$), 120.2 (2*C*), 115.1 (2*C*$H_{arom.}$), 41.3 (N–CH_2); *m*/*z* 392 (M+1), 409 (M+18); (Anal. Calcd for $C_{21}H_{13}NO_7$: C, 64.45; N, 3.58; H, 3.35. Found: C, 64.55; N, 3.61; H, 3.50).

4.4. 3,4-Dibromomaleic anhydride (7)

Under an inert atmosphere, a solution of maleic anhydride (1.50 g, 15.29 mmol), aluminium chloride (28 mg, 0.21 mmol) and bromine (1.50 mL, 30.58 mmol) was heated at 120 °C during 16 h in a sealed tube. After cooling the tube to room temperature, the mixture was taken up in ethyl acetate, filtered and the filtrate was concentrated in vacuo to afford the title compound **7** (3.64 g, 93%) as a yellow solid, mp 113–114 °C.[10]

4.5. 3,4-Dibromo-2,5-dihydro-1*H*-pyrrol-2,5-dione (8a)

To a solution of 3,4-dibromomaleic anhydride **7** (4 g, 15.63 mmol) in acetic acid (50 mL) was added ammonium acetate (1.76 g, 23.44 mmol). The mixture was heated at reflux during 16 h. After solvent removal under reduced pressure, the crude residue was purified by column chromatography over silica gel (eluent: light petroleum–ethyl acetate: 7/3) to give compound **8a** (2.40 g, 60%) as a yellow solid, mp 198 °C.[17]

4.6. 3,4-Dibromo-2,5-dihydro-1-(substituted)-1*H*-pyrrol-2,5-dione (8b–e): General procedure

To a solution of 3,4-dibromomaleic anhydride **7** (4.40 g, 17.19 mmol) in acetic acid (50 mL) was added anilines (18.91 mmol). The mixture was heated at reflux during 3 h. After solvent removal under reduced pressure, the crude mixture was purified by column chromatography over silica gel (eluent: light petroleum–ethyl acetate) to afford the desired products **8b–e**.

4.6.1. 3,4-Dibromo-2,5-dihydro-1-phenyl-1*H*-pyrrol-2,5-dione (8b). Yellow solid (81%), mp 162–163 °C.[10]

4.6.2. 3,4-Dibromo-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (8c). Yellow solid (92%) mp 107–108 °C.[10]

4.6.3. 3,4-Dibromo-2,5-dihydro-1-(ethylphenyl)-1*H*-pyrrol-2,5-dione (8d). Yellow solid (75%), mp 165–166 °C; ν_{max}(KBr)/cm^{-1} 3054, 2987, 1727, 1595, 1421, 1361, 1166, 1102, 896; δ_H (200 MHz, $CDCl_3$) 7.31–7.18 (5H, m, $H_{arom.}$),

3.85 (2H, t, $J=6.4$ Hz, CH_2), 2.92 (2H, t, $J=6.4$ Hz, CH_2); δ_C (200 MHz, $CDCl_3$) 163.7 (2*C*=O), 137.2 (*C*), 129.3 (2*C*Br), 128.7 (4*C*H$_{arom.}$), 126.9 (*C*H$_{arom.}$), 40.8 (*C*H$_2$), 34.4 (*C*H$_2$); *m/z* 359 (M), 268 ^{79}Br, 361 (M), 270 ^{81}Br, 104; (Anal. Calcd for $C_{12}H_9Br_2NO_2$: C, 40.15; N, 3.90; H, 2.53. Found: C, 40.12; N, 3.87; H, 2.50).

4.7. 3,4-Dibromo-2,5-dihydro-1-(4-methoxybenzyl)-1*H*-pyrrol-2,5-dione (8e)

Yellow solid (90%), mp 120–121 °C.[10]

4.7.1. 3,4-Diiodo-2,5-dihydro-1-(substituted)-1*H*-pyrrol-2,5-dione (6a–e). General procedure. A solution of 3,4-dibromo-2,5-dihydro-1-(substituted)-1*H*-pyrrol-2,5-dione **8a–e** (4.40 g, 17.26 mmol) and sodium iodide (7.86 g, 51.78 mmol) in acetic acid (65 mL) was heated at reflux during 2 h, afterwards water (50 mL) was added. The yellow precipate obtained was filtered off, washed with water and dried to provide the title compounds **6a–f**.

4.7.2. 3,4-Diiodo-2,5-dihydro-1*H*-pyrrol-2,5-dione (6a). Yellow solid (70%), mp 254–255 °C.[18]

4.7.3. 3,4-Diiodo-2,5-dihydro-1-phenyl-1*H*-pyrrol-2,5-dione (6b). Yellow solid (84%), mp 184–186 °C.[19]

4.7.4. 3,4-Diiodo-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (6c). Yellow solid (89%), mp 127–128 °C; ν_{max}(KBr)/cm^{-1} 3057, 2955, 1777, 1715, 1550, 1433, 1388, 1331, 1056, 908; δ_H (200 MHz, $CDCl_3$) 7.31–7.17 (5H, m, *H*$_{arom.}$), 4.72 (2H, s, C*H*$_2$); δ_C (200 MHz, $CDCl_3$) 165.9 (2*C*=O), 135.3 (*C*), 128.6 (4*C*H$_{arom.}$), 128.0 (*C*H$_{arom.}$), 117.2 (2*C*I), 43.4 (*C*H$_2$); *m/z* 439 (M+1); (Anal. Calcd for $C_{11}H_7I_2NO_2$: C, 30.1; N, 3.19; H, 1.61. Found: C, 30.06; N, 3.11; H, 1.73).

4.7.5. 3,4-Diiodo-2,5-dihydro-1-(ethylphenyl)-1*H*-pyrrol-2,5-dione (6d). Yellow solid (87%), mp 163–164 °C; ν_{max}(KBr)/cm^{-1} 3055, 2987, 1762, 1718, 1555, 1435, 1399, 1098, 1058, 896; δ_H (200 MHz, $CDCl_3$) 7.28–7.10 (5H, m, *H*$_{arom.}$), 3.89–3.75 (2H, m, C*H*$_2$), 2.96–2.85 (2H, m, C*H*$_2$); δ_C (200 MHz, $CDCl_3$) 166.2 (2*C*=O), 137.3 (*C*), 128.8 (4*C*H$_{arom.}$), 126.9 (*C*H$_{arom.}$), 117.2 (2*C*I), 41.3 (*C*H$_2$), 34.5 (*C*H$_2$); *m/z* 454 (M+1); (Anal. Calcd for $C_{12}H_9I_2NO_2$: C, 31.82; N, 3.09; H, 2.00. Found: C, 31.93; N, 3.01; H, 2.11).

4.7.6. 3,4-Diiodo-2,5-dihydro-1-(4-methoxybenzyl)-1*H*-pyrrol-2,5-dione (6e). Yellow solid (88%), mp 136–137 °C; ν_{max}(KBr)/cm^{-1} 3054, 2986, 1781, 1722, 1612, 1575, 1515, 1390, 1178, 1033, 896; δ_H (200 MHz, $CDCl_3$) 7.31 (2H, d, $J=8.5$ Hz, *H*$_{arom.}$), 6.84 (2H, d, $J=8.5$ Hz, *H*$_{arom.}$), 4.7 (2H, s, C*H*$_2$), 3.78 (3H, s, C*H*$_3$); δ_C (200 MHz, $CDCl_3$) 166.1 (2*C*=O), 159.5 (*C*–OMe), 130.4 (2*C*H$_{arom.}$), 127.7 (*C*), 117.4 (2*C*I), 114.1 (2*C*H$_{arom.}$), 55.3 (*C*H$_3$), 43.1 (*C*H$_2$); *m/z* 469 (M), 342, 215, 121; (Anal. Calcd for $C_{12}H_9I_2NO_3$: C, 30.73; N, 2.99; H, 1.93. Found: C, 30.69; N, 2.93; H, 1.91).

4.7.7. 3,4-Diiodo-2,5-dihydro-1-(4-hydroxybenzyl)-1*H*-pyrrol-2,5-dione (6f). A solution of **6e** (5 g, 10.6 mmol) and boron tribromide (3.5 mL, 37.3 mmol) in dichloromethane (150 mL) was stirred at −10 °C to room temperature during 90 min. The reaction was then hydrolysed slowly and extracted with ethyl acetate. The combined organic layers were washed with a saturated sodium hydrogenocarbonate solution and dried over anydrous $MgSO_4$. After solvent removal, the crude was purified by column chromatography (eluent: light petroleum–ethyl acetate: 8/2) to give **6f** (4.08 g, 84%) as orange needles, mp 222 °C; ν_{max}(KBr)/cm^{-1} 3055, 1762, 1698, 1610, 1514, 1441,1390, 1211, 1072, 915; δ_H (200 MHz, DMSO) 9.39 (1H, br s, O*H*), 7.07 (2H, d, $J=8.2$ Hz, *H*$_{arom.}$), 6.69 (2H, d, $J=8.2$ Hz, *H*$_{arom.}$), 4.52 (2H, s, C*H*$_2$); δ_C (200 MHz, DMSO) 167.5 (2*C*=O), 157.2 (*C*–OH), 129.4 (2*C*H$_{arom.}$), 126.9 (*C*), 119.5 (2CI), 115.6 (2*C*H$_{arom.}$), 42.6 (*C*H$_2$); *m/z* 455 (M+1); (Anal. Calcd for $C_{11}H_7I_2NO_3$: C, 29.04; N, 3.08; H, 1.55. Found: C, 28.99; N, 3.02; H, 1.51).

4.7.8. 2-(Diethoxymethyl)-4-bromofuran (9). *4,5-Dibromofuran*. Furaldehyde (20.00 g, 208.14 mmol) was added dropwise to aluminium chloride (61.06 g, 457.91 mmol) at 0 °C under an inert atmosphere with mechanical stirring. Bromine (21.32 mL, 416.28 mmol) was then added dropwise in a similar manner still at 0 °C. The temperature was then allowed to rise to room temperature while stirring was maintained for 16 h. Then the reaction was cautiously hydrolysed with ice and water and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (eluent: light petroleum–ethyl acetate: 98/2) to give 4,5-dibromofuran (33 g, 63%) as a brown solid, mp 31–32 °C.[11]

2-(Diethoxymethyl)-4,5-dibromofuran. Triethyl orthoformate (18.21 mL, 109.4 mmol) was added to a solution of 4,5-dibromofuran (7.00 g, 27.35 mmol) and ammonium chloride (350 mg) in ethanol (140 mL). The mixture was refluxed during 16 h. After cooling the solution to room temperature, the solvent was removed under reduced pressure and the residue diluted in ethyl acetate. The organic layer was washed with a saturated sodium hydrogenocarbonate solution and dried over anhydrous $MgSO_4$. After solvent removal, the crude mixture was chromatographied over silica gel (eluent: light petroleum–ethyl acetate: 99/1) to afford the desired product (8.9 g, 98%) as a brown oil.[11]

2-(Diethoxymethyl)-4-bromofuran. Under an inert atmosphere, *n*-butyllithium (10.85 mL, 27.13 mmol, 2.5 M in hexane) was added dropwise to a solution of 2-(diethoxymethyl)-4,5-dibromofuran (8.9 g, 27.13 mmol) in ether at −78 °C. The mixture was then stirred for 1 h while allowing the temperature to rise to room temperature, and neutralised (pH=5). The mixture was extracted and the combined organic layers were washed and dried over anhydrous $MgSO_4$. After solvent removal, the crude residue was chromatographied over silica gel (eluent: light petroleum–ethyl acetate: 8/2) to afford **9** (4.9 g, 73%) as a yellow oil.[11]

4.7.9. 3,4-Bis[(5-diethoxymethyl)fur-3-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (11). Under an inert atmosphere, bis(pinacolato)diborane (324 mg, 1.28 mmol), potassium acetate (380 mg, 3.84 mmol), [1,1′-bis(diphenylphosphinoferrocene]dichloropalladium (II) (30 mg,

0.038 mmol) were added to a stirred solution of **9** (320 mg, 1.28 mmol) in dry DMF (5 mL). The mixture was refluxed under nitrogen with stirring for 2 h. After cooling the solution to room temperature, **6c** (280 mg, 0.64 mmol), [1,1′bis(diphenylphosphino)ferrocene] dichloropalladium (II) (30 mg, 0.038 mmol) and 2 M Na_2CO_3 (1.2 mL, 1.60 mmol) were added, and the mixture was stirred at 80 °C, under nitrogen for another 2 h. The solution was cooled to room temperature and was extracted with ethyl acetate (15 mL). The combined organic layers were washed with water (15 mL), brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel (eluent: light petroleum–ethyl acetate: 8/2) gave 57 mg (20%) of 3,4-bis[(5-diethoxymethyl)fur-3-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-one **11** as a yellow oil, ν_{max} (film)/cm^{-1} 3054, 2986, 1708, 1682, 1434, 1398, 1114, 1057, 1020; δ_H (200 MHz, $CDCl_3$) 8.11 (2H, s, $H_{furan.}$), 7.44–7.25 (5H, m, $H_{arom.}$), 6.72 (2H, s, $H_{furan.}$), 5.55 (2H, s, 2C*H*$(OEt)_2$), 4.76 (2H, s, N–CH_2), 3.62 (8H, dq, J=2.6, 7.0 Hz, 4C$H_2$$CH_3$), 1.24 (12H, t, J=7.0 Hz, 4CH_2CH_3); δ_C (200 MHz, $CDCl_3$) 168.9 (2*C*=O), 152.8 (2*C*), 144.9 (2C$H_{furan.}$), 136.3 (2*C*), 128.7 (2C$H_{arom.}$), 128.5 (2C$H_{arom.}$), 127.8 (C$H_{arom.}$), 126.8 (*C*), 114.8 (2*C*), 107.7 (2C$H_{furan.}$), 95.8 (2*C*H$(OEt)_2$), 61.4 (4*C*H_2), 41.9 (N–CH_2), 15.1 (4CH_3); *m/z* 524 (M+1), 541 (M+18), 546 (M+23); (Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; N, 2.68; H, 6.35. Found: C, 66.49; N, 2.66; H, 6.29).

4.7.10. 3-Bromo-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (12). A solution of maleic anhydride (16 g, 163 mmol) and benzylamine (17.82 mL, 163 mmol) in acetic acid (150 mL) was heated at reflux during 2 h. After the solution was cooled to 0 °C, bromine (24.6 mL, 489 mmol) and potassium acetate (16 g, 163 mmol) were added and the mixture was refluxed under stirring for 3 h. Then water (200 mL) was added. The precipate obtained was filtered off, washed with water, dried and purified by column chromatography to give dibromo compound **8c** (28.48 g, 51%) and **12** (18.22 g, 42%) as a yellow solid, mp 51–52 °C; ν_{max}(KBr)/cm^{-1} 3055, 2986, 1727, 1430, 1383, 1150, 1075, 892; δ_H (200 MHz, $CDCl_3$) 7.34–7.24 (5H, m, $H_{arom.}$), 6.82 (1H, s, C*H*–C=O), 4.67 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 168.2 (*C*=O), 165.0 (*C*=O), 135.7 (*C*), 131.9 (*C*H), 131.3 (C_{Br}), 128.8 (2C$H_{arom.}$), 128.6 (2C$H_{arom.}$), 128.1 (C$H_{arom.}$), 42.3 (N–CH_2); *m/z* 266 (M+1) ^{79}Br, 268 (M+1) ^{81}Br; (Anal. Calcd for $C_{11}H_8BrNO_2$: C, 49.65; N, 5.26; H, 3.03. Found: C, 49.71; N, 5.21; H, 3.09).

4.7.11. 3-[(5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (13). According to the general procedure in Section 4.2, the title compound was obtained as a red oil (55%); ν_{max} (film)/cm^{-1} 3054, 2979, 1708, 1684, 1430, 1401, 1110, 1057, 1020; δ_H (200 MHz, $CDCl_3$) 7.31–7.17 (6H, m, 1 $H_{furan.}$, 5 $H_{arom.}$), 6.55 (2H, d, J=3.4 Hz, $H_{furan.}$), 6.51 (1H, s, C*H*–C=O), 5.53 (1H, s, C*H*$(OEt)_2$), 4.63 (2H, s, N–CH_2), 3.59 (4H, q, J=6.9 Hz, 2 O–C$H_2$$CH_3$), 1.20 (6H, t, J=6.9 Hz, 2 O–CH_2CH_3); δ_C (200 MHz, $CDCl_3$) 170.3 (*C*=O), 168.6 (*C*=O), 156.2 (*C*), 144.6 (*C*), 136.3 (*C*), 133.6 (*C*H), 128.6 (2C$H_{arom.}$), 128.3 (2C$H_{arom.}$), 127.7 (C$H_{arom.}$), 117.9 (C$H_{furan.}$, *C*), 111.4 (C$H_{furan.}$), 95.9 (2*C*H$(OEt)_2$), 61.5 (2*C*H_2), 41.4 (N–CH_2), 15.1 (2CH_3); *m/z* 310 (M), 373 (M+18), 378 (M+23); (Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; N, 3.94; H, 5.96. Found: C, 67.55; N, 3.88; H, 5.91).

4.7.12. 4-Bromo-3-[(5-diethoxymethyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (14). Under an inert atmosphere, bromine (80 μL, 1.56 mmol) was added dropwise to a solution of **13** (0.53 g, 1.49 mmol) in dichloromethane (5 mL). After triethylamine (270 μL, 1.56 mmol) was added, the mixture was stirred for 1 h while allowing the temperature to rise to room temperature. It was then taken up in ethyl acetate and washed with water. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographied on silica gel (eluent: light petroleum–dichloromethane: 1/1) to give **14** (1.04 g, 70%) as a yellow oil; ν_{max} (film)/cm^{-1} 3054, 2979, 1710, 1679, 1432, 1395, 1114, 1057, 1018, 893; δ_H (200 MHz, $CDCl_3$) 7.48 (1H, d, J=3.5 Hz, $H_{furan.}$), 7.51–7.22 (5H, m, $H_{arom.}$), 6.62 (1H, d, J=3.5 Hz, $H_{furan.}$), 5.58 (1H, s, C*H*$(OEt)_2$), 4.72 (2H, s, N–CH_2), 3.65 (4H, q, J=7.1 Hz, 2 O–C$H_2$$CH_3$), 1.24 (6H, t, J=7.1 Hz, 2 O–CH_2CH_3); δ_C (200 MHz, $CDCl_3$) 167.0 (*C*=O), 165.7 (*C*=O), 156.8 (*C*), 143.9 (*C*), 135.8 (*C*), 129.5 (*C*), 128.7 (2C$H_{arom.}$), 128.6 (2C$H_{arom.}$), 128.0 (C$H_{arom.}$), 119.4 (C$H_{furan.}$), 114.2 (*C*), 111.3 (C$H_{furan.}$), 96.0 (2*C*H$(OEt)_2$), 61.7 (2*C*H_2), 42.4 (N–CH_2), 15.2 (2CH_3); *m/z* 434 (M+1), 456 (M+23), ^{79}Br. 436 (M+1), 458 (M+23) ^{81}Br; (Anal. Calcd for $C_{20}H_{20}BrNO_5$: C, 55.31; N, 3.23; H, 4.64. Found: C, 55.42; N, 3.19; H, 4.72).

4.7.13. 4-Bromo-3-[(5-carboxyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (15). *4-Bromo-3-[(5-formyl)-fur-2-yl]-2,5-dihydro-1-benzyl-1H-pyrrol-2,5-dione*. According to the general procedure in Section 4.3, the desired formylfuryl intermediate was obtained as a yellow solid (79%), mp 145–146 °C; ν_{max} (KBr)/cm^{-1} 3054, 2986, 1706, 1679, 1664, 1396, 1400, 1115, 981; δ_H (200 MHz, $CDCl_3$) 9.78 (1H, s, C*H*O), 7.61 (2H, d, J=3.8 Hz, $H_{furan.}$), 7.38–7.30 (6H, m, $H_{arom.}$), 4.75 (2H, s, N–CH_2); δ_C (200 MHz, $CDCl_3$) 178.2 (C*H*O), 166.4 (*C*=O), 164.8 (*C*=O), 153.8 (*C*), 147.8 (*C*), 135.4 (*C*), 128.9 (*C*), 128.8 (2C$H_{arom.}$), 128.7 (2C$H_{arom.}$), 128.2 (C$H_{arom.}$), 120.7 (C$H_{furan.}$), 119.1 (*C*), 119.0 (C$H_{furan.}$), 42.7 (N–CH_2); *m/z* 377 (M+18), 382 (M+23), 392 (M+33) ^{79}Br. 378 (M+18), 384 (M+23), 394 (M+33) ^{81}Br; (Anal. Calcd for $C_{16}H_{10}BrNO_4$: C, 53.36; N, 3.89; H, 2.80. Found: C, 53.19; N, 3.75; H, 2.69).

4.7.14. 4-Bromo-3-[(5-carboxyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione. A solution of $NaClO_2$ (60 mg, 0.66 mmol) in water (1 mL) was added dropwise to a stirred mixture of 4-bromo-3-[(5-formyl)fur-2-yl]-2,5-dihydro-1-benzyl-1H-pyrrol-2,5-dione (200 mg, 0.55 mmol) in acetonitrile (1 mL), NaH_2PO_4 (32 mg) in water (0.5 mL) and of 30% H_2O_2 (95 μL, 0.83 mmol), keeping the temperature at 15 °C with water cooling. Oxygen evolved from the solution until the end of the reaction (1 h) with a bubbler connected to the apparatus. A small amount of Na_2SO_3 (~10 mg) was added to destroy the unreacted HOCl and H_2O_2. After acidification with HCl 6 N, the mixture was extracted with tetrahydrofuran/dichloromethane 1:3. The combined organic layers were washed with little water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue mixture was purified

by fash column chromatography (eluent: dichloromethane/acetic acid 99:1) to give **15** (141 mg, 72%) as a yellow solid, mp 170–171 °C; ν_{max} (KBr)/cm^{-1} 3447, 3055, 2987, 1710, 1683, 1445, 1112, 1030, 896; δ_H (200 MHz, DMSO) 7.41 (7H, m, $H_{furan.}$, $H_{arom.}$), 4.62 (2H, s, CH_2); δ_C (200 MHz, DMSO) 164.3 (*C*=O), 163.2 (*C*=O), 158.6 (*C*OOH), 145.1 (*C*), 143.9 (*C*), 134.6 (*C*), 128.7 (2$CH_{arom.}$), 128.5 (2$CH_{arom.}$), 128.1 ($CH_{arom.}$), 126.9 (*C*), 119.3 ($CH_{furan.}$), 118.1 (*C*), 117.3 ($CH_{furan.}$), 42.5 (N–CH_2); *m/z* 358 (M+1), 380 (M+23); (Anal. Calcd for $C_{16}H_{10}BrNO_5$: C, 51.09; N, 3.72; H, 2.68. Found: C, 51.01; N, 3.64; H, 2.54).

4.7.15. 4-[(5-formyl)fur-2-yl]-3-[(5-carboxyl)fur-2-yl]-2,5-dihydro-1-benzyl-1*H*-pyrrol-2,5-dione (16). Compound **16** was prepared according to the general procedure in Section 4.2, until the final crude residue was obtained. Then, this latter was purified by flash column chromatography (eluent: dichloromethane/acetic acid 99:1) to give **16** as a red solid (17%), mp 175 °C; ν_{max} (KBr)/cm^{-1} 3446, 3054, 2986, 1706, 1687, 1401, 1116, 1057, 891; δ_H (200 MHz, DMSO) 9.79 (1H, s, C*H*O), 7.65–7.25 (9H, m, $H_{arom.}$, $H_{furan.}$), 4.71 (2H, s, N–CH_2); δ_C (200 MHz, DMSO) 180.2 (*C*HO), 168.3 (2*C*=O), 159.3 (*C*OOH), 153.9 (*C*), 148.6 (*C*), 147.9 (*C*), 147.1 (*C*), 136.6 (*C*), 129.1 ($CH_{arom.}$), 129.0 (2$CH_{arom.}$), 127.9 (2$CH_{arom.}$), 121.2 ($CH_{furan.}$), 120.5 ($CH_{furan.}$), 120.2 (2*C*), 120.0 ($CH_{furan.}$), 119.7 ($CH_{furan.}$), 41.8 (N–CH_2); *m/z* 392 (M+1), 406 (M−17+MeOH), 414 (M+23); (Anal. Calcd for $C_{21}H_{13}NO_7$: C, 64.45; N, 3.58; H, 3.35. Found: C, 64.42; N, 3.51; H, 3.28).

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Nucleophilic addition to dimethylvinylphosphine sulfide as a convenient route to polydentate ligands containing the 2-dimethylphosphinoethyl unit

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Abstract—The synthesis of a range of new phosphine-containing polydentate ligands has been achieved by addition of sulfur and nitrogen nucleophiles to dimethylvinylphosphine sulfide, followed by reduction of the resulting phosphine sulfides with lithium aluminium hydride.

1. Introduction

Metal complexes containing phosphine ligands have a wide range of uses including both medical and industrial applications. Phosphines are known to coordinate well to a range of metals and their inclusion in polydentate ligands can facilitate complex formation in some circumstances. However, the tendency of alkyl substituted phosphines to oxidise in air makes it difficult to prepare pure samples of some complex phosphine-containing polydentate ligands and this has often inhibited the synthesis of polydentate ligands containing trialkylphosphine centres in favour of those containing diphenylphosphino groups.

Our interest in phosphine-containing polydentate ligands developed from our work on ^{99m}Tc-based radiopharmaceutical imaging agents.[1] Here, the ligand must be prepared in a high state of purity and the overall complex must have an appropriate lipophilicity if it is to exhibit a useful biodistribution. In this context the presence of phenyl substituents on the phosphorus is highly undesirable due to the high lipophilicity of the resulting systems while the incorporation of a terminal dimethylphosphino group is often highly desirable. In some cases, such as the bisphosphines we have prepared as potential myocardial imaging agents[2,3] incorporation of the dimethylphosphino group was achieved by nucleophilic substitution of appropriately substituted alkyl halides by the dimethylphosphide anion. However, this latter material is particularly unpleasant to handle and it often proved necessary to purify the resulting ligand via temporary formation of the corresponding sulfide or oxide in order to obtain material of sufficient purity for subsequent testing.

We now report a convenient route to a range of new polydentate ligands containing the dimethylphosphino group based on the use of dimethylvinylphosphine sulfide **1** as the precursor for the 2-dimethylphosphinoethyl unit. Previous workers[4] have reported the use of this compound in the synthesis of a number of polyphosphine ligands. We have exploited the susceptibility of the dimethylvinylphosphine sulfide to nucleophilic attack to include the use of both sulfur and nitrogen nucleophiles, thus offering scope for the synthesis of a wide range of new polydentate phosphine ligands such as those shown in Scheme 1 and Figure 1.

2. Results and discussion

In general, the nucleophilic additions to dimethylvinylphosphine sulfide **1** were carried out in ethanol and while the addition of the more nucleophilic thiolate anions could be achieved at room temperatures, addition of aliphatic amines usually required an extended period of heating under reflux. Aromatic amines were found to be unreactive towards **1** under these conditions, but they did react rapidly if first converted into their amide anions by the action of

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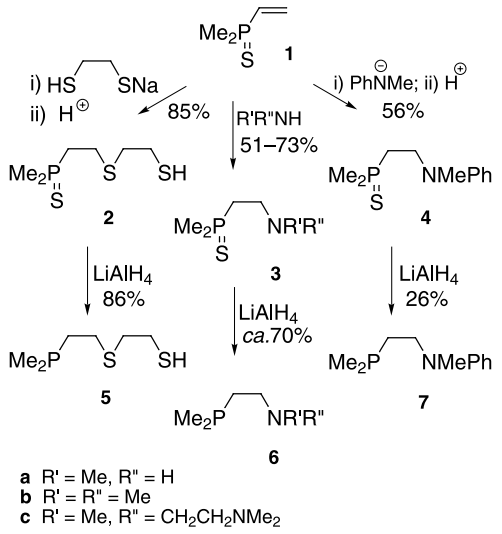


Scheme 1.

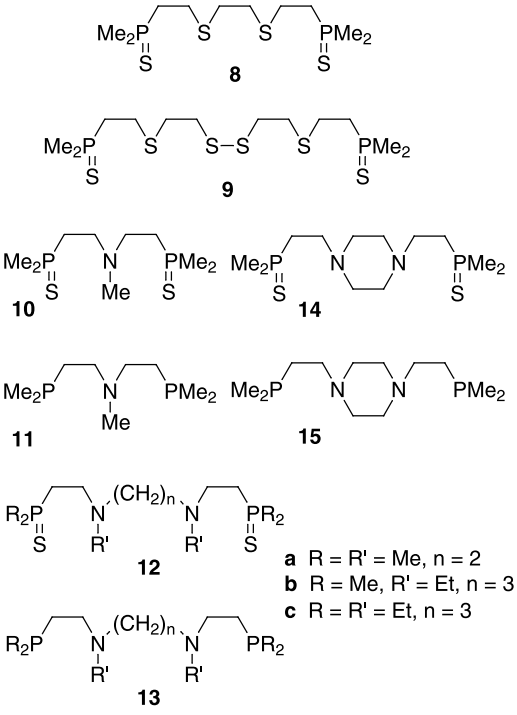


Figure 1.

n-butyllithium. Thus, for example, the lithium salt of methylaniline readily added to **1** to give the phosphine sulfide **4**.

In some cases reported here, reaction of more than one dimethylvinylphosphine sulfide molecule with the nucleophile is possible, although in general we found that this could be avoided if the nucleophile was kept in excess. This approach enabled the preparation of the phosphine sulfide **2** to be achieved from the thiolate of ethane-1,2-dithiol without significant formation of the bis(phosphine sulfide) **8**, and likewise the formation of the phosphine sulfide **3a** rather than **10** from the reaction of **1** with methylamine.

The phosphine sulfides produced in these studies were very stable, often crystalline solids, which could be readily purified. Reduction of these materials with reducing agents such as lithium aluminium hydride gave the corresponding phosphine ligands in good yield and in a high state of purity.

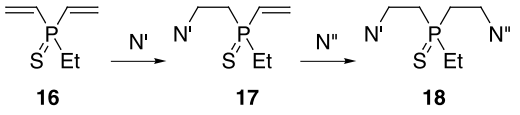
Additional support of the structure of the polydentate phosphine ligands produced in this way was obtained by adding sulfur, which led to regeneration of the phosphine sulfide precursors.

It should be noted that some of the phosphine ligands were found to readily co-distil with the dioxane used as the solvent in the reduction step. This could result in significant loss of the phosphine ligand from the distillation flask unless particular care was taken during the distillation. An alternative approach was to convert the phosphine ligand into its hydrochloride salt before removing the dioxane. The phosphine was then regenerated and recovered via extraction into diethyl ether. Fortunately, in general, this was unnecessary, as a dioxane solution of the phosphine ligand was suitable for our purposes.

We have also prepared other dialkylvinylphosphine sulfides for use in ligand synthesis. Thus, for example, diethylvinylphosphine sulfide was prepared by an analogous route to that used for the dimethyl analogue **1** and used to prepare the bisphosphine **12c**.

Preliminary work has also been carried out on the use of alkyldivinylphosphine sulfides such as **16**,[5] for the preparation of polydentate ligands containing a trialkylphosphine site at a non-terminal position.

We have already established that it is possible to react **16** with *N*,*N*,*N*′-trimethylethylenediamine to give **17** ($N'=$ $NMeCH_2CH_2NMe_2$) and that this can be converted into **18** ($N'=N''=NMeCH_2CH_2NMe_2$) in a subsequent step (Scheme 2). The stepwise addition of two different nucleophiles to the divinylphosphine sulfide **16** should therefore provide a route for the preparation of a wide range of new unsymmetrical ($N'\neq N''$) polydentate ligand systems. This is currently being investigated.



Scheme 2.

3. Conclusions

The susceptibility of dialkylvinylphosphine sulfides, such as **1**, to nucleophilic attack by both sulfur and nitrogen nucleophiles can be exploited to provide a convenient route for the synthesis of a wide range of new phosphine-containing polydentate ligands via the initial formation of the corresponding air-stable phosphine sulfide precursors. The range of ligands that are accessible by this approach can also be extended by the stepwise addition of two nucleophilic units to an alkyldivinylphosphine sulfide such as **16**.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ (on JEOL GSX270, FX100, PMX60 and Bruker AMX 600 spectrometers), dm, doublet of multiplets. Melting points were taken in open capillaries on an electrically heated Buchi SMP-20 melting point apparatus and are uncorrected. Elemental analyses were obtained on a Carlo Erba 1106 Elemental Analyser.

4.1.1. Dimethylvinylphosphine sulfide (1). Dimethylvinylphosphine sulfide was prepared by a previously reported procedure.[4]

4.1.2. Diethylvinylphosphine sulfide. Diethylvinylphosphine sulfide was obtained from diethylphosphinothioylbromide by the procedure used to prepare the corresponding dimethyl analogue **1** and isolated as a colourless oil, (0.93 g, 20% overall yield after 3 steps), bp 44 °C, 0.05 mmHg, (lit.[6] bp 98–99 °C, 1.5 mmHg). δ_P ($CDCl_3$) 48.5; δ_H (270 MHz, $CDCl_3$), 0.81 (6H, td, J_{P-H}= 19.3 Hz, J_{H-H}=7.4 Hz, CH_2*Me*), 1.57 (4H, dq, J_{P-H}= 11.4 Hz, J_{H-H}=7.4 Hz, CH_2), 5.99 (3H, m, CH=CH_2); δ_C ($CDCl_3$), 5.77 (d, J_{P-C}=4.2 Hz, CH_2*Me*), 23.9 (d, J_{P-C}= 56.1 Hz, CH_2–P), 129.1 (d, J_{P-C}=69.5 Hz, P–CH), 135.3 (s, CH=*CH_2*). EI-MS: 148 ($[M]^+$, 37%), 147 (92), 120 (84), 92 (100), 63 (52), 57 (35). ESI-HRMS: Found $[M+Na]^+$ 171.0368, $[C_6H_{13}PS+Na]^+$ requires 171.19772.

4.1.3. 2-(2-Dimethylphosphinothioylethylsulfanyl)-ethanethiol (2). 1,2-Dimercaptoethane (20 g, 213 mmol) was added to a solution of sodium ethoxide, prepared by adding sodium (1.5 g, 65 mmol) to ethanol (300 cm^3). The mixture was stirred for 1 h at room temperature and then cooled in ice before dimethylvinylphosphine sulfide **1**[4] (8 g, 66 mmol) was added. The mixture was allowed to warm to room temperature and left to stir overnight. The solvent and excess dithiol were removed under reduced pressure and water (250 cm^3) was added. The mixture was acidified by addition of hydrochloric acid and extracted with chloroform (3×200 cm^3). The chloroform extracts were dried with anhydrous $MgSO_4$, filtered and the solvent evaporated to give the phosphine sulfide **2** (12 g, 85%) as a colourless oil, containing a small quantity of the bis(phosphine sulfide) **8**. The phosphine sulfide **2** was further purified by distillation (bp 155–160 °C at 0.001 mmHg), although care was needed since some decomposition occurred at higher temperatures. δ_P ($CDCl_3$) 36.0; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, d, J_{PH}= 13 Hz, P(S)Me_2), 2.10–2.20 (2H, m, α-CH_2), 2.72–2.95 (6H, m, β-CH_2 and SCH_2CH_2S); δ_C ($CDCl_3$) 21.1 (d, J_{PC}= 54 Hz, P(S)Me_2), 24.4 (CH_2), 24.8 (d, J_{PC}=2 Hz, β-CH_2), 34.3 (d, J_{PC}=49 Hz, α-CH_2), 36.0 (CH_2).

On prolonged exposure to the air the thiol **2** (R=CH_2CH_2-SH) oxidised to the corresponding disulfide **9**, a colourless waxy solid (Found: C, 33.52; H, 6.5. $C_{12}H_{28}P_2S_6$ requires C, 33.8; H, 6.6%). δ_P ($CDCl_3$) 36.2; δ_H (270 MHz, $CDCl_3$) 1.78 (12H, d, J_{PH}=13 Hz, P(S)Me_2), 2.12–2.22 (4H, m, α-CH_2) 2.92 (8H, br s, SCH_2CH_2S) 2.87–2.97 (4H, m, β-CH_2); δ_C ($CDCl_3$) 21.3 (d, J_{PC}=54 Hz, P(S)Me_2), 25.2 (d, J_{PC}= 2 Hz, β-CH_2), 31.6 (CH_2), 34.6 (d, J_{PC}=50 Hz, α-CH_2), 38.3 (CH_2).

4.1.4. 2-(2-Dimethylphosphinoethylsulfanyl)ethanethiol (5). The following reduction procedure and subsequent work-up was carried out in an inert atmosphere of nitrogen using degassed solvents. To a suspension of lithium aluminium hydride (2.2 g, 56 mmol) in dry dioxane (200 cm^3) was added 2-(2-dimethylphosphinothioylethylsulfanyl)ethane-thiol **2** (6 g, 28 mmol), and the mixture heated under reflux for 24 h (N.B. After a short initiation period a vigorous exothermic reaction often occurs which may necessitate cooling the reaction mixture). The mixture was allowed to cool and 25% aqueous dioxane (10 cm^3) was added dropwise. Aqueous sodium hydroxide (5 cm^3, 2 M) was then added followed by water (7 cm^3). The resulting mixture was filtered through a glass sinter and the solvent was removed under reduced pressure (50 °C at 40 mmHg). The residue, which contained a little solid, was redissolved in dry dioxane, filtered, and the solvent then removed under reduced pressure (50 °C at 40 mmHg) to give the phosphine **5** (ca. 4.5 g, 86%) containing a small quantity of solvent. δ_P ($CDCl_3$) −50.2; δ_H (60 MHz, $CDCl_3$) 0.94 (6H, d, J_{PH}=2 Hz, PMe_2), 1.40–1.68 (2H, m, β-CH_2), 1.70 (1H, br s, SH), 2.38–2.78 (6H, m, CH_2); δ_C ($CDCl_3$) 13.8 (d, J_{PC}=13 Hz, PMe_2), 24.7 (CH_2), 28.5 (d, J_{PC}=18 Hz, α-CH_2), 32.1 (d, J_{PC}=13 Hz, β-CH_2), 36.1 (CH_2).

4.1.5. *N*-(2′-Dimethylphosphinothioylethyl)methylamine (3a). Dry methylamine was passed into ethanol (100 cm^3) until it no longer readily dissolved. Dimethylvinylphosphine sulfide **1** (8 g, 66 mmol) was added and the mixture was heated at 80 °C overnight in a Teflon-lined (Berghof) autoclave. Volatile components were removed under reduced pressure (60 °C at 18 mmHg) and the residue distilled under vacuum, bp 100 °C at 0.1 mmHg, to give the pure phosphine sulfide **3a** as a colourless low melting solid (6 g, 60%), mp 35–36 °C (Found: C, 39.8; H, 9.53; N, 9.3. $C_5H_{14}NPS$ requires C, 39.7; H, 9.3; N, 9.3%). δ_P ($CDCl_3$) 35.2; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, d, J_{PH}=13 Hz, P(S)Me_2), 1.82 (1H, br s, NH), 2.10 (2H, dt, J_{PH}=12 Hz, J_{HH}=7 Hz, α-CH_2), 2.44 (3H, s, NMe), 2.97 (2H, dt, J_{PH}= 14 Hz, J_{HH}=7 Hz, β-CH_2); δ_C ($CDCl_3$) 21.2 (d, J_{PC}= 55 Hz, P(S)Me_2), 33.6 (d, J_{PC}=53 Hz, α-CH_2), 35.4 (Me), 45.2 (β-CH_2); IR (ν max cm^{-1}, thin film): 3472, 3287, 2974, 2936, 2905, 2851, 2797, 1474, 1451, 1420, 1289, 1115, 945, 918, 856, 744.5, 713.6, 575.

4.1.6. *N*-(2′-Dimethylphosphinoethyl)methylamine (6a). *N*-(2′-Dimethylphosphinothioylethyl)methylamine **3a** (3 g, 26 mmol) was reduced cleanly to the corresponding phosphine **6a** using the method previously given for the preparation of **5**. Because the resulting *N*-(2′-dimethylphosphinoethyl)methylamine **6a** tended to co-distil when efforts were made to remove the reaction solvent, it was generally used as a solution in dioxane in subsequent studies. The dioxane could be removed carefully at 53 °C at 100 mmHg but this resulted in significant loss of product from the reaction flask.[7] δ_P ($CDCl_3$) −55.5; δ_H (270 MHz, $CDCl_3$) 0.95 (6H, d, J_{PH}=2 Hz, PMe_2), 1.50 (2H, br t, J_{HH}=8 Hz, α-CH_2), 2.08 (1H, br s, NH), 2.35 (3H, s, NMe), 2.62 (2H, dt, J_{PH}=7.5 Hz, J_{PH}=8 Hz, β-CH_2); δ_C ($CDCl_3$) 13.5 (d, J_{PC}=13 Hz, PMe_2), 32.0 (d, J_{PC}=10 Hz, α-CH_2), 35.6 (NMe), 48.2 (d, J_{PC}=17 Hz, β-CH_2).

4.1.7. *N*,*N*-Bis(2′-dimethylphosphinothioylethyl)-methylamine (10). A mixture of *N*-(2′-dimethylphosphinothioylethyl)-methylamine **3a** (11 g, 73 mmol) and dimethyl-vinylphosphine sulfide **1** (9 g, 75 mmol) in ethanol (150 cm^3) was heated under reflux for 24 h. The mixture was cooled in ice and the resulting precipitate was isolated by filtration. The solid was then recrystallised from ethanol to give the pure product **10** (11.5 g, 58%), mp 189 °C, (Found: C, 39.9; H, 8.8; N, 4.9. $C_9H_{23}NP_2S_2$ requires C, 39.8; H, 8.54; N, 5.2%), δ_P ($CDCl_3$) 36.0; δ_H (270 MHz, $CDCl_3$) 1.77 (12H, d, $J_{PH}=13$ Hz, P(S)Me_2), 2.09 (4H, dt, $J_{PH}=12$ Hz, $J_{PH}=7$ Hz, α-CH_2), 2.27 (3H, s, NMe), 2.82 (4H, dt, $J_{PH}=13$ Hz, $J_{PH}=7$ Hz, β-CH_2); δ_C ($CDCl_3$) 21.5 (d, $J_{PC}=54$ Hz, P(S)Me_2), 31.7 (d, $J_{PH}=53$ Hz, α-CH_2), 41.6 (NMe), 50.8 (β-CH_2).

4.1.8. *N*,*N*-Bis(2′-dimethylphosphinoethyl)methylamine (11). *N*,*N*-Bis(2′-dimethylphosphinothioylethyl)methylamine **10** (5 g, 18 mmol) was cleanly reduced to the phosphine **11** (3.5 g, 91%) using the procedure previously given for the preparation of **5**, allowing for the presence of two phosphine sulfide centres in the molecule. δ_P ($CDCl_3$) −53.6; δ_H (60 MHz, $CDCl_3$) 0.96 (12H, d, $J_{PH}=2$ Hz, PMe_2), 1.42 (4H, m, α-CH_2), 2.15 (3H, s, NMe), 2.42 (4H, m, β-CH_2); δ_C ($CDCl_3$) 14.0 (d, $J_{PC}=13$ Hz, PMe_2), 29.4 (d, $J_{PC}=10$ Hz, α-CH_2), 41.4 (s, NMe), 53.7 (d, $J_{PC}=19$ Hz, β-CH_2).

4.1.9. *N*-(2′-Dimethylphosphinothioylethyl)dimethylamine (3b). Dry dimethylamine was passed into ethanol (100 cm^3) until it no longer readily dissolved. Dimethyl-vinylphosphine sulfide **1** (10 g, 83 mmol) was added and the mixture was heated at 80 °C overnight in a Teflon-lined (Berghof) autoclave. The crystalline product was filtered off and purified by vacuum sublimation (100 °C at 0.1 mmHg) to give the pure product **3b** as a colourless solid (10 g, 73%), mp 79–80 °C (lit.[8] mp 125–129 °C)[9] (Found: C, 43.50; H, 9.8; N, 8.4. $C_6H_{16}NPS$ requires C, 43.6; H, 9.8; N, 8.50%). δ_P ($CDCl_3$) 35.8; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, d, $J_{PH}=13$ Hz, P(S)Me_2), 2.07 (2H, dm, $J_{PH}=12$ Hz, α-CH_2), 2.56 (6H, s, NMe_2), 2.68 (2H, dm, $J_{PH}=12$ Hz, β-CH_2); δ_C ($CDCl_3$) 21.3 (d, $J_{PC}=54$ Hz, P(S)Me_2), 32.6 (d, $J_{PC}=53$ Hz, α-CH_2), 45.1 (NMe_2), 53.2 (β-CH_2).

4.1.10. *N*-(2′-Dimethylphosphinoethyl)dimethylamine (6b). *N*-(2′-Dimethylphosphinothioylethyl)dimethylamine **3b** (3 g, 26 mmol) was cleanly reduced to the corresponding phosphine **6b** using the method previously given for the preparation of **5**. Because the resulting *N*-(2′-dimethylphosphinothioylethyl)dimethylamine tended to co-distil when efforts were made to remove the reaction solvent, it was generally used as a solution in dioxane in subsequent studies. The dioxane could be removed under reduced pressure (53 °C at 100 mmHg) but this resulted in significant loss of product. δ_P ($CDCl_3$) −53.8; δ_H (60 MHz, $CDCl_3$) 0.96 (6H, d, $J_{PH}=2$ Hz, PMe_2), 1.44 (2H, m, α-CH_2), 2.17 (6H, s, NMe_2), 2.32 (4H, m, β-CH_2); δ_C ($CDCl_3$) 14.1 (d, $J_{PC}=12$ Hz, PMe_2), 30.2 (d, $J_{PC}=10$ Hz, α-CH_2), 45.2 (s, NMe_2), 56.3 (d, $J_{PC}=19$ Hz, β-CH_2).

4.1.11. *N*,*N*′-Bis(2′-dimethylphosphinothioylethyl)-*N*,*N*′-dimethylethylenediamine (12a). A mixture of *N*,*N*′-dimethylethylenediamine (5 g, 57 mmol) and dimethyl-vinylphosphine sulfide (14 g, 117 mmol) in ethanol (75 cm^3) was heated under reflux for approximately 1 week and monitored by ^{31}P NMR spectroscopy. After this time the reaction mixture was cooled to afford a crystalline solid which was isolated by filtration. The bulk of the solvent was then removed under reduced pressure (60 °C at 18 mmHg) to give a further quantity of the crystalline product. Recrystallisation of this material from ethyl acetate gave the pure product **12a** (15 g, 80%) as a colourless solid, mp 120 °C, (Found: C, 43.6; H, 9.2; N, 8.51. $C_{12}H_{30}N_2P_2S_2$ requires C, 43.9; H, 9.2; N, 8.53%). δ_P ($CDCl_3$) 36.0; δ_H (270 MHz, $CDCl_3$) 1.77 (12H, d, $J_{PH}=13$ Hz, P(S)Me_2), 2.07 (4H, dm, $J_{PH}=12$ Hz, α-CH_2), 2.26 (6H, s, NMe), 2.53 (4H, s, CH_2), 2.82 (4H, dm, $J_{PH}=13$ Hz, β-CH_2); δ_C ($CDCl_3$) 21.3 (d, $J_{PC}=55$ Hz, P(S)Me_2), 31.5 (d, $J_{PC}=53$ Hz, α-CH_2), 41.9 (NMe), 51.1 (β-CH_2), 54.8 (CH_2).

4.1.12. *N*,*N*′-Bis(2′-dimethylphosphinoethyl)-*N*,*N*′-dimethylethylenediamine (13a). *N*,*N*′-Bis(2′-Dimethylphosphinothioylethyl)-*N*,*N*′-dimethyl-ethylenediamine **12a** (6 g, 18 mmol) was cleanly reduced to the phosphine **13a** (4.0 g, 83%) using the procedure previously indicated for the preparation of **11**. δ_P ($CDCl_3$) −53.8; δ_H (60 MHz, $CDCl_3$) 0.95 (12H, d, $J_{PH}=2$ Hz, PMe_2), 1.48 (4H, m, α-CH_2), 2.17 (6H, s, NMe), 2.40 (4H, br s, CH_2), 2.42 (4H, m, β-CH_2); δ_C ($CDCl_3$) 13.8 (d, $J_{PC}=13$ Hz, PMe_2), 29.0 (d, $J_{PC}=10$ Hz, α-CH_2), 41.9 (NMe), 54.4 (d, $J_{PC}=19$ Hz, β-CH_2), 54.6 (CH_2).

4.1.13. *N*,*N*′-Bis(2′-dimethylphosphinothioylethyl)-*N*,*N*′-diethylpropylenediamine (12b). A mixture of *N*,*N*′-dimethylpropylene-1,3-diamine (5 g, 38 mmol) and dimethylvinylphosphine sulfide **1** (10.5 g, 87 mmol) in ethanol (125 cm^3) was heated under reflux for 48 h in an atmosphere of dry nitrogen. The solvent was removed under reduced pressure to give an orange oil which was recrystallised in ethyl acetate. This yielded the pure bis(phosphine sulfide) **12b** (7.9 g, 56%) as a colourless solid, mp 79 °C, (Found: C, 48.9; H, 9.9; N, 7.5. $C_{15}H_{36}N_2P_2S_2$ requires C, 48.6; H, 9.8; N, 7.56%). δ_P ($CDCl_3$) 36.1; δ_H (270 MHz, $CDCl_3$) 1.03 (6H, t, $J_{HH}=7$ Hz, Me), 1.58–1.69 (2H, m, CH_2), 1.76 (12H, d, $J_{PH}=13$ Hz, P(S)Me_2), 1.98–2.08 (4H, dm, $J_{PH}=12$ Hz, α-CH_2), 2.45 (4H, t, $J_{HH}=7$ Hz, NCH_2), 2.53 (4H, q, $J_{HH}=7$ Hz, CH_3CH_2), 2.83–2.93 (4H, dm, $J_{PH}=12$ Hz, β-CH_2); δ_C ($CDCl_3$) 11.9 (Me), 21.4 (d, $J_{PC}=55$ Hz, P(S)Me_2), 24.8 (CH_2), 31.5 (d, $J_{PC}=53$ Hz, α-CH_2), 47.0 (β-CH_2), 47.1 (CH_2), 51.3 (CH_2). EI-MS: 371 ($[M+H]^+$ 99%), 355 (15), 339 (6), 251 (8), 325 (4), 178 (21), 166 (7). ES-HRMS: Found $[M+H]^+$ 371.18762 $C_{15}H_{36}N_2P_2S_2$ requires 371.18732.

4.1.14. *N*,*N*′-Bis(2′-dimethylphosphinoethyl)-*N*,*N*′-diethyl-propylenediamine (13b). *N*,*N*′-Bis(2′-dimethylphosphinothioylethyl)-*N*,*N*′-diethyl-propylenediamine **12b** (1.9 g) was reduced to the phosphine **13b** using the procedure previously indicated for the preparation of **11**. However, to obtain a pure sample of the bisphosphine **13b** the reduction mixture was evaporated prior to hydrolysis. This caused the pure bisphosphine (0.52 g, 33%) to separated from the remaining creamy oil. δ_P ($CDCl_3$) −53.8; δ_H (270 MHz, $CDCl_3$) 0.95–1.03 (18H, m,

J_{PH}=2 Hz, Me, PMe_2), 1.46 (4H, m, α-CH_2) 1.56 (2H, m, CH_2), 2.40 (4H, m, β-CH_2), 2.49–2.56 (8H, m, NCH_2, CH_2CH_3); δ_C ($CDCl_3$) 11.4 (Me), 13.7 (d, J_{PC}=12 Hz, PMe_2), 24.2 (CH_2), 28.5 (d, J_{PC}=10 Hz, α-CH_2), 46.5 (CH_2), 49.3 (d, J_{PC}=19 Hz, β-CH_2), 50.8 (CH_2).

4.1.15. *N,N′*-Bis(2′-diethylphosphinothioylethyl)-*N,N′*-diethylpropylenediamine (12c). A mixture of *N,N′*-diethylpropylene-1,3-diamine (1.83 g, 14 mmol) and diethylvinylphosphine sulfide (4.8 g, 32 mmol) in ethanol (45 cm^3) was heated under reflux in an atmosphere of dry nitrogen for 72 h. After cooling, the solvent was removed under reduced pressure and the crude product recrystallised from diethyl ether/cyclohexane. The pure bis(phosphine sulfide) **12c** (2.75 g, 46%) was isolated as a colourless solid, mp 56 °C, (Found: C, 53.4; H, 10.5; N, 6.9. $C_{19}H_{44}N_2P_2S_2$ requires C, 53.50; H, 10.4; N, 6.6%). δ_P ($CDCl_3$) 52.2; δ_H (270 MHz, $CDCl_3$) 1.01 (6H, t, J_{HH}=7 Hz, N–CH_2CH_3), 1.18 (12H, dt, J_{PH}=19 Hz, J_{HH}=7.5 Hz, P(S)CH_2CH_3), 1.63 (2H, m, CH_2), 1.86 (8H, dm, J_{PH}=12 Hz, PCH_2CH_3), 1.90–2.00 (4H, m, α-CH_2), 2.49 (4H, m, N–CH_2), 2.53 (4H, q, J_{HH}=7 Hz, N–CH_2CH_3), 2.83 (4H, m, β-CH_2); δ_C ($CDCl_3$), 6.7 (d, J_{PC}=5 Hz, P(S)CH_2CH_3), 12.1 (N-CH_2CH_3), 24.2 (d, J_{PC}=52, P(S)CH_2CH_3), 24.9 (CH_2), 26.8 (d, J_{PC}=48 Hz, α-CH_2), 46.9 (βCH_2), 47.3 (CH_2), 51.5 (CH_2). EI-MS: 427 ($[M+H]^+$, 99%), 399 (10), 305 (30), 279 (39), 232 (10), 220 (5), 206 (69), 183 (20), 149 (68). ES-HRMS: Found $[M+H]^+$ 427.24935 $C_{19}H_{44}N_2P_2S_2$ requires 427.24992.

4.1.16. *N,N′*-(2′-Diethylphosphinoethyl)-*N,N′*-diethylethylenediamine (13c). *N,N′*-Bis(2′-diethylphosphinothioylethyl)-*N,N′*-diethyl-propylenediamine **12c** (1.45 g, 3 mmol) was cleanly reduced to the bisphosphine **13c** (0.63 g, 51%) using the procedure previously indicated for the preparation of **11**. δ_P ($CDCl_3$) −25.7; δ_H (600 MHz, $CDCl_3$) 0.95 (6H, t, J_{HH}=7.5 Hz, NCH_2CH_3), 0.99 (12H, dt, J_{PH}=14 Hz, J_{HH}=7.5 Hz, PCH_2CH_3), 1.35 (8H, q, J_{HH}=7.5 Hz, PCH_2CH_3), 1.46 (4H, m, J_{PH}=6.5 Hz, α-CH_2), 1.53 (2H, quintet, J_{HH}=7.2 Hz, CH_2), 2.37 (4H, 't', J_{HH}=7.2 Hz, $CH_2CH_2CH_2$), 2.46 (4H, q, J_{HH}=7.5 Hz, N–CH_2), 2.51 (4H, dm, J_{PH}=12 Hz, β-CH_2); δ_C ($CDCl_3$) 9.1 (d, J_{PC}=13 Hz, PCH_2CH_3), 11.6 (N-CH_2CH_3), 18.6 (d, J_{PC}=13 Hz, PCH_2CH_3), 23.4 (d, J_{PC}=16 Hz, α-CH_2), 24.8 (CH_2), 46.6 (CH_2), 49.8 (d, J_{PC}=20 Hz, β-CH_2), 50.7 (CH_2).

4.1.17. *N,N′*-(2′-Dimethylphosphinothioylethyl)piperazine (14). Piperazine (1.8 g, 21 mmol) and dimethylvinylphosphine sulfide **1** (5.1 g, 42 mmol) were dissolved in ethanol (150 cm^3) and the mixture heated under reflux for 6 days. After cooling the product was filtered off and dried to give the pure product **14** as a colourless solid (5 g, 73%), mp 212 °C, (Found: C, 44.3; H, 8.7; N, 8.4. $C_{12}H_{28}N_2P_2S_2$ requires C, 44.1; H, 8.65; N, 8.6%). δ_P ($CDCl_3$) 36.0; δ_H (270 MHz, $CDCl_3$) 1.77 (12H, d, J_{PH}=13 Hz, P(S)Me), 2.06 (4H, dt, J_{PH}=12 Hz, J_{HH}=7 Hz, α-CH_2), 2.51 (8H, br m, NCH_2), 2.77 (4H, dt, J_{PH}=14 Hz, J_{HH}=7 Hz, β-CH_2); δ_C ($CDCl_3$) 21.5 (d, J_{PC}=54 Hz, P(S)Me), 31.9 (d, J_{PC}=53 Hz, α-CH_2), 51.8 (β-CH_2), 52.9 (NCH_2).

4.1.18. *N,N′*-(2′-Dimethylphosphinoethyl)piperazine (15). *N,N′*-(2′-Dimethylphosphinothioylethyl)piperazine **14** (7 g, 21 mmol) was cleanly reduced to the phosphine **15** (4.83 g, 86%) using the procedure previously indicated for the preparation of **11** and isolated as a colourless viscous oil which solidified on standing. δ_P ($CDCl_3$) −53.1; δ_H (60 MHz, $CDCl_3$) 0.92 (12H, d, J_{PH}=2 Hz, PMe), 1.45 (4H, m, α-CH_2), 2.35 (4H, m, β-CH_2), 2.40 (8H, br s, CH_2); δ_C ($CDCl_3$) 14.0 (d, J_{PC}=12 Hz, PMe), 29.2 (d, J_{PC}=10 Hz, β-CH_2), 52.8 (NCH_2), 55.1 (d, J_{PC}=19 Hz, α-CH_2).

4.1.19. *N*-(2′-Dimethylphosphinothioylethyl)-*N,N′,N′*-trimethylethylenediamine (3c). A mixture of *N,N′,N′*-trimethylethylenediamine (8.5 g, 83 mmol) and dimethylvinylphosphine sulfide **1** (10 g, 83 mmol) in ethanol (100 cm^3) was heated under reflux for 3 days. Evaporation of the solvent gave the title product as a yellow oil, in a good state of purity. A pure sample of the product **3c** (9.6 g, 51%) was obtained by distillation (bp 114 °C at 0.1 mmHg), (Found: C, 48.6; H, 10.2; N, 12.35. $C_9H_{23}N_2PS$ requires C, 48.6; H, 10.4; N, 12.6%). δ_P ($CDCl_3$) 36.4; δ_H (270 MHz, $CDCl_3$, 30 °C), 1.57 (6H, d, J_{PH}=13 Hz, P(S)Me), 1.87 (2H, dm, J_{PH}=12 Hz, β-CH_2), 2.05 (6H, s, NMe_2), 2.08 (3H, s, NMe), 2.22 (2H, m, CH_2NMe_2), 2.32 (2H, m, CH_2NMe), 2.64 (2H, dm, J_{PH}=13 Hz, α-CH_2); δ_C ($CDCl_3$), 21.4 (d, J_{PC}=55 Hz, P(S)Me), 32.1 (d, J_{PC}=52 Hz, α-CH_2), 42.0 (N-Me), 45.8 (N-Me_2), 51.6 (CH_2), 55.3 (CH_2), 57.3 (CH_2). EI-MS: 223 ($[M+H]^+$ 99%), 207 (6), 189 (10), 178 (12), 164 (48), 150 (3). ES-HRMS: Found $[M+H]^+$ 223.13982 $C_9H_{23}N_2PS$ requires 223.13977.

4.1.20. *N*-(2′-Dimethylphosphinoethyl)-*N,N′,N′*-trimethyl-ethylenediamine (6c). *N*-(2′-Dimethylphosphinothioylethyl)-*N,N′,N′*-trimethyl-ethylenediamine **3c** (3.7 g, 17 mmol) was reduced cleanly to the phosphine **6c** using the method previously given for the preparation of **5** and isolated as a colourless oil (2.2 g, 69%), δ_P ($CDCl_3$) −53.4; δ_H (270 MHz, $CDCl_3$) 0.96 (6H, d, J_{PH}=2 Hz, PMe), 1.46–1.53 (2H, m, α-CH_2), 2.21 (3H, s, NMe), 2.24 (6H, s, NMe_2), 2.41–2.53 (6H, m, CH_2); δ_C ($CDCl_3$) 13.4 (d, J_{PC}=13 Hz, PMe), 28.8 (d, J_{PC}=11 Hz, α-CH_2), 41.5 (NMe), 45.2 (NMe), 54.2 (d, J_{PC}=19 Hz, β-CH_2), 54.5 (CH_2), 56.8 (CH_2).

4.1.21. *N*-(2′-Dimethylphosphinothioylethyl)methylamino-benzene (4). To a solution of *N*-methylaniline (1 g, 9.3 mmol) and dimethylvinylphosphine sulfide **1** (1.25 g, 10.4 mmol) in dry toluene (50 cm^3), at room temperature and under an atmosphere of dry nitrogen, was added a solution of *n*-butyl lithium in pentane (5.5 cm^3, 1.7 M). The resulting cloudy orange solution was stirred for 30 min and ethanol (20 cm^3) was then slowly added. The mixture was acidified with hydrochloric acid (2 M) and then extracted with chloroform. The aqueous layer was basified by the addition of aqueous sodium hydroxide (2 M) and re-extracted with chloroform. The latter chloroform extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to give a solid. This was recrystallised from diethyl ether to yield the phosphine sulfide **4** as a colourless solid (1.2 g, 56%) (Found: C, 57.9; H, 8.15; N, 6.2. $C_{11}H_{18}NPS$ requires C, 58.1; H, 8.0; N, 6.2%). δ_P ($CDCl_3$) 34.6; δ_H (270 MHz, $CDCl_3$) 1.67 (6H, d, J_{PH}=11 Hz, P(S)Me), 2.06 (2H, dm, J_{PH}=12 Hz, α-CH_2), 2.90 (3H, s, NMe), 3.72 (2H, dm, J_{PH}=14 Hz, β-CH_2), 6.65–6.71 (3H, m, ArH), 7.15–7.22 (2H, m, ArH); δ_C ($CDCl_3$)

21.4 (d, $J_{PC}=55$ Hz, P(S)Me), 30.6 (d, $J_{PC}=50$ Hz, α-CH_2), 38.6 (NMe), 46.9 (β-CH_2), 113.0 (C-2,6), 117.3 (C-4), 129.4 (C-3,5), 148.4 (C-1). EI-MS: 227 ($[M+H]^+$, 22%), 152 (5), 132 (100), 120 (81), 104 (63), 94 (58), 77 (65), 65 (15), 51 (12), 42 (23). ES-HRMS: Found $[M+H]^+$ 228.0970 $C_{11}H_{19}NPS$ requires 228.0976.

4.1.22. *N*-(2′-Dimethylphosphinoethyl)methylaminobenzene (7). *N*-(2′-Dimethylphossphinoethyl)methylaminobenzene **4** (0.5 g, 2.6 mmol) was reduced cleanly to the phosphine **7** using the method previously given for the preparation of **5** and isolated as a colourless oil (0.13 g, 26%), δ_P ($CDCl_3$) −54.9; δ_H (270 MHz, $CDCl_3$) 0.96 (6H, d, $J_{PH}=2$ Hz, PMe), 1.51–1.56 (2H, m, α-CH_2), 2.81 (3H, s, NMe), 3.34–3.38 (6H, m, CH_2), 6.63–6.69 (3H, m, ArH), 7.17–7.20 (2H, m, ArH); δ_C ($CDCl_3$) 13.4 (d, $J_{PC}=14$ Hz, PMe), 28.1 (d, $J_{PC}=13$ Hz, α-CH_2), 37.5 (NMe), 49.2 (d, $J_{PC}=21$ Hz, β-CH_2),), 112.0 (C-2,6), 115.8 (C-4), 128.7 (C-3,5), 148.4 (C-1)

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Synthesis of 3,3-dimethoxy-2-aryl-2,3-dihydro-1-oxa-cyclopenta[*l*]phenanthren-2-ols and their conversion to 2(3*H*)- and 3(2*H*)-furanones

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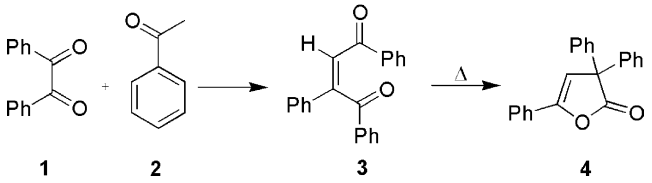
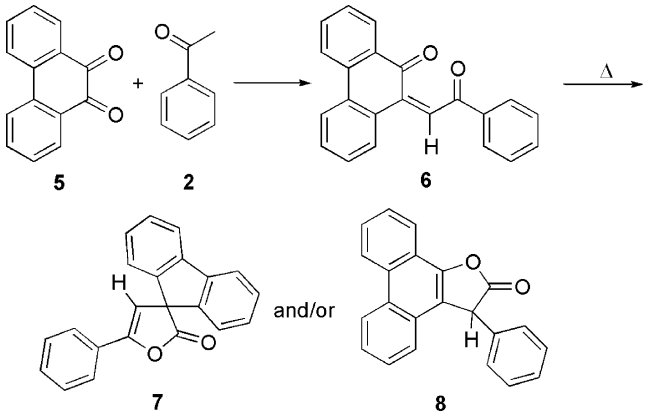
Abstract—A number of new 3,3-dimethoxy-2-aryl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ols were synthesized by the base-catalyzed reaction between phenanthrenequinone and 4-substituted acetophenones in methanol. These furanols are unstable and are easily converted to stable 3-methoxy-3-aryl-3*H*-1-oxacyclopenta[*l*]phenathren-2-ones in excellent yields. The furanols are converted to 2-aryl-1-oxacyclopenta[*l*]phenanthren-3-ones on treatment with acids. Plausible mechanisms for some of these new transformations are proposed.

1. Introduction

α,β-Unsaturated ketones are conveniently prepared by Aldol condensation.[1–4] Dibenzoylstyrene (**3**), for example, is synthesized by the base-catalyzed condensation between benzil (**1**) and acetophenone (**2**). Thermolysis of **3** and related systems leads to 2(3*H*)-furanones **4**, which exhibit rich photochemistry (Scheme 1).[5,6] Furthermore, due to their common occurrence in nature, oxygen containing heterocycles are frequent and important targets for synthesis either as final products or as useful synthetic intermediates. The synthesis of lactones can be achieved by the lactonization of hydroxy acids, Baeyer–Villiger oxidation, the insertion of a carbonyl group by transition metals, intramolecular cyclization of 1,4-diones, etc.[7] We reasoned that the condensation between phenanthrenequinone (**5**) and acetophenone (**2**) should lead to phenanthrenone-9-ylidene ketones **6**, which may be regarded as novel analogues of dibenzoylalkenes. Accordingly, these ketones, in principle,



Scheme 1.



Scheme 2.

should undergo thermal rearrangement to give 2(3*H*)-furanone derivatives **7** and/or **8** (Scheme 2).

Close examination of the structural features of **6** reveals that it can be considered as a quinonemethide as well. Hence, **6** and its derivatives are expected to undergo transformations typical of other quinonemethides including Diels–Alder reactions, nucleophilic additions, etc. The reported procedure for the preparation of **6** involves the Wittig reaction between phenanthrenequinone and the triphenylphosphonium ylide prepared from phenacyl bromide.[8] Dimerization of **6** through a hetero Diels–Alder pathway is a major side reaction here making this procedure synthetically unviable. So, we explored the possibility of synthesizing **6** through the base-catalyzed reaction between phenanthrenequinone and acetophenones. In this article, we report our findings on the

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base-catalyzed reaction between phenanthrenequinone and acetophenones.

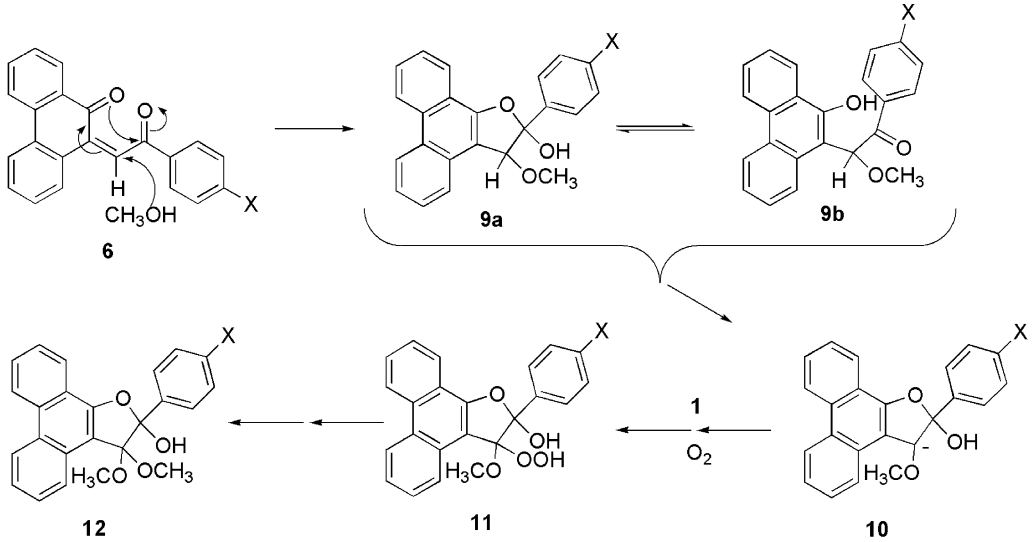
2. Results and discussion

We proposed to synthesize phenanthrenone-9-ylidene ketones **6a–f** by the condensation of phenanthrenequinone (**5**) with selected acetophenones **2a–f** in methanol in the presence of potassium hydroxide as catalyst (Scheme 2). Aryl ketones of our choice were acetophenone (**2a**), 4-methylacetophenone (**2b**), 4-methoxyacetophenone (**2c**), 4-bromoacetophenone (**2d**), 4-chloroacetophenone (**2e**), and 4-phenylacetophenone (**2f**).

The condensation of phenanthrenequinone with acetophenones in the presence of potassium hydroxide in methanol gave a product in 20–50% yield. These compounds were unstable and underwent slow degradation in solution. However, we obtained reliable elemental analysis and mass spectral data on freshly prepared samples. The UV spectra of all these compounds were dominated by absorption due to the phenanthrene residue present in them. Surprisingly, the IR spectra of the products did not indicate the presence of carbonyl groups, but showed absorption at 3400 cm^{-1} indicating the presence of a hydroxy group in the molecule. ^1H NMR spectra of **12a–f** showed the presence of two methoxy groups.[9] ^{13}C NMR spectra (noise decoupled) of two representative examples such as **12b**,**d** also indicated the absence of carbonyl groups in the molecule, but indicated the presence of two signals attributable to methoxy groups and another signal at $\sim\delta$ 108 attributable to a ketal group. Based on spectral and analytical data, the structure of the products was assigned as dihydrofuranols **12a–f**.

A possible mechanism for the formation of dihydro-2-furanol **12** involving the intermediacy of phenanthrenone-9-ylidene ketones **6** is presented in Scheme 3. Nucleophilic addition of methanol to **6** leads to the formation of **9**. The carbanion intermediate **10** generated by abstraction of the moderately acidic proton at the 3-position of **9** undergoes oxidation by single electron transfer to either oxygen[10] or phenanthrenequinone[11] followed by further transformations to give the hydroperoxide intermediate **11**.[12–14] Under the conditions of work up, **11** is transformed to the dihydrofuranol **12**.[15–18] The effect of oxygen on this reaction was studied by bubbling oxygen through the reaction mixture. No increase in the yield of **12** was observed by this method. When the reaction was repeated in degassed methanol, no noticeable change in yield or product distribution was observed. However, when the reaction was repeated with phenanthrenequinone and acetophenone taken in a 2:1 ratio, the yield of **12** improved moderately (35% vs 30%) suggesting a possible additional role for phenanthrenequinone on the course of the reaction. The poor solubility of phenanthrenequinone in other solvents such as ethanol, and *t*-butanol prevented us from carrying out the reaction in these solvents.

The dihydrofuranol derivatives **12a–f** underwent facile thermal rearrangement when heated up to their respective melting points. Neat thermolysis of **12a–f** in sealed tubes gave **14a–f** as colorless crystalline solids in high yield (>80%). The structures of **14a–f** were arrived at on the basis of spectral and analytical data. All the thermolysis products **14a–f** showed strong IR absorptions at $\sim$1813 cm^{-1} indicating the presence of a γ-lactone component in the molecule. UV absorption spectra of these compounds are similar to that of phenanthrene indicating the presence of phenanthrene components. ^1H NMR spectra of **14a–f** showed a singlet at $\sim\delta$ 3.4 (3H) indicating the presence of a single methoxy group. In the ^{13}C NMR spectra, signals were observed at $\sim\delta$ 54 (OCH_3), 85, 114–150 (aromatic) and 175 (C=O). Mass spectral data suggested the loss of elements of methanol from the furanol precursors. Based on these data, the compounds were assigned the phenanthro-2(3*H*)-furanone structures **14a–f**. The structures of these compounds were unequivocally determined by single crystal X-ray diffraction analysis of a representative example such as **14a** (Fig. 1).[19] The mechanism for the formation of phenanthro-2(3*H*)-furanones is given in Scheme 4. Upon heating, loss of a molecule of methanol from **12** and consequent bond



Scheme 3. X= (a) H, (b) CH_3, (c) OCH_3, (d) Br, (e) Cl, (f) Ph.

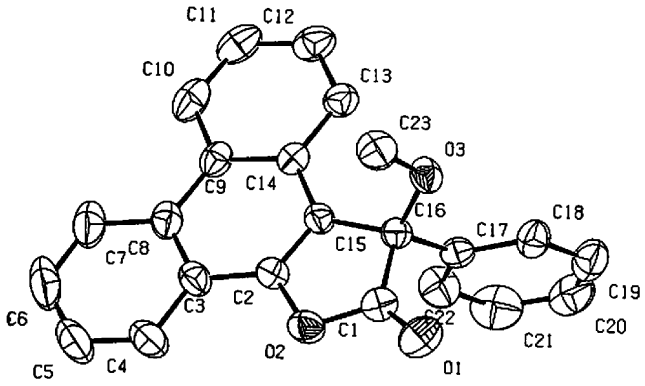
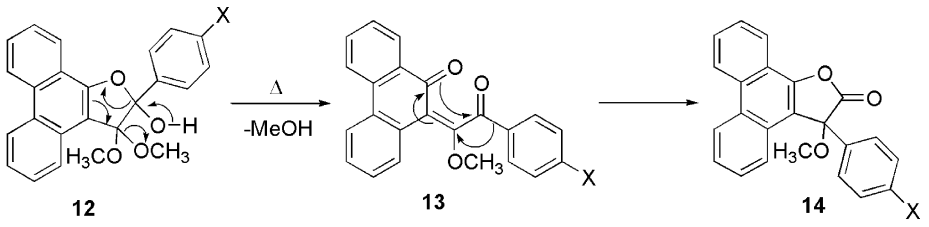


Figure 1. ORTEP diagram of molecular structure of **14a** in the crystal.

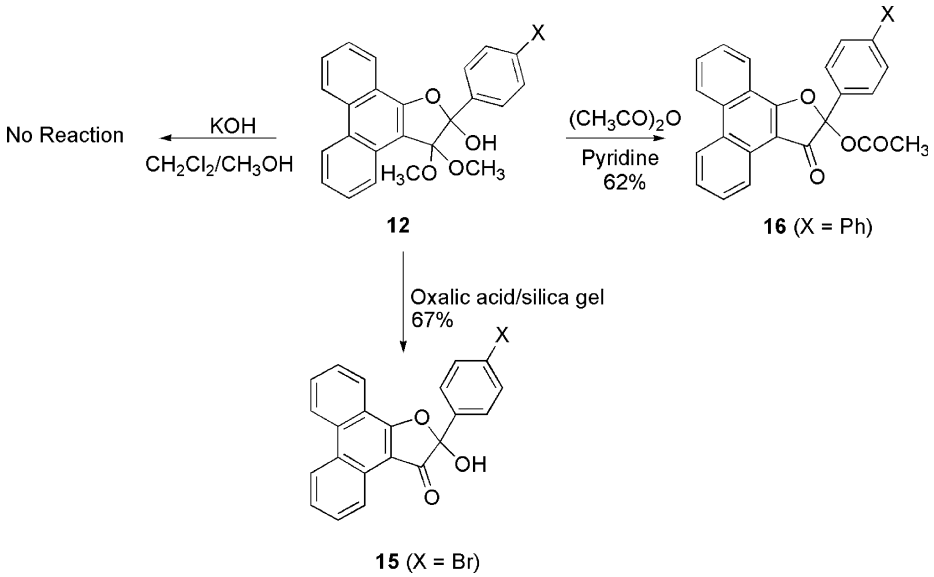
reorganizations lead to the formation of methoxydibenzoylalkene **13**. Subsequently **13** undergoes thermal transformation analogous to that reported for other dibenzoylalkenes to yield the corresponding 2(3*H*)-furanone **14**.[5,6] Our attempts to isolate **13** were not successful.

The thermolysis of **12** in refluxing *o*-dichlorobenzene also yielded **14** in comparable yields. In continuation, we carried out the neat thermolysis of **12** in an open vessel and obtained the furanones **14** in near quantitative amounts. Thermogravimetric analysis of **12a** indicated that its decomposition is completed in the narrow temperature range between 130 and 140 °C. The observed transformation appears to be a three-stage process.[20] The unstable nature of **12a–f** was further illustrated by a simple NMR experiment: ^{1}H NMR spectra of **12a–f** were collected over a period of 0–120 h. Freshly prepared samples of **12a–f** in $CDCl_3$ gave acceptable ^{1}H NMR spectra. However, ^{1}H NMR spectra of these samples recorded after storing at room temperature for 48–120 h indicated complete transformation of **12a–f** to **14a–f**. While this experiment gave no evidence in support of the formation of the dibenzoylalkene-type intermediate **13**, it indicated that the nature of the substituents on the 2-aryl group has a remarkable effect on the relative stability of these furanols. Bromo (**12d**), chloro (**12e**), and phenyl (**12f**) substituents at the fourth position of the 2-aryl moiety seem to impart higher stability to these furanols. On the other hand, compounds **12a**,**b** were particularly unstable and underwent fast conversion to **14a**,**b**.

Furanol **12** may be considered as the dimethylketal of 3(2*H*)-furanone **15**. 3(2*H*)-Furanone moiety is identified as a central structural unit in a growing number of natural products including simple compounds such as bullatenone[21] and geipavarin[22] and more complex compounds such as jatrophone, eremantholide,[23] and lychnophorolide.[24] Many of these natural products possess significant tumor-inhibiting properties. Therefore, the synthesis of 3(2*H*)-furanones has attracted considerable attention.[25–28] So, it was of interest to us to study the conversion of **12** to **15**. Treatment of **12** with base did not lead to any reaction. However, treatment of **12** with acid led to the transformation to 3(2*H*)-furanone **15**. Further, we acetylated a representative furanol derivatives, **12f** using acetic anhydride in



Scheme 4. X= (a) H, (b) CH_3, (c) OCH_3, (d) Br, (e) Cl, (f) Ph.



Scheme 5.

pyridine. Under these conditions, the acetylated phenanthro-3(2*H*)-furanone **16** was formed in 62% yield (Scheme 5).

3. Conclusions

In summary, we have synthesized several phenanthrofuranols by the base-catalyzed reaction between phenanthrenequinone and acetophenones. These phenanthrofuranols are converted to 2(3*H*)- or 3(2*H*)-furanones in near-quantitative yields under suitable reaction conditions. The furanone derivatives thus obtained have immense potential for further investigations.

4. Experimental section

4.1. General procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminum sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualization was achieved by exposure to iodine vapor or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Qualigens 60–120 mesh). Absorption spectra were recorded using Shimadzu 160A spectrometer and infrared spectra were recorded using Shimadzu-DR-8001 series FTIR spectrophotometer, respectively. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Brucker 300 FT-NMR spectrometer with tetramethylsilane as internal standard.

4.2. Starting materials

Phenanthrenequinone (**1**) and acetophenone (**2**) were purchased from E. Merck and were used as obtained. Ketones **2b–f** were prepared using a known procedure.[29]

4.3. Preparation of 12a–f

12a–f were prepared by the condensation of phenanthrenequinone with appropriate acetophenone derivatives in the presence of potassium hydroxide in methanol. In a typical experiment, a mixture of phenanthrenequinone (0.025 mol), acetophenone (0.027 mol), and powdered potassium hydroxide (1 g) in methanol (30 mL) was stirred at 60 °C for 1 h and then kept in a refrigerator for 48 h. The solid product separated out was filtered and purified by recrystallization from a mixture (2:1) of methanol and dichloromethane.

4.3.1. 3,3-Dimethoxy-2-phenyl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12a). Light yellow solid (30%); mp 116–118 °C (dec.); IR ν_{max} (KBr) 3408 cm^{-1} (OH); UV λ_{max} (CH_3CN) 224 (ε 20,000), 248 (ε 30,000), 302 nm (ε 5100), 359 nm (ε 2400); ^{1}H NMR ($CDCl_3$) δ 3.3 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 5.6 (s, 1H, OH), 7.0–8.8 (m, 12H, aromatic); ESI-MS (*m/z*): calcd for $C_{24}H_{20}NaO_4$ $[M+Na]^+$ 395.1. Found 394.9; HRMS $(M-CH_3OH+Na)^+$ found 363.0995. $C_{23}H_{16}NaO_3$ requires 363.0997; Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.10; H, 5.04.

4.3.2. 3,3-Dimethoxy-2-*p*-tolyl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12b). Light yellow solid (20%); mp 118–120 °C (dec.); IR ν_{max} (KBr) 3406 (OH), and 2941, 1633, 1500 cm^{-1}; UV λ_{max} (CH_3CN) 215 (ε 14,000), 251 (ε 5800), 341 nm (ε 1500); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3); 3.2 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 5.6 (s,1H, OH), 7.0–8.6 (m, 12H, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.1, 51.2, 52.2, 108.7, 110.5, 121.6, 122.8, 123, 123.1, 123.5, 123.9, 124.1, 125.7, 126.6, 126.9, 127.1, 128.3, 128.4, 129.3, 130.1, 132.7, 134.6, 138.6; MS (*m/z*) 354 $\{(M-CH_3OH)^+\}$, 326, 221, 119, 91, and other peaks; ESI-MS (*m/z*): calcd for $C_{25}H_{22}NaO_4$ $[M+Na]^+$: 409.14. Found 409.2; HRMS $(M-CH_3OH+Na)^+$ found 377.1156. $C_{24}H_{18}NaO_3$ requires 377.1154; Anal. Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.98; H, 5.63.

4.3.3. 3,3-Dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12c). Light yellow solid (50%); mp 136–138 °C (dec.); IR ν_{max} (KBr) 3408, 2992, and 1635 cm^{-1}; UV λ_{max} (CH_3CN) 248 (ε 42,000), 302 (ε 8300), 359 nm (ε 2600); ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 3.6 (s, 3H, OCH_3), 5.6 (s, 1H, OH), 6.9–8.7 (m, 12H, aromatic); MS (*m/z*) 370 $\{(M-CH_3OH)^+\}$, 342, 107, and other peaks; ESI-MS (*m/z*): calcd for $C_{25}H_{22}NaO_5$ $[M+Na]^+$: 425.14. Found 425.1; Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.43; H, 5.28.

4.3.4. 2-(4-Bromophenyl)-3,3-dimethoxy-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12d). Light brown crystals (25%); mp 140–141 °C (dec.); IR ν_{max} (KBr) 3400, 2943, 1614, 1589, and 1520 cm^{-1}; UV λ_{max} (CH_3CN) 224 (ε 32,200), 248 (ε 37,000), 308 (ε 7100) 341 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 5.6 (s, 1H, OH), 7.2–8.8 (m, 12H, aromatic); ^{13}C NMR δ 51.3, 52.2, 108.7, 109.9, 111.0, 122.9, 124.1, 124.2, 126.8, 127.2, 128.9, 130.8, 132.8, 136.9, 154.2; MS (*m/z*) 420 $\{(M-CH_3OH)^+\}$, 390, 221, 185, and other peaks; FABMS, *m/z* 453 $\{(M+H)^+\}$. ESI-MS (*m/z*): calcd for $C_{24}H_{20}BrO_4$ $[M+1]^{+:}$ 451.9. Found: 451.1; Anal. Calcd for $C_{24}H_{19}O_4Br$: C, 63.87; H, 4.24. Found: C, 63.82; H, 4.17.

4.3.5. 2-(4-Chlorophenyl)-3,3-dimethoxy-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12e). Light yellow crystals (20%); mp 142–143 °C (dec.); IR ν_{max} (KBr) 3419 (OH), 2949, 1637, 1603, 1506, 756 cm^{-1}; UV λ_{max} (CH_3CN) 209 (ε 55,000), 263 (ε 56,000), 320 (ε 8200), 410 nm (ε 3300); ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 5.6 (s, 1H, OH), 6.5–8.5 (m, 13H, aromatic); MS (*m/z*) 374 $\{(M-CH_3OH)^+\}$, 346, 315, 139, 111, and other peaks; Anal. Calcd for $C_{24}H_{20}O_4$: C, 70.85; H, 4.71. Found: C, 71.03; H, 4.53.

4.3.6. 3-Biphenyl-4-yl-3,3-dimethoxy-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol (12f). Light yellow solid (30%); mp 132–134 °C (dec.); IR ν_{max} (KBr), 3404 (OH), 1635, 1610 and 1506 cm^{-1}; UV λ_{max} (CH_3CN) 203 (ε 60,000), 257 (ε 59,000), 308 (ε 9200), 341 nm (ε 2400); ^{1}H NMR ($CDCl_3$) δ 3.3 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3),

5.6 (s, 1H, OH), 7.4–8.8 (m, 17H, aromatic); MS (*m/z*) 416 $\{(M-CH_3OH)^+\}$, 416, 388, 357, 181, and other peaks; ESI-MS (*m/z*) calcd for $C_{30}H_{25}O_4$ $[M+1]^+$: 449.1. Found: 448.0; HRMS $(M-CH_3OH+Na)^+$ Found: 439.1313. $C_{29}H_{20}NaO_3$ requires 439.1310; Anal. Calcd for $C_{30}H_{24}O_4$: C, 80.34; H, 5.39. Found: C, 80.30; H, 5.14.

4.4. Reaction of phenanthrenequinone and acetophenone under oxygen bubbling

A mixture of phenanthrenequinone (0.025 mol), acetophenone (0.027 mol), and powdered potassium hydroxide (1 g) in methanol (30 mL) was stirred at 60 °C, under oxygen bubbling for 1 h and later kept in a refrigerator for 48 h. The solid product separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **12a** (28%); mp 116–118 °C.

4.5. Reaction of phenanthrenequinone and 4-phenylacetophenone in degassed methanol

A mixture of phenanthrenequinone (0.025 mol), 4-phenylacetophenone (0.027 mol), and powdered potassium hydroxide (1 g) in degassed methanol (30 mL) was stirred at 60 °C, for 4 h and later kept in a refrigerator for 48 h. The solid product separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **12f** (28%); mp 132–134 °C.

4.6. Reaction of 2 equiv of phenanthrenequinone with 1 equiv of acetophenone

A mixture of phenanthrenequinone (0.05 mol), acetophenone (0.025 mol), and powdered potassium hydroxide (1 g) in methanol (30 mL) was stirred at 60 °C for 1 h and later kept in a refrigerator for 48 h. The solid product separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **12a** (35%); mp 116–118 °C.

4.7. Thermolysis experiments

4.7.1. Neat thermolysis of 12a. The samples **12a–f** were heated in sealed tubes to give phenanthro-2(3*H*)-furanones **14a–f**. In a typical experiment, a sample of **12a** (100 mg, 0.27 mmol) was heated in a sealed tube at 150 °C for 4 h. The solid residue was chromatographed over silica gel. Elution with a mixture (4:1) of hexane and dichloromethane gave **14a** (79 mg, 0.232 mmol).

4.7.2. -Methoxy-3-phenyl-3*H*-1-oxacyclopenta[*l*]phenanthren-2-one (14a). White solid (86%); mp 214–216 °C; IR ν_{max} (KBr) 1813 cm^{-1} (lactone C=O); UV λ_{max} (CH_3CN) 208 (ε 17,200), 222 (ε 13,000), 245 (ε 17,600), 257 (ε 14,100), 276 (ε 6300), 308 (ε 3000), 337 (ε 900), 355 nm (ε 800); ^1H NMR ($CDCl_3$) δ 3.4 (3H, s, OCH_3), 7.2–8.9 (13H, m, aromatic); MS (*m/z*) 340 (M^+), 312, 281, 239, 125, and other peaks; Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found: C, 81.22; H, 4.74.

Crystal data of (**14a**). $C_{23}H_{16}O_3$. $M=340.36$, triclinic, space group *P*1, $a=8.4695(7)$ Å, $b=10.2384(9)$ Å, $c=10.9698(5)$ Å, $\alpha=100.368(5)°$, $\beta=110.282(4)°$, $\gamma=102.529(7)°$, $U=836.51(11)$ $Å^3$, $Z=4$, $D_C=1.351$ g cm^{-3}, $\mu=0.715$ mm^{-1}, (Cu Kα, $\lambda=1.54180$ Å), $T=293$ K. Of 3402 reflections measured on an Enraf-Nonius CAD4 diffractometer and corrected by Psi scan for absorption, 3172 were unique ($R_{int}=0.0280$). The structure was solved by direct methods and refined on F^2 values. Hydrogen atoms were refined isotropically. $R=0.0537$ [*F* values, $I>2\sigma(I)$]. $wR2=0.1521$ (F^2 values, all data), goodness-of-fit=1.141, final difference map extremes +0.316 and −0.225 eA^{-3}. Software: SHELXS-97, SHELXL-97.

4.7.3. 3-Methoxy-3-*p*-tolyl-3*H*-1-oxacyclopenta[*l*]phenanthren-2-one (14b). White solid (82%); mp 160–162 °C; IR ν_{max} (KBr) 1813 cm^{-1} (lactone C=O); UV λ_{max} (CH_3CN) 208 (ε 19,600), 223 (ε 14,000), 245 (ε 19,300), 256 (ε 15,900), 276 (ε 7100), 308 (ε 3400), 337 (ε 800), 355 nm (ε 700); ^1H NMR ($CDCl_3$) δ 2.3 (3H, s, methyl); δ 3.4 (3H, s, OCH_3); 7.0–8.9 (12H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.5, 54.3, 85.3, 114.0, 120.1, 122.6, 122.8, 123.4, 123.5, 123.7, 124.0, 124.2, 126.0, 127.5, 127.5, 127.7, 128.0, 128.3, 128.8, 128.9, 129.1, 132.6, 149.6, 175.3.; MS (*m/z*) 354 (M^+), 326, 91, and other peaks; Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.62; H, 5.34.

4.7.4. 3-Methoxy-3-(4-methoxyphenyl)-3*H*-1-oxacyclopenta[*l*]phenanthren-2-one (14c). White solid (86%); mp 135–138 °C; IR ν_{max} (KBr) 1815 cm^{-1} (lactone C=O); UV λ_{max} (CH_3CN) 208 (ε 23,300), 225 (ε 20,000), 246 (ε 29,900), 257 (ε 22,000), 275 (ε 10,500), 304 (ε 5000), 339 (ε 2400), 355 nm (ε 2000); ^1H NMR ($CDCl_3$) δ 3.3 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 6.8–8.9 (12H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 54.2, 55.3, 85.1, 114.1, 120.0, 122.6, 122.9, 123.4, 123.5, 123.7, 124.0, 124.2, 126.0, 127.5, 127.5, 127.7, 128.0, 128.3, 128.8, 128.9, 129.2, 132.5, 149.6, 175.3.; MS (*m/z*) 371 (M^+), 341, 204, 135, and other peaks; Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.9. Found: C, 78.1; H, 4.94.

4.7.5. 3-(4-Bromophenyl)-3-methoxy-3*H*-1-oxacyclopenta[*l*]phenanthren-2-one (14d). White solid (82%); mp 191–193 °C; IR ν_{max} (KBr) 1811 cm^{-1} (lactone C=O); UV λ_{max} (CH_3CN) 205 (ε 23,000), 226 (ε 19,500), 244 (ε 29,200), 257 (ε 21,000), 274 (ε 10,000), 304 (ε 4000), 339 (ε 2400), 355 nm (ε 2000); ^1H NMR ($CDCl_3$) δ 3.3 (3H, s, OCH_3), 7.2–8.9 (12H, m, aromatic); MS (*m/z*) 420 (M^+), 394, 361, 155, and other peaks; Anal. Calcd for $C_{23}H_{15}O_3Br$: C, 65.9; H, 3.61. Found: C, 65.56; H, 3.76.

4.7.6. 3-(4-Chlorophenyl)-3-methoxy-3*H*-1-oxacyclopenta[*l*]phenanthren-2-one (14e). White solid (81%); mp 193–194 °C; IR ν_{max} (KBr) 1813 cm^{-1} (lactone C=O);); UV λ_{max} (CH_3CN) 208 (ε 21,400), 245 (ε 21,500), 258 (ε 17,800), 276 (ε 7900), 308 (ε 24,100), 338 (ε 1000), 354 nm (ε 900); ^1H NMR ($CDCl_3$) δ 3.3 (3H, s, OCH_3), 7.2–8.8 (12H, m, aromatic); MS (*m/z*) 374 (M^+), 346, 239, 163,111, and other peaks; Anal. Calcd for $C_{23}H_{15}O_3Cl$: C, 73.85; H, 4.03. Found: C, 74.02; H, 4.05.

4.7.7. 3-Biphenyl-4yl-3-methoxy-3*H*-1-oxacyclopenta-[*l*]phenanthren-2-one (14f). White solid (82%); mp 152–154 °C; IR ν_{max} (KBr), 1813 cm^{-1} (lactone C=O); UV

λ_{max} (CH_3CN) 207 (ε 41,000), 262 (ε 39,000), 306 (ε 8000), 342 nm (ε 4600) 338 (ε 2800), 356 nm (ε 1800); ^{1}H NMR ($CDCl_3$) δ 3.4 (3H, s, OCH_3), 7.3–8.8 (17H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 54.3, 85.4, 114.1, 120.1, 122.7, 123.5, 123.6, 124.2, 126.2, 126.7, 127.5, 127.6, 128.8, 128.9, 132.7, 136.2, 140.5, 142.0, 149.8, 175.1.; MS (*m/z*) 416 (M^+), 388, 357, 281, and other peaks; Anal. Calcd for $C_{29}H_{20}O_3$: C, 83.64; H, 4.84. Found: C, 83.48; H, 4.86.

4.8. Thermolysis in open vessel

The samples **12a–f** were thermolyzed in open vessels to give phenanthro-2(3*H*)-furanones. In a typical experiment, a sample of **12a** (100 mg, 0.27 mmol) was heated in conical flask at 150 °C for 4 h. The solid was extracted with dichloromethane. Column chromatography using a mixture (4:1) of hexane and dichloromethane gave **14a** as a white solid (75 mg, 83%).

4.9. Thermolysis in *o*-dichlorobenzene

The samples **12a–f** were refluxed in *o*-dichlorobenzene to give the corresponding phenanthro-2(3*H*)-furanones. In a typical experiment, a sample of **12a** (100 mg, 0.27 mmol) was dissolved in *o*-dichlorobenzene and refluxed for 4 h. Solvent was removed under reduced pressure. The solid was extracted with dichloromethane. Column chromatography by using a mixture of hexane and dichloromethane (4:1) gave **14a** as a white solid (71 mg, 79%).

4.10. Reaction of 12a with base

A sample of **12a** (100 mg, 0.27 mmol) was dissolved in dichloromethane (10 mL) and potassium hydroxide (0.5 g) in methanol (2 mL) was added and stirred for 12 h. The progress of the reaction was monitored by TLC. No change was observed. The solution was then refluxed for 6 h. and was monitored by TLC. The unchanged **12a** was recovered almost quantitatively (90 mg).

4.11. Reaction of 3b in acidic medium

A sample of **12d** (100 mg, 0.26 mmol) was dissolved in dichloromethane (10 mL) and oxalic acid adsorbed on silica gel was added. The mixture was stirred for 12 h. The progress of the reaction was monitored by TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane to give **15d** as a white solid.

4.11.1. 2-(4-Bromophenyl)-2-hydroxy-2-hydroxy-1-oxacyclo-penta[l]phenanthren-3-one (15d). 67%. Mp 195–197 °C; IR ν_{max} (KBr), 3236 (OH), 1690 (C=O), 1618 and 1506 cm^{-1}; UV λ_{max} (CH_3CN) 202 (ε 40,000), 254 (ε 28,000), 306 (ε 5300), 338 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 7.2–8.6 (m, aromatic and hydroxy). Anal. Calcd for $C_{22}H_{13}O_3Br$: C, 65.20; H, 3.23. Found: C, 65.30; H, 3.26.

4.12. Reaction of 12f with acetic anhydride

A sample of **12f** (100 mg, 0.22 mmol) was dissolved in dichloromethane (20 mL) and pyridine (5 mL) was added. Acetic anhydride was added dropwise to the mixture over 30 min and then refluxed for 2 h. The mixture was cooled and diluted with dichloromethane. Then it was washed with dil. H_2SO_4, sodium bicarbonate, and with water. The organic layer was separated, dried over anhydrous sodium sulfate, and solvent was evaporated to give **16f**. It was then recrystallised from a mixture (2:1) of dichloromethane and hexane.

4.12.1. 2-Biphenyl-4-yl-3-oxo-2,3-dihydro-1-oxacyclo-penta-[*l*]phenanthren-2-yl acetate (16f). White solid (62%); mp 182–185 °C; IR ν_{max} (KBr), 1774, 1713, 1620, 1600 cm^{-1}; UV λ_{max} (CH_3CN) 202 (ε 45,000), 255 (ε 31,000), 306 (ε 8200), 340 nm (ε 2100); ^{1}H NMR ($CDCl_3$) δ 2.3 (3H, s, acetoxy), 7.2–8.8 (17H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.7, 102.0, 108.0, 109.0, 120.8, 122.9, 123.1, 123.7, 124.0, 126.1, 126.9, 127.1, 127.3, 127.5, 127.7, 128.8, 131.8, 132.0, 136.0, 140.3, 143.0, 168.3, 171.2, 194.2; MS (*m/z*) 444 (M^+), 386, 263, 181, and other peaks; Anal. Calcd for $C_{30}H_{20}O_4$: C, 81.07; H, 4.54. Found: C, 81.30; H, 4.14.

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Aza-Michael addition of chiral hydrazines to alkylidene malonates

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Abstract—The conjugate spontaneous addition of chiral *N*,*N*-dialkylhydrazines **1** to dimethyl alkylidene/arylidene malonates **2**, **5**–**10** affords the corresponding β-hydrazino esters in moderate-to-good yields and selectivities. D-Mannitol-derived hydrazine **1a** afforded best results, mainly due to the higher stability of the products **3**, **11**–**16**.

1. Introduction

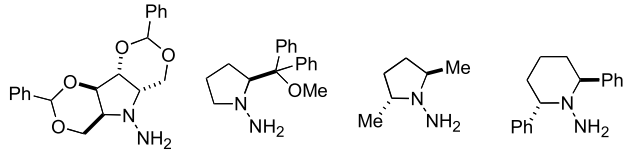
During the last years the interest for β-aminoacids has grown notably due to their presence in a number of natural products and to their application as precursors of other interesting compounds, such as β-lactams.[1] Among the different approaches described for the stereoselective synthesis of β-aminoacids, the aza-Michael addition of ammonia equivalents to α,β-unsaturated carboxylates appears as one of the more attractive methods for its simplicity. Pyrrolidine derived chiral hydrazines have been previously used as neutral nitrogen nucleophiles in the Lewis acid catalyzed 1,4-addition to reactive Michael acceptors as α,β-unsaturated sulfones,[2] and sulfonates.[3] However, the extension of the methodology to α,β-unsaturated esters has not been reported. The use of lithiated *N*-silylhydrazines as ammonia equivalents in their addition to prochiral enoates has been reported instead, but the procedure requires protection and activation of the nucleophile, and strong basic conditions are associated with anionic reagent.[4]

The enhanced electrophilic reactivity provided by the geminal carboxylate functions in alkylidene malonates has been frequently exploited in the conjugate nuclephilic addition of weak nucleophiles under mild conditions.[5] Additionally, these substrates are easily available through Knoevenagel condensation of malonates and carbonyl compounds and due to the presence of identical carboxylate groups, do not require any considerations regarding *E*/*Z* isomerizations.

On the other hand, the precedent of the spontaneous addition of chiral hydrazines to nitroalkenes,[6] which exhibit similar levels of reactivity to that of alkylidene malonates,[7] suggests that the addition of chiral *N*,*N*-dialkylhydrazines to the latter should also be possible under non-catalyzed conditions or at least, under mild conditions compatible with the use of free hydrazines as the nucleophiles. We now wish to present the results collected on the basis of this hypothesis.

2. Results and discussion

Preliminary reactivity experiments were carried out using several chiral hydrazines based in different types of cyclic dialkylamino auxiliaries. These include D-mannitol-derived hydrazine **1a**,[8] (*S*)-1-amino-2-(1-diphenylmethoxymethyl)-pyrrolidine **1b**[9] as a sterically demanding proline derivative, and other C_2-symmetric hydrazines such (*R*,*R*)-1-amino-2,5-dimethylpyrrolidine **1c**[10] and (*S*,*S*)-1-amino-2,5-diphenylpyperidine **1d**[11] (Fig. 1).



1a 1b 1c 1d

Figure 1. Chiral hydrazines **1a**–**d** used in the preliminary screening.

Keywords: Conjugate addition; Hydrazines; Synthetic methods.
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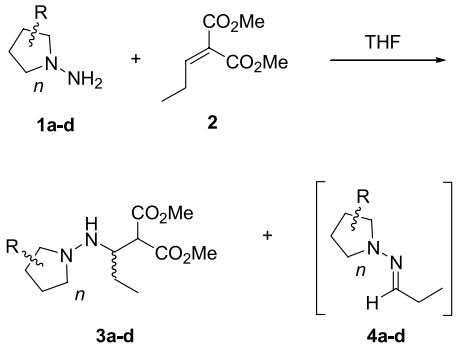
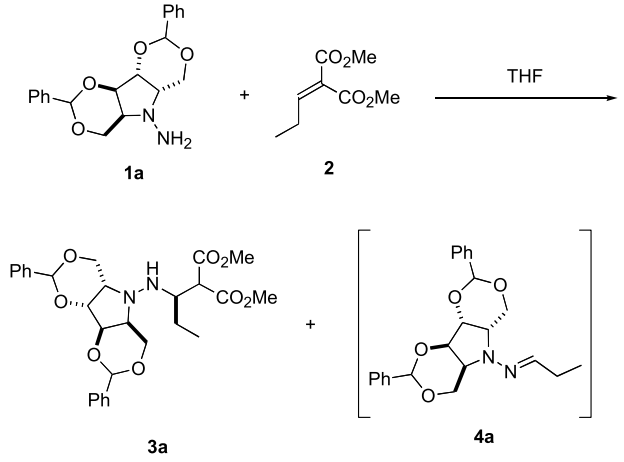
Addition experiments carried out with hydrazines **1a–d** and 2-propylidene malonic acid dimethyl ester **2** confirmed the expected reactivity, as the conjugate addition took place in the absence of promoter or catalyst in all cases. Though the reactivities exhibited by the different hydrazines tested were similar, D-mannitol-derived hydrazine **1a** proved to be the reagent of choice, mainly due to the higher stability of the obtained adduct. On the other hand, adducts obtained from hydrazines **1b–d** showed a higher tendency to suffer a side-reaction to give hydrazones **4b–d**. These by-products, presumably formed by β-elimination of dimethylmalonate, can be viewed as the condensation products of the different hydrazines **1a–d** used with propionaldehyde, formally resulting from a retro-Knoevenagel reaction from **2** (Scheme 1).



Scheme 1. Additions of hydrazines **1a–d** to propylidene dimethylmalonate **2**.

Therefore, a further optimization of the reaction conditions was carried out using hydrazine **1a** and alkylidene malonate **2** as reactants (Scheme 2). The effect of some Lewis acids [MgI_2, $ZnCl_2$, $Zn(TfO)_2$ and $Mg(TfO)_2$], added in catalytic or stoichiometric amounts, was investigated in reactions carried out in THF at room temperature. Though faster additions were observed in all cases, these species also favoured the undesired β-elimination side-reaction, leading to mixtures containing adduct **3a** and hydrazone **4a** in variable amounts. On the basis of these results the effect of different parameters as the solvent and the temperature on the non-catalyzed addition was studied.



Scheme 2.

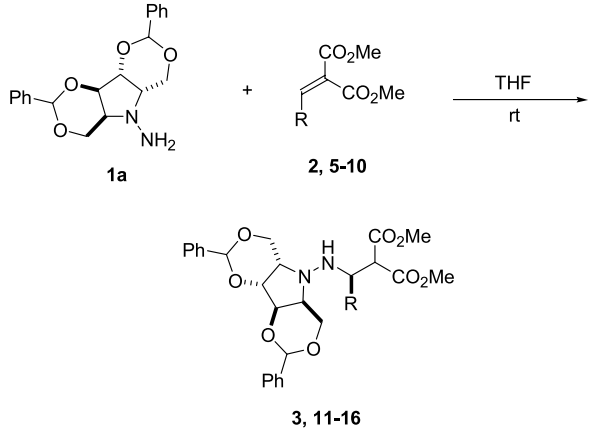
The results collected in Table 1 indicate that THF provides the best result (entry 1), leading to a similar yield (70%) but better diasteroselectivity (d.r.=4:1) than other solvents such as toluene, diethyl ether, methylene chloride or DMF (entries 2–5). Interestingly, the reaction performed in the latter (Table 1, entry 5) resulted in a reversion of the stereoselectivity (d.r. 1:1.8). The undesired β-elimination reaction leading to **4a** was only observed when the reaction was performed in MeOH. Although **3a** was also initially formed in this solvent, this compound was spontaneusly transformed into hydrazone **4a** and dimethyl malonate, observed as the only isolable products after consumption of the starting material.

Table 1. Addition of hydrazine **1a** to dimethyl propylidene malonate **2** in different solvents[a]

Entry	Solvent	Time (h)	Yield of **3a**[b] (%)	d.r.[c]
1	THF	4	70	4:1
2	Toluene	5	68	2:1
3	Et_2O	12	65	2.4:1
4	CH_2Cl_2	4	62	2.5:1
5	DMF	7	68	1:1.8

[a] Reactions performed at room temperature with a 1:1.5 hydrazine:ester ratio.
[b] Overall yield of the product after chromatographic purification.
[c] Determined by ^{13}C NMR analysis of the reaction mixtures.

On the other hand, experiments performed at lower temperatures (0 or −40 °C) resulted in similar yields and selectivities. Therefore, the extension of the procedure to other substrates was carried out at room temperature to get faster reactions. The optimized conditions (THF, room temperature) were applied to the addition of hydrazine **1a** to other aliphatic (**2**, **5**, **6**) and aromatic (**7–10**) alkylidene malonates (Scheme 3). The reactions were carried out using hydrazine **1a** as limiting reagent and 1.1 equiv of alkylidene malonates for the most reactive substrates **2**, **5** and 1.5 equiv in the case of the less reactive **6–10**. Yields



Comp.	**2,3**	**5,11**	**6,12**	**7,13**	**8,14**	**9,15**	**10,16**
R	Et	Me	^{i}Pr	Ph	2-naphthyl	*p*-$C_6H_4NO_2$	4-biphenyl

Scheme 3. Addition of hydrazine **1a** to alkylidene and arylidene malonates **2**, **5–10**.

Table 2. Addition of hydrazine **1a** to alkylidene malonates **2**,**5–10** Synthesis of hydrazines **3**, **11–16**

Entry	Substrate	R	*t* (h)	Prod.	Yield (%)[a]	d.r.[b]	Conf.
1	**2**	Et	4	**3**	70[c]	80:20	*R*
2	**5**	Me	5	**11**	85[c]	55:45	*R*
3	**6**	i-Pr	12	**12**	60[d] (40)	67:33[e] (98%)	*R*
4	**7**	Ph	8	**13**	70[d] (42)	81:19[f] (98%)	*S*
5	**8**	2-Naphthyl	12	**14**	46[d]	82:18	*S*
6	**9**	*p*-$C_6H_4NO_2$	22	**15**	54[d]	77:23	*S*
7	**10**	4-biphenyl	29	**16**	53[d]	82:18	*S*

[a] Overall yield of the product after chromatographic purification. In brackets yields of pure major isomers.
[b] Determined by ^{13}C NMR of the reaction mixtures. In brackets d.e. of pure major isomers.
[c] Reactions carried out at room temperature with a 1:1.1 hydrazine:ester ratio.
[d] Reactions performed with a ratio hydrazine:ester 1:1.5.
[e] Separable by flash chromatography.
[f] Major (*S*)-isomer was obtained in pure form by crystallization.

and diastereomeric ratio of adducts **3**, **11–16** obtained under these conditions are summarized in Table 2.

The chromatographic purification of the addition products and subsequent removal of the solvent had to be performed as rapidly as possible in order to avoid undesired, spontaneous β-elimination reactions. Once in solid state, however, pure adducts **3**, **11–16** are stable compounds, even at room temperature, and do not need to be stored with any special precaution provided that solvents have been completely removed.

The major isomer of compound **13** was purified by fractional crystallization of the diastereomeric mixture, and the (*S*) configuration of the newly created stereogenic centre could be determined by single-crystal X-ray diffraction analysis (Fig. 2).[12] Assuming a uniform stereochemical pathway for all the conjugate additions, the absolute configurations indicated in Table 2 for compounds **3**, **11**, **12**, and **14–16** have been assigned by analogy.

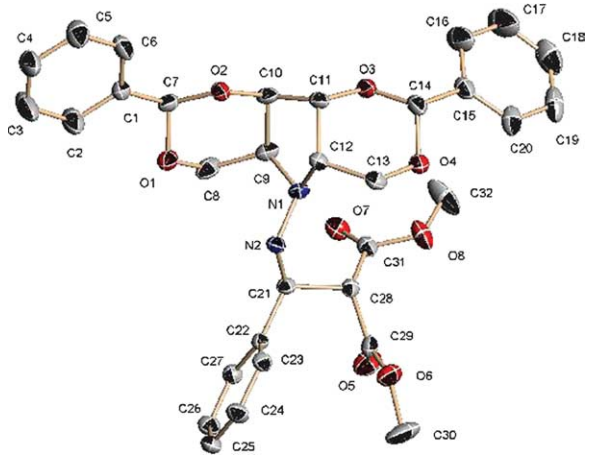


Figure 2. Crystal structure of (*S*)-**13**. Hydrogen atom are ommited for clarity.

Concluding, the high electrophilicity of alkylidene malonates provides the required reactivity for the spontaneous conjugate addition of *N*,*N*-dialkylhydrazines. The D-mannitol-derived hydrazine **1a** confers stability to the addition products, which were obtained with moderate-to-good selectivites in most cases.

3. Experimental

Et_2O, toluene and THF were distilled from sodium benzophenone ketyl and CH_2Cl_2 from calcium hydride inmediately prior use; Et_3N from KOH. All other reagents and solvents were purified by standard procedures or were used as obtained from commercial sources as appropriate. Light petroleum ether used had a bp 40–65 °C. Aqueous solutions were all saturated, unless otherwise stated. Flash column chromatography was carried out using silica-gel Merck 60 (0.063–0.200 mm, 0.040–0.063 mm or 0.015–0.040 mm) or prepacked silica columns. Analytical thin layer chromatography was performed on precoated plates (Merck silica-gel 60 F254). Melting points were recorded using a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured using an Perkin–Elmer 241 MC polarimeter. Infrared spectra were recorded on a FT-IR Bomen MB-120 spectrometer. Spectra were recorded for KBr pellets or films. Proton magnetic resonance spectra (^1H NMR) were recorded at 300 or 500 MHz on a Bruker AMX 300 or Bruker AMX 500 instruments, respectively, and are reported as follows: chemical shift δ in ppm, (multiplicity, number of protons, coupling constant *J* in Hz). Residual protic solvent was used as the internal reference. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 75.5 or 125.5 MHz on a Bruker AMX 300 or Bruker AMX 500 instruments, respectively. Chemical shifts are quoted in ppm and referenced to the appropriate solvent peak. Microanalyses were determined in microanalytical laboratories at the Instituto de Investigaciones Químicas Isla de la Cartuja (Seville). Mass spectra were obtained on a Kratos MS 80 RFA or Micromass AutoSpecQ spectrometers.

3.1. Addition of 1a to alkylidene/arylidene malonates 2, 5–10. General procedure

Alkylidene malonate **2**, **5–10** (1.1–1.5 mmol) was added to a solution of hydrazine **1a** (354 mg, 1 mmol) in dry THF under an argon atmosphere and the mixture was stirred at rt until TLC indicated total consumption of the starting material. The reaction mixture was concentrated and the residue purified by flash chromatography. Eluants, yields and spectral and analytical data for compounds **3**, **11–16** are as follows:

3.1.1. Compound 3. From **2** (189 mg, 1.1 mmol), flash

chromatography (1:4 Et_2O–petroleum ether) gave 368 mg (70%) of **3** as a 80:20 inseparable mixture of (2*R*)-**3** and (2*S*)-**3**. IR (film, cm^{-1}): 2959, 2905, 2866, 1732, 1603, 1452, 1391, 1302, 1094, 1013, 758, 700; mass spectrum (FAB) *m/z* (rel intensity): 527 (60%, $M^+ + 1$), 526 (100, M^+), 353 (50), 289 (39). Anal. Calcd $C_{28}H_{34}N_2O_8$: C, 63.86; H, 6.51; N, 5.32; found: C, 63.94; H, 6.62; N, 5.35. NMR data for (2*R*)-**3**: ^1H NMR (300 MHz, C_6D_6) δ 1.00 (t, 3H, $J=7.2$ Hz), 1.54–1.66 (m, 1H), 1.76–1.90 (m, 1H), 3.32 (s, 3H), 3.37 (s, 3H), 3.66–3.70 (m, 2H), 3.97–4.01 (m, 1H), 4.07–4.09 (m, 2H), 4.24 (d, 1H, $J=6.1$ Hz), 4.48–4.80 (m, 5H), 5.23–5.25 (m, 2H), 7.11–7.25 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 10.3, 24.1, 51.2, 51.7, 54.8, 60.8, 64.7, 65.0, 77.9, 99.2, 126.2, 126.3, 128.5, 168.7, 168.7. NMR data for (2*S*)-**3**: ^1H NMR (300 MHz, C_6D_6) δ 0.98 (t, 3H, $J=7.3$ Hz), 1.98–2.06 (m, 2H), 3.33 (s, 3H), 3.35 (s, 3H), 3.55–3.67 (m, 2H), 3.78–4.83 (m, 1H), 3.87 (d, 1H, $J=6.7$ Hz), 4.13–4.18 (m, 2H), 4.48–4.80 (m, 5H), 5.23–5.25 (m, 2H), 7.11–7.25 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 9.8, 22.9, 51.3, 51.4, 54.5, 57.5, 60.6, 65.0, 77.9, 99.0, 126.2, 126.3, 128.5, 168.4, 168.4.

3.1.2. Compound 11. From **5** (174 mg, 1.1 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 435 mg (85%) of **11** as a 55:45 inseparable mixture of (2*R*)-**11** and (2*S*)-**11**. IR (film, cm^{-1}): 2918, 2852, 1740, 1446, 1387, 1302, 1112, 1014, 922, 870, 765; mass spectrum (CI) *m/z* (rel intensity): 513 (4%, $M^+ + 1$), 381 (56), 275 (42), 133 (100), 107 (95), 101 (77); *m/z* calcd for $C_{27}H_{32}N_2O_8$ 512.2159, found 512.2156. Anal. Calcd $C_{27}H_{32}N_2O_8$: C, 63.36; H, 6.29; N, 5.47; found: C, 63.56; H, 6.17; N, 5.63. NMR data for (2*R*)-**11**: ^1H NMR (500 MHz, C_6D_6) δ 1.24 (d, 3H, $J=6.5$ Hz), 3.31 (s, 3H), 3.39 (s, 3H), 3.68–3.74 (m, 4H), 4.01–4.42 (m, 1H), 4.09–4.10 (m, 2H), 4.19 (d, 1H, $J=5.8$ Hz), 4.45–4.58 (m, 2H), 5.21–5.34 (m, 3H), 7.14–7.26 (m, 8H), 7.58–7.66 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 16.2, 51.5, 52.0, 55.6, 55.9, 67.4, 67.7, 78.0, 78.9, 99.5, 126.6, 126.7, 128.9, 139.1, 139.3, 168.9, 169.0. NMR data for (2*S*)-**11**: ^1H NMR (500 MHz, C_6D_6) δ 1.48 (d, 3H, $J=6.1$ Hz), 3.31 (s, 3H), 3.33 (s, 3H), 3.64 (d, 1H, $J=8.1$ Hz), 3.68–3.74 (m, 4H), 3.88–3.92 (m, 1H), 4.08–4.10 (m, 2H), 4.82–4.92 (m, 2H), 5.21–5.34 (m, 3H), 7.14–7.26 (m, 8H), 7.58–7.66 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 17.4, 51.8, 52.1, 54.7, 57.6, 64.2, 64.8, 77.6, 79.0, 99.5, 126.6, 126.7, 128.9, 139.1, 139.3, 168.3, 168.7.

3.1.3. Compound 12. From **6** (279 mg, 1.5 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 216 mg (40%) of (2*R*)-**12** and 108 mg (20%) of (2*S*)-**12**. Data for (2*R*)-**12**: $[\alpha]_D$ +132.0 (c 0.9, CH_2Cl_2); IR (film, cm^{-1}): 3057, 1739, 1391, 1094, 1020, 872, 802, 750, 698; mass spectrum (EI) *m/z* (rel intensity): 540 (7%, M^+), 409 (19), 408 (69), 354 (42), 149 (100); *m/z* calcd for $C_{29}H_{36}N_2O_8$ 540.2472, found 540.2446; ^1H NMR (500 MHz, C_6D_6) δ 1.06 (d, 3H, $J=7.1$ Hz), 1.10 (d, 3H, $J=6.8$ Hz), 1.97–2.19 (m, 1H), 3.10–3.17 (m, 1H), 3.35 (s, 3H), 3.36 (s, 3H), 3.46–3.51 (m, 1H), 3.65–3.77 (m, 2H), 4.03 (d, 1H, $J=9.0$ Hz), 4.08 (sa, 2H), 4.27–4.29 (m, 1H), 4.50–4.60 (m, 1H), 4.69 (sa, 1H), 4.72–4.82 (m, 1H), 5.22–5.26 (m, 2H), 7.14–7.26 (m, 6H), 7.49–7.70 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 15.6, 20.7, 29.7, 51.7, 52.5, 56.1, 58.0, 63.2, 65.4, 65.9, 67.5, 78.3, 78.8, 99.3, 126.4, 126.5, 126.7, 126.7, 128.3, 168.7, 169.2. Data for (2*S*)-**12**: $[\alpha]_D$ +62.3 (c 1.1, CH_2Cl_2); IR (film, cm^{-1}): 3057, 1739, 1391, 1094, 1020, 872, 802, 750, 698; mass spectrum (EI) *m/z* (rel intensity): 540 (15%, M^+), 409 (16), 408 (69), 149 (100); *m/z* calcd for $C_{29}H_{36}N_2O_8$ 540.2472, found 540.2455; ^1H NMR (500 MHz, C_6D_6) δ 0.96 (d, 3H, $J=7.0$ Hz), 1.02 (d, 3H, $J=7.0$ Hz), 2.27–2.32 (m, 1H), 3.10–3.17 (m, 1H), 3.36 (s, 3H), 3.46 (s, 3H), 3.46–3.51 (m, 1H), 3.65–3.77 (m, 2H), 3.89–3.92 (m, 1H), 3.94 (d, 1H, $J=7.7$ Hz), 4.11 (sa, 2H), 4.50–4.60 (m, 1H), 4.69 (sa, 1H), 4.72–4.82 (m, 1H), 5.22–5.26 (m, 2H), 7.14–7.26 (m, 6H), 7.49–7.70 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 18.7, 19.6, 29.0, 52.2, 52.5, 54.6, 58.0, 65.4, 65.6, 66.2, 67.5, 78.0, 79.9, 99.0, 99.4, 126.3, 126.5, 126.7, 128.3, 168.9, 169.2.

3.1.4. Compound 13. From **7** (330 mg, 1.5 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 403 mg (70%) of **13** as 81:19 inseparable mixture of (2*S*)-**13** and (2*R*)-**13**. Recrystallization of this mixture from Et_2O–Petroleum ether gave pure, crystalline (2*S*)-**13**. Mp 128–131 °C. IR (film, cm^{-1}): 3034, 2951, 2907, 2849, 1734, 1454, 1393, 1034, 1117, 1094, 1013, 934, 756, 700; mass spectrum (CI) *m/z* (rel intensity): 575 (6%, M^+), 443 (95), 189 (95), 133 (92), 107 (98), 101 (100). Anal. Calcd $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.88; found: C, 66.64; H, 5.99; N, 4.96. Data for (2*R*)-**13**: $[\alpha]_D$ +84.6 (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.35 (s, 3H), 3.35–3.42 (m, 2H), 3.90 (d, 1H, $J=9.1$ Hz), 4.07–4.13 (m, 2H), 4.30–4.33 (m, 3H), 4.54–4.62 (m, 2H), 4.90 (dd, 1H, $J=9.1$, 2.6 Hz), 5.49 (s, 2H), 7.23–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.0, 52.6, 57.9, 64.2, 64.8, 65.2, 65.8, 78.3, 99.4, 126.0, 128.2, 128.6, 137.8, 138.6, 168.1, 168.3. NMR data for (2*S*)-**13** ^1H NMR (500 MHz, $CDCl_3$) δ 3.35–3.42 (s, 2H), 3.43 (s, 3H), 3.67 (s, 3H), 3.88–3.92 (m, 1H), 4.02–4.05 (m, 2H), 4.30–4.33 (m, 3H), 4.54–4.62 (m, 2H), 4.78–4.82 (m, 1H), 5.42 (s, 2H), 7.23–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 52.9, 57.6, 64.2, 64.8, 65.2, 65.8, 78.3, 99.5, 126.0, 128.2, 128.6, 137.8, 138.6, 168.1, 168.5.

3.1.5. Compound 14. From **8** (405 mg, 1.5 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 287 mg (46%) of **14** as a 82:18 inseparable mixture of (2*S*)-**14** and (2*R*)-**14**. IR (film, cm^{-1}): 3117, 1739, 1395, 1094, 1020, 872, 802, 754, 700; mass spectrum (FAB) *m/z* (rel intensity): 647 (10%, $M^+ + 23$), 625 (32, $M^+ + 1$), 515 (40), 353 (100), 171 (94); *m/z* calcd for $C_{36}H_{36}N_2O_8Na$ 647.2369, found 647.2349. NMR data for (2*S*)-**14**: ^1H NMR (300 MHz, C_6D_6) δ 2.77 (s, 3H), 3.26 (s, 3H), 3.62–3.69 (m, 4H), 3.98–3.99 (m, 2H), 4.30 (d, 1H, $J=9.0$ Hz), 4.57 (sa, 1H), 4.68–4.72 (m, 2H), 5.05 (s, 1H), 5.16 (s, 1H), 5.42 (d, 1H, $J=9.1$ Hz), 6.95–7.94 (m, 17H); ^{13}C NMR (75 MHz, C_6D_6) δ 51.6, 52.5, 58.3, 65.0, 65.5, 65.9, 78.0, 99.3, 123.5, 125.6, 126.1, 126.2, 126.5, 126.6, 126.6, 126.7, 127.7, 128.5, 128.6, 128.7, 128.8, 129.1, 133.7, 133.9, 137.1, 168.1, 168.5. NMR data for (2*S*)-**14**: ^1H NMR (300 MHz, C_6D_6) δ 2.67 (s, 3H), 3.36 (s, 3H), 3.54–3.62 (m, 4H), 3.90 (d, 2H, $J=2.5$ Hz), 4.35 (d, 1H, $J=10.0$ Hz), 4.57 (sa, 1H), 4.82–4.86 (m, 2H), 5.09 (s, 1H), 5.06–5.12 (m, 3H), 6.95–7.94 (m, 17H); ^{13}C NMR (75 MHz, C_6D_6) δ 51.7, 52.5, 58.6, 65.2, 65.5, 65.9, 78.9, 99.3, 123.5, 125.6, 126.1, 126.2, 126.5, 126.6, 126.6, 126.7, 127.7, 128.5, 128.6, 128.7, 128.8, 129.1, 133.7, 133.9, 137.1, 167.3, 168.6.

3.1.6. Compound 15. From **9** (398 mg, 1.5 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 334 mg (54%) of **15** as a 77:23 inseparable mixture of (2*S*)-**15** and minor isomer (2*R*)-**15**. IR (film, cm^{-1}): 2934, 2850, 1610, 1528, 1461, 1352, 1122, 1007, 932, 864, 763, 695; mass spectrum (EI) *m/z* (rel intensity): 619 (10%, M^+), 353 (100), 166 (52), 149 (28); *m/z* calcd for $C_{32}H_{34}N_3O_{10}$ 620.2244, found 620.2239. Anal. Calcd $C_{32}H_{33}N_3O_{10}$: C, 62.03; H, 5.37; N, 6.78; found: C, 62.38; H, 5.53; N, 6.73. NMR data for (2*R*)-**15**: ^1H NMR (500 MHz, C_6D_6) δ 2.93 (s, 3H), 3.32 (s, 3H), 3.74–3.78 (m, 4H), 4.09–4.15 (m, 3H), 4.49 (sa, 1H), 4.60–4.64 (m, 2H), 5.17–5.23 (m, 3H), 7.14–8.00 (m, 14H); ^{13}C NMR (125 MHz, C_6D_6) δ 51.4, 52.3, 57.1, 63.6, 64.8, 77.6, 98.9, 123.0, 128.0, 128.1, 138.6, 145.9, 147.8, 167.3, 167.7. NMR data for (2*S*)-**15**: ^1H NMR (500 MHz, C_6D_6) δ 3.03 (s, 3H), 3.38 (s, 3H), 3.74–3.78 (m, 4H), 3.99–4.01 (m, 2H), 4.42 (sa, 1H), 4.90–4.93 (m, 2H), 5.17–5.23 (m, 3H), 7.14–8.00 (m, 14H); ^{13}C NMR (125 MHz, C_6D_6) δ 51.6, 52.4, 56.9, 63.7, 64.8, 77.6, 98.9, 123.0, 126.0, 128.1, 128.7, 138.2, 147.1, 147.7, 166.5, 167.9.

3.1.7. Compound 16. From **10** (444 mg, 1.5 mmol), flash chromatography (1:4 Et_2O–petroleum ether) gave 345 mg (53%) of **16** as a 82:18 inseparable mixture of (2*S*)-**16** and (2*R*)-**16**. IR (film, cm^{-1}): 3032, 2913, 1729, 1455, 1392, 1308, 1126, 1000, 936, 845, 761, 705; mass spectrum (EI) *m/z* (rel intensity): 651 (20%, $M^+ + 1$), 541 (58), 353 (78), 197 (100); *m/z* calcd for $C_{38}H_{39}N_2O_8$ 651.2706, found 651.2669. Anal. Calcd $C_{38}H_{38}N_2O_8$: C, 70.14; H, 5.89; N 4.31; found: C, 70.31; H, 6.295; N, 4.00. NMR data for (2*S*)-**16**: ^1H NMR (300 MHz, C_6D_6) δ 3.05 (s, 3H), 3.37 (s, 3H), 3.77–3.80 (m, 4H), 4.11–4.12 (m, 2H), 4.64 (sa, 1H), 4.75–4.80 (m, 2H), 5.26 (m, 2H), 5.40 (d, 1H, $J=9.0$ Hz), 7.12–7.81 (m, 19H); ^{13}C NMR (125 MHz, C_6D_6) δ 51.3, 52.1, 58.1, 64.1, 77.6, 98.9, 125.9, 126.2, 128.7, 129.1, 138.2, 138.5, 140.6, 140.9, 167.8, 168.1. NMR data for (2*S*)-**16**: ^1H NMR (300 MHz, C_6D_6) δ 3.01 (s, 3H), 3.27 (s, 3H), 3.64–3.68 (m, 4H), 4.20–4.21 (m, 2H), 4.64 (sa, 1H), 4.90–4.94 (m, 2H), 5.26 (m, 2H), 5.28 (m, 1H), 7.12–7.81 (m, 19H); ^{13}C NMR (125 MHz, C_6D_6) δ 51.4, 52.9, 57.6, 64.7, 78.7, 98.9, 126.3, 126.8, 126.9, 128.6, 136.9, 139.6, 141.1, 167.8, 168.1.

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Laccase-catalyzed carbon–carbon bond formation: oxidative dimerization of salicylic esters by air in aqueous solution

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Abstract—The laccase catalyzed oxidative dimerization of salicylic esters, a rare example of a laccase-catalyzed carbon–carbon bond formation, was studied. This reaction allows the use of air as stoichiometric oxidant and proceeds in aqueous solution. The preparative scope and the mechanism of the method, which provides a new and convenient access to functionalized biaryls under mild conditions, were investigated.

1. Introduction

The research for new environmentally friendly oxidations represents an important field in green chemistry (development of sustainable processes). In this context, enzyme catalyzed oxidations by air are of considerable current interest. These reactions represent new, low-cost processes, which allow the use of aqueous solvent systems and non-toxic starting materials. Laccases (EC 1.10.3.1) are multi-copper oxidases, widely distributed in plants and fungi, with the capability to catalyze the oxidation of a broad range of substrates, such as phenols or lignin-derivatives.[1,2] Laccase catalyzed oxidations of phenols proceed by formation of radical cations (involving molecular oxygen as electron acceptor) and subsequent deprotonation of the phenolic hydroxy groups to give phenoxy radicals which can undergo a broad variety of reactions. Laccases have been applied so far mainly in the fields of waste detoxification, transformations of textile dyes, and food industry.

Recently, increasing interest has been focussed on the application of laccase as a new biocatalyst in organic synthesis.[3] In fact, the high stability of laccases in solution, the mild reaction conditions and the enzymes selectivity for phenol moieties make them to promising biocatalysts. For example, decolouration reactions of aromatic dyes by *N*-demethylation[3a] and depolymerisations of lignin and non-lignin fractions[4] have proven useful for biotechnological processes. In addition, a number of other laccase-catalyzed reactions have been reported; this includes polymerizations of phenols and lignins,[5] dimerizations of penicillins,[6] syntheses of secondary metabolites such as cinnabarinic acid,[7] and oxidative cross-coupling reactions of phenols with amines.[8] Furthermore, the laccase-catalyzed oxidation of benzylic alcohols to the corresponding aldehydes, in the presence of 2,2′-azinobis-(3-ethylbenzylthiozoline-6-sulphate) (ABTS) or *N*-hydroxybenzotriazole, has been reported.[9] Quinones have been prepared by laccase-catalyzed oxidation of polycyclic aromatic hydrocarbons (PAH).[10]

Herein, we wish to report what are, to the best of our knowledge, the first laccase-catalyzed dimerizations of salicylic esters to give functionalized biaryls. These reactions represent rare examples of laccase-catalyzed carbon–carbon bond formations[11] and allow the synthesis of functionalized biaryls under mild conditions. The reactions require only air as stoichiometric oxidant and proceed in aqueous solution.

2. Results and discussion

A number of alkyl-substituted salicylic esters, readily available by [3+3] cyclization of 1,3-bis-silyl enol ethers[12] with 3-silyloxyalk-2-en-1-ones[13] or 1,1-diacylcyclopropanes,[14] were subjected to laccase oxidation. The reactions

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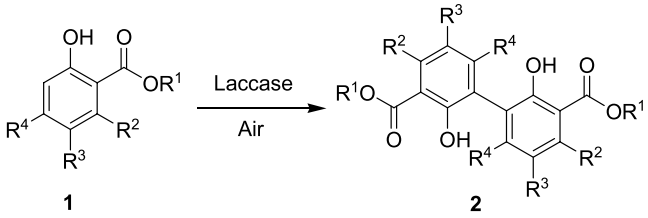
Table 1. Products and yields

1, 2	R^1	R^2	R^3	R^4	% (2)[a]	Products[b]
a	H	H	H	H	0	0
b	Me	H	H	H	0	0
c	Me	Me	Me	Me	84	1
d	Me	Me	Et	Me	85	1[c]
e	Me	Me	$(CH_2)_2Cl$	Me	85	5
f	Et	Me	$(CH_2)_2Cl$	Me	74	5
g	Et	Me	$(CH_2)_2Cl$	H	0	>7
h	Me	H	Me	H	78	3
i	Me	Me	H	Me	0	>7

[a] Isolated yields.
[b] Number of products formed in the reaction.
[c] Besides **2d**, a small amount of starting material was recovered.

showed remarkable differences in terms of substrate depletion, kinetics and product distribution, dependent on the position and number of the alkyl substituents (Table 1). The main products, symmetrical biaryls, were formed by oxidative dimerization and proved stable in aqueous solution and in organic solvents (MeOH, EtOAc, CH_2Cl_2, $CHCl_3$). Notably, parent salicylic acid and methyl salicylate were not oxidized by laccase.

The laccase catalyzed reaction of 4,5,6-trialkylsalicylic esters **1c** and **1d** afforded the corresponding biaryls **2c** and **2d**, respectively (Scheme 1). Control experiments showed that the presence of laccase was required to induce dimerization. The salicylates **1c–d** showed high reactivity towards laccase and biaryls **2c–d** were formed as the main products. In case of the methyl salicylate **1c** (1 mM), a conversion of more than 90% was observed during the first 20 min of the reaction (Fig. 1A). The biaryl **2c** proved to be less soluble in water compared to the starting material and precipitated during the reaction. It was the only product formed (HPLC) and was isolated in 84% yield. Similar results were observed for ethyl salicylate **1d**. Besides **2d**, a small amount of starting material was recovered in this reaction.



Scheme 1. Laccase-catalyzed dimerization of salicylates.

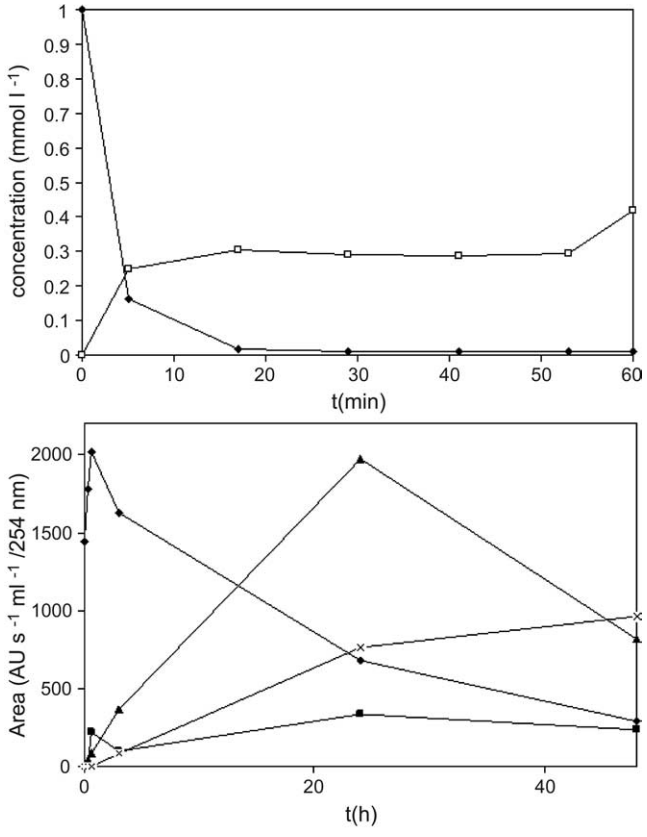


Figure 1. Kinetics of substrate depletion (1 mM) and product formation by laccase from *Trametes* spec. A: **1c** ♦, **2c** □, 20 min; B: **1h** ♦, coupling product 1 ■, coupling product 2 ▲, coupling product 3 ×, 24 h.

Due to the mild reaction conditions, a good chemoselectivity was generally observed. This was demonstrated by the successful dimerization of the chloroethyl-substituted salicylic esters **1e** and **1f**, prepared by cyclization of 1,3-bis-silyl enol ethers with 1,1-diacetylcyclopropane,[14] to give the highly functionalized biaryls **2e** and **2f**. The decreased hydrophilicity of **1e** and **1f** resulted in a poor water-solubility of the starting materials (below 1 mM). Therefore, the amount of methanol in the assay had to be increased up to 5% (v/v), which caused no inhibition of the enzyme activity. Nevertheless, only 20% of methyl salicylate **1e** and 8% of the even less water-soluble ethyl salicylate **1f** were transformed into the products within the first 20 min. The product formation was completed within 24 h. The oxidation of the substrate was accompanied by the formation of small amounts of four side-products. Biaryls **2e** and **2f**, the most hydrophobic products, were formed as the main products (more than 90% by HPLC).

Salicylate **1g** was also readily oxidized by laccase and 40% of the substrate was consumed within 20 min. However, the formation of a complex mixture was observed by HPLC. Some of these peaks were also obtained in the control experiment without addition of laccase, which indicated that the compound was unstable. The oxidation rate for **1h** was much lower than for **1c–g**. Within 24 h about 60% of the substrate had been oxidized to give a mixture of three compounds (Fig. 1B). The desired dimer **2h** could be isolated after reaction for 48 h in 78% yield (Table 1). The conversion rate of salicylate **1i** (55%/24 h) was comparable

to that of **1h**. The formation of seven products in various amounts was observed. Due to the low product formation rate and the unspecific product pattern, this reaction was not further investigated.

As mentioned above, the laccase catalyzed dimerization of **1c–f** resulted in the selective formation of only one major product. The presence of impurities in commercial laccase disturbed the purification process of biaryls **2c–d** and **2f** by solid phase extraction. Therefore, a laccase derived from *Pycnoporus cinnabarinus*, exhibiting a higher degree of purity, was used for preparative scale experiments. Product **2e** was isolated by liquid–liquid extraction (dichloromethane) and was purified by silica gel chromatography.

The results outlined above indicate that the presence of a substituent at carbon C-5 in *para*-position to the hydroxyl group of the salicylate is important for clean transformations. The laccase reactions reported herein presumably proceed by formation of a radical cation, subsequent deprotonation of the hydroxy group to give a radical, dimerization and rearomatization (vide supra). The presence of a substituent located at C-5 seems to be important for the stabilization of the radical formed during the reaction.

In summary, we have reported a new laccase-catalyzed oxidative dimerization reaction, which represents a rare example of a laccase-catalyzed carbon–carbon bond formation. The reactions provide a convenient access to functionalized biaryls under very mild conditions. Air can be used as stoichiometric oxidant and the reactions can be carried out in aqueous solution.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectral data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O) or the electrospray ionization (ESI). For preparative scale chromatography silica gel (60–200 mesh) was used. Melting points are uncorrected. Salicylic acid and salicylic acid methyl ester were obtained from Sigma-Aldrich (Deisenhofen, Germany). Salicylates **1c–d,i**[13] and **1e–g**[14] were prepared according to literature procedures.

3.2. Enzymes

Analytical assays were carried out in the presence of commercially available laccase C (ASA Spezialenzyme, Wolfenbüttel, FRG) from *Trametes* spec. For production scale, a laccase preparation with higher purity obtained from the white rot fungus *Pycnoporus cinnabarinus* SBUG-M, deposited at the strain collection of the Department of Biology of the University of Greifswald (SBUG), was used. The fungus was cultivated on a shaker at 30 °C in a liquid, nitrogen-rich medium containing 5.00 g of glucose, 1 g of KH_2PO_4, 0.50 g of L-asparagine, 0.5 g of yeast extract, 0.50 g of KCl, 0.50 g of $MgSO_4 \cdot 7H_2O$, 50 mL of an aqueous solution of various salts (1.00 g of $Ca(NO_3)_2 \cdot 4H_2O$, 0.06 g of $CuSO_4 \cdot 5H_2O$, and 0.04 g of $ZnSO_4 \cdot 7H_2O$ per liter) and 50 mL of an aqueous solution of $FeSO_4$ (0.2 g L^{-1}). For higher yields of laccase, cultures were incubated with 3,4-dimethoxybenzylic alcohol (10 mM)—a known inducer of laccase.[11] After 7 days of cultivation, mycelium was separated from the culture supernatant by filtration through a glass fiber filter using a Buechner funnel. The cell-free culture medium was stirred with DEAE-Sephacel (Sigma, Steinheim, FRG) for 1 h and the adsorbed enzyme was eluted from the anion exchange resin using an aqueous buffer solution (20 mM sodium acetate, pH 5, 700 mM sodium chloride). This enzyme extract was subsequently desalted using a Sephadex G-25 Superfine column (Pharmacia, Freiburg, Germany).

3.3. Determination of laccase activity

The laccase activity was determined spectrophotometrically at 420 nm using ABTS as a substrate[15] and an adapted method.[11]

3.4. Analytical HPLC

For routine analysis, the reaction mixtures were analyzed using an HPLC system LC-10ATvP (Shimadzu, Germany) consisting of a FcV-10ATvP pump, a SPD-M10AvP photodiode array detector, and a SCL-10AvP control unit controlled by VPClass 5.0. The separation of the substances was achieved on an endcapped, 5-μm, LiChroCart 125-4 RP 18 column (Merck, Darmstadt, Germany) using a flow rate of 1 mL/min. A solvent system consisting of methanol (eluent A) and phosphoric acid (0.1%, eluent B), starting from an initial ratio of 55% A and 45% B and reaching 100% methanol within 8 min, was used.

3.5. Procedure for the laccase catalyzed dimerization of salicylic esters

For analytical scale reactions, the assays were carried out in 5-mL-brown-glass bottles with 2-mL-sample volumes. An aqueous solution of a sodium acetate buffer (20 mM, pH5) of salicylates (concentration: 1 mM, stock solution: 50 mM in methanol) was incubated and the reaction started upon addition of laccase (974 nmol/mL min^{-1}). The reaction mixtures were incubated at room temperature with agitation at 100 rpm for appropriate times and the product formation was followed by HPLC. Preparative scale transformations were performed in 500-mL-flasks using a magnetic stirrer. Aqueous buffer solutions (40–200 mL) were used employing the substrate concentration and enzyme activity as described above.

3.6. Isolation of the products

Some of the products were isolated by repeated solid phase extraction. A RP18 silicagel column (polypropylene, 500 mg–2000 mg adsorbent material, Merck, Darmstadt, Germany) was charged with the reaction mixture. Remaining starting material was eluted with less concentrated methanol solutions in water (40–80%) before the products were eluted using pure methanol. The products, which could

not be isolated by SPE on RP phases, were isolated by normal phase chromatography. The products were removed from the incubation assay by liquid–liquid-extraction (ethyl acetate), the solvent was evaporated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/*n*-hexane).

3.6.1. Dimethyl 2,2′-dihydroxy-4,5,6,4′,5′,6′-hexamethylbiphenyl-3,3′-dicarboxylate (2c). Starting with **1c** (11.6 mg, 0.06 mmol), **2c** was isolated as a colourless solid (9.8 mg, 84%), mp 192–193 °C; R_f=0.47 (hexane/ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3428 (br), 2929 (w), 1729 (w), 1657 (s), 1597 (w), 1440 (m), 1231 (s), 1072 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=10.49 (s, 2H, OH), 3.92 (s, 6H, OCH_3), 2.48 (s, 6H, CH_3), 2.21 (s, 6H, CH_3), 2.98 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.34 (2C), 156.21 (2C), 142.77 (2C), 137.39 (2C), 127.47 (2C), 123.38 (2C), 111.77 (2C, C), 52.08 (2C, OCH_3), 19.33 (2C), 17.99 (2C), 16.21 (2C, CH_3); MS (EI, 70 eV): *m/z* (%)=385.8 (M^+, 27), 353.7 (6), 338.7 (21), 306.7 (100), 193.7 (12), 161.7 (43), 133.9 (12), 90.8 (10), 27.9 (55).

3.6.2. Dimethyl 5,5′-diethyl-2,2′-dihydroxy-4,6,4′,6′-tetramethylbiphenyl-3,3′-dicarboxylate (2d). Starting with **1d** (38.8 mg, 0.186 mmol), **2d** was isolated as a colourless solid (33 mg, 85%); mp 168–169 °C; R_f=0.59 (hexane/ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3421 (br), 2968 (m), 1730 (w), 1651 (s), 1595 (m), 1565 (w), 1440 (s), 1349 (m), 1223 (s), 1074 (m), 811 (w); ^1H NMR (300 MHz, $CDCl_3$): δ=10.47 (s, 2H, OH), 3.93 (s, 6H, OCH_3), 2.71 (q, 4H, J=7.5 Hz, CH_2), 2.52 (s, 6H, CH_3), 2.07 (s, 6H, CH_3), 1.12 (t, 6H, J=7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.31 (2C), 156.21 (2C), 142.32 (2C), 136.85 (2C), 133.32 (2C), 123.78 (2C), 119.97 (2C, C), 52.02 (2C, OCH_3), 22.94 (2C, CH_2), 18.35 (2C), 16.98 (2C), 13.78 (2C, CH_3); MS (EI, 70 eV): *m/z* (%)=415.4 (M^+, 38), 382.0 (6), 367.0 (22), 353.0 (12), 334.9 (100), 306.0 (7), 175.0 (4), 43.0 (5), 28.1 (7). Elemental analysis calcd for $C_{24}H_{28}O_6$: C, 69.64; H, 7.29. Found: C, 69.27; 7.61.

3.6.3. Dimethyl 5,5′-bis(2″-chloroethyl)-2,2′-dihydroxy-4,6,4′,6′-tetramethylbiphenyl-3,3′-dicarboxylate (2e). Starting with **1e** (4.8 mg, 0.02 mmol), **2e** was isolated as a colourless solid (4.1 mg, 85%), mp 168–169 °C; R_f=0.71 (hexane/ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3428 (br), 2988 (m), 1657 (s), 1601 (m), 1574 (m), 1468 (m), 1435 (s), 1336 (m), 1355 (s), 1317 (m), 1240 (s), 1072 (m), 804 (m), 762 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=10.79 (s, 2H, OH), 3.96 (s, 6H, OCH_3), 3.58–3.52 (m, 4H, CH_2Cl), 3.22–3.16 (m, 4H, CH_2), 2.55 (s, 6H, CH_3), 2.02 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.12 (2C), 157.44 (2C), 143.09 (2C), 138.35 (2C), 127.29 (2C), 124.00 (2C), 111.50 (2C, C), 52.30 (2C, CH_3), 42.32 (2C), 33.66 (2C, CH_2), 18.81 (2C), 17.44 (2C, CH_3); MS (EI, 70 eV): *m/z* (%)=487.2 (M^+, 8), 485.0 (M^+, 52), 483.4 (M^+, 56), 424.3 (52), 403.9 (100), 375.7 (11), 210.4 (21), 161.3 (26), 28.0 (39); elemental analysis: calcd (%) for $C_{24}H_{28}O_6Cl_2$: C 59.63, H 5.84; found: C 59.53, H 6.46.

3.6.4. Diethyl 5,5′-bis(2-chloroethyl)-2,2′-dihydroxy-4,6,4′,6′-tetramethylbiphenyl-3,3′-dicarboxylate (2f). Starting **1f** (5.8 mg, 0.0225 mmol), **2f** (4.2 mg, 74%) was obtained as a colourless solid, mp 176–177 °C; R_f=0.53 (hexane/ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3426 (br), 2927 (w), 1727 (w), 1654 (s), 1595 (w), 1447 (m), 1374 (m), 1232 (s), 1071 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=10.84 (s, 2H, OH), 4.43 (q, 4H, J=7.2 Hz, OCH_2), 3.59–3.48 (m, 4H, CH_2Cl), 3.22–3.16 (m, 4H, CH_2), 2.57 (s, 6H, CH_3), 2.02 (s, 6H, CH_3), 1.42 (t, 6H, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.61 (2C), 157.46 (2C), 142.92 (2C), 138.36 (2C), 127.23 (2C), 124.07 (2C), 112.29 (2C, C), 61.75 (2C), 42.33 (2C), 33.68 (2C, CH_2), 18.83 (2C), 17.44 (2C), 14.20 (2C, CH_3); MS (EI, 70 eV): *m/z* (%)=511.6 (M^+, 17), 509.6 (M^+, 26), 450.6 (16), 448.7 (25), 404.6 (65), 402.6 (100), 368.7 (5), 159.8 (11), 28.0 (25).

3.6.5. Dimethyl 2,2-dihydroxy-5,5′-dimethylbiphenyl-3,3′-dicarboxylate (2h). Starting with **1h** (33.2 mg, 0.2 mmol), **2h** was obtained (26 mg, 78%) as a colourless solid, mp 194–195 °C; R_f=0.63 (hexane/ethyl acetate=3:1); IR (KBr): $\tilde{\nu}$=2958 (w), 1672 (s), 1601 (m), 1435 (s), 1330 (m), 1247 (s), 1220 (s), 1098 (m), 796 (m), 725 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=10.94 (s, 2H, OH), 7.68 (s, 2H, ArH), 7.30 (s, 2H, ArH), 3.94 (s, 6H, OCH_3), 2.32 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.85 (2C), 157.04 (2C, C), 138.32 (2C), 129.48 (2C, CH), 127.79 (2C), 15.98 (2C), 112.08 (2C, C), 52.29 (2C), 20.40 (2C, CH_3); MS (EI, 70 eV): *m/z* (%)=330.1 (M^+, 96), 298.0 (100), 266.0 (67), 238.0 (35), 182.0 (11), 148.3 (14), 28.0 (79). Elemental analysis calcd (%) for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 64.98; H, 6.06.

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Leontopodic acid—a novel highly substituted glucaric acid derivative from Edelweiss (*Leontopodium alpinum* Cass.) and its antioxidative and DNA protecting properties

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Abstract—Leontopodic acid—a novel full substituted hexaric acid derivative, was isolated from the aerial parts of Edelweiss (*Leontopodium alpinum* Cass.) as one of the major compounds. The complex structure of leontopodic acid-2-[(3*S*)-3-hydroxybutanoate]-3,4,5-tris-[(2*E*)-3-(3,4-dihydroxyphenyl)-2-propenoate]-D-glucaric acid—was elucidated by mass spectrometry, 1D- and 2D NMR spectroscopy and HPLC monitored transesterification. Leontopodic acid exhibited pronounced antioxidative effects in the Briggs-Rauscher (BR) model [$(r.a.c.)_m$ 3.4 ± 0.5] and the trolox equivalent antioxidant capacity (TEAC) method (TEAC value of 1.53 ± 0.11). The antioxidative properties of this compound were confirmed by the 3D method, an in vitro assay evaluating DNA protection against oxidative damage (IC_{50}: 1.89 μM).

1. Introduction

Free radicals and reactive oxygen species (ROS) are produced by most cells. They play a crucial role in cellular metabolism and mediate critical biochemical reactions and physiologic effects, for example, eicosanoid synthesis, phagocyte activity, cytochrome P-450 and peroxidase function, pyruvate and coenzyme A metabolism, carboxylation of glutamic acid by vitamin K-dependent enzymes, and the reduction of ribonucleosides. Maintenance of the normal redox balance of a cell, ensuring a transitory ROS generation, is controlled by compounds that are antioxidants (e.g., the antioxidant vitamins) or by enzymes, both constitutive and inducible. If the antioxidant defense systems fail ROS are produced in excess and oxidative stress-an imbalance between oxidants and antioxidants in favor of the former, and potentially leading to damage—can arise.[1] As a result, ROS can damage cells by interactions with critical macromolecules, including DNA, proteins, and lipids, which leads to toxicity. They are believed to be involved in the etiology of a wide array of human disorders. For example, reactive oxygen species have been linked to coronary heart disease, atherosclerosis, cancer, diabetes, cataract, arthritis, toxic liver injury, adverse drug reactions, immune hypersensitivity, inflammation, reperfusion injury, neurological disease, and aging.[2] Plant constituents, widely

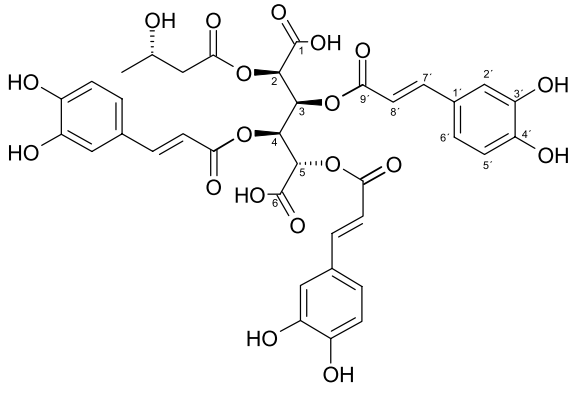

Figure 1. Structure of leontopodic acid.

Keywords: *Leontopodium alpinum*; Asteraceae; Glucaric acid; Caffeic acid; Briggs-Rauscher reaction; TEAC; 3D; Leontopodic acid.
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discussed as potential antioxidant prophylactic agents for both health and disease management belong to different compound classes ranging from vitamins to polyphenols to sulfur containing constituents. In this study a novel highly substituted hexaric acid derivative (Fig. 1) with pronounced antioxidative properties was isolated from the aerial parts of *Leontopodium alpinum* Cass. (Asteraceae), commonly known as Edelweiss. The structure of the constituent was elucidated by NMR spectroscopy, mass spectrometry and transesterification. *L. alpinum* is one of the most famous plants of the European Alps and shows a wide diversity of secondary plant metabolites such as phenolic acids, lignans, flavonoids, sesquiterpenes, coumarins, benzofuran and —pyrane derivatives, polyacetylenes, diterpene acids and others.[3–6] In folk medicine extracts of this plant are used as therapy for abdominal aches, tonsillitis, bronchitis, cancer, diarrhea, dysentery and fever.[7]

Today, this highly protected plant, *L. alpinum*, is cultivated in large quantities in Switzerland.

2. Results and discussion

2.1. Structure elucidation of leontopodic acid

High resolution FAB (*m/z*: 781.16340 $[M-H]^-$ for $C_{37}H_{33}O_{19}$; calculated: 781.1611) and ESI mass spectra (negative mode, pseudo molecular ion *m/z*=781 $[M-H]^-$) displayed a molecular weight of 782. The fragmentation pattern (Fig. 2) exhibited prominent fragment ions at *m/z*=619 ($[M-H]^-$–$C_9H_6O_3$), *m/z*=457 ($[M-H]^--2\times C_9H_6O_3$), and *m/z*=295 ($[M-H]^--3\times C_9H_6O_3$) confirming the presence of three caffeic acid units (anion at *m/z*=179). Further fragment signals were observed at *m/z*=695 ($[M-H]^-$–$C_4H_6O_2$), *m/z*=533 ($[M-H]^-$–$C_4H_6O_2-1\times C_9H_6O_3$), *m/z*=371 ($[M-H]^-$–$C_4H_6O_2-2\times C_9H_6O_3$), and *m/z*=209 ($[M-H]^-$–$C_4H_6O_2-3\times C_9H_6O_3$) indicating the presence of an additional acid moiety with the molecular ion formula $C_4H_6O_2$.

The ^{1}H NMR spectrum displayed three resonance clusters

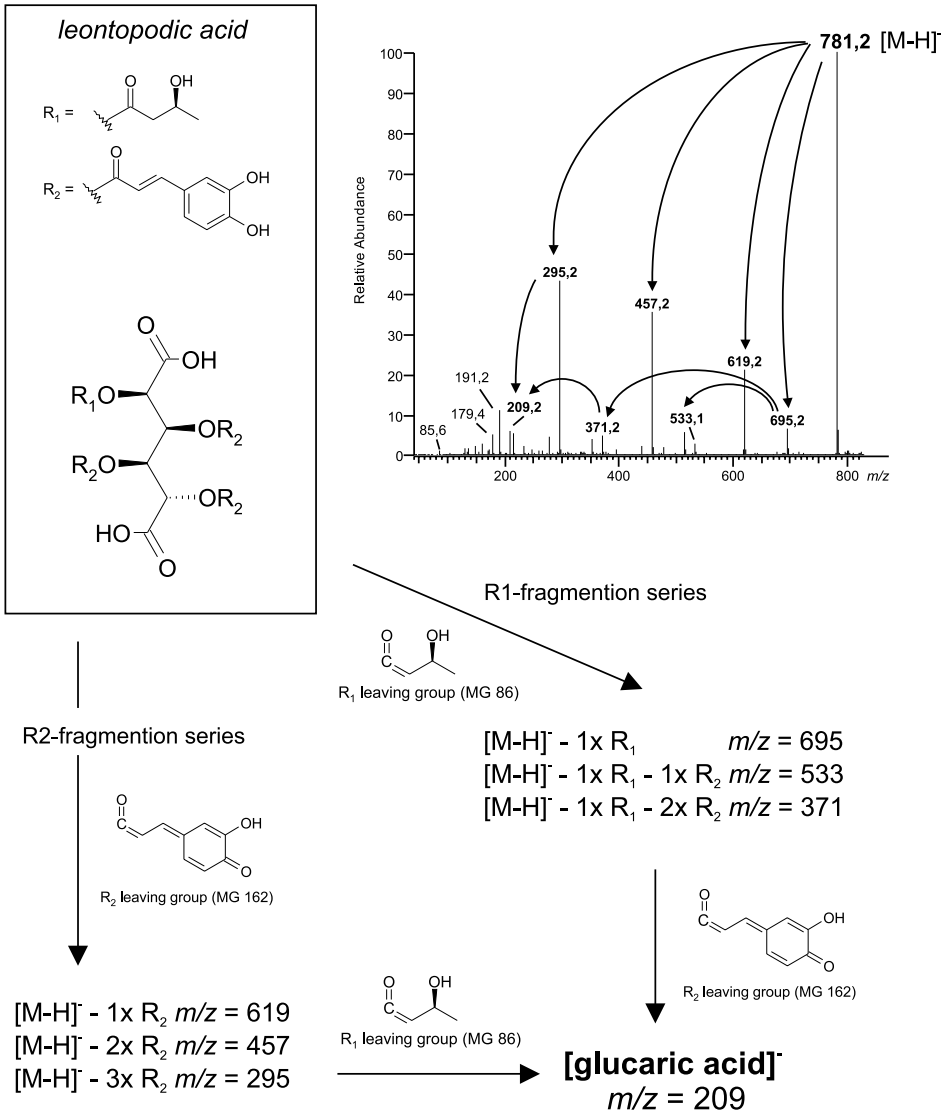

Figure 2. Simplified syringe pump negative ESI-MS based breakdown of leontopodic acid.

of aromatic protons at δ_H 7.50–7.70, 6.70–7.10, and 6.20–6.45 ppm; five methine protons at δ_H 6.17 (dd), 5.86 (dd), 5.56 (d), 5.33 (d), and 4.20 (sext), respectively; a methylene moiety at δ_{Ha} 2.62 (dd) and δ_{Hb} 2.52 (dd) and a methyl group at δ_H 1.21 (d). The ^{13}C NMR spectrum showed six signals in the range of δ_C 167.66–171.75 ppm, indicating the presence of six carboxylic acid derivative moieties. A total of 24 aromatic resonances in the range of δ_C 114.00–149.85 ppm (nine quaternary carbons and 15 methine carbons according to the DEPT experiment) correspond with the presence of three caffeic acid units as indicated by MS data. Furthermore, five oxygenated methine (δ_C 65.40–72.71 ppm), one methylene (δ_C 44.50 ppm) and one methyl (δ_C 23.17 ppm) resonances were observed. HSQC and HMBC contacts within the aromatic systems confirmed the presence of three (*E*)-caffeoylic acid ester units connected to three methine carbons (δ_H/δ_C 6.17/71.08, 5.86/71.90, and 5.56/72.71 ppm). The remaining non-aromatic signals combine with the acyl resonance at $\delta_C = 171.75$ ppm to a 3-hydroxybutryric acid unit, which is esterified with the fourth CH(O) residue at δ_H/δ_C 5.33/72.37 ppm. This assignment is in accordance to the $C_4H_6O_3$ fragment ($m/z = 86$) found in the ESI-MS spectrum. DQF-COSY and HMBC correlations within the group of four substituted methines as well as the coupling constant patterns did prove the presence of a linear 1,2,3,4-tetrahydroxybutyl fragment and therefore allowed to exclude the presence of a quinic acid derivative. Furthermore, the unequivocal assignment of the individual positions of the obtained δ_H/δ_C resonance pairs was possible. HMBC cross-peaks finally allowed us to place the remaining two acyl resonances at $\delta_C = 170.26$ and 170.46 ppm in the proximity of the first (δ_C 72.37 ppm) and the fourth (δ_C 72.71 ppm) carbon of the tetraol fragment, resulting in the presence of a hexaric acid backbone. For the full assignment of the NMR data see Table 1.

Table 1. ^1H (300 MHz) and ^{13}C NMR (75 MHz) data of leontopodic acid

Carbon-number	δ_H, mult (*J*)	δ_C, mult
Hexaric acid		
1	—	170.26 s
2	5.33 d (4.2)	72.37 d
3	5.86 dd (6.9; 4.2)	71.90 d
4	6.17 dd (6.9; 2.9)	71.08 d
5	5.56 d (2.9)	72.71 d
6	—	170.46 s
3-Hydroxybutyric acid at position 2		
α	—	171.75 s
β	H_a 2.62 dd (15.1; 7.0)	
H_b 2.52 dd (15.1; 6.2)	44.50 t	
γ	4.20 sext (6.6)	65.40 d
δ	1.21 d (6.4)	23.17 q
Caffeic acid at position 3		
1‴	—	127.57 s
2‴	7.07 d (2.0)	115.44 d
3‴	—	146.77 s
4‴	—	149.85 s
5‴	6.75 d (8.2)	116.54 d
6‴	6.95 dd (8.2; 2.0)	123.27 d
7‴	7.65 d (15.9)	148.42 d
8‴	6.26 d (15.9)	114.00 d
9‴	—	167.66 s
Caffeic acid at position 4		
1″	—	127.67 s
2″	7.00 d (2.0)	115.20 d
3″	—	146.77 s
4″	—	149.83 s
5″	6.73 d (8.2)	116.54 d
6″	6.89 dd (8.2; 2.0)	123.31 d
7″	7.56 d (15.9)	148.55 d
8″	6.20 d (15.9)	113.91 d
9″	—	167.71 s
Caffeic acid at position 5		
1′	—	127.57 s
2′	6.98 d (2.0)	115.27 d
3′	—	146.77 s
4′	—	149.83 s
5′	6.74 d (8.2)	116.51 d
6′	6.86 dd (8.2; 2.0)	123.36 d
7′	7.53 d (15.9)	148.55 d
8′	6.38 d (15.9)	114.02 d
9′	—	167.92 s

(CD_3OD, 300 K, δ in ppm, *J* in Hz).

Since previously described methods of hydrolysis, used for the splitting of similar constituents[8,9] did not yield hexaric acid in suitable amounts and purity, a transesterification protocol was established. The reaction progress was monitored by HPLC (Fig. 3) and the purification of the desired hexaric acid was achieved by a multistep washing procedure that was applied to the evaporated crude reaction mixture. Comparison of the ^1H NMR data of the reaction product with the reported values obtained from the literature[10] lead to the identification of glucaric acid as the reaction product. Unambiguous proof was finally obtained by performing a ^1H NMR mixing experiment with commercial available glucaric acid (Fig. 4). Identity of sign and size of the obtained optical rotations of the methanolysis product and commercial D-glucaric acid proved identical absolute configurations. The absolute configuration of the 3-hydroxybutyric acid residue was assigned in the same methanolysis experiment. The obtained diethyl ether fraction contained a mixture of 3-hydroxybutyric acid, its methyl ester and the ester of both substances, which was proved by MS experiments. The observed positive optical rotation of the mixture indicated the presence of the (*S*)-3-hydroxybutyric acid isomer. Thus, the isolated compound was identified as 2-[(3*S*)-3-hydroxybutanoate]-3,4,5-tris-[(2*E*)-3-(3,4-dihydroxy-phenyl)-2-propenoate]-D-glucaric acid. Leontopodic acid as trivial name is proposed for this novel unusual secondary plant metabolite.

2.2. Relative antioxidant activity

2.2.1. Briggs-Rauscher method (BR). Antioxidant activity of leontopodic acid was measured using the chemical in vitro method reported by Cervellati et al.[11] This method is based on the inhibition of oscillations produced by the presence of ROS scavengers. Oscillations are measured potentiometrically. The BR system consists of hydrogen peroxide, acidic iodate, malonic acid and Mn(II) as catalyst and works at the physiological pH of the human stomach (pH ~ 2).[12] Similar to other methods, the BR reaction method is based on the generation of free radicals in the reaction mixture. The generated hydroperoxyl radicals ($HOO^{\cdot}$) are among the main intermediates of the BR system. The mechanism of the action of antioxidants against $HOO^{\cdot}$ radicals has been described in detail elsewhere.[11,13] When ROS scavengers are added to an active oscillating BR

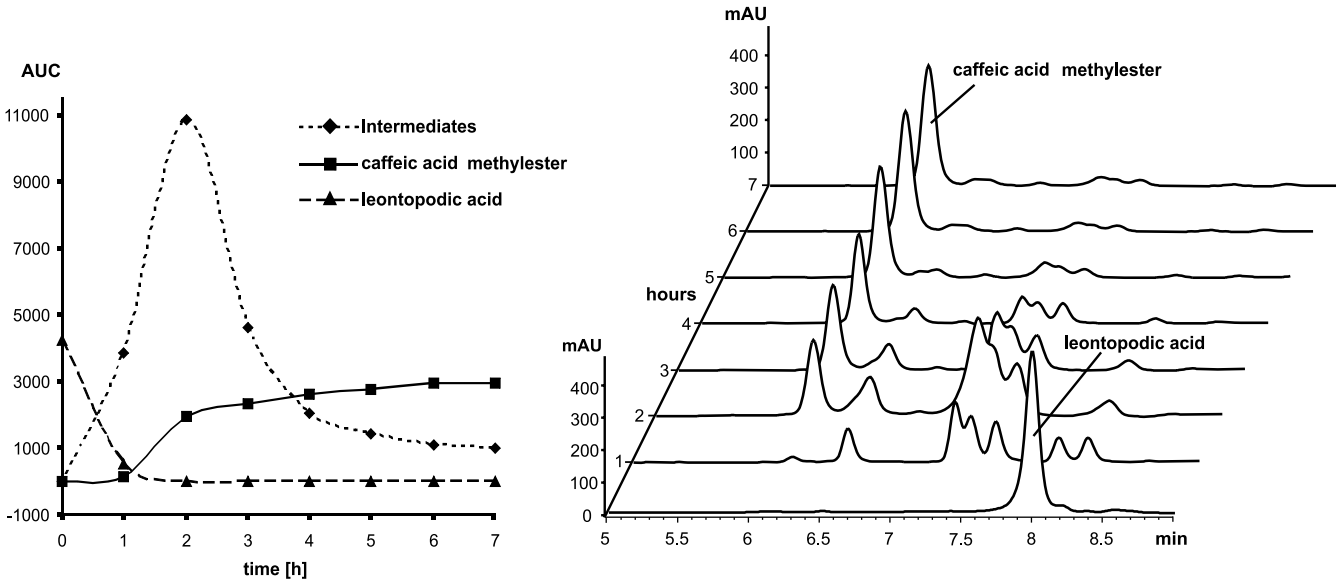

Figure 3. Results of the HPLC monitored transesterification. Left graph: Conversion of leontopodic acid into intermediates and caffeic acid methylester during transesterification process [time/AUC from LC/DAD, 350 nm]. Right graph: LC-DAD chromatograms (350 nm) of reaction control samples.

mixture there is an immediate quenching of the oscillations, depending on the linear relationship of the concentration and activity of the antioxidant, followed by regeneration of the oscillations. Relative antioxidant activities with respect to a substance chosen as a standard are determined on the basis of the inhibition times.

The graphs t_{inhib} versus concentration for leontopodic acid and resorcinol (standard) are given in Figure 5. Data are well fitted by straight lines. Behavior deviates from linearity below a certain concentration of antioxidant added (different for each antioxidant).

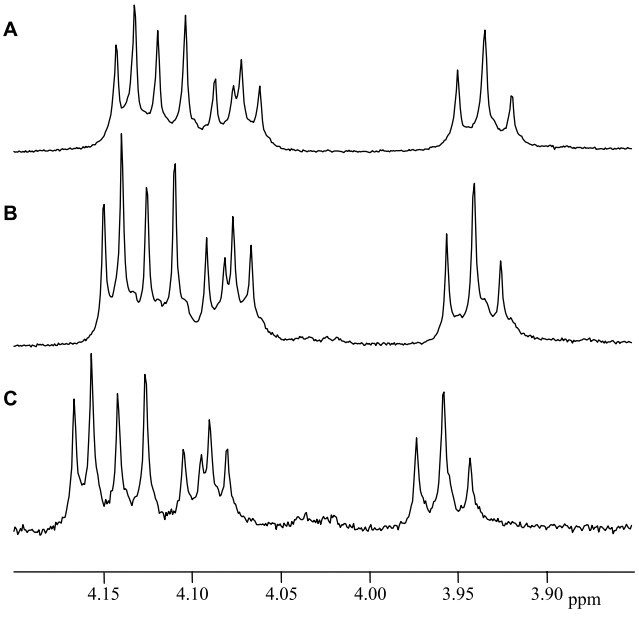

Figure 4. ^{1}H NMR mixing experiment of transesterification product (disodium glucaric acid) and commercial available Ca^{2+}-glucarat. A: ^{1}H NMR methanolysis product in D_2O (Di-sodium salt; $c=5.7$ mg/ml = 0.23 M); B: ^{1}H NMR mixture (1 part disodium glucarat solution + 3 parts Ca^{2+}-glucarat solution); C: ^{1}H NMR Ca^{2+}-glucarat in D_2O ($c=12.5$ mg/ml = 0.72 M).

At the low concentration of antioxidant added, the inhibition time becomes too low to be measured: there is a threshold under which inhibition time cannot be detected. Under these lower limits the straight line curves towards zero. At higher concentrations of antioxidants the amplitude of the resumed oscillations becomes too low, until up to a given concentration (different for each antioxidant) oscillations do not restart. This means that the reaction reaches the end, thereby, loosing the ability to produce radicals.

As shown in Figure 5, the slopes of the straight lines are different, so the calculation of the relative antioxidant activity will depend on the substance chosen as the standard and the concentration of the sample. For this reason, it is

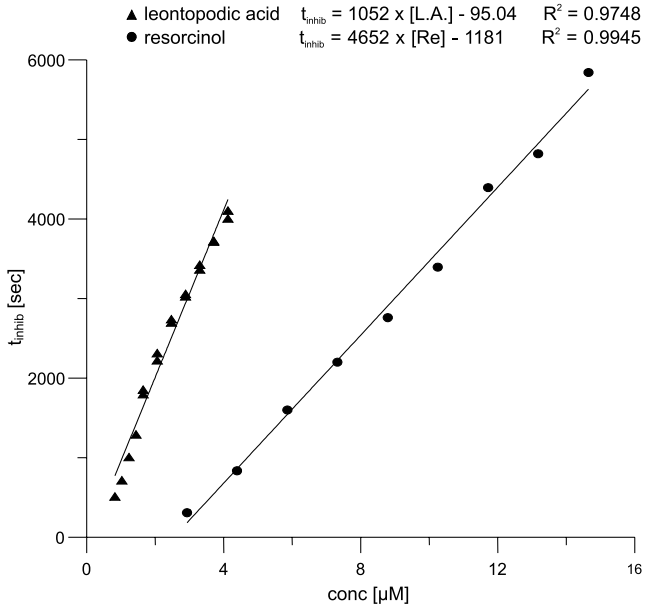

Figure 5. Graphs t_{inhib} versus concentration for leontopodic acid [L.A.] and resorcinol [Re]. Parameters of the straight line equations and R^2 values are given in the legend.

Table 2. Inhibition times of leontopodic acid measured in Briggs-Rauscher reaction. r.a.c.=[std]/[smp]

Conc.in mixture ((M)	Inhibition time (s)	r.a.c.[a]	$(r.a.c.)_m \pm \sigma$
1.03	717	3.96±0.12	3.39±0.5
1.24	1008	3.81±0.11	
1.44	1293	3.69±0.11	
1.65	1799	3.88±0.12	
1.65	1855	3.96±0.12	
2.06	2223	3.55±0.11	
2.06	2314	3.64±0.11	
2.48	2699	3.37±0.10	
2.48	2741	3.41±0.10	
2.89	3027	3.13±0.09	
2.89	3059	3.16±0.09	
3.30	3425	3.00±0.09	
3.30	3367	2.96±0.09	
3.71	3725	2.84±0.09	
3.71	3716	2.84±0.09	
4.13	4106	2.76±0.08	
4.13	4007	2.70±0.08	

Standard: resorcinol.
[a] Quoted errors calculated according to the procedure suggested by Harris.[14]

convenient to calculate a mean value of r.a.c., $(r.a.c.)_m$, in a range of inhibition times common to the sample and the standard. Leontopodic acid was tested in different concentration levels from 1.03 μM (r.a.c. 3.96±0.12) to 4.13 μM (r.a.c. 2.70±0.08) (Table 2).

The mid-range of the inhibition times for resorcinol is 2766 s; the experimental inhibition time for leontopodic acid nearer to this mid-range value is 2741 s resulting in a r.a.c. of 3.41, very close to the $(r.a.c.)_m$ of 3.39.

It can be concluded that the $(r.a.c.)_m$ reported in Table 2 is the most significant indicator of the BR relative antioxidant activity of leontopodic acid. This mean value is used for the comparison with $(r.a.c.)_m$ values of other compounds. In Table 3 a comparison of $(r.a.c.)_m$ for different natural antioxidants is given.

2.2.2. TEAC assay. This method works at physiological pH (pH=7.4). The original TEAC assay of Miller et al.,[16] based on the activation of metmyoglobin with hydrogen peroxide in the presence of ABTS, 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt, to produce the radical cation $ABTS^{\cdot+}$, was modified by a decolorization technique in which the $ABTS^{\cdot+}$ is generated directly in a stable form prior to the addition of the antioxidants. The generation of the blue/green $ABTS^{\cdot+}$ chromophore resulted from the reaction between ABTS and the potassium persulfate.[17]

Table 3. Comparison of $(r.a.c.)_m$ of different natural antioxidants

Compound	$(r.a.c.)_m$
Rosmarinic acid[a]	3.99
Leontopodic acid	3.39
Ferulic acid[b]	2.12
Pyrocatechol[b]	2.10
Caffeic acid[b]	1.68
Homovanillic acid[b]	1.35
Resorcinol	1.00

[a] Cervellati et al.[11]
[b] Cervellati et al.[15]

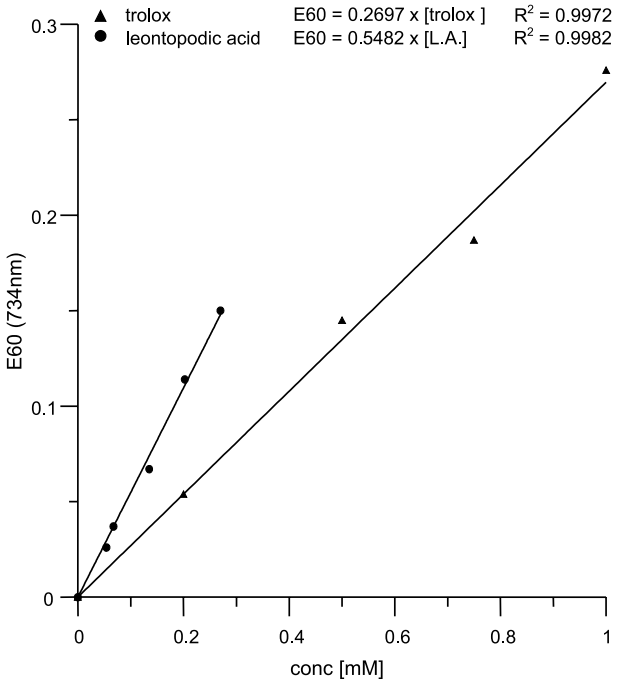

Figure 6. Graphs ΔE60 at 743 nm versus concentration for trolox and leontopodic acid [L.A.]. Parameters of the straight line equations and R^2 values are given in the legend.

Addition of antioxidants to the preformed radical cation causes a decolorization of the solution. The extent of the decolorization is a function of concentration and time. The absorbance at 734 nm of a blank (a suitable diluted $ABTS^{\cdot+}$ mixture plus an amount of a pH=7.4 PBS) was prerecorded before each measurement of diluted $ABTS^{\cdot+}$ mixture plus the same amount of diluted Trolox solution in PBS. The graphs ΔE60 versus concentration for leontopodic acid and Trolox are reported in Figure 6. Data are well fitted by straight lines through the origin. Slopes of the straight lines are different, so the calculation of the TEAC will depend on the concentration of the sample. The obtained values of TEAC are reported in Table 4. Variability in the TEAC values calculated at different concentrations was noted. Therefore, it is convenient to calculate a mean value of TEAC, $(TEAC)_m$, in a range of concentration of the sample. The greater variability in the BR measurements compared to that of the TEAC measurements is probably due to the higher sensitivity of inhibition time to concentration ratios rather than absorbance to concentration ratios. In both the TEAC and BR methods, the quoted standard deviations of the mean values are not in relation with the inaccuracy of

Table 4. Measured ΔE60 in the $ABTS^{\cdot+}$ reaction and calculated TEAC values TEAC=[trolox]/[leontopodic acid]

Leontopodic acid (mM)	Leontopodic acid (ΔE60 exptl.)	Trolox (mM calc. from its s.l.)	TEAC (mM)	$(TEAC)_m+\sigma$
0.0690	0.026	0.0964	1.397	1.53+0.11
0.0862	0.037	0.1371	1.591	
0.1725	0.067	0.2484	1.440	
0.2587	0.114	0.4227	1.634	
0.3450	0.150	0.5562	1.612	

Table 5. Comparison of TEAC values of different natural antioxidants

Compound	TEAC values
Rosmarinic acid	2.79[a]
Quercetin	2.77[b]; 2.76[a]
β-Carotene	2.47[b]
Cyaniding	2.30[b]
Ferulic acid	2.07[c]; 1.69[b]
Malvidin	1.76[b]
Caffeic acid	1.66[c]; 0.99[b]
Leontopodic acid	1.53±0.11
Homovanillic acid	1.34[c]
Gluthatione	1.13[b]
Kaempferol	1.02[b]
α-Tocopherol	0.89[b]; 0.96[a]

[a] Koleva et al.[21]
[b] Re et al.[17]
[c] Cervellati et al.[11]

the measurements, but with the variability of the values obtained at different concentrations.

In Table 5 a comparison of different TEACs for different natural antioxidants is given. For leontopodic acid a TEAC of 1.53 was determined thus positioning this compound in the range of caffeic acid, which is presented three times as a subunit in the Edelweiss molecule. However, published TEAC values for secondary plant metabolites show a wide range of variability, depending on the different test conditions (concentration of tested compounds, solvent system, reaction time, etc.).[18] Additionally, the moderate TEAC of leontopodic acid (1.53) when compared to relative high antioxidative activities of other natural constituents might be related to their possibility of intermediate formation with $ABTS^{\cdot+}$ scavenging properties.[19]

2.3. Structure–activity relations

A theoretical method to calculate the bond dissociation enthalpies (BDE), ΔH_D, for molecules belonging to the class of phenolic antioxidants, and to correlate them with their free radical scavenging activities, has been reported by Wright et al.[20] They also found that it is not the number of phenolic groups, but their relative position in the molecule that determines the antioxidant activity of the compound. The H_D value for the OH group of the phenol was calculated to be 87 kcal mol^{-1}. All molecules, in which the HD value of the active OH group is less than that in the phenol, are more active. In general, the value of $\Delta H_D = H_D(comp) - H_D(phenol)$ is given. Therefore, the number of active sites must be taken into account in comparing the calculated antioxidant power of a series of compounds.

Wright et al.[20] proposed empirical additivity rules that take into account the electronic, H-bonding, conjugation, and the steric effects of subunits in the phenol parent molecule to evaluate antioxidant power and structure/activity relationship. This empirical calculation was made for phenylpropanoid glycosides isolated from *W. carinthiaca*.[22] We believe that in the case of leontopodic acid there is not the need to make calculations because the phenolic portions and the –C═C– attached to the phenols and to the main chain of the molecule are similar to that of piceatannol (Fig. 7). For piceatannol a ΔH_D of -15.6 kcal mol^{-1} was calculated.[13] The active OH groups underlined in Figure 7, are in *para* position with respect to the main chain. The OH groups in *ortho* position stabilize the compound radical formed by reaction of the compound with $HOO^{\cdot}$ radicals. For leontopodic acid a ΔH_D of -15 kcal mol^{-1} can be assumed, which is comparable to the value found for the three phenylpropanoid glycosides of *W. carinthiaca* (-16.2 kcal mol^{-1}).[22] For these compounds $(r.a.c.)_m$ values of 2.05 to 2.40 were found,[22] respectively. Leontopodic acid has three active sites while phenylpropanoid glycosides have only two. Therefore, each molecule of leontopodic acid can react simultaneously with three free radicals.

2.4. Damaged DNA detection (3D) assay

The different results obtained in the chemical assays (BR and TEAC), as shown in Tables 3 and 5, prompted us to investigate the antioxidative properties of leontopodic acid with an additional biological test system. The chosen assay was the Damaged DNA Detection assay (3D test). It evaluates the ability of an antioxidant to protect DNA which is one of the most important biological targets from ROS (generated by Fe^{2+} and H_2O_2). The 3D test draws near the frequently used COMET test,[23] but has the great advantage that the assay can be automated for a better reproducibility and in consequence be used for biological screening. Results of the 3D assay show a typical sigmoid concentration/activity curve (Fig. 8) and allow determination of IC_{50} values with corresponding confidence limits by regular statistic methods. The resulting IC_{50} value expresses the concentration of an antioxidant which is necessary to inhibit

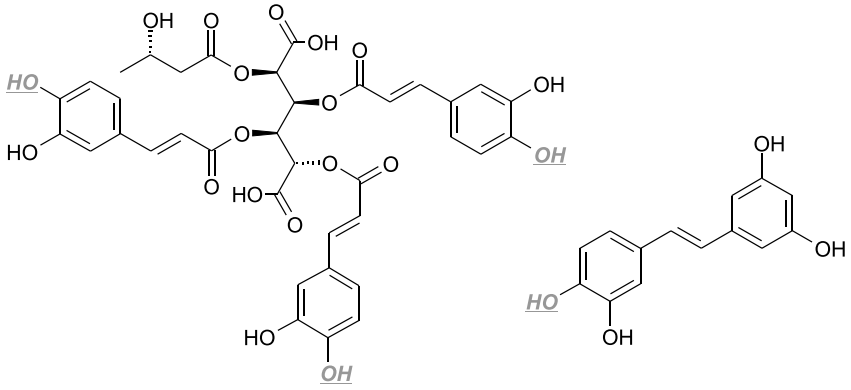

Figure 7. Structure of leontopodic acid in comparison to piceatannol. Active sites involved in antioxidative activity are shown underlined.

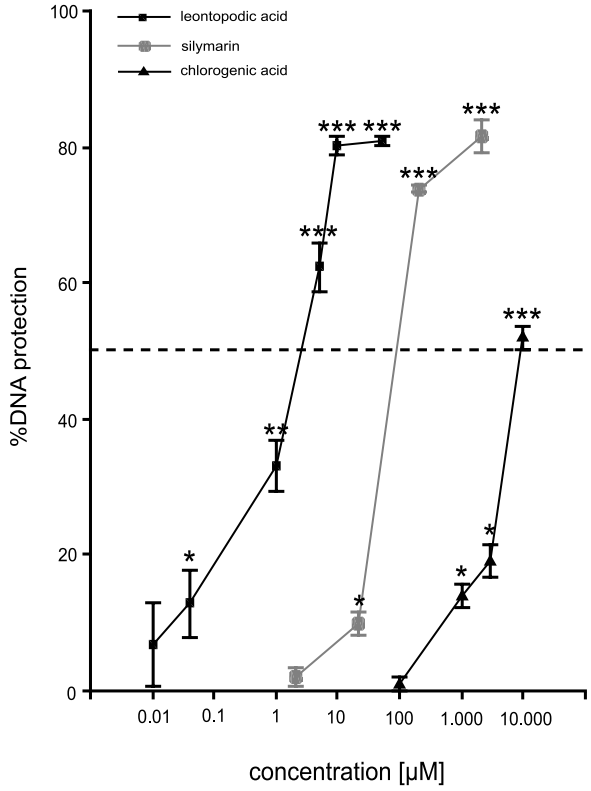

Figure 8. Obtained results from 3D test of leontopodic acid, silymarin and chlorogenic acid (concentration [µM]/%DNA protection: mean ($n=3$) ± SD; ***$p<0.001$, **$p<0.01$, *$p<0.05$, at the analysis of variance, as compared with control).

50% of a defined oxidative DNA damage or the concentration of an antioxidant which is necessary to protect 50% of DNA against a defined oxidative damage. In addition to leontopodic acid, the DNA protecting properties of silymarin (used as positive control) and chlorogenic acid (structural elements similar to those constituted leontopodic acid) were evaluated. The results of the 3D assay showed unexpected high differences in the obtained IC_{50} values of the tested compounds. The found IC_{50} of 1.89 µM (CI_{95} 1.26–2.80 µM) of leontopodic acid in relation to 149.60 µM (CI_{95} 77.20–288.82 µM) for silymarin and IC_{50} 10714.21 µM (CI_{95} 8510.94–14353.80 µM) for chlorogenic acid (Fig. 8) proved the outstanding antioxidative potential of leontopodic acid.

3. Conclusion

Leontopodic acid is a novel full substituted hexaric acid derivative, which turned out to be one of the major constituents of the flowering aerial parts of *Leontopodium alpinum*. The structure of this rather unusual compound was established by means of mass spectrometry, NMR spectroscopy and methanolysis into the methyl esters of caffeic and 3-hydroxybutyric acid and the sodium salt of D-glucaric acid. As expected this compound exhibited pronounced antioxidant effects in the Briggs-Rauscher and TEAC assay. In the TEAC assay the antioxidant activity of leontopodic acid was comparable with that of caffeic acid. In contrast in the Briggs-Rauscher model leontopodic acid exhibited much higher antioxidative effects, comparable to that of rosmarinic acid. The degree of antioxidant effects of natural compounds depends strongly on the chosen in vitro assay as confirmed by different authors.[11,18,24] Especially, the TEAC assay may not reflect the antioxidant effect of some measured compounds, since further products formed during the reaction with $ABTS^{\cdot+}$ may remarkably contribute to the overall TEAC value.[19] Results of the DNA protecting properties confirmed the outcome of the BR assay and allowed to verify leontopodic acid as a potent natural antioxidant.

4. Experimental

4.1. General

All reagents used were of puriss. or analytical grade and were purchased from Sigma Aldrich (Sigma-Aldrich, Vienna, Austria) if not otherwise specified. HPLC solvents were of gradient grade. Water was produced by reverse osmosis followed by distillation. Puriss. grade solvents were distilled before use. HPLC: HP 1090 system (Agilent, Waldbronn, Germany) equipped with auto sampler, DAD and column thermostat; stationary phase: Waters (Waters, Milford, MA, USA) X-Terra column RP 3.5 µm (4.6 mm×150 mm), guard column: LiChroCART 4-4, with LiChrospher 100 RP 18 (5 µm) material from Merck (VWR Darmstadt, Germany); temp.: 45 °C; mobile phases: water with 0.1% TFA (A), acetonitrile with 25% methanol and 0.1% TFA (B); flow rate: 1.00 ml/min, injected sample volume 10 µl; detection: 350 and 280 nm; gradient: start: A 75%; 20 min: A 40%; 25 min: A 2%; 30 min: stop; post-time: 10 min. TLC: silica gel 60 F_{254} plates (Merck, No. 5554); mobile phase: ethyl acetate/acetone/formic acid (8/1/1; v/v/v); detection: natural product reagent. Mp: Kofler hot-stage; uncorrected. Optical rotation: Perkin-Elmer 341 polarimeter. FT-IR-spectra: ZnSe disc (2 mm thickness) Bruker IFS 25 FTIR-spectrometer, transmission mode within 4000 to 600 cm−1: values in cm^{-1}. NMR: 2D and 1D measured at a Bruker AM-300 at 300 MHz (^1H) and 75 MHz (^{13}C); chemical shifts δ in ppm, coupling constants J in Hz; $SiMe_4$ as internal standard. MS-parameters: ESI-MS (neg. mode): Finnigan MAT SSQ 7000 (Finnigan MAT, San Jose, CA, USA) equipped with a Digital DEC 3000 data station (Digital Equipment Corporation, Maynard, MA, USA); sample introduction by syringe pump (flow 20 µl/min); capillary temperature: 200 °C; negative mode: spray voltage −4.7 kV; CID (collision induced dissociation) 90 V; nebulizer 40 psi. FAB-HR-MS (neg. mode): Finnigan MAT SSQ 7000 (Finnigan MAT, San Jose, CA, USA); Cs-Gun: 20 kV, 4 µA, matrix: m-Nitrobenzylalcohol; R=6000.

4.2. Extract preparation and isolation of the compound

Dried aerial parts of *L. alpinum* were obtained from cultured sources as a gift from Alpaflor Ltd/Pentapharm, Basel, Switzerland. A voucher specimen (CH 4002) is deposited at the herbarium of the Institut für Pharmazie, Abteilung Pharmakognosie, Leopold-Franzens-Universität Innsbruck. The grounded flowering aerial parts (2.03 kg) were exhaustively macerated with dichloromethane followed by methanol (12.5 l DCM; 12.0 l MeOH, at rt). Extracts were

evaporated to dryness yielding 60.5 g of the dichloromethane and 160.5 g of the methanol extract. Approximately 75.2 g of the semisolid MeOH-extract was suspended in 500 ml of distilled water, and distributed with 1.5 l (in six equal steps) of petrol ether, 900 ml ethyl acetate (in three equal steps) followed by 1.7 l of *n*-butanol (in six equal steps). Each of the combined organic layers was washed two times with 50 ml distilled water. The resulting water fraction was added to the starting water fraction. Each of the obtained fractions was evaporated under reduced pressure to dryness. The desired analyte was found in the residual water fraction (40.65 g). Further separation was done by VLC on a bed (∅ 10 cm; *h*: 6 cm) of 90.0 g LiChroprep® RP-18 material (40–63 μm; Merck, Darmstadt, Germany). The stationary phase was preconditioned with 200 ml of methanol followed by 200 ml of acetonitrile and 500 ml of distilled water, the water fraction (40.65 g) was suspended in 50 ml distilled water and applied at the top. The sample was eluted with 250 ml water, 250 ml 10% (v/v) acetonitrile in water, 250 ml 15% (v/v) acetonitrile in water, 250 ml 20% (v/v) acetonitrile in water, 250 ml 25% (v/v) acetonitrile in water, 500 ml 30% (v/v) acetonitrile in water and finally with 500 ml pure acetonitrile. Each gradient step was collected separately. The compound was detected in different purity grades in the fractions eluted with 15, 20 and 25% acetonitrile. Furthermore, the 20% acetonitrile fraction (1.79 g) was fractionated by Sephadex® LH-20 (Pharmacia Biotech, Sweden) column chromatography using MeOH as solvent that yielded 70.0 mg of a light yellow amorphous powder.

4.3. Methanolysis of the isolated compound

The isolated compound (25.0 mg) was dissolved in 10.0 ml water free methanol (Merck, Darmstadt, Germany; gradient grade, dried with Na_2SO_4 Merck, Darmstadt, Germany) followed by the addition of 20.7 mg sodium methoxide (Fluka Chemie, Switzerland). The mixture was heated at 50° for 7 h. The reaction was controlled by HPLC every hour until the starting product (retention time: 7.9 min) was no longer detectable and the observed intermediates and the caffeic acid methyl ester peak (retention time: 6.1 min) equilibrated (Figure 2). After 7 h the reaction mixture was evaporated to dryness, suspended in diethyl ether and filtered (100 ml solvent). The obtained residue was fractionated with DCM, acetone, EtOAc, $EtOH_{abs.}$, MeOH and water (each 100 ml). The obtained diethyl ether fraction was dried yielding 0.64 mg of a colorless liquid (17.0% of theoretical yield) with a strong smell like butyric acid. Optical rotation: $[\alpha]_D^{20} = +12.50$ ($CHCl_3$; $c = 0.064$). ESI-MS (neg. mode): $m/z = 203$ (4); 177 (100); 162 (24); 145 (73); 117 (57); 103 (2). The obtained water fraction was dried yielding 8.14 mg of a light brown solid (100.2% of theoretical yield) which was resolved in D_2O and submitted to NMR measurements. Optical rotation: $[\alpha]_D^{20} = +4.39$ (H_2O; $c = 0.057$).

4.4. Spectroscopic and physical data

Light yellow amorphous solid (70.0 mg); $C_{37}H_{34}O_{19}$; mp: under decomposition 165–168 °C; LC-online UV: $\lambda_{max} = 329$, 305, 245, 219 nm; FT-IR: ν_{max} cm^{-1}: 3383 (–OH),1714, 1604, 1518, 1446, 1358, 1284, 1153, 1116, 979, 851, 814; optical rotation: $[\alpha]_D^{20} = -257.59$ (MeOH; $c = 0.4232$), $[\alpha]_D^{20} = -138.88$ (H_2O; $c = 0.1080$); FAB-HR-MS (neg. modus): m/z 781.1634 $[M-H]^-$ (calculated for C_{37} $H_{33}O_{19}$: 781.1611); ESI-MS: $m/z = 781$ (100) $[M-H]^-$, fragments: $m/z = 695$ (6) $[(M-H) - C_4H_6O_2]^-$ (−hydroxybutyric acid), $m/z = 619$ (22) $[(M-H)-C_9H_6O_3]^-$ (−1× caffeoyl), $m/z = 533$ (3) $[(M-H)-C_4H_6O_2-1\times C_9H_6O_3]^-$ (−hydroxybutyric acid unit −2× caffeoyl), $m/z = 457$ (36) $[(M-H)-2\times C_9H_6O_3]^-$ (−2×caffeoyl), $m/z = 371$ (5) $[(M-H)-C_4H_6O_2-2\times C_9H_6O_3]^-$ (−hydroxybutyric acid unit−2×caffeoyl), $m/z = 295$ (43) $[(M-H)-3\times C_9H_6O_3]^-$ (−3×caffeoyl), $m/z = 209$ (6) $[(M-H)-3\times C_9H_6O_3-C_4H_7O_2]^-$ (−3× caffeoyl−hydroxybutyric acid unit). ^1H and ^{13}C NMR data: see Table 1.

4.5. Antioxidant activity assays

4.5.1. Briggs-Rauscher oscillating reaction method. BR mixtures were prepared by mixing the appropriate amounts of stock solutions from reagents using pipettes or burettes in a 100 ml beaker to a total volume of 30 ml. The order of addition was malonic acid, $MnSO_4$, $HClO_4$, $NaIO_3$ and H_2O_2. Oscillations started after the addition of H_2O_2. The initial composition of the BR mixture was: [malonic acid] = 0.05 M, $[Mn^{2+}] = 0.00667$ M, $[HClO_4] = 0.0226$ M, $[IO_3^-] = 0.0667$ M, $[H_2O_2] = 1.20$ M. An aqueous solution (1.0 ml) of sample was then added to the active, well stirred, thermostated (25.0±0.1 °C)(oscillating BR mixture after the third oscillation. The inhibition times were then measured in duplicate for different concentrations of leontopodic acid and the standard (resorcinol). The antioxidant activity relative to this standard was then calculated as the ratio:

$$\text{r.a.c.} = [\text{std}]/[\text{smp}]$$

where r.a.c. is the relative activity with respect to concentrations, whereas, [std] and [smp] are the concentrations of the standard and the sample that give the same inhibition time. The BR reaction method was successfully tested on several white wines,[25] fruit and vegetable extracts,[26] some natural polyphenolic compounds,[15] extracts of *Cynara scolymus*,[27] and compounds isolated from *Wulfenia carinthiaca*.[22]

4.5.2. TEAC (Trolox Equivalent Antioxidant Capacity) assay. Measurements were performed in triplicate at four different concentrations of trolox. The absorbance measurements (734 nm) were performed at exactly 1 min after the mixing of the reactants. A graph ΔE60 [Abs(blank)−$Abs(trolox)_{av}$] versus conc(trolox) in mMol was then constructed. In a similar way a graph was constructed using leontopodic acid instead of trolox. All solutions and the cuvette compartment were thermostated at 30.0 °C (±0.1 °C). The antioxidant activity relative to trolox (TEAC) was calculated as the ratio:

$$\text{TEAC} = [\text{trolox}]/[\text{smp}]$$

where [trolox] and [smp] are the concentrations of the standard and the sample that give the same ΔE60.

4.5.3. Damaged DNA detection (3D) assay. The 3D assay

was performed using a commercial available kit (SFRI, IDN 003, F-33127 Saint-Jean d'Illac). The microplate screening system used an immobilized plasmidic DNA, which is treated with the tested substance (dissolved in $EtOH_{abs}/H_2O$; 1/1) followed by a treatment with a mixture of Fe^{2+} and H_2O_2 (Fenton reaction) to generate hydroxide radicals causing the DNA damage. For the quantification of the induced damage or protection, specific repair protein complexes as well as labeled nucleotides (Biotin-21-dUTP) were added. The incorporated biotinylated nucleotides of the resulting newly synthesized DNA were detected with an avidin-peroxidase conjugate and chemiluminescent substrate of peroxidase, which measured the emitted light using a luminometer. The repair signal intensity of the emitted light is proportional to the concentration of DNA lesions and expressed in percent protection in relation to non-protected DNA (negative control) and inhibition of the repair enzyme complex. Each experiment was done in triplicate. Mean values and the standard deviations were determined (Microsoft, Excel). Data were analyzed by one-way analysis of variance followed by Dunnett's test for multiple comparisons of unpaired data. Probability levels lower than 0.05 were considered as statistically significant. IC_{50} values with confidence limits (CI_{95}) were calculated by probit-log analysis using SPSS 11.5 for MS Windows. Additional tested compounds silymarin and chlorogenic acid were obtained from Indena and Sigma Chemical, respectively.

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Synthesis of chlorinated 2-(aminomethyl)- and 2-(alkoxymethyl)pyrroles

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Abstract—The synthesis of chlorinated 2-(hydroxymethyl)-, 2-(alkoxymethyl)- and 2-(aminomethyl)pyrroles via aromatization of 2-aryl-3,3-dichloro-5-(bromomethyl)pyrrolines and via reduction of 2-formyl- and 2-cyanopyrroles is described. The former methodology also provided new 2-[(alkyl- or phenylamino)methyl]pyrroles and a 2-(phosphonomethyl)pyrrole. Halogenated and methylene-spaced functionalized pyrroles are of particular interest for their pronounced physiological activities.

1. Introduction

Entries towards regiospecifically halogenated pyrroles, especially 3-halopyrroles, are not widespread in the current literature because of the difficult regiocontrol and problems of overhalogenation in halogenation reactions of pyrroles.[1–9] Physiologically active 3-halogenated pyrroles have been isolated from a diversity of micro-organisms and have been used as lead structures to develop 3-halogenated pyrroles with current use in agrochemistry and medicine, for example, the antifungal pyrrolnitrin.[10–14] Another structural feature which is often associated with pronounced physiological activities of pyrroles, is the presence of hydroxymethyl or aminomethyl functionalities at the 2-position. 2-(Aminomethyl)- and 2-(hydroxymethyl)pyrroles are versatile intermediates in the synthesis of natural products, especially porphyrins and related pyrrole oligomers.[15] In addition to their use as intermediates in porphyrin syntheses, methylene-spaced substituted pyrroles also display a variety of physiologically interesting activities.[16–22] Recently, 2-(hydroxymethyl)pyrroles, for example, **1**, were discovered as a new class of inhibitors of α-chymotrypsin, a member of serine protease enzymes (Fig. 1).[16] Viminol **2** is a central analgesic and can be used for the treatment of drug dependency.[17]

Substituted 2-(aminomethyl)pyrroles have attracted renewed interest due to their specific binding properties to dopamine receptors. Pyrrole **3** (DU 122290) and **4** bind specifically at the dopamine D3 receptor and can be used for antipsychotic therapy,[18] whereas pyrrole **5** (FAUC 356) is a selective dopamine D4 receptor partial agonist and might be of interest in the treatment of ADHD (attention deficit hyperactive disorder).[19] 2-(Aminomethyl)pyrrole derivatives were patented as analgesics[20] and used as building blocks for pyrrolo[2,1c][1,4]benzodiazepines, compounds with pronounced antitumor activities.[21] Other 2-(aminomethyl)pyrroles are mono-amine oxidase inhibitors and show antidepressant activities.[22]

2. Results and discussion

In order to establish a short and convenient method to synthesize 2-(hydroxymethyl)-, 2-(alkoxymethyl)- and 2-(aminomethyl)pyrroles bearing a halogen at the 4-position, efforts were performed to synthesize these new pyrroles via a base-induced aromatization of suitable 2,2-dichloro-1-pyrrolines. 1-Pyrrolines are known to serve as good precursors for the synthesis of halogenated pyrroles by dihalogenation and subsequent dehydrohalogenation.[9] In this respect, the known cyclic imines **7a**,**b**[23] were prepared according to literature procedures[23] from benzonitriles **6**. The scope of this synthetic pathway was extended towards the synthesis of the new 5-(chloromethyl)-1-pyrroline **7c** using NCS as an electrophile (Scheme 1). Subsequently, the synthesized 5-(halomethyl)-1-pyrrolines **7** were treated with halogenating agents to obtain 3,3-dihalo-1-pyrrolines **8**.

Reactions of pyrroline **7a** with NBS resulted in tarry reaction mixtures, while reactions with NCS in refluxing CCl_4 or $CHCl_3/CH_3CN$ (4:1) for 15 h yielded 3,3-dichloro-

Keywords: Pyrroles; Trichloroisocyanuric acid; Pyrrolines.
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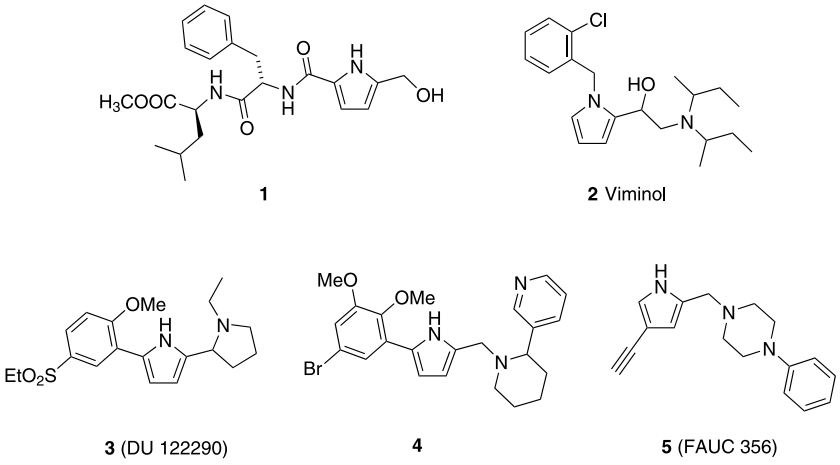
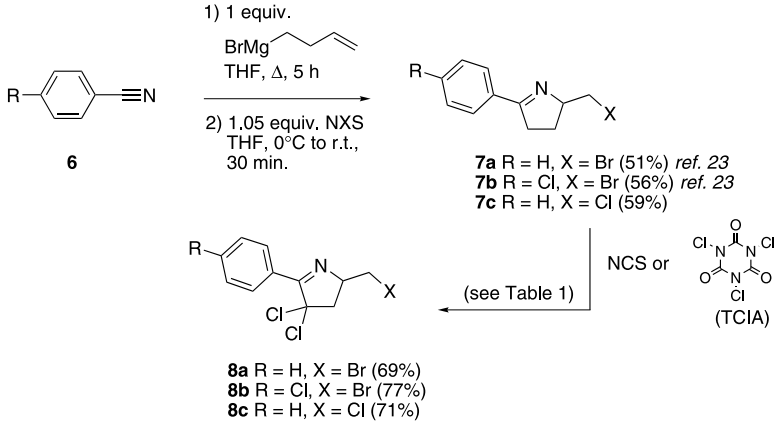


Figure 1.



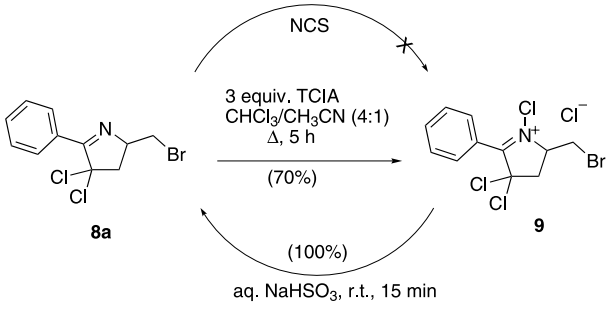
Scheme 1.

Table 1. Chlorination of pyrroline **7a** using NCS or TCIA

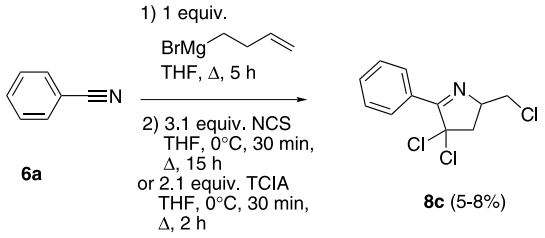
Reaction conditions	Ratio **8a/9**[a]	Isolated yield
2.1 equiv NCS, $CHCl_3/CH_3CN$ (4:1), Δ, 15 h	100:0	**8a** (63%)
1 equiv TCIA, $CHCl_3/CH_3CN$ (4:1), Δ, 5 h	91:9	**8a** (51%) **9** (4%)
(1) 1 equiv TCIA, $CHCl_3/CH_3CN$ (4:1), Δ, 5 h (2) aq $NaHSO_3$, rt, 15 min	100:0	**8a** (69%)
3 equiv TCIA, $CHCl_3/CH_3CN$ (4:1), Δ, 5 h	0:100	**9** (70%)

[a] Ratios calculated from ^1H NMR spectra.

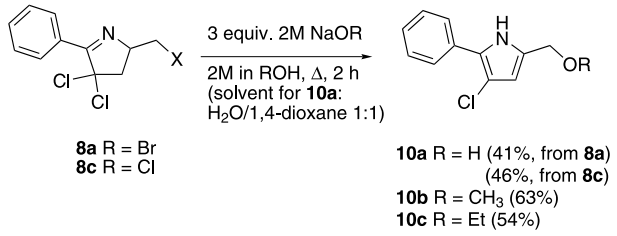
1-pyrroline **8a**. However, the reaction mixture contained some decomposition material (ca. 5%) due to the inherent instability of the halogenated pyrrolines **8**. A better result was obtained when the reaction was performed using trichloroisocyanuric acid (TCIA) as the halogenating agent (Table 1). The fact that this reagent is cheaper as compared to NCS and the fact that less molar quantities of the reagent are necessary due to the presence of three chloro atoms per molecule, should re-establish its use in organic synthesis. Treatment of pyrroline **7a** with 1 equiv of TCIA resulted in a clean reaction mixture consisting of almost exclusively dichlorinated pyrroline **8a**. In the reaction mixture a second compound was formed and could be separated from the major compound **8a** by flash chromatography. This



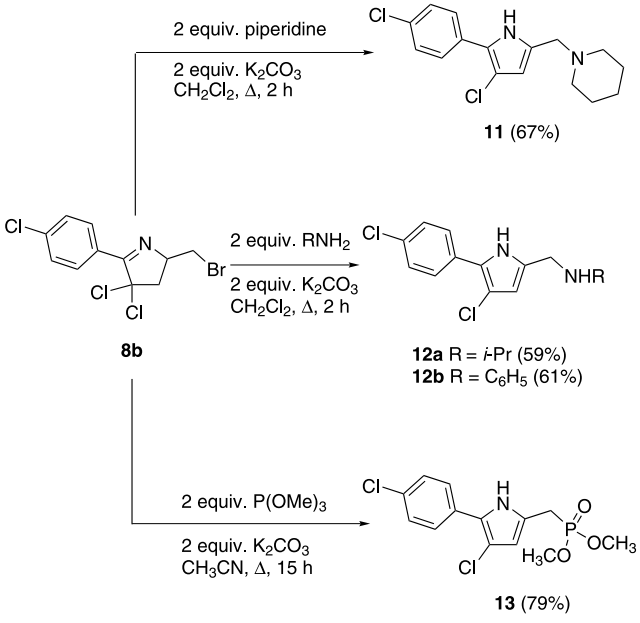
Scheme 2.



Scheme 3.



Scheme 4.



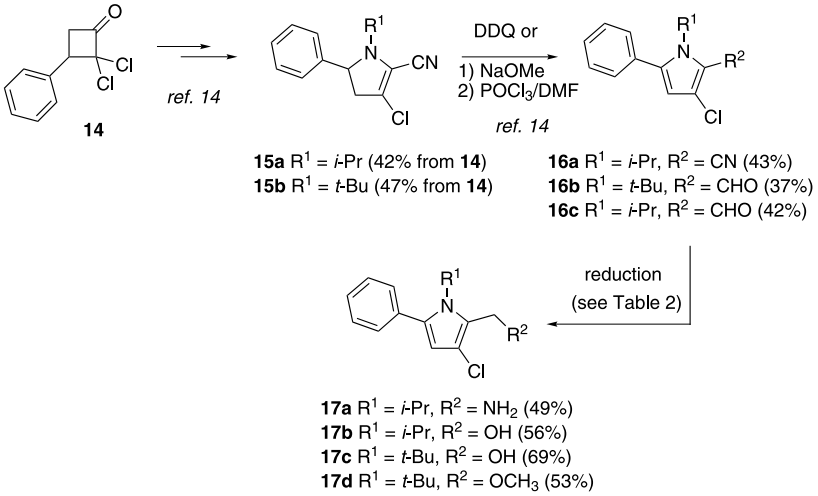
Scheme 5.

compound was characterized as the *N*-chlorinated analogue **9** (Scheme 2).

A complete conversion of dichloropyrroline **8a** towards the overchlorinated product **9** could be established with an excess of TCIA in a refluxing mixture of $CHCl_3/CH_3CN$ (ratio 4:1) for 5 h (Scheme 2). This result probably arises due to the formation of small amounts of chlorine in the reaction mixture. An analogous reaction with NCS in CCl_4 or $CHCl_3/CH_3CN$ (9:1) did not yield any **9**, even after reflux overnight. Treatment of *N*-chloroiminium compound **9** with a saturated aqueous $NaHSO_3$-solution at room temperature for 15 min yielded dichlorinated pyrroline **8a** quantitatively. Attempts to synthesize 3,3-dichloro-5-chloromethyl-2-phenyl-1-pyrroline **8c** in one pot from benzonitrile by an initial reaction of benzonitrile with 3-butenylmagnesium bromide followed by reaction with 3.1 equiv of NCS or 2.1 equiv of TCIA in THF resulted in complex reaction mixtures containing only traces (<8%) of the desired pyrroline **8c** (Scheme 3).

The obtained 2-aryl-3,3-dichloro-5-(halomethyl)pyrrolines **8** were treated with triethylamine to induce a dehydrochlorination towards 2-(halomethyl)pyrroles. However, despite the various attempts, no clean reaction could be accomplished. In contrast, a one-pot procedure using sodium hydroxide in water/1,4-dioxane (ratio 1:1), 2 M sodium methoxide in methanol or 2 M sodium ethoxide in ethanol resulted in a simultaneous nucleophilic substitution and dehydrohalogenation yielding the corresponding new 2-(alkoxymethyl)pyrroles **10** in good yield (Scheme 4). When using chloromethylpyrroline **8c** as a starting product, a virtually equal yield of pyrrole **10a** was obtained.

Analogous reactions with aliphatic, aromatic or heterocyclic amines in CH_2Cl_2 in the presence of potassium carbonate also yielded new 2-(aminomethyl)pyrroles **11** and **12** in good yield (Scheme 5). In addition, the reaction of pyrroline **8b** with trimethyl phosphite in acetonitrile to accomplish a synthesis of dimethyl (4-chloro-5-(4-chlorophenyl)pyrrol-2-yl)methylphosphonate **13** via an Arbuzov-reaction proceeded in good yield (Scheme 5).



Scheme 6.

Table 2. Reduction of pyrroles **16**

Entry	Reaction conditions	Product (yield)
16a	1 equiv $LiAlH_4$, THF, Δ, 4 h	**17a** (49%)
16b	1 equiv $NaBH_4$, THF, rt, 20 h	**17b** (56%)
16c	1 equiv $NaBH_4$, THF, rt, 20 h	**17c** (69%)
16b	1 equiv $NaBH_4$, MeOH, rt, 2 h	**17d** (53%)

In addition to the synthesis of pyrroles bearing a chloro atom at the 3-position as described above, another methodology to access 4-chlorinated 2-(aminomethyl)-, 2-(hydroxymethyl)- or 2-(alkoxymethyl)pyrroles was developed via the reduction of chlorinated 2-cyano- and 2-formylpyrroles **16** (Scheme 6). Recently, we disclosed a new synthetic pathway towards 1-alkyl-5-aryl-3-chloro-2-cyano-2-pyrrolines **15** from 3-aryl-2,2-dichlorocyclobutanones **14**.[14] These compounds were treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or with sodium methoxide followed by a Vilsmeier formylation to yield pyrroles **16a** and **16b**,**c**, respectively (Scheme 6).[14] In the present paper, these pyrroles **16** were reduced with sodium borohydride or lithium aluminum hydride to produce new 2-(hydroxymethyl)- and 2-(aminomethyl)-pyrrole derivatives **17** bearing a chloro atom at the 4-position (Table 2). 2-(Methoxymethyl)pyrrole **17d** was obtained directly by reducing pyrrole **16b** with sodium borohydride in methanol instead of THF, resulting in a substitution of the hydroxyl function by methanol.

In conclusion, it can be stated that a short and generally applicable synthesis is developed to access chlorinated 2-(hydroxymethyl)-, 2-(alkoxymethyl)- and 2-(aminomethyl)pyrroles, a class of compounds with currently renewed interest as physiologically active heterocycles.

3. Experimental

3.1. General methods

^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Jeol Eclipse FT 300 NMR spectrometer, respectively. Peak assignments were performed with the aid of the DEPT-technique, 2D-COSY and HETCOR spectra. IR assignments were obtained from a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series VL mass spectrometer (ES) or a HP 5973 MSD spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 Elemental Analyser. Melting points were measured with a Büchi B-450 apparatus. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm).

3.2. Synthesis of 5-(chloromethyl)-2-phenyl-1-pyrrolines 7

Compounds **7a** and **7b** were synthesized according to literature procedures in 69 and 72% yield, respectively (lit. yields: **7a**: 51%, **7b**: 56%).[23] Compound **7c** was synthesized using the following adapted procedure. To 5.0 mmol of 3-butenylmagnesium bromide in 5 mL of THF was added 0.52 g (5.0 mmol) of benzonitrile in 5 mL of dry THF. After reflux for 5 h, the reaction mixture was cooled to 0 °C and was reacted with 0.73 g (5.5 mmol, 1.1 equiv) of NCS. The mixture was stirred at 0 °C for 30 min and subsequently poured in 25 mL of water. Extraction with 3×20 mL of Et_2O yielded 5-(chloromethyl)-2-phenyl-1-pyrroline **7c** after evaporation of the solvents.

3.2.1. 5-(Chloromethyl)-2-phenyl-1-pyrroline 7c. Flash chromatography (EtOAc/hexane 9:1, R_f=0.16). Yield 59%. ^{1}H NMR ($CDCl_3$): δ 1.86–2.04 (1H, m, CH_aH_b), 2.21–2.33 (1H, m, CH$_a$H$_b$), 2.89–3.16 (2H, m, CH_2C=N), 3.63 (1H, dd, J=10.0, 6.3 Hz, ClCH_aH_b), 3.79 (1H, dd, J=10.0, 4.0 Hz, ClCH$_a$H$_b$), 4.57–4.61 (1H, m, NCH), 7.38–4.47 (3H, m, 3×CH$_{ar}$), 7.83–7.86 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 27.8 (CH_2), 35.7 (CH_2), 38.5 (CH_2), 73.2 (NCH), 2×127.9 (2×CH$_{ar}$), 2×128.6 (2×CH$_{ar}$), 130.9 (CH$_{ar}$), 134.2 (C$_{quat}$), 174.6 (C=N). IR (NaCl): ν_{max} 1615, 1574 cm^{-1}. MS (ES+) m/z (%): 193/95 (M+H$^+$, 100). Anal. Calcd for $C_{11}H_{12}NCl$: C, 68.22; H, 6.25; N, 7.23. Found: C, 68.46; H, 6.41; N, 7.01.

3.3. Dichlorination of pyrrolines 7

To a solution of 1.00 g (4.20 mmol) of 5-(bromomethyl)-2-phenyl-1-pyrroline **7a**[23] in 25 mL of $CHCl_3$/CH_3CN (4:1) was added 0.97 g (4.20 mmol, 1.0 equiv) of trichloroisocyanuric acid. The mixture was refluxed for 5 h and was poured in 25 mL water after cooling to room temperature. The dichlorinated pyrroline **8a** was extracted from the mixture with chloroform (3×20 mL). After drying ($MgSO_4$) and evaporation of the solvent, a mixture of dichlorinated product **8a** and *N*-chlorinated pyrroline **9** (ratio 9:1) was obtained. The latter was converted to the desired 5-(bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline **8a** by simple washing of the reaction mixture (dissolved in 25 mL of dichloromethane) with a saturated aqueous solution of $NaHSO_3$ during 15 min. Standard workup yielded almost pure product **8a**. Flash chromatography was used to remove the last traces of impurities.

3.3.1. 5-(Bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline 8a. Flash chromatography (hexane/EtOAc 95:5, R_f=0.19); yield 69%. ^{1}H NMR ($CDCl_3$): δ 2.90 (1H, dd, J=14.5, 7.0 Hz, CH_aH_b), 3.31 (1H, dd, J=14.5, 6.1 Hz, CH$_a$H$_b$), 3.74 (1H, dd, J=10.5, 6.9 Hz, BrCH_aH_b), 3.80 (1H, dd, J=10.5, 4.1 Hz, BrCH$_a$H$_b$), 4.57–4.65 (1H, m, NCH), 7.44–7.57 (3H, m, 3×CH$_{ar}$), 8.17–8.21 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 34.9 (CH_2), 53.2 (CH_2Br), 68.5 (NCH), 86.8 (CCl_2), 2×128.4 (2×CH$_{ar}$), 129.2 (2×CH$_{ar}$), 129.3 (C$_{quat}$), 131.6 (CH$_{ar}$), 170.1 (C=N). IR (NaCl): ν_{max} 1606, 1574, 1297 cm^{-1}. MS m/z (%): 305/7/9/11 (M$^+$, 13), 189 (18), 154 (21), 130 (100), 104 (45). Anal. Calcd for $C_{11}H_{10}NBrCl_2$: C, 43.03; H, 3.28; N, 4.56. Found: C, 42.82; H, 3.40; N, 4.41.

3.3.2. 5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline 8b. Flash chromatography (hexane/EtOAc 9:1, R_f=0.20); yield 77%. ^{1}H NMR ($CDCl_3$): δ 2.88 (1H, dd, J=14.6, 7.2 Hz, CH_aH$_b$), 3.28 (1H, dd, J=14.6, 6.3 Hz, CH$_a$$H_b$), 3.69 (1H, dd, J=10.5, 6.9 Hz, BrCH_aH$_b$), 3.76 (1H, dd, J=10.5, 4.3 Hz, BrCH$_a$$H_b$), 4.57 (1H, 'dq', J=6.8, 4.3 Hz, NCH), 7.40–7.45 (2H, m, 2×CH$_{ar}$), 8.09–8.13 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 34.7 (CH_2), 53.2 (CH_2Br), 68.5 (NCH), 86.6 (CCl_2), 127.7 (C$_{quat}$), 2×128.8 (2×CH$_{ar}$), 2×130.6 (2×CH$_{ar}$), 137.9 (C$_{quat}$) 169.0 (C=N). IR (NaCl): ν_{max} 1607, 1492, 1093 cm^{-1}. MS *m/z* (%): 339/41/43/45 (M$^+$, 8), 164/66 (100), 138 (35). Anal. Calcd for $C_{11}H_9NBrCl_3$: C, 38.69; H, 2.66; N, 4.10. Found: C, 38.48; H, 2.75; N, 3.81.

3.3.3. 3,3-Dichloro-5-(chloromethyl)-2-phenyl-1-pyrroline 8c. Flash chromatography (hexane/EtOAc 9:1, R_f= 0.25); yield 71%. ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 2.87 (1H, dd, J=14.6, 7.2 Hz, CH_aH$_b$), 3.27 (1H, dd, J= 14.6, 6.3 Hz, CH$_a$$H_b$), 3.69 (1H, dd, J=10.4, 7.0 Hz, ClCH_aH$_b$), 3.77 (1H, dd, J=10.4, 4.4 Hz, ClCH$_a$$H_b$), 4.52–4.60 (1H, m, NCH), 7.40–7.54 (3H, m, 3×CH$_{ar}$), 8.14–8.18 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 34.9 (CH_2), 53.2 (CH_2Cl), 68.5 (NCH), 86.8 (CCl_2), 2×128.5 (2×CH$_{ar}$), 2×129.2 (2×CH$_{ar}$), 129.3 (C$_{quat}$), 131.6 (CH$_{ar}$) 170.1 (C=N). IR (NaCl): ν_{max} 1606, 1574, 1495, 1447 cm^{-1}. MS (ES+) *m/z* (%): 261/63/65/67 (M+H$^+$, 100). Anal. Calcd for $C_{11}H_{10}NCl_3$: C, 50.32; H, 3.84; N, 5.33. Found: C, 50.17; H, 3.98; N, 5.20.

3.3.4. 5-(Bromomethyl)-1,4,4-trichloro-2-phenyl-1-pyrrolinium 9. Flash chromatography (hexane/EtOAc 95:5, R_f=0.23); yield 70%, purity >95% (determined via ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 3.02 (1H, dd, J=16.0, 4.8 Hz, CH_aH$_b$), 3.23 (1H, dd, J=16.0, 5.5 Hz, CH$_a$$H_b$), 3.79 (1H, dd, J=11.1, 6.6 Hz, BrCH_aH$_b$), 3.99 (1H, dd, J=11.1, 5.8 Hz, BrCH$_a$$H_b$), 4.15–4.23 (1H, m, NCH), 7.46–7.52 (2H, m, 2×CH$_{ar}$), 7.54–7.64 (1H, m, CH$_{ar}$), 8.22–8.33 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 31.1 (CH_2), 45.0 (CH_2Br), 77.0 (NCH), 84.3 (CCl_2), 2×128.4 (2×CH$_{ar}$), 2×131.1 (2×CH$_{ar}$), 131.5 (C$_{quat}$), 133.9 (CH$_{ar}$), 187.7 (C=N). IR (NaCl): ν_{max} 1693, 1597, 1250 cm^{-1}. MS (ES+) *m/z* (%): 306/8/10/12 (M−Cl$_2$+H$^+$, 100).

3.4. Synthesis of 2-(hydroxymethyl)- and 2-(alkoxymethyl)pyrroles 10

5-(Bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline **8a** (1.70 g, 5.54 mmol) was dissolved in 8 mL of 1,4-dioxane and 8.31 mL (16.61 mmol, 3 equiv) of an aqueous 2 M NaOH solution was added. The resulting homogeneous mixture was refluxed for 2 h and subsequently acidified with aq 2 M HCl until neutral. Extraction was performed with dichloromethane (3×20 mL). After drying and evaporation of the solvents ($MgSO_4$), 2-(hydroxymethyl)pyrrole **10a** was obtained which could be purified by flash chromatography (short column). The synthesized 2-(hydroxymethyl)- and 2-(alkoxymethyl)pyrroles **10** were acid-sensitive and decomposed on silica gel during flash chromatography, leaving an intensely colored red material on the silica. For that reason it is of importance to perform the purificatrion step as fast as possible on a small silica column. For the synthesis of 2-(methoxymethyl)- and 2-(ethoxymethyl)pyrroles **10b**,**c**, no dioxane was used as a solvent for the reaction, but the corresponding alcohols instead.

3.4.1. 3-Chloro-5-(hydroxymethyl)-2-phenylpyrrole 10a. Flash chromatography (hexane/EtOAc 1:1, R_f=0.30); yield 41%. ^{1}H NMR ($CDCl_3$): δ 2.70 (1H, s(b), OH), 4.45 (2H, s, CH_2OH), 6.06 (1H, d, J=3.0 Hz, NC=CH), 7.20–7.36 (3H, m, 3×CH$_{ar}$), 7.53–7.57 (2H, m, 2×CH$_{ar}$), 8.95 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 57.8 (CH_2OH), 109.4 (C$_{quat}$), 109.7 (NC=*C*H), 2×126.1 (2×CH$_{ar}$), 127.2 (CH$_{ar}$), 127.5 (C$_{quat}$), 2×128.9 (2×CH$_{ar}$), 130.3 (C$_{quat}$), 131.1 (C$_{quat}$). IR (NaCl): ν_{max} 3547, 3411, 1604, 1017 cm^{-1}. MS (ES+) *m/z* (%): 190/92 (M+H$^+$–H_2O, 100). Anal. Calcd for $C_{11}H_{10}NOCl$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.89; H, 5.05; N, 6.57.

3.4.2. 3-Chloro-5-(methoxymethyl)-2-phenylpyrrole 10b. Flash chromatography (hexane/EtOAc 4:1, R_f= 0.21); yield 63%, mp 94–97 °C. ^{1}H NMR ($CDCl_3$): δ 3.32 (3H, s, OCH_3), 4.39 (2H, s, OCH_2), 6.17 (1H, d, J=3.0 Hz, NC=CH), 7.22–7.28 (1H, m, CH$_{ar}$), 7.34–7.40 (2H, m, 2×CH$_{ar}$), 7.55–7.59 (2H, m, 2×CH$_{ar}$), 8.89 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 57.5 (CH_3O), 67.0 (CH_2O), 109.3 (C$_{quat}$), 110.9 (NC=*C*H), 2×126.2 (2×CH$_{ar}$), 127.1 (CH$_{ar}$), 2×127.7 (2×C$_{quat}$), 2×128.8 (2×CH$_{ar}$), 131.3 (C$_{quat}$). IR (KBr): ν_{max} 3230, 1605, 1067 cm^{-1}. MS (ES+) *m/z* (%): 190/92 (M+H$^+$–CH_3OH, 100). Anal. Calcd for $C_{12}H_{12}NOCl$: C, 65.02; H, 5.46; N, 6.32. Found: C, 64.87; H, 5.57; N, 6.56.

3.4.3. 3-Chloro-5-(ethoxymethyl)-2-phenylpyrrole 10c. Flash chromatography (hexane/EtOAc 9:1, R_f=0.11); yield 54%. ^{1}H NMR ($CDCl_3$): δ 1.21 (3H, t, J=7.0 Hz, CH_3), 3.53 (2H, q, J=7.0 Hz, CH_2CH$_3$), 4.45 (2H, s, CH_2O), 6.15 (1H, d, J=2.8 Hz, NC=CH), 7.24–7.30 (1H, m, CH$_{ar}$), 7.37–7.43 (2H, m, 2×CH$_{ar}$), 7.59–7.63 (2H, m, 2×CH$_{ar}$). ^{13}C NMR ($CDCl_3$): δ 15.2 (CH_3), 65.2 (OCH_2), 65.6 (OCH_2), 109.4 (NC=*C*), 110.3 (NC=*C*H), 2×126.1 (2×CH$_{ar}$), 127.1 (CH$_{ar}$), 127.3 (C$_{quat}$), 128.3 (C$_{quat}$), 2× 128.8 (2×CH$_{ar}$), 131.3 (C$_{quat}$). IR (NaCl): ν_{max} 3422, 3270, 1605, 1073 cm^{-1}. MS *m/z* (%): 235/37 (M$^+$, 51), 190/92 (100), 154 (41). Anal. Calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.02; H, 6.13; N, 5.78.

3.5. Synthesis of 2-(aminomethyl)pyrroles 11, 12

5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline **8b** (0.65 g, 1.90 mmol) was dissolved in 25 mL of dichloromethane containing 0.53 g (3.81 mmol, 2 equiv) of potassium carbonate and 0.22 g (3.81 mmol, 2 equiv) of isopropylamine. After heating the heterogeneous mixture at reflux temperature for 2 h, the mixture was poured in 25 mL water and extracted with dichloromethane (3×25 mL). The extracts were dried over $MgSO_4$ and the solvent evaporated in vacuo. After a fast flash chromatography of the obtained reaction product, 2-(isopropylaminomethyl)pyrrole **12a** was obtained.

3.5.1. 3-Chloro-2-(4-chlorophenyl)-5-(isopropylaminomethyl)pyrrole 12a. Flash chromatography (hexane/EtOAc 3:1, R_f=0.3); yield 59%, mp 73–74 °C. ^{1}H NMR ($CDCl_3$): δ 1.01 (6H, d, J=6.3 Hz, CH(CH_3)$_2$), 1.33 (1H,

s(b), NH), 2.84 (1H, sept, $J=6.3$ Hz, C*H*(CH_3)$_2$), 3.73 (2H, s, NCH_2), 6.07 (1H, s, NC=CH), 7.19–7.28 (4H, m, C_6H_4), 10.40 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 2×22.8 (2×CH_3), 44.2 and 49.1 (CH_2N and CHN), 108.8 (NC=*C*H), 109.5 (C_{quat}), 125.8 (C_{quat}), 2×127.7 (2×CH_{ar}), 128.8 (2×CH_{ar}), 130.1 (C_{quat}), 130.5 (C_{quat}), 132.4 (C_{quat}). IR (KBr): ν_{max} 3435, 1632, 1518, 1091 cm^{-1}. MS (ES+) *m/z* (%): 224/26/28 ($M+H^+$–*i*PrNH, 100). Anal. Calcd for $C_{14}H_{16}N_2Cl_2$: C, 59.38; H, 5.69; N, 9.89. Found: C, 59.09; H, 5.87; N, 9.72.

3.5.2. 5-(Anilinomethyl)-3-chloro-2-(4-chlorophenyl)-pyrrole 12b. Flash chromatography (hexane/EtOAc 3:2, $R_f=0.63$); yield 61%. ^{1}H NMR ($CDCl_3$): δ 3.89 (1H, s(b), NH), 4,19 (2H, s, NCH_2), 6.10 (1H, d, $J=2.8$ Hz, NC=CH), 6.57–6.65 (2H, m, 2×CH_{ar}), 6.74–6.76 (1H, m, CH_{ar}), 7.14–7.22 (2H, m, 2×CH_{ar}), 7.28 and 7.44 (2×2H, 2×dt, $J=8.9$, 2.3 Hz, C_6H_4), 8.39 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 42.0 (NCH_2), 108.8 (NC=*C*H), 110.2 (C_{quat}), 2×113.6 (2×CH_{ar}), 118.9 (CH_{ar}), 125.3 (C_{quat}), 2×127.1 (2×CH_{ar}), 2×129.0 (2×CH_{ar}), 2×129.6 (2×CH_{ar}), 129.7 (C_{quat}), 130.0 (C_{quat}), 132.6 (C_{quat}), 147.9 (C_{quat}). IR (NaCl): ν_{max} 3419, 1603, 1504 cm^{-1}. MS (ES+) *m/z* (%): 317/19/21 ($M+H^+$, 24), 224/26/28 (M^+ − aniline, 100). Anal. Calcd for $C_{17}H_{14}N_2Cl_2$: C, 64.37; H, 4.45; N, 8.83. Found: C, 64.20; H, 4.37; N, 8.69.

3.5.3. 3-Chloro-2-(4-chlorophenyl)-5-(piperidinomethyl)pyrrole 11. Purified by washing with cold diethyl ether; yield 67%, mp 179 °C. ^{1}H NMR ($CDCl_3$): δ 1.35 (6H, m, 3×CH_2), 2.36–2.48 (4H, m, 2×NCH_2), 3.40 (2H, s, NCH_2), 6.09 (1H, d, $J=2.5$ Hz, NC=CH), 7.28 (4H, s, C_6H_4), 9.67 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 24.1 (CH_2), 2×25.5 (2×CH_2), 2×55.0 (2×NCH_2), 56.2 (NCH_2), 109.4 (C_{quat}), 110.6 (NC=*C*H), 126.0 (C_{quat}), 2×127.7 (2×CH_{ar}), 128.5 (C_{quat}), 2×128.7 (2×CH_{ar}), 130.0 (C_{quat}), 132.5 (C_{quat}). IR (KBr): ν_{max} 3436, 3091, 1586, 1516, 1471, 1339 cm^{-1}. MS (ES+) *m/z* (%): 224/26/28 (M^+ − piperidine, 14), 86 (100). Anal. Calcd for $C_{16}H_{18}N_2Cl_2$: C, 62.14; H, 5.87; N, 9.06. Found: C, 62.44; H, 5.95; N, 8.85.

3.6. Synthesis of dimethyl (4-chloro-5-(4-chlorophenyl)-pyrrol-2-yl)methylphosphonate 13

5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline **8b** (1.00 g, 2.93 mmol) was dissolved in 25 mL of acetonitrile containing 0.81 g (5.86 mmol, 2 equiv) of potassium carbonate and 0.73 g (5.86 mmol, 2 equiv) of trimethyl phosphite. After heating the heterogeneous mixture at reflux overnight (15 h), the mixture was filtered and the filtrate was evaporated under a N_2-stream in a fume hood. The obtained crystalline compound was redissolved in 25 mL of dichloromethane and washed twice with 25 mL water. After drying of the organic phase and evaporation of the solvent in vacuo, the resulting pyrrolylmethylphosphonate **13** was washed with cold diethyl ether. Residual solvent was removed by evaporation at high vacuum (0.01 mmHg).

3.6.1. Dimethyl (4-chloro-5-(4-chlorophenyl)pyrrol-2-yl)methylphosphonate 13. Purified by washing with cold diethyl ether; yield 79%, mp 141 °C. ^{1}H NMR ($CDCl_3$): δ 3.24 (2H, d, $J=20.4$ Hz, CH_2P), 3.75 (6H, d, $J=11.0$ Hz, P(OCH_3)$_2$), 6.05 (1H, 't', $J=2.9$ Hz, NC=CH), 7.19–7.22 (2H, m, 2×CH_{ar}), 7.26–7.31 (2H, m, 2×CH_{ar}), 10.19 (1H, s(b), NH). ^{13}C NMR ($CDCl_3$): δ 24.8 (d, $J=143.1$ Hz, CH_2P), 2×53.4 (d, $J=6.9$ Hz, P(OCH_3)$_2$), 109.8 (C_{quat}), 110.4 (d, $J=8.1$ Hz, NC=*C*H), 120.3 (d, $J=10.4$ Hz, *C*CH_2P), 126.0 (C_{quat}), 2×126.8 (2×CH_{ar}), 2×128.4 (2×CH_{ar}), 129.7 (C_{quat}), 131.9 (C_{quat}). ^{31}P NMR ($CDCl_3$): δ 28.13 (O=P(OCH_3)$_2$). IR (KBr): ν_{max} 3436, 1585, 1512, 1227, 1059 cm^{-1}. MS (ES+) *m/z* (%): 334/36/38 ($M+H^+$, 21), 224/26/28 ($M+H^+$–O=P(OCH_3)$_2$, 100). Anal. Calcd for $C_{13}H_{14}NO_3Cl_2P$: C, 46.73; H, 4.22; N, 4.19. Found: C, 46.93; H, 4.41; N, 3.98.

3.7. Synthesis of 2-(aminomethyl)pyrrole 17a

To a solution of 3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole **16a** (1.00 g, 4.09 mmol) in 25 mL of dry THF was added 0.16 g (4.09 mmol, 1 equiv) of $LiAlH_4$. The mixture was refluxed for 4 h and after cooling to room temperature, the reaction was stopped by adding slowly (dropwise) 5 mL of ice water. The reaction mixture was subsequently poured in 25 mL water and extracted with 3×25 mL of diethyl ether. The solvents were evaporated in vacuo after drying over $MgSO_4$. To remove minor impurities a flash chromatography over a small column was applied.

3.7.1. 2-(Aminomethyl)-3-chloro-1-isopropyl-5-phenylpyrrole 17a. Flash chromatography (hexane/EtOAc/Et_3N 48:50:2, $R_f=0.50$); yield 49%. ^{1}H NMR ($CDCl_3$): δ 1.45 (6H, d, $J=7.0$ Hz, CH(C*H*$_3$)$_2$), 3.99 (2H, s, CH_2), 4.54 (1H, sept, $J=7.0$ Hz, C*H*(CH_3)$_2$), 6.02 (1H, s, NC=CH), 7.29–7.44 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 2×23.5 (2×CH_3), 36.4 (CH_2NH_2), 48.8 (NCH), 108.4 (NC=*C*H), 111.4 (C_{quat}), 127.7 (CH_{ar}), 2×128.4 (2×CH_{ar}), 129.9 (C_{quat}), 2×130.0 (2×CH_{ar}), 133.4 (C_{quat}), 133.7 (C_{quat}). IR (NaCl): ν_{max} 3374, 1602, 1470, 1332 cm^{-1}. MS *m/z* (%): 248/50 (M^+, 69), 232/34 (55), 190/92 (100). Anal. Calcd for $C_{14}H_{17}N_2Cl$: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.47; H, 7.00; N, 11.02.

3.8. Synthesis of 2-(hydroxymethyl)- and 2-(methoxymethyl)pyrroles 17b,c and 17d

To a solution of 3-chloro-2-formyl-1-isopropyl-5-phenylpyrrole **16b** (0.50 g, 2.02 mmol) in 10 mL of dry THF was added 0.08 g (2.02 mmol, 1 equiv) sodium borohydride at room temperature and under N_2-atmosphere. The mixture was stirred overnight (20 h) and subsequently poured in 25 mL water. Extraction was performed with diethyl ether (3×25 mL) and the combined extracts were dried over $MgSO_4$. After removal of the solvents in vacuo, a clean reaction mixture was obtained containing only traces of impurities. To remove these impurities, pyrrole **17b** was chromatographed over a small column (3 cm) of silica gel. Pyrrole **17d** was prepared via an analogous procedure in methanol (reaction time of 2 h).

3.8.1. 3-Chloro-2-(hydroxymethyl)-1-isopropyl-5-phenylpyrrole 17b. Flash chromatography (hexane/EtOAc 9:1, $R_f=0.35$); yield 56%. ^{1}H NMR ($CDCl_3$): δ 1.42 (6H, d, $J=7.1$ Hz, CH(C*H*$_3$)$_2$), 4.54 (1H, sept, $J=7.1$ Hz, C*H*(CH_3)$_2$), 4.70 (2H, s, CH_2O), 6.04 (1H, s,

NC=CH), 7.29–7.42 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 2×23.3 (2×CH_3), 49.4 (CH), 61.0 (OCH_2), 108.6 (NC=*C*H), 114.4 (C_{quat}), 124.5 (C_{quat}), 127.9 (CH_{ar}), 2×128.3 (2×CH_{ar}), 2×130.1 (2×CH_{ar}), 133.8 (C_{quat}), 134.9 (C_{quat}). IR (NaCl): ν_{max} 3396, 1603, 1552, 1468, 1333 cm^{-1}. MS *m/z* (%): 232/34 ($M^+ - OH$, 88), 190 (100). Anal. Calcd for $C_{14}H_{16}NOCl$: C, 67.33; H, 6.46; N, 5.61. Found: C, 67.43; H, 6.62; N, 5.74.

3.8.2. 1-*t*-Butyl-3-chloro-2-(hydroxymethyl)-5-phenylpyrrole 17c. Flash chromatography (hexane/EtOAc 9:1, R_f=0.18); yield 69%. ^{1}H NMR ($CDCl_3$): δ 1.51 (9H, s, $C(Me)_3$), 4.77 (2H, s, CH_2), 5.91 (1H, s, CH), 7.28–7.38 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 3×33.2 (3×CH_3), 60.8 (C_{quat}), 62.6 (CH_2), 111.2 (CH), 115.4 (C_{quat}), 125.8 (C_{quat}), 3×127.5 (3×CH_{ar}), 2×130.7 (2×CH_{ar}), 135.6 (C_{quat}), 137.7 (C_{quat}). IR (NaCl): ν_{max} 3400, 1602, 1469, 1397 cm^{-1}. MS (ES+) *m/z* (%): 246/8 ($M+H^+-H_2O$, 12), 190/92 (100). Anal. Calcd for $C_{15}H_{18}NOCl$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.04; H, 7.03; N, 5.17.

3.8.3. 3-Chloro-1-isopropyl-2-(methoxymethyl)-5-phenylpyrrole 17d. Flash chromatography (hexane/EtOAc 4:1, R_f=0.24); yield 53%. ^{1}H NMR ($CDCl_3$): δ 1.48 (9H, s, $C(Me)_3$), 3.38 (3H, s, CH_3), 4.64 (2H, s, CH_2), 5.91 (1H, s, CH), 7.28–7.33 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 3×32.9 (3×CH_3), 59.9 (CH_3), 60.8 (C_{quat}), 65.0 (CH_2), 111.2 (CH), 115.4 (C_{quat}), 125.6 (C_{quat}), 2×127.5 (2×CH_{ar}), 127.6 (CH_{ar}), 2×130.7 (2×CH_{ar}), 135.7 (C_{quat}), 137.7 (C_{quat}). IR (NaCl): ν_{max} 1602, 1471, 1395 cm^{-1}. MS (ES+) *m/z* (%): 278/80 ($M+H^+$, 4), 190/92 (100). Anal. Calcd for $C_{16}H_{20}NOCl$: C, 69.18; H, 7.26; N, 5.04. Found: C, 68.92; H, 7.43; N, 4.96.

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Niobium pentachloride–silver perchlorate as an efficient catalyst in the Friedel–Crafts acylation and Sakurai–Hosomi reaction of acetals

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Abstract—Friedel–Crafts acylation catalyzed by niobium pentachloride with silver salt is described. Aromatic compounds with Ac_2O or Bz_2O were smoothly converted into the corresponding ketones in good to excellent yields. This system was also applied to the Sakurai–Hosomi reaction using acetals. The reaction proceeded quite rapidly to give the desired products in excellent yields.

1. Introduction

Niobium pentachloride, a strong Lewis acid, has recently been recognized as a useful reagent in organic synthesis because of its stability, low hygroscopic characteristics and ease of handling compared to other Lewis acids and some examples of organic transformation promoted by stoichiometric amount of $NbCl_5$ have been reported.[1] Moreover, the catalytic use of $NbCl_5$ in the acylative cleavage of ethers[2] and C–P bond formation[3] have been reported. Quite recently, we developed a highly selective dealkylation of alkylarylethers with a stoichiometric amount of $NbCl_5$.[4] To establish the utility of $NbCl_5$ as a catalyst, catalytic version of Friedel–Crafts acylation, one of the most fundamental reactions in organic synthesis,[5–7] was examined.

2. Results and discussion

Initially, the acylation of 1,2-dimethoxybenzene **1a** with Ac_2O was investigated in the presence of $NbCl_5$ (Table 1).[8] The reaction of **1a** and acetic anhydride (1.5 equiv) in CH_2Cl_2 at rt with 110 mol% of $NbCl_5$ gave **2a** in 89% yield, however catalytic amount of $NbCl_5$ (10 mol%) under similar conditions resulted in 19% yield (entry 1). Niobium pentachloride alone did not act as a catalyst because coordination of **1a** or **2a** to $NbCl_5$ reduces its catalytic activity. On the other hand, the addition of silver perchlorate (20 mol%)[9] with $NbCl_5$ (10 mol%), which would cationic Nb complex, dramatically enhanced the reactivity to give **2a** in 63% yield (entry 2). $AgClO_4$ alone (20 mol%) gave the product in only 12% yield (entry 3). These results show that both metal salts are essential for successful conversion to the acylated product. The reaction in nitromethane proceeded faster to complete within 3.5 h and the product was obtained in 87% yield (entry 4). Further optimization revealed that at 80 °C a lower catalyst loading ($NbCl_5$: 2.5 mol%, $AgClO_4$: 5 mol%) was enough to complete the reaction within 1 h, and gave **2a** in 93% yield (entry 5), but a lower catalyst loading required a longer reaction time (entry 6). When acetyl chloride was used as an electrophile under similar conditions to entry 4, **2a** was obtained in 52% yield even after 4 h. Furthermore, even in the presence of 1 mol% of $NbCl_5$ with $AgClO_4$ (3 mol%), the reaction proceeded smoothly within 1.5 h under similar conditions (entry 7). Subsequent screening of co-catalysts revealed that $AgClO_4$ was the best additive of choice (entries 8 and 9). Although the reaction of **1a** with stoichiometric amount of $NbCl_5$ alone at 80 °C gives mono-demethylated compound,[4] the addition of silver salt proceeded Friedel–Crafts acylation very rapidly without demethylation. These results are summarized in Table 1. The proposed catalytic cycle of this reaction is outlined in Figure 1. The initial abstraction of chloride from $NbCl_5$ by a silver salt would gives a cationic Nb species,[9a] which promotes the generation of acylium cation with the reaction of acetic anhydride. Subsequent acylation of **1a** gives **2a** and $HClO_4$ which promotes regeneration of a catalyst by proton exchange between niobium acetate and $HClO_4$.

Next, various substrates were acylated under the optimized conditions, as shown in Table 2. For example, **1a** with Bz_2O gave the desired product **3a** quantitatively (entry 1). 1,3-Dimethoxybenzene **1b** gave a mixture of **2b/3b** (94:6) in

Keywords: Catalyst; Friedel–Crafts acylation; Niobium; Sakurai–Hosomi reaction.
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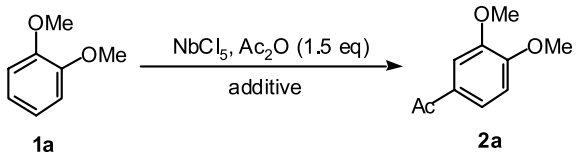
Table 1. Catalytic Friedel–Crafts acylation using $NbCl_5$



1a 2a

Entry	$NbCl_5$ (mol%)	Additive (mol%)	Conditions	Yield (%)
1	10	None	CH_2Cl_2, rt, 24 h	19
2	10	$AgClO_4$ (20)	CH_2Cl_2, rt, 24 h	63
3	None	$AgClO_4$ (20)	CH_2Cl_2, rt, 24 h	12
4	10	$AgClO_4$ (20)	$MeNO_2$, rt, 3.5 h	87
5	2.5	$AgClO_4$ (5)	$MeNO_2$, 80 °C, 1 h	93
6	1	$AgClO_4$ (2)	$MeNO_2$, 80 °C, 25 h	89
7	1	$AgClO_4$ (3)	$MeNO_2$, 80 °C, 1.5 h	91
8	1	$AgSbF_6$ (3)	$MeNO_2$, 80 °C, 1.5 h	62
9	1	AgOTf (3)	$MeNO_2$, 80 °C, 1.5 h	82

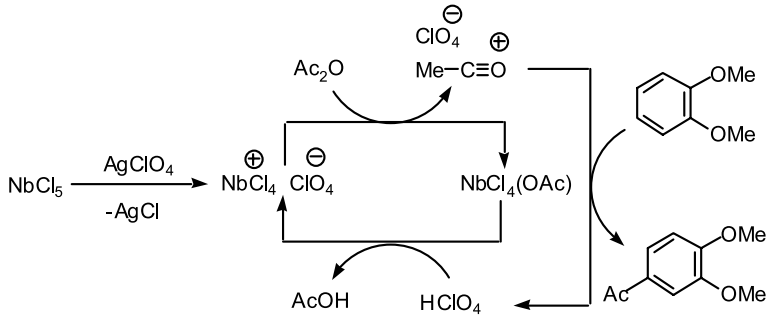


Figure 1. Proposed catalytic cycle for Friedel–Crafts acylation using $NbCl_5$ with $AgClO_4$.

58% yield. Anisole **1c** was also smoothly acylated to give **2c** in 79% yield, exclusively (entry 3). 1-Methoxynaphthalene **1d** and 1,3,5-trimethylbenzene **1e** were smoothly converted into the corresponding ketones **2d** and **2e** in respective yields of 99% and 95% yields (entries 4 and 5). In the case of thiophene **1f**, furan **1g** and *N*-tosylindole **1h**, the reactions gave the corresponding acylated products in respective yields of 86, 52 and 92% (entries 6–8). In case of **1b** and **1g**, the corresponding products could coordinate to niobium species as bidentate ligands to form stable niobium complexes and reduce their Lewis acidity, so that the catalytic cycle does not work effectively (entries 2 and 7). Reactions using less reactive substrates such as naphthalene and toluene were unsuccessful, and gave the desired products in less than 15% yield.

The direct use of carboxylic acid as an electrophile is quite effective in this protocol. For example, the reaction of **1a** with acetic acid (1.5 equiv) in the presence of *p*-nitrobenzoic anhydride[10] with Nb(V) and silver salt (in situ preparation of mixed anhydride) gave **2a** in 88% yield as a single product. Intramolecular acylation of **1i** under similar conditions proceeded smoothly to give **2i** in 85% yield (Scheme 1).

Having succeeded in the development of a catalytic system using Nb(V) with a silver salt, we next applied this protocol to the Sakurai–Hosomi reaction using acetals **4** with allyltrimethylsilane **5**.[11] As expected, the use of $NbCl_5$ alone with **4a** and **5** gave poor results because Nb(V) is too strong as a Lewis acid and the catalytic cycle cannot be established (entry 1). On the other hand, the addition of $AgClO_4$ (15 mol%) was quite effective even at −20 °C and the reaction proceeded to give **6a** in excellent yield (entry 2). Finally, optimization revealed that a catalytic amount of $NbCl_5$ and $AgClO_4$ (0.5 mol% each) at 0 °C furnished the product in 87% yield (entry 3). Other aromatic and aliphatic acetals **4b–d** gave the desired products **6b–d** in 84–98% yields.[12] These results are summarized in Table 3.

In summary, we have developed a $NbCl_5$–$AgClO_4$-catalyzed Friedel–Crafts acylation and Sakurai–Hosomi reaction using acetals with excellent chemical yields under quite mild conditions. These reaction system allow to use $NbCl_5$ of 1 and 0.5 mol% each. The further application of this system to organic synthesis is presently under investigation.

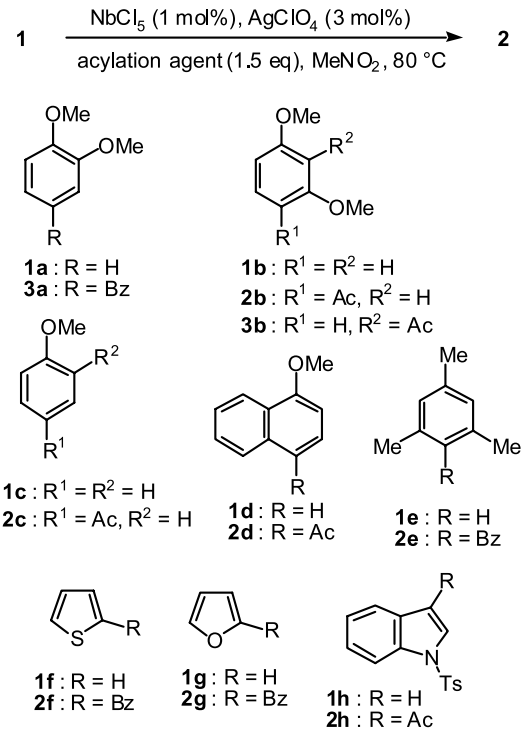
3. Experimental

Registry number of the products described are following; **2a** (1131-62-0), **3a** (4038-14-6), **2b** (829-20-9), **3b** (2040-04-2), **3c** (579-74-8), **2d** (24764-66-7), **2e** (954-16-5), **2f** (135-00-2), **2g** (2689-59-0), **2h** (104142-24-7), **2i** (529-34-0), **5a** (22039-97-0), **5b** (125310-48-7), **5c** (111874-57-8) and **5d** (60753-91-5).

3.1. Typical experimental procedure for Friedel–Crafts acylation of 1: synthesis of 2a (Table 1, entry 6)

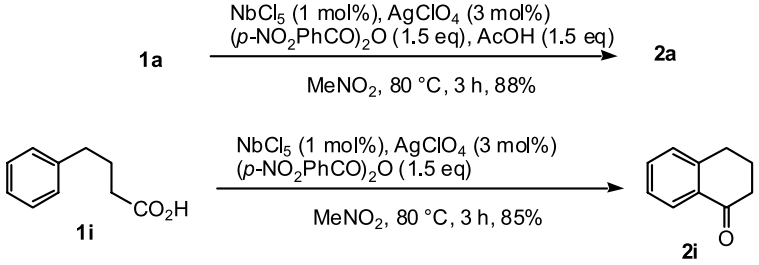
To a mixture of $NbCl_5$ (5.4 mg, 0.02 mmol, 1 mol%) and

Table 2. Niobium-catalyzed Friedel–Crafts acylation using various substrates



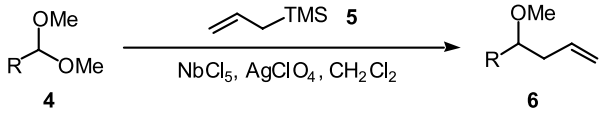
Entry	Substrate	Acylating agent	Time (h)	Result
1	**1a**	Bz_2O	7	**3a**: 100%
2	**1b**	Ac_2O	10	**2b**+**3b**: 58%[a]
3	**1c**	Ac_2O	7	**2c**: 79%
4	**1d**	Ac_2O	2	**2d**: 99%
5	**1e**	Bz_2O	7	**2e**: 95%
6	**1f**	Bz_2O	2[b]	**2f**: 86%
7	**1g**	Bz_2O	30[b,c]	**2g**: 52%
8	**1h**	Ac_2O	7	**2h**: 92%

[a] **2b**:**3b**=94:6.
[b] Two equiv of Bz_2O was used.
[c] The reaction was carried out at rt.



Scheme 1. Direct use of carboxylic acid as an electrophile in Friedel–Crafts acylation.

Table 3. Catalytic Sakurai–Hosomi reaction of acetals promoted by a Nb–Ag system



Entry	Acetal	Nb (mol%)	Ag (mol%)	Conditions	Yield (%)
1	**4a**: R=Ph	5	None	rt, 15 min	**6a**: 3
2	**4a**: R=Ph	5	15	−20 °C, 10 min	**6a**: 90
3	**4a**: R=Ph	0.5	0.5	0 °C, 10 min	**6a**: 87
4	**4b**: R=4-ClPh	0.5	0.5	0 °C, 20 min	**6b**: 98
5	**4c**: R=4-MeOPh	0.5	0.5	0 °C, 20 min	**6c**: 94
6	**4d**: R=Ph$(CH_2)_2$	0.5	0.5	0 °C to rt, 2 h	**6d**: 84

$AgClO_4$ (12.4 mg, 0.06 mmol, 3 mol%), nitromethane (2.0 mL) was added under argon atmosphere and then mixture was stirred for 10 min at room temperature. Then **1a** (0.24 mL, 2.0 mmol) and acetic anhydride (0.28 mL, 3.0 mmol) were added at room temperature. After the mixture was stirred for 1.5 h at 80 °C, the reaction was quenched with sat. $NaHCO_3$ (1.0 mL). The mixture was extracted with CH_2Cl_2 (5 mL, 3 times), washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane: AcOEt = 2:1) gave **2a** as a colorless oil (326.6 mg, 1.81 mmol, 91%).

3.2. Typical experimental procedure for Sakurai–Hosomi reaction of acetal 4, synthesis of 6a (Table 3, entry 3)

To a mixture of $NbCl_5$ (1.4 mg, 0.005 mmol, 0.5 mol%) and $AgClO_4$ (1.0 mg, 0.005 mmol, 0.5 mol%) in CH_2Cl_2 (1.0 mL) was added **4a** (150 μL, 1.0 mmol) and **5** (191 μL, 1.2 mmol) at 0 °C. After stirring for 10 min, the reaction was quenched by addition of saturated $NaHCO_3$ (1.0 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 mL three times). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude residue was purified by the following flash column chromatography (hexane:Et_2O = 10:1) to give **6a** as a colorless oil (141.2 mg, 0.87 mmol, 87%).

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Electrochemical studies of biologically active indolizines

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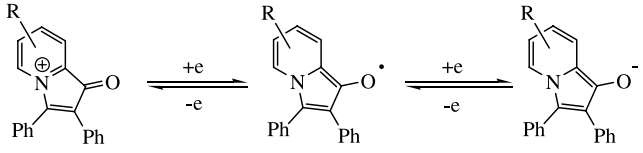
Abstract—The electrochemical behavior of indolizine ethers, esters, tosylates, sulfonates and other indolizine and azaindolizine derivatives has been investigated by cyclic voltammetry and preparative electrolysis. The cyclic voltammetric data show that the E° values, taken as the midpoints between the anodic and cathodic peak potentials, are sensitive to the identities of the substituents at C-1, C-2 and C-7 positions. The E° values have been correlated with the Hammett substituent parameters. As expected, low E° values are seen for electron donating substituents and higher E° values are seen for electron withdrawing substituents. The cyclic voltammograms of indolizine derivatives with an oxygen atom connected to the C-1 position exhibit a one-electron reversible oxidation and a further, less well-defined, one-electron irreversible oxidation at higher E° values. The cyclic voltammograms of indolizines with hydrogen atom or thienyl substituents connected to the C-1 position exhibit only a one-electron irreversible oxidation. Electrochemical bulk oxidations of indolizines with an oxygen atom at the C-1 position afforded oxoindolizinium salts in decent yields, whereas indolizines with a hydrogen atom at C-1 afforded 1,1′ dimers of indolizines as products in good yields. Bulk oxidation of 1-(α-hydroxybenzyl)-2,3-diphenylindolizine-7-carbonitrile afforded an unexpected ketone product in which the carbonyl group of the indolizine is connected at C-8 instead of at the C-1 position of the starting material. The findings described herein support our hypothesis that certain indolizine derivatives may inhibit lipid peroxidation by an electron transfer mechanism.

1. Introduction

It is well documented that certain 1-indolizinols are easily oxidized to stable free radicals.[1] We therefore envisaged that *O*-protected indolizinols may act as stable precursors for highly potent antioxidants, and we found high inhibitory activity against lipid peroxidation (LPO) in vitro for esters, ethers, carbonates, carbamates and sulfonates of indolizines as well as azaindolizines.[2] Regardless of the identity of the *O*-substituent, otherwise identical indolizines exhibited comparable activities in the test system. Effective cleavages of all *O*-substituted indolizines, especially the ethers, in the test medium were highly unlikely. Also boiled rat liver microsomes were employed in the assay, and enzymatic cleavage of for instance esters would not be possible. This led us to propose that all active indolizines inhibit lipid peroxidation by an electron donor mechanism. The oxygen in the indolizine 1-position was crucial for antioxidant activity. All 1-alkyl-, 1-aryl- or unsubstituted indolizines were essentially inactive.

Later, we examined several indolizine derivatives as inhibitors of 15-lipoxygenase (15-LO).[3] Again, we found high activity for several compounds studied, but no correlation between inhibitory activity against the enzyme in the previously described lipid peroxidation assay.[2] Hence, we believe that the indolizines may be regarded as so-called non-antioxidant inhibitors of 15-LO which exhibit activity by direct binding to the enzyme.[4]

In order to gain further insight into antioxidant properties of indolizines, we decided to carry out a detailed study of electrochemical activity of bioactive indolizines. Cyclic voltammograms for some indolizines are reported,[1b] but no systematic electrochemical investigations of indolizines can be found in the literature. One-electron oxidation products of a variety of indolizinols have been isolated as a family of crystalline radical species that exhibit a remarkable stability at room temperature.[1b] Upon further oxidation, indolizinyl radicals formed stable oxoindolizinium ions (Scheme 1).[1b] Such ions were most conveniently prepared in good yield



Scheme 1.

Keywords: Electrochemistry; Cyclic voltammetry; Indolizine; Bulk oxidation.
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(70–95%) by direct two-electron oxidation of the desired 1-indolizinol. The oxidative dimers of 3-indolizinols were also prepared by aerating a solution of an appropriate diarylcyclopropenone in pyridine containing 2.5 mol% cupric acetate. Cyclic voltammetry of the dimers revealed two reversible one-electron oxidations and two reversible one-electron reductions.[1b]

2. Results and discussion

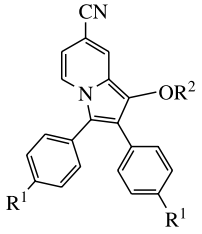
2.1. Cyclic voltammetry studies of indolizines with an oxygen atom connected at the C-1

The synthetic methodology for the preparations of the indolizines studied have been described previously,[2,3] and novel compounds are included in the Section 4. Biological activities (inhibition of 15-LO and LPO) have also been reported before.[2,3] Cyclic voltammetry (CV) data for indolizine ethers, esters and acetals are summarized in Table 1. All CV data were recorded at a Pt disk electrode ($d=1.0$ mm) for ca. 1 mM acetonitrile solutions of the substrate containing 0.1 M $Bu_4N^+BF_4^-$ as the supporting electrolyte at 20 °C and a voltage scan rate of 1 V/s unless otherwise noted.

The cyclic voltammograms of the indolizine derivatives **1–3** in Table 1 reveal that all of the compounds undergo a one-electron reversible oxidation in the range 0.36–0.69 V versus the Cp_2Fe/Cp_2Fe^+ (Fc) couple[5] with peak-to-peak separations of 68–110 mV. In comparison, the separation for Cp_2Fe was found to be 59–64 mV, close to the ideal 58 mV value for a reversible (Nernstian) wave. This suggests that the electron transfer process for the indolizine derivatives is quasi-reversible. Additionally, a chemically irreversible oxidation wave was seen in the range 0.89–1.35 V versus Fc. The cyclic voltammograms of the indolizines **1–3** are qualitatively quite similar, and the CV of compound **1j** is illustrated as an example and used for the discussion below.

Figure 1a and b show cyclic voltammograms for the oxidation of compound **1j** at two different sweep widths. In Figure 1a, it is seen that the oxidation of the indolizine occurs reversibly at 0.443 V versus Fc with peak-to-peak separation of ca. 100 mV. The anodic and cathodic peak currents are approximately equal and it may be inferred that the indolizine is oxidized to the corresponding stable radical cation reversibly on the experimental time scale (ca. 1 s). Figure 1b shows the cyclic voltammogram of compound **1j** taken to higher anodic potential, and it is evident that a second anodic peak has emerged at a potential of 1.25 V versus Fc. There is no associated reduction peak during the reverse (cathodic) scan, so it is concluded that the second oxidation process at 1.25 V versus Fc is a chemically irreversible process. Furthermore, a new cathodic peak can be seen at −0.12 V versus Fc. This wave was absent during the scan in Figure 1a, which did not include the second oxidation. Thus, it appears that the −0.12 V wave must be caused by reduction of a species that is formed subsequent

Table 1. Cyclic voltammetry data for Indolizine ethers, esters and acetals[a]



Compound	R^1	R^2	E°_1[b] (V)	E_2[c] (V)
1a	H	$-CH_3$	0.386	0.98
1b	F	$-CH_3$	0.429	1.12
1c	Cl	$-CH_3$	0.461	1.14
1d	CH_3	CH_3	0.385	1.10
1e	OCH_3	CH_3	0.362	0.89
1f	H	$-CH_2Ph$	0.435	1.21
1g	H	$-CH_2$-*p*-MeO–Ph	0.446	1.26
1h	H	$-CH_2$-*m*-MeO–Ph	0.647	nd
1i	H	$-CH_2$-*o*-MeO–Ph	0.671	1.21
1j	H	$-CH_2$-*p*-F–Ph	0.443	1.25
1k	H	$-CH_2$-*p*-Cl–Ph	0.522	1.14
1l	H	$-CH_2$-*m*-Cl–Ph	0.450	1.20
1m	H	$-CH_2$-*p*-Me–Ph	0.436	1.06
1n	H	$-CH_2-C_6H_{11}$	0.391	1.12
2a	H	$-CH_2OCH_2Ph$	0.492	1.16
2b	H	$-CH_2-O-CH(CH_2OCH_2Ph)_2$	0.443	1.12
3a	H	–CO-*o*-MeO–Ph	0.676	1.10
3b	H	–CO-*m*-MeO–Ph	0.688	1.35
3c	H	–CO-*p*-MeO–Ph	0.679	1.26
3d	H	$-COCH_3$	0.692	No peak

nd, not determined.
[a] Conditions: 1.0 mM substrate in acetonitrile/0.1 M Bu_4NBF_4, 20 °C, Pt-disk electrodes ($d=1.0$ mm), $\nu=1.0$ V/s.
[b] Chemically reversible. E°_1 is taken as the midpoint between the anodic and cathodic peaks.
[c] Peak potential for chemically irreversible process.

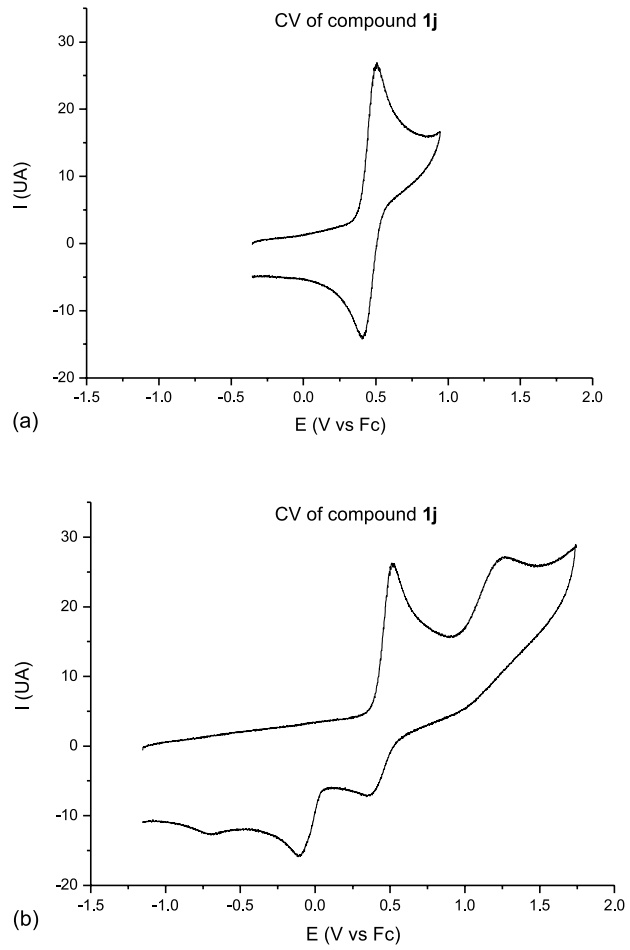
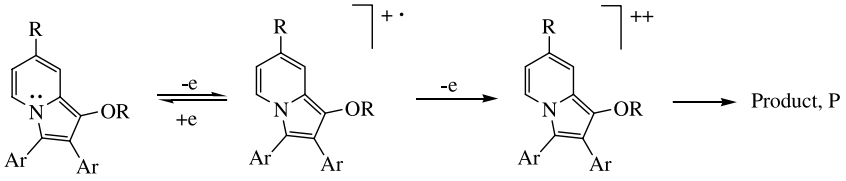


Figure 1. Cyclic voltammograms for the oxidation of compound **1j** at different sweep widths. Conditions: 1.0 mM solution of **1j** in acetonitrile/0.1 M Bu_4NBF_4 at 20 °C (d=1.0 mm Pt disk electrode, voltage sweep rate ν=1.0 V/s). The oxidative scans are done with freshly conditioned electrode surface.

with electron donating groups such as methyl (**1d**) and methoxy (**1e**) substituents by as much as 0.044–0.067 V. The sensitivity of the E° values to the identity of the substituent has been correlated with the Hammett substituent constants based on the ionization of the substituted benzoic acids.[6] A linear correlation of E° versus σ_p gives a slope $\delta E/d\sigma = 0.19 \pm 0.04$ V (Fig. 2).

As is evident from Figure 2, the E° values increase with increasing σ_p values. Thus, the donor methoxy and methyl substituents cause a thermodynamic stabilization of the cation radicals, observed by a lowering of the oxidation potential for their neutral indolizine precursor. Conversely, the electron withdrawing F and Cl substituents destabilize the cation radicals. Interestingly, the highest E° value is obtained for **1c** with a chlorine substituent, and not for **1b** with a fluorine substituent. The difference observed between these two is opposite of what may be expected on the basis of electronegativity arguments alone and nicely manifests the delicate interplay between σ and π effects of the susbtituents. The π-electron system has been responsible for the well-known deviations of *para* donor substituents in the literature.[6,7] Introduction of substituted benzyl groups as R^2 substituents (**1f–m**) in Table 1 led to little variation in the corresponding oxidation potentials, except for compounds **1h–i** which perhaps surprisingly are found to have significantly higher E° values than the others. The indolizine esters **3a–d** are more difficult to oxidize than the ethers and the acetals by 0.22–0.33 and 0.20–0.25 V, respectively, most probably because of the radical cation destabilizing effect of the electron withdrawing acyl groups. This effect is even more profound for the sulfonates **4**, see below, where the radical cation formed after oxidation is expected to be severely destabilized by the strongly electron withdrawing substituents.

We extended the electrochemical studies of indolizines and the cyclic voltammetry data of a variety of indolizine



Scheme 2. General scheme for the oxidations of indolizines as shown in the cyclic voltammetry experiment.

to the second oxidation step at 1.25 V. A general scheme for the oxidations of the indolizines that is based on this analysis is depicted in Scheme 2. The indolizines with an oxygen atom connected to the C-1 position are oxidized to the corresponding radical cations reversibly and the radical cations are further oxidized to reactive dication species, which ultimately are converted to a product P (see the cyclic voltammograms in Figure 1 and Scheme 2).

When the oxidation potentials for compounds **1a–e** (Table 1) are compared, it is evident that the E° values, taken as the midpoints between the anodic and cathodic peaks, are sensitive to the identity of the substituent, R^1. The indolizines with electron withdrawing groups such as F (**1b**) and Cl (**1c**) atoms are more difficult to oxidize than those

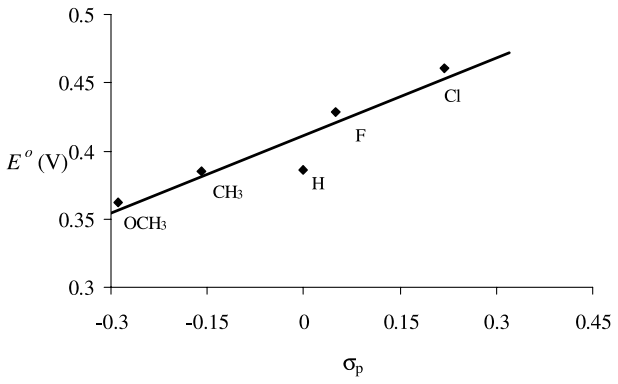
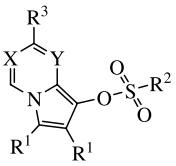


Figure 2. Correlation between E° and Hammett σ_p values[5] for **1a–e**.

Table 2. Cyclic voltammetry data of indolizine sulfonates[a]



Comp.	X	Y	R^1	R^2	R^3	E°_1[b] (V)	E_2[c] (V)
4a	C	C	Ph	4-MeC_6H_4	CN	0.770	1.46
4b	C	C	*p*-FC_6H_4	4-MeC_6H_4	CN	0.807	1.51
4c	C	C	*p*-ClC_6H_4	4-MeC_6H_4	CN	0.825	1.71
4d	C	C	*p*-MeC_6H_4	4-MeC_6H_4	CN	0.740	1.77
4e	C	C	*p*-$MeOC_6H_4$	4-MeC_6H_4	CN	0.680	1.29
4f	C	C	Ph	$-CH_3$	CN	0.792	1.49
4g	C	C	Ph	$-(CH_2)_3CH_3$	CN	0.773	1.50
4h	C	C	Ph	$-CF_3$	CN	0.966	1.75
4i	C	C	Ph	$-N(Me)_2$	CN	0.743	No peak
4j	C	C	Ph	4-$CF_3C_6H_4$	CN	0.776	1.51
4k	C	C	Ph	4-ClC_6H_4	CN	0.815	1.40
4l	C	C	Ph	4-$MeOC_6H_4$	CN	0.804	1.50
4m	C	C	Ph	4-MeC_6H_4	H	0.477	1.46
4n	C	C	Ph	4-MeC_6H_4	$COCH_3$	0.688	1.48
4o	C	C	Ph	4-MeC_6H_4	CHO	0.711	1.51
4p	C	C	Ph	4-MeC_6H_4	$C(CH_3)_3$	0.411	1.31
4q	C	C	$-CH_2CH_3$	4-MeC_6H_4	CN	0.686	No peak
4r	C	C	$-(CH_2)_3CH_3$	4-MeC_6H_4	CN	0.683	No peak
4s	C	C	Ph	3,4-$(MeO)_2C_6H_3$	CN	0.791	1.63
4t	C	C	Ph	2,5-$(MeO)_2C_6H_3$	CN	0.772	1.35
4u	C	C	Ph	2,4-$(MeO)_2C_6H_3$	CN	0.754	1.49
4v	C	C	Ph	2-MeC_6H_4	CN	0.782	1.51
4w	C	C	Ph	4-^{i}Pr-C_6H_4	CN	0.788	1.50
4x	C	C	Ph	2,4,6-$(Me)_3C_6H_2$	CN	0.780	1.49
4y	C	C	Ph	2-thienyl	CN	0.809	1.52
4z	C	C	Ph	3-thienyl	CN	0.790	1.51
4aa	N	C	Ph	4-MeC_6H_4	H	0.722	1.48
4ab	C	N	Ph	4-MeC_6H_4	H	0.669	nd

nd, not determined.
[a] Conditions: 1.0 mM substrate in acetonitrile/0.1 M Bu_4NBF_4, 20 °C, Pt-disk electrodes ($d=1.0$ mm), $\nu=1.0$ V/s
[b] Chemically reversible. E° is taken as midpoint between anodic and cathodic peaks.
[c] Peak potential for chemically irreversible process.

sulfonates are shown in Table 2. Most sulfonates are powerful inhibitors of 15-lipoxygenase[3] and triflates are even capable of lipid peroxidation inhibition.[2] The tosylates **4a–e** are generally more difficult to oxidize than the ethers **1a–e** by as much as 0.28–0.46 V. The sensitivity of the E° values of **4a–e** to the identity of the substituent has also been correlated with the Hammett substituent constants and the same pattern is observed as described above. A linear correlation of E° versus σ_p now gives a slope $\delta E/d\sigma = 0.28 \pm 0.04$ V (Fig. 3). These compounds are, therefore, more sensitive to changes in the R^1 groups than **1a–e**.

The oxidation potential data for compounds **4a–4g** reveal that the E° values are essentially insensitive to the identity of the substituent on the $\mathbf{SO_2}$-moiety of the sulfonate (R^2 in Table 2). When R^2 is methyl, butyl, or a *para*-substituted phenyl group, the E° values fall in the range 0.680–0.825 V versus Fc. The R^2 group is further removed from the electroactive indolizine moiety in these species than in the compound included in Table 1, and less E° variation might, therefore, be anticipated. The indolizine triflate **4h**, on the other hand, shows a higher E° value, certainly due to the presence of the electron-withdrawing trifluoro moiety directly attached to the sulfonate group. The dimethylamino substituent in the sulfonamide derivative **4i** stabilizes the radical cation somewhat. This compound displays one of the lowest E° values among the 7-cyano-2,3-diaryl indolizine sulfonates examined.

Significant substituent effects on the E° values were observed when different substituents R^3 were attached to the C-7 position of the indolizines, compare compounds **4a** and **4m–p** in Table 2. The relationship between the Hammett σ_p substituent constants and the E° values are shown in Figure 4. A linear correlation of E° versus σ_p gives a slope $\delta E/d\sigma = 0.42 \pm 0.01$ V. The E° values are, therefore,

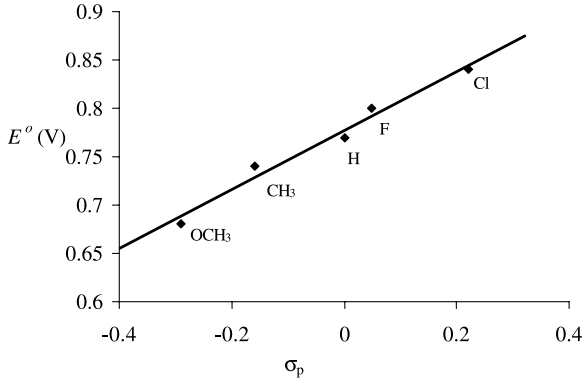


Figure 3. Correlation between E° and Hammett σ_p values[5] for **4a–e**.

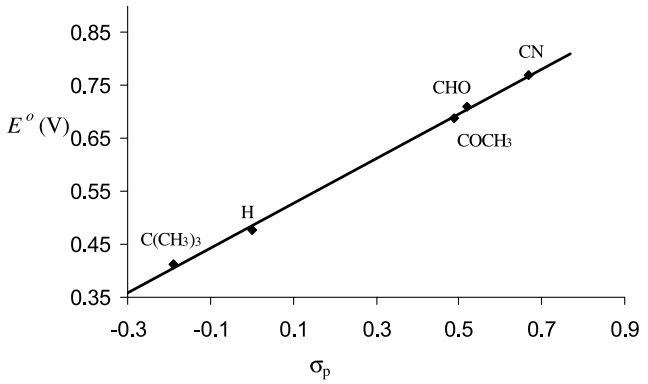


Figure 4. Comparison between E° and Hammett σ_p values[6] for **4a** and **4m–p**.

considerably more sensitive to changes in R^3 than to R^1 and R^2. As expected the E° values increase with increasing values for σ_p. When the cyano group in **4a** is replaced by another electron withdrawing substituents such as an acetyl (**4n**) or formyl (**4o**) group, the oxidation potential slightly drops from 0.770 to 0.688 and 0.711 V versus Fc, respectively. However, when the cyano group was replaced by H (**4m**) or *tert*-butyl (**4p**) groups, the E° values drop substantially to 0.477 and 0.411 V versus Fc, respectively. Replacement of the phenyl groups at the C-2 and C-3 positions of **4a** (0.770 V versus Fc) with ethyl (**4q**) and butyl (**4r**) substituents lowers the E° values by 0.084–0.087 V. This suggests that the two phenyl groups in **4a** are not capable of stabilizing the cation radical by resonance effects, presumably because the phenyl rings cannot be coplanar with the indolizine moiety for steric reasons. We have previously published the X-ray structure of another 1-substituted 7-cyano-2,3-diphenylindolizine. For that structure we found the phenyl group at C-2 to be 34° out of the indolizine ring plane and the phenyl group in the 3-position was 63° out of the same plane.[2b] (Note, see next paragraph, that **4q** and **4r** are *irreversibly* oxidized. This may introduce an unknown kinetic potential shift in the cathodic direction and, therefore, the true E° difference may be less pronounced than suggested by the tabulated data).

The cyclic voltammograms of the indolizine sulfonates **4a–p** (Table 2) revealed that all these compounds exhibit a one-electron reversible oxidation in the range 0.41–0.97 V versus Fc with peak-to-peak separations ranging from 53–110 mV, followed by a one-electron irreversible oxidation in the range 1.29–1.77 V versus Fc. Cyclic voltammograms for compounds **4j**, **4n** and **4o** are shown as examples in Figure 5. The behavior of these systems is quite similar to that found for **1–3**. The same general scheme for the oxidations (Scheme 2) is, therefore, implied also for the indolizine sulfonates. In contrast, the voltammograms of compounds **4q** and **4r** showed only a one-electron irreversible oxidation (0.686 and 0.683 V versus Fc, respectively) and no second oxidation wave. In these cases, it is the cation radicals that undergo a chemical reaction. Compounds **4q** and **4r** only differ from **4a–p** in bearing *n*-alkyl groups rather than phenyl rings at C-2 and C-3. The phenyl rings at C-2 and C-3, therefore, appear to be crucial for kinetically stabilizing the indolizine cation radicals. It is not known what the origin of the reduced

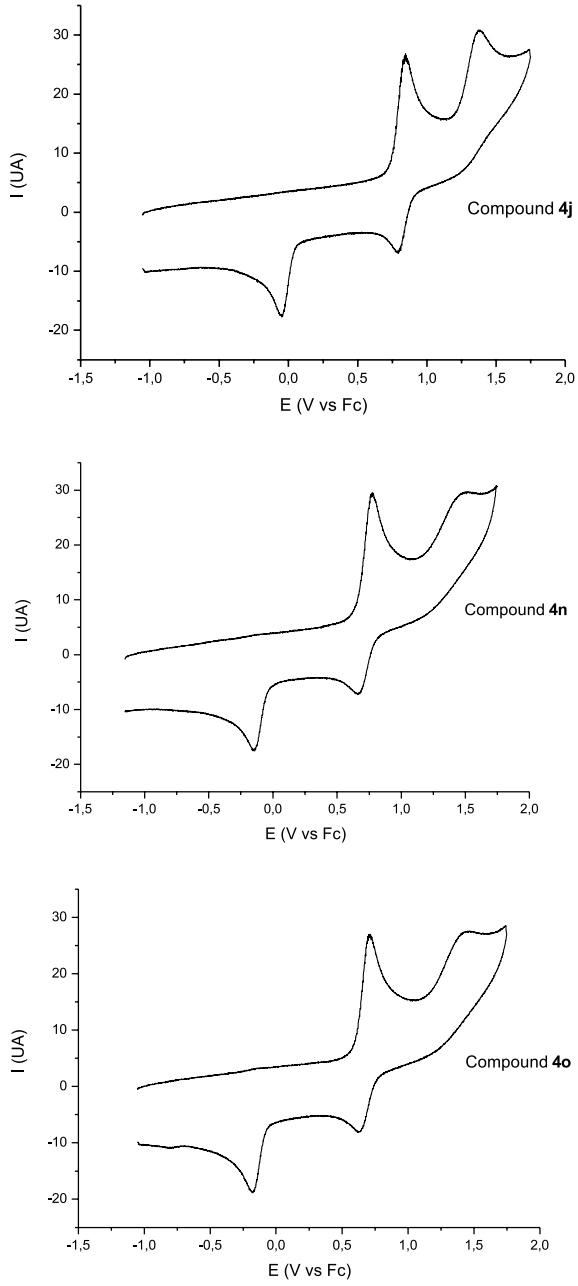


Figure 5. Cyclic voltammograms for the oxidations of compounds **4j**, **4n** and **4o**. Conditions: 1.0 mM solution of appropriate compound in acetonitrile/0.1 M Bu_4NBF_4 at 20 °C (d=1.0 mm Pt disk electrode, voltage sweep rate ν=1.0 V/s). The oxidative scans are done with freshly conditioned electrode surface.

chemical stability of the cation radicals of **4q** and **4r** might be. They might, however, be susceptible to proton loss from the α position of the alkyl groups. Such behavior is commonly observed for methylarene cation radicals.[8]

The electrochemical investigation of indolizine sulfonates was expanded to include other aromatic groups at R^2. CV data for the indolizine sulfonates **4s–z** are also included in Table 2. The introduction of additional electron donating groups at different positions of the sulfonate benzene ring did not show a significant influence on the E° values. This supports the notion that the redox active moiety of the molecules is the indolizine core, and that the sulfonate

substituents at R^2 are too far removed from the core to significantly affect the E° values. The cyclic voltammetry of the compounds **4s–z** reveals that all of the compounds have one-electron reversible oxidations in the range 0.75–0.81 V versus Fc. Again, the cyclic voltammograms for **4s–z** qualitatively are very much similar to the ones shown in Figure 5, and these compounds are concluded to react according to Scheme 2.

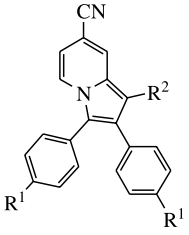
We also have briefly investigated the cyclic voltammetry of some azaindolizines and the voltammetric data are shown in Table 2. Compounds **4aa–4ab** undergo one-electron reversible oxidations at 0.724 and 0.669 V versus Fc, respectively. Furthermore, **4aa** exhibits an irreversible oxidation wave at 1.48 V versus Fc.

2.2. Cyclic voltammetry studies of indolizines without an oxygen atom connected at C-1

Cyclic voltammetry data for some indolizines without an oxygen atom at the C-1 position are shown in Table 3. Compounds **5–6** undergo irreversible oxidations at 0.55–0.80 V versus Fc. Disregarding the effects of kinetic potential shifts caused by the follow-up homogeneous reactions, the data indicate that **5a–d** are more difficult to oxidize than the correspondingly substituted **6a–d** by 0.10–0.20 V, and more difficult to oxidize than the corresponding alcohols **7a–d** by 0.04–0.10 V. The data do suggest that the 2-thienyl group is better at stabilizing the cation radical than the –CH(OH)Ph moiety, which is again better than a H atom.

The cyclic voltammograms of the indolizine compounds **5–6** show irreversible oxidation waves with peak potentials at 0.55–0.80 V versus Fc. Figure 6 depicts typical examples, **5b** and **6b**. The irreversibility of the oxidation waves indicates that these radical cations spontaneously react to give new products. Figure 6a also shows that there is a small cathodic peak at ca. 0.45 V versus Fc, which presumably arises from a product that was formed subsequent to the electron transfer event. A similar feature is seen at 0.28 V versus Fc in Figure 6b. A general scheme that describes this behavior is shown in Scheme 3.

Table 3. CV data for indolizines without oxygen atom connected to C-1 position[a]



Compound	R^1	R^2	E_1^b (V)	E_2^c (V)
5a	H	H	0.709[c]	No peak
5b	F	H	0.727[c]	No peak
5c	Cl	H	0.798[c]	No peak
5d	CH_3	H	0.644[c]	No peak
6a	H	-2-thienyl	0.677[c]	No peak
6b	F	-2-thienyl	0.579[c]	No peak
6c	Cl	-2-thienyl	0.600[c]	No peak
6d	CH_3	-2-thienyl	0.549[c]	No peak
7a	H	–CH(OH)Ph	0.606	1.35
7b	F	–CH(OH)Ph	0.671	1.39
7c	Cl	–CH(OH)Ph	0.698	nd
7d	CH_3	–CH(OH)Ph	0.601	1.26

nd, not determined.

[a] Conditions: 1.0 mM substrate in acetonitrile/0.1 M Bu_4NBF_4, 20 °C, Pt-disk electrodes ($d=1.0$ mm), $\nu=1.0$ V/s.

[b] E° for chemically reversible unless otherwise noted, taken as midpoint between cathodic and anodic peaks.

[c] Oxidation peak potential for chemically irreversible process.

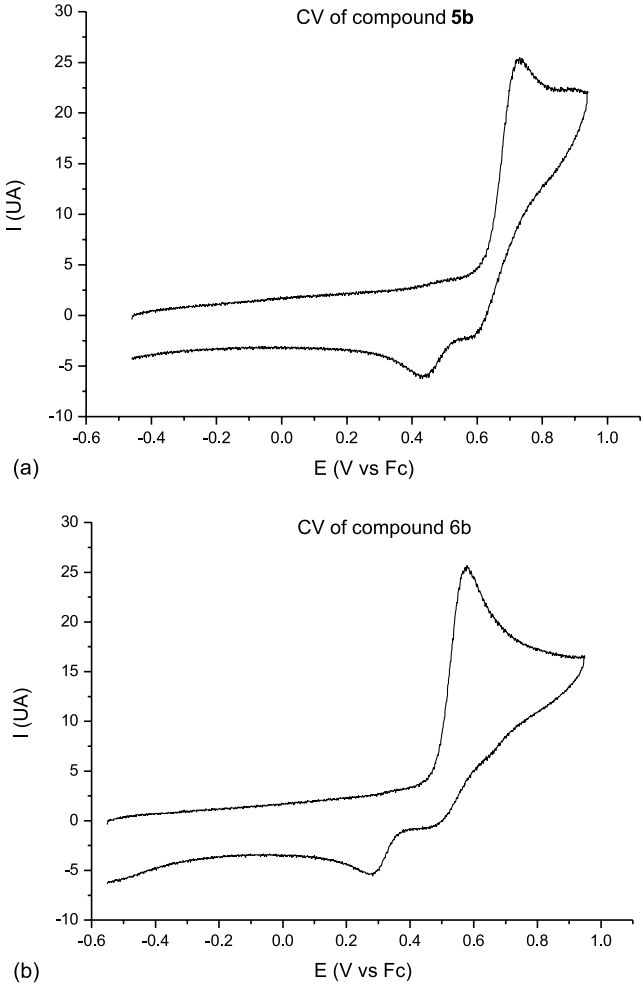
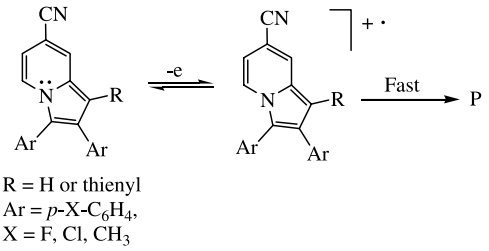


Figure 6. Cyclic voltammograms for the oxidations of compounds **5b** and **6b**. Conditions: 1.0 mM solution of appropriate indolizine compound in acetonitrile/0.1 M Bu_4NBF_4 at 20 °C ($d=1.0$ mm Pt disk electrode, voltage sweep rate $\nu=1.0$ V/s). The oxidative scans are done with freshly conditioned electrode surface.

The voltammograms of compounds **7a–d** reveal that they undergo one-electron reversible oxidations at 0.60–0.70 V versus Fc with peak-to-peak separations of ca. 116–136 mV and one-electron irreversible oxidations at 1.26–1.39 V versus Fc. Thus, the CH(OH)Ph group is kinetically more capable at stabilizing the cation radical than is the thienyl group (expressed by the reversibility of the electron transfer), whereas the opposite applies to the thermodynamic stabilities of the cation radicals (expressed by the E° values).



Scheme 3. General scheme for oxidations of indolizines without oxygen atom connected to C-1.

2.3. Electrochemical bulk oxidations of indolizines with oxygen atom connected at C-1

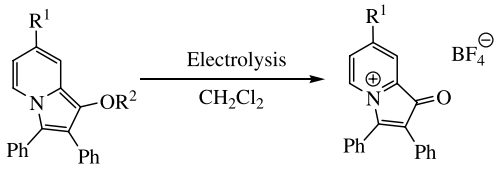
Constant-potential bulk electrolysis followed by isolation of oxidation products was performed for selected substrates. The bulk oxidations of compounds **4h**, **4m–n** and **4p** (from Table 2) were performed at Pt gauze electrodes. The current that passed through the electrolysis cell was measured and the measured coulometric data are tabulated in Table 4. It is important to note that the time scale of a coulometry experiment is at least several minutes (plus work-up), contrasting with the approximate one-second time scale of the cyclic voltammetry measurements. Thus, processes that are reversible on the CV time scale may turn out to be irreversible on the electrolysis time scale. For this reason, among others, processes that appear to be one-electron transfers in CV need not necessarily result in overall 1 Faraday/mol coulometric measurements.

Table 4. Coulometric data during bulk oxidations

Compound	*E* applied versus Fc (V)	Charge (Faraday/mol)
4h	1.95	2.0
4m	0.85	1.3
4n	1.85	1.2
4p	1.85	2.1
5a	1.15	1.2
5d	1.95	2.0

The oxidations of the indolizines were performed at the electrode working potentials shown in Table 4. For compound **4m** this means that the working electrode will oxidize the substrate to the mono cation but not to the dication. For the other substrates, complete oxidation to the dication is, in principle, possible. The charges that passed through the electrolysis cell are also shown in Table 4.

In the electrolysis experiments (see the Section 4 for details), the indolizine triflate **4h** and sulfonates **4m–n** and **4p** are converted to the corresponding oxoindolizinium salts **8a–d** (Scheme 4). The isolated products were analyzed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectra of the isolated products confirmed the introduction of a new carbonyl group adsorbing at 1735–1746 cm^{-1}. The ^{1}H NMR data of the isolated oxoindolizinium salts are in accordance with the literature data.[1b] It is also shown in the literature[1b] that oxoindolizinium salts are the products from chemical oxidations of 1-indolizinols, after homolytic cleavage of the O–H bond at C-1.



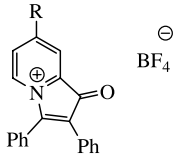
4h,m-n,p **8a-d**

Compd.	R^1	R^2	Compd.	R^1	Yield (%)
4h	CN	$-S(=O)_2-CF_3$	**8a**	CN	55
4m	H	Ts	**8b**	H	64
4n	$COCH_3$	Ts	**8c**	$COCH_3$	55
4p	$C(CH_3)_3$	Ts	**8d**	$C(CH_3)_3$	18

Scheme 4. Oxidations of indolizines to oxoindolizinium salts.

Cyclic voltammmetry of oxoindolizinium ions showed two-reversible, one-electron reductions in the literature.[1b] We have also seen two-reversible one-electron reductions for the oxoindolizium ions that were produced during electrolysis. Table 5 lists redox potentials for several representative oxoindolizinium ions. These E° values agree with those previously reported[1b] for the oxoindolizinium ions **8a–d** to within 0.10–0.01V. (The potentials in the literature were given relative to SCE employing acetonitrile as a solvent and we corrected the values to Fc by subtracting 0.307 V for comparison).[5] This agreement is good, considering differences in solvent, electrolyte and reference electrode used.

Table 5. Redox potentials for representative oxoindolizinium ions[a]



Compound	R	E_1[b] (V)	E_2[c] (V)
8a	CN	0.07	−0.58[b]
8b	H	−0.31	−0.85[b]
8c	$COCH_3$	−0.11	−0.76
8d	$C(CH_3)_3$	−0.37	−0.88

[a] Conditions: 1.0 mM substrate in acetonitrile/0.1 M Bu_4NBF_4, 20 °C, Pt-disk electrodes (d=1.0 mm), ν=1.0 V/s.
[b] Chemically reversible unless otherwise noted.
[c] Reduction peak potential for chemically irreversible process.

A typical coulometry experiment and bulk oxidation of the triflate **4h** is discussed in the following section. Compound **4h** was dissolved in MeCN with supporting electrolyte and the coulometry experiment was conducted. Cyclic voltammograms were recorded at a separate Pt disk electrode before and after the coulometry and are shown in Figure 7. Figure 7.1 shows cyclic voltammogram before the electrolysis and as it is shown, **4h** is oxidized to the corresponding radical cation at 0.97 V versus Fc and the radical cation is

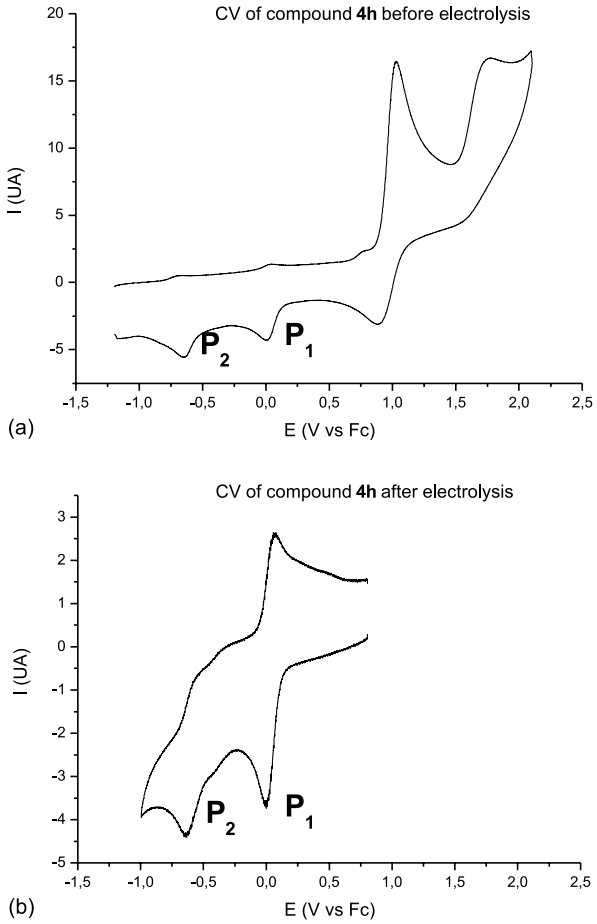


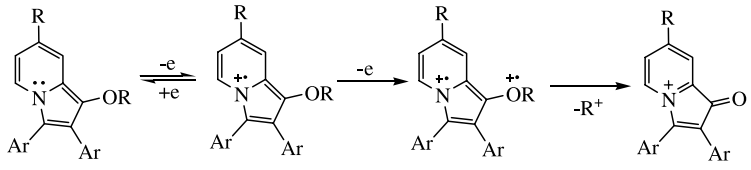
Figure 7. CV of compound **4h** before and after electrolysis. Conditions: 1.0 mM solution of appropriate compound in acetonitrile/0.05 M Me_4NBF_4 at 20 °C (d=1.0 mm Pt disk electrode, voltage sweep rate ν=1.0 V/s). The oxidative scans are done with freshly conditioned electrode surface.

further oxidized to the dication species at 1.75 V versus Fc. The dication species then reacts rapidly to give two products detected at P_1 and P_2. After work-up, P_1 was identified to be the corresponding oxoindolizinium salt **8a** (Scheme 4) by IR and NMR spectroscopy. In Figure 7.2, P_1 was shown to be reduced to the corresponding indolizine radical reversibly at ca. 0.07 V versus Fc as shown in Scheme 1 and described in the literature.[1b] Further reduction of the indolizine radical at ca. −0.55 V gave rise to the corresponding indolizine anion P_2 as described in the literature.[1b] The redox behavior of the indolizinium ion **8a** follows the behavior shown in Scheme 1.[1b] Even though the formations of the indolizine radical and anion were obvious from Figure 7.2, isolation of them was impractical because of difficulty in separating the products from the electrolyte. The oxoindolizinium salts **8b**, **8c** and **8d** (Scheme 4) were made in the same way described for **8a** from the appropriate precursors.

From the coulometry experiments, the charges that are passed in the system are roughly 2 Faraday/mol for compounds **4h** and **4p** (Table 4). The formation of the corresponding oxoindolizinium salts **8a** and **8d** (Scheme 4) can be rationalized by the removal of two electrons from the neutral indolizines as shown in Scheme 5, and therefore, the product formation is consistent with the coulometry data. (Alternatively, the radical cation may undergo homolysis to produce the oxoindolizinium product and the R radical (R˙), in which case the second oxidation wave must originate from a subsequent oxidation of the radical or species derived from R˙). For compounds **4m** and **4n**, the charge that is passed in the system is somewhat greater than 1 Faraday/mol (Table 4). It is not known whether the apparently different stoichiometry can be attributed to different reaction mechanisms, the non-quantitative reaction yields, or other factors. In the reaction of the 7-unsubstituted **4m**, we only got compound **8b** in decent yield and we saw no indication of dimerization in the indolizine 7-position.[1b]

We have previously observed a higher inhibition of lipid peroxidation (LPO) in vitro for compound **4h** than the corresponding tosylate **4a**.[2b] Since effective cleavage of all *O*-substituted indolizines in the test medium were highly unlikely, this led us to propose that all active indolizines including **4h** inhibit lipid peroxidation by an electron transfer mechanism.[2b] However, the very efficient LPO inhibition found for the triflate cannot easily be explained by an electron transfer mechanism alone, since we now have shown that the triflate is much more difficult to oxidize electrochemically than the other sulfonates examined. The triflate **4h** was cleaved to the parent indolizinol when subjected to Pd-catalyzed coupling conditions,[2b] and we cannot rule out that the triflate is also labile under LPO conditions and, at least partly, is cleaved to the indolizinol which may scavenge LPO. The 1-indolizinol is known to spontaneously be oxidized to the corresponding neutral radical by donating a hydrogen atom to for instance atmospheric oxygen,[1b] hence part of the LPO inhibition reported earlier might be due to hydrogen atom donation by the 1-indolizinol formed from the triflate **4h** and not only by electron transfer as suggested earlier.[2a] The ability of 1-indolizinol to donate a hydrogen atom can of course not be investigated by the CV investigations since no change in charge is involved in such a process.

In this study, we considered that the peak at 1.75 V versus Fc in Figure 7.1 could be due to the oxidation of 1-indolizinol, which could be obtained as a result of the hydrolysis of the triflate **4h**. However, we find that 1-indolizinol is irreversibly oxidized at 0.363 V versus Fc (Fig. 8) to the corresponding radical cation, which rapidly reacts to give a product that is reduced at ca. 0.07 V versus



Scheme 5. Oxoindolizinium ions by removal of two electrons.

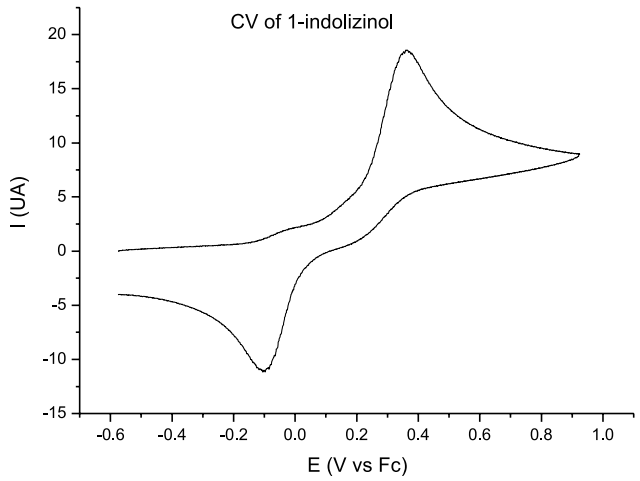


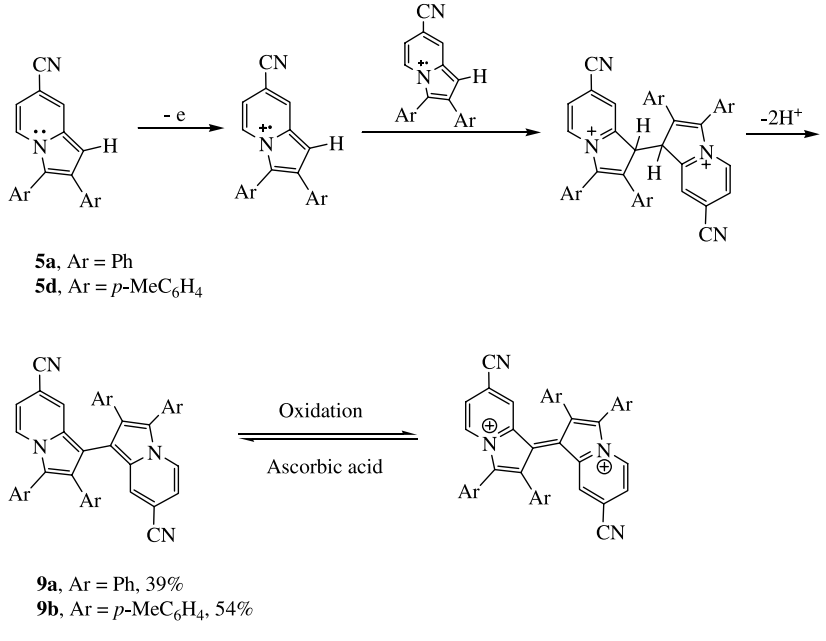
Figure 8. Cyclic voltammogram of 1-indolizinol. Conditions: 1.0 mM solution of 1-indolizinol in acetonitrile/0.1 M Bu_4NBF_4 at 20 °C (d= 1.0 mm Pt disk electrode, voltage sweep rate ν=1.0 V/s). The oxidative scans are done with freshly conditioned electrode surface.

Fc. This product was also isolated and identified as the oxoindolizinium ion **8a**. As discussed above, the peak at 1.75 V versus Fc is, therefore, obtained as a result of the oxidation of the indolizine radical cation to a dication species, which rapidly produces the indolizinium ion. The indolizinium ion is hence reversibly reduced to the indolizine radical at ca. −0.55 V versus Fc (see Scheme 1 and Fig. 7).

2.4. Electrochemical bulk oxidations of indolizines without a substituent in the 1 position

Similarly, bulk oxidations of 2,3-diphenylindolizine-7-carbonitrile **5a** and **5d** (Table 3) were performed at Pt mesh electrodes. The working potentials at which oxidations of the indolizines were performed and the charges that are passed in the coulometry experiment are also shown in Table 4. The cyclic voltammograms of compounds **5a** and **5d**, which are similar to the cyclic voltammograms shown in Figure 6, indicate that they both undergo one-electron irreversible oxidations giving rise to one compound in each case. The electrolysis products were analyzed by ^1H and ^{13}C NMR spectroscopy and in both cases the 1,1′-dimers (**9a** and **9b**) of the indolizines were formed in decent yields. The NMR spectroscopic data of compound **9a** are in good agreement with literature data.[2b] The reaction scheme for the formation of the dimers is shown in Scheme 6. Earlier work has revealed that the dimer 1,1′-dioxo-$\Delta^{7,7'}$(3H,3′H)-bisindolizine undergoes two reversible one-electron oxidations and two reversible one-electron reductions.[1b] Cyclic voltammograms of the isolated dimers **9a** and **9b** also reveal two reversible one-electron oxidations as shown in Figure 9. The cyclic voltammogram of the dimer **9a** shows two reversible one-electron oxidations at 0.473 and 0.687 V versus Fc. The cyclic voltammogram of the dimer **9b** shows two reversible one-electron oxidations at 0.462 and 0.643 V versus Fc. The E° values of the dimer **9b** are somewhat lower than those of **9a** presumably due to the inductive effects of the four methyl substituents connected at the *para* positions of the phenyl groups.

The oxidative dimerizations of indolizines and other heterocyclic compounds have been previously reported.[1b,9–13] A possible mechanism for the dimerization of the indolizines is shown in Scheme 6. Initial oxidation of the neutral indolizine gives rise to the corresponding indolizine radical cation. Cation radical dimerizations are frequently encountered.[14] The dicationic dimer is expected to be highly acidic and readily undergoes proton loss to give the neutral dimer. Based on the electrode potentials for the dimers, these will spontaneously undergo oxidation by one electron per monomeric unit to provide the dimeric dication (Scheme 6) in an overall two-electron process per monomeric unit. (Alternatively, the radical cation may react with the neutral indolizine to give an intermediate that is subsequently oxidized to give the same dication dimer).



5a, Ar = Ph
5d, Ar = *p*-MeC_6H_4

9a, Ar = Ph, 39%
9b, Ar = *p*-MeC_6H_4, 54%

Scheme 6. Proposed mechanism for dimerization of compounds **5a**,**d**.

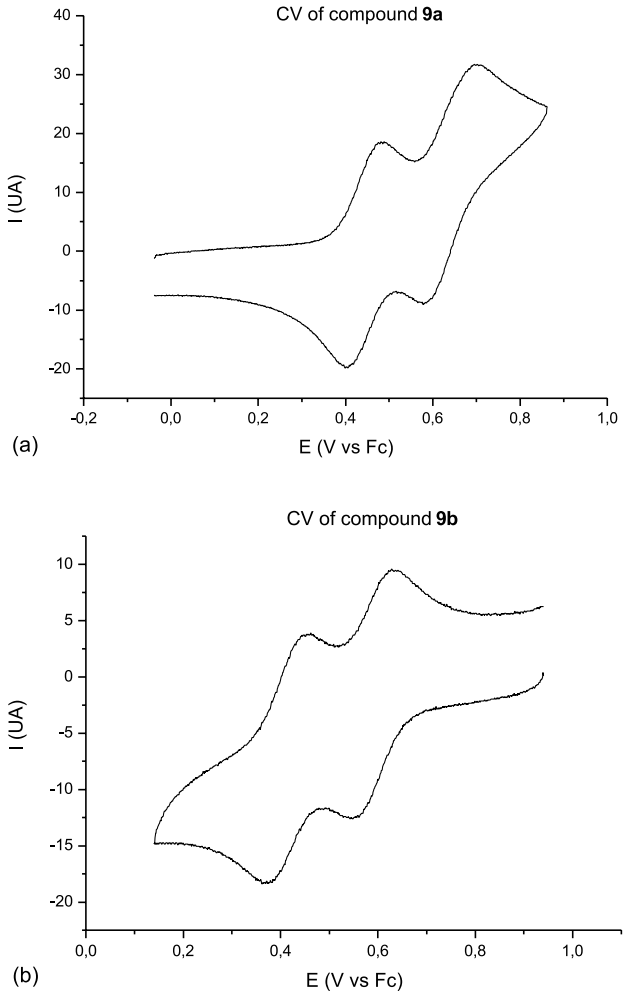
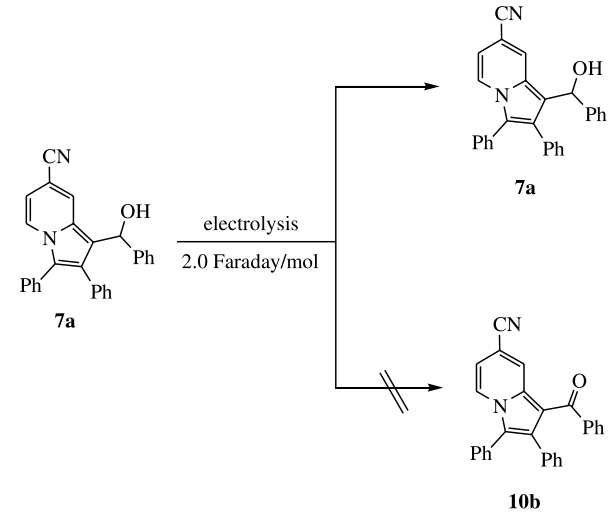


Figure 9. Cyclic voltammograms for the oxidations of the dimers **9a** and **9b**. Conditions: 1.0 mM solution of appropriate dimer in acetonitrile/0.1 M Bu_4NBF_4 at 20 °C (d=1.0 mm Pt disk electrode, voltage sweep rate ν=1.0 V/s). The oxidative scans are done with freshly conditioned electrode surface.

2.5. Electrochemical bulk oxidations of indolizines with aryl or alkyl substituents connected to C-1

Bulk oxidation of 1-(α-hydroxybenzyl)-2,3-diphenylindolizine-7-carbonitrile **7a** (Scheme 7) was also performed at Pt mesh electrodes. The charge that passed through the cell was 2.0 Faraday/mol at a working electrode potential of 1.5 V versus Fc. The yellowish colour of the starting alcohol changed to reddish during electrolysis and when 2.0 Faraday/mol was passed through the electrolysis cell, the coulometry experiment was stopped. The reaction was not complete, but NMR and MS data revealed that a phenyl indolizinyl ketone was present together with unreacted starting material **7a**. Isolation of the ketone was not successful, but the NMR data revealed that the product formed was not the expected ketone **10b** which we have prepared before.[15]



Scheme 7. Electrolysis reaction of **7a**.

3. Conclusion

We have, for the first time, carried out a detailed study of the electrochemical behavior of a large variety of in vitro biologically active indolizine derivatives. Indolizines with electron withdrawing substituents at the C-1 and C-7 positions are more difficult to oxidize than those with electron donating substituents. Good correlations between Hammett σ_p and E° values have been obtained. The cyclic voltammetry studies revealed that indolizines with an oxygen atom connected at C-1 position have one-electron reversible oxidations and one-electron irreversible oxidations. The bulk oxidations of these types of indolizines afforded the oxoindolizinium salts. Indolizines with a hydrogen atom connected at the C-1 position showed a one-electron irreversible oxidation and bulk oxidations of these types of indolizines afforded 1,1′ dimers of indolizines. The results described herein support our hypothesis that indolizine ethers, esters and to some extent sulfonates, can inhibit lipid peroxidation by an electron transfer mechanism in which the indolizines are oxidized to stable radical cations. In the case of the triflate **4h**, which is not readily oxidized electrochemically, the profound ability to inhibit LPO may be explained by partial hydrolysis to the parent indolizinol. Among the indolizine derivatives examined as LPO inhibitors, 1-(α-hydroxybenzyl)-2,3-diphenylindolizine-7-carbonitrile **7a** is the only indolizine without oxygen in the 1-position which is able to inhibit LPO. We have now demonstrated that this compound may also act as an antioxidant by an electron transfer mechanism.

4. Experimental

4.1. General procedures

Acetonitrile was distilled from $AlCl_3$, alkaline permanganate and Li_2CO_3, $KHSO_4$ and CaH_2 according to a literature procedure.[16] Dichloromethane was distilled from CaH_2. Acetonitrile and dichloromethane containing the supporting electrolyte were passed through a column of active neutral alumina prior to use to remove water and protic impurities before electrochemical measurements. The electrolyte was freed of air by purging with purified solvent-saturated argon, and all measurements and electrolyses were carried out under a blanket of argon. Silica gel for flash

chromatography was available from Merck (Darmstadt, Germany) (Merck No. 9385) or Fluka (Fluka No. 60752). DCE was distilled from CaH_2 and THF from Na/benzophenone. Other reagents were used as received. The ^1H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the instruments mentioned above. Unless otherwise stated, the spectra are recorded at 20 °C. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane, with the residual solvent proton resonance as internal standard. Mass spectra (EI) were recorded with a VG Prospec instrument at 70 eV ionizing voltage unless otherwise stated, and are presented as *m/z* (% rel. int.). Electrospray MS spectra (ESI) were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. IR spectra were recorded on a Nicolet 550 Magna-IR spectrometer and are reported as cm^{-1}. Melting points are uncorrected. Electrochemical measurements were performed with an EG&G-PAR Model 273 potentiostat/galvanostat driven by an external HP 33120 function generator. The signals were fed to an on-line personal computer for processing with home-made National Instruments LabView software through a National Instruments DAQ interface card. The working electrodes were Pt-disk electrodes ($d=1.0$ mm), the counter electrode was a Pt wire, and the Ag-wire reference electrode assembly was filled with acetonitrile/0.01 M $AgNO_3$/0.1 M $Bu_4N^+BF_4^-$. The reference electrode was calibrated against Cp_2Fe, which was also used as the reference in this work. The positive-feedback *iR* compensation circuitry of the potentiostat was employed and adjusted such that the separation of anodic and cathodic peaks for the Cp_2Fe oxidation was 59–64 mV under the CV conditions.

4.2. Syntheses

4.2.1. 1-Methoxy-2,3-di(4-flurophenyl)indolizine-7-carbonitrile (1b). A mixture of 2,3-di(4-flurophenyl)cyclopropenone (121 mg, 0.5 mmol) and 4-cyanopyridine (52 mg, 0.5 mmol) was refluxed in dry DCE (10 mL) under N_2 for 22 h, cooled and evaporated under N_2. The residue was dissolved in dry THF (30 mL), and sodium hydride (26 mg, 1.1 mmol) was added. The resulting mixture was stirred under N_2 at ambient temperature for 1 h, after which iodomethane (249 mg, 1.75 mmol) was added. After stirring at ambient temperature for 24 h, the reaction mixture was evaporated in vacuo, the residue was dissolved in diethyl ether (100 mL) and washed with water (50 mL). The dried ($MgSO_4$) organic solution was evaporated in vacuo and the product was purified by flash chromatography, eluting with EtOAc–hexane (1:19). Yield 150 mg (83%) of yellow crystals, mp 153–155 °C. $R_f=0.39$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.80$ (s, 3H, OMe), 6.47 (dd, 1H, $J=7.4$, 1.8 Hz, 6-H), 6.98–7.34 (m, 8H, Ph), 7.81 (dd, 1H, $J=7.4$, 1.0 Hz, 5-H), 7.94 (m, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=62.92$ (–OCH_3), 97.58, 110.52, 115.65, 115.96, 116.82, 117.11, 119.68, 120.63, 121.23, 121.86, 122.53, 124.69, 126.07 (d, $J_{CF}=3.5$ Hz, C–F), 128.31 (d, $J_{CF}=3.3$ Hz, C–F), 131.88, 132.07, 132.72, 132.83, 139.86, 162.73 (d, $J=250.5$ Hz, C–F). ^{19}F NMR (188 MHz, $CDCl_3$): $\delta=-111.80$ (C–F), −115.10 (C–F). MS (EI); *m/z* (%): 360 [M^+] (63), 345 (100), 214 (5), 131 (27), 103 (52). HRMS $C_{22}H_{14}F_2N_2O$: Calcd 360.1074; found 360.1075.

4.2.2. 1-Methoxy-2,3-di(4-chlorophenyl)indolizine-7-carbonitrile (1c). A mixture of 2,3-di(4-chlorophenyl)-cyclopropenone (136 mg, 0.5 mmol) and 4-cyanopyridine (52 mg, 0.5 mmol) was refluxed in dry DCE under N_2 for 22 h, cooled and evaporated under N_2. The title compound was then prepared as described for compound **1b** above. Yield 143 mg (77%) of yellow crystals, mp 165–167 °C. $R_f=0.42$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.77$ (s, 3H, OMe), 6.48 (dd, 1H, $J=7.4$, 1.7 Hz, 6-H), 7.20–7.48 (m, 8H, Ar), 7.85 (br d, 1H, $J=7.4$ Hz, 5-H), 7.94 (br s, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=63.11$ (–OCH_3), 98.09, 110.78, 119.58, 120.48, 121.54, 121.89, 122.31, 124.79, 128.38, 129.13, 130.15, 130.71, 131.46, 132.11, 133.62, 135.28, 139.97. MS (EI); *m/z* (%): 393 [M^+] (12), 377 (100), 246 (2), 176 (8), 171 (3), 161 (3), 153 (4), 131 (469, 103 (85). HRMS $C_{22}H_{14}Cl_2N_2O$: Calcd 392.0483; found 392.0501.

4.2.3. 1-Methoxy-2,3-di(*p*-tolyl)indolizine-7-carbonitrile (1d). A mixture of di-*p*-tolylcyclopropenone (117 mg, 0.5 mmol) and 4-cyanopyridine (52 mg, 0.5 mmol) was refluxed in dry DCE (10 mL) under N_2 for 22 h, cooled and evaporated under N_2. The title compound was then prepared as described for compound **1b** above. Yield 143 mg (81%) of yellow crystals, mp 143–146 °C. $R_f=0.48$ (SiO_2, EtOAc–hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.25$ (s, 3H, Me), 2.27 (s, 3H, Me), 3.75 (s, 3H, OMe), 6.35 (dd, 1H, $J=7.4$, 1.8 Hz, 6-H), 7.06–7.08 (m, 2H, Ar), 7.14–7.24 (m, 6H, Ar), 7.80 (br d, 1H, $J=7.4$ Hz, 5-H), 7.86 (br s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=21.64$ (CH_3), 21.80 (CH_3), 62.91 (OCH_3), 96.99, 110.03, 120.02, 121.11, 121.33, 121.95, 123.89, 124.54, 127.31, 129.41, 129.57, 130.06, 130.30, 130.67, 137.01, 138.93, 139.99. MS (EI); *m/z* (%): 352 [M^+] (47), 337 (100), 205 (8), 189 (5), 161 (6), 131 (8), 103 (29). HRMS $C_{22}H_{20}N_2O$: Calcd 352.1576; found 352.1567.

4.2.4. 1-Methoxy-2,3-bis(*p*-anisyl)indolizine-7-carbonitrile (1e). A mixture of bis(*p*-anisyl)cyclopropenone (341 mg, 1.0 mmol) and 4-cyanopyridine (104 mg, 1.0 mmol) was refluxed in dry DCE (15 mL) under N_2 for 22 h, evaporated and cooled under N_2. The title compound was then prepared as described for compound **1b** above. Yield 265 mg (69%) of yellow wax. $R_f=0.60$ (SiO_2, EtOAc–hexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.72$ (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.41 (dd, 1H, $J=7.4$, 1.8 Hz, 6-H), 6.85–7.02 (m, 4H, Ar), 7.25–7.32 (m, 4H, Ar), 7.83 (dd, 1H, $J=7.4$, 0.9 Hz, 5-H), 7.91 (dd, 1H, $J=1.73$, 0.96 Hz, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=55.56$ (OMe), 55.71 (OMe), 62.84 (OMe), 96.83, 109.97, 114.18, 115.09, 120.07, 120.99, 121.85, 122.45, 123.51, 124.42, 124.89, 131.28, 132.14, 139.01, 158.95, 160.09. MS (EI); *m/z* (%): 384 [M^+] (58), 369 (100), 238 (11), 223 (12), 192 (3), 152 (3), 103 (18). HRMS: Calcd for $C_{24}H_{20}N_2O_3$ 384.1464, found 384.1474.

4.2.5. 1-(3-Methoxyphenyl)methoxy-2,3-diphenyl-7-indolizinecarbonitrile (1h). The title compound was prepared as described for compound **1b** above. After

addition of the alkyl halide (3-methoxybenzyl chloride, 548 mg, 3.5 mmol), the reaction mixture was heated to 60 °C and stirred for 24 h. The resulting mixture was evaporated in vacuo, and purified by flash chromatography, eluting with EtOAc–hexane (1:19). Yield 312 mg (72%) of yellow crystals, mp 160–162 °C. R_f=0.28 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.77 (3H, s), 4.77 (2H, s), 6.37 (1H, dd, J=7.4, J=1.8 Hz), 6.82–6.87 (2H, m, Ph), 7.21–7.44 (12H, m, Ph), 7.72 (1H, dd, J=1.67, J=1.10 Hz, 8-H), 7.83 (1H, dd, J=7.4, 0.9 Hz, 5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.67 (–OCH_3), 97.58 (–OCH_2), 110.36, 114.16, 114.39, 119.84, 120.98, 121.97, 122.09, 123.86, 124.72, 127.50, 128.74, 129.05, 129.60, 129.93, 130.19, 130.42, 130.86, 132.60, 138.48, 138.78, 160.11. MS (EI); *m/z* (%): 430 [M^+] (4), 309 (100), 281 (5), 178 (7), 131 (9), 103 (24). HRMS $C_{29}H_{22}N_2O_2$: Calcd 430.1681; found 430.1681.

4.2.6. 1-(Cyclohexyl)methoxy-2,3-diphenyl-7-indolizinecarbonitrile (1n). The title compound was prepared as described for compound **1b** above. After addition of the alkyl halide (bromomethyl cyclohexane, 305 μL, 2.2 mmol), the reaction mixture was heated to 65 °C and stirred for 70 h. The resulting mixture was evaporated in vacuo, and purified by flash chromatography, eluting with EtOAc–hexane (1:29 and 1:19). Yield 165 mg (41%) of yellow crystals, mp 168–170 °C. R_f=0.42 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–1.01 (2H, m, CH_2), 1.14–1.24, (3H, m, CH_2 and CH), 1.61–1.77 (6H, m, 3×CH_2), 3.59 (2H, d, J=6.1 Hz), 6.37 (1H, dd, J=7.3, 1.9 Hz, 6-H), 7.16–7.29 (6H, m, Ph), 7.29–7.38 (4H, m, Ph), 7.81 (1H, d, J=7.3 Hz, 5-H), 7.83 (1H, br s, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.20 (CH_2), 26.86 (CH_2), 30.15 (CH_2), 38.79 (CH), 81.44 (–OCH_2), 97.12, 110.23, 120.04, 121.63, 121.93, 123.79, 124.73, 127.30, 128.54, 128.97, 129.56, 130.31, 130.38, 130.83, 132.59, 139.45. MS (EI); *m/z* (%): 407 [M^+] (7), 406 (26), 310 (100), 282 (1), 178 (6), 131 (8), 103 (25), 55 (14), 41 (6). HRMS $C_{28}H_{26}N_2O$: Calcd 406.2045; found 407.2058.

4.2.7. 2,3-Di(4-flurophenyl)indolizine-1-(2-thienyl)indolizine-7-carbonitrile (6b). Tetrakis (triphenylphosphine)-palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (26 mg, 25 μmol) and triphenylphosphine (52 mg, 200 μmol)] in dry DMF (7 mL) was added to a solution of 1-bromo-2,3-di(4-flurophenyl)indolizine-7-carbonitrile (200 mg, 0.50 mmol) and 2-thienyl(tributyl)tin (0.227 mL, 0.720 mmol) in DMF (5 mL). The resulting mixture was stirred for 24 h under N_2 at 100 °C, cooled and evaporated in vacuo. The residue was dissolved in a saturated solution of KF in MeOH and stirred for 2 h. The mixture was evaporated in vacuo and the product was purified by flash chromatography, eluting with EtOAc–hexane (1:29 and 1:19). Yield 171 mg (83%) of yellow crystals, mp 193–196 °C. R_f=0.46 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.58 (dd, 1H, J=7.3, 1.6 Hz, 6-H), 6.85–6.92 (m, 3H in thienyl), 7.00–7.29 (m, 8H, Ar), 7.89 (br d, 1H, J=7.3 Hz, 5-H), 8.09 (br s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=100.94, 111.47, 115.51, 115.79, 116.74, 117.03, 119.35, 122.87, 125.84 (d, J=2.8 Hz, C–F), 125.96, 126.11, 126.26, 127.31, 127.80, 128.80, 129.16 (d, J=3.2 Hz, C–F), 129.38, 132.71, 132.81, 132.91, 134.56, 162.64 (d, J=250.5 Hz, C–F). MS (EI); *m/z* (%): 412 [M^+] (100), 316 (2), 309 (3), 158 (3). HRMS: Calcd for $C_{25}H_{14}F_2N_2S$ 412.0846, found 412.0856.

4.2.8. 2,3-Di(4-chlorophenyl)-1-(2-thienyl)indolizine-7-carbonitrile (6c). The title compound was prepared from 1-bromo-2,3-di(4-chlorophenyl)indolizine-7-carbonitrile (220 mg, 0.50 mmol) and 2-thienyl(tributyl)tin (0.227 mL, 0.720 mmol) as described for compound **6b** above. Yield 207 mg (91%) of yellow crystals, mp 195–197 °C. R_f=0.45 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.66 (dd, 1H, J=7.4, 1.8 Hz, 6-H), 6.92 (dd, 1H, J=3.5, 1.1 Hz, 3-H in thienyl), 7.03–7.08 (m, 2H, Ar), 7.09–7.12 (m, 1H, 4-H in thienyl), 7.21–7.30 (m, 4H, Ar), 7.36 (dd, 1H, J=5.1, 1.1 Hz, 5-H in thienyl), 7.42–7.48 (m, 2H, Ar), 8.04 (dd, 1H, J=7.4 and 0.8 Hz, 5-H), 8.15 (br s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=101.23, 111.67, 112.20, 118.5, 122.89, 125.70, 126.30, 126.34, 127.52, 127.90, 128.15, 128.93, 129.16, 129.50, 130.07, 131.87, 132.11, 132.52, 133.75, 134.27, 135.36. MS (EI); *m/z* (%): 444 [M^+] (100), 408 (6), 374 (2), 186 (15). HRMS: Calcd for $C_{25}H_{14}Cl_2N_2S$ 444.0242, found 444.0254.

4.2.9. 2,3-Di(*p*-tolyl)-1-(2-thienyl)indolizine-7-carbonitrile (6d). The title compound was prepared from 1-bromo-2,3-di(*p*-tolyl)indolizine-7-carbonitrile (200 mg, 0.50 mmol) and 2-thienyl(tributyl)tin (0.227 mL, 0.720 mmol) as described for compound **6b** above. Yield 262 mg (72%) of yellow crystals, mp 198–201 °C. R_f=0.50 (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.17 (s, 3H, Me), 2.20 (s, 3H, Me), 6.52 (dd, 1H, J=7.3, 1.7 Hz, 6-H), 6.86 (dd, 1H, J=3.4, 1.1 Hz, 3-H in thienyl), 6.97–7.02 (m, 4H, Ar), 7.14–7.24 (m, 6H, Ar), 7.85 (br d, 1H, J=7.3 Hz, 5-H), 8.08 (br s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.69 (CH_3), 21.82 (CH_3), 100.24, 110.99, 112.34, 119.70, 123.01, 125.80, 126.13, 127.07, 127.17, 127.22, 127.68, 129.07, 129.18, 129.39, 129.96, 130.23, 130.39, 130.64, 130.70, 131.16, 135.17, 137.09, 138.97. MS (EI); *m/z* (%): 404 [M^+] (100), 356 (2), 312 (2), 186 (2). HRMS: Calcd for $C_{27}H_{20}N_2S$ 404.1353, found 404.1347.

4.2.10. 1-(α-Hydroxybenzyl)-2,3-di(4-flurophenyl)indolizine-7-carbonitrile (7b). *n*-Butyllithium (0.310 mL of 1.6 M solution in hexane, 0.56 mmol) was added dropwise to a stirred solution of 1-bromo-2,3-di(4-flurophenyl)indolizine-7-carbonitrile (200 mg, 0.50 mmol) in dry THF (20 mL) at −78 °C under N_2 and the mixture was stirred at −78 °C for 30 min, after which benzaldehyde (0.167 mL, 1.50 mmol) was added. The resulting mixture was stirred at 78 °C for an additional 1.5 h. EtOAc (25 mL), diethyl ether (25 mL) and saturated aqueous ammonium chloride (30 mL) were added to the cold reaction mixture. The phases were separated and the organic layer was washed with water (2×30 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc–hexane (1:19 and 1:9). Yield 153 mg (70%) of yellow wax. R_f=0.17 (1:4 EtOAc–hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.36 (br s, 1H, OH), 6.17 (br s, 1H, CH), 6.60 (dd, 1H, J=7.4, 1.7 Hz, 6-H), 6.96–7.33 (m, 13H, Ar), 7.98 (br d, J=7.4 Hz, 1H, 5-H), 8.02 (br s, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=59.05 (CH–OH), 99.95, 111.18, 115.60, 116.03, 116.58, 117.02, 119.49, 119.71, 122.83, 125.17, 125.99 (d, J_{CF}=3.5 Hz, C–F),

126.37, 127.31, 128.03, 128.39, 129.67 (d, $J_{CF}=3.2$ Hz, C–F), 132.53, 132.58, 132.70, 132.74, 143.81, 163.50 (d, $J_{CF}=250.0$ Hz, C–F). ^{19}F NMR (188 MHz, $CDCl_3$): $\delta=-112.07$ (C–F), -114.84 (C–F). MS (EI); *m/z* (%): 436 [M^+] (100), 419 (67), 359 (68), 330 (14), 235 (2), 105 (7), 77 (2). –$C_{28}H_{18}F_2N_2O$ (436.14): Calcd C, 77.05; H, 4.16; N, 6.42; found C, 76.75; H, 4.25; N, 6.09.

4.2.11. 1-(α-Hydroxybenzyl)-2,3-di(4-chlorophenyl)-indolizine-7-carbonitrile (7c). *n*-Butyllithium (0.310 mL of 1.65 M solution in hexane, 0.56 mmol) was added dropwise to a stirred solution of 1-bromo-2,3-di(4-chlorophenyl)indolizine-7-carbonitrile (221 mg, 0.50 mmol) in dry THF (10 mL) at -78 °C under N_2. The title compound was then prepared as described for compound **7b** above. Yield 166 mg (71%) of yellow crystals, mp 108–109 °C. $R_f=0.30$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.32$ (br s, 1H, OH), 6.10 (br s, 1H, CH), 6.55 (dd, 1H, $J=7.5$, 1.7 Hz, 6-H), 7.04–7.36 (m, 13H, Ar), 7.94 (br d, $J=7.5$ Hz, 1H, 5-H), 7.97 (br s, 1H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=70.04$ (CH–OH), 100.26, 111.35, 119.71, 122.82, 124.86, 126.35, 127.37, 128.08, 128.26, 129.01, 129.05, 129.45, 129.94, 131.91, 132.10, 132.28, 134.05), 135.05. MS (EI); *m/z* (%): 468 [M^+] (59), 452 (75), 393 (32), 363 (11), 339 (10), 292 (4), 105 (12), 77 (5). HRMS: Calcd for $C_{28}H_{18}Cl_2N_2O$: 468.0784; found 468.0796.

4.2.12. 1-(α-Hydroxybenzyl)-2,3-di(*p*-tolyl)indolizine-7-carbonitrile (7d). *n*-Butyllithium (0.310 mL of 1.6 M solution in hexane, 0.56 mmol) was added dropwise to a stirred solution of 1-bromo-2,3-di(*p*-tolyl)indolizine-7-carbonitrile (200 mg, 0.50 mmol) in dry THF (20 mL) at -78 °C under N_2. The title compound was then prepared as described for compound **7b** above. Yield 153 mg (77%) of yellow crystals, mp 84–87 °C. $R_f=0.43$ (SiO_2, EtOAc–hexane, 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.27$ (br s, 1H, OH), 2.34 (s, 3H, Me), 2.37 (s, 3H, Me), 6.14 (br s, 1H, CH), 6.48 (dd, 1H, $J=7.4$, 1.7 Hz, 6-H), 6.97–7.03 (m, 5H, Ar), 7.04–7.26 (m, 8H, Ar), 7.86 (br s, 1H, H-8), 7.94 (br d, 1H, $J=7.5$ Hz, 5-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 21.65 (Me), 21.79 (Me), 66.27 (CH–OH), 99.14, 110.73, 119.79, 119.87, 122.94, 126.41, 127.14, 127.23, 127.75, 128.21, 128.86, 129.43, 130.16, 130.57, 130.94, 137.30, 138.71, 144.11. MS (EI); *m/z* (%): 428 [M^+] (100), 413 (10), 351 (49), 323 (12), 105 (5). HRMS: Calcd for $C_{30}H_{24}N_2O$ 428.1906, found 428.1889.

4.3. Constant-potential electrochemical oxidation of compounds 4h, 4m–n and 4p

All electrolysis experiments were performed in an H-shaped cell, the compartments of which were separated by a medium-frit glass junction. Platinum gauze working electrodes were used. In the experiments, an appropriate indolizine (20–60 mg, 0.04–0.15 mmol) was suspended in acetonitrile/0.05 M $Me_4N^+BF_4^-$ (20 mL) in the electrolysis cell and the appropriate working electrode potential was applied to the cell. The electrolyzed solutions were immediately transferred to round-bottomed flasks, and the solvent was removed under vacuum. The residue was extracted with dichloromethane (leaving the electrolyte behind), and the extract was filtered and precipitated from chlorobenzene to give the corresponding oxoindolizinium salts **8a–d**.

4.3.1. 2,3-Diphenyl-7-cyano-1-oxoindolizinium tetrafluoroborate (8a). Reddish precipitate, yield 55%; mp 151–154 °C; IR ν_{max} 1746 (C=O), 1637, 1447, 1407, 1321, 1133, 1061, 1007, 844, 736 cm^{-1}. ^{1}H NMR is in accordance with the literature values.[1b] ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=207.18$ (C=O), 134.08, 131.24, 130.33, 130.14, 129.59, 129.54, 129.33, 129.18, 128.89, 128.82, 127.57, 127.36. MS (ESI); *m/z* (%): 309 [M^+] (46), 279 (7), 178 (10), 176 (5), 131 (7), 103 (15).

4.3.2. 2,3-Diphenyl-1-oxoindolizinium tetrafluoroborate (8b). Reddish precipitate, yield 64%; mp 178–182 °C; IR ν_{max} 1739 (C=O), 1625, 1498, 1448, 1356, 1032, 739 cm^{-1}. ^{1}H NMR is in accordance with literature values.[1b] ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=185.65$ (C=O), 150.96, 133.72, 132.75, 131.30, 130.92, 130.79, 130.59, 131.13, 128.19, 126.99, 124.40, 123.59; MS (ESI), *m/z* (%): 285 [M^+] (100).

4.3.3. 2,3-Diphenyl-7-acetyl-1-oxoindolizinium tetrafluoroborate (8c). Reddish precipitate; yield 55%; mp 165–170 °C; IR ν_{max} 1740 (C=O), 1708 (C=O), 1636, 1595, 1446, 1363, 1278, 1177, 1057, 899, 731 cm^{-1}. ^{1}H NMR is in accordance with the literature values.[1b]

4.3.4. 2,3-Diphenyl-7-tert-butyl-1-oxoindolizinium tetrafluoroborate (8d). Reddish wax; yield 18%; IR ν_{max} 2971, 1735 (C=O), 1632, 1481, 1372, 1181, 1154, 1055, 1035, 698 cm^{-1}. ^{1}H NMR is in accordance with the literature values.[1b]

4.4. Constant-potential electrochemical oxidations of compounds 5a and 5d

All experiments were performed in the same way described for **4h**, **4m–n** and **4p** above. The electrolyzed solutions were immediately transferred to round-bottomed flasks, and the solvent was removed. The residue was extracted with dichloromethane (leaving the electrolyte behind) and the extract was filtered. The solvent was removed and transferred to an NMR tube by dissolving with $CDCl_3$ (4 mL). D_2O (ca. 3 mL) and 2–3 mg of *L*-ascorbic acid were added to the NMR tube and the tube was thoroughly shaken. The tube was let to stand for a few minutes and the colour of the organic layer was then changed to yellow. The aqueous layer was then taken out and the rest was purified by flash chromatography, eluting with CH_2Cl_2 to afford the dimers **9a** and **9b**. All the spectroscopic data for compound **9a** were in accordance with the literature data.[2b]

4.4.1. 2,2′3,3′-Tetra(*p*-tolyl)-1,1′-biindolizine-7-7′-dicarbonitrile (9b). Yellowish powder; yield 54%, R_f 0.57 (SiO_2, EtOAc–hexane; 1:4), mp 253–256 °C; ^{1}H NMR (200 MHz, $CDCl_3$), $\delta=2.16$ (s, 6H, 2×CH_3), 2.37 (s, 6H, 2×CH_3), 6.49 (dd, 2H, $J=7.4$, 1.78 Hz, 6-H, 6′-H), 6.58 (d, 4H, $J=8.1$ Hz, Ar), 7.13 (d, 4H, $J=8.0$ Hz, Ar), 7.19 (m, 8H, Ar), 7.42 (br s, 2H, 8-H, 8′-H), 7.98 (dd, 2H, $J=7.4$, 0.83 Hz, 5-H, 5′-H). ^{13}C NMR (50 MHz, $CDCl_3$), $\delta=$ 138.77, 136.21, 131.07, 130.95, 130.74, 130.17, 129.58, 128.87, 127.38, 126.87, 125.92, 122.91, 119.65, 110.65,

110.29, 99.25, 21.80, 21.52. MS (EI); *m/z* (%): 642 [M^+] (100), 555 (2), 321 (12), 98 (2), 44 (8). HRMS ($C_{46}H_{34}N_4$):Calcd 642.2783; found 642.2767.

4.5. Constant-potential electrochemical oxidations of compound 7a

All experiments were performed in the same way described for **4h**, **4m–n** and **4p** above. The electrolyzed solution was immediately transferred to a round-bottomed flask, and the solvent was removed. The residue was extracted with dichloromethane (leaving the electrolyte behind) and the extract was filtered and purified by flash chromatography eluting with EtOAc–hexane (1:29) followed by (1:19), (1:9) and finally (1:4) to get the novel ketone **10a** together with the starting material **7a** in 49% total yield. The ratio of **10a** to **7a** was roughly 1:1 as observed by ^{1}H NMR spectroscopy.

4.5.1. 8-Benzoyl-2,3-diphenyl-7-indolizinecarbonitrile (10a). Yellowish wax; ^{1}H NMR (200 MHz, $CDCl_3$), δ= 6.50 (d, J=8.0 Hz, H-6), 7.03 (s, 1H, H-1), 7.12–7.24 (m, 10H, Ph), 7.26–7.32 (m, 5H, Ph), 7.89 (d, J=7.8 Hz, H-5). ^{13}C NMR (50 MHz, $CDCl_3$), δ=104.00, 112.31, 115.33, 122.84, 126.14, 126.42, 127.21, 128.03, 128.55, 128.68, 129.08, 129.32, 129.67, 129.74, 130.38, 130.49, 134.05, 138.35, 170.56, 192.05. MS (EI); *m/z* (%): 398 [M^+] (100), 321 (50), 293 (18), 292 (12), 199 (3), 105 (32).

Acknowledgements

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Stereoselective allylation of chiral monoperoxyacetals

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Abstract—Neighboring iodo-, alkoxy-, acetoxy- and silyl groups impart useful levels of diastereoselection in the Lewis acid-mediated allylation of monoperoxyacetals. Although monoperoxyacetals are found to be considerably less reactive than corresponding nonperoxidic acetals, similar stereochemical trends are observed in the two series.

1. Introduction

Although the number of reported peroxide natural products continues to increase, methodology for peroxide synthesis remains limited.[1,2] For example, there exist only a handful of approaches to homoallyl peroxides and 3-peroxyalkanoates, common subunits in peroxide natural products; some typical examples are illustrated in Figure 1. We have reported new methodology for introduction of these substructures based upon Lewis acid-mediated reactions of monoperoxyacetals with electron-rich alkenes.[3,4] We sought to extend this methodology to asymmetric synthesis and we now report the stereoselective allylation of monoperoxyacetals based upon stereoinduction from neighboring chiral centers.

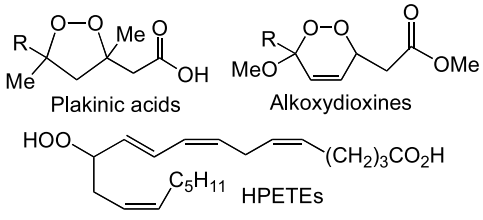

Figure 1. Naturally occurring homoallyl peroxides and 3-peroxyalkanoates.

The Lewis acid-mediated reactions of peroxyacetals appear to involve ionization to intermediate peroxycarbenium ions,[3] a mechanism which limits the stereochemical influence of the departing alkoxide, the Lewis acid, or the acetal center. We therefore chose to investigate induction from a resident stereocenter in the peroxyacetal backbone. This approach, while unexplored in peroxide chemistry, has precedent in the chemistry of simple acetals. For example, Cram–Felkin–Anh (CFA) stereoinduction has been demonstrated in reactions of acetals.[5] However, effective CFA directing groups are rarely practical in terms of the conditions required for synthetic modification or removal. We were intrigued by reports of diastereoselective displacements of nonperoxidic acetals based upon induction from neighboring heteroatoms.[6,7] We now report on the Lewis acid-mediated displacement of halo-, alkoxy, acyloxy, and silyl-substituted monoperoxyacetals. (Fig. 2).

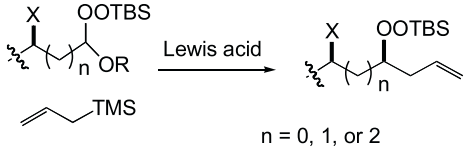

Figure 2. Overview.

2. Results and discussion

Our studies focused on induction from 2-, 3-, and 4-substituted monoperoxyacetals (Fig. 2).

2.1. Preparation of substrates

Preparation of 2-halo- and 2-mercurioperoxyacetals is illustrated in Table 1. Enol ethers **1** and **2** were prepared as isomeric mixtures and reacted with *t*-butyl hydroperoxide in the presence of NIS, NBS, or mercuric acetate to furnish 2-halo or 2-mercurioperoxyacetals as mixtures of diastereomers.[8] The diastereomeric 2-mercurioperoxyacetals were easily separated. The isomeric 2-haloperoxyacetals were inseparable but mixtures enriched in one diastereomer

Keywords: Peroxide; Monoperoxyacetal; Allylation; Lewis acid; Stereoinduction; Neighbouring group.
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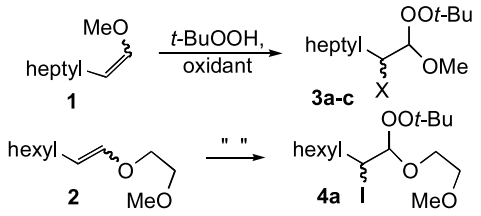
Table 1. Synthesis of 2-halo/mercurioperoxyacetals

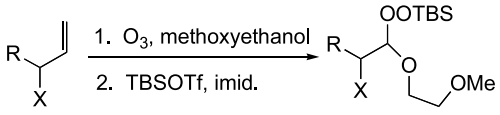


Substrate	Oxidant	Product	X	Yield (%)
1	NIS	**3a**	I	60
1	NBS	**3b**	Br	45
1	$Hg(OAc)_2$	**3c**	HgCl	80
2	NIS	**4a**	I	47

were available based upon peroxyhalogenation of samples of enol ether enriched in the *E*-isomer. The halo- and chloromercurioperoxyacetals were quite stable, except for iodoacetal **3a**, which decomposed upon prolonged storage.

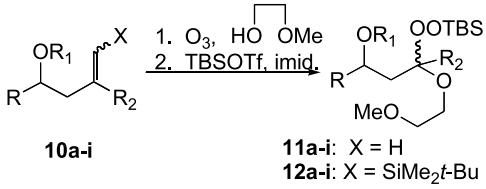
The preparation of 2-silyl peroxyacetals, an unknown class of compounds, was initially modeled for an achiral substrate (Table 2). Ozonolysis of allyltriphenylsilane in 2-methoxyethanol cleanly furnished a 2-triphenylsilyl hydroperoxyacetal, which underwent *O*-silylation to furnish peroxyacetal **5**.[9] Ozonolysis of chiral trialkylsilane **6** furnished an 85:15 mixture of diastereomeric 2-silyl hydroperoxyacetals, a result demonstrating significant influence of the trialkylsilyl group on the intermediate carbonyl oxide. Curiously, ozonolysis of the analogous

Table 2. Synthesis of 2-silyl monoperoxyacetals



Substrate	R	X	Product
$AllySiPh_3$	H	$SiPh_3$	**5** (45%)
6	Hexyl	$SiMe_2tBu$	**8** (54%)
7	Hexyl	$SiPh_3$	—

Table 3. Synthesis of 3-oxygenated peroxyacetals

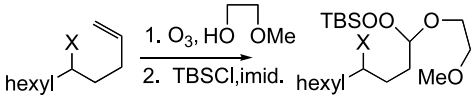


	R	R_1	R_2	X	**11a–i** (%)	**12a–i** (%)
10a	Heptyl	TBS	H	OMe	73	85
10b	Heptyl	Me	H	H	45	87
10c	Heptyl	Bn	H	H	45	88
10d	Heptyl	Ac	H	H	60	77
10e	Heptyl	Bz	H	H	40	75
10f	Heptyl	Piv	H	H	50	60
10g	Heptyl	MOM	H	H	55	82
10h	Ph	Ac	H	H	50	55
10i	Hexyl	Ac	Me	H	62	75

triphenylsilane (**7**) led only to decomposition. Attempts to prepare 2-mercapto monoperoxyacetals by a similar approach involving ozonolysis of allyl sulfides (not shown) were uniformly unsuccessful.

A series of 3-oxygenated peroxyacetals **12a–i** were prepared through ozonolysis of unsaturated ethers and esters, followed by silylation of the derived hydroperoxyacetals (Table 3). In each case, the new peroxyacetals were formed as 1:1 mixtures of epimers. Two 4-substituted peroxyacetals were prepared by a similar procedure (Table 4).

Table 4. Synthesis of 4-substituted monoperoxyacetals

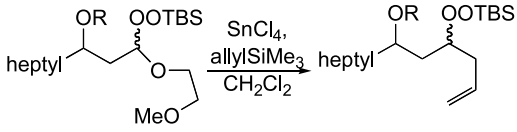


Substrate	X	Product	Yield
13a	OMe	**14a**	40
13b	I	**14b**	34

2.2. Lewis acid-mediated reactions

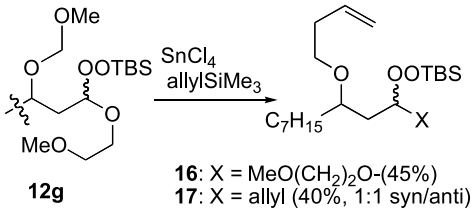
Allylations were initially investigated for 3-substituted peroxyacetals (Table 5). Optimal conditions were found to involve addition of stoichiometric $SnCl_4$ to a 0 °C solution of the peroxyacetal and allylsilane.[3] Reactions were generally complete within one to 2 h. The products were isolated and purified by standard methods, with diastereoselectivity determined by NMR integration; control experiments demonstrated no difference in diastereomer ratios before or after purification. Ether **12b** and the pivaloate ester **12f** reacted with moderate *syn* selectivity (vide infra); diastereoselection was reduced in the case of the acetate (**12d**) or benzoate (**12e**) and nonexistent for the silyloxy peroxyacetal (**12a**). A benzylic monoperoxyacetal (**12h**) and the sole monoperoxyketal (**12i**) underwent predominant decomposition under the reaction conditions (not shown).

Table 5. Allylation of 3-oxygenated peroxyacetals



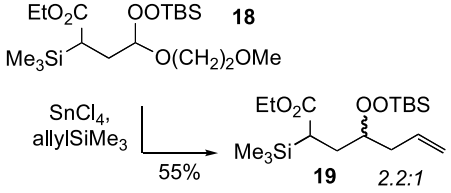
S. mat.	R	Product	Yield (%)	*syn*/*anti*
12a	$SiMe_2t$-Bu	**15a**	65	50:50
12b	Me	**15b**	60	75:25
12c	Bn	**15c**	50	60:40
12d	Ac	**15d**	60	60:40
12e	Bz	**15e**	55	62:38
12f	Piv	**15f**	55	73:27

Monoperoxyacetal **12g**, a substrate intended to explore 1,5-stereoinduction via ethereal oxygen, instead revealed the tremendous difference in reactivity between peroxidic and nonperoxidic acetals; both major products resulted from initial allylation of the MOM group (Eq. 1). To our knowledge, this is the first direct comparison of the reactivity of an acetal and a monoperoxyacetal under ionizing conditions.



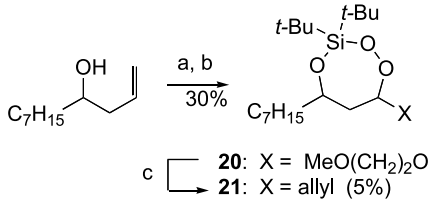
(1)

Peroxyacetal **18** was investigated as a substrate in which interaction of the ester carbonyl with the developing peroxycarbenium ion would provide a transient cyclic framework for stereoinduction from the 3-trimethylsilyl group. Diastereoselection in formation of the homoallyl peroxide was similar to that obtained for the 3-alkoxy and 3-acyloxy substrates shown above (Eq. 2).



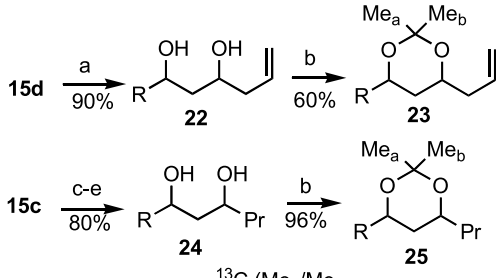
(2)

We also investigated 1,3-stereoinduction through a temporary scaffold (Scheme 1). Ozonolysis of a homoallylic alcohol followed by bissilylation of the derived hydroperoxyalcohol achieved the first synthesis of a 3-sila-1,2,4-trioxepane (**20**). Unfortunately, this substrate was nearly unreactive, furnishing <5% yield of allylated silatrioxepane under typical reaction conditions; attempted reaction at higher temperatures resulted in decomposition.



Scheme 1. Allylation of alkoxysilatrioxepane. (a) O_3, 2-methoxyethanol; (b) t-$Bu_2Si(OTf)_2$, DMF, imidazole; (c) allyltrimethylsilane, $SnCl_4$, 0 °C.

Stereochemical correlation. The major diastereomers for the 3-alkoxy- and 3-acyloxyhomoallyl peroxides **15c** and **15d** were assigned as *syn* based upon the ^{13}C chemical shifts of the derived 1,3-dioxanes **23** and **25** (Scheme 2).[10]

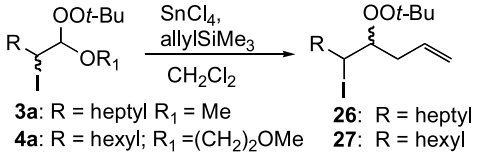


Acetonide	R	^{13}C (Me_a/Me_b, major diast.)	stereochem.
23	heptyl	30.3, 19.8	syn
25	heptyl	30.4, 19.8	syn

Scheme 2. Stereochemical correlation. (a) $LiAlH_4$; (b) 2,2-dimethoxypropane, CSA; (c) THF/HOAc/H_2O; (d) PPh_3; (e) Pd/H_2.

1,2-Stereoinduction. The observed diastereoselectivity for allylation of 2-iodoperoxyacetal **3a** varied somewhat depending upon the composition of the starting material but consistently afforded one major diastereomer (Table 6). The major product was assigned as *anti* based upon spectral correlations with reports for 2-iodoethers[5] and 2-iodoperoxides.[11] Intriguingly, iodoacetal **3a** underwent allylation at −78 °C, whereas most other peroxyacetals, including the closely related **4a**, undergo reaction only at temperatures near 0 °C. In addition, significant decomposition of **3a** was observed under the reaction conditions. The 2-bromoperoxyacetal **3b** was unreactive while the 2-chloromercurioperoxyacetal underwent rapid decomposition in the presence of either $SnCl_4$ or TMSOTf (not shown).

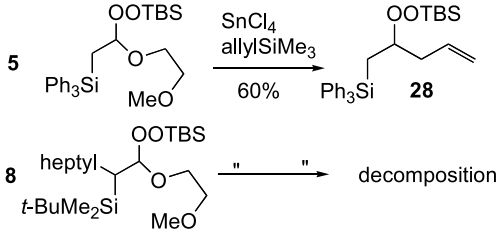
Table 6. Allylation of 2-iodoperoxyacetals



S. mat.	dr	T (°C)	Product (yield)	*syn/anti*
3a	40:60	−78	**26** (30%)	1:1.4
3a	75:25	−78	**26** (28%)	1:9
4a	76:24	0	**27** (23%)	1:3
4a	71:29[a]	0	**27** (20%)	1:5

[a] Conducted in 25% CH_3NO_2/CH_2Cl_2.

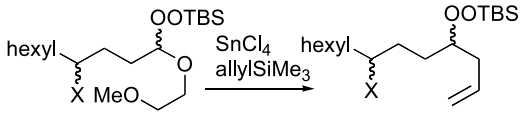
Investigation of 1,2 stereoinduction from a silyl group was thwarted by the decomposition of silyl peroxyacetal **8** under the reaction conditions (Scheme 3). This failure was curious, given the successful allylation of the achiral model (**5**).



Scheme 3. Allylation of 2-silyl monoperoxyacetals.

1,4-Stereoinduction. Allylation of the 4-methoxyl peroxyacetal **14a** proceeded in good yield and with moderate stereoselection; the 4-iodoperoxyacetal (**14b**) underwent allylation in lower yield and with reduced diastereoselection (Table 7).

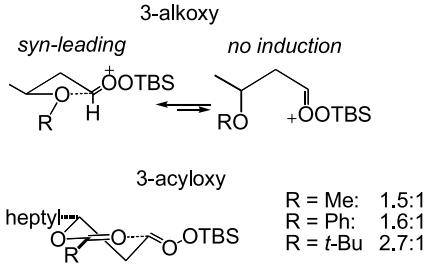
Table 7. Allylation of 4-substituted monoperoxyacetals



Substrate	X	Product	Yield (%)	dr
14a	OMe	**29a**	78	71:29
14b	I	**29b**	30	60:40

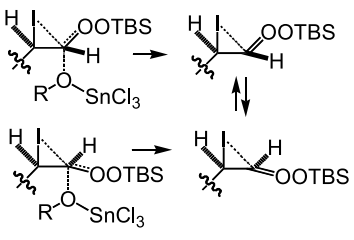
2.3. Discussion

Our results demonstrate the influence of neighboring heteroatoms on the reactivity of peroxyacetals and the stereoselectivity of peroxyacetal displacement. The degree of influence is dependent upon the nature and location of the group. Peroxyacetals bearing 3-alkoxy and 3-acyloxy substituents are as reactive as unsubstituted monoperoxyacetals,[2] suggesting only limited influence of β-oxygenation on the barriers to substrate ionization. However, the *syn* selectivity observed for reactions of 3-methoxy and 3-pivaloyloxy peroxyacetals, and the complete lack of selectivity for the 3-trialkylsiloxy substrate, indicates the importance of interactions with the intermediate peroxycarbenium ion; in the case of the 3-acyloxy groups, the diastereoselection varies with the bulk of the side chain. The outcome with the trialkylsiloxy group is similar to results observed with 3-silyloxyaldehydes (Eq. 3).[12] Our results provide a mechanistic underpinning for results reported for reactions of 3-alkoxy acetals.[5] Moderate stereochemical induction is also observed for the 4-methoxyperoxyacetal, although the selectivity is lower than that reported for reactions of 4-alkoxyacetals.[7]



(3)

The enhanced reactivity of 2-iodo and 2-triphenylsilyl peroxyacetals suggests a significant influence on substrate ionization. Allylation of the 2-iodoperoxyacetals proceeds with higher diastereoselectivity than for any of the other substrates studied. This, combined with the consistent preference for formation of the anti diastereomer, suggests a strong interaction with a peroxycarbenium ion or similar species. At the same time, the variation in product diastereoselection depending upon the composition of the starting material suggests the possibility of reaction through both intimate versus separated ion pairs (Eq. 4). While the chiral 2-trialkylsilyl peroxyacetals underwent decomposition under reaction conditions, it is interesting to note that the 2-trialkylsilyl group exerted a very strong influence on the stereochemistry of trapping of a neighboring carbonyl oxide.



(4)

3. Conclusion

Easily installed and synthetically tractable neighboring groups are shown to impart useful levels of stereoinduction to the allylation of monoperoxyacetals. The results, while paralleling previous findings for reactions of nonperoxidic acetals, are influenced by the unique reactivity patterns of the peroxyacetals. Application of these results to the synthesis of peroxide natural products is under investigation.

4. Experimental

4.1. General

Standard experimental procedures have been described elsewhere.[13] All new compounds were determined to be >95% pure based upon ^{1}H or ^{13}C NMR. Unless otherwise noted NMR spectra were recorded at 500 (^{1}H) or 125 (^{13}C) MHz in $CDCl_3$. FT-IR spectra were recorded as CH_2Cl_2 or $CDCl_3$ solutions; selected absorbances are reported in cm^{-1}. Most hydroperoxides and peroxides failed to generate identifiable molecular or fragmentation ions (HRFAB or HREI).

4.1.1. (*E*)- and (*Z*)-1-Methoxy-1-nonene (1). The title compounds were prepared as a mixture from octanal.[14]

4.1.2. (*E*)- and (*Z*)-1-(2-Methoxyethoxy)-oct-1-ene (2). The title compounds were prepared using a variation of a reported procedure.[15] Into a solution of 1-octanal (2.0 g, 16 mmol) in 2-methoxyethanol (50 mL) was added *p*-TsOH·H_2O (cat., 100 mg). The reaction was stirred for 15 min and then quenched with sat. NH_4Cl solution. (100 mL) The Et_2O extracts (2×50 mL) were dried over Na_2SO_4 and concentrated. Flash chromatography (20% EA/Hex) furnished 1,1-bis-(2-ethoxymethoxy)-octane (3.7 g, 90%). R_f=0.48 (20% EA/hex); ^{1}H δ 4.53 (t, 1H, J=6.0 Hz), 3.65 (m, 2H), 3.56 (m, 2H), 3.47 (t, 4H, J=4.7 Hz), 3.30 (s, 6H), 1.59–1.55 (2H), 1.30–1.20 (10H), 0.80 (t, 3H, J=6.6 Hz); ^{13}C δ 103.2, 71.9, 63.9, 58.7, 32.9, 31.6, 29.2, 29.0, 24.5, 22.4, 13.8; IR 1129; HRFAB calcd for $C_{14}H_{30}O_4Li$ $(M+Li)^+$: 269.2304; found: 269.2317, 4.9 ppm.

A solution of the bis-methoxyethoxy acetal (2.9 g, 11 mmol) and diisopropylethylamine (50 mL) was heated to 115–120 °C in an oil bath whereupon trimethylsilyl trifluoromethanesulfonate (2.7 g, 12 mmol, 2.2 mL) was rapidly added. After 2 min, the oil bath was removed and the reaction was quenched with 10% NaOH (50 mL) and hexanes (100 mL). The organic layer was washed with 10% NaOH (2×25 mL) and water (50 mL), dried over Na_2SO_4 and concentrated. The DIPEA was removed under vacuum and the crude product was purified by flash chromatography to furnish 1-2-(methoxyethoxy)-oct-1-ene (**2**) as a colorless liquid consisting of a 1:4.2 mixture of *E* and *Z* isomers (1.4 g, 70%): R_f=0.44 (2% EA/hex); ^{1}H δ 6.25 (d, 0.2H, J=12.6 Hz), 5.94 (d, 0.8H, J=6.3 Hz), 4.78 (dt, 0.2H, J=12.6, 7.2 Hz), 4.34 (dd, 0.8H, J=6.9, 7.2 Hz), 3.84 (t, 1.6H, J=4.7 Hz), 3.78 (t, 0.4H, J=4.7 Hz), 3.59 (t, 0.4H, J=4.7 Hz), 3.56 (t, 1.6H, J=4.7 Hz), 3.39 (s, 0.8H), 3.387 (s,

2.2H), 2.09–2.05 (1.6H), 1.91–1.87 (0.4H), 1.31–1.27 (8H), 0.87 (t, 3H, J=6.9 Hz); ^{13}C δ 146.0, 144.7, 107.8, 104.7, 71.7, 71.24, 71.21, 68.2, 59.09/59.04, 31.74/31.70, 30.6, 29.7, 28.9, 28.6, 27.6, 23.9, 22.6, 14.0; IR 1660, 1101; HRFAB calcd for $C_{11}H_{22}O_2Li$ $(M+Li)^+$: 193.1780; found: 193.1774 (3.1 ppm).

4.1.3. (*syn*)- and (*anti*)-1-*tert*-Butylperoxy-2-iodo-1-methoxynonane (3a). A solution of 70% aqueous *tert*-BuOOH (10 mL) was extracted with CH_2Cl_2 (10 mL). The organic layer was successively dried over Na_2SO_4 and $MgSO_4$ and 4 mL of the resulting solution was added into solution of enol ether **1** (1.0 equiv, 3.6 mmol, 570 mg) in CH_2Cl_2 (10 mL). The mixture was cooled to −78 °C and *N*-iodosuccinimide (1.5 equiv, 5.5 mmol, 1.23 g) was added. The reaction flask was briefly removed from cooling bath whenever the mixture solidified. After 15 min the reaction was quenched with DI water and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was redissolved into 2% EA/hex (50 mL) and stirred over a pinch of charcoal until the reddish violet color was lost (ca. 15 min). The solution was filtered through a plug of cotton and concentrated under reduced pressure. Flash chromatography furnished 0.82 g (60%) of **3a** as a mixture of diastereomers which could not be completely separated. R_f=0.6 (2% EA/hex); ^{1}H δ 4.78 (d, 0.7H, 4.4), 4.57 (d, 0.3H, 5.0), 4.09–4.04 (m, 1H), 3.575 (s, 1.8H), 3.57 (s, 1.2H), 1.78–1.73 (2H), 1.55–1.47 (2H), 1.32–1.19 (17H, including obscured singlets from *tert*-Bu), 0.85 (t, 3H, J=6.9 Hz); ^{13}C δ 108.3/107.8, 80.9/80.7, 58.0/57.9, 34.8, 33.9, 33.2, 32.6, 31.7, 29.4, 29.37, 29.3, 29.0, 28.7, 28.6, 26.5, 22.5, 13.96; IR 2977–2851, 1358, 1249, 1199, 1110; HRFAB calcd for $C_{13}H_{26}IO_2$ $(M-OMe)^+$: 341.0978; found: 341.1177 (58.3 ppm).

4.1.4. *syn*- and *anti*-2-Bromo-1-*tert*-butylperoxy-1-methoxy-nonane (3b). Into a −20 °C solution of enol ether (522 mg, 3.3 mmol) and *tert*-BuOOH in CH_2Cl_2 (5 mL) was added NBS (2.0 equiv, 1.2 g). After 15 min, the reaction mixture was quenched with DI water, and extracted with recycled EA/Hex (3×30 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes or *n*-pentane) furnished 490 mg (45%) of a mixture of diastereomeric bromo peroxy acetals: R_f=0.7 (*n*-pentane); ^{1}H δ 4.88 (d, 0.5H, J=4.7 Hz), 4.79 (d, 0.5H, J=5.4 Hz), 4.04–3.98 (m, 1H), 3.59 (s, 1.7H), 3.58 (s, 1.3H), 1.99–1.89 (2H), 1.8–1.71 (2H), 1.41–1.21 (17H), 0.87 (t, 3H, J=6.9 Hz); ^{13}C δ 108.0/107.7, 81.0, 58.02/57.94, 53.6/52.8, 33.2, 32.7, 31.8, 31.7, 29.0, 28.9, 28.8, 27.25, 27.24, 26.6, 26.5, 22.5, 14.0; IR 2924–2858, 1238, 1192, 1102; HRMS: no identifiable ions were observed.

4.1.5. *syn*- and *anti*-1-*tert*-Butylperoxy-2-chloromercurio-1-methoxynonane (3c). To a solution of $Hg(OAc)_2$ (1.1 equiv, 3.70 mmol, 1.18 g) and *tert*-BuOOH in CH_2Cl_2 (5 mL) in an ice bath was added, dropwise, enol ether **1** (1.0 equiv, 3.4 mmol, 525 mg) as a solution in CH_2Cl_2 (10 mL). After the addition was complete, the reaction was allowed to warm to room temperature and stirred until the salt had dissolved (5 min). Solvent was removed under reduced pressure and the residue was diluted with hexanes (50 mL). The solution was washed with satd NaCl (3×100 mL) and dried over Na_2SO_4 The precipitate obtained upon concentration was suspended in hexanes (50 mL) and filtered through a plug of cotton. Removal of solvent in vacuo followed by purification through flash silica (5% EA/hex) furnished colorless oil (1.3 g, 80%) as a mixture of diastereomers, which were easily separated by HPLC (4.6×25 mm Si, 5% EA/hex, 10 mL/min, 13.6 min, 17.0 min). *First eluting diastereomer*: R_f=0.33 (5% EA/hex); ^{1}H δ 4.96 (d, 1H, J=2.5 Hz), 3.55 (s, 3H), 2.68–2.64 (m, 1H), 1.80–1.58 (2H), 1.48–1.28 (8H), 1.26–1.25 (11H), 0.87 (t, 3H, J=6.6 Hz). ^{13}C 109.2, 80.9, 57.3, 32.5, 31.7, 31.0, 29.3, 29.0, 26.6, 24.7, 22.5, 14.0. *Second eluting diastereomer*: R_f=0.33 (5% EA/hex); ^{1}H 4.98 (d, 1H, J=3.8 Hz), 3.49 (s, 3H), 2.6–2.56 (m, 1H), 1.83–1.57 (2H), 1.47–1.29 (6H), 1.27–1.23 (13H), 0.86 (t, 3H, J=6.9 Hz); ^{13}C δ 108.8, 80.9, 56.79, 56.77, 54.6, 32.3, 31.7, 30.5, 29.3, 29.0, 26.6, 22.5, 13.93, 13.91; IR (cm^{-1}): 2924–2854, 1464, 1366, 1181, 1105; HRMS (FAB/EI) observed only high molecular weight ion aggregates.

4.1.6. *syn*- and *anti*-1-*tert*-Butylperoxy-2-iodo-1-(2-methoxyethoxy)-octane (4a). Into a −25 °C solution of enol ether **2** (845 mg, 4.5 mmol) in CH_2Cl_2 (10 mL) was added *tert*-BuOOH (5 mL of a 5.0–6.0 M solution in nonane), followed by *N*-iodosuccinimide (1.5 g, 6.8 mmol, 1.5 equiv). The reaction was stirred for 5 min and then quenched with DI water. The Et_2O extracts (2×50 mL) were dried over Na_2SO_4 and concentrated. Workup and purification as for iodoacetal **3a** furnished 0.85 g (47%) of **4a** as a 4:1 mixture of diastereomers which could not be cleanly separated. R_f=0.38 (2% EA/hex); ^{1}H δ 4.92 (d, 0.8H, J=5.0 Hz), 4.77 (d, 0.2H, J=5.0 Hz), 4.10–4.03 (2H), 3.86–3.81 (1H), 3.61–3.54 (2H), 3.38 (s, 3H), 1.84–1.74 (2H), 1.58–1.32 (8H), 1.27 (s, 6.3H), 1.268 (s, 2.7H), 0.87 (t, 3H, J=6.9 Hz); ^{13}C δ 107.4, 107.0, 81.0, 71.95/71.91, 69.79/69.76, 59.0, 34.3, 32.8, 31.60/31.57, 29.3, 28.41, 28.36, 26.6, 22.5, 14.0; IR 1242, 1195, 1125; HRFAB calcd for $C_{15}H_{31}IO_4Li$ $(M+Li)^+$: 409.1427; found: 409.1432 (1.1 ppm).

4.1.7. 1-(2-Methoxyethoxy)-2-triphenylsilyl ethyl *tert*-butyl dimethylsilyl peroxide (5). Yield=0.65 g, 50%. 1-(2-Methoxyethoxy)-2-triphenylsilyl ethyl hydroperoxide was prepared by ozonolysis of allyltriphenylsilane in 2-methoxyethanol using the procedure described for homoallyl ethers and esters (vide infra). R_f=0.52 (50% EA/hex); ^{1}H (400 MHz) δ 10.58 (s, 1H), 7.72–7.69 (6H), 7.49–7.40 (9H), 5.19 (dd, 1H, J=4.5, 8.3 Hz), 3.62–3.48 (3H), 3.47–3.41 (1H), 3.4 (s, 3H), 2.24 (dd, 1H, J=8.3, 14.9 Hz), 2.05 (dd, 1H, J=4.5, 15.2 Hz). ^{13}C (100 MHz) δ 135.5, 134.1, 129.2, 127.5, 105.5, 72.2, 65.1, 58.5, 17.5; IR 3306 (broad), 1481, 1350, 1196, 1128; HRMS: no identifiable ions were observed.

Silylation of the hydroperoxyacetal under standard conditions (vide infra) furnished the silyl peroxyacetal **5**: Yield=429 mg, 90%. R_f=0.35 (5% EA/hex); ^{1}H (400 MHz) δ 7.66–7.64 (6H), 7.48–7.40 (9H), 5.11 (dd, 1H, J=4.3, 8.1 Hz), 4.06 (m, 1H), 3.43 (m, 1H), 3.32 (m, 1H), 3.32 (t, 2H, J=5.05 Hz) 3.296 (s, 3H), 2.13 (dd, 1H, J=8.1, 14.9 Hz), 1.92 (dd, 1H, J=4.3, 14.9 Hz), 0.98 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H). ^{13}C (100 MHz) δ 135.7,

134.6, 129.4, 127.7, 106.9, 71.6, 69.4, 58.6, 26.1, 18.0, −5.7, −5.8; IR 1473, 1326, 1188, 1124. HRFAB calcd for $C_{29}H_{40}O_4Si_2Li$ $(M+Li)^+$: 515.2625; found: 515.2620 (1.0 ppm).

4.1.8. *tert*-Butyldimethyl(1-nonen-3-yl)silane (6). The title compound was prepared by C-silylation of octanal *tert*-butylimine followed by Wittig methylenation of the derived aldehyde.[16]

4.1.9. 1-Nonen-3-yl triphenylsilane (7). The title compound was prepared by a similar procedure as for **6**; the yield for methylenation was less than 5% (812 mg). R_f=0.72 (2% EA/hex); ^{1}H (400 MHz) δ 7.58–7.55 (6H), 7.43–7.33 (9H), 5.71 (ddd, 1H, J=16.9, 10.1, 7.0 Hz), 4.96 (broad d, 1H, J=10.4, 1.5 Hz), 4.90 (broad d, 1H, J=17.2 Hz), 2.48 (td, 1H, J=10.6, 7.5 Hz), 1.75–1.70 (1H), 1.50–1.42 (2H), 1.26–1.14 (7H), 0.85 (t, 3H, J=7.3 Hz). ^{13}C (100 MHz) δ 138.9, 136.2, 134.2, 129.3, 127.7, 114.6, 32.1, 31.8, 29.0, 28.9, 22.6, 14.1; IR 1623, 1489, 1469, 1429; HRFAB calcd for $C_{27}H_{32}SiLi$ $(M+Li)^+$: 391.2433, found: 391.2442 (2.3 ppm).

4.1.10. 2-(*tert*-Butyldimethylsilyl)-1-(2-methoxyethoxy)-oct-1-yl *tert*-butyldimethylsilyl peroxide (8). Ozonolysis of allylsilane **6** as above gave 2-(*tert*-butyldimethylsilyl)-1-(2-methoxyethoxy)-octyl hydroperoxide (1.7 g, 60% yield). R_f=0.48 (10% EA/hex); ^{1}H δ 10.38 (s, 1H), 5.04 (d, 0.2H, J=5.36 Hz), 4.88 (d, 0.8H, J=6.6 Hz), 3.94–3.82 (m, 2H), 3.67–3.63 (m, 1H), 3.55–3.53 (m, 1H), 3.44 (s, 3H), 1.44–1.26 (13H), 0.89 (s, 9H), 0.07 (s, 0.5H), 0.04 (s, 0.8H), 0.017 (s, 2H), 0.01 (s, 2.7H). ^{13}C δ 111.5/111.3, 73.4/73.3, 68.2, 67.7, 59.1, 59.0, 31.8, 31.7, 30.6, 30.5, 30.1, 29.7, 29.0, 28.4, 27.8, 27.5, 27.3, 27.25, 27.17, 26.7, 22.7/22.6, 17.7, 17.5, 14.1, −5.04/-5.15, −5.4/-5.8; IR 3324 (b), 1136 cm^{-1}. HRMS: no identifiable ions were observed.

Silylation of this hydroperoxide under standard conditions furnished silyl peroxyacetal **8** in 1.1 g, 90% yield: R_f=0.63 (10% EA/hex); ^{1}H δ 5.04 (d, 0.1H, J=2.5 Hz), 5.0 (d, 0.9H, J=3.5 Hz), 4.17 (m, 0.1H), 4.13 (m, 0.9H), 3.77 (m, 1H), 3.52 (m, 2H), 3.359 (s, 2.5H), 3.554 (s, 0.5H), 1.53–1.253 (13H), 1.11 (m, 1H), 0.93 (s, 9H), 0.89–0.87 (3H), 0.88 (s, 9H), 0.17 (s, 2.8H), 0.16 (s, 3.2H), 0.05 (s, 2.9H), 0.03 (s, 3H); ^{13}C δ 111.7, 111.5, 72.4, 72.3, 70.6, 58.8, 31.9, 31.8, 30.3, 29.6, 28.9, 27.7, 27.2, 27.1, 26.2, 25.6, 22.7, 18.0, 17.4, 14.1, 14.0, −4.56, −5.47, −5.5, −5.9; IR 1132, 1104. HRFAB calcd for $C_{23}H_{52}O_4Si_2Na$ $(M+Na)^+$: 471.3304, found: 471.3313 (2.3 ppm).

4.2. Preparation of homoallyl ethers and esters (10a–10i)

Compounds **10a–i** were prepared by etherification or esterification of the corresponding homoallyl alcohol.[17]

4.2.1. 4-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1-undecene (10a).[18] R_f=0.76 (5% EtOAc/Hex); ^{1}H δ 5.90 (d, 1H, 6.3), 4.39 (dd, 1H, J=7.2, 13.6 Hz), 3.65 (m, 1H), 3.55 (s, 3H), 2.23–2.19 (2H), 1.27–1.44 (12H), 0.88–0.90 (12H), 0.05 (6H); ^{13}C δ 147.0, 103.0, 72.2, 59.3, 36.8, 31.8, 31.7, 29.7, 29.3, 25.9, 25.4, 22.7, 14.1, −4.4, −4.6; IR 1667, 1251, 1108; HRMS calcd for $C_{18}H_{37}O_2Si$ $(M-H)^+$: 313.2562, found: 313.2556 (2.1 ppm).

4.2.2. 4-Methoxyundec-1-ene (10b). To a 1.0 M solution of undec-1-ene-4-ol (650 mg, 3.8 mmol) in DMF was added NaH (305 mg, 60% suspension in mineral oil, 7.6 mmol), MeI (0.3 mL, 5 mmol), 6.8 mmol), Py (0.6 mL, 6.8 mmol) at 0 °C and the reaction mixture was stirred overnight (convenience). The reaction mixture was quenched with satd NH_4Cl and extracted with recycled 20% EA/hexanes (3×25 mL), the organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (5% EA/hexanes) of the crude product furnished 493 mg (70%) of the methyl ether. R_f=0.42 (5% EA/hex); ^{1}H δ 5.89 (ddt, 1H, J=17.6, 10.1, 6.9 Hz), 5.07 (dd, 1H, J=17.3, 1.9 Hz), 5.04 (dd, 1H, J=10.1, 1.8 Hz), 3.33 (s, 3H), 3.19–3.18 (m, 1H), 2.28–2.24 (m, 2H), 1.47–1.35 (12H), 0.87 (t, 3H, J=6.9 Hz); ^{13}C δ 135.1, 116.6, 80.6, 56.5, 37.8, 33.4, 31.8, 29.7, 29.3, 25.3, 22.6, 14.0; IR 1643, 1100; HREI: calcd for $C_{12}H_{23}O$ $(M-H)^+$: 183.1747, found: 183.1744 (2.8 ppm).

4.2.3. 4-Benzyloxy-undec-1-ene (10c). To a 1.0 M solution of undec-1-ene-4-ol (2.0 g, 12.0 mmol) in DMF was added neat NaH (0.58 g 24 mmol), BnBr (2.2 mL, 18 mmol), and a catalytic amount of Bu_4NI at 0 °C and the reaction mixture was stirred overnight (convenience). The reaction mixture was quenched with satd NH_4Cl and extracted with recycled 20% EA/hexanes (3×50 mL), the organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (5% EA/hexanes) of the crude product furnished 2.12 g (70%) of the methyl ether (∼5 g scale, 63%). R_f=0.69 (5% EA/hex); ^{1}H δ 7.43–7.40 (5H), 5.93 (ddt, 1H, J=17.3, 10.1, 7.2 Hz), 5.23 (dd, 1H, J=17.3, 2.2 Hz), 5.17 (dd, 1H, J=10.1, 2.2 Hz), 4.60 (d, 1H, J=2.7 Hz), 4.58 (d, 1H, J=2.7 Hz), 3.50 (m, 1H), 2.39 (dd, 2H, J=2.9, 1.4 Hz), 1.65–1.30 (12H), 0.96 (t, 3H, J=6.9 Hz); ^{13}C δ 139.1, 135.1, 128.2, 127.6, 127.3, 116.6, 70.9, 38.3, 33.8, 31.8, 29.7, 29.2, 25.3, 22.6, 14.0; IR 1639, 1492, 1454, 1205, 1096; HREI: calcd for $C_{18}H_{28}O$ $(M)^+$: 260.2140, found: 260.2134 (2.3 ppm).

4.2.4. Acetic acid, 1-undecene-4-yl ester (10d). To a 1.0 M solution of undec-1-ene-4-ol (579 mg, 3.4 mmol) in CH_2Cl_2 was added Ac_2O (0.7 mL, 6.8 mmol), and pyridine (0.6 mL, 7 mmol) at 0 °C and the reaction mixture was stirred overnight (convenience). The solvent was removed under reduced pressure, and excess Ac_2O, Py were removed under high vacuum. Flash chromatography (5% EA/hexanes) furnished 581 mg (75%) of the acyl ester (∼5 g scale, 78–80%). R_f=0.54 (5% EA/hex); ^{1}H δ 5.69 (ddt, 1H, J=17.1, 10.0, 7.0 Hz), 5.02 (broad dd, 1H, J=17.0, 1.5 Hz), 4.99 (broad dd, 1H, J=10.0, 0.8 Hz), 4.86 (m, 1H), 2.24 (m, 2H), 2.0 (s, 3H), 1.40 (2H), 1.25 (broad, 10H), 0.83 (t, 3H, J=7.0 Hz); ^{13}C δ 170.5, 133.7, 117.3, 73.2, 38.5, 33.5, 31.7, 29.3, 29.1, 25.3, 22.5, 21.0, 13.9; IR 1739, 1641; HRFAB calcd for $C_{13}H_{24}OLi$ $(M+Li)^+$: 219.1936, found: 219.1186 (88 ppm).

4.2.5. Benzoic acid, undecene-4-yl ester (10e). To a 1.0 M solution of undec-1-ene-4-ol (740 mg, 4.3 mmol) in CH_2Cl_2/Py (1:3) was added benzoyl chloride (1.5 mL, 13 mmol). The reaction mixture turns pink after the addition of reagents is complete. After 1 h the reaction mixture is quenched with sat. NH_4Cl at 0 °C and extracted with 30% recycled EA/hexanes (3×50 mL). The organics were dried

over Na_2SO_4. The solvent was removed under reduced pressure and flash chromatography of the crude product (10% EA/hexanes) furnished 1.1 g (90%) of the benzoyl ester. R_f=0.68 (10% EA/hex); ^{1}H (400 MHz) δ 8.05 (broad d, 2H, J=7.6 Hz), 7.55 (dt, 1H, J=7.3, 1.3 Hz), 7.43 (broad t, 2H, J=7.3 Hz) 5.83 (ddt, 1H, J=17.2, 10.4, 7.0 Hz), 5.20–5.15 (m, 1H), 5.11 (dd, 1H, J=17.2, 1.5 Hz), 5.06 (dd, 1H, J=10.4, 1.7 Hz), 2.45 (t, 2H, J=6.6 Hz), 1.76–1.61 (2H), 1.43–1.25 (10H), 0.87 (t, 3H, J=6.8 Hz); ^{13}C (100 MHz) δ 166.2, 133.7, 132.7, 130.7, 129.5, 128.3, 117.7, 74.0, 38.7, 33.6, 31.7, 29.4, 29.1, 25.3, 22.6, 14.0; IR 1719, 1643; HRFAB calcd for $C_{18}H_{26}O_2Li$ $(M+Li)^+$: 281.2093; found: 281.2095 (0.7 ppm).

4.2.6. 4-(Methoxymethoxy)-undec-1-ene (10g). To a 1.0 M solution of undec-1-ene-4-ol (1.6 g, 9.2 mmol) in DIPEA/CH_2Cl_2 (1:1) was added chloromethyl methyl ether (1.4 mL, 18 mmol) at 0 °C and the reaction mixture was stirred overnight (convenience). The reaction mixture was quenched with satd NH_4Cl at 0 °C and the aqueous layer was extracted with recycled 20% EA/hexanes (3×25 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (5% EA/hexanes) of the crude product furnished 1.51 g (75%) of the methoxymethyl ether. R_f= 0.39 (5% EA/hex); ^{1}H δ 5.76 (ddt, 1H, J=17.0, 10.1, 6.9 Hz), 5.0 (dd, 1H, J=17.3, 1.9 Hz), 4.97 (dd, 1H, J= 10.1, 1.9 Hz), 4.5 (dd, 2H, J=12.9, 6.9 Hz), 3.54 (m, 1H), 3.31 (s, 3H), 2.23 (broad t, 2H, J=6.6 Hz), 1.45–1.23 (12H), 0.83 (t, 3H, J=6.9 Hz); ^{13}C δ 135.0, 116.7, 95.5, 76.8, 55.3, 39.0, 34.3, 31.8, 29.7, 29.3, 25.3, 22.6, 13.9; IR 1646, 1149, 1099; HREI calcd for $C_{10}H_{21}O_2$ $(M-allyl)^+$: 173.1542, found: 173.1547 (2.8 ppm).

4.2.7. Acetic acid, 1-phenyl-3-buten-1-yl ester (10h). To a 1.0 M solution of benzaldehyde (10.6 g, 100 mmol), in THF was added a 2.0 M solution of allylmagnesium chloride (76 mL, 150 mmol) in THF at 0 °C. The color of the reaction mixture changed from reddish brown to dark green as the reaction progressed. After 24 h the reaction mixture was quenched with sat. NH_4Cl at 0 °C and extracted with recycled 20% EA/hexanes (3×150 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was distilled under reduced pressure to furnish 6.9 g (46%) of 1-phenyl-3-butenol. A portion of the alcohol (4.5 g, 30.3 mmol) was acylated using a procedure similar to compound **10d** to furnish the acetate ester in 4.15 g (72%) yield. R_f=0.5 (4% EA/hex); ^{1}H δ 7.48–7.25 (5H), 5.80 (t, 1H, J=6.3 Hz), 5.69 (ddt, 1H, J=17.3, 10.4, 6.9 Hz), 5.05 (dd, 1H, J=17.9, 1.9 Hz), 5.03 (dd, 1H, J=10.1, 1.6 Hz), 2.67–2.52 (m, 2H), 2.03 (s, 3H); ^{13}C δ 170.0, 140.0, 133.2, 128.3, 127.8, 126.4, 117.8, 75.0, 40.6, 21.0; IR 1748, 1637, 1492, 1458, 1424; HRFAB calcd for $C_{12}H_{14}O_2Li$ $(M+Li)^+$: 197.1154, found: 197.115 (0.9 ppm).

4.2.8. Acetic acid, 2-methyl-1-undecene-4-yl ester (10i). To a 1.0 M solution of heptanal (5 g, 43.8 mmol) in THF was added a solution of methallyl magnesium bromide (1.1 equiv) in THF at 0 °C. After 24 h stirring the reaction mixture was quenched with satd NH_4Cl and the aqueous layer was extracted with recycled 20% EA/hexanes. The organics were washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Distillation of the crude product furnished 2-methyl-1-decene-4-ol in (5.6 g, 75%) yield. Acylation of the alcohol by a similar procedure as employed for the preparation of compound **10d** furnished the desired acetate ester in 62% yield. R_f=0.74 (5% EA/hex); ^{1}H δ 5.02 (m, 1H), 4.74 (d, 1H, J=6.3 Hz), 4.67 (d, 1H, J=6.3 Hz), 2.27–2.14 (2H), 1.98 (s, 3H), 1.72 (s, 3H), 1.49 (2H), 1.24 (broad, 8H), 0.85 (t, 3H, J=6.9 Hz); ^{13}C δ 170.5, 141.8, 113.0, 72.1, 42.9, 34.0, 31.7, 29.0, 25.3, 22.5, 22.4, 21.0, 13.9; IR 1735, 1643; HR-EI calcd for $C_{11}H_{19}$ $(M-AcOH)^+$: 152.1643; found: 152.1571 (47 ppm).

4.3. Ozonolysis of homoallyl ethers/esters (illustrated for 11d)

Into a −78 °C solution of alkene **10d** (4.70 g, 20.6 mmol) in 2-methoxyethanol (100 mL, excess) tinted slightly pink with a trace of Sudan Red B was bubbled a gaseous solution of O_3/O_2. After the reddish color had faded to light yellow and TLC analysis displayed little or no starting material, ozonolysis was stopped and residual ozone was removed by sparging with O_2 or N_2. The reaction mixture was allowed to warm to room temperature and was diluted with DI water (100 mL). The organic extracts (recycled EA/hex, 3× 100 mL), were dried over Na_2SO_4 and the solution was concentrated in vacuo. Residual methoxyethanol was removed under high vacuum, and the residue was purified by flash chromatography (20% EA/hex) to furnish 3.7 g (59%) of hydroperoxy acetal **11d**. Compounds **11a–i** were prepared by a similar procedure. Unless otherwise noted, the hydroperoxyacetals were formed as approximately 1:1 mixtures of diastereomers.

4.3.1. 3-*tert*-Butyldimethylsilyloxy-1-hydroperoxy-1-(2-methoxyethoxy)decane (11a). Yield=1.8 g, 73%. R_f= 0.39 (10% EA/hex); ^{1}H δ 10.30 (s, 0.5H), 10.25 (s, 0.5H), 4.97–4.92 (1H), 3.85–3.78 (3H), 3.66–3.60 (1H), 3.56–3.52 (1H), 3.43 (s, J=1.6 Hz), 3.42 (s, 1.4H), 1.97–1.89 (2H), 1.83–1.79 (2H), 1.46–1.41 (2H), 1.29–1.24 (8H), 0.87 (s, 5H), 0.86 (s, 4H), 0.86–0.87 (3H), 0.05 (s, 1.4H), 0.04 (s, 1.4H), 0.38 (s, 3.2H); ^{13}C δ 105.1, 105.0, 72.9, 72.8, 69.0, 68.9, 65.4, 65.3, 58.6, 38.7, 38.4, 37.62, 37.59, 31.8, 31.7, 29.72, 29.68, 29.2, 25.9, 25.8, 24.7, 22.6, 18.01, 18.0, 14.0, −4.3, −4.4, −4.6, −4.7; IR 3428, 2857–2848, 1255, 1102–1124; HRMS: no identifiable ions were observed.

4.3.2. (1-Hydroperoxy)-3-methoxy-1-(2-methoxyethoxy)-decane (11b). Yield=204 mg, 45%. R_f=0.6 (40% EA/hex); ^{1}H δ 10.31 (s, 0.6H), 10.27 (s, 0.3H), 4.97–4.93 (m, 1H), 3.87–3.77 (m, 1H), 3.64–3.59 (2H), 3.56–3.49 (2H), 3.41 (s, 1.2H), 3.40 (s, 1.8H), 3.30 (s, 1.2H), 3.29 (s, 1.8H), 1.96–1.23 (m, 14H), 0.83 (t, 3H, J=6.3 Hz); ^{13}C δ 105.1, 104.8, 77.5, 77.4, 72.7, 72.5, 65.7, 65.5, 58.9, 58.8, 56.7, 56.4, 35.9, 35.8, 33.3, 33.0, 31.7, 29.6, 29.1, 24.7, 22.5, 14.0; IR 3331, 1198, 1104; HRMS: no identifiable ions were observed.

4.3.3. 3-Benzyloxy-1-hydroperoxy-1-(2-methoxyethoxy)-decane (11c). Yield=300 mg, 50%. R_f=0.45 (20% EA/hex); ^{1}H δ 10.27 (s, 0.8H), 9.73 (t, 0.2H, J=1.9 Hz), 7.35–7.24 (5H), 5.05–5.02 (m, 0.4H), 4.99 (broad t, 0.6H, J= 6.0 Hz), 4.60–4.50 (2H), 3.86–3.78 (m, 0.7H), 3.72–3.68

(m, 0.3H), 3.65–3.57 (m, 2H), 3.56–3.45 (m, 2H), 3.43 (s, 1.2H), 3.42 (s, 1.8H), 2.40 (m, 0.4H), 2.05–1.79 (m, 1.6H), 1.65–1.27 (12H), 0.89 (t, 3H, J=6.9 Hz); ^{13}C δ 138.7, 128.3, 128.24/128.22, 127.77, 127.73, 127.66, 127.51, 127.48, 127.43, 127.41, 127.38, 105.2, 105.0, 75.9, 75.7, 72.8, 72.7, 72.6, 71.3, 70.9, 69.9, 65.9, 58.8, 43.7, 36.3, 34.9, 33.9, 31.7, 29.64/29.62, 29.4, 29.1, 25.8, 24.9, 24.8, 22.5, 21.8, 14.0; IR 3331, 1495, 1451, 1198, 1096; HRMS: no identifiable ions were observed.

4.3.4. Acetic acid, 1-hydroperoxy-1-(2-methoxyethoxy) decane-3-yl ester (11d). Yield=2.9 g, 60%. R_f=0.39 (20% EA/hex); ^{1}H δ 10.33 (s, 0.8H), 10.23 (s, 0.2H), 4.94 (m, 1H), 4.79 (m, 1H), 3.94–3.83 (m, 2H), 3.72–3.59 (m, 2H), 3.50 (s, 1.8H), 3.49 (s, 1.2H), 2.09 (s, 1.8H), 2.08 (s, 1.2H), 1.99–1.94 (m, 2H), 1.62–1.60 (m, 2H), 1.31 (broad s, 10H), 0.92 (t, 3H, J=6.6 Hz); ^{13}C δ 170.5/170.4, 104.8/104.5, 72.5/72.4, 71.7/71.6, 66.5, 65.4, 58.7, 36.3, 35.9, 34.4, 34.1, 31.5, 31.0, 29.1, 28.9, 28.3, 24.9, 24.86, 22.4, 20.93, 20.9, 13.8; IR 3300 (b), 1734, 1124, 1100; HRMS: no identifiable ions were observed.

4.3.5. Benzoic acid, 1-hydroperoxy-1-(2-methoxyethoxy) decane-3-yl ester (11e). Yield=510 mg, 40%. R_f=0.47 (20% EA/hex); ^{1}H δ 10.46 (s, 0.6H), 10.30 (s, 0.4H), 8.0 (broad d, 2H, J=7.9 Hz), 7.53–7.51 (1H), 7.41 (broad t, 2H, J=7.6 Hz), 5.31–5.25 (m, 1H), 4.96 (t, 0.5H, J=6.0 Hz), 4.93 (t, 0.5H, J=6.0 Hz), 3.8–3.7 (2H), 3.66–3.62 (2H), 3.40 (s, 1.8,H), 3.38 (s, 1.2H), 2.16–2.02 (2H), 1.76–1.61 (4H), 1.39–1.22 (8H), 0.83 (broad t, 3H, J=6.3 Hz); ^{13}C δ 166.0, 132.8, 132.7, 130.5, 130.3, 129.5, 129.4, 128.25, 128.2, 104.8, 104.5, 72.6, 72.5, 71.6, 66.5, 65.3, 58.83, 58.76, 36.4, 36.1, 34.6, 34.3, 31.6, 29.3, 29.0, 25.01, 24.99, 22.5, 13.9; IR 3315 (b), 1719, 1581, 1450, 1192, 1102, 1071; HRMS: no identifiable ions were observed.

4.3.6. 2,2-Dimethylpropionic acid, 1-hydroperoxy-1-(2-methoxyethoxy) decane-3-yl ester (11f). The title compound was prepared by esterification of undecen-4-ol followed by ozonolysis of the crude pivaloate ester in 325 mg, 50% yield. R_f=0.26 (20% EA/hex); ^{1}H δ 10.38 (0.4H), 10.25 (0.6H), 5.04–4.92 (1H), 4.88 (t, 0.6H, J=6.0 Hz), 4.83 (t, 0.4H, J=5.7 Hz), 3.86–3.78 (2H), 3.67–3.51 (2H), 3.425 (s, 1.8H), 3.429 (s, 1.2H), 1.93–1.85 (2H), 1.67–1.55 (4H), 1.179 (s, 3.6H), 1.173 (s, 5.4H), 1.17–1.50 (8H), 0.85 (t, 3H, J=6.9 Hz); ^{13}C δ 178.0/177.9, 105.1, 104.7, 72.8, 72.7, 70.7, 70.6, 70.3, 70.2, 66.6, 65.2, 63.5, 58.9, 58.87, 58.83, 39.2, 38.8, 38.76, 36.5, 36.1, 34.5, 34.2, 33.9, 31.7, 29.3, 29.2, 29.1, 27.16, 27.13, 27.0, 24.97, 24.94, 22.5, 13.1; IR 1725, 1159, 1130, 1101; HRMS: no identifiable ions were observed.

4.3.7. 1-(2-Ethoxymethoxy)-3-(methoxymethoxy)decyl hydroperoxide (11g). Yield=0.8 g, 55%. R_f=0.39 (20% EA/hex); ^{1}H δ 10.27 (s, 1H), 4.90 (s, 0.1H), 4.77 (t, 1H, J=6 Hz), 4.52 (s, 1.9H), 3.77–3.75 (1H), 3.57–3.47 (2H), 3.43 (t, 2H, J=6.3 Hz), 3.37 (s, 3H), 3.30 (s, J=0.3 Hz), 3.27 (s, 2.7H), 1.68–1.28 (17H); ^{13}C δ 107.2, 99.0, 96.3, 77.2, 72.6, 72.3, 67.0, 67.5, 65.3, 58.7, 54.8, 31.1, 29.4, 28.3, 25.5 25.8, 24.4, 24.2, 12.0; IR 3316, 1196, 1102, 1044; HRMS: no identifiable ions were observed.

4.3.8. Acetic acid, 1-hydroperoxy-1-(2-methoxyethoxy)-3-phenyl propane-3-yl ester (11h). Yield=2.8 g, 50%. R_f=0.44 (40% EA/hex); ^{1}H δ 10.53 (s, 1H), 7.53–7.40 (5H), 6.07–5.99 (1H), 4.97–4.95 (0.7H), 4.88 (t, 0.3H, J=6.0 Hz), 3.96–3.92 (2H), 3.79–3.70 (2H), 3.56 (s, 1H), 3.55 (s, 2H), 2.16 (s, 3H), 1.85–1.43 (2H); ^{13}C δ 169.9, 140.0, 128.4, 128.0, 126.42, 126.38, 104.37, 104.0, 72.65, 72.63, 72.57, 72.54, 72.4, 66.2, 58.8, 38.3, 37.9, 21.0; IR 3330 (b), 1740, 1490, 1600, 1124; HRMS: no identifiable ions were observed.

4.3.9. Acetic acid, 2-hydroperoxy-2-methoxyethoxy-decane-4-yl ester (11i). Yield=493 mg, 62%. R_f=0.64 (40% EA/hex); ^{1}H δ 10.14 (s, 0.6H), 10.10 (s, 0.4H), 5.0 (m, 1H), 3.50–3.41 (4H), 3.329 (s, 1.3H), 3.326 (s, 1.7H), 1.98 (s, 1H), 1.90 (s, 2H), 1.88–1.87 (1H), 1.45–1.14 (m, 3H), 1.24 (s, 1.8H), 1.22 (s, 1.2H), 1.18–1.15 (8H), 0.76 (t, 3H, J=7.0 Hz); ^{13}C δ 170.4, 170.2, 105.7, 105.5, 72.6, 70.5, 70.3, 59.8, 59.7, 58.6, 39.64, 39.59, 35.1, 35.0, 31.4, 28.8, 24.7, 22.3, 21.03, 21.0, 19.6, 19.4, 13.8; IR 3308, 1734, 1125; HRMS: no identifiable ions were observed.

4.4. Silylation of hydroperoxyacetals (illustrated for 12d)

Into a 0 °C solution of hydroperoxyacetal **11d** (3.70 g, 12.0 mmol) in DMF (15 mL) under N_2, was added imidazole (1.5 equiv, 1.22 g, 18 mmol) followed by TBSOTf (18 mmol, 4.2 mL, dropwise). The reaction was stirred for 25–30 min and then quenched with DI water (50 mL). The combined organic extracts (recycled EA/hexane, 3×100 mL) were dried over Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by flash chromatography (10% EA/hex) to furnish 4.5 g (88%) of the silyl peroxyacetal **12d**. Compounds **12a–i** were prepared by similar procedures.

4.4.1. 1-(*tert*-Butyldimethylsilyldioxy)-3-(*tert*-butyldimethylsilyloxy)-1-(2-methoxyethoxy)-decane (12a). Yield=427 mg, 85%. R_f=0.65 (10% EA/hex); ^{1}H δ 4.99–4.94 (1H), 4.10–4.05 (0.5H), 4.02–3.98 (0.5H), 3.83–3.71 (2H), 3.59–3.49 (2H), 3.36 (s, 1.6H), 3.356 (s, 1.4H), 1.89–1.68 (2H), 1.43 (broad peak, 2H), 1.25 (broad peak, 12H), 0.92 (s, 9H), 0.87 (s, 9H), 0.88–0.85 (3H), 0.15 (s, 6H), 0.05 (s, 1.6H), 0.04 (4.4H); ^{13}C δ 106.5, 105.9, 72.1, 72.0, 69.2, 69.0, 68.9, 68.7, 58.9, 58.87, 39.8, 39.5, 37.6, 37.5, 31.79, 31.78, 29.7, 29.2, 26.12, 26.1, 25.8, 24.9, 24.7, 22.6, 18.1, 18.01, 18.0, 14.0, −4.3, −4.4, −4.6, −4.6, −5.7; IR 2959–2851, 1101, 1252, 1203; HRMS: no identifiable ions were observed.

4.4.2. 1-(*tert*-Butyldimethylsilyldioxy)-3-methoxy-1-(2-methoxyethoxy) decane (12b). Yield=135 mg, 87%. R_f=0.68 (20% EA/hex); ^{1}H δ 5.02 (m, 1H), 4.10–4.03 (m, 1H), 3.83–3.75 (m, 2H), 3.61–3.51 (2H), 3.38 (s, 1.7H), 3.37 (s, 1.3H), 3.32 (s, 3H), 1.87–1.66 (m, 2H), 1.50–1.25 (12H), 0.92 (s, 3.8H), 0.91 (s, 5.2H), 0.85 (t, 3H, J=6.6 Hz), 0.26 (s, 3.4H), 0.16 (s, 2.6H); ^{13}C δ 106.4/106.1, 77.4, 72.1, 72.0, 69.4, 69.0, 58.82, 58.78, 56.3, 37.0, 33.7, 33.6, 31.8, 29.75, 29.68, 29.2, 26.1, 25.7, 25.6, 24.9, 22.6, 18.1, 14.0, −3.0, −5.7; IR 2962–2851, 1249, 1199, 1095; HRFAB calcd for $C_{20}H_{44}O_5SiLi$ $(M+Li)^+$: 399.3118; found: 399.3125 (1.6 ppm).

4.4.3. 1-(*tert*-Butyldimethylsilyldioxy)-3-benzyloxy-1-(2-methoxyethoxy)-decane (12c). Yield=2.8 g, 88%. R_f=0.71 (20% EA/hex); ^{1}H δ 7.37–7.27 (5H), 5.14–5.07 (1H), 4.50–4.49 (2H), 4.10–3.96 (1H), 3.65–3.46 (2H), 3.39–3.34 (2H), 3.36 (s, 3H), 1.95–1.78 (2H), 1.63–1.50 (2H), 1.48–1.3 (10H), 0.97 (s, 4.6H), 0.969 (s, 4.4H), 0.92 (t, 3H, J=6.6 Hz), 0.19 (s, 2.7H), 0.18 (s, 3.3H); ^{13}C δ 139.0, 138.97, 128.2, 128.1, 127.6, 127.58, 127.5, 127.46, 127.43, 127.3, 127.26, 106.3, 106.0, 75.8, 75.7, 72.8, 72.0, 70.9, 70.8, 69.4, 38.9, 58.73, 58.69, 37.35, 37.26, 34.1, 34.0, 31.7, 29.7, 29.6, 29.1, 26.1, 25.7, 25.0, 24.9, 22.5, 18.05, 18.03, 13.9, −4.1, −4.2, −5.73, −5.7; IR 2962–2855, 1494, 1462, 1249, 1106; HRFAB calcd for $C_{26}H_{48}O_5SiNa$ $(M+Na)^+$: 491.3171; found: 491.3151 (3.6 ppm).

4.4.4. Acetic acid, 1-(*tert*-butyldimethylsilyldioxy)-1-(2-methoxyethoxy)-decane-3-yl ester (12d). Yield=4.5 g, 88%. R_f=0.42 (10% EA/hex); ^{1}H δ 5.0 (m, 1H), 3.99–3.96 (m, 1H), 3.74–3.68 (2H), 3.54–3.47 (2H), 3.46 (s, 1.2H), 3.45 (s, 1.8H), 2.0 (s, 1.8H), 1.99 (s, 1.2H), 1.95–1.76 (4H), 1.60–1.40 (broad peak, 2H), 1.15–1.30 (8H), 0.9 (s, 6.7H), 0.89 (s, 2.3H), 0.83 (t, 3H, J=6 Hz), 0.125 (s, 4H), 0.11 (s, 1.9H). ^{13}C δ 170.24/170.21, 105.9/105.5, 72.0/71.97, 71.1/71.0, 69.76/68.74, 58.78/58.71, 37.0, 36.8, 34.5, 34.2, 31.6, 29.3, 29.0, 26.04, 26.02, 25.7, 25.6, 25.0, 22.5, 21.1, 21.0, 18.0, 13.9, −5.8; IR 2928–2850, 1734, 1233, 1130, 1101; HRMS: no identifiable ions were observed.

4.4.5. Benzoic acid, 1-(*tert*-butyldimethylsilyldioxy)-1-(2-methoxyethoxy)-decane-3-yl ester (12e). Yield=291 mg, 75%. R_f=0.5 (10% EA/hex); ^{1}H δ 8.03 (broad d, 2H, J=8.2 Hz), 7.55–7.51 (m, 1H), 7.43–7.40 (m, 2H), 5.31–5.21 (m, 0.4H), 5.03–4.96 (m, 0.6H), 4.06 (broad t, 1H, J=5.0 Hz), 3.76–3.70 (m, 2H), 3.52–3.42 (m, 2H), 3.30 (s, 1H), 3.29 (s, 2H), 2.02–1.98 (m, 2H), 1.75–1.64 (m, 2H), 1.40–1.20 (m, 10H), 0.91 (s, 9H), 0.84 (broad t, 3H, J=6 Hz), 0.16 (s, 3.9H), 0.13 (s, 2.1H); ^{13}C δ 165.8, 165.78, 132.7, 132.6, 130.6, 130.5, 129.5, 128.23, 128.19, 105.9, 105.4, 72.0, 71.9, 71.8, 71.7, 69.9, 68.7, 58.8, 58.7, 37.1, 36.8, 34.6, 34.3, 31.7, 29.36, 29.32, 29.0, 26.0, 24.99, 24.97, 22.5, 18.04, 18.02, 14.0, −5.8; IR 2859–2849, 1710, 1601, 1580, 1462, 1441, 1275, 1175, 1106, 1023; HRFAB calcd for $C_{26}H_{46}O_6SiLi$ $(M+Li)^+$: 489.3224; found: 489.3243 (3.9 ppm).

4.4.6. 2,2-Dimethylpropionic acid, 1-(*tert*-butyldimethylsilyldioxy)-1-(2-methoxyethoxy)-decane-3-yl ester (12f). Yield=212 mg, 60%. R_f=0.72 (20% EA/hex); ^{1}H δ 5.03–4.81 (m, 1H), 4.07–3.96 (1H), 3.75–3.68 (2H), 3.56–3.48 (2H), 3.35 (s, 1.2H), 3.33 (1.8H), 1.56–1.48 (2H), 1.28–1.20 (12H), 1.17 (s, 3.7H), 1.16 (s, 5.3H), 0.91 (s, 9H), 0.84 (broad t, 3H), 0.14 (s, 3.4H), 0.13 (s, 2.6H); ^{13}C δ 177.57, 177.55, 106.0, 105.4, 72.0, 71.9, 70.7, 70.68, 70.0, 68.6, 58.84, 58.80, 45.2, 38.73, 38.7, 37.1, 36.8, 34.5, 34.1, 31.7, 29.3, 29.1, 27.2, 27.1, 26.08, 26.06, 25.7, 25.6, 25.5, 24.8, 22.5, 18.07, 18.05, 14.0; IR 2953–2855, 1729, 1246, 1158, 1109; HRFAB calcd for $C_{24}H_{50}O_6SiLi$ $(M+Li)^+$: 469.3537; found: 469.3541 (0.8 ppm).

4.4.7. 1-(*tert*-Butyldimethylsilyldioxy)-3-methoxymethoxy-1-(2-methoxyethoxy)decane (12g). Yield=293 mg, 82%. R_f=0.6 (20% EA/hex); ^{1}H δ 4.97 (s, 0.1H), 4.80 (t, 0.9H, J=5.7 Hz), 4.53 (s, 1.9H), 4.15 (t, 0.1H, J=4.73 Hz), 3.99 (m, 1H), 3.78–3.70 (2H), 3.52–3.42 (2H), 3.30 (s, 3H), 3.27 (s, 3H), 1.59–1.49 (6H), 1.40–1.30 (8H), 0.86 (s, 9H), 0.83 (broad t, 3H, J=6.6 Hz), 0.10 (s, 6H); ^{13}C δ 108.2, 99.7, 96.2, 72.0, 71.7, 69.1, 68.7, 67.4, 58.8, 58.7, 54.8, 32.1, 30.1, 29.4, 26.0, 25.8, 24.4, 17.9, −5.8, −6.0; IR 1111, 1045; HRMS: no identifiable ions were observed.

4.4.8. Acetic acid, 1-(*tert*-butyldimethylsilyldioxy)-3-phenyl-1-(2-methoxyethoxy)-decane-3-yl ester (12h). Yield=2.0 g, 55%. R_f=0.5 (20% EA/hex); ^{1}H δ 7.49–7.17 (5H), 5.91–5.85 (1H), 4.96–4.94 (0.8H), 4.81 (t, 0.2H, J=6.0 Hz), 4.07–3.70 (2H), 3.71–3.49 (2H), 3.38 (s, 1.2H), 3.36 (s, 1.8H), 2.36–2.33 (m, 2H), 2.03 (s, 1.8H), 2.02 (s, 1.2H), 0.94 (5.6H), 0.93 (3.4H), 0.18 (s, 3.4H), 0.17 (s, 2.6H); ^{13}C δ 169.66, 169.62, 140.3, 140.1, 128.39, 128.36, 127.9, 127.8, 126.4, 126.3, 105.3, 105.1, 72.7, 72.66, 72.0, 71.8, 69.5, 68.8, 58.8, 58.7, 39.1, 38.8, 26.03, 26.0, 25.6, 21.0, 20.96, 18.0, 17.8, −3.7, −5.8; IR 2930–2848, 1741, 1464, 1366, 1230, 1116; HRFAB calcd for $C_{20}H_{34}O_6SiNa$ $(M+Na)^+$: 421.2025, found: 421.2036 (2.6 ppm).

4.4.9. Acetic acid, 2-(*tert*-butyldimethylsilyldioxy)-2-(2-methoxyethoxy)-nonane-4-yl ester (12i). Yield=584 mg, 75%. R_f=0.65 (20% EA/hex); ^{1}H δ 5.03 (m, 1H), 3.59 (broad t, 2H, J=5.0 Hz), 3.47 (broad t, 2H, J=5 Hz), 3.30 (s, 3H), 1.95 (s, 3H), 2.08–2.04 (1.2H), 1.78–1.74 (0.8H), 1.53–1.49 (3H), 1.29 (s, Me, 1.4H), 1.27 (s, Me, 1.6H), 1.21 (broad peak, 7H), 0.88 (s, 9H), 0.81 (t, 3H, J=6.3 Hz), 0.10 (s, 1.5H), 0.08 (s, 4.5H); ^{13}C δ 170.2, 170.1, 105.6, 105.4, 71.9, 71.8, 71.1, 70.6, 60.9, 60.4, 58.8, 40.4, 40.3, 35.5, 35.2, 31.6, 29.1, 29.0, 26.05, 26.03, 24.95, 24.87, 22.4, 21.2, 21.1, 20.4, 19.8, 18.15, 18.11, 13.9, −5.8; IR 2928–2855, 1739, 1247, 1130; HRFAB calcd for $C_{21}H_{44}O_6SiNa$ $(M+Na)^+$: 443.2807; found: 443.2822 (3.3 ppm).

4.4.10. Undecene-5-ol.[19] The title compound was prepared by a reported procedure.

4.4.11. 5-Methoxyundecene (13a). The title compound was prepared using a reported procedure[7]. Yield=1.3 g, 75%. R_f=0.2 (2% EA/hex); ^{1}H δ 5.82 (ddt, 1H, J=17.0, 10.4, 6.6 Hz), 5.01 (broad dd, 1H, J=17.0, 1.9 Hz), 4.98 (dd, 1H, J=10.1, 1.9 Hz), 3.31 (s, 3H), 3.14 (m 1H), 2.19–2.01 (2H), 1.69–1.21 (12H), 0.88 (t, 3H, J=6.9 Hz); ^{13}C δ 138.8, 114.3, 80.3, 56.4, 33.5, 32.85, 29.6, 29.5, 25.2, 22.6, 14.0; IR 1633, 1103, 1158; HREI calcd for $C_{12}H_{25}O$ $(M+H)^+$: 185.1905; found: 185.1896 (4.8 ppm).

4.4.12. 5-Iodoundecene (13b). Into a 0 °C solution of undec-1-ene-5-ol (3.6 g, 21.1 mmol) in CH_2Cl_2 (50 mL) were successively added PPh_3 (6.1 g, 23.2 g), I_2 (7.5 g, 29.5 mmol) and imidazole (2.0 g, 29.5 mmol). The reaction was stirred overnight (convenience), diluted with CH_2Cl_2 (50 mL) and then quenched with DI water and washed with aqueous sodium thiosulphate solution (3×100 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a white solid which was washed with hexanes (3×100 mL). The hexanes were removed under reduced pressure to give a colorless liquid which was purified by flash chromatography (10% EA/hex) to furnish the iodide (5.2 g, 88%): R_f=0.88 (10% EA/hex); ^{1}H (400 MHz) δ 5.77

(ddt, 1H, $J=17.2$, 10.4, 6.8 Hz), 5.07 (broad dd, 1H, $J=$ 17.2, 1.5 Hz), 5.0 (broad dd, 1H, $J=10.4$, 1.8 Hz), 4.1 (m, 1H), 2.34–2.12 (2H), 2.0–1.65 (4H), 1.56–1.28 (8H), 0.88 (t, 3H, $J=6.8$ Hz); ^{13}C (100 MHz) δ 137.0, 115.6, 40.6, 39.6, 39.4, 33.6, 31.6, 29.4, 28.5, 22.6, 14.0; IR 1636, 1300, 1225, 1151; HREI calcd for $C_{11}H_{21}I$ $(M)^+$: 280.0688; found: 280.0685 (1.0 ppm).

4.4.13. [1-*tert*-Butyldimethylsilyldioxy]-4-methoxy-1-(2-methoxyethoxy) decane (14a). Ozonolysis of 5-methoxyundecene in 2-methoxyethanol furnished 4-methoxy-1-(2-methoxyethoxy)-dec-1-yl-hydroperoxide in 307 mg, 50% yield: $R_f=0.33$ (20% EA/hex); ^{1}H δ 10.32 (s, 0.6H), 10.30 (0.4H), 4.81 (t, 1H, $J=6.0$ Hz), 3.83–3.76 (2H), 3.62–3.58 (1H), 3.55–3.51 (1H), 3.41 (s, 3.0H), 3.274 (s, 1.5H), 3.271 (s, 1.5H), 3.15–3.09 (m, 1H), 1.79–1.24 (14H), 0.84 (t, 3H, $J=6.3$ Hz); ^{13}C δ 107.4, 80.4, 72.7, 65.3, 65.1, 58.8, 56.2, 56.1, 33.3, 31.7, 29.45, 29.38, 28.4, 28.2, 27.06, 25.15, 25.13, 22.5, 13.9; IR 3332, 1174, 1086; HRMS: no identifiable ions were observed.

Silylation of the hydroperoxyacetal under standard conditions furnished silyl peroxyacetal **14a** in 268 mg, 87% yield: $R_f=0.68$ (20% EA/hex); ^{1}H δ 4.81 (broad t, 1H, $J=$ 5.7 Hz), 4.0–3.96 (m, 1H), 3.74–3.69 (m, 1H), 3.51–3.43 (m, 2H), 3.29 (s, 3H), 3.22 (s, 3H), 3.06 (m, 1H), 1.70–1.20 (14H), 0.87 (s, 9H), 0.8 (t, 3H, $J=6.0$ Hz), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C δ 108.41, 108.36, 80.4, 80.2, 72.1, 69.1, 69.0, 58.7, 56.1, 33.3, 33.2, 31.7, 29.3, 28.2, 28.1, 28.0, 27.9, 26.0, 25.0, 22.4, 17.9, 13.8, −5.8; IR 2955–2819, 1198, 1247, 1106; HRFAB calcd for $C_{20}H_{44}O_5SiLi$: (M+Li): 399.3118; found: 399.3132 (3.6 ppm).

4.4.14. [1-*tert*-Butyldimethylsilyldioxy]-4-iodo-1-(2-methoxyethoxy)-decane (14b). Ozonolysis of iodoundecene in 2-methoxyethanol furnished 4-iodo-1-(2-methoxyethoxy)-dec-1-yl-hydroperoxide in 1.7 g, 45% yield: $R_f=0.42$ (20% EA/hex); ^{1}H δ 10.36 (s, 0.5H), 10.33 (s, 0.5H), 4.83 (t, 0.8H, $J=6.31$ Hz), 4.21 (t, 0.2H, $J=$ 4.73 Hz), 4.12–4.06 (m, 1H), 3.86–3.78 (2H), 3.65–3.53 (2H), 3.434 (s, $J=1.6$ Hz), 3.431 (s, 1.4H), 1.87–1.63 (6H), 1.49–1.26 (8H), 0.86 (t, 3H, $J=6.9$ Hz); ^{13}C δ 106.4, 106.3, 72.8, 70.4, 65.5, 65.23, 63.5, 58.9, 40.71, 40.68, 40.5, 38.9, 38.7, 38.0, 35.8, 35.6, 35.4, 34.2, 31.6, 31.3, 29.35, 29.32, 28.4, 22.5, 13.9; IR 3370 (b), 1371, 1192, 1084; HRMS: no identifiable ions were observed.

Silylation of the hydroperoxyacetal furnished **14b** in 1.3 g, 79% yield. $R_f=0.36$ (2% EA/hex); ^{1}H δ 4.89–4.86 (1H), 4.10–4.01 (2H), 3.77 (m, 1H), 3.57–3.49 (2H), 3.36 (s, 1.5H), 3.356 (s, $J=1.5$ Hz), 1.92–1.62 (6H), 1.52–1.26 (8H), 0.92 (s, 9H), 0.86 (t, 3H, $J=6.9$ Hz), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C δ 107.6, 107.5, 72.2, 69.4, 69.3, 58.9, 58.89, 40.65, 40.6, 38.99, 38.9, 35.64, 35.56, 32.5, 32.3, 31.6, 29.4, 28.4, 26.1, 25.7, 25.6, 22.5, 18.1, 14.0, −3.0, −5.7; IR 2949–2849 (several bands), 1356, 1202, 1102; HRFAB calcd for $C_{19}H_{41}IO_4SiLi$ $(M+Li)^+$: 495.1229; found: 495.1995 (3.2 ppm).

4.5. Allylation of peroxyacetals (illustrated for 15d)

Into a 0 °C solution of silyl peroxy acetal **12d** (171 mg, 0.35 mmol) and allylsilane (2.0 equiv, 0.7 mmol, 0.1 mL) in CH_2Cl_2 (4 mL) under N_2, was added a solution of $SnCl_4$ in CH_2Cl_2, (nominally 1.0 M solution, 0.4 mL, dropwise). The reaction mixture was allowed to stir for 1hr, and then quenched with DI water. The organic extracts (50% recycled EA/hex, 3×15 mL) were dried over Na_2SO_4, and solvent was removed under reduced pressure. Flash chromatography (5% EA/hex) furnished 95 mg (60%) of the allylated peroxide (**15d**). Compounds **15a–f**, **16**, **17**, **19** and **21** were prepared similarly.

4.5.1. 4-(*tert*-Butyldimethylsilyldioxy)-6-(*tert*-butyldimethylsilyloxy)-1-tridecene (15a). Yield=63 mg, 65%. $R_f=0.82$ (5% EA/hex); ^{1}H δ 5.82 (m, 1H), 5.08 (dd, 1H, $J=$ 17.0, 1.9 Hz), 5.04 (dd, 1H, $J=9.1$, 1.9 Hz), 4.10–4.01 (m, 1H), 3.85–3.76 (m, 1H), 2.55–2.25 (2H), 1.80–1.27 (broad, 17H), 0.94 (s, 5.4H), 0.93 (s, 3.6H), 0.88 (s, 9H), 0.15 (s, 6H), 0.06 (s, 2.8H), 0.05 (s, 3.2H); ^{13}C δ 135.0/134.7, 116.9, 116.7, 81.94, 81.87, 69.8, 69.6, 39.7, 38.2, 37.8, 37.4, 37.0, 31.9, 29.8, 29.3, 26.2, 26.0, 25.96, 25.2, 24.9, 22.6, 18.2, 18.1, 14.0, 12.2, −4.2, −4.37, −4.41, −5.58, −5.61; IR 2962–2851, 1641, 1249; HRMS: no identifiable ions were observed.

4.5.2. 4-(*tert*-Butyldimethylsilyldioxy)-6-methoxy-1-tridecene (15b). Yield=61 mg, 60%. $R_f=0.64$ (5% EA/hex); ^{1}H δ 5.82 (ddt, 1H, $J=17.3$, 10.1, 6.9 Hz), 5.07 (broad dd, 1H, $J=15.1$, 1.9 Hz), 5.04 (broad dd, 1H, $J=10.4$, 1.6 Hz), 4.16–4.11 (m, 1H), 4.06–4.01 (m, 1H), 3.33 (s, 0.9H), 3.29 (s, 2.1H), 2.53–2.28 (m, 2H), 1.88 (m, 0.3H), 1.68–1.58 (m, 1.7H), 1.54–1.27 (12H), 0.94 (s, 9H), 0.88 (t, 3H, $J=6.9$ Hz), 0.16 (s, 1.4H), 0.15 (s, 4.5H); ^{13}C δ 134.8/134.6, 117.04/117.01, 81.9, 78.0, 56.0, 37.7, 37.2, 35.8, 35.7, 33.8, 31.8, 29.8, 29.3, 26.2, 25.2, 25.0, 22.6, 18.2, 14.0, 14.02, −5.6; IR 2948–2854, 1635, 1246, 1130; HRMS: no identifiable ions were observed.

4.5.3. 6-Benzyloxy-4-(*tert*-butyldimethylsilyldioxy)-1-tridecene (15c). Yield=60 mg, 50%. $R_f=0.55$ (5% EA/hex); ^{1}H δ 7.35–7.27 (5H), 5.85–5.77 (ddt, 1H, $J=17.0$, 10.1, 6.9 Hz), 5.19 (dd, 1H, $J=17.0$, 1.3 Hz), 5.15 (dd, 1H, $J=$ 10.4, 1.3 Hz), 4.50 (s, 1.2H), 4.49 (s, $J=0.8$ Hz), 4.11–4.06 (m, 0.4H), 3.71–3.66 (m, 0.6H), 3.57–3.53 (m, 0.4H), 3.47 (m, 0.6H), 2.52–2.17 (2H), 1.75–1.28 (14H), 0.94 (s, 3.7H), 0.89 (s, 5.3H), 0.90–0.88 (3H, along with *tert*-Bu) 0.05 (s, 3.6H), 0.049 (s, 2.4H); ^{13}C δ 139.0, 138.7, 135.4, 134.7, 134.6, 128.3, 128.7, 127.7, 127.6, 127.5, 127.43, 127.37, 117.1, 116.9, 116.5, 81.9, 76.5, 76.0, 72.9, 72.0, 71.2, 70.4, 41.9, 37.7, 37.5, 37.2, 36.7, 36.2, 34.4, 34.0, 31.8, 29.8, 29.7, 29.3, 26.3, 26.2, 25.9, 25.3, 25.2, 25.1, 22.6, 18.2, 18.1, 14.0, −1.0, −4.4, −4.5, −5.6; IR 2951–2848, 1638, 1502, 1469, 1247, 1209, 1095; HRMS: no identifiable ions were observed.

4.5.4. Acetic acid, 4-(*tert*-butyldimethylsilyldioxy)-1-tridecen-6-yl ester (15d). Yield=95 mg, 65%. $R_f=0.62$ (5% EA/hex); ^{1}H δ 5.78 (ddt, 1H, $J=17.0$, 9.0, 7.0 Hz), 5.18–4.99 (3H), 3.99–3.94 (m, 1H), 2.008 (s, 1.2H), 2.006 (s, 1.8H), 2.50–2.26 (m, 2H), 1.92–1.63 (m, 2H), 1.21 (broad, 12H), 0.92 (s, 3.2H). 0.91 (s, 5.8H), 0.83 (t, 3H, $J=6.9$ Hz), 0.13 (s, 3.4H), 0.12 (s, 2.6H); ^{13}C δ 170.46/170.42, 134.3/134.1, 117.4/117.2, 81.6/81.5, 71.9/71.5, 37.4, 36.7, 36.6, 36.0, 34.7, 34.3, 31.7, 34.3, 31.7, 29.4, 29.3, 29.1, 26.15,

26.13, 25.9, 25.8, 25.7, 25.2, 25.0, 22.6, 21.2, 18.1, 14.0, −5.72/-5.74; IR 2954–2853, 1736, 1640, 1232; HRFAB calcd for $C_{21}H_{42}O_4SiLi$ $(M+Li)^+$: 393.3012; found: 393.3009 (0.9 ppm).

4.5.5. Benzoic acid, 4-(*tert*-butyldimethylsilyldioxy)-1-tridecen-6-yl ester (15e). Yield=57 mg, 55%. R_f=0.43 (5% EA/hex); ^1H δ 8.04 (broad dd, 2H, J=5.4, 2.2 Hz), 7.56–7.53 (1H), 7.45–7.42 (2H), 5.8 (ddt, 1H, J=17.3, 10.7, 6.9 Hz), 5.29–5.22 (1H), 5.08 (broad dd, J=17.0, 1.9 Hz), 5.05 (broad dd, 1H, J=10.1, 1.9 Hz), 4.10–4.04 (1H), 2.55–2.42 (2H), 1.97–1.81 (2H), 1.76–1.60 (2H), 1.40–1.24 (10H), 0.92 (s, 3.5H), 0.916 (s, 5.4H), 0.86 (t, 3H, J=6.9 Hz), 0.13 (s, 4.3H), 0.10 (s, 1.7H); ^{13}C δ 166.05/166.01, 134.3, 134.1, 132.74/132.66, 130.8, 130.6, 129.56/129.51, 128.3, 117.5, 117.3, 81.58/81.55, 72.7, 72.1, 37.4, 36.7, 36.67, 36.0, 34.8, 34.4, 31.7, 29.5, 29.2, 26.1, 26.13, 25.2, 25.1, 22.6, 18.1, 14.0, −5.7; IR 2924–2859, 1719, 1638, 1458, 1500; HRMS: no identifiable ions were observed.

4.5.6. 2,2-Dimethylpropionic acid, 4-(*tert*-butyldimethylsilyldioxy)-1-tridecen-6-yl ester (15f). Yield=35 mg, 55%. R_f=0.69 (5% EA/hex); ^1H δ 5.76 (ddt, 1H, J=17.0, 10.4, 7.0 Hz), 5.07 (dd, 1H, J=11.3, 1.6 Hz), 5.05 (dd, 1H, J=6.6, 1.9 Hz), 4.99–4.93 (m, 1H), 4.91–4.86 (0.2H), 3.99–3.93 (0.8H), 2.51–2.26 (m, 2H), 1.82–1.65 (2H), 1.59–1.50 (2H), 1.31–1.22 (10H), 1.19 (s, 2.3H), 1.18 (s, 6.7H), 0.93 (s, 2.3H), 0.926 (s, J=6.7 Hz), 0.87 (t, 3H, J=6.9 Hz), 0.15 (s, 4.5H), 0.14 (s, 1.5H); ^{13}C δ 177.9, 177.8, 134.4, 134.2, 117.3, 117.2, 81.6, 81.58, 72.8, 71.6, 70.9, 45.2, 38.8, 38.7, 37.5, 36.8, 36.6, 36.1, 34.7, 34.3, 33.6, 31.7, 30.8, 29.43, 29.38, 29.2, 27.2, 26.2, 25.2, 25.1, 24.9, 22.6, 18.1, 14.0, −5.67, −5.68; IR 2928–2855, 1734, 1642, 1286; HRMS: no identifiable ions were observed.

4.5.7. Acetic acid, 3-(*tert*-butyldimethylsilyldioxy)-1-phenyl-hex-5-enyl ester (15h). Yield=11 mg, 10%. R_f=0.33 (5% EA/hex); ^1H δ 7.40–7.30 (5H), 5.90 (ddt, 1H, J=17.3, 10.7, 6.9 Hz), 5.20 (broad dd, 1H, J=17.0, 1.9 Hz), 5.12 (broad dd, 1H, J=9.1, 1.9 Hz), 5.19–5.09 (1H), 4.05–3.90 (t, 0.5H, J=6.6 Hz), 3.91 (t, 0.5H, J=6.0 Hz), 2.05 (s, 1.5H), 2.04 (s, 1.5H), 1.64–1.56 (2H), 1.38–1.25 (2H), 0.944 (s, 4.6H), 0.936 (s, 4.4H), 0.152–0.148 (s, 6H); ^{13}C δ 171.1, 169.9, 141.1, 134.7, 134.2, 128.6, 128.5, 128.2, 127.8, 127.0, 126.5, 117.9, 117.4, 116.9, 84.6, 82.2, 81.0, 80.4, 73.2, 72.7, 64.5, 47.7, 39.3, 37.5, 37.3, 36.9, 31.7, 28.6, 26.2, 25.1, 21.1, 20.9, 18.2, −1.09, −5.6, −5.7; IR 2957–2859, 1741, 1638, 1496, 1475, 1238; HRMS: no identifiable ions were observed.

4.5.8. 3-But-3-enyloxy-1-(2-methoxyethoxy)-1-(*tert*-butyldimethylsilyldioxy)-decane (16). Yield=63 mg, 45%. R_f=0.34 (10% EA/hex); ^1H δ 5.81 (ddt, 1H, J=17.0, 10.1, 0.9 Hz), 5.07 (broad dd, 1H, J=17.3, 1.6 Hz), 5.01 (broad dd, 1H, J=10.1, 0.9 Hz), 4.86 (t, 0.5H, J=6.0 Hz), 4.07–4.03 (m, 0.5H), 3.80–3.76 (m, 1H), 3.58–3.50 (m, 2H), 3.40 (t, 2H, J=6.9 Hz), 3.39 (2H, t, J=6.6 Hz), 3.36 (s, 3H), 2.31 (broad q, 2H, J=6.6 Hz), 1.66–1.53 (6H), 1.44–1.31 (8H), 0.93 (s, 9H), 0.88 (t, 3H, J=6.3 Hz), 0.16 (s, 3.1H), 0.15 (s, 2.8H); ^{13}C δ 135.4, 116.1, 108.5, 72.3, 70.8, 70.2, 69.2, 58.9, 34.2, 32.3, 29.6, 26.1, 26.0, 24.6, 18.1, −5.7; IR 2923–2855, 1632, 1642, 1106; HRMS: no identifiable ions were observed.

4.5.9. 6-But-3-enyloxy-tridec-1-en-4-yl *tert*-butyl dimethylsilyl peroxide (17). Yield=52 mg, 40%. R_f=0.7 (10% EA/hex); ^1H δ 5.86–5.75 (ddt, 2H, J=16.1, 10.4, 6.6 Hz), 5.08 (dd, 2H, J=16.7, 1.9 Hz), 5.03 (dd, 2H, J=10.4, 1.6 Hz), 3.90 (m, 1H), 3.45 (t, 1H, J=6.9 Hz), 3.40 (t, 1H, J=6.6 Hz), 3.40–3.50 (1H), 2.47–2.25 (4H), 1.57–1.22 (14H), 0.93 (s, 9H), 0.89–0.88 (3H), 0.15 (s, 3.1H), 0.14 (2.9H); ^{13}C δ 135.3, 134.7, 116.2, 84.6, 70.8, 70.1, 36.8, 34.2, 31.7, 29.7, 29.6, 26.2, 25.9, 25.3, 18.1, −5.6; IR 2928–2855, 1632, 1642, 1111; HRMS: no identifiable ions were observed.

4.5.10. Ethyl-4-*tert*-butyldimethylsilyldioxy-4-(2-methoxyethoxy)-2-trimethylsilylbutyrate (18). 4-Hydroperoxy-4-(2-methoxyethoxy)-2-trimethylsilyl-butyric acid ethyl ester was prepared by ozonolysis of 2-trimethylsilyl-pent-4-enoic acid ethyl ester in 2.9 g, 58% yield: R_f=0.33 (20% EA/hex); ^1H δ 10.1 (s, 0.5H), 10.0 (s, 0.5H), 4.71 (broad q, 2H, J=5.7 Hz), 4.08–3.99 (1H), 3.81–3.68 (2H), 3.60–3.44 (2H), 3.36 (s, 1.4H), 3.35 (s, 1.6H), 2.23–2.15 (m, 0.5H), 2.09–1.96 (0.5H), 1.80 (broad dd, 1H, J=7.88 Hz),1.65 (broad dd, 1H, J=6.3 Hz), 1.17 (broad dd, 3H, J=6.9, 7.2 Hz), 0.16 (s, 5H), 0.01 (s, 4H); ^{13}C δ 175.7, 175.0, 106.9, 106.3, 72.5, 72.2, 66.1, 65.8, 60.0, 59.7, 58.8, 58.7, 33.2, 32.5, 28.1, 27.9, 14.2, −2.9, −3.0; IR 3335, 1716, 1252, 1100–1130; HRMS: no identifiable ions were observed.

Silylation of the hydroperoxide under standard conditions afforded silyl peroxide **18** in 916 mg, 88% yield: R_f=0.67 (20% EA/hex); ^1H δ 4.86 (dd, 0.8H, J=3.8, 7.9 Hz), 4.82–4.80 (dd, 0.2H, J=3.8, 7.9 Hz), 4.11–4.04 (1.4H), 4.03–3.98 (0.6H), 3.76–3.71 (1.3H), 3.53–3.46 (2.7H), 3.34 (s, 0.6H), 3.33 (s, 2.4H), 2.22 (t, 0.7H, J=2.2 Hz), 2.20 (0.3H), 2.14–1.56 (2H), 1.21 (broad t, 3H, J=6.9 Hz), 0.90 (s, 6H), 0.83 (s, 3H), 0.14 (s, 2H), 0.04 (s, 4H), −0.01 (s, 9H); ^{13}C δ 174.7, 174.6, 107.7, 107.2, 72.0, 71.9, 69.7, 68.9, 59.7, 58.8, 58.7, 32.7, 32.6, 30.2, 28.9, 26.1, 25.63, 25.6, 18.06, 18.0, 14.4, 14.3, −2.76, −2.8, −3.0, −5.8. IR 2952–2859, 1714, 1464, 1252, 1160, 1100; HRFAB calcd for $C_{18}H_{40}O_6Si_2Li$ $(M+Li)^+$: 415.2523, found: 415.2527 (0.8 ppm).

4.5.11. 4-*tert*-Butyldimethylsilyldioxy-2-trimethylsilyl-6-heptenoic acid ethyl ester (19). The title compound was prepared by allylation of **18** under standard conditions: Yield=200 mg, 55%. R_f=0.48 (5% EA/hex); ^1H δ 5.8 (ddt, 1H, J=17.6, 10.4, 7.2 Hz), 5.08 (broad dd, 1H, J=17.3, 1.6 Hz), 5.04 (broad dd, 1H, J=10.1, 1.6 Hz), 4.14–4.04 (m, 2.3H), 3.93–3.83 (m, 0.7H), 2.55–1.96 (2H), 1.77–1.66 (0.5H), 1.70–1.66 (0.5H), 1.60–1.56 (2H), 1.21 (t, 2H, J=2.0 Hz), 1.99 (t, 1H, J=2.0 Hz), 0.92 (s, 2.8H), 0.91 (s, 6.2H), 0.16 (s, 0.7H), 0.14 (s, 1.2H), 0.13 (s, 2H), 0.11 (s, 2.1H), 0.06 (s, 3.4H), 0.05 (s, 5.6H); ^{13}C δ 175.07/175.04, 134.6, 134.4, 117.0, 116.8, 101.6, 84.6, 84.2, 59.7, 59.6, 37.5, 35.7, 33.8, 33.1, 31.6, 29.4, 28.3, 26.2, 25.8, 22.6, 18.2, 18.1, 14.4, 14.0, −2.6, −2.68, −2.75, −5.7; IR 2949–2855, 1714, 1638, 1252; HRMS: no identifiable ions were observed.

4.5.12. Formation of silatrioxepane: 3,3-di-*tert*-butyl-5-heptyl-7-(2-methoxyethoxy)-3-sila-[1,2,4]-trioxepane (20). 1-Hydroperoxy-1-(2-methoxyethoxy)-decan-3-ol was prepared by ozonolysis of undecen-4-ol in

2-methoxyethanol in 530 mg, 65% yield: R_f=0.37 (40% EA/hex); ^{1}H δ 10.8 (s, 0.1H), 10.46 (s, 0.9H), 5.09 (t, 0.1H, J=4.7 Hz), 5.05–4.99 (0.9H), 3.91–3.85 (0.6H), 3.84–3.76 (2H), 3.64–3.52 (2H), 3.40 (s, 1.3H), 3.40 (s, J=1.7 Hz), 3.36–3.34 (0.4H), 2.84 (broad peak, 2H), 1.91–1.23 (13H), 0.84 (broad t, 3H, J=6.3 Hz); ^{13}C δ 106.2, 106.1, 72.6, 72.5, 68.4, 68.3, 66.9, 66.3, 66.5, 58.8, 38.7, 38.5, 37.4, 31.7, 31.0, 29.5, 29.1, 25.5, 25.4, 25.3, 22.5, 13.9; IR 3364, 1198, 1143, 1095; HRMS: no identifiable ions were observed.

A solution of *tert*-BuSi(OTf)$_2$ (700 mg, 0.6 mL, 1.6 mmol, 3.0 equiv) and imidazole (180 mg, 2.6 mmol, 5 equiv) in DMF (2 mL) was stirred for few minutes, after which was added a dropwise solution of the hydroperoxyalcohol (140 mg, 0.53 mmol) in DMF (2 mL). After 15 min the reaction mixture was quenched with DI water and extracted into recycled 50% EA/hex (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (20% EA/Hex) furnished 85 mg (45%) of silatrioxepane (**20**): R_f=0.68 (20% EA/hex); ^{1}H δ 5.02 (t, 0.4H, J=4.1 Hz), 4.93–4.91 (m, 0.6H), 4.10–4.12 (0.4H), 4.00–3.96 (0.6H), 3.71–3.59 (2H), 3.56–3.51 (2H), 3.375 (s, 1.1H), 3.372 (s, 1.9H), 2.23–2.18 (0.8H), 1.92–1.83 (m, 1.2H), 1.57–1.26 (12H), 1.07 (s, 5.7H), 1.05 (s, 3.3H), 1.03 (s, 2.8H), 1.0 (s, 6.2H), 0.87 (broad t, 3H, J=6.0 Hz); ^{13}C δ 107.4, 104.4, 71.9, 71.5, 70.6, 67.2, 67.1, 59.0, 58.98, 40.6, 40.4, 38.6, 37.5, 31.8, 31.7, 29.5, 29.44, 29.37, 29.3, 29.1, 28.1, 28.0, 27.9, 27.7, 27.5, 27.2, 27.0, 26.9, 26.7, 25.9, 25.3, 24.9, 22.6, 21.9, 21.5, 20.5, 20.3, 14.1; IR 2933–2850, 1111; HRFAB calcd for $C_{21}H_{44}O_5SiNa$ $(M+Na)^+$: 427.2858, found: 427.2867 (2.7 ppm).

4.5.13. 3,3-Di-*tert*-butyl-5-heptyl-7-(2-propenyl)-1,2,4,3-trioxasilepane (21). The title compound was prepared by allylation of **20** under conditions similar to those described for compound **15d**: yield=4 mg, 5%. R_f=0.78 (5% EA/hex); ^{1}H δ 5.86 (ddt, 1H, J=17.3, 10.1, 6.9 Hz), 5.07 (dd, 1H, J=17.3, 1.6 Hz), 5.05 (dd, 1H, J=9.1, 1.3 Hz), 4.16 (m, 1H), 4.08 (m, 1H), 2.43–2.37 (1H), 2.24–2.18 (m, 1H), 1.78–1.67 (2H), 1.63–1.56 (1H), 1.43–1.28 (11H), 1.0 (s, 4.6H), 0.99 (s, 4.4H), 0.96 (s, 4.6H), 0.95 (s, 4.4H), 0.88 (broad t, 3.0H, J=6.9 Hz); ^{13}C δ 135.3, 116.7, 100.8, 70.0, 42.3, 38.2, 37.9, 31.8, 29.7, 29.5, 29.3, 27.6, 27.5, 27.3, 27.1, 25.6, 22.6, 21.0, 14.1, 9.4, 2.1; IR 2930–2848, 1638, 1247, 1073; HRMS: no identifiable ions were observed.

4.5.14. Reduction of peroxides: tridec-1-ene-4,6-diol (22). Into a solution of allylated peroxide **15d** (201 mg, 0.52 mmol) in THF (6 mL) was added $LiAlH_4$ (2.6 mmol, 99 mg). The reaction was stirred overnight, and then quenched with dilute HCl. The extracts (50% recycled EA/hex, 3×15 mL) were dried over Na_2SO_4, and solvent was removed in vacuo. The crude product was purified by flash chromatography (20% EA/hex) to furnish 62 mg (55%) and 35 mg (35%) of diastereomeric diols.

Minor diastereomer. R_f=0.51 (40% EA/hex); ^{1}H δ 5.81 (ddt, 1H, J=16.4, 9.5, 6.9 Hz), 5.08 (dd, 1H, J=17.0, 1.9 Hz), 5.04 (dd, 1H, J=10.4, 2.2 Hz), 3.93–3.88 (m, 1H), 3.87–3.82 (m, 1H), 2.88 (broad s, 2H), 2.29–2.19 (m, 2H), 1.64–1.60 (2H), 1.52–1.39 (4H), 1.33–1.24 (8H), 0.88 (t, 3H, J=6.6 Hz); ^{13}C δ 134.4, 118.2, 72.9, 71.9, 42.64/42.60, 38.2, 31.8, 29.6, 29.2, 25.4, 22.6, 14.0.

Major diastereomer. R_f=0.49 (40% EA/hex); ^{1}H δ 5.8 (ddt, 1H, J=16.4, 9.1, 5.4 Hz), 5.15–5.11 (2H), 4.01–3.96 (m, 1H), 3.93–3.90 (m, 1H), 2.44 (broad s, 2.0H), 2.28–2.25 (m, 2H), 1.62–1.60 (2H), 1.53–1.28 (12H), 0.88 (t, 3H, J=6.9 Hz); ^{13}C δ 134.7, 118.0, 69.3, 68.27, 42.1, 37.5, 31.8, 29.6, 29.2, 25.7, 22.6, 14.6, 14.0; IR 3347 (b), 1637; HRFAB calcd for $C_{13}H_{26}O_2Li$ $(M+Li)^+$: 221.2093, found: 221.2086 (3.2 ppm).

4.5.15. Formation of acetonides: 4-(2-propenyl)-6-heptyl-2,2-dimethyl-1,3-dioxane (23). Into a solution of diol **22** (100 mg, 0.46 mmol) in 2,2-dimethoxypropane (6 mL, excess), was added a catalytic amount of *S*-(+)-camphor sulphonic acid (5 mg). The reaction mixture was stirred for twenty minutes, after which solvent was removed in vacuo. The crude product was purified by flash chromatography (5% EA/hex) to furnish 71 mg (60%) of a mixture of diastereomeric acetonides: R_f=0.65 (10% EA/hex); ^{1}H δ 5.88 (ddt, 1H, J=17.3, 10.0, 6.9 Hz), 5.09 (broad dd, 1H, J=17.3, 1.9 Hz), 5.04 (broad dd, 1H, J=10.4, 1.8 Hz), 3.88–3.81 (m, 1H), 3.79–3.72 (m, 1H), 2.32–2.26 (1H), 2.20–2.11 (1H), 1.51–1.47 (4H), 1.38 (s, 3H), 1.339 (s, 3H), 1.30–1.27 (10H), 0.87 (t, 3H, J=6.9 Hz).

Mixture of diastereomers. DEPT 135 ^{13}C δ 134.6 (+), 134.3 (+), 116.9 (−), 116.7 (−), 100.1 (−), 98.3 (−), 69.0 (+), 68.7 (+), 66.6 (+), 66.2 (+), 40.9 (−), 40.2 (−), 38.2 (−), 36.5 (−), 36.49 (−), 36.0 (−), 31.8 (−), 30.3 (+), 29.7 (−), 29.55 (−), 29.5 (−), 29.23 (−), 29.21 (−), 25.3 (−), 24.95 (+), 24.87, 24.8 (+), 22.6 (−), 19.8 (+), 14.0 (+); IR 1638, 1165, 1116; HREI calcd for $C_{15}H_{27}O_2$ $(M-CH_3)^+$: 239.2011; found: 239.2012 (0.4 ppm).

4.5.16. Tridecane-4, 6-diol (24). Peroxide **15c** (345 mg, 0.8 mmol), and BHT (5 mg), were dissolved in THF/AcOH/H_2O (5:3:2, 10 mL). Following disappearance of starting material (2 days, TLC), triphenyl phosphine (4 mmol, 1 g) was added. After an additional 24 h, the reaction mixture was diluted with 50 mL of 40% recycled EA/hex, and washed sequentially with saturated NH_4Cl (4×20 mL) solution and brine solution (2×15 mL). The separated organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (5% EA/hex) furnished 217 mg (89%) of 4-hydroxy 6-benzyloxy tridecene as an inseparable mixture of diastereomers. R_f=0.2 (5% EA/hex); ^{1}H δ 7.35–7.27 (5H), 5.84 (ddt, 1H, J=17.3, 10.4, 7.2 Hz), 5.14 (dd, 1H, J=17.0, 1.9 Hz), 5.12 (dd, 1H, J=10.0, 2.0 Hz), 4.64 (d, 0.6H, J=11.3 Hz), 4.44 (d, 0.6H, J=11.3 Hz), 4.56 (dd, 0.5H, J=11.3, 15.3 Hz), 3.99–3.94 (0.3H), 3.86–3.81 (1H), 3.73–3.65 (1H), 3.53 (s, 0.9H), 2.78 (s, 0.1H), 2.27–2.17 (2H), 1.72–1.50 (4H), 1.37–1.24 (broad, 10H), 0.90 (t, 3H, J=6.9 Hz); ^{13}C δ 138.2, 135.0, 134.9, 128.4, 128.3, 127.8, 127.7, 127.6, 117.3, 117.1, 79.6, 71.2, 70.7, 70.6, 67.8, 42.2, 42.1, 40.5, 39.7, 33.6, 33.5, 31.7, 29.8, 29.7, 29.2, 25.4, 24.7, 22.6, 13.9; IR 3449, 1647, 1494, 1451; HREI calcd for $C_{20}H_{33}O_2$ $(M+H)^+$: 305.2481; found: 305.2483 (0.9 ppm).

A mixture of 4-hydroxy-6-benzyloxy tridecene (217 mg,

0.71 mmol) and 10% Pd/C (10 mol%, 76 mg) in MeOH (5 mL) was placed under an atmosphere of H_2 (balloon). After 3 days, the reaction mixture was filtered through a plug of cotton and the solvent was removed under reduced pressure. Flash chromatography (20% EA/Hex) furnished tridecane-4,6-diol (**24**) as a mixture of two diastereomers in a total yield of 78%. The first eluting diastereomer was a colorless oil (86 mg). The second eluting isomer was a white solid (35 mg).

Major diastereomer. R_f=0.3 (20% EA/hex); ^{1}H δ 3.81–3.80 (2H), 3.53 (broad peak, 2H), 1.58–1.26 (18H), 0.9 (t, 3H, J=6.3 Hz), 0.85 (t, 3H, J=6.3 Hz); ^{13}C δ 73.1, 72.8, 42.7, 40.32, 38.2, 31.8, 29.6, 29.2, 25.3, 22.6, 18.5, 14.0, 13.99; IR 3294, 1062.

Minor diastereomer. Mp 55–56 °C; ^{1}H δ 3.93–3.89 (2H), 2.53 (broad peak, 2H), 1.60–1.28 (18H), 0.92 (t, 3H, J=6.3 Hz), 0.87 (t, 3H, J=6.3 Hz); ^{13}C δ 69.4, 69.1, 42.3, 39.6, 37.5, 31.8, 29.6, 29.2, 25.8, 22.6, 18.9, 14.0, 12.1; HRFAB calcd for $C_{13}H_{28}O_2Li$ $(M+Li)^+$: 223.2249, found: 223.2240 (4.1 ppm).

4.5.17. 2,2-Dimethyl- 4-heptyl-6-propyl-1,3-dioxane (25). Into a solution of diol **24** (70 mg, 0.32 mmol) in 2,2 dimethoxypropane (4 mL, excess), was added (*S*)-(+)-camphor sulfonic acid (5 mg). After 30 min solvent was removed in vacuo. Flash chromatography (5% EA/hex) furnished 80 mg (96%) of acetonide. R_f=0.5 (5% EA/hex) ^{1}H δ 3.80–3.73 (2H), 1.54–1.44 (3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.34–1.25 (14H), 1.07 (q, 1H, J=11.9 Hz), 0.88 (t, 3H, J=6.6 Hz), 0.86 (t, 3H, J=6.6 Hz); DEPT 135 ^{13}C δ 69.0 (+), 68.7 (+), 38.6 (−), 37.0 (−), 36.5 (−), 31.8 (−), 30.3 (−), 29.5 (−), 29.2 (−), 24.9 (−), 22.6 (−), 19.8 (+), 18.1 (−), 14.0 (+), 13.97 (+), 12.1 (−); IR 1165, 1116; HREI calcd for $C_{13}H_{28}O_2Li$ $(M+H)^+$: 257.2481, found: 257.2483 (0.9 ppm).

4.5.18. 4-*tert*-Butyldioxy-5-iodo-dodec-1-ene (26). Into a −78 °C solution of iodoperoxy acetal (0.35 mmol, 134 mg) **3a** and allylsilane (2 equiv, 0.7 mmol, 0.1 mL) in CH_2Cl_2 (5 mL) was added drop wise $SnCl_4$ (1.1 equiv, 0.4 mL, 1.0 M in CH_2Cl_2). After 30 min the reaction mixture was quenched with DI water and allowed to warm to room temperature. The combined extracts (recycled 50% EA/hex, 3×30 mL) were dried over Na_2SO_4 and concentrated. Flash chromatography (2% EA/Hex) furnished allylated peroxide in 48 mg, 35% yield. R_f=0.88 (2% EA/hex); ^{1}H δ 5.89 (ddt, 1H, J=17.0, 10.0, 6.9 Hz), 5.14 (dd, 1H, J=17.3, 1.6 Hz), 5.08 (dd, 1H, J=10.1, 1.8 Hz), 4.51 (dt, 1H, J=9.8, 4.1 Hz), 4.41 (m, 0.1H), 3.95 (m, 0.1H), 3.46 (m, 0.9H), 2.40–2.37 (2H), 1.86–1.58 (3H), 1.40–1.26 (broad 9H), 1.25 (s, 8.2H), 1.23 (s, 1.1H), 0.88 (t, 3H, J=6.6 Hz); ^{13}C δ 134.7/134.3, 117.3/117.2, 85.0, 80.4, 40.4, 36.5, 36.0, 31.8, 29.9, 29.8, 29.11/29.07, 28.8, 26.7, 26.5, 22.6; IR 2977–2844, 1643, 1358, 1252, 1196; HRFAB calcd for $C_{13}H_{26}IO_2$ $(M-allyl)^+$: 341.0978; found: 341.0207 (22 ppm).

4.5.19. 4-*tert*-Butyldioxy-5-iodo-undec-1-ene (27). The title compound was prepared by allylation of iodoperoxy acetal **4a** at 0 °C (43 mg, 23%). R_f=0.63 (2% EA/hex); ^{1}H δ 5.90 (ddt, 1H, J=17.3, 10.4, 7.2 Hz), 5.15 (broad dd, 1H, J=17.0, 1.6 Hz), 5.08 (broad dd, 1H, J=10.1, 1.6 Hz), 4.56–4.54 (m, 0.8H), 4.47–4.43 (0.2H), 4.01–3.98 (m, 0.2H), 3.49–3.46 (0.8H), 2.44–2.30 (2H), 1.75–1.59 (2H), 1.36–1.29 (8H), 1.25 (s, 7.5H), 1.23 (s, 1.5H), 0.89 (t, 3H, J=6.9 Hz); ^{13}C δ 134.7, 134.3, 117.3, 117.2, 85.7, 85.0, 80.5, 80.4, 40.8, 38.6, 36.4, 36.0, 34.4, 34.2, 31.6, 30.3, 29.9, 29.7, 28.53, 28.49, 26.7, 26.5, 22.6, 22.2, 14.1; IR 1642, 1243, 1199; HRMS: no identifiable ions were observed.

Allylation of peroxyacetals **5** and **14a,b** was carried out under similar procedures as described earlier.

4.5.20. 1-Triphenylsilyl-4-penten-2-yl *tert*-butyldimethylsilylperoxide (28). The title compound was prepared by allylation of triphenylsilyl peroxyacetal **5**. Yield= 118 mg, 60%. R_f=0.33 (2% EA/hex); ^{1}H δ 7.75–7.64 (6H), 7.48–7.40 (9H), 5.80 (ddt, 1H, J=17.0, 10.1, 6.9 Hz), 5.05 (dd, 1H, J=10.7, 1.9 Hz), 4.88 (1H, dd, J=17.0, 1.6 Hz), 4.35 (m, 1H), 2.24 (m, 2H), 0.96 (d, 2H, J= 7.8 Hz), 0.98 (s, 9H), 0.18–0.10 (overlapping s, 6H). ^{13}C δ 135.7, 134.9, 134.5, 129.5, 127.8, 117.2, 82.2, 38.9, 26.1, 18.1, 16.9, 2.0, −5.5, −5.6; IR 1639, 1493, 1477, 1362; HRFAB calcd for $C_{29}H_{38}O_2Si_2Li$ $(M+Li)^+$: 481.2571; found: 481.2583 (2.4 ppm).

4.5.21. 7-Methoxy-tridec-1-en-4-yl *tert*-butyldimethylsilyl peroxide (29a). The title compound was prepared by allylation of peroxyacetal **14a**. Yield=87 mg, 78%. R_f= 0.73 (10% EA/hex); ^{1}H δ 5.80 (ddt, 1H, J=17.0, 10.1, 6.9 Hz), 5.06 (dd, 1H, J=17.0, 1.6 Hz), 5.04 (dd, 1H, J= 9.1, 1.9 Hz), 3.91 (m, 1H), 3.30 (s, 3H), 3.11 (m, 1H), 2.49–2.43 (1H), 2.31–2.20 (1H), 1.64–1.18 (14H), 0.93 (s, 9H), 0.88 (t, 3H, J=6.3 Hz), 0.15 (s, 3.4H), 0.14 (s, 2.6H); ^{13}C δ 134.7, 116.8, 84.9, 84.7, 80.9, 80.7, 56.3, 56.2, 37.0, 33.45/ 33.41, 31.8, 29.7, 29.5, 29.2, 28.8, 27.6, 26.2, 26.1, 25.3, 25.2, 22.6, 18.2, 14.0, −5.6; IR 2954–2810, 1650, 1193, 1093; HRMS: no identifiable ions were observed.

4.5.22. 4-*tert*-Butyldimethyl silyldioxy-7-iodo-tridec-1-ene (29b). The title compound was prepared by allylation of acetal **14b** under standard conditions. Yield=68 mg, 30%. R_f=0.8 (2% EA/hex); ^{1}H δ 5.80 (ddt, 1H, J=17.0, 10.1, 6.9 Hz), 5.08 (broad dd, 1H, J=17.0, 1.6 Hz), 5.06 (broad dd, 1H, J=10.1, 1.6 Hz), 4.15–4.07 (1H), 3.95–3.89 (1H), 2.49–2.42 (1H), 2.31–2.23 (1H), 1.95–1.63 (5H), 1.47–1.24 (9H), 0.94 (s, 9H), 0.90 (t, 3H, J=6.6 Hz), 0.16 (s, 2.4H), 0.15 (s, 3.6H); ^{13}C δ 134.43/134.40, 84.2, 83.7, 40.71, 40.68, 39.8, 39.76, 36.9, 36.7, 36.2, 32.0, 31.8, 31.7, 29.7, 29.5, 29.4, 28.5, 26.2, 22.6, 18.2, 14.0, −5.62, −5.64; IR 1642, 1247, 1151; HRMS: no identifiable ions were observed.

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Hemiacetal and hemiaminal formation at fluoroacyl moiety

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Abstract—Hemiacetals and hemiaminals were produced not only at a trifluoroacetyl (CF_3CO) moiety but also at difluoroacetyl (CHF_2CO) and pentafluoroalkanoyl (C_2F_5CO) moieties. As larger was the electron-withdrawing nature and less bulky was the fluoroalkyl (R_f) group and smaller was the size of an alcohol, the ratio of hemiacetal form increased. Not only a CF_3CO moiety but also monofluoroacetyl (CH_2FCO), CHF_2CO, and C_2F_5CO moieties produced the hemiaminals. As larger was the electron-withdrawing nature of R_f group and smaller was an amine, the ratio of hemiaminal form increased.

1. Introduction

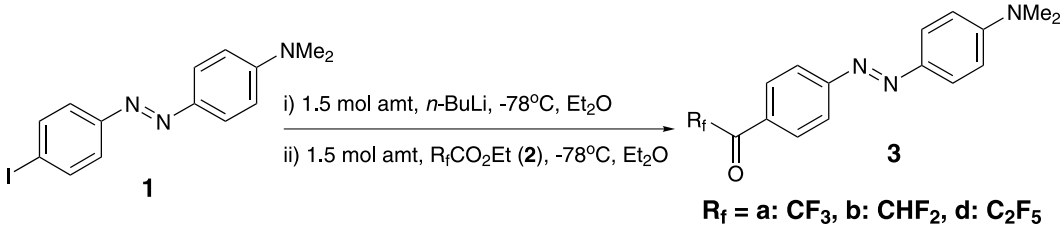
A CF_3CO moiety forms hemiacetals, hemiaminals, and zwitterions with alcohols, primary and secondary amines, and tertiary amines, respectively.[1] The basic properties of CF_3CO-substituted azobenzenes and stylbenes have been reported.[2] PMMA polymer pendant with a CF_3CO-substituted azobenzene derivative was used as quantitative analysis of amines.[3] The application of CF_3CO-substituted compounds as selective reorganization of amino acids[4] have been also reported.[4] Thus, the properties of CF_3CO moiety have been examined in detail, no systematic studies of fluoroacyl (R_fCO) moieties on the formation of hemiacetals and hemiaminals have been reported so far. It is of significance to examine the relationship among the formation of hemiacetals and hemiaminals, the properties of R_f group, alcohols, and amines. We report herein the formation of hemiacetals and hemiaminals at CH_2FCO, CHF_2CO, CF_3CO, and C_2F_5CO moieties on the basis of the solvatochromism of R_fCO-substituted azobenzenes.

2. Results and discussion

CF_3CO-, CHF_2CO-, and C_2F_5CO-substituted azobenzenes **3a**, **3b**, and **3d** were synthesized as shown in Scheme 1. 4-Dimethylamino-4′-iodoazobenzene (**1**) reacted with butyl lithium followed by the reaction with ethyl fluoroacetates **2a**, **2b**, and **2d** gave the corresponding azobenzenes **3a**, **3b**, and **3d** in moderate yields.

Since monofluoroacetic acid is toxic, the method described above was not used to prepare the CH_2FCO derivative **3c**. 2,3,3-Trifluoro-1-{4-[4-(dimethylamino)phenylazo]phenyl}-1-propenyl-*p*-toluenesulfonate (**3′c**) was prepared as described in the paper.[5] The hydrolysis of this compound provided **3c** in a 71% yield as shown in Scheme 2.

Change in the UV–vis absorption spectra of **3d** in 2-methyl-1-propanol at 25 °C is shown in Figure 1. The spectra showed the hypsochromic shift of absorption maximum (λ_{max}) from 470 to 419 nm with isosbestic points at 343 and 436 nm. The equilibrium was reached in 6 h. In the case of



Scheme 1.

Keywords: Perfluoroacyl; Hemiacetal; Hemiaminal; Steric effect; Electronic effect.
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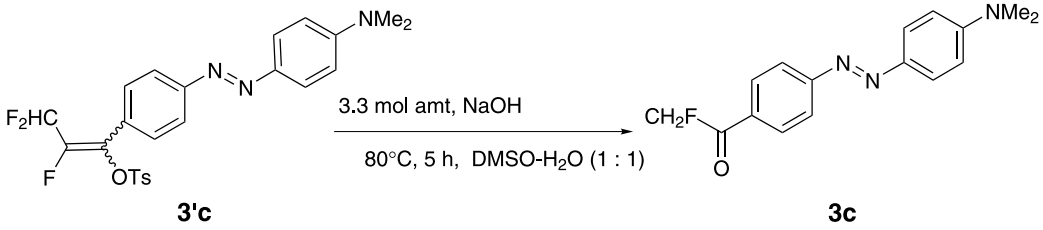

Scheme 2.

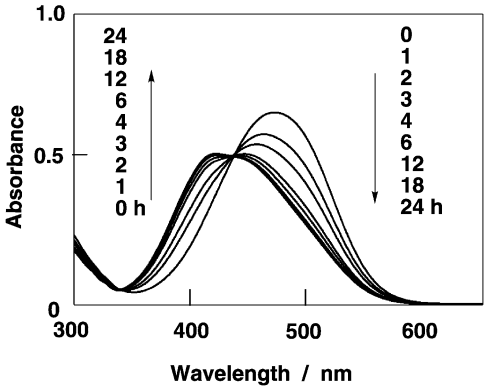

Figure 1. Change in UV–vis absorption spectrum of **3d** in 2-methyl-1-propanol at 25 °C. The spectra were measured on 3.0×10^{-5} mol dm^{-3} of **3d**.

amines, the UV–vis absorption spectrum immediately changed. Therefore, all the UV–vis absorption spectra of R_fCO-substituted azobenzenes **3** in alcohols and amines were measured at 25 °C after 24 h to examine the formation of hemiacetals and hemiaminals.

The UV–vis absorption spectra of CHF_2CO derivative **3b** in toluene, acetonitrile, methanol, and 2-methyl-1-propanol are shown in Figure 2. The λ_{max} of **3b** in toluene and acetonitrile were observed at 457 and 470 nm, respectively, indicating slightly positive solvatochromism as normally observed for neutral azo dyes. No shoulder peak of **3b** was observed around 418 nm in toluene and acetonitrile. Meanwhile, the absorption spectrum in methanol showed the λ_{max} at 418 nm and no shoulder peak around 457 nm. The

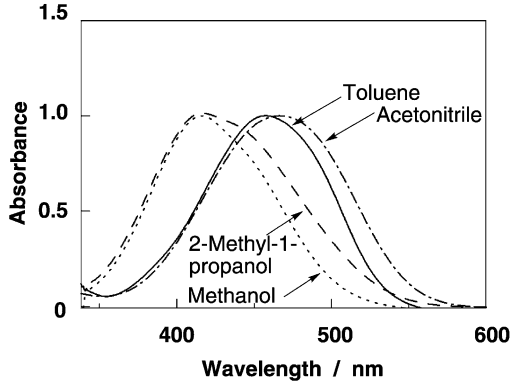

Figure 2. UV–vis absorption spectra of **3b** in toluene, acetonitrile, methanol, and 2-methyl-1-propanol. The spectra are normalized.

hypsochromicity in methanol comes from decrease in the electron-withdrawing nature of the CHF_2CO moiety in the push–pull chromophoric azobenzene **3b**. The UV–vis absorption spectrum of **3b** in 2-methyl-1-propanol showed the λ_{max} at 418 nm with a shoulder peak around 457 nm, suggesting that both the keto and hemiacetal forms exist in the solution.

The NMR spectra of **3b** in $CDCl_3$ and CD_3OD–$CDCl_3$ (9:1) mixed solution are shown in Figures 3 and 4. Since the solubility of **3b** in CD_3OD was not high enough to measure the ^{13}C NMR spectrum, the mixed solvent was used. The ^1H NMR spectrum of **3b** in $CDCl_3$ showed a characteristic triplet peak at 6.32 ppm ($J=55.9$ Hz) attributed to the difluoromethyl proton H^a and a doublet peak at 8.18 ppm ($J=8.5$ Hz) of *o*-aromatic protons H^d (Fig. 3a). Meanwhile, the spectrum of **3b** in the CD_3OD–$CDCl_3$ mixed solution showed a triplet peak at 5.74 ppm ($J=55.9$ Hz, $H^{a'}$) and a doublet peak at 7.66 ppm ($J=8.8$ Hz, $H^{d'}$), being upfielded due to the formation of the hemiacetal with CD_3OD (Fig. 3b). Small proton peaks assigned to the keto form were also observed in the range of 6.7 to 8.2 ppm. The ^{13}C NMR spectra of **3b** in $CDCl_3$ showed a small triplet peak at 186.9 ppm ($J=24.8$ Hz) based on the carbonyl carbon C^b (Fig. 4a). In the CD_3OD–$CDCl_3$ mixed solvent, this peak upfielded to 98.2 ppm ($J=24.8$ Hz, $C^{b'}$) (Fig. 4b). Small carbon peaks come from the keto form were also observed in the aromatic region. Thus, it is clear that the CHF_2CO moiety could form the hemiacetal with methanol.

The ^1H NMR spectra of **3b** in $CDCl_3$ in the presence 25 molar amounts of butylamine is shown in Figure 3c. When more amount of butylamine was added to the solution, the *S*/*N* ratio of the spectrum markedly decreased. The spectrum showed a triplet peak at 5.70 and a doublet peak at 7.66 ppm, which are assigned to the difluoromethine and *o*-aromatic protons in the aminal form, respectively.

Figure 5 shows the UV–vis absorption spectra of **3b** and **3c** in butylamine and diethylamine. The λ_{max} of **3b** in butylamine was observed at 408 nm without a shoulder peak around 460 nm. That of **3b** in diethylamine was observed at 408 nm with a shoulder peak around 460 nm. The λ_{max} of **3c** in diethylamine was observed at 438 nm without a shoulder peak around 408 nm. Compound **3c** showed the λ_{max} at 408 nm with a small shoulder peak around 460 nm in butylamine. These results indicate that both the keto and hemiaminal forms of **3b** and **3c** can exist depending on the kinds of amines.

The UV–vis absorption spectra of **3a–d** were measured in

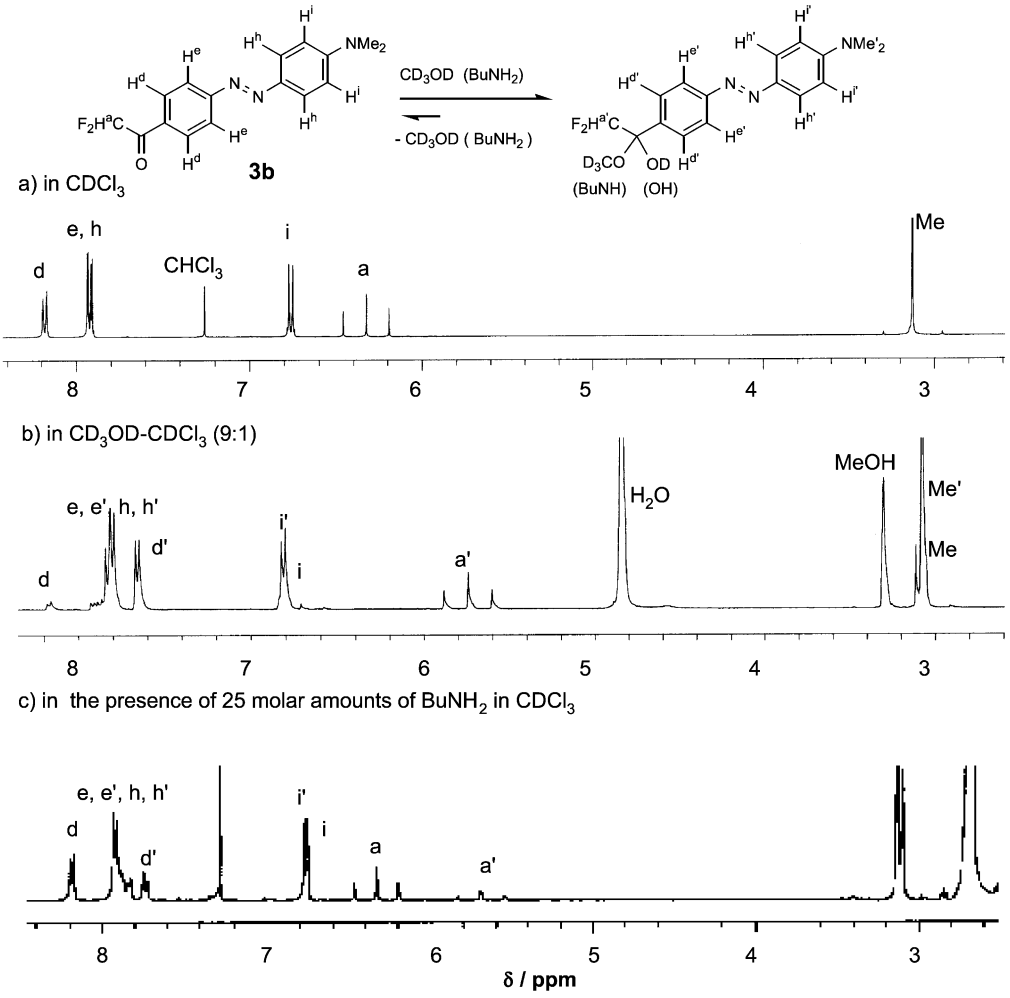

Figure 3. ^{1}H NMR spectra of **3b** in (a) $CDCl_3$, (b) CD_3OD–$CDCl_3$ (9:1) mixed solution, and (c) in the presence of 25 molar amounts of $BuNH_2$ in $CDCl_3$.

neat solvents. The ratios of hemiacetal and hemiaminal forms were calculated on the basis of the UV–vis absorption spectra of R_fCO-substituted azobenzenes. The calculation of the ratio of hemiacetal and hemiaminal forms are described in Section 4.

The relationship between the ratio of hemiacetal and hemiaminal forms at the R_fCO moieties and the steric parameter (ν) of alcohols and amines are shown in Figure 6. The pK_a values of methanol, ethanol, and 2-propanol in DMSO have been reported to be 28.99 ± 0.13, 29.80 ± 0.08 and 30.25 ± 0.06, respectively, suggesting no remarkable difference in nucleophilicity among the alcohols.[9] Hemiacetals were produced at the CHF_2CO, CF_3CO, and C_2F_5CO moieties. The ratio of hemiacetal form was highest in methanol. The electronic parameters (σ_i constants) of CHF_2, CHF_2, CF_3, and C_2F_5 groups have been reported to be 0.13, 0.26, 0.39 and 0.41, respectively.[7] Thus, the strong electron-withdrawing nature of R_f group was essential to form hemiacetals. Though no remarkable difference in the electron-withdrawing nature between CF_3 and C_2F_5 groups has been reported, the ratio of hemiacetal form at the CF_3CO moiety was significantly larger than that at the C_2F_5CO moiety. The steric parameters (E_s constants) of Me, CHF_2, CHF_2, and CF_3 groups have been reported to be -1.24, -1.48, -1.91 and -2.4, respectively.[8] Though, no parameter for C_2F_5 group has been reported, it is clear that the C_2F_5 group is much more bulky than CF_3 group. Therefore, it is reasonable that less bulky CF_3CO moiety could more easily form hemiacetals than C_2F_5CO moiety. In small size alcohols such as methanol and ethanol, the ratio of hemiacetal form increased in the following order of R_fCO moiety: $CF_3CO > C_2F_5CO > CHF_2CO$. In propanol, butanol, 2-methyl-1-propanol, and 2-ethyl-1-butanol, the ratio was in the following order: $CF_3CO > CHF_2CO > C_2F_5CO$. In rather big size alcohols such as 2-propanol, 2-butanol, 2-octanol, and 2-methyl-2-butanol, the ratio at C_2F_5CO moiety was considerably small compared with those at CHF_2CO and CF_3CO moieties, in spite of its strong electron-withdrawing nature. Thus, stronger electron-withdrawing and less bulky R_fCO moiety could form larger amount of hemiacetals with small size alcohols. As more bulky was the R_fCO moiety, the formation of hemiacetal with large size alcohols was inhibited due to steric effect between the R_f group and the alcohol. The pK_a values of conjugated bases of butyl- and diethylamines in DMSO have been reported to be 10.7 ± 0.2 and 10.5 ± 0.1, respectively, indicating that amines have larger nucleophilicity than alcohols and that no marked difference in nucleophilicity is observed between the amines.[9] Though the bulkiness of

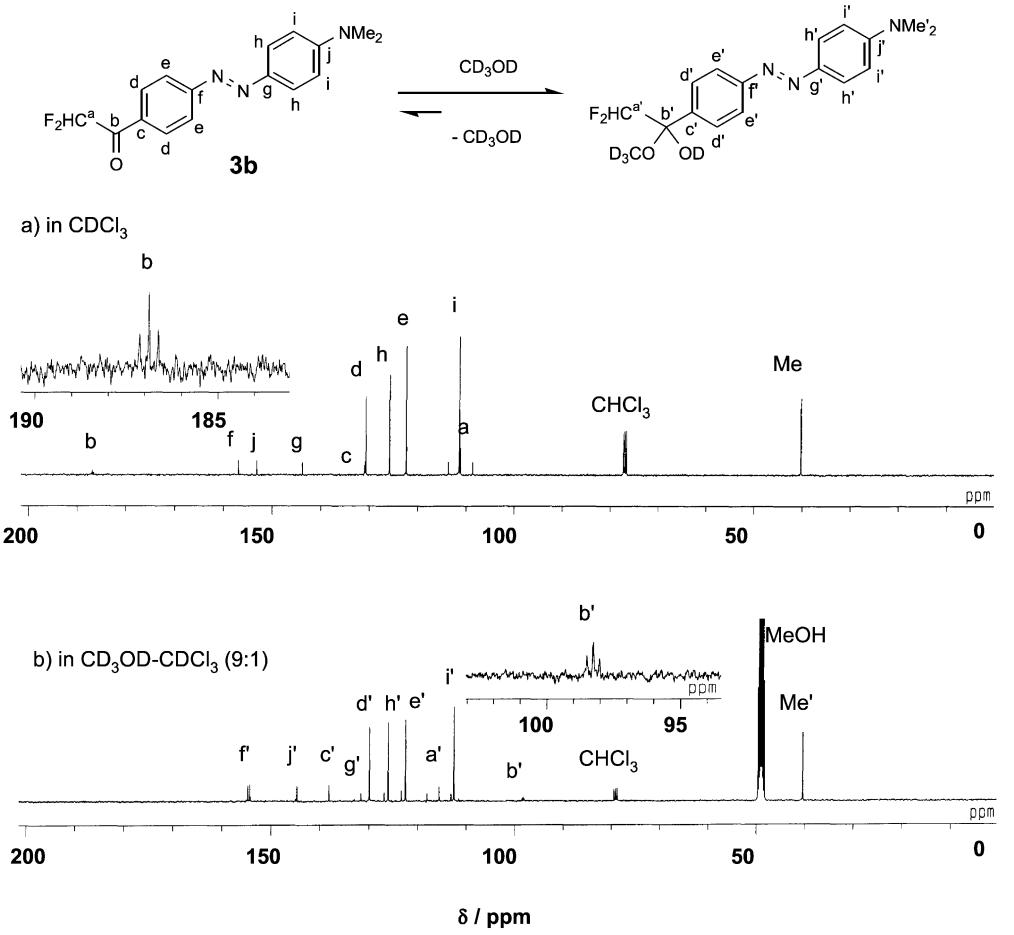

Figure 4. ^{13}C NMR spectra of **3b** in (a) $CDCl_3$ and (b) CD_3OD–$CDCl_3$ (9:1) mixed solution.

butylamine ($\nu=0.70$) and 2-ethyl-1-butanol (0.71) and diethylamine (1.37) and 2-methyl-2-butanol (1.35) are similar, the ratios of hemiaminal forms at all the R_fCO moiety were larger than those of hemiacetal forms, due to higher nucleophilicity of the amines than the alcohols. Hemiaminals were produced at the CF_3CO, CHF_2CO, CH_2FCO, and C_2F_5CO moieties. The ratio of hemiaminal form increased as smaller was the amine. The ratio of hemiaminal form increased in the following order of R_fCO moiety: $CF_3CO > C_2F_5CO > CHF_2CO > CH_2FCO$. Strongly electron-withdrawing and less bulky CF_3CO moiety could

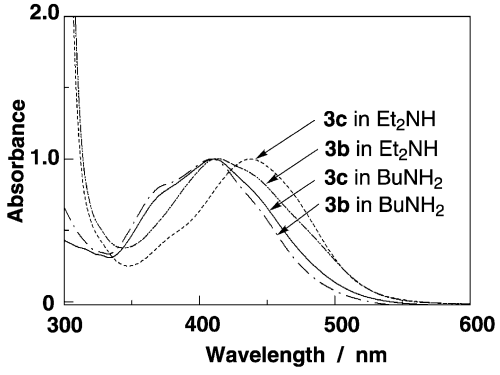

Figure 5. UV–vis absorption spectra of **3b** and **3c** in butylamine and diethylamine. All the spectra are normalized.

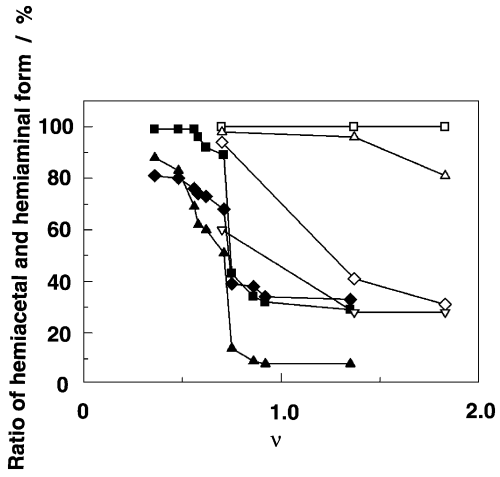

Figure 6. Relationship between the ratio of hemiacetal and hemiaminal form at R_fCO group and steric parameter of solvents. Hemiacetal form; ■: CF_3CO, ◆: CHF_2CO, ▲: C_2F_5CO. Hemiaminal form; □: CF_3CO, ◇: CHF_2CO, ▽: CH_2FCO, △: C_2F_5CO. ν values;[6] methanol: 0.36, ethanol: 0.48, propanol: 0.56, butanol: 0.58, 2-methyl-1-propanol: 0.62, 2-ethyl-1-butanol: 0.71, 2-propanol: 0.75, 2-butanol: 0.86, 2-octanol: 0.92, 2-methyl-2-butanol: 1.35, butylamine: 0.70, diethylamine: 1.37, *tert*.-butylamine: 1.83, di(*iso*-propyl)amine: 2.01.

form hemiaminals not only with small size amines but also big size amines. Thus, the hemiacetal and hemiaminal formation depend on both the electronic and steric factors of R_f groups and solvents.

3. Conclusion

The formation of hemiacetals and hemiaminals at R_fCO moiety was examined by measuring the solvatochromism of 4-dimethylamino-4′-(fluoroacyl)azobenzenes in neat solvents. A few new information were found:

(1) not only a CF_3CO but also CHF_2CO and C_2F_5CO moiety formed the hemiacetals,
(2) hemiaminals were produced at CH_2FCO, CHF_2CO, CF_3CO, and C_2F_5CO moieties,
(3) the ratio of hemiaminal and hemiaminal forms increased as stronger was the electron-withdrawing nature, less bulky was the R_f group, and smaller were the size of alcohols and amines.

4. Experimental

4.1. Instruments

Melting points were measured with a Yanagimoto MP-52 micro-melting-point apparatus. NMR spectra were recorded on a JEOL α-400 spectrometer. Mass spectra were taken on a Shimadzu QP-1000 spectrometer. UV–vis absorption spectra were measured with a Hitachi UV-3500 spectrometer. IR spectra were taken by a Shimadzu FTIR 8100A spectrometer. Elemental analysis was performed with a Yanaco MT-6 CHN corder.

4.2. Materials

4-Dimethylamino-4′-iodoazobenzene (**1**), 4-aminoacetophenone, ethyl trifluoroacetate (**2a**), ethyl difluoroacetate (**2b**), ethyl perfluoropropionate (**2d**) and *N*,*N*-dimethylaniline were purchased from Tokyo Kasei Co., Ltd, 2,3,3-Trifluoro-1-{4-[4-(dimethylamino)phenylazo]phenyl}-1-propenyl-*p*-toluenesulfonate (**3′c**) was synthesized as described in the paper.[5] All solvents were refluxed with calcium hydride, and then distilled to obtain anhydrous ones before measuring the UV–vis spectra.

4.3. Synthesis of fluoroacyl-substituted azobenzenes 3a, 3b, and 3d

To an ether solution (4 mL) of 4-dimethylamino-4′-iodoazobenzene **1** (0.353 g, 1.01 mmol) was added butyl lithium (2.86 mol dm^{-3}, hexane solution). The mixture was stirred for 10 min under an argon atmosphere at −78 °C. To this solution was slowly added ethyl fluoroacetates **2** (1.795 mmol) and stirred for 3 h at −78 °C. After the reaction was completed, to this mixture was added an aqueous saturated solution (30 mL) of sodium hydrogencarbonate. The product was extracted with dichloromethane (50 mL×3). The extract was dried over anhydrous sodium sulfate. The product was isolated by column chromatography (SiO_2, hexane–benzene=1:1) and recrystallized from hexane.

4.3.1. 4-Dimethylamino-4′-(trifluoroacetyl)azobenzene (3a). Yield 244 mg (76%); mp 169.0–169.5 °C; ^{1}H NMR ($CDCl_3$) δ=3.18 (s, 6H), 6.77 (d, J=9.0 Hz, 2H), 7.94 (d, J=9.0 Hz, 2H), 7.93 (d, J=8.3 Hz, 2H), 8.18 (d, J=8.3 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ=6.58 (s, 3F); ElMS (70 eV) *m/z* (rel intensity) 321 (M^+; 58), 120 (100), 77 (31); IR (KBr) 1699.5 ($\nu_{C=O}$) cm^{-1}; UV–vis (toluene) λ_{max}=467 nm (ε=33,000). Anal. Found: C, 59.79; H, 4.57; N, 13.00%. Calcd for $C_{16}H_{14}F_3N_3O$: C, 59.81; H, 4.39; N, 13.08%.

4.3.2. 4-Difluoroacetyl-4′-(dimethylamino)azobenzene (3b). Yield 127 mg (42%); mp 158.5–159.0 °C; ^{1}H NMR ($CDCl_3$) δ=3.12 (s, 6H), 6.32 (t, J=55.9 Hz, 1H), 6.75 (d, J=9.3 Hz, 2H), 7.91 (d, J=9.3 Hz, 2H), 7.92 (d, J=8.5 Hz, 2H), 8.18 (d, J=8.5 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ=−44.08 (d, J=55.9 Hz, 2F); ElMS (70 eV) *m/z* (rel intensity) 303 (M^+; 59), 120 (100), 77 (28); IR (KBr) 1695.6 ($\nu_{C=O}$) cm^{-1}; UV–vis (toluene) λ_{max}=457 nm (ε=21,000). Anal. Found: C, 63.23; H, 5.07; N, 13.72%. Calcd for $C_{16}H_{15}F_2N_3O$: C, 63.36; H, 4.98; N, 13.85%.

4.3.3. 4-Dimethylamino-4′-(perfluoropropanoyl)azobenzene (3d). Yield 234 mg (63%); mp 178.0–178.5 °C; ^{1}H NMR ($CDCl_3$) δ=3.14 (s, 6H), 6.77 (d, J=9.3 Hz, 2H), 7.91 (d, J=9.3 Hz, 2H), 7.93 (d, J=8.8 Hz, 2H), 8.20 (d, J=8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ=−3.72 (s, 3F), −37.53 (s, 2F); ElMS (70 eV) *m/z* (rel intensity) 371 (M^+; 59), 120 (10), 77 (25); IR (KBr) 1697.6 ($\nu_{C=O}$) cm^{-1}; UV–vis λ_{max} (toluene)=472 nm (ε=31,000). Anal. Found: C, 54.57; H, 3.94; N, 11.19%. Calcd for $C_{17}H_{14}F_5N_3O$: C, 53.99; H, 3.80; N, 11.32%.

4.4. Synthesis of 4-dimethylamino-4′-(monofluoroacetyl)azobenzene (3c)

To water (3.6 mL) were added sodium hydroxide (159 mg, 3.6 mmol), 2,3,3-trifluoro-1-{4-[4-(dimethylamino)phenylazo]phenyl}-1-propenyl-*p*-toluenesulfonate (**3′c**, 538 mg, 1.1 mmol) and DMSO (3.6 mL) under an argon atmosphere. The mixture was heated at 80 °C for 5 h. After the reaction was completed, the mixture was poured into brine (100 mL). The product was extracted with ethyl acetate (50 mL×3) and dried over anhydrous sodium sulfate. The product was purified by column chromatography (SiO_2, benzene) and recrystallized from a hexane–ethyl acetate mixed solvent. Yield 223 mg (71%); mp 182.0–183.5 °C; ^{1}H NMR ($CDCl_3$) δ=3.12 (s, 6H), 5.57 (d, J=46.8 Hz, 2H), 6.76 (d, J=9.0 Hz, 2H), 8.01 (d, J=9.0 Hz, 2H), 7.80–7.97 (m, 4H); ElMS (70 eV) *m/z* (rel intensity) 285 (M^+; 40), 120 (100); IR (KBr) 1693.6 ($\nu_{C=O}$) cm^{-1}; UV–vis (toluene) λ_{max}=472 nm (ε=31,000). Anal. Found: C, 67.03; H, 5.92; N, 14.60%. Calcd for $C_{16}H_{16}FN_3O$: C, 67.35; H, 5.65; N, 14.73%.

4.5. Calculation of ratio of hemiacetal form

The UV–vis absorption spectra of **3b** in the methanol–chloroform mixed solution are shown in Figure 7.

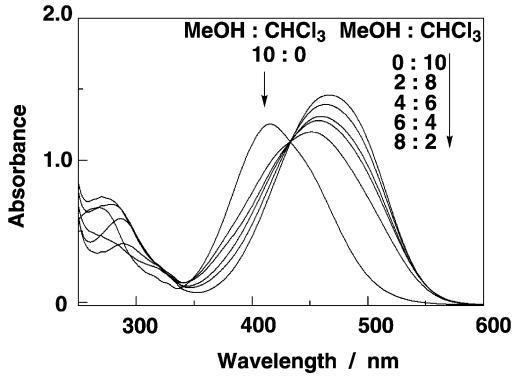

Figure 7. Change in UV–vis absorption spectra of **3b** in various ratio of methanol–chloroform mixed solution. The spectra were measured on 5.0×10^{-5} mol dm^{-3} of **3b** at 25 °C.

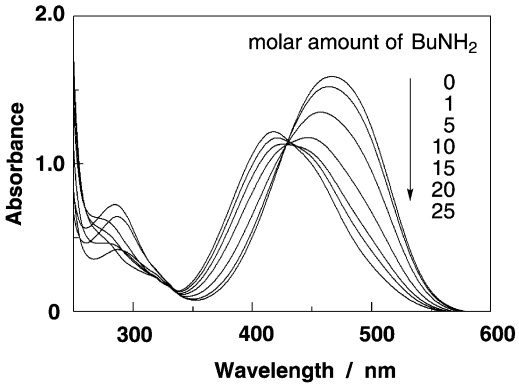

Figure 9. Change in UV–vis absorption spectra of **3b** in chloroform in the presence of various molar amount of butylamine. The spectra were measured on 5.0×10^{-5} mol dm^{-3} of **3b** at 25 °C.

Since the absorbance of **3b** at 418 and 457 nm corresponds to the amount of hemiacetal and keto forms, respectively, the parameter for the hemiacetal form is assumed by an (Eq. 1)

$$\text{parameter for hemiacetal form} = \text{A418}/(\text{A418} + \text{A457}) \quad (1)$$

where A418 and A457 represent the absorbance at 418 and 457 nm, respectively. The ratio of hemiacetal form of **3b** was determined by measuring the ^{1}H NMR spectrum in the same ratio of CD_3OD–$CDCl_3$ mixed solution. The relationship between the parameter for hemiacetal form and the ratio of hemiacetal forms of **3a** and **3d** were obtained in the same way. In the cases of **3b** and **3d**, A417 and A419 as the hemiacetal forms and A467 and A472 as the keto forms were used for the calculation, respectively. The results are shown in Figure 8.

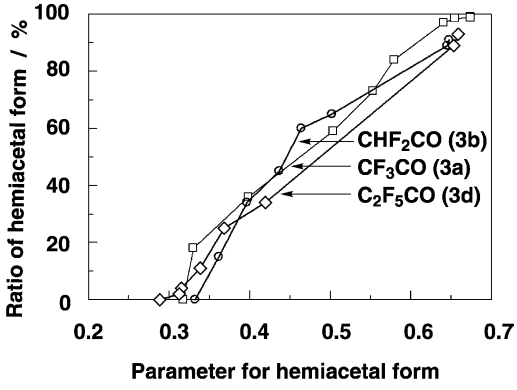

Figure 8. Relationship between the parameter of hemiacetal form of **3a**, **3b**, and **3d** and the ratio of hemiacetal form.

4.6. Calculation of ratio of hemiaminal form

The UV–vis absorption spectra of **3b** in the chloroform in the presence of butylamine are shown in Figure 9. The λ_{max} were observed at 415 and 467 nm. The ratio of hemiaminal form of **3b** was determined by measuring the ^{1}H NMR spectrum of **3b** in $CDCl_3$ in the presence of butylamine.

The parameter for the hemiaminal form is assumed by an (Eq. 2)

$$\text{parameter for hemiaminal form} = \text{A415}/(\text{A415} + \text{A467}) \quad (2)$$

where A415 and A467 represent the absorbance at 415 and 467 nm, respectively.

The relationship between the parameter of hemiaminal form of **3a** and **3d** and the ratio of hemiaminal form was obtained in the same way. In the cases of **3a** and **3d**, A410 and A413 as the hemiaminal forms and A472 and A475 as the keto forms were used for the calculation, respectively. In the case of **3c**, the change in the UV–vis absorption spectra required higher concentration (>50 molar amounts) of butylamine. Unfortunately, the ^{1}H NMR spectrum of this high concentration of butylamine could not be measured due to extremely low *S/N* ratio in the spectrum. Therefore, the test curve for **3b** was used to obtain the ratio of hemiaminal for **3c**. The relationship between the parameter for hemiaminal form of **3a**, **3b**, and **3d** and the ratio of hemiaminal form is shown in Figure 10.

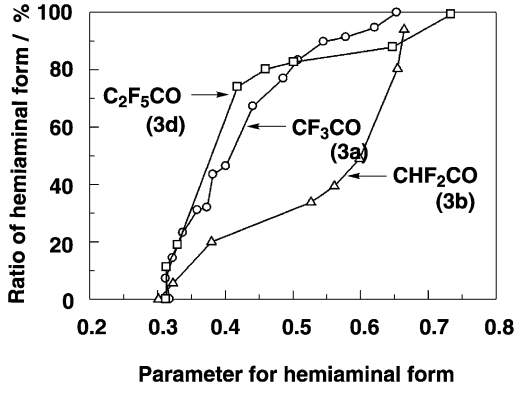

Figure 10. Relationship between the parameter of hemiaminal form of **3a**, **3d**, and **3d** and the ratio of hemiaminal form.

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Micellar effect on the electron transfer reaction of chromium(V) ion with organic sulfides

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Abstract—The rate of electron transfer from organic sulfides to $[Cr^{V}(ehba)_2]^-$ (ehba-2-ethyl-2-hydroxy butyric acid) decreases with a decrease in the polarity of the medium. The anionic surfactant, SDS and the cationic surfactant, CTAB have different effects on the kinetics of this reaction. The micellar inhibition observed in the presence of SDS is probably due to the decrease in the polarity and the electrostatic repulsion faced by the anionic oxidant from the anionic micelle and the partition of the hydrophobic substrate between the aqueous and micellar phases. The micellar catalysis in the presence of CTAB is attributed to the increase in the concentration of both reactants in the micellar phase. This micellar catalysis is observed to offset the retarding effects of the less polar micellar medium and the unfavorable charge–charge interaction between the + charge developed on S center in the transition state and the cationic micelle. This catalysis is contrary to the enormous micellar inhibition observed with IO_4^-, HSO_5^- and HCO_4^- oxidation of organic sulfides.

1. Introduction

The carcinogenicity and toxicity of chromium(VI) compounds has been well established.[1,2] The mechanism by which these compounds induce cancer is yet to be established.[3–12] The reduction of chromium(VI) by cellular reductants leads to the formation of chromium(III) via chromium(IV) and chromium(V) as intermediates. A fundamental question concerns the role of chromium(V) in the overall mechanism of carcinogenesis by chromium(VI), since the DNA damage by chromium(VI) compounds is likely due to the reactivity of the other valance states of Cr or free radicals known to be formed from the reduction reaction.[10] In order to understand the role of the intermediate chromium(V) state towards the toxicity of chromium compounds, several model compounds have been synthesized.[13–16] Of these chromium(V) complexes isolated and characterized to date, few show appreciable stability in aqueous system and under physiological conditions making biologically relevant studies difficult. Some of the best known and studied chromium(V) complexes are those chelated to the α-hydroxy acids and salens shown in Figure 1.

The aqueous solution of carboxylato bound chromium(V) complexes is reasonably stable at pH = 3 and the complexes have interesting reactions with a large number of organic compounds.[17–20] Of these different organic compounds, thioethers play a special role in bio-systems.[21] Methionine residues, due to the unique combination of hydrophobicity and nucleophilic reactivity provided by the thioether group in the side chain, participate in the maintenance of the structure of the protein molecules, take part in the transfer of electrons and/or also act as a part of substrate binding sites.[21–25] The nucleophilic sulfur atom in methionine is very susceptible to oxidation. The oxidation of methionine has received particular attention because of its possible role in the biological inactivation of several hormones.[25] Insight into damage to the biological system can be gained by analyzing simpler systems such as organic sulfides. Furthermore, organic sulfides serve an important function in many biological macromolecules.[26] They are highly susceptible to oxidation and different pathways have been established depending on the nature of the oxidizing species.[26–31] In recent reports we have established that the two different Cr(V) complexes $[Cr^{V}(ehba)_2]^-$ and

Keywords: Organic sulfides; Cr(V) complexes; Electron transfer; Micellar effect.
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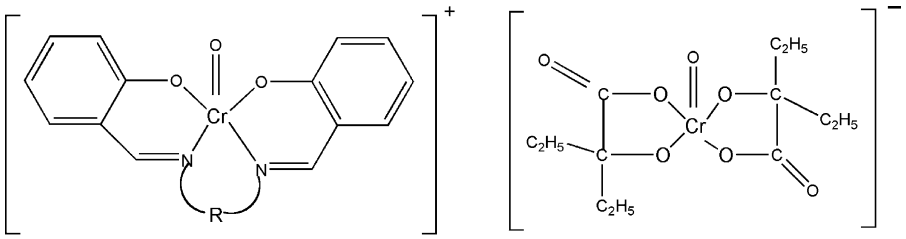


Figure 1. Structure of the Chromium(V) complexes. Complex **I** = $[OCr^{V}(salen)]^{+}$; complex **II** $R_1 = R_2 = CH_3 = [Cr^{V}(hmpa)_2]^{-}$; complex **III** $R_1 = CH_3$, $R_2 = C_2H_5 = [Cr^{V}(hmba)_2]^{-}$; complex **IV** $R_1 = C_2H_5$, $R_2 = C_2H_5 = [Cr^{V}(ehba)_2]^{-}$.

$[OCr^{V}(salen)]^{+}$ oxidize organic sulfides via two different routes.[28,29] The oxidation by the anionic chromium complex, $[Cr^{V}(ehba)_2]^{-}$ proceeds through an electron transfer mechanism and that by the cationic oxidant, $[OCr^{V}(salen)]^{+}$, through an S_N2 mechanism.

The electron transfer reaction of $[Cr^{V}(ehba)_2]^{-}$ with organic sulfides yielding a sulfide cation radical is important because the –OH and CO_2H groups present in the biological system and the oxidation of proteins and lipids by single electron transfer process has been associated with the onset of several diseases and ageing.[32,33] If the metal ion oxidizes the thioether moiety by an electron transfer mechanism, the system is more prone to carcinogenesis. In biological systems, apart from other factors, hydrophobic interactions also play an important role. In a recent article Zewail and co-workers[34] have indicated that the surface of the protein is similar to a micellar surface. Thus the study of electron transfer reaction in a micellar medium may throw light on the details of electron transfer reaction in biological system. Realizing the important role of chromium(V) ion in the carcinogenesis of chromium compounds, the high reactivity of thioether moiety and hydrophobic interaction in biological system, we planned to study the effect of micelles on the electron transfer reaction of the chromium complex, $[Cr^{V}(ehba)_2]^{-}$ and related complexes with organic sulfides. $[Cr(ehba)_2]^{-}$, an anionic electrophile and organic sulfides should be taken up by the cationic micelles and concentrated at the micellar surface, which should speed up the reaction.

The kinetics of the reaction has been followed spectrophotometrically in the absence and presence of anionic and cationic surfactants and the observed kinetic results are analyzed in terms of pseudo phase ion exchange model of micelle. As all the sulfides are water insoluble, the reaction has been studied in an aqueous phase containing 1% acetonitrile. A similar solvent system has been chosen by Blasko et al.,[35] for the IO_4^- oxidation of organic sulfides in SDS and CTAC. It is pertinent to point out that an increase in [surfactant] increases the micellar solubilization of the sulfides.

2. Ionic micelles

Ionic micelles typically catalyze the reaction of a reactive counter ion with hydrophobic substrates that bind to the micelles.[36–40] This catalysis is due to the higher local concentrations of both reactants at the micelle–water interface as compared to their stoichiometric concentrations. Though a large number of reports are available on the oxidation of organic sulfides with particular focus on the synthetic applications and mechanistic details of the reactions, results on the micellar effects on the redox reactions of organic sulfides particularly with metal ion oxidants are rare except the recent report on the peroxomolybdate and Cr(VI) oxidation of thioanisole.[41,42] On the other hand, a detailed study on the micellar effect on the oxidation of organic sulfides with periodate and peroxomonosulphate ions has been reported by Bunton[35,43] and oxidation with bicarbonate-activated hydrogen peroxide by Richardson.[44]

Reactions of anionic oxidants in the presence of surfactants can be treated by the distribution model that considers the bulk solvent and the surfactant as distinct reaction regions, that is, pseudo phases. The observed first order rate constant of overall reaction (rate = k_{obs} [sub]) in micelles or similar assemblies, is given by (Eq. 1).

$$k_{obs} = \frac{k_w[O]_w + k_2^m K_S[D_n]\{O\}_m}{1 + K_S[D_n]} \quad (1)$$

Here, the second-order rate constant in the micellar pseudo phase k_2^m ($M^{-1}\,s^{-1}$) is defined in terms of the local molarity of oxidant, $\{O\}_m$ is the concentration of the oxidant in the micelle reactive region (local molarities are indicated by {}brackets). The term k_w is the second order rate constant in aqueous phase and K_S is the substrate binding constant, written in terms of the concentration of micellized surfactant (Eq. 2).

$$K_S = \frac{[S_m]}{[S_w][D_n]} \quad (2)$$

where $[D_n] = [D_T] - cmc$, and S_W and S_m denote substrate in the aqueous and micellar pseudo phases, respectively.

Blasko et al.[35] observed that in the presence of cationic surfactant the value of the ratio of the second order rate constant in the micellar to the aqueous phase, that is, k_2^m/k_w (where k_2^m is the second order rate constant in the micellar phase and k_w is the second order rate constant in the aqueous phase) is very small in the IO_4^- oxidation of organic sulfides. This observation was rationalized in terms of unfavorable interactions between the cationic head group of the micelle and the developing positive charge on S of the substrate in the transition state. This interaction should be

Table 1. Effect of varying solvent composition on Cr(V) oxidation of MPS at 303 K

	$k_2\times10^3\ M^{-1}\ s^{-1}$		
CH_3CN–H_2O	Complex **II**	Complex **III**	Complex **IV**
30–70	11.5±0.17	10.1±0.09	1.33±0.06
40–60	9.32±0.15	9.16±0.08	1.00±0.07
50–50	7.48±0.10	7.22±0.03	0.858±0.10
60–40	6.44±0.04	5.59±0.11	0.764±0.03
70–30	5.46±0.19	4.39±0.05	0.676±0.09
80–20	4.80±0.07	3.58±0.06	0.601±0.05
90–10	4.47±0.05	2.44±0.07	0.519±0.11
100–0	3.29±0.07	1.81±0.03	0.373±0.01

[Cr(V)]=0.001 M; [MPS]=0.01 M; [H^+]=0.001 M.

absent if the reaction is carried out in the anionic micelle but the reaction may still be slow due to columbic repulsion which is actually observed.[35,43]

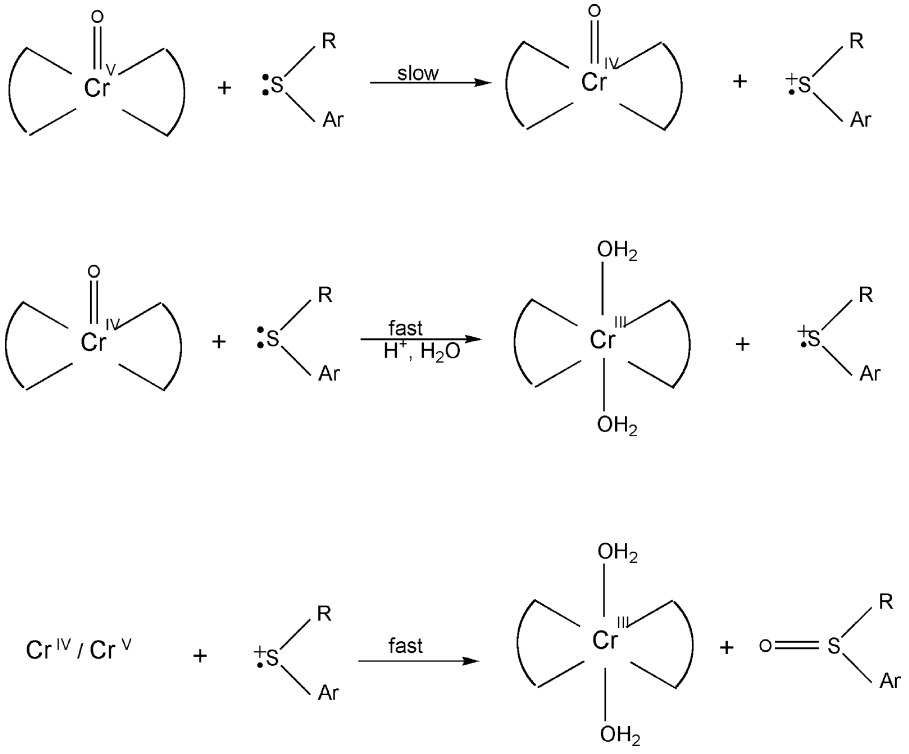
2.1. Kinetics of the reaction in the absence of surfactants

The kinetics of oxidation of 19 alkyl aryl sulfides and five dialkyl sulfides with three oxochromium(V) complexes **II**–**IV** have been studied spectrophotometrically in acetonitrile–water mixture under pseudo first-order conditions and already reported.[28] The reaction is of total second order, first order in the oxidant and in the substrate. Aromatic sulfides containing electron-withdrawing substituents in the benzene ring retard the rate while those containing electron-donating substituents accelerate the rate of oxidation. The second order rate constants for the oxygenation reaction, k_2 are better correlated with σ^+/σ^- values than the Hammett σ constants. The reactivity of different alkyl phenyl sulfides, C_6H_5SR(R=Me, Et, *n*-Pr, *i*-Pr, *n*-Bu and *t*-Bu) has been analyzed successfully in terms of Taft's polar, σ^* and steric, E_s, substituent constants. The reaction has been studied using different solvent composition of acetonitrile and water and the data collected in Table 1. The solvent effect study shows that the rate of reaction decreases with the decrease in the polarity of the medium. In this respect, the reaction behaves similarly to that of IO_4^- and HSO_5^- towards organic sulfides. The kinetics of the reaction has also been followed by EPR technique and the rate constant data obtained from this technique are similar to the values observed from the spectrophotometric technique.[28] To account for these kinetics results, an electron transfer mechanism shown in Scheme 1 has been proposed.

2.2. Reactions in the presence of anionic surfactant, SDS

The oxidation of organic sulfides by oxochrominum(V) ions **II**–**IV** was carried out in the presence of SDS and the kinetic data obtained for the reaction of complex **IV** with several organic sulfides are collected in Table 2. Though the k_2 values are little affected at [SDS]<cmc, further increase in [SDS] decreases the rate constant enormously. The variation of rate constant with [surfactant] is generally explained using the assumption that substrate, S is distributed between the aqueous and micellar pseudo phases designated by subscripts w and m, respectively (Scheme 2), where k_w and k_2^m are the second order rate constants in aqueous and micellar pseudo phases.

Provided the equilibrium is maintained between reactants in the pseudo phases, the second order rate constant, k_2 ($k_2=k_{obs}$/[sub]), can be obtained from the (Eq. 1) and can be readily resolved for spontaneous reaction and for micellar inhibited reactions. For micellar inhibited reactions, as

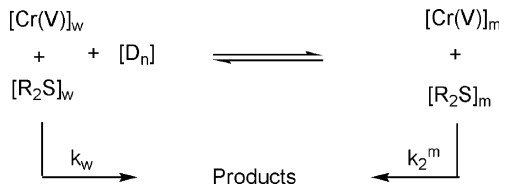


Scheme 1.

Table 2. Effect of SDS on the $[Cr^{V}(ehba)_2]^-$ oxidation of MPS and dialkyl sulfides at 303 K

	$k_2\times10^2$ (s^{-1})					
[SDS], M	MPS	DES	DPS	DBS	DTBS	DIPS
0.000	6.91	12.4	11.0	10.8	10.7	9.88
0.001	7.59	12.6	10.8	9.57	10.0	10.9
0.005	7.01	12.1	11.2	9.03	11.0	10.0
0.008	6.85	11.2	10.5	8.81	10.6	9.71
0.010	6.31	10.6	9.91	8.24	9.89	9.22
0.020	5.03	6.16	5.15	4.14	5.71	4.00
0.030	2.98	3.47	3.09	2.88	3.25	2.77
0.050	0.652	1.17	1.24	0.868	1.23	1.17
0.100	0.398	0.714	0.701	0.513	0.745	0.699
0.200	0.331	0.688	0.652	0.471	0.662	0.622

[Cr(V)]=0.0001 M; [Sulfide]=0.001 M; $[H]^+$=0.001 M ($HClO_4$); solvent=1% CH_3CN:99% H_2O. MPS, Methyl phenyl sulfide; DES, Diethyl sulfide; DPS, Di *n*-propyl sulfide; DBS, Di *n*-butyl sulfide; DTBS, Di-*tert*-butyl sulfide; DIPS-Di-*i*-propyl sulfide.



Scheme 2.

given in Table 3 are very similar to Bunton's reported values.[35] Further, in order to assess the success of this model, computer simulation of rate constant values at different [SDS] has been attempted. Good agreement is observed between the experimental and theoretical values. A sample plot is shown in Figure 2. The observed micellar inhibition in the presence of SDS can be ascribed to two important factors: (i) the rate of electron transfer from the substrate to Cr(V) ion is retarded with a decrease in the

Table 3. The substrate binding constants, K_S, micellar rate constant, k_2^m, the ratio of the rate constants in micelle to water (k_2^m/k_w) evaluated for the various sulfides in the presence of anionic surfactant, SDS

Sulfide	Complex **II**			Complex **III**			Complex **IV**		
	K_S	$10^6\,k_m$	k_2^m/k_w	K_S	$10^6\,k_2^m$	k_2^m/k_w	K_S	$10^6\,k_2^m$	k_2^m/k_w
MPS	174	2.72	0.021	185	9.47	0.09	164	4.53	0.07
DES	138	1.02	0.007	99	11.5	0.07	107	6.23	0.05
DPS	143	2.03	0.014	128	14.9	0.10	108	7.69	0.07
DBS	149	4.18	0.026	142	21.7	0.15	109	20.9	0.19
DTBS	121	4.67	0.03	99	25.2	0.18	94	23.9	0.22
DIPS	95	1.32	0.013	75	15.4	0.12	88	7.18	0.08

$k_2^m\rightarrow0$ (Eq. 1) can be rearranged to (Eq. 3).

$$k_2=\frac{k_w}{1+K_S[D_n]} \tag{3}$$

However, the use of Eq. 3 requires estimation of the concentration of monomeric surfactant which, often, is assumed to be cmc. Compared to the concentration of surfactant used in the present study, the value of cmc is small and it can be ignored here. It is to be remembered that in the presence of additives the value of cmc is lowered. For many micellar inhibited reactions the reverse of Eq. 3 given as Eq. 4 can be used to analyze the data.

$$\frac{1}{k_2}=\frac{1}{k_w}+\frac{k_S[D_n]}{k_w} \tag{4}$$

If the above assumptions are valid, Eq. 4 can be used to account for micellar inhibition in the presence of SDS.

If Eq. 4 is applicable to the present system the plot of $1/k_2$ versus $[D_n]$ should be linear. However, the plot of $1/k_2$ against $[D_n]$ is not linear but a curve (figure not shown). This implies that the (Eq. 4) is not applicable to the redox system used in this study. Hence Eq. 1 has been used to get the values of K_S and k_2^m by an iterative procedure and the values are collected in Table 2. The K_S values for different sulfides

polarity of the medium. The kinetic data collected in Table 1 show that the change of the acetonitrile content from 30 to 100% in the aqueous acetonitrile decreases the rate constant by 4–5 times. The dielectric constant of SDS is ~40. Thus,

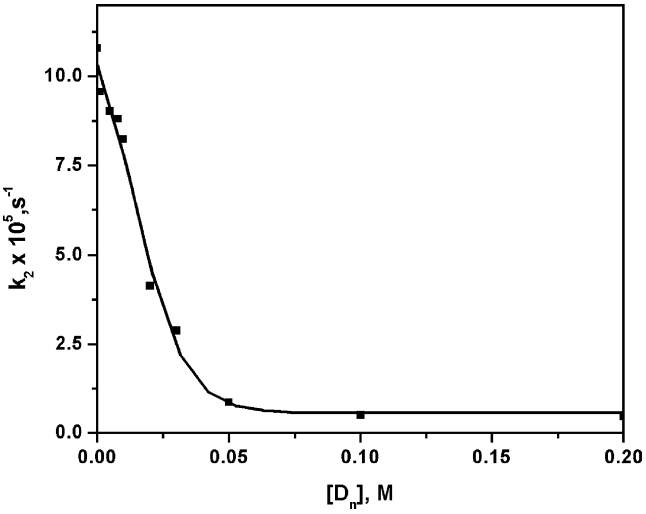


Figure 2. Plot of experimental (■) and calculated values (———) for the reaction of DBS with complex (**IV**) in SDS.

Table 4. Effect of CTAB on the $[Cr^{V}(hmpa)_2]^-$ oxidation of MPS and dialkyl sulfides at 303 K

	$k_2\times10^2$ (s^{-1})					
[CTAB], M	MPS	DES	DPS	DBS	DTBS	DIPS
0.000	13.0	18.6	17.0	16.0	15.8	14.4
0.001	16.5	24.7	25.9	27.1	18.7	17.1
0.005	19.6	31.2	32.3	33.3	22.0	19.9
0.008	23.7	35.6	36.9	37.5	28.5	25.0
0.010	19.8	30.8	31.5	32.2	23.1	21.7
0.030	18.4	29.5	30.4	31.0	22.3	20.6

[Cr(V)]=0.0001 M; [Sulfide]=0.001 M; $[H]^+$=0.001 M (H_2SO_4); solvent=1% CH_3CN:99% H_2O.

one of the factors responsible for rate retardation in the presence of SDS is the decrease in the polarity of the medium. (ii) As the oxidant, $[Cr(ehba)_2]^-$, is an anion, it remains in aqueous phase due to Columbic repulsion from the surface of the anionic micelle. On the other hand, the substrate is hydrophobic and binds strongly with the anionic micelle and the binding constant is ~100. Thus the concentration of substrate available in the aqueous phase is small and the rate is retarded with the increase in [SDS].

2.3. Reactions in the presence of cationic micelle

The rate constant data given in Table 4 shows that the increase in [CTAB] increases the k_2 value but at high [CTAB], the rate constant attains a limiting value and shows a downward trend, Figure 3. The cationic micelle, CTAB, accelerates the Cr(V) oxidation of organic sulfides. If we compare the reactivity of three sulfides DES, DPS and DBS the catalytic activity of micelle increases with the increase in the hydrophobicity of the substrates because the percentage of reaction taking place in the micellar phase is a function of the concentration of the sulfide in the micellar phase, $[R_2S]_m$. The value of $[R_2S]_m$ increases with the increase in the hydrophobicity of sulfide as well as [surfactant]. Perez-Bentio and Rodenas[37] have observed similar results in the Cr(VI) oxidation of water insoluble alcohols. On the other hand, the catalytic activity observed with DIPS and DTBS is comparatively less which may be attributed to steric effects.

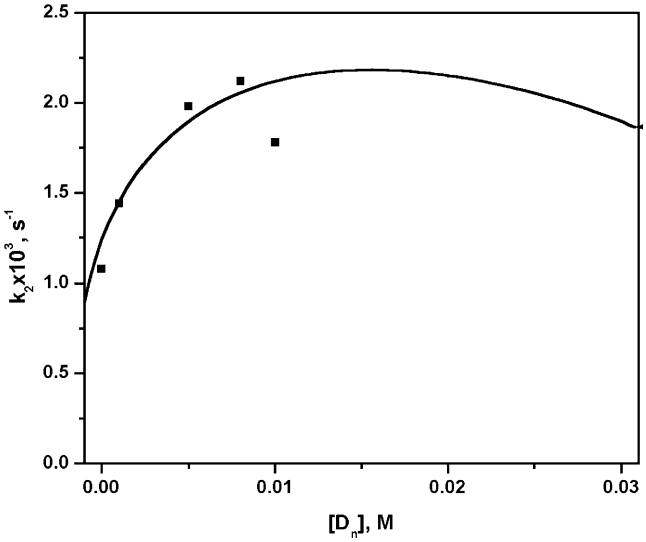


Figure 3. Plot of experimental (■) and calculated values (———) for the reaction of DBS with $[Cr^{V}(ehba)_2]^-$ in the presence of CTAB.

In most of the studies reported so far the micellar catalysis in bimolecular reactions has been attributed to higher concentration of the reactants in the micellar phase.[36–40] Hence, the rate acceleration observed in this reaction may also be due to higher local concentration of both reactants at the micelle, as compared to their stoichiometric concentrations in the aqueous phase. The decrease in rate after reaching maximum value may be taken as evidence for the bimolecular micellar surface reaction.

Thus the kinetic results in the cationic micellar phase can be analyzed by assuming Scheme 2 as the mechanism for the Cr(V) oxidation of organic sulfides in cationic micellar phase also. Both $[Cr^{V}(ehba)_2]^-$ and sulfide bind with CTAB. The micellar catalysis is observed though development of positive charge on sulfur in the transition state and a decrease in polarity may retard the rate of the reaction in the presence of CTAB. It is pertinent to recall that these factors led to micellar inhibition on IO_4^-, HSO_5^- and HCO_4^- oxidation of organic sulfides.[35,43,44]

Thus, the oxidation reaction takes place in the aqueous as well as in the micellar phase. With an increase in [surfactant], the concentration of the reactants in the micellar phase, $[Cr(V)]_m$ and $[sulfide]_m$ also increase which may also partly be responsible for the increase in k_2 value with initial increase in concentration of micelles. A similar explanation has been given by Drummond and Grieser[40] for micellar catalysis in H_2O_2-mediated oxidation reactions.

Eq. 1 cannot be used when both the reactants bind with the micelle and to compute the individual binding constants of the reactants in the micelle or the partition of the reactants between the aqueous and the micellar phase. Therefore, the phase separation approach of Berezin et al.,[45] applicable to the case in which both reactants are strongly bound to the micelle, was considered useful in the present study. The effect of CTAB on the rate of oxidation was analyzed quantitatively using the appropriate Berezin Eq. 5, with k_2^m being the second order rate constant in the micellar phase and k_w being the experimental second order rate constant in the aqueous phase, K_{Cr} and K_S being the binding constants of Cr(V) and sulfide to the micelle, respectively, defined by (Eqs. 6 and 7).

$$k_1 = (k_2^m K_{Cr} K_S C + k_w)/(1 + K_{Cr}C)(1 + K_S C) \quad (5)$$

$$K_{Cr} = (P_{Cr} - 1)V \quad (6)$$

$$K_S = (P_S - 1)V \quad (7)$$

Table 5. The binding constant, K_{Cr},K_S and the second order rate constant k_m, values calculated for the micellar (CTAB) catalyzed oxidation of organic sulfides by complex(**II**)

Sulfide	K_{Cr}	K_S	$10^2\ k_m$	$10^3 k_2^m$	K_2^m/k_w
MPS	8.00	106	6.12	8.57	0.66
DES	8.00	193	5.62	7.87	0.42
DPS	8.00	206	5.62	7.83	0.46
DBS	8.00	218	5.59	7.83	0.49
DTBS	8.00	128	5.95	8.33	0.53
DIPS	8.00	112	6.07	8.50	0.59

P_{Cr} and P_S are partition coefficients of the reactants namely Cr(V) and sulfides species, respectively, between the aqueous and micellar phases and C is the concentration of the micelle less cmc value and V is the molar volume of the hydrated surfactant, which is taken to be 0.14 $dm^3\ mol^{-1}$.

Since the values of K_S have been estimated from a spectral method, a non-linear iterative method used to evaluate K_{Cr}, and k_2^m. By assuming K_{Cr} as different values we have evaluated k_2^m values, which can be fitted to our experimental data with minimum error. Utilizing the k_2^m value thus evaluated, K_{Cr} values are evaluated. The parameters K_{Cr} and k_2^m, determined by this method are listed in Table 5. Such low K_{Cr} value indicates that a part of the oxidant is in aqueous phase and the moderate micellar catalysis is due to the small K_{Cr} value.

The data given in the last column of Table 5 indicate that the rate constants of the reaction in the aqueous phase and micellar phase are of the comparable magnitude, that is, $k_w \approx k_2^m$. Thus the micellar catalysis observed in the presence of CTAB is attributed to the high concentrations of the reactants in the micellar phases. Similar results have been observed in several micellar catalyzed reactions.[36–40]

2.4. Comparison with the reactivity of anionic peroxidants at micellar surface

As already indicated in the previous sections, the micellar effect on the oxidation of organic sulfides has been studied by choosing IO_4^-, HSO_5^- and HCO_4^- as oxidants.[35,43,44] In all these reactions, the rate constant in a cationic micelle pseudo phase is significantly lower than that for the aqueous phase. The observed oxidation rates with IO_4^-, HSO_5^- and HCO_4^- are not accelerated by cationic micelles, although both reactants should bind strongly with micellar surfaces. The much lower values of second-order rate constants at micellar surface as compared to those in the aqueous phase are responsible for the reduced oxidation rates by IO_4^-, HSO_5^- and HCO_4^- in aqueous CTAB solutions. The second-order rate constants at the cationic micellar surface are lower than those in water by a factor of $\sim$1000, $\sim$400 and $\sim$100, respectively. The low values of k_2^m compared to k_w are attributed to the unfavorable interactions between the increased positive charge on sulfur in the proposed transition state and the positive charge on micellar head groups. It is important to recall that all these reactions are retarded with the decrease in the polarity of the medium. The polarity of the Stern layer is generally considered to be lower than that of bulk water. But Bunton and co-workers have suggested the effect of polarity of the medium to be less important than the charge–charge interaction.[35,43]

In contrast to the above observations, micellar catalysis is observed and the value of $k_2^m/k_w \sim 1$ for the oxidation of organic sulfides with $[Cr^V(ehba)_2]^-$ in the cationic micelle. This micellar catalysis is interesting because the rate of the titled reaction also decreased with the decrease in the polarity of the medium (cf. Table 1) and a partial positive charge is developed on the sulfur center in the transition state of the reaction (cf. Scheme 1). The inference from this observation is that the rate retardation by the lower polarity of a micellar medium and unfavorable charge–charge interaction is compensated to a large extent by the increase in the concentration of the reactants in the micellar phase. It is important to recall that $[Cr^V(ehba)_2]^-$ oxidation of organic sulfides proceeds by an electron transfer mechanism and of anionic peroxidants by the electrophilic attack of the oxidant at the sulfur center of the substrate, that is, S_N2 type mechanism. Thus the positive charge developed on the S centre in the transition state is less with $[Cr^V(ehba)_2]^-$ oxidation compared to the anionic peroxidants oxidation. These results also support the importance of charge–charge interaction in the transition state on the overall rate of the reaction in the micellar phase.

2.5. Comparison with Cr(VI) oxidation

From our study on the effect of micelles on the Cr(VI) oxidation of dialkyl sulfides[42] we have observed that SDS catalyzes the reaction while the cationic surfactant, CTAC retards the reaction. Similar results have been observed on the micellar effect on the Cr(VI) oxidation of dimethyl sulfoxide.[38,46] The catalytic role of SDS is explained in terms of the acid catalysis of the reaction. The H^+ ion gets preferentially concentrated in the anionic micellar phase. The cationic surfactant inhibits the reaction because the approach of H^+ ion to the cationic micellar surface (in which both the reactants, R_2S and $HCrO_4^-$, are preferentially concentrated) is unfavorable due to an electrostatic repulsion.

These results observed for the Cr(VI) and Cr(V) oxidation of thioethers in microheterogeneous systems like micelles are important from the point of view carcinogenicity of Cr compounds.[38] In the carcinogenicity of Cr compounds, it is realized that Cr(V) and free radicals generated from the reaction of Cr compounds are considered to play a dominant role. The present study indicates that forces like hydrophobicity, charge–charge interactions in the transition state and change of polarity of the medium decide the reactivity of Cr(VI) and Cr(V) compounds, particularly with thioethers, in a microheterogeneous medium. Thus these aspects should be taken into account when we consider the mechanism responsible for the carcinogenicity of Cr compounds.

3. Conclusion

Though the results for the reaction of anionic Cr(V) ion with thioethers in SDS are similar to those observed for the oxidation with IO_4^-, HSO_5^- and HCO_4^-, the results observed in CTAB are novel and micellar catalysis is observed. These results highlight the importance of the nature of electron transfer of the reaction and the development of less positive charge on sulfur in the transition state leading to micellar catalysis.

4. Experimental

The ligand acids 2-hydroxy-2-methylpropionic acid (HMPA) (Fluka 99%), 2-hydroxy-2-methylbutyric acid (HMBA) (Aldrich 99%), and 2-ethyl-2-hydroxybutyric acid (HEBA) (Aldrich 99%) were used as received. Spectroscopic grade solvent acetonitrile and doubled distilled water were used throughout the course of the present study. Dialkyl sulfides were used as received from Aldrich. Methyl phenyl sulfide was prepared by known procedure[27,28] and the purity was checked. Sodium bis(2-hydroxy-2-methylpropionato)oxochromium(V) (complex **II**), Sodium bis(2-hydroxy-2-methylbutyrato)oxochromium(V) (complex **III**), and Sodium bis(2-ethyl-2-hydroxy-butyrato)oxochromium(V) (complex **IV**) were synthesized from their corresponding ligand acids and sodium dichromate (Merck, AR grade) in acetone and hexane (Merck AR grade) as described previously.[13,47]

4.1. Kinetics of Cr(V) oxidation of organic sulfides in micelles

Redox reactions of methyl phenyl and dialkyl sulfides with Cr(V) were followed spectrophotometrically using a Hitachi 200-UV–visible spectrophotometer at 30 °C in the presence of appropriate $[H]^+$ and 99% H_2O–1% CH_3CN medium. The small percentage of organic solvent is essential as the sulfides are insoluble in the aqueous phase. In the case of anionic micelle (SDS) the reactions were carried out in perchloric acid medium while in the case of the cationic micelle (CTAB) the reactions were followed in sulfuric acid medium since perchlorate salts were precipitated in the presence of cationic surfactant.

The progress of the reaction in the presence of SDS was followed by measuring the decrease in absorbance of Cr(V) ion at 350 nm under pseudo first order conditions keeping the substrate–oxidant ratio always greater than 10. Sulfides were added as solutions in acetonitrile, so that the reaction solution contained 1 vol% of acetonitrile. The kinetics of the reaction in the presence of CTAB was followed at 370 nm (vide infra).

4.2. Spectral studies in the presence of surfactants

4.2.1. Studies at SDS. In the absence of surfactant (SDS), oxidant (complex **IV**) shows an absorption maximum at 350 nm ($\varepsilon = 1500\ M^{-1}\ cm^{-1}$). In the presence of SDS there is no shift in the λ_{max} of Cr(V) ion and no appreciable change in OD at 350 nm. On the other hand, in the presence of surfactants, sulfides showed an increase in absorbance at 260 nm ($\varepsilon = 8000\ M^{-1}\ cm^{-1}$).

4.2.2. Studies at CTAB. In the absence of CTAB, complex **IV** shows an absorption maximum at 350 nm ($\varepsilon = 1500\ M^{-1}\ cm^{-1}$) and at 260 nm ($\varepsilon = 6475\ M^{-1}\ cm^{-1}$). In the presence of micelle we observed an increase in absorbance at 260 nm which indicate the micellization of substrate. The incorporation of the anionic oxidant $[Cr^V(ehba)_2]^-$ into the cationic micelle is evidenced from the observed spectral shift of Cr(V) ion, λ_{max} shifts from 350 to 370 nm in the presence of CTAB (Fig. 4). The increase in the absorbance of organic sulfides in the presence of surfactants has been used for the estimation of binding constants of these with the micelles. As the λ_{max} of Cr(V) shifts from 350 to 370 nm in the presence of CTAB the kinetics of the reaction in the presence of CTAB were followed by observing the change in OD with time at 370 nm.

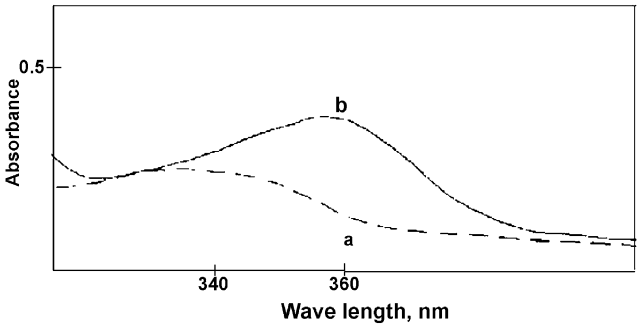


Figure 4. Absorption spectra of $[Cr^V(ehba)_2]^-$ in the absence (a) and presence (b) of CTAB.

4.3. Evaluation of binding constants

4.3.1. Spectrophotometric method. The binding constant of MPS and dialkyl sulfides with the micelles has been evaluated spectrophotometrically by measuring the absorbance at different concentrations of sulfides in the presence of SDS and CTAB, respectively.

If the surfactant is in excess, the binding constant is given by (Eq. 2). The extent of micellar binding can be estimated from the spectral shifts provided the Beer's law is followed. The experimental data were collected to fit into the following (Eq. 8).

$$1/(A_s - A_w) + 1/(A_m - A_w) = 1/(1 + K_s D_n) \quad (8)$$

where A_w and A_m are absorbance in the absence of surfactant and limiting absorbance upon complete incorporation into the micellar phase, respectively. The term A_s is the absorbance in the presence of surfactant. (Eq. 8) can be transformed to (Eq. 9).

$$(A_s - A_w)/D_n = A_m K_s - A_s K_s \quad (9)$$

A plot of $(A_s - A_w)/D_n$ versus A_s gave the negative slope $= -K_S$ and from the slope the value of K_S can be evaluated. A similar approach has been adopted by Bunton et al., for the estimation of binding constants of organic sulfides with micelles.[35] The binding constants estimated

for MPS in the presence of SDS and CTAB were 171 and 335 M^{-1}, respectively.

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Accurate molecular weight measurements of nucleoside phosphoramidites: a suitable matrix of mass spectrometry

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Abstract—Nucleoside phosphoramidites (PAs) are the most widely used building blocks in contemporary solid-phase synthesis of oligonucleotides. The accurate molecular weight (MW) measurements of such molecules, which contain acid-labile moieties, may be easily determined by mass spectrometry using a matrix system, triethanolamine (TEOA)–NaCl, on liquid secondary ion mass spectrometry (LSIMS) equipped with a double-focusing mass spectrometer. The present method measures rapidly and easily the accurate MWs of various PAs as adduct ions $[M+Na]^+$ with average mass error smaller than 0.4 ppm, allowing the formulas of various PAs in place of elemental analysis. Further, it was found that intensities of molecular-related ions could be enhanced to the highest degree by adjustment of the mole ratio of PA and NaCl fixing the amount of TEOA on LSIMS, making the present method powerful tool for the MS identification of PAs.

1. Introduction

DNA and RNA oligonucleotides are usually synthesized through phosphoramidite (PA) chemistry on polymeric support by sequential addition of nucleoside building blocks to a growing oligonucleotide chain which is covalently attached to the solid support.[1] Nucleoside PAs containing *O*-cyanoethyl (CNEt)-*N*,*N*-diisopropyl groups are the starting materials in the automatic synthesis.[2] The *tert*-butyldimethylsilyl (TBDMS) group is the most widely used protecting group for 2′-hydroxy functions of RNA monomers. The *N*,*N*-diisopropyl PA group can be activated by mild acidic treatment followed by reaction with nucleophiles (e.g., with the free 5′-hydroxy group of the growing nucleotide bound to a solid support) to furnish the phosphite triester linkage which on oxidation is converted to stable phosphotriester linkage. The *O*-CNEt group is removed by base treatment through β-elimination at the end of the synthesis and the monomers are transiently protected by an acid-labile 5′-*O*-dimethoxytrityl (DMT) group. These inherent properties render the above building blocks extremely sensitive toward acids, bases and nucleophiles.

Very recently, we were able to successfully incorporate an imidazole base into RNA sequence to investigate the functions of imidazole as a pseudo nucleobase in ribozyme catalysis (Fig. 1).[3a] A novel C4-linked imidazole ribonucleoside (ICN) PA **1a**[3b,c] with a pivaloyloxymethyl (POM) group, which is easily removed under basic condition and is compatible with TBDMS synthesis of RNA, was first synthesized as a key ribonucleoside variant. However, in the course of analytical investigation of **1a**, we encountered difficulty in mass spectrometric characterization of **1a**, which decomposed even on a standard TLC plate (Merck 60 F_{254}).

Mass spectrometry (MS) is now used as a very common and indispensable tool in the fields of nucleic acid chemistry. Routine handling of the samples for MS can be carried out at the nanogram level compared to elementary analysis requiring several milligrams. Since crystallization of PAs is not easy, MS has been effective and extensively used for their characterization. However, MS is problematic for nucleoside PAs owing to their labile properties. Szabó et al. reported an application of nanoelectrospray MS to only six standard 2′-deoxynucloside PAs.[4] Although the mildest ionization methods[5] [fast atom bombardment (FAB) MS and liquid secondary ion (LSI) MS] are effective for PAs,[4,6] it is not always possible for the molecular-related ions (MRIs) of various PAs to be detected by them. On the other hand, little attention has been paid to the study of suitable matrices on LSIMS or FABMS for MS measurements of the

Keywords: Nucleoside; Phosphoramidite; Molecular weight; Mass spectrometry; Matrix.
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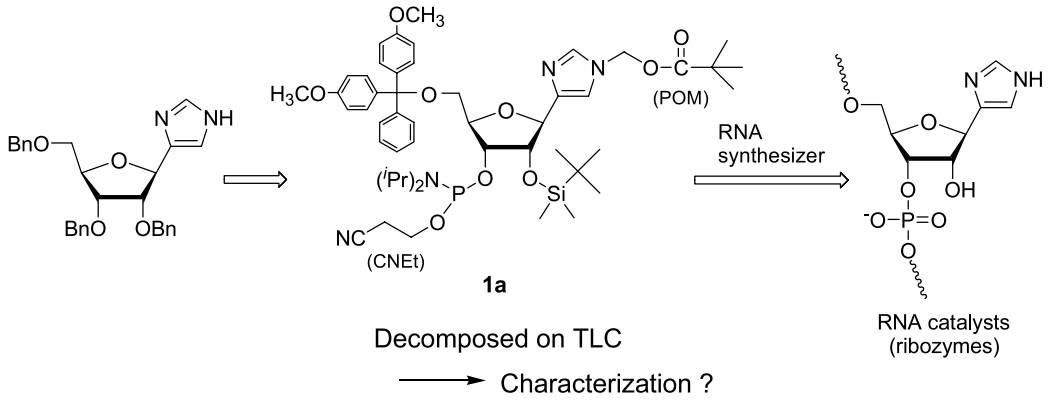


Figure 1. Chemical steps to incorporate imidazole base into RNA sequence.

PAs. If the accurate molecular weights (MWs) of PAs can be easily measured by MS, it would greatly enhance the reliability of PA-mass measurements. We herein report a suitable matrix system, triethanolamine [$N(CH_2CH_2OH)_3$, (TEOA)]–NaCl, for detection of the MRIs of a variety of PAs. It may be employed on LSIMS or FABMS equipped with double-focusing mass spectrometers, which are currently available. The present method measures the accurate MWs of various PAs as adduct ions $[M+Na]^+$ with average mass error smaller than 0.4 ppm, thus providing the formulas of various PAs.

2. Results and discussion

2.1. Accurate MW-measurements of ICN-PAs

We first measured MS of ICN PA **1a** using the conventional electron ionization (EI) and chemical ionization (CI) (Table 1), but they could not afford the MRI of **1a** (entries 1–3), only showing DMT group as the base peak. Our attention was next directed to LSIMS which has been exploited for a mild and soft ionization of various types of labile materials.[5] The matrix on LSIMS analysis plays a

Table 1. MS conditions for ICN phosphoramidite (PA) **1a**

Entry	Ionization Method	Matrix [a]	MRI [b]	RI [c] (%)	Observed mass [d] (m/z)	Error [e] (ppm)
1	EI (70eV)		-	ND [f]		
2	(20eV)		-	ND		
3	CI (i-C_4H_{10})		-	ND		
4	LSIMS	G	-	ND		
5		NBA	-	ND		
6		DEOA	-	ND		
7		MB	-	ND		
8		DTT/TG	-	ND		
9		TEOA	-	ND		
10		G + NaCl	$[M+Na]^+$	0.2		
11		NBA + NaCl	$[M+Na]^+$	0.6		
12		DEOA + NaCl	$[M+Na]^+$	0.7		
13		MB + NaCl	$[M+Na]^+$	0.4		
14		DTT/TG + NaCl	$[M+Na]^+$	0.3		
15		TEOA + NaCl	$[M+Na]^+$	20.1	953.4625 [g]	0.4
16	FAB	G	-	ND		
17		G + NaCl	-	ND		
18		TEOA + NaCl	$[M+Na]^+$	2.6		
19	ESI		-	ND		
20	MALDI-TOF	THAP	$[M+Na]^+$	- [h]	953.5199 [g]	60.6

[a] G, glycerol; NBA, *m*-nitrobenzyl alcohol; DEOA, diethanolamine; MB, dithiothreitol/dithioerythritol (3/1); DTT/TG, dithiothreitol/thioglycerol (1:1); TEOA, triethanolamine; THAP, 2′,4′,6′-trihydroxyacetophenone.
[b] MRI, molecular-related ion.
[c] RI, intensity relative to the base peak ion (100%).
[d] The mass was measured by HRMS.
[e] See Ref. 10.
[f] ND, not detected; <0.1%.
[g] **1a**: $C_{50}H_{71}N_4O_9PSi$, $[M+Na]^+$, theoretical mass (m/z)=953.4621.
[h] RI was not determined due to numerous peaks (<MW 500) resulted from THAP.

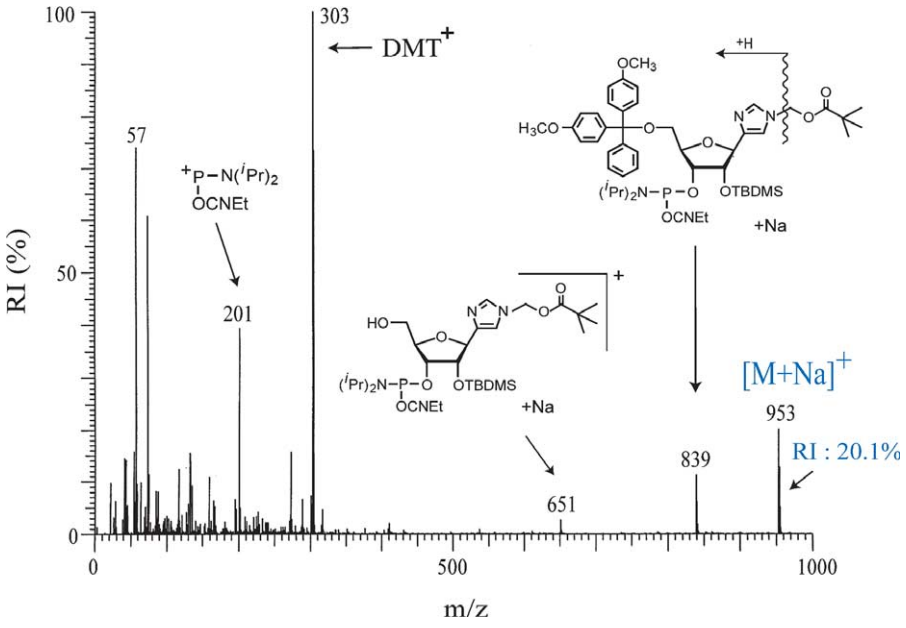
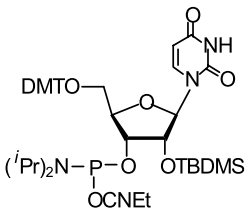
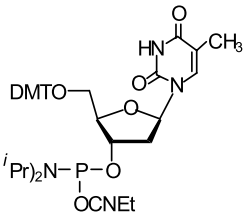


Figure 2. Positive ionization LSIMS spectrum of **1a** (MW 930) introduced in TEOA–NaCl matrix.

Table 2. MS conditions for *N*-nucleoside PAs **2a** and **3a**



2a

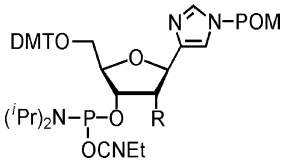
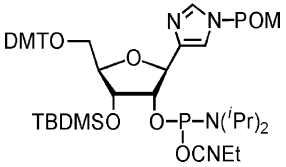
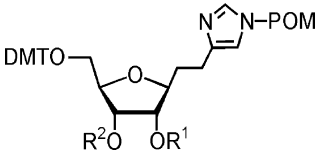
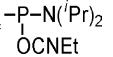
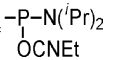
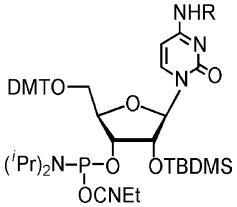
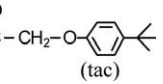
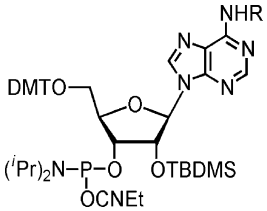
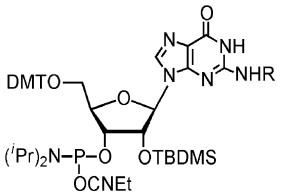


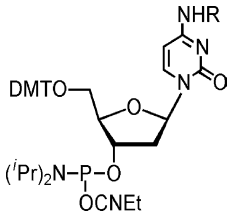
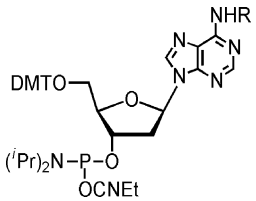
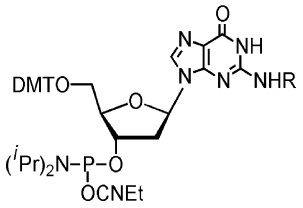
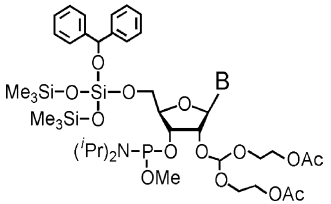
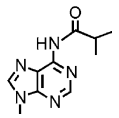
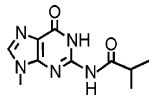
3a

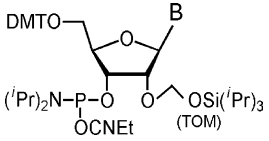
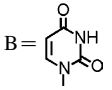
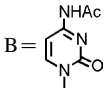
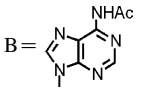
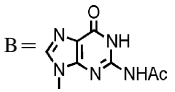
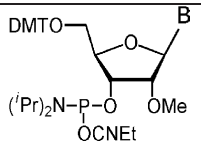
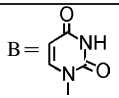
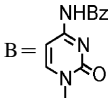
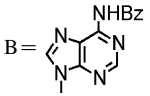
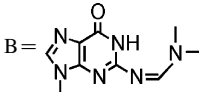
Entry	Ionization Method	Matrix [a]	MRI [a]	**2a** [b]		**3a** [c]	
				RI (%) [a]	Error [d] (ppm)	RI (%)	Error (ppm)
1	EI (70eV)		-	ND [a]		ND	
2	(20eV)		-	ND		ND	
3	CI (i-C_4H_{10})		-	ND		ND	
4	LSIMS	G	-	ND		ND	
5		NBA	-	ND		ND	
6		DEOA	$[M+H]^+$	0.2		ND	
7		MB	$[M+H]^+$	0.1		ND	
8		TEOA	$[M+H]^+$	0.1		ND	
9		G + NaCl	-	ND		ND	
10		NBA + NaCl	$[M+Na]^+$	0.1		0.2	
11		DEOA + NaCl	$[M+Na]^+$	3.1		3.5	
12		MB + NaCl	$[M+Na]^+$	2.5		ND	
13		TEOA + NaCl	$[M+Na]^+$	19.1	0.1 [e]	35.9	−0.3 [f]
14	FAB	G	-	ND		ND	
15		G + NaCl	-	ND		ND	
16		TEOA + NaCl	$[M+Na]^+$	2.5		4.2	

[a] See Table 1.
[b] **2a**; $C_{45}H_{61}N_4O_9PSi$, $[M+Na]^+$, theoretical mass (m/z)=883.3840.
[c] **3a**; $C_{40}H_{49}N_4O_8P$, $[M+Na]^+$, theoretical mass (m/z)=767.3182.
[d] See Ref. 10.
[e] Observed mass (m/z) of **2a**: 883.3841.
[f] Observed mass (m/z) of **3a**: 767.3180

Table 3. LSIMS measurements using TEOA–NaCl matrix: accurate MWs of standard PAs

Entry	PA	No.		Theoretical mass[a]	Observed mass[a]	RI[b] (%)	Error[c] (ppm)
1		**1b**	R=–O 	879.4070 $C_{47}H_{61}N_4O_9P$	879.4069	2.2	−0.1
2		**c**	R=–H	823.3809 $C_{44}H_{57}N_4O_8P$	823.3801	3.5	−1.0
3		**d**		953.4621 $C_{50}H_{71}N_4O_9PSi$	953.4618	14.6	−0.3
4		**e**	R^1=-TBDMS R^2= 	981.4934 $C_{52}H_{75}N_4O_9PSi$	981.4935	1.6	0.1
5		**f**	R^1=  R^2=-TBDMS	981.4934 $C_{52}H_{75}N_4O_9PSi$	981.4932	0.4	−0.2
6		**2b**	R=–Ac	924.4105 $C_{47}H_{64}N_5O_9PSi$	924.4106	3.6	0.1
7		**c**	R=  (tac)	1072.4993 $C_{57}H_{76}N_5O_{10}PSi$	1072.4991	3.0	−0.2
8		**d**	R=-Bz	1010.4373 $C_{53}H_{66}N_7O_8PSi$	1010.4375	5.5	0.2
9		**e**	R=-tac	1096.5105 $C_{58}H_{76}N_7O_9PSi$	1096.5109	4.8	0.4
10		**f**	R=-^{i}Bu	992.4479 $C_{50}H_{68}N_7O_9PSi$	992.4476	7.7	−0.3
11		**g**	R=-tac	1112.5054 $C_{58}H_{76}N_7O_{10}PSi$	1112.5056	6.1	0.2

Entry	PA	No.		Theoretical mass[a]	Observed mass[a]	RI[b] (%)	Error[c] (ppm)
12		**3b**	R = -Ac	794.3291 $C_{41}H_{50}N_5O_8P$	794.3290	1.3	−0.1
13		**c**	R = -Bz	856.3448 $C_{46}H_{52}N_5O_8P$	856.3448	2.1	0.0
14		**d**	R = -tac	942.4179 $C_{51}H_{62}N_5O_9P$	942.4182	2.8	0.3
15		**e**	R = -Bz	880.3561 $C_{47}H_{52}N_7O_7P$	880.3560	15.3	−0.1
16		**f**	R = -tac	966.4292 $C_{52}H_{62}N_7O_8P$	966.4294	15.5	0.2
17		**g**	R = -^{i}Bu	862.3666 $C_{44}H_{54}N_7O_8P$	862.3669	8.6	0.3
18		**h**	R = -tac	982.4241 $C_{52}H_{62}N_7O_9P$	982.4242	9.3	0.1
19		**4a**	B = 	1034.3695 $C_{44}H_{70}N_3O_{16}PSi_3$	1034.3699	3.5	0.4
20		**b**	B = 	1075.3961 $C_{46}H_{73}N_4O_{16}PSi_3$	1075.3963	2.4	0.2
21		**c**	B = 	1127.4386 $C_{49}H_{77}N_6O_{15}PSi_3$	1127.4387	6.9	0.1
22		**d**	B = 	1143.4335 $C_{49}H_{77}N_6O_{16}PSi_3$	1143.4340	9.3	0.4

Entry	PA	No.		Theoretical mass[a]	Observed mass[a]	RI[b] (%)	Error[c] (ppm)
23		**5a**		955.4414 $C_{49}H_{69}N_4O_{10}PSi$	955.4416	11.0	0.2
24		**b**		996.4680 $C_{51}H_{72}N_5O_{10}PSi$	996.4680	1.3	0.0
25		**c**		1020.4792 $C_{52}H_{72}N_7O_9PSi$	1020.4791	15.4	−0.1
26		**d**		1036.4741 $C_{52}H_{72}N_7O_{10}PSi$	1036.4742	7.6	0.1
27		**6a**		783.3132 $C_{40}H_{49}N_4O_9P$	783.3133	20.7	0.1
28		**b**		886.3554 $C_{47}H_{54}N_5O_9P$	886.3551	10.9	−0.3
29		**c**		910.3666 $C_{48}H_{54}N_7O_8P$	910.3670	12.1	0.4
30		**d**		877.3775 $C_{44}H_{55}N_8O_8P$	877.3777	17.4	0.2

[a] $[M+Na]^+$.
[b] See Table 1.
[c] See Ref. 10.

significant role as a supporting base (a relatively involatile solvent which holds the sample in position on the sample target) to achieve effective and stable ionizations.[7a] Glycerol (G) or *m*-nitrobenzyl alcohol (NBA), which were the popular choice for LSIMS matrices,[7b] did not give any useful peaks of **1a** (entries 4 and 5). Many matrices were tried to find the most suitable condition on LSIMS for **1a**. Uses of diethanolamine (DEOA), magic bullet (MB, a 3:1 mixture of dithiothreitol: dithioerythritol), a 1:1 mixture of dithiothreitol and α-thioglycerol (DTT/TG), or TEOA as matrices failed (entries 6–9). Use of a matrix in the presence of a metal ion has been known to be effective.[8] Then, when saline (NaCl)[9a] was added to G, NBA, DEOA, MB, or DTT/TG, the desired MRI peaks could be detected as $[M+Na]^+$ with low 0.2–0.7% relative intensities (RIs) (entries 10–14). Further, a combination of TEOA and NaCl produced an optimum result, remarkably increasing the peak of the ion to 20.1% (entry 15). The MRI of **1a** appeared at *m/z* 953.4625 in the externally calibrated spectrum (polyethylene glycol) by high-resolution (HR)-MS and the error[10] was only 0.4 ppm from the expected mass number. The MRI of **1a**, on the contrary, was not found in negative mode of LSIMS using various matrices.[9b] In addition, this matrix has an advantage of permitting use on FAB, as shown in entry 18. Use of electrospray ionization (ESI) for **1a** did not show any useful peaks either (entry 19). On the other hand, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) MS was investigated for analysis of **1a**. After examination of various matrices, a matrix, 2′, 4′, 6′-trihydroxyacetophenone (THAP), led to $[M+Na]^+$ of **1a** at *m/z* 953.5199 with the error of 60.6 ppm from the theoretical mass number (entry 20). The error of MALDI-TOF is 152-times larger than the low error (0.4 ppm) of the TEOA–NaCl matrix on LSIMS. As determination of the molecular composition requires mass error smaller than ±3 ppm, MALDI-TOF MS cannot give the molecular composition of **1a**. In this manner, MALDI-TOF MS is still a limited state and it is generally difficult to determine the compositions because of the large errors.[11]

The LSIMS spectrum (low MS level) of **1a** using the TEOA–NaCl matrix characterized the structure as shown in Figure 2, where the fragment ions at *m/z* 839 and 651 correspond to the Na^+-adducted ions generated by removal of POM or DMT from **1a**, together with a base peak due to DMT^+ ion at *m/z* 303.

2.2. Application of TEOA–NaCl matrix to C- and N-nucleoside PAs[12]

Next, PAs **2a** (U) and **3a** (T) of protected uridine and thymidine were similarly analyzed by various MS conditions (Table 2). EI and CI were ineffective for **2a** and **3a** (entries 1–3). Uses of matrices DEOA, MB, and TEOA on LSIMS for **2a** showed only 0.1–0.2% abundance of MRIs in the absence of NaCl, but not for DNA monomer **3a** (entries 6–8). On the other hand, the TEOA–NaCl matrix system on LSIMS provided excellent MRI peaks (19.1 and 35.9%) of **2a** and **3a** with small errors (0.1 and −0.3 ppm), respectively (entry 13). Efficiency of the TEOA–NaCl system on FAB was also indicated by MRI peaks of **2a** or **3a**, although with lower intensities (entry 16).

The above results encouraged us to examine the scope and limitation of the TEOA–NaCl matrix on LSIMS for nucleoside PAs. The observed and theoretical mass of the PAs are summarized in Table 3. Use of the MS method to labile C4-linked ICN-PAs **1b–f** containing 2′-deoxy- and two-carbon-elongated ribonucleosides successfully provided the MRIs with low-ppm-level mass accuracy (error: <0.3 ppm) (entries 1–5). Cytidine PAs **2b** (Ac-C) and **2c** (tac-C), adenosine PAs **2d** (Bz-A) and **2e** (tac-A), and guanosine PAs **2f** (*i*Bu-G) and **2g** (tac-G), which are commercial available building blocks used in typical RNA synthesizer programs, fitted the matrix to give their MRIs (Ac = acetyl, tac = 4-*tert*-butylphenoxyacetyl, Bz = benzoyl, *i*Bu = isobutyryl) (entries 6–11). It also provided MRIs of the other standard monomers **3b–h** for routine synthesis of DNA oligonucleotides: **3b** (Ac-dC), **3c** (Bz-dC), **3d** (tac-dC), **3e** (Bz-dA), **3f** (tac-dA), **3g** (*i*Bu-dG), and **3h** (tac-dG) (entries 12–18). Newly improved RNA synthons,[13] 5′-*O*-BzH-2′-*O*-ACE-protected PAs **4a** (U), **4b** (Ac-C), **4c** (*i*Bu-A), and **4d** (*i*Bu-G) were subjected to the LSIMS condition to give the corresponding MRIs [BzH, benzhydryloxybis(trimethylsilyloxy)silyl; ACE, bis(2-acetoxyethoxy)methyl] (entries 19–22). 5′-*O*-DMT-2′-*O*-triisopropyloxymethyl (TOM)-ribonucleoside PAs **5a** (U), **5b** (Ac-C), **5c** (Ac-A), and **5d** (Ac-G) in TOM chemistry[14] were characterized by use of the present matrix (entries 23–26). Further, the matrix was successfully applied to a set of 5′-*O*-DMT-2′-OMe-RNA monomers[15] **6a** (U), **6b** (Bz-C), **6c** (Bz-A), and N^2-dimethylaminomethylene protected G **6d** which were designed to produce synthetic oligonucleotides containing nuclease-resistant 2′-OMe ribonucleotide linkage (entries 27–30).

2.3. Extension to a variety of PAs[12]

The present method was further extended to a variety of PAs bonded to functional molecules (Table 4): 3-nitropyrrole 2′-deoxynucleoside **7** as a universal nucleoside, two halo-nucleosides **8** (Br-dU) and **9** (2′-F-Ac-C), T-5′-PA **10**, 5′-amino modifier **11**, photocleavable biotin PA **12**,[16] PA synthon **13** for oligonucleotide dendrimers, disulfide thiol modifier **14**, amino-modified C6 dC **15**, fluorescein PA **16**, Cy3 PA **17**, and abasic PA **18**.[17] As shown in Table 4, their accurate MWs were easily measured with low errors (<0.5 ppm) by TEOA–NaCl on LSIMS. In some cases, extremely high $[M+Na]^+$ species were observed (entries 4, 5, 10 and 11). These facts demonstrate the potential of the method.

2.4. Suitable mole-ratios of PA, NaCl, and TEOA as the matrix

In the course of our study, we became aware that the MRIs of PAs were influenced by the concentration of NaCl in the matrix. Thus, relationship between MRI intensity and the mole-ratio of a NaCl/sample was examined closely fixing the amount of TEOA (0.5 μl), and was plotted successively in a diagram (Fig. 3). As shown in the diagram, the MRI intensities of **3a** were gradually enhanced, as the mole-ratios of NaCl/**3a** were increased. When the mole-ratio of NaCl/**3a** was 6, the RI was attained to the highest degree (30.4%), but above 6 it was rather suppressed (e.g., NaCl/**3a** = 12). The same mole-ratio of NaCl/**2a** also provided a high RI of **2a**

Table 4. LSIMS measurements using TEOA–NaCl matrix: accurate MWs of various PAs

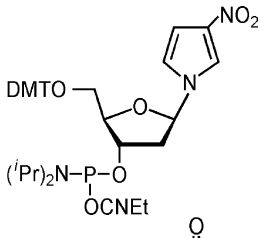
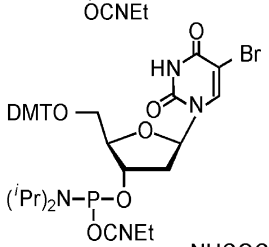
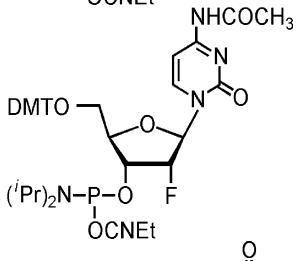
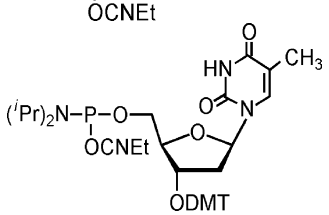
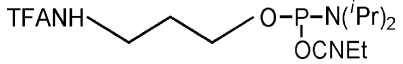
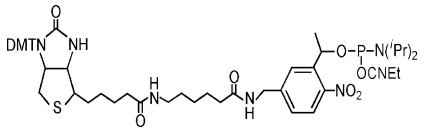
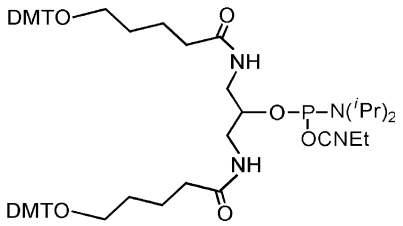
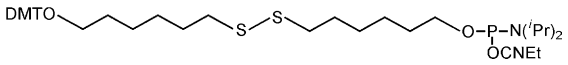
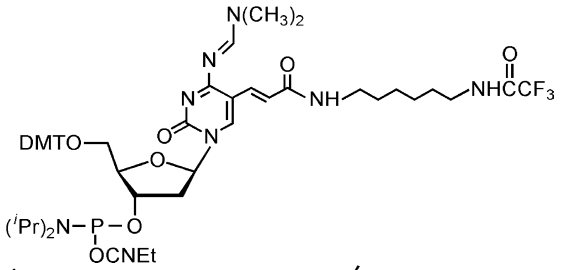
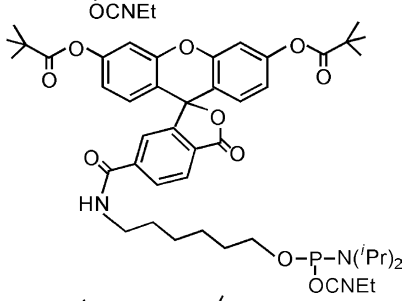
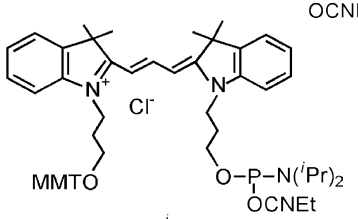
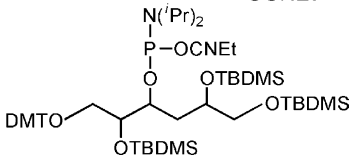
Entry	PA	No.	Theoretical mass[a]	Observed mass [a]	RI[b] (%)	Error[c] (ppm)
1		**7**	753.3026 $C_{39}H_{47}N_4O_8P$	753.3024	8.5	−0.3
2		**8**	831.2131 $C_{39}H_{46}BrN_4O_8P$	831.2129	4.5	−0.2
3		**9**	812.3197 $C_{41}H_{49}FN_5O_8P$	812.3200	8.3	0.4
4		**10**	767.3183 $C_{40}H_{49}N_4O_8P$	767.3180	63.3	−0.4
5		**11**	394.1482 $C_{14}H_{25}F_3N_3O_3$	394.1482	42.0	0.0
6		**12**[16]	1060.4744 $C_{55}H_{72}N_7O_9PS$	1060.4747	2.6	0.3
7		**13**	1117.5427 $C_{64}H_{79}N_4O_{10}P$	1117.5425	6.0	−0.2

Table 4 (*continued*)

Entry	PA	No.	Theoretical mass[a]	Observed mass [a]	RI[b] (%)	Error[c] (ppm)
8		**14**	791.3654 $C_{42}H_{61}N_2O_5PS_2$	791.3655	1.0	0.1
9		**15**	1071.4692 $C_{53}H_{68}F_3N_8O_9P$	1071.4688	5.3	−0.4
10		**16**	866.3754 $C_{46}H_{58}N_3O_{10}P$	866.3750	100.0	−0.5
11		**17**[d]	917.5131 $C_{58}H_{70}N_4O_4P(Cl^-)$	917.5130	76.1	−0.1
12		**18**[17]	1033.5713 $C_{54}H_{91}N_2O_8PSi_3$	1033.5712	7.5	−0.1

[a] $[M+Na]^+$.
[b] See Table 1.
[c] See Ref. 10.
[d] Compound **17** was detected as $[M-Cl^-]^+$.

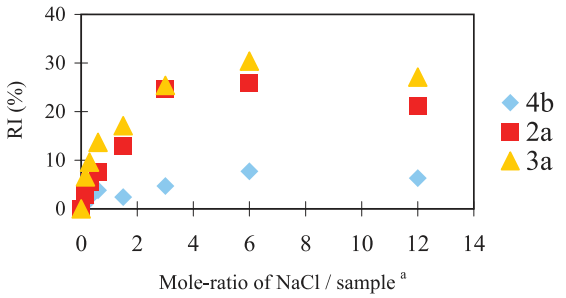


Figure 3. A relationship between RIs of MRIs and mole-ratios of NaCl/sample. [a]TEOA is fixed to 0.5 µl.

the secondary sample ions were accelerated to 6 keV. Most of the samples for LSIMS were primarily prepared as a mixture of PA (0.02 µmol), NaCl (0.03 µmol), and TEOA (0.5 µl) (entry 5 in Table 5), then all of them placed on the LSIMS target. All mass spectra were acquired at 8 s intervals from *m/z* 0 to 1500 in the positive ion mode, and about 10 spectra were averaged. The mass resolution was 2000–3000 ($M/\Delta m$). FABMS were measured on JEOL JMS-700. MALDI-TOF MS were carried out on an Applied Biosystem Voyager-DE TMSTR. ESIMS were measured using a Hitachi M-8000 (LC3DQ/MS).

Table 5. Suitable mole-ratios of NaCl/TEOA[a]

Entry		1	2	3	4	5	6	7	8
PA (µmol)		0.1	0.1	0.1	0.05	0.02	0.01	0.01	0.005
NaCl (µmol)		0	0.015	0.03	0.03	0.03	0.03	0.06	0.06
NaCl / Sample		0	0.15	0.3	0.6	1.5	3	6	12
relative intensity of $[M+Na]^+$	**2a**	0	2.9	5.5	7.6	12.9	24.7	25.8	21.2
	3a	0	6.6	9.6	13.7	17.1	25.4	30.4	27.1
	4b	0	1.1	2.4	3.8	2.4	4.7	7.7	6.3

[a]TEOA is fixed to 0.5 µl.

(25.8%). A similar tendency could be seen in 2′-ACE-Ac-C **4b** showing 7.7% RI. Therefore, we may recommend a combination of PA (0.01 µmol), NaCl (0.06 µmol), and TEOA (0.5 µl) as a composition of the matrix on LSIMS for PAs (Table 5).

3. Conclusion

The TEOA–NaCl matrix on LSIMS equipped with a double-focusing mass spectrometer was quite useful for the measurements of nucleoside PAs. The present method measures rapidly and easily the accurate MWs of various PAs as adduct ions $[M+Na]^+$ with average mass error smaller than 0.4 ppm. All of the 45 PAs investigated gave MRIs using the present method. This matrix on FAB may be used for PAs. These facts successfully prove the generality and potential of the method. Hence, the proposed method is a powerful tool for the MS identification of PAs.

4. Experimental

4.1. General

EI-, CI-MS and LSIMS were performed on Hitachi M-4000H double-focusing mass spectrometer of a magnetic–electric (*B–E*) sector geometry with a cesium ion source. EI- and CI-MS were measured at a chamber temperature of 180 °C (ionization voltage of 70 or 20 eV), accelerating voltage of 6 kV. The direct inlet temperature was increased from 0 to 500 °C. The sample was introduced into the ion source using a direct inlet system. A Cs^+ ion primary beam with an energy of 15 keV was used, and

4.2. Measurement of 2a under the most suitable condition of matrix

A 20 mM chloroform solution of **2a** was prepared in advance as follows: **2a** (8.6 mg, 10 µmol) was dissolved in chloroform (50 µl), 2 µl of which was diluted with chloroform (18 µl). A mixture of the prepared chloroform solution of **2a** (0.5 µl) (corresponding to 0.01 µmol of **2a**), neat TEOA (0.5 µl), and saline (0.4 µl: 0.06 µmol of NaCl) was subjected to LSIMS to give the MRI (25.8% RI) (Table 5, entry 7).

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9. (a) NaCl was used in the state of 0.9% saline. (b) For measurements of negative mode of **1a**, six matrices on LSIMS (G, NBA, TEOA, G + NaCl, NBA + NaCl, and TEOA + NaCl) were examined.
10. The error can be calculated using the following equation: error (ppm) = $10^6 \times$ (observed mass − theoretical mass)/theoretical mass.
11. For examples of MALDI-TOF MS data, see: (a) Korshun, V. A.; Stetsenko, D. A.; Gait, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1092–1104. (b) Zatsepin, T. S.; Ivanova, Y. M.; Oretskaya, T. S. *Chem. Biodiver.* **2004**, *1*, 1537–1545. (c) Ashraf, M. A.; Notta, J. K.; Snaith, J. S. *Tetrahedron Lett.* **2003**, *44*, 9115–9119. (d) Lu, X.; He, X.; Feng, L.; Shi, Z.; Gu, Z. *Tetrahedron* **2004**, 3713–3716. (e) Kirk, J. S.; Bohn, P. W. *J. Am. Chem. Soc.* **2004**, *126*, 5920–5926. (f) Zhu, X.; Schmidt, R. R. *Synthesis* **2003**, 1262. (g) McKeen, C. M.; Brown, L. J.; Nicol, J. T. G.; Mellor, J. M.; Brown, T. *Org. Biomol. Chem.* **2003**, *1*, 2267–2275.
12. Compounds **1a** and **1d** were prepared according to reference **3b**. The synthesis of **1b**, **1c**, **1e**, and **1f** will be published later. Other investigated PAs were purchased from Cruachem (**2a**, **2b**, **2d**, **2f**, and **3c**), PrOligo (**2c**, **2e**, **2g**, **3d**, **3f**, and **3h**), Glen Research (**3a**, **3b**, **3e**, **3g**, **5a**–**5d**, **6a**–**6d**, **7**–**16**, and **18**), Dharmacon (**4a**–**d**), and Amersham Biosciences (**17**).
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Nucleophilic aromatic substitution reactions of fluorobenzenechromium complexes with P-chiral secondary phosphine–boranes: synthesis of optically pure P-chiral (dialkyl)arylphosphine–boranes

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Abstract—Optically pure P-chiral (dialkyl)arylphosphine–boranes having high structural diversity were prepared by two- or three-component coupling of fluorobenzenechromium complexes, P-chiral secondary phosphine–boranes, and other nucleophiles. The stereochemical integrity at the P-stereogenic center was completely retained during the S_NAr process when the reaction was carried out in THF at low temperature.

1. Introduction

Optically active phosphines have played an important role in various metal-catalyzed asymmetric transformations, and numerous phosphines have been prepared for the development of effective catalytic asymmetric processes.[1,2] Among them, P-chiral diphosphines have attracted increasing attention in the field of asymmetric catalysis, because some examples of this class of phosphines, such as 1,2-bis-(alkylmethylphosphino)ethanes (BisP*) and bis(alkylmethylphosphino)methanes (MiniPHOS), exhibit not only almost perfect enantioselectivity in rhodium-catalyzed asymmetric hydrogenation but also high utility in the detailed mechanistic study of the hydrogenation.[3,4]

The synthesis of optically active P-chiral phosphines has a long history, and many synthetic methods have been reported so far.[2h,j] The most conventional method involves the introduction of a chiral auxiliary and the subsequent separation of diastereomers.[5] Enantioselective syntheses have also been achieved by means of asymmetric deprotonation,[6] crystallization-induced asymmetric transformation,[7] dynamic kinetic resolution,[8] or asymmetric catalysis.[9] In these protocols, however, only a limited range of substrates can be employed for achieving high enantioselectivity and hence the development of new synthetic methods for various P-chiral phosphines remains an important research subject.

On the other hand, the electrophilic alkylation or arylation of chiral tetracoordinate organophosphorus compounds having a P–H bond is known to proceed with retention of configuration at the phosphorus atom, and the reaction is recognized as an effective method for the preparation of functionalized P-chiral phosphines in the optically pure form.[10] It is noted that the introduction of aryl groups to the P-chiral center has been achieved by means of the Pd-catalyzed coupling of optically active P-chiral secondary phosphine derivatives with haloarenes. These reports have inspired us to hypothesize that P-chiral (dialkyl)-arylphosphines can be synthesized by coupling P-chiral secondary phosphine–boranes with aryl cation equivalents. Arenechromium complexes are extremely electron-deficient aromatic compounds and recognized as one of the representative aryl cation equivalents.[11,12] In particular, haloarenechromium complexes have been proven to be good substrates for the S_NAr process owing to their strong electrophilicity at the *ipso* position. In this paper, we report a new method for the preparation of various P-chiral arylphosphines in enantiomerically pure form based on the

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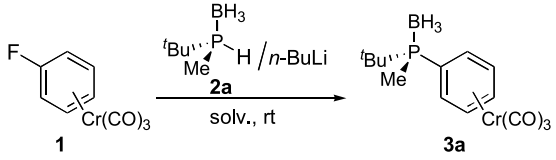
S_NAr reaction of secondary phosphine–boranes with halobenzenechromium complexes.

2. Results and discussion

Our first trial for the synthesis of P-chiral (dialkyl)-arylphosphines involved the reaction of (*S*)-*t*-butyl-methylphosphine–borane (**2a**) with fluorobenzene tricarbonylchromium (**1**) by using *n*-butyllithium as the deprotonation agent in various solvents. The results are summarized in Table 1. In THF, the reaction proceeded at ambient temperature to give the corresponding coupling product **3a** in 61% yield (entry 1). The chemical yield was improved by using an excess amount of **2a**. Thus, product **3a** was obtained in 81% yield by the use of 2.2 equiv of **2a** (entry 2). Similarly, the use of 3.3 equiv of **2a** afforded 90% yield of **3a** with 62% recovery of **2a** (entry 3). The reaction in acetonitrile required a longer time to give the product in 60% yield (entry 4). Slightly lower reactivity was also observed when diethyl ether, 1,4-dioxane and toluene were used as solvents (entries 5–7).

Table 1. Coupling of *t*-butylmethylphosphine–borane and fluorobenzenechromium tricarbonyl in various solvents[a]

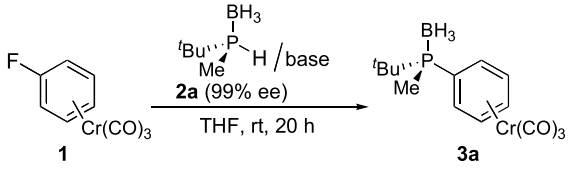


Entry	Solvent	Time (h)	Yield of **3a** (%)[b]
1	THF	8	61
2[c]	THF	8	81[d]
3[e]	THF	8	90[f]
4	MeCN	18	60
5	Et_2O	18	51
6	Dioxane	18	41
7	Toluene	18	37

[a] All reactions were carried out with **1** (1 mmol) and 1.1 equiv of **2a**/*n*-BuLi at rt unless otherwise noted.
[b] Isolated yield.
[c] 2.2 equiv of **2a**/*n*-BuLi was used.
[d] 50% of **2a** was recovered.
[e] 3.3 equiv of **2a**/*n*-BuLi was used.
[f] 62% of **2a** was recovered.

The stability of the P-stereogenic center during the coupling reaction was examined by using almost enantiomerically pure **2a** (99% ee).[13] The reaction at room temperature gave product **3a** with 84% ee (entry 1, in Table 2). The decreased ee of the product is responsible for the partial racemization of the anionic phosphorus species under the conditions.[14] This racemization was suppressed by lowering the reaction temperature, giving rise to 99% ee of the product (entries 2 and 3). However, the reaction in acetonitrile at −40 °C produced the product with decreased ee (84%), although the chemical yield was excellent (entry 4). Both the satisfactory chemical yield and the almost complete retention of configuration were obtained by the use of *s*-butyllithium as the base (entries 5). The high yield of this reaction was maintained under the same conditions on multigram scale (entries 6).

Table 2. Coupling of P-chiral *t*-butylmethylphosphine–borane and fluorobenzenechromium tricarbonyl under various conditions[a]

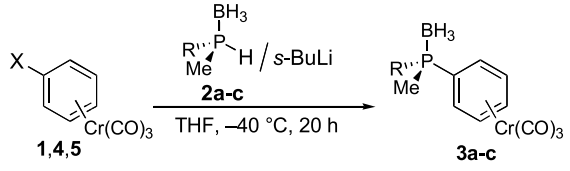


Entry	Base	Temp./°C	Yield/%[b]	ee/%[c]
1[d]	*n*-BuLi	rt	83	84
2	*n*-BuLi	−40	81	99
3	*n*-BuLi	−78	7	99
4[e]	*n*-BuLi	−40	95	84
5	*s*-BuLi	−40	93	99
6[f]	*s*-BuLi	−40	89	99
7[g]	NaH	−40	75	87

[a] All reactions were carried out with **1** (1 mmol) and 2.2 equiv of **2a**/base for 20 h unless otherwise noted.
[b] Isolated yield.
[c] Determined by CSP-HPLC analysis after conversion to di-phenyl-hydroxy-methyl derivatives (see Ref. 13).
[d] Reaction time: 8 h.
[e] Acetonitrile was used as a solvent.
[f] The reaction was carried out with 7 mmol of **1**.
[g] DMF was used as a solvent.

Based on the results mentioned above, (*S*)-1-adamantyl-methylphosphine–borane (**2b**) (99% ee) and (*S*)-cyclohexyl-methylphosphine–borane (**2c**) (75% ee) were allowed to react with the fluorobenzenechromium complex at −40 °C in THF using *s*-BuLi as the deprotonation agent. In both cases, no racemization took place and the corresponding coupling products were obtained in high yields (entries 2 and 3 in Table 3). On the other hand, we attempted to react **2a** with chlorobenzene tricarbonyl-chromium (**4**) or bromobenzenechromium complex (**5**) under the same conditions. The former reaction was very sluggish, giving the product in only 7% yield, whereas the latter reaction did not take place at all under the given conditions (entries 4 and 5). These results indicate that this aromatic nucleophilic substitution (S_NAr) reaction proceeds through an addition–elimination process and the highly electronegative fluorine atom accelerates the initial addition step. It is also clear that the

Table 3. Coupling of P-chiral alkylmethylphosphine–boranes and halobenzene–chromium tricarbonyls[a]



Entry	R	X	Product	Yield/%[b]	ee/%[c]
1	*t*-Bu (**2a**)	F (**1**)	**3a**	93	99
2	Ad (**2b**)	F (**1**)	**3b**	86	99
3[d]	*c*-Hex (**2c**)	F (**1**)	**3c**	81	75
4	*t*-Bu (**2a**)	Cl (**4**)	**3a**	7	99
5	*t*-Bu (**2a**)	Br (**5**)	**3a**	0	—

[a] All reactions were carried out with haloarenechromium tricarbonyl (1 mmol) and 2.2 equiv of **2**/*s*-BuLi in THF at −40 °C for 20 h.
[b] Isolated yield.
[c] Determined by CSP-HPLC analysis after conversion to di-phenyl-hydroxy-methyl derivatives (see Ref. 13).
[d] 75% ee of **2c** was used.

less electronegative and bulkier chlorine and bromine atoms retard the nucleophilic attack of the phosphorus anion at the *ipso* position.

We envisioned that the substituent at the *ortho* position of P-chiral phosphinobenzene may significantly affect the enantiodifferentiation in asymmetric catalysis via the stereo and electronic effects.[15] This led us to develop a new method for the synthesis of *ortho*-substituted P-chiral phosphines. Figure 1 illustrates our protocol consisting of three-component coupling of secondary phosphine–borane, *o*-difluorobenzenechromium complex, and various nucleophiles. First, we tried to prepare the key intermediate by reacting of **2a** with *o*-difluoro-benzene-chromium tricarbonyl (**6**) in the presence of *s*-BuLi. The reaction proceeded smoothly to give monosubstituted product **7** with an 85/15 diastereomeric ratio in 97% combined yield (Eq. 1). Each diastereomer was easily separated by column chromatography on silica gel. The subsequent attempted reaction of the major diastereomer with methylmagnesium was unsuccessful, probably owing to the large steric hindrance of the boranatophosphino group (Eq. 2). We therefore carried out deboranation by treatment with 1-methylpyrrolidine to obtain (*R*)-2-(*t*-butyl-methyl-phosphino)-fluorobenzene tricarbonylchromium (**9**) as a yellow solid (Eq. 3).[16] It is noteworthy that this phosphine was not readily oxidized in air; approximately 5% of **9** was oxidized on exposure to air for one week. The air-stable property of **9** is responsible for the electron-withdrawing nature of the chromium tricarbonyl group.

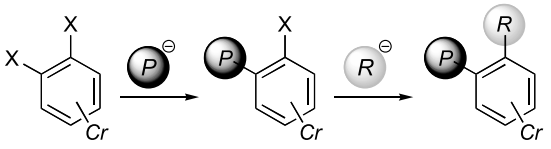
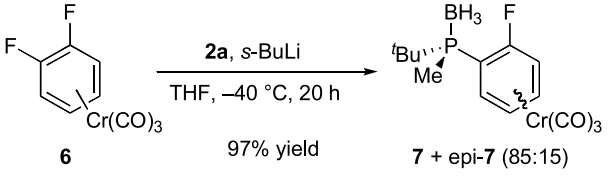
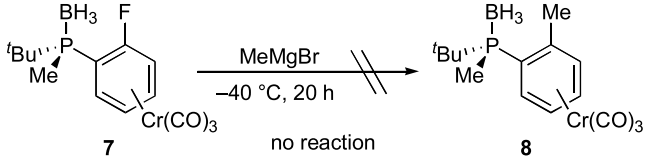


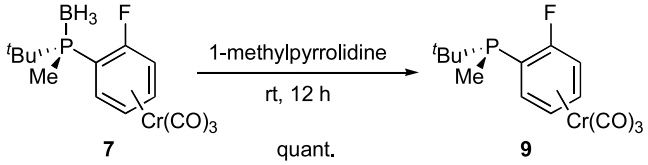
Figure 1. Preparation of various P-chiral arylphosphine by combinatorial approach.



(1)

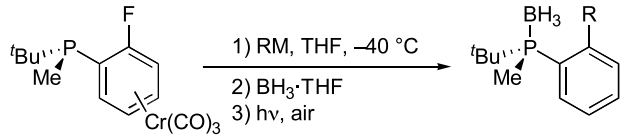


(2)



(3)

Table 4. S_NAr reaction of **9** with various nucleophiles[a]

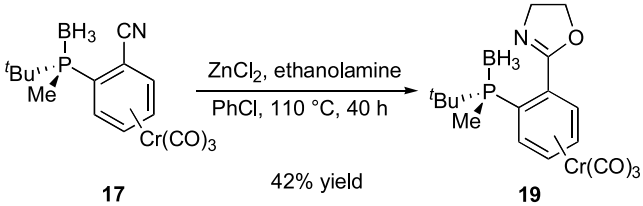


Entry	RM	Time (h)	Product	Yield (%)[b]
1	MeMgBr	20	**10**	90
2	*n*-BuMgBr	20	**11**	75
3	*n*-BuLi	20	**11**	22
4[c]	*n*-BuLi	20	**11**	60
5	*c*-HexMgBr	20	**12**	41
6	*c*-HexLi	20	**12**	69
7	PhMgBr	24	**13**	87
8	PhLi	24	**13**	88
9	PhSLi	20	**14**	40
10	*t*-BuSLi	20	**15**	55
11	PhSeLi	20	**16**	52
12[d]	TMSCN	20	**17**	91
13[d]	$TMSN_3$	20	**18**	68

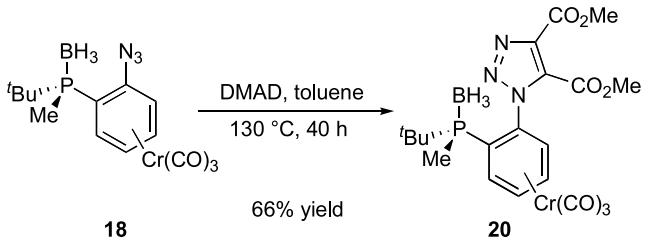
[a] All reactions were carried out with **9** and 2.0 equiv of RM in THF at −40 °C. The products were isolated as Cr-free phosphine–borane derivatives.
[b] Isolated yield.
[c] TMEDA (2.0 equiv) was added.
[d] 2-Propanol (2.0 equiv) was added.

Compound **9** was reacted with various nucleophiles in THF at −40 °C, and the products were isolated as Cr-free phosphine–borane derivatives. The results are summarized in Table 4. It is noted that the reactions with Grignard reagents and organolithium compounds afforded the corresponding substitution products in good to high yields (entries 1–8). Thiolate and selenide nucleophiles also underwent the substitution reaction to yield the respective *ortho*-substituted products, which are potentially useful as chiral P/S and P/Se hybrid ligands.[17] In addition, cyano derivative **17** and azido derivative **18** were obtained in 91 and 68% yields, respectively, by reacting with trimethylsilyl cyanide or azidotrimethylsilane in the presence of 2-propanol.

Compounds **17** and **18** were further transformed into oxazoline and triazine derivatives, respectively, as shown in Eqs. 4 and 5.[18,19] It is noted that the phosphine–borane moiety remained intact under these considerably drastic conditions to produce the heterocycles in moderate to good yields. Although the reaction examples are still limited, we believe that new P-chiral P/N hybrid ligands can be prepared by this method.



(4)



18 20 (5)

3. Conclusion

Optically pure P-chiral (dialkyl)arylphosphine–boranes were prepared by the S_NAr reaction of P-chiral secondary phosphine–boranes with fluorobenzenechromium complexes in the presence of *s*-butyllithium. Complete retention at the P-stereogenic center was observed during this coupling process when the reaction was carried out in THF at −40 °C. In addition, the three-component coupling of secondary P-chiral phosphine–borane, fluoroarene–chromium complexes, and other nucleophiles was also achieved to provide P-chiral arylphosphine–borane derivatives bearing a functional group at the *ortho* position.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere. Dehydrated tetrahydrofuran (THF) and diethyl ether were purchased from Kanto Chemical Co., Inc. and Wako Pure Chemical Industries Ltd, respectively, and used as received. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a JNM-LA400, a JNM-LA500, a JNM-400s or a JNM-ECA (400 MHz) spectrometer. In both ^{1}H NMR and ^{13}C NMR measurements, the chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS). The ^{31}P NMR chemical shifts are relative to 85% H_3PO_4. FT-IR spectra were recorded on a Hitachi IR 215 spectrometer by using KBr disks or NaCl plates. Mass spectra were obtained by a JMS-700 spectrometer equipped with a FAB source. HPLC analysis was performed on a Shimadzu LC10AD liquid chromatography system, and a Hitachi High-Technologies Corporation L-2450 liquid chromatography system with chiral stationary phase columns. Fluorobenzene tricarbonylchromium (**1**)[20] and P-chiral secondary phosphine–boranes **2a**–**c**[21] were prepared according to the reported procedures.

4.1.1. (*R*)-Boranato(*tert*-butyl)methylphosphinobenzene-tricarbonylchromium (3a). To a solution of (*S*)-*tert*-butylmethylphosphine–borane (**2a**) (1.82 g, 15.4 mmol) in THF (15 mL) was added 1.0 M *sec*-BuLi (1.0 M cyclohexane and *n*-hexane solution, 15.4 mL, 15.4 mmol) at −78 °C under nitrogen atmosphere. After stirring for 1 h, a solution of **1** (1.62 g, 7 mmol) in THF (21 mL) was added at −40 °C, and the mixture was stirred for 20 h at intact temperature. The reaction was quenched with 1 M HCl aq., and the mixture was extracted three times with AcOEt. The combined extracts were washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (AcOEt/hexane, 1:5) to give **3a** (2.06 g, 89% yield) as a yellow solid. Mp 156–157 °C; $[\alpha]_D$ −12.7° (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.41–1.31 (m, 3H), 1.22 (d, J=14.6 Hz, 9H), 1.60 (d, J=9.2 Hz, 3H), 5.09 (m, 1H), 5.18 (m, 1H), 5.46 (m, 1H), 5.61 (m, 1H), 6.02 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.59; IR (KBr) 3091, 2906, 2340, 1993, 1931, 1439 1070 cm^{-1}; FAB-MS (NBA): *m*/*z* 329 (M^+-H); HRMS: *m*/*z* calcd for $C_{14}H_{20}BCrO_3P$: 329.0648. Found 329.0650. The enantiomeric excess of **3a** was determined according to the reported procedure.[8,13]

4.1.2. (*R*)-1-Adamantyl(boranato)methylphosphino-benzene tricarbonylchromium (3b). Yield: 86% as a yellow solid; mp 184–186 °C; $[\alpha]_D$ −26.3° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.41–1.31 (m, 3H), 1.22 (d, J=14.6 Hz, 9H), 1.60 (d, J=9.2 Hz, 3H), 5.09 (m, 1H), 5.17 (m, 1H), 5.41 (m, 1H), 5.61 (m, 1H), 5.97 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 29.76; IR (KBr) 3090, 2906, 2360, 1931, 1439 1070 cm^{-1}; FAB-MS: *m*/*z* 407 (M^+-H); HRMS: *m*/*z* calcd for $C_{20}H_{26}BCrO_3P$: 407.1118. Found 407.1112.

4.1.3. (*R*)-Boranato(cyclohexyl)methylphosphino-benzene tricarbonylchromium (3c). Yield: 81% as a yellow solid; mp 161–162 °C; $[\alpha]_D$ −2.2° (75% ee, *c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.41–1.31 (m, 3H), 1.22 (d, J=14.6 Hz, 9H), 1.60 (d, J=9.2 Hz, 3H), 4.76 (m, 1H), 5.25 (m, 1H), 5.54 (m, 1H), 5.71 (m, 1H), 6.00 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.59; IR (KBr) 3090, 2340, 1993, 1931, 1439 1060 cm^{-1}; FAB-MS: *m*/*z* 355 (M^+-H); HRMS: *m*/*z* calcd for $C_{16}H_{22}CrBFO_3P$: 355.1022. Found 355.1032.

4.1.4. Difluorobenzene tricarbonylchromium (6). Difluorobenzene (9.9 mL, 100 mmol) was added to a suspension of hexacarbonylchromium (2.2 g, 10 mmol) in dry THF (5 mL) and dry dibutyl ether (50 mL) at room temperature under nitrogen. The mixture was stirred at 140 °C for 12 h (gradually turned into a dark yellow solution). The resulting yellow solution was cooled to room temperature, and then passed through a short pad of Celite (Et_2O washings) to remove unreacted hexacarbonylchromium. The volatiles were removed under reduced pressure and the residue was washed with hexane to give difluorobenzene tricarbonylchromium (**6**) in 31% yield as a yellow solid. Mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 5.01 (m, 2H), 5.58 (m, 2H); IR (KBr) 1990, 1541, 1478, 1259, 1220 cm^{-1}; FAB-MS: *m*/*z* 250 (M^+); HRMS: *m*/*z* calcd for $C_9H_4CrF_2O_3$: 249.9534. Found 249.9554.

4.1.5. 2-(Boranato(*tert*-butyl)methylphosphino)fluorobenzene tricarbonylchromium (7). To a solution of **2a** (182 mg, 1.54 mmol) in THF (1.5 mL) was added *sec*-BuLi (1.0 M in hexane solution, 1.54 mL, 1.54 mmol) at −78 °C under nitrogen atmosphere, and the reaction mixture was stirred for 1 h. To this mixture was added difluorobenzene tricarbonyl chromium (**6**) (175 mg, 0.7 mmol) in THF (2.1 mL) at −40 °C, and the mixture was stirred for 20 h at intact temperature. The reaction was quenched with 1 M

HCl aq. and the mixture was extracted three times with AcOEt. The combined extracts were washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (AcOEt/hexane, 1:5) to give **7** (131 mg, 77% yield) as yellow crystal. Mp 162–163 °C; $[\alpha]_D$ −19.1° (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.41–1.31 (m, 3H), 1.22 (d, $J=14.6$ Hz, 9H), 1.60 (d, $J=9.2$ Hz, 3H), 4.76 (dt, $J=2.8$, 6.4 Hz, 1H), 5.25 (dt, $J=1.8$, 6.0 Hz, 1H), 5.54 (dq, $J=0.9$, 5.0 Hz, 1H), 5.71 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.59; IR (KBr) 3091, 2383, 1993, 1512, 1475, 1211 cm^{-1}; FAB-MS: *m/z* 347 (M^+-H); HRMS: *m/z* calcd for $C_{14}H_{18}BCrFO_3P$: 347.0479. Found 347.0485.

epi-**7**. Yield: 12%; mp 161–162 °C; $[\alpha]_D$ −20.5° (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.31–0.95 (m, 3H), 1.21 (d, $J=14.6$ Hz, 9H), 1.73 (dd, $J=2.7$, 10.3 Hz, 3H), 4.84 (dt, $J=3.1$, 6.3 Hz, 1H), 5.18 (m, 1H), 5.70 (m, 1H), 6.11 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.94; IR (KBr) 3089, 2384, 1993, 1513, 1475, 1211, 1070 cm^{-1}; FAB-MS: *m/z* 347 (M^+-H); HRMS: *m/z* calcd for $C_{14}H_{18}BCrFO_3P$: 347.0479. Found 347.0498.

4.1.6. 2-(*tert*-Butylmethylphosphino)fluorobenzene tricarbonylchromium (9). A mixture of 2-(boranato(*tert*-butyl)methylphosphino)fluorobenzene tricarbonyl-chromium (**7**) (34.8 mg, 0.1 mmol) and 1-methylpyrrolidine (1 mL, 10 mmol) was stirred under nitrogen atmosphere at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:5) to give 2-(*tert*-butyl)methylphosphinofluorobenzene tricarbonyl-chromium (**9**) as a yellow solid. Yield: 90%; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 1.04 (d, $J=12.4$ Hz, 9H), 1.32 (d, $J=5.5$ Hz, 3H), 4.84 (m, 1H), 5.30 (m, 1H), 5.47 (m, 1H), 5.59 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ −21.0 (d, $J_{PF}=16.0$ Hz).

4.1.7. 1-Boranato(*tert*-butyl)methylphosphino-2-methylbenzene (10). To a solution of 2-(*tert*-butylmethylphosphino)fluorobenzene tri-carbonyl-chromium (**9**) (16.7 mg, 0.05 mmol) in THF (1 mL) was added 1.0 M methyllithium (0.1 mL, 0.1 mmol) or 1.0 M methylmagnesium bromide (0.1 mL, 0.1 mmol) under nitrogen atmosphere for 20 h at −40 °C. The reaction was quenched with 1 M HCl aq., and the mixture was extracted three times with AcOEt. The combined extracts were washed with saturated $NaHCO_3$, water, and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in THF (1 mL). To this solution was added borane-tetrahydrofuran complex (1 M, 0.15 mL, 0.15 mmol) under nitrogen atmosphere at 0 °C, and the mixture was stirred for 3 h. The mixture was exposed to air under irradiation with sunlight for 3 h. It was purified by chromatography on silica gel (AcOEt/hexane, 1:5) to give **10** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.40–1.10 (m, 3H) 1.11 (d, $J=12.3$ Hz, 9H), 1.43 (d, $J=9.2$ Hz, 3H), 2.67 (s, 3H), 7.15–7.19 (m, 2H), 7.32 (m, 1H), 7.50–7.53 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 33.5; IR (KBr) 2977, 2370, 1604, 1474, 1215, 1080, 884 cm^{-1}; FAB-MS: *m/z* 207 (M^+-H); HRMS: *m/z* calcd for $C_{12}H_{21}BP$: 207.1474. Found 207.1482.

4.1.8. 1-Boranato(*tert*-butyl)methylphosphino-2-butylbenzene (11). Yield: 75% as a white solid; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.40–1.12 (m, 3H), 0.95–1.00 (m, 1H), 1.03–1.06 (d, $J=12.3$ Hz, 9H), 1.08–1.37 (m, 6H), 1.31 (d, $J=5.5$ Hz, 3H), 1.67–1.87 (m, 2H), 7.11–7.18 (m, 2H), 7.31 (m, 1H), 7.52–7.54 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.20; IR (KBr) 3080, 2377, 1439, 1211, 1070, 885 cm^{-1}; FAB-MS: *m/z* 249 (M^+-H); HRMS: *m/z* calcd for $C_{15}H_{27}BP$: 249.2022. Found 249.2026.

4.1.9. 1-Boranato(*tert*-butyl)methylphosphino-2-cyclohexyl-benzene (12). Yield: 69% as a white solid; mp 77–79 °C; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.43–1.12 (m, 3H), 0.83–0.91 (m, 3H), 0.97–1.01 (m, 2H), 1.11 (d, $J=12.3$ Hz, 9H), 1.34 (d, $J=7.3$ Hz, 3H), 1.45–1.51 (m, 2H), 1.67–1.83 (m, 4H), 6.89 (dd, $J=8.8$ Hz, 1H), 7.07–7.12 (m, 1H), 7.43–7.46 (m, 1H), 7.52–7.54 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 33.42; IR (KBr) 3353, 2962, 2340, 1604, 1148, 1070, 817 cm^{-1}; FAB-MS: *m/z* 275 (M^+-H); HRMS: *m/z* calcd for $C_{17}H_{29}BP$: 275.2100. Found 275.2118.

4.1.10. 1-Boranato(*tert*-butyl)methylphosphino-(2-phenylthio)benzene (14). Yield: 40% as a white solid; mp 113–114 °C; $[\alpha]_D$ −13.5° (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.40–1.12 (m, 3H), 1.13 (dd, $J=2.8$, 14.7 Hz, 9H), 1.81 (dd, $J=2.8$, 12.8 Hz, 3H), 6.84–6.88 (m, 1H), 6.99–7.12 (m, 2H), 7.29–7.33 (m, 1H), 7.42–7.54 (m, 2H), 7.69–7.72 (m, 1H), 7.97–8.01 (m, 2H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 30.12; IR (KBr) 2361, 1604, 1148, 1080, 883 cm^{-1}; FAB-MS: *m/z* 301 (M^+-H); HRMS: *m/z* calcd for $C_{17}H_{23}BPS$: 301.1454. Found 301.1476.

4.1.11. 1-Boranato(*tert*-butyl)methylphosphino-(2-*tert*-butylthio)benzene (15). Yield: 55% as a white solid; mp 121–123 °C; $[\alpha]_D$ −18.2° (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.41–1.10 (m, 3H), 1.07 (d, $J=14.7$ Hz, 9H), 1.25(d, $J=6.0$ Hz, 9H), 2.12 (d, $J=13.3$ Hz, 3H), 7.45–7.54 (m, 2H), 7.65–7.72 (m, 2H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 25.22; IR (KBr) 2379, 1602, 1461, 1070, 878 cm^{-1}; FAB-MS: *m/z* (M^+-H) 281;HRMS: *m/z* calcd for $C_{15}H_{27}BPS$: 281.1664. Found 281.1667.

4.1.12. 1-Boranato(*tert*-butyl)methylphosphino-(2-phenylseleno)benzene (16). Yield: 52% as a white solid; mp 87–89 °C; $[\alpha]_D$ −9.2° (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.39–1.10 (m, 3H), 1.15 (d, $J=15.6$ Hz, 9H), 1.81 (dd, $J=2.8$, 12.8 Hz, 3H), 6.83–6.88 (m, 1H), 7.04–7.12 (m, 2H), 7.51–7.56 (m, 2H), 7.65–7.71 (m, 2H), 7.95–8.03 (m, 2H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 37.20; IR (KBr) 2374, 1604, 1474, 1080, 884 cm^{-1}; FAB-MS: *m/z* 349 (M^+-H); HRMS: *m/z* calcd for $C_{17}H_{23}BPSe$: 349.0796. Found 349.0811.

4.1.13. 1-Boranato(*tert*-butyl)methylphosphino-2-cyanobenzene (17). Yield: 91% as a white solid; ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.39–1.11 (m, 3H), 1.19 (d, $J=16.0$ Hz, 9H), 1.82 (dd, $J=2.8$, 12.8 Hz, 3H), 7.06–7.12 (m,

1H), 7.29–7.33 (m, 1H), 7.50–7.54 (m, 1H), 7.97–7.99 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 34.49; IR (KBr) 2380, 1604, 1470, 1080, 883 cm^{-1}.

4.1.14. 1-Azide-2-boranato(*tert*-butyl)methylphosphinobenzene (18). Yield: 68% as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.40– 1.10 (m, 3H), 1.20 (d, J= 16.0 Hz, 9H), 1.82 (dd, J=2.8, 12.8 Hz, 3H), 7.08 (m, 1H), 7.29–7.33 (m, 1H), 7.51–7.54 (m, 1H), 7.97 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 27.30; IR (KBr) 2340, 1604, 1477, 1148, 884 cm^{-1}.

4.1.15. 1-Boranato(*tert*-butyl)methylphosphino-2-oxazolinobenzene (19). A mixture of 1-boranato(*tert*-butyl)-methylphosphino-2-cyanobenzene (**17**) (11 mg, 0.05 mmol), ethanolamine (0.90 mL, 0.15 mmol), anhydrous $ZnCl_2$ (0.78 mg, 0.005 mmol), and anhydrous chloro-benzene (0.3 mL) was stirred at 110 °C for 40 h, and it was passed through a short silica gel column with CH_2Cl_2. The solvent was removed under reduced pressure to give **19** in 42% yield (5.5 mg, 0.021 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.28–1.12 (m, 3H), 1.15 (d, J= 15.7 Hz, 9H), 1.47 (dd, J=2.5, 11.8 Hz, 3H), 3.86 (m, 2H), 4.22 (m, 2H), 7.10–7.12 (m, 1H), 7.30–7.33 (m, 1H), 7.51–7.54 (m, 1H), 7.76–7.88 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 30.02.

4.1.16. 1-Boranato(*tert*-butyl)methylphosphino-2-(4′,5′-bis(methoxycarbonyl))benzene (20). Dimethyl acetylene dicarboxylate (18.4 μL, 0.15 mmol) was added to a solution of 1-azide-2-boranato(*tert*-butyl)methylphosphino benzene (**18**) (11.7 mg, 0.05 mmol) in anhydrous toluene (0.3 mL). The mixture was heated at 130 °C for 40 h and cooled to ambient temperature. The reaction mixture was passed through a short silica gel column with AcOEt. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:5) to give **20** in 66% yield (12.4 mg, 0.03 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.30–1.08 (m, 3H), 1.15 (d, J=15.9 Hz, 9H), 1.46 (dd, J=2.8, 12.4 Hz, 3H), 3.86 (s, 3H), 4.02 (s, 3H), 7.15 (m, 1H), 7.24–7.28 (m, 1H), 7.49–7.51 (m, 1H), 7.76 (m, 1H); ^{31}P NMR ($CDCl_3$, 400 MHz, 25 °C) δ 32.14.

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