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Tetrahedron

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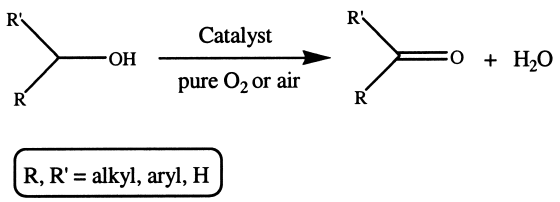

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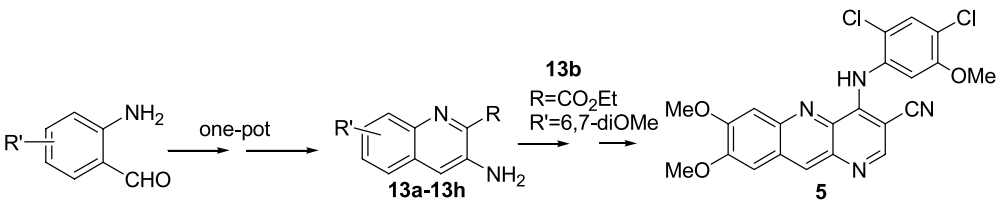

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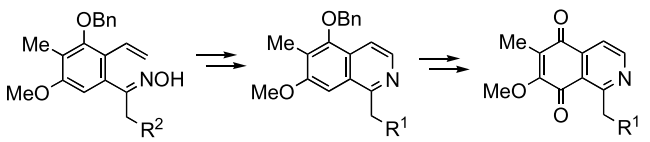

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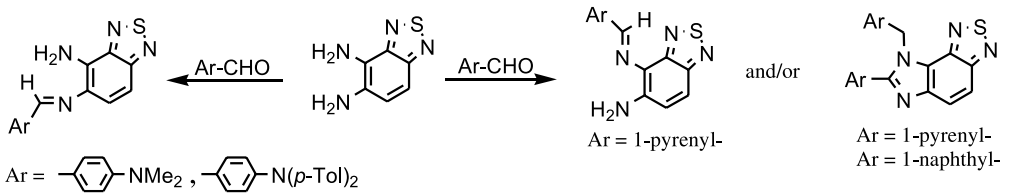

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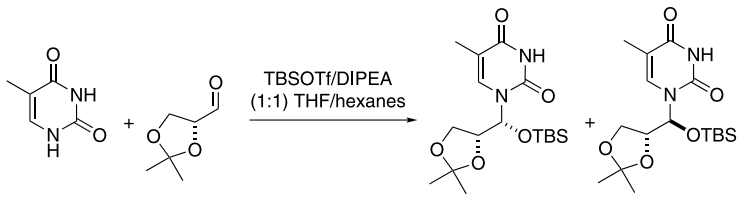

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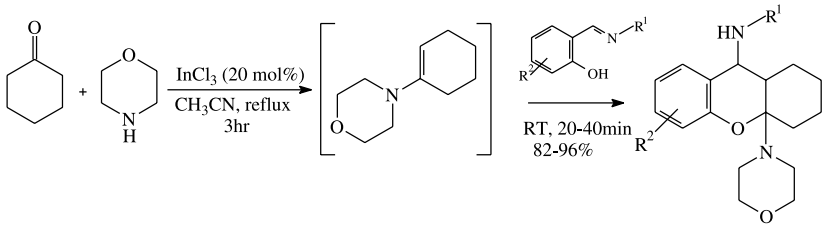

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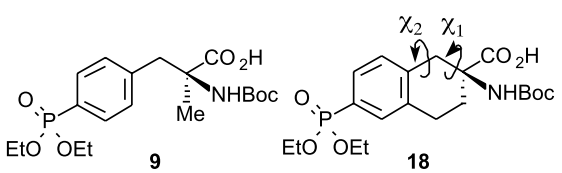

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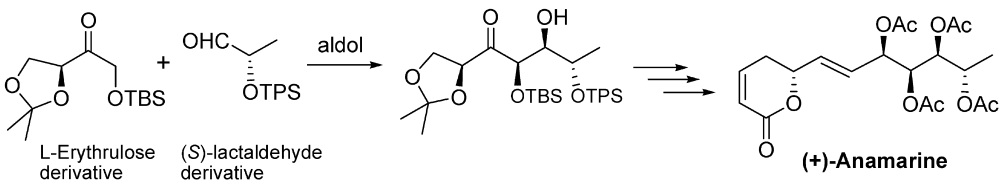

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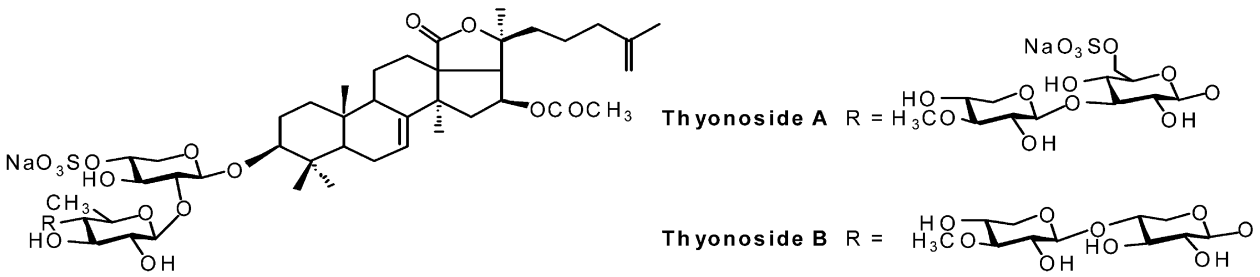

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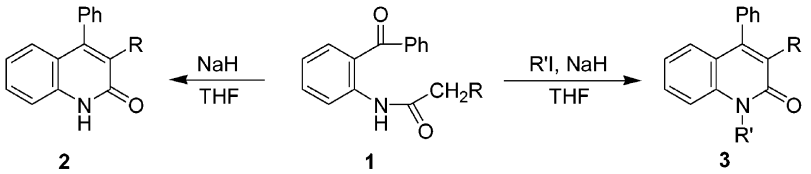

The reaction of **1** (R=H, CH_3, *n*-C_5H_{11}) with NaH gave **2** in 62–83% yields, and the reaction in the presence of R′I gave **3** (R′=Me, Et, *n*-Octyl) in 75–95% yields.

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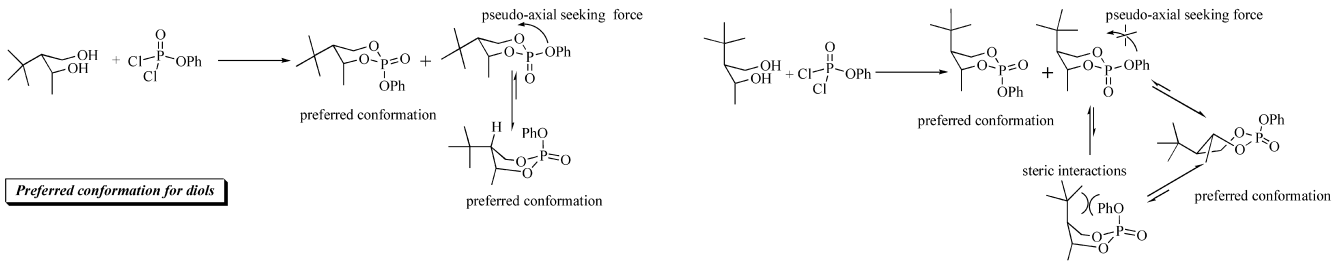

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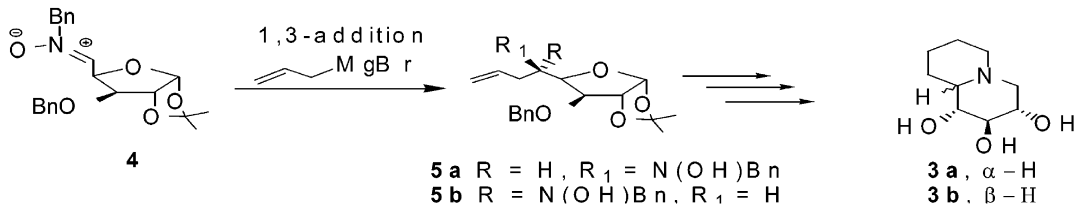

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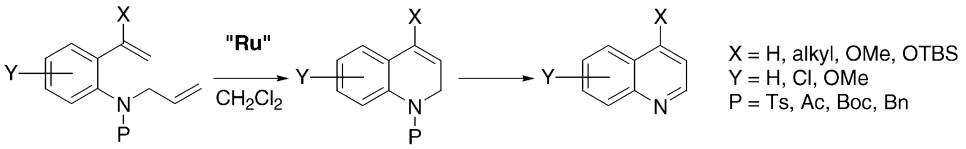

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U. Deva Priyakumar, M. Punnagai, G. P. Krishna Mohan and G. Narahari Sastry*

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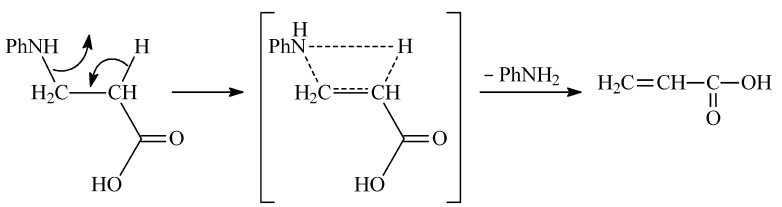

Thermal gas-phase elimination of 3-(*N*-phenylamino)propanoic acid together with four of its aryl analogues reveal the formation of acrylic acid in addition to aniline or substituted anilines. Theoretical study using an ab initio SCF method lend support to a reaction pathway involving a 4-membered cyclic transition state.

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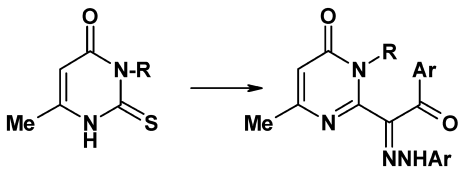

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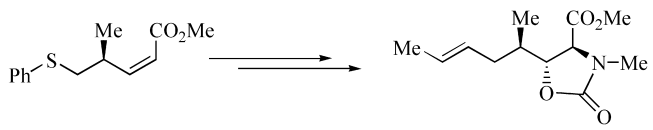

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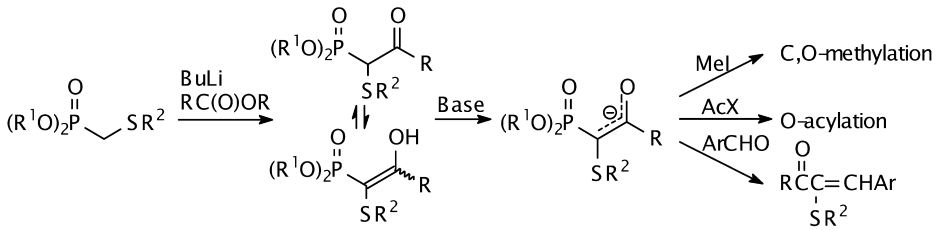

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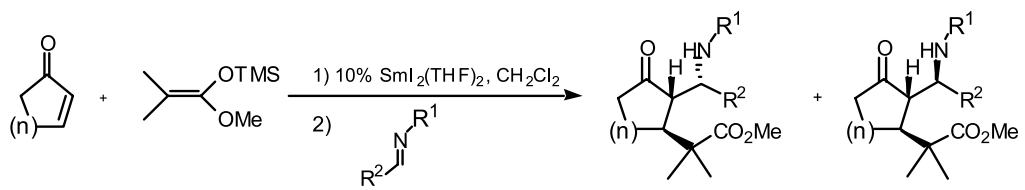

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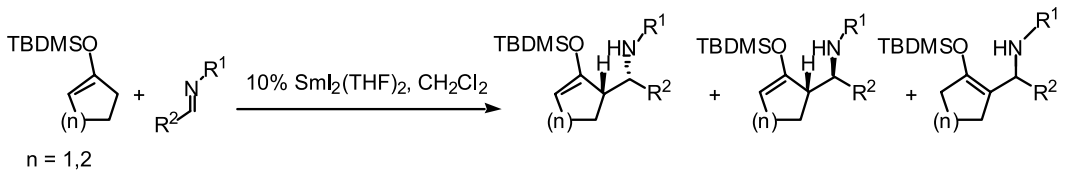

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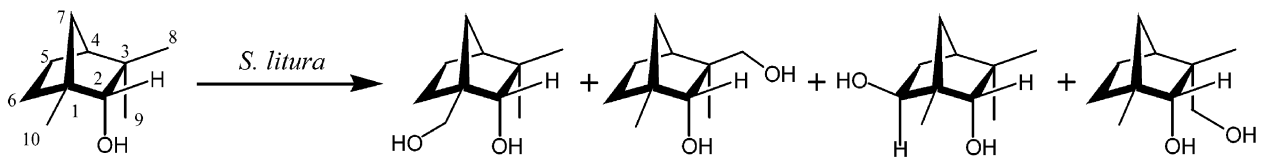

Biotransformation of (+)-(1*R*,2*S*)-fenchol in *Spodoptera litura* larvae has been investigated and isolated four metabolites (three new).

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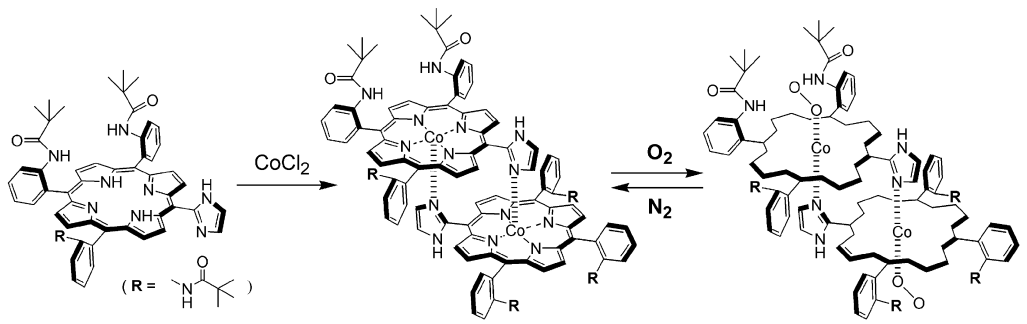

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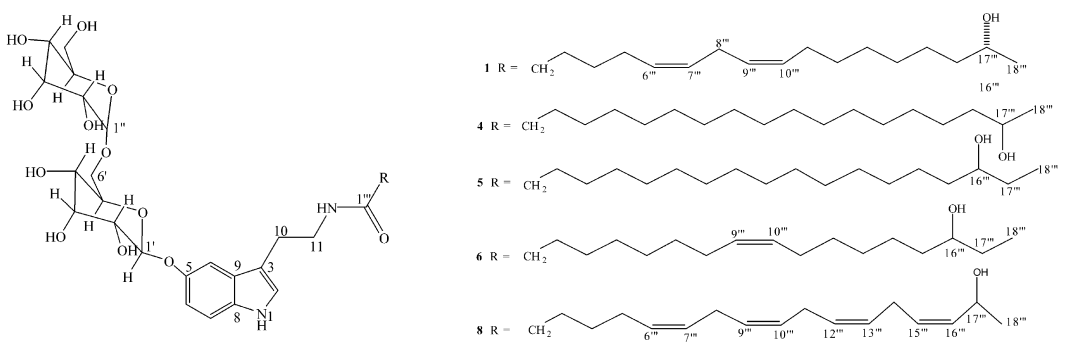

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Recent developments in the aerobic oxidation of alcohols

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Department of Chemistry and Institute for Research in Materials, Dalhousie University, Halifax, NS, Canada B3H 4J3

Received 12 December 2003

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1. Introduction

The oxidation of alcohols to their corresponding aldehydes and ketones is of significant importance in organic chemistry, both for fundamental research and industrial manufacturing.[1–3] The world-wide annual production of carbonyl compounds is over 10^7 tonnes and many of these compounds are produced from the oxidation of alcohols.[4]

The oxidation of alcohols is traditionally carried out with stoichiometric amounts of oxidants such as chromium reagents,[5–9] permanganates,[10,11] ruthenium (VIII) oxide,[12,13] TPAP/NMO (tetra-*N*-propylammonium perruthenate/*N*-methyl-morpholine-*N*-oxide),[14,15] activated dimethyl sulfoxide (DMSO) reagents,[16] or Dess–Martin periodinane reagent.[17] Unfortunately, these methods often require one or more equivalents of these relatively expensive oxidizing agents. Some of these processes also generate equal amounts of metal waste. Furthermore, oxidation reactions are usually carried out in halogenated organic solvents, typically chlorinated hydrocarbons, which are environmentally undesirable. Therefore, developing green, selective and efficient aerobic catalysts for the oxidation of alcohols, that can use air or pure dioxygen (O_2) as oxidants, is of paramount importance for both economic and environmental reasons (Scheme 1). These green processes produce water as the only by-product. Due to the obvious advantages of using air or dioxygen as the ultimate and stoichiometric oxidant, considerable effort has been invested in the last few years to develop novel catalysts for the aerobic oxidation of alcohols to their corresponding aldehydes and ketones. This topic has been discussed in various books and reviews, but with restrictions to specific catalytic systems.[18] The aim of this report is to give an

Keywords: Alcohol; Aerobic oxidation; Homogeneous catalysis; Heterogeneous catalysis.

Abbreviations: ARP-Pd, palladium nanoparticles dispersed on an amphiphilic resin; convn., conversion; DABCO, 1,4-diazabicyclo-[2,2,2]octane; DMF, dimethylformamide; dba, dibenzylideneacetone; DMSO, dimethyl sulfoxide; FAU, faujasite zeolite; GO, galactose oxidase; HAP, hydroxyapatite; MTBE, methyl *tert*-butyl ether; MS3Å, 3 Å molecular sieves; nbd, norbornyldiene; NaX, faujasite zeolite-X in sodium form; NMO, *N*-methyl-morpholine-*N*-oxide; Phen, 1,10-phenanthroline; PhenS*, bathophenanthroline disulfonate; PIPO, polyamine immobilized piperidinyl oxyl; PSP, polymer supported perruthenate; sel., selectivity; TEMPO, 2,2′,6,6′-tetramethylpiperidine-*N*-oxyl; TMAO, trimethylamine-*N*-oxide; TOF, turn over frequency; TON, turn over number; TPAP, tetra-propylammonium perruthenate; XPS, X-ray photoelectron spectroscopy.

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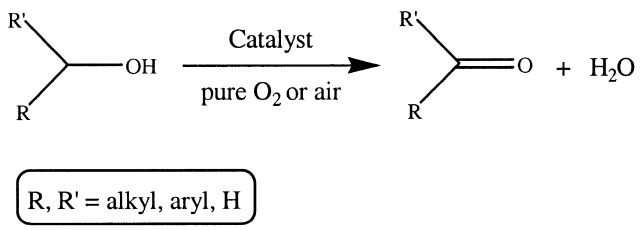


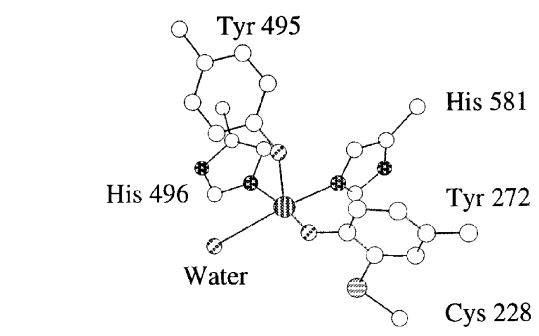
Scheme 1. Catalytic aerobic oxidation of alcohols.

overview of the recent developments in this rapidly growing area, covering both homogeneous and heterogeneous catalytic systems. The mechanistic features of some catalytic systems will be briefly discussed herein.

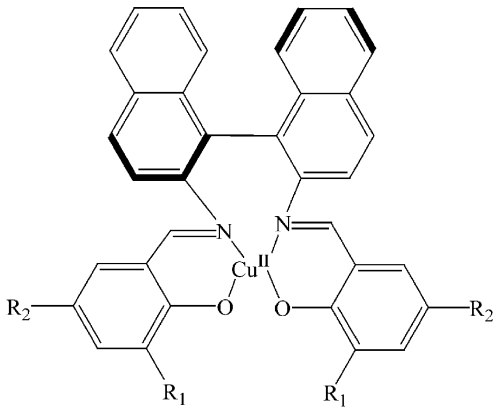
2. Homogeneous catalysis

There are several advantages to using homogeneous catalysis, including high activity and selectivity (especially enantioselectivity) since the reactants and catalysts co-exist in the same phase.

Homogeneous catalysts often have structures similar to the active sites of natural enzymes. A typical example in the study of the aerobic oxidation of alcohols is the biomimetic chemistry of the copper(II)-containing metalloprotein galactose oxidase (GO), which selectively catalyzes the aerobic oxidation of primary alcohols to aldehydes with the formation of 1 equiv. of hydrogen peroxide (Eq. 1) under very mild conditions.[19,20] The active centre of GO is a single copper(II) ion coordinated with a tyrosinate anion, a (thioether-modified) tyrosyl radical and two histidine residues, as shown in Scheme 2.[21,22] The mechanism of the oxidation of primary alcohols by GO has been thoroughly studied and defined. Initially, the alcohol coordinates to the Cu(II) ion, and then the O-coordinated alkoxide ligand undergoes H-abstraction from the α-carbon atom of the alkoxide by the coordinated tyrosyl radical. This is considered to be the rate-determining step, leading to the generation of a bound ketyl radical anion and tyrosine. The ketyl radical ligand is then intramolecularly converted to the aldehyde through one-electron oxidation with concomitant formation of a Cu(I) species. Re-oxidation of the latter by dioxygen regenerates the active Cu(II)-tyrosyl form of the enzyme and H_2O_2, and the process is thus stoichiometric in dioxygen.[23] A great number of model compounds containing Cu(II)-phenoxyl, having a structure around the Cu(II) ion similar to that in GO, have been synthesized and characterized by measuring their catalytic properties for the aerobic oxidation of alcohols.[24] Scheme 3 presents a typical model compound. Recently, Stack and co-workers have published a review paper with the title 'Biomimetic modeling of copper oxidase reactivity'.[18c] Therefore, discussion of the synthesis and catalysis of copper(II)-phenoxyl modeling complexes is abbreviated in this report. However, it is necessary to point out that the catalytic activity of the synthesized Cu(II) model complexes is still low and is mostly limited to activated (e.g., benzylic and allylic) primary alcohols.[24] Furthermore, base is required.



Scheme 2. Copper active site of GOase at pH 7.0.[22]



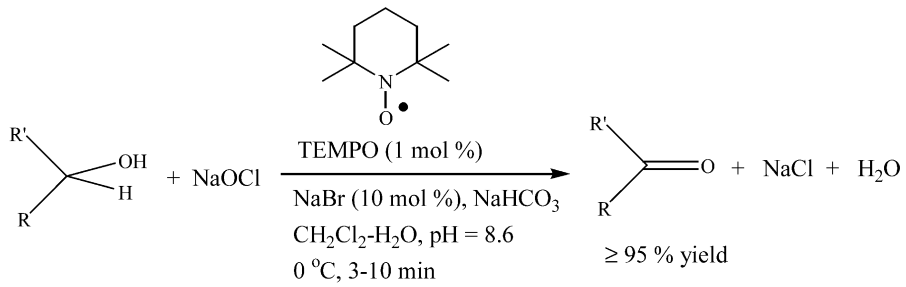
Scheme 3. A typical copper(II)-phenoxyl complex with a structure similar to GO, where R_1=SPh and R_2=*tert*-butyl.[24a]

$$RCH_2OH + O_2 \xrightarrow{[GO]} RCHO + H_2O_2 \quad (1)$$

The mechanistic studies involving the GO enzyme clearly indicate that the dioxygen molecule is actually activated by the Cu(I) species. Therefore, it was anticipated that Cu(I)-containing complexes could be useful as aerobic oxidation catalysts. Markó and co-workers successfully demonstrated that a CuCl/1,10-phenanthroline (Phen) complex is able to catalytically oxidize activated primary alcohols to aldehydes in the presence of appropriate solvents, additives and base (usually K_2CO_3).[25] However, both saturated primary and secondary aliphatic alcohols, for example, unactivated alcohols, proved to be poor substrates. The conversions were only modest even though a larger amount of CuCl/Phen catalyst (20 mol%) was employed.[25]

2.1. M/TEMPO Complexes

Nitroxyl radicals are well-established catalysts for oxidation processes. They are increasingly applied on both industrial and laboratory scales for the oxidation of alcohols.[26,27] Typically, the oxidation reactions are carried out in the presence of 1 mol% of 2,2′,6,6′-tetramethylpiperidine-*N*-oxyl (also known as TEMPO) and a stoichiometric amount of sodium hypochlorite (bleach) as shown in Eq. 2.[28] The oxoammonium cation, which is formed via the oxidation of TEMPO with hypochlorite, is the active oxidant. Oxidation of alcohols gives the corresponding carbonyl compounds and the reduced form of TEMPO (e.g., the hydroxylamine,



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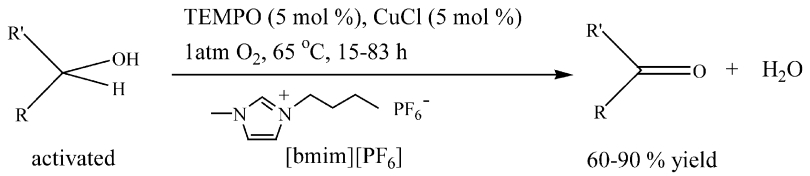


(3)

or TEMPOH). The latter is then re-oxidized by hypochlorite to regenerate the oxoammonium cation. Sodium bromide (10 mol%) is usually exploited as a co-catalyst, as the re-oxidation of TEMPOH is more favorable with hypobromite, and the hypobromite is steadily produced via oxidation of the sodium bromite with hypochlorite.[28]

In 1984, Semmelhack et al. first reported that the CuCl/TEMPO catalytic system can catalyze the aerobic oxidation of activated primary alcohols using dioxygen as a stoichiometric oxidant.[29] A turn over frequency (TOF) of up to 9.6 h^{-1} was reached in the oxidation of *p*-methoxybenzyl alcohol at room temperature. The catalytic properties are significantly enhanced if the reaction is conducted at high temperature with a co-catalyst, in both biphasic and ionic liquid conditions.[30,31] For instance, a CuCl/TEMPO catalytic system aerobically oxidizes both activated primary and secondary alcohols to the corresponding aldehydes and ketones in the ionic liquid [bmim][PF_6], for example, Eq. 3.[31] The product was isolated by a simple extraction with organic solvent, and the ionic liquid can be recycled or re-used. However, the oxidation of unactivated aliphatic and cyclic alcohols is slower and incomplete. No oxidation is observed when the solubility of alcohols in the ionic solvent is poor.[31] Very recently, Sheldon and co-workers reported that [Cu(II)-(2,2′-bipyridine)]/TEMPO systems selectively catalyze the aerobic oxidation of primary alcohols to aldehydes at room temperature with a base as co-catalyst.[32] However, these catalysts are completely inert to secondary alcohols.

Recently, the catalytic properties of TEMPO-based aerobic oxidation catalysts have been found to be significantly enhanced if Cu(I)Cl is replaced by other transition metal compounds. For example, Sheldon and co-workers reported that a $Ru(PPh_3)_3Cl_2$/TEMPO system can smoothly oxidize both activated and unactivated alcohols to the corresponding aldehydes and ketones with a selectivity of over 99% in a reasonable length of time (2.5–7 h), for example, Eq. 4 and entries 1–5 in Table 1.[33] Interestingly, primary alcohols were found to be more active than secondary alcohols in this catalytic system: in a competitive oxidation of 1-octanol and

Table 1. Selected aerobic oxidation results with $Ru(PPh_3)_3Cl_2$/TEMPO and Mn(II)-Co(II)/TEMPO catalytic systems[32,35]

Entry	Substrate	Product	Time (h)	Temperature (°C)	Convn. (%)[a]
1[b]	Benzyl alcohol	Benzaldehyde	2.5	100	>99 (90)
2[c]	2-Octanol	2-Octanone	7	100	98 (90)
3[d]	1-Octanol	Octanal	7	100	85
4[c]	Cyclooctanol	Cyclooctanone	7	100	92
5[c]	2-Adamantanol	2-Adamantanone	6	100	98
6[d]	2-Octanol/1-octanol	2-Octanone/octanal	7	100	10/80
7[e]	Benzyl alcohol	Benzaldehyde	10	20	(98)
8	1-Heptanol	Heptanal	6	40	(97)
9	2-Nonanol	2-Nonanone	5	40	(100)
10	Cyclohexanol	Cyclohexanone	9	20	(96)
11	2-Adamantanol	2-Adamantanone	6	20	(97)

Reaction conditions for entries 1–6 (Ref. 32): 15 mmol of substrate, $Ru(PPh_3)_3Cl_2$/TEMPO mole ratio 1:3, 30 mL PhCl, 10 mL min^{-1} O_2/N_2 (8:92; v/v), p=10 bar, T=100 °C.

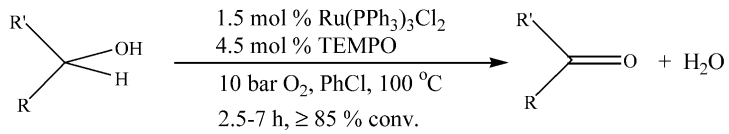
[a] Conversions based on GC results (selectivity >99% in all cases); numbers in parentheses are isolated yields.

[b] Ru(II)=0.075 mmol.

[c] Ru(II)=0.15 mmol.

[d] Ru(II)=0.30 mmol, 1 atm of dioxygen.
Reaction conditions for entries 7–11 (Ref. 35): 12.5 mmol alcohol, 1.25 mmol TEMPO, 0.25 mmol $Mn(NO_3)_2$, 0.25 mmol $Co(NO_3)_2$ in AcOH (12.5 mL) and 1 atm of dioxygen.

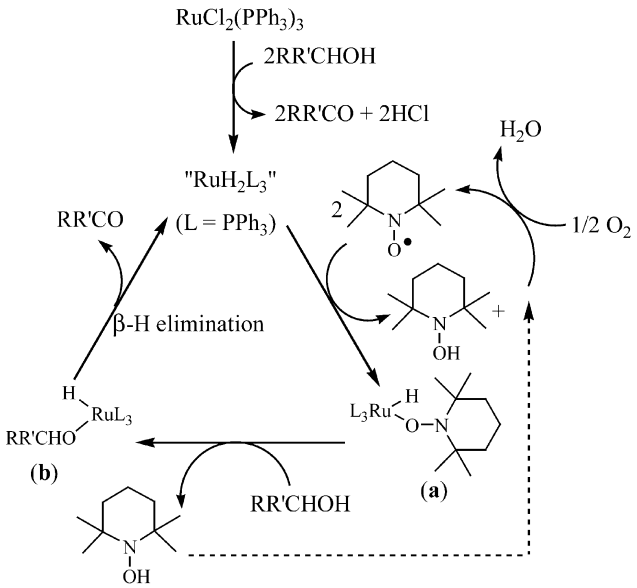
[e] 1 atm of air.



(4)

2-octanol, the conversion for 1-octanol was 80%, while it was only 10% for 2-octanol (entry 6, Table 1). However, these oxidations must be carried out at relatively high pressure (10 bar) and temperature (100 °C), and an intrinsically oxidatively unstable triphenylphosphine ligand is required. Furthermore, alcohols containing additional heteroatoms, that is, S, N and O, are inert due to their coordination to, and poisoning of, the ruthenium ion leading to the deactivation of catalyst.

Mechanistic studies suggest that the formation of ruthenium hydride ($RuH_2(PPh_3)_3$) is the key intermediate for the aerobic oxidation of alcohols with the $Ru(PPh_3)_3Cl_2$/TEMPO catalyst (Scheme 4):[33d] initially, the alcohol substrate is dehydrogenated by the $Ru(PPh_3)_3Cl_2$, giving the corresponding carbonyl compound and a ruthenium hydride. The latter then reacts with 2 equiv. of TEMPO to produce TEMPOH and complex, (a) in Scheme 4, which contains a hydride and a piperidinyloxyl ligand. The latter is displaced by an alcohol to form another TEMPOH molecule and an alkoxy ruthenium hydride, (b) in Scheme 4. The alkoxy ruthenium hydride then undergoes β-hydride elimination, releasing the carbonyl compound and regenerating the ruthenium hydride. TEMPO is regenerated via rapid oxidation of TEMPOH by dioxygen with concomitant formation of water by-product.



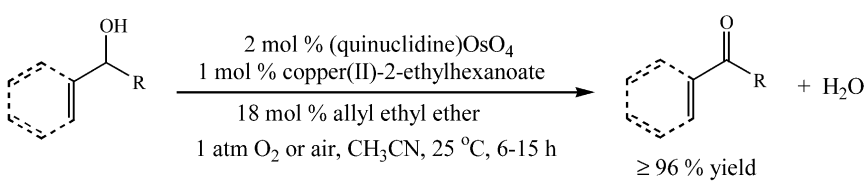
Scheme 4. Suggested mechanism for the $Ru(PPh_3)_3Cl_2$/TEMPO-catalyzed aerobic oxidation of alcohols.[33d]

Hydroquinone can also be used in oxidations of this type, replacing TEMPO. Ishii and co-workers reported that $Ru(PPh_3)_3Cl_2$ is an active catalyst in the presence of hydroquinone and K_2CO_3.[34] The $Ru(PPh_3)_3Cl_2$/hydroquinone/K_2CO_3 system can efficiently convert a variety of alcohols to the corresponding aldehydes and ketones at 60 °C and 1 atm of dioxygen.[34] For instance, the oxidation of 1-decanol proceeds smoothly with catalytic amounts of $Ru(PPh_3)_3Cl_2$ (20 mol%), hydroquinone (20 mol%), and K_2CO_3 (3 mol%) in trifluorotoluene solvent under 1 atm of dioxygen at 60 °C for 20 h. The conversion is 90% with over 99% selectivity for decanal production.

Minisci and co-workers reported that the aerobic oxidation of both activated and unactivated alcohols can be performed under relatively mild conditions, such as in 1 atm of dioxygen or even 1 atm of air at temperatures of 20–40 °C, if copper is replaced by a bimetallic salt, such as Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates.[35] Some of their oxidation results are given in entries 7–11 of Table 1. Benzyl alcohol was oxidized to benzaldehyde with an isolated yield of 98% in 10 h at 20 °C in 1 atm of dioxygen (Table 1, entry 7). A primary aliphatic alcohol, 1-heptanol, was oxidized to heptanal in an isolated yield of 97% in 6 h at 40 °C (Table 1, entry 8). Unactivated secondary alcohols were oxidized to their corresponding ketones (Table 1, entries 9–11). For example, the oxidation of cyclohexanol gave an isolated yield of 96% of cyclohexanone in 9 h at 20 °C (Table 1, entry 10). However, acetic acid had to be used as solvent as non-acidic media, such as acetonitrile, resulted in almost no oxidation. It should be noted that relatively large amounts of somewhat expensive TEMPO (10 mmol%) are necessary for these oxidation reactions.

2.2. OsO_4-Copper catalysts

Other efficient bimetallic systems include OsO_4–Cu(I), OsO_4–Cu(II), Mo(VI)–Cu(II), and Mo(VI)–Fe(II).[36] Osborn and co-workers reported that OsO_4–CuCl is an efficient catalytic system for the aerobic oxidation of primary allylic and benzylic alcohols to the corresponding aldehydes in the presence of pyridine base and molecular sieves.[36a,b] Activation of OsO_4 with quinuclidine and copper(II)-2-ethylhexanoate was found to significantly improve both reactivity and selectivity in the aerobic



(5)

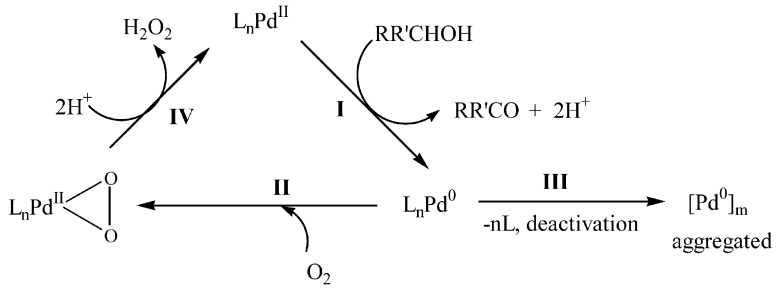
oxidation of alcohols.[36c] Both allylic and benzylic alcohols oxidized completely in acetonitrile solvent within 6–15 h at room temperature (e.g., Eq. 5), and the products were easily isolated. A $K_2[OsO_2(OH)_4]$/1,4-diazabicyclo[2,2,2]octane (DABCO) system has also been investigated for potential application in the aerobic oxidation of alcohols.[37]

2.3. Pd(II) Catalysts

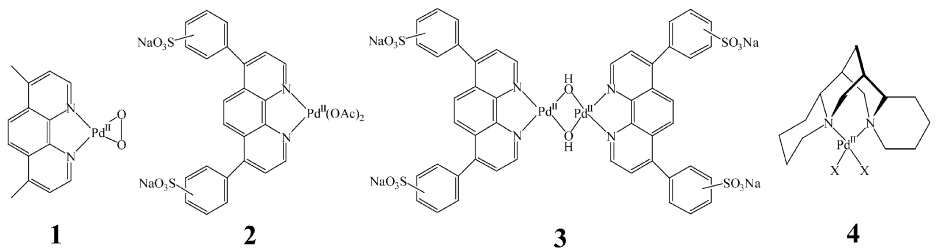
The Wacker process, that is, Pd/Cu-catalyzed aerobic oxidation of ethylene to acetaldehyde (Eq. 6), was developed more than 40 years ago,[38] but the use of palladium as catalyst for the aerobic oxidation of alcohols was first reported by Schwartz in 1977.[39] Since then, considerable research has resulted in the development of more selective and efficient Pd(II)-containing catalytic systems.[33,40–50] For example, a catalytic system of $Pd(OAc)_2$/dimethyl sulfoxide (DMSO) was found to effectively and selectively oxidize allylic and benzylic alcohols to the corresponding aldehydes and ketones.[42] The reaction rates and yields are further improved by adding appropriate bases such as Na_2CO_3. The success of DMSO as the solvent suggested several mechanistic possibilities, including the prospect that DMSO itself participates in the redox process. DMSO is a stoichiometric oxidant in a variety of chemical and biological oxidation reactions, yielding dimethyl sulfide as by-product.[16] However, Stahl and co-workers have recently proposed an oxidation mechanism excluding the involvement of DMSO in the redox process (Scheme 5).[45] The Pd(II)-catalyzed aerobic oxidation of alcohols likely proceeds through a reduction of Pd(II) to Pd(0) by the alcohol. Pd(0) then reacts with dioxygen to produce a palladium peroxo intermediate (step II). The role of DMSO as a solvent corresponds to its ability to coordinate palladium(0), preventing the formation of aggregated palladium metal (step III).[45b] This oxidation mechanism is supported by several facts:[45a,b] successful separation of a structurally characterized peroxopalladium(II) species (e.g., **1** in Scheme 6) in reacting bathocuproine–palladium(0) complex with dioxygen; a first order dependence on dioxygen pressure; a substantial negative entropy of activation, $\Delta S^{\neq} = -180\ \mathrm{J\ K^{-1}\ mol^{-1}}$. The exclusion of DMSO in the redox process is also supported by the success of a $Pd(OAc)_2$/pyridine (Py) catalyst system, in which the Py ligand plays a similar role as DMSO in preventing the Pd(0) aggregation.[45c]

$$H_2C = CH_2 + 1/2O_2 \xrightarrow{\text{Pd/Cu cat.}} CH_3CHO \qquad (6)$$

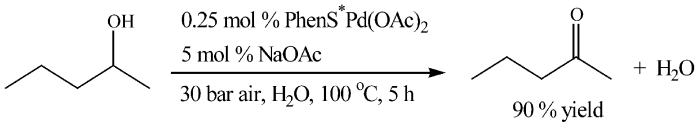
Sheldon et al. have created a novel, active and cleaner/greener catalytic system, in which the aerobic oxidation of alcohols can be carried out in water using a water-soluble bathophenanthroline disulfonate palladium complex ($PhenS^*Pd(OAc)_2$, **2** in Scheme 6 and Eq. 7) as catalyst in the presence of a small amount of sodium acetate at 100 °C under high air pressure.[46] Small secondary aliphatic and cyclic alcohols, with relatively high water solubility, are very active and are easily oxidized to the corresponding ketones using this system. For instance, 2-pentanol was completely converted to 2-pentanone in 5 h with a TOF of 80 h^{-1} (Eq. 7). Surprisingly, benzylic alcohols reacted more slowly than expected, even accounting for their low solubility in water. Lower activity was also found in the oxidation of allylic alcohols, due to the competing coordination of the olefinic double bonds to the palladium. These results are very different from the systems discussed above. For alcohols containing terminal olefinic double bonds, at a distance from the alcohol moieties, Wacker-type reactions strongly dominate. This is in contrast to the catalytic system with DMSO as solvent.[42] Furthermore, due to the use of high temperature (100 °C) and high pressure (30 bar) reaction conditions for the aqueous reactions, the formed aldehydes further oxidize to the corresponding carboxylic acids. As such, radical scavengers, such as TEMPO, are required to prevent the over-oxidation. As with many procedures, alcohols containing other functionalities, for example, N, S and multiple O atoms which are able to coordinate strongly to the palladium, were shown to be inert



Scheme 5. Oxidation mechanism for the aerobic oxidation of alcohols in $Pd(OAc)_2$/DMSO system.[45a,b]



Scheme 6. Some Pd(II) complexes.

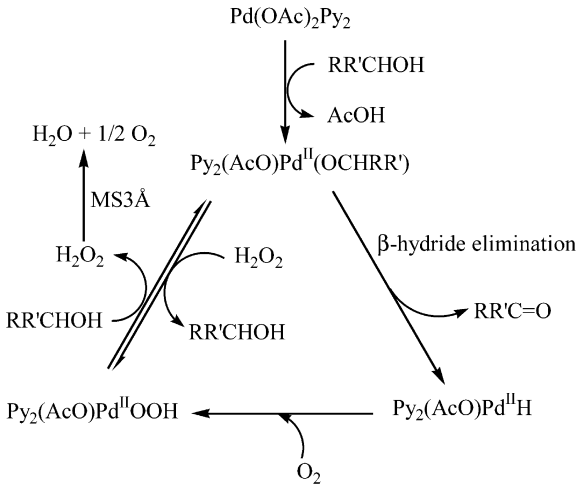


(7)

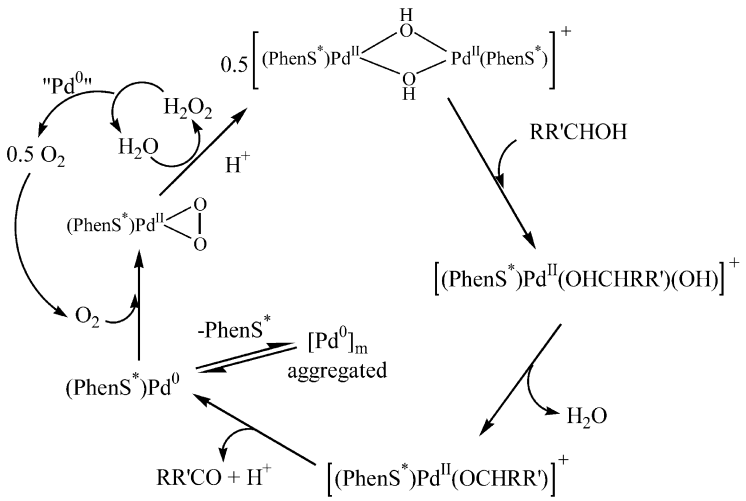
in this PhenS*Pd(OAc)$_2$ catalyst system, and alcohols with low solubilities in water were less efficient. Interestingly, the ability to recycle the catalyst solution has been demonstrated using 2-hexanol as the substrate.[46]

Mechanistic studies suggested the oxidation mechanism shown in Scheme 7,[46] which is similar to that proposed by Stahl for the Pd(OAc)$_2$/DMSO catalytic system.[45] The starting complex is believed to be a dihydroxy-bridged palladium dimer (e.g., **3** in Scheme 6) that is in equilibrium with 2 equiv. of a palladium monomer, [(PhenS*)-Pd(II)OH]$^+$. After alcohol coordination, the bridged-palladium dimer decomposes. The alcohol-coordinated Pd(II) complex undergoes a water elimination, affording a palladium alkoxide, [(PhenS*)Pd(II)OCHRR′]$^+$. The palladium alkoxy intermediate then undergoes β-elimination, the rate-determining step, affording a carbonyl compound, (PhenS*)Pd(0), and a proton. The results of mechanistic studies on the Pd(OAc)$_2$/DMSO and PhenS*Pd(OAc)$_2$/NaOAc/H$_2$O systems (e.g., Schemes 5 and 7) clearly suggest the key factor to developing more efficient and stable Pd(II)-based catalysts for the aerobic oxidation of alcohols, namely, accelerating the re-oxidation rate of palladium(0) with dioxygen and suppressing the aggregation of palladium(0), which leads to deactivation.

The Pd(II)-catalyzed aerobic oxidation of alcohols seems to be very sensitive to the nature of organic ligands and reaction media. Uemura and co-workers have demonstrated that the Pd(OAc)$_2$/pyridine/MS3Å catalytic system is more than 10 times as efficient as the Pd(OAc)$_2$/DMSO catalytic system in the aerobic oxidation of alcohols using toluene as solvent at 80 °C under anhydrous conditions.[43] Using these conditions, a variety of primary and secondary (both activated and unactivated) alcohols may be oxidized to the corresponding aldehydes and ketones with high yields. Interestingly, air can be used instead of dioxygen (with a resulting longer reaction time). The use of other palladium compounds, such as PdCl$_2$, PdCl$_2$(MeCN)$_2$, Pd(OCOCF$_3$)$_2$, Pd(PPh$_3$)$_4$, or Pd(dba)$_2$ (dba=dibenzylideneacetone), was found to be ineffective, and lower yields were observed using other solvents or bases. However, there are some limitations to using the Pd(OAc)$_2$/pyridine/MS3Å system, including lower activity in the oxidation of 1-dimethylamino-2-propanol, 1-methoxy-1-phenyl-2-ethanol or 1-phenyl-1-propynol, etc. and dominant olefin oxidation over alcohol oxidation in the presence of trace amounts of water. This difference in reactivity was attributed to an alternative mechanism as shown in Scheme 8. In contrast to the Pd(OAc)$_2$/DMSO and PhenS*Pd(OAc)$_2$ systems, the valence state of the palladium(II) ion does not change in the catalytic cycle. The reaction starts by binding the alcohol to the Pd(II)-pyridine complex, giving the Pd(II)-alkoxide. The latter then undergoes β-hydride elimination, affording



Scheme 8. Suggested aerobic oxidation mechanism for Pd(OAc)$_2$/-pyridine/MS3Å system.[43]



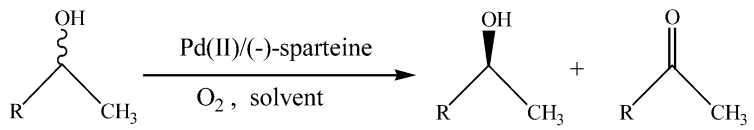
Scheme 7. Reaction cycle proposed for PhenS*Pd(OAc)$_2$-catalyzed alcohol oxidation.[46]

the corresponding Pd(II)-hydride species. This active hydride species reacts with dioxygen, forming Pd(II)-hydroperoxide. The Pd(II)-alkoxide complex is regenerated via ligand exchange of Pd(II)-hydroperoxide with alcohol, releasing H_2O_2 as by-product.[43] The in situ formation of H_2O_2 has been demonstrated: its decomposition into water and dioxygen is promoted by molecular sieves. The removal of H_2O_2 by the use of molecular sieves accelerates the oxidation of alcohols as its competition with the alcohol for binding to the palladium(II) ion is eliminated. The mechanism is also supported by an dioxygen uptake experiment.[43b] However, it is worth pointing out that, in the absence of molecular sieves, the $Pd(OAc)_2$/pyridine-catalyzed aerobic alcohol oxidation can proceed via a different mechanism.[45c]

The successes of the Pd(II)-catalyzed aerobic oxidation of alcohols using bidentate nitrogen ligands inspired research into the oxidative kinetic resolution of alcohols. In early 2001, the successful application of Pd(II) catalysts to the oxidative kinetic resolution of secondary alcohols (Eq. 8) using Pd(II) salts and a natural diamine, that is, (−)-sparteine, was reported by two independent teams led by Sigman[48] and Stoltz.[49] In these reactions, the Pd(II)-sparteine complex (e.g., **4** in Scheme 6) is formed in situ from 5 mol% of either $Pd(OAc)_2$, or a soluble $PdCl_2$ source such as $Pd(MeCN)_2Cl_2$ or $Pd(nbd)Cl_2$ (nbd=norbornyldiene), and 20 mol% of (−)-sparteine. The choice of solvent, counter ion for the Pd(II) ion, and base significantly influences both the reaction rates and the enantioselectivities.

The isolation of enantiomerically enriched alcohols with over 50% total yield can be achieved by the oxidative kinetic resolution as the ketones are recyclable, as demonstrated by Stoltz and Ferreira.[49a] For example, in the oxidative kinetic resolution of (±)-2-naphthylethanol, the first cycle gave a 44% yield of (−)-2-naphthylethanol in 99% ee. After isolation of the enantiomerically enriched alcohol, the ketone was reduced back to the racemic alcohol by treatment with $NaBH_4$ (99% yield). A second oxidative kinetic resolution cycle gave a 24% yield in 99% ee (Eq. 9).

Additionally, Pd(II)/(−)-sparteine-catalyzed oxidative kinetic resolution has been employed in the enantioselective synthesis of two pharmaceuticals, (*S*)-fluoxetine–HCl and (*R*)-tomoxetine–HCl.[50] Furthermore, the $PdCl_2$/(−)-sparteine catalytic system has also been employed in the desymmetrization of *meso* diols. For example, desymmetrization of 1,3-*meso*-diol (Eq. 10) provided the enantiomerically enriched hydroxy-ketone product in 69% yield and 82% ee (59% yield, 93% ee after recrystallization).[48a]



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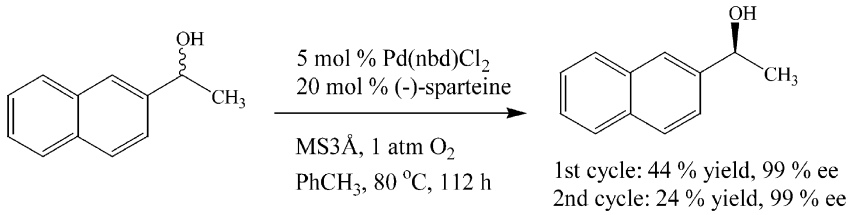

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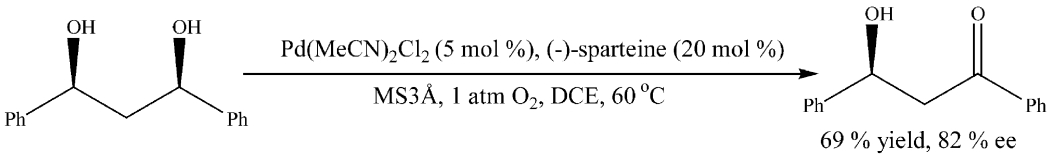

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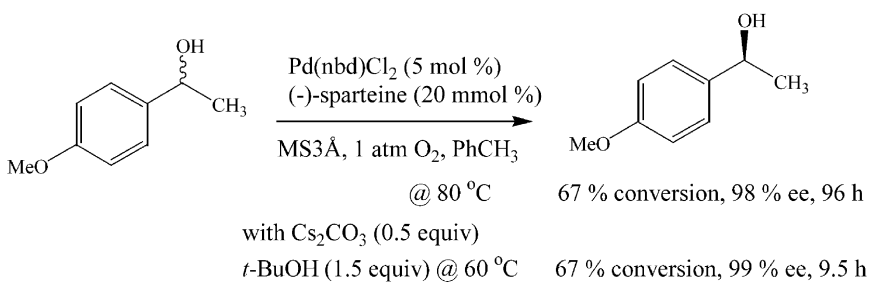


(11)

Very recently, Stoltz and co-workers reported that the addition of Cs_2CO_3/*t*-BuOH can dramatically accelerate the palladium-catalyzed aerobic oxidative kinetic resolution while maintaining enantioselectivity.[49b] A typical example is given in Eq. 11: with similar conversion, the required reaction time for this oxidative kinetic resolution decreases from 96 to 9.5 h by the addition of Cs_2CO_3/*t*-BuOH.

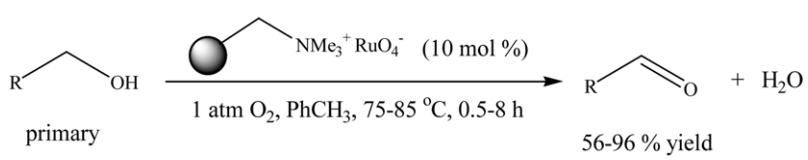
3. Heterogeneous catalysis

Heterogeneous catalysis has several advantages over homogeneous processes, including simple product isolation as well as catalyst separation and recycling.

It has been known for a long time that the aerobic oxidation of alcohols to the corresponding aldehydes and ketones can be performed in aqueous media using platinum, palladium and other noble metals as catalysts under mild conditions (20–80 °C and atmospheric pressure).[51–53] Considerable advances have been made in this area over the last 20 years. These catalytic reactions proceed in an environmentally-friendly solvent (water), replace expensive stoichiometric oxidants[5–17] with dioxygen, and produce water as the only by-product. Such heterogeneous oxidations proceed via an oxidative dehydrogenation mechanism, in which the substrates are adsorbed and dehydrogenated on the metal surfaces. The adsorbed hydrogen atoms are then oxidized to water by oxygen. This field is maturing rapidly with research led by Heyns,[51] Kuster,[52] van Bekkum,[53] Mallat,[54] Gallezot,[55] and Kimura.[56] However, severe deactivation of the catalysts is often found in the noble metal-catalyzed aerobic oxidation processes, causing serious concern and limitations for process development. Several causes of deactivation have been defined: metal oxidation and leaching, blocking of active sites by the strong absorption of side-products, and the aggregation of fine metal-crystals. Several recent reviews, including one in 2000 regarding the aerobic oxidation of alcohols over noble metal catalysts, have already been published,[57–60] therefore, no detailed discussion of this field will be covered in this review. However, it is worth pointing out that supported noble metals have been found to be excellent catalysts for the selective oxidation of alcohols to the corresponding aldehydes and ketones with high yields, using dioxygen as an oxidant in a supercritical CO_2 fluid medium.[61,62] Bimetals and metallic nanoparticles also act as efficient catalysts for the aerobic oxidation of alcohols.[63,64] For example, it was reported that the polystyrene–poly(ethylene glycol) resin-supported nanopalladium (~9 nm) displays high efficiency and selectivity in the aerobic oxidation of a variety of alcohols, and this has been attributed to the huge external surface area of nanomaterials.[64] The catalytic activity of palladium nanoparticles dispersed on an amphiphilic resin (ARP-Pd) was examined for the catalytic aerobic oxidation of alcohols in refluxing water.[64] Benzyl alcohol was oxidized to benzaldehyde almost quantitatively in 90 min under 1 atm of dioxygen using 1 mol% palladium as ARP-Pd. Secondary activated alcohols, such as 1-phenylethanol, diphenylmethanol, and 1-hydroxyindane undergo aerobic oxidation in water giving acetophenone, benzophenone, and indanone in 99, 85, and 95% yield, respectively. However, in the oxidation of unactivated alcohols, longer reaction times and larger amounts of Pd catalyst (20 mol%) are required, and over-oxidation products are obtained in the oxidation of saturated aliphatic primary alcohols. The experimental results from the oxidation of cyclooctanol indicate that the supported palladium nanoparticles can be recycled without losing catalytic activity.

3.1. Supported TPAP

In combination with *N*-methyl-morpholine-*N*-oxide (NMO), tetra-*N*-propylammonium perruthenate (TPAP) is an efficient reagent for the conversion of primary and secondary alcohols to the corresponding aldehydes and ketones.[14,15] TPAP alone is an active catalyst for the oxidation of alcohols at room temperature if the water formed can be removed in situ by adding activated molecular sieves to the reaction system.[65,66b] However, it is difficult to remove the expensive and relatively large amount (10 mol%) of TPAP catalyst and side products.[66] Ley and co-workers tried to solve these problems by grafting perruthenate onto the polymer of Amberlyst A-26 (Fluka) through strong ionic interactions.[66a,c] Results of alcohol oxidation reactions indicated that both activated and unactivated primary alcohols are aerobically oxidized to the corresponding aldehydes over polymer-supported perruthenate (PSP) catalyst in toluene at a temperature of 75–85 °C under 1 atm of dioxygen, similar to the conditions employed for homogeneous catalysis.[65] The yields of aldehydes were 56–96% within 0.5–8 h (Eq. 12).[66c] Interestingly, the PSP catalyst displays significant selectivity for the oxidation of primary over secondary alcohols:[66c] using a 1:1 mixture of benzyl alcohol and 1-phenylethanol at 75 °C for 3 h, benzaldehyde was the only oxidation product. No oxidation product of 1-phenylethanol was found under these reaction conditions. Similar results were obtained in the competitive oxidation of 1-octanol versus 2-octanol. Indeed, 83% of 1-octanol was oxidized to octanal, while only 13% of 2-octanol was converted to 2-octanone within 6 h at 85 °C.[66c] However, it is worth pointing out that relatively large amounts of catalyst (10 mol%) are required (Eq. 12). These results demonstrate that the PSP catalyst could provide a practical synthetic alternative for the oxidation of alcohols. However, it is still quite difficult to recycle the PSP reagent, possibly due to oxidative degradation of the



(12)

polymer support. The use of inorganic materials, such as SiO_2 and molecular sieves, as supports could potentially overcome these problems.[67]

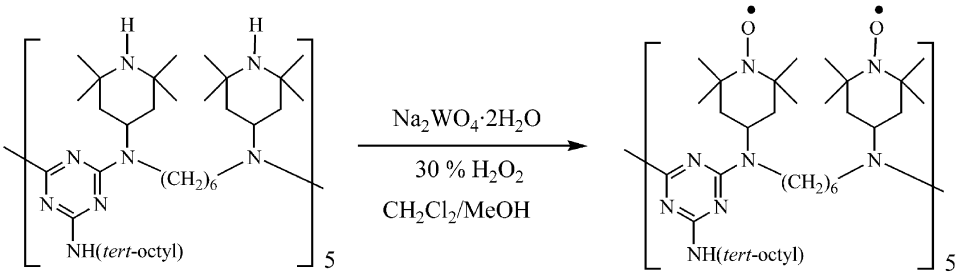
Mesoporous silica molecular sieves, MCM-41 for example, have multiple silanol groups (SiOH) on their internal and external surfaces. These silanol groups can potentially provide active sites to immobilize catalytically active species. Ley and co-workers have successfully immobilized perruthenates to the channels of MCM-41 molecular sieves through strong ionic interactions.[67] A MCM-41-supported propylamine-tethered triethylammonium perruthenate catalyst with a loading of 1.1 wt% Ru was found to be most active.[67] It quantitatively oxidizes various benzylic alcohols to the corresponding aldehydes in 0.5–3 h at 80 °C under 1 atm of dioxygen. No over-oxidation products were found with these supported-catalysts. Furthermore, experimental results indicated that no deactivation and no leaching were found after 12-recycle runs. However, these MCM-41-supported catalysts are much less active than the homogeneous TPAP catalytic system,[65] and neither cyclohexanol nor cyclohexenol was oxidized to the corresponding ketones. The use of NMO or TMAO (trimethylamine *N*-oxide) in place of dioxygen, gives good yields of oxidized products although contamination of the products by ruthenium species and organic impurities was observed.[67]

TPAP-incorporated silica gels have been prepared by directly adding TPAP to the sol–gel polymerization processes for silica gels.[68] It has been demonstrated that the TPAP/gel catalysts are stable under operational conditions, and that the leaching of ruthenium into the organic solvent is negligible. Results from catalysis studies indicated that the nature of the gel supports significantly affects the oxidation activity of the resultant catalysts. It was found that the catalyst made with TPAP and pure methyltrimethoxysilan, called ormosil-doped TPAP, was about 30 times more active than the catalyst prepared with TPAP and pure tetramethoxysilane.[68] The ormosil-doped TPAP catalyst is quite active toward the aerobic oxidation of benzyl alcohol. However, its activity towards other alcohols is quite low. For instance, in the oxidation of 1-octanol a TOF of only 1 h^{-1} was observed.[68] Recently, potassium perruthenate-impregnated zeolite X was reported.[69] Experiments to oxidize alcohols indicated that this zeolite-supported perruthenate catalyst displays interesting shape-selective ability on the substrates of benzyl alcohol and 1-pyrenemethanol, although the reactivity was quite low under the reported conditions.[69] Benzyl alcohol, being smaller than the open channels of zeolite X, was selectively oxidized to benzaldehyde, while 1-pyrenemethanol, which is too large to enter the channels of zeolite X, was inert under the same conditions.[69]

3.2. Supported TEMPO/M

3.2.1. Polymer-supported TEMPO/M. As we have described in the homogeneous catalysis section of this review, nitroxyl radicals are well-established catalysts for the oxidation of alcohols. Indeed, the protocol introduced by Anelli et al., involving TEMPO and bleach, is very useful, especially for large scale oxidations (Eq. 2);[28] a few polymer-bound nitroxyl radical systems have been used as oxidation catalysts, based on the Anelli protocol. These studies have encouraged efforts to develop efficient and green heterogeneous systems, which allow simple catalyst separation and recycling. One of the most advanced polymer-immobilized TEMPO derivative catalysts reported so far was developed by Sheldon and co-workers.[70–72] Polyamine-immobilized piperidinyl oxyl, PIPO, was prepared from a commercially available oligomeric sterically hindered amine, known as Chimassorb 944. Nitroxyl species were formed by treating Chimassorb 944 with hydrogen peroxide and a catalytic amount of $Na_2WO_4 \cdot 2H_2O$ (Eq. 13).

PIPO-catalyzed oxidations of alcohols can be either homogeneous or heterogeneous depending on the nature of the solvents used.[70–72] PIPO is soluble in dichloromethane, thus the catalysis is homogeneous if dichloromethane is adopted as solvent. Both activated and unactivated alcohols are oxidized to the corresponding aldehydes and ketones in PIPO/CH_2Cl_2/NaOCl/KBr systems, akin to the conventional TEMPO-bleach



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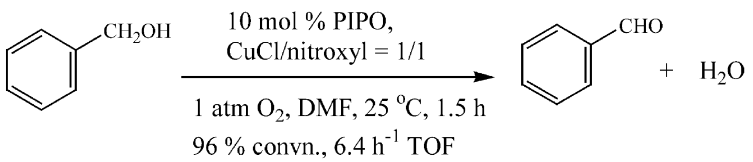


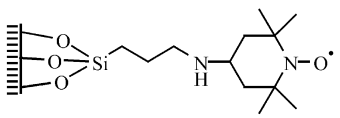
(14)

homogeneous oxidation system in which CH_2Cl_2 is the solvent and KBr is a co-catalyst (Eq. 2).[28]

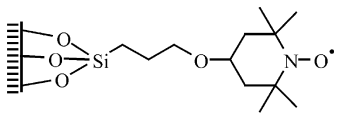
Besides sodium hypochlorite, dioxygen can also be used as the oxidant in PIPO-catalyzed oxidations. For example, PIPO/CuCl catalyzes the aerobic oxidation of benzyl alcohol to benzaldehyde with a TOF of 6.4 h^{-1} in dimethylformamide (DMF) solvent (Eq. 14).[71] This reactivity is comparable to the homogeneous TEMPO/CuCl system, in which a TOF of 4.7 h^{-1} was observed.[29] The PIPO/CuCl system also catalyzes the aerobic oxidation of alcohols under solvent-free conditions, but this is limited to activated benzylic and allylic alcohols as for the homogeneous TEMPO/CuCl catalytic system.[29] However, in contrast to the homogeneous system of TEMPO/$Ru(PPh_3)_3Cl_2$,[32] the PIPO/$Ru(PPh_3)_3Cl_2$ in chlorobenzene does not catalyze the aerobic oxidation of alcohol. This is believed to be due to coordination of ruthenium to the polyamine.[70]

3.2.2. Silica-supported TEMPO/M. There have been reports of silica-supported nitroxyl radicals as catalysts for the oxidation of alcohols.[73–75] For instance, TEMPO can be grafted to silica surfaces through reductive amination, affording SiO_2-amine-TEMPO (**5** in Scheme 9).[74] According to Anelli's protocol,[28] various alcohols were successfully oxidized in high yield to give the corresponding aldehydes and ketones using the SiO_2-amine-TEMPO system as catalyst.[74] Furthermore, the silica-supported catalyst exhibits behavior similar to that of the unsupported TEMPO catalyst, such as in the selective oxidation of the primary alcohols within mixtures of primary and secondary alcohols. Recycling experiments showed that the silica-bound TEMPO derivative was stable under the reaction conditions, thus allowing it to be recovered without significant loss of catalytic activity.[74]

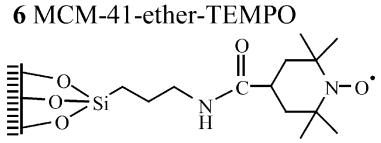
TEMPO derivatives have also been immobilized on the internal surfaces of mesoporous silica of MCM-41 through both ether and amide linkages, for example, MCM-41-ether-TEMPO (**6**) and MCM-41-amide-TEMPO (**7**), as shown in Scheme 9.[76] α-Methyl glucoside was oxidized to 1-*O*-methyl glucuronate with over 95% selectivity using the MCM-41 supported TEMPOs/NaOCl catalytic systems, and no obvious difference was found between the MCM-41-ether-TEMPO and MCM-41-amide-TEMPO catalysts.



5 SiO_2-amine-TEMPO



6 MCM-41-ether-TEMPO



7 MCM-41-amide-TEMPO

Scheme 9. Silica supported TEMPO derivatives.[74,76]

Aerobic oxidation results for benzyl alcohol over the MCM-41-ether-TEMPO/CuCl catalytic system are given in Table 2, along with controlled CuCl and unsupported TEMPO/CuCl results for comparison.[76a] The MCM-41-ether-TEMPO/CuCl catalytic system was much more active than CuCl alone (Table 2, entries 2 and 3). However, in comparison to the homogeneous TEMPO/CuCl system, the MCM-41-ether-TEMPO/CuCl system gave relatively low oxidation activity, although the selectivity for aldehydes is similar (Table 2, entries 3 and 4). In the oxidation of benzyl alcohol, for example, a conversion of 35% in 48 h (Table 2, entry 3) was found, corresponding to an average TOF of ~0.5 h^{-1},[76a] which is much lower than that of the homogeneous TEMPO/CuCl system (4.7 h^{-1} TOF, Table 2, entry 4)[29] and the PIPO/CuCl system (6.4 h^{-1} TOF, Eq. 14).[71] According to the proposal by Semmelhack et al.[29] the re-oxidation step involves disproportionation, which requires two TEMPO molecules to be in close proximity. The loading in the immobilized TEMPO system is probably not optimal for this reaction step. No over-oxidation to benzoic acid was found in the MCM-41-ether-TEMPO/CuCl system, which can be attributed to the low water content in the reaction mixture (only stoichiometric amounts of water are produced in the reaction), leading to a low concentration of the hydrated aldehyde. The latter is the intermediate in the production of carboxylic acid.

Table 2. Benzyl alcohol aerobic oxidation using MCM-41 supported TEMPO/CuCl catalyst[76a]

Entry	Catalyst	Convn. (%)	Sel. (%)[a]
1	None	0	—
2	CuCl	1.2	50
3	MCM-41-TEMPO/CuCl	35	>99
4	TEMPO/CuCl[b]	94	>99

Reaction conditions: 10 mmol benzyl alcohol, 0.25 mmol CuCl and 0.25 g MCM-41-ether-TEMPO in 25 mL DMF, reaction mixture was analyzed by GC after 48 h at room temperature and 1 atm of dioxygen.

[a] Selectivity to benzaldehyde.

[b] 10 mmol benzyl alcohol, 0.5 mmol TEMPO and 0.5 mol CuCl in 25 mL DMF, 4 h.[29]

3.3. Supported Pd(II) complexes

As we have already discussed in Section 2.3, Pd(II) complexes are important homogeneous catalysts in the aerobic oxidation of alcohols. However, there are very few reports concerning the synthesis of supported-Pd(II) complexes and their use as aerobic oxidation catalysts. Based on the success in developing the $Pd(OAc)_2$/pyridine/MS3Å catalytic systems for the aerobic oxidation of alcohols using dioxygen oxidant,[43] Uemura and co-workers synthesized a $Pd(OAc)_2$-pyridine complex on the surface of hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$) to give a heterogeneous palladium catalyst, denoted as Pd(II)-hydrotalcite.[77–79] The Pd(II)-hydrotalcite catalyst efficiently catalyzes the aerobic oxidation of benzyl alcohol to benzaldehyde in the presence of pyridine as co-catalyst (Eq. 15).[78] Unactivated secondary

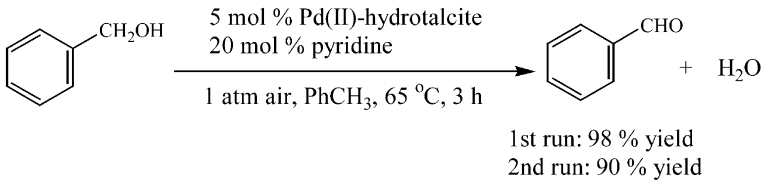


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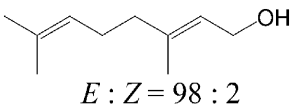
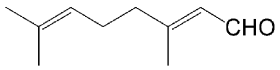
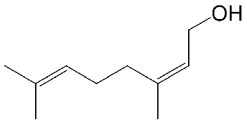
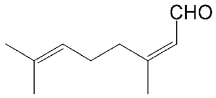
Table 3. Catalytic oxidation of geraniol and nerol using Pd(II)-hydrotalcite and $Pd(OAc)_2$/pyridine/MS3Å[77]

Entry	Substrate	Product	Pd(II)-hydrotalcite[a]		$Pd(OAc)_2$/pyridine/MS3Å[b]	
			Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	 $E:Z=98:2$		4.5	91 (98) *E*:*Z*=95:5	15	56 (76) *E*:*Z*=63:37
2	 $E:Z=2:98$		4.5	89 (100) *E*:*Z*=6:94	15	39 (71) *E*:*Z*=31:69

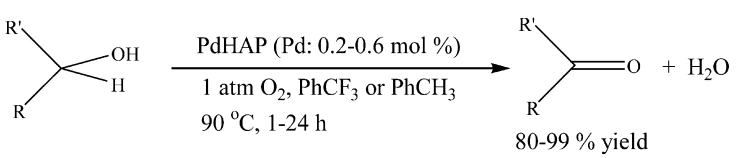
Reaction conditions: alcohol (1.0 mmol), pyridine (5.0 mmol), 1 atm of dioxygen, 80 °C.
[a] Pd(II)-hydrotalcite (300 mg, 0.05 mmol Pd).
[b] Pd(OAc) (0.05 mmol), MS3Å (500 mg).
[c] The value in parentheses is the conversion of alcohol in%. *E*:*Z* ratio was determined by ^{1}H NMR spectroscopy.

aliphatic alcohols were also oxidized, although an excess amount of pyridine was required.

Interesting results were found in the oxidation of alkenic alcohols using the Pd(II)-hydrotalcite catalyst;[77] these are summarized in Table 3. The Pd(II)-hydrotalcite system smoothly catalyzed the aerobic oxidation of geraniol to the corresponding aldehyde in 91% isolated yield in 4.5 h without geometrical isomerization (*E*:*Z*=95:5), while the reaction is incomplete even after long reaction times (76% conversion in 15 h) using the homogeneous $Pd(OAc)_2$/pyridine/MS3Å catalytic system. Furthermore, the *E*:*Z* ratio was significantly disturbed (*E*:*Z*=63:37), entry 1 in Table 3, under the $Pd(OAc)_2$/pyridine/MS3Å conditions. Similar results were found in the oxidation of nerol. The Pd(II)-hydrotalcite catalyst gives a yield of 89% with *E*:*Z*=6:94 (entry 2, Table 3), while both yield and selectivity were low using the $Pd(OAc)_2$/pyridine/MS3Å system (39% yield, *E*:*Z*=31:69). Although the reason for the high activity and selectivity of the Pd(II)-hydrotalcite catalyst is not yet clear (inhibition of strong complexation between Pd(II) and olefin due to the steric bulk of hydrotalcite surface may be a reason for the very low geometric isomerization observed in the heterogeneous system), this catalyst has shown its usefulness for the oxidation of unsaturated alcohols. However, it is still unclear how the Pd(II) complex is bound to the hydrotalcite surface, and how to overcome the leaching of the immobilized catalyst, especially in the presence of an excess amount of pyridine co-catalyst. In the oxidation of benzyl alcohol, the yield decreased from 98% with fresh catalyst (first run) to about 90% in the second run (Eq. 15, the catalyst was separated and washed after the first run, and then re-used for the second run).[78] The oxidation of alcohols to aldehydes or ketones using $PdCl_2(PhCN)_2$-exchanged hydroxyapatites (PdHAP) has been reported recently.[80] PdHAP exhibits high activity for benzylic and allylic alcohols, giving the corresponding carbonyl compounds in excellent yields.[80] Aliphatic and heterocyclic alcohols are also smoothly oxidized to the corresponding ketones and aldehydes (Eq. 16). Furthermore, a turn over number (TON) up to 236,000 was reached in a solvent-free oxidation of 1-phenylethanol to acetophenone in 24 h at 160 °C under 1 atm of dioxygen. In addition, no leaching of palladium occurred, allowing the re-use of catalyst without loss of catalytic activity and selectivity.

3.4. Polyoxometalate catalysts

Polyoxometalate catalysts have attracted much attention because of their strong acidity and rich redox properties.[81] However, polyoxometalate-catalyzed aerobic oxidation of alcohols was not reported until 1991 when Neumann and Levin discovered that benzyl alcohol is smoothly oxidized to benzaldehyde with 100% selectivity by a Keggin-type



(16)

polyoxometalate salt, $Na_5PV_2Mo_{10}O_{40}$, supported on activated carbon at 100 °C under 1 atm of air.[82] Substituted benzyl alcohols such as 4-bromobenzyl-, 4-nitrobenzyl-, 4-methoxy- and 4-methylbenzyl alcohols are also oxidized to their corresponding aldehydes in good yields (93–98%). However, unactivated secondary alcohols were only moderately reactive, and saturated primary alcohols were found to be inert under these reaction conditions. Interestingly, further studies indicated that the non-supported $PV_2Mo_{10}O_{40}^{5-}$ and silica or alumina supported $PV_2Mo_{10}O_{40}^{5-}$ were catalytically inactive.[83] These results suggest that activated carbon is not an inert support, but instead plays an integral part in the catalytic cycle. Indeed, it is known that there are multiple oxygen-containing groups present on the surface of activated carbon.[84] The intermediate or promoter, formed by these groups and $PV_2Mo_{10}O_{40}^{5-}$, could play a key role in the oxidation. This speculation was confirmed by using catalytic systems of $Na_5PV_2Mo_{10}O_{40}$ and quinones.[83] Experimental results indicate that the $Na_5PV_2Mo_{10}O_{40}$ is active for the aerobic oxidation of benzylic and allylic alcohols in the presence of quinines, which could be promoters. Furthermore, $H_5PV_2Mo_{10}O_{40}$ alone was active for the oxidation of benzylic alcohol if the reaction was conducted at 100 °C under 2 atm of dioxygen using polyethylene glycol as solvent.[85] PVMo-based polyoxometalates were also found to be efficient catalysts in the aerobic oxidation of 2-butyl-5-hydroxymethylimidazole to 2-butyl-5-formyl-imidazole under high pressure and temperature conditions.[86]

Using DMSO as solvent, the $H_5PV_2Mo_{10}O_{40}$ catalyst was found to be active for the oxidation of aliphatic alcohols, such as cyclooctanol, 3-octanol, etc.[87] Mechanistic studies revealed that DMSO is in fact the oxygen donor.[87] The catalytic properties of $H_5PV_2Mo_{10}O_{40}$ are significantly enhanced (over 100 times in most cases) if TEMPO is employed as co-catalyst.[88] Table 4 gives some catalytic results for $H_5PV_2Mo_{10}O_{40}$ catalyst with and without TEMPO. The catalytic activity of the $H_5PV_2Mo_{10}O_{40}$/TEMPO system is comparable to that of the $Ru(PPh_3)_3Cl_2$/TEMPO system as we have discussed in section 2.1.

The catalytic activities of polyoxometalates can be improved by introducing other substitution patterns. For example, $Q_4PSb^{v}(O)Mo_{11}O_{39}$ and $Q_3PSb^{v}(Br)Mo_{11}O_{39}$, where Q^+=tetra-*n*-butylammonium cation, are much more active than $Q_5PV_2Mo_{10}O_{40}$ in the aerobic oxidation of alcohols.[89] Recently, Neumann et al. reported that ruthenium and osmium-containing polyoxometalates, $[M(DMSO)_3Mo_7O_{24}]^{4-}$ (M=Ru(II) or Os(II)), are very active catalysts for the aerobic oxidation of alcohols.[90] Benzylic alcohols are efficiently and selectively oxidized to the corresponding benzaldehyde derivatives at 120 °C with 0.2 mol% catalyst in the absence of solvent. Although the use of toluene as solvent gave good yields of products, the reactions were about 20–50% slower than when no solvent was used. Secondary allylic alcohols were also oxidized effectively to the corresponding β-unsaturated ketones, generally with over 90% selectivity. However, primary aliphatic allylic alcohols were less active with only about 50% selectivity for β-unsaturated aldehydes. Lower activities were also found in the oxidation of unactivated alcohols.

Table 4. Selected aerobic oxidation results for $H_5PV_2Mo_{10}O_{40}$/TEMPO catalyst[87]

Entry	Substrate	Product	Time (h)	Convn. (%)[a]
1	Benzyl alcohol	Benzaldehyde	6	>99
2	Benzyl alcohol (no TEMPO)	Benzaldehyde	6	8.4
3	1-Octanol	Octanal	18	98
4	1-Octanol (no TEMPO)	Octanal	18	0.2
5	*cis*-2-Hexen-1-ol	2-Hexenal	10	>99
6	*cis*-2-Hexen-1-ol (no TEMPO)	2-Hexenal	10	1.1

Reaction conditions: 1 mmol of substrate, 0.01 mmol of $H_5PV_2Mo_{10}O_{40}$, 0.03 mmol of TEMPO, 0.15 mL of acetone. 2 atm of dioxygen at room temperature, T=100 °C.

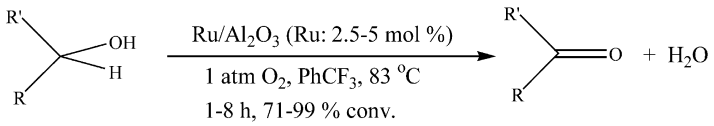
[a] Conversions based on GC results.

Ru(III)-substituted polyoxometalate is also an efficient oxidation catalyst. Mizuno et al. reported that a monoruthenium(III) substituted silicotungstate, $[(C_4H_9)_4N]_4H[SiW_{11}Ru^{III}(H_2O)O_{39}]\cdot 2H_2O$, synthesized by the reaction of the lacunary polyoxometalate $[SiW_{11}O_{39}]^{8-}$ with Ru^{3+}, is an efficient catalyst for the aerobic oxidation of various alkanes and alcohols in 1 atm of dioxygen.[91] Very high TONs (over 1000) were achieved in the aerobic oxidation of secondary alkanes, such as adamantane and cyclohexane, and alcohols in the absence of co-catalysts or reductants. However, the selectivity was lower in the oxidation of primary alcohols due to over-oxidation, forming carboxylic acids. Furthermore, a relatively long reaction period, 48–120 h, lead to low TOFs and reduced the practicality of these systems.

3.5. Supported Ru(III) catalysts

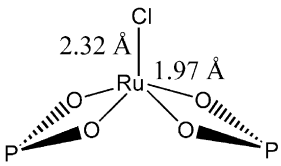
The catalytic activity of Ru(III) was significantly improved by using Al_2O_3 as support in an dioxygen atmosphere.[92] The Ru/Al_2O_3 catalyst shows high catalytic activities in the oxidation of both activated and unactivated alcohols under 1 atm of dioxygen, and all primary and secondary benzylic alcohols were quantitatively converted into the corresponding benzaldehydes and ketones, respectively. Also, enals and enones were prepared from the corresponding primary and secondary allylic alcohols, with no hydrogen transfer or isomerization of double bonds, and unactivated alcohols were oxidized smoothly (Eq. 17).[92] However, over-oxidation of unactivated primary alcohols to the carboxylic acids was found, but this can be overcome by the addition of a small amount of hydroquinone. The Ru/Al_2O_3 catalyst efficiently catalyzes the oxidation of unactivated 2-octanol and activated 1-phenylethanol under solvent-free conditions. Thus, solvent-free oxidation of 2-octanol and 1-phenylethanol gave TOFs of 300 and 340 h^{-1}, and TONs of 950 and 980, respectively, albeit at relatively high temperature (150 °C). These oxidations can be performed in air, instead of dioxygen, without influencing the conversion or selectivity. However, it is still not clear either how the Ru species resides on the Al_2O_3 support, or what kind of interaction prevents Ru from leaching during reactions. The ability to recycle this catalyst was demonstrated through the oxidation of benzyl alcohol at 83 °C.

Another Ru(III)-containing heterogeneous catalyst that has been reported is ruthenium-exchanged hydroxyapatite



(17)

(RuHAP), prepared by ion exchange of hydroxyapatite (HAP) powder with aqueous $RuCl_3$ solution at 25 °C for 24 h.[93] The presence and chemical environment of the Ru(III) species on the surface of HAP have been fully characterized and defined by elemental analysis, X-ray photoelectron spectroscopy (XPS), and X-ray absorption techniques (Scheme 10). Various alcohols are efficiently oxidized to the corresponding aldehydes and ketones using RuHAP as catalyst at 80 °C under 1 atm of dioxygen. Benzylic and allylic compounds show especially high reactivity for oxidative dehydrogenation. Interestingly, 1-octanol was oxidized to 1-octanal without any over-oxidation products being observed. Primary alcohols are more reactive than secondary alcohols with the RuHAP catalyst: in a competitive oxidation where equimolar 1-octanol and 4-octanol were mixed as substrates, octanal was obtained with 95% selectivity; in the intramolecular competitive oxidation of 1,7-octanediol, 7-hydroxyoctanal was obtained with 80% chemoselectivity. Furthermore, the RuHAP catalyst is active in the oxidation of various heterocyclic alcohols containing nitrogen and sulfur atoms. For example, 2-pyridinemethanol and 2-thiophenemethanol were oxidized to the corresponding aldehydes in good yields. These substrates were inert to the $Ru(PPh_3)_3Cl_2$ and Pd(II) catalytic systems as we have discussed in the homogeneous catalysis sections.

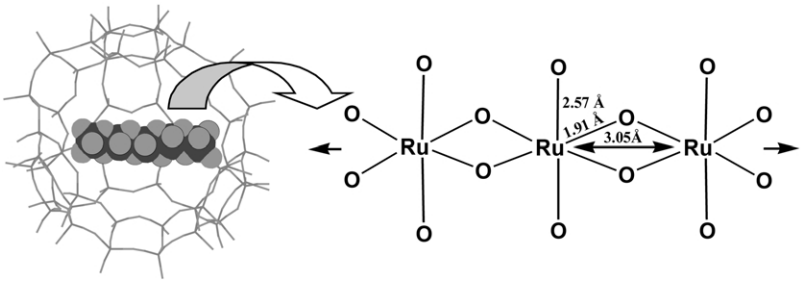


Scheme 10. Proposed environment of Ru^{3+} on hydroxyapatite.[93]

3.6. Functionalized zeolites

Zeolites form a major subclass of microporous materials.[94] Microporous zeolitic materials have several special features: very high surface area, well-defined pores/cages, polarity-controlled frameworks, tunable acid sites, molecular sieve and ion exchange capabilities. These unique advantages make them one of the most widely used catalysts in the petrochemical industry. Zeolites can be functionalized as acid catalysts by generating acidic sites in the framework, with the opportunity to tailor strength and concentration for particular applications.[94] Zeolites can be functionalized as redox catalysts by introducing various transition metals into their frameworks,[95] or confining nanometer-sized transition metal compounds into their pores/cages. The latter was named a ship-in-a-bottle (or host–guest) system,[96–99] in which the zeolitic frameworks serve only as an inert support. One of the most interesting zeolites is faujasite (FAU) zeolite, in which ~13 Å supercages are tetrahedrally connected via open channels of diameter ~7.4 Å.[94] This specific structure allows physical trapping of molecules of size ~1 nm into its supercages. The guest molecules, once encapsulated, do not diffuse out during various chemical processes unless the zeolitic frameworks are destroyed.[96–99] Furthermore, the catalytic properties of these ship-in-a-bottle systems mainly depend on the properties of the guest molecules. Various transition-metalloporphyrins have been synthesized inside the supercages of faujasite zeolites using the build-bottle-around-ship strategy.[97–99] These zeolite-confined metalloporphyrins display rich catalysis-chemistry such as oxidation,[97] hydrogenation[98] and hydroxylation.[99] It is well known that a variety of transition-metal oxides, such as RuO_2, MnO_2, CrO_3, etc.[1] act as oxidants or catalysts in the oxidative dehydrogenation of alcohols to carbonyl compounds. For example, for the oxidation of cinnamyl alcohol, hydrated RuO_2 was found to be more efficient than MnO_2.[100] Recently, microporous manganese oxide was found active for the aerobic oxidation of alcohols and its reactivity was accelerated in the presence of Brønsted acids.[101]

Cognizant of the oxidative ability of RuO_2, and the ability of the faujasite zeolite to promote catalytic reactions, Zhan and co-workers have synthesized nanometer-sized RuO_2 clusters (~1 nm) in the supercages of faujasite zeolite,[102,103] using an organic-template-free approach:[104,105] the system was named RuO_2-FAU. Ru K-edge X-ray adsorption experiments indicate that RuO_2-FAU has a two-dimensional chain structure, similar to amorphous hydrous RuO_2, in which the RuO_6 units are connected together by two shared oxygen atoms (Scheme 11).[102,106] RuO_2-FAU is a green, selective and efficient catalyst for the aerobic oxidation of alcohols. It catalytically and aerobically oxidizes a variety of alcohols using air as the sole oxidant under very mild conditions (e.g., 80 °C and 1 atm). Table 5 gives some of the aerobic oxidation results for benzyl alcohol.[102] No oxidation product was detected from GC analysis using unmodified faujasite zeolite (NaX) as catalyst, indicating that the unmodified faujasite zeolite itself is inert under the experimental conditions (Table 5, entry 1). Using pure hydrous RuO_2 as a catalyst and toluene as solvent, benzyl alcohol was converted to benzaldehyde in 16% in 1.5 h at 80 °C (Table 5, entry 2). However, benzyl alcohol was completely and selectively converted to benzaldehyde in 1.5 h when RuO_2-FAU was used as catalyst under the same reaction conditions (Table 5, entry 3), indicating that the FAU-confined RuO_2 nanocluster is much more active than bulk RuO_2. Furthermore, aerobic oxidation with this system can be carried out without using an organic solvent. For example, neat benzyl alcohol was selectively oxidized to benzaldehyde with a conversion of 22% in 20 h at 80 °C and 1 atm of air (Table 5, entry 4). The RuO_2-FAU catalyst in toluene is active in the aerobic oxidation of benzyl alcohol even at ambient temperature without the need for any co-catalysts or reductants (Table 5, entry 5).



Scheme 11. The 2D-chain structure of nano-RuO_2 in the faujasite zeolite.

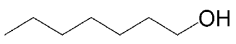
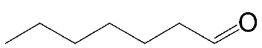
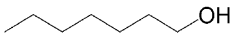
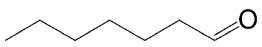
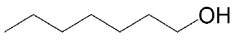
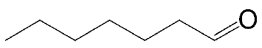
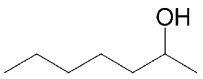
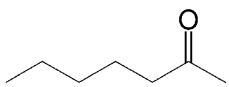
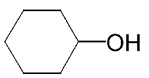
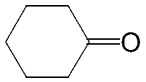
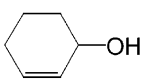
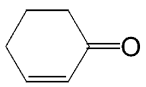
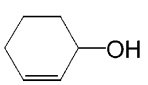
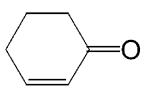
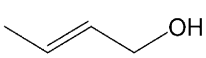
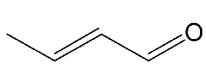
Table 5. RuO_2-FAU catalyzed aerobic oxidation of benzyl alcohol[102]

Entry	Catalyst	Time (h)	Conditions	Convn. (%)	TON
1[a,b]	NaX	4	80 °C, air	0	0
2[b]	RuO_2	1.5	80 °C, air	16	2
3[b]	RuO_2-FAU	1.5	80 °C, air	100	13
4[c]	RuO_2-FAU	20	80 °C, air	22	28
5[d]	RuO_2-FAU	24	RT, O_2	58	7

[a] Unmodified faujasite zeolite (0.1 g) was used as 'catalyst'.
[b] 0.078 mmol RuO_2 (or 0.1 g RuO_2-FAU, for example, 0.078 mmol Ru), 1 mmol alcohol, 3 mL toluene.
[c] 30 mmol alcohol, 0.3 g RuO_2-FAU.
[d] 10 mL toluene. All reactions were conducted at ambient pressure and benzaldehyde was the only oxidation product.

The RuO_2-FAU catalyst is active in the oxidation of various alcohols, including unactivated alcohols (Table 6), which are rarely oxidized by RuO_2 or RuO_2/dioxygen.[100] For example, *n*-heptanol was selectively oxidized to *n*-heptaldehyde with 44% conversion in 4 h (Table 6, entry 1). The oxidation was essentially complete in 20 h with over 99% selectivity for *n*-heptaldehyde (Table 6, entry 2). No over-oxidation product was detected by GC analysis. In comparison with unactivated primary aliphatic alcohols, secondary acyclic aliphatic alcohols are more reactive with the RuO_2-FAU catalyst: 69% of 2-heptanol was oxidized to 2-heptanone in 4 h (Table 6, entry 4). This trend is very different from that observed in the monomeric ruthenium catalysts, such as $Ru(PPh_3)_3Cl_2$,[32] Ru/Al_2O_3[92] and RuHAP.[93] Unfortunately, only 17% of cyclohexanol was oxidized to cyclohexanone under the RuO_2-FAU conditions (Table 6, entry 5). This is further confirmed by a competitive reaction, in which heptanol is found to be about 3 times more reactive than cyclohexanol.[102] This result agrees very well with the individual reactions (Table 6, entries 1 and 5). The oxidation of alcohols using RuO_2-FAU is significantly promoted in 1 atm of dioxygen (Table 6, entries 1 and 3). Furthermore, allylic alcohols are oxidized easily: 68% of 2-cyclohexenol was selectively oxidized to 2-cyclohexenone in 4 h (Table 6, entry 6). This oxidation was complete in 8 h (Table 6, entry 7). 2-Buten-1-ol was selectively converted to 2-butenal in 95% yield after 4 h. The physically trapped nano-RuO_2 in FAU is very stable during the oxidation processes, allowing the catalyst to be recycled without losing activity and selectivity.[102] The shape-selectivity of zeolites, derived from their well-defined pores/cages, was observed in the RuO_2-FAU-catalyzed

Table 6. RuO_2-FAU catalyzed aerobic oxidation of alcohols[102]

Entry	Time (h)	Substrate	Product	Convn. (%)
1	4			44
2	20			93
3	4[a]			98
4	4			69
5	4			17
6	4			68
7	8			100
8	4			95

Reaction conditions: 0.1 g nanoRuO_2-FAU (0.078 mmol Ru); 1 mmol alcohol; 3 mL toluene; 80 °C and 1 atm of air.
[a] 1 atm of dioxygen. For all reactions, aldehydes or ketones are the only oxidation product.

competitive aerobic oxidation of benzyl alcohol over 9-hydroxyfluorene.[102] Similar phenomena were observed in the $KRuO_4$ impregnated NaX system.[69]

4. Conclusion

The environmental and economic significance of the aerobic oxidation of alcohols to the corresponding carbonyls is continuing to inspire research to develop novel, green and efficient oxidation catalysts. In homogeneous catalysis, TEMPO-based systems are the most important and widely investigated catalysts for the aerobic oxidation of alcohols. The development of supported TEMPOs could potentially provide a solution to re-use the expensive TEMPO-based catalysts, even though the catalytic abilities of heterogenized TEMPO catalysts are still much lower than their homogeneous counterparts. Progress has been made in the development of polyoxometalate-based catalytic systems, and the catalytic abilities of these systems are significantly improved by the introduction of various catalytically active species as building units. The unique Pd(II)/Pd(0) catalytic cycle and the rich redox chemistry of ruthenium compounds have enabled tremendous development in the aerobic oxidation of alcohols. In the Pd(II)-catalytic system, mechanistic studies reveal that the prevention of Pd(0) aggregation and the promotion of Pd(0) re-oxidation to Pd(II) with dioxygen are key factors in improving the performance of Pd(II) catalysts. In preliminary studies, the supported Pd(II) complexes and Pd nanoparticle have already displayed useful chemistry. A variety of ruthenium compounds, for example, Ru(II, III, and IV), have shown very significant reactivity and diversity for the catalytic aerobic oxidation of alcohols. Due to significant advances in product and catalyst separation, heterogeneous catalysis has gained increasing attention in the last few years. The availability of various supports with differing physical properties and porosities, for example, hydroxyapatite, microporous zeolite, and mesoporous silica, allows chemists to design and create many catalytic systems and to explore and understand their oxidation mechanisms. Porous supports with well-defined cages and channels provide a nano-reactor environment, which can introduce shape-selectivity for substrates, products, and transition states.

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References and notes

1. Larock, R. C. *Comprehensive organic transformations*; VCH: New York, 1999; pp 1234–1250.
2. Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed oxidation of organic compounds*; Academic: New York, 1981; pp 350–382.
3. Trost, B. M.; Fleming, I.; Ley, S. V. *Comprehensive organic synthesis*; Pergamon: Oxford, 1991; Vol. 7.
4. Weissermel, K.; Arpe, H.-J. In *Industrial organic chemistry*, 3rd ed; Lindley, C. R., Ed.; VCH: New York, 1997; Translated.
5. Holum, J. R. *J. Org. Chem.* **1961**, *26*, 4814–4816.
6. Lee, D. G.; Spitzer, U. A. *J. Org. Chem.* **1970**, *35*, 3589–3590.
7. Cainelli, G.; Cardillo, G. *Chromium oxidants in organic chemistry*; Springer: Berlin, 1984.
8. Ley, S. V.; Madin, A. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 251–289.
9. Muzart, J. *Chem. Rev.* **1992**, *92*, 113–140.
10. Regen, S. L.; Koteel, C. *J. Am. Chem. Soc.* **1977**, *99*, 3837–3838.
11. Menger, F. M.; Lee, C. *Tetrahedron Lett.* **1981**, *22*, 1655–1656.
12. Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682–6684.
13. Griffith, W. P. *Chem. Soc. Rev.* **1992**, *21*, 179–185.
14. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
15. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
16. Lee, T. V. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 291–303.
17. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
18. (a) Sheldon, R. A.; Arend, I. W. C. E.; Dijksman, A. *Catal. Today* **2000**, *57*, 157–166. (b) Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816. (c) Mahadevan, V.; Gebbink, R. J. M. K.; Stack, T. D. P. *Curr. Opin. Chem. Biol.* **2000**, *4*, 228–234, and references therein. (d) Sheldon, R. A.; Arends, I. W. C. E. *Catal. Met. Complexes* **2003**, *26*, 123–155.
19. Whittaker, J. W. *Metal ions in biological systems*; Sigel, H., Sigel, A., Eds.; Marcel Dekker: New York, 1994; Vol. 30, pp 315–360.
20. Knowles, P. F.; Ito, N. *Perspectives in bio-inorganic chemistry*; Hay, R. W., Dilworth, J. R., Nolan, K. B., Eds.; Jai: London, 1994; Vol. 2, pp 207–244.
21. (a) Ito, N.; Phillips, S. E.; Stevens, C.; Ogel, Z. B.; McPherson, M. J.; Keen, J. N.; Yadav, K. D.; Knowles, P. F. *Nature* **1991**, *350*, 87–90. (b) Ito, N.; Phillips, S. E.; Stevens, C.; Ogel, Z. B.; McPherson, M. J.; Keen, J. N.; Yadav, K. D.; Knowles, P. F. *Faraday Discuss.* **1992**, *93*, 75–84.
22. Ito, N.; Phillips, S. E.; Yadav, K. D.; Knowles, P. F. *J. Mol. Biol.* **1994**, *238*, 794–814.
23. Whittaker, M. M.; Whittaker, J. W. *Biophys. J.* **1993**, *64*, 762–772.
24. (a) Wang, Y.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. *Science* **1998**, *279*, 537–540. (b) Chaudhuri, P.; Hess, M.; Flörke, U.; Wieghardt, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2217–2220. (c) Chaudhuri, P.; Hess, M.; Müller, J.; Hildenbrand, K.; Bill, E.; Weyhermüller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **1999**, *121*, 9599–9610. (d) Chaudhuri, P.; Hess, M.; Weyhermüller, T.; Wieghardt, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1095–1098. (e) Nagata,

Y.; Miyamoto, C.; Matsushima, Y.; Matsumoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 71–76.
25. (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044–2046. (b) Markó, I. E.; Gautier, A.; Chellé-Regnaut, I.; Giles, P. R.; Tsukazaki, M.; Urch, C. J.; Brown, S. M. *J. Org. Chem.* **1998**, *63*, 7576–7577. (c) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433–2439.
26. Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509–533.
27. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.
28. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
29. Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376.
30. (a) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343–4346. (b) Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P. *Tetrahedron* **2002**, *58*, 3985–3991.
31. Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507.
32. Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414–2415.
33. (a) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591–1592. (b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Platinum Met. Rev.* **2001**, *45*, 15–19. (c) Dijksman, A.; Marino-Gonzalez, A.; Mairata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826–6833. (d) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774–781.
34. Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 5557–5560.
35. Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651–6653.
36. (a) Coleman, K. S.; Coppe, M.; Thomas, C.; Osborn, J. A. *Tetrahedron Lett.* **1999**, *40*, 3723–3726. (b) Lorber, C. Y.; Smidt, S. O.; Osborn, J. A. *Eur. J. Inorg. Chem.* **2000**, *4*, 655–658. (c) Muldoon, J.; Brown, S. N. *Org. Lett.* **2002**, *4*, 1043–1045.
37. Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* **2001**, *42*, 8447–8449.
38. Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.
39. Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157–158.
40. (a) Heck, R. F. *Palladium reagents in organic syntheses*; Academic: London, 1985; pp 110–115. (b) Bellosta, V.; Benhaddou, R.; Czernecki, S. *Synlett* **1993**, 861–863.
41. Tsuji, J. *Palladium reagents and catalysis*; Wiley: New York, 1995.
42. Peterson, K. P.; Larcock, R. C. *J. Org. Chem.* **1998**, *63*, 3185–3189.
43. (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011–6014. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755. (c) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645–2646. (d) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1915–1918. (e) Nishimura, T.; Maeda, Y.; Kakiuchi, N.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4301–4305.
44. Bortolo, R.; Bianchi, D.; D'Aloisio, R.; Querci, C.; Ricci, M. *J. Mol. Catal. A: Chem.* **2000**, *153*, 25–29.
45. (a) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766–767. (c) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179–4181.
46. (a) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639. (b) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355–369. (c) ten Brink, G.-J.; Arends, I. W. C. E.; Hoogenraad, M.; Verspui, G.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 497–505.
47. Hallman, K.; Moberg, C. *Adv. Synth. Catal.* **2001**, *343*, 260–263.
48. (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476. (b) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202–8203. (c) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63–65. (d) Sigman, M. S.; Jensen, D. R.; Rajaram, S. *Curr. Opin. Drug Discovery Dev.* **2002**, *6*, 860–869.
49. (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835–837.
50. Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435–5436.
51. (a) Heyns, K.; Paulsen, H. *Angew. Chem.* **1957**, *69*, 600–608. (b) Heyns, K.; Paulsen, H. *Adv. Carbohydr. Chem.* **1962**, *17*, 169–211.
52. (a) de Wilt, H. G. J.; Lindhout, J.; Kuster, B. F. M. *Carbohydr. Res.* **1971**, *19*, 5–15. (b) Dijkgraaf, P. J. M.; Duisters, H. A. M.; Kuster, B. F. M.; van der Wiele, K. *J. Catal.* **1988**, *112*, 337–344. (c) Schuurman, Y.; Kuster, B. F. M.; van der Wiele, K.; Marin, G. B. *Appl. Catal.* **1992**, *89*, 47–68. (d) Jelemensky, L.; Kuster, B. F. M.; Marin, G. B. *Catal. Lett.* **1995**, *30*, 269–277. (e) Markusse, A. P.; Kuster, B. F. M.; Koningsberger, D. C.; Marin, G. B. *Catal. Lett.* **1998**, *55*, 141–145. (f) Markusse, A. P.; Kuster, B. F. M.; Schouten, J. C. *J. Mol. Catal. A: Chem.* **2000**, *158*, 215–222. (g) Kluytmans, J. H. J.; Markusse, A. P.; Kuster, B. F. M.; Marin, G. B.; Schouten, J. C. *Catal. Today* **2000**, *57*, 143–155.
53. (a) de Wit, G.; de Vlieger, J. J.; Kock-van Daten, A. C.; Heus, R.; Laroy, R.; van Hengstum, A. J.; Kieboom, A. P. G.; van Bekkum, H. *Carbohydr. Res.* **1981**, *91*, 125–138. (b) van Dam, H. E.; Duijverman, P.; Kieboom, A. P. G.; van Bekkum, H. *Appl. Catal.* **1987**, *33*, 373–382. (c) Venema, F. R.; Peters, J. A.; van Bekkum, H. *J. Mol. Catal.* **1992**, *77*, 75–85. (d) Abbadi, A.; van Bekkum, H. *Appl. Catal. A* **1996**, *148*, 113–122. (e) Verraest, D. I.; Peters, J. A.; van Bekkum, H. *Carbohydr. Res.* **1998**, *306*, 197–203.
54. (a) Mallat, T.; Baiker, A. *Appl. Catal. A* **1991**, *79*, 41–58. (b) Brönnimann, C.; Bodnar, Z.; Hug, P.; Mallat, T.; Baiker, A. *J. Catal.* **1994**, *150*, 199–211. (c) Brönnimann, C.; Bodnar, Z.; Aeschimann, R.; Mallat, T.; Baiker, A. *J. Catal.* **1996**, *161*, 720–729. (d) Mallat, T.; Seyler, L.; Mir Alai, M.; Baiker, A. *Sepc. Publ.—R. Soc. Chem.* **1998**, *216*, 66–71. (e) Keresszegi, C.; Burgi, T.; Mallat, T.; Baiker, A. *J. Catal.* **2002**, *211*, 244–251. (f) Grunwaldt, J.-D.; Keresszegi, C.; Mallat, T.; Baiker, A. *J. Catal.* **2003**, *213*, 291–295.
55. (a) Gallezot, P.; de Mésanstourne, R.; Christidis, Y.;

Mattioda, G.; Schoutecten, A. *J. Catal.* **1992**, *133*, 479–485. (b) Besson, M.; Gallesot, P.; Lahmer, F.; Fléche, G.; Fuertes, P. *J. Catal.* **1995**, *152*, 116–121. (c) Fordham, P.; Besson, M.; Gallesot, P. *Catal. Lett.* **1997**, *46*, 195–199. (d) Crozon, A. B.; Besson, M.; Gallesot, P. *New J. Chem.* **1998**, *22*, 269–273.

56. (a) Kimura, H.; Kimura, A.; Kokubo, I.; Wakisaka, T.; Mitsuda, Y. *Appl. Catal. A* **1993**, *95*, 143–169. (b) Kimura, H. *J. Polym. Sci.* **1998**, *36*, 189–196. (c) Kimura, H. *J. Polym. Sci.* **1998**, *36*, 195–205.
57. Vinke, P.; de Wit, D.; de Goede, A. T. J. W.; van Bekkum, H. *Stud. Surf. Sci. Catal.* **1992**, *72*, 1–20.
58. Mallat, T.; Baiker, A. *Catal. Today* **1994**, *19*, 247–283.
59. Gallezot, P. *Catal. Today* **1997**, *37*, 405–418.
60. Besson, M.; Gallezot, P. *Catal. Today* **2000**, *57*, 127–141.
61. Jenzer, G.; Sueur, D.; Mallat, T.; Baiker, A. *Chem. Commun.* **2000**, 2247–2248.
62. Steele, A. M.; Zhu, J.; Tsang, S. C. *Catal. Lett.* **2001**, *73*, 9–13.
63. Lee, A. F.; Gee, J. J.; Theyers, H. J. *Green Chem.* **2000**, *2*, 279–282.
64. Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194–197.
65. Markó, I. S.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661–12662.
66. (a) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907–1908. (b) Lenz, R.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291–3292. (c) Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977–979.
67. Bleloch, A.; Johnson, B. F. G.; Ley, S. V.; Price, A. J.; Shephard, D. S.; Thomas, A. W. *Chem. Commun.* **1999**, 1907–1908.
68. Pagliaro, M.; Ciriminna, R. *Tetrahedron Lett.* **2001**, *42*, 4511–4514.
69. Wu, D. L.; Wight, A. P.; Davis, M. E. *Chem. Commun.* **2003**, 758–759.
70. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271–272.
71. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 102–104.
72. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Special publication*; Royal Society of Chemistry, 2001; Vol. 266 (Supported Catalysts and Their Applications) pp 118–124.
73. Tsubokawa, N.; Kimoto, T.; Endo, T. *J. Mol. Catal. A: Chem.* **1995**, *101*, 45–50.
74. (a) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795–1796. (b) Fey, T.; Fisher, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154–8159.
75. Heeres, A.; van Doren, H. A.; Gotlieb, K. F.; Bleeker, I. P. *Carbohydr. Res.* **1997**, *299*, 221–227.
76. (a) Brunel, D.; Fajula, F.; Nagy, J. B.; Deroide, B.; Verhoef, M. J.; Veum, L.; Peters, J. A.; van Bekkum, H. *Appl. Catal. A: Gen.* **2001**, *213*, 73–82. (b) Brunel, D.; Lentz, P.; Sutra, P.; Deroide, B.; Fajula, F.; Nagy, J. B. *Stud. Surf. Sci. Catal.* **1999**, *125*, 237–244. (c) Verhoef, M. J.; Peters, J. A.; van Bekkum, H. *Stud. Surf. Sci. Catal.* **1999**, *125*, 465–472.
77. Nishimura, T.; Kakiuchi, N.; Inoue, M.; Uemura, S. *Chem. Commun.* **2000**, 1245–1246.
78. Kakiuchi, N.; Nishimura, T.; Inoue, M.; Uemura, S. *Bull. Chem. Soc. Jpn* **2001**, *74*, 165–172.
79. Kakiuchi, N.; Maeda, Y.; Nishimura, M.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620–6625.
80. Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572–11573.
81. (a) Hill, C. L.; Prosser-McCartha, C. M. *Coord. Chem. Rev.* **1995**, 143–407. (b) Fujibayashi, S.-Y.; Nakayama, K.; Hamamoto, M.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Mol. Catal. A: Chem.* **1996**, *110*, 105–117. (c) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171–198. (d) Nizuno, N.; Misono, M. *Chem. Rev.* **1998**, *98*, 199–217. (e) Neumann, R. *Prog. Inorg. Chem.* **1998**, *47*, 317–370.
82. Neumann, R.; Levin, M. *J. Org. Chem.* **1991**, *56*, 5707–5710.
83. Neumann, R.; Khenkin, A. M.; Vigdergauz, I. *Chem. Eur. J.* **2000**, *6*, 875–882.
84. van Krevelen, D. W. Coal: typology, chemistry, physics, constitution. Elsevier: Amsterdam, 1961.
85. Haimov, A.; Neumann, R. *Chem. Commun.* **2002**, 876–877.
86. Desrosiers, P.; Guram, A.; Hagemeyer, A.; Jandeleit, B.; Poojary, D. M.; Turner, H.; Weinberg, H. *Catal. Today* **2001**, *67*, 397–402.
87. Khenkin, A. M.; Neumann, R. *J. Org. Chem.* **2002**, *67*, 7075–7079.
88. Ben-Daniel, R.; Alster, P.; Neumann, R. *J. Org. Chem.* **2001**, *66*, 8650–8653.
89. Khenkin, A. M.; Shimon, L. J. W.; Neumann, R. *Eur. J. Inorg. Chem.* **2001**, 789–794.
90. Khenkin, A. M.; Shimon, L. J. W.; Neumann, R. *Inorg. Chem.* **2003**, *42*, 3331.
91. Yamaguchi, K.; Mizuno, N. *New J. Chem.* **2002**, *26*, 972–974.
92. Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538–4551.
93. Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144–7145.
94. Corma, A. *Chem. Rev.* **1995**, *95*, 559–614.
95. (a) Raja, R.; Thomas, J. M. *J. Mol. Catal. A: Chem.* **2002**, *181*, 3–14. (b) Thomas, J. M.; Raja, R. *Chem. Commun.* **2001**, 675–687, and references therein. (c) Schuchardt, U.; Cardoso, D.; Sercheli, R.; Pereira, R.; da Cruz, R. S.; Guerreiro, M. C.; Mandelli, D.; Spinace, E. V.; Pires, E. L. *Appl. Catal. A: Gen.* **2001**, *211*, 1–17, and references therein.
96. (a) Zakharov, V. Yu.; Romanovskii, B. V. *Vestnik Moskovskogo Universiteta, Seriya 2: Khimiya* **1977**, *18*, 143–145. (b) Herron, N. *Inorg. Chem.* **1986**, *25*, 4714–4717. (c) Knops-Gerrits, P.-P.; De Vos, D.; Thibault-Starzyk, F.; Jacobs, P. A. *Nature* **1994**, *369*, 543–546. (d) Parton, R. F.; Vankelecom, I. F. J.; Casselman, M. J. A.; Bezoukhanova, C. P.; Uytterhoeven, J. B.; Jacobs, P. A. *Nature* **1994**, *370*, 541–544. (e) Balkus, Jr. K. J.; Eissa, M.; Levado, R. *J. Am. Chem. Soc.* **1995**, *117*, 10753–10754.
97. Zhan, B.-Z.; Li, X.-Y. *Chem. Commun.* **1998**, 349–350.
98. Zhan, B. -Z.; Jacobs, P. A.; Li, X. -Y. *Proceedings of the 12th International Zeolite Conference*; 1999, 2897–2904.
99. Zhan, B. -Z.; Jacobs, P. A.; Li, X. -Y. *Proceedings of the 12th International Zeolite Conference*; 1999, 2905–2912.
100. Matsumoto, M.; Watanabe, N. *J. Org. Chem.* **1984**, *49*, 3435–3436.
101. Son, Y.-C.; Makwana, V. D.; Howell, A. R.; Suib, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4280–4283.
102. Zhan, B.-Z.; White, M. A.; Sham, T.-K.; Pincock, J. A.; Doucet, R. J.; Rao, K. V. R.; Robertson, K. N.; Cameron, T. S. *J. Am. Chem. Soc.* **2003**, *125*, 2195–2199.
103. Zhan, B.-Z.; White, M. A.; Pincock, J. A.; Robertson, K. N.;

Cameron, T. S.; Sham, T.-K. *Can. J. Chem.* **2003**, *81*, 764–769.
104. Zhan, B.-Z.; White, M. A.; Robertson, K. N.; Cameron, T. S.; Gharghouri, M. *Chem. Commun.* **2001**, 1176–1177.
105. Zhan, B.-Z.; White, M. A.; Lumsden, M.; Mueller-Neuhaus, J.; Robertson, K. N.; Cameron, T. S.; Gharghouri, M. *Chem. Mater.* **2002**, *14*, 3636–3642.
106. Mckeown, D. A.; Hagans, P. L.; Carette, L. P. L.; Russell, A. E.; Swider, K. E.; Rolison, D. R. *J. Phys. Chem. B* **1999**, *103*, 4825–4832.

Biographical sketch

Bi-Zeng Zhan was born in Huli (Liangjian, Fujian), China in 1964. He studied chemistry at the Zhongshan (Sun Yat-Sen) University and received his B.Sc. in 1985 and M.Sc in 1988. He was an assistant lecturer and then lecturer (1988-1994) at the Zhongshan University, Guangzhou, China. He moved to Hong Kong in 1994 and received his Ph.D. from the Hong Kong University of Science and Technology in 1998 for his work with Professor Xiao-Yuan Li on nanoscale-confined biomimetic catalysts. With an award of Killam Postdoctoral Fellowship (2000-2002), he joined Dalhousie University in 2000. He is now a research associate in Professor Mary Anne White's materials research group in the Department of Chemistry and Institute for Research in Materials at Dalhousie University. His current research interests concentrate on the design and development of zeolite-based nano-materials, with potential as aerobic oxidation catalysts and solid polymer electrolytes.

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A facile one-pot synthesis of 2-substituted-3-aminoquinolines: preparation of benzo[*b*]naphthyridine-3-carbonitriles

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Abstract—A facile one-pot synthesis of 3-aminoquinolines from *ortho*-aminobenzaldehydes was developed. Ethyl 6,7-dimethoxy-3-aminoquinoline-2-carboxylate, a key intermediate for the preparation of a 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile, was efficiently prepared by this method. Synthetic routes to 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile and 4-anilino-benzo[*b*][1,8]-naphthyridine-3-carbonitrile are described

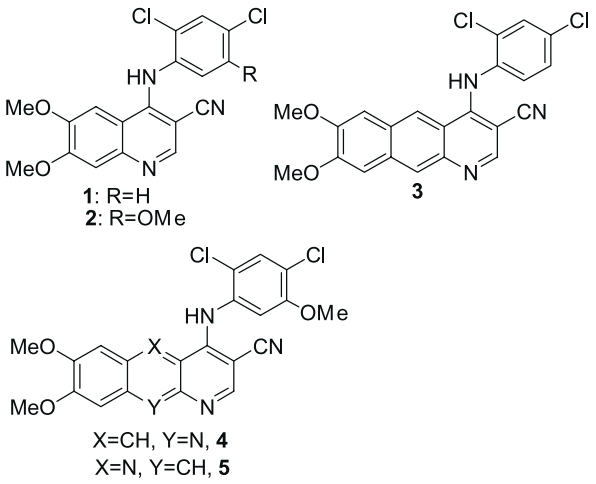
1. Introduction

Protein tyrosine kinases (PTKS), including Src,[1] are key elements in signal transduction pathways regulating a number of cellular functions such as cell growth and differentiation. The activation and over-expression of Src has been implicated in a number of diseases, including cancer.[2] Small molecule inhibitors of Src activity could be beneficial for the treatment of various diseases. Several classes of Src kinase inhibitors have been reported in the literature.[3]

We previously reported that 4-anilino-3-quinolinecarbonitriles,[4,5] **1** and **2**, were potent inhibitors of Src kinase activity. It was subsequently shown that 4-anilino-benzo[*g*]-quinoline-3-carbonitrile **3**,[6] which has a phenyl ring fused to the 3-quinolinecarbonitrile, also inhibited Src kinase activity. Aza analogs of 3-quinolinecarbonitriles (**1** and **2**), which have [1,7], [1,5] or [1,8]-naphthyridine bicyclic cores, were also reported to be inhibitors of PTKs.[7] Compounds **4** and **5**, which have a 5-aza/10-aza tricyclic scaffold, were therefore designed as potential Src inhibitors.

2. Results and discussion

Treatment of 6-nitroveratraldehyde with methyl cyanoacetate followed by reduction provided 2-aminoquinoline **8** (Scheme 1). Reaction of **8** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) followed by addition of the anion of acetonitrile gave **10**. Subsequent chlorination of **10** and coupling reaction of **11** with 2,4-dichloro-5-methoxy-aniline gave the final product **4**.



To synthesize 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile **5** using an analogous approach to the one described above, the major challenge would be the preparation of 3-amino-2-quinolinecarboxylate **C** (Scheme 2). At the inception of our work, there was only one report of the synthesis of a 3-amino-2-quinoline-carboxylate in the literature.

Westphal et al. disclosed[8] that the condensation of *ortho*-aminobenzaldehyde with 1-(2-ethoxycarbonyl-2-oxoethyl)-pyridinium bromide **D**, prepared from pyridine and ethyl 2-bromopyruvate, gave 3-pyridino-quinoline **E** (Scheme 3). Upon treatment with pyrrolidine, **E** was converted to 3-aminoquinoline **F**. A major drawback of this approach

Keywords: 3-Aminoquinolines; Benzo[*b*]naphthyridine-3-carbonitriles.
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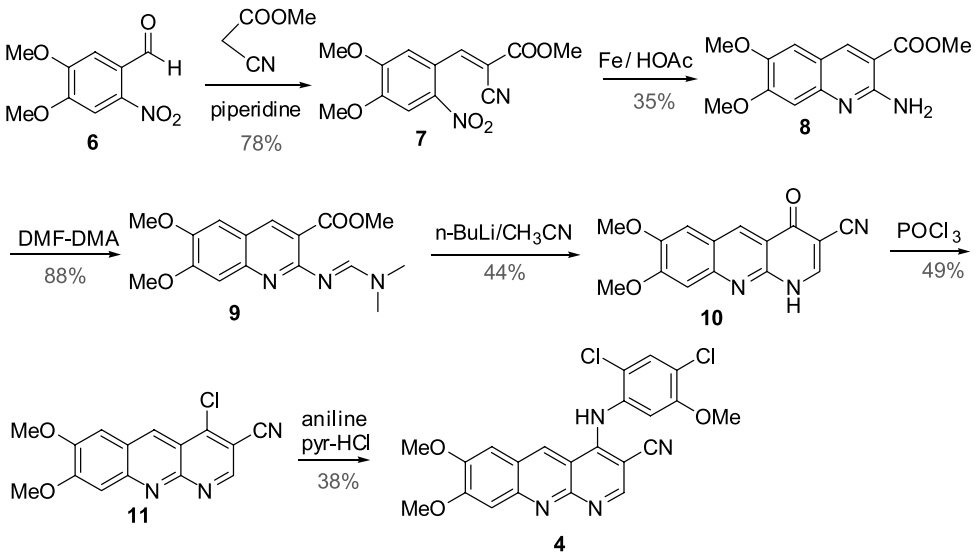
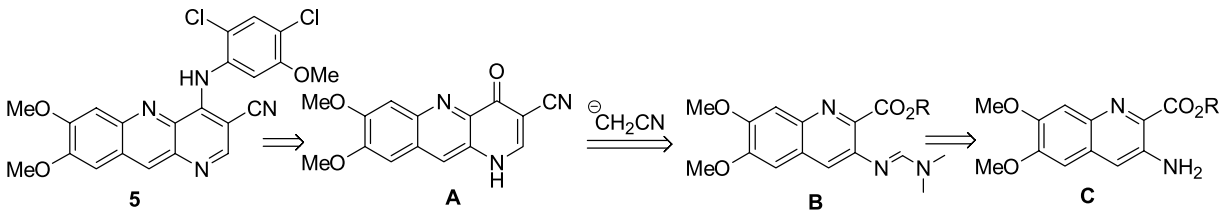
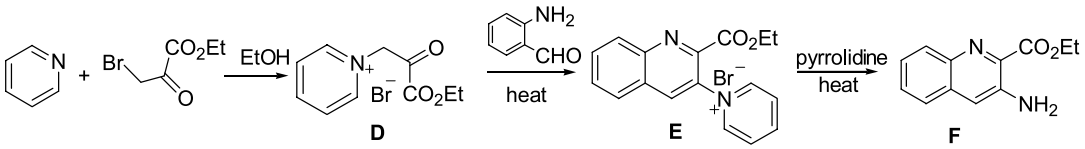


Scheme 1.



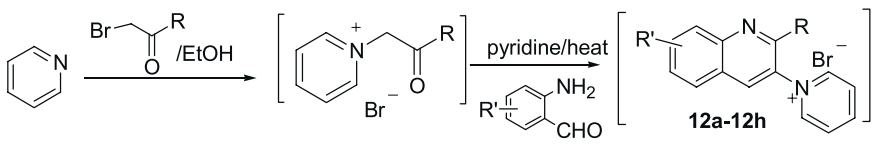
Scheme 2.



Scheme 3.

was that the coupling reaction of **D** with *ortho*-aminobenzaldehyde gave a poor yield (~30%) of **E**. It did, however, offer an efficient and concise approach to functionalized 3-aminoquinolines from readily accessible starting materials.

This prompted us to investigate possible modifications to improve the existing procedure. We found that the poor reproducibility in pyridinium formation and the low yield in its subsequent condensation with *ortho*-aminobenzaldehydes were mainly due to the hydroscopicity and instability of compounds **D** and **E** when exposed to the atmosphere. A one-pot procedure, that did not require separation and purification of intermediates **D** and **E**, was therefore

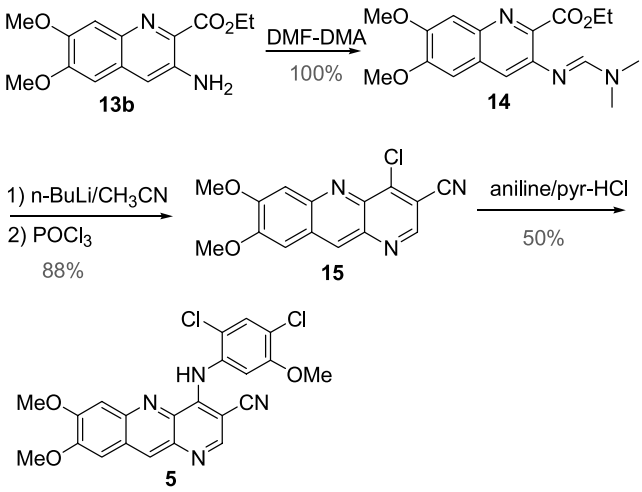


13a R=CO_2Et, R'=H, 90%
13b R=CO_2Et, R'=6,7-dimethoxy, 79%
13c R=CO_2Et, R'=6-Cl, 48%
13d R=CO_2Et, R'=7-Cl, 71%
13e R=CO_2Et, R'=6,8-dibromo, 39%
13f R=phenyl, R'=H, 65%
13g R=phenyl, R'=6,7-dimethoxy, 75%
13h R=methyl, R'=H, 52%

Scheme 4.

developed. In order to improve the overall yield of this one-pot approach, we also optimized the reaction conditions, including temperature, time and the ratio of reagents and substrates. Under the optimal reaction conditions, **13a** (Scheme 4) was obtained in 90% overall yield from *ortho*-aminobenzaldehyde. This method also provided satisfactory yields for the condensations of various substituted *ortho*-aminobenzaldehydes (**13b**-**13e** and **13g**, Scheme 4). By preparing other 2-substituted-3-aminoquinolines (**13f**-**13h**, Scheme 4), the versatility of this methodology was demonstrated. It is worthwhile to note that the coupling reactions of the pyridinium salt with *ortho*-aminobenzaldehydes, when the R group is Me or Ph, were somewhat sluggish. We found that the addition of a catalytic amount of a relatively strong base such as 4-(dimethylamino)pyridine facilitated the reaction.

With ethyl 3-aminoquinoline-2-carboxylate **13b** in hand, we embarked on converting it to the target 4-anilino-benzo-[*b*][1,5]-naphthyridine-3-carbonitrile **5** (Scheme 5). Treatment of **13b** with DMF-DMA gave amidine **14**. Reaction of **14** with the anion of acetonitrile followed by chlorination with phosphorus oxychloride provided **15**. Coupling of **15** with 2,4-dichloro-5-methoxyaniline gave target compound **5**.



Scheme 5.

In summary, we present here an efficient one-pot synthesis of 2-substituted-3-aminoquinolines from *ortho*-amino-benzaldehydes. We demonstrated that this method can potentially be utilized for the preparation of other 3-aminoquinolines with different functional groups at C-2. In addition, first synthetic routes to a benzo[*b*][1,5]-naphthyridine-3-carbonitrile and a benzo[*b*][1,8]-naphthyridine-3-carbonitrile were described. The activities of target molecules **4** and **5** will be disclosed elsewhere.

3. Experimental

3.1. General

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a NT-300 WB spectrometer. Electrospray (ES) mass spectra were recorded on a Microma Platform mass spectrometer. Flash chromatography was performed with Baker 40 μM silica gel. Reactions were generally carried out under an inert atmosphere of nitrogen.

3.2. Compounds 7-11 and 4

3.2.1. Methyl (*E*)-2-cyano-3-(4,5-dimethoxy-2-nitrophenyl)-2-propenoate (7). To a mixture of 6-nitroveratraldehyde (80%) (7.00 g, 33.2 mmol) and methyl cyanoacetate (3.4 mL, 38.4 mmol) in methanol (170 mL) was added piperidine (0.70 mL). The reaction mixture was stirred at room temperature for 1 h. The resultant solid was collected by filtration washing with methanol and diethyl ether to provide **7** (7.57 g, 78%) as a pale yellow solid; mp 162–164 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.90 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.56 (s, 1H), 7.83 (s, 1H), 8.77 (s, 1H); *m*/*z* (ES) $(MH)^-$=292.1. Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.03; H, 4.02; N, 9.59.

3.2.2. Methyl 2-amino-6,7-dimethoxy-3-quinolinecarboxylate (8). A mixture of **7** (7.00 g, 24.0 mmol) and iron (5.00 g, 89.6 mmol) in acetic acid (100 mL) was heated at reflux for 10 min. The reaction mixture was cooled slightly and the solids were removed by filtration, washing with ethyl acetate. The filtrate was concentrated in vacuo and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Trituration of the residue with diethyl ether provided **8** (652 mg, 10%) as a pale yellow solid. Acidification of the aqueous layer with concentrated hydrochloric acid caused additional product to precipitate out. This material was collected by filtration, washed with water and ethyl acetate to provide an additional amount of **8** (1.57 g, 25%); mp 227–229 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.81 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.89 (s, 1H), 6.95 (br s, 2H), 7.27 (s, 1H), 8.59 (s, 1H); *m*/*z* (ES) $(MH)^+$=263.1. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.56; H, 5.46; N, 10.55.

3.2.3. Methyl 2-{[(*E*)-(dimethylamino)methylidene]-amino}-6,7-dimethoxy-3-quinoline-carboxylate (9). A mixture of **8** (3.6 g, 13.0 mmol), *N*,*N*-dimethylformamide dimethyl acetal (4.1 mL, 31.0 mmol) and *p*-toluenesulfonic acid (40 mg) in toluene (60 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and the solid was collected by filtration to provide **9** (737 mg, 18%) as an off-white solid. Concentration of the filtrate provided an additional 2.86 g (70%) of **9**; mp 166–168 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.00 (s, 3H), 3.12 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 7.14 (s, 1H), 7.29 (s, 1H), 8.20 (s, 1H), 8.50 (s, 1H); *m*/*z* (ES) $(MH)^+$=318.1. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.63; H, 6.08; N, 13.32.

3.2.4. 4-Hydroxy-7,8-dimethoxybenzo[*b*][1,8]-naphthyridine-3-carbonitrile (10). To a −78 °C solution of *n*-butyl lithium (9.0 mL of a 2.5 M solution, 22.5 mmol) in tetrahydrofuran (40 mL) was added acetonitrile (1.3 mL,

24.9 mmol). After stirring for 15 min, a solution of **9** (2.86 g, 9.0 mmol) in tetrahydrofuran (100 mL) was added dropwise over 30 min. The mixture was stirred at −78 °C for 30 min then allowed to come to room temperature. The reaction mixture was cooled to −78 °C and acetic acid (3 mL) was added. The reaction mixture was allowed to warm to room temperature. The solids were collected by filtration washing with water, methanol, and ethyl acetate to provide **10** (1.11 g, 44%) as a light yellow solid; mp >300 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.93 (s, 3H), 4.00 (s, 3H), 7.29 (s, 1H), 7.60 (s, 1H), 8.68 (s, 1H), 8.97 (s, 1H); *m/z* (ES) $(MH)^+$=281.9. Anal. Calcd for $C_{15}H_{11}N_3O_3$ −0.65 H_2O: C, 61.49; H, 4.23; N, 14.34. Found: C, 61.40; H, 4.40; N, 14.70.

3.2.5. 4-Chloro-7,8-dimethoxybenzo[*b*][1,8]-naphthyridine-3-carbonitrile (11). A mixture of **10** (500 mg, 1.8 mmol) and phosphorous oxychloride (5 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and hexane was added. The resultant solid was collected by filtration washing with hexane, water, methanol and ethyl acetate to provide **11** (258 mg, 49%) as a brown solid; mp >300 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 4.01 (s, 3H), 4.07 (s, 3H), 7.58 (s, 1H), 7.77 (s, 1H), 9.27 (s, 1H), 9.34 (s, 1H); *m/z* (ES) $(MH)^+$=299.9. Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ −0.40 H_2O: C, 58.70; H, 3.55; N, 13.69. Found: C, 58.85; H, 3.33; N, 13.97.

3.2.6. 4-(2,4-Dichloro-5-methoxyanilino)-7,8-dimethoxybenzo[*b*][1,8]naphthyridine-3-carbonitrile (4). A mixture of **11** (150 mg, 0.50 mmol), 2,4-dichloro-5-methoxyaniline (160 mg, 0.83 mmol) and pyridine hydrochloride (70 mg, 0.60 mmol) in 2-ethoxyethanol (15 mL) was heated at reflux for 25 min. The resultant black solution was cooled to room temperature and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to provide 143 mg of a 10:1 mixture of **4** and **10**. This material was dissolved in ethyl acetate and washed with a solution of saturated aqueous sodium bicarbonate and sodium hydroxide (pH 11) to remove **10**. The organic layer was dried over magnesium sulfate, filtered and reduced in vacuo to about 10 mL. The solids were collected by filtration washing with diethyl ether to provide **4** (86 mg, 38%) as a bright orange solid; mp >290 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.82 (s, 3H), 3.92 (s, 3H), 4.00 (s, 3H), 6.78 (s, 1H), 7.28 (s, 1H), 7.47 (s, 1H), 7.62 (s, 1H), 8.28 (s, 1H), 9.19 (s, 1H); *m/z* (ES) $(MH)^+$=455.0. Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_3$: C, 58.04; H, 3.54; N, 12.31. Found: C, 57.86; H, 3.48; N, 12.30.

3.3. Compounds 13a-13h

3.3.1. Ethyl 3-amino-2-quinolinecarboxylate (13a). To a mixture of pyridine (342 mg, 4.34 mol) and ethanol (12 mL) was added ethyl 2-bromopyruvate (846 mg, 4.34 mmol) in ethanol (8 mL) dropwise over 20 min. The resulting mixture was heated at 60–70 °C for one hour and cooled to room temperature. *ortho*-Aminobenzaldehyde (500 mg, 4.13 mmol) and pyridine (0.80 mL) were added. After heating at reflux for 5 h, pyrrolidine (698 mg, 9.83 mmol) was added. The resulting mixture was heated for an additional 2 h and concentrated. The residue was chromatographed (ethyl acetate/hexanes 1:3) to give **13a** as a yellow solid (762 mg, 90%); mp 148–150 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.38 (t, *J*=5 Hz, 3H), 4.40 (q, *J*=5 Hz, 2H), 6.42 (s, 2H), 7.41 (dt, *J*=5, 1 Hz, 1H), 7.47 (dt, *J*=5, 1 Hz, 1H), 7.51 (s, 1H), 7.67 (d, *J*=5 Hz, 1H), 7.86 (d, *J*=5 Hz, 1H); *m/z* (ES) $(MH)^+$=217.1. Anal. Calcd for $C_{12}H_{12}N_2O_2$ −0.10H_2O: C, 66.10; H, 5.62; N, 12.85. Found: C, 65.82; H, 5.50; N, 12.74.

3.3.2. Ethyl 3-amino-6,7-dimethoxy-2-quinolinecarboxylate (13b). Following the route used to prepare **13a**, **13b** was obtained from 2-amino-4,5-dimethoxybenzaldehyde (1.0 g, 4.74 mmol) as a yellow solid (1.04 g, 79%); mp 168–170 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.35 (t, *J*=5 Hz, 3H), 3.32 (s, 6H), 4.35 (q, *J*=5 Hz, 2H), 6.31 (s, br, 2H), 7.00 (s, 1H), 7.16 (s, 1H), 7.40 (s, 1H); *m/z* (ES) $(MH)^+$=277.2. Anal. Calcd for $C_{14}H_{16}N_2O_4$ −0.10 H_2O: C, 60.46; H, 5.85; N, 10.08. Found: C, 60.20; H, 6.00; N, 9.91.

2-Amino-4,5-dimethoxybenzaldehyde was prepared as follows: A mixture of 3,4-dimethoxy-6-nitrobenzaldehyde (2.0 g, 9,47 mmol) and 10% Pd–C (200 mg) in ethanol (50 mL) was hydrogenated at 40 psi for 2 h. The resulting suspension was filtered and washed with ethanol. The filtrate was used directly in the next step.

3.3.3. Ethyl 3-amino-6-chloro-2-quinolinecarboxylate (13c). Following the route used to prepare **13a**, **13c** was obtained from 2-amino-5-chlorobenzaldehyde (500 mg, 3.21 mmol) as a yellow solid (385 mg, 48%): mp 151–153 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.37 (t, *J*=5 Hz, 3H), 4.41 (q, *J*=5 Hz, 2H), 6.58 (s, 2H), 7.36 (dt, *J*=7, 2 Hz, 1H), 7.46 (s, 1H), 7.82 (d, *J*=2 Hz, 1H), 7.85 (d, *J*=7 Hz, 1H); *m/z* (ES) $(MH)^+$=251.1. Anal. Calcd for $C_{12}H_{11}ClN_2O_2$ −0.1 $C_4H_8O_2$: C, 57.39; H, 4.57; N, 10.80. Found: C, 57.35; H, 4.33; N, 10.53.

3.3.4. Ethyl 3-amino-7-chloro-2-quinolinecarboxylate (13d). Following the route used to prepare **13a**, **13d** was obtained from 2-amino-4-chlorobenzaldehyde[9] (500 mg, 3.21 mmol) as a yellow solid (71%); mp 128–130 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.37 (t, *J*=5 Hz, 3H), 4.40 (q, *J*=5 Hz, 2H), 6.51 (s, 2H), 7.48 (dt, *J*=7, 2 Hz, 1H), 7.55 (s, 1H), 7.74 (d, *J*=7 Hz, 1H), 7.90 (d, *J*=2 Hz, 1H); *m/z* (ES) $(MH)^+$=251.0. Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.22; N, 11.05.

3.3.5. Ethyl 3-amino-6,8-dibromo-2-quinolinecarboxylate (13e). Following the route used to prepare **13a**, **13e** was obtained from 2-amino-3,5-dibromobenzaldehyde (896 mg, 3.21 mmol) as a yellow solid (470 mg, 39%); mp 143–145 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.36 (t, *J*=5 Hz, 3H); 4.41 (q, *J*=5 Hz, 2H), 6.71 (s, br, 2H), 7.48 (s, 1H), 7.88 (d, *J*=2 Hz, 1H), 8.03 (d, *J*=2 Hz, 1H); (*m/z* (ES) $(MH)^+$=374.9. Anal. Calcd for $C_{12}H_{10}Br_2N_2O_2$: C, 38.53; H, 2.53; N, 7.49. Found: C, 38.22; H, 2.53; N, 7.30.

3.3.6. 2-Phenyl-quinoline-3-ylamine (13f). A mixture of 1-phenacylpyridinium bromide (1.20 g, 4.34 mmol), *ortho*-aminobenzaldehyde (0.5 g, 4.13 mmol), pyridine (0.2 mL)

and DMAP (catalytic amount) in ethanol was heated at reflux for 48 h. The reaction mixture was cooled to room temperature and pyrrolidine (0.82 mL, 9.83 mmol) was added. After heating at reflux overnight, the resulting mixture was concentrated. The residue was partitioned between saturated aqueous sodium bicarbonate and methylene chloride. The combined organics were dried over sodium sulfate, concentrated and chromatographed (ethyl acetate/hexanes 1:3) to give **13f** (588 mg, 65%) as a yellow solid; mp 100–101 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 5.25 (s, br, 2H), 7.36–7.40 (m, 3H), 7.47–7.55 (m, 3H), 7.64 (d, J=6 Hz, 1H), 7.73 (dd, J=1, 6 Hz, 2H), 7.79 (d, J=5 Hz, 1H); m/z (ES) $(MH)^+$=221.1. Anal. Calcd for $C_{15}H_{12}N_2$ −0.05 H_2O C, 81.45; H, 5.50; N, 12.67. Found: C, 81.29; H, 5.35; N, 12.69.

3.3.7. 6,7-Dimethoxy-2-phenyl-quinoline-3-ylamine (13g). Following the route used to prepare **13f**, **13g** was obtained from 2-amino-4,5-dimethoxybenzaldehyde (1.0 g, 4.75 mmol) as a yellow solid (996 mg, 75%); mp 148–149 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.84 (s, 3H), 3.87 (s, 3H), 4.98 (s, br, 2H), 7.03 (s, 1H), 7.19 (s, 1H), 7.32 (s, 1H), 7.41–7.52 (m, 3H), 7.72–7.74 (m, 2H); m/z (ES) $(MH)^+$=281.1. Anal. Calcd for $C_{17}H_{16}N_2O_2$ C, 72.84; H, 5.75; N, 9.99. Found: C, 72.44; H, 5.56; N, 9.66.

3.3.8. 2-Methyl-quinoline-3-ylamine (13h). Following the route used to prepare **13f**, **13h** was obtained from *ortho*-aminobenzaldehyde (388 mg, 3.21 mmol) and N-acetonyl-pyridinium bromide (762 mg, 3.53 mmol) as a off-white solid (262 mg, 52%): mp 142–143 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 2.48 (s, 3H), 5.39 (s, br, 2H), 7.16 (s, 1H), 7.27–7.34 (m, 2H), 7.57 (dd, J=6, 3 Hz, 1H), 7.70 (dd, J=6, 3 Hz, 1H); m/z (ES) $(MH)^+$=159.0. Anal. Calcd for $C_{10}H_{10}N_2$ −0.1 CH_2Cl_2 C, 71.31; H, 6.06; N, 16.39. Found: C, 71.33; H, 5.67; N, 16.28.

3.4. Compounds 13-15 and 5

3.4.1. Ethyl 3-{([(*E*)-(dimethylamino)methylidene]-amino}-6,7-dimethoxy-2-quinoline-carboxylate (14). A mixture of **13b** (1.0 g, 3.61 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.34 g, 9.04 mmol) in toluene (30 mL) was heated at 80 °C for 5 h and concentrated. The solid residue was slurried in hexanes, filtered and washed with hexanes to give **14** (1.22 g, 100%) as an off-white solid; mp 135–140 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.31 (t, J=5 Hz, 3H), 2.93 (s, 3H), 3.05 (s, 3H), 4.31 (q, J=5 Hz, 2H), 3.89 (s, 6H), 7.16 (s, 1H), 7.29 (s, 1H), 7.69 (s, 1H), 7.89 (s, 1H); m/z (ES) $(MH)^+$=332.2. Anal. Calcd for $C_{17}H_{21}N_3O_4$ C, 61.62; H, 6.39; N, 12.68. Found: C, 61.78; H, 6.37; N, 12.65.

3.4.2. 4-Chloro-7,8-dimethoxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (15). To an oven-dried three-necked flask was charged tetrahydrofuran (10 mL) and n-butyl lithium (2.5 M in hexanes, 2.8 mL, 6.93 mmol). The mixture was cooled to −78 °C and acetonitrile (284 mg, 6.93 mmol) was added dropwise over 20 min. The resulting mixture was stirred for 30 min and **14** (1.12 g, 3.30 mmol) in tetrahydrofuran (20 mL) was added dropwise via syringe over 30 min. The reaction was allowed to stir at −78 °C for 3 h and quenched with acetic acid (590 mg, 9.90 mmol). The resulting mixture was stirred at room temperature overnight and concentrated. The residue was dissolved in tetrahydrofuran (50 mL) and a few drops of conc. hydrochloric acid were added. The reaction mixture was heated to 70 °C, stirred for 2 h and concentrated. The solid residue was slurried in water (30 mL), filtered and washed with water and ether to provide 7,8-dimethoxy-4-hydroxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (525 mg, 58%) as an off-white solid that was used as it is in next step;

A mixture of 7,8-dimethoxy-4-hydroxy-benzo[*b*][1,5]-naphthyridine-3-carbonitrile (428 mg, 1.52 mmol) and phosphorous oxychloride (4.94 g, 32.2 mmol) was heated at reflux for 1 h and concentrated. The residue was carefully neutralized with saturated sodium bicarbonate with cooling on an ice-bath, filtered and washed thoroughly with water to give **15** (454 mg, 88%) as a light brown solid; mp >340 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 4.02 (s, 3H), 4.07 (s, 3H), 7.56 (s, 1H), 7.57 (s, 1H), 9.04 (s, 1H), 9.18 (s, 1H); m/z (ES) $(MH)^+$=300.1. Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ −2.0 HCl 48.34; H, 3.24; N, 11.08. Found: C, 48.57; H, 3.42; N, 10.75.

3.4.3. 4-(2,4-Dichloro-5-methoxyanilino)-7,8-dimethoxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (5). A mixture of **15** (100 mg, 0.334 mmol), 2,4-dichloro-5-methoxy-aniline (67 mg, 0.351 mmol) and pyridine-HCl (43 mg, 0.368 mmol) in 2-ethoxyethanol (2.2 mL) was heated at 100 °C for 5 h. The resultant reaction mixture was diluted with saturated sodium bicarbonate and was allowed to stir one hour at room temperature. The suspension was filtered and washed thoroughly with water, followed by a minimum amount of methanol and hexanes to give **5** (75 mg, 50%) as a light yellow solid; mp >360 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.76 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.14 (s, 1H), 7.32 (s, 2H), 7.98 (s, 1H), 8.20 (s, 1H); m/z (ES) $(MH)^+$=455.1. Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_3$ −0.5 H_2O C, 56.91; H, 3.67; N, 12.07. Found: C, 56.74; H, 3.70; N, 11.77.

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References and notes

1. Abram, C. L.; Courtneidge, S. A. *Exp. Cell Res.* **2000**, *254*, 1.
2. Frame, M. C. *Biochim. Biophys. Acta* **2002**, *1602*, 114.
3. Boschelli, D. H.; Boschelli, F. *Drug Fut.* **2000**, *25*, 717.
4. Boschelli, D. H.; Wang, Y. D.; Ye, F.; Wu, B.; Zhang, N.; Dutia, M.; Powell, D. W.; Wissner, A.; Weber, J. M.; Boschelli, F. *J. Med. Chem.* **2001**, *44*, 822.
5. Boschelli, D. H.; Ye, F.; Wang, Y. D.; Dutia, M.; Johnson, S. L.; Wu, B.; Miller, K.; Powell, D. W.; Yaczko, D.; Young, M.; Tischler, M.; Arndt, K.; Discafani, C.; Etienne, C.; Gibbons, J.; Grod, J.; Lucas, J.; Weber, J. M.; Boschelli, F. *J. Med. Chem.* **2001**, *44*, 3965.
6. Zhang, N.; Wu, B.; Wissner, A.; Powell, D. W.; Rabindran,

S. K.; Kohler, C.; Boschelli, F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 423.
7. Wissner, A.; Hamann, P. R.; Yamashita, A. WO 0066583, 2000; *CAN* 133,350203.
8. Westphal, G.; Scheybal, A.; Lipke, B.; Weber, F. G. *Pharmazie* **1976**, *31*, 770.
9. Tom, N. J.; Whritenour, D. C. US Patent 2002042516, 2002; *CAN* 136,294741.

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Syntheses of the antibiotic alkaloids renierone, mimocin, renierol, renierol acetate, renierol propionate, and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione

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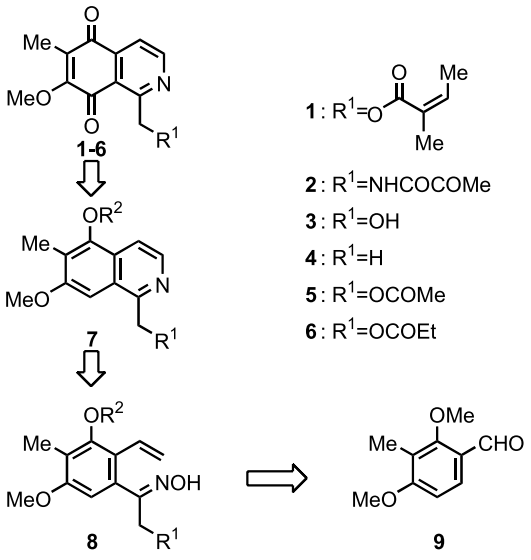
Abstract—The total synthesis of renierone, mimocin, renierol, renierol acetate, renierol propionate, and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione was successfully achieved by the regioselective oxidation of 5-oxygenated isoquinoline. The synthetic method of the 5-oxygenated isoquinoline is based on the thermal electrocyclic reaction of 1-azahexatriene system involving the benzene 1,2-bond.

1. Introduction

Many naturally occurring isoquinoline-5,8-diones have been isolated both from marine sponges and from *Actinomycetes*.[1] The isoquinolinequinones possess significant biological activity,[2] which suggests their potential value as promising structures for the development of new pharmaceuticals. In 1979, renierone (**1**) was isolated from the major metabolite of *Reniera* sp.[3] Mimocin (**2**), isolated from a metabolite of *Streptomyces lavendulae*, contains a pyruvamide side chain in place of the angelate ester side chain of **1**.[4] Renierol (**3**) was isolated from the hard blue sponge *Xestospongia caycedoi*.[6] Further studies of the metabolites of *Reniera* sp. have resulted in the isolation of 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**),[3b,5] which was also found in a blue Philippine marine sponge of the genus *Xestospongia* sp.[6] In addition, renierol acetate (**5**) and renierol propionate (**6**) were isolated from the marine sponge *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*[7] (Scheme 1).



Scheme 1.

Synthetic studies of these antibiotic alkaloids have been conducted by five groups. The total synthesis of renierone (**1**) was established by the groups of Danishefsky[8] and Kubo.[2d,9] Mimocin (**2**) was totally synthesized by the groups of Matsuo[10] and Kubo.[11] The total syntheses of renierol (**3**), renierol acetate (**5**), and renierol propionate (**5**) were reported by the Kubo group.[2d,7c,9a,c] 7-Methoxy-1,6-dimethyl-5,8-dihydro-isoquinoline-5,8-dione (**4**) was synthesized by the groups of Kubo,[9a,c] Liebskind,[12] and Molina.[13] Among these efforts, two regioselective syntheses of the isoquinoline-5,8-dione system have been reported that employ either the oxidation of an 8-aminoisoquinoline derivative with Fremy's salt (Kubo group)[2d,9] or the oxidative demethylation of a 5,7,8-trimethoxyisoquinoline derivative with Ag_2O (Liebskind group).[12] However, it remains difficult to estimate the regioselectivity of oxidative demethylation from the 5,7,8-trimethoxyisoquinoline to

Keywords: Antibiotic alkaloids; Isoquinoline-5,8-diones; Electrocyclic reaction; Azahexatriene system.
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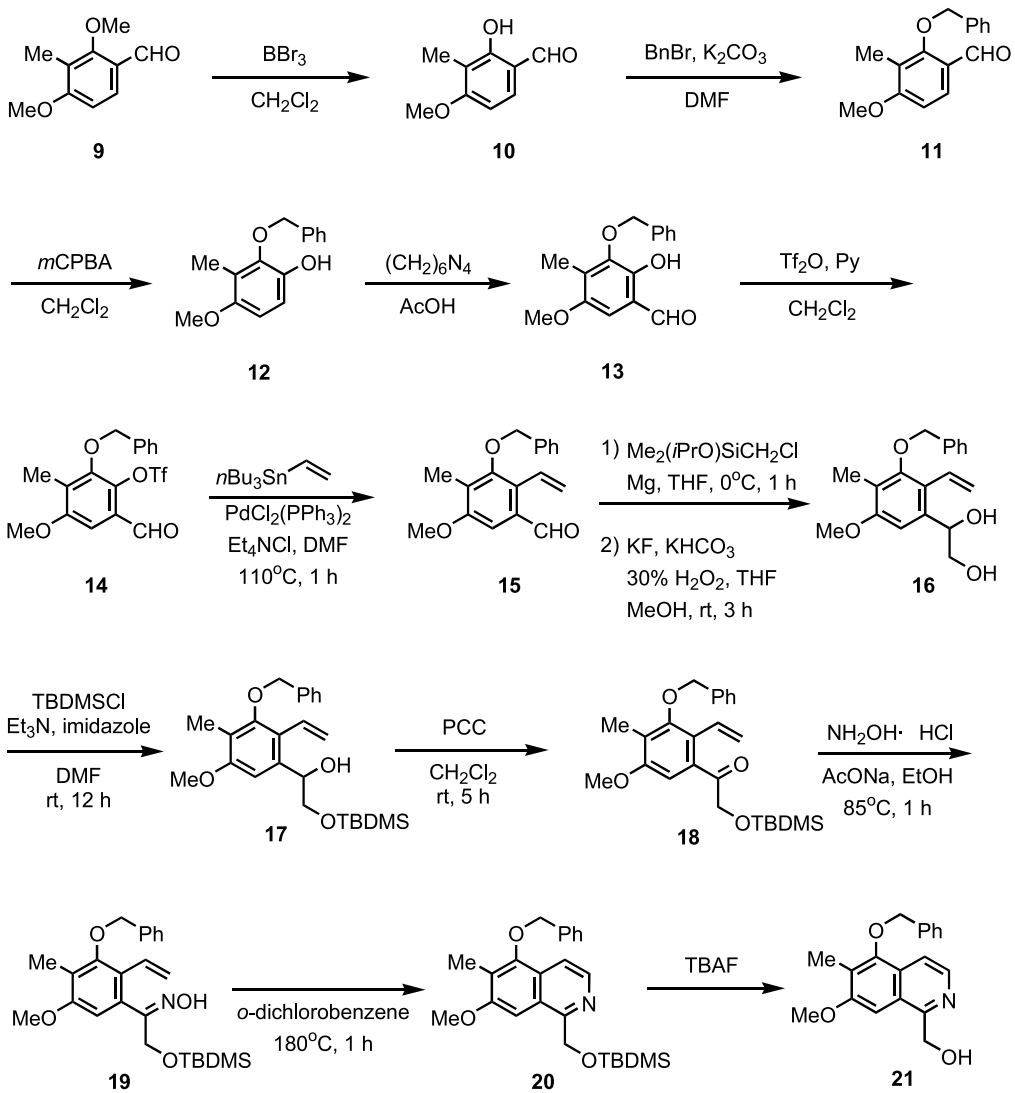
either the isoquinoline-5,8-dione or isoquinoline-7,8-dione using the above synthetic works.

In the course of our studies directed towards the synthesis of biologically active, condensed nitrogen-containing heterocyclic compounds including natural products based on the electrocyclic reaction of a 6π-electron system,[14] we developed thermal electrocyclic reactions using either hexatriene[14c,15] or azahexatriene[14c,16] systems incorporating one double bond of the aromatic or heteroaromatic ring. Recently, we preliminarily reported the total syntheses of renierol (**3**), renierol acetate (**5**), and renierol propionate (**6**) based on the application of our methodology.[17] In this paper, we describe the details of these former studies[17] and the additional total syntheses of renierone (**1**), mimocin (**2**), and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**6**). All of these alkaloids have a common skeleton, 1-hydroxymethyl (or methyl)-7-methoxy-6-methylisoquinoline-5,8-dione, and they differ only in terms of the side chain at C-1 of the isoquinoline ring. There are several classical methods currently used for the synthesis of this type of isoquinoline, e.g., the Bischler-Napieralski reaction. However, we adopted our methodology for the present syntheses, because it has been shown to be advantageous over other approaches due to the cleanliness of the reaction associated with the loss of water.[16] As shown in a retro-synthetic analysis (Scheme 1), we initially planned the synthesis of the common precursor, 5-oxygenated 7-methoxy-6-methylisoquinoline (**7**), in order to achieve the regioselective syntheses of six isoquinoline-5,8-dione antibiotic alkaloids. Namely, a required precursor (**7**) would be obtained by a thermal electrocyclic reaction of *o*-alkenylbenzketoxime (**8**) as a 1-aza-6π-electron system, which would be derived from the known 2,4-dimethoxy-3-methylbenzaldehyde (**9**).[18]

2. Results and discussion

For the preparation of a required precursor (**7**), we began as follows (Scheme 2). The benzaldehyde (**9**) was treated with boron tribromide to produce the 2-hydroxybenzaldehyde (**10**) (88%), which was converted into the benzyl ether (**11**) (99%). The benzaldehyde (**11**) was subjected to the Baeyer–Villiger reaction with *m*-chloroperbenzoic acid (*m*CPBA) to give the phenol (**12**) (88%). The Duff reaction



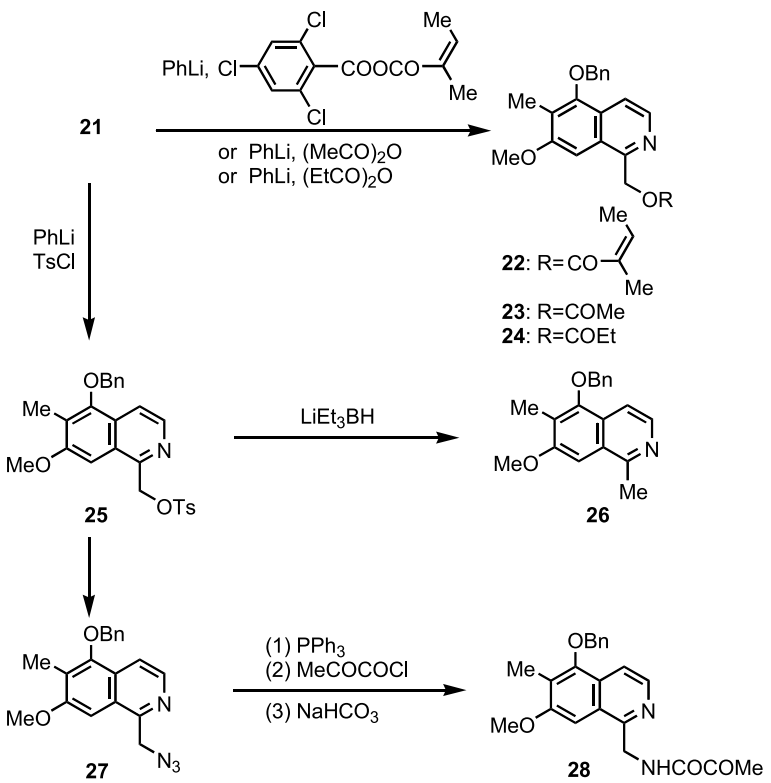
Scheme 2.

of **12** was carried out by hexamethylenetetramine in acetic acid to yield the 2-hydroxybenzaldehyde (**13**) (53%), which was treated with trifluoromethanesulfonic anhydride (Tf_2O) to yield the triflate (**14**) (81%). The cross-coupling reaction of **14** with vinyl tributyltin in the presence of palladium dichlorobistriphenylphosphine [$PdCl_2(PPh_3)_2$] gave the *o*-ethenylbenzaldehyde (**15**) (90%). The Grignard reaction of **15** with dimethylisopropyloxysilylmethylmagnesium chloride,[19] followed by treatment with potassium fluoride and 30% hydrogen peroxide, afforded the 1,2-diol (**16**) (87%). Selective protection of **16** with *tert*-butyldimethylsilyl chloride (TBDMSCl) produced the TBDMS ether (**17**) (92%), which was oxidized with pyridinium chlorochromate (PCC) to obtain the ketone (**18**). Subsequent treatment of **18** with hydroxylamine afforded the ketoxime (**19**) as a 1-azahexatriene system (**8**) (57%), which was subjected to a thermal electrocyclic reaction in *o*-dichlorobenzene at 180 °C to furnish the desired 5-benzyloxyisoquinoline (**20**) (42%). Although the electrocyclic reaction of the highly substituted substrate (**19**) also proceeded, the yield of **20** was only marginally better than that of the simple *o*-alkenylbenzaldoxime.[20] Deprotection of the TBDMS group of **20** was carried out using tetrabutylammonium fluoride (TBAF) to provide the expected 5-benzyloxy-1-hydroxymethylisoquinoline (**21**) as the common precursor, 5-oxygenated isoquinoline (**7**), with the appropriate substitutents (Scheme 2).

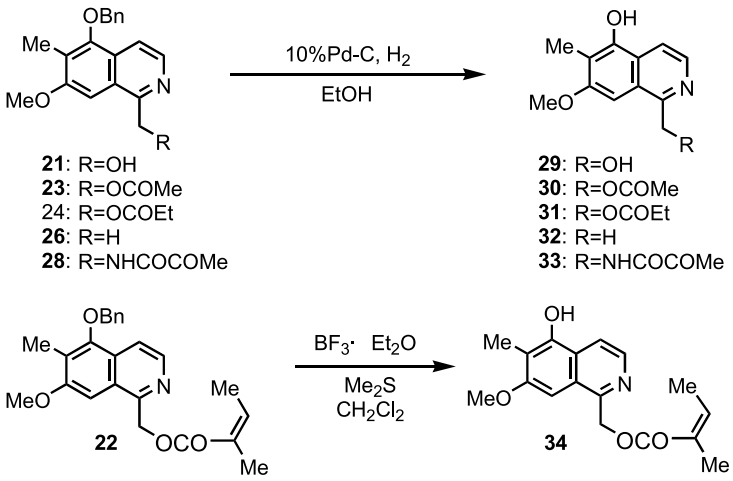
For the next step, the 1-hydroxymethylisoquinoline (**21**) was converted to the corresponding esters; angelate (**22**) (78%), acetate (**23**) (83%), and propionate (**24**) (80%) by treatment of **21** with phenyllithium, followed by the addition of the mixed anhydride[21] of angelic acid with 2,4,6-trichlorobenzoyl chloride, acetic anhydride, and propionic anhydride, respectively. For the conversion of **21** into the 1-methylisoquinoline (**26**), 1-hydroxymethylisoquinoline (**21**) was tosylated by treatment with phenyllithium, followed by the addition of *p*-toluenesulfonyl chloride (*p*-TsCl) (64%). Subsequent reduction of the tosylate (**25**) with lithium triethylborane ($LiEt_3BH$)[9] afforded the 1-methylisoquinoline (**26**) (85%). Furthermore, the nucleophilic substitution reaction of tosyloxymethylisoquinoline (**25**) was carried out by sodium azide to obtain the azide derivative (**27**) (81%), which was treated with triphenylphosphine (PPh_3) in situ, followed by the addition of pyruvoyl chloride,[22] prepared from pyruvic acid and α,α-dichloromethyl methyl ether at 50 °C,[23] to furnish the 1-pyruvoylaminomethylisoquinoline (**28**) (45%). Thus, all of the side chains at the C-1 position of these isoquinoline-5,8-dione alkaloids (**1**–**6**) could be arranged (Scheme 3).

The sequential cleavage of the benzyl groups of **21**, **23**, **24**, **26**, and **28** was carried out by 10% Pd–C and hydrogen in ethanol to give the phenols (**29**–**33**) in excellent yields (91–99%). However, these conditions could not be utilized for **22** because of the reduction of the alkene of the C-1 side chain. Debenzylation of 5-benzyloxyisoquinoline (**22**) successfully proceeded using Fuji's conditions of $BF_3{\cdot}Et_2O$ and Me_2S in dichloromethane[24] to obtain the phenol (**34**) (98%) (Scheme 4).

At the final stage, the oxidation of all of the 5-hydroxyisoquinolines (**29**–**34**) was attempted using two types of oxidizing agents, ceric ammonium nitrate (CAN; Method A),[25] and a combination of salcomine with oxygen (Method

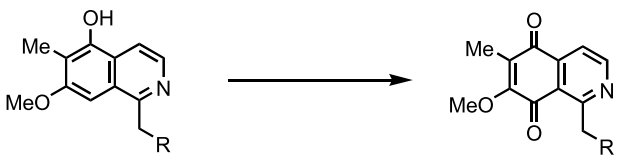


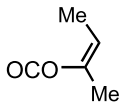
Scheme 3.



Scheme 4.

Table 1. Oxidation of phenols to isoquinoline-5,8-diones



Phenols compounds No.	R	Quinones compounds No.	Oxidizing agents CAN (%)[a]	Salcomine+O_2 (%)[b]
29	OH	**3**	52	78
30	OCOMe	**5**	91	96
31	OCOEt	**6**	87	99
32	H	**4**	81	85
33	NHCOCOMe	**2**	79	85
34		**1**	90	95

[a] Method A.
[b] Method B.

B)[26] to exclusively provide the corresponding isoquinoline-5,8-diones (**1**–**6**) in excellent yields, as shown in Table 1. It was demonstrated that both oxidizing agents produced similar results for the same substrate. The physical data for these isoquinoline-5,8-dione derivatives (**1**–**6**) were consistent with those of natural[3–7] and synthetic[2d,8–13]products in all respects.

3. Conclusions

The total syntheses of the isoquinolinequinone antibiotics, renierone (**1**), mimocin (**2**), renierol (**3**), renierol acetate (**5**), renierol propionate (**6**), and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**) were newly established through the construction of 5-oxygenated isoquinoline (**7**) based on the thermal electrocyclic reaction of 1-aza-6π-electron system (**8**), followed by the regioselective oxidation with both oxidizing agents. Based on this result, it was found that the 5-oxygenated isoquinoline (**7**) is an effective precursor of isoquinoline-5,8-diones (**1**–**6**).

4. Experimental

4.1. General

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Horiba FT-720 spectrophotometer. ^{1}H NMR spectra were taken by JEOL PMX60Si and JNM AL-300 spectrometers using $SiMe_4$ as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on Shimadzu QP-5050 and GC–MS 9020DF spectrometers (EI). Silica gel (60–100 mesh, Merck Art 7734) was used for the column chromatography.

4.1.1. 2-Hydroxy-4-methoxy-3-methylbenzaldehyde (10). A solution of benzaldehyde **9** (6 g, 33.3 mmol) in CH_2Cl_2 (30 mL) was slowly added to a stirred solution of BBr_3 (3.7 mL, 40 mmol) in CH_2Cl_2 (40 mL) at −78 °C under N_2 atmosphere. After gradually being warmed to rt, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated.

The residue was purified by column chromatography (silica gel, 100 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the phenol **10** (4.6 g, 83%), mp 60.5–61.5 °C (Et_2O). IR (KBr) ν: 3400, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.92 (3H, s), 6.56 (1H, d, J=9 Hz), 7.37 (1H, d, J=9 Hz), 9.71 (1H, s), 11.44 (1H, s); MS m/z: 166 (M^+). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.36; H, 6.35.

4.1.2. 2-Benzyloxy-4-methoxy-3-methylbenzaldehyde (11). A mixture of phenol **10** (6 g, 54.2 mmol), benzyl bromide (6.4 mL, 54.2 mmol) and K_2CO_3 (10 g, 72.2 mmol) in DMF (60 mL) was heated at 60 °C for 4 h under N_2 atmosphere. After being cooled to an ambient temperature, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 100 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzyl ether **11** (9.2 g, 99%), mp 57.5–58.5 °C (Et_2O). IR (KBr) ν: 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.19 (3H, s), 3.92 (3H, s), 4.95 (2H, s), 6.77 (1H, d, J=9 Hz), 7.75 (1H, d, J=9 Hz), 10.13 (1H, s); MS m/z: 256 (M^+). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.23; H, 6.52.

4.1.3. 2-Benzyloxy-4-methoxy-3-methylphenol (12). A mixture of benzaldehyde **11** (250 mg, 0.98 mmol), and *m*CPBA (252 mg, 1.46 mmol) in CH_2Cl_2 (15 mL) was heated at 60 °C for 1 h under N_2 atmosphere. After being cooled to an ambient temperature, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated. A solution of the residue in EtOH (5 mL) was added an aqueous KOH solution (10%, 5 mL), and then stirred at rt for 1 h. The mixture was acidified with 1 M HCl, which was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily phenol **12** (209 mg, 88%). IR (neat) ν: 3528 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.79 (3H, s), 4.88 (2H, s), 6.55 (1H, d, J=9 Hz), 6.74 (1H, d, J=9 Hz), 7.45–7.55 (5H, m); MS m/z: 244 (M^+). HRMS calcd for $C_{15}H_{16}O_3$: 244.1099; observed: 244.1105.

4.1.4. 3-Benzyloxy-2-hydroxy-5-methoxy-4-methylbenzaldehyde (13). Hexamethyltetramine (688 mg, 4.91 mmol) was added to a solution of the phenol **12** (200 mg, 0.82 mmol) in AcOH (10 mL), which was heated at 110 °C for 3 h. After being cooled to an ambient temperature, the solution was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzaldehyde **13** (118 mg, 53%), mp 73–74 °C (Et_2O). IR (KBr) ν: 3528, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.82 (3H, s), 5.09 (2H, s), 6.70 (1H, s), 7.32–7.49 (5H, m), 9.83 (1H, s); MS m/z: 272 (M^+). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.85; H, 6.18.

4.1.5. 3-Benzyloxy-5-methoxy-4-methyl-2-(trifluoromethylsulfonyloxy)benzaldehyde (14). Tf_2O (93 μL, 0.55 mmol) was added to an ice-cooled solution of benzaldehyde **13** (100 mg, 0.37 mmol), and pyridine (59 μL, 0.73 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere. After being stirred at the same temperature for 1 h, an aqueous $NaHCO_3$ solution (saturated) was added to the reactant, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the triflate **14** (120 mg, 81%), mp 72–73 °C (Et_2O). IR (KBr) ν: 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.89 (3H, s), 4.96 (2H, s), 7.17 (1H, s), 7.32–7.45 (5H, m), 10.18 (1H, s); MS m/z: 404 (M^+). Anal. Calcd for $C_{17}H_{15}F_3O_6S$: C, 50.50; H, 3.74. Found: C, 50.75; H, 3.90.

4.1.6. 3-Benzyloxy-2-ethenyl-5-methoxy-4-methylbenzaldehyde (15). A mixture of the triflate **14** (843 mg, 2.08 mmol), vinyl *n*-tributyltin (913 mL, 3.13 mmol), Et_4NCl (345 mg, 2.08 mmol) and $PdCl_2(PPh_3)_2$ in DMF (5 mL) was heated at 110 °C for 1.5 h under Ar atmosphere. After being cooled to an ambient temperature, an aqueous KF solution (30%) was added to the reactant, and then the mixture was stirred at rt for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzaldehyde **15** (530 mg, 90%), mp 87–87.5 °C (Et_2O). IR (KBr) ν: 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.90 (3H, s), 4.81 (2H, s), 5.35 (1H, d, J=18 Hz), 5.72 (1H, d, J=12 Hz), 7.03 (1H, d, J=12, 18 Hz), 7.35–7.47 (6H, m), 10.18 (1H, s); MS m/z: 282 (M^+). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.88; H, 6.59.

4.1.7. 1-(3-Benzyloxy-2-ethenyl-5-methoxy-4-methylphenyl)ethane-1,2-diol (16). A solution of the benzaldehyde **15** (60 mg, 0.21 mmol) in THF (3 mL) was added to the Grignard reagent [prepared from chloromethyldimethylisopropoxysilane (191 μL, 1.06 mmol), 1,2-dibromoethane (20 μL, 0.23 mmol), and Mg (26 mg, 1.06 mmol) in THF (2 mL) according to the Tamao's procedure[19]] under N_2 atmosphere. After being stirred at rt for 2 h, the mixture was quenched with an aqueous NH_4Cl solution (10%), and then the mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4, and concentrated at 0 °C. A solution of H_2O_2 (28%, 216 mL, 1.19 mmol) was added to the mixture of the residue, $KHCO_3$ (64 mg, 0.64 mmol), and KF (37 mg, 0.64 mmol) in THF (2 mL) and MeOH (2 mL). After being stirred at rt for 3 h, an aqueous $Na_2S_2O_3$ solution (50%) was added slowly to the mixture. Et_2O was added to the mixture, which was filtered through a pad of Celite. The filtrate was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the diol **16** (58 mg, 87%), mp 79–80 °C (Et_2O). IR (KBr) ν: 3279 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (3H, s), 3.50–3.67 (2H, m), 3.84 (3H, s), 4.72 (2H, s), 5.07–5.11 (1H, m), 5.50 (1H, dd, J=2, 12 Hz), 5.55 (1H, dd, J=2, 18 Hz), 6.82 (1H,

d, J=12, 18 Hz), 6.97 (1H, s), 7.28–7.43 (5H, m); MS m/z: 314 (M^+). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.81; H, 7.32.

4.1.8. 1-(3-Benzyloxy-2-ethenyl-5-methoxy-4-methylphenyl)-2-(*tert*-butyldimethylsilyloxy)ethanol (17). *tert*-Butyldimethylsilyl chloride (57 mg, 0.38 mmol) was added to a solution of the diol **16** (100 mg, 0.32 mmol) and imidazole (65 mg, 0.96 mmol) in DMF (10 mL) at rt under N_2 atmosphere. The mixture was stirred at the same temperature for 1 h. After being quenched with water, the mixture was extracted with EtOAc. The EtOAc layer was washed with an aqueous $NaHCO_3$ solution (saturated), water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the alcohol **17** (126 mg, 92%), mp 68.5–69.5 °C (Et_2O). IR (KBr) ν: 3470 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.92 (9H, s), 2.15 (3H, s), 3.48 (1H, d, J=9 Hz), 3.78 (1H, dd, J=3, 9 Hz), 3.86 (3H, s), 4.68 (1H, d, J=11 Hz), 4.76 (1H, d, J=11 Hz), 5.08 (1H, dd, J=3, 9 Hz), 5.50 (1H, dd, J=2, 12 Hz), 5.57 (1H, dd, J=2, 18 Hz), 6.75 (1H, dd, J=12, 18 Hz), 6.95 (1H, s), 7.32–7.46 (5H, m); MS m/z: 428 (M^+). Anal. Calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.29; H, 8.68.

4.1.9. 2-Benzyloxy-4-[α-(*tert*-butyldimethylsilyloxy)-acetyl]-3-ethenyl-6-methoxytoluene (18). A solution of the alcohol **17** (432 mg, 2.02 mmol) in CH_2Cl_2 (5 mL) was added to an ice-cooled mixture of PCC (434 mg, 2.02 mmol) and Celite (800 mg) in CH_2Cl_2 under N_2 atmosphere. After being stirred at rt for 10 h, the reaction mixture was diluted with Et_2O, and then the mixture was filtrated through a pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily ketone **18** (365 mg, 85%). IR (neat) ν: 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 2.17 (3H, s), 3.83 (3H, s), 4.56 (2H, s), 4.75 (2H, s), 5.41 (1H, dd, J=1.5, 12 Hz), 5.39 (1H, dd, J=1.5, 18 Hz), 6.62 (1H, s), 6.96 (1H, dd, J=12, 18 Hz), 7.30–7.45 (5H, m); MS m/z: 426 (M^+). HRMS calcd for $C_{25}H_{34}O_4Si$: 426.2226; observed: 426.2233.

4.1.10. 2-Benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)-1-(hydroxyimino)ethyl]-3-ethenyl-6-methoxytoluene (19). A mixture of the ketone **18** (240 mg, 0.56 mmol), NH_2-OH·HCl (196 mg, 2.82 mmol) and AcONa (231 mg, 2.82 mmol) in EtOH (10 mL) were heated at 85 °C for 1 h. After being cooled to an ambient temperature, the mixture was concentrated. The water was added to the resulting residue, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the gummy oxime **19** (141 mg, 57%). IR (neat) ν: 3250, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: −0.06 (4H, s), −0.04 (2H, s), 0.71 (6H, s), 0.83 (3, s), 2.16 (2/3H, s), 2.17 (1/3H, s), 3.82 (3H, s), 4.73 (4/3H, s), 4.74 (2/3H, s), 5.31 (1/3H, dd, J=2, 12 Hz), 5.36 (2/3H, dd, J=2, 12 Hz), 5.61 (2/3H, dd, J=2, 18 Hz), 5.69 (1/3H, dd, J=2, 18 Hz), 6.49 (1/3H, s), 6.59 (2/3H, s), 6.75 (1/3H, dd, J=12, 18 Hz), 6.84 (2/3H, dd, J=12, 18 Hz), 7.33–7.47 (5H, m); MS m/z: 441 (M^+). HRMS calcd for $C_{25}H_{35}NO_4Si$: 441.2335; observed: 441.2321.

4.1.11. 1-(*tert*-Butyldimethylsilyloxymethyl)-5-benzyloxy-7-methoxy-6-methylisoquinoline (20). A solution of the oxime **19** (141 mg, 0.32 mmol) in *o*-dichlorobenzene (5 mL) was heated at 180 °C for 1 h. After being cooled to an ambient temperature, the solvent was evaporated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily isoquinoline **20** (66 mg, 49%). ^1H NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 2.34 (3H, s), 3.98 (3H, s), 4.98 (2H, s), 5.22 (2H, s), 7.38–7.55 (6H, m), 7.74 (1H, d, J=6 Hz), 8.29 (1H, dd, J=6 Hz); MS m/z: 423 (M^+). HRMS calcd for $C_{25}H_{33}NO_3Si$: 463.2230; observed: 463.2228.

4.1.12. 5-Benzyloxy-1-hydroxymethyl-7-methoxy-6-methylisoquinoline (21). A solution of TBAF (1.0 M in THF, 107 μL, 0.11 mmol) was added to an ice-cooled solution of the isoquinoline **20** (45.5 mg, 0.11 mmol) in THF (3 mL). After being stirred at rt for 1 h, the reaction mixture was treated with water. The mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the alcohol **21** (30 mg, 89%), mp 144.5–146.5 °C (Et_2O). IR (KBr) ν: 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.98 (3H, s), 4.98 (2H, s), 5.15 (2H, s), 6.85 (1H, s), 7.36–7.54 (5H, m), 7.74 (1H, d, J=6 Hz), 8.33 (1H, dd, J=6 Hz); MS m/z: 309 (M^+). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.97; H, 6.35; N, 4.49.

4.1.13. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl angelate (22). A solution of PhLi (0.88 M in cyclohexane–Et_2O, 771 μL, 0.68 mmol) was added dropwise to an ice-cooled solution of the alcohol **21** (100 mg, 0.32 mmol) in dioxane (5 mL) and Et_2O (5 mL) under N_2 atmosphere. After being stirred at the same temperature for 10 min, the mixed anhydride (angelic 2,4,6-trichlorobenzoic anhydride) [prepared from 2,4,6-trichlorobenzoyl chloride (202 μL, 1.29 mmol), triethylamine (244 μL, 1.62 mmol) and angelic acid (136 mg, 1.36 mmol) in toluene (10 mL) under N_2 atmosphere, according to the Greene's procedure[21]] was added to the mixture. After being stirred at rt for 12 h, the mixture was quenched with water, which was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily ester **22** (98 mg, 78%). IR (neat) ν: 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.90 (3H, dq, J=1.5, 1.5 Hz), 1.98 (3H, dq, J=1.5, 7.2 Hz), 2.34 (3H, s), 3.95 (3H, s), 4.98 (2H, s), 5.77 (2H, s), 6.09 (1H, qq, J=1.5, 7.2 Hz), 7.20 (1H, s), 7.36–7.54 (5H, m), 7.81 (1H, d, J=5.5 Hz), 8.40 (1H, d, J=5.5 Hz); MS m/z: 391 (M^+). HRMS calcd for $C_{24}H_{25}NO_4$: 391.1784; observed: 391.1795.

4.1.14. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl acetate (23). A solution of PhLi (0.88 M in cyclohexane–Et_2O, 154 μL, 0.14 mmol) was added dropwise to an ice-cooled solution of the alcohol **21** (20 mg,

0.06 mmol) in dioxane (2 mL) and Et_2O (2 mL) under N_2 atmosphere. After being stirred at the same temperature for 10 min, $(MeCO)_2O$ (7 μL, 0.07 mmol) was added to the mixture. The mixture was stirred at ambient temperature for 30 min, which was quenched with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the acetate **23** (19 mg, 83%), mp 112.5–113.5 °C (Et_2O). IR (KBr) ν: 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.34 (3H, s), 3.98 (3H, s), 4.97 (2H, s), 5.70 (2H, s), 7.15 (1H, s), 7.38–7.54 (5H, m), 7.80 (1H, d, J=6 Hz), 8.40 (1H, d, J=6 Hz); MS m/z: 351 (M^+). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.98; H, 4.30; N, 3.86.

4.1.15. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl propionate (24). The same procedure as above was carried out using the alcohol **21** (50 mg, 0.16 mmol), PhLi (0.88 M in cyclohexane–Et_2O, 386 μL, 0.34 mmol) and $(EtCO)_2O$ (23 μL, 0.18 mmol) to give the propionate **24** (47.5 mg, 80%), mp 97.5–98.5 °C (Et_2O). IR (KBr) ν: 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.18 (3H, t, J=8 Hz), 2.34 (3H, s), 2.44 (2H, q, J=8 Hz), 3.97 (3H, s), 4.97 (2H, s), 5.70 (2H, s), 7.15 (1H, s), 7.37–7.54 (5H, m), 7.80 (1H, d, J=6 Hz), 8.39 (1H, d, J=6 Hz); MS m/z: 365 (M^+). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.59; H, 6.33; N, 3.74.

4.1.16. 5-Benzyloxy-7-methoxy-6-methyl-1-(4-toluenesulfonyloxymethyl)isoquinoline (25). The same procedure as above was carried out using the alcohol **21** (77 mg, 0.33 mmol), PhLi (0.88 M in cyclohexane–Et_2O, 830 μL, 0.73 mmol) and *p*-TsCl (69 mg, 0.36 mmol) to give the oily tosylate **25** (82 mg, 64%). IR (neat) ν: 1371, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.36 (3H, s), 3.95 (3H, s), 4.88 (2H, s), 5.50 (2H, s), 7.22–7.72 (10H, m), 7.75 (1H, d, J=6 Hz), 8.20 (1H, d, J=6 Hz); MS m/z: 463 (M^+). HRMS calcd for $C_{26}H_{25}NO_5S$: 463.1453; observed: 463.1466.

4.1.17. 5-Benzyloxy-1,6-dimethyl-7-methoxyisoquinoline (26). A solution of $LiEt_3BH$ (1.0 M in THF, 470 mL, 0.48 mmol) was added dropwise to an ice-cooled solution of the tosylate **25** (110 mg, 0.24 mmol) in THF (1 mL). After being stirred at the same temperature for 10 min, the reaction mixture was quenched with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the 1-methylisoquinoline **26** (59 mg, 85%), mp 123–124 °C (Et_2O). ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.92 (3H, s), 4.00 (3H, s), 4.97 (2H, s), 7.09 (1H, s), 7.39–7.55 (5H, m), 7.67 (1H, d, J=6 Hz), 8.27 (1H, d, J=6 Hz); MS m/z: 293 (M^+). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.93; H, 6.49; N, 4.65.

4.1.18. 1-Azidomethyl-5-benzyloxy-7-methoxy-6-methylisoquinoline (27). A solution of NaN_3 (24 mg, 0.37 mmol) in water (3 mL) was added dropwise to an ice-cooled solution of the tosylate **25** (115 mg, 0.25 mmol) in dioxane (15 mL), and then the mixture was stirred at 60 °C for 1 h. After being cooled to an ambient temperature, the mixture was diluted with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the azide **27** (67 mg, 81%), mp 82–83 °C (Et_2O). IR (KBr) ν: 2100, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.99 (3H, s), 4.86 (2H, s), 4.97 (2H, s), 7.10 (1H, s), 7.36–7.53 (5H, m), 7.79 (1H, d, J=6 Hz), 8.36 (1H, d, J=6 Hz); MS m/z: 334 (M^+). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.46; H, 5.54; N, 16.63.

4.1.19. 5-Benzyloxy-7-methoxy-6-methyl-1-(pyruvoylaminomethyl)isoquinoline (28). A solution of PPh_3 (54 mg, 0.21 mmol) in benzene (3 mL) was added dropwise to a solution of the azide **27** (63 mg, 0.19 mmol) in benzene (2 mL) under N_2 atmosphere, and then the solution was stirred at rt for 12 h. The pyruvoyl chloride [prepared from pyruvic acid (52 μL, 0.75 mmol) and α,α-dichloromethyl methyl ether (68 μL, 0.75 mmol) at 50 °C for 30 min[22]] was added dropwise to the ice-cooled solution. After being stirred at rt for 5 min, an aqueous $NaHCO_3$ solution (saturated, 30 mL) and MeOH (10 mL) was added to the ice-cooled mixture, which was stirred at the same temperature for 1 h. The mixture was diluted with water, and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the amide **28** (33 mg, 45%), mp 129.5–131 °C (Et_2O). IR (KBr) ν: 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.55 (3H, s), 400 (3H, s), 4.97 (2H, s), 4.99 (2H, s), 7.04 (1H, s), 7.36–7.53 (5H, m), 7.76 (1H, d, J=6 Hz), 8.34 (1H, d, J=6 Hz), 8.90 (1H, br s),; MS m/z: 378 (M^+). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.98; H, 5.97; N, 7.36.

4.1.20. 5-Hydroxy-1-hydroxymethyl-7-methoxy-6-methylisoquinoline (29). A mixture of the alcohol **21** (52 mg, 0.19 mmol) and 10% Pd–C (10 mg) in EtOH (15 mL) was stirred at rt for 2 h under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the 5-hydroxyisoquinoline **29** (19 mg, 99%), mp 189.5–190 °C (MeOH). IR (KBr) ν: 3017 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.98 (3H, s), 5.09 (2H, s), 7.13 (1H, s), 7.93 (1H, d, J=6 Hz), 8.19 (1H, d, J=6 Hz); MS m/z: 219 (M^+). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 6.15; N, 6.22.

4.1.21. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl acetate (30). The same procedure as above was carried out using the acetate **23** (20 mg, 0.057 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **30** (14.5 mg, 98%), mp 204–205 °C (benzene). IR (KBr) ν: 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.23 (3H, s), 3.96 (3H, s), 5.68 (2H, s), 6.95 (1H, s), 7.86 (1H, d, J=6 Hz), 8.40 (1H, d, J=6 Hz); MS m/z: 261 (M^+), 218. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.56; H, 5.98; N, 5.19.

4.1.22. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl propionate (31). The same procedure as above was carried out using the propionate **24** (42 mg, 0.11 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **31** (31 mg, 98%), mp 167.5–168 °C (benzene). IR (KBr) ν: 3450, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.17 (3H, t, J=8 Hz), 2.30 (3H, s), 2.42 (1H, q, J=8 Hz), 3.94 (3H, s), 5.68 (2H, s), 6.95 (1H, s), 7.87 (1H, d, J=6 Hz), 8.37 (1H, d, J=6 Hz); MS m/z: 275 (M^+), 218. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.75; H, 6.34; N, 4.93.

4.1.23. 5-Hydroxy-7-methoxy-1,6-dimethylisoquinoline (32). The same procedure as above was carried out using the 1-methylisoquinoline **26** (52 mg, 0.12 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **32** (33 mg, 91%), mp 238–240 °C (decomp.) (benzene). IR (KBr) ν: 3439 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.78 (3H, s), 3.89 (3H, s), 6.80 (1H, s), 7.73 (1H, d, J=6 Hz), 8.07 (1H, d, J=6 Hz); MS m/z: 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.14; H, 6.56; N, 6.73.

4.1.24. 5-Hydroxy-7-methoxy-6-methyl-1-(pyruvoylaminomethyl)isoquinoline (33). The same procedure as above was carried out using the 1-methylisoquinoline **28** (62 mg, 0.16 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **33** (42 mg, 91%), mp 174.5–175.5 °C (Et_2O). IR (KBr) ν: 3302, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.30 (3H, s), 2.55 (3H, s), 3.97 (3H, s), 4.95 (2H, d, J=4 Hz), 6.84 (1H, s), 7.82 (1H, d, J=6 Hz), 8.33 (1H, d, J=6 Hz), 8.75–8.85 (1H, br s); MS m/z: 288 (M^+), 202. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.68; H, 5.80; N, 9.62.

4.1.25. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl angelate (34). $BF_3{\cdot}Et_2O$ (214 μL, 1.69 mmol) and Me_2S (170 μL, 2.32 mmol) were added dropwise to an ice-cooled solution of the angelate **28** (33 mg, 0.084 mmol) in CH_2Cl_2 (8 mL), and then the mixture was stirred at rt for 12 h. In Addition, $BF_3{\cdot}Et_2O$ (214 μL, 1.69 mmol) and Me_2S (170 μL, 2.32 mmol) were added to an ice-cooled mixture, which was stirred at rt for 6 h. The mixture was quenched with water, which was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the 5-hydroxyisoquinoline **34** (25 mg, 96%), mp 154–155 °C (Et_2O). IR (KBr) ν: 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.26 (3H, dq, J=1.5, 1.5 Hz), 1.75 (3H, dq, J=1.5, 7.2 Hz), 1.84 (3H, s), 2.29 (3H, s), 3.92 (3H, s), 5.72 (2H, s), 6.90 (1H, qq, J=1.5, 7.2 Hz), 7.00 (1H, s), 7.86 (1H, d, J=6 Hz), 8.38 (1H, d, J=6 Hz); MS m/z: 301 (M^+), 218. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.97; H, 6.58; N, 4.51.

4.1.26. Renierone (1). *Method A*. A solution of CAN (150 mg, 0.27 mmol) of CH_3CN (2 mL) and H_2O (1 mL) was added dropwise to an ice-cooled solution of the phenol **34** (16.5 mg, 0.055 mmol) of CH_3CN (2 mL) and H_2O (1 mL). After being stirred at the same temperature for 30 min, the mixture was diluted with water, which was neutralized with an aqueous $NaHCO_3$ solution (saturated). The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7 v/v) as an eluent to give renierone **1** (15.5 mg, 90%), mp 92–92.5 °C (Et_2O) (lit.,[3a] 91.5–92.5 °C). IR (KBr) ν: 1707, 1666, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.83 (3H, dq, J=1.5, 1.5 Hz), 1.90 (3H, dq, J=1.5, 7.3 Hz), 2.09 (3H, s), 4.14 (3H, s), 5.76 (2H, s), 6.09 (1H, qq, J=1.5, 7.3 Hz), 7.86 (1H, d, J=5 Hz), 8.92 (1H, d, J=5 Hz); MS m/z: 315 (M^+), 83.

Method B. A stirred solution of the phenol **34** (17.3 mg, 0.057 mmol) and salcomine (3.6 mg, 0.011 mmol) in DMF (5 mL) was bubbled with oxygen at rt for 2 h. The reaction mixture was diluted with water, and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give renierone **1** (17.2 mg, 95%).

4.1.27. Mimocin (2). *Method A*. The same procedure as above was carried out using the amide **33** (15.7 mg, 0.055 mmol) and CAN (149 mg, 0.27 mmol) to give mimocin **2** (13 mg, 79%), mp 189–191 °C (decomp.) (Et_2O) (lit.,[4] 189–191 °C). IR (KBr) ν: 3391, 1722, 1684, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.53 (3H, s), 4.17 (3H, s), 5.10 (2H, d, J=5.1 Hz), 8.62 (1H, br s), 8.94 (1H, d, J=5 Hz); MS m/z: 302 (M^+).

Method B. The same procedure as above was carried out using the amide **33** (14.8 mg, 0.051 mmol) and salcomine (3.2 mg, 0.01 mmol) with O_2 to give mimocin **2** (13.2 mg, 85%).

4.1.28. Renierol (3). *Method A*. The same procedure as above was carried out using the 1-hydroxymethylisoquinoline **29** (11 mg, 0.05 mmol) and CAN (143 mg, 0.26 mmol) to give renierol **3** (6.2 mg, 52%), mp 128–130 °C (Et_2O) (lit.,[9c] 131–133 °C). IR (KBr) ν: 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10 (3H, s), 4.15 (3H, s), 4.48 (1H, br s), 5.20 (2H, s), 7.92 (1H, d, J=5 Hz), 8.84 (1H, d, J=5 Hz); MS m/z: 233 (M^+), 233.

Method B. The same procedure as above was carried out using the 1-hydroxymethylisoquinoline **29** (11 mg, 0.05 mmol) and salcomine (3 mg, 0.01 mmol) with O_2 to give renierol **3** (9.1 mg, 78%).

4.1.29. 7-Methoxy-1,6-dimethylisoquinoline-5,8-dione (4). *Method A*. The same procedure as above was carried out using the 1-methylisoquinoline **32** (17.2 mg, 0.084 mmol) and CAN (231 mg, 0.42 mmol) to give the compound **4** (14.9 mg, 81%), mp 186–188.5 °C (Et_2O) (lit.,[3b] 188–190 °C). IR (KBr) ν: 1668, 1628, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.98 (3H, s), 4.14 (3H, s), 7.80 (1H, d, J=5 Hz), 8.84 (1H, d, J=5 Hz); MS m/z: 217 (M^+).

Method B. The same procedure as above was carried out using the 1-methylisoquinoline **32** (15.8 mg, 0.078 mmol) and salcomine (4.9 mg, 0.016 mmol) with O_2 to give the compound **4** (14.3 mg, 85%).

4.1.30. Renierol acetate (5). *Method A*. The same procedure as above was carried out using the acetate **30** (3.9 mg, 0.015 mmol) and CAN (41 mg, 0.075 mmol) to give renierol acetate **5** (2.4 mg, 91%), mp 108–109 °C (Et_2O) (lit.,[7c] 118–119 °C). IR (KBr) ν: 1749, 1674, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.23 (3H, s), 4.15 (3H, s), 5.71 (2H, s), 7.89 (1H, d, J=5 Hz), 8.94 (1H, d, J=5 Hz); MS *m/z*: 275 (M^+), 233.

Method B. The same procedure as above was carried out using the acetate **30** (8.3 mg, 0.032 mmol) and salcomine (2 mg, 0.0064 mmol) with O_2 to give renierol acetate **5** (8.4 mg, 96%).

4.1.31. Renierol propionate (6). *Method A*. The same procedure as above was carried out using the propionate **31** (5.3 mg, 0.019 mmol) and CAN (53 mg, 0.097 mmol) to give renierol propionate **6** (4.9 mg, 87%), mp 88–90 °C (Et_2O) (lit.,[2d] 89–90 °C). IR (KBr) ν: 2960, 1751, 1672, 1653, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.5 Hz), 2.09 (3H, s), 2.52 (2H, d, J=7.5 Hz), 4.15 (3H, s), 5.71 (2H, s), 7.88 (1H, d, J=5 Hz), 8.92 (1H, d, J=5 Hz); MS *m/z*: 289 (M^+), 233.

Method B. The same procedure as above was carried out using the propionate **31** (7.4 mg, 0.027 mmol) and salcomine (3 mg, 0.096 mmol) with O_2 to give renierol propionate **6** (7.7 mg, 99%).

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References and notes

1. (a) Arai, T.; Kubo, A. *The alkaloid*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, pp 44–100. (b) Christopherson, C. *The alkaloid*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 24, pp 25–111. (c) Thompson, R. H. *Naturally occurring quinones*; Chapman and Hall: London, 1987; Vol. III. pp 633–671. (d) Pettit, G. R.; Collins, J. C.; Herald, D. L.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A.; Tackett, L. P. *Can. J. Chem.* **1992**, *70*, 1170–1175. (e) Venkateswarlu, Y.; Reddy, M. V. K.; Srivas, K. V. N.; Rao, J. V. *Indian J. Chem.* **1993**, 704. (f) Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793–798. (g) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A. *J. Nat. Prod.* **2003**, *66*, 544–547.
2. (a) Take, Y.; Oogose, K.; Kubo, T.; Inouye, Y.; Nakamura, S.; Kitahara, Y.; Kubo, A. *J. Antibiotic.* **1987**, *40*, 679–684. (b) Inouye, Y.; Oogose, K.; Take, Y.; Kubo, A.; Nakamura, S. *J. Antibiotic.* **1987**, *40*, 702–705. (c) Take, Y.; Inouye, Y.; Nakamura, S.; Allaudeen, H. S.; Kubo, A. *J. Anitbiotic.* **1989**, *42*, 107–115. (d) Kubo, A.; Kitahara, Y.; Nakahara, S. *Chem. Pharm. Bull.* **1989**, *37*, 1384–1386.
3. (a) McIntire, D. E.; Faulkner, D. J.; Engen, D. V.; Clardy, J. *Tetrahedron Lett.* **1979**, *20*, 4163–4166. (b) Flinke, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 265–269.
4. Kubo, A.; Nakahara, S.; Iwata, R.; Takahashi, K.; Arai, T. *Tetrahedron Lett.* **1980**, *21*, 3207–3208.
5. McKee, T.; Ireland, C. M. *J. Nat. Prod.* **1987**, *50*, 754–756.
6. Edrada, R. A.; Proksch, P.; Wray, V.; Christ, R.; Witte, L.; Van Soest, R. W. M. *J. Nat. Prod.* **1996**, *59*, 973–976.
7. (a) de Silva, E. D.; Glavita, N. K. 16th IUPAC International Symposium on the Chemistry of Natural Products; Kyoto, May 1988, Abstract Pa 8, p 610. (b) Glavita, N. K. University of Hawaii, PhD Dissertation. (c) Kitahara, Y.; Nakahara, S.; Numata, R.; Inaba, K.; Kubo, A. *Chem. Pharm. Bull.* **1985**, *33*, 823–830.
8. Danishefsky, S.; Berman, E.; Cvetovich, R.; Minamikawa, J. *Tetrahedron Lett.* **1980**, *21*, 4819–4822.
9. (a) Kubo, A.; Nakahara, S. *Chem. Pharm. Bull.* **1981**, *29*, 595–596. (b) Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2582–2584. (c) Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4056–4068.
10. (a) Matsuo, K.; Okumura, M.; Tanaka, K. *Chem. Lett.* **1982**, 1339–1340. (b) Matsuo, K.; Okumura, M.; Tanaka, K. *Chem. Pharm. Bull.* **1982**, *30*, 4170–4174.
11. Kubo, A.; Kitahara, Y.; Nakahara, S.; Iwata, R.; Numata, R. *Chem. Pharm. Bull.* **1988**, *36*, 4355–4363.
12. Iyer, S.; Liebskind, S. *J. Am. Chem. Soc.* **1987**, *109*, 2759–2770.
13. Molina, P.; Vidal, A.; Tover, F. *Synthesis* **1997**, 963–966.
14. (a) Okamura, W. H.; de Lera, A. R. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: New York, 1994; Vol. 5, pp 697–750. (b) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443–457. (c) Hibino, S.; Sugino, E. *Advances in nitrogen heterocycles*; Moody, C. J., Ed.; JAI: Greenwich CT, 1995; Vol. 1, pp 205–227.
15. (a) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1996**, *37*, 2593–2596. (b) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535–2545. (c) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1998**, *46*, 1948–1949. (d) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Tetrahedron* **2000**, *58*, 5807–5811. (e) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881–886.
16. (a) Yoshioka, H.; Choshi, T.; Sugino, E.; Hibino, S. *Heterocycles* **1995**, *41*, 161–174. (b) Choshi, T.; Yamada, S.; Sugino, E.; Hibino, S. *Synlett* **1995**, 147–148. (c) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899–5904. (d) Yoshioka, H.; Matsuya, Y.; Chsohi, T.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1996**, *44*, 709–714. (e) Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, E. *Heterocycles* **1996**, *43*, 1847–1854. (f) Choshi, T.; Yamada, S.; Nobuhiro, J.; Mihara, Y.; Sugino, E.; Hibino, S. *Heterocycles* **1998**, *48*, 11–14. (g) Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1998**, *39*, 2341–2344. (h) Sugino, E.; Choshi, T.; Hibino, S. *Heterocycles* **1999**, *50*, 543–559. (i) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108–113. (j) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S. *Heterocycles* **2000**, *53*,

1877–1880. (k) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793–8798.
17. Kuwabara, N.; Hayashi, H.; Hiramatsu, N.; Choshi, T.; Hibino, S. *Chem. Pharm. Bull.* **1999**, *47*, 1805–1807.
18. Godfrey, I. M.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353–1354.
19. Tamao, R.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245–4248.
20. (a) Hibino, S.; Sugino, E.; Adachi, Y.; Nomi, K.; Sato, K. *Heterocycles* **1989**, *28*, 275–282. (b) Hibino, S.; Sugino, E.; Choshi, T.; Sato, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2429–2432.
21. Hartmann, B.; Kanazawa, A. M.; Depres, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077–5080.
22. Barluenga, N.; Fererro, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497–3500.
23. Ottenheijm, H. C.; de Man, J. H. M. *Synthesis* **1975**, 163–164.
24. (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662–3664. (b) Miki, Y.; Fujita, R.; Matsushita, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2533–2536.
25. (a) Joseph, J. R., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629. (b) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521–522. (c) Kubo, A.; Kitahara, Y.; Nakahara, S.; Numata, R. *Chem. Pharm. Bull.* **1983**, *31*, 341–343. (d) Kitahara, Y.; Nakai, T.; Nakahara, S.; Akazawa, M.; Shimizu, M.; Kubo, A. *Chem. Pharm. Bull.* **1991**, *39*, 2256–2263.
26. (a) Bailes, R. H.; Calvin, M. *J. Am. Chem. Soc.* **1947**, *69*, 1886–1893. (b) VanDort, H. M.; Geursen, H. J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 520–526. (c) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232–236. (d) Wakamatsu, T.; Nishi, T.; Ohnuma, T.; Ban, Y. *Synth. Commun.* **1984**, *14*, 1167–1173.

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Site-selective formation of *N*-arylmethylimidazoles and *C*-arylimines in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with aromatic aldehydes

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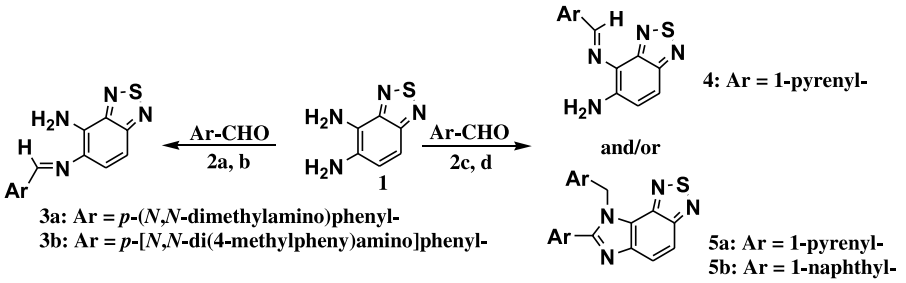
Abstract—Regioselective formation of *N*-arylmethylimidazoles and *C*-arylimines was found in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with selected aromatic aldehydes. The regiochemistry of the reaction products was confirmed by single crystal X-ray analysis. Gibbs free energy calculation using DFT method at the B3LYP/6-31G(d) level supports the regio-selectivity observed. The 4-imine obtained in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with pyrene-1-carboxaldehyde showed an unusually low magnetic field shift of the imine proton that was reproduced by molecular calculations.

1. Introduction

Since introduction of hetero atoms perturbs the photo- and electro-chemical properties of aromatic π-systems, various types of heteroaromatic compounds have been studied as carrier (hole and electron) transporting and light emitting materials for electroluminescent (EL) devices.[1] In this context, condensed heterocyclic ring systems with thiadiazole, imidazole, and oxadiazole substructures have been extensively studied.[2] During the course of our investigation for heteroaromatic EL materials, it was found that *N*-arylmethylimidazoles and *C*-arylimines were formed in the reactions of 4,5-diamino-2,1,3-benzothiadiazole (**1**) with arylaldehydes **2** in a regioselective manner, depending upon the nature of **2**. Imine **4** resulting from the reaction of pyrene-1-carboxaldehyde (**2c**) and **1** showed an unusual ^{1}H NMR chemical shift of the imine proton at 11 ppm. This unusual chemical shift is explained by use of a molecular orbital calculation, which is also applied to explain the regioselective formation of arylmethylenimidazole **5**.

2. Results and discussion

The reactions of 4,5-dibromo-2,1,3-benzothiadiazole (**1**) with arylaldehydes **2** are represented in Scheme 1. The



Scheme 1.

Keywords: Thiadiazole; Regioselective formation; Chemical shift; B3LYP/6-31G(d).
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reactions with *p*-(*N*,*N*-dimethylamino)benzaldehyde (**2a**) and *p*-[*N*,*N*-di(4-methylphenyl) amino]benzaldehyde (**2b**) in toluene under reflux conditions gave the corresponding 5-imino derivatives **3a** and **3b** in 30 and 40% yields, respectively. Corresponding isomeric 4-imines were not found in the reaction mixtures. On the other hand, the reaction of **1** with pyrene-1-carboxaldehyde (**2c**) afforded 4-imino compound **4** and 8-arylmethylenimidazole **5a** in 9 and 15% yields, respectively. Similar reaction of **1** with naphthalene-1-carboxaldehyde (**2d**) gave imidazole **5b** as the only product in 20% yield. The formation of 8-arylmethylen-7-arylbenz[*d*]imidazoles is well documented in the reaction of *o*-phenylenediamine with aromatic aldehydes.[3]

The product structures are deduced from spectral data and confirmed by single crystal X-ray analysis of **3a**, **4**, and **5b**. The ORTEP drawings are shown in Figures 1–3.

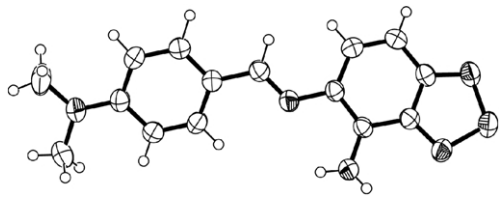


Figure 1. ORTEP drawing of **3a**.

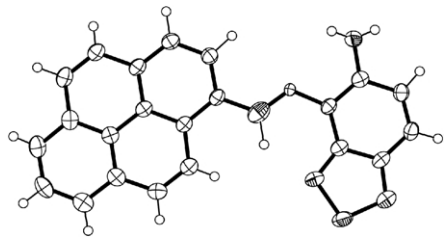


Figure 2. ORTEP drawing of **4**.

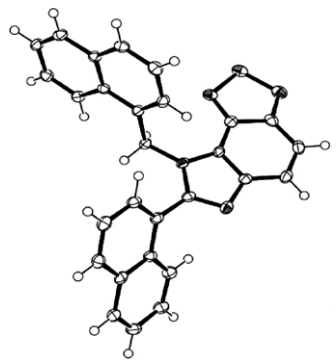
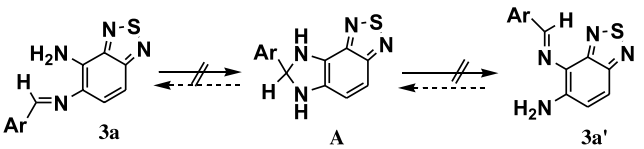


Figure 3. ORTEP drawing of **5b**.

In the reaction of **1** with aromatic aldehydes **2**, the regioselective formation of imines was observed with selected aromatic aldehydes **2**. Isomerization of 5-imino derivative **3a** to the corresponding regioisomer via the cyclic imidazoline intermediate **A** (Scheme 2) was not observed. The starting imine **3a** was recovered quantitatively after toluene reflux for 24 h, while under the same conditions, 4-imino compound **4** was inert.



Scheme 2.

Gibbs free energy calculation using DFT method at the B3LYP/6-31G(d) level[4–6] supports the selective formation of 5-imine **3a** and 4-imine **4** over the corresponding isomers, respectively, although the difference is not large. The molecular calculation estimates that **3a** is 0.81 kcal/mol more stable than **3a**′ and *C*-pyrenyl-4-imino derivative **4** is 0.45 kcal/mol more stable than the 5-imino isomer **4**′.[7]

Imidazole **5** seems less congested than the regioisomeric 6-arylmethyl derivative **5**′, in which the steric repulsion between the arylmethyl group and the proton on the *peri*-position is expected. The molecular calculation supports the selective formation of the imidazole **5**; 8-arylmethyl compound **5a** is 1.98 kcal/mol more stable than the corresponding **5**′.[4–6] As one of possible routes to **5**, a cyclization of the imino compound such as **4** to produce the imidazoline intermediate like **A**, followed by the reaction of the imidazoline with the additional aldehyde could be considered. Electron-donating groups of **3a** and **3b** would reduce the electrophilicity of the imino carbon, which prevents the following cyclization. In the *C*-pyrenylimine **4** with the large substituent compared to naphthyl group, the cyclization from **4** would not proceed perfectly due to the steric factor, which resulted in a mixture of **4** and **5a**.

The most characteristic difference between imines **3** and **4** in the ^{1}H NMR spectra is the imine proton of **4** appearing at an extraordinarily low magnetic field (11.28 ppm). On the other hand, the imine protons of **3a** and **3b** were observed in the usual position at 8.55 and 8.56 ppm, respectively. The single crystal X-ray analysis of **4** shows the close proximity of the imine proton with the nitrogen atom of benzo-2,1,3-thiadiazole ring (0.209 nm) induces the formation of a six-membered ring, that in turn deshields by the nitrogen atom of the 2,1,3-thiadiazole ring with the imine proton.

To compare with the theoretical value of ^{1}H NMR signals, the molecular geometries of **3** and **4** were fully optimized at B3LYP/6-31G(d) level. The calculation of ^{1}H NMR chemical shift was carried out using the Gauge-Independent

Table 1. Chemical shift (ppm) of imine protons of **3** and **4**

Compound	Observed[a]	Calculated[b]	Compound	Observed[a]	Calculated[b]
3a	8.55	8.60	**4**	11.28	11.86
3a′	—	10.48	**4′**	—	9.94
3b	8.56	—	—		

[a] Measured in $CDCl_3$.
[b] Calculated values using HF/6-31G(d).

Atomic Orbitals (GIAO) method[4,8] at Hartree–Fock (HF)/6-31G(d) level, to well reproduce the low field shift of the imine proton of **4**, as summarized in Table 1.

3. Conclusion

Regioselective formation of imines **3** and **4** and imidazole **5** was found in the reaction of 4,5-diamino-2,1,3-benzothiadiazole (**1**) and arylaldehydes **2** and molecular calculation of Gibbs free energy supports the product selectivity. Interestingly, considerable low magnetic field shift was observed for the imine proton of **4** in the ^{1}H NMR spectrum. The single-crystal X-ray analysis gave evidence of a deshielding mechanism by the nitrogen atom of the thiadiazole ring with the imine proton.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400. IR spectra were measured as KBr pellets using a JASCO FT/IR-420. High-resolution mass spectra (HRMS) were measured using JEOL JMS-70. Melting points were determined by differential scanning calorimeter (DSC) of a Perkin–Elmer Pyris 1. Column chromatography was conducted using silica gel 60 (70–230 mesh, Merck). In general, all organic reagents were used as received. Toluene was dried over activated molecular sieves 4A.

4.2. General procedure for the reaction of 4,5-diamino-2,1,3-benzothiadiazole (1) with aryl aldehydes 2

In a 300 ml three-necked flask equipped with Dean-Stark trap, a solution of **2** (6.02 mmol) in toluene (10 ml) was added to a solution of **1** (1.00 g, 6.02 mmol) in toluene (140 ml). The mixture was heated under reflux for 6 h and the solvent was evaporated in vacuo. The residue was column-chromatographed using a 5:1 mixture of toluene and ethyl acetate for **3a** and **3b**, a 19:1 mixture of toluene and ethyl acetate for **4**, **5a**, and **5b**.

4.2.1. 4-Amino-5-[*p*-(*N*,*N*-dimethylamino)benzylidene]-2,1,3-benzothiadiazole 3a. Red crystal (ethyl acetate/hexane); mp 145 °C; IR (KBr) cm^{-1} 3478, 3369, 1600, 1525, 1358, 1163, 818; ^{1}H NMR ($CDCl_3$) δ: 3.08 (s, 6H), 5.18 (brs, 2H), 6.76 (d, 2H, J=8.8 Hz), 7.34 (d, 1H, J=9.2 Hz), 7.59 (d, 1H, J=9.2 Hz), 7.83 (d, 2H, J=8.8 Hz), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 109.09, 120.17, 122.55, 125.64, 128.86, 129.43, 129.56, 130.07, 133.39, 133.88, 144.23, 148.16, 150.98, 154.37, 155.43; HRMS (EI) *m*/*z* calcd for $C_{15}H_{15}N_5S$ 297.1048. Found 297.1053; Anal. calcd for $C_{15}H_{15}N_5S$: C, 60.58; H, 5.08; N, 23.55. Found: C, 60.45; H, 5.06; N, 23.32.

4.2.2. 4-Amino-5-[*p*-[*N*,*N*-di(4-methylphenyl)amino]-benzylidene]-2,1,3-benzothiadiazole 3b. Red crystal (ethyl acetate/*n*-hexane), mp 153 °C; IR cm^{-1} 3455, 3353, 3031, 1596, 1502, 1322, 1275, 823; ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 6H), 5.21 (brs, 2H), 7.02–7.14 (m, 10H), 7.33 (d, 1H, J=9.2 Hz), 7.58 (d, 1H, J=9.2 Hz), 7.75 (d, 2H, J=8.8 Hz), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 109.09, 120.17, 122.55, 125.64, 128.86, 129.43, 129.56, 130.07, 133.39, 133.88, 144.23, 148.16, 150.98, 154.37, 155.43; HRMS (EI) *m*/*z* calcd for $C_{27}H_{23}N_5S$ 449.1671. Found 449.1674; Anal. calcd for $C_{27}H_{23}N_5S$: C, 72.13; H, 5.16; N, 15.58. Found: C, 71.88; H, 5.18; N, 15.32.

4.2.3. 5-Amino-4-[(pyren-1-yl)methylidene]-2,1,3-benzothiadiazole 4. Deep orange crystal (chloroform/acetone); mp 200 °C; IR (KBr) cm^{-1} 3427, 3330, 3038, 1608, 1515, 1302, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.23 (brs, 2H), 7.28 (d, 1H, J=9.2 Hz), 7.75 (d, 1H, J=9.2 Hz), 8.03–8.28 (m, 7H), 8.94–9.00 (m, 2H), 11.28 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 117.19, 120.87, 121.73, 123.83, 124.50, 124.97, 125.05, 125.55, 125.84, 125.89, 126.31, 127.35, 128.14, 128.56, 129.33, 130.05, 130.32, 130.74, 132.00, 147.65, 150.18, 150.75, 152.77; HRMS (EI) *m*/*z* calcd for $C_{23}H_{14}N_4S$ 378.0939. Found 378.0943; Anal. calcd for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; Found: C, 72.59; H, 3.84; N, 14.57.

4.2.4. 7-[4-(*N*,*N*-Dimethylamino)phenyl]-8-[(peren-1-yl)methyl]imidazo[4,5-*e*]-2,1,3-benzothiadiazole 5a. Yellow crystal (chloroform/acetone); mp 262 °C. IR (KBr) cm^{-1} 3039, 1604, 1523, 1430, 1288, 837. ^{1}H NMR ($CDCl_3$) δ: 6.64 (s, 2H), 7.21 (d, 1H, J=8.2 Hz), 7.60–7.82 (m, 7H), 7.85–8.10 (m, 10H), 8.16 (d, 1H, J=8.0 Hz), 8.25 (d, 1H, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 48.1, 116.3, 121.5, 123.8, 124.0, 124.3, 124.6, 125.7, 127.0, 127.4, 128.6, 128.7, 130.4, 130.5, 131.1, 132.5, 142.6, 144.6, 153.1, 154.7; HRMS (FAB) *m*/*z* calcd for $C_{40}H_{22}N_4S$ 590.1555. Found 590.1565; Anal. calcd for $C_{23}H_{14}N_4S$: C, 81.33; H, 3.75; N, 9.48. Found: C, 81.32; H, 3.86; N, 9.30.

4.2.5. 7-[4-(*N*,*N*-Dimethylamino)phenyl]-8-[(naphth-1-yl)methyl]imidazo[4,5-*e*]-2,1,3-benzothiadiazole 5b. Yellow crystal (chloroform/acetone); mp 220 °C. IR (KBr) cm^{-1} 3062, 1607, 1515, 1287, 1072, 804. ^{1}H NMR ($CDCl_3$) δ: 6.32 (s, 2H), 6.54 (d, 1H, J=7.4 Hz), 7.10 (dd, 1H, J=7.4, 7.4 Hz), 7.31 (dd, 1H, J=8.2, 8.2 Hz), 7.40–7.53 (m, 5H), 7.64 (d, 1H, J=8.2 Hz), 7.77–7.94 (m, 6H), 8.18 (d, 1H, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 48.1, 116.3, 122.3, 123.0, 125.1, 125.2, 126.0, 126.5, 126.9, 128.1, 128.5, 128.9, 130.2, 130.6, 132.2, 132.3, 133.6, 133.7, 142.5, 144.5, 152.5, 154.5; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{19}N_4S$

$[M+H]^+$: 443.1328. Found 443.1330; Anal. calcd for $C_{28}H_{18}N_4S$: C, 75.99; H, 4.10; N, 12.66. Found: C, 76.13; H, 3.77; N, 12.22.

4.3. X-ray crystallography

All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation.

4.3.1. Crystal data: for $C_{15}H_{15}N_5S$ 3a. Monoclinic space group $P21/n$, a=12.9379 (6) Å, b=8.1971 (4) Å, c=14.8002 (7) Å, β=114.075 (2)°, V=1433.1 (1) Å^3, Z=4, crystal size 0.35×0.30×0.15 mm^3, T=300 K; Of the 3513 reflections that were collected, 3276 were unique; equivalent reflections were merged (maximum 2θ=55.0°, R_{int}=0.000). Refinement gave R_1=0.043 [$I>3\sigma(I)$] and wR_2 [$I>3\sigma(I)$]=0.121.

4.3.2. Crystal data: for $C_{23}H_{14}N_4S$ 4. Triclinic space group P-1, a=8.040 (3) Å, b=15.349 (8) Å, c=15.42 (1) Å, α=107.80 (4)°, β=104.23 (4)°, γ=95.50 (7)°, V=1725.9 (2) Å^3, Z=4, crystal size 0.50×0.20×0.02 mm^3, T=123 K; Of the 16,268 reflections that were collected, 7617 were unique (maximum 2θ=55.0° R_{int}=0.093); equivalent reflections were merged. Refinement gave R_1=0.073 [$I>3\sigma(I)$] and wR_2 [$I>3\sigma(I)$]=0.200.

4.3.3. Crystal data: for $C_{28}H_{18}N_4S$ 5b. Triclinic space group P-1, a=9.210 (7) Å, b=11.505 (7) Å, c=11.614 (7) Å, α=111.55 (2)°, β=93.37 (2)°, γ=112.31 (3)°, V=1030 (1) Å^3, Z=2, crystal size 0.30×0.12×0.10 mm^3, T=123 K; Of the 38,986 reflections that were collected, 4687 were unique; equivalent reflections were merged (maximum 2θ=55.0°, R_{int}=0.070). Refinement gave R_1=0.043 [$I>2\sigma(I)$] and wR_2 [all reflections]=0.112.

Crystal data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC deposition numbers **3b** (227522), **4** (227523) and **5b** (227524). The supplementary crystallographic data for this paper can be obtained free of charge from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

References and notes

1. (a) Tang, C. W.; VanSlyke, S. A. *Appl. Phys. Lett.* **1987**, *51*, 913. (b) Suzuki, K.; Ueno, K. *J. Photopolym. Sci. Technol.* **2001**, *14*, 311. (c) Suzuki, K.; Seno, A.; Tanabe, H.; Ueno, K. *Synth. Met.* **2004**. in press. (d) Hung, L. S.; Chen, C. H. *Mater. Sci. Engng* **2002**, *R39*, 143.
2. (a) Koga, T.; Takase, A.; Yasuda, S.; Yamashita, S.; Gorohmaru, H.; Thiemann, T.; Mataka, S.; Takahashi, K. *Chem. Phys. Lett.* **2002**, *354*, 173. (b) Gorohmaru, H.; Thiemann, T.; Sawada, T.; Takahashi, K.; Nishi-I, K.; Ochi, N.; Kosugi, Y.; Mataka, S. *Heterocycles* **2002**, *56*, 421. (c) Mataka, S.; Gorohmaru, H.; Thiemann, T.; Sawada, T.; Takahashi, K.; Tori-i, A. *Heterocycles* **1999**, *50*, 895. (d) Mataka, S.; Isomura, K.; Sawada, T.; Tsukinoki, T.; Tashiro, M.; Takahashi, K.; Tori-i, A. *Heterocycles* **1998**, *48*, 113. (e) Mataka, S.; Ikezaki, Y.; Shimojo, Y.; Tori-i, A.; Tashiro, M. *Chemische Berichte* **1993**, *126*, 2767. (f) Mataka, S.; Misumi, O.; Lin, W-H.; Tashiro, M.; Takahashi, K.; Torii, A. *J. Heterocyclic Chem.* **1992**, *29*, 87. (g) Mataka, S.; Ikezaki, Y.; Takahashi, K.; Tori-i, A.; Tashiro, M. *Heterocycles* **1992**, *33*, 791.
3. (a) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279. (b) Katrisky, A. R.; Rees, C. W. *Comprehensive heterocyclic chemistry*; Elsevier Science: Amsterdam, 1997; 5. p 471, and references cited therein. The formation of *N*-benzylimidazole resulted from a reaction of *C*-phenylendiamine and benzaldehyde was reported though the detailed mechanism was not cleared.
4. The present calculation was performed using the Gaussian 98 program. Gaussian 98, Revision A.9: Frisch, J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1998..
5. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
6. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
7. Gibbs free energies are calculated as the gas phase at 1.0 atm. and 298.15 K.
8. Wolinski, K. W.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

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Silylative *N*-hydroxyalkylation of amide compounds: application to the synthesis of acyclic alditol-based nucleoside analogues

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Abstract—A rare silylative hydroxyalkylation of amide compounds with chiral aldehydes has been developed utilizing a Lewis acid–Lewis base promoter system consisting of an equimolecular mixture of *tert*-butyldimethylsilyl trifluoromethanesulfonate and *N*-diisopropylethylamine. This approach culminated in the synthesis of several enantiopure acyclic nucleoside representatives comprising thymidine analogues **6**, **7**, **9**, **10**, **12** and **13**, uridine analogues **15** and **16**, and 6-chloropurine derivatives **18** and **19**.

1. Introduction

Tandem processes where two or more discrete reactions are triggered sequentially by the same reagent or catalyst system are inherently attractive for several reasons.[1,2] For example, they are simple and expeditious and can be managed with a substantial level of atom economy and stereocontrol. Their practical impact is markedly enhanced when a highly efficient, irreversible step terminates a scarcely productive cascade of reversible events, to give stable products which can be easily isolated.

A few years ago, the discovery was made in these laboratories that when a critical intramolecular aldol reaction, which is typically unproductive under conventional aldol coupling conditions,[3] was followed up by an irreversible silylation and used as the final step in the sequence of reversible events leading up to carbon–carbon bond formation, it became highly productive, as shown in Figure 1 (eq 1).[4] In the event, the combined use of a bulky silyl triflate with a suitable tertiary amine co-mediated enolsilane formation (**A** to **C**) as well as both carbon–carbon bond construction and aldolate oxygen silylation (**C** to **E**) to finally give *O*-silylated cycloaldols with complete conversion of the starting aldehyde substrate and excellent diastereocontrol.

In this paper, we establish that analogous Lewis acid–Lewis base combinations trigger sequential intermolecular hydroxyalkylation–silylation reactions of amide compounds with aldehydes leading to stable and easily isolated *N*-silyloxyalkylamides (*N*-acyl-*O*-silyl acetals) in high yields (Fig. 1, eq 2).

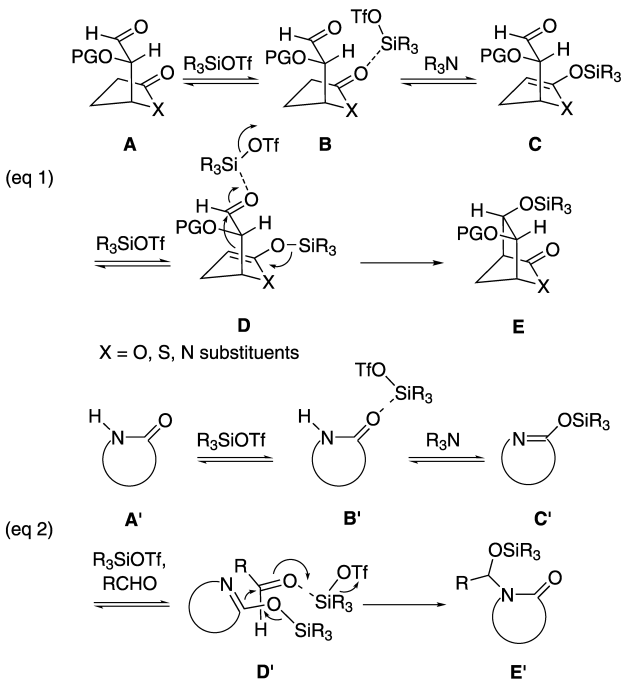

Figure 1. Parallelism between the silylative cycloaldolization cascade and the silylative hydroxyalkylation.

In this current study, we also demonstrate the utility of this silylative carbon–nitrogen bond-forming protocol in the mild synthesis of acyclic, alditol-based nucleoside

Keywords: Amide compounds; *N*-Hydroxyalkylation; Silylation; Acyclic nucleosides.
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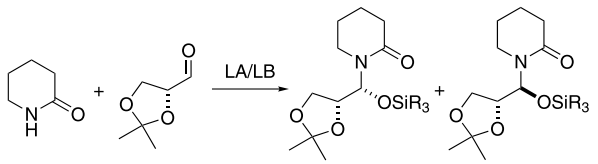
analogues in a chiral nonracemic format (e.g. compounds **6**, **7**, **9**, **10**, **12**, **13**, **15**, **16**, **18**, **19**).[5]

2. Results and discussion

To initiate our study, we examined the ability of the Lewis acid–Lewis base combinations (R_3SiOTf/R_3N) in promoting the silylative coupling between δ-valerolactam (**1**) and 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) delivering *anti*- and *syn*-configured silyloxypiperidinones **3** and **4** (Table 1).

Table 1. The optimum reaction conditions of silylative coupling between lactam **1** and aldehyde **2**: concerning the triflate/amine promoter system[a,b]



1 **2** **3a:** $R_3 = Bu^tMe_2$ **4a:** $R_3 = Bu^tMe_2$ **3b:** $R_3 = Et_3$ **4b:** $R_3 = Et_3$

Entry	LA (equiv.)	LB (equiv.)	Yield **3**+**4** [%]	Products	dr (**3**:**4**)
1	TBSOTf (1.0)	DIPEA (1.0)	<1		
2	TBSOTf (2.0)	DIPEA (2.0)	28	**3a**, **4a**	75:25
3	TBSOTf (3.0)	DIPEA (3.0)	70	**3a**, **4a**	77:23
4	TBSOTf (3.0)	—	<1		
5	—	DIPEA (3.0)	<1		
6	TBSOTf (4.0)	DIPEA (3.0)	5[c]	**3a**, **4a**	66:34
7	TBSOTf (3.0)	DIPEA (4.0)	<1		
8	TESOTf (3.0)	DIPEA (3.0)	95	**3b**, **4b**	55:45
9	TIPSOTf (3.0)	DIPEA (3.0)	<1		
10	TMSOTf (3.0)	DIPEA (3.0)	<1		
11	TBSOTf (3.0)	Et_3N (3.0)	<1		
12	TBSOTf (3.0)	Sparteine (3.0)	51	**3a**, **4a**	52:48

[a] The reactions were carried out with δ-valerolactam (1.0 equiv., 0.1 M) and 2,3-*O*-isopropylidene-D-glyceraldehyde (2.0 equiv.) at room temperature in THF, for 4 h.
[b] The diastereomeric ratio was determined from analysis of ^1H NMR spectra of the crude product.
[c] Aldehyde **2** was completely consumed.

Well aware of the fragile nature of the *N*-acyl hemiaminal functionality in **3** and **4**, we carefully selected the Lewis acid–Lewis base candidates, reasoning that truly acidic or basic conditions may be incompatible with the *N*,*O*-acetal group, as well as other functionalities in these compounds. The optimum reaction conditions of R_3SiOTf/R_3N-promoted silylative amination of **2** with lactam **1** are shown in Table 1. The nature of the acid–base pair as well as the amine/triflate ratio and the substrate/promoter stoichiometry were found to have a significant influence on the efficiency and reproducibility of the reaction.

On their own, neither the triflate Lewis acid nor the tertiary amine Lewis base are activators. Yet, a freshly prepared combination of 3.0 equiv. TBSOTf and 3.0 equiv. Hünig's base (DIPEA) in THF at room temperature was found to be a superb activator, with the best result summarized in entry 3.[6] When this reaction was carried out by changing the triflate acid–base ratio, it was found that an excess of triflate irremediably contaminated the reaction, whilst an excessive amount of amine rendered the reaction sluggish and unproductive (entries 6 and 7). Changing TBSOTf for TESOTf raised the reaction yield but resulted in a decrease in diastereoselectivity. On the contrary, sterically cumbersome triflates did not activate the reaction, as was the case for TMS. These experiments support the inference that silylation of the aldolate is the key to the success of this reaction. Indeed, when this key step is slowed down (use of TIPSOTf, entry 9) or when the protecting group of the aldolate oxygen is too labile to survive reaction conditions, (use of TMSOTf, entry 10) the reaction as a whole fails. Furthermore, the nature of the base proved critical as only encumbered tertiary amines proved to be efficacious agents. Among the solvents tested (Table 2), aprotic low polarity solvents proved to be effective for the reaction, and a 1:1 (v/v) mixture of THF/hexanes provided the best results (entry 5). Hydroxyalkylation at high concentration did not increase the chemical yield, and dilution only reduced the reaction rate with a negligible gain in diastereoselection (entries 6 and 7). Several reaction temperatures were examined, and coupling at −20 °C markedly reduced the yield, with no increase in diastereoselectivity (entry 8).

Table 2. The optimum reaction conditions of silylative coupling between lactam **1** and aldehyde **2**: concerning solvent, concentration and temperature[a,b]

Entry	Solvent (mL)	*T* (°C)	Yield **3**+**4** [%]	Products	dr (**3**:**4**)
1	THF (20)	25	70	**3a**, **4a**	77:23
2	CH_2Cl_2 (20)	25	33	**3a**, **4a**	58:42
3	Et_2O (20)	25	20	**3a**, **4a**	70:30
4	CH_3CN (20)	25	<1		
5	THF/hexanes (20)[c]	25	78	**3a**, **4a**	80:20
6	THF/hexanes (2)[c]	25	45	**3a**, **4a**	71:29
7	THF/hexanes (60)[c]	25	40	**3a**, **4a**	81:19
8	THF/hexanes (20)[c]	−20	21	**3a**, **4a**	78:22

[a] The reactions were carried out with δ-valerolactam (2.0 mmol) and 2,3-*O*-isopropylidene-D-glyceraldehyde (4.0 mmol) in the presence of TBSOTf (6.0 mmol) and DIPEA (6.0 mmol) in the specified solvent and temperature, for 4 h.
[b] The diastereomeric ratio was determined from analysis of ^1H NMR spectra of the crude product.
[c] 1:1 solvent mixture.

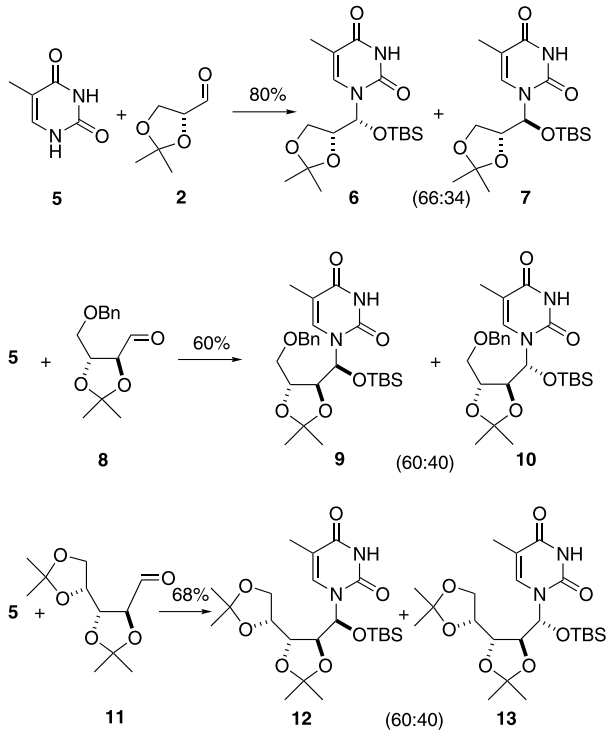
The assignment of the relative stereochemistry for *N*-substituted valerolactams **3a**,**b** and **4a**,**b** was only tentative at this point, with the *anti*-configured isomers **3a**,**b** (Felkin-type preference) predominating over the *syn*-counterparts **4a**,**b** (vide infra).[7]

With the groundwork laid, we then moved ahead to the silylative addition of three representative nucleobases to enantiopure hydroxylated aldehydes, with the intent of producing novel alditol-based acyclic nucleoside analogues.

The superior levels of coupling efficiency observed with the TBSOTf/DIPEA mixture in the optimization exercises mentioned above prompted us to select these reaction conditions for our further investigations.

As highlighted in Scheme 1, thymine (**5**) may be used as a nitrogen nucleophile with certain chiral pool-derived aldehyde acceptors, including glyceraldehyde **2**, threose **8**, and arabinose **11**.

Silylative coupling to **2** gave a mixture of two



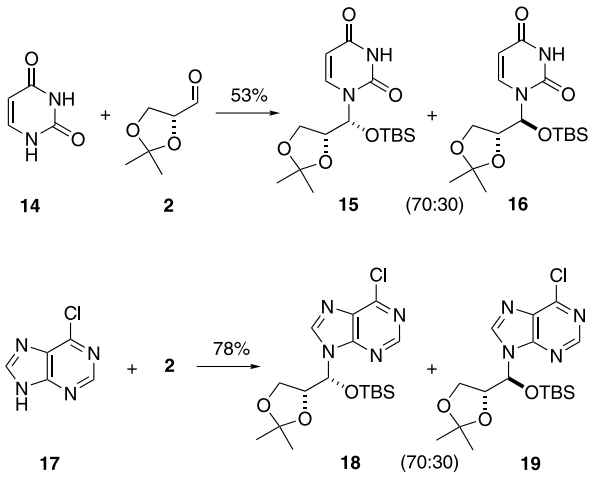
Scheme 1. Silylative hydroxyalkylation of thymine (**5**) with aldehydes **2**, **8** and **11**. The reactions were carried out in the presence of TBSOTf/DIPEA, in 1:1 THF/hexanes at room temperature for 4 h.

chromatographically separable diastereoisomers, **6** and **7**, in a 80% global yield (66:34 isomer ratio). These two C(1′) epimers were readily distinguished by their ^{1}H NMR data; 1′,2′-*anti*-configured glycerol **6** revealed H-1′ to be the expected doublet at 5.92 ppm ($J_{1',2'}$=3.6 Hz), whilst in *syn* isomer **7** the coupling value was markedly larger (5.90 ppm, d, $J_{1',2'}$=6.9 Hz). Based on many experimental analogies with related glycerol adducts[8] and semi-empirical molecular mechanics calculations the stereochemical disposition in **6** and **7** was assessed as shown.[9]

Similarly, threose **8** under the same conditions gave two thymine alditols, **9** and **10**, (60:40 dr) in 60% yield, whereas arabinose **11** produced **12** and **13** in a 68% combined yield and 60:40 *anti*/*syn* diastereomeric ratio. Using the same optimal experimental conditions, the applications of this reaction were further investigated using uracil (**14**) and 6-chloropurine (**17**) as nitrogen donors and glyceraldehyde **2** as the common acceptor (Scheme 2). The expected *anti*- and *syn*-configured C(1′) epimeric couples **15/16** (53% global yield) and **18/19** (78% yield) were obtained with 70:30 diastereomeric ratio.

Inspection of the results in Schemes 1 and 2 reveals that in all experiments 1′,2′-*anti* isomers invariably dominated over the 1′,2′-*syn* counterparts indicating that transition states **A** and **B** are probable models for this silylative addition (Fig. 2).

The Felkin-type model rotamer **A** seems to be favoured over the model rotamer **B** (*anti*-Felkin) where an unfavourable stereoelectronic interaction between the large electronegative aldehyde α-substituent and the incoming heterocyclic nitrogen nucleophile arises.



Scheme 2. Silylative hydroxyalkylation of uracil (**14**) and 6-chloropurine (**17**) with glyceraldehyde **2**. The reactions were carried out in the presence of TBSOTf/DIPEA, in 1:1 THF/hexanes at room temperature for 4 h.

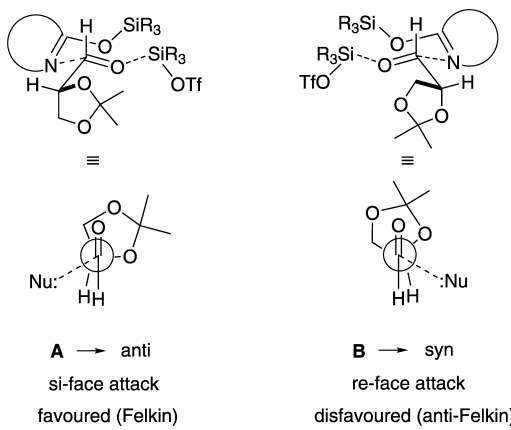
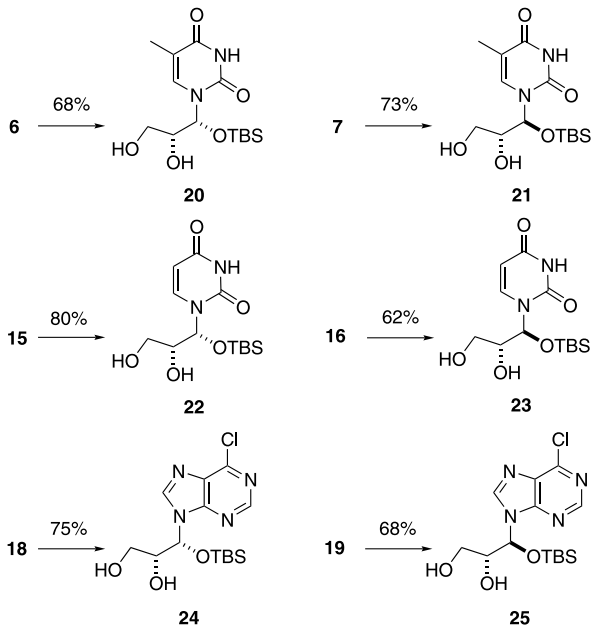


Figure 2. Probable transition state structures in the silylative hydroxyalkylation of amide compounds with chiral α-alkoxyaldehydes.

The alditol-based nucleoside analogues of this study were found to be very stable when in the absence of highly acidic conditions or desilylating reagents (e.g. fluoride ions). As test compounds, thymidine analogues **6** and **7**, uridine analogues **15** and **16**, and 6-chloropurine derivatives **18** and **19** were subjected to acidic removal of the isopropylidene blockage (80% aqueous AcOH, 50 °C) furnishing the respective diols **20**–**25** in very good yields with complete retention of the integrity of the TBS-protected hemiaminal functionalities (Scheme 3).

On the other hand, exposure of the same products to TBAF in THF at room temperature caused a desilylative retrograde addition with recovery of the glyceraldehyde and nucleobase components.

To conclude, the silylation-terminated addition of amide compounds to α-chiral hydroxyaldehydes establishes an efficient methodology for the installation of a stabilized carbon–nitrogen linkage.[10] Under the assistance of a selected Lewis acid–Lewis base combination, TBSOTf/DIPEA, the delicate *N*-acyl hemiaminal motif in the expected adducts is silylated in situ, and stable *N*-silyloxyalkylamides are formed in high isolated yields. The use of



Scheme 3. Selective deacetonidation of nucleosides **6**, **7**, **15**, **16**, **18** and **19**. The reactions were carried out in 80% aqueous AcOH at 50 °C.

nucleobase donors and sugar-derived aldehyde acceptors both expands and ennobles this chemistry further towards the formation of novel chiral nonracemic alditol nucleoside analogues in a single step.

3. Experimental

3.1. General

Flash chromatography was performed on 32–63 μm silica gel, using the indicated solvent mixtures. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} plates (0.25 mm). The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate, followed by charring with a heat gun. Proton and carbon NMR spectra were recorded on a Bruker Avance 300 spectrometer at the frequency indicated. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (0.0 ppm) as an internal reference, with coupling constants in hertz (Hz). Connectivity was determined by $^1H-^1H$ COSY and $^1H-^{13}C$ HETCOR experiments. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at ambient temperature, using a 100 mm cell with a 1 mL capacity and specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}. FT-IR spectra were recorded on a JASCO FT/IR-300E spectrometer. High-resolution mass spectral analyses were carried out using JEOL JMS-SX 102A. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari. Melting points were determined on an optical thermomicroscope Optiphot2-Pol Nikon. All anhydrous solvents were distilled before use: THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2.

3.2. Materials

2,3-*O*-Isopropylidene-D-glyceraldehyde (**2**) was prepared from D-mannitol (Aldrich) according to a recently optimized protocol.[11] 2,3-*O*-Isopropylidene-4-*O*-benzyl-D-threose (**8**) was prepared from commercial 2,3-*O*-isopropylidene-D-threitol (Aldrich).[12,13] 2,3:4,5-Di-*O*-isopropylidene-D-arabinose (**11**) was prepared from the corresponding sugar via dithioacetal formation, acetonidation, and liberation of the aldehyde function, by following the procedures of Zinner.[14]

3.3. Data for compounds

3.3.1. (1′*R*,4″*R*)-1-[(*tert*-Butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]piperidin-2-one (3a) and (1′*S*,4″*R*)-1-[(*tert*-butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]piperidin-2-one (4a). *Typical procedure*. To a solution of diisopropylethylamine (DIPEA) (1.03 mL, 5.94 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (10 mL) at 25 °C under argon atmosphere was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (1.36 mL, 5.94 mmol). The resulting mixture was stirred at the same temperature for 10 min before adding lactam **1** (196 mg, 1.98 mmol) and aldehyde **2** (516 mg, 3.96 mmol) dissolved in 10 mL of the same solvent mixture. The reaction was monitored by TLC and was judged complete after 4 h. The solution was then quenched with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (4:6 hexanes/EtOAc) to give adducts **3a** (422 mg, 62%) and **4a** (109 mg, 16%).

Compound **3a**. Colourless crystals, mp 43–48 °C; $[\alpha]_D^{20}=-14.6$ (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, *J*=6.0 Hz, 1H), 4.18 (q, *J*=6.7 Hz, 1H), 3.95 (dd, *J*=8.4, 6.8 Hz, 1H), 3.78 (dd, *J*=8.4, 6.8 Hz, 1H), 3.56 (m, 1H), 3.20 (m, 1H), 2.3–2.5 (m, 2H), 1.6–1.8 (m, 4H), 1.44 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H) 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 109.9, 77.7, 76.5, 65.5, 41.3, 32.4, 26.3, 25.7 (3C), 25.6, 23.0, 20.8, 18.0, −5.0, −5.1. FT-IR (KBr): 2950, 1681, 1470, 1090 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{17}H_{34}NO_4Si$ (M+H$^+$), 344.2257; found, 344.2269. Anal. calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.59; H, 9.55; N, 4.15.

Compound **4a**. Colourless crystals, mp 72–80 °C; $[\alpha]_D^{20}=-10.7$ (*c* 3.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, *J*=7.6 Hz, 1H), 4.0–4.2 (m, 2H), 3.88 (m, 1H), 3.47 (dtd, *J*=11.8, 4.8, 1.1 Hz, 1H), 3.23 (ddd, *J*=11.9, 9.5, 4.4 Hz, 1H), 2.50 (bdt, *J*=17.9, 5.8 Hz, 1H), 2.34 (ddd, *J*=17.7, 8.9, 6.6 Hz, 1H), 1.6–2.0 (m, 4H), 1.42 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 109.7, 76.1, 74.8, 66.8, 40.1, 32.5, 26.5, 25.5 (3C), 25.4, 22.8, 20.6, 17.6, −4.9, −5.5. FT-IR (KBr): 2954, 1680, 1477, 1070 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{17}H_{34}NO_4Si$ (M+H$^+$), 344.2257; found, 344.2264. Anal. calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.62; H, 9.57; N, 4.20.

3.3.2. (1′*R*,4″*R*)-1-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-(triethylsilanyloxy)methyl]piperidin-2-one (3b) and (1′*S*,4″*R*)-1-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-(triethylsilanyloxy)methyl]piperidin-2-one (4b). The title

compounds were prepared by starting with DIPEA (1.03 mL, 5.94 mmol), triethylsilyl trifluoromethanesulfonate (TESOTf) (1.34 mL, 5.94 mmol), lactam **1** (196 mg, 1.98 mmol) and aldehyde **2** (516 mg, 3.96 mmol) in anhydrous THF (20 mL) according to the above procedure described for compounds **3a** and **4a**. After flash chromatographic purification (4:6 hexanes/EtOAc) there were obtained 354 mg (52%) of pure adduct **3b** along with 293 mg (43%) of pure **4b**.

Compound **3b**. A glassy solid, mp 45–47 °C; $[\alpha]_D^{20}=-13.0$ (*c* 1.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J*=6.0 Hz, 1H,), 4.15 (q, *J*=6.7 Hz, 1H), 3.95 (dd, *J*=8.5, 6.9 Hz, 1H), 3.77 (dd, *J*=8.5, 6.7 Hz, 1H), 3.51 (m, 1H), 3.22 (m, 1H), 2.2–2.4 (m, 2H), 1.6–1.8 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 0.95 (t, *J*=8.1 Hz, 9H), 0.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 110.2, 77.7, 76.4, 66.0, 41.3, 32.0, 26.3, 25.2, 23.0, 21.0, 6.4 (3C), 4.3 (3C). Anal. calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.28; H, 9.67; N, 4.36.

Compound **4b**. A glassy solid, 39–41 °C; $[\alpha]_D^{20}=-11.3$ (*c* 2.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, *J*=7.5 Hz, 1H), 4.0–4.2 (m, 2H), 3.85 (m, 1H), 3.48 (dtd, *J*=11.8, 4.9, 1.0 Hz, 1H), 3.23 (ddd, *J*=11.8, 9.2, 4.3 Hz, 1H), 2.50 (bdt, *J*=17.9, 5.7 Hz, 1H), 2.37 (ddd, *J*=17.9, 8.5, 6.3 Hz, 1H), 1.7–2.0 (m, 4H), 1.40 (s, 3H), 1.28 (s, 3H), 0.94 (t, *J*=8.2 Hz, 9H), 0.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 110.2, 76.6, 74.2, 66.0, 40.8, 33.7, 26.0, 25.2, 23.0, 21.4, 6.4 (3C), 4.2 (3C). Anal. calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.63; H, 9.44; N, 4.32.

3.3.3. (1′*R*,4″*R*)-1-[(*tert*-Butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (6) and (1′*S*,4″*R*)-1-[(*tert*-butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (7). *Typical procedure*. To a solution of DIPEA (1.03 mL, 5.94 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (20 mL) at 25 °C under argon atmosphere was added TBSOTf (1.36 mL, 5.94 mmol). The resulting mixture was stirred at the same temperature for 10 min before adding thymine (**5**) (250 mg, 1.98 mmol) and aldehyde **2** (516 mg, 3.96 mmol) dissolved in 20 mL of the same solvent mixture. The reaction was monitored by TLC and was judged complete after 4 h. The solution was then quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (45:55 hexanes/EtOAc) to give adducts **6** (390 mg, 53%) and **7** (198 mg, 27%).

Compound **6**. Colourless crystals, mp 106–115 °C; $[\alpha]_D^{20}=-74.5$ (*c* 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.32 (bs, 1H), 7.38 (q, *J*=1.2 Hz, 1H), 5.92 (d, *J*=3.6 Hz, 1H), 4.22 (ddd, *J*=6.8, 5.7, 3.6 Hz, 1H), 4.05 (dd, *J*=8.6, 6.9 Hz, 1H), 3.88 (dd, *J*=8.6, 5.7 Hz, 1H), 1.95 (d, *J*=1.2 Hz, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.3, 136.8, 110.6, 110.4, 77.8, 77.7, 65.3, 26.1, 25.5 (3C), 25.3, 17.9, 12.6, −5.2, −5.3. FT-IR (KBr): 3210, 3030, 1740, 1680, 1480, 1080 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{17}H_{31}N_2O_5Si$ ($M+H^+$), 371.2002; found, 371.2013. Anal. calcd for $C_{17}H_{30}N_2O_5Si$: C, 55.11; H, 8.16; N, 7.56. Found: C, 55.20; H, 8.07; N, 7.48.

Compound **7**. Colourless crystals, mp 111–120 °C; $[\alpha]_D^{20}=-5.3$ (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (bs, 1H), 7.22 (q, *J*=1.2 Hz, 1H), 5.90 (d, *J*=6.9 Hz, 1H), 4.17 (m, 1H), 4.14 (dd, *J*=8.3, 6.1 Hz, 1H), 3.93 (dd, *J*=8.5, 3.6 Hz, 1H), 1.96 (d, *J*=1.2 Hz, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.6, 135.6, 111.1, 110.6, 78.3, 76.9, 66.2, 26.3, 25.5 (3C), 25.1, 17.4, 12.5, −5.0, −5.3. FT-IR (KBr): 3210, 3035, 1740, 1680, 1476, 1070 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{17}H_{31}N_2O_5Si$ ($M+H^+$), 371.2002; found, 371.2010. Anal. calcd for $C_{17}H_{30}N_2O_5Si$: C, 55.11; H, 8.16; N, 7.56. Found: C, 55.20; H, 8.07; N, 7.48.

3.3.4. (1′*S*,4″*S*,5″*R*)-1-[(5-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-(*tert*-butyldimethylsilanyloxy)-methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (9) and (1′*R*,4″*S*,5″*R*)-1-[(5-benzyloxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-(*tert*-butyldimethylsilanyloxy)-methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (10). The title compounds were prepared by starting with DIPEA (1.03 mL, 5.94 mmol), TBSOTf (1.36 mL, 5.94 mmol), thymine (**5**) (250 mg, 1.98 mmol) and protected threose **8** (991 mg, 3.96 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (40 mL) according to the above procedure described for compounds **6** and **7**. After flash chromatographic purification (1:1 hexanes/EtOAc) there were obtained 350 mg (36%) of pure adduct **9** along with 233 mg (24%) of pure **10**.

Compound **9**. A colourless oil; $[\alpha]_D^{20}=-44.6$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (bs, 1H), 7.25–7.40 (m, 6H), 6.04 (d, *J*=3.8 Hz, 1H), 4.55 (bs, 2H), 4.22 (dt, *J*=7.7, 5.4 Hz, 1H), 3.95 (dd, *J*=7.8, 3.8 Hz, 1H), 3.60 (dd, *J*=9.7, 5.2 Hz, 1H), 3.49 (dd, *J*=9.7, 5.6 Hz, 1H), 1.92 (d, *J*=1.2 Hz, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.0, 137.5, 136.9, 128.4 (2C), 127.7, 127.6 (2C), 111.6, 110.3, 81.3, 77.2, 75.5, 73.6, 70.2, 27.2, 26.6, 25.5 (3C), 17.9, 12.5, −5.3, −5.4. FT-IR (film): 3260, 3060, 1736, 1677, 1501, 1230, 1024, 710 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{25}H_{39}N_2O_6Si$ ($M+H^+$), 491.2577; found, 491.2565. Anal. calcd for $C_{25}H_{38}N_2O_6Si$: C, 61.20; H, 7.81; N, 5.71. Found: C, 61.33; H, 7.92; N, 5.57.

Compound **10**. A colourless oil; $[\alpha]_D^{20}=+21.6$ (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (bs, 1H), 7.2–7.4 (m, 6H), 6.02 (d, *J*=6.9 Hz, 1H), 4.63 (bs, 2H), 4.15 (m, 1H), 3.90 (m, 1H), 3.6–3.8 (m, 2H), 1.95 (d, *J*=1.0 Hz, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 0.85 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.1, 137.6, 135.6, 128.3 (2C), 127.8, 127.6 (2C), 111.0, 110.2, 81.9, 78.8, 78.1, 73.6, 70.5, 27.1, 26.5, 25.4 (3C), 17.7, 12.4, −5.2, −5.3. FT-IR (film): 3261, 3051, 1739, 1680, 1500, 1225, 1020, 710 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{25}H_{39}N_2O_6Si$ ($M+H^+$), 491.2577; found, 491.2586. Anal. calcd for $C_{25}H_{38}N_2O_6Si$: C, 61.20; H, 7.81; N, 5.71. Found: C, 61.33; H, 7.92; N, 5.57.

3.3.5. (1′*S*,4″*R*,4‴*R*,5″*S*)-1-[(*tert*-Butyldimethylsilanyloxy)-(2,2,2′,2′-tetramethyl-[4,4′]bis[[1,3]dioxolanyl]-5-yl)methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (12) and (1′*R*,4″*R*,4‴*R*,5″*S*)-1-[(*tert*-butyldimethylsilanyloxy)-(2,2,2′,2′-tetramethyl-[4,4′]bis[[1,3]dioxolanyl]-5-yl)methyl]-5-methyl-1*H*-pyrimidine-2,4-dione (13). The title compounds were prepared by starting with DIPEA (1.03 mL, 5.94 mmol), TBSOTf (1.36 mL, 5.94 mmol), thymine (**5**) (250 mg, 1.98 mmol) and protected arabinose **11** (912 mg, 3.96 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (40 mL) according to the above procedure described for compounds **6** and **7**. After flash chromatographic purification (55:45 hexanes/EtOAc) there were obtained 382 mg (41%) of pure adduct **12** along with 252 mg (27%) of pure **13**.

Compound **12**. A white foam; $[\alpha]_D^{20}=-3.5$ (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (bs, 1H,), 7.38 (q, *J*=1.2 Hz, 1H), 6.08 (d, *J*=4.3 Hz, 1H), 4.15 (m, 1H), 4.06 (dd, *J*=6.5, 4.3 Hz, 1H), 3.9–4.0 (m, 2H), 3.81 (dd, *J*=8.3, 6.4 Hz, 1H), 1.96 (d, *J*=1.2 Hz, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.92 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.3, 135.6, 110.4, 109.7, 109.5, 79.0, 78.2, 77.8, 77.2, 65.3, 26.7, 26.4, 25.8 (3C), 25.2, 24.6, 17.4, 12.3, −5.2, −5.3. FT-IR (KBr): 3240, 3010, 1735, 1670, 1500, 1085 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{22}H_{39}N_2O_7Si$ ($M+H^+$), 471.2526; found, 471.2539. Anal. calcd for $C_{22}H_{38}N_2O_7Si$: C, 56.15; H, 8.14; N, 5.95. Found: C, 56.32; H, 7.83; N, 5.75.

Compound **13**. A white foam; $[\alpha]_D^{20}=+4.1$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (bs, 1H), 7.38 (q, *J*=1.2 Hz, 1H), 6.11 (d, *J*=4.6 Hz, 1H), 3.8–4.2 (m, 5H), 1.97 (d, *J*=1.1 Hz, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 0.92 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 150.6, 136.4, 111.1, 110.2, 109.3, 79.2, 78.6, 78.3, 76.8, 66.2, 26.9, 26.2, 25.8, 25.5 (3C), 25.0, 17.9, 12.5, −5.0, −5.3. FT-IR (KBr): 3241, 3012, 1740, 1677, 1506, 1080 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{22}H_{39}N_2O_7Si$ ($M+H^+$), 471.2526; found, 471.2517. Anal. calcd for $C_{22}H_{38}N_2O_7Si$: C, 56.15; H, 8.14; N, 5.95. Found: C, 56.27; H, 8.06; N, 6.04.

3.3.6. (1′*R*,4″*R*)-1-[(*tert*-Butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-1*H*-pyrimidine-2,4-dione (15) and (1′*S*,4″*R*)-1-[(*tert*-butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-1*H*-pyrimidine-2,4-dione (16). The title compounds were prepared by starting with DIPEA (1.03 mL, 5.94 mmol), TBSOTf (1.36 mL, 5.94 mmol), uracil (**14**) (222 mg, 1.98 mmol) and aldehyde **2** (516 mg, 3.96 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (40 mL) according to the above procedure described for compounds **6** and **7**. After flash chromatographic purification (6:4 hexanes/EtOAc) there were obtained 261 mg (37%) of pure adduct **15** along with 113 mg (16%) of pure **16**.

Compound **15**. A colourless oil; $[\alpha]_D^{20}=-61.1$ (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.30 (bs, 1H), 7.59 (d, *J*=8.2 Hz, 1H), 5.94 (d, *J*=3.0 Hz, 1H), 5.77 (dd, *J*=8.1, 2.0 Hz, 1H), 4.23 (ddd, *J*=6.9, 5.6, 3.1 Hz, 1H), 4.07 (dd, *J*=8.5, 6.9 Hz, 1H), 3.90 (dd, *J*=8.5, 5.6 Hz, 1H), 1.49 (s, 3H), 1.36 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.4, 141.2, 110.6, 102.0, 77.7, 77.5, 65.3, 26.0, 25.5 (3C), 25.3, 17.9, −5.1, −5.4. FT-IR (film): 3270, 3140, 3004, 1736, 1700, 1670, 1500, 1030 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{16}H_{29}N_2O_5Si$ ($M+H^+$), 357.1846; found, 357.1835. Anal. calcd for $C_{16}H_{28}N_2O_5Si$: C, 53.91; H, 7.92; N, 7.86. Found: C, 54.12; H, 7.81; N, 8.01.

Compound **16**. A colourless oil; $[\alpha]_D^{20}=+12.9$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (bs, 1H), 7.41 (d, *J*=8.1 Hz, 1H), 5.91 (d, *J*=6.5 Hz, 1H), 5.79 (dd, *J*=8.1, 2.2 Hz, 1H), 4.15 (m, 2H), 3.93 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 150.7, 140.0, 110.6, 102.7, 78.4, 77.1, 65.5, 26.2, 25.5 (3C), 25.0, 17.7, −5.1, −5.4. FT-IR (film): 3269, 3136, 3000, 1730, 1697, 1645, 1500, 1020 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{16}H_{29}N_2O_5Si$ ($M+H^+$), 357.1846; found, 357.1852. Anal. calcd for $C_{16}H_{28}N_2O_5Si$: C, 53.91; H, 7.92; N, 7.86. Found: C, 54.03; H, 8.05; N, 7.73.

3.3.7. (1′*R*,4″*R*)-9-[(*tert*-Butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-6-chloro-9*H*-purine (18) and (1′*S*,4″*R*)-9-[(*tert*-butyldimethylsilanyloxy)-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]-6-chloro-9*H*-purine (19). The title compounds were prepared by starting with DIPEA (1.03 mL, 5.94 mmol), TBSOTf (1.36 mL, 5.94 mmol), 6-chloropurine (**17**) (306 mg, 1.98 mmol) and aldehyde **2** (516 mg, 3.96 mmol) in a 1:1 (v/v) mixture of anhydrous THF/hexanes (40 mL) according to the above procedure described for compounds **6** and **7**. After flash chromatographic purification (65:35 hexanes/EtOAc) there were obtained 435 mg (55%) of pure adduct **18** along with 182 mg (23%) of pure **19**.

Compound **18**. A colourless oil; $[\alpha]_D^{20}=-51.6$ (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.42 (s, 1H), 6.18 (d, *J*=3.9 Hz, 1H), 4.38 (m, 1H), 4.0–4.1 (m, 2H), 1.32 (s, 6H), 0.86 (s, 9H), 0.13 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 151.0, 150.9, 144.1, 131.8, 110.8, 78.6, 77.8, 64.8, 26.0, 25.4 (3C), 25.0, 17.9, −5.3, −5.4. FT-IR (film): 2950, 1620, 1351, 1091, 696 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{17}H_{28}N_4ClO_3Si$ ($M+H^+$), 399.1619; found, 399.1610. Anal. calcd for $C_{17}H_{27}N_4ClO_3Si$: C, 51.18; H, 6.82; N, 14.04; Cl, 8.89. Found: C, 51.36; H, 6.90; N, 13.93; Cl, 8.71.

Compound **19**. A colourless oil; $[\alpha]_D^{20}=+22.1$ (*c* 2.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (s, 1H), 5.93 (d, *J*=7.1 Hz, 1H), 4.45 (m, 1H), 4.0–4.2 (m, 2H), 1.25 (s, 3H), 1.18 (s, 3H), 0.79 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 151.4, 150.8, 143.3, 131.1, 110.6, 79.3, 77.9, 66.0, 26.3, 25.3 (3C), 24.7, 17.8, −5.3, −5.4. FT-IR (film): 2964, 1614, 1350, 1090, 700 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{17}H_{28}N_4ClO_3Si$ ($M+H^+$), 399.1619; found, 399.1627. Anal. calcd for $C_{17}H_{27}N_4ClO_3Si$: C, 51.18; H, 6.82; N, 14.04; Cl, 8.89. Found: C, 50.97; H, 6.95; N, 14.14; Cl, 8.76.

3.3.8. (1′*R*,2′*R*)-1-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-dihydroxypropyl]-5-methyl-1*H*-pyrimidine-2,4-dione (20). *Typical procedure*. Protected adduct **6** (390 mg, 1.05 mmol) was dissolved in 8.4 mL of 80% aqueous acetic

acid, and the resulting solution was allowed to react at 50 °C. The reaction was monitored by TLC and was judged complete after 24 h. The solution was diluted with water and extracted with EtOAc. The combined extracts were washed with saturated $NaHCO_3$ solution and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to afford a crude residue which was purified by silica gel flash chromatography (EtOAc). Terminal diol **20** was isolated (236 mg) in a 68% yield as a glassy solid; $[\alpha]_D^{20}=-13.3$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (bs, 1H), 7.40 (q, *J*=1.2 Hz, 1H), 5.97 (d, *J*=4.4 Hz, 1H), 3.80 (m, 1H), 3.68 (m, 2H), 3.11 (bs, 1H), 2.70 (bs, 1H), 1.92 (d, *J*=1.1 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 150.8, 137.4, 109.6, 78.9, 73.3, 62.7, 25.5 (3C), 17.9, 12.3, −5.2, −5.3. FT-IR (KBr): 3300, 2960, 1735, 1676, 1501, 1260, 1060 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{14}H_{27}N_2O_5Si$ (M+H$^+$), 331.1689; found, 331.1699. Anal. calcd for $C_{14}H_{26}N_2O_5Si$: C, 50.86; H, 7.93; N, 8.48. Found: C, 50.98; H, 7.81; N, 8.57.

3.3.9. (1′*S*,2′*R*)-1-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-dihydroxypropyl]-5-methyl-1*H*-pyrimidine-2,4-dione (21). The title compound was prepared starting from 198 mg of protected adduct **7** (0.53 mmol) and 4.2 mL of 80% aqueous acetic acid according to the above procedure described for compound **20**. After flash chromatographic purification (EtOAc) there was obtained diol **21** (128 mg, 73%) as a colourless semisolid; $[\alpha]_D^{20}=-25.4$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (bs, 1H), 7.30 (q, *J*=1.1 Hz, 1H), 6.11 (d, *J*=7.4 Hz, 1H), 4.49 (bs, 1H), 3.90 (dd, *J*=11.8, 3.2 Hz, 1H), 3.79 (dd, *J*=11.8, 3.9 Hz, 1H), 3.69 (m, 1H), 3.47 (bs, 1H), 1.90 (d, *J*=1.0 Hz, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 151.7, 136.3, 111.1, 78.5, 74.5, 62.8, 25.5 (3C), 17.8, 12.4, −5.2, −5.5. FT-IR (film): 3300, 2956, 1730, 1680, 1500, 1259, 1050 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{14}H_{27}N_2O_5Si$ (M+H$^+$), 331.1689; found, 331.1695. Anal. calcd for $C_{14}H_{26}N_2O_5Si$: C, 50.86; H, 7.93; N, 8.48. Found: C, 51.01; H, 8.08; N, 8.23.

3.3.10. (1′*R*,2′*R*)-1-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-dihydroxypropyl]-1*H*-pyrimidine-2,4-dione (22). The title compound was prepared starting from 261 mg of protected adduct **15** (0.73 mmol) and 5.8 mL of 80% aqueous acetic acid according to the above procedure described for compound **20**. After flash chromatographic purification (EtOAc) there was obtained diol **22** (185 mg, 80%) as a waxy solid; $[\alpha]_D^{20}=-21.4$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (bs, 1H), 7.58 (d, *J*=8.1 Hz, 1H), 5.97 (d, *J*=3.6 Hz, 1H), 5.72 (d, *J*=8.1 Hz, 1H), 3.6–3.9 (m, 3H), 3.24 (bs, 1H), 2.81 (bs, 1H), 0.91 (s, 9H), 0.17 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 150.6, 141.0, 102.0, 78.8, 73.6, 62.6, 25.6 (3C), 17.9, −5.1, −5.4. FT-IR (film): 3300, 2961, 1736, 1670, 1500 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{13}H_{25}N_2O_5Si$ (M+H$^+$), 317.1533; found, 317.1541. Anal. calcd for $C_{13}H_{24}N_2O_5Si$: C, 49.35; H, 7.64; N, 8.85. Found: C, 49.50; H, 7.53; N, 8.92.

3.3.11. (1′*S*,2′*R*)-1-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-dihydroxypropyl]-1*H*-pyrimidine-2,4-dione (23). The title compound was prepared starting from protected adduct **16** (113 mg, 0.32 mmol) and 2.5 mL of 80% aqueous acetic acid according to the above procedure described for compound **20**. After flash chromatographic purification (EtOAc) there was obtained diol **23** (63 mg, 62%) as colourless crystals, mp 141–145 °C; $[\alpha]_D^{20}=-8.3$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (bs, 1H), 7.50 (d, *J*=8.1 Hz, 1H), 6.08 (d, *J*=5.7 Hz, 1H), 5.80 (d, *J*=8.1 Hz, 1H), 3.6–3.8 (m, 3H), 3.01 (bs, 1H), 2.51 (bs, 1H), 0.92 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 150.2, 140.4, 102.8, 78.6, 74.4, 62.5, 25.5 (3C), 17.8, −5.2, −5.5. FT-IR (KBr): 3300, 2960, 1740, 1681, 1500 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{13}H_{25}N_2O_5Si$ (M+H$^+$), 317.1533; found, 317.1521. Anal. calcd for $C_{13}H_{24}N_2O_5Si$: C, 49.35; H, 7.64; N, 8.85. Found: C, 49.46; H, 7.72; N, 8.63.

3.3.12. (2*R*,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(6-chloro-purin-9-yl)propane-1,2-diol (24). The title compound was prepared starting from protected adduct **18** (435 mg, 1.09 mmol) and 8.7 mL of 80% aqueous acetic acid according to the above procedure described for compound **20**. After flash chromatographic purification (2:8 hexanes/EtOAc) there was obtained diol **24** (293 mg, 75%) as a white foam; $[\alpha]_D^{20}=-18.9$ (*c* 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.48 (s, 1H), 6.29 (d, *J*=4.1 Hz, 1H), 3.95 (q, *J*=4.7 Hz, 1H), 3.75 (dd, *J*=11.6, 4.8 Hz, 1H), 3.66 (dd, *J*=11.6, 5.2 Hz, 1H), 3.28 (bs, 2H), 0.89 (s, 9H), 0.16 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 151.0, 150.6, 144.3, 131.0, 79.0, 74.1, 62.3, 25.4 (3C), 17.8, −5.3, −5.4. FT-IR (KBr): 3300, 2920, 1612, 1351, 1060, 702 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{14}H_{24}N_4ClO_3Si$ (M+H$^+$), 359.1306; found, 359.1320. Anal. calcd for $C_{14}H_{23}N_4ClO_3Si$: C, 46.85; H, 6.46; N, 15.61; Cl, 9.88. Found: C, 46.97; H, 6.37; N, 15.48; Cl, 9.96.

3.3.13. (2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(6-chloro-purin-9-yl)propane-1,2-diol (25). The title compound was prepared starting from protected adduct **19** (182 mg, 0.46 mmol) and 3.7 mL of 80% aqueous acetic acid according to the above procedure described for compound **20**. After flash chromatographic purification (2:8 hexanes/EtOAc) there was obtained diol **25** (122 mg, 68%) as a white foam; $[\alpha]_D^{20}=-12.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.39 (s, 1H), 6.24 (d, *J*=5.5 Hz, 1H), 4.17 (q, *J*=5.0 Hz, 1H), 3.74 (dd, *J*=11.5, 4.9 Hz, 1H), 3.64 (dd, *J*=11.6, 5.0 Hz, 1H), 2.98 (bs, 2H), 0.89 (s, 9H), 0.15 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 151.1, 150.2, 143.9, 131.0, 79.3, 74.3, 62.1, 25.4 (3C), 17.9, −5.2 (2C). FT-IR (KBr): 3300, 2930, 1610, 1350, 1050, 700 cm^{-1}. HRMS (FAB$^+$, *m/z*): calcd for $C_{14}H_{24}N_4ClO_3Si$ (M+H$^+$), 359.1306; found, 359.1317. Anal. calcd for $C_{14}H_{23}N_4ClO_3Si$: C, 46.85; H, 6.46; N, 15.61; Cl, 9.88. Found: C, 47.01; H, 6.36; N, 15.74; Cl, 9.74.

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References and notes

1. For recent reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–166. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194. (e) Parsons, P. J.; Penkett, C. S.; Shell, A. *J. Chem. Rev.* **1996**, *96*, 195–206. (f) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207–222. (g) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269. (h) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (i) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (j) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163. (k) Ho, T.-L. *Tandem organic reactions*; Wiley: New York, 1992. (l) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.
2. Some examples of reagents and promoters that perform at least two roles in a reaction sequence: (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045–1048. (b) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500–6501. (c) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413. (d) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. (e) Hafez, A. M.; Dudding, T.; Wagerle, T. R.; Shah, M. H.; Taggi, A. E.; Lectka, T. *J. Org. Chem.* **2003**, *68*, 5819–5825. (f) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368–2378.
3. (a) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213–1215. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307–6318.
4. (a) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070–8075. (b) Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Rassu, G.; Pinna, L.; Auzzas, L.; Zambrano, V.; Casiraghi, G. *Eur. J. Org. Chem.* **2002**, 1956–1965. (c) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2002**, *67*, 5338–5342. (d) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881–5885.
5. For biologically and pharmaceutically relevant acyclic nucleoside analogues, see: (a) Périgaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903–945. (b) Chu, C. K.; Cutler, *J. Heterocycl. Chem.* **1986**, *23*, 289–319. (c) Remy, R. J.; Secrist, J. A. *Nucleosides Nucleotides* **1985**, *4*, 411–427. (d) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716–5720. (e) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759–761. (f) Smee, D. F.; Martin, J. C.; Verheyden, J. P. H.; Matthews, T. R. *Antimicrob. Agents Chemother.* **1983**, *23*, 676–682. (g) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. *J. Med. Chem.* **1987**, *30*, 1636–1642. (h) Tanaka, H.; Baba, M.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1991**, *34*, 1394–1399.
6. When a clear THF solution of TBSOTf and DIPEA (1:1 molar ratio) was stored at 4 °C for several days, colourless crystals separate. This mixture did not work as a promoter, nor did the solid precipitate from the liquid layer. From these results TBSOTf and DIPEA are believed to act separately, yet synergistically, as promoters because the crystalline TBSOTf·DIPEA complex formed is insoluble in our THF/hexanes reaction medium.
7. Despite intense investigation, no conditions were found to obtain single crystals suitable for X-ray analysis for both compounds **3** and **4**, as well as several solid derivatives in this study.
8. (a) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477–5480. (b) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919–4922. (c) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869–2874. (d) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065–1074.
9. For *anti*- and *syn*-configured compounds **6** and **7** a molecular mechanics calculation was performed (Sybyl 6.3, Tripos Inc. St. Louis MO), simulating a rotation around the C(1′)–C(2′) bond. The calculation of the relative populations of *anti* and *gauche* conformations allowed the prediction of the mean $J_{1'-2'}$ values, which were in good accordance with the experimental data, thus confirming the discussed assignments. The calculated and observed values were: compound **6**, 3.9 Hz (obsd 3.6 Hz); compound **7**, 7.1 Hz (obsd 6.9 Hz).
10. For related amide hydroxyalkylation experiments, see: (a). *O/N Acetale (Houben-Weyl, Methoden der organischen chemie)*; Hagemann, H., Klamann, D., Eds.; Georg Thieme: Stuttgart, 1991; Vol. E14a/2. (b) Henriksen, U. *Nucleosides Nucleotides* **2000**, *19*, 1093–1100. (c) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509–2512.
11. Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048–2064.
12. Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265–276.
13. Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687–702.
14. (a) Zinner, H.; Brandner, H.; Rembarz, G. *Chem. Ber.* **1956**, *89*, 800–813. (b) Zinner, H.; Wittenburg, E.; Rembarz, G. *Chem. Ber.* **1959**, *92*, 1614–1617.

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Indium(III) chloride catalyzed in situ generation of enamines and cyclization with imines: a novel route for synthesis of hexahydroxanthene-9-*N*-arylamines

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Abstract—A simple, efficient, and novel method has been developed for the synthesis of hexahydroxanthene-9-*N*-arylamine derivatives through a one-pot reaction of cyclohexanone and morpholine with salicylaldehyde imines in the presence of indium(III) chloride as a catalyst. 1-(4-Morpholino)-cyclohexene enamine prepared in situ from cyclohexanone and morpholine in presence of 20 mol% $InCl_3$ in acetonitrile under reflux condition was used without further purification, for the cyclization reaction with salicylaldehyde Schiff's bases.

1. Introduction

Xanthone derivatives are parent compounds of a large number of naturally occurring, as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry.[1] Ishiguro et al. have reported the isolation of clusone (1,3,4,5,6-pentamethoxy-9*H*-xanthen-9-one) from the fresh flowers of Clusia insignis.[2] 4-Methoxyxanthen-9-amine derivatives have been used for the synthesis of pharmacologically important Clavizepine alkaloids.[3] Boyd et al. have reported that 9-aryl or alkylimino-xanthene derivatives have been used for solid phase synthesis of (*RS*)-1-aminophosphinic acid.[4] Broggini et al. have reported the synthesis of (−)-(1*S*,4a*R*,9*R*,9a*S*)-9-amino-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol using intra-molecular nitrone cycloadditions to the cyclohexene ring.[5] Schemidt has reported the synthesis of linear fused cyclohexyl benzopyrans via 4+2 cycloaddition reaction of *o*-hydroxybenzyl carbocation with cyclohexene using $SnCl_4$ as a catalyst.[6]

Enamines have been intensively studied and used in organic synthesis in a wide variety of ways following Stork's report on the application of enamines in the alkylation and acylation of carbonyl compounds.[7] Weidinger et al. have reported that 1,3-diaza-1,3-butadiene have been shown to participate in [4+2] cycloaddition reactions with 1-[4-morpholino]cyclohexene.[8] Enamines have been used in natural product synthesis, for example the total synthesis of fabianine[9] and quaipyridines,[10] including heteroaromatic azadiene Diels–Alder reaction.

Indium trichloride has been effectively employed as a Lewis acid catalyst for various transformations[11] in organic synthesis, such as aldol condensations, imino Diels–Alder reactions, rearrangement of epoxides and prins-type cyclization.[12] $InCl_3$ is readily available and found to retain its activity even in the presence of water and other active functional groups such as NO_2, COOH, CN, NH_2 in the substrates.[13] In continuation of our research interest on the catalytic applications of $InCl_3$,[14] we herein describe another remarkable catalytic activity of $InCl_3$ in the synthesis of novel xanthene-9-*N*-arylamine derivatives from salicylaldehyde imines and 1-(4-morpholino)-cyclohexene enamine in CH_3CN at room temperature in excellent yields within 40 min. 1-(4-Morpholino)-cyclohexene enamine is moisture sensitive and undergoes hydrolysis easily.[15] In order to overcome this difficulty we have attempted the generation of 1-(4-morpholino)-cyclohexene enamine in situ using $InCl_3$ (20 mol%) under reflux conditions.

1-(4-Morpholino)-cyclohexene enamine **3** prepared in situ from cyclohexanone **1** and morpholine **2** in the presence of 20 mol% $InCl_3$ in acetonitrile under reflux conditions for 2–3 h was used without further purification, for the cyclization with salicylaldehyde Schiff's bases **4**. A wide range of salicylaldehyde Schiff's bases **4** with various substituent groups were subjected to this procedure and converted to the corresponding linear fused hexahydroxanthene-9-*N*-arylamines **5** derivatives in high yields (Scheme 1). In all these reactions, a single product **5** was

Keywords: Indium trichloride; Imines; Enamine; Xanthene.
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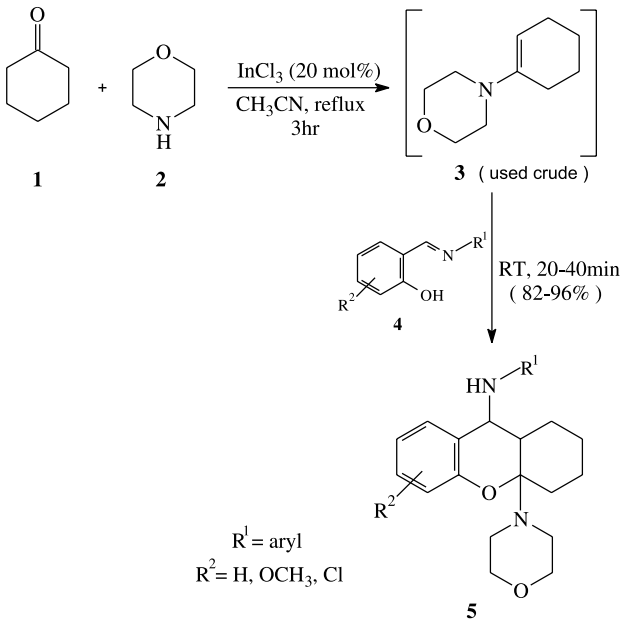


Scheme 1. Synthesis of hexahydroxanthene-9-*N*-arylamine.

Table 1. $InCl_3$ catalyzed formation of hexahydroxanthene-9-*N*-arylamine[a]

Entry	R^1	R^2	Time (min)	Yield (%)	Mp (°C)
a	C_6H_5	H	20	96	156–158
b	2-CH_3–C_6H_4	H	30	89	140–143
c	4-CH_3O–C_6H_4	H	20	93	160–162
d	4-Br–C_6H_4	H	40	90	164–166
e	2-Pyridine	H	30	87	166–168
f	C_6H_5	5-CH_3O	30	95	174–178
g	4-NO_2–C_6H_4	H	35	82	187–189
h	C_6H_5	7-Cl	25	87	132–134
i	4-CH_3–C_6H_4	7-Cl	20	90	148–149
j	4-CH_3–C_6H_4	5-CH_3O	30	92	180–182
k	2-Pyridine	5-CH_3O	40	86	152–154
l	2-Naphthyl	5-CH_3O	20	91	128–130

[a] All the products were characterized by ^1H NMR, ^{13}C NMR, IR and MS. All compounds gave satisfactory CHN values.

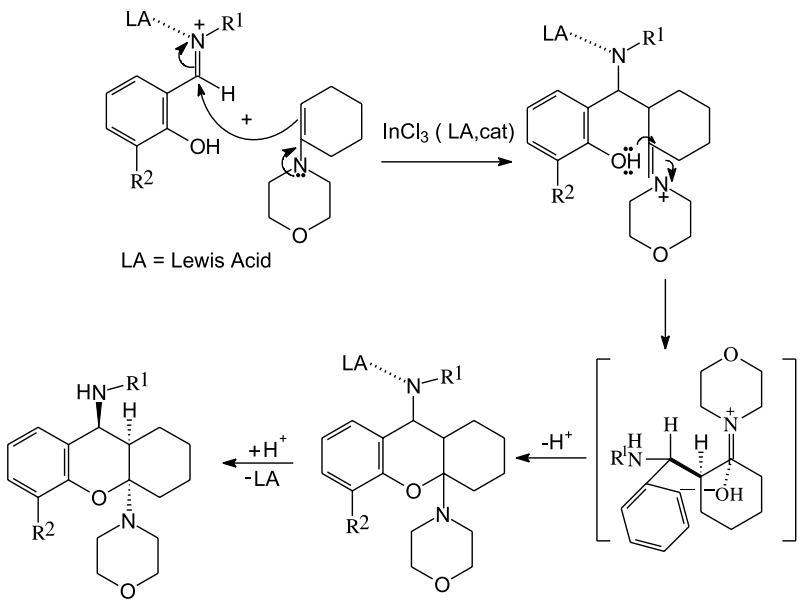
obtained, which upon recrystallization with ethyl acetate yielded pure crystalline products. The results are summarized in Table 1.

The reaction is expected to proceed through the activation of the imine nitrogen by co-ordination of the catalyst $InCl_3$, followed by nucleophilic addition at imine (C═N) bond and subsequent cyclization of the iminium ion, resulting in the formation of the linear fused hexahydroxanthene-9-*N*-arylamines (Scheme 2).

The structures of **5a**–**l** were confirmed by ^1H and ^{13}C NMR spectroscopy. The structure assignment of **5e** was supported by an X-ray crystallography determination.[16] The X-ray crystal structure of **5e** is shown in Figure 1.

The experimental procedure is simple and the products are obtained in excellent yields. However, when the substituent group R^1 was benzyl, cyclohexyl, methyl and ethyl, the cyclization under these reaction conditions was not favoured. We have substituted different cyclic ketones, such as cyclopentanone, cycloheptanone and cyclooctanone instead of cyclohexanone in the reaction with morpholine and salicylaldehydimine, under similar reaction conditions and no reaction was observed, the starting materials, being recovered as such. When the reaction was carried out at ambient temperature using equimolar ratio of reagents and 20 mol% $InCl_3$, the cyclization reaction was not observed which led to the recovery of unchanged starting materials.

The influence of various solvents on the yield of the reaction was investigated using *o*-hydroxy benzaldimine (entry a in Table 1) as the substrate. The results indicate that acetonitrile is the best solvent for the enamine formation and cyclization reaction of 1-(4-morpholino)-cyclohexene enamine with salicylaldehyde Schiff's bases (Table 2). The increased yield in the acetonitrile medium may be attributed to the higher polarity of the solvent and miscibility with water, formed during the enamine formation.



Scheme 2. Mechanism for the $InCl_3$ catalysed synthesis of hexahydroxanthene-9-*N*-arylamines.

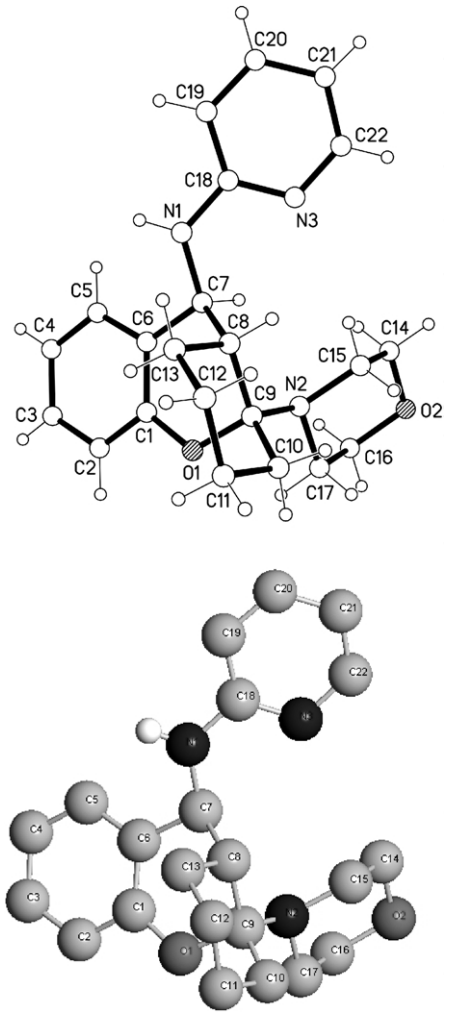


Figure 1. A perspective view of one of the two independent molecules in the asymmetric unit of **5e**.

Table 2. Effect of the solvent medium on the reaction yield of *o*-hydroxy benzaldimine with 20 mol% $InCl_3$

Entry	Solvent	Yield (%)
1	Benzene	94
2	Toluene	89
3	CH_3CN	97
4	$CHCl_3$	65
5	THF	37

In summary, this paper describes a general method for the synthesis of hexahydroxanthene-9-*N*-arylamines from salicylaldimines and 1-(4-morpholino)-cyclohexene enamine using sub-stoichiometric amounts of $InCl_3$. The catalyst is mild which has an advantage in that only 20 mol% is required for the reactions. In addition to its efficiency, operational simplicity, mild reaction conditions and easier work-up procedure make it a useful method for the synthesis of fused hexahydroxanthene-9-*N*-arylamines derivatives.

2. Experimental

o-Hydroxybenzaldimines prepared from appropriate *o*-hydroxybenzaldehyde and aniline. Salicylaldehyde, substituted anilines, cyclohexanone and morpholine were purchased from s. d. Fine Chem Ltd, India. Reagent grade acetonitrile and other solvents were used as supplied. The procedure does not require anhydrous solvent and inert atmosphere. All the products obtained were purified by recrystallization with ethyl acetate. IR measurements were done as KBr pellets for solids using Perkin Elmer Spectrum RXI FT-IR. The ^1H and ^{13}C NMR was recorded in $CDCl_3$ with JEOL 400 MHz (model GSX 400) high resolution NMR spectrometer. $CDCl_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in ppm with TMS as internal standards. The products Mass were analyzed by using a VG70-70H instrument. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

2.1. Preparation of hexahydroxanthene-9-*N*-arylamines: general procedure

To a mixture of cyclohexanone (0.3 g, 3.06 mmol) and morpholine (0.27 g, 3.10 mmol), in acetonitrile (20 mL), was added a catalytic amount of $InCl_3$ (0.136 g, 20 mol%). The reaction mixture was refluxed on a water bath under nitrogen atmosphere for 3 h and then allowed to cool to room temperature before the addition of *o*-hydroxy benzaldimine **1a** (0.6 g, 3.05 mmol). The stirring was continued for 20 min. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by addition of water (30 mL) and extracted with ethylacetate (2×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo, kept at 0 °C overnight in a fridge to obtain the crude product. The crude solid was recrystallized from ethylacetate to give the corresponding xanthene derivative **5a** (1.064 g, 96%).

2.1.1. Product 5a: *N*-phenyl-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl) amine. Yield 1.064 g (96%); colorless solid, mp 156–158 °C; IR (KBr) 3361 (NH), 3050, 3015, 2926, 2855, 2821, 1599, 1488, 1450, 1360, 1299, 1260, 1234, 1151, 1112, 1064, 1026, 973, 973, 770, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–6.57 (m, 9H), 4.12 (d, 1H, J=9.8 Hz), 3.60–3.67 (m, 4H), 2.55–2.70 (m, 3H), 2.35–2.38 (m, 2H), 2.02 (t, 2H, J=13.2 Hz), 1.72–1.10 (m, 7H, including NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 146.9, 129.6, 128.5, 123.3, 121.1, 116.9, 112.9, 112.2, 89.6, 67.4, 52.4, 45.3, 35.8, 29.0, 26.7, 25.1, 21.9; MS (*m*/*z*): 364 (M^+). Anal. calcd for $C_{23}H_{28}N_2O$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.92; H, 7.69; N, 7.58%.

2.1.2. Product 5b: *N*-(2-methylphenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl) amine. Yield 0.797 g (89%); colorless solid, mp 140–143 °C; IR (KBr) 3438 (NH), 3064, 3021, 2919, 2886, 2848, 2754, 1604, 1582, 1514, 1482, 1450, 1294, 1257, 1234, 1203, 1146, 1116, 1029, 975, 957, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 1H, J=7.82 Hz), 7.23 (m, 3H), 6.95 (t, 1H, J=7.3 Hz), 6.83–6.81 (m, 1H), 6.69–6.62 (m, 2H), 5.26 (brs, 1H), 3.68–3.63 (m, 4H), 2.74–2.64 (m, 3H),

2.35–2.34 (m, 2H), 2.18 (s, 3H, CH_3), 2.09–2.00 (m, 2H), 1.68–1.12 (m, 7H, including NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.4, 130.6, 128.2, 127.3, 126.7, 124.5, 121.8, 120.8, 116.8, 116.4, 108.9, 90.9, 67.5, 47.4, 45.4, 34.1, 27.0, 24.6, 21.9, 21.8, 17.7; MS (*m*/*z*): 378 (M^+). Anal. calcd for $C_{24}H_{30}N_2O$: C, 76.16; H, 7.79; N, 7.40. Found: C, 76.29; H, 7.67; N, 7.29%.

2.1.3. Product 5c: *N*-(4-methoxyphenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro 1*H*-xanthen-9-yl) amine. Yield 0.807 g (93%); colorless solid, mp 160–162 °C; IR (KBr) 3375 (NH), 3375, 3049, 3004, 2943, 2855, 2826, 1589, 1511, 1455, 1297, 1240, 1182, 1149, 1116, 1038, 975, 944, 819, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–7.29 (m, 4H), 6.81 (d, 2H, *J*=8.8 Hz), 6.55 (d, 2H, *J*=8.8 Hz), 4.03 (d, 1H, *J*=10.3 Hz), 3.76 (s, 3H), 3.59 (m, 4H), 2.57 (m, 4H), 2.39–1.27 (m, 10H, including NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.5, 141.3, 130.7, 128.5, 123.5, 121.0, 116.9, 115.2, 113.7, 89.6, 67.4, 55.7, 53.4, 45.5, 35.6, 29.1, 26.8, 25.1, 21.9; MS (*m*/*z*): 394 (M^+) Anal. calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.31; H, 7.77; N, 7.18%.

2.1.4. Product 5d: *N*-(4-bromophenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl) amine. Yield 0.722 g (90%); colorless solid, mp 164–166 °C; IR (KBr) 3398 (NH), 3050, 3011, 2926, 2856, 1593, 1493, 1454, 1312, 1261, 1238, 1147, 1114, 1070, 976, 950, 811, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 2H, *J*=8.3 Hz), 7.25–7.17 (m, 2H), 6.95–6.80 (m, 2H), 6.46 (d, 2H, *J*=8.8 Hz) 4.05 (d, 1H, *J*=10.3 Hz), 3.57 (m, 4H), 2.63–2.54 (m, 3H), 2.34–2.30 (m, 2H), 2.06–2.02 (m, 2H), 1.70–1.24 (m, 7H, including NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 145.9, 132.3, 130.6, 128.8, 122.8, 121.2, 117.1, 113.8, 108.5, 89.5, 67.5, 52.7, 48.1, 45.3, 35.7, 29.0, 26.7, 25.1, 21.9; MS (*m*/*z*):443 (M^+). Anal. calcd for $C_{23}H_{27}N_2O_2Br$: C, 62.31; H, 6.14; N, 7.10. Found: C, 62.18; H, 6.01; N, 7.23%.

2.1.5. Product 5e: *N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl) pyridin-2-amine. Yield 0.802 g (87%); colorless solid, mp 164–166 °C; IR (KBr) 3348 (NH), 3062, 2936, 2854, 2817, 2744, 1607, 1513, 1487, 1450, 1344, 1283, 1241, 1198, 1139, 1108, 1033, 956, 850, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.06 (m, 1H), 7.44–7.38 (m, 2H), 7.18–7.14 (m, 1H), 6.93–6.91 (m, 1H), 6.89–6.80 (m, 1H), 6.59–6.57 (m, 1H), 6.43 (d, 1H, *J*=8.3 Hz), 4.53 (d, 1H, *J*=9.8 Hz), 3.71–3.62 (m, 2H), 2.86–2.73 (m, 2H), 2.46–2.41 (m, 1H), 2.03–1.99 (m, 2H), 1.87 (brs, 1H, NH), 1.68–1.54 (m, 2H), 1.44–1.36 (m, 2H), 1.18–1.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 152.4, 148.7, 137.6, 128.4, 126.6, 124.4, 120.9, 116.8, 113.3, 107.9, 91.3, 67.9, 46.7, 45.5, 34.8, 27.2, 24.9, 22.3, 22.2; MS (*m*/*z*): 365 (M^+). Anal. calcd for $C_{22}H_{27}N_3O$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.45; H, 7.53; N, 11.61%.

2.1.6. Product 5f: *N*-(phenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-5-methoxy xanthen-9-yl) amine. Yield 0.825 g (95%); colorless solid, mp 174–178 °C; IR (KBr) 3372 (NH), 3058, 3018, 2949, 2849, 2832, 1582, 1516, 1443, 1245, 1147, 1118, 978, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2H), 6.93–6.64 (m, 5H), 6.59 (d, 1H, *J*=8.0 Hz), 4.66 (d, 1H, *J*=10.3 Hz), 4.12 (d, 1H, *J*=10.3 Hz), 3.86 (s, 3H), 3.72–3.61 (m, 2H), 2.56 (m, 2H), 2.39–2.12 (m, 3H), 1.80–1.61 (m, 6H), 1.52–1.1 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 147.0, 140.1, 129.8, 124.3, 122.5, 120.6, 117.2, 112.4, 123.0, 110.7, 89.8, 67.7, 56.2, 52.7, 45.5, 36.0, 29.2, 26.9, 25.2; MS (*m*/*z*): 394 (M^+). Anal. calcd for $C_{24}H_{30}N_2O$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.87; H, 7.57; N, 7.22.

2.1.7. Product 5g: *N*-(4-nitrophenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-9-yl) amine. Yield 0.693 g (82%); pale yellow colored solid, mp 187–189 °C IR (KBr) 3392 (NH), 3053, 3015, 2928, 2849, 1596, 1493, 1459, 1321, 1234, 1119, 981, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.10 (m, 2H), 7.30–7.18 (m, 3H), 6.96–6.83 (m, 2H), 6.61(d, 1H, *J*=9.2 Hz), 5.26 (dd, 1H, J_1=5.8 Hz, J_2=9.8 Hz), 4.60 (d, 1H, *J*=10.3 Hz), 3.67–3.61 (m, 2H), 2.78–2.02 (m, 6H), 1.84–1.14 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.9, 138.4, 130.4, 129.5, 129.1, 126.9, 126.5, 122.5, 121.1, 116.9, 90.9, 67.5, 48.2, 45.5, 34.9, 27.0, 24.5, 22.1, 21.1; MS (*m*/*z*): 409 (M^+). Anal. calcd for $C_{23}H_{27}N_3O$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.23; H, 6.56; N, 10.38%.

2.1.8. Product 5h: *N*-(phenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-7-chloroxanthen-9-yl) amine. Yield 0.749 g (87%); colorless solid, mp 132–134 °C; IR (KBr) 3368 (NH), 3055, 3021, 2926, 2852, 2823, 1591, 1482, 1457, 1298, 1235, 1117, 975, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, 1H, *J*=2.2 Hz), 7.25–7.13 (m, 4H), 6.78–6.71 (m, 2H), 6.57–6.56 (d, 1H, *J*=7.4 Hz), 3.76–3.47 (m, 1H), 2.69–2.53 (m, 3H), 2.37–2.02 (m, 2H), 1.72–1.24 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 146.6, 130.4, 129.8, 128.8, 125.9, 125.1, 118.4, 117.5, 112.3, 90.0, 67.5, 52.4, 46.1, 35.7, 29.1, 26.7, 25.1, 21.9; MS (*m*/*z*): 398 (M^+). Anal. calcd for $C_{23}H_{27}N_2O_2Cl$: C, 69.25; H, 6.82; N, 7.02. Found: C, 69.18; H, 6.89; N, 6.89%.

2.1.9. Product 5i: *N*-(4-methylphenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-7-chloroxanthen-9-yl) amine. Yield 0.757 g (90%); colorless solid, mp 148–149 °C; IR (KBr) 3445 (NH), 3067, 3018, 2915, 2879, 2843, 1603, 1578, 1518, 1469, 1451, 1298, 1238, 1156, 965, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.02 (m, 5H), 6.73 (d, 1H, *J*=8.6 Hz), 6.58 (d, 1H, *J*=8.6 Hz), 5.01 (brs, 1H, NH), 4.49 (d, 1H, *J*=9.2 Hz), 4.05 (d, 1H, *J*=8.6 Hz), 4.49 (d, 1H, *J*=9.2 Hz), 3.69–3.60 (m, 4H), 2.80–2.53 (m, 2H), 2.37–2.25 (m, 2H), 2.37–2.25 (m, 5H), 2.06–1.97 (m,1H), 1.71–1.02 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 144.9, 130.3, 128.7, 128.3, 126.9, 126.3, 125.7, 117.8, 113.4, 112.4, 91.4, 67.5, 52.6, 48.2, 45.3, 34.1, 24.5, 21.8, 21.7, 20.4; MS (*m*/*z*): 412 (M^+). Anal. calcd for $C_{24}H_{29}N_2O_2Cl$: C, 69.80; H, 7.08; N, 6.78. Found: C, 69.92; H, 7.19; N, 6.86%.

2.1.10. Product 5j: *N*-(4-methylphenyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-5-methoxyxanthen-9-yl) amine. Yield 0.779 g (92%); colorless solid, mp 180–182 °C; IR (KBr) 3365 (NH), 3052, 3008, 2945, 2851, 2828, 1578, 1518, 1459, 1252, 1141, 1112, 972, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–6.70 (m, 6H), 6.60 (d,

J=8.0 Hz), 6.50 (d, 1H, J=8.0 Hz), 4.61 (d, 1H, J=10.1 Hz), 4.09 (d, 1H, J=9.7 Hz), 3.93 (s, 3H), 3.87–3.38 (m, 3H), 2.97–2.96 (m, 2H), 2.72–2.41 (m, 4H), 2.37 (s, 3H), 2.32–1.03 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 151.5, 148.5, 145.6, 137, 130.1, 129.8, 123.7, 121.1, 119.2, 118.5, 114.5, 90.2, 66.8, 56.2, 48.2, 45.4, 36.4, 29.5, 26.7, 21.9, 21.1; MS (*m*/*z*): 408 (M^+). Anal. calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86. Found; C, 73.35; H, 7.97; N, 6.77%.

2.1.11. Product 5k: *N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-5-methoxyxanthen-9-yl)pyridin-2-amine. Yield 0.745 g (86%); colorless solid, mp 152–154 °C; IR (KBr) 3355 (NH), 3068, 2938, 2855, 2812, 1605, 1521, 1472, 1461, 1232, 1121, 951, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.32 (m, 1H), 6.88–6.37 (m, 5H), 5.58 (d, 1H, J=5.2 Hz), 3.98–3,49 (m, 2H), 3.35 (s, 3H), 2.64–1.88 (m, 6H), 1.70–1.06 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.4, 148.2, 141.5, 137.0, 125.4, 120.1, 118.9, 112.1, 117.0, 109.9, 91.4, 67.3, 56.1, 45.5, 34.2, 31.2, 26.7, 24.6, 22.7, 22.4; MS (*m*/*z*): 395 (M^+). Anal. calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.72; H, 7.18; N, 10.33%.

2.1.12. Product 5l: *N*-(2-naphthyl)-*N*-(4a-morpholin-4yl-2,3,4,4a,9,9a-hexahydro-1*H*-5-methoxyxanthen-9-yl) amine. Yield 0.726 g (91%); brown colored solid, mp 128–130 °C; IR (KBr) 3349 (NH), 3045, 2932, 2855, 2822, 1593, 1492, 1453, 1281, 1260, 1237, 1122, 975, 772, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 3H), 7.37–6.79 (m, 7H), 4.83 (d, 1H, J=9.7 Hz), 4.25 (d, 1H, J=8.6 Hz), 3.88 (s, 3H), 3.75–3.46 (m, 2H), 3.09 (m, 1H), 2.63–1.24 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 144.6, 140.1, 135.4, 129.6, 127.8, 127.4, 126.6, 125.9, 124.1, 122.5, 122.1, 120.7, 117.8, 110.8, 103.0, 89.8, 68.1, 56.2, 52.7, 44.6, 35.4, 29.2, 26.9, 25.3, 22.2; MS (*m*/*z*): 442 (M^+). Anal. calcd for $C_{28}H_{32}N_2O$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.78; H, 7.14; N, 6.38%.

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References and notes

1. (a) Robak, J.; Gryglewski, R. J. *Pol. J. Pharmacol.* **1996**, *48*, 55. (b) Wang, H. K.; Morris-Natschke, S. L.; Lee, K. H. *Med. Res. Rev.* **1997**, *17*, 367. (c) Rukavishnikov, A. V.; Smith, M. P.; Birrell, G. B.; Keana, J. F. W.; Griffith, O. H. *Tetrahedron Lett.* **1998**, *39*, 6637.
2. Ishiguro, K.; Chaudhuri, S. K.; Kubo, I. *Phytochemistry* **1998**, *49*, 2531.
3. Garcia, A.; Paz, S.; Dominguez, D. *Tetrahedron Lett.* **2001**, *42*, 665.
4. Boyd, E. A.; Chan, W. C.; Loh, V. M., Jr. *Tetrahedron Lett.* **1996**, *37*, 1647.
5. Broggini, G.; Folcin, F.; Sardone, N.; Zecchi, G. *Tetrahedron* **1996**, *52*, 11849.
6. Schemidt, R. R. *Tetrahedron Lett.* **1969**, 5279.
7. Stork, G.; Terrel, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.
8. Weidinger, H.; Slurm, H. J. *Justus Liebigs Ann. Chem.* **1968**, *716*, 143.
9. (a) Sugita, T.; Koyama, J.; Tagahara, K.; Suzuta, Y. *Heterocycles* **1986**, *24*, 29. (b) Sugita, T.; Koyama, J.; Tagahara, K.; Suzuta, Y. *Heterocycles* **1985**, *23*, 2789.
10. Okatani, T.; Koyama, J.; Tagahara, K.; Suzuta, Y. *Heterocycles* **1987**, *26*, 595.
11. (a) Babu, G.; Perumal, P. T. *Aldrichemica Acta* **2000**, *33*, 16. (b) Loh, T. P.; Pei, J.; Cao, G.-Q. *Chem. Commun.* **1996**, 1819. (c) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 5025. (d) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323. (e) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212. (f) Miyai, T.; Onshi, Y.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 6291. (g) Hirashita, T.; Kamei, T.; Horie, T.; Yamamura, H.; Kawai, M.; Araki, S. *J. Org. Chem.* **1999**, *64*, 172. (h) Loh, T.-P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315.
12. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
13. Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141.
14. (a) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 5025. (b) Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627. (c) Babu, G.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2000**, 661. (d) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215.
15. Hunig, S.; Lucke, E.; Brenninger, W. *Org. Synth. Collect. Vol. V* **1973**, *5*, 808.
16. CCDC No: 226164.

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Synthesis of α,α-disubstituted 4-phosphonophenylalanine analogues as conformationally-constrained phosphotyrosyl mimetics☆

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Abstract—Syntheses of *N*-Boc (*S*)-4-(diethylphosphono)-(α-methyl)phenylalanine [Boc-(α-Me)Phe(4-PO_3Et_2)-OH] (**9**) and *N*-Boc (*S*)-2-amino-6-(diethylphosphono)tetralin-2-carboxylic acid [Boc-Atc(6-PO_3Et_2)-OH] (**18**) are reported as conformationally-constrained phosphotyrosyl mimetics suitably protected for peptide synthesis. Both syntheses proceeded through chiral arylhalides that are converted to arylphosphonates by palladium-catalyzed cross coupling with diethylphosphite. These amino acid analogues may be useful in the study of cellular signal transduction processes.

1. Introduction

The biological dependence of peptides on tertiary structure has made restriction of conformational flexibility an important component of peptide mimetic design.[1–6] A variety of non-proteinogenic constrained α-amino acids have been developed for this purpose. In the case of tyrosine (Tyr, **1a**), analogues have been reported that limit rotational freedom either through the addition of substituents at the α- or β-positions or through side chain inclusion in an appended ring structure (Fig. 1).[7] One example is α-methyl-Tyr (**2a**), which is a member of the broader class of α-methyl-containing amino acids known to promote turn geometries.[8] Another example is 2-amino-6-hydroxy-tetralin-2-carboxylic acid (**3a**), which can induce turn conformations similar to **2a** as well as severely restrict χ_1 and χ_2 angles.[9,10]

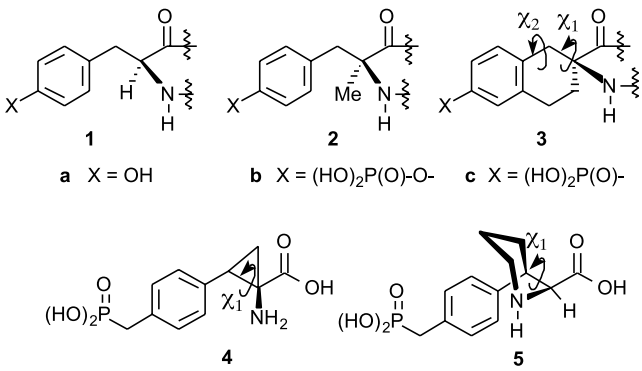

Figure 1. Structures of pTyr and pTyr mimetics.

The biological activities of proteins are also highly influenced by post-translational modifications. This is exemplified by the conversion of Tyr residues to phosphotyrosyl residues (pTyr, **1b**) via protein-tyrosine kinases (PTKs). In aberrant cellular signal transduction this process can be critical to several diseases, including certain cancers.[11,12] Derivatives of pTyr such as α-methyl-pTyr (**2b**) that include elements of conformational constraint can be useful in the design of pTyr-dependent signaling antagonists.[13,14] This type of analogue is of limited use in cellular systems where the phosphoryl ester bond is labile to protein-tyrosine phosphatases (PTPs). Accordingly, the development of PTP-stable phosphonate-based congeners has been undertaken, as exemplified by **1c**[15,16] and (α-methyl)-*p*-phosphonophenylalanine ((α-methyl)-Ppp, **2c**).[17] These compounds can retain much of the biological potency of the parent phosphate-containing analogues.[17,18] Although

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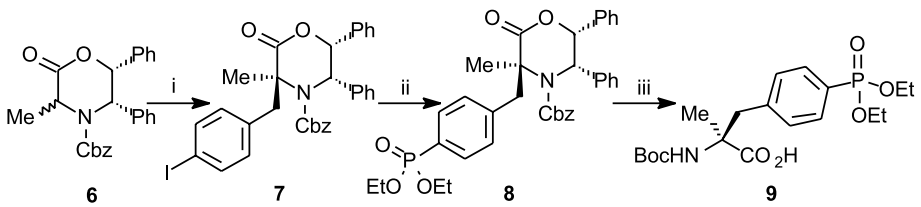


Scheme 1. (i) 4-Iodobenzyl bromide, KHMDS (86% yield); (ii) $(EtO)_2PHO$, Et_3N, $Pd(PPh_3)_4$ (74% yield); (iii) (a) H_2, Pd·C, (b) Boc_2O, Et_3N (61% yield).

phosphonate-containing χ_1-constrained pTyr mimetics such as **4**[19] and **5**[20] have been disclosed, to date the χ_1, χ_2-restricted pTyr mimetic **3c** has yet to be reported, in spite of its potential usefulness. Work was therefore undertaken to prepare **3c** in its enantio-pure form, suitably protected for incorporation into peptides using standard methodologies. Efforts were also devoted to develop a new enantioselective synthesis of orthogonally-protected **2c**.

1.1. Synthesis of *N*-Boc (*S*)-4-(diethylphosphono)-(α-methyl)phenylalanine

The synthesis of (α-methyl)-Ppp (**2c**) in racemic form as the diethyl phosphonate ester bearing *N*-Fmoc protection has been achieved previously[17] via a Schiff base approach.[19] In the current work, enantioselective synthesis of the (*S*)-*N*-Boc variant of this compound (*N*-Boc (α-methyl)-Ppp$(OEt)_2$, **9**) was accomplished using the 3-methyl-substituted Williams oxazinone **6**[21] in a protocol similar to that used to prepare non-phosphorus-containing (α-methyl)-pTyr mimetics (Scheme 1).[14] Reaction of **6** with 4-iodobenzyl bromide in the presence of KHMDS afforded the fully-protected (α-methyl)-(4-iodo)phenylalanine (**7**),[22] which represents a potential common intermediate for the enantioselective synthesis of a variety of 4-substituted phenylalanines. While attempted $Pd(PPh_3)_4$-mediated replacement of iodine using $(Bu^tO)_2P(O)H$ failed, product **8** could be obtained in good yield using the sterically less demanding $(EtO)_2P(O)H$. Hydrogenolytic deprotection and reaction with Boc anhydride provided the desired target compound **9** in 39% overall yield.

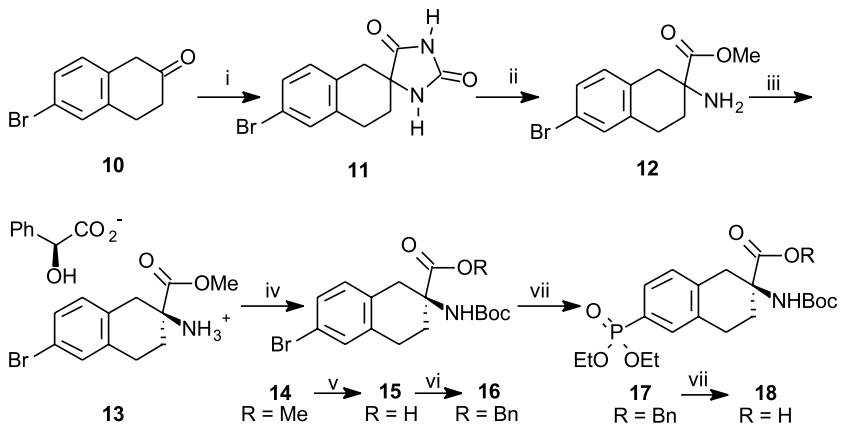
1.2. Synthesis of *N*-Boc (*S*)-2-amino-6-(diethylphosphono)tetralin-2-carboxylic acid

The route to cyclic α,α-substituted analogue **18** involved the synthesis of racemic 2-amino-6-bromo-tetralin-2-carboxylic acid methyl ester (**12**), which was obtained in classic fashion[23,24] from commercially available 6-bromo-2-tetralone **10** through the intermediacy of spirohydantoin **11** (Scheme 2). Resolution of (±)-**12** as the (L)-(+)-mandelic acid salt according to literature procedures[23] provided the ammonium salt **13** bearing the L-configuration as determined by single crystal X-ray crystallography. The optical purity of **13** was verified by HPLC analysis of **14** using a chiral stationary phase (ee >98%). Amino ester **13** was converted in two steps to the *N*-Boc amino acid **15** (77% yield), which represents a versatile intermediate for the preparation of a variety of 6-substituted analogues using cross-coupling chemistries. Transient protection of **15** as its benzyl ester (**16**) allowed $Pd(PPh_3)_4$-mediated introduction of the 6-$(EtO)_2PO$-group, which provided the conformationally-constrained pTyr mimetic **18** following hydrogenolytic de-esterification.

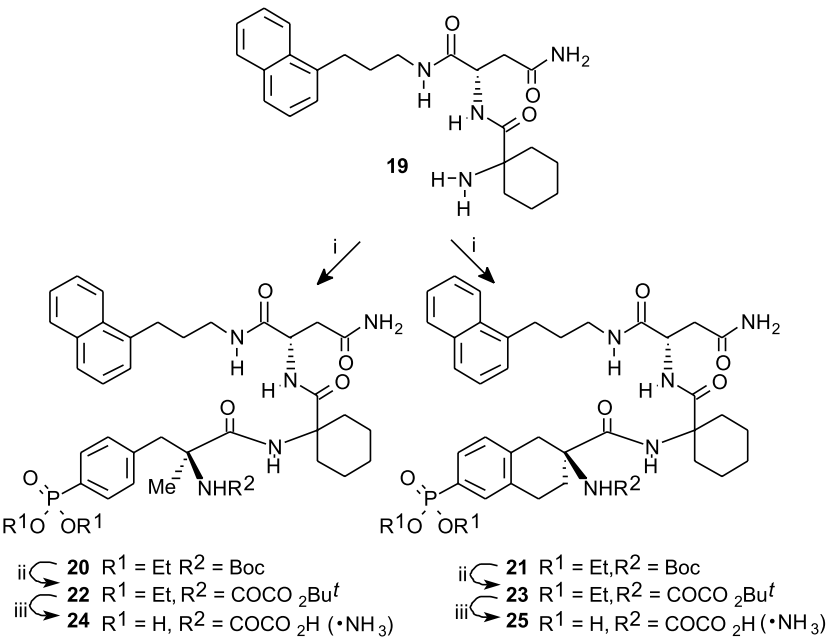
1.3. Incorporation of pTyr mimetics 9 and 18 in Grb2 SH2 domain-directed peptides

In order to demonstrate the suitability of conformationally-constrained pTyr mimetics **9** and **18** for peptide synthesis, Grb2 SH2 domain-directed tripeptides **24** and **25** were prepared, respectively (Scheme 3). This platform has been used extensively to investigate a variety of pTyr mimetics, including the χ_1-constrained analogue **5**.[20] Coupling of the α,α-disubstituted residues with the sterically-crowded amino group of dipeptide **19**[25] was achieved using tetramethylfluoroformamidinium hexafluorophosphate (TFFH).[26] Final products **24** and **25** were obtained as their ammonium salts following deprotection using trimethylsilyl iodide (TMSI) and TFA.

Although the primary purpose in preparing peptides **24** and



Scheme 2. (i) KCN, $(NH_4)_2CO_3$ (81% yield); (ii) (a) $Ba(OH)_2$, (b) $SOCl_2$, MeOH (54% yield); (iii) L-(+)-mandelic acid (25% yield); (iv) Boc_2O, Et_3N (79% yield); (v) LiOH (98% yield); (vi) BnBr, Pr^i_2EtN (97% yield); (vii) $(EtO)_2PHO$, Et_3N, $Pd(PPh_3)_4$ (93% yield); (iii) (a) H_2, Pd·C (99% yield).



Scheme 3. (i) **9** or **18**, TFFH, Pr^i_2EtN; (ii) (a) TFA, anisole, (b) Bu^tO_2CCOCl, Pr^i_2EtN; (iii) (a) TMSI, (b) TFA–H_2O (95:5).

25 was to verify the suitability of amino acid analogues **9** and **18** for peptide synthesis, once in hand, it was also of interest to determine the Grb2 SH2 domain-binding potency of these peptides. In an ELISA-based extracellular binding assay, the unconstrained N^{α}-oxalyl Pmp-containing variant of **24** and **25** had previously been shown to exhibit low nanomolar Grb2 SH2 domain-binding potency.[25] Therefore, it was surprising that in a similar ELISA-based Grb2 SH2 domain binding assay,[27] peptides **24** and **25** displayed poor affinity (IC_{50} >10 μM). This was reminiscent of a report that conformational constraint of the pTyr-mimicking residue is deleterious to SH2 domain-binding potency.[20] However, it was in marked contrast to the findings of a recent study employing a cyclopropane-based pTyr mimetic that was equipotent to the unconstrained parent.[28]

2. Conclusions

Reported herein are the syntheses of two conformationally-constrained pTyr mimetics in protected forms suitable for incorporation into peptides using standard methodologies. Chiral arylhalide intermediates in both approaches represent potential starting points for the cross-coupling synthesis of additional constrained phenylalanyl analogues.

3. Experimental

3.1. General synthetic

Reactions were carried out under argon in oven-dried glassware using standard gas-tight syringes, cannulas and septa. Anhydrous solvents were purchased from Aldrich Chemical Corporation and used without further drying. Melting points were measured using a MEL-TEMP II apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA. ^1H NMR data were recorded on a Varian 400 MHz spectrometer and are reported in ppm relative to TMS and referenced to the solvent in which they were run. Fast atom bombardment mass spectra (FABMS) were acquired with a VG analytical 7070E mass spectrometer under the control of a VG 2035 data system. HPLC separations were conducted using a Cosmosil $5C_{18}$-ARII (20×250 mm) with a solvent system of 0.1% aqueous NH_3 (v/v, solvent A)/0.1% NH_3 in MeCN (v/v, solvent B) or a CHIRALCEL OD (10×250 mm) using hexanes (solvent C) and *i*-PrOH (solvent D).

3.1.1. (3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(4-iodo)benzyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7). To a stirred solution of **6**[21] (2.00 g, 4.98 mmol) in dry THF (40 mL) was added a solution of KHMDS in toluene (0.5 M, 12.0 mL, 6.0 mmol) at −78 °C under argon. After 5 min, a solution of 4-iodobenzyl bromide (1.84 g, 6.22 mmol) was added dropwise at −78 °C, and stirring was continued for 30 min, followed by quenching with a saturated NH_4Cl solution. The mixture was extracted with EtOAc, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes–EtOAc (20:1) provided **7** as colorless crystals (2.67 g, 86% yield): mp 98–100 °C; $[\alpha]_D^{21}$ +156.0 (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.08 (d, *J*=13.2 Hz, 1H), 3.88 (m, 1H), 4.22 (d, *J*=13.4 Hz, 1H), 5.01 (m, 1H), 5.10 (d, *J*=12.2 Hz, 1H), 5.23 (d, *J*=12.2 Hz, 1H), 6.60–7.63 (m, 19H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.3, 43.8, 59.9, 66.3, 67.6, 78.8, 93.1, 126.2, 128.1, 128.2, 128.6, 128.9, 132.0, 134.3, 135.6, 136.0, 136.3, 137.9, 153.5, 172.8. Anal. calcd for $C_{32}H_{28}INO_4$: C, 62.24; H, 4.57; N, 2.27. Found: C, 62.30; H, 4.63; N, 2.26. FABMS *m/z* 618 (MH^+).

3.1.2. (3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(4-diethylphosphono)benzyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8). A mixture of **7** (2.53 g, 4.09 mmol), diethyl phosphite (0.580 mL, 4.50 mmol),

Et_3N (0.627 mL, 4.50 mmol) and $Pd(PPh_3)_4$ (236 mg, 0.204 mmol) in dry toluene (5 mL) was stirred at reflux for 6 h at 90 °C under argon. The whole was extracted with EtOAc, and the extract was washed with H_2O and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes–EtOAc (1:1) provided **8** as a colorless oil (1.90 g, 74% yield): $[\alpha]_D^{22}$ +189.9 (*c* 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J*=7.0 Hz, 3H), 1.27 (t, *J*=7.0 Hz, 3H), 1.57 (s, 9H), 2.02 (s, 3H), 3.17 (d, *J*=13.4 Hz, 1H), 3.80 (m, 1H), 3.83–4.16 (m, 4H), 4.37 (d, *J*=13.4 Hz, 1H), 5.02 (m, 1H), 5.14 (d, *J*=12.3 Hz, 1H), 5.24 (d, *J*=12.1 Hz, 1H), 6.64 (d, *J*=7.2 Hz, 2H), 6.86 (d, *J*=6.8 Hz, 2H), 6.96–7.56 (m, 13H), 7.72 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.2, 16.3, 5.4, 44.2, 59.6, 62.1, 62.2, 66.4, 67.7, 78.7, 125.8, 128.0, 128.1, 128.2, 128.4, 128.6, 128.8, 130.2, 132.2, 134.2, 135.4, 135.9, 141.3, 153.5, 172.6. FABMS *m*/*z* 628 (MH^+). Anal. calcd for $C_{36}H_{38}NO_7P$: C, 68.89; H, 6.10; N, 2.23. Found: C, 68.49; H, 6.24; N, 2.41.

3.1.3. (2*S*)-2-(*tert*-Butyloxycarbonyl)amino-3-(4-diethylphosphono)phenylpropionic acid [Boc-(α-Me)Phe(4-PO_3Et_2)-OH] (9). Oxazinone **8** (4.70 g, 7.48 mmol) was treated using Pd·C (10%, 1.0 g) in THF–EtOH (1:1, 300 mL) under H_2. After filtration through Celite, the solution was concentrated under reduced pressure to yield the amino acid. This was taken up in DMF–H_2O (4:1, 25 mL) and reacted with Boc_2O (2.45 g, 11.23 mmol) and Et_3N (3.13 mL, 22.4 mmol) at 0 °C and with stirring for 4 days at room temperature. The mixture was acidified with saturated citric acid solution and extracted with EtOAc. The extract was washed with H_2O and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel using CH_2Cl_2–MeOH (10:1) provided **9** as colorless gum (1.92 g, 61% yield): $[\alpha]_D^{22}$ +22.0 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (m, 6H), 1.45 (s, 9H), 1.74 (s, 3H), 3.28 (d, *J*=13.3 Hz, 1H), 3.69 (m, 1H), 4.00–4.25 (m, 4H), 5.56 (s, 1H), 7.35 (dd, *J*=8.2, 4.2 Hz, 2H), 7.66 (dd, *J*=13.3, 8.0 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.1, 16.2, 24.2, 28.4, 41.1, 60.4, 62.5, 62.7, 79.1, 124.2, 126.1, 130.2, 131.5, 142.8, 154.3, 175.3. FABMS *m*/*z* 416 (MH^+). Anal. calcd for $C_{19}H_{30}NO_7P$: C, 54.93; H, 7.28; N, 3.37. Found: C, 55.24; H, 7.42; N, 3.22.

3.1.4. 3′,4′-Dihydro-6′-bromo-spiro[imidazolidine-4,2′(1′*H*)-naphthalene]-2,5-dione (11). A mixture of 6-bromo-2-tetralone **10** (20.3 g, 90.2 mmol), KCN (7.63 mL, 117 mmol), $(NH_4)_2CO_3$ (78.0 g, 811 mmol) in 50% aqueous EtOH (540 mL) was stirred at reflux for 1 h. After evaporation of EtOH, the suspension was filtrated to provide **11** as brown powder (21.7 g, 81% yield): mp 285–287 °C (decomp.); ^1H NMR (400 MHz, DMSO-d_6) δ 1.80 (m, 1H), 1.92 (m, 1H), 2.75 (d, *J*=17.0 Hz, 1H), 2.90 (m, 2H), 3.04 (d, *J*=17.3 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 7.30 (dd, *J*=8.0, 2.2 Hz, 1H), 7.35 (d, *J*=2.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.5, 29.5, 36.3, 60.3, 118.8, 128.5, 130.9, 131.0, 132.1, 137.7, 156.2, 177.9. FABMS *m*/*z* 295 (MH^+). Anal. calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.84; H, 3.76; N, 9.49. Found: C, 49.27; H, 3.79; N, 9.20.

3.1.5. Methyl 2-amino-1,2,3,4-tetrahydro-6-bromo-2-naphthalenecarboxylate (12). A suspension of **11** (21.5 g, 72.9 mmol) and $Ba(OH)_2$ in H_2O (750 mL) was stirred at reflux for 36 h. The mixture was acidified with 6 N H_2SO_4, and filtered and the filter pad was washed with MeOH repeatedly. The combined filtrate was concentrated under reduced pressure to yield a suspension, which was adjusted to pH 6.0 with NH_4OH and the resulting solid was collected by filtration to provide the crude amino acid (18.7 g, 95%). A mixture of amino acid (17.7 g) and $SOCl_2$ (14.3 mL, 197 mmol) in MeOH (350 mL) was stirred at reflux for 3 h. After filtration, the filtrate was concentrated under reduced pressure to give the methyl ester as an HCl salt. This was neutralized with excess $NaHCO_3$ in toluene–H_2O (5:9, 840 mL) and the organic phase was separated and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes–EtOAc (1:1) gave **12** as a pale yellow oil (10.7 g, 57% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 2H), 1.87 (m, 1H), 2.12 (ddd, *J*=13.4, 9.6, 6.1 Hz, 1H), 2.68 (d, *J*=16.5 Hz, 1H), 2.78 (dt, *J*=17.2, 5.5 Hz, 1H), 2.98 (m, 1H), 3.21 (d, *J*=16.4 Hz, 1H), 3.74 (s, 3H), 6.94 (d, *J*=8.0 Hz, 1H), 7.20–7.28 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.3, 31.6, 38.8, 52.4, 56.2, 119.6, 129.0, 130.9, 131.4, 132.7, 137.1, 177.0. FABMS *m*/*z* 284 (MH^+). Anal. calcd for $C_{12}H_{14}BrNO_2$; C: 50.72; H: 4.97; N: 4.93. Found: C, 50.90; H, 5.00; N, 4.93.

3.1.6. (*S*)-2-Amino-1,2,3,4-tetrahydro-6-bromo-2-naphthalenecarboxylic acid methyl ester (*S*)-mandelic acid salt (13). To a solution of amino ester **12** (10.4 g, 36.8 mmol) in Et_2O–MeOH (3:1, 150 mL) was added L-(+)-mandelic acid (5.55 g, 36.5 mmol). Repeated recrystalization from Et_2O–MeOH (3:1) provided salt **13** as colorless crystals (4.07 g, 25% yield): mp 138–140 °C; Anal. calcd for $C_{20}H_{22}BrNO_5$: C, 55.06; H, 5.08; N, 3.21. Found: C, 54.77; H, 5.08; N, 3.21.

3.1.7. Methyl (*S*)-2-(*tert*-butyloxycarbonyl)amino-1,2,3,4-tetrahydro-6-bromo-2-naphthalenecarboxylate (14). To a stirred suspension of **13** (50 mg, 0.114 mmol) in $CHCl_3$ (0.160 mL) were added Boc_2O (55 mg, 0.252 mmol) and Et_3N (0.070 mL, 0.504 mmol) at 0 °C, and stirring was continued for 2 days at room temperature. The mixture was extracted with EtOAc, and the extract was successively washed with 5% citric acid solution, brine, 5% $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes–EtOAc (7:1) provided **14** as colorless crystals (35 mg, 79% yield): mp 115–117 °C; $[\alpha]_D^{21}$ +30.6 (*c* 0.68, $CHCl_3$). Enantiomeric purity, determined by HPLC analysis using a CHIRALCEL column (isocratic, 10% D in C), was >98%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.10 (m, 1H), 2.46 (m, 1H), 2.82 (dd, *J*=8.3, 4.8 Hz, 2H), 2.92 (d, *J*=16.8 Hz, 1H), 3.22 (d, *J*=16.7 Hz, 1H), 3.76 (s, 3H), 4.72 (s, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 7.23–7.29 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.1, 28.2, 37.6, 52.5, 57.6, 120.0, 129.2, 130.9, 131.4, 131.6, 137.2, 154.9, 174.2. FABMS *m*/*z* 384 (MH^+). Anal. calcd for $C_{17}H_{22}BrNO_4$: C, 53.14; H, 5.77; N, 3.65. Found: C, 53.27; H, 5.78; N, 3.70.

3.1.8. (*S*)-2-(*tert*-Butyloxycarbonyl)amino-1,2,3,4-tetrahydro-6-bromo-2-naphthalenecarboxylic acid (15). To a

stirred solution of amino ester **14** (2.00 g, 5.20 mmol), in THF (25 mL) was added 1 N LiOH (15.6 mL, 15.6 mmol) at 0 °C, and stirring was continued overnight at room temperature. The mixture was acidified with saturated citric acid solution, concentrated under reduced pressure and extracted with EtOAc. The extract was washed with H_2O and brine, and dried over $MgSO_4$. Concentration and recrystalization from Et_2O–MeOH (5:1) gave **15** as colorless crystals (1.90 g, 98% yield): mp 183–185 °C; $[\alpha]_D^{22}$ +22.8 (*c* 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.10 (ddd, *J*=13.6, 10.5, 6.8 Hz, 1H), 2.53 (m, 1H), 2.84 (m, 2H), 2.94 (d, *J*=17.1 Hz, 1H), 3.31 (d, *J*=16.8 Hz, 1H), 4.79 (br, 1H), 6.95 (d, *J*=8.0 Hz, 1H), 7.27 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.6, 28.1, 56.6, 77.9, 118.3, 128.2, 130.5, 131.3, 133.5, 137.7, 155.0,175.4. FABMS *m*/*z* 370 (MH^+). Anal. calcd for $C_{16}H_{20}BrNO_4$; C, 51.90; H, 5.44; N, 3.78. Found: C, 51.90; H, 5.47; N, 3.66.

3.1.9. Benzyl (*S*)-2-(*tert*-butyloxycarbonyl)amino-1,2,3,4-tetrahydro-6-bromo-2-naphthalenecarboxylate (16). To a stirred solution of **15** (1.88 g, 5.07 mmol) in DMF (5.5 mL) were added BnBr (0.664 mL, 5.58 mmol) and Pr^i_2EtN (1.06 mL, 6.09 mmol) at 0 °C and stirring was continued for 24 h at room temperature. The mixture was extracted with EtOAc, and the extract was washed with saturated citric acid solution, H_2O, 5% $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (7:1) provided **16** as colorless crystals (2.27 g, 97% yield): mp 89–91 °C; $[\alpha]_D^{22}$ +16.9 (*c* 0.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.12 (ddd, *J*=13.6, 9.7, 7.5 Hz, 1H), 2.46 (m, 1H), 2.79 (m, 2H), 2.92 (d, *J*=16.5 Hz, 1H), 3.26 (d, *J*=16.6 Hz, 1H), 4.75 (br, 1H), 5.18 (s, 2H), 6.91 (d, *J*=8.0 Hz, 1H), 7.21–7.27 (m, 2H), 7.29–7.38 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.1, 28.2, 37.6, 57.7, 67.2, 120.0, 128.1, 128.2, 128.5, 129.2, 130.9, 131.5, 135.6, 137.2, 149.1, 154.8, 173.5. FABMS *m*/*z* 460 (MH^+). Anal. calcd for $C_{23}H_{26}BrNO_4$: C, 60.01; H, 5.69; N, 3.04. Found: C, 59.64; H, 5.70; N, 2.92.

3.1.10. (*S*)-2-(*tert*-Butyloxycarbonyl)amino-1,2,3,4-tetrahydro-6-(diethylphosphono)-2-naphthalenecarboxylic acid benzyl ester (17). Treatment of **16** (2.21 g, 4.80 mmol) with diethyl phosphite using a procedure similar to that described for the preparation **8** from **7**, gave **17** as a colorless oil (1.91 g, 93% yield): $[\alpha]_D^{22}$ +9.30 (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=7.0 Hz, 6H), 1.38 (s, 9H), 2.15 (ddd, *J*=13.6, 9.2, 7.3 Hz, 1H), 2.45 (m, 1H), 2.86 (m, 2H), 3.04 (d, *J*=17.3 Hz, 1H), 3.40 (d, *J*=17.0 Hz, 1H), 4.11 (m, 4H), 4.79 (s, 1H), 5.19 (s, 2H), 7.15 (dd, *J*=7.8, 4.3 Hz, 1H), 7.28–7.38 (m, 5H), 7.49–7.60 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.3, 25.1, 28.2, 28.9, 38.0, 57.7, 62.0, 67.2, 125.2, 127.1, 128.1, 128.2, 128.5, 129.1, 129.5, 132.4, 135.3, 135.6, 137.7, 154.8, 173.5. HR-FABMS *m*/*z* calcd for $C_{27}H_{37}NO_7P$ (MH^+) 518.2308, found: 518.2264.

3.1.11. (*S*)-2-(*tert*-Butyloxycarbonyl)amino-1,2,3,4-tetrahydro-6-(diethylphosphono)-2-naphthalenecarboxylic acid [Boc-Atc(6-PO_3Et_2)-OH] (18). Benzyl ester **17** (1.84 g, 3.55 mmol) was treated using Pd·C (10%, 300 mg) in EtOAc (100 mL) under an H_2 atmosphere. After filtration through Celite and concentration under reduced pressure, purification by flash chromatography over silica gel with CH_2Cl_2–MeOH (10:1) provided **18** as a colorless powder (1.51 g, 99% yield): mp 75–77 °C; $[\alpha]_D^{22}$ +7.19 (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=7.0 Hz, 6H), 1.42 (s, 9H), 2.14 (m, 1H), 2.51 (m, 1H), 2.91 (m, 2H), 3.07 (d, *J*=17.3 Hz, 1H), 3.43 (d, *J*=17.3 Hz, 1H), 4.13 (m, 4H), 4.87 (br, 1H), 7.17 (dd, *J*=7.8, 4.1 Hz, 1H), 7.53 (dd, *J*=12.9, 7.8 Hz, 1H), 7.59 (d, *J*=14.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.3, 25.1, 28.2, 37.8, 57.6, 62.3, 80.6, 124.7, 126.6, 129.1, 129.6, 132.4, 135.4, 138.0, 155.6, 177.0. FABMS *m*/*z* 428 (MH^+). Anal. calcd for $C_{20}H_{30}NO_7P$: C, 56.20; H, 7.07; N, 3.28. Found: C, 56.07; H, 7.10; N, 3.22.

3.1.12. Boc-(α-Me)Phe(4-PO_3Et_2)-Ac_6c-Asn-$(CH_2)_3$-(1-naphthyl) (20). To a stirred solution of **9** (215 mg, 0.518 mmol) in dry DMF (2 mL) was added TFFH (136 mg, 0.518 mmol) at room temperature. After 10 min, amine **19**[25] (200 mg, 0.471 mmol) and Pr^i_2EtN (0.180 mL, 1.03 mmol) were added to the above mixture at room temperature, and stirring was continued for 24 h at 50 °C. The mixture was extracted with EtOAc, and the extract was washed successively with saturated citric acid solution, brine, saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Concentration followed by flash chromatography over silica gel with CH_2Cl_2–MeOH (100:0 to 10:1) gave **20** as colorless semisolid (282 mg, 71% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.53 (m, 21H), 1.58–1.77 (m, 3H), 1.82 (m, 1H), 1.90–2.11 (m, 4H), 2.17 (m, 1H), 2.65 (dd, *J*=15.3, 5.1 Hz, 1H), 2.90 (d, *J*=13.6 Hz, 1H), 3.04 (dd, *J*=15.3, 5.6 Hz, 1H), 3.12 (m, 2H), 3.35 (m, 1H), 3.41 (m, 1H), 3.51 (d, *J*=13.6 Hz, 1H), 4.14 (m, 4H), 4.66 (s, 1H), 4.71 (m, 1H), 5.35 (br, 1H), 6.22 (br, 1H), 7.04 (m, 3H), 7.34 (m, 2H), 7.43 (m, 2H), 7.53 (t, *J*=5.6 Hz, 1H), 7.66 (m, 3H), 7.79 (m, 1H), 7.85 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=8.3 Hz, 1H). FABMS *m*/*z* 822 (MH^+). Anal. calcd for $C_{43}H_{60}N_5O_9P{\cdot}0.5H_2O$: C, 62.15; H, 7.40; N, 8.43. Found: C, 62.00; H, 7.38; N, 8.37.

3.1.13. Boc-Atc(6-PO_3Et_2)-Ac_6c-Asn-$(CH_2)_3$-(1-naphthyl) (21). Using a procedure similar to that described for the preparation of peptide **20** from **19**, coupling of **18** (200 mg, 0.471 mmol) with **19** provided **21** as a colorless semisolid (282 mg, 71% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.43 (m, 18H), 1.52–1.84 (m, 5H), 1.85–2.09 (m, 5H), 2.22 (m, 1H), 2.39 (m, 1H), 2.57–2.91 (m, 5H), 3.08 (m, 2H), 3.25 (d, *J*=17.0 Hz, 1H), 3.34 (m, 2H), 4.13 (m, 4H), 4.79 (dt, *J*=8.2, 5.8 Hz, 1H), 4.81 (s, 1H), 5.35 (br, 1H), 6.36 (br, 1H), 7.02 (dd, *J*=7.8, 4.1 Hz, 1H), 7.20 (br, 1H), 7.30 (m, 2H), 7.40 (m, 2H), 7.50 (dd, *J*=17.9, 7.5 Hz, 1H), 7.55 (m, 2H), 7.64 (m, 1H), 7.80 (m, 2H), 8.01 (d, *J*=8.3 Hz, 1H). FABMS *m*/*z* 834 (MH^+). Anal. calcd for $C_{44}H_{60}N_5O_9P{\cdot}H_2O$: C, 62.03; H, 7.34; N, 8.22. Found: C, 62.29; H, 7.30; N, 8.32.

3.1.14. *tert*-Bu^{t}O-$(CO)_2$-(α-Me)Phe(4-PO_3Et_2)-Ac_6c-Asn-$(CH_2)_3$-(1-naphthyl) (22). Protected peptide **20** (93 mg, 0.113 mmol) was treated with TFA-anisole (10:1, 5.5 mL) for 2 h at room temperature then the reaction mixture was concentrated and dissolved in dry DMF (1 mL). To this were added *tert*-butyl oxalyl chloride

(24 mg, 0.169 mmol) and Pr^i_2EtN (0.059 mL, 0.339 mmol) at 0 °C, and stirring was continued for 2 h at 50 °C. The mixture was extracted with EtOAc, and the extract was washed successively with saturated citric acid solution, brine, saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Concentration followed by flash chromatography over silica gel with CH_2Cl_2–MeOH (100:0 to 10:1) gave **20** as colorless semisolid (56 g, 58% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18–1.45 (m, 12H), 1.49 (s, 9H), 1.56–1.82 (m, 5H), 1.99 (m, 3H), 2.29 (m, 1H), 2.71 (dd, J=14.6, 5.3 Hz, 1H), 2.82 (dd, J=14.6, 6.3 Hz, 1H), 3.03 (d, J=13.6 Hz, 1H), 3.11 (m, 2H), 3.34 (m, 2H), 3.46 (d, J=13.4 Hz, 1H), 4.12 (m, 4H), 4.65 (m, 1H), 5.65 (br, 1H), 6.89 (br, 1H), 7.23 (dd, J=8.0, 3.6 Hz, 2H), 7.28 (s, 1H), 7.32–7.38 (m, 2H). 7.40–7.50 (m, 3H), 7.52 (m, 1H), 7.66 (dd, J=6.5, 2.6 Hz, 1H), 7.70–7.84 (m, 4H), 8.04 (d, J=8.0 Hz, 1H). FABMS m/z 850 (MH^+). Anal. calcd for $C_{44}H_{60}N_5O_{10}P{\cdot}H_2O$: C, 60.89; H, 7.20; N, 8.07. Found: C, 61.11; H, 7.03; N, 8.09.

3.1.15. *tert*-BuO-(CO)$_2$-Atc(6-PO$_3$Et$_2$)-Ac$_6$c-Asn-(CH$_2$)$_3$-(1-naphthyl) (23). Using a procedure similar to that described for the preparation of peptide **22** from **20**, coupling of **21** (265 mg, 0.317 mmol) with *tert*-butyl oxalyl chloride gave **23** as colorless semisolid (183 mg, 66% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (m, 2H), 1.14 (m, 1H), 1.33 (m, 6H), 1.36–1.62 (m, 12H), 1.65 (m, 2H), 1.86–2.06 (m, 3H), 2.24 (m, 3H), 2.78 (m, 4H), 3.10 (m, 3H), 3.23 (m, 1H), 3.37 (m, 1H), 3.61 (d, J=17.3 Hz, 1H), 4.11 (m, 4H), 4.66 (m, 1H), 5.52 (br, 1H), 6.74 (br, 1H), 6.93 (s, 1H), 7.20 (dd, J=4.3, 3.9 Hz, 1H), 7.35 (m, 3H), 7.44 (m, 3H), 7.60 (m, 3H), 7.68 (dd, J=7.0, 2.2 Hz, 1H), 7.82 (m, 1H), 8.04 (d, J=8.2 Hz, 1H). FABMS m/z 862 (MH^+). Anal. calcd for $C_{45}H_{60}N_5O_{10}P{\cdot}H_2O$: C, 61.42; H, 7.10; N, 7.96. Found: C, 61.58; H, 7.13; N, 7.90.

3.1.16. HO-(CO)$_2$-(α-Me)Phe(4-PO$_3$H$_2$)-Ac$_6$c-Asn-(CH$_2$)$_3$-(1-naphthyl) (24). To a stirred solution of protected peptide **22** (43 mg, 0.050 mmol) in MeCN (1 mL) were added thioanisole (0.100 mL) and TMSI (0.711 mL) at 0 °C and the mixture was stirred for 30 min at 0 °C and for an additional 1 h at room temperature. After concentration, the residue was dissolved in 95% TFA (10 mL), and stirring was continued for 2 h at room temperature. The mixture was concentrated and extracted with 0.1% NH_4OH, and the extract was washed with Et_2O. The aqueous solution was purified by preparative HPLC (linear gradient 3–13% B in A over 30 min) to give **24** as colorless powder (39 mg, 98% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (s, 3H), 1.21 (m, 2H), 1.40–1.60 (m, 4H), 1.66 (m, 1H), 1.74–1.96 (m, 4H), 2.29 (m, 1H), 2.37 (m, 1H), 2.90 (m, 2H), 3.05 (t=8.0 Hz, 2H), 3.18 (m, 2H), 3.30 (d, J=12.6 Hz, 1H), 4.25 (m, 1H), 6.62 (br, 1H), 7.29 (m, 2H), 7.37 (m, 2H), 7.47 (m, 3H), 7.61 (m, 2H), 7.73 (d, J=7.8 Hz, 1H), 7.87 (m, 1H), 7.96 (d, J=7.5 Hz, 1H), 8.07 (m, 2H), 8.30 (br, 1H), 8.35 (s, 1H). FABMS m/z 736 [$(M-H)^-$].

3.1.17. HO-(CO)$_2$-Atc(6-PO$_3$H$_2$)-Ac$_6$c-Asn-(CH$_2$)$_3$-(1-naphthyl) (25). Using a procedure similar to that described for the preparation of **24** from **22**, treatment of **23** (49 mg, 0.0568 mmol) gave **25** as a colorless powder (34 mg, 74% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (m, 2H), 1.38–1.66 (m, 5H), 1.70–1.98 (m, 6H), 2.20–2.52 (m, 4H), 2.84–3.34 (m, 7H), 4.25 (m, 1H), 6.66 (s, 1H), 7.06 (m, 1H), 7.30–7.54 (m, 7H), 7.74 (m, 1H), 7.82 (d, J=7.3 Hz, 1H), 7.86–7.96 (m, 2H), 8.09 (m, 1H), 8.26 (br, 1H). FABMS m/z 748 [$(M-H)^-$].

4. Supplementary Material

Single crystal X-ray crystallographic data for salt **13**, including a thermal ellipsoid plot at the 50% confidence interval and tables of atomic coordinates and parameters are provided (10 pages). Supplementary material can be found in the online version of this paper.

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References and notes

1. Mutter, M. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 639–653.
2. Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472.
3. Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441–452.
4. Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945–970.
5. Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541–558.
6. Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553–5566.
7. Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585–615.
8. Prasad, B. V. V.; Balaram, P. *CRC Crit. Rev. Biochem.* **1984**, *14*, 307–348.
9. Rastogi, S. N.; Bindra, J. S.; Anand, N. *Ind. J. Chem.* **1971**, *9*, 1175–1182.
10. Obrecht, D.; Altorfer, M.; Bohdal, U.; Daly, J.; Huber, W.; Labhardt, A.; Lehmann, C.; Muller, K.; Ruffieux, R.; Schonholzer, P.; Spiegler, C.; Zumbrunn, C. *Biopolymers* **1997**, *42*, 575–626.
11. Tsatsanis, C.; Spandidos, D. A. *Int. J. Mol. Med.* **2000**, *5*, 583–590.
12. Renhowe, P. A. *Ann. Rep. Med. Chem.* **2001**, *36*, 109–118.
13. Kzardenings, A. K.; Gordeev, M. F.; Patel, D. V. *Tetrahedron Lett.* **1996**, *37*, 3635–3638.
14. Liu, W. Q.; Vidal, M.; Gresh, N.; Rogues, B. P.; Garbay, C. *J. Med. Chem.* **1999**, *42*, 3737–3741.
15. Petrakis, K. S.; Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831–2833.
16. Bayle-Lacoste, M.; Moulines, J.; Collignon, N.; Boumekouez, A.; De Tinguy-Moreaud, E.; Neuzil, E. *Tetrahedron* **1990**, *46*, 7793–7802.
17. Garbay, C.; Liu, W.-Q.; Vidal, M.; Roques, B. P. Preparation of pseudopeptides having an inhibiting activity with respect to

paths activated by proteins with active tyrosine kinase activity and pharmaceutical compositions containing same. US Pat. Appl. Publ. No. US 2002/0055463 A1 (May 9, 2002) for US Appl. No. 09/977,349, filed October 16, 2001. Priority Fr 98/16459 (December 24, 1998).
18. Stankovic, C. J.; Surendran, N.; Lunney, E. A.; Plummer, M. S.; Para, K. S.; Shahripour, A.; Fergus, J. H.; Marks, J. S.; Herrera, R.; Hubbell, S. E.; Humblet, C.; Saltiel, A. R.; Stewart, B. H.; Sawyer, T. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1909–1914.
19. Liu, W. Q.; Carreaux, F.; Meudal, H.; Roques, B. P.; GarbayJaureguiberry, C. *Tetrahedron* **1996**, *52*, 4411–4422.
20. Liu, D.-G.; Wang, X.-Z.; Gao, Y.; Li, B.; Yang, D.; Burke, T. R., Jr. *Tetrahedron* **2002**, *58*, 10423–10428.
21. Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286.
22. Compound **7** was diastereomerically pure to H NMR.
23. Ishizumi, K.; Ohashi, N.; Tanno, N. *J. Org. Chem.* **1987**, *52*, 4477–4485.
24. Obrecht, D.; Spiegler, C.; Schoenholzer, P.; Mueller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta* **1992**, *75*, 1666–1696.
25. Yao, Z. J.; King, C. R.; Cao, T.; Kelley, J.; Milne, G. W. A.; Voigt, J. H.; Burke, T. R. *J. Med. Chem.* **1999**, *42*, 25–35.
26. Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401–5402.
27. Gao, Y.; Luo, J.; Yao, Z.-J.; Guo, R.; Zou, H.; Kelley, J.; Voigt, J. H.; Yang, D.; Burke, T. R., Jr. *J. Med. Chem.* **2000**, *43*, 911–920.
28. Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 205–215.

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Stereoselective synthesis of anamarine

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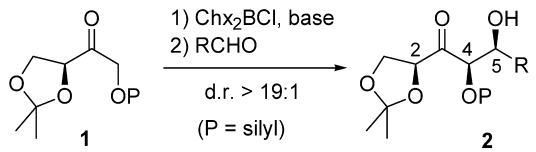
Abstract—A stereoselective synthesis of the naturally occurring, α,β-unsaturated lactone anamarine is described. The key step was a highly stereoselective aldol reaction of a protected erythrulose derivative with a chiral aldehyde. Another relevant step was an asymmetric aldehyde allylation with a chiral allylborane. The lactone ring was made by means of a ring-closing metathesis.

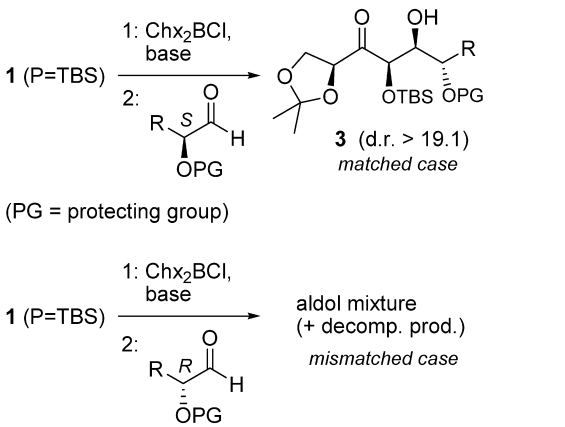
1. Introduction

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon–carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] Our current interest in the development of erythrulose[3] as a useful chiral building block for the stereocontrolled construction of polyfunctionalized structures has led us to investigate the enolization of protected derivatives thereof and the subsequent addition of the resulting enolates to aldehydes. We recently reported that L-erythrulose acetals with the general formula **1** (Scheme 1, protecting group P=silyl), readily prepared in two steps from L-erythrulose,[4] were transformed into boron enolates provided that chlorodicyclohexylborane (Chx_2BCl) was used as the enolization reagent.[5–7] The boron enolates were then allowed to react with a range of achiral aldehydes to yield aldol adducts of the general formula **2** with a high degree of *syn* 1,2- and 1,3-induction (the 2,4-*syn*/4,5-*syn* relationship in **2**, diastereomeric ratio, d.r.>19:1).



Scheme 1. Boron aldol reactions of erythrulose derivatives with achiral aldehydes.

Very recently, we have shown that such aldol reactions can be carried out with high stereoselectivity also in the case of α-chiral aldehydes. The sense of induction of these doubly diastereoselective processes was found to depend on the type of α-substituents (carbon vs heteroatom groups), matched and mismatched cases being observed. As a matter of fact, (*S*)-α-oxygenated aldehydes were found to react with ketones **1** to yield aldols **3** with a high degree of stereoselectivity, whereas those having the *R* configuration turned out to give sluggish and nonstereoselective reactions (Scheme 2). Mechanistic models were proposed to explain these diverging results.[8]



Scheme 2. Boron aldol reactions of erythrulose derivatives with chiral, α-oxygenated aldehydes.

In order to show the synthetic utility of these aldol reactions, we have now performed a total, stereoselective synthesis of the naturally occurring lactone anamarine (Fig. 1). This α,β-unsaturated lactone and several structural analogues thereof such as spicigerolide, hyptolide and synrotolide have been isolated from species of *Hyptis* and other botanically related genera (natural configurations depicted in Fig. 1).[9] These compounds contain a polyoxygenated chain connected with an α,β-unsaturated six-membered lactone and show a range of pharmacological properties,

Keywords: Erythrulose; Boron aldol reactions; Asymmetric allylboration; Stereoselectivity; Ring-closing metathesis; Anamarine.
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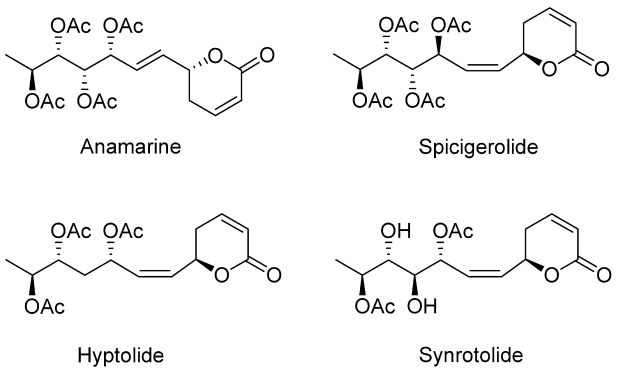
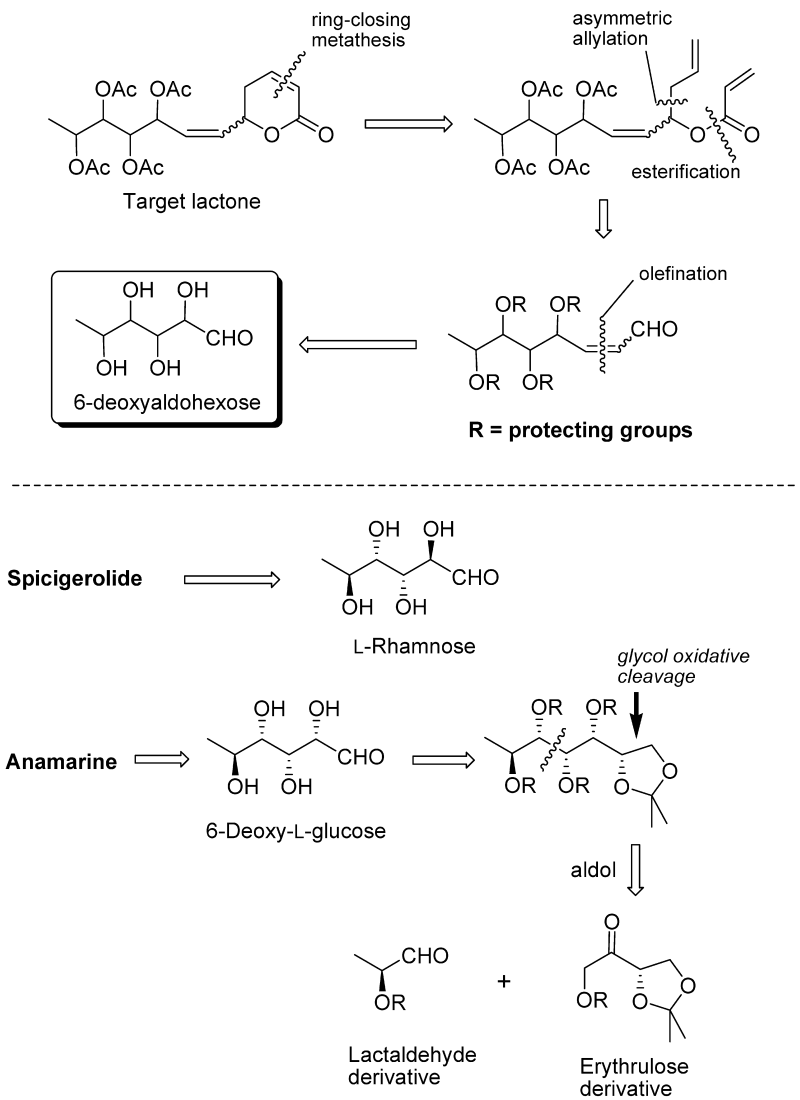


Figure 1. Naturally occurring γ-pyrones isolated from *Hyptis* spp. and related genera.

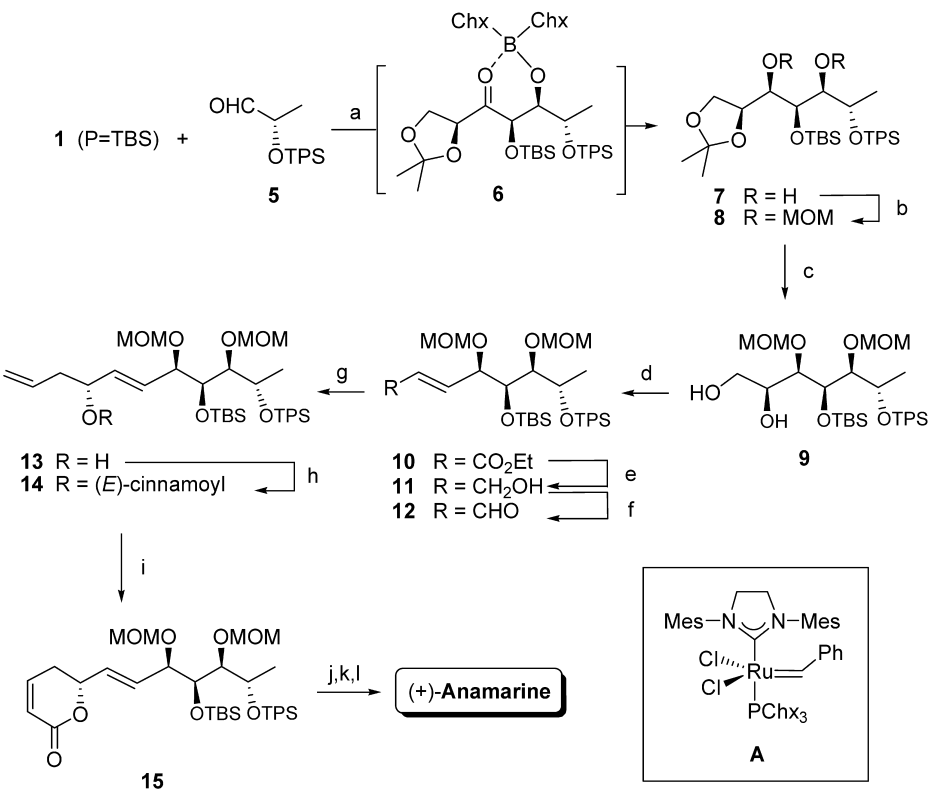
such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc. Pharmacological properties of these types make these compounds interesting synthetic goals. Efforts in this direction were limited for many years to the syntheses of natural (+)-anamarine (Fig. 1) and its nonnatural (−)-enantiomer.[10] Very recently, we have published stereoselective syntheses of the natural enantiomers of spicigerolide and hyptolide.[11]

2. Results and discussion

The previous syntheses of both enantiomers of anamarine were carbohydrate-based, with all stereogenic carbons being already present in the chiral starting materials.[10] Our synthesis relies upon the same general concept used in our recent syntheses of structurally similar lactones, where asymmetric allylations and ring-closing metatheses played a key role.[11] As shown in Scheme 3, the generic retrosynthetic analysis for such lactones points to a 6-deoxyaldohexose as the starting material. In our synthesis of spicigerolide, for instance,[11b] we used to advantage the fact that the polyoxygenated chain has the same absolute configuration as L-rhamnose (6-deoxy-L-mannose), a commercially available sugar. In the case of anamarine, however, the same analysis leads to the nonavailable sugar 6-deoxy-L-glucose. A synthesis for this compound in suitably protected



Scheme 3. Retrosynthetic analysis for anamarine and related polyoxygenated lactones.



Scheme 4. Synthesis of (+)-anamarine. Reaction conditions: (a) Chx_2BCl, Et_3N, Et_2O, 0 °C, then **5**, from −78 °C to 0 °C, 5 h, then $LiBH_4$, −78 °C, 2 h (75% of **7**); (b) MOMCl, DIPEA, 4 days, △ (72%); (c) PPTS, aq MeOH, rt, overnight (70%); (d) $Pb(OAc)_4$, CH_2Cl_2, rt, 1 h, then $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, rt, overnight (88% overall); (e) DIBAL, hexane–toluene, 0 °C, 4 h, (82%); (f) PCC, celite, CH_2Cl_2, rt, 1.5 h (90%); (g) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 3 h (88:12 diastereoisomer mixture, 74% of pure **13** after chromatography); (h) cinnamoyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h (81%); (i) catalyst **A** (10%), CH_2Cl_2, reflux, 3 h (98%); (j) $BF_3{\cdot}Et_2O$, SMe_2, −10 °C, 30 min; (k) aq HF, rt, 7 h; (l) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, overnight (62% overall for the three steps). Abbreviations: Chx, cyclohexyl; MOMCl, methoxymethyl chloride; DIPEA, ethyl *N*,*N*-di*iso*propylamine; PPTS, pyridinium *p*-toluenesulfonate; DIP-Cl, di*iso*pinocampheylboron chloride; PCC, pyridinium chlorochromate; DMAP, *N*,*N*-dimethylaminopyridine; DIBAL, di*iso*butylaluminum hydride.

form was then designed with reliance on our aldol methodology with erythrulose derivatives (Scheme 3).

As we have recently reported, the reaction between the boron enolate of ketone **1** (P=TBS) and the (*S*)-lactaldehyde derivative **5** generates with high diastereoselectivity the boron aldolate **6** which, by means of an oxidative hydrolytic work-up, gives rise to the corresponding aldol adduct (Scheme 4).[8] In the present case, however, aldolate **6** was reduced in situ with $LiBH_4$ to yield the *syn*-1,3-diol **7**.[12] After protection of the hydroxyl groups and hydrolytic cleavage of the acetonide ring,[13] diol **9** was oxidatively cleaved to an intermediate α-alkoxy aldehyde (not depicted) which, without purification, was olefinated by means of a modified Horner–Emmons reaction[14] to conjugated ester **10**. Standard functional group manipulations afforded conjugated aldehyde **12**, which was then subjected to asymmetric allylation[15] to alcohol **13**. Acylation of the latter with cinnamoyl chloride,[16] followed by ring-closing metathesis in the presence of the second-generation Grubbs ruthenium catalyst **A**,[17] provided conjugated lactone **15**. Finally, cleavage of all protecting groups and per-acetylation furnished synthetic (+)-anamarine, identical in its physical and spectral properties[9a] to the natural product (Scheme 4). The overall yield was about 8% (based on ketone **1**), a figure which compares well with the previous synthetic efforts.[10]

3. Conclusions

Erythrulose derivatives are able to give highly stereoselective aldol reactions with α-oxygenated aldehydes provided that the configurations of both chiral components are suitably matched (doubly diastereoselective process). The synthetic utility of these reactions has been shown here with the stereoselective synthesis of the naturally occurring, pharmacologically active lactone (+)-anamarine. Further applications of this methodology to the synthesis of natural products are being currently developed by our group and will be described in near future.

4. Experimental

4.1. General

NMR spectra were measured at 400 or 500 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^{1}H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C NMR signals were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR

data are given only for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O was freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into 5% aq $NaHCO_3$ (if acids had been utilized in the reaction) or into satd aq NH_4Cl (if bases had been utilized), then washing again the organic layer with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent in vacuo. When solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent, and the washing liquids incorporated into the main organic layer. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60–200 μ) with the indicated eluent. Reagent acronyms are explained in the caption of Scheme 4.

4.1.1. (1*R*,2*S*,3*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-1-((4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-pentane-1,3-diol (7). The aldol reaction of ketone **1** with aldehyde **5** promoted by Chx_2BCl, followed by in situ $LiBH_4$ reduction was performed as previously reported[8] to yield **7** in 75% overall yield: oil, IR ν_{max} (cm^{-1}) 3400 (br, OH); ^1H NMR (500 MHz) δ 7.75–7.65 (4H, m), 7.45–7.35 (6H, m), 4.25 (1H, br q, *J*=6.5 Hz), 4.10 (1H, dd, *J*=8, 4.5 Hz), 4.00–3.80 (3H, m), 3.55–3.45 (2H, m), 1.43 (3H, s), 1.36 (3H, s), 1.07 (9H, s), 1.07 (3H, d, *J*=6.5 Hz, overlapped), 0.86 (9H, s), 0.12 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 134.0, 133.8, 109.2, 19.2, 19.1 (C), 135.9, 135.8, 129.7, 129.6, 127.7, 127.5, 76.0, 74.4, 72.5, 70.2, 68.2 (CH), 66.3 (CH_2), 27.1 (×3), 26.7, 26.0 (×3), 25.8, 18.2, −4.2, −4.5 (CH_3).

4.1.2. (4*S*)-4-[(1*R*,2*S*,3*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-1,3-bis(methoxymethoxy)pentyl]-2,2-dimethyl-[1,3]dioxolane, 8. Diol **7** (2.355 g, 4 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and treated dropwise with DIPEA (8 mL, 46 mmol) and MOM chloride (3 mL, ca. 40 mmol). The reaction was then stirred at reflux for 4 days. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 95:5) afforded compound **8** (1.95 g, 72%): oil, $[\alpha]_D$=−25.5 (*c* 0.9; $CHCl_3$); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 4.86 (2H, AB system, *J*=6.2 Hz), 4.60 (1H, d, *J*=6.7 Hz), 4.40 (1H, d, *J*=6.7 Hz), 4.20 (1H, br q, *J*=6.5 Hz), 3.95–3.90 (2H, m), 3.85 (1H, m), 3.77 (1H, br d, *J*=8 Hz), 3.56 (1H, dd, *J*=8, 3.6 Hz), 3.49 (1H, dd, *J*=8, 3.7 Hz), 3.48 (3H, s), 3.20 (3H, s), 1.31 (3H, s), 1.20 (3H, s), 1.07 (9H, s), 1.02 (3H, d, *J*=6.5 Hz), 0.87 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz) δ 134.2, 134.1, 108.2, 19.1, 18.0 (C), 136.1, 135.9, 129.6, 129.5, 127.5, 127.4, 80.8, 80.1, 76.5, 73.7, 70.1 (CH), 97.7, 97.0, 65.8 (CH_2), 56.1, 55.6, 27.1 (×3), 26.8, 26.0 (×3), 25.7, 17.7, −4.7, −5.0 (CH_3). Anal. Calcd for $C_{36}H_{60}O_8Si_2$: C, 63.87; H, 8.93. Found, C, 64.01; H, 9.00.

4.1.3. (2*S*,3*R*,4*S*,5*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3,5-bis(methoxymethoxy)-heptane-1,2-diol, 9. Acetonide **8** (1.354 g, 2 mmol) was dissolved in MeOH (20 mL) and treated with a solution of pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) in water (1 mL). The solution was stirred overnight at room temperature and then carefully neutralized with aq Na_2CO_3. After removal of all volatiles in vacuo, the residue was subjected to column chromatography on silica gel (hexanes–EtOAc, 70:30) to furnish diol **9** (892 mg, 70%): oil, $[\alpha]_D$=+7.3 (*c* 0.9; $CHCl_3$); IR ν_{max} (cm^{-1}) 3400 (br, OH); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 4.87 (2H, AB system, *J*=6 Hz), 4.48 (2H, AB system, *J*=6.5 Hz), 4.08 (1H, br q, *J*=6.5 Hz), 3.94 (1H, br d, *J*=6 Hz), 3.72 (2H, m), 3.55 (2H, m), 3.47 (3H, s), 3.44 (1H, t, *J*=5 Hz), 3.25 (3H, s), 2.60 (1H, d, *J*=5 Hz, OH), 2.50 (1H, t, *J*=6 Hz, OH), 1.08 (3H, d, *J*=6.5 Hz), 1.05 (9H, s), 0.84 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz) δ 134.5, 133.9, 19.1, 18.4 (C), 136.1, 135.9, 129.6, 129.5, 127.6, 127.4, 81.5, 80.8, 73.0, 70.2, 69.9 (CH), 98.2, 97.7, 64.1 (CH_2), 56.1 (×2), 27.1 (×3), 26.0 (×3), 18.0, −4.6, −4.8 (CH_3). HR FABMS *m*/*z* 659.3393 $(M+Na)^+$, calcd for $C_{33}H_{56}NaO_8Si_2$, 659.3411. Anal. Calcd for $C_{33}H_{56}O_8Si_2$: C, 62.23; H, 8.86. Found, C, 62.03; H, 9.02.

4.1.4. Ethyl (2*E*,4*R*,5*S*,6*S*,7*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2-enoate, 10. Lead tetraacetate (488 mg, 1.1 mmol) was added to a solution of diol **9** (636 mg, ca. 1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 1 h at room temperature, then filtered through a Celite pad and evaporated in vacuo. The residue was redissolved in Et_2O, cooled in an ice bath and stirred with powdered K_2CO_3 (1.38 g, 10 mmol) for 30 min. The mixture was then filtered and evaporated in vacuo. The oily residue was dissolved in dry acetonitrile (45 mL) and treated with DIPEA (610 μL, 3.5 mmol), LiCl (212 mg, 5 mmol) and $(EtO)_2POCH_2COOEt$ (790 μL, 4 mmol). The reaction mixture was then stirred overnight at room temperature and worked up (extraction with Et_2O). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes–EtOAc, 90:10) provided ethyl ester **10** (594 mg, 88%): oil, $[\alpha]_D$=−22.5 (*c* 1; $CHCl_3$); IR ν_{max} (cm^{-1}) 1724 (C=O); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 7.00 (1H, dd, *J*=16, 4.5 Hz), 5.86 (1H, dd, *J*=16, 1.7 Hz), 4.84 and 4.76 (2H, AB system, *J*=6 Hz), 4.35 (2H, AB system, *J*=6.6 Hz), 4.17 (3H, m), 3.98 (1H, dq, *J*=2, 6.5 Hz), 3.68 (1H, dd, *J*=7.7, 2 Hz), 3.60 (1H, dd, *J*=7.7, 4.5 Hz), 3.46 (3H, s), 3.20 (3H, s), 1.29 (3H, t, *J*=7 Hz), 1.04 (9H, s), 1.02 (3H, d, *J*=6.5 Hz), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz) δ 165.9, 134.7, 133.8, 19.1, 18.0 (C), 144.5, 136.1, 136.0, 129.5, 129.4, 127.5, 127.4, 122.2, 81.5, 77.5, 74.1, 70.1 (CH), 97.8, 95.3, 60.3 (CH_2), 56.1, 55.8, 27.1 (×3), 25.9 (×3), 18.1, 14.2, −4.5, −5.0 (CH_3). HR FABMS *m*/*z* 697.3599 $(M+Na)^+$, calcd for $C_{36}H_{58}NaO_8Si_2$, 697.3562. Anal. Calcd for $C_{36}H_{58}O_8Si_2$: C, 64.06; H, 8.66. Found, C, 64.03; H, 8.88.

4.1.5. (2*E*,4*R*,5*S*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2-en-1-ol, 11. DIBAL (2.4 mL of a 1 M solution in toluene, 2.4 mmol) was added to an ice-cooled solution of ester **10** (540 mg, 0.8 mmol) in hexanes (10 mL). The solution was stirred for 4 h at 0 °C and quenched with satd

aq NH_4Cl. After filtering through a Celite pad, the solution was evaporated in vacuo. Column chromatography of the residue on silica gel (hexanes–EtOAc, 80:20) afforded alcohol **11** (415 mg, 82%): oil, $[\alpha]_D=-37.8$ (*c* 1.7; $CHCl_3$); IR ν_{max} (cm^{-1}) 3430 (br, OH); ^1H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 5.70 (1H, dt, *J*=16, 5.2 Hz), 5.55 (1H, dd, *J*=16, 5.5 Hz), 4.86 and 4.73 (2H, AB system, *J*=6.2 Hz), 4.38 and 4.26 (2H, AB system, *J*=6.6 Hz), 4.02 (2H, m), 3.96 (2H, m), 3.78 (1H, dd, *J*=7.5, 2 Hz), 3.50 (1H, dd, *J*=7.5, 4 Hz), 3.46 (3H, s), 3.16 (3H, s), 1.04 (9H, s), 1.03 (3H, d, *J*=6.5 Hz), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz) δ 134.4, 134.3, 19.1, 18.1 (C), 136.1, 136.0, 132.3, 129.5, 127.5, 127.4, 80.0, 77.8, 74.1, 70.4 (CH), 97.2, 94.4, 63.1 (CH_2), 55.9, 55.5, 27.1 (×3), 25.9 (×3), 17.7, −4.5, −4.9 (CH_3). HR FABMS *m/z* 655.3475 $(M+Na)^+$, calcd for $C_{34}H_{56}NaO_7Si_2$, 655.3462. Anal. Calcd for $C_{34}H_{56}O_7Si_2$: C, 64.51; H, 8.92. Found, C, 64.44; H, 8.80.

4.1.6. (4*R*,5*S*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-4,6-bis(methoxymethoxy)-oct-2*E*-enal, 12. PCC (194 mg, 0.9 mmol) and Celite (180 mg) were added to a solution of alcohol **11** (380 mg, 0.6 mmol) in dry CH_2Cl_2 (6 mL). The solution was stirred for 1.5 h at room temperature, then filtered through a Celite pad and evaporated in vacuo. The oily residue was subjected to column chromatography on silica gel (hexanes–EtOAc, 90:10) to provide aldehyde **12** (341 mg, 90%): oil, $[\alpha]_D=-10.8$ (*c* 1.5; $CHCl_3$); IR ν_{max} (cm^{-1}) 1697 (C=O); ^1H NMR (500 MHz) δ 9.40 (1H, d, *J*=8 Hz), 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 6.82 (1H, dd, *J*=16, 4.3 Hz), 6.10 (1H, ddd, *J*=16, 8, 1 Hz), 4.80 and 4.76 (2H, AB system, *J*=6 Hz), 4.39 (2H, AB system, *J*=6.7 Hz), 4.28 (1H, m), 4.00 (1H, br q, *J*=6.5 Hz), 3.70–3.60 (2H, m), 3.43 (3H, s), 3.20 (3H, s), 1.06 (3H, d, *J*=6.5 Hz), 1.05 (9H, s), 0.87 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 193.1, 134.5, 133.8, 18.1, 18.0 (C), 153.5, 136.0, 135.9, 132.3, 129.7, 129.5, 127.6, 127.4, 81.3, 77.6, 74.2, 70.2 (CH), 97.7, 95.7 (CH_2), 56.1, 55.9, 27.0 (×3), 25.9 (×3), 19.1, −4.6, −5.0 (CH_3). HR FABMS *m/z* 653.3325 $(M+Na)^+$, calcd for $C_{34}H_{54}NaO_7Si_2$, 653.3305.

4.1.7. (4*R*,7*R*,8*S*,9*S*,10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-7,9-bis(methoxymethoxy)-undeca-1,5*E*-dien-4-ol, 13. Allylmagnesium bromide (commercial 1 M solution in Et_2O, 750 μL, 0.75 mmol) was added dropwise via syringe to a solution of (+)-di*iso*pinocampheylboron chloride (289 mg, 0.9 mmol) in dry Et_2O (5 mL) cooled in a dry ice–acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was then allowed to stand, which caused precipitation of magnesium chloride. The supernatant solution was then carefully transferred to another flask via canula. After cooling this flask at −78 °C, a solution of aldehyde **12** (378 mg, 0.6 mmol) in dry Et_2O (5 mL) was added dropwise via syringe. The resulting solution was further stirred at the same temperature for 3 h. The reaction mixture was then quenched through addition of phosphate pH 7 buffer solution (2 mL), MeOH (3 mL) and 30% H_2O_2 (2 mL). After stirring for 30 min, the mixture was poured onto satd aq $NaHCO_3$ and worked up as usual (extraction with Et_2O). An NMR examination of the crude reaction product revealed that an 88:12 diastereoisomer mixture was present. A careful column chromatography on silica gel (hexanes–EtOAc, 90:10) afforded pure alcohol **13** (299 mg, 74%): oil, $[\alpha]_D=-47.6$ (*c* 1.8; $CHCl_3$); IR ν_{max} (cm^{-1}) 3450 (br, OH); ^1H NMR (400 MHz) δ 7.70–7.60 (4H, m), 7.40–7.30 (6H, m), 5.77 (1H, m), 5.62 (1H, ddd, *J*=15.7, 5.4, 1 Hz), 5.47 (1H, ddd, *J*=15.7, 6.6, 1 Hz), 5.15–5.10 (2H, m), 4.86 and 4.75 (2H, AB system, *J*=6.2 Hz), 4.37 and 4.22 (2H, AB system, *J*=6.6 Hz), 4.05 (1H, dq, *J*=2.2, 6.5 Hz), 4.00 (2H, m), 3.76 (1H, dd, *J*=7.5, 2.2 Hz), 3.53 (1H, dd, *J*=7.5, 4.3 Hz), 3.46 (3H, s), 3.17 (3H, s), 2.20 (2H, m), 1.70 (1H, br s, OH), 1.05 (3H, d, *J*=6.5 Hz), 1.04 (9H, s), 0.86 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz) δ 134.5, 134.3, 19.1, 18.1 (C), 136.5, 136.1 (×2), 134.3, 129.6, 129.5, 127.6, 127.5, 126.1, 80.6, 78.2, 74.4, 70.8, 70.4 (CH), 118.2, 97.5, 94.1, 41.7 (CH_2), 56.0, 55.5, 27.1 (×3), 26.0 (×3), 18.0, −4.5, −4.8 (CH_3). HR FABMS *m/z* 695.3757 $(M+Na)^+$, calcd for $C_{37}H_{60}NaO_7Si_2$, 695.3775. Anal. Calcd for $C_{37}H_{60}O_7Si_2$: C, 66.03; H, 8.99. Found, C, 65.93; H, 9.08.

4.1.8. (4*R*,7*R*,8*S*,9*S*,10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-7,9-bis(methoxymethoxy)-undeca-1,5*E*-dien-4-yl (*E*)-3-phenylacrylate, 14. Alcohol **13** (270 mg, 0.4 mmol) was dissolved in dry CH_2Cl_2 (8 mL) and treated with triethyl amine (140 μL, 1 mmol), (*E*)-cinnamoyl chloride (133 mg, 0.8 mmol) and DMAP (5 mg, ca. 0.04 mmol). The mixture was then stirred overnight at room temperature and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 95:5) provided ester **14** (260 mg, 81%): oil, $[\alpha]_D=-60.4$ (*c* 3; $CHCl_3$); IR ν_{max} (cm^{-1}) 1716 (C=O); ^1H NMR (500 MHz) δ 7.70–7.60 (5H, m), 7.50 (3H, m), 7.40–7.30 (8H, m), 6.42 (1H, d, *J*=16 Hz), 5.78 (1H, m), 5.66 (1H, dd, *J*=15.7, 5.1 Hz), 5.62 (1H, dd, *J*=15.7, 6.5 Hz), 5.45 (1H, m), 5.15–5.10 (2H, m), 4.84 and 4.76 (2H, AB system, *J*=6.2 Hz), 4.43 and 4.28 (2H, AB system, *J*=6.6 Hz), 4.07 (1H, dq, *J*=2.2, 6.5 Hz), 4.03 (1H, m), 3.79 (1H, dd, *J*=7.2, 2.5 Hz), 3.58 (1H, dd, *J*=7.5, 4.7 Hz), 3.45 (3H, s), 3.20 (3H, s), 2.22 (2H, m), 1.06 (9H, s), 1.05 (3H, d, *J*=6.5 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz) δ 165.9, 134.8, 134.5, 134.1, 18.3, 18.1 (C), 144.8, 136.0, 135.9, 133.3, 132.2, 130.2, 129.6, 129.4, 128.8, 128.4, 128.1, 127.6, 127.4, 118.4, 80.8, 78.2, 74.2, 72.8, 70.6 (CH), 118.0, 97.6, 94.2, 39.0 (CH_2), 56.0, 55.5, 27.1 (×3), 26.0 (×3), 19.1, −4.4, −4.8 (CH_3). Anal. Calcd for $C_{46}H_{66}O_8Si_2$: C, 68.79; H, 8.28. Found, C, 68.93; H, 8.10.

4.1.9. (6*R*)-6-[(3*R*,4*S*,5*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3,5-bis(methoxymethoxy)-hept-1-enyl]-5,6-dihydropyran-2-one, 15. Ester **14** (240 mg, 0.3 mmol) and ruthenium catalyst **A** (26 mg, 0.03 mmol) were dissolved in dry, degassed CH_2Cl_2 (42 mL) and heated under N_2 at reflux until consumption of the starting material (3–4 h, TLC monitoring!). Solvent removal under reduced pressure was followed by column chromatography on silica gel (hexanes–EtOAc, 4:1) to yield α,β-unsaturated lactone **15** (206 mg, 98%): oil, $[\alpha]_D=-15.2$ (*c* 1.5; $CHCl_3$); IR ν_{max} (cm^{-1}) 1733 (C=O); ^1H NMR (500 MHz) δ 7.75–7.65 (4H, m), 7.40–7.30 (6H, m), 6.74 (1H, m), 6.00 (1H, br d, *J*=10 Hz), 5.74 (1H, dd, *J*=16, 5.1 Hz), 5.64 (1H, dd, *J*=16, 5.5 Hz), 4.83 and 4.76 (2H, AB system, *J*=6.2 Hz), 4.70 (1H, m), 4.36 and 4.26

(2H, AB system, J=6.5 Hz), 4.04 (2H, m), 3.70 (1H, dd, J=7.7, 1.5 Hz), 3.53 (1H, dd, J=7.5, 4.5 Hz), 3.46 (3H, s), 3.16 (3H, s), 2.15 (2H, m), 1.06 (3H, d, J=6.5 Hz), 1.04 (9H, s), 0.86 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz) δ 163.8, 134.4, 134.3, 19.1, 18.1 (C), 144.6, 136.0, 135.9, 130.3, 129.6, 129.5, 129.3, 127.5, 127.4, 121.5, 80.7, 77.6, 77.4, 74.0, 70.2 (CH), 97.5, 94.7, 29.5 (CH_2), 55.9, 55.5, 27.0 (×3), 25.9 (×3), 17.9, −4.5, −5.0 (CH_3). FABMS m/z 721 $(M+Na)^+$, calcd for $C_{38}H_{58}NaO_8Si_2$, 721. Anal. Calcd for $C_{38}H_{58}O_8Si_2$: C, 65.29; H, 8.36. Found, C, 65.23; H, 8.16.

4.1.10. (6*R*)-6-[(3*R*,4*S*,5*S*,6*S*)-3,4,5,6-Tetraacetoxyhept-1-enyl]-5,6-dihydropyran-2-one, Anamarine. Lactone **15** (196 mg, 0.28 mmol) was dissolved in SMe_2 (3 mL) and cooled to −10 °C. Then, $BF_3{\cdot}Et_2O$ (710 μL, 5.6 mmol) was added to the solution, which was stirred at the same temperature for 30 min. Work-up (extraction with CH_2Cl_2) and solvent removal under reduced pressure gave an oily material which was dissolved in MeCN (5 mL) and treated at room temperature with 48% aq HF (115 μL, 2.8 mmol). After stirring at room temperature for 7 h, the reaction mixture was worked up (extraction with CH_2Cl_2) and evaporated in vacuo. The oily residue was then dissolved in dry CH_2Cl_2 (10 mL) and treated with Et_3N (310 μL, 2.2 mmol), acetic anhydride (190 μL, 2 mmol) and DMAP (4 mg, 0.03 mmol). After stirring overnight, the reaction mixture was worked up (extraction with CH_2Cl_2) and chromatographed on a silica gel column (hexanes–EtOAc, 1:1) to give (+)-anamarine (74 mg, 62% overall): white crystals, mp 110–111 °C (from Et_2O), lit.[9a] for natural anamarine, mp 110–112 °C; $[\alpha]_D$=+14.5 (c 0.06; $CHCl_3$); lit.[9a] for natural anamarine, $[\alpha]_D$=+28.2 (c 0.52; $CHCl_3$), value later revised to +18.8; lit.[10b] for synthetic (+)-anamarine, $[\alpha]_D$=+15.9 (c 0.8; $CHCl_3$); lit.[10c] for synthetic (−)-anamarine, $[\alpha]_D$=−15 (c 0.02; $CHCl_3$); IR ν_{max} (cm^{-1}) 1738 (C=O); ^{1}H NMR (500 MHz) δ 6.88 (1H, ddd, J=10, 5.2, 3 Hz), 6.04 (1H, dt, J=10, 1.5 Hz), 5.85–5.75 (2H, m), 5.36 (1H, dd, J=7, 6.5 Hz), 5.30 (1H, dd, J=7, 3.5 Hz), 5.17 (1H, dd, J=7, 3.5 Hz), 4.95 (1H, m), 4.90 (1H, quint, J=6.5 Hz), 2.45 (2H, m), 2.12 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.02 (3H, s), 1.17 (3H, d, J=6.5 Hz); ^{13}C NMR (125 MHz) δ 170.0, 169.8, 169.7, 169.6, 163.4 (C), 144.5, 133.0, 125.7, 121.6, 75.9, 71.9, 71.7, 70.5, 67.4 (CH), 29.2 (CH_2), 21.0, 20.9, 20.8, 20.6, 15.8 (CH_3).

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References and notes

1. (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (d) Heathcock, C. H.; Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 111–212. (e) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99–111. (f) *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2. (g) Mekelburger, H. B.; Wilcox, C. S. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2, pp 99–131. (h) Heathcock, C. H. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2, pp 133–179, see also pp 181–238. (i) Kim, B. M.; Williams, S. F.; Masamune, S. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2, pp 239–275. (j) Rathke, M. W.; Weipert, P. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2, pp 277–299. (k) Paterson, I. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2, pp 301–319. (l) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317–338. (m) Braun, M. *Houben-Weyl's methods of organic chemistry, stereoselective synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; Vol. 3, pp 1603–1666, see also pp 1713–1735.
2. (a) In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (b) Tatsuta, K. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 1–38. (c) Blizzard, T.; Fisher, M.; Mrozik, H.; Shih, T. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 65–102. (d) Isobe, M. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 103–134. (e) Beau, J.-M. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 135–182. (f) Yonemitsu, O.; Horita, K. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 447–466. (g) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041–2114.
3. Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, M. *J. Org. Chem.* **1998**, *63*, 698–707, and references cited therein.
4. For an improved preparation of silylated L-erythrulose acetonides **1** (P=TES, TBS, TPS) from L-erythrulose hydrate, see: (a) Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999**, *29*, 2601–2610. For the preparation of protected D- and L-erythrulose derivatives using chiral precursors other than erythrulose itself, see: (b) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801–1810.
5. For a general review of boron aldol reactions: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.
6. For the enolization of ketones with Chx_2BCl/tertiary amine to yield *E* boron enolates, see, for example: (a) Brown, H. C.;

Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147–153. (b) Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996**, *37*, 8243–8246.

7. (a) Falomir, E. Ph.D. Thesis, University of Castellón, Spain, 1998. (b) Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tetrahedron Lett.* **1999**, *40*, 1065–1068. (c) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677–683.
8. Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577–8582.
9. (a) Alemany, A.; Márquez, C.; Pascual, C.; Valverde, S.; Martínez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, *20*, 3583–3586. (b) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47–53. (c) Achmad, S. A.; Høyer, T.; Kjær, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, *41B*, 599–609. (d) Coleman, M. T. D.; English, R. B.; Rivett, D. E. A. *Phytochemistry* **1987**, *26*, 1497–1499.
10. (a) Lichtenthaler, F.; Lorenz, K.; Ma, W. *Tetrahedron Lett.* **1987**, *28*, 47–50. (b) Lorenz, K.; Lichtenthaler, F. *Tetrahedron Lett.* **1987**, *28*, 6437–6440. (c) Valverde, S.; Hernández, A.; Herradón, B.; Rabanal, R. M.; Martín-Lomas, M. *Tetrahedron* **1987**, *43*, 3499–3504, The overall yield in these rather lengthy syntheses was less than 1%.
11. (a) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737–1739. (b) Falomir, E.; Murga, J.; Ruiz, P.; Carda, M.; Marco, J. A.; Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *J. Org. Chem.* **2003**, *68*, 5672–5676.
12. Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797–800.
13. When the synthesis was started with lactaldehyde protected with a TBS group, the latter did not resist the acidic conditions of acetonide cleavage (step c in Scheme 4). The internal and more hindered TBS group survived, however, these conditions.
14. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
15. The allylborane used in step (g) was prepared as described in the literature from allylmagnesium bromide and (+)-di*iso*-pinocampheylboron chloride. See: Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417–2420. For a very recent review on asymmetric allylborations, see: Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23–35.
16. Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547–7550. We have previously used this acyl residue in cases where acryloyl chloride did not react efficiently: García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2003**, *5*, 1447–1449.
17. Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29, The standard ruthenium catalyst $PhCH{=}RuCl_2(PChx_3)_2$ proved ineffective in this case.

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Thyonosides A and B, two new saponins isolated from the holothurian *Thyone aurea*

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Abstract—The structures of two saponins, thyonosides A and B, isolated from the holothurian *Thyone aurea* collected in Namibia, were elucidated by 1D and 2D NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{1}H J-resolved, TOCSY, HMQC, HMBC and NOESY). The two compounds have the same aglycon but different oligosaccharidic chains. Thyonoside A has a 3-*O*-methyl-β-D-xylopyranosyl-(1→3)-6-*O*-sodium sulphate-β-D-glucopyranosyl-(1→4)-β-D-quinovopyranosyl-(1→2)-4-*O*-sodium sulphate-β-D-xylopyranosyl chain, and thyonoside B a 3-*O*-methyl-β-D-xylopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-quinovopyranosyl-(1→2)-4-*O*-sodium sulphate-β-D-xylopyranosyl chain. The holostane-type aglycon features an endocyclic double bond at position 7–8, a double bond at position 25–26 and a β-acetoxy group at C16.

1. Introduction

More than 100 saponins found in holothurians have been described to date. Most of them present a sugar chain of up to six monosaccharide units [principally D-glucose (Glu), D-xylose (Xyl), D-fucose (Fuc), D-quinovose (Qui), D-3-*O*-methylglucose (3-*O*-Me-Glu), and D-3-*O*-methylxylose (3-*O*-Me-Xyl)] linked to C-3 of the aglycon, which is usually represented by a triterpene 18(20)-lactone with a lanostane skeleton (holostane). Another notable feature of many of the glycosides from marine organisms is the sulphatation of the aglycon or the sugar moiety. Traditionally, structural studies of saponins have involved hydrolytic removal of the sugars, which usually results in the decomposition of the aglycon to give complex mixtures including many artifacts. The development of high-resolution NMR techniques in the last two decades, and more specifically ^{13}C NMR spectroscopy, now permits the structural studies on intact saponins and avoids the need for large quantities of material. The advent of modern high-field two-dimensional (2D) NMR techniques provides an extremely useful tool for the characterization of complex molecules since these techniques often allow unambiguous assignment of most signals observed in conventional unidimensional ^{1}H and ^{13}C NMR spectra. This paper illustrates the use of these 2D-NMR experiments to determine the structures of the two saponins isolated from the holothurian *Thyone aurea*.

2. Results and discussion

Thyonosides A and B were isolated from an alcoholic extract of the sea cucumber *Thyone aurea* collected in Namibia in December 1995. The extract showed interesting activity against murine tumor cell line, L1210, and herpes simplex virus type 1, HSV-1. After subsequent chromatography, the final isolation was accomplished by reverse phase HPLC and Counter Current Chromatography (CCC). The structures were elucidated mainly by 500 MHz NMR analyses including 1D and 2D (^{1}H–^{1}H COSY, TOCSY, ^{1}H–^{1}H J-resolved, HMQC, HMBC and NOESY) spectroscopy.

2.1. Aglycon portion

The assignments for the NMR signals associated with the aglycon moiety (Table 1) show the same aglycon for both thyonosides A and B. Since the ^{13}C NMR spectra gave inadequate results, most of the ^{13}C assignment were established by HMQC, HMBC, and by comparison with those of other saponins (frondoside A,[1] frondogenin,[2] eximisoside A[3]…).

Signals at 145.5 and 119.9 ppm for thyonoside A (145.5 and 120.0 for thyonoside B) in the downfield region, are indicative of the presence of an endocyclic double bond at

Keywords: *Thyone aurea*; Holothurian; Triterpene saponin; Holostane aglycon.
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Table 1. ^{13}C and ^{1}H NMR data and assignments for the aglycon moieties of thyonosides A (**1**) and B (**2**) in $C_5D_5N–D_2O$ 9:1

	^{13}C NMR in ppm			^{1}H NMR in ppm, mult. (*J* in Hz)	
C	(**1**)	(**2**)	H	(**1**)	(**2**)
1	35.5	35.6	1α;1β	1.33 m	1.40 m
2		26.4	2α;2β	1.83 m; 2.05 m	1.86 m; 2.07 m
3	88.5	89.0	3α	3.18 dd (3.7, 11.5)	3.22 dd (3.5, 11.7)
4	39.0	39.6			
5	47.3	48.0	5α	0.92 m	0.99 t (7.8)
6	22.7 or 20.8[a]	23.3	6α;6β	1.95 m	2.00 m
7	119.9	120.0	7	5.63 m	5.54 m
8	145.5	145.5			
9	46.5	47.0	9β	3.41 bd (14.5)	3.43 bd (14.4)
10		36.1			
11		22.6	11α;11β	1.47 m; 1.72 m	1.51 m; 1.76 m
12		31.6	12α;12β	2.07 m; 1.96 m	1.94 m; 2.15 m
13	59.0	59.3			
14	47.0	47.5			
15	43.0	43.2	15α	2.56 dd (7.3, 12.5)	2.60 dd (7.3, 12.0)
			15β	1.67 m	1.74 m
16	74.8	74.8	16α	5.88 ddd (7.3, 8.9, 9.0)	5.91 ddd (7.3, 8.7, 9.3)
17	54.2	54.5	17α	2.63 d (9.0)	2.61 d (9.3)
18	180.0	179.6			
19	23.6	24.1	19	1.12 s	1.19 s
20	85.0	85.0			
21	27.8	28.2	21	1.47 s	1.46 s
22	38.0	38.4	22; 22′	2.32 m; 1.82 m	2.36 m; 1.88 m
23			23; 23′	1.45 m; 1.35 m	1.50 m
24	37.8	38.4	24; 24′	1.93 m	1.96 m
25	145.6	145.8			
26	110.6	110.0	26; 26′	4.74 b	4.77 b
27	21.7	22.2	27	1.64 s	1.66 s
28	31.8	32.2	28	1.15 s	1.09 s
29	16.7	17.3	29	0.97 s	1.12 s
30	28.2	28.7	30	1.16 s	1.25 s
31	170.0	170.4	31		
32	22.7 or 20.8[a]	21.5	32	1.99 s	2.01 s

[a] Assignments may be reversed.

the 7, 8-position (9, 8-double bond feature chemical shifts around 140 and 130 ppm, whereas 9, 11-double bond resonate around 150 and 110 ppm). Signals at 145.6 and 110.6 ppm for thyonoside A (145.8 and 110.0 for thyonoside B) show an another double bond consistent with a terminal isoprenyl function.[4,5] Two low field resonances at 180.0 and 170.0 ppm for thyonoside A (179.6 and 170.4 ppm for thyonoside B) are assigned to the γ-lactone and acetoxy carbonyl carbons, respectively.

The high field region of the ^{1}H NMR spectrum shows a pattern characteristic of most holothurins, featuring many overlapping signals. In this instance, the use of the COSY experiment allowed the establishment of the connectivities within the framework and thus permitted the assignment of the chemical shifts for the overlapping proton signals. Assignments were confirmed by TOCSY and completed using 2D-NOESY experiments. Of particular interest, the presence of two double bonds in the aglycon was confirmed by: (1) the 1H multiplet at 5.63 ppm (5.54 ppm for thyonoside B), correlated to H-6 at 1.95 ppm (2.00 ppm for thyonoside B), which can be attributed to the H-7 vinylic proton, (2) the strong broad 2H singlet at 4.74 ppm (4.77 ppm for thyonoside B) correlated to H_3-27 and H-24, which can be attributed to *exo* H-26 methylenic proton. The presence of an acetoxy group at C-16 was deduced from the chemical shift of the H-16 signal which shows coupling signals with H-17, Hα-15 and Hβ-15 in the 2D-COSY spectrum.

The relative stereochemistry of the aglycon was deduced using 2D-NOESY experiments (mixing time of 250 ms) for

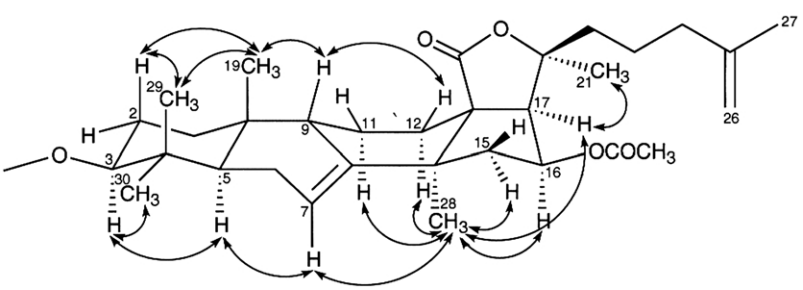


Figure 1. NOE correlations for the aglycon of thyonoside A (**1**).

Table 2. Experimental and calculated vicinal proton coupling constants for the D-ring protons of thyonosides A and B

	Thyonoside A	Thyonoside B	Frondoside A[a]		
H–H	$J_{exp.}$	$J_{exp.}$	$J_{exp.}$	$J_{calc.}$[b]	Dihedral angle (deg.)
15α 16α	7.32	7.33	7.4	8.0	32
15β 16α	8.92	8.75	8.6	9.0	155
16α 17α	9.03	9.28	9.0	9.2	345
16β 17α				1.5	110
15β 16β				6.0	32
15α 16β				1.2	270

[a] Ref. 1.
[b] Calculated assuming a distorted envelope conformation.

NOEs and 2D-^{1}H–^{1}H J-resolved experiments for coupling constants (Fig. 1 and Table 2). The orientation of the hydroxyl function at C-3 proved to be β-equatorial from the large coupling constant (J=11.5 Hz for thyonoside A and J=11.7 Hz for thyonoside B) due to H-3α (axial) and H-2β (axial). Strong NOEs between H-3α and H_3-30, and between H-3α and H-5α (even between H_3-30 and H-5α for thyonoside B) indicate the α position of the C-30 methyl group and H-5. Strong NOEs between H-2β and H_3-29, H-2β and H_3-19, and between H_3-29 and H_3-19, indicate the 1,3-axial orientation of these methyl groups. These suggest that the A/B ring has a *trans* junction. The H-9β configuration was confirmed by: (1) the presence of a broad doublet at 3.41 ppm for thyonoside A and 3.43 ppm for thyonoside B, the downfield shift of which have been previously attributed to the anisotropic effect of the γ-lactone carbonyl[6] and (2) a strong NOE between H-9β and H_3-19. NOEs observed between H-9β and H-12β and between H-12α and H_3-28 indicate the α-position of the C-28 methyl group. This methyl group is also correlated via NOEs with H-7, H-15α, H-16α, H-17α. These data show that the C/D-ring has a *trans* junction and the D/E-ring a *cis* junction. The α configuration of the H_3-21 group was determined by the observation of a NOE between the H_3-21 singlet and H-17α. The β configuration of the C-16 acetoxy group was deduced from the NOE mentioned between H_3-28 and H-16α, and from coupling constants for the four-proton system 2H-15/H-16/H-17. Comparisons between our values and the calculated coupling constants for the D-ring protons of frondoside A[1], support the β configuration for the C-16 acetoxy group (Table 2).

The aglycon appears to be the same as that in neothyonidioside C[7] from *Neothyone magnum*, in cucumarioside A_0-2[8] from *Cucumaria japonica*, in lefevreioside D[9] from *Cucumaria lefevrei* and in cucumarioside G_1[10] from *Eupenctata fraudatrix*.

2.2. Oligosaccharide chain

The nature of the sugar units, the oligosaccharide sequence, and the position of interglycosidic linkages were determined using a combination of ^{1}H–^{1}H COSY, TOCSY, ^{1}H–^{1}H J-resolved, ^{13}C–^{1}H correlations and NOESY experiments. The carbon and proton chemical shift assignments, and coupling constant values are summarized in Table 3.

Firstly, the proton and carbon resonances corresponding to the sugar part of the molecule suggested the presence of four monosaccharide units for both saponins. This conclusion is clearly indicated by signals for four anomeric carbons at

Table 3. ^{13}C and ^{1}H NMR data and assignments for the oligosaccharide subunits of thyonosides A (**1**) and B (**2**) in C_5D_5N–D_2O 9:1

Sugars		^{13}C NMR in ppm		^{1}H NMR in ppm, mult. (J in Hz)	
		(**1**)	(**2**)	(**1**)	(**2**)
Xyl-4-OSO_3Na	1	104.6	105.0	4.65 d (7.1)	4.69 d (7.3)
	2	82.0	84.0	3.83 dd (7.1, 8.7)	3.98 dd (7.3, 9.0)
	3	74.3	75.5	4.23 dd (8.7, 8.7)	4.32 dd (9.0, 9.0)
	4	75.3	75.0	5.07 ddd (5.5, 8.7, 9.6)	5.12 m
	5	64.0	64.2	4.68 m	4.82 dd (5.1, 11.5)
				3.68 dd (9.6, 11.8)	3.72 dd (9.7, 11.5)
Qui	1	104.3	105.5	4.79 d (7.8)	5.09 d (7.6)
	2	75.3	73.8	3.89 dd (7.8, 9.9)	3.99 dd (7.6, 9.5)
	3	74.3	68.8	3.98 dd (8.4, 9.9)	4.02 dd (9.5, 8.9)
	4	87.0	86.1	3.37 dd (8.4, 9.5)	3.63 dd (8.9, 8.9)
	5	71.0	71.8	3.55 dd (5.9, 9.5)	3.74 dd (5.9, 8.9)
	6	17.4	17.9	1.57 d (5.9)	1.71 d (5.9)
Glu-6-OSO_3Na or Xyl	1	104.2	105.5	4.73 d (7.8)	4.85 d (7.6)
	2	74.6[a]	75.5	3.86 dd (7.8, 10.4)	3.98 dd (7.6, 9.0)
	3	85.7	75.5	4.13 dd (10.4, 10.4)	4.12 dd (9.0, 9.0)
	4	69.2	86.6	3.73 dd (8.7, 10.4)	4.04 ddd (5.6, 9.0, 10.6)
	5	74.6	66.5	4.15 m	4.19 dd (5.6, 11.5)
					3.65 dd (10.6, 11.5)
	6	67.3		5.10 m	
				4.70 m	
3-*O*-Me-Xyl	1	105.4	106.0	5.19 d (7.8)	5.25 d (8.0)
	2	73.6[a]	74.5	3.85 dd (7.8, 9.2)	3.94 dd (8.0, 8.9)
	3	87.0	87.8	3.55 dd (8.8, 9.2)	3.60 dd (8.9, 8.9)
	4	69.3	70.2	4.02 ddd (5.6, 8.8, 10.6)	4.08 ddd (5.7, 8.9, 10.4)
	5	66.4	67.1	4.15 dd (5.6, 11.2)	4.20 dd (5.7, 11.6)
				3.55 dd (10.6, 11.2)	3.61 dd (10.4, 11.6)
	OMe	60.3	60.7	3.81 s	3.84 s

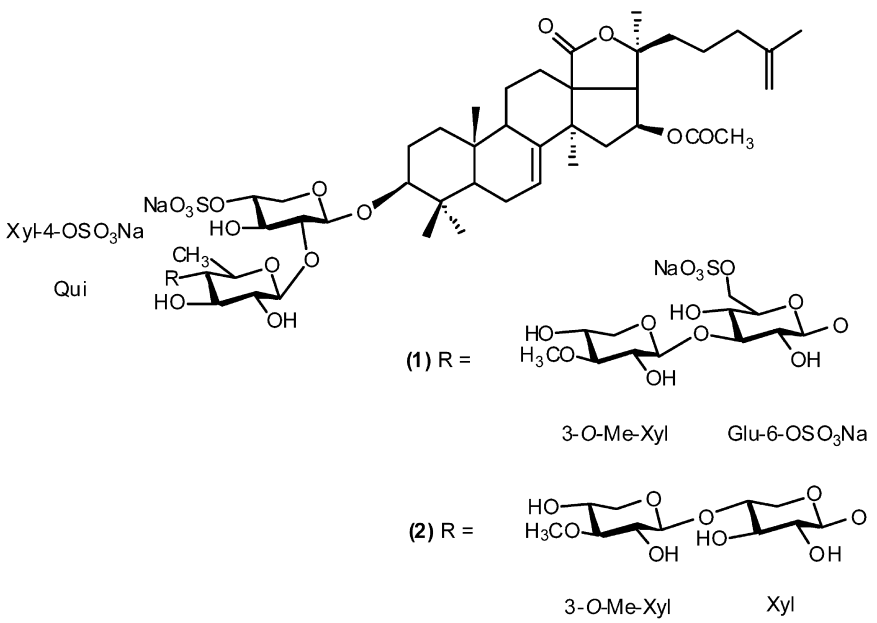
[a] Assignment may be reversed in the vertical column.

105.4, 104.6, 104.3, 104.2 ppm for thyonoside A (106.0, 105.5, 105.5, 105.0 ppm for thyonoside B) and four anomeric protons at 5.19, 4.79, 4.73, 4.65 ppm for thyonoside A (5.25, 5.09, 4.85, 4.69 ppm for thyonoside B). All anomeric protons resonate as doublets with coupling constants between 7 and 8 Hz, indicating a β stereochemistry of the glycoside bond. Furthermore, the 104–106 ppm range of the anomeric carbon signals is indicative of a β configuration.[11,12] A doublet at 1.57 ppm (J=5.9 Hz, 3H) for thyonoside A (1.71 ppm, J=5.9 Hz, 3H for thyonoside B), and a singlet at 3.81 ppm (s, 3H) for thyonoside A (3.84 ppm, s, 3H for thyonoside B) in both ^{1}H spectra are ascribable to a 6-deoxy sugar and an *O*-methyl sugar, respectively. The ^{1}H–^{1}H COSY and TOCSY-NMR spectra allowed the identification of the separate carbohydrate ring spin systems. NOESY-NMR spectra (t_{mix}=250 ms) were used to define completely the relative stereochemistry of each carbohydrate unit with ^{1}H–^{1}H J-resolved for coupling constants. Coupling constants in the 8–9 Hz range are indicative of axial–axial coupling[13,14] for proton 2–3, 3–4, 4–5. For xylose units, a coupling constant of 5–6 Hz can be observed between H-4 axial and H-5 equatorial protons.[13,14] The four sugars for thyonoside A appear to be xylose-4-sulphate, quinovose, glucose-6-sulphate and 3-*O*-methylxylose; the sugars in thyonoside B are xylose-4-sulphate, quinovose, xylose and 3-*O*-methylxylose.

The sequence of the oligosaccharide chains was deduced from the NOESY and HMBC experiments (Fig. 2). The position of the interglycosidic linkages was determined by comparing the carbon chemical shifts observed with those of the corresponding methyl glycopyranoside[15,16] and taking into account the downfield shift resulting from glycosidation. The Xyl-4-OSO_3Na subunit of thyonoside A must be linked to the aglycon at C-3 due to the strong NOE and the HMBC correlation observed between H-1 of Xyl-4-OSO_3Na and the H-3α proton or C-3 carbon of the aglycon. The interglycosidic position of attachment of Xyl-4-OSO_3Na is assigned to C-2 based on the significant downfield shift ($\Delta\delta$=82.0−74.6=7.4 ppm difference from the corresponding methyl glycopyranoside).[16] This residue appears to be linked to Qui, according to the NOE observed between H-1 of Qui and H-2 of Xyl-4-OSO_3Na. Another important downfield shift ($\Delta\delta$=75.3−70.9=4.4 ppm), observed at C-4 of Xyl-4-OSO_3Na is attributed to the presence of a sulphate group at that position. This shift cannot be the consequence of a glycosidic linkage since no inter-residue NOE involving H-4 of Xyl-4-OSO_3Na is observed. The presence of an inter-residue NOE between H-1 of Glu-6-OSO_3Na and H-4 of Qui, as well as a large glycosidation shift on C-4 of Qui ($\Delta\delta$=87.0−73.8=13.2 ppm) suggest that Glu-6-OSO_3Na is β1-4 linked to Qui. A distinctive downfield shift for the C-6 of Glu-6-OSO_3Na (67.0 instead of 60–62 ppm), indicates the C-6 attachment of the sulphate group.[15,17] The absence of any ^{13}C glycosidation shift for 3-*O*-Me-Xyl (except the one due to the methylation on C-3 hydroxyl function and identified by HMBC and NOESY), suggests that this residue must be the terminal unit. A NOE between H-1 of 3-*O*-Me-Xyl and H-3 of Glu-6-OSO_3Na, and the downfield shift of C-3 of Glu-6-OSO_3Na ($\Delta\delta$=85.7−78.3=7.4 ppm) confirmed that 3-*O*-Me-Xyl is β1-3 linked to Glu-6-OSO_3Na. The glycoside sequence is supported by the following HMBC correlations: H-1 of Qui with C-2 of Xyl-4-OSO_3Na, H-1 of Glu-6-OSO_3Na with C-4 of Qui, H-1 of 3-*O*-Me-Xyl with C-3 of Glu-6-OSO_3Na.

Therefore, based on the above results and the HRFAB data (see Section 3), thyonoside A possesses structure **1**; that is, 16β-acetoxy-3β-*O*-{3-*O*-methyl-β-D-xylopyranosyl-(1→3)-6-*O*-sodium sulphate-β-D-glucopyranosyl-(1→4)-β-D-quinovopyranosyl-(1→2)-4-*O*-sodium sulphate-β-D-xylopyranosyl}-holosta-7(8),25(26)-diene, assuming that each monosaccharide belongs to the D series.

The difference between thyonosides A and B resides not only in one glycosidic residue, Xyl instead of Glu-6-OSO_3Na, but also in the linkage between 3-*O*-Me-Xyl and Xyl which is β1-4 according to the downfield shift of C-4 of Xyl. The absence of a strong NOE between these two



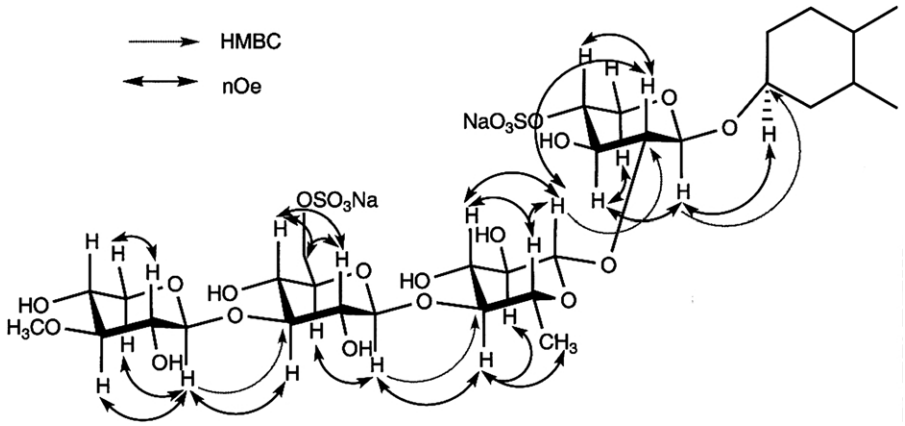


Figure 2. NOE and HMBC correlations for the oligosaccharide chain of thyonoside A (**1**).

residues and a HMBC correlation between H-1 of 3-*O*-Me-Xyl and C-4 of Xyl establishes the linkage position. Otherwise, similar correlations and glycosidation shifts are observed for this saponin. Hence, thyonoside B possesses structure **2**; that is, 16β-acetoxy-3β-*O*-{3-*O*-methyl-β-D-xylopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-quinovopyranosyl-(1→2)-4-*O*-sodium sulphate-β-D-xylopyranosyl}-holosta-7(8), 25(26)-diene.

The extensive use of ^{1}H and ^{13}C NMR techniques led us to the structure determination of two new saponins, thyonosides A and B, isolated from *Thyone aurea*. They possess a classical holostane-type aglycon which has been found previously in neothyonidioside C,[7] cucumarioside A_0-2,[8] lefevreioside D,[9] and in cucumarioside G_1.[10] Differences between thyonosides A and B and these known saponins appear in the oligosaccharide chain, principally due to the combination of the two final sugars: glucose-6-sulphate and 3-*O*-methylxylose, or xylose and 3-*O*-methylxylose.

3. Experimental

3.1. General methods

High resolution FAB mass experiments were recorded on a VG 70-4SE mass spectrometer. NMR spectra were obtained on a Varian 500NB spectrometer at 300 K using 5 mg of thyonoside A and 7 mg of thyonoside B in 0.75 mL of pyridine-d_5 plus one drop of D_2O. ^{13}C Experiments were run on a Varian 500 MHz. HPLC was carried out on a Econosil C_{18} (10 μm) column (10×250 mm) at 1 mL/min, UV detection at 210 nm. CCC separations were performed under 150 psi at 12 mL/min.

3.2. Extraction and purification

The specimen of the sea cucumber *Thyone aurea* was collected in Namibia. Extraction of 70 g of material with a mixture of methanol–acetone 5:5 gave 3.43 g of dry extract. This crude extract was partitioned between hexane, then chloroform, and a mixture of methanol–water, then between butanol and water. The alcoholic fraction (590 mg) showed interesting activities against L1210 cells and HSV-1. This part of the extract was submitted to silica gel chromatographies (eluent CH_2Cl_2 to MeOH) to give 115 mg of a glycoside mixture. After a first purification on HPLC reversed-phase (eluent CH_3CN-H_2O 5:5), a final purification was performed using CCC with $CHCl_3$–MeOH–H_2O–*i*PrOH–EtOH (9:6:8:1:8) as solvent, upper phase as mobile phase. Pure thyonoside A (6.2 mg) and pure thyonoside B (8.0 mg) were collected as white amorphous powders. The molecular formula of thyonoside A was determined as $C_{55}H_{84}O_{28}S_2Na_2$ by pseudo-molecular ion at *m/z* 1325.4260 $[M+Na]^+$ in the HRFABMS (positive ion mode), calcd for $C_{55}H_{84}O_{28}S_2Na_3$ 1325.428366. Fragment ion peaks at *m/z* 1223.5 $[M-SO_3Na+Na+H]^+$, and 1121.6 $[M-2SO_3Na+Na+2H]^+$ indicate the presence of two sulphate groups in the glycoside. The molecular formula of thyonoside B was determined as $C_{54}H_{83}O_{24}SNa$ by pseudo-molecular ion at *m/z* 1193.4766 $[M+Na]^+$ in the HRFABMS (positive ion mode), calcd for $C_{54}H_{83}O_{24}SNa_2$ 1193.479041. Fragment ion peaks at *m/z* 1091.6 $[M-SO_3Na+Na+H]^+$ indicate the presence of one sulphate group in the glycoside.

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References and notes

1. Girard, M.; Belanger, J.; Apsimon, J. N.; Garneau, F.-X.; Harvey, C.; Brisson, J.-R. *Can. J. Chem.* **1990**, *68*, 11–18.
2. Findlay, J. A.; Daljeet, A. *J. Nat. Prod.* **1984**, *47*, 320–324.
3. Kalinin, V. I.; Avilov, S. A.; Kalinina, E. Y.; Korolkova, O. G.; Kalinovsky, A. I.; Stonik, V. A.; Riguera, R.; Jiménez, C. *J. Nat. Prod.* **1997**, *60*, 817–819.
4. Miyamoto, T.; Togawa, K.; Higuchi, R.; Komori, T.; Sasaki, T. *J. Nat. Prod.* **1992**, *55*, 940–946.
5. Bedoya Zurita, M.; Ahond, A.; Poupat, C.; Potier, P.; Menou, J.-L. *J. Nat. Prod.* **1986**, *49*, 809–813.
6. Kitagawa, I.; Kobayashi, M.; Inamoto, T.; Yasuzawa, T.;

Kyogoku, Y.; Kido, M. *Chem. Pharm. Bull.* **1981**, *29*, 1189–1192.
7. Avilov, S. A.; Kalinovsky, A. I.; Stonik, V. A. *Khim. Prir. Soedin.* **1990**, 53–57.
8. Drozdova, O. A.; Avilov, S. A.; Kalinovsky, A. I.; Stonik, V. A.; Milgrom, Y. M.; Rashkes, Y. W. *Khim. Prir. Soedin.* **1993**, 242–248.
9. Rodriguez, J.; Riguera, R. *J. Chem. Res. Synop.* **1989**, 342–343.
10. Kalinin, V. I.; Avilov, S. A.; Kalinovsky, A. I.; Stonik, V. A. *Khim. Prir. Soedin.* **1992**, 729–730.
11. Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933–1944.
12. Beier, R. C.; Mundy, B. P.; Strobel, G. A. *Can. J. Chem.* **1980**, *58*, 2800–2804.
13. Findlay, J. A.; Jaseja, M.; Brisson, J.-R. *Can. J. Chem.* **1987**, *65*, 2605–2611.
14. Findlay, J. A.; Jaseja, M.; Burnell, D. J.; Brisson, J.-R. *Can. J. Chem.* **1987**, *65*, 1384–1391.
15. Archibald, P. J.; Fenn, M. D.; Roy, A. R. *Carbohydrate Res.* **1981**, *93*, 177–190.
16. Kitagawa, I.; Nishino, M.; Kobayashi, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1951–1956.
17. Kitagawa, I.; Nishino, M.; Kyogoku, Y. *Tetrahedron Lett.* **1979**, *16*, 1419–1422.

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Facile synthesis of 4-phenylquinolin-2(1*H*)-one derivatives from *N*-acyl-*o*-aminobenzophenones

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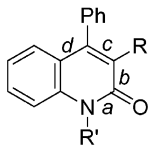
This paper is dedicated to Professor Dong H. Kim on the occasion of his retirement from the Department of Chemistry, Postech

Abstract—An efficient synthesis of 4-phenylquinolin-2(1*H*)-one derivatives has been achieved in a one-pot reaction from *N*-acyl-*o*-aminobenzophenones **1a**-**c** (**a**: acyl=acetyl; **b**: acyl=propanoyl; **c**: acyl=heptanoyl) using NaH as a base. Treatment of **1** with NaH provided the quinolones **2a**-**c** with 62–83% yields, whereas the reaction in the presence of alkyl iodide (alkyl=methyl, ethyl, *n*-octyl) gave the corresponding N-alkylated quinolones **3a**-**g** in 75–95% yields. The alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide gave a mixture of N-alkylated and O-alkylated products. Comparison of IR and NMR data of the N-alkylated and O-alkylated compounds with those of **2a**-**c** indicated that **2a**-**c** exist as the lactam form.

1. Introduction

Quinolines and their derivatives occur in numerous natural products and have interesting biological properties.[1] Their wide-ranging applicabilities such as pharmaceuticals, agrochemicals and synthetic building blocks have been discovered.[2] Thus, development of efficient methods for their syntheses is still attracting much interest of organic chemists,[3,4] even though the syntheses of quinolines have been known for more than a century. 4-Phenylquinolin-2(1*H*)-ones **2** and **3** are found to be useful intermediates in organic synthesis[5–7] and some of them show interesting biological profiles.[7–10]



2: R' = H
3: R' = alkyl

Quinolin-2(1*H*)-one skeletons usually have been prepared by acid-catalyzed cyclization of acylacetoanilides[9–11] forming bond *d* in the benzo-fused pyridine ring. The synthetic methods involving the final ring closure at bond *a*,[6,12] *b*[13] or *c*[7,8,14] and via cyclization/rearrangement[15] or desulfurization reaction[16] have also been reported. Most of these synthetic methods for 2-quinolones have their own drawbacks such as difficult accessibility of the starting materials, low yields, and/or harsh reaction conditions. Here, we wish to report a facile and efficient synthesis of 4-phenylquinolin-2(1*H*)-one derivatives **2** and **3** by forming the bond *c* from *N*-acyl-*o*-aminobenzophenones **1** using NaH as a base. It provides various 4-phenylquinolin-2(1*H*)-one derivatives in high yields from readily available starting materials by one-pot reaction. The tautomeric form of **2** was also clarified.

2. Results and discussions

2.1. Synthesis of 4-phenylquinolin-2(1*H*)-ones 2 from *N*-acyl-*o*-aminobenzophenones 1 and study on the alkylation reaction of 2

N-Acyl-*o*-aminobenzophenones **1a**-**c** were obtained in quantitative yields by reacting *o*-aminobenzophenone with the corresponding acyl chlorides in dichloromethane in the presence of pyridine. Treatment of **1a**-**c** with 6 equiv. of NaH in THF at refluxing temperature for 2.5–20 h provided 4-phenylquinolin-2(1*H*)-ones **2a**-**c** in 62–83% yields with the deacylated side product, *o*-aminobenzophenone in 16–23% yields (Scheme 1). There are scattered reports for the synthesis of **2a**[7–9,11b,12,13,15,16] and **2b**[13,14,17] by various methods, but the yields are low and/or the methodologies are rather too specific. We believe that the

Keywords: *N*-Acyl-*o*-aminobenzophenones; 4-Phenylquinolin-2(1*H*)-one; *N*-Alkyl-4-phenylquinolin-2(1*H*)-ones; 2-Alkoxy-4-phenylquinolines; Lactam–lactim tautomeric form.
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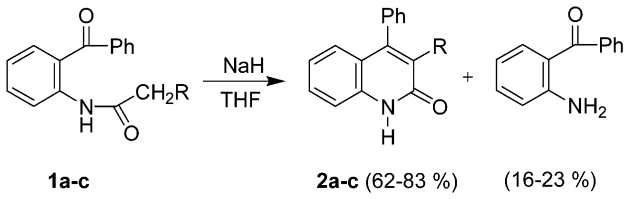


Scheme 1. Reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with NaH.

present method is very simple general route for the synthesis of 4-phenyl-quinoline-2(1*H*)-ones.

We studied the alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide. The reaction of **2a** with alkyl halide in DMF at 70 °C in the presence of various bases gave mixtures of the corresponding N-alkylated and O-alkylated products, **3** and **4** (Table 1). The reaction with methyl iodide in the presence of K_2CO_3 gave mostly N-alkylated product **3a**. However, with the alkyl halides of larger alkyl group, the proportion of the O-alkylated product **4** increases (see entries 1–3), presumably due to the steric interaction between the bulky *N*-alkyl group and the adjacent H atom in the 8-position of the quinoline ring. Using Cs_2CO_3 or NaH instead of K_2CO_3 as a base gave almost the same results. Changing the reaction medium from DMF to THF resulted in much slower reaction, but the yield of the N-alkylated product was higher (compare entries 2 and 4 vs. 5). This is reminiscent of the previous reports that pyridin-2-ones undergo alkylation at either nitrogen or oxygen.[18]

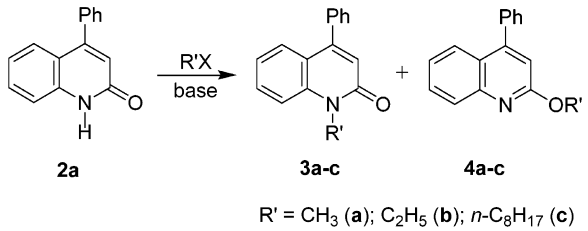
2.2. One-pot synthesis of *N*-alkyl-4-phenylquinolin-2(1*H*)-ones 3 from 1

The unsatisfactory yields of **2** from **1** and the formation of both N and O-alkylated products **3** and **4** in the alkylation reaction of **2** made us to search an alternative route for the synthesis of **3**. For the cyclization of the compounds **1** to the quinoline ring, the hydrogen atom attached to the alpha carbon to the carbonyl group needs to be removed. However, the hydrogen is less acidic than the hydrogen atom attached to the nitrogen of the amide group. We envisioned that N-alkylation of **1** prior to the treatment with the base would increase the yield of the cyclization reaction and also give the N-alkylated quinolones. Thus, we carried out the reaction of **1a-c** with NaH in the presence of alkyl iodide to achieve the alkylation and cyclization reactions in one pot. The product distributions obtained from the reactions of **1a** with NaH and methyl iodide under various conditions are listed in Table 2.

Table 2 shows that the yield of *N*-methyl-4-phenylquinolin-2(1*H*)-one **3a** is as high as 92% when 2.5 equiv. of CH_3I and 6 equiv. of NaH are used at the refluxing temperature of THF. Either lowering the reaction temperature or using less amount of NaH or CH_3I resulted in N-alkylated, but not-cyclized product, **5a**. The yields of *N*-alkyl-2-quinolone derivatives obtained from the reactions of *N*-acyl-*o*-aminobenzophenones **1a-c** with 6 equiv. of NaH in the presence of 2.5 equiv. of various alkyl iodides are summarized in Table 3. It shows that *N*-alkyl-4-phenylquinolin-2(1*H*)-ones **3a-g** can be efficiently prepared in the one-pot reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with alkyl iodide and NaH. Unlike the reaction of **2a** with alkyl halides, O-alkylated products **4** were not detected, suggesting that N-alkylation of **1** precedes the cyclization reaction.

Based on the data in Tables 2 and 3, we propose the mechanism for the reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with alkyl iodide and NaH as Scheme 2. To support the involvement of **5** as an intermediate, we prepared *N*-ethyl-*o*-benzoylacetanilide (**5b**: R=H; R′=Et) from the reaction of **1a** with ethyl iodide in the presence of cesium carbonate in acetone, and then it was reacted with 3 equiv. of NaH in refluxing THF. The yield of *N*-ethyl-4-phenylquinolin-2(1*H*)-one **3b** was higher in shorter reaction time (92% yield after 4 h) compared to the reaction of **1a** (85% yield after 7 h: see entry 2 of Table 3). The fact that the reaction of **2a** with alkyl iodide in THF is very slow and

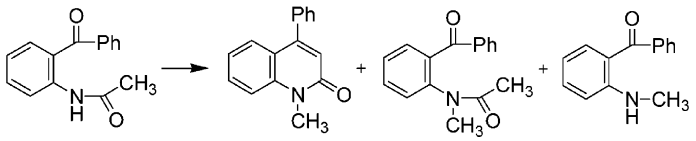
Table 1. Alkylation reaction of **2a** with alkyl halides



Entry	R′X	Base	Solvent	Temperature	Time (h)	Yields (%)	
						3	**4**
1	CH_3I	K_2CO_3	DMF	70 °C	0.5	84	8
2	C_2H_5I	K_2CO_3	DMF	70 °C	1	60	34
3	n-$C_8H_{17}Br$	K_2CO_3	DMF	70 °C	1.5	42	48
4	C_2H_5I	Cs_2CO_3	DMF	70 °C	0.5	59	31
5[a]	C_2H_5I	NaH	THF	Reflux	120	66 (72)[b]	13 (14)[b]
6	n-$C_8H_{17}I$	NaH	DMF	70 °C	0.5	43	52

[a] 8% of the starting material was remained unreacted.
[b] The yield in the parenthesis is the yield based on the consumed starting material.

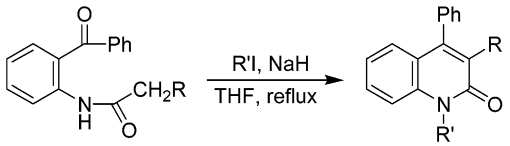
Table 2. Reaction of **1a** with methyl iodide and NaH in THF



1a **3a** **5a** **6a**

Entry	Equiv. of CH_3I	Equiv. of NaH	T (°C)	Time (h)	Yields (%)		
					3a	**5a**	**6a**
1	2.5	3	0	3	nd	100	nd
2	2.5	3	25	2	16	81	nd
3	2.5	6	0	2	13	77	8
4	2.5	6	25	1	60	31	8
5	2.5	6	40	1	67	24	7
6	2.5	3	Reflux	2	78	18	2
7	1.5	6	Reflux	2	85	9	nd
8	2.5	6	Reflux	2	92	nd	6

Table 3. The yields of *N*-alkyl-2-quinolones **3a-g** obtained from the reaction of **1a-c** with various alkyl iodide and NaH in THF



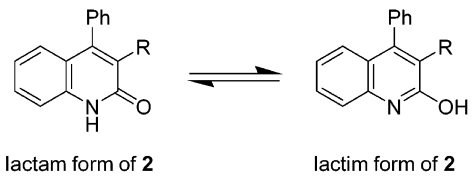
1a-c **3a-g**

Entry	Starting material	R	R′	Time (h)	Product	Yields (%)
1	**1a**	H	CH_3	2	**3a**	92
2	**1a**	H	C_2H_5	7	**3b**	85
3	**1a**	H	n-C_8H_{17}	40	**3c**	75
4	**1b**	CH_3	CH_3	4	**3d**	85
5	**1b**	CH_3	C_2H_5	5	**3e**	88
6	**1c**	n-C_5H_{11}	CH_3	4	**3f**	95
7	**1c**	n-C_5H_{11}	C_2H_5	8	**3g**	84

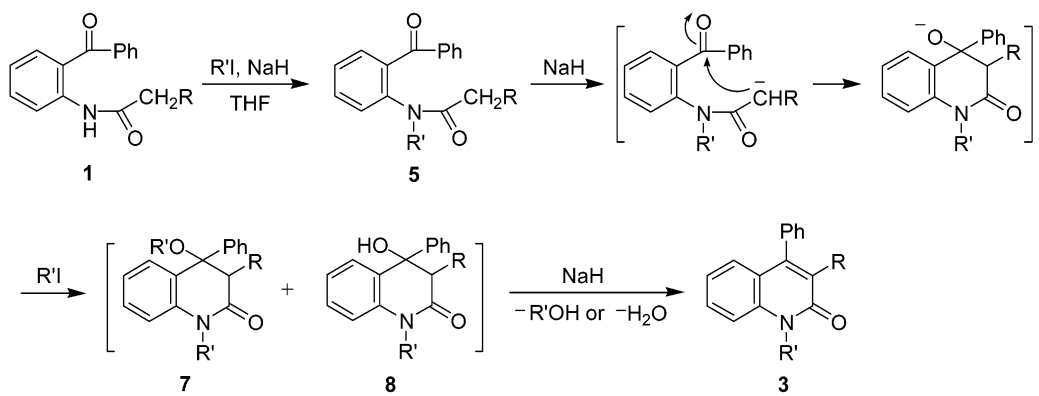
gives appreciable amount of O-alkylated product **4** (see entry 5 of Table 1) further supports the involvement of the intermediate **5** in the transformation of **1** to **3** in the presence of alkyl halide. We propose the involvement of the intermediate **7** in addition of **8** based on the following two facts. One is that the yield of **3a** becomes lower with less than 2 equiv. of alkyl iodide (compare entries 7 and 8 of Table 2). The other is that the yield of **3b** is increased from 92 to 99% in the reaction of **5b** with NaH when 1.5 equiv. of ethyl iodide is added to the reaction mixture.

2.3. Tautomeric form of 4-phenylquinolin-2(1*H*)-ones 2a-c

The tautomeric equilibrium of lactam–lactim continues to attract much attention owing to its chemical, biological, and theoretical importance.[19] Compounds **2a-c** can exist in either lactam or lactim forms. Of the two tautomers, the lactim form of **2a** (R=H) is reported to be more stable than the lactam by ca. 1 kJ/mol in the gas phase,[20] and the lactam is slightly more stable in solution, especially in polar solvent (ca. 20 kJ/mol in water).[21] It was also reported that both the lactam and lactim tautomers of **2a** exist in the supersonic jet expansion.[22] On the other hand, a paper suggested that the compound **2a** exists in the lactim form as 2-hydroxyquinoline, based on a singlet signal for one proton present at δ 12 in the ^{1}H NMR spectrum.[12b] The crystal structure of **2a** has recently been reported, showing that **2a** has the lactam structure.[23]



lactam form of **2** lactim form of **2**



Scheme 2. Proposed mechanism for the reaction of *N*-acyl-*o*-aminobenzophenones **1** with alkyl iodide and NaH.

Since both N-alkylated and O-alkylated compounds **3a-c** and **4a-c**, which correspond to the lactam and lactim forms, respectively, are at our hands, we compare the spectroscopic characteristics between the N-alkylated compounds **3** and the O-alkylated ones **4** and deduce the tautomeric structure of **2**. The NMR data of **3** are significantly different from those of **4** (see Section 4 for data): major differences are ^{1}H and ^{13}C peaks of CH_2 (or CH_3) bonded to the heteroatoms and ^{1}H peaks of the aromatic protons. The chemical shift of the carbon atom at the 2-position of the quinoline ring is almost same for both **3a-c** and **4a-c** as δ 161–162. As expected, ^{1}H and ^{13}C peaks of CH_2 (or CH_3) bonded to the oxygen atom in **4a-c** have larger δ values than those bonded to the nitrogen atom in **3a-c**: the O-alkylated compounds **4a-c** have the ^{1}H peaks at δ 4.11, 4.57, and 4.50, and the ^{13}C peaks at δ 53.39, 61.65, and 66.00, respectively, while **3a-c** have the corresponding ^{1}H peaks at 3.78, 4.43, and 4.34, and ^{13}C peaks at 29.45, 37.26, and 42.34, respectively.

^{1}H Peaks of the aromatic protons of **4a-c** are more downfield-shifted than those of **3a-c**: the singlet signal of the hydrogen atom at the 3-position of the quinoline ring appears at δ 6.84–6.85 for **4a-c**, but δ 6.66–6.68 for **3a-c**, and the protons at the 5-, 6-, 7-, and 8-positions of the quinoline ring of **4a-c** are well resolved as a doublet at δ 7.74–7.75, a triplet at δ 7.29–7.31, a triplet at δ 7.60–7.62, and a doublet at δ 7.89–7.91, respectively, while those of **3a-c** appear unresolved at higher field.

It is also seen that the characteristic IR peaks of **3a-c** and **4a-c** exhibit clear differences: N-alkylated compounds **3a-c** have a very strong peak around 1648–1665 cm^{-1}, while O-alkylated ones **4a-c** have a medium peak at 1608–1611 cm^{-1}. Comparison of the IR and NMR spectral data of **2a** with those of **3a-c** and **4a-c** indicates that the pattern and positions of the NMR peaks of the aromatic protons and the characteristic IR peak of **2a** are very much similar with those of N-alkylated compounds **3a-c**, but not with those of **4a-c**. Also, the spectroscopic characteristics of **2b** and **2c** are very alike with their N-alkylated products **3d** and **3e**, and **3f** and **3g**, respectively. Thus, we can conclude unequivocally that the compound **2a-c** exist as the lactam form in our experimental conditions, either in chloroform solution or in KBr pellet.

3. Conclusions

We have described an efficient synthesis of 4-phenylquinolin-2(1*H*)-ones **2** from *N*-acyl-*o*-aminobenzophenones **1** using NaH as a base. The alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide gave a mixture of N-alkylated and O-alkylated products **3** and **4**. The reaction of **1** with NaH in the presence of alkyl iodide gave the corresponding N-alkylated quinolones **3** in 75–95% yields, resulting from N-alkylation followed by cyclization reaction in one pot. Comparison of IR and NMR data of **3** and **4** with those of **2a-c** clearly indicates that **2a-c** exist as the lactam form.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using tetramethylsilane as an internal standard in $CDCl_3$. Melting points are uncorrected.

4.2. General procedure for the preparation of *N*-acyl-*o*-aminobenzophenones

To a mixture of 2-aminobenzophenone (5.00 g, 25.4 mmol) and pyridine (12.3 ml, 152 mmol) in dichloromethane (150 ml) was added slowly acyl chloride (30.4 mmol). After stirring at room temp for 0.5 h, the reaction mixture was concentrated to ca. 50 ml and washed with 10% aqeous HCl solution. Then the aqueous solution was extracted with dichloromethane 2–3 times. The combined organic layers were dried over sodium sulfate, filtered, and evaporated to afford a residue. Purification of the residue by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 3:1) provided the corresponding *N*-acyl-*o*-aminobenzophenones **1a-c** in 99–100% yields.

4.2.1. Compound 1a. R_f 0.49 (hexane–ethyl acetate, 2:1); mp 90–91 °C (lit.[24] 89–90 °C); ^{1}H NMR δ 10.82 (broad s, 1H), 8.63 (d, 1H, *J*=8 Hz), 7.70 (d, 2H, *J*=8 Hz), 7.60–7.46 (m, 5H), 7.08 (t, 1H, *J*=8 Hz), 2.23 (s, 3H). IR (KBr): 3161, 1668, 1645, 1603 cm^{-1}.

4.2.2. Compound 1b. R_f 0.56 (hexane–ethyl acetate, 2:1); mp 83–84 °C; ^{1}H NMR δ 10.89 (broad s, 1H), 8.67 (d, 1H, *J*=8 Hz), 7.69 (d, 2H, *J*=8 Hz), 7.62–7.53 (m, 3H), 7.48 (t, 2H, *J*=8 Hz), 7.07 (t, 1H, *J*=8 Hz), 2.48 (q, 2H, *J*=8 Hz), 1.28 (t, 3H, *J*=8 Hz). IR (KBr): 3223, 1667, 1647, 1601 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.49; H, 5.88; N, 5.35.

4.2.3. Compound 1c. R_f 0.78 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 10.87 (s, 1H), 8.67 (d, 1H, *J*=8 Hz), 7.69 (d, 2H, *J*=7 Hz), 7.62–7.52 (m, 3H), 7.48 (t, 2H, *J*=8 Hz), 7.06 (t, 1H, *J*=7 Hz), 2.43 (t, 2H, *J*=8 Hz), 1.75 (quintet, 2H, *J*=8 Hz), 1.43–1.25 (m, 6H), 0.87 (t, 3H, *J*=7 Hz). IR (KBr): 3309, 1699, 1635, 1603 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.74; H, 7.74; N, 4.66.

N-Alkylation of *N*-acyl-*o*-aminobenzophenone was carried out using cesium carbonate as a base. To a mixture of **1a** (0.10 g, 0.42 mmol) and cesium carbonate (0.82 g, 2.5 mmol) in acetone (10 ml) was added slowly ethyl iodide (67 μl, 0.84 mmol). After heating at reflux for 19 h, the reaction mixture was concentrated. Dichloromethane was added to the residue and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, concentrated, and then purified by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 1:1) to provide *N*-ethyl-*o*-benzoylacetanilide **5b** (0.105 g, 0.393 mmol) in 94% yield: R_f 0.30 (*n*-hexane–ethyl acetate, 1:1); mp 87–88 °C; ^{1}H NMR δ 7.80–7.76 (m, 2H), 7.63–7.42 (m, 6H), 7.28 (d, 1H, *J*=8 Hz), 4.05–3.95 (m, 1H), 3.08–2.98 (m, 1H), 1.86 (s, 3H), 1.03 (t, 3H, *J*=7 Hz). IR (KBr): 1659, 1594, 1577 cm^{-1}. Anal. Calcd for

$C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.22; H, 6.56; N, 5.14.

4.3. General procedure for the synthesis of 4-phenylquinolin-2(1*H*)-ones 2a-c

The mixture of *N*-acyl-*o*-aminobenzophenones **1a-c** (0.84 mmol) and sodium hydride (121 mg, 5.04 mmol) in THF (4 ml) was heated at reflux for 2.5 h for **1a**, 9 h for **1b**, and 20 h for **1c**. Dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and concentrated. Silica gel column chromatography of the residue (eluent: hexane–ethyl acetate, 2:1 for **2a**; hexane–ethyl acetate, 3:1 for **2b**; hexane–ethyl acetate, 5:1 and then 2:1 for **2c**) provided the corresponding **2a-c** in 83, 62, and 65% yields, together with the deacylated compound, *o*-aminobenzophenone with 16, 23, and 22% yields, respectively.

4.3.1. Compound 2a. R_f 0.10 (hexane–ethyl acetate, 2:1); mp 259–261 °C (lit.[16a] 260 °C; lit.[12b] 260–262 °C; lit.[15] 257–259 °C); ^{1}H NMR δ 12.87 (s, 1H), 7.58–7.45 (m, 8H), 7.16 (t, 1H, J=7 Hz), 6.71 (s, 1H); ^{13}C NMR δ 164.16, 153.33, 138.87, 137.05, 130.61, 128.78, 128.72, 128.53, 126.64, 122.46, 120.69, 119.52, 116.66. IR (KBr): $\nu_{C=O}$ 1663 cm^{-1}.

4.3.2. Compound 2b. R_f 0.13 (hexane–ethyl acetate, 2:1); mp 227–228 °C (lit[13] 227–230 °C); ^{1}H NMR δ 12.61 (s, 1H), 7.55–7.41 (m, 5H), 7.27–7.24 (m, 2H), 7.09–7.03 (m, 2H), 2.10 (s, 3H); ^{13}C NMR δ 164.46, 148.68, 137.02, 136.90, 129.17, 128.70, 128.57, 127.86, 127.37, 126.63, 122.07, 121.02, 115.85, 14.38. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}.

4.3.3. Compound 2c. R_f 0.28 (hexane–ethyl acetate, 2:1); mp 166–168 °C; ^{1}H NMR δ 12.47 (s, 1H), 7.53–7.39 (m, 5H), 7.28–7.22 (m, 2H), 7.07–6.98 (m, 2H), 2.49 (t, 2H, J=8 Hz), 1.54 (quintet, 2H, J=7 Hz), 1.28–1.17 (m, 4H), 0.83 (t, 3H, J=7 Hz); ^{13}C NMR δ 164.08, 148.50, 137.06, 136.70, 132.12, 129.11, 128.72, 128.37, 127.77, 126.82, 121.96, 121.27, 115.67, 31.97, 28.83, 28.19, 22.31, 14.00. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.72; H, 7.30; N, 5.04.

4.4. General procedure for the synthesis of *N*-alkyl-4-phenylquinolin-2(1*H*)-one derivatives 3a-g

The mixture of *N*-acyl-*o*-aminobenzophenones **1a-c** (0.84 mmol), alkyl iodide (2.10 mmol), and sodium hydride (121 mg, 5.04 mmol) in THF (4 ml) was heated at reflux. After the reaction, dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and evaporated to afford a residue. Silica gel column chromatography (eluent: hexane–ethyl acetate, 5:1 for **3c** and *n*-hexane–ethyl acetate, 2:1 for others) provided **3a-g**. The yields and reaction times are listed in Table 3.

4.4.1. Compound 3a. R_f 0.37 (hexane–ethyl acetate, 2:1); mp 146 °C (lit.[16a] 146 °C); ^{1}H NMR δ 7.60–7.40 (m, 8H), 7.16 (t, 1H, J=8 Hz), 6.68 (s, 1H), 3.78 (s, 3H); ^{13}C NMR δ 161.71, 150.73, 140.12, 136.90, 130.51, 128.76, 128.52, 128.40, 127.55, 121.77, 121.08, 120.32, 114.32, 29.45. IR (KBr): $\nu_{C=O}$ 1665 cm^{-1}.

4.4.2. Compound 3b. R_f 0.46 (hexane–ethyl acetate, 2:1); mp 99–100 °C (lit.[11c] 98–99 °C); ^{1}H NMR δ 7.59–7.39 (m, 8H), 7.14 (t, 1H, J=8 Hz), 6.67 (s, 1H), 4.43 (q, 2H, J=7 Hz), 1.42 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.27, 150.69, 139.10, 137.02, 130.47, 128.75, 128.49, 128.41, 127.80, 121.56, 121.21, 120.62, 114.21, 37.26, 12.80. IR (KBr): $\nu_{C=O}$ 1648 cm^{-1}.

4.4.3. Compound 3c. R_f 0.84 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 7.59–7.39 (m, 8H), 7.14 (t, 1H, J=8 Hz), 6.66 (s, 1H), 4.34 (t, 2H, J=8 Hz), 1.80 (quintet, 2H, J=8 Hz), 1.50 (quintet, 2H, J=7 Hz), 1.43–1.24 (m, 8H), 0.89 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.43, 150.60, 139.32, 137.02, 130.37, 128.74, 128.45, 128.38, 127.73, 121.49, 121.19, 120.57, 114.35, 42.34, 31.79, 29.36, 29.22, 27.54, 27.07, 22.63, 14.10. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.87; H, 8.28; N, 4.32.

4.4.4. Compound 3d. R_f 0.31 (hexane–ethyl acetate, 2:1); mp 132–133 °C; ^{1}H NMR δ 7.53–7.42 (m, 4H), 7.39 (d, 1H, J=8 Hz), 7.23–7.19 (m, 2H), 7.12–7.05 (m, 2H), 3.82 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 162.50, 146.49, 138.47, 136.92, 129.17, 128.77, 128.53, 127.78, 127.54 (two overlapped C's), 121.63, 121.56, 113.75, 29.95, 15.33. IR (KBr): $\nu_{C=O}$ 1636 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.98; H, 6.05; N, 5.58.

4.4.5. Compound 3e. R_f 0.44 (hexane–ethyl acetate, 2:1); mp 111 °C (lit. 107–109 °C[25]); ^{1}H NMR δ 7.53–7.39 (m, 5H), 7.23–7.19 (m, 2H), 7.11 (dd, 1H, J=8, 2 Hz), 7.06 (t, 1H, J=8 Hz), 4.47 (q, 2H, J=7 Hz), 2.02 (s, 3H), 1.43 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.95, 146.47, 137.42, 137.03, 129.13, 128.74, 128.53, 127.78, 127.73, 127.54, 121.83, 121.39, 113.64, 37.77, 15.20, 12.80. IR (KBr): $\nu_{C=O}$ 1629 cm^{-1}.

4.4.6. Compound 3f. R_f 0.54 (hexane–ethyl acetate, 2:1); mp 78–79 °C; ^{1}H NMR δ 7.52–7.43 (m, 4H), 7.37 (d, 1H, J=8 Hz), 7.22 (d, 2H, J=8 Hz), 7.09–7.01 (m, 2H), 3.81 (s, 3H), 2.41 (t, 2H, J=8 Hz), 1.46 (quintet, 2H, J=8 Hz), 1.23–1.12 (m, 4H), 0.79 (t, 3H, J=7 Hz); ^{13}C NMR δ 162.05, 146.42, 138.53, 136.73, 132.16, 129.17, 128.77, 128.35, 127.72 (two overlapped C's), 121.78, 121.56, 113.69, 32.06, 29.86, 29.18, 28.79, 22.27, 13.98. IR (KBr): $\nu_{C=O}$ 1647 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.65; H, 7.64; N, 4.69.

4.4.7. Compound 3g. R_f 0.66 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 7.52–7.37 (m, 5H), 7.27–7.17 (m, 2H), 7.08–6.99 (m, 2H), 4.45 (q, 2H, J=7 Hz), 2.40 (t, 2H, J=8 Hz), 1.51–1.37 (m, 5H), 1.23–1.13 (m, 4H), 0.79 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.47, 146.33, 137.49, 136.83, 132.16, 129.10, 128.75, 128.35, 127.95, 127.66, 122.02, 121.30, 113.55, 37.70, 32.08, 29.09, 28.76, 22.23, 13.98, 12.82. IR (KBr): $\nu_{C=O}$ 1637 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.80; H, 7.81; N, 4.39.

4.5. Alkylation reaction of 2a with alkyl halides

To a mixture of **2a** (100 mg, 0.47 mmol) and K_2CO_3 (393 mg, 2.84 mmol) in DMF (5 ml) was added slowly alkyl halide (0.95 mmol) and the reaction mixture was heated at 70 °C. After the reaction, dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and evaporated to afford a residue. Separation of the residue by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 5:1 and then 2:1 or 1:1) provided the corresponding N-alkylated product (**3a-c**) and O-alkylated product (**4a-c**): O-alkylated product eluted first and then followed by N-alkylated product. The reactions using Cs_2CO_3 or NaH instead of K_2CO_3 as a base and THF instead of DMF as a solvent were carried out similarly. The product distributions and reaction times are listed in Table 1. The characterization data of **3a-c** are given in Section 4.4.

4.5.1. Compound 4a. R_f 0.76 (hexane–ethyl acetate, 5:1); mp 79–80 °C (lit.[26] 78–80 °C); ^{1}H NMR δ 7.91 (d, 1H, J=8 Hz), 7.75 (d, 1H, J=8 Hz), 7.62 (t, 1H, J=8 Hz), 7.53–7.44 (m, 5H), 7.31 (t, 1H, J=8 Hz), 6.85 (s, 1H), 4.11 (s, 3H); ^{13}C NMR δ 161.93, 151.03, 147.10, 137.89, 129.33, 129.27, 128.40, 128.26, 127.55, 125.72, 123.97, 123.88, 112.75, 53.39. IR (KBr): $\nu_{C=N}$ 1611 cm^{-1}.

4.5.2. Compound 4b. R_f 0.79 (hexane–ethyl acetate, 5:1); oil (lit.[27] 54–55 °C); ^{1}H NMR δ 7.89 (d, 1H, J=8 Hz), 7.74 (d, 1H, J=8 Hz), 7.60 (t, 1H, J=8 Hz), 7.52–7.43 (m, 5H), 7.29 (t, 1H, J=7 Hz), 6.84 (s, 1H), 4.57 (q, 2H, J=7 Hz), 1.46 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.64, 150.92, 147.19, 137.95, 129.26 (two overlapped C's), 128.38, 128.20, 127.55, 125.67, 123.90, 123.75, 112.98, 61.65, 14.72. IR (KBr): $\nu_{C=N}$ 1608 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.87; H, 6.04; N, 5.68.

4.5.3. Compound 4c. R_f 0.87 (hexane–ethyl acetate, 5:1); oil; ^{1}H NMR δ 7.89 (d, 1H, J=8 Hz), 7.74 (d, 1H, J=8 Hz), 7.60 (t, 1H, J=8 Hz), 7.52–7.43 (m, 5H), 7.29 (t, 1H, J=8 Hz), 6.85 (s, 1H), 4.50 (t, 2H, J=7 Hz), 1.84 (quintet, 2H, J=7 Hz), 1.49 (quintet, 2H, J=7 Hz), 1.43–1.24 (m, 8H), 0.88 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.85, 150.89, 147.20, 137.96, 129.26, 129.23, 128.36, 128.20, 127.53, 125.66, 123.88, 123.72, 113.01, 66.00, 31.89, 29.46, 29.34, 29.12, 26.22, 22.74, 14.19. IR (KBr): $\nu_{C=N}$ 1608 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 83.06; H, 8.22; N, 4.00.

Acknowledgements

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References and notes

1. Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476–493, and references therein.
2. (a) Balasubramanian, M.; Keay, J. G. *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 5, pp 245–300. (b) Yates, F. S. *Comprehensive heterocyclic chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2, pp 511–524.
3. (a) Jones, G. *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 5, pp 167–243. (b) Jones, G. *Comprehensive heterocyclic chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2, pp 395–510. (c) Claret, P. A. *Comprehensive organic chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: New York, 1979; Vol. 4, pp 157–166.
4. (a) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257–4259. (b) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371–9378. (c) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *Tetrahedron* **2003**, *59*, 9887–9893. (d) Fan, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 7001–7003. (e) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron Lett.* **2002**, *43*, 5537–5540. (f) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488. (g) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467–477. (h) Kobayashi, K.; Yoneda, K.; Mizumoto, T.; Umakoshi, H.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **2003**, *44*, 4733–4736, and references therein. (i) Kobayashi, K.; Yoneda, K.; Mano, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2003**, *32*, 76–77. (j) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455–1458.
5. (a) Cookson, R. F.; Rodway, R. E. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1854–1857. (b) Nakahara, S.; Tanaka, Y.; Kubo, A. *Heterocycles* **1993**, *36*, 1139–1144.
6. Holzapfel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 215–219.
7. Hino, K.; Furukawa, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1980**, *28*, 2618–2622.
8. Hino, K.; Kawashima, K.; Oka, M.; Nagai, Y.; Uno, H.; Matsumoto, J. *Chem. Pharm. Bull.* **1989**, *37*, 110–115.
9. Huang, L.; Hsieh, M.; Teng, C.; Lee, K.; Kuo, S. *Biorg. Med. Chem.* **1998**, *6*, 1657–1662.
10. Beier, N.; Labitzke, E.; Mederski, W. W. K. R.; Radunz, H.; Rauschenbach-Ruess, K.; Schneider, B. *Heterocycles* **1994**, *39*, 117–131.
11. (a) Hauser, C. R.; Reynolds, G. A. *J. Am. Chem. Soc.* **1948**, *70*, 2402–2404. (b) Staskun, B. *J. Org. Chem.* **1964**, *29*, 1153–1157. (c) Koelsch, C. F.; Britain, J. W. *J. Org. Chem.* **1959**, *24*, 1551–1553. (d) Kaslow, C. E.; Cook, D. J. *J. Am. Chem. Soc.* **1945**, *67*, 1969–1972. (e) Hodgkinson, A. J.; Staskun, B. *J. Org. Chem.* **1969**, *34*, 1709–1713.
12. (a) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952–2958. (b) Chorbadjiev, S. *Synth. Commun.* **1990**, *20*, 3497–3505.
13. Kobayashi, K.; Kitamura, T.; Yoneda, K.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2000**, 798–799.
14. Ferrer, P.; Avendano, C.; Soellhuber, M. *Liebigs Ann. Chem.* **1995**, 1895–1899.
15. Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281–5283.
16. (a) Kaupp, G.; Gründken, E.; Matthies, D. *Chem. Ber.* **1986**, *119*, 3109–3120. (b) Kano, S.; Ozaki, T.; Hibino, S. *Heterocycles* **1979**, *12*, 489–492.

17. Fuerstner, A.; Jumban, D. N.; Shi, N. *Z. Naturforsch. B* **1995**, *50*, 326–332, CAN 123, 143616.
18. Scriven, E. F. V. *Comprehensive heterocyclic chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2, pp 176–178.
19. Johnson, C. D. *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 5, pp 15–18.
20. Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186–192.
21. Cook, M. J.; Katritzky, A. R.; Linda, P.; Tack, R. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1080–1086.
22. Nimlos, M. R.; Kelley, D. F.; Bernstein, E. R. *J. Phys. Chem.* **1987**, *91*, 6610–6614.
23. Rajnikant; Gupta, V. K.; Deshmukh, M. B.; Varghese, B.; Dinesh, *Crystallogr. Rep.* **2002**, *47*, 449–496.
24. Gribble, G. W.; Bousquet, F. P. *Tetrahedron* **1971**, *27*, 3785–3794.
25. Nesvadba, P.; Kuthan, J. *Collect. Czech. Chem. Commun.* **1983**, *48*, 2965–2969.
26. Hofmann, H.; Fischer, H.; Bremer, M. *Chem. Ber.* **1987**, *120*, 2087–2089.
27. Sindler-Kulyk, M.; Neckers, D. C. *J. Org. Chem.* **1982**, *47*, 4914–4919.

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Conformational and configurational analysis of 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes. Conformational and configurational dependence upon conformation of the diol precursor

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Abstract—Diastereomeric 5-*tert*-butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes were synthesized, and studied by NMR and computational methods in order to determine their predominant conformations as well as their relative configurations. The study was performed assuming a novel criteria, in which, the conformation and configuration of the diastereomeric 5-*tert*-butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes depend upon the conformation of the corresponding diol precursors. In other words, the orientation or pseudo orientation of the groups into the ring framework of the heterocyclic is initially acquired by the direct phosphorylation reaction with the diol precursor in the most stable conformation, and then, once the heterocyclic is formed, the final conformation is dictated by stereoelectronic and steric effects.

1. Introduction

The conformational and configurational study of the well-known 1,3,2-dioxaphosphorinanes is one of the most exciting in the field of the physic-organic chemistry.[1] These studies have found more popularity since the report from the Bentrude's group, which suggests that the twist conformation of the cAMP and cGMP is the predominant in the cell metabolism.[2] Apparently, the ΔG^0 for the chair-twist equilibria is provided by binding forces within an enzyme active sites.[2] Thus, attention turned to the conformational study of 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes fused in *transoid* fashion, in which, a small molecular distortion is observed and two twist forms and only one boat form can be assumed as accessible.[1] Similar behavior is observed for those analogous fused in *cisoid* fashion.[1,3,4]

In this regard, we recently reported the trapping of two different molecules into a crystal asymmetric unit, one molecule in chair conformation and another one in boat conformation.[4] Thus, the ready dynamic equilibrium between the chair and the boat conformation in solution was absolutely corroborated in solid state. This finding, put forward that the boat conformation should be considered as a further appropriate conformation for intermolecular interaction between the cAMP and cGMP and the enzyme active site that regulate the role in the cell metabolism.[5]

For less strained 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes, the chair–non-chair and the chair–chair equilibria are spontaneous operations. So, their configurational and conformational analyses turn very complicated due to the existence of more conformational forms than those 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes fused in *trans* or *cisoid* fashion.[1]

Apparently, one of the best ways for monitoring the specific conformational equilibria is by means of analysis of the well-known stereospecificity between the vicinal coupling constant and its dihedral angle.[1] Additionally, assignments of the preferred configuration and conformation of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes and related compounds could be performed by the analysis of the vicinal $^1H-^1H$ scalar coupling constants, and the well-established $^3J_{H,P}$ coupling constant relationship. Herein, the equatorial H–P coupling constant is typically $\geq$20 Hz, while the corresponding axial H–P coupling is usually $\leq$5 Hz.[1] A further key factor in these assignments is the preference of the P–OR bond to be axially oriented, which is clearly observed in the phosphorus chemical shift value, i.e. signals which are up-field shifted can be attributed to phosphorinanes having their phenoxy group at the axial position.[1,6]

Previously, we reported that the chair–boat equilibria for 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes derived from

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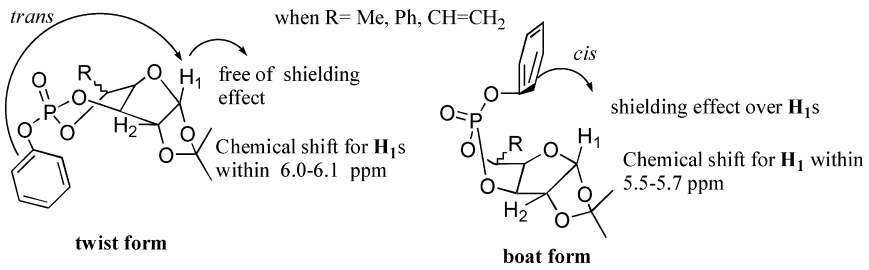
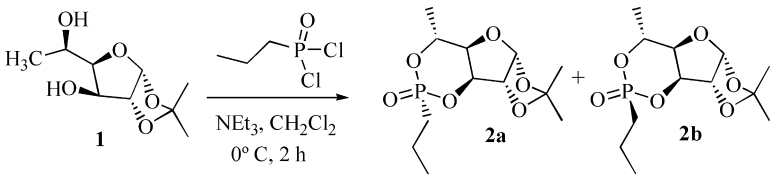
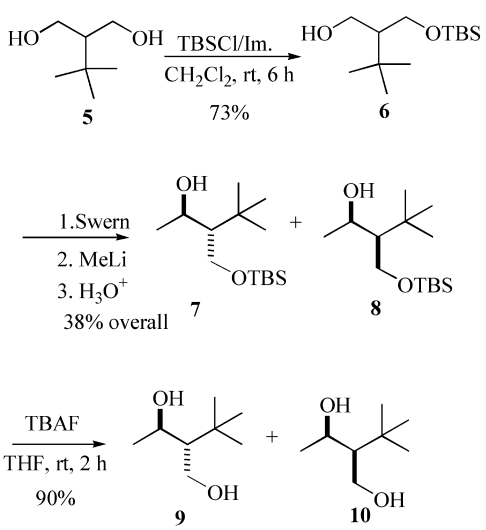


Figure 1. Aromatic ring current effect in the chemical shift of the anomeric furanose protons.



Scheme 1. Synthesis of cyclic phosphonates.



Scheme 2. Synthesis of diols **9** and **10**.

1,2-*O*-isopropylidene-α-D-xylofuranose can be observed by the analysis of the chemical shift of anomeric protons, which are oriented *cis* to the P-phenoxy group (Fig. 1).[4]

In fact, the driving force that aid to get the above non-chair conformations is the strain imposed by the presence of a *cisoid*-like fused bicyclic structure bearing methyl, phenyl and vinyl groups attached at the *C*′5 position of the 1,2-*O*-isopropylidene-α-D-xylofuranose moiety (see Figure 1) and the strong pseudo-axial seeking force caused by phenoxy group. In this sense, herein, we report further information that allows, in a way, to observe and predict specific conformational equilibria and relative configurational assignment of non-fused 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes disubstituted at C5 and C3.

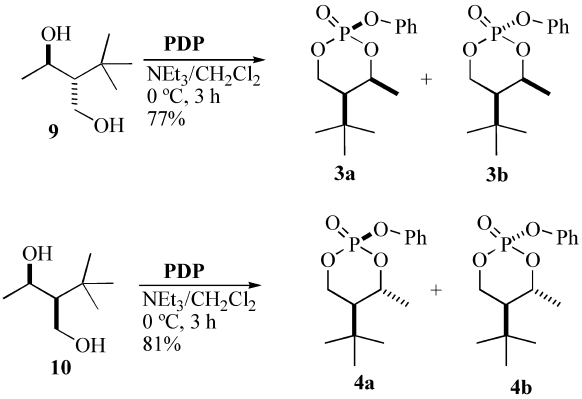
2. Results and discussion

As just mentioned, the strong anisotropic shielding effect of the aromatic ring of the phenoxy group, generates an up-field shift in the H_1 furanose anomeric hydrogen atoms when are oriented *cis* to the P-phenoxy group. Therefore, the replacement of the phenoxy group with an alkyl group should not generate any up-field shift in the H_1 furanose anomeric hydrogen atoms. Thus, cyclic phosphonates **2a** and **2b** were synthesized from diol **1** and propylphosphonic dichloride in the presence of triethylamine, in 80% yield, on a 2:1 ratio, respectively, Scheme 1.

As expected, due to the absence of the benzene ring current effect, there was not observed any shielding effect over the anomeric hydrogen (5.96 ppm for **2a** and 6.09 ppm for **2b**). Furthermore, on the basis of the vicinal H,P H,H coupling constants, and 2D-NOESY interactions, and due also to the absence of the stronger anomeric effect that phenoxy group incorporates into the dynamic motion, the chair-twist equilibrium for both phosphonates is proposed.[7]

Then, we proceed to synthesize four diasteromeric 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes incorporating the methyl group at C4 and *tert*-butyl group at C5 (**3a**, **3b**, **4a** and **4b**). First, the monosilylation of diol **5** is performed. Then, a sequential Swern[8] oxidation, followed by methyl addition affords the *anti* and *syn* monosilylated alcohols **7** and **8** in a 1:1 ratio. Finally, desilylation of **7** and **8** yielded to the *anti* and *syn* diols **9** and **10** (Scheme 2).

Diols **9** and **10** are converted in a mixture of two pairs of



Scheme 3. Synthesis of phosphorinanes **3a**, **3b**, **4a** and **4b**.

Table 1. Coupling constants (Hz) for dioxaphosphorinanes **3a**, **3b**, **4a**, and **4b**[a]

	$^3J_{H4,P}$	$^3J_{H6,P}$	$^3J_{H6',P}$	$^3J_{H4,H5}$	$^3J_{H5,H6'}$	$^3J_{H5,H6}$	$^3J_{H4,H6}$	$^3J_{H6,H6'}$
3a	21.0	22.1	2.4	3.8	11.0	3.5	1.3	11.4
3b	15.4	11.1	11.0	4.0	10.3	4.4	0	11.2
4a	14.0	17.1	8.9	6.6	9.0	5.3	0	11.5
4b	19.8[b]	20.0[b]	7.3[b]	2.8[b]	4.0[b]	3.3[b]	0.8[b]	12.3[b]

[a] $CDCl_3$ solution unless otherwise noted.
[b] Spectrum recorded on C_6D_6 (insufficient resolution in $CDCl_3$).

Table 2. ^1H and ^{31}P chemical shift for dioxaphosphorinanes **3a**, **3b**, **4a**, and **4b**[a]

	δ_{H4}	δ_{H5}	δ_{H6}	$\delta_{H6'}$	$\delta_{t\text{-Bu}}$	δ_{Me}	δ_P
3a	4.87	2.45	4.54	4.38	0.98	1.57	−12.7
3b	4.85	2.16	4.58	4.40	1.00	1.62	−12.3
4a	4.61	1.82	4.43	4.22	0.97	1.60	−9.00
4b	4.48[b]	0.70[b]	4.12[b]	4.04[b]	0.80[b]	1.22[b]	−11.0[b]

[a] $CDCl_3$ solution unless other wise noted.
[b] Spectrum recorded on C_6D_6 (insufficient resolution in $CDCl_3$).

Doing a preliminary evaluation for all the diasteromeric dioxaphosphorinanes, it can be said that each pair of dioxaphosphorinanes has one conformer with a permanent chair and another one with a non-chair conformation (Fig. 2).

Nevertheless, the correct assignment of the non-chair conformation without crystallographic studies, continues being a difficult task; the vicinal H,P coupling constants from 8 to 16 Hz may describe either twist, boat or twist-boat conformations.

The primary interest of this conformational and configurational study of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes bearing the methyl and *tert*-butyl groups at C4 and C5, respectively, concerns in the introduction of a novel way of rationalize and predict the preferred conformations of these heterocyclic compounds by virtue of the specific conformation of the diol precursors.

Till now, it is considered that the chair–chair and

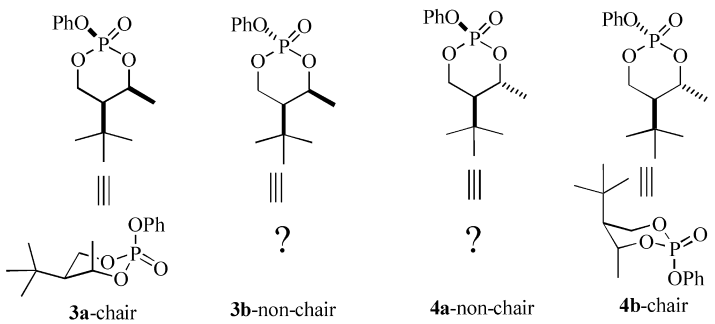


Figure 2. Predominant chair conformation for **3a** and **4b** and known non-chair for **4a** and **4b**.

cyclic phosphates **3a** and **3b**, **4a** and **4b** by treatment with phenyl dichlorophosphate (**PDP**), and triethylamine in dichloromethane. Both pairs of diasteromeric phosphorinanes are separated by column chromatography on silica gel giving **3a**, **3b** and **4a**, **4b** in good yields (77 and 81%, respectively). The diastereomeric ratio was 1:1 in both cases (Scheme 3).

Table 1 shows the $^3J_{H,P}$, $^3J_{H,H}$ and ^4J_w values. It is clear for compounds **3a** and **4b** that they are predominantly in a chair conformation. The H4 and H6 are quite comfortable in equatorial position leading to the methyl group in axial position ($^3J_{H4,P}$=20.1 Hz, $^3J_{H6,P}$=22.1 Hz for **3a** and $^3J_{H4,P}$=19.4 Hz, $^3J_{H6,P}$=20.0 Hz for **4b**). The analysis of the H4,H5 coupling constants for **3a** are in agreement with the equatorial position for *tert*-butyl group ($^3J_{H4,H5}$=3.8 Hz). Additionally, if the *tert*-butyl is equatorially and the methyl axially oriented, the stereochemistry for diol **9** should be *anti*, and obviously **10** have to be *syn*. NMR data for the another two phosphorinanes **3b** and **4a** revealed that both are away from the chair conformation ($^3J_{H4,P}$=15.4 Hz, $^3J_{H6,P}$=11.1 Hz for **3b** and $^3J_{H4,P}$=14.0 Hz, $^3J_{H6,P}$=17.1 Hz for **4a**). The configuration of the phosphorus atom was determined on the bias of the ^{31}P chemical shift: phosphorinanes that appear at upper field than their diastereomer congener suggest that phenoxy group is oriented in axial position (see Table 2).[6]

chair–non-chair equilibria of 1,3,2-dioxaphosphorinanes (and similar others) is dictated after phosphorylation reaction is achieved. To our best knowledge, any work has considered that the predominant conformation of these heterocycles may depend on the most stable conformation of 1,3-diols precursors; especially those disubstituted.

The above idea was originated from the absence of the expected chair conformations for **3bc′** and **4ac′**. In the case of **3bc′**, the anomeric effect caused by the phenoxy group, and the lack of 1,3-diaxial interactions between the

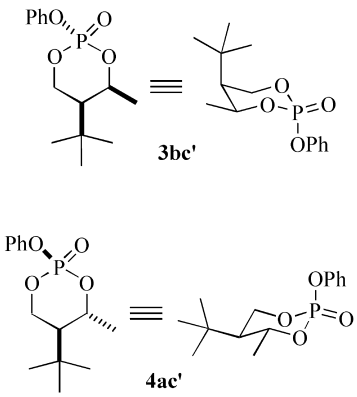


Figure 3. Expectable conformations for **3b** and **4a**.

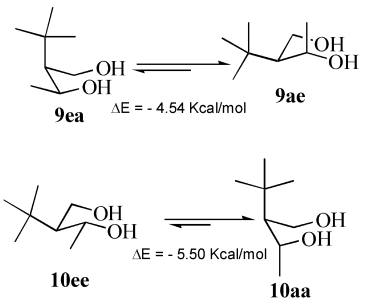


Figure 4. Preferred conformation of diols **9** and **10**.

tert-butyl and methyl groups should afford a very comfortable chair conformation (see Figure 3). Similar criteria should be applied for **4ac′**, although in this case the gauche interaction between the *tert*-butyl and methyl groups might appear as a lightly unfavorable situation for the chair conformation (see Figure 3).

In this sense, it was found by computational calculations (using the PC GAMESS program, with the 6-31G** basis set[9]) that conformers **9ae** and **10aa** are more stable by 4.54 and 5.50 kcal/mol, respectively (see Figure 4).

Thus, direct phosphorylation reaction of diol **9** in the preferred conformation **9ae** should afford **3ac** and **3bc**. Phosphorinane **3ac** is locked in a comfortable chair conformation (as previously was described). On the other hand, **3bc** escapes from the chair conformation to the boat conformation **3bb** due to the strong pseudo-axial seeking force caused by phenoxy group (see Figure 5). Chemical shift of H5 revealed for phosphorinane **3bb** to be exposed to a shielding effect caused by phenoxy group (δ: 2.45 ppm for **3ac** and 1.95 ppm for **3bb**) indicating that the boat conformation **3bb** with H5 and phenoxy group in proximity is predominant (Fig. 5).[4] Computational calculations (geometry optimization with semi-empirical PM3 level and ab initio calculations at HF/6-31G** level[9]) and NMR data support the boat conformation.

On the other hand, direct phosphorylation of diol **10** in the preferred conformation **10aa** affords phosphorinanes **4ac** and **4bc**. Now, phosphorinane **4bc** is locked in a comfortable chair conformation (Fig. 6). Apparently, **4bc** should be more stable in the chair conformation than **3ac** because in this case, the *tert*-butyl and methyl groups are oriented *anti*-diaxial minimizing most of the steric destabilizing contributions (Fig. 6). Nevertheless, larger values of $^{3}J_{H4,P}$ and $^{3}J_{H6,P}$ for **3ac** suggest that **3ac** is more predominant in chair conformation than **4bc**. Computational calculations are in agreement with this assessment: it was found that **3ac** is more stable than **4bc** by 2.7 kcal/mol. It is important to mention that in both cases, the methyl and phenoxy groups are oriented *syn*-1,3-diaxial, and steric repulsions may destabilize the chair conformation. Reports

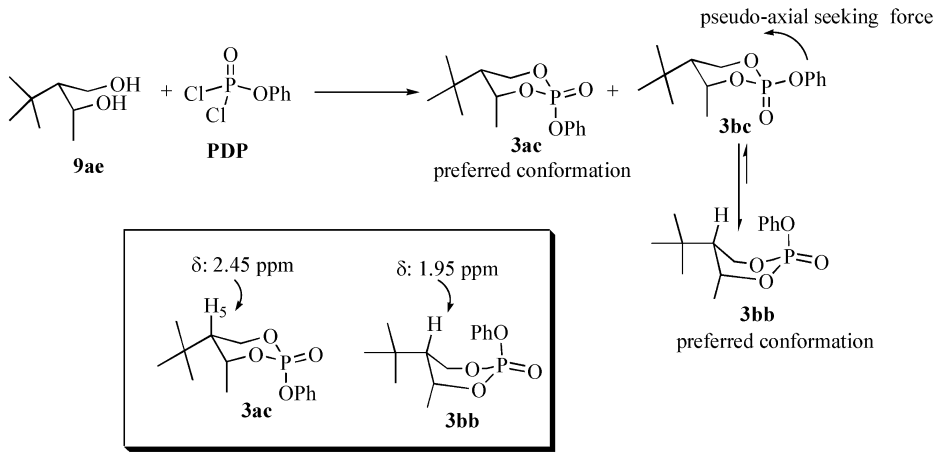


Figure 5. Direct phosphotylation reaction of diol **9** in the preferred **9ae** conformation.

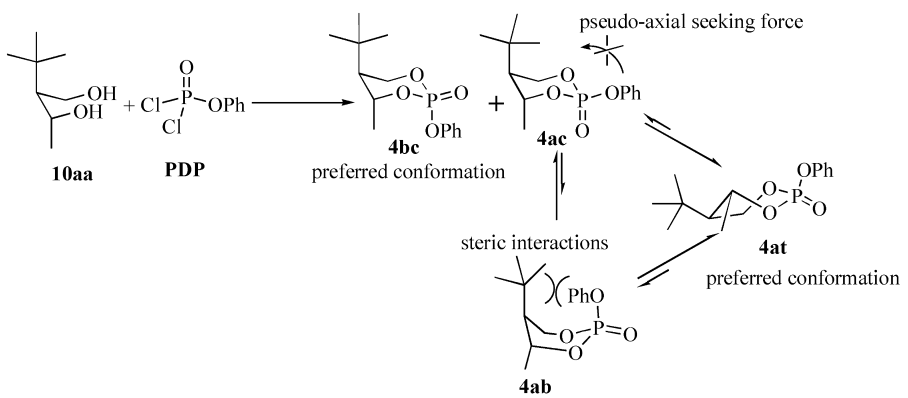


Figure 6. Direct phosphorylation reaction of diol **10** in the preferred **10aa** conformation.

from Majoral[10] and us[11] have showed that *syn*-1,3 diaxial interactions between methyl or benzyl and phenoxy groups appear do not considerably affect the chair conformation.

On the other hand, **4ac** places the phenoxy group in unstable equatorial position, very similar to **3bc**. However, in this case, the non-chair conformation in the boat fashion **4ab** cannot be assumed. The pseudo-axial seeking force caused by phenoxy group is now considerably diminished by the strong steric interaction that the phenoxy and *tert*-butyl groups encounter when the boat conformation is operating. Now, the non-chair conformation is accommodated in a classical twist conformation **4at**. Thus, applying the same computational treatment, phosphorinane **4a** found the lowest relative energy in the twist conformation **4at** (Fig. 6).

By use of the H,P dihedral angle values of the phosphorinanes **3a**, **3b**, **4a** and **4b** in the conformation given by the computational calculations and applying them to the Lee and Sarma correlation[12] ($^3J_{POCH}$=18.1 $\cos^2\theta$−4.8 $\cos\theta$), we found close agreement values with the experimental ones, especially for phosphorinanes **3a**, **3b** and **4b**, where the difference between the calculated and observed are less than 2 Hz. In the case of **4a** some values are slightly higher; this means that the degree of twisting of phosphorinane ring is affected by the presence (in very small contribution) of further boat conformation (see Fig. 6).

It is important to consider the direct phosphorylation reaction of the diols **9** and **10** in the unfavorable **9ea** and **10ee** conformations. Phosphorinanes **3ac′** and **4ac′** should be expected as the major conformers along with their corresponding non-chair conformers. Unfortunately, small values of $^3J_{H4,P}$ and $^wJ_{Me,P}$ for those diastereomeric phosphorinanes were not observed (Fig. 7).[10,11]

Although the conformation and configuration study developed herein is well applied for 1,3-diols-1,2-disubstituted with methyl and *tert*-butyl groups, it is necessary to take some cautions with 1,3-diols-1,2-disubstituted

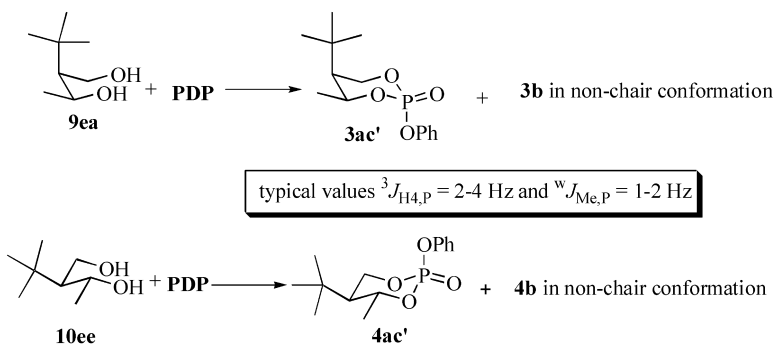
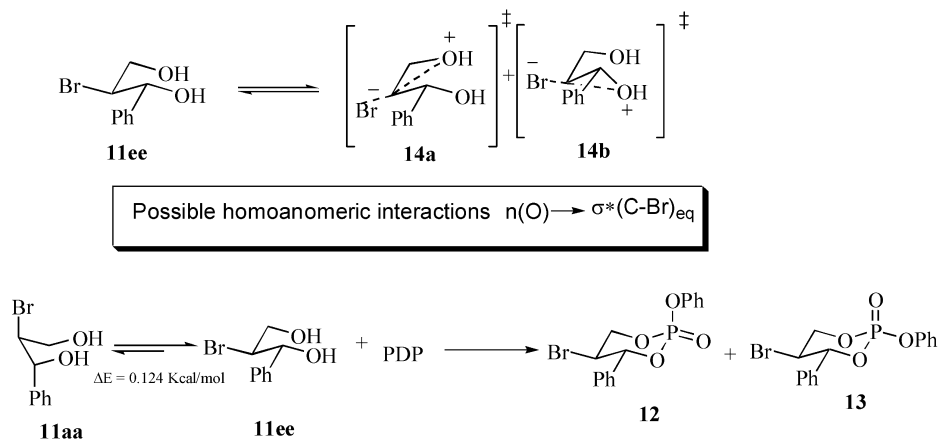


Figure 7. Hypothetic direct phosphorylation reactions of diols **9** and **10** in the unfavorable **9ea** and **10ee** conformations.



	δ_P [a]	$^3J_{H4,P}$ [b]	$^3J_{H4,H5}$ [b]	$^3J_{H6,P}$ [b]	$^3J_{H6',P}$ [b]
12	-13.5	0.8	10.4	26.1	1.0
13	-9.1	2.2	10.1	25.9	3.5

a: ppm, b: Hz

Figure 8. Homoanomeric interactions controlling diol and phosphorinanes conformation.

bearing electronegative groups like halides. In that case, stereoelectronic effects[13] turn more important than steric ones, and reversal behaviors may appear.

In this regard, we reviewed the phosphorylation reaction of the diol **11**.[14] Applying the same computational treatment, it was found that conformer **11ee** is more stable for 0.124 kcal/mol than **11aa**. Direct phosphorylation reaction of the diol **11** in the preferred conformation **11ee** affords phosphorinanes **12** and **13** in very comfortable chair conformation. In both cases, the bromine atom in placed in equatorial position (Fig. 8).

It is very well-known that the classic anomeric interactions[15] are stronger than any homoanomeric ones,[16] but the latter turns more important when the ability of σ^* orbitals increases as a result of bond stretching and/or polarization.[15] So, homoanomeric interactions involving W-and/or Plough effects[16,17] (n(O)→σ^*(C–Br)eq) are present when diol **11** is found in the **11ee** conformation. Besides, the above interactions may be also interpreted as a typical homoconjugation between n(O)→σ^*(C–Br)eq orbitals leading to a type of close shell solvolysis **14a** and **14b** intermediates (Fig. 7).

3. Conclusion

To the best of our knowledge, herein it has been introduced a novel way to predict and rationalize the conformational equilibria and relative configurational assignment of 5,4-disustituted-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes. Although this study only involved two different types of 1,3-diols 1,2-disubstituted with different chemical properties, we anticipate very similar behavior for those with few variants into the framework, and will function analogously albeit on different time scales. Besides, due to few reports about the homoanomeric interactions in non-cyclic system (even in cyclic systems), further efforts in design and study new model molecules with specific structural featuring are currently underway and will be reported soon.

4. Experimental

4.1. Calculation methods

All geometries were fully optimized, and the nature of the resulting stationary point was characterized by vibrational frequencies at HF/6-31G(d,p) and PM3 levels for diols and phosphorinanes, respectively. The PC GAMESS[9a] program resided on a PIV computer and all optimized structures were visualized by using the MOLEKEL 4.3 program.[9b,c] The application of more accurate basis sets such as HF/6-31G(d,p) for phosphorinanes would exert enormous demand on our available computers.

4.1.1. (5*R*,S_P)-1,2-Isopropyliden-5-methyl-3,5-*O*-propylphosphoryl-α-D-xylofuranose (2a) and (5*R*,R_P)-1,2-Isopropyliden-5-methyl-3,5-*O*-propylphosphoryl-α-D-xylofuranose (2b). A solution of diol (**1**) (120 mg, 0.59 mmol) and triethylamine (0.2 mL, 0.88 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added dropwise propyldichlorophosphonate (0.12 mL, 0.88 mmol) dissolved in 5 mL of CH_2Cl_2. The reaction mixture was allowed to stir for 2 h before quenched with H_2O (20 mL). Extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated under pressure reduced. The residue was purified by column chromatography (2:1, mixture of hexane/ethyl acetate) affording **2a** and **2b** in 80% yield with a ratio of 2:1 respectively.

Compound **2a**. $[\alpha]_D$=22.4 (c=1, $CHCl_3$); ^{1}H NMR δ: 1.01 (td, 3H,. J=7.5, 2.0 Hz), 1.34 (s, 3H), 1.5 (s, 3H), 1.64 (d, 6H, J=7.2 Hz), 1.75–1.85 (m, 4H), 4.21 (dd, 1H, J=2.4, 2.0 Hz), 4.58 (ddd, 1H, J=14.1, 7.2, 2.0 Hz), 4.65 (d, 1H, J=3.6 Hz), 4.95 (apparent t, 1H, J=2.0 Hz), 5.96 (d, 1H, J=3.6 Hz); ^{13}C NMR δ: 15.0, 15.8, 20.3, 26.0, 26.5, 27.5, 74.0, 76.2, 77.7, 83.9, 104.6, 112.5; ^{31}P NMR δ: 27.9; FABS m/z: 293.1159 $[M+H]^+$ (calcd for $C_{12}H_{22}O_6P$ 293.1154).

Compound **2b**. Mp 130–132 °C; $[\alpha]_D$=78.1 (c=1, $CHCl_3$); ^{1}H NMR δ: 1.04 (td, 3H, J=7.6, 1.5 Hz), 1.3 (s, 3H), 1.50 (s, 3H), 1.51 (d, 3H, J=6.3 Hz), 1.6–1.9 (m, 4H), 4.27 (apparent t, 1H, J=3.6 Hz), 4.57 (dd, 1H, J=5.2, 3.6 Hz), 4.62 (ddd, 1H, J=13.4, 6.3, 1.8 Hz), 4.75 (d, 1H, J=3.6 Hz), 6.01 (d, 1H, J=3.6 Hz); ^{13}C NMR δ: 15.2, 15.9, 19.8, 26.3, 26.9, 27.4, 72.9, 79.8, 81.0, 84.1, 105.6, 112.5; FABS m/z: 293. 1159 $[M+H]^+$ (calcd for $C_{12}H_{22}O_6P$ 293.1156).

4.1.2. 2-*tert*-Butyl-3-(*tert*-butyldimethylsiloxy)-1-propanol (6). To solution of **5** (1.2 g, 9 mmol) and imidazole (0.71 g, 9.8 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise *tert*-butyldimethylsilyl chloride (1.4 g, 10.8 mmol) in CH_2Cl_2 (15 mL). The mixture was allowed to stir for 12 h, then, reaction was quenched with water and organic phase extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (eluent hexane/ethyl acetate: 8:1) gave **3** (1.55 g, 71%). ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 6H), 0.9 (s, 18H), 1.59 (m, 1H), 3.3 (d, 1H, J=6 Hz), 3.73 (t, 1H, J=9.4 Hz), 3.81 (t broad, 1H, J=9 Hz), 3.9 (dd, 1H, J=8.0, 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ: −5.3, 18.1, 23.3, 29.0, 33.1, 51.2, 64.9, 65.7; EIHRMS: m/z: 189.1327 (M+·−t-Bu), calcd for $C_9H_{21}O_2Si$: m/z: 189.1311.

4.1.3. *anti* and *syn*-2-*tert*-Butyl-1-(*tert*-butyldimethylsiloxy)-3-butanol (8 and 9). To a solution of oxalyl chloride (1 mL) in CH_2Cl_2 (30 mL) at −70 °C was added dropwise dry DMSO (5 mL) and, after stirring for 15 min, a solution of **6** (1 g, 4 mmol) in CH_2Cl_2 (5 mL) followed by triethylamine (3.5 mL). The reaction mixture was then allowed to warm to room temperature then quenched with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$) and evaporated in vacuo. The crude reaction mixture was dissolved in dry THF (10 mL) and cooled to 0 °C and MeLi (6 mL, of 1.4 M in ether) was added. After 2 h the reaction was quenched with aqueous NH_4Cl (10 mL) and the organic phase was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography on silica gel (eluent hexane/ethyl acetate: 4/1) gave of *anti*-**7** (0.21 g, 18%) and *syn*-**8** (0.19 g, 15%).

anti-2-tert-Butyl-1-(tert-butyldimethylsiloxy)-2-butanol (**7**). ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 6H), 0.9 (s, 9H), 1.0 (s, 9H), 1.1 (m, 1H), 1.28 (d, 3H, J=6.6 Hz), 3.43 (d, 1H, J=8.7 Hz),

3.81 (dd, 1H, J=11.0, 4.2 Hz), 4.02 (dd, 1H, J=11.0, 4.0 Hz), 4.14 (qd, 1H, J=6.6, 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ: −5.5, 17.1, 25.4, 25.9, 29.1, 33.2, 53.7, 61.6, 68.4; EIHRMS: m/z: 245.1942 (M+·−Me), calcd for $C_{13}H_{29}O_2Si$: m/z: 245.1937.

syn-2-tert-Butyl-1-(tert-butyldimethylsiloxy)-2-butanol (**8**). ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 6H), 0.87 (s, 9H), 0.95 (s, 9H), 1.35 (d, 3H, J=6.5 Hz), 1.85 (m, 1H), 3.73 (d, 1H, J=10 Hz), 3.9 (d, 1H, J=9.5 Hz), 4.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: −4.5, 19.2, 25.8, 27.1, 29.0, 31.0, 53.9, 61.4, 68.8; EIHRMS: m/z: 245.1930 (M+·−Me), calcd for $C_{13}H_{29}O_2Si$: m/z: 245.1937.

4.1.4. *anti*-2-*tert*-Butyl-1,3-butandiol (9). To solution of **8** (100 mg, 0.4 mmol) in THF (3 mL) was added Bu_4NF (0.8 mL, 1.0 M in THF, 0.8 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and allowed to stir for 3 h before it was diluted with water and extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel (eluent: hexane/ethyl acetate: 2/1) gave **9** (50 mg, 90%). ^{1}H NMR ($CDCl_3$) δ: 1.0 (s, 9H), 1.12 (m, 1H), 1.32 (d, 3H, J=6.5 Hz), 2.5 (broad, 1H), 2.7 (broad, 1H), 4.0 (m, 2H), 4.25 (qd, 1H, J=6.5, 1.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 25.8, 28.9, 33.1, 54.3, 61.2, 68.6. EIHRMS: m/z: 147.1377 (M+·+H), calcd for $C_8H_{19}O_2$: m/z: 147.1385.

4.1.5. *syn*-2-*tert*-Butyl-1,3-butandiol (10). Was obtained analogously to **9**, also in 90% yield. ^{1}H NMR ($CDCl_3$) δ: 0.92 (s, 9H), 1.32 (d, 3H, J=6.5 Hz), 1.86 (m, 1H), 2.8 (broad, 1H), 3.9 (m, 2H), 4.23 (qd, 1H, J=6.5, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 19.5, 29.1, 31.5, 54.6, 61.3, 69.7. EIHRMS: m/z: 147.1383 (M+·+H), calcd for $C_8H_{19}O_2$: m/z: 147.1385.

4.1.6. 2*S,4*S**,5*R**-5-*tert*-Butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (3a) and 2*R**,3*S**,5*R**-5-*tert*-butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (3b).** $PhOPOCl_2$ (0.04 mL, 0.28 mmol) was added dropwise to solution of **9** (40 mg, 0.276 mmol) and triethylamine (0.08 mL, 0.56 mmol) in CH_2Cl_2 (8 mL). The mixture stirred for 6 h before the reaction was quenched with water and the aqueous phase extracted with ethyl acetate and the combined organic layers dried ($MgSO_4$) and evaporated in vacuo. Chromatography over column chromatography (eluent: hexane/ethyl acetate: 5/1) gave **3a** (15 mg, 38%) and **3b** (16 mg, 39%). **3a**, a white solid, mp 90 °C; ^{13}C NMR ($CDCl_3$) δ 17.2, 28.1, 31.5, 48.1, 66.1, 80.2, 119.5, 124.7, 129.7, 152.8. Anal. Calcd for $C_{14}H_{21}O_4P$: C, 59.15; H, 7.45. Found: H, 59.02; C, 7.41. Compound **2**, a white solid mp 82 °C; ^{13}C NMR ($CDCl_3$) δ: 18.9, 28.9, 31.6, 47.3, 67.9, 80.4, 120.2, 125.2, 129.8, 152.2. EIHRMS: m/z: 284.1188 (M+·), calcd for $C_{14}H_{21}O_4P$: m/z: 284.1178.

4.1.7. 2*S,4*R**,5*R**-5-*tert*-Butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (4a) and 2*R**,3*R**,5*R**-5-*tert*-butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane (4b).** Were obtained analogously to **3a** and **3b**, in 40% for **4a** and 41% for **4b**.

Compound **4a**, a white solid, mp 70 °C; ^{13}C NMR ($CDCl_3$) δ: 23.0, 28.5, 32.6, 49.8, 66.4, 78.1, 119.2, 124.0, 129.7, 150.2; EIHRMS: m/z: 284.1181 (M+·), calcd for $C_{14}H_{21}O_4P$: m/z: 284.1175.

Compound **4b**. ^{13}C NMR ($CDCl_3$) δ: 25.1, 28.1, 32.0, 51.2, 68.4, 78.8, 120.1, 125.2, 129.8, 153.0; EIHRMS: m/z: 284.1179 (M+·), calcd for $C_{14}H_{21}O_4P$: m/z: 284.1178.

Acknowledgements

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References and notes

1. (a) Bentrude, W. G.; Setzer, W. N. Stereospecificity in ^{31}P-element coupling: proton-phosphorus couplings. In *Phosphorus-31 NMR spectroscopy in stereochemical analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Weinheim, 1987; Chapter 12. (b) Bentrude, W. G. Steric and stereoelectronic effects in 1,3,2-dioxaphosphorinanes. In *Methods in stereochemical analysis*; Juaristi, E., Ed.; VCH: New York, 1995; Chapter 7. (c) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187. (d) Gallagher, M. J. In *Phosphorus-31 NMR spectroscopy in stereochemical analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH: Deerfield Beach, FL, 1987; Chapter 11.
2. Nelson, K. A.; Bentrude, W. G.; Setzer, W. N.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 4058.
3. Neeser, J. R.; Tronchet, J. M. J.; Charollais, E. J. *Can. J. Chem.* **1983**, *61*, 1387.
4. Sartillo-Piscil, F.; Cruz, S.; Sanchez, M.; Höpfl, H.; Anaya de Parrodi, C.; Quintero, L. *Tetrahedron* **2003**, *59*, 4077.
5. (a) Taylor, S. S.; Buechler, J. A.; Yonemoto, W. *Ann. Rev. Biochem.* **1990**, *59*, 971. (b) Revenkar, G. R.; Robin, R. K. *Handbook of experimental pharmacology*; Nelson, J. A., Kebabain, J. W., Eds.; Springer: Berlin, 1982; Vol. 58/I. Chapter 2, and references cited therein.
6. (a) Gorenstein, D. G.; Rowell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925. (b) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 5077.
7. A detailed conformational study of cyclic phosphonates analogues to **2a** and **2b** will be reported in a subsequent paper.
8. (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
9. (a) Schimidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jense, J. J.; Kosiki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comp. Chem.* **1993**, *14*, 1347. (b) Flükiger, P.; Lüthi, H. P.; Portmann, S.; Weber, J. *MOLEKEL 4.3*; Swiss Center for Scientific Computing: Manno, Switzerland, 2000–2002. (c) Stefan Portmann and Hans Peter Lüthi. MOLEKEL: an interactive molecular graphics tool. *CHIMIA* **2000**, *54*, 766.
10. Majoral, J. P.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, 96.
11. Crich, D.; Sartillo-Piscil, F.; Quintero, L.; Wink, D. J. *J. Org. Chem.* **2002**, *67*, 3360.
12. (a) Lee, C. H.; Sarma, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 3541. Further references where this correlation has been successfully

used: (b) Maccoss, M.; Ainsworth, C. F.; Leo, G.; Ezra, F. S.; Danyluk, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7353. (c) Maccoss, M.; Ezra, F. S.; Robins, M. J.; Danyluk, S. S. *Carbohydr. Res.* **1978**, *62*, 203.
13. Deslongchamps, P. Stereoelectronic effects in organic chemistry; Pergamon: Oxford, 1983.
14. Sartillo-Piscil, F.; Meza, R.; Quintero, L. *Rev. Soc. Quim. Méx.* **2002**, *46*, 330.
15. (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (b) Juaristi, E.; Cuevas, G. *The anomeric effect*; CRC: Boca Raton, FL, 1994.
16. Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014.
17. Homoanomeric interaction are observed in cyclohexane, dioxane, 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane compounds Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910, and references cited therein.

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Synthesis of trihydroxy quinolizidine alkaloids: 1,3-addition reaction of allylmagnesium bromide to a sugar nitrone

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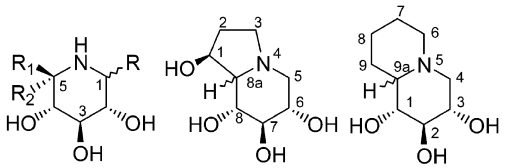
Abstract—The synthesis of (1*R*,2*R*,3*S*,9a*R*) and (1*R*,2*R*,3*S*,9a*S*) trihydroxy quinolizidine alkaloids **3a** and **3b** from D-glucose derived nitrone **4** is described. The key transformation involves the 1,3-addition of allylmagnesium bromide to nitrone **4** that afforded high diastereoselectivity in the presence of TMSOTf. The N–O bond reductive cleavage, *N*-Cbz protection, ozonolysis, Wittig olefination, lactum formation and reductive amination cascade afforded the target compounds **3a** and **3b** in good overall yield.

1. Introduction

Nitrones are becoming increasingly important in providing intermediates for the synthesis of complex molecules, including natural products and bioactive compounds.[1] In general, nitrones are employed in the 1,3-dipolar cycloaddition pathway with different olefinic compounds both in the inter- and intramolecular version. Alternatively, the reactions of nitrones as electrophiles with organometallic reagents (1,3-addition) are gaining a lot of interest in recent years.[2] Easy availability of organometallic compounds as nucleophiles (different metals combined with aryl or alkyl substituents), high electrophilicity of nitrones and feasibility to manipulate the stereoselectivity at the prochiral nitrone-carbon, under different chelation and non-chelation conditions by the use of suitable Lewis acids, made this approach versatile in organic synthesis. This approach is now finding applications in carbohydrate chemistry, especially in the synthesis of polyhydroxylated indolizidine, pyrrolidine and piperidine alkaloids.[3] In this context, we have recently reported on the diastereoselective 1,3-addition of methylmagnesium chloride and silyl ketene acetals to D-glucose derived nitrones in the synthesis of 6-deoxynojirimycin **1a** (Fig. 1) and 1-deoxy-D-*gluco*/L-*ido*-homonojirimycin, **1b**/**1c**, respectively.[4] This class of compounds, in particular polyhydroxylated piperidine (e.g. nojirimycin **1d**), indolizidine (e.g. castanospermine **2**) and quinolizidine-alkaloids **3a** and **3b** have attracted considerable attention because of their promising glycosidase inhibitory activity—the process that plays a crucial role in many biological processes, including breakdown of edible carbohydrates, eukaryotic glycoprotein processing and polysaccharide and glycoconjugate anabolism and catabolism.[5]



1a R = OH, R_1 = CH_3, R_2 = H
1b R = R_2 = H, R_1 = CH_2CH_2OH
1c R = R_1 = H, R_2 = CH_2CH_2OH
1d R = OH, R_1 = CH_2OH, R_2 = H

Figure 1.

The quinolizidine alkaloids are frequently encountered in nature especially in ant species and in the skin of frogs and toads.[6] Although a variety of structurally complex quinolizidine alkaloids are known, the synthesis of polyhydroxylated quinolizidine alkaloids and evaluation of their glycosidase inhibitory activity is a topic of current interest.[7] As part of our continuing efforts in the synthesis of azasugars,[4,8] we are now describing a synthesis of trihydroxy quinolizidine alkaloids **3a** and **3b** using the 1,3-addition reaction of allylmagnesium bromide to a D-glucose derived nitrone **4** as a key step. Although, a few reports are available for the synthesis of polyhydroxylated quinolizidine alkaloids only a single report describes the synthesis of **3b**,[9] while the synthesis of **3a** is not reported so far.

Keywords: Nitrone; Azasugar; Carbohydrate; Quinolizidine; Glycosidase; Inhibitor.
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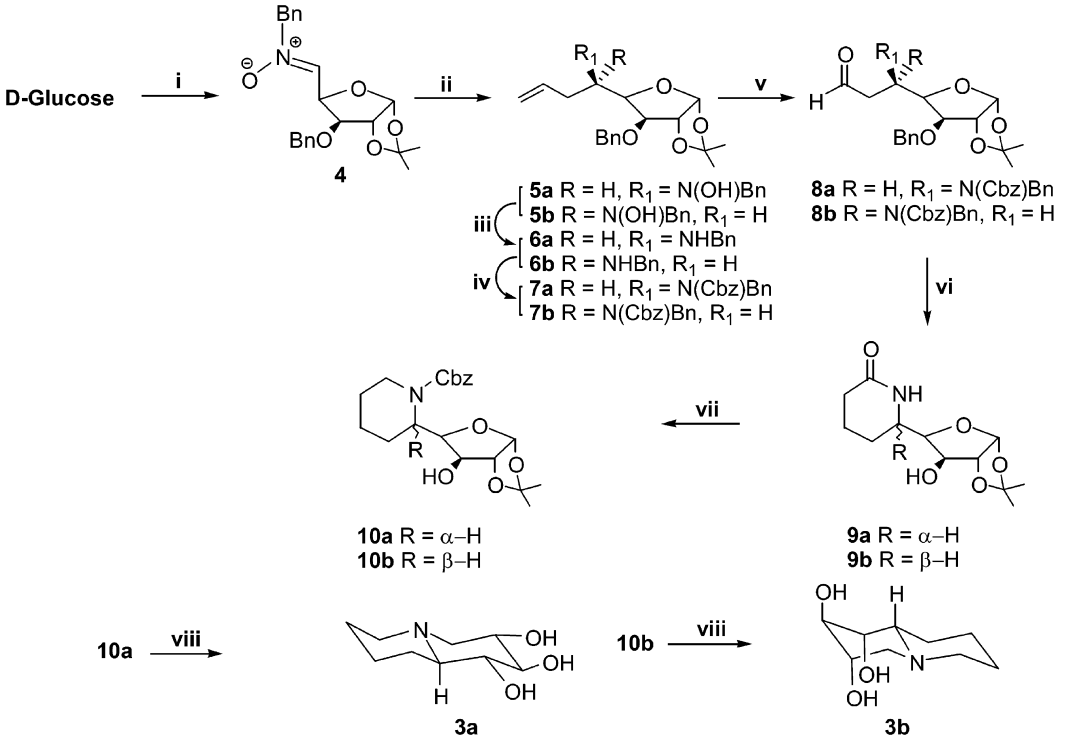
2. Results and discussion

2.1. Stereoselective 1,3-addition of allylmagnesium bromide to sugar derived nitrone 4

The desired sugar nitrone **4** was prepared by the reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pento-dialdose with *N*-benzylhydroxylamine hydrochloride, in the presence of sodium acetate in ethanol-water, as reported earlier by us.[4a] The 1,3-addition of allylmagnesium bromide to **4** at −78 °C in dry THF for 2 h afforded a diastereomeric mixture of *N*-benzylhydroxylamines **5a** and **5b** in 92% yield in the ratio D-*gluco*:L-*ido*=7:3, as evident from the ^{1}H NMR spectrum of the crude product (Scheme 1). To improve the stereoselectivity at the prochiral C5 center, various reaction conditions (e.g. change of solvent, temperature and stoichiometry of reactants) were tried (Table 1). Performing the reaction using ether as solvent had no effect on the stereoselectivity while no product was obtained when dichloromethane was used (entries 2 and 3). Change in the stoichiometry of the reactants (i.e. decreasing the Grignard to nitrone ratio) lowered the combined yield with no significant change in the stereoselectivity (entries 4 and 5). In case of nitrones it is known that the presence of an oxygen atom, formally carrying a net negative charge, allows a strong complexation with Lewis acid to occur. The resulting *N*-*oxy*-immonium species thus displayed enhanced reactivity and, in some cases, different stereochemical outcomes in reaction with nucleophiles.[10] In this context, we have demonstrated the utility of trimethylsilyltriflate (TMSOTf) as a promoter that leads to good stereoselectivity with high yield under kinetic and non-chelation controlled conditions.[10d–h] Inspired by this observation, the reaction of nitrone **4** with allylmagnesium bromide (2.5 equiv.) in the presence of TMSOTf (1 equiv.) was performed. The product on desilylation afforded **5a** and **5b** in the ratio



Scheme 1. Reagents and conditions: (i) Ref. 4a 78%; (ii) Allylmagnesium bromide (2.5 equiv.), THF, −78 °C, 2 h, 93%; (iii) Zn (2 equiv.), $Cu(OAc)_2$, AcOH, 70 °C, 1 h, 78%; (iv) Cbz-Cl (1.5 equiv.), $NaHCO_3$, aq. EtOH, 2 h, 75%; (v) O_3, DCM, DMS, −40 °C, 1 h, 90%; (vi) a) Ph_3P=CHCOOEt (1.5 equiv.), MeOH, rt, 2 h; (b) H_2, 10% Pd–C, MeOH, 25 °C, 12 h; (c) CH_3COONa (4 equiv.), MeOH, reflux, 6 h, 69%; (vii) a) LAH (5 equiv.), THF, 0 °C, 1 h; (b) Cbz-Cl (1.5 equiv.), $NaHCO_3$, aq. EtOH, 2 h, 74%; (Viii) (a) TFA/H_2O (3:2), 0 °C to rt, 2.5 h; (b) H_2, 10% Pd–C, MeOH, 25 °C, 12 h, 87%.

Table 1. 1,3-Addition reaction of allylmagnesium bromide to sugar derived nitrone **4**

Entry	RMgBr R=allyl (equiv.)	Solvent	Lewis acid	Temperature (°C)	Time (h)	Product ratio[a] **5a** and **5b**	Yield[b] (%)
1	2.5	THF	—	−78	2	70/30	92
2	2.5	Et_2O	—	−30	4	65/35	94
3	2.5	CH_2Cl_2	—	−30	48	No reaction[c]	—
4	2.0	THF	—	−78	2	69/31	78[d]
5	1.5	THF	—	−78	5	65/35	48[d]
6	2.5	THF	TMSOTf	−78	2	86/14	93

[a] Ratio was calculated by ^{1}H NMR data of the crude product.
[b] Yields refer to the isolated yields after chromatography.
[c] Starting was recovered ~100%.
[d] Starting was recovered.

86:14, respectively, resulting in a significant improvement of the diastereoselective in favor of D-*gluco* isomer with high yield.

2.2. Assignment of the relative stereochemistry at C5 of the 5a and 5b

The relative stereochemistry at C5 in **5a** and **5b** was assigned on the basis of ^{1}H NMR data. It is known that for a given C5-epimeric pair, derived from the D-*gluco*-furanose, the $J_{4,5}$ in the L-*ido* isomer (*threo*-relationship) is consistently larger than that of the corresponding D-*gluco* isomer (*erythro*-relationship).[11] The higher value of $J_{4,5}$ observed in the diastereomer **5b** (9.5 Hz), as compared to **5a** (8.3 Hz) indicated the L-*ido* configuration for **5b** and the D-*gluco* configuration for **5a**. This assignment was further supported by comparison of the chemical shifts of H3 in both the isomers. The chemical shift of H3 is reported to be diagnostic such that in the L-*ido* isomer, which is significantly upfield ($\delta\sim3.6$) as compared to that in the D-*gluco* ($\delta\sim4.0$).[11] In **5b** H3 appeared upfield at δ 3.84 as compared to **5a** at δ 4.01, further supporting the D-*gluco* and L-*ido* configuration at C5 to **5a** and **5b**, respectively. Thus, the absolute configurations at C-5 in **5a** and **5b** were assigned as (5*R*) and (5*S*), respectively.

2.3. Explanation for the observed stereochemistry

The observed facial selectivity in the 1,3-addition of allylmagnesium bromide to nitrone **4** could be rationalized by Felkin-Anh like transition states (TS) **A** and **B** (Fig. 2). According to Felkin-Anh model[12] the large substituent is kept perpendicular to the C=N bond. We believe that the C–O bond will adopt this position; in fact it is known that nucleophilic attack seeks the LUMO of the nitrone which may be stabilized through mixing of the π^* C=N orbital with the lowest energy σ^* orbital of a substituent, generally associated with the most electronegative substituent.[13] Amongst the two transition states, the TS **A** offers the more favorable Burgi–Dunitz trajectory for the incoming nucleophile[14] thus favoring the formation of D-*gluco* isomer in a major amount and this effect is magnified in the presence of TMSOTf.

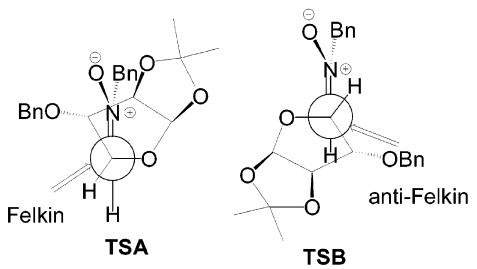


Figure 2.

2.4. Synthesis of 3a and 3b

The utility of **5a** and **5b** were demonstrated in the formation of the corresponding quinolizidine alkaloids **3a** and **3b**. As shown in Scheme 1, the N–O bond reductive cleavage of *N*-benzylhydroxylamine **5a** with zinc in acetic acid–water (85:15) at 70 °C for 1 h afforded the *N*-benzylamino sugar **6a** in good yield. The amino functionality in **6a** was protected with benzyloxycarbonyl chloride in the presence of sodium bicarbonate in aq. ethanol to afford *N*-Cbz protected compound **7a** in 95% yield.[15] Ozonolysis of **7a** at −40 °C in dry CH_2Cl_2 for 2 h afforded aldehyde **8a** in 80% yield. Wittig reaction of aldehyde **8a** with Ph_3-P=CHCOOEt in methanol gave a geometric mixture of α,β-unsaturated-δ-amino esters in 92% yield which was directly subjected to hydrogenation followed by treatment with sodium acetate in methanol to afford six membered δ-lactam **9a** in 70% yield. In the subsequent steps, reduction of the lactam functionality in **9a** with LAH in THF and N-protection with benzyl chloroformate gave **10a** in 78% yield. Finally, compound **10a** was reacted with TFA–H_2O and the hemiacetal thus obtained was subjected to hydrogenation to give (1*R*,2*R*,3*S*,9a*R*)-octahydro-2*H*-quinolizine-1,2,3-triol **3a**. The same reaction sequence was repeated for the *N*-hydroxylamine **5b** (Scheme 1). The corresponding C5-epimeric compounds **6b**, **7b**, **8b** and **9b** were isolated and characterized by spectral and analytical data. Comparison of the IR and ^{1}H NMR spectra of C5-epimeric compounds **9a** and **9b** led to an interesting observation. In the IR spectrum, compound **9a** (D-*gluco*) showed the amide carbonyl stretching frequency at 1658 cm^{-1} while; in compound **9b** (L-*ido*) amide stretching frequency was appeared at 1624 cm^{-1}. The decrease in IR carbonyl frequency in **9b** could be attributed to the intramolecular hydrogen bonding between C3–OH and amide carbonyl oxygen as shown in Figure 3. This observation is substantiated by the fact that, in the ^{1}H NMR spectra, the observed $J_{4,5}$ is found to be larger in D-*gluco* isomer **9a** (9.3 Hz) than the corresponding C5 epimeric L-*ido* isomer **9b** (4.8 Hz). This finding is opposite to that reported ($J_{4,5}$ in L-*ido*>D-*gluco*)[11] and could be attributed to the possible six membered intramolecular hydrogen bonding in **9a** and **9b** between NH and C3 oxygen by rotation about the C4–C5 bond (Fig. 3). In this situation, the molecule is held in such a way that, for the hydrogen bonded D-*gluco* isomer **9a**, the dihedral angle between H4 and H5 is ~180° and that for L-*ido* isomer **9b** is ~45° thus resulting in the observed coupling constants.

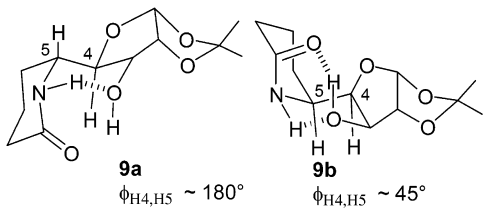


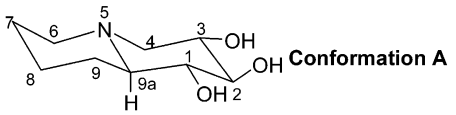
Figure 3.

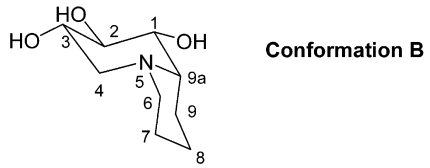
In the next step, reduction of the lactam functionality in **9b** with LAH in THF followed by the *N*-Cbz protection afforded **10b**.[16] Compound **10b** was reacted with TFA–H_2O and the hemiacetal thus obtained was subjected for hydrogenation to give (1*R*,2*R*,3*S*,9a*S*)-octahydro-2*H*-quinolizine-1,2,3-triol **3b**.

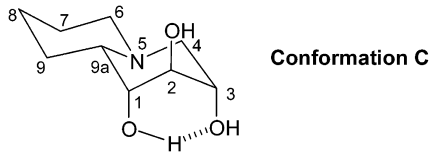
2.5. Conformational assignment of 3a and 3b

Azasugars can exist in different conformations. For example, nojirimycin exists in $^4C_1$ conformation and the castanospermine and 1-deoxy-castanospermine are present

in $^{8}C_{5}$ conformation while; we have reported that the 1-deoxy-8a-*epi*-castanospermine is present in $^{5}C_{8}$ conformation.[8h] The quinolizidine alkaloids **3a** and **3b** have the framework of aza-decalin system wherein one can expect *trans* or *cis* ring fusion. In order to know the conformations, we studied the ^{1}H NMR spectra of **3a** and **3b** and the coupling constant information was obtained by decoupling experiments. In the ^{1}H NMR spectra of **3a** the doublet of triplet ($J_{3,4e}$=4.4 Hz and $J_{3,4a}$=$J_{3,2}$=9.5 Hz), corresponding to H3 proton, indicated the axial orientation of this proton. The triplet ($J_{2,3}$=$J_{2,1}$=9.5 Hz), corresponding to H2, requires *trans*-diaxial relationship with H3 and H1. As the *trans* aza-decalin is conformationally rigid chair-chair system, the conformation **A** was assigned to **3a**. Since the ^{1}H NMR spectrum of **3b** is very different from **3a** it was thought that **3b** could exist in different conformation. Thus, for **3b** we considered two conformations—one with *cis* ring fusion and equatorially oriented OH substituents (conformation **B**) and the other *trans* ring fusion with axially oriented OH substituents (conformation **C**). The initial geometry in the precursor **10b** ensures that in the product **3b** the substituents at C1, C2 and C2, C3 should be *trans*. The ^{1}H NMR of **3b** showed the low coupling constant values ($J_{1,2}$=$J_{2,3}$~3 Hz) between the H1-H2 and H2-H3. This indicated the equatorial orientation of these protons at C1/C2/C3. This fact is supported by the noticeable downfield shift of H1/H2/H3 as compared to the respective protons in **3a**. Based on this observation, we assigned the preferred *trans* ring fused conformation **C**, with axial orientation of the OH substituents, for compound **3b**.[17]







In conclusion, we have demonstrated that the 1,3-addition reaction of allylmagnesium bromide to sugar derived nitrone **4** can be stereocontrolled in favor of D-*gluco* isomer by the use of TMSOTf. The two diastereomeric γ-alkenylamines thus obtained were successfully utilized in the synthesis of trihydroxy quinolizidine alkaloids **3a** and **3b**.

3. Experimental

3.1. General

Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR spectrophotometer as a thin film or in nujol mull and are expressed in cm^{-1}. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ as a solvent unless otherwise noted. NMR Chemical shifts are reported in δ (ppm) downfield from TMS. Elemental analyses were carried out with an elemental analyzer. Optical rotations were measured with a polarimeter using sodium light (D line 589.3 nm) at 25 °C. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with 100–200 mesh silica gel. The reactions were carried out in oven-dried glassware under dry N_2. Allylmagnesium bromide was prepared from Mg and allyl bromide in dry ether prior to use. *N*-Benzylhydroxylamine hydrochloride, LAH, Cbz-Cl was purchased from Aldrich and/or Fluka. Methanol, diethyl ether, dichloromethane, THF were purified and dried before use. Petroleum ether (PE) is a distillation fraction between 40–60 °C. After work up, organic layer was washed with water, brine and dried over anhydrous sodium sulfate and evaporated at reduced pressure. Sugar nitrone **4** was prepared from 1,2-*O*-benzyl-α-D-*xylo*-pento-dialdose in 78% yield as reported earlier.[4a] ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) of compounds **7a**, **7b** and **8a**, **8b** showed doubling of signals and therefore not stated in the experimental.[15]

3.1.1. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-(*N*-benzyl-*N*-hydroxyamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (5a) and 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetra-deoxy-5-(*N*-benzyl-*N*-hydroxyamino)-β-L-*ido*-7-eno-octo-1,4-furanose (5b). To a stirred solution of nitrone **4** (1 g, 2.61 mmol) in THF under nitrogen atmosphere, at −10 °C, was added dropwise TMSOTf (0.47 mL, 2.61 mmol). After stirring for 10 min. the mixture was cooled to −78 °C and allylmagnesium bromide (1 M in diethylether, 1.4 mL, 6.52 mmol) was added dropwise with stirring at −78 °C for 2 h. Quenching was performed with 2 M HCl (2 mL), with stirring at room temperature for 30 min. The reaction mixture was neutralized with saturated solution of $NaHCO_3$ and was extracted with diethyl ether (3×15 mL). The ethereal layer on work up afforded a thick oil. Column chromatograph using (2% EtOAc/Pet. Ether) gave **5a** (0.890 g, 80%) as thick liquid; [Found: C, 70.51; H, 7.30. $C_{25}H_{31}NO_5$ requires C, 70.57; H, 7.34%]; R_f (30% EtOAc/Hexane) 0.52; $[\alpha]_D$ −30.0 (*c* 2.40, $CHCl_3$); ν_{max}(neat) 3510–3160 (br), 1639 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, s, *Me*), 1.44 (3H, s, *Me*), 2.49–2.69 (2H, m, *H*6), 3.41 (1H, ddd, *J*=8.3, 7.8, 4.8 Hz, *H*5), 3.76 (1H, d, *J*=13.6 Hz, CH_2Ph), 3.94 (1H, d, *J*=13.6 Hz, CH_2Ph), 4.01 (1H, d, *J*=3.0 Hz, *H*3), 4.37 (1H, dd, *J*=8.3, 3.0 Hz, *H*4), 4.40–4.45 (1H, bs, exchanges with D_2O, O*H*), 4.50 (1H, d, *J*=11.7 Hz, CH_2Ph), 4.54 (1H, d, *J*=3.9 Hz, *H*2), 4.63 (1H, d, *J*=11.7 Hz, CH_2Ph), 4.98 (1H, dd, *J*=11.1, 1.6 Hz, =CH_2), 5.10 (1H, dd, *J*=17.0, 1.6 Hz, =CH_2), 5.87 (1H, d, *J*=3.9 Hz, *H*1), 5.92–6.10 (1H, m, =C*H*), 7.12–7.28 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.2, 26.7, 31.4, 60.8, 63.4, 72.0, 79.6, 81.9, 82.5, 104.5, 111.3, 115.6, 127.1, 127.5, 127.6, 128.2, 128.4, 129.1, 137.6, 137.7, 138.3. Further elution with (5% EtOAc/Pet. Ether) afforded **5b** (0.145, 13%) as a thick liquid; [Found: C, 70.29; H, 7.59. $C_{25}H_{31}NO_5$ requires C, 70.57; H, 7.34%]; R_f (30% EtOAc/Hexane) 0.44; $[\alpha]_D$ −48.0 (*c* 0.25, $CHCl_3$); ν_{max}(neat) 3530–3150 (br), 1639 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, s, *Me*), 1.46 (3H, s, *Me*),

1.91–2.09 (1H, m, *H*6$_a$), 2.21–2.35 (1H, m, *H*6$_b$), 3.38 (1H, ddd, *J*=9.5, 8.1, 4.3 Hz, *H*5), 3.84 (1H, d, *J*=3.0 Hz, *H*3), 3.92 (1H, d, *J*=13.9 Hz, C*H*$_2$Ph), 4.09 (1H, d, *J*=13.9 Hz, C*H*$_2$Ph), 4.39 (1H, d, *J*=11.6 Hz, C*H*$_2$Ph), 4.44 (1H, dd, *J*=9.5, 3.0 Hz, *H*4), 4.57 (1H, d, *J*=3.8 Hz, *H*2), 4.61 (1H, d, *J*=11.6 Hz, C*H*$_2$Ph), 4.84–4.92 (2H, m, =C*H*$_2$), 4.93–4.96 (1H, bs, exchanges with D_2O, O*H*), 5.83–6.05 (1H, m, =C*H*), 5.93 (1H, d, *J*=3.8 Hz, *H*1), 7.10–7.38 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.5, 26.8, 34.3, 49.4, 57.3, 72.0, 81.3, 81.9, 83.5, 104.9, 111.3, 115.0, 126.2, 127.4, 127.5, 127.7, 128.2, 128.4, 137.9, 138.2, 141.5.

3.1.2. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-*N*-(benzylamino)-α-D-*gluco*-7-eno-octo1,4-furanose (6a). Zinc dust (0.275 g, 4.23 mmol) was added to a solution of copper(II) acetate (0.015 g) in glacial acetic acid (1 mL) under nitrogen and the mixture was stirred at 25 °C for 15 min until the color disappeared. *N*-Benzylhydroxylamine **5a** (0.30 g, 0.70 mmol) in glacial acetic acid (0.7 ml) and water (0.3 mL) was successively added; the reaction mixture was heated at 70 °C for 1 h and cooled to room temperature. The sodium salt of EDTA (0.1 g) was added to the mixture and stirred for 10 min and then made alkaline to pH 10 by addition of 3 M NaOH. The resulting solution was extracted with chloroform (3×15 mL) and the combined organic layer was evaporated to give an oil. Purification by column chromatography (15% EtOAc/Pet. Ether) gave **6a** (0.22 g, 76%) as a thick liquid; [Found: C, 73.26; H, 7.58. $C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63]; R_f 0.19 (50% EtOAc/Hexane); $[\alpha]_D$ −31.0 (*c* 1.55, $CHCl_3$); ν_{max}(neat) 3640–3310 (br), 1588 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, s, *Me*), 1.47 (3H, s, *Me*), 1.59–1.62 (1H, bs, exchanges with D_2O, O*H*), 2.31–2.42 (1H, m, *H*6$_a$), 2.51–2.61 (1H, m, *H*6$_b$), 3.20 (1H, ddd, *J*=9.3, 6.0, 4.0 Hz, *H*5), 3.68 (1H, d, *J*=12.7 Hz, C*H*$_2$Ph), 3.85 (1H, d, *J*=12.7 Hz, C*H*$_2$Ph), 3.99 (1H, dd, *J*=9.3, 3.1 Hz, *H*4), 4.09 (1H, d, *J*=3.1 Hz, *H*3), 4.53 (1H, d, *J*=11.5 Hz, C*H*$_2$Ph), 4.60 (1H, d, *J*=3.8 Hz, *H*2), 4.68 (1H, d, *J*=11.5 Hz, C*H*$_2$Ph), 5.10–5.20 (2H, m, =C*H*$_2$), 5.71–6.00 (1H, m, =C*H*), 5.92 (1H, d, *J*=3.8 Hz, *H*1), 7.18–7.38 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.3, 26.8, 34.8, 51.5, 54.0, 71.9, 81.7, 81.8, 81.9, 104.7, 111.4, 118.1, 126.8, 127.7, 127.8, 128.1, 128.3, 128.4, 134.5, 137.5, 140.7.

3.1.3. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-5-*N*-(benzylamino)-β-L-*ido*-7-eno-octo-1,4-furanose (6b). The reaction of *N*-benzylhydroxylamine **5b** (0.30 g, 0.70 mmol) with Zn/Cu couple under the same reaction conditions reported for **6a**, gave *N*-benzylamine **6b** (0.23 g, 80%) as a thick liquid; [Found: C, 73.22; H, 7.51. $C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63%]; R_f (50% EtOAc/Hexane) 0.11; $[\alpha]_D$ −60.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat) 3620–3260 (br), 1638.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.80–1.97 (1H, bs, exchanges with D_2O, O*H*), 2.01–2.14 (1H, m, *H*6$_a$), 2.20–2.32 (1H, m, *H*6$_b$), 3.19 (1H, ddd, *J*=10.0, 9.3, 5.1 Hz, *H*5), 3.83 (2H, ABq, *J*=12.3 Hz, C*H*$_2$Ph), 3.89 (1H, d, *J*=3.0 Hz, *H*3), 4.08 (1H, dd, *J*=9.3, 3.0 Hz, *H*4), 4.44 (1H, d, *J*=11.7 Hz, C*H*$_2$Ph), 4.64 (1H, d, *J*=3.9 Hz, *H*2), 4.86 (1H, d, *J*=11.7 Hz, C*H*$_2$Ph), 4.93–5.08 (2H, m, =C*H*$_2$), 5.81–5.98 (1H, m, =C*H*), 5.93 (1H, d, *J*=3.9 Hz, *H*1), 7.19–7.39 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.4, 26.7, 34.8, 51.7, 55.3, 71.4, 81.3, 81.7, 82.6, 104.5, 111.4, 116.7, 126.6, 127.8, 127.9, 128.1, 128.2, 128.3, 135.1, 136.9, 140.5.

3.1.4. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-α-D-*gluco*-7-eno-octo-1,4-furanose (7a). To a stirred solution of *N*-benzylamine **6a** (0.622 g, 1.52 mmol) in methanol (5 mL) was added benzyloxycarbonyl chloride (0.322 g, 2.28 mmol) and sodium bicarbonate (0.253 g, 3.00 mmol) and the reaction mixture was stirred at room temperature for 2 h. The methanol was evaporated under reduced pressure and water (10 mL) was added and extracted with chloroform (20 mL×3). Usual work up gave an oil which on purification by column chromatography (5% EtOAc/Pet. Ether) gave **7a** (0.610 g, 73%) as a thick liquid; [Found: C, 73.11; H, 7.09. $C_{33}H_{37}NO_6$ requires C, 72.91; H, 6.86%]; R_f (30% EtOAc/Hexane) 0.72; $[\alpha]_D$ −43.8 (*c* 3.75, $CHCl_3$); ν_{max}(neat) 1695, 1601 cm^{-1}.

3.1.5. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-β-L-*ido*-7-eno-octo-1,4-furanose (7b). The reaction of **6b** (1.5 g, 3.66 mmol) with benzyloxycarbonyl chloride (0.775 g, 5.50 mmol) and sodium bicarbonate (0.610 g, 7.26 mmol) was performed under the same conditions as reported for **7a**. Column chromatography (5% EtOAc/Pet. Ether) afforded **7b** (1.5 g, 79%) as a thick liquid; [Found: C, 72.98; H, 7.13. $C_{33}H_{37}NO_6$ requires C, 72.91; H, 6.86%]; R_f (30% EtOAc/Hexane) 0.59; $[\alpha]_D$ −8.1 (*c* 1.85, $CHCl_3$); ν_{max}(neat) 1697, 1598 cm^{-1}.

3.1.6. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-α-D-*gluco*-heptodialdo-1,4-furanose (8a). Ozone was bubbled through a solution of **7a** (0.3 g, 0.55 mmol) in dichloromethane (10 mL) at −40 °C until a blue color persisted. The reaction mixture was purged with O_2 until the blue color disappeared Dimethyl sulfide (1 mL, 5.5 mmol) was added and the reaction mixture was allow to attain room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure to give a crude product that was purified by column chromatography (10% EtOAc/Pet. Ether) to give aldehyde **8a** (0.275 g, 91%) as a thick liquid; [Found: C, 70.31; H, 6.38. $C_{32}H_{35}NO_7$ requires C, 70.44; H, 6.47%]; R_f (30% EtOAc/Hexane) 0.65; $[\alpha]_D$ −28.7 (*c* 3.35, $CHCl_3$); ν_{max}(neat) 2731, 1722.3, 1697.2 cm^{-1}.

3.1.7. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-β-L-*ido*-heptodialdo-1,4-furanose (8b). The reaction of **7b** (1.0 g, 1.84 mmol)) with ozone in dichloromethane at −40 °C was performed under the same conditions as reported for **8a**. Column chromatography (10% EtOAc/Pet. Ether) afforded **8b** (0.900 g, 89%) as a thick liquid; [Found: C, 70.29; H, 6.32. $C_{32}H_{35}NO_7$ requires C, 70.44; H, 6.47%]; R_f (30% EtOAc/Hexane) 0.61; $[\alpha]_D$ −23.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 2722, 1726, 1697 cm^{-1}.

3.1.8. 1,2-*O*-Isopropylidene-5,6,7,8-tetra-deoxy-5,9-imino-α-D-*gluco*-nona-1,4-furan-9-ulose (9a). To a solution of aldehyde **8a** (1 g, 1.83 mmol) in methanol (5 mL), Wittig reagent, triphenylethoxycarbonylmethylene phosphorane (0.957 g, 2.75 mmol) was added and reaction mixture was stirred for 2.5 h at room temperature. The methanol was evaporated the thick liquid obtained which on usual work up gave an oil. The crude product was directly

subjected to hydrogenation with 10% Pd/C (0.200 g) in methanol (10 mL) at 80 psi for 12 h. The solution was filtered through Celite and washed with methanol. To the filtrate anhydrous sodium acetate (0.265 g, 3.18 mmol) was added and refluxed for 6 h. The pH of the solution was adjusted to eight by addition of 1 M NaOH. Methanol was removed and the solution was extracted with chloroform (3×15 mL). The combined chloroform layer was dried and evaporated to give gummy solid, which was purified by column chromatography (2% MeOH/$CHCl_3$) to give **9a** (0.321 g, 68%) as a white solid; melting point 166–168 °C; [Found: C, 55.94; H, 7.29. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44%]; R_f (10% MeOH/$CHCl_3$) 0.61; $[\alpha]_D$ −24.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 3330–2880, 1658 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, *Me*), 1.50 (3H, s, *Me*), 1.62–2.08 (4H, m, *H*6, *H*7), 2.19–2.36 (2H, m, *H*8), 3.64–3.76 (1H, m, *H*5), 3.95 (1H, dd, *J*=9.3, 2.4 Hz, *H*4), 4.27 (1H, d, *J*=2.4 Hz, *H*3), 4.55 (1H, d, *J*=3.6 Hz, *H*2), 4.78–5.11 (1H, bs, exchanges with D_2O, O*H*), 5.91 (1H, d, *J*=3.6 Hz, *H*1), 8.05–8.22 (1H, bs, exchanges with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 17.8, 24.5, 26.1, 26.9, 31.2, 50.3, 73.4, 82.1, 85.5, 104.8, 111.3, 174.4.

3.1.9. 1,2-*O*-Isopropylidene-5,6,7,8-tetra-deoxy-5,9-imino-β-L-*ido*-nona-1,4-furan-9-ulose (9b). The reaction of **8b** (0.91 g, 1.67 mmol) with Wittig reagent triphenylethoxycarbonylmethylene phosphorane (0.871 g, 2.50 mmol) and followed by hydrogenation with 10% Pd/C (0.180 g) and sodium acetate (0.242 g, 2.96 mmol) was performed under the same conditions as reported for **9a**. Column chromatography (4% MeOH/$CHCl_3$) afforded **9b** (0.330 g, 70%) as a white solid; melting point 156–157 °C; [Found: C, 55.91; H, 7.25. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44%]; R_f (10% $CHCl_3$/MeOH) 0.58; $[\alpha]_D$ −11.5 (*c* 2.25, $CHCl_3$); ν_{max}(neat) 3330– 2880, 1624,cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.59–1.81 (2H, m, *H*6), 1.82 (2H, m, *H*7), 2.21–2.49 (2H, m, *H*8), 3.65–3.80 (1H, m, *H*5), 3.95 (1H, dd, *J*=4.8, 2.7 Hz, *H*4), 4.22 (1H, d, *J*=2.7 Hz, *H*3), 4.51 (1H, d, *J*=3.6 Hz, *H*2), 5.01–5.21 (1H, bs, exchanges with D_2O, O*H*), 5.95 (1H, d, *J*=3.6 Hz, *H*1), 7.10–7.22 (1H, bs, exchanges with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 19.8, 25.9, 26.2, 26.8, 30.9, 52.6, 75.7, 81.3, 85.2, 104.6, 111.5, 173.16.

3.1.10. 1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzoxycarbonyl-imino)-α-D-*gluco*-nona-1,4-furanose (10a). To an ice cooled suspension of LAH (0.223 g, 6.03 mmol) in dry THF (10 mL) was added a solution of **9a** (0.310 g, 1.20 mmol) in dry THF (15 mL) over a period of 10 min. The mixture was allowed to attain the room temperature and stirred for 2 h. Ethyl acetate (10 mL) was added at 0 °C and stirred for 10 min. The reaction was quenched by slow addition of saturated aq. solution of NH_4Cl (2 mL), filtered and residue rinsed with ethyl acetate (5 mL). The usual work up afforded a thick oil that was dissolved in ethanol/water (2 mL, 1/1). The solution was cooled to 0 °C and sodium bicarbonate (0.299 g, 2.41 mmol), benzyloxycarbonyl chloride (0.304 g, 1.80 mmol) was added successively. The mixture was stirred at 25 °C for 2 h. Ethanol was evaporated at reduced pressure and the residue was extracted with chloroform (3×15 mL). The usual work up afforded a thick liquid, that was purified by column chromatography (15% EtOAc/Pet. Ether) to give **10a** (0.365 g, 80%) as a thick liquid; [Found: C, 63.51; H, 7.09. $C_{20}H_{27}NO_6$ requires C, 64.63; H, 7.21%]; R_f (60% EtOAc/Hexane) 0.76; $[\alpha]_D$ −43.0 (*c* 2.0, $CHCl_3$); ν_{max}(neat) 3475, 1674 cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.31 (3H, s, *Me*), 1.48 (3H, s, *Me*), 1.88–2.02 (4H, m, *H*6, *H*7), 2.20–2.35 (2H, m, *H*8), 3.38–3.48 (2H, m, *H*9), 3.79 (1H, dd, *J*=9.9, 1.8 Hz, *H*4), 4.02 (1H, d, *J*=1.8 Hz, *H*3), 4.08–4.19 (1H, m, *H*5), 4.58 (1H, d, *J*=3.6 Hz, *H*2), 5.12 (2H, ABq, *J*=12.0 Hz, CH_2Ph), 5.88 (1H, d, *J*=3.6 Hz, *H*1), 7.22–7.41 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.9, 25.1, 25.3, 26.2, 27.0, 41.1, 48.5, 67.8, 73.6, 76.6, 84.5, 104.8, 111.3, 127.8, 128.4, 128.5, 135.9, 156.9.

3.1.11. 1,2-*O*-Isopropylidine-5,6,7,8,9-penta-deoxy-5,9-(*N*-benzoxycarbonyl-imino)-β-L-*ido*-nona-1,4-furanose (10b). The reaction of **9b** (0.342 g, 1.33 mmol) with LAH (0.250 g, 6.65 mmol) followd by reaction with sodium bicarbonate (0.223 g, 2.66 mmol) and benzyloxycarbonyl chloride (0.340 g, 1.99 mmol) under the same conditions as reported for **10a** and column chromatography (15% EtOAc/Pet. Ether) afforded **10b** (0.350 g, 69%) as a thick liquid; [Found: C, 63.86; H, 7.45. $C_{20}H_{27}NO_6$ requires C, 64.63; H, 7.21%]; R_f (60% EtOAc/ Hexane) 0.68; $[\alpha]_D$ −72.3 (*c* 1.55, $CHCl_3$); ν_{max}(neat) 3110–3620, 1674 cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.32 (3H, s, *Me*), 1.51 (3H, s, *Me*), 1.60–1.80 (2H, m, *H*6), 1.81–1.98 (2H, m, *H*7), 2.01–2.22 (2H, m, *H*8), 3.41–3.60 (2H, m, *H*9), 3.98 (1H, dd, *J*=3.0, 1.8 Hz, *H*4), 4.13 (1H, d, *J*=1.8 Hz, *H*3), 4.28–4.35 (1H, m, *H*5), 4.47 (1H, d, *J*=3.6 Hz, *H*2), 5.13 (2H, ABq, *J*=12.3 Hz, CH_2Ph), 5.87 (1H, d, *J*=3.6 Hz, *H*1), 7.21–7.41 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.6, 25.2, 26.1, 26.2, 26.8, 40.0, 48.9, 66.9, 74.6, 77.6, 85.4, 104.1, 111.1, 127.3, 127.5, 128.2, 136.8, 156.2.

3.1.12. (1*R*,2*R*,3*S*,9a*R*)-Octahydro-2*H*-quinolizine-1,2,3-triol (3a). A solution of **10a** (0.100 g, 0.26 mmol) in TFA–H_2O (2 mL, 3/2) was stirred at 25 °C for 2 h. Trifluroacetic acid was co-evaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. To a solution of above product in methanol (5 mL) was added 10% Pd/C (0.01 g) and solution was hydrogenated at 80 psi for 16 h. The solution was filtered through Celite and washed with methanol and the filtrate concentrated to get a sticky solid which was purified by column chromatography (5% MeOH/$CHCl_3$) to give **3a** (0.042 g, 85%) as a thick liquid; [Found: C, 51.51; H, 10.99. $C_9H_{17}NO_3 3H_2O$ requires C, 51.65; H, 11.08%]; R_f (30% chloroform/methanol) 0.29; $[\alpha]_D$ −36.0 (*c* 0.2, MeOH); ν_{max}(neat) 3676–3250 cm^{-1}; δ_H (300 MHz, D_2O) 1.24–1.53 (2H, m, *H*7), 1.55–1.72 (1H, m, *H*9), 1.79–1.98 (3H, m, *H*8, *H*9), 2.26 (1H, brd, *J*=13.2 Hz, $H6_a$), 2.60–2.86 (3H, m, *H*4, $H6_b$), 3.22–3.36 (2H, m, *H*1, *H*9a), 3.41 (1H, t, *J*=9.5 Hz, *H*2), 3.69 (1H, dt, *J*=9.5, 4.5 Hz, *H*3); δ_C (75 MHz, D_2O) 21.6, 23.4, 26.9, 55.3, 56.8, 65.0, 67.0, 72.7, 76.5.

3.1.13. (1*R*,2*R*,3*S*,9a*S*)-Octahydro-2*H*-quinolizine-1,2,3-triol (3b). The reaction of **10b** (0.13 g, 0.34 mmol) with TFA–H_2O (3 mL, 3/2) followed by hydrogenation with 10% Pd/C (0.02 g) as reported for **3a**. Column chromatography (10% MeOH/$CHCl_3$) afforded **3b** (0.058 g, 91%) as a thick liquid; [Found: C, 51.95; H, 10.30. $C_9H_{17}NO_3.2H_2O$ requires C, 52.15; H, 10.21%]; R_f (30% chloroform/methanol) 0.25; $[\alpha]_D$ −80.0 (*c* 0.1, MeOH); ν_{max}(neat)

3640–3180 cm^{-1}; δ_H (300 MHz, D_2O) 1.42–1.80 (6H, m, *H*7, *H*8, *H*9), 2.79–2.91 (1H, m, $H6_a$), 3.15–3.38 (4H, m, *H*4, $H6_b$, *H*9a), 3.65 (1H, bs, W_H 6 Hz, *H*3), 3.87 (2H, bs, W_H 6 Hz, *H*2, *H*1); δ_C (75 MHz, D_2O) 21.7, 22.9, 25.7, 55.7, 61.6, 66.4, 67.2, 70.2 (strong).

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References and notes

1. For reviews see: (a) Padwa, A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123. (b) Tufariello, J. J. In *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 9, p 83. (c) In *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 9, p 277. (d) Balasubramanian, N. *Org. Prep. Proced.* **1985**, *17*, 23. (e) Torssell, K. B. G. Nitrile oxides, nitrones and nitronates. *Organic synthesis*; VCH: New York, 1988. (f) Wade, P. A. Intramolecular 1,3-dipolar cycloadditions. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 1111. (g) Fisera, L.; Al-Timari, U. A. R.; Ertl, P. *Cycloadditions in carbohydrate chemistry*. *ACS Monograph*; American Chemical Society: Washington, 1992; p 158. (h) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (i) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (j) Merino, P.; Tejero, T. *Molecules* **1999**, *4*, 169. (k) Osborn, H.; Gemmell, N.; Harwood, L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.
2. Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695, and references cited therein.
3. (a) Merino, P.; Castello, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Teterahedron* **1998**, *54*, 12301. (b) Merino, P.; Franco, S.; Gascon, J. M.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1867. (c) Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tunon, V.; Tejero, T. *Synth. Commun.* **2000**, 2989. (d) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
4. (a) Dhavale, D.; Desai, V.; Sindkhedkar, M.; Mali, R.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, 1475. (b) Saha, N.; Desai, V.; Dhavale, D. *Tetrahedron* **2001**, 39.
5. (a) Hughes, A. B.; Rudge, A. *J. Nat. Prod. Rep.* **1994**, *11*, 135. (b) Sears, P.; Wong, C. *J. Chem. Soc., Chem, Commun.* **1998**, 1161. (c) Butters, T. D.; Van den Brock, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormold, M. R.; Dwek, R. A.; Platt, F. M. *Tetrahedron: Asymmetry* **2000**, *11*, 113. (d) Elbein, A. D.; Molyneux, R. J. *Alkoloids: chemical and biological prespectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1, p 1. (e) Howard, A. S.; Micheal, J. P. *Alkoliods (N.Y.)* **1986**, *28*, 183. (f) Micheal, J. P. *Nat. Prod. Rep.* **1990**, 485. (g) Asano, N.; Nash, R.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (h) Elbein, A. D.; Molyneux, R. J. Alkaloid glycosidase inhibitors. *Comprehensive natural products chemistry*; Barton, D., Nakanishi, K., Meth-cohn, O., Eds.; Elsevier: Oxford, 1999; Vol. 3, p 129. (i) Sears, P.; Wong, C.-H. *Chem. Commun.* **1998**, 1161. (j) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (k) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (l) Kaushal, G. P.; Elbein, A. D. *Meth. Enzymol.* **1994**, *230*, 316. (m) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (n) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (o) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171. (p) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471. (q) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (r) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J. *Phytochemistry* **2001**, *56*, 265. (s) Michael, J. P. *Nat. Prod. Rep.* **2002**, *18*, 719.
6. Jones, T.; Gorman, J.; Snelling, R.; Delabie, J.; Blum, M.; Garraffo, H.; Jain, P.; Daly, J.; Spande, T. *J. Chem. Ecol.* **1999**, *25*, 1179.
7. (a) Michael, J. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Michael, J. *Nat. Prod. Rep.* **2000**, *17*, 579. (c) Gradnig, G.; Berger, A.; Stutz, A. *Tetrahedron Lett.* **1991**, *32*, 4889. (d) Liu, P.; Rogers, R.; Kang, M.; Sankara, P. *Tetrahedron Lett.* **1991**, *32*, 5853. (e) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Sztaricskai, F. *Tetrahedron* **1995**, *51*, 2969. (f) Carretero, J.; Arrayas, R.; Gracia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (g) Overkleeft, H.; Bruggeman, P.; Pandit, U. *Tetrahedron Lett.* **1998**, *39*, 3869. (h) Pearson, W.; Hembre, E. *J. Org. Chem.* **1996**, *61*, 5537. (i) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (j) Gebarowski, P.; Sas, W. *Chem. Commun.* **2001**, 915. (k) Pandit, U. K.; Overkleeft, H.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959.
8. (a) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1997**, *62*, 7482. (b) Dhavale, D.; Saha, N.; Desai, V. *J. Org. Chem.* **1999**, *64*, 1715. (c) Dhavale, D.; Saha, N.; Desai, V. *J. Chem. Soc., Chem. Commun.* **1999**, 1719. (d) Patil, N.; Tilekar, J.; Dhavale, D. *Tetrahedron Lett.* **2001**, *42*, 747. (e) Dhavale, D.; Patil, N.; John, S.; Sabharwal, S. *Bioorg. Med. Chem.* **2002**, *10*, 2155. (f) Dhavale, D.; Saha, N.; Desai, V.; Tilekar, J. *Arkivoc* **2002**, *VII*, 91. (g) Patil, N.; Tilekar, J.; Jadhav, H.; Dhavale, D. *Tetrahedron* **2003**, *59*, 1873. (h) Patil, N.; Tilekar, J.; Dhavale, D. *J. Org. Chem.* **2001**, *66*, 1065.
9. Pandit, U. K. et al. claimes the synthesis of **3b**, no spectral and analytical data is given for the compound **3b**, See Ref. 7g.
10. (a) Dondoni, A.; Franco, S.; Merchan, F.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505. (c) Merchan, F.; Merino, P.; Rojo, I.; Tejero, T.; Dondoni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 667. (d) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059. (e) Trombini, C.; Dhavale, D. *Heterocycles* **1992**, *34*, 2253. (f) Trombini, C.; Dhavale, D. *J. Chem. Soc. Chem. Commun.* **1992**, 1268. (g) Camiletti, C.; Dhavale, D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3157. (h) Camiletti, C.; Dhavale, D.; Donati, F.; Trombini, C. *Tetrahedron Lett.* **1995**, *36*, 7239.
11. Cornia, M.; Casiraghi, G. *Tetrhedron* **1989**, *45*, 2869.
12. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrhedron Lett.* **1968**, 2199. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrhedron Lett.* **1968**, 2205. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
13. Houk, K. N.; Paddon-Row, N. M.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.
14. Burgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065.
15. The ^1H and ^{13}C NMR spectra of compounds **7a**, **8a**, and **7b**, **8b**, in which a *N*-Cbz group is present, showed doubling of

signals. This was due to isomerisation by restricted rotation around C=N, see: In *Applications of NMR spectroscopy in organic chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon: Elmsford, NY, 1978; p 361. An analogous observation was also noticed by us and others see Ref. 8h.

16. Here also we have observed an analogues observation as in case of **9a** and **9b**. The ^{1}H NMR data of **10a** and **10b** showed coupling constant between H4 and H5 as 9.9 and 3.0 Hz, respectively, (for **9a** and **9b** $J_{4,5}$ is 9.3 and 4.8 Hz). Similar findings we have reported earlier see Ref. 8h.
17. Although, the OH substituents are equatorial in the conformation **B**, the butane–gauche interactions destabilize this conformation while; in the conformation **C** the butane–guache interactions are minimum and in addition the intramolecular hydrogen bonding in the six membered transition state stabilize the conformation **C** for **3b**. The counting of butane–guache interactions in the decalin systems reveal three such interactions in the cis isomer and none in the *trans*. Therefore, the calculated difference in heats of formation between the decalins is 2.7 kcal/mol, the *trans* isomer being the more stable. See: In *Stereochemistry of organic compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; p 777.

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A novel synthesis of substituted quinolines using ring-closing metathesis (RCM): its application to the synthesis of key intermediates for anti-malarial agents

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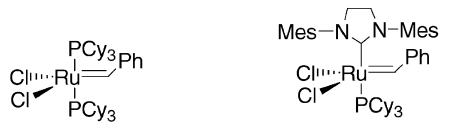
Abstract—A method for synthesizing substituted quinolines using ruthenium-catalyzed ring-closing metathesis as a key step has been developed. Substituted 1,2-dihydroquinolines, 4-silyloxy-1,2-dihydroquinoline and 4-methoxy-1,2-dihydroquinoline, were successfully synthesized in excellent yields via ene–ene metathesis and silyl or alkyl enol ether–ene metathesis, respectively. The synthetic intermediates of the antimalarial agents quinine, chloroquine, and PPMP–quinine hybrid were efficiently synthesized by this methodology.

Quinolines are a major class of alkaloids and play an important role in the fields of natural products and medicinal chemistry. Several methods for synthesizing quinoline have been known since the late 1800s.[1] However, despite their versatility, these conventional methods have several drawbacks. First, these reactions usually require high temperature and/or strongly acidic conditions, which lead to the decomposition of products and a tedious isolation procedure. Regioselectivity is another problem with the intramolecular electrophilic substitution of unsymmetrically substituted aniline derivatives. To overcome these problems, modern synthetic methods for quinoline using a transition metal-catalyst, such as ruthenium, palladium, rhodium, iron, copper, manganese or cobalt, have been investigated.[2]

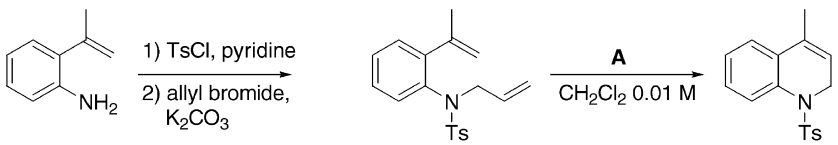


A B

Figure 1. Ruthenium carbene catalysts.

We have been studying the synthesis of some nitrogen-containing cyclic compounds by ring-closing metathesis (RCM) using ruthenium carbene catalysts **A**[3] and **B**[4] (Fig. 1).[5] We previously developed a novel method for synthesizing substituted 1,2-dihydroquinolines using ene–ene metathesis and silyl or alkyl enol ether–ene metathesis, which proceeds under mild conditions and gives an excellent yield.[6] This process leads to spontaneous air oxidation to quinoline after deprotection. In this article, we report the details of this reaction and its application to the synthesis of key intermediates for antimalarial agents, such as quinine, chloroquine, and PPMP–quinine hybrid.

We first investigated RCM conditions for α,ω-diene **1** derived from commercially available 2-isopropenylaniline (Scheme 1). When **1** was reacted with 30% Grubbs' catalyst **A** in CH_2Cl_2 (0.01 M, degassed by freezed–pump–thaw



1 2

Scheme 1. Synthesis of 1,2-dihydroquinoline **2** using RCM.

Keywords: Quinine; Chloroquine; Quinoline alkaloid; Anti-malaria; Ring-closing metathesis (RCM); Silylenol-ether.
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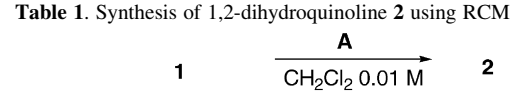
Table 1. Synthesis of 1,2-dihydroquinoline **2** using RCM

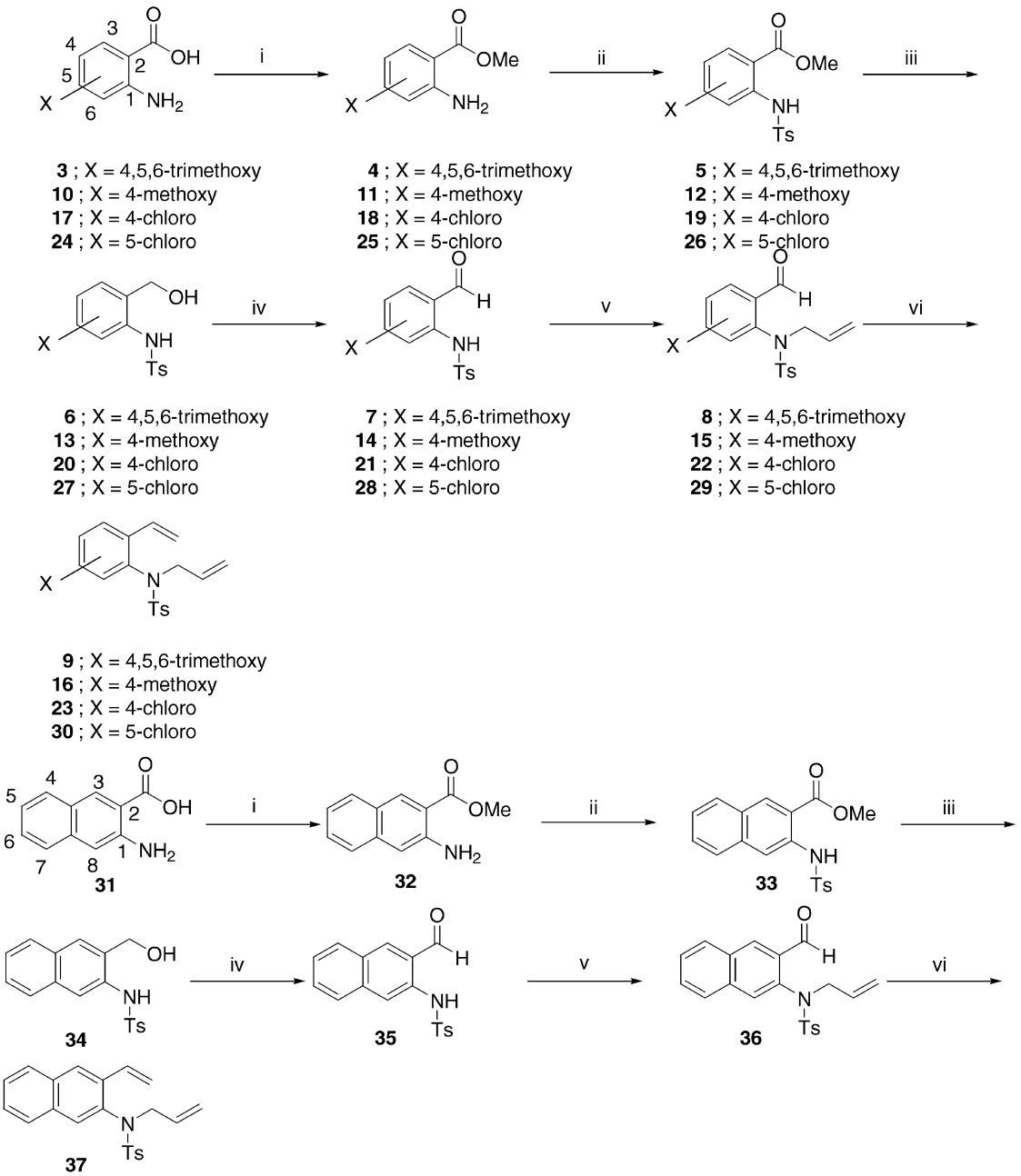


Run	Catalyst **A** (mol%)	Conditions		Yield (%)
1	30	Room temperature	3 h	94
2	5	Room temperature	3 h	72
3	5	Reflux	1 h	92

(FPT) cycle) at room temperature for 3 h, the corresponding 1,2-dihydroquinoline **2** was obtained in 94% yield (Table 1, run 1), whereas the use of 5 mol% of catalyst **A** reduced the yield to 72% (run 2). However, the reaction at reflux temperature gave **2** in 92% yield within 1 h (run 3).

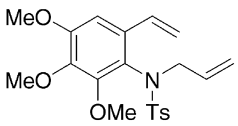
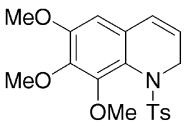
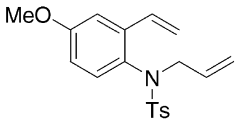
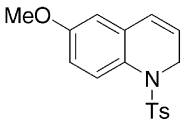
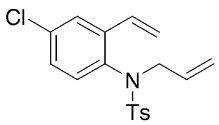
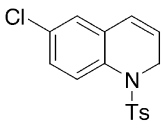
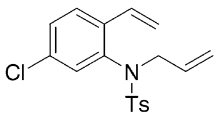
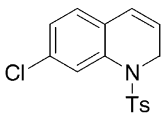
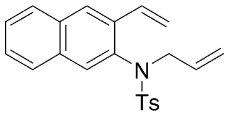
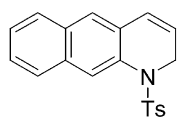
Under these optimized reaction conditions, we examined the scope and limitations of RCM for 1,2-dihydroquinoline synthesis. Various dienes were prepared from anthranilic acid derivatives (Scheme 2) and subjected to RCM reaction. The results are summarized in Table 2.

Initially, dienes (**9**, **16**, **23**, **30**, **37**) were subjected to the optimized RCM conditions described above. As a result, cyclized 1,2-dihydroquinolines (**38**–**42**) were isolated in good to excellent yields, regardless of the substitution pattern on the aromatic ring (–OMe, runs 1 and 2 or –Cl, runs 3–5). Benzoquinoline was obtained in 98% yield (run 6). According to recent reports, catalyst **B** is more reactive in a metathesis reaction.[4] Therefore, substrate **30** was re-examined with catalyst **B**, which confirmed its superior



Scheme 2. Preparation of α,ω-dienes. (i) $Me_2C(OMe)_2$, HCl; (ii) TsCl, pyridine; (iii) DIBAH; (iv) MnO_2, benzene; (v) allyl bromide, K_2CO_3; (vi) $Ph_2P{=}CH_2$.

Table 2. RCM of dienes **9**, **16**, **23**, **30** and **37** using catalysts **A** and **B**[a]

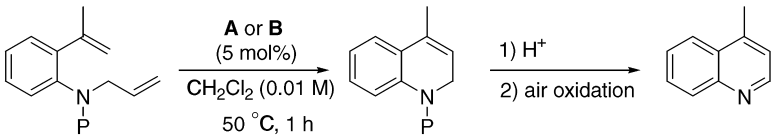
Run	Substrate		Ru-catalyst	Product		Yield (%)
1		**9**	**A**		**38**	90
2		**16**	**A**		**39**	95
3		**23**	**A**		**40**	90
4		**30**	**A**		**41**	74
5			**B**			100
6		**37**	**A**		**42**	98

[a] Conditions: 5 mol% of catalyst **A** or **B** in CH_2Cl_2 (0.01 M, degassed) under Ar for 1 h at reflux temperature.

efficacy, the desired chloroquinoline **41** was obtained in 100% yield.

Having established the RCM conditions, we next examined the effect of protecting groups on nitrogen. Dienes **43a**–**43c**, which were readily prepared from the commercially available *o*-aminostyrene, were reacted with both Grubbs' catalysts **A** and **B**. The reaction of *N*-benzyl derivative **43a** with catalyst **A** gave **44a** in excellent yield (Table 3, run 1), while *N*-acetyl derivative **43b** did not give the desired cyclized product (run 2). In this case, catalyst **A** probably reacted with the terminal double bond in **43b** to form a chelated intermediate **46**, which prohibited further RCM. When *N-tert*-butoxycarbonyl derivative **43c** was treated with catalyst **A** under similar conditions, 1,2-dihydroquinoline **44c** was obtained in modest yield. On the other hand, with catalyst **B**, the yields of **43b** and **43c** dramatically increased to give **44b** and **44c**, respectively, in almost quantitative yields (runs 3 and 5). The protective groups on nitrogen of products **44a**–**c** were readily removed during

Table 3. Effect of protective groups on nitrogen



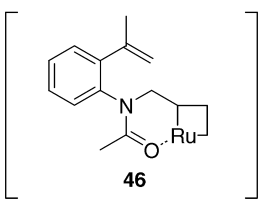
43

43a ; P = Bn
43b ; P = Ac
43c ; P = Boc

44

44a ; P = Bn
44b ; P = Ac
44c ; P = Boc

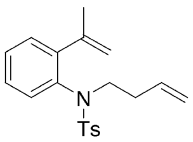
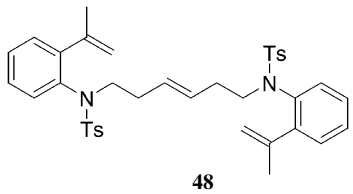
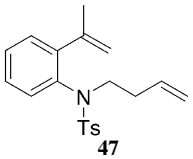
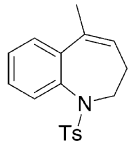
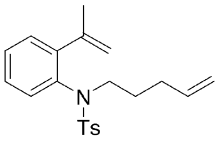
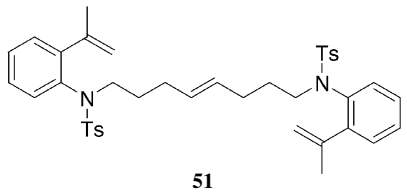
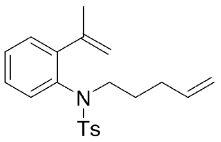
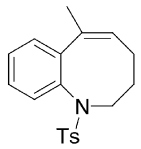
45



46

Run	Substrate	Ru-catalyst	Product (%)
1	**43a**	**A**	**45** (95)
2	**43b**	**A**	**45** (0)
3	**43b**	**B**	**45** (98)
4	**43c**	**A**	**45** (63)
5	**43c**	**B**	**45** (97)

Table 4. Effect of Ru-catalysts on the RCM of dienes **47** and **50**

Run	Substrate	Ru-catalyst	Product	Yield (%)
1	 **47**	**A**	 **48**	100
2	 **47**	**B**	 **49**	100
3	 **50**	**A**	 **51**	95
4	 **50**	**B**	 **52**	99

silica gel column chromatography to give 1,2-dihydroquinolines, which were spontaneously oxidized to give 4-methylquinoline **45** quantitatively.

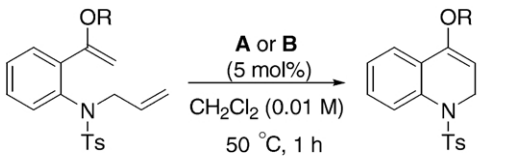
We next investigated a similar RCM for medium-sized rings such as in benzoazepine and benzoazocine. Dienes **47** and **50** were subjected to the above reaction conditions using both Grubbs' catalysts **A** and **B**. The reaction of **47** and **50** in the presence of catalyst **A** gave only the dimeric products **48** and **51**, respectively. In sharp contrast, the corresponding benzoazepine **49** and benzoazocine **52** were obtained with catalyst **B** in excellent yields (Table 4). Interestingly, isolated **48** and **51** were converted to **49** (5 h, 98%) and **52** (6 h, 97%), respectively, under the same conditions using catalyst **B**.

Many quinoline alkaloids which show important bioactivities, such as quinine and chloroquine, contain substituents at the 4-position. Therefore, we next focused our attention on extending this reaction to the synthesis of 4-substituted quinolines. For this purpose, we studied the synthesis of 4-methoxy- and 4-siloxy-1,2-dihydroquinolines, which, in turn, could be converted to various 4-substituted quinolines, using ene–enol ether metathesis (Table 5).

Enol methyl ether **53a** and enol silyl ether **53b** were prepared from commercially available *o*-aminoacetophenone and subjected to our reaction conditions using Grubbs' catalysts **A** and **B**, respectively. Surprisingly, when enol methyl ether **53a** and enol silyl ether **53b** were treated with **A**, the cyclized product was not obtained at all and the starting materials were recovered (runs 1 and 3). In contrast, treatment of the same substrates with Grubbs' catalyst **B** gave the corresponding 4-methoxy-1,2-dihydroquinoline **54a** and 4-siloxy-1,2-dihydroquinoline **54b** in 95% yield, respectively (runs 2 and 4). This novel synthetic method could be applied to large-scale, multigram, syntheses.

In the general procedure for RCM, degassing of the solution is an important process to prevent deactivation of the catalyst, although the highly active catalyst **B** was designed to tolerate oxygen, moisture and some impurities in the solvent.[7] High dilution was also required, such as 0.01 and

Table 5. Effect of Ru-catalyst on the ene–enol metathesis of **53a** and **53b**



53a ; R = Me
53b ; R = TBS

54a ; R = Me
54b ; R = TBS

Run	Substrate	Ru-catalyst	Concentration (M)	Product (%)
1	**53a**	**A**	0.01[a]	**54a** (0)
2	**53a**	**B**	0.01[a]	**54a** (95)
3	**53b**	**A**	0.01[a]	**54b** (0)
4	**53b**	**B**	0.01[a]	**54b** (95)
5	**53b**	**B**	0.01[b]	**54b** (99)
6	**53b**	**B**	0.1[a]	**54b** (96)
7	**53b**	**B**	0.1[b]	**54b** (97)

[a] Degassed conditions.
[b] Without degassing.

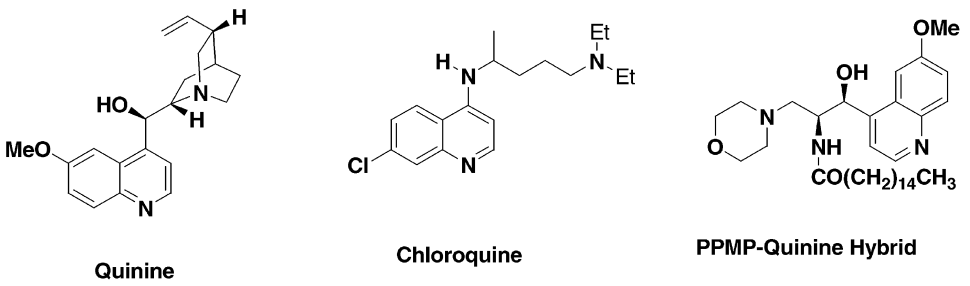


Figure 2. Natural products with anti-malarial activity.

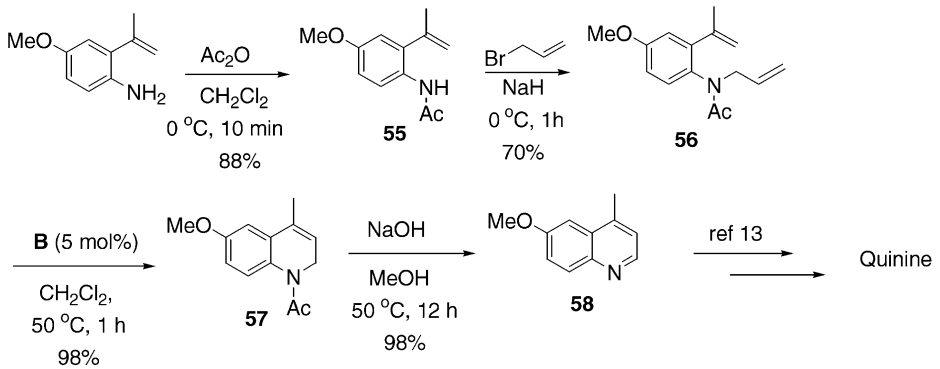
0.001 M, to prevent an intermolecular reaction, however this procedure is inconvenient, especially in large-scale synthesis. Thus, we tried this silyl enol ether–ene metathesis without degassing at a concentration of 0.1 M. As a result, the reaction of **53b** in 0.01 M solution gave **54b** in almost quantitative yield regardless of degassing the reaction mixture (runs 5 and 7).

Encouraged by these results, we applied this novel method to the synthesis of key intermediates of anti-malarial agents, such as quinine,[8] chloroquine,[9]and PPMP–quinine hybrid,[10] which are shown in Figure 2.

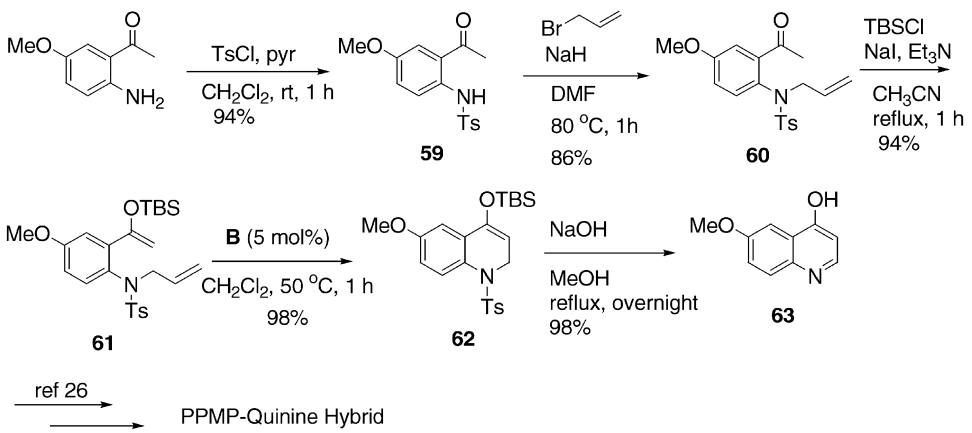
Malaria is one of the world's most devastating human infections and causes millions of deaths every year. Some effective anti-malarial agents are currently available, such as quinine, chloroquine, mefloquine, premaquine, and arteminicin. However, the development of new anti-malarial agent is still required against resistant Plasmodium species, the most virulent of malarias. We previously reported the synthesis of an inhibitor of sphingolipid synthase, PPMP (1-phenyl-2-palmitoylamino-3-morpholino-1-propanol),[10] which has been reported to have anti-malarial activity by Haldar.[11] A PPMP–quinine hybrid is an interesting potential anti-malarial agent.

Acetylation of 2-isopropenyl-4-methoxyaniline[12] gave **55** in 88% yield, which was in turn allylated with allyl bromide in the presence of sodium hydride to provide **56** in 70% yield. Highly efficient RCM was achieved by treatment of **56** with catalyst **B** (5 mol %) at 50 °C for 1 h to give the corresponding 1,2-dihydroquinoline **57** in 98% yield. The acetyl group was removed by treatment of NaOH in MeOH to give 4-methyl-6-methoxyquinoline (**58**),[13] a key intermediate for the synthesis of quinine, in 98% yield (Scheme 3).

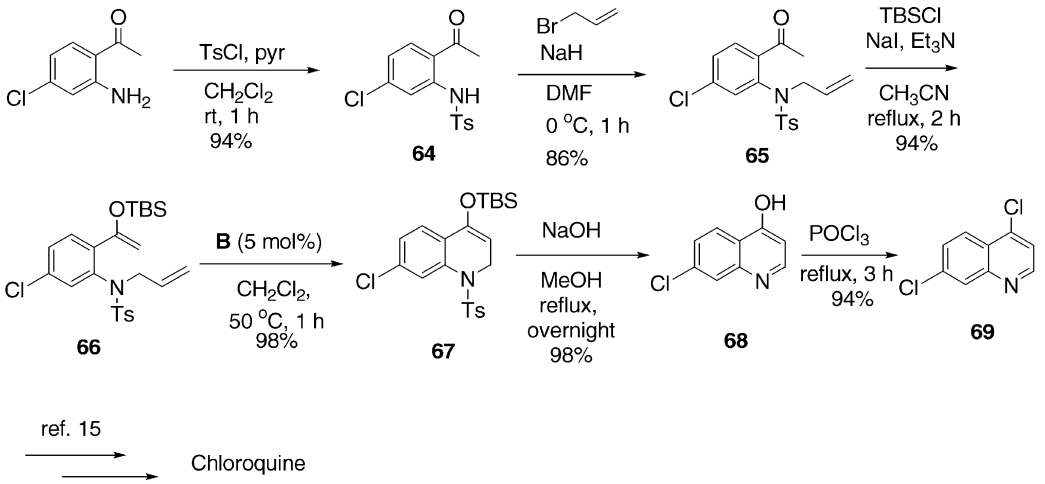
The synthesis of 4-hydroxy-6-methoxyquinoline as a key



Scheme 3. Preparation of 4-methyl-6-methoxy-quinoline (**58**).



Scheme 4. Preparation of 4-hydroxy-6-methoxy-quinoline (**63**).[26]



Scheme 5. Preparation of 4,7-dichloro-quinoline (**69**).

intermediate of PPMP–quinine hybrid is demonstrated to emphasize the effectiveness of RCM.

2-Amino-5-methoxyacetophenone, prepared according to a procedure developed by Fürstner and co-workers,[14] was converted to **60** by tosylation followed by allylation. Allylated **60** was transformed to silyl enol ether **61**, which was readily subjected to silyl enol ether–ene metathesis. The expected 1,2-dihydroquinoline (**62**) was obtained with catalyst **B** at 50 °C in CH_2Cl_2 (0.01 M) for 1 h. Subsequent deprotection of both the silyl and tosyl groups gave **63** in excellent yield (Scheme 4).

4,7-Dichloroquinoline (**69**), a key intermediate for chloroquine synthesis,[15] was also prepared in 6 steps from 2-amino-6-chloroacetophenone by a similar methodology (Scheme 5). Tosylation of 2-amino-6-chloroacetophenone[14] followed by *N*-allylation gave **65**, which was converted to silyl enol ether **66**. RCM of **66** using catalyst **B** at 50 °C in CH_2Cl_2 (0.01 M) for 1 h gave **67** in 98% yield. Deprotection of the silyl and tosyl groups of **67** afforded **68**. Treatment of **68** with $POCl_3$ gave the 4,7-dichloroquinoline (**69**)[16] in 92%.

1. Conclusion

The development of a novel method for synthesizing substituted quinolines and 1,2-dihydroquinolines was achieved by applying RCM using well-defined Grubbs' catalysts and α,ω-dienes, prepared from anthranilic acid, *o*-isopropylaniline and *o*-aminoacetophenone. The reaction proceeded efficiently under mild conditions, which are suitable for the large-scale synthesis of substituted quinolines. Moreover, the highly regioselective synthesis of cyclic silyl enol ether was also developed as a powerful method for synthesizing 4-hetero-substituted quinolines. The utility of this novel quinoline synthesis was demonstrated by the efficient synthesis of 4-methyl-6-methoxyquinoline, the key intermediate for quinine, 4,7-dichloroquinoline, the key intermediate of chloroquine, and 4-hydro-6-methoxyquinoline, the key intermediate of PPMP–quinine hybrid. We believe that these findings could lead to a new methodology for the synthesis of antimalarial agents as well as other biologically active natural products containing a quinoline ring system.

2. Experimental

2.1. General

All melting points are uncorrected. ^1H NMR (and ^{13}C NMR) spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 400 MHz, with TMS as an internal standard. Silica gel 60 N (Spherical, neutral, Kanto Chemical Co., Inc.) was used for column chromatography and E. Merck precoated TLC plates, silica gel $60F_{254}$, were used for preparative thin layer chromatography. The organic layers were dried over anhydrous Na_2SO_4. Ruthenium carbene catalysts **A** and **B** and substrates **4**, **18**, **24**, and **31** were obtained commercially.

2.1.1. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-isopropenylaniline (1). To a solution of 2-isopropenylaniline (400 mg, 3.00 mmol) in 20 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.72 mL, 9.00 mmol) and TsCl (686 mg, 3.60 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of water. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 838 mg (97%) of *N*-*p*-toluenesulfonyl-2-isopropenylaniline as off white solid.

To a solution of *N*-*p*-toluenesulfonyl-2-isopropenylaniline (241 mg, 0.84 mmol) and K_2CO_3 (174 mg, 1.26 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.15 mL, 1.26 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 266 mg (97%) of **1** as white plates.

Mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (2H, d, J=8.3 Hz), 7.27–7.31 (4H, m), 7.12 (1H, ddd, J=2.4, 7.8, 6.6 Hz), 6.74 (1H, d, J=8.0 Hz), 5.69 (1H, dddd, J=6.8, 6.9, 11.2, 17.1 Hz), 5.22 (1H, dd, J=1.4, 1.6 Hz), 5.05 (1H, dd, J=0.9, 1.2 Hz), 4.98 (1H, d, J=3.1 Hz), 4.94 (1H, dd, J=1.4, 11.2 Hz), 4.12 (2H, d, J=6.9 Hz), 2.44 (3H, s), 2.18 (3H, s); ^{13}C NMR ($CDCl_3$) δ 144.9, 143.6, 143.4, 136.9, 136.4, 132.6, 130.1, 129.4, 128.6, 128.2, 128.1, 127.2, 119.2, 116.6, 54.6, 24.3, 21.5: IR (KBr) 3461, 3070, 2958, 2902, 2865, 1646, 1596, 1491, 1450, 1341; HRMS (FAB) calcd for $C_{19}H_{22}NO_2S$ 328.1371, found 328.1348.

2.1.2. *N*-*p*-Toluenesulfonyl-4-methyl-1,2-dihydroquinoline (2). To a solution of olefin **1** (80 mg, 0.24 mmol) in 24 mL of CH_2Cl_2 under an Ar atmosphere, was added Grubbs' catalyst **A** (10.2 mg, 0.012 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1), and then recrystallized from *n*-hexane/AcOEt to give 66 mg (92%) of **2** as colorless needles. Mp 82 °C (lit.[17] 105–106 °C from methanol); ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, dd, J=1.5, 8.1 Hz), 7.30 (1H, ddd, J=1.4, 7.6, 7.6 Hz), 7.21–7.26 (3H, m), 7.11 (1H, dd, J=1.5, 7.6 Hz), 7.05 (2H, d, J=8.3 Hz), 5.31 (1H, t, J=1.5 Hz), 4.32 (2H, d, J=2.7 Hz), 2.33 (3H, s), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.1, 136.1, 135.1, 131.6, 131.4, 128.8, 127.8, 127.4, 127.2, 126.7, 123.2, 120.3, 45.3, 21.4, 17.7; IR (KBr) 3395, 3042, 2921, 2846, 1609, 1451, 1321, 1153; LRMS (FAB) *m*/*z* 300 [10, M^++H], 299 [15, M^+], 144 [100].

2.1.3. *N*-*p*-Toluenesulfonyl-3,4,5-trimethoxyanthranilic acid methyl ester (5). To a solution of 3,4,5-trimethoxyanthranilic acid methyl ester (2.40 g, 10.0 mmol) in 40 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (2.4 mL, 30.0 mmol) and TsCl (2.29 g, 12.0 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from acetone to give 3.28 g (83%) of **5** as white needles. Mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 8.96 (1H, s), 7.71 (2H, d, J=8.3 Hz), 7.26 (2H, d, J=8.3 Hz), 7.16 (1H, s), 3.90 (3H, s), 3.86 (3H, s), 3.80 (3H, s), 3.41 (3H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.31, 150.43, 148.35, 146.76, 142.93, 137.72, 128.96, 127.17, 127.13, 117.66, 108.28, 60.90, 60.12, 56.08, 52.32, 21.38; IR (KBr) 3163, 2933, 1684; LRMS (FAB) *m*/*z* 396 [40, M^++H], 395 [40, M^+], 241 100]. Anal. Calcd for $C_{18}H_{21}NO_7S$; C, 54.67; H, 5.35; N, 3.54; found C, 54.64; H, 5.41; N, 3.52.

2.1.4. *N*-*p*-Toluenesulfonyl-2-hydroxymethyl-4,5,6-trimethoxyaniline (6). To a cooled (−78 °C) solution of ester **5** (3.28 g, 8.30 mmol) in 50 mL of toluene under an Ar atmosphere, was added a solution of DIBAL in toluene (1 M, 24.9 mL, 24.9 mmol). The mixture was stirred at −78 °C for 1 h and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt, then the solution was allowed to stir at room temperature until it was separated into two layers. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane/AcOEt to give 222 mg (73%) of **6** as colorless needles. Mp 166–167 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.5 Hz), 6.82 (1H, s), 6.33 (1H, br), 4.75 (2H, s), 3.89 (3H, s), 3.60 (3H, s), 3.29 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.21, 148.04, 143.65, 140.35, 136.25, 135.54, 129.19, 127.71, 119.36, 107.75, 61.60, 60.49, 60.15, 55.94, 21.35; IR (KBr) 3518, 3181, 2929; LRMS (FAB) *m*/*z* 368 [20, M^++H], 367 [57, M^+], 212 [100]. Anal. Calcd for $C_{17}H_{21}NO_6S$; C, 55.57; H, 5.76; N, 3.81; found C, 55.55; H, 5.75; N, 3.79.

2.1.5. *N*-*p*-Toluenesulfonyl-2-formyl-4,5,6-trimethoxyaniline (7). To a solution of alcohol **6** (500 mg, 1.36 mmol) in 70 mL of benzene, was added MnO_2 (355 mg, 4.08 mmol). The mixture was refluxed for 4 h and filtered through a celite pad. After removal of the solvent, the residue was purified by recrystallization from acetone to give 309 mg (62%) of **7** as a white amorphous solid. Mp 97–99 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (1H, s), 7.49 (2H, d, J=8.3 Hz), 7.22 (1H, s), 7.21 (2H, d, J=8.1 Hz), 7.03 (1H, br), 3.92 (3H, s), 3.75 (3H, s), 3.31 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 189.53, 152.41, 147.09, 145.94, 144.06, 135.81, 129.42, 127.60, 127.52, 125.42, 105.42, 60.78, 60.51, 56.12, 21.48; IR (KBr) 3248, 1685, 1164; LRMS (FAB) *m*/*z* 366 [30, M^++H], 365 [30, M^+], 211 [100]. Anal. Calcd for $C_{17}H_{19}NO_6S$; C, 55.88; H, 5.24; N, 3.83; found C, 55.49; H, 5.43; N, 3.72.

2.1.6. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-formyl-4,5,6-trimethoxyaniline (8). To a solution of aldehyde **7** (0.79 g, 2.17 mmol) and K_2CO_3 (0.45 g, 3.26 mmol) in 60 mL of DMF under an Ar atmosphere, was added allyl bromide (0.28 mL, 3.26 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give 875 mg (99%) of **8** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 10.04 (1H, s), 7.61 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.4 Hz), 7.22 (1H, s), 5.71–5.81 (1H, m), 5.00–5.05 (2H, m), 4.59 (1H, dd, J=5.7, 14.1 Hz), 3.98 (1H, dd, J=8.4, 14.1 Hz), 3.92 (3H, s), 3.82 (3H, s), 3.52 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 189.86, 154.03, 151.35, 146.53, 143.51, 136.91, 132.39, 131.95, 129.52, 127.55, 127.07, 120.02, 103.98, 60.74, 60.45, 56.03, 53.75, 21.49; IR (neat) 2945, 2845, 1688; HRMS (FAB) calcd for $C_{20}H_{24}NO_6S$ 406.1324, found 406.1314.

2.1.7. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-ethenyl-4,5,6-trimethoxyaniline (9). To a cooled (−78 °C) solution of $BrPh_3PMe$ (2.30 g, 6.48 mmol) in 72 mL of THF under an Ar atmosphere, was added a solution of $KN(TMS)_2$ in THF (0.5 M, 13 mL, 6.48 mmol). The mixture was stirred at −78 °C for 15 min. Then, aldehyde **8** (875 mg, 2.16 mmol) was added to this solution, and the mixture was warmed to room temperature with stirring for 1 h. The solution was quenched by the addition of saturated aqueous Rochelle's salt. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue

was purified by recrystallization from *n*-hexane/AcOEt to give 760 mg (87%) of **9** as white prisms. Mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.1 Hz), 6.88 (1H, dd, J=11.0, 17.8 Hz), 6.83 (1H, s), 5.70–5.77 (1H, m), 5.63 (1H, d, J=17.6 Hz), 5.22 (1H, d, J=12.0 Hz), 4.95–4.99 (2H, m), 4.29 (1H, dd, J=6.1, 14.2 Hz), 3.97 (1H, dd, J=7.8, 14.4 Hz), 3.90 (3H, s), 3.77 (3H, s), 3.63 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.72, 151.81, 142.90, 141.24, 137.87, 134.72, 133.47, 133.12, 129.21, 127.80, 122.46, 118.68, 114.80, 102.04, 60.63, 60.41, 55.77, 53.71, 21.47; IR (KBr) cm^{-1} 2942, 1491, 1334; LRMS (FAB) *m/z* 404 [23, M$^+$+H], 149 [100]. Anal. Calcd for $C_{21}H_{25}NO_5S$; C, 62.51; H, 6.25; N, 3.47; found C, 62.29; H, 6.36; N, 3.42.

2.1.8. *N*-*p*-Toluenesulfonyl-6,7,8-trimethoxy-1,2-dihydroquinoline (38). To a solution of olefin **9** (100 mg, 0.29 mmol) in 29 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **A** (12.2 mg, 0.0245 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give 98 mg (90%) of **38** as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, J=8.2 Hz), 7.15 (2H, d, J=8.2 Hz), 6.28 (1H, s), 5.94 (1H, d, J=9.5 Hz), 5.50 (1H, td, J=4.2, 9.5 Hz), 4.29 (2H, br), 4.00 (3H, s), 3.90 (3H, s), 3.85 (3H, s), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 152.6, 150.6, 143.2, 142.0, 136.8, 128.9, 127.8, 126.9, 126.0, 124.6, 120.8, 104.2, 61.0, 60.8, 56.0, 45.5, 21.5; IR (KBr) 3451, 2930, 2837, 1560, 1458, 1348; LRMS (EI) *m/z* 375 [60, M$^+$], 221[100]. Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73, found: C, 60.72; H, 5.64; N, 3.60.

2.1.9. 5-Methoxyanthranilic acid (10). To a solution of 5-methoxy-2-nitrobenzoic acid (5.05 g, 25.6 mmol) in 100 mL of EtOH) was added 5% palladium on charcoal (105 mg and stirred at room temperature for 12 h under an Ar atmosphere. After the starting material was disappeared on TLC, the solution was filtered through a celite pad and solvent was removed to give 4.00 g (97%) of **10** as a violet solid. ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, d, J=1.8 Hz), 7.03 (1H, dd, J=3.1, 9.0 Hz), 6.66 (1H, d, J=8.8 Hz), 3.78 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.7, 150.6, 145.8, 124.7, 118.5, 113.3, 109.4, 55.8; IR (KBr) 3500, 2951, 2598, 1930, 1707, 1583; HRMS (FAB) calcd for $C_8H_{10}NO_3$ 168.0661, found 168.0653.

2.1.10. 5-Methoxyanthranilic acid methyl ester (11).[18] To a solution of **10** (15.0 g, 89.7 mmol) in 550 mL of 2,3-dimethoxypropane, was added 79 mL of 36% hydrochloric acid. The mixture was stirred at room temperature for 12 h and the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The product was extracted with AcOEt, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=3:1) to give 5.20 g (32%) of **11** as a yellow-orange oil. ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, d, J=3.1 Hz), 6.96 (1H, dd, J=3.1, 8.8 Hz), 6.63 (1H, d, J=8.9 Hz), 5.42 (2H, br), 3.88 (3H, s), 3.76 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.3, 150.5, 145.1, 123.3, 118.2, 113.1, 110.7, 55.8, 51.6; IR (KBr) 3373, 2995, 2952, 2837, 1691, 1593; HRMS (FAB) calcd for $C_9H_{11}NO_3$; 181.0739, found 181.0747.

2.1.11. *N*-*p*-Toluenesulfonyl-5-methoxyanthranilic acid methyl ester (12). To a solution of ester **11** (100 mg, 0.55 mmol) in 4 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.13 mL, 1.65 mmol) and TsCl (126 mg, 0.66 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 150 mg (82%) of **12** as pale yellow prisms. Mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 10.0 (1H, s), 7.66 (1H, d, J=9.2 Hz), 7.63 (2H, d, J=8.3 Hz), 7.34 (1H, d, J=2.9 Hz), 7.18 (2H, d, J=8.5 Hz), 7.04 (1H, dd, J=2.9, 9.0 Hz), 3.81 (3H, s), 3.76 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.7, 155.4, 143.6, 136.1, 133.4, 129.4, 127.2, 122.6, 120.9, 118.1, 114.6, 55.6, 52.4, 21.5; IR (KBr) 3174, 2951, 2843, 1691, 1612; LRMS (FAB) *m/z* 336 [50, M$^+$+H], 335 [80, M$^+$], 181 [100]. Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18, found: C, 57.16; H, 5.06; N, 4.10.

2.1.12. *N*-*p*-Toluenesulfonyl-2-hydroxymethyl-4-methoxyaniline (13). To a cooled (−78 °C) solution of ester **12** (5.50 g, 16.4 mmol) in 120 mL of toluene under an Ar atmosphere, was added a solution of DIBAL in toluene (1 M, 54.1 mL, 54.1 mmol). The mixture was stirred at −78 °C for 1 h and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt, then the solution was allowed to stir at room temperature until two layers were separated. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from MeOH to give 4.57 g (91%) of **13** as colorless needles. Mp 130 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (2H, d, J=8.4 Hz), 7.30 (1H, br), 7.21 (2H, d, J=7.9 Hz), 7.10 (1H, d, J=8.4 Hz), 6.74 (1H, d, J=3.1 Hz), 6.72 (1H, dd, J=3.3 Hz), 4.30 (2H, s), 3.76 (3H, s), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 158.0, 143.8, 136.6, 136.3, 129.6, 127.9, 127.4, 127.2, 114.7, 113.8, 63.1, 55.4, 21.5; IR (KBr) 3489, 3130, 2964, 2837, 1612, 1498; LRMS (FAB) *m/z* 308 [30, M$^+$+H], 307 [100, M$^+$]. Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56, found: C, 58.52; H, 5.53; N, 4.42.

2.1.13. *N*-*p*-Toluenesulfonyl-2-formyl-4-methoxyaniline (14). To a solution of alcohol **13** (75 mg, 0.24 mmol) in 10 mL of benzene, was added MnO_2 (510 mg, 0.59 mmol). The mixture was refluxed for 4 h and filtered through a celite pad. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 70 mg (91%) of **14** as yellow plates. Mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 10.22 (1H, s), 9.74 (1H, s), 7.68 (2H, d, J=8.3 Hz), 7.67 (1H, d, J=9.2 Hz), 7.20 (2H, d, J=8.1 Hz), 7.09 (1H, dd, J=2.9, 9.0 Hz), 7.05 (1H, d, J=2.9 Hz), 3.81 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 194.5, 155.7, 143.9, 136.2, 132.9, 129.6, 127.2, 123.5, 122.0, 121.0, 119.3, 55.7, 21.5; IR (KBr) 3390, 1652, 1583; LRMS (FAB) *m/z* 306 [5, M$^+$+H], 305 [7, M$^+$], 154 [100]. Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 59.00; H, 4.95; N, 4.59, found: C, 58.87; H, 5.04; N, 4.49.

2.1.14. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-formyl-4-methoxyaniline (15). To a solution of aldehyde **14** (100 mg, 0.33 mmol) and K_2CO_3 (68 mg, 0.50 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.04 mL, 0.50 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane/AcOEt to give 110 mg (97%) of **15** as orange needles. Mp 77 °C; ^{1}H NMR ($CDCl_3$) δ 10.27 (1H, s), 7.37 (2H, d, J=8.3 Hz), 7.33 (1H, d, J=3.2 Hz), 7.19 (2H, d, J=8.3 Hz), 6.88 (1H, dd, J=3.2, 8.8 Hz), 6.50 (1H, d, J=8.8 Hz), 5.62 (1H, dddd, J=6.8, 6.8, 8.5, 17.1 Hz), 4.95 (^{1}H, d, J=4.6 Hz), 4.92 (1H, d, J=11.6 Hz), 4.48 (2H, br), 3.71 (3H, br), 2.33 (3H, s); ^{13}C NMR (CDCl3) δ 190.1, 159.3, 144.1, 136.9, 134.5, 134.0, 131.7, 129.6, 129.2, 127.9, 121.5, 120.4, 110.6, 55.7, 54.5, 21.6; IR (KBr) 3367, 3068, 2864, 2750, 1693; LRMS (FAB) *m*/*z* 346 [40, M^++H], 191 [100]. Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; found: C, 62.44; H, 5.44; N, 3.93.

2.1.15. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-ethenyl-4-methoxyaniline (16). To a cooled (−78 °C) solution of $BrPh_3PMe$ (34.1 mg, 0.96 mmol) in 5 mL of THF under an Ar atmosphere, was added a solution of $KN(TMS)_2$ in THF (0.5 M, 1.91 mL, 0.96 mmol). The mixture was stirred at −78 °C for 15 min. To this solution, aldehyde **15** (110 mg, 0.32 mmol) was added and the mixture was warmed to room temperature with stirring for 1 h. The reaction was quenched by the addition of saturated aqueous Rochelle's salt. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give 107 mg (98%) of **16** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.59 (2H, d, J=6.6 Hz), 7.28 (2H, d, J=7.9 Hz), 7.10 (1H, d, J=2.9 Hz), 7.00 (1H, dd, J=2.2, 7.8 Hz), 6.67 (1H, dd, J=2.9, 8.8 Hz), 6.57 (1H, d, J=8.8 Hz), 5.67–6.77 (2H, m), 5.29 (1H, dd, J=1.2, 11.2 Hz), 5.00 (1H, dd, J=1.2, 5.8 Hz), 4.96 (1H, dd, J=1.2, 4.9 Hz), 4.23 (1H, br), 3.93 (1H, br), 3.81 (3H, s), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 159.2, 152.0, 143.4, 139.7, 136.1, 132.8, 132.5, 130.1, 129.4, 127.8, 119.2, 115.8, 113.9, 110.3, 55.3, 54.9, 21.5; IR (neat) 3091, 3012, 2939, 2837, 1603, 1571; LRMS (FAB) *m*/*z* 344 [25, M^++H], 188 [100]. Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08, found: C, 66.31; H, 6.09; N, 3.93.

2.1.16. *N*-*p*-Toluenesulfonyl-6-methoxy-1,2-dihydroquinoline (39). To a solution of olefin **16** (34 mg, 0.10 mmol) in 10 mL of CH_2Cl_2 under an Ar atmosphere, was added Grubbs' catalyst **A** (4.11 mg, 0.005 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=3:1) followed by recrystallization from *n*-hexane/AcOEt to give 30 mg (95%) of **39** as colorless needles. Mp 152 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, d, J=8.8 Hz), 7.27 (2H, d, J=8.2 Hz), 7.07 (2H, d, J=8.4 Hz), 6.81 (1H, dd, J=2.9, 8.8 Hz), 6.46 (1H, d, J=2.9 Hz), 5.94 (1H, d, J=9.7 Hz), 5.55 (1H, td, J=4.0, 9.7 Hz), 4.40 (2H, d, J=4.0 Hz), 3.80 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 158.1, 143.2, 136.1, 130.6, 129.0, 128.3, 127.7, 127.3, 125.8, 124.5, 112.9, 111.5, 55.4, 45.5, 21.5; IR (KBr) 3383, 2962, 1574, 1485; HRMS (FAB) calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0943.

2.1.17. *N*-*p*-Toluenesulfonyl-5-chloro-anthranilic acid methyl ester (19). To a solution of commercially available 5-chloro-anthranilic acid methyl ester (0.50 g, 2.69 mmol) in 20 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.64 mL, 8.08 mmol) and TsCl (0.62 g, 3.23 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from acetone to give 0.83 g (91%) of **19** as colorless needles. Mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 10.50 (1H, s), 7.87 (1H, d, J=2.4 Hz), 7.71 (2H, d, J=8.5 Hz), 7.66 (1H, d, J=9.0 Hz), 7.39 (1H, dd, J=2.4, 9.0 Hz), 7.22 (2H, d, J=8.1 Hz), 3.88 (3H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.1, 144.1, 139.0, 136.1, 134.3, 130.7, 129.7, 128.1, 127.2, 120.4, 117.0, 52.7, 21.5; IR (KBr) 3451, 3170, 2954, 1935, 1696; LRMS (FAB) *m*/*z* 342 [25, M^++H], 340 [63, M^++H], 154 [100]. Anal. Calcd for $C_{15}H_{14}ClNO_4S$: C, 53.02; H, 4.15; N, 4.12, found: C, 52.94; H, 4.28; N, 4.05.

2.1.18. *N*-*p*-Toluenesulfonyl-4-chloro-2-hydroxymethylaniline (20). To a cooled (−78 °C) solution of ester **19** (0.74 g, 2.17 mmol) in 10 mL of toluene under an Ar atmosphere, was added a solution of DIBAL in toluene (1 M, 6.51 mL, 6.51 mmol). The mixture was stirred at −78 °C for 1 h and the reaction was quenched by the addition of MeOH and Rochelle's salt, and then the solution was allowed to stir at room temperature until two layers were separated. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from MeOH to give 417 mg (62%) of **20** as colorless prisms. Mp 174 °C; ^{1}H NMR (acetone-d_6) δ 8.58 (1H, br), 7.60 (2H, d, J=6.4 Hz), 7.30 (2H, d, J=7.9 Hz), 7.26 (1H, d, J=7.1 Hz), 7.23 (1H, s), 7.19 (1H, dd, J=2.6, 8.6 Hz), 4.73 (1H, br), 4.44 (2H, s), 2.34 (3H, s); ^{13}C NMR (acetone-d_6) δ 144.3, 137.7, 137.1, 134.9, 130.6, 130.0, 128.2, 128.0, 127.4, 125.5, 61.6, 20.9; IR (KBr) 3468, 3120, 2921, 2809, 1586, 1480, 1327; LRMS (FAB) *m*/*z* 314 [8, M^++H], 312 [20, M^++H], 154 [100]. Anal. Calcd for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49, found: C, 53.80; H, 4.63; N, 4.49.

2.1.19. *N*-*p*-Toluenesulfonyl-4-chloro-2-formylaniline (21). To a solution of alcohol **20** (0.22 g, 0.69 mmol) in 10 mL of benzene, was added MnO_2 (0.18 g, 2.07 mmol). The mixture was refluxed for 4 h and filtered through a celite pad. After removal of the solvent, the residue was purified by recrystallization from acetone to give 116 mg (54%) of **21** as colorless needles. Mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 10.88 (1H, s), 9.79 (1H, s), 7.79 (2H, d, J=6.6 Hz), 7.72 (1H, d, J=1.7 Hz), 7.51 (1H, d, J=8.3 Hz), 7.28 (2H, d, J=8.1 Hz), 7.12 (1H, dd, J=1.7, 8.1 Hz), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 193.7, 144.4, 138.4, 136.0, 135.6, 135.1, 129.8, 128.3, 127.2, 122.8, 119.5, 21.5; IR (KBr) 3433, 3178, 3051, 2753, 1667, 1573, 1489; LRMS

(FAB) *m/z* 312 [20, M^++H], 310 [50, M^++H], 154 [100]. Anal. Calcd for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.90; N, 4.52, found: C, 54.28; H, 4.03; N, 4.47.

2.1.20. *N*-Allyl-*N*-*p*-toluenesulfonyl-4-chloro-2-formylaniline (22). To a solution of aldehyde **21** (0.24 g, 0.77 mmol) and K_2CO_3 (0.16 g, 1.16 mmol) in 20 mL of DMF under an Ar atmosphere, was added allyl bromide (0.1 mL, 1.16 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=2:1) to give 260 mg (97%) of **22** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 10.32 (1H, s), 7.94 (1H, d, *J*=2.6 Hz), 7.48 (2H, d, *J*=8.1 Hz), 7.40 (1H, dd, *J*=2.5, 8.4 Hz), 7.30 (2H, d, *J*=8.4 Hz), 6.64 (1H, d, *J*=8.6 Hz), 5.70 (1H, dddd, *J*=6.8, 6.9, 10.1, 17.0 Hz), 5.08 (1H, d, *J*=10.1 Hz), 5.03 (1H, d, *J*=17.0 Hz), 4.68 (1H, br), 3.89 (1H, br), 2.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 188.7, 144.5, 139.6, 137.2, 135.0, 134.1, 133.8, 131.3, 129.8, 129.3, 128.4, 127.9, 120.9, 54.3, 21.6; IR (neat) 3451, 3070, 2921, 2874, 1690; HRMS (FAB) calcd for $C_{17}H_{17}ClNO_3S$ 350.0618, found 350.0586.

2.1.21. *N*-Allyl-*N*-*p*-toluenesulfonyl-4-chloro-2-ethenylaniline (23). To a cooled (−78 °C) solution of $BrPh_3PMe$ (270 mg, 0.75 mmol) in 20 mL of THF under an Ar atmosphere, was added a solution of $KN(TMS)_2$ in THF (0.5 M, 1.5 mL, 0.75 mmol). After the mixture was stirred at −78 °C for 15 min, aldehyde **22** (220 mg, 0.63 mmol) was added and the mixture was warmed to room temperature for 1 h. The reaction was quenched by the addition of Rochelle's salt. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=2:1) to give 210 mg (96%) of **23** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, s), 7.57 (2H, d, *J*=6.6 Hz), 7.29 (2H, d, *J*=7.9 Hz), 7.09 (1H, dd, *J*=2.5, 8.6 Hz), 6.96 (1H, dd, *J*=11.0, 17.6 Hz), 6.60 (1H, d, *J*=8.4 Hz), 5.65–5.75 (2H, m), 5.34 (1H, d, *J*=11.1 Hz), 5.00 (1H, dd, *J*=1.1, 8.7 Hz), 4.96 (1H, dd, *J*=1.3, 7.0 Hz), 4.23 (1H, br), 3.94 (1H, s), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.8, 140.4, 135.7, 135.1, 134.4, 132.0, 131.7, 130.3, 129.6, 127.9, 127.8, 126.1, 119.6, 117.0, 54.7, 21.5.; IR (neat) 3087, 3023, 2977, 2923, 2856, 1477; HRMS (FAB) calcd for $C_{18}H_{19}ClNO_2S$ 348.0825, found: 348.0825.

2.1.22. *N*-*p*-Toluenesulfonyl-6-chloro-1,2-dihydroquinoline (40). To a solution of olefin **23** (100 mg, 0.29 mmol) in 29 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **A** (12.2 mg, 0.0245 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give 84 mg (90%) of **40** as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.63 (1H, d, *J*=8.5 Hz), 7.30 (2H, d, *J*=8.3 Hz), 7.20 (1H, dd, *J*=2.4, 8.5 Hz), 7.09 (2H, d, *J*=8.1 Hz), 6.92 (1H, d, *J*=2.4 Hz), 5.96 (1H, d, *J*=9.8 Hz), 5.63 (1H, td, *J*=4.1, 4.2 Hz), 4.42 (2H, dd, *J*=1.7, 4.1 Hz), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.6, 135.9, 133.3, 132.0, 130.7, 129.1, 128.0, 127.6, 127.1, 126.1, 125.4, 124.8, 60.3, 21.4; IR (KBr) 3451, 3060, 2921, 1560, 1179, 1354; HRMS (FAB) calcd for $C_{16}H_{14}ClNO_2S$ 319.0434, found: 319.0427.

2.1.23. 4-Chloro-anthranilic acid methyl ester (25). To solution of purified 2-amino-4-chlorobenzoic acid **24** (5.00 g, 29.1 mmol) in 291 mL of 2,2-dimethoxypropane, was added 58.2 mL of hydrochloric acid (36%). The mixture was stirred at 50 °C for 12 h and the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The product was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane to give 3.59 g (67%) of **25** as white needles. Mp 60–61 °C (lit.[19] 66–68 °C); ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d, *J*=8.5 Hz), 6.66 (1H, d, *J*=2.2 Hz), 6.60 (1H, dd, *J*=2.2, 8.5 Hz), 5.80 (2H, s), 3.86 (3H, s); ^{13}C NMR ($CDCl_3$) δ 149.3, 138.9, 131.9, 118.8, 115.4, 115.2, 67.5, 51.1; IR (KBr) 3454, 3357, 1685; LRMS (EI) *m/z* 187 [10, M^+], 185 [40, M^+], 98 [100]. Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55, found: C, 51.76; H, 4.29; N, 7.42.

2.1.24. *N*-*p*-Toluenesulfonyl-4-chloro-anthranilic acid methyl ester (26). To a solution of ester **25** (1.80 g, 9.70 mmol) in 30 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (2.31 mL, 29.1 mmol) and TsCl (2.22 g, 11.6 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from acetone to give 2.37 g (72%) of **26** as colorless needles. Mp 143 °C (lit.[20] 134–136 °C from ethanol); ^{1}H NMR ($CDCl_3$) δ 10.72 (1H, s), 7.84 (1H, d, *J*=8.4 Hz), 7.77 (2H, d, *J*=8.0 Hz), 7.72 (1H, d, *J*=1.8 Hz), 7.25 (2H, d, *J*=8.0 Hz), 6.98 (1H, dd, *J*=1.8, 8.5 Hz), 3.88 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.1, 143.7, 136.3, 136.0, 133.5, 128.9, 128.7, 127.3, 125.8, 116.9, 116.5, 52.6, 21.4; IR (KBr) 3114, 2956, 1687, 1597; LRMS (FAB) *m/z* 342 [25, M^++H], 340 [65, M^++H], 154 [100]. Anal. Calcd for $C_{15}H_{14}ClNO_4S$: C, 53.02; H, 4.15; N, 4.12, found: C, 52.84; H, 4.09; N, 3.84.

2.1.25. *N*-*p*-Toluenesulfonyl-5-chloro-2-hydroxymethylaniline (27). To a cooled (−78 °C) solution of ester **26** (0.16 g, 0.47 mmol) in 5 mL of toluene under an Ar atmosphere, was added a solution of DIBAL in toluene (1 M, 1.55 mL, 1.55 mmol). After the mixture was stirred at −78 °C for 1 h, the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt. Then the solution was allowed to stir at room temperature until two layers were separated. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from MeOH to give 100 mg (70%) of **27** as colorless prisms. Mp 123–124 °C (lit.[20] 108–110 °C from ethanol); ^{1}H NMR ($CDCl_3$) δ 7.65 (2H, d, *J*=8.4 Hz), 7.45 (1H, d, *J*=1.5 Hz), 7.24 (2H, d, *J*=8.4 Hz), 7.02 (1H, dd, *J*=1.5, 8.1 Hz), 6.99 (1H, d, *J*=8.1 Hz), 4.37 (2H, s), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 144.2, 137.6, 136.5, 134.7, 129.9, 129.8, 129.4, 127.0, 125.0, 122.7, 63.3, 21.5; IR (KBr) 3500, 3249, 1600, 1491;

LRMS (FAB) *m/z* 314 [8, M^++H], 312 [20, M^++H], 154 [100]. Anal. Calcd for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49, found: C, 53.78; H, 4.52; N, 4.37.

2.1.26. *N*-*p*-Toluenesulfonyl-5-chloro-2-formylaniline (28). To a solution of alcohol **27** (590 mg, 1.89 mmol) in 100 mL of benzene, was added MnO_2 (400 mg, 4.54 mmol). The mixture was refluxed for 4 h and filtered through a celite pad. After removal of the solvent, the residue was purified by recrystallization from acetone to give 420 mg (71%) of **27** as colorless prisms. Mp 139–140 °C (lit.[20] 138–140 °C from ethanol); ^{1}H NMR ($CDCl_3$) δ 10.88 (1H, s), 9.78 (1H, s), 7.79 (2H, d, *J*=6.6 Hz), 7.72 (1H, d, *J*=1.7 Hz), 7.51 (1H, d, *J*=8.3 Hz), 7.28 (2H, d, *J*=8.2 Hz), 7.12 (1H, dd, *J*=1.7, 8.1 Hz), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 193.9, 144.6, 142.6, 141.0, 137.0, 136.1, 129.9, 127.3, 123.2, 120.1, 117.7, 21.6; IR (KBr) 3153, 3105, 2858, 1672, 1597; LRMS (FAB) *m/z* 312 [20, M^++H], 310 [50, M^++H], 154 [100]. Anal. Calcd for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.90; N, 4.52, found: C, 54.17; H, 3.90; N, 4.35.

2.1.27. *N*-Allyl-*N*-*p*-toluenesulfonyl-5-chloro-2-formylaniline (29). To a solution of aldehyde **28** (1.11 g, 3.58 mmol) and K_2CO_3 (740 mg, 5.38 mmol) in 100 mL of DMF under an Ar atmosphere, was added allyl bromide (0.47 mL, 5.38 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 1.15 g (92%) of **29** as white prisms. Mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 10.31 (1H, s), 7.94 (1H, d, *J*=2.6 Hz), 7.50 (2H, d, *J*=8.3 Hz), 7.42 (1H, dd, *J*=2.0, 8.3 Hz), 7.33 (2H, d, *J*=8.0 Hz), 6.67 (1H, d, *J*=8.6 Hz), 5.22 (1H, dddd, *J*=3.4, 6.6, 10.0, 17.0 Hz), 5.10 (1H, dd, *J*=0.7, 10.0 Hz), 5.06 (1H, dd, *J*=1.2, 17.1 Hz), 4.53 (1H, br), 3.82 (1H, br), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$) δ 188.9, 144.7, 142.4, 134.6, 131.2, 129.9, 129.6, 129.1, 128.3, 127.9, 121.0, 60.4, 54.4, 21.6, 14.2; IR (KBr) 3089, 3068, 2924, 2870, 1691; LRMS (FAB) *m/z* 352 [40, M^++H], 350 [100, M^++H]. Anal. Calcd for $C_{17}H_{16}ClNO_3S$: C, 58.37; H, 4.61; N, 4.00; found: C, 58.30; H, 4.59; N, 3.82.

2.1.28. *N*-Allyl-*N*-*p*-toluenesulfonyl-5-chloro-2-ethenylaniline (30). To a cooled (−78 °C) solution of $BrPh_3PMe$ (613 mg, 1.72 mmol) in 20 mL of THF under an Ar atmosphere, was added a solution of $KN(TMS)_2$ in THF (0.5 M, 3.43 mL, 1.72 mmol). The mixture was stirred at −78 °C for 15 min. Then, to the mixture, aldehyde **29** (200 mg, 0.57 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The solution was quenched by the addition of saturated aqueous Rochelle's salt and MeOH. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane to give 193 mg (97%) of **30** as orange prisms. Mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (3H, m), 7.29 (2H, d, *J*=7.9 Hz), 7.09 (1H, dd, *J*=2.4, 8.6 Hz), 6.97 (1H, dd, *J*=11.0, 17.6 Hz), 6.60 (1H, d, *J*=8.4 Hz), 5.65–5.75 (2H, m), 5.34 (1H, d, *J*=11.0 Hz), 4.94–5.02 (2H, m), 4.23 (1H, br), 3.94 (1H, br), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.9, 137.5, 137.3, 135.5, 132.9, 131.8, 131.7, 129.6, 129.1, 128.7, 127.8, 127.0, 119.6, 116.3, 54.6, 21.7; IR (KBr) 3448, 3074, 2925, 2867, 1699, 1595, 1352; LRMS (FAB) *m/z* 350 [20, M^++H], 348 [40, M^++H], 192 [100]. Anal. Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03, found: C, 62.27; H, 5.40; N, 3.94.

2.1.29. *N*-*p*-Toluenesulfonyl-7-chloro-1,2-dihydroquinoline (41). To a solution of olefin **30** (197 mg, 0.57 mmol) in 57 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (24 mg, 0.0285 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) and recrystallization from MeOH to give 181 mg (100%) of **41** as colorless needles. Mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, d, *J*=2.0 Hz), 7.35 (2H, d, *J*=8.1 Hz), 7.14 (1H, dd, *J*=2.0, 8.2 Hz), 7.10 (2H, d, *J*=8.2 Hz), 6.86 (1H, d, *J*=8.0 Hz), 6.01 (1H, d, *J*=9.5 Hz), 5.60 (1H, td, *J*=4.2, 9.4 Hz), 4.43 (2H, d, *J*=4.2 Hz), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.8, 136.2, 136.1, 133.2, 129.3, 127.4, 126.8, 125.2, 124.2, 45.3, 29.8, 21.6, 1.09, 0.07; IR (KBr) 3448, 3065, 2926, 2858, 1593; LRMS (FAB) *m/z* 322 [10, M^++H], 320 [35, M^++H], 164 [100]. Anal. Calcd for $C_{16}H_{14}ClNO_2S$: C, 60.09; H, 4.41; N, 4.38, found: C, 59.97; H, 4.51; N, 4.28.

2.1.30. 2-Aminonaphthalene-3-carboxylic acid methyl ester (32). To a solution of 2-aminonaphthalene-3-carboxylic acid (0.10 g, 0.53 mmol) in 5 mL of 2,2-dimethoxypropane, was added 1 mL of 36% hydrochloric acid. The mixture was stirred at room temperature for 12 h and the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The product was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane to give 43 mg (40%) of **32** as yellow needles. Mp 102 °C (lit.[21] 104–105 °C); ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, s), 7.71 (1H, d, *J*=8.3 Hz), 7.52 (1H, d, *J*=8.3 Hz), 7.38 (1H, dd, *J*=7.6, 8.3 Hz), 7.17 (1H, dd, *J*=7.6, 8.3 Hz), 6.95 (1H, s), 5.56 (2H, br), 3.94 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.3, 145.9, 137.3, 133.4, 129.2, 128.8, 126.0, 125.1, 122.5, 114.7, 109.9, 51.9; IR (KBr) 3496, 3389, 2961, 1694; LRMS (FAB) *m/z* 202 [50, M^++H]. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96, found: C, 71.48; H, 5.51; N, 6.86.

2.1.31. *N*-*p*-Toluenesulfonyl-2-aminonaphthalene-3-carboxylic acid methyl ester (33). To a solution of ester **32** (50 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.06 mL, 0.75 mmol) and TsCl (57.2 mg, 0.30 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from acetone to give 40 mg (78%) of **33** as colorless needles. Mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 10.39 (1H, s), 8.50 (1H, s), 8.07 (1H, s), 7.77 (2H, d, *J*=9.1 Hz), 7.73 (2H, d, *J*=8.2 Hz), 7.56 (1H, dd, *J*=7.1, 8.1 Hz), 7.42 (1H, dd, *J*=7.3, 8.3 Hz), 7.17 (2H, d, *J*=8.4 Hz), 3.92 (3H, s), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.1, 143.7, 136.3, 136.0, 135.2, 133.5, 129.5, 129.4, 128.9, 128.7, 127.32, 127.30, 125.8, 116.9, 116.5,

52.6, 21.4; IR (KBr) 3445, 3173, 2952, 1941, 1830, 1682; LRMS (FAB) *m/z* 356 [60, M^++H], 355 [65, M^+], 154 [100]. Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94, found: C, 64.05; H, 4.95; N, 3.85.

2.1.32. *N*-(*p*-Toluenesulfonyl)-2-amino-3-hydroxymethylnaphthalene (34). To a cooled (−78 °C) solution of ester **33** (0.10 g, 0.28 mmol) in 3 mL of toluene under an Ar atmosphere, was added a solution of DIBAL in toluene (1 M, 1.13 mL, 1.13 mmol). The mixture was stirred at −78 °C for 1 h and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt. Then the solution was allowed to stir at room temperature until two layers were separated. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from MeOH to give 88 mg (96%) of **34** as light brown needles. Mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 7.94 (1H, s), 7.78 (1H, d, *J*=8.0 Hz), 7.72 (1H, d, *J*=8.0 Hz), 7.68 (2H, d, *J*=8.3 Hz), 7.54 (1H, s), 7.48 (2H, dd, *J*=7.1, 7.9 Hz), 7.42 (1H, dd, *J*=7.8, 6.8 Hz), 7.18 (2H, d, *J*=8.0 Hz), 4.52 (2H, d, *J*=4.9 Hz), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 144.6, 140.9, 136.3, 131.6, 126.5, 126.3, 125.9, 125.8, 125.4, 124.0, 123.9, 120.9, 116.3, 106.6, 59.8, 21.1; IR (KBr): 3455, 3110, 2917, 2867, 2806, 2710, 1597; LRMS (FAB) *m/z* 328 [10, M^++H], 327 [25, M^+], 154 [100]. Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28, found: C, 65.85; H, 5.14; N, 4.14.

2.1.33. *N*-(*p*-Toluenesulfonyl)-2-amino-3-formylnaphthalene (35). To a solution of alcohol **34** (0.42 g, 1.28 mmol) in 100 mL of benzene, was added MnO_2 (0.40 g, 3.08 mmol). The mixture was refluxed for 4 h and filtered through a celite pad. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 350 mg (84%) of **35** as yellow prisms. Mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 10.44 (1H, s), 9.95 (1H, s), 8.12 (1H, s), 8.03 (1H, s), 7.85 (1H, d, *J*=8.3 Hz), 7.79 (1H, d, *J*=2.3 Hz), 7.76 (2H, d, *J*=8.3 Hz), 7.62 (1H, dd, *J*=7.1, 7.1 Hz), 7.45 (1H, dd, *J*=7.1, 7.1 Hz), 7.18 (2H, d, *J*=7.1 Hz), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 194.9, 144.0, 140.3, 136.6, 136.4, 134.7, 130.7, 129.7, 129.2, 128.9, 127.7, 127.4, 126.1, 123.1, 115.9, 21.6; IR (KBr) 3204, 3066, 2843, 1670; LRMS (FAB) *m/z* 326 [60, M^++H], 325 [50, M^+], 154 [100]. Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30, found: C, 66.15; H, 4.62; N, 4.20.

2.1.34. *N*-Allyl-*N*-(*p*-toluenesulfonyl)-2-amino-3-formylnaphthalene (36). To a solution of aldehyde **35** (36 mg, 0.11 mmol) and K_2CO_3 (23 mg, 0.17 mmol) in 10 mL of DMF, was added allyl bromide (0.01 mL, 0.17 mmol) under an Ar atmosphere. The mixture was stirred at 80 °C for 1 h and quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 35.7 mg (89%) of **36** as colorless prisms. Mp 137–138 °C; ^{1}H NMR ($CDCl_3$) δ 10.49 (1H, s), 8.52 (1H, s), 8.00 (1H, dd, *J*=3.6, 6.0 Hz), 7.66 (1H, dd, *J*=4.8, 4.9 Hz), 7.58–7.61 (2H, m), 7.51 (2H, d, *J*=8.4 Hz), 7.28 (2H, d, *J*=8.1 Hz), 7.19 (1H, s), 5.80 (1H, dddd, *J*=6.8, 6.8, 10.2, 16.8 Hz), 5.05 (1H, d, *J*=3.1 Hz), 5.01 (1H, d, *J*=7.9 Hz), 4.58 (1H, s), 4.02 (1H, s), 2.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 190.3, 144.1, 136.8, 135.4, 134.5, 132.9, 131.9, 131.7, 130.6, 129.9, 129.6, 129.0, 128.0, 127.9, 127.7, 127.6, 120.4, 55.0, 21.6; IR (KBr) 3447, 3055, 2979, 2892, 1685; LRMS (FAB) *m/z* 366 [40, M^++H], 211 [100]. Anal. Calcd for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; N, 3.83, found: C, 68.92; H, 5.22; N, 3.77.

2.1.35. *N*-Allyl-*N*-(*p*-toluenesulfonyl)-2-amino-3-ethenylnaphthalene (37). To a cooled (−78 °C) solution of $BrPh_3PMe$ (68 mg, 0.19 mmol) in 5 mL of THF, was added a solution of $KN(TMS)_2$ in THF (0.5 M, 0.38 mL, 0.19 mmol) under an Ar atmosphere. After the mixture was stirred at −78 °C for 15 min, aldehyde **36** (35 mg, 0.10 mmol) in THF (5 mL) was added and the mixture warmed to room temperature for 1 h. The solution was quenched by the addition of saturated aqueous Rochelle's salt. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from *n*-hexane to give 34 mg (97%) of **37** as white needles. Mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, s), 7.83 (1H, d, *J*=7.5 Hz), 7.61 (2H, d, *J*=8.2 Hz), 7.58 (1H, d, *J*=8.2 Hz), 7.48 (1H, ddd, *J*=1.3, 6.8, 6.8 Hz), 7.43 (1H, ddd, *J*=1.3, 6.8, 6.8 Hz), 7.29 (2H, d, *J*=7.9 Hz), 7.24 (1H, s), 7.13 (1H, dd, *J*=11.0, 17.4 Hz), 5.86 (1H, dd, *J*=1.3, 16.3 Hz), 5.72–5.82 (1H, m), 5.35 (1H, dd, *J*=1.3, 11.0 Hz), 4.99 (1H, d, *J*=1.3 Hz), 4.95 (1H, dd, *J*=1.3, 6.4 Hz), 4.29 (1H, br), 4.13 (1H, br), 2.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.6, 136.4, 136.1, 135.3, 133.3, 133.0, 132.6, 132.3, 129.5, 128.4, 128.0, 127.8, 127.4, 126.9, 126.2, 125.4, 119.4, 116.1, 55.1, 21.6; IR (KBr) 3447, 3059, 2918, 2849, 1645, 1596; LRMS (FAB) *m/z* 364 [25, M^++H], 208 [100]. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.58, found: C, 72.55; H, 5.79; N, 3.77.

2.1.36. *N*-(*p*-Toluenesulfonyl)-1,2-dihydrobenzo[*g*]quinoline (42). To a solution of olefin **37** (20 mg, 0.055 mmol) in 5.5 mL of CH_2Cl_2, was added catalyst **A** (2.26 mg, 0.00275 mmol) under an Ar atmosphere. The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography (*n*-hexane/AcOEt=4:1) on silica gel followed by recrystallization from *n*-hexane/AcOEt to give 19.1 mg (98%) of **42** as pale yellow needles. Mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, s), 7.87 (1H, d, *J*=9.0 Hz), 7.73 (1H, d, *J*=7.0 Hz), 7.43–7.49 (2H, m), 7.36 (1H, s), 7.29 (2H, d, *J*=8.4 Hz), 7.03 (2H, d, *J*=7.9 Hz), 6.23 (1H, d, *J*=9.7 Hz), 5.72 (1H, ddd, *J*=1.3, 4.0, 9.7 Hz), 4.51 (2H, dd, *J*=1.3, 4.0 Hz), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.4, 136.4, 132.9, 132.7, 131.9, 129.1, 128.3, 127.6, 127.5, 127.3, 126.4, 126.3, 126.2, 125.3, 125.1, 125.0, 45.5, 21.5; IR (KBr) 3347, 3052, 2923, 2865, 1918, 1636, 1598; LRMS (FAB) *m/z* 336 [35, M^++H], 335 [40, M^+], 180 [100]. Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18, found: C, 71.60; H, 5.11; N, 4.13.

2.1.37. *N*-Allyl-*N*-benzyl-2-isopropenylaniline (43a). To a solution of 2-isopropenylaniline (400 mg, 3.00 mmol) in 2 mL of CH_2Cl_2 under an Ar atmosphere, was added BnBr (0.31 mL, 3.30 mmol). The mixture was stirred at room temperature for 4 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was

extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give 315 mg (61%) of *N*-benzyl-2-isopropenylaniline as a pale yellow oil. To a mixture of *N*-benzyl-2-isopropenylaniline (223 mg, 1.00 mmol) and 60% NaH in mineral oil (43.9 mg, 1.10 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.1 mL, 1.10 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give 54 mg (20%) of **43a** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.13–7.28 (7H, m), 6.95 (1H, dd, *J*=1.2, 7.3 Hz), 6.90 (1H, d, *J*=8.1 Hz), 5.71–5.81 (1H, m), 5.05–5.22 (4H, m), 4.21 (2H, s), 3.60 (2H, d, *J*=6.3 Hz), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$) δ 148.1, 147.8, 138.5, 138.4, 124.8, 130.3, 128.9, 128.1, 127.4, 126.8, 122.3, 121.1, 117.5, 114.7, 56.1, 54.3, 22.3: IR (KBr) 3080, 2975, 2924, 1661, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{22}N$ 264.1752, found 264.1771.

2.1.38. *N*-Allyl-*N*-acetyl-2-isopropenylaniline (43b). To a solution of 2-isopropenylaniline (266 mg, 2.00 mmol) in 2 mL of CH_2Cl_2, was added Ac_2O (0.20 mL, 2.20 mmol). The mixture was stirred at 0 °C for 10 min and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 316 mg (90%) of *N*-acetyl-2-isopropenylaniline as a colorless oil. To a solution of *N*-acetyl-2-isopropenylaniline (250 mg, 1.43 mmol) and NaH (60% in mineral oil, 114 mg, 2.86 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.25 mL, 2.86 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 209 mg (68%) of **43b** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.28–7.32 (3H, m), 7.07 (1H, d, *J*=7.3 Hz), 5.82–5.92 (1H, m), 5.21 (1H, t, *J*=1.7 Hz), 4.95–5.10 (3H, m), 4.92 (1H, dd, *J*=5.2, 14.6 Hz), 3.45 (1H, dd, *J*=7.8, 14.8 Hz), 2.04 (3H, s), 1.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1, 143.1, 141.1, 139.5, 133.0, 130.0, 129.7, 128.1, 127.9, 117.7, 116.9, 51.2, 22.9, 22.5: IR (KBr) 3080, 2975, 2924, 1661, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1394.

2.1.39. *N*-Allyl-*N*-(*t*-butoxycarbonyl)-2-isopropenylaniline (43c). To a solution of 2-isopropenylaniline (266 mg, 2.00 mmol) in 3 mL of 1 N NaOH, was added di-*t*-butyl dicarbonate (655 mg, 3.00 mmol). The mixture was stirred at 50 °C for 3 h and the reaction was quenched by the addition of water. The mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) to give 234 mg (50%) of *N*-(*t*-butoxycarbonyl)-2-isopropenylaniline as yellow oil. To a solution of *N*-(*t*-butoxycarbonyl)-2-isopropenylaniline (233 mg, 1.00 mmol) and NaH (60% in mineral oil, 43.9 mg, 1.10 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.10 mL, 1.10 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give 52 mg (19%) of **43c** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.26 (4H, br), 5.82–5.92 (1H, m), 5.15 (1H, s), 5.06 (2H, d, *J*=11.2 Hz), 4.98 (1H, s), 4.55 (1H, d, *J*=2.8 Hz), 3.57 (1H, dd. *J*=6.8, 15.6 Hz), 2.04 (3H, s), 1.34 (9H, s); ^{13}C NMR ($CDCl_3$) δ 153.7, 143.8, 141.3, 139.5, 134.0, 129.6, 128.6, 127.4, 126.3, 116.0, 114.7, 78.7, 52.2, 27.6, 22.3: IR (KBr) 3080, 2976, 2928, 1698, 1490 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{24}NO_2$ 274.1807, found 274.1780.

2.1.40. 4-Methylquinoline (45).[12] *Method A*. To a solution of olefin **43a** (65 mg, 0.25 mmol) in 25 mL of CH_2Cl_2 under an Ar atmosphere, was added Grubbs' catalyst **A** (10.5 mg, 0.012 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 34 mg (95%) of **45** as a colorless oil.

Method B. To a solution of olefin **43b** (86 mg, 0.40 mmol) in 40 mL of CH_2Cl_2 under an Ar atmosphere, was added Grubbs' catalyst **B** (17 mg, 0.02 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 55.6 mg (97%) of **45** as a colorless oil.

Method C. To a solution of olefin **43c** (49.2 mg, 0.18 mmol) in 18 mL of CH_2Cl_2 under an Ar atmosphere, was added Grubbs' catalyst **B** (7.64 mg, 0.009 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=20:1) to give 25 mg (97%) of **45** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, d, *J*=8.1 Hz), 8.10 (1H, d, *J*=7.6 Hz), 7.92 (1H, d, *J*=4.4 Hz), 7.67 (1H, dd, *J*=8.3, 8.3 Hz), 7.53 (1H, dd, *J*=8.1, 8.1 Hz), 7.15 (1H, d, *J*=4.1 Hz), 2.62 (3H, s); ^{13}C NMR ($CDCl_3$) δ 150.1, 148.0, 144.1, 130.0, 129.0, 128.2, 126.2, 123.7, 121.7, 18.5; IR (KBr) 3408, 3397, 3061, 2981, 2924, 1618, 1597, 1571; LRMS (EI) *m*/*z* 143 [100, M$^+$].

2.1.41. *N*-*n*-Butenyl-*N*-*p*-toluenesulfonyl-2-isopropenylaniline (47). To a solution of *N*-*p*-toluenesulfonyl-2-isopropenylaniline (287 mg, 1.00 mmol) and K_2CO_3 (207 mg, 1.50 mmol) in 10 mL of DMF under an Ar atmosphere, was added 4-bromo-1-butene (0.15 mL, 1.50 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was

purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 266 mg (97%) of **47** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.66 (2H, d, *J*=8.3 Hz), 7.27–7.31 (4H, m), 7.16 (1H, dd, *J*=2.7, 8.0 Hz), 6.80 (1H, d, *J*=7.6 Hz), 5.54–5.64 (1H, m), 5.22 (1H, s), 5.05 (1H, s), 4.91–4.96 (2H, m), 3.53 (2H, br), 2.44 (3H, s), 2.18 (3H, s), 2.08 (2H, br); ^{13}C NMR ($CDCl_3$) δ 144.9, 143.6, 143.4, 136.7, 136.4, 134.5, 130.2, 129.4, 128.3, 128.2, 128.1, 127.4, 116.9, 116.7, 50.8, 32.3, 24.4, 21.5; IR (neat) 3461, 3070, 2958, 2902, 2865, 1646, 1596, 1491, 1450, 1341, 1158, 1091 cm^{-1}; LRMS (EI) *m/z* 341 [20, M$^+$], 186 [100]. Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10; found: C, 70.26; H, 6.94; N, 3.96.

2.1.42. [*N*,*N*′-Bis(*o*-isopropenylphenyl)-*N*,*N*′-bis-*p*-toluenesulfonyl]hex-3-ene-1,6-diamine (48). To a solution of olefin **47** (102 mg, 0.30 mmol) in 30 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **A** (12.3 mg, 0.006 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2=1:1) to give 36 mg (70%, *E*/*Z* mixture) of **48** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.62 (4H, dd, *J*=8.3, 11.5 Hz), 7.26–7.30 (8H, m), 7.09–7.16 (2H, m), 6.72 (2H, dd, *J*=4.9, 7.6 Hz), 5.14–5.19 (4H, m), 5.01 (2H, s), 3.40 (4H, br), 2.44 (6H, s), 2.15 (6H, s), 1.97 (4H, br); ^{13}C NMR ($CDCl_3$) δ 144.8, 143.6, 143.4, 136.6, 130.2, 129.5, 128.5, 128.2, 128.1, 128.0, 127.6, 127.4, 127.3, 116.7, 53.4, 51.1, 50.8, 31.2, 26.2, 24.3, 21.5, 14.1; IR (neat) 3451, 3060, 3023, 2921, 2846, 1637, 1598, 1489, 1346, 1160 cm^{-1}; LRMS (FAB) *m/z* 655 [10, M$^+$+H], 144 [100]. Anal. Calcd for $C_{38}H_{42}N_2O_4S_2$: C, 69.69; H, 6.46; N, 4.28; found: C, 69.35; H, 6.54; N, 4.15.

2.1.43. 5-Methyl-1-*p*-toluenesulfonyl-2,3-dihydro-1*H*-benzo[*b*]azepine (49). To a solution of olefin **47** (102 mg, 0.30 mmol) in 30 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (12.7 mg, 0.006 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1), followed by recrystallization from *n*-hexane/AcOEt to give 90 mg (96%) of **49** as white prisms. Mp 92 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, dd, *J*=1.7, 7.5 Hz), 7.42 (2H, d, *J*=8.3 Hz), 7.23–7.34 (2H, m), 7.15–7.17 (3H, m), 5.61 (1H, dd, *J*=1.2, 6.6 Hz), 4.13 (2H, br), 2.37 (3H, s), 2.05–2.10 (2H, m), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$) δ 142.6, 140.8, 137.8, 136.5, 136.2, 131.9, 129.0, 128.1, 127.5, 127.4, 127.1, 125.6, 57.2, 26.3, 22.0, 21.4; IR (KBr) 3451, 2921, 2884, 2846, 1655, 1339, 1160 cm^{-1}; LRMS (EI) *m/z* 313 [100, M$^+$]. Anal. Calcd for $C_{18}H_{19}NO_2S$ C, 68.98; H, 6.11; N, 4.47; found C, 68.76; H, 6.07; N, 4.33.

2.1.44. *N*-*n*-Pentenyl-*N*-*p*-toluenesulfonyl-2-isopropenylaniline (50). To a solution of *N*-*p*-toluenesulfonyl-2-isopropenylaniline (287 mg, 1.00 mmol) and K_2CO_3 (207 mg, 1.50 mmol) in 10 mL of DMF under an Ar atmosphere, was added 5-bromo-1-pentene (0.18 mL, 1.50 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 347 mg (98%) of **50** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.66 (2H, d, *J*=8.3 Hz), 7.25–7.31 (4H, m), 7.16 (1H, dd, *J*=2.7, 6.3 Hz), 6.78 (1H, d, *J*=8.3 Hz), 5.60–5.70 (1H, m), 5.21 (1H, s), 5.05 (1H, s), 4.91 (2H, d, *J*=12.4 Hz), 3.47 (2H, br), 2.44 (3H, s), 2.18 (3H, s), 1.94 (2H, d, *J*=7.0 Hz), 1.48 (2H, br); ^{13}C NMR ($CDCl_3$) δ 145.0, 143.6, 143.3, 137.3, 136.72, 136.69, 130.2, 129.4, 128.2, 128.12, 128.07, 127.4, 116.7, 115.2, 51.2, 30.9, 26.9, 24.4, 21.5; IR (neat) 3461, 3076, 2977, 2924, 1638, 1598, 1488, 1347, 1162, 1092 cm^{-1}; LRMS (EI) *m/z* 355 [10, M$^+$], 200 [100]. Anal. Calcd for $C_{21}H_{25}NO_2S$ C, 70.95; H, 7.09; N, 3.94; found C, 71.03; H, 7.31; N, 3.81.

2.1.45. [*N*,*N*′-Bis(*o*-isopropenylphenyl)-*N*,*N*′-bis-*p*-toluenesulfonyl]oct-4-ene-1,8-diamine (51). To a solution of olefin **50** (60 mg, 0.17 mmol) in 17 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **A** (7.0 mg, 0.0085 mmol). The mixture was degassed and stirred at 50 °C for 4 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2=1:1) to give 26 mg (70%, *E*/*Z* mixture) of **51** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.64 (4H, dd, *J*=1.7, 8.2 Hz), 7.24–7.30 (8H, m), 7.11–7.15 (2H, m), 6.77 (2H, dd, *J*=8.1, 8.1 Hz), 5.16–5.19 (4H, m), 5.01 (2H, s), 4.43 (4H, br), 2.43 (6H, s), 2.16 (6H, s), 1.82 (4H, s), 1.39 (4H, br); ^{13}C NMR ($CDCl_3$) δ 144.9, 143.62, 143.61, 143.4, 143.3, 136.6, 136.66, 136.63, 130.2, 129.6, 129.4, 129.2, 128.2, 128.17, 128.09, 128.05, 127.4, 116.6, 51.24, 51.18, 29.7, 27.7, 27.5, 24.5, 24.4, 21.5; IR (neat) 3442, 2921, 2856, 1637, 1441, 1345, 1159 cm^{-1}; LRMS (EI) 682 [15, M$^+$] 158 [100]. Anal. Calcd for $C_{40}H_{46}N_2O_4S_2$1/2H_2O C, 69.43; H, 6.85; N, 4.05; found C, 69.17; H, 6.94; N, 3.77.

2.1.46. 6-Methyl-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-1*H*-benzo[*b*]azocine (52). To a solution of olefin **50** (275 mg, 0.77 mmol) in 77 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (32.9 mg, 0.015 mmol). The mixture was degassed and stirred at 50 °C for 4 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) followed by recrystallization from *n*-hexane/AcOEt to give 234 mg (86%) of **52** as white prisms. Mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (2H, d, *J*=7.9 Hz), 7.25–7.34 (4H, m), 7.15 (1H, dd, *J*=2.4, 8.3 Hz), 6.76 (1H, d, *J*=7.6 Hz), 5.73 (1H, dd, *J*=1.2, 7.9 Hz), 4.21 (1H, br), 2.84 (1H, br), 2.43 (3H, s), 2.18 (1H, br), 2.06 (3H, s), 1.60 (3H, br); ^{13}C NMR ($CDCl_3$) δ 143.7, 142.8, 138.6, 138.1, 133.7, 129.3, 129.0, 128.6, 128.3, 127.8, 127.3, 126.9, 51.5, 26.7, 26.4, 24.3, 21.5; IR (KBr) 3451, 2934, 2856, 1488, 1342, 1159 cm^{-1}; LRMS (EI) *m/z* 327 [3, M$^+$], 91 [100]. Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; found C, 69.72; H, 6.47; N, 4.23.

2.1.47. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-(1-methoxyvinyl)-aniline (53a). To a solution of 2-aminoacetophenone (400 mg, 3.00 mmol) in 20 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.72 mL, 9.00 mmol) and TsCl (686 mg, 3.60 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the

residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 838 mg (97%) of *N*-*p*-toluenesulfonyl-2-aminoacetophenone as off white solid. To a solution of *N*-*p*-toluenesulfonyl-2-aminoacetophenone (241 mg, 0.84 mmol) and K_2CO_3 (174 mg, 1.26 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.15 mL, 1.26 mmol). The solution was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 266 mg (97%) of *N*-allyl-*N*-*p*-toluenesulfonyl-2-aminoacetophenone as a white solid. To a solution of *N*-allyl-*N*-*p*-toluenesulfonyl-2-aminoacetophenone (50 mg, 0.15 mmol) and trimethoxymethane (0.04 mL, 0.38 mmol), was added *p*-toluenesulfonic acid monohydrate (2.85 mg, 0.15 mmol) in 3 mL of MeOH. The solution was stirred at room temperature for 4 h and the reaction was quenched by the addition of Et_3N. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 55 mg (99%) of *N*-allyl-*N*-*p*-toluenesulfonyl-2-(1,1-dimethoxyethyl)aniline as a yellow solid. To *N*-allyl-*N*-*p*-toluenesulfonyl-2-(1,1-dimethoxyethyl)aniline (55 mg, 0.15 mL), were added pyridine (1.0 mL), TMSCl (1.0 mL, 0.80 mmol) and benzoic acid (1.83 mg, 0.015 mmol). The solution was stirred at 65 °C for 2 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 41 mg (80%) of **53a** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.66 (2H, d, J=8.2 Hz), 7.43 (1H, dd, J=1.7, 7.5 Hz), 7.27–7.31 (4H, m), 6.94 (1H, dd, J=1.1, 7.7 Hz), 5.54–5.64 (1H, m), 4.91–4.96 (2H, m), 4.40 (1H, s), 4.31 (1H, s), 4.13 (2H, d, J=6.6 Hz), 3.59 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 160.2, 143.1, 138.5, 137.5, 136.8, 133.1, 130.6, 130.4, 129.3, 128.6, 128.1, 128.0, 118.8, 86.4, 55.1, 54.2, 21.5: IR (neat) 3070, 2933, 2846, 1597, 1490, 1474, 1347 cm^{-1}; LRMS (EI) *m*/*z* 343 [100, M^+]. HRMS (FAB) calcd for $C_{19}H_{21}NO_3SK$ 382.0879, found 382.0873.

2.1.48. *N*-*p*-Toluenesulfonyl-4-methoxy-1,2-dihydroquinoline (54a). To a solution of olefin **53a** (24 mg, 0.07 mmol) in 7 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (3.1 mg, 0.0035 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=5:1) to give 21 mg (97%) of **54a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.69 (1H, dd, J=1.1, 8.1 Hz), 7.38 (1H, dd, J=1.7, 7.7 Hz), 7.34 (1H, dd, J=1.6, 7.5 Hz), 7.30 (2H, d, J=8.2 Hz), 7.23 (1H, ddd, J=1.2, 7.5, 15.0 Hz), 7.07 (2H, d, J=7.9 Hz), 4.44 (3H, s), 3.31 (3H, s), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 151.1, 143.3, 136.4, 135.8, 128.9, 128.6, 127.5, 127.4, 126.7, 126.5, 122.2, 91.2, 54.4, 44.9, 21.4; IR (neat) 3447, 3086, 3020, 2985, 2869, 2840, 1920, 1651, 1599 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{18}NO_3S$ 316.1007, found 316.1013.

2.1.49. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-[1-(*t*-butyldimethylsilyloxy)vinyl]aniline (53b). To *N*-allyl-*N*-*p*-toluenesulfonyl-2-aminoacetophenone (100 mg, 0.30 mmol) under an Ar atmosphere, were added NaI (180 mg, 1.20 mmol) and TBSCl (180.8 mg, 1.20 mmol) in 10 mL of CH_3CN and Et_3N (0.18 mL, 1.32 mmol). The mixture was stirred at 100 °C for 2 h. and quenched by the addition of Et_3N. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on basic alumina (*n*-hexane/acetone=5:1) to give 106 mg (85%) of **53b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.69 (2H, d, J=8.1 Hz), 7.51 (1H, dd, J=1.4, 7.0 Hz), 7.28 (2H, d, J=8.1 Hz), 7.26 (1H, d, J=7.0 Hz), 7.52 (1H, ddd, J=1.6, 7.7, 10.7 Hz), 6.81 (1H, d, J=7.1 Hz), 5.75 (1H, dddd, J=4.4, 6.7, 11.4, 17.0 Hz), 4.97 (1H, d, J=4.4 Hz), 4.93 (1H, d, J=11.4 Hz), 4.74 (2H, dd, J=1.3, 17.0 Hz), 4.17 (2H, dd, J=6.7 Hz), 2.43 (3H, s), 0.95 (9H, s), 0.22 (6H, s); ^{13}C NMR ($CDCl_3$) δ 153.2, 143.3, 139.6, 137.3, 136.3, 132.7, 129.9, 129.6, 129.4, 128.0, 127.9, 119.1, 96.3, 54.5, 29.6, 25.8, 21.5, 18.2, −4.6: IR (neat) 3429, 3084, 2924, 2867, 1697, 1596, 1487 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{34}NO_3SSi$ 444.2029, found 444.2030.

2.1.50. *N*-*p*-Toluenesulfonyl-4-(*tert*-butyldimethylsilyloxy)-1,2-dihydroquinoline (54b). To a solution of olefin **53b** (31 mg, 0.07 mmol) in 7 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (3.12 mg, 0.0035 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on basic alumina gel (*n*-hexane/acetone=5:1) to give 21 mg (95%) of **54b** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, dd, J=1.3, 8.1 Hz), 7.57 (1H, dd, J=1.7, 7.7 Hz), 7.48–7.55 (3H, m), 7.43 (1H, ddd, J=1.3, 7.5, 7.5 Hz), 7.29 (2H, d, J=8.6 Hz), 4.83 (1H, t, J=4.4 Hz), 4.67 (2H, d, J=4.4 Hz), 2.53 (3H, s), 1.11 (9H, s), 0.15 (6H, s); ^{13}C NMR ($CDCl_3$) δ 155.1, 141.2, 136.3, 129.5, 128.5, 127.0, 125.4, 116.8, 112.3, 88.0, 42.6, 42.5, 40.9, 20.8, 20.5, 15.1, −6.1; IR (neat) 3422, 2956, 2856, 1920, 1686, 1597 cm^{-1}; LRMS (EI) *m*/*z* 415 [15, M^+], 374 [100]. HRMS (FAB) calcd for $C_{22}H_{30}NO_3SSi$ 416.1716, found 416.1727.

2.1.51. *N*-Acetyl-2-isopropenyl-4-methoxyaniline (55). To the stirring solution of 2-isopropenyl-4-methoxyaniline[7] (40 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 at 0 °C, was added Ac_2O (0.25 mL, 0.27 mmol) and the mixture was stirred at 0 °C for 10 min. The reaction mixture was quenched by $NaHCO_3$ until pH 8 and was extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was recrystallized from AcOEt to give 45 mg (88%) of **55** as pale yellow plates. Mp 73 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (1H, d, J=8.8 Hz), 7.31 (1H, br), 6.81 (1H, dd, J=3.0, 9.0 Hz), 6.69 (1H, d, J=2.9 Hz), 5.35 (1H, s), 5.05 (1H, s), 3.79 (3H, s), 2.13 (3H, s), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.0, 156.0, 142.9, 135.7, 127.0, 123.3, 116.6, 113.4, 112.6, 55.4, 24.4, 24.2; IR (KBr) 3451, 3237, 1641, 1545 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1191.

2.1.52. *N*-Allyl-*N*-acetyl-2-isopropenyl-4-methoxyaniline (56). To a solution of **55** (44 mg, 0.21 mmol) and NaH (60% in mineral oil, 11.3 mg, 0.26 mmol) in 5 mL of DMF under

an Ar atmosphere, was added allyl bromide (0.01 mL, 0.26 mmol). The mixture was stirred at 0 °C for 1 h and quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:1) to give 35 mg (70%) of **56** as a yellow oil. ^1H NMR ($CDCl_3$) δ 6.97 (1H, d, J=8.4 Hz), 6.82 (1H, d, J=2.9 Hz), 6.79 (2H, dd, J=2.9, 8.4 Hz), 5.85 (1H, dddd, J=5.1, 11.0, 14.6, 17.0 Hz), 5.20 (1H, dd, J=1.7, 1.7 Hz), 5.08 (1H, d, J=11.0 Hz), 5.00 (1H, d, J=17.0 Hz), 4.90 (1H, dd, J=5.1, 14.6 Hz), 3.83 (3H, s), 3.40 (1H, dd, J=7.9, 14.6 Hz), 2.03 (3H, s), 1.86 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.78, 158.89, 143.27, 142.42, 133.18, 132.51, 130.85, 117.76, 116.92, 115.14, 112.95, 55.39, 51.54, 23.03, 22.60; IR (neat) 2921, 1655, 1491, 1395, 1311 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{20}NO_2$ 246.1494, found 246.1513.

2.1.53. *N*-Acetyl-4-methyl-6-methoxy-1,2-dihydroquinoline (57). To a solution of olefin **56** (35 mg, 0.14 mmol) in 14 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (6.1 mg, 0.007 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=3:1) to give 30 mg (98%) of **57** as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 7.04 (1H, d, J=8.4 Hz), 6.84 (1H, d, J=2.7 Hz), 6.77 (1H, dd, J=2.7, 8.6 Hz), 5.91 (1H, s), 4.39 (2H, s), 3.88 (3H, s), 2.15 (3H, s), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.91, 157.32, 132.35, 131.28, 130.26, 125.20, 124.51, 111.28, 109.48, 55.47, 41.23, 21.97, 18.07; IR (neat) 3448, 2921, 2856, 1655, 1237 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1098.

2.1.54. 6-Methoxy-4-methylquinoline (58). A solution of **57** (10 mg, 0.05 mmol) in a mixture of 1 mL of 10% aq. NaOH and 2 mL of MeOH was stirred at 50 °C overnight. The reaction was diluted with water and extracted with CH_2Cl_2. Combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/acetone=5:2) followed by recrystallization from acetone to give 8.0 mg (98%) of **58** as white prisms. Mp 55–56 °C (lit.[22] 52 °C); ^1H NMR ($CDCl_3$) δ 8.65 (1H, d, J=4.4 Hz), 8.01 (1H, d, J=9.2 Hz), 7.36 (1H, dd, J=2.8, 9.2 Hz), 7.20 (2H, dd, J=4.8, 3.2 Hz), 3.96 (3H, s), 2.67 (3H, s); ^{13}C NMR ($CDCl_3$) δ 157.6, 147.7, 144.0, 142.7, 131.5, 129.1, 122.1, 121.4, 101.8, 55.5, 18.9; IR (KBr) 3372, 3209 2921, 2828, 1619, 1509 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0927.

2.1.55. *N*-*p*-Toluenesulfonyl-2-acetyl-4-methoxyaniline (59). To a solution of 2-acetyl-4-methoxyaniline[13] (100 mg, 0.61 mmol) in 10 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.15 mL, 1.82 mmol) and TsCl (139 mg, 0.73 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from AcOEt to give 184 mg (94%) of **59** as yellow crystals. Mp 120 °C; ^1H NMR ($CDCl_3$) δ 10.66 (1H, s), 7.86 (1H, d, J=9.0 Hz), 7.61 (2H, d, J=8.2 Hz), 7.21 (1H, d, J=2.9 Hz), 7.18 (2H, d, J=8.0 Hz), 7.05 (1H, dd, J=2.9, 9.8 Hz), 3.80 (3H, s), 2.43 (3H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.43, 155.23, 143.59, 136.34, 132.56, 129.47, 127.26, 124.90, 122.75, 119.84, 116.63, 55.67, 28.05, 21.49; IR (KBr) 3423, 3070, 2920, 2846, 1654, 1503 cm^{-1}; LRMS (EI) *m/z* 319 [20, M^++H], 317 [100, M^+]. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39; found: C, 60.22; H, 5.56; N, 4.34.

2.1.56. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-acetyl-4-methoxyaniline (60). To a solution of ketone **59** (180 mg, 0.56 mmol) and K_2CO_3 (117 mg, 0.85 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.07 mL, 0.85 mmol). The mixture was stirred at 80 °C for 1 h and reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture were extracted with Et_2O and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=2:1) to give 174 mg (86%) of **60** as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 7.46 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=9.2 Hz), 7.14 (1H, d, J=3.1 Hz), 6.82 (1H, dd, J=2.9, 8.8 Hz), 6.57 (1H, d, J=8.8 Hz), 5.80–5.90 (1H, m), 5.10 (1H, s), 5.06 (1H, d, J=5.9 Hz), 4.39 (1H, s), 4.00 (1H, s), 3.83 (3H, s), 2.64 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.4, 158.9, 143.7, 142.7, 134.9, 132.3, 129.7, 129.4, 128.9, 128.0, 119.9, 116.8, 113.7, 55.6, 54.5, 30.3, 21.5; IR (neat) 3427, 3065, 3005, 2909, 2841, 1654, 1502 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1250.

2.1.57. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-[1-(*tert*-butyldimethylsiloxy)-vinyl]-4-methoxyaniline (61). To a mixture of **60** (170 mg, 0.47 mmol), NaI (283 mg, 1.89 mmol) and Et_3N (0.28 mL, 2.07 mmol), was added a solution of TBSCl (285 mg, 1.89 mmol) in 20 mL of MeCN. The mixture was refluxed for 1 h and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$. After the mixture was extracted with Et_2O, combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on alumina (*n*-hexane/AcOEt=3:1) to give 210 mg (94%) of **61** as a light brown oil. ^1H NMR ($CDCl_3$) δ 7.66 (2H, d, J=8.3 Hz), 7.26 (2H, d, J=8.0 Hz), 7.06 (1H, dd, J=1.7, 1.7 Hz), 6.65 (2H, d, J=1.7 Hz), 5.70–5.79 (1H, m), 4.96 (2H, d, J=1.5 Hz), 4.93 (2H, dd, J=1.5, 15.4 Hz), 4.57 (2H, d, J=1.7 Hz), 3.78 (3H, s), 2.41 (3H, s), 0.94 (9H, s), 0.85 (6H, s); ^{13}C NMR ($CDCl_3$) δ 158.7, 152.7, 143.2, 137.1, 132.7, 130.6, 129.4, 128.9, 128.0, 119.1, 114.4, 113.6, 96.5, 55.2, 54.6, 25.8, 21.5, 18.2, −3.0, −4.6; IR (neat) 2960, 2924, 2851, 1513, 1260 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{36}NO_4SSi$ 474.2134, found 474.2105.

2.1.58. *N*-*p*-Toluenesulfonyl-4-(*tert*-butyldimethylsiloxy)-6-methoxy-1,2-dihydroquinoline (62). To a solution of olefin **61** (100 mg, 0.21 mmol) in 21 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (8.9 mg, 0.01 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was recrystallized from acetone to give 91 mg (98%) of **62** as pale yellow needles. Mp 108 °C; ^1H NMR ($CDCl_3$) δ 7.62 (1H, d, J=8.8 Hz), 7.30 (2H, d, J=8.1 Hz), 7.08 (2H, d,

J=8.1 Hz), 6.89 (1H, d, J=2.6 Hz), 6.85 (1H, dd, J=2.8, 8.8 Hz), 4.59 (1H, d, J=4.1 Hz), 4.22 (2H, d, J=4.2 Hz), 3.80 (3H, s), 2.32 (3H, s), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR ($CDCl_3$) δ 158.00, 146.34, 143.04, 136.54, 130.29, 129.17, 128.75, 127.87, 127.25, 113.59, 107.65, 99.49, 55.30, 45.09, 25.43, 21.40, 17.94, −5.07; IR (KBr) 3428, 2949, 2860, 1639, 1604, 1491 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{31}NO_4SSi$ 445.1743, found 445.1700.

2.1.59. 4-Hydroxy-6-methoxyquinoline (63). A mixture of **62** (50 mg, 0.11 mmol), 2 mL of 20% aq. NaOH and 5 mL of MeOH was refluxed overnight. The reaction was diluted with water and the mixture was extracted with CH_2Cl_2. Combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/MeOH=10:1) followed by recrystallization from acetone to give 17 mg (98%) of **63** as pale yellow prisms. Mp 246 °C (lit.[23] 244–247 °C from ethanol); ^{1}H NMR ($CDCl_3$) δ 119 (1H, s) 7.84 (1H, d, J=7.1 Hz), 7.52 (1H, d, J=9.0 Hz), 7.47 (1H, d, J=2.9 Hz), 7.27 (1H, dd, J=2.9, 9.0 Hz), 5.99 (1H, d, J=7.3 Hz), 3.81 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.12, 155.44, 138.40, 134.70, 126.78, 122.08, 120.09, 107.45, 104.12, 55.30; IR (KBr) 3428, 3076, 1594, 1385, 1229 cm^{-1}.

2.1.60. *N*-*p*-Toluenesulfonyl-2-acetyl-5-chloroaniline (64). To a solution of 2-acetyl-5-chloroaniline[14] (280 mg, 1.65 mmol) in 20 mL of CH_2Cl_2 under an Ar atmosphere, were added pyridine (0.41 mL, 4.95 mmol) and TsCl (378 mg, 1.98 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water. The mixture was extracted with AcOEt and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 400 mg (75%) of **64** as yellow needles. Mp 182 °C; ^{1}H NMR ($CDCl_3$) δ 11.59 (1H, s), 7.76 (2H, dd, J=2.0, 8.3 Hz), 7.73 (1H, d, J=3.9 Hz), 7.71 (1H, d, J=2.7 Hz), 7.27 (2H, d, J=8.5 Hz), 7.00 (1H, dd, J=2.1, 8.7 Hz), 2.55 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 201.4, 144.2, 141.3, 141.2, 136.3, 133.0, 129.8, 127.2, 122.6, 120.2, 118.6, 28.1, 21.5; IR (KBr) 3451, 3060, 1656, 1572, 1497, 1405 cm^{-1}; LRMS (EI) m/z 325 [45, M^+], 323 [100, M^+]. Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33; Found: C, 55.67; H, 4.41; N, 4.29.

2.1.61. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-acetyl-5-chloroaniline (65). To a solution of aldehyde **64** (300 mg, 0.93 mmol) and K_2CO_3 (192 mg, 1.40 mmol) in 10 mL of DMF under an Ar atmosphere, was added allyl bromide (0.11 mL, 1.40 mmol). The mixture was stirred at 80 °C for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O and combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from AcOEt to give 320 mg (95%) of **65** as pale yellow plates. Mp 103 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (1H, d, J=8.3 Hz), 7.45 (2H, d, J=8.3 Hz), 7.34 (1H, dd, J=2.0, 8.3 Hz), 7.30 (2H, d, J=7.8 Hz), 6.63 (1H, d, J=2.2 Hz), 5.77–5.87 (1H, m), 5.13 (1H, s), 5.09 (1H, dd, J=1.2, 6.8 Hz), 4.09 (2H, br), 2.64 (3H, s), 2.45 (3H, s); ^{13}C NMR ($CDCl_3$) δ 199.2, 144.2, 139.9, 137.9, 136.6, 134.3, 131.7, 130.4, 129.6, 128.6, 128.4, 127.9, 120.4, 54.3, 30.1, 21.5; IR (KBr) 3442, 1693, 1646, 1591, 1469, 1404 cm^{-1}; LRMS (EI) m/z 365 [2, M^+], 363 [3, M^+], 210 [100]. Anal. Calcd for $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.99; N, 3.85; Found: C, 59.60; H, 5.05; N, 3.83.

2.1.62. *N*-Allyl-*N*-*p*-toluenesulfonyl-2-[1-(*tert*-butyldimethylsilyloxy)vinyl]-5-chloroaniline (66). To a mixture of **65** (290 mg, 0.80 mmol), NaI (480 mg, 3.20 mmol) and Et_3N (0.47 mL, 3.52 mmol), was added a solution of TBSCl (482 mg, 3.20 mmol) in 20 mL of MeCN. The mixture was refluxed for 1 h and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$. After the mixture was extracted with Et_2O, combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from CH_2Cl_2 to give 375 mg (98%) of **66** as light brown needles. Mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (2H, d, J=8.2 Hz), 7.45 (1H, d, J=8.4 Hz), 7.29 (2H, d, J=8.4 Hz), 7.23 (1H, dd, J=2.0, 8.4 Hz), 6.75 (1H, d, J=2.0 Hz), 5.65–5.75 (1H, m), 4.97 (2H, d, J=9.8 Hz), 4.70 (2H, dd, J=1.6, 26.1 Hz), 4.11 (2H, d, J=6.8 Hz), 2.42 (3H, s), 0.92 (9H, s), 0.20 (6H, s); ^{13}C NMR ($CDCl_3$) δ 152.2, 143.7, 138.2, 137.4, 136.7, 133.0, 132.1, 130.8, 129.5, 128.2, 128.0, 119.6, 96.7, 54.4, 25.7, 25.6, 21.5, 18.2, −3.0, −4.6; IR (KBr) 3433, 1693, 1656, 1590, 1367 cm^{-1}; LRMS (FAB) m/z 480 [1, M^++H], 478 [3, M^++H], 364 [100].

2.1.63. *N*-*p*-Toluenesulfonyl-4-(*t*-butyldimethylsilyloxy)-7-chloro-1,2-dihydroquinoline (67). To a solution of olefin **66** (200 mg, 0.42 mmol) in 42 mL of CH_2Cl_2 under an Ar atmosphere, was added catalyst **B** (17.8 mg, 0.02 mmol). The mixture was degassed and stirred at 50 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) followed by recrystallization from CH_2Cl_2 to give 180 mg (95%) of **67** as pale yellow crystals. Mp 124 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, d, J=2.2 Hz), 7.44 (2H, d, J=8.4 Hz), 7.34 (1H, d, J=8.2 Hz), 7.24 (1H, dd, J=2.2, 8.2 Hz), 7.17 (2H, d, J=8.2 Hz), 4.71 (1H, dd, J=4.4, 4.4 Hz), 4.52 (2H, d, J=4.2 Hz), 2.40 (3H, s), 0.95 (9H, s), 0.00 (6H, s); ^{13}C NMR ($CDCl_3$) δ 146.0, 143.5, 137.0, 136.5, 133.6, 129.3, 127.4, 127.1, 126.3, 126.2, 123.5, 99.3, 60.3, 45.1, 25.4, 21.4, 17.9, 14.1, −5.1; IR (KBr) 3442, 2958, 2926, 2856, 1641, 1596, 1474, 1352 cm^{-1}; LRMS (EI) m/z 451 [50, M^+], 449 [100, M^+]. Anal. Calcd for $C_{22}H_{28}ClNO_3SSi$: C, 58.71; H, 6.27; N, 3.11; Found: C, 58.74; H, 6.27; N, 3.13.

2.1.64. 4-Hydroxy-7-chloroquinoline (68). A mixture of **67** (100 mg, 0.22 mmol), 1.1 mL of aq NaOH, and 5 mL MeOH was refluxed overnight. The reaction was quenched by water and the mixture was extracted with CH_2Cl_2. Combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt=10:1) followed by recrystallized from MeOH to give 32 mg (81%) of **68** as white prisms. Mp 272 °C (lit.[24] 277–279 °C from water); ^{1}H NMR (DMSO-d_6) δ 11.76 (1H, br), 8.06 (1H, d, J=8.8 Hz), 7.92 (1H, d, J=7.1 Hz), 7.57 (1H, s), 7.31 (1H, d, J=7.3 Hz), 7.04 (1H, d, J=6.8 Hz); ^{13}C NMR (DMSO-d_6) 176.3, 145.2, 139.9, 136.2, 127.3, 124.4, 123.4, 117.4, 109.3; IR (KBr) 3421, 3239,

3056, 2801, 2634, 1635, 1555, 1458, 1361 cm^{-1}; LRMS (EI) *m/z* 181 [35, M^+], 179 [100, M^+], 163 [100].

2.1.65. 4,7-Dichloroquinoline (69). A solution of **68** (180 mg, 1.00 mmol) in 2 mL of $POCl_3$ was refluxed for 1 h. To this mixture, was added 10% HCl and the mixture was extracted with Et_2O. Combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/MeOH=10:1) followed by recrystallization from CH_2Cl_2 to give 186 mg (94%) of **69** as white needles. Mp 84–85 °C (lit.[25] 84–85.5 °C from aqueous ethanol): ^1H NMR ($CDCl_3$) δ 8.77 (1H, d, J=4.8 Hz), 8.17 (1H, d, J=9.0 Hz), 8.14 (1H, d, J=2.0 Hz), 7.59 (1H, dd, J=2.2, 9.0 Hz), 7.47 (1H, d, J=4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 150.4, 149.4, 142.5, 136.4, 128.7, 128.5, 125.5, 124.9, 121.3; IR (KBr) 3449, 3057, 2924, 1609, 1556, 1488 cm^{-1}; LRMS (EI) *m/z* 201 [10, M^+], 199 [65, M^+], 197 [100, M^+].

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References and notes

1. For examples, (a) Skraup, Z. H. *Ber.* **1880**, *13*, 2086–2087. (b) Doebner, O.; Miller, W. V. *Ber* **1883**, *16*, 2464–2472. (c) Comb, A. *Bull. Soc. Chim. Fr.* **1888**, *49*, 89–92. (d) Friedländer, P. *Ber.* **1882**, *15*, 2572–2575. (e) Pfitzinger, W. *J. Prakt. Chem.* **1886**, *33*(2), 100. (f) Niementowski, W. V. *Ber.* **1894**, *27*, 1394–1403.
2. For examples, ruthenium-catalyzed versions; (a) Tsuji, Y.; Huh, K. T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673–1680. (b) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T. J.; Shim, S. C. *Chem. Commun.* **2000**, 1885–1886. (c) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269–3271. Palladium-catalyzed versions; (d) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952–2958. (e) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (f) Laborde, E.; Lesheski, L. E.; Kiely, J. S. *Tetrahedron Lett.* **1990**, *31*, 1837–1840. (g) Larock, R. C.; Kuo, M. Y. *Tetrahedron Lett.* **1991**, *32*, 569–572. (h) Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett.* **1993**, *34*, 1625–1628. (i) Dupont, J.; Halfen, R. A. P.; Zinn, F. K.; Pfeffer, M. *J. Organomet. Chem.* **1994**, *484*, c8–c9. (j) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1999**, 401–404. (k) Pita, B.; Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **2002**, *43*, 7929–7932. (l) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704–4705. Rhodium-catalyzed versions; (m) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490–491. (n) Watanabe, Y.; Yamamoto, M.; Shim, S. C.; Mitsudo, T.; Takegami, Y. *Chem. Lett.* **1979**, 1025–1026. (o) Watanabe, Y.; Suzuki, N.; Shim, S. C.; Yamamoto, M.; Mitsudo, T.; Takegami, Y. *Chem. Lett.* **1980**, 429–430. (p) Boyle, W. J.; Mares, F. *Organometallics* **1982**, *1*, 1003–1006. (q) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109–1112. Iron-catalyzed version; (r) Watanabe, Y.; Takatsuki, K.; Shim, S. C.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn* **1978**, *51*, 3397–3398. Copper-catalyzed version; (s) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488. (6) Manganese-catalyzed version; (t) Kobayashi, K.; Nakahashi, R.; Mano, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn* **2003**, *76*, 1257–1259. Cobalt-catalyzed version; (u) Domínguez, G.; Casarrubios, L.; Rodríguez-Noriega, J.; Pérez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856–2861.
3. (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041. (b) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960–961.
4. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
5. (a) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179–1180. (b) Nakagawa, M.; Torisawa, Y.; Uchida, H.; Nishida, A. *J. Synth. Org. Chem. Jpn* **1999**, *57*, 1004–1015. (c) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1873–1876. (d) Arisawa, M.; Kaneko, H.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *Synlett* **2000**, 841–843. (e) Arisawa, M.; Takahashi, M.; Takezawa, E.; Yamaguchi, T.; Torisawa, Y.; Nishida, A.; Nakagawa, M. *Chem. Pharm. Bull.* **2000**, *48*, 1593–1596. (f) Arisawa, M.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc. Perkin Trans. 1* **2002**, 959–964. (g) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4732–4734.
6. Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029–8033.
7. For reviews, see (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3012–3043. (d) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 1900–1923.
8. (a) Turner, R. B.; Woodward, R. B. In *The chemistry of the cinchona alkaloids. The alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1953; Vol. 3, pp 1–63 Chapter 16. (b) Uskokoviac, M. R.; Grethe, G. In *The cinchona alkaloids. The alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1973; Vol. 14, pp 181–223. (c) Grethe, G.; Uskokovic, M. R. *The chemistry of heterocyclic compounds*; Sexton, J. E., Ed.; Wiley-Interscience: New York, 1983; Vol. 23, p 279 Part 4. (d) Dutta, N. L.; Quasim, C. *Indian J. Chem.* **1968**, *6*, 566–567. For stereoselective total synthesis (e) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239–3242.
9. (a) Andersag, H.; Breitner, S.; Jung, H. German Patent 683, 692, October 26, 1939; *C.A.* **1942**, *36*, 4973. (b) Andersag, H.; Breitner, S.; Jung, H. US Patent 2,233,970, March 4, 1941; *C.A.* **1941**, *35*, 3771.
10. Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Nakagawa, M. *Synlett* **1998**, 389–390.
11. (a) Lauer, S. A.; Ghori, N.; Haldar, K. *Proc. Natl. Acad. Sci.*

U. S. A. **1995**, *92*, 9181–9185. (b) Lauer, S. A.; Rathod, P. K.; Ghori, N.; Haldar, K. *Science* **1997**, *276*, 1122–1125. (c) Akompong, T.; VanWye, J.; Ghori, N.; Haldar, K. *Mol. Biochem. Parasitol.* **1999**, *101*, 71–79.
12. Shishido, K.; Azuma, T.; Shibuya, M. *Tetrahedron Lett.* **1990**, *31*, 219–220.
13. Wilson, S. R.; Grandi, M. J. D. *J. Org. Chem.* **1991**, *56*, 4766–4772.
14. Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127*, 1125–1130.
15. Bailey, D. M. *J. Med. Chem.* **1969**, *12*, 184–185.
16. Heindel, N. D.; Bechara, I. S.; Ohnmacht, C. J.; Molnar, J.; Lemke, T. F.; Kennewell, P. D. *J. Med. Chem.* **1969**, *12*, 797–801.
17. Schweizer, E. E.; Smucker, L. D. *J. Org. Chem.* **1966**, *31*, 3146–3149.
18. Rewcastle, G. W.; Denny, W. A. *Synthesis* **1985**, *2*, 220–222.
19. Cai, S. X.; Zhon, Z.; Huang, J.; Whittemore, E. R.; Egbuwoku, Z. O.; Lü, Y.; Hawkinson, J. E.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *J. Med. Chem.* **1996**, *39*, 3248–3255.
20. Hewson, A. T.; Hughes, K.; Richardson, S. K.; Sharpe, D. A.; Wadsworth, A. H. *J. Chem. Soc. Perkin Trans. 1* **1991**, *6*, 1565–1569.
21. Hambly, A. N.; O'Grady, B. V. *Aust. J. Chem.* **1963**, *16*, 459–474.
22. Campbell, K. N.; Schaffner, I. J. *J. Am. Chem. Soc.* **1945**, *67*, 86–89.
23. Elderfield, R. C.; Maggiolo, A. *J. Am. Chem. Soc.* **1949**, *71*, 1906–1911.
24. Surrey, A. R.; Hammer, H. F. *J. Am. Chem. Soc.* **1946**, *68*, 113–116.
25. Kwart, H.; Miller, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 884–887.
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A computational study of cation–π interactions in polycyclic systems: exploring the dependence on the curvature and electronic factors☆

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Abstract—Density functional theory (B3LYP) calculations with double and triple-ζ quality basis sets were performed on the Li^+ and Na^+ π-complexes of corannulene **2**, sumanene **3CH$_2$**, heterosumanenes **3X**, triphenylene **4** and heterotrindenes **5X**. The metal ions bind to both convex and concave faces of buckybowls, with a consistent preference to bind to the convex surface by about 1–4 kcal/mol. The metal ion complexation with the π-framework of the central six-membered ring span wider range compared to benzene, indicating the control of size, curvature and electronic perturbations over the strength of cation–π interactions. Computations show that the bowl-to-bowl inversion barriers are only slightly altered upon metal complexation, indicating the continuity of bowl-to-bowl inversion despite metal complexation. We have calculated the binding energies of model systems, triphenylene (**4**) and heterotrindenes (**5X**), which indicate that the interaction energies are controlled by electronic factors. While the inversion barrier is dependent mainly on the size of the heteroatom, the extent of binding is independent of the size of the atom or the bowl depth.

1. Introduction

Non-covalent interactions such as van der Waals interactions, hydrogen bonding, dispersive forces, hydrophilic and hydrophobic interactions play a major role in dictating the structures and functions of biological macromolecules and supramolecular assemblies.[1,2] These interactions are responsible for molecular recognition like substrate–enzyme, antigen–antibody, neurotransmitter–neuroreceptor, protein–protein, protein–DNA interactions, etc. Dougherty and co-workers have identified the interaction between a cation and the π-face of an aromatic ring namely the cation–π interaction.[3] Cation–π interactions are ubiquitous in biological systems and arguably the strongest among the non-covalent interactions.[3–5] The interaction of metal ions with the π-system of various aromatic hydrocarbons and aminoacids containing aromatic rings have generated interest recently.[6,7] A recent study of the dependence of the strength of cation–π interaction on the curvature of polycyclic system showed a marginal preference for binding to the convex face.[8] Thus, the curvature was expected to show only a slight facial selectivity in cation–π interaction. To our knowledge, the influence of electronic factors and the aromaticity of the π-system on the cation binding ability have not been explored.

A theoretical study on a designed series of model systems where the curvature and electronic factors can be systematically modulated should help in discerning the causative factors of the binding energies. The C_{20} and C_{21} fragments of C_{60} along its C_5 and C_3 axes have been subjects of a number of experimental and theoretical studies.[9,10] There has been a lot of interest in this class of compounds, which resulted in a flurry of research activity concentrating on this C_3-fragment of fullerene.[9–13] Theoretical study on trisubstituted trindenes and sumanenes indicated that the type of substituent imparts a marked effect on the central six-membered ring of both the systems.[13] Thus, these systems provide benzene rings modified by varied extents and we felt a systematic study of M^+ (Li^+, Na^+) ion binding to the central six-membered ring (Scheme 1) would be worthwhile. Many experimental studies on the endohedral and exohedral complexes of fullerene with various metal ions, which have potential applications in superconductivity, are available.[14,15] Similarly, a buckybowl bound to a transition metal fragment has been synthesized and theoretical studies on a similar class of compounds have been reported.[16,17] In the present paper, we report a density functional theory study of the cation–π interactions of a series of polycyclic aromatic compounds (**2**, **3X**, **4** and **5X**) (Scheme 1). Unlike planar aromatics, the cation has the possibility to bind to the

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Keywords: Cation–π interaction; Polycylic aromatic hydrocarbons; Buckybowls; Heterobuckybowls; Computational.

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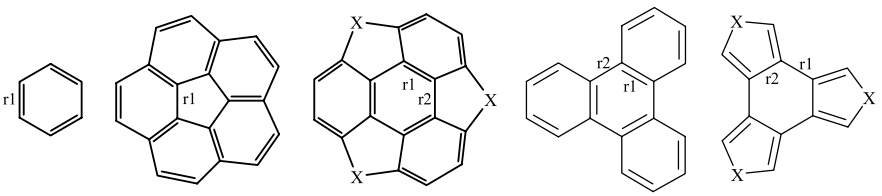
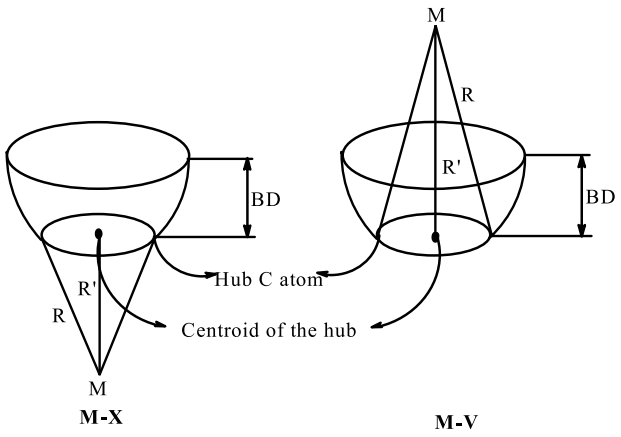


X = O, NH, CH_2, BH, S, PH, PH_3, Si, SiH_2, AlH

Scheme 1.

two distinct faces, namely convex, **X** and concave, **V** (Scheme 2) of these bowl structures. The relative binding of the metal ions namely, Li^+ and Na^+, to either face of the buckybowls are analyzed. The buckybowls considered in the present study exhibit bowl depth (BD) ranging from 0.0 to 1.5 Å and possess substituents with varying electronegativities.[13] Hence, it would be interesting to see how these factors dictate the binding energies and other physicochemical properties such as curvature, BD, in this class of compounds. Cation–π interactions of model systems, **4** and **5X**, are studied to understand the electronic factor dependence on the binding energies. The heterotrindenes (**5X**) which are devoid of curvature (except **5PH**) are expected to single out the effect of electronic perturbations on the binding energies. We have also examined the effect of cation binding on the bowl-to-bowl inversion barriers of the bowl structures. Hybrid density functional theory (B3LYP) calculations were performed to address the above points.



Scheme 2.

2. Methodology

All the structures considered in the study were optimized within the given symmetry constraints using the hybrid density functional theory B3LYP level using the 6-31G* basis set. The nature of the stationary points thus obtained was assessed based on frequency calculations. The planar forms of corannulene (**2**) and sumanenes, **3X**, (X=O, NH, CH_2, BH and S) were computed to be transition states corresponding to the bowl-to-bowl inversion. The planar forms of **3X** (X=PH_3, Si, SiH_2 and AlH) were characterized as minima on the potential energy surface, thus, precluding the possibility for a bowl structure. The planar form of **3PH** is a third order saddle point; the normal modes of the imaginary frequencies correspond to the out-of-plane bending of the hydrogen atoms connected to phosphorus. The minimum energy structures corresponding to the bowl forms of **3X** (X=O, NH, CH_2, BH and S) have been located and the frequency calculations characterize them as minima. The Li^+ and Na^+ complexes of all the minimum energy structures were optimized and characterized as minima except **3O-Na^+-V**, which is a second order saddle point. The transition states corresponding to the bowl-to-bowl inversion barriers of the metal ion complexed buckybowls were also obtained and their nature was confirmed by frequency calculations. **4**, **5X** and their Li^+ and Na^+ complexes were optimized at the B3LYP/6-31G* level. Planar structures were considered for all except **5PH**, where the three hydrogen atoms connected to P lie out-of-plane. **5Si** and **5AlH** were third order saddle points, which was traced to the *peri*-hydrogen interactions.[13] The complexes of these two trindenes and **5BH** are also higher order saddle points (Table 1). Previous computational studies on buckybowls and cation–π interactions reveal that employing the triple-ζ basis set is crucial in obtaining reliable inversion barriers of buckybowls and cation–π binding energies.[18–21] Therefore, single point calculations were employed at the B3LYP level using the 6-311+G** basis set for all the systems considered in the present study. The discussion on the energetics will be based on those obtained at the B3LYP/6-311+G** basis set unless otherwise specified. All computations were performed using Gaussian 98 suite of programs.[22] The curvature of the buckybowls and their complexes were assessed based on the π-orbital axis vector (POAV) angles.[23,24]

3. Results and discussion

The equilibrium geometries and effect of metal ion binding on the geometric parameters of all the compounds and curvature of buckybowls are discussed first. This is followed by a discussion on the variation of the interaction energies arising from binding to the convex and the concave faces of the buckybowls and the role of varying heteroatoms in the strength of binding. Finally, the deviation of the bowl-to-bowl inversion barriers of the parent buckybowl molecules upon cation binding is presented.

3.1. Equilibrium geometries

The principal equilibrium geometries of **1**, **2**, **3X**, **4**, **5X**, and their metal ion complexes are given in Table 1 The notations used in Table 1 are to be deciphered from Schemes 1 and 2. POAV angle is the angle between the vector normal to the

Table 1. The principal geometric parameters (r, $r2$, R and R'), bowl depth (BD) and POAV angles at the hub position of **1**, **2**, **3X**, **4** and **5X**, their metal ion (Li^+ and Na^+) complexes and bowl-to-bowl inversion transition states. The notations used in this table are illustrated in Schemes 1 and 2. All bond lengths are given in Å and angles in degrees. The number of imaginary frequencies are also given

Structure	$r1$	$r2$	R	R'	BD	POAV (hub)	N_{Img}	Structure	$r1$	$r2$	R	R'	N_{Img}
1	1.397	—	—	—	—	—	0	**2-TS**	1.398	—	—	—	1
1-Li$^+$	1.406	—	2.349	1.882	—	—	0	**2-Li$^+$-TS**	1.401	—	2.254	1.913	1
1-Na$^+$	1.404	—	2.761	2.377	—	—	0	**2-Na$^+$-TS**	1.401	—	2.672	2.392	1
2	1.385	—	—	—	0.862	98.1	0	**3O-TS**	1.348	1.369	—	—	1
2-Li$^+$-X	1.393	—	2.281	1.934	0.876	98.1	0	**3O-Li$^+$-TS**	1.354	1.375	2.345	1.907	1
2-Li$^+$-V	1.393	—	2.252	1.899	0.883	98.3	0	**3O-Na$^+$-TS**	1.353	1.374	2.766	2.406	1
2-Na$^+$-X	1.391	—	2.680	2.391	0.892	98.4	0	**3NH-TS**	1.354	1.375	—	—	1
2-Na$^+$-V	1.391	—	2.690	2.403	0.905	98.4	0	**3NH-Li$^+$-TS**	1.362	1.381	2.294	1.839	1
3O	1.399	1.428	—	—	1.486	101.9	0	**3NH-Na$^+$-TS**	1.361	1.380	2.700	2.326	1
3O-Li$^+$-X	1.406	1.436	2.398	1.931	1.484	101.9	0	**3CH$_2$-TS**	1.366	1.400	—	—	1
3O-Li$^+$-V	1.405	1.435	2.373	1.901	1.504	103.3	0	**3CH$_2$-Li$^+$-TS**	1.372	1.406	2.302	1.836	1
3O-Na$^+$-X	1.405	1.435	2.771	2.379	1.491	102.0	0	**3CH$_2$-Na$^+$-TS**	1.371	1.405	2.709	2.327	1
3O-Na$^+$-V	1.403	1.432	2.861	2.485	1.513	102.0	2	**3BH-TS**	1.367	1.420	—	—	1
3NH	1.399	1.422	—	—	1.325	100.6	0	**3BH-Li$^+$-TS**	1.373	1.425	2.310	1.839	1
3NH-Li$^+$-X	1.407	1.428	2.341	1.863	1.303	100.6	0	**3BH-Na$^+$-TS**	1.371	1.425	2.727	2.341	1
3NH-Li$^+$-V	1.408	1.428	2.380	1.785	1.308	100.8	0	**3S-TS**	1.382	1.403	—	—	1
3NH-Na$^+$-X	1.407	1.428	2.709	2.308	1.315	100.6	0	**3S-Li$^+$-TS**	1.390	1.409	2.342	1.878	1
3NH-Na$^+$-V	1.405	1.426	2.721	2.324	1.315	98.7	0	**3S-Na$^+$-TS**	1.388	1.408	2.754	2.373	1
3CH$_2$	1.387	1.433	—	—	1.121	98.5	0	**4**	1.421	1.467	—	—	0
3CH$_2$-Li$^+$-X	1.392	1.440	2.343	1.866	1.109	99.0	0	**4-Li$^+$**	1.431	1.475	2.342	1.837	0
3CH$_2$-Li$^+$-V	1.393	1.442	2.288	1.796	1.161	98.7	0	**4-Na$^+$**	1.428	1.475	2.734	2.316	0
3CH$_2$-Na$^+$-X	1.392	1.440	2.726	2.329	1.126	99.1	0	**5O**	1.452	1.453	—	—	0
3CH$_2$-Na$^+$-V	1.391	1.440	2.714	2.315	1.190	96.5	0	**5O-Li$^+$**	1.459	1.464	2.357	1.850	0
3BH	1.377	1.439	—	—	0.890	96.5	0	**5O-Na$^+$**	1.458	1.462	2.741	2.320	0
3BH-Li$^+$-X	1.383	1.443	2.345	1.871	0.891	96.7	0	**5NH**	1.451	1.445	—	—	0
3BH-Li$^+$-V	1.383	1.445	2.387	1.798	0.902	96.9	0	**5NH-Li$^+$**	1.458	1.456	2.291	1.764	0
3BH-Na$^+$-X	1.382	1.445	2.743	2.351	0.915	96.9	0	**5NH-Na$^+$**	1.458	1.453	2.663	2.230	0
3BH-Na$^+$-V	1.381	1.444	2.719	2.323	0.934	94.0	0	**5CH$_2$**	1.460	1.489	—	—	0
3S	1.391	1.414	—	—	0.642	95.1	0	**5CH$_2$-Li$^+$**	1.467	1.500	2.348	1.819	0
3S-Li$^+$-X	1.398	1.420	2.367	1.902	0.643	95.1	0	**5CH$_2$-Na$^+$**	1.466	1.467	2.709	2.267	0
3S-Li$^+$-V	1.400	1.421	2.319	1.841	0.677	95.4	0	**5BH**	1.390	1.483	—	—	0
3S-Na$^+$-X	1.398	1.421	2.761	2.374	0.679	95.4	0	**5BH-Li$^+$**	1.393	1.493	2.458	1.988	2
3S-Na$^+$-V	1.398	1.421	2.748	2.360	0.703	95.6	0	**5BH-Na$^+$**	1.397	1.492	2.825	2.428	2
3PH	1.388	1.423	—	—	0.107	90.0	0	**5S**	1.462	1.449	—	—	0
3PH-Li$^+$-X	1.396	1.430	2.324	1.854	0.094	90.0	0	**5S-Li$^+$**	1.469	1.457	2.352	1.841	0
3PH-Li$^+$-V	1.396	1.430	2.329	1.851	0.102	90.0	0	**5S-Na$^+$**	1.468	1.455	2.732	2.308	0
3PH-Na$^+$-X	1.395	1.431	2.735	2.342	0.273	91.8	0	**5PH**	1.468	1.480	—	—	0
3PH-Na$^+$-V	1.394	1.429	2.745	2.355	0.028	90.0	0	**5PH-Li$^+$**	1.474	1.487	2.368	1.849	0
3PH$_3$	1.390	1.432	—	—	0.027	90.0	0	**5PH-Na$^+$**	1.474	1.485	2.732	2.297	0
3PH$_3$-Li$^+$	1.400	1.442	2.308	1.820	0.018	90.0	0	**5PH$_3$**	1.469	1.500	—	—	0
3PH$_3$-Na$^+$	1.396	1.441	2.711	2.314	0.102	91.1	0	**5PH$_3$-Li$^+$**	1.479	1.512	2.365	1.833	0
3Si	1.386	1.435	—	—	0.000	90.0	0	**5PH$_3$-Na$^+$**	1.479	1.509	2.756	2.289	0
3Si-Li$^+$	1.394	1.442	2.313	1.827	0.094	90.0	0	**5Si**	1.464	1.527	—	—	3
3Si-Na$^+$	1.392	1.442	2.728	2.331	0.177	91.1	0	**5Si-Li$^+$**	1.471	1.533	2.415	1.891	2
3SiH$_2$	1.401	1.446	—	—	0.000	90.0	0	**5Si-Na$^+$**	1.470	1.530	2.775	2.334	2
3SiH$_2$-Li$^+$	1.402	1.453	2.322	1.831	0.003	90.0	0	**5SiH$_2$**	1.478	1.512	—	—	0
3SiH$_2$-Na$^+$	1.401	1.452	2.730	2.328	0.034	90.0	0	**5SiH$_2$-Li$^+$**	1.478	1.522	2.388	1.855	0
3Al	1.404	1.468	—	—	0.000	90.0	0	**5SiH$_2$-Na$^+$**	1.484	1.519	2.756	2.311	0
3Al-Li$^+$	1.412	1.474	2.298	1.788	0.008	90.0	0	**5AlH**	1.487	1.537	—	—	3
3Al-Na$^+$	1.410	1.474	2.699	2.282	0.023	90.0	0	**5AlH-Li$^+$**	1.497	1.547	2.359	1.803	3
								5AlH-Na$^+$	1.495	1.544	2.722	2.259	3

triangle formed by the three idealized C–C bonds[23,24] and BD is the distance between the two planes formed by the hub and the rim atoms. The parameter R is the distance between the hub carbon atom and the metal ion, and R' is the distance from the centroid of the hub to the metal ion. All the bond lengths of the central six-membered ring are uniformly elongated in all cases upon complexation with either Li^+ or Na^+. However, the variation of the other bond lengths upon cation binding is marginal in most of the cases. Among **3X**, R is longer in case of **3O** and among **5X**, M–C bond length is longer in case of **5BH** indicating the weak interaction in these two compounds. The weak binding is also reflected in the low binding energies compared to that of the other systems (vide infra). BD and POAV angles have been extensively used to evaluate the curvature of buckybowls. The BD of the heterosumanenes decreases upon increasing the size of the heteroatom. The planar structures are the minima, when X=PH_3, Si, SiH_2 and AlH; hence, these do not have two distinct faces (convex and concave). In general, Na^+ imparts more curvature on the buckybowl skeleton compared to Li^+. When Li^+ binds to the convex face of the bowls, the BD slightly decreases or remains almost the same compared to that of the parent buckybowl. On the other hand, those complexes where Li^+ is bound to the concave face or Na^+ is bound to either of the faces, exhibit a comparatively deeper bowl skeleton. In the case of

3NH, all the complexes exhibit lower BDs compared to the parent buckybowl. A similar trend is observed when POAV angle is used as a measure of curvature (Table 1).

3.2. Binding energies

The interaction energies of the compounds under study when binding with Li^+ and Na^+ obtained at the B3LYP level using the 6-31G* and 6-311+G** basis sets are given in Table 2. The binding energies are uniformly overestimated when 6-31G* basis set was used except for **5NH**. Importantly, the trend of the binding energies between the convex and concave faces obtained using the 6-31G* basis set is different compared to those obtained using 6-311+G** basis set in many cases, emphasizing the importance of employing triple-ζ quality basis set. Thus, the complexation energy mainly depends on the quality of the basis set and this is in agreement with our recent study on metal ion complexation with corannulene and suamanene.[8] A comparison of the binding energies of the convex and concave bound complexes reveals that the selectivity between the two is marginal. However, binding to the convex face is consistently preferred over the concave face in all cases. The preference is about 3–4 kcal/mol when X=O, NH and BH, whereas in case of X=CH_2, S and PH, the selectivity for binding between the two faces is marginal. The binding energies of the cation complexes exhibit wide ranges with both Li^+ (25–59 kcal/mol) and Na^+ (15–43 kcal/mol) with varying substituents. The correlation of the interaction energies of all the compounds considered in the study with Li^+ and Na^+ is depicted in Figure 1. As the difference between the binding energies of the convex and concave bound complexes are marginal, those of only the convex complexes are depicted in the figure for clarity. Consistent with the previous studies, Li^+ binds strongly to the π-systems compared to Na^+ in all the cases. The trend of the binding energies of the Li^+ and Na^+ complexes remains the same with respect to the varying substituents. Any straight correlation of the BD, curvature or electronegativity of the heteroatom with the complexation energy could not be obtained, indicating the intricate factors involved in deciding the affinity. The two factors affecting the binding energies are the curvature and the electronic perturbation caused by the substitutents. A comparison of the binding energies of the bowl molecules (**2**, **3X**) and the corresponding planar molecules (**2-TS** and **3X-TS**) reveals that they are comparable; the qualitative trend of the variation of binding energies with varying

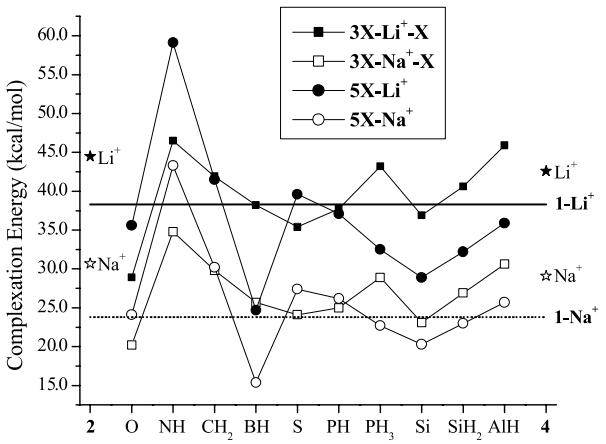


Figure 1. The correlation of the interaction energies of benzene (**1**), corannulene (**2**), heterosumanenes (**3X**), triphenylene (**4**) and heterotrindenes (**5X**) with Li^+ and Na^+ obtained at the B3LYP/6-311+G** level.

Table 2. The interaction energies (in kcal/mol) of the compounds considered in the present study with Li^+ and Na^+ ions obtained at the B3LYP level using the 6-31G* (in parentheses) and 6-311+G** basis sets

Structure	Li^+-X	Li^+-V	Na^+-X	Na^+-V
1	38.3 (42.3)	—	23.8 (28.5)	—
2	44.5 (48.2)	40.3 (46.5)	30.7 (34.2)	28.0 (33.6)
2-TS	42.4 (46.1)	—	28.3 (31.6)	—
3O	28.9 (33.5)	25.5 (33.9)	20.2 (24.3)	17.4 (25.2)
3O-TS	28.1 (32.3)	—	17.2 (21.1)	—
3NH	46.5 (51.4)	42.9 (51.0)	34.8 (39.2)	30.5 (38.1)
3NH-TS	46.3 (50.8)	—	31.9 (36.4)	—
3CH_2	41.9 (45.6)	40.9 (47.4)	29.8 (33.2)	28.5 (34.4)
3CH_2-TS	42.5 (45.9)	—	28.7 (31.9)	—
3BH	38.2 (41.5)	34.7 (40.2)	25.7 (28.9)	21.9 (26.9)
3BH-TS	37.4 (40.8)	—	23.6 (27.0)	—
3S	35.4 (37.6)	33.8 (37.9)	24.1 (26.1)	22.5 (25.9)
3S-TS	35.0 (37.4)	—	22.8 (25.3)	—
3PH	37.7 (40.2)	37.2 (40.2)	25.0 (27.1)	24.4 (27.4)
3PH_3	43.2 (45.9)	—	28.9 (31.6)	—
3Si	36.9 (39.6)	—	23.1 (25.6)	—
3SiH_2	40.6 (43.3)	—	26.9 (29.6)	—
3AlH	45.9 (48.8)	—	30.6 (33.5)	—
4	42.6 (46.4)	—	29.1 (33.1)	—
5O	35.6 (40.3)	—	24.1 (28.5)	—
5NH	59.1 (54.7)	—	43.3 (38.6)	—
5CH_2	41.5 (44.9)	—	30.2 (33.5)	—
5BH	24.7 (27.5)	—	15.4 (18.2)	—
5S	39.6 (42.2)	—	27.4 (30.1)	—
5PH	37.1 (39.6)	—	26.2 (28.6)	—
5PH_3	32.5 (35.2)	—	22.7 (25.3)	—
5Si	28.9 (30.2)	—	20.3 (21.4)	—
5SiH_2	32.2 (34.7)	—	23.0 (25.3)	—
5AlH	35.9 (38.3)	—	25.7 (27.9)	—

Table 3. NICS values calculated at 1 Å above the centroid of the six-membered ring, total charge and the perimeter at the central six-membered ring obtained at the B3LYP level using 6-31G* basis set

Structure	NICS	Charges	Perimeter
1	−11.2	−0.771	8.380
2[a]	2.6, *−2.3*, **5.3**	−0.257	7.085
3O[a]	1.7, *−9.5*, **−6.3**	−0.110	8.481
3NH[a]	1.4, *−9.1*, **−6.5**	−0.155	8.463
3CH_2[a]	−1.6, *−10.6*, **−6.7**	0.074	8.460
3BH[a]	−2.7, *−8.0*, **−6.5**	0.004	8.448
3S[a]	−2.4, *−7.6*, **−5.4**	0.462	8.415
3PH	−6.3	0.465	8.433
3PH_3	−6.3	0.535	8.466
3Si	−7.4	0.470	8.463
3SiH_2	−6.4	0.254	8.526
3AlH	−6.7	0.253	8.616
4	−6.1	0.422	8.541
5O	−12.0	0.362	8.715
5NH	−3.2	0.280	8.688
5CH_2	−1.0	0.711	8.847
5BH	22.8	0.344	8.619
5S	0.8	0.821	8.733
5PH	0.7	0.710	8.844
5PH_3	0.9	0.881	8.907
5Si	0.8	0.787	8.973
5SiH_2	0.6	0.555	8.970
5AlH	0.6	0.554	9.072

[a] The three values correspond to the NICS values calculated for the bowl structure from the convex (underlined) and concave (italicized) face and calculated for the planar form (bold).

Table 4. The bowl-to-bowl inversion barriers (in kcal/mol) of the buckybowls (**2** and **3X**) and their metal ion complexes obtained at the B3LYP level using 6-31G* (in parentheses) and 6-311+G** basis set

Structure	Convex (**X**)	Transition state (**TS**)	Concave (**V**)
2	0.0 (0.0)	10.7 (8.6)	0.0 (0.0)
2-Li$^+$	0.0 (0.0)	8.5 (9.0)	4.2 (1.6)
2-Na$^+$	0.0 (0.0)	10.4 (10.6)	2.7 (−0.6)
3O	0.0 (0.0)	70.4 (68.3)	0.0 (0.0)
3O-Li$^+$	0.0 (0.0)	67.8 (69.9)	3.4 (−0.4)
3O-Na$^+$	0.0 (0.0)	70.6 (72.4)	2.8 (1.0)
3NH	0.0 (0.0)	44.6 (42.1)	0.0 (0.0)
3NH-Li$^+$	0.0 (0.0)	41.1 (42.4)	3.6 (0.4)
3NH-Na$^+$	0.0 (0.0)	43.2 (43.9)	4.3 (−1.2)
3CH$_2$	0.0 (0.0)	19.1 (16.8)	0.0 (0.0)
3CH$_2$-Li$^+$	0.0 (0.0)	17.5 (18.3)	1.0 (−1.8)
3CH$_2$-Na$^+$	0.0 (0.0)	18.9 (19.3)	1.3 (1.2)
3BH	0.0 (0.0)	7.4 (5.9)	0.0 (0.0)
3BH-Li$^+$	0.0 (0.0)	4.7 (5.3)	3.5 (1.3)
3BH-Na$^+$	0.0 (0.0)	5.7 (5.9)	3.8 (−2.0)
3S	0.0 (0.0)	2.9 (1.8)	0.0 (0.0)
3S-Li$^+$	0.0 (0.0)	1.8 (2.3)	1.6 (−0.3)
3S-Na$^+$	0.0 (0.0)	2.6 (2.5)	1.6 (−0.2)

substituents remain unaltered. This indicates that the BD has very little effect on the binding energies of the buckybowls. Hence, the complexation energies are mainly controlled by electronic factors. The qualitative trend of the binding energies of **3X** and **5X** for the various substituents are comparable except when X=S and PH_3. While the lowest binding energy is observed for **3X** when X=O; the complexation energy is lowest for **5X** when X=BH, when binding to either Li^+ or Na^+. The weak binding in these compounds is also witnessed in the long M−C bond lengths (Table 1). The π-complexes exhibit higher binding energies when X=NH, in both **3X** and **5X**, which is about 21 kcal/mol higher than that of benzene in **5NH-Li$^+$**. We have studied the effect of aromaticity of the central six-membered ring on the binding energies using the nucleus independent chemical shift (NICS) criterion.[25] The NICS (1) values are calculated both in the convex and concave surfaces for the bowl shaped molecules and are given in Table 3. The six-membered ring in **5X** exhibits non-aromatic character in all the cases except when X=O and BH. While **5O** is designated as highly aromatic, **5BH** is found to have antiaromatic character according to NICS. This is in line with our observation that the bond length alternation in **3O** is close to zero and that of **3BH** is around 0.09 Å.[13,26] We also have examined the total charge and the perimeter of the hub six-membered ring (Table 3). No straightforward correlation between any of these parameters and the binding energy could be drawn. Thus we feel that the electronic effects of the substituent atoms are not of columbic origin and operate in a more intricate way.

3.3. Bowl-to-bowl inversion barriers

The bowl-to-bowl inversion barriers of the parent buckybowls (**2** and **3X**; X=O, NH, CH_2, BH and S) and their corresponding Li^+ and Na^+ complexed bowl structures are given in Table 4. In the case of parent buckybowls, the inversion process normally leads to identical bowl structures. In contrast, the metal ion bound buckybowls generate two distinct species upon inversion (Fig. 2). Among the heterosumanenes (**3X**), the bowl-to-bowl inversion barriers decrease with the increase in the size of the heteroatom; calculations predict that the bowl-to-bowl inversion process does not happen when X=PH_3, Si, SiH_2 and AlH. Metal ion (both Li^+ and Na^+) complexation to the bowl molecules results in a slight lowering of the inversion barrier for the bowl-to-bowl. The maximum difference between the inversion barriers of the parent buckybowl and its corresponding metal ion complex is 3.5 kcal/mol in the case of **3NH-Li$^+$**. Therefore, the inversion barrier corresponding to the bowl-to-bowl inversion process is controlled mainly by the size of the substituent and not due to the electronic perturbations.

4. Conclusions

B3LYP/6-311+G** calculations were performed to assess the effect of curvature and remote electronic perturbations on the cation−π interactions of a large series of aromatic hydrocarbons and their hetero analogs. In all cases, except corannulene, the π-system is a structurally and electronically modified aromatic six-membered ring. The metal ions (Li^+ and Na^+) bind to both the faces of the buckybowls arising to two possibilities for π-complexes; convex face binding is preferred over concave binding in all the cases by about 1−4 kcal/mol. Both the bowl and planar forms yield similar binding energies, indicating that the curvature of the buckybowls has very little effect on the complexation energies. The strength of cation binding to the six-membered ring is mainly controlled by electronic factors, while the curvature plays only a marginal role. Heterosumanene or heterotrindene has a very high complexation energy compared to other compounds when X=NH. The present study indicates that there is no straightforward correlation between either the charge on

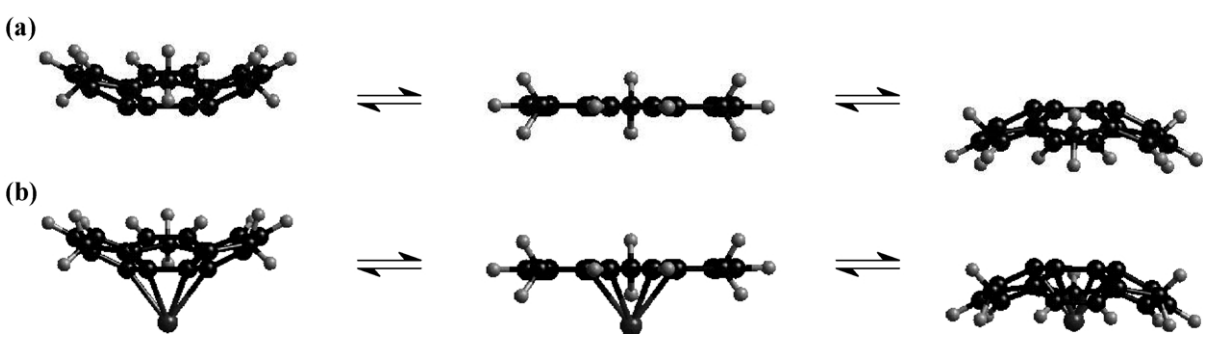


Figure 2. The bowl-to-bowl inversion processes of parent buckybowls (a) and their metal ion complexes (b).

the hub or the size of the system with the binding energies. The interaction energies observed in this class of compounds exhibit a wide range from 25–59 and 15–43 kcal for Li^+ and Na^+ ions, respectively. Importantly, the present study reveals that the curvature and flexibility of the curved surfaces are virtually undisturbed upon metal ion complexation and the solvation might have an important role in cation–π interactions but it is not considered in the present study due to the computational demand at this level of theory. A careful tuning of the electronic factors can make the strength of cation–π interactions comparable to that of covalent interactions! While the strength of binding is controlled by electronic factors, the bowl-to-bowl inversion barrier is exclusively controlled by the size of the heteroatom.

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References and notes

1. (a) Weber, G. *Protein interactions*; Chapman & Hall: London, 1992. (b) Rubin, H. *Touchstone of life: molecular information, cell communication, and the foundations of life*; Oxford University Press: New York, 1999.
2. Jones, S.; Thornton, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, 13–20.
3. Dougherty, D. A. *Science* **1996**, *271*, 163–168.
4. Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.
5. (a) Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307–2308. (b) Gallivan, J. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 870–874. (c) Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459–9464. (d) Ngola, M.; Kearney, P. C.; Mecozzi, S.; Russell, K.; Dougherty, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 1192–1201. (e) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103–105. (f) Ngola, S. M.; Dougherty, D. A. *J. Org. Chem.* **1998**, *63*, 4566–4567. (g) Coates, G. W.; Dunn, A. R.; Henling, L. M.; Dougherty, D. A.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 248–251.
6. (a) Doetschman, D. C.; Gilbert, D. C.; Dwyer, D. W. *Chem. Phys.* **2000**, *256*, 37–43. (b) Bruce, G.; Jack, D. H. *J. Bioorg. Med. Chem.* **2003**, *11*, 311–314. (c) Dasiewicz, B.; Fuks, L.; Lewandowski, W. *J. Mol. Struct.* **2001**, *565–566*, 1–6. (d) Ekaterina, V. P.; Alain, T. L.; Bruce, D. F.; Nenad, M. K. *J. Am. Chem. Soc.* **2001**, *123*, 6232–6245. (e) Marianne, R.; Jacky, L.; Eric, B. *J. Mol. Biol.* **2002**, *316*, 67–76.
7. (a) Sundaram, A.; Toshihiro, F.; Hiroaki, T. *J. Chem. Phys.* **1999**, *250*, 237–242. (b) David, F.; David, A. D.; John, B. N. *J. Phys. Chem. A* **2000**, *104*, 11414–11419.
8. Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett.* **2003**, *44*, 6043–6046.
9. (a) Rabideau, P. W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235–241. (b) Mehta, G.; Rao, H. S. P. *Tetrahedron* **1998**, *54*, 13325–13329. (c) Mehta, G.; Panda, G. *Proc. Indian Natl. Sci. Acad., Part A* **1998**, *64*, 587–608. (d) Scott, L. T.; Bronstein, H. E.; Preda, D. V.; Ansems, R. B. M.; Bratcher, M. S.; Hagen, S. *Pure Appl. Chem.* **1999**, *71*, 209–219.
10. (a) Priyakumar, U. D.; Sastry, G. N. *J. Phys. Chem. A* **2001**, *105*, 4488–4494. (b) Priyakumar, U. D.; Sastry, G. N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 30–40. (c) Priyakumar, U. D.; Sastry, G. N. *J. Mol. Graphics Modell.* **2001**, *19*, 266–269. (d) Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett.* **2001**, *42*, 1379–1381. (e) David, D.; Nguyen, M. T.; Vanquickenborne, L. G. *Chem. Phys. Lett.* **2001**, *333*, 103–112. (f) Sastry, G. N.; Rao, H. S. P.; Bednarek, P.; Priyakumar, U. D. *Chem. Commun* **2000**, 843–844. (g) Klemm, L. H.; Hall, E.; Cousins, L.; Klopfenstein, C. E. *J. Heterocycl. Chem.* **1989**, *26*, 345–348.
11. (a) Imamura, K.; Takimiya, K.; Aso, Y.; Otsubo, T. *Chem. Commun.* **1999**, 1859–1860. (b) Sygula, A.; Rabideau, P. W. *J. Am. Chem. Soc.* **1999**, *121*, 7800–7803. (c) Ansems, R. B. M.; Scott, L. T. *J. Am. Chem. Soc.* **2000**, *122*, 2719–2724. (d) Sygula, A.; Marcinow, Z.; Fronczek, F. R.; Guzei, H.; Rabideau, P. E. *Chem. Commun.* **2000**, 2439–2440. (e) Mehta, G.; Sarma, P. V. V. S. *Chem. Commun.* **2000**, 19–20. (f) Steiner, E.; Fowler, P. W.; Jenneskens, L. W. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 362–365.
12. (a) Dinadayalane, T. C.; Priyakumar, U. D.; Sastry, G. N. *J. Mol. Struct. (Theochem)* **2001**, *543*, 1–10. (b) Dinadayalane, T. C.; Priyakumar, U. D.; Sastry, G. N. *J. Chem. Soc., Perkin Trans. 2* **2002**, 94–101. (c) Dinadayalane, T. C.; Sastry, G. N. *J. Org. Chem.* **2002**, *67*, 4605–4607. (d) Dinadayalane, T. C.; Sastry, G. N. *Tetrahedron* **2003**, *59*, 8347–8351. (e) Dinadayalane, T. C.; Deepa, S.; Sastry, G. N. *Tetrahedron Lett.* **2003**, *44*, 4527–4529.
13. Priyakumar, U. D.; Sastry, G. N. *J. Org. Chem.* **2001**, *66*, 6523–6530.
14. (a) Saunders, M.; Jimenez-Varzquez, H. A.; Cross, R. J. *Science* **1993**, *259*, 1428–1430. (b) Wieske, T.; Bohme, D. K.; Hrusak, J.; Kratschmer, W.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 884–886.
15. (a) Fagan, P. J.; Calabrese, J. C.; Malone, B. *Science* **1991**, *252*, 1160–1161. (b) Balsh, A. L. *Chem. Rev.* **1998**, *98*, 2123–2166. (c) Hsu, H.; Shapley, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 9192–9193.
16. Shaltout, R. M.; Sygula, R.; Sygula, A.; Fronczek, F. R.; Stanley, G. G.; Rabideau, P. W. *J. Am. Chem. Soc.* **1998**, *120*, 835–836.
17. Jemmis, E. D.; Manoharan, M.; Sharma, P. K. *Organometallics* **2000**, *19*, 1879–1887.
18. (a) Biedermann, P. U.; Pogodin, S.; Agranat, I. *J. Org. Chem.* **1999**, *64*, 3655–3662. (b) Baldridge, K. K.; Siegel, J. S. *Theor. Chem. Acc.* **1997**, *97*, 67–71. (c) Schulman, J. M.; Disch, R. L. *J. Comput. Chem.* **1998**, *19*, 189–194. (d) Baldridge, K. K.; Seigel, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 5332–5333.
19. (a) Seiders, T.; Baldridge, K. K.; Elliott, E. L.; Grube, G. H.; Seigel, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 7439–7440. (b) Seiders, T. J.; Baldridge, K. K.; Grube, G. H.; Siegel, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 517–525.
20. Zhong, W.; Gallivan, J. P.; Zhang, Y.; Li, L.; Lester, H. A.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12088–12093.
21. (a) Bhattacharjee, A. K. *J. Mol. Struct. (Theochem)* **2000**, *529*, 193–201. (b) Ikuta, S. *J. Mol. Struct. (Theochem)* **2000**, *530*, 201–207. (c) Jursic, B. S. *J. Mol. Struct. (Theochem)* **1999**, *491*, 193–203. (d) Shuichi, H.; Shigeru, I. *J. Mol. Struct. (Theochem)* **1999**, *468*, 85–94. (e) Malone, J. F.; Murray,

C. M.; Charlton, M. H.; Rober, D.; Lavery, A. *J. Chem. Soc., Faraday Trans.* **1997**, *93*(19), 3429–3436.

22. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, *Revision A.11.2*; Gaussian, Inc., Pittsburgh PA, 2001.
23. (a) Haddon, R. C. *J. Am. Chem. Soc.* **1990**, *112*, 3385–3389. (b) Haddon, R. C.; Scott, L. T. *Pure Appl. Chem.* **1986**, *58*, 137–142. (c) Haddon, R. C. *Acc. Chem. Res.* **1988**, *25*, 243–249.
24. Haddon, R. C. *POAV3*: *Release 3.0*, 1993.
25. Schleyer, P. v. R.; Maerker, C.; dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318.
26. (a) Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1721–1723. (b) Lu, Y.; Lemal, D. M.; Jasinski, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 2440–2445. (c) Burgi, H.-B.; Baldridge, K. K.; Hardcastle, K.; Frank, N. L.; Gantzel, P.; Siegel, J. S.; Ziller, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1454–1456. (d) Shaik, S.; Shurki, A.; Danovich, D.; Hiberty, P. C. *Chem. Rev.* **2001**, *101*, 1501–1540.

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Kinetics and mechanism of thermal gas-phase elimination of α- and β- (*N*-arylamino)propanoic acid: experimental and theoretical analysis

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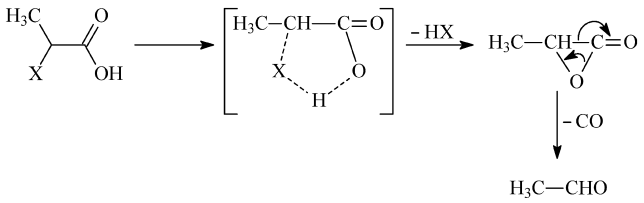
Abstract—2-(*N*-Phenylamino)propanoic acid **1a** and 3-(*N*-phenylamino)-propanoic acid **2a** together with four of their aryl analogues were pyrolysed in the gas-phase. The reactions were homogeneous and free from catalytic and radical pathways. Analysis of the pyrolysate of **1** showed the elimination products to be carbon monoxide, acetaldehyde and aniline, while the pyrolysate of **2** reveals the formation of acrylic acid in addition to aniline. Theoretical study of the pyrolysis of **2** using an ab initio SCF method lend support to a reaction pathway involving a 4-membered cyclic transition state.

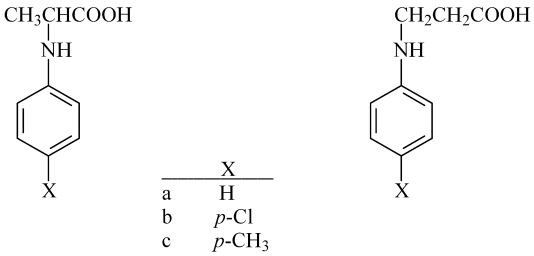
1. Introduction

We have recently reported on the kinetics and mechanism of thermal gas-phase elimination of α-substituted carboxylic acids, namely 2-phenoxypropanoic acid together with five of its aryl derivatives; phenylthio and *N*-phenylamino analogues were also investigated.[1] The reaction pathway is considered to involve a cyclic five-membered transition state associated with elimination of HX and formation of an α-lactone intermediate (Scheme 1). The effect of the α-substituent (X) is related to the basicity of X.



Scheme 1.

In this study, we look at the pyrolysis reaction of 2-(*N*-arylamino)propanoic acid **1a**–**c** and 3-(*N*-arylamino)propanoic acid **2a**–**c**; the two systems are α- and β-derivatives of propanoic acid. Substituents which make up the aryl moiety for **1a** and **2a**, phenyl group; for **1b** and **2b**, *p*-chlorophenyl for **1c** and **2c** *p*-methylphenyl group.



	X
a	H
b	*p*-Cl
c	*p*-CH_3

2. Results and discussion

2.1. Kinetics

Percent (10–20%) pyrolysis at the reaction temperature is used to evaluate the rate constant of reaction on the basis of HPLC retention data. Each recorded rate constant represents an average from at least three kinetic runs, which are in agreement to within ±2%. Rate coefficients were determined at different temperatures of 5–10 °C intervals for ≥95% reaction. The kinetic measurements of each substrate were followed over a temperature range of >50 K, an experimental requirement in thermal gas-phase elimination studies. The homogeneity of the reaction was tested by comparing the kinetic rate using an empty carbonized tube with that of similar vessel packed with glass helices. The results show that no pyrolysis occurred due to activation at the reactor surface. Since six-fold change in the amount of substrate used per kinetic run gave no significant change in rate coefficient, these reactions were deemed to be of first order. The presence or absence of a radical mechanism was

Keywords: α- and β- (*N*-Arylamino)propanoic acid; Thermal gas-phase elimination; Theoretical analysis.
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Table 1. Rate coefficients and Arrhenius parameters for pyrolysis of **1a–c** and **2a–c**

Compound	T (K)	10^4 k (s^{-1})	Log A (s^{-1})	*E*a (kJ mol^{-1})	10^3 $k_{600\ K}$ (s^{-1})
1a	550.50	2.320	12.13±0.50	166.18±6.12	3.68
	560.85	4.640			
	570.75	9.070			
	572.05	9.810			
	591.65	30.03			
	602.15	53.38			
1b	548.50	2.320	10.04±0.15	143.58±1.64	6.63
	552.55	2.890			
	570.65	7.930			
	589.05	20.75			
	606.75	46.72			
1c	475.55	0.900	4.86±0.09	81.21±1.01	5.47
	516.15	4.210			
	537.05	8.990			
	556.35	18.29			
	576.55	31.40			
	596.85	57.54			
2a	547.50	3.260	8.53±0.34	125.96±3.63	4.64
	558.65	5.720			
	568.55	9.080			
	578.55	13.88			
	589.05	23.46			
	605.50	46.10			
2b	540.50	4.320	8.68±0.61	124.77±6.70	3.46
	543.65	5.010			
	557.35	10.34			
	567.75	14.15			
	581.95	31.90			
	590.50	44.33			
2c	506.25	4.060	3.93±0.41	71.17±5.47	6.21
	519.45	6.080			
	532.05	9.130			
	544.45	11.55			
	569.95	28.54			

also tested by adding a radical trap, the presence of cyclohexene which was used in this test had no effect on the rate.[2,3] Arrhenius plots of log *k* vs 1/*T* (K) showed strict linearity up to >90% reaction. Kinetic data, Arrhenius parameters, and rate coefficients of reaction at 600 K are summarized in Table 1. The rates at 600 K are calculated using the kinetic equation for first order reactions:

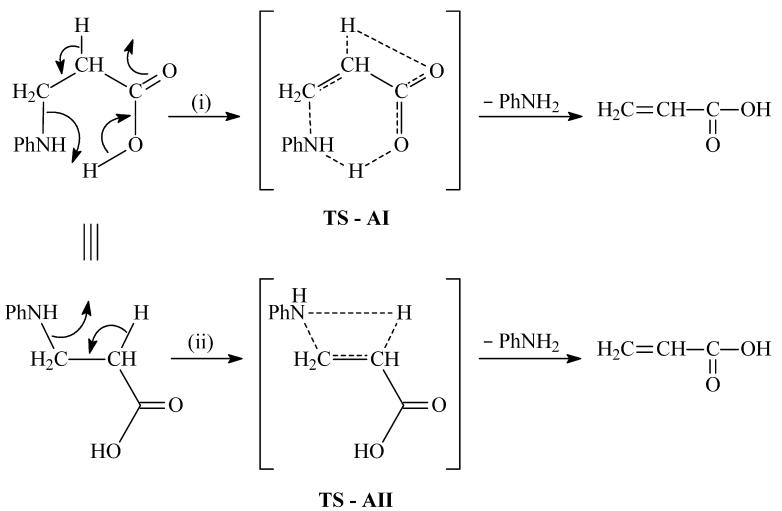
$$\log k = \log A - E_a/4.575\ T$$

The noteworthy observation in this kinetic study is that in the earlier paper[1] we reported reactivity correlations for α-substituents in propanoic acid in which the order of reactivity of the aryl groups was: –NHPh >–OPh>–SPh. On the basis of re-evaluation of the rate constant of 2-(*N*-phenylamino)propanoic acid, the order now is: –OPh >–SPh>–NHPh. This order corresponds more closely to the trend expected from the nature of the incipient phenol, thiophene and aniline fragments. It is of interest to note that there seems to be no opposing substituent effect from the *p*-position of the aryl moiety of the amino group consistent with the electron-donating character of the methyl and the electron-withdrawing character of the chloro substituent. The pyrolysates from the complete gas-phase pyrolysis of α-substituted carboxylic acids [2-(*N*-arylamino)propanoic acid **1a–c**] and β-substituted carboxylic acids [3-(*N*-arylamino)propanoic acid **2a–c**] were analysed and their constituents fully characterized using LC retention data, MS and NMR techniques.

The pyrolysates from substrates **1a–c** were ascertained to be $ArNH_2$, CH_3CHO and CO. The reaction pathway shown in Scheme 1 is compatible with the products of pyrolysis from **1a–c** and follows earlier findings by us and others.[4–7]

The pyrolysates from the pyrolytic reaction of substrates **2a–c** were identified as $ArNH_2$ and acrylic acid. A plausible mechanism is outlined in Scheme 2 to account for the formation of acrylic acid and substituted anilines from the pyrolysis of **2a–c**. This proposed pathway proceeds either through a six-membered transition state (route i) or through a four-membered transition state (route ii). Elimination of aniline in route (i) involves the acidic proton of the carboxylic group, while in route (ii) it involves the less acidic proton of the α-carbon atom.

Examining and characterizing in detail both routes (Scheme 2) in the suggested mechanism was carried out



Scheme 2.

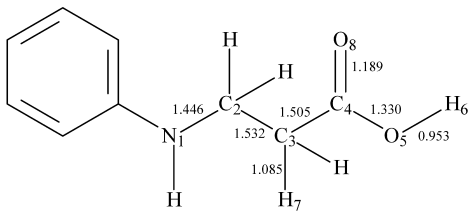


Figure 1. Schematic representation of optimized structure of **2a** to show main distances (Å), obtained by HF/6-31G* basis set.

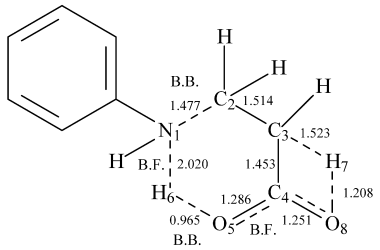


Figure 2. Schematic representation of the optimized structure of TS-AI to show main distances (Å) obtained by HF/6-31G*.

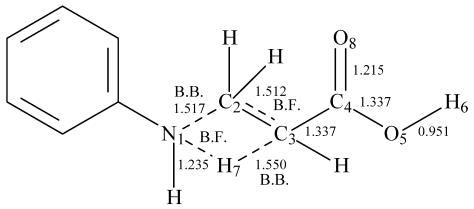


Figure 3. Schematic representation of the optimized structure of TS-AII, to show main distances (Å), obtained by HF/6-31G* basis set.

Table 2. Main distances (Å) in the substrate **2a** and transition states (AI, AII), calculated at the HF/6-31G* level

Distance, Å	**2a**	TS-AI	TS-AII
N_1-C_2	1.446	1.477	1.517
C_2-C_3	1.532	1.514	1.512
C_3-C_4	1.505	1.453	1.438
C_3-H_7	1.085	1.523	1.550
C_4-O_8	1.189	1.251	1.215
C_4-O_5	1.330	1.286	1.337
O_5-H_6	0.953	0.965	0.951
N_1-H_7	2.770	3.916	1.235
N_1-H_6	5.631	2.020	4.638
O_8-H_7	3.102	1.208	2.705

by theoretical calculation of the thermal elimination of aniline and acrylic acid from substrate **2a** using ab initio SCF method.

2.2. Computational studies

Theoretical studies on the thermolysis of β-substituted carboxylic acids in the gas phase were carried out using an ab initio SCF method. Calculations were carried out to explore the nature of the reaction mechanism of the unimolecular decomposition of molecule **2a**. Two competitive reaction pathways for the decomposition process have been studied. All the calculations have been performed with the TITAN computational package.[8]

The geometric parameters of the substrate **2a**, the transition states A and B, were fully optimized at the HF/6-31G* level to obtain the energy profile corresponding to the studied reaction. Each stationary structure characterized by frequency calculations was a minimum or saddle point of first-order. A scaling factor of 0.9135 for the zero-point vibrational energies has been used.[9] The structures obtained from the optimization calculations are represented in Figures 1–3.

Table 2 shows the main distances in each optimized structure. During the thermolysis process, when **2a** is being transformed into TS-AII, the N_1-C_2 and C_3-C_4 distances are increasing, whereas the C_2-C_3 and N_1-H_7 distances are decreasing.

Electronic energies, zero-point vibrational energies, enthalpies and entropies were evaluated at the HF/6-31G* level of theory for the substrate **2a**, TS-AI and TS-AII, and the products involved in the two pathways of the studied reaction are collected in Table 3.

The free energy profile for the decomposition process of the studied reaction is re-presented in Figure 4, obtained at the HF/6-31G* level.

Examination of the free energy of the two suggested transiting states shows that TS-AII has a lower free energy barrier than TS-AI (Fig. 4). The calculated activation free energies are 89.59 and 66.41 kJ mol^{-1} for the reaction via the transition states TS-AI and TS-AII, respectively. The overall process is exergonic; with reaction free energy equal to -92.89 kJ mol^{-1}.

From the results obtained, it appears that the single cyclic 4-membered ring transition state, TS-AII, is more favored than the cyclic 4- and 6-membered ring transition state, TS-AI.

Table 3. Total energy zero-point vibrational energy (ZPE) and thermal correction to enthalpy and entropy at HF/6-31G* and 573 K for **2a**, transition states and products

Species	Total energy (Hartrees)	ZPE (kcal mol^{-1})	Enthalpy (kcal mol^{-1})	Entropy (cal mol^{-1} K^{-1})
2a	−551.410335	127.988	134.533	104.899
TS-AI	−551.266869	124.854	130.937	99.273
TS-AII	−551.301672	125.137	131.305	100.440
$PhNH_2$	−285.730756	78.870	82.269	74.352
$H_2C{=}CHCOOH$	−265.653665	45.866	48.866	70.635

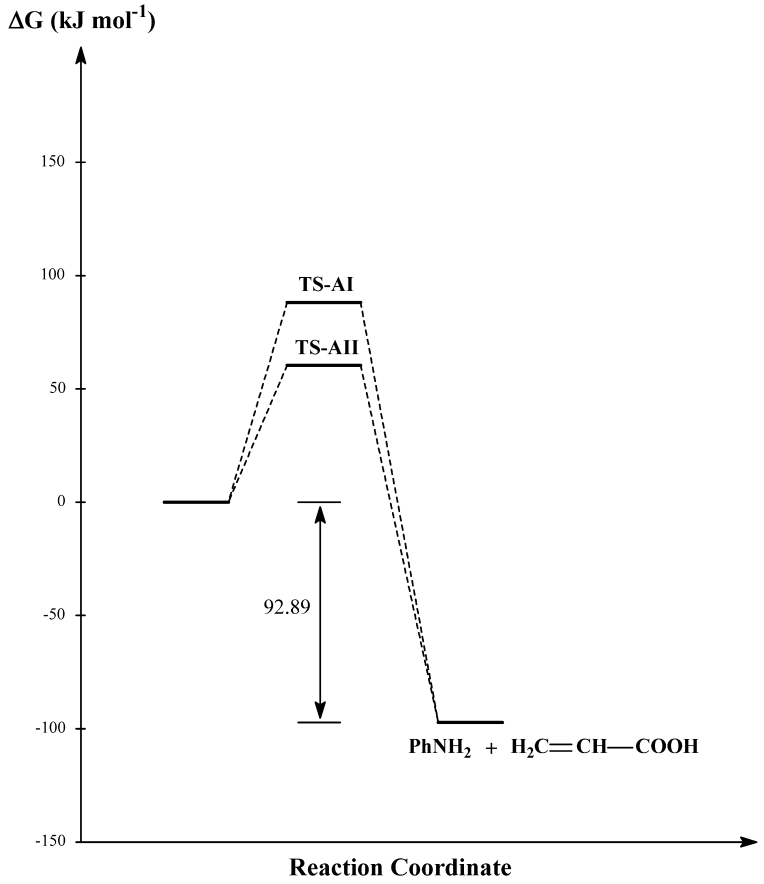


Figure 4. Free energy profile evaluated at the HF/6-31G* level for **2a** decomposition process.

3. Experimental

3.1. Synthesis

3.1.1. Ethyl 2-arylaminopropionate. A mixture of ethyl 2-bromopropionate (0.10 mol), aniline or its *p*-substituted analogues (0.10 mol) and sodium acetate (0.20 mol) was refluxed at 125 °C for 12 h. The reaction mixture was cooled, filtered free of the salt and repeatedly washed with ether. The ether was removed in vacuo and the remaining product was distilled to afford the title compounds.[10]

3.1.2. 2-Arylaminopropanoic acid, 1a–c. Ethyl 2-arylaminopropionate was hydrolysed by heating under reflux with 10% aqueous sodium hydroxide solution (100 ml) for 4–5 h. After cooling, the product was acidified by dropwise addition of diluted hydrochloric acid, the crystals of the products were filtered and recrystallized from ethyl acetate and petroleum ether to afford the title compounds in 55–75% yield. The following compounds were thus synthesized.

2-Phenylaminopropanoic acid, **1a**. Light brown crystals, mp 165.5 °C. ^{1}H NMR (acetone-d^6): δ 1.47 (d, J=7.2 Hz, 3H, CH_3), 4.12 (q, J=7.2 Hz, 1H, CH), 6.62–6.68 (m, 3H, ArH), 7.12 (t, J=7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.3, 52.9, 115.6, 119.6, 129.8, 146.5, 177.6. Anal. calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.66; N, 8.48. Found: C, 64.95; H, 6.61; N, 8.6%. MS: *m*/*z* 165 (M^+). IR (cm^{-1}): 3420 (NH), 1570 (CO).

2-(4-Chlorophenylamino)propanoic acid, **1b** White crystals, mp 143 °C. ^{1}H NMR (acetone-d^6): δ 1.47 (d, J=6.9 Hz, 3H, CH_{-3}), 4.1 (q, J=6.9 Hz, 1H, CH), 6.67 (d, J=8.6 Hz, 2H, ArH), 7.11 (d, J=8.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.2, 52.6, 115.1, 124.1, 129.7, 145.2, 177.9. Anal. calcd for $C_9H_{10}NO_2Cl$:, 54.13; H, 5.01; N, 7.02. Found: C, 54.0; H, 5.16; N, 7.03%. MS: *m*/*z* 199 (M^+). IR (cm^{-1}): 3400 (NH), 1592 (CO).

2-(p-Methylphenylamino)propanoic acid, **1c**. Light brown crystals, mp 142 °C. ^{1}H NMR (acetone-d^6): δ 1.45 (d, J=6.9 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.07 (q, J=6.9 Hz, 1H, CH), 6.58 (d, J=8.2 Hz, 2H, ArH), 6.93, (d, J=8.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 19.0, 21.0, 54.4, 115.3, 129.6, 130.4, 143.6, 179.3. Anal. Calcd. For $C_{10}H_{13}NO_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 67.39; H, 7.26; N, 8.06%. MS: *m*/*z* 179.1 (M^+). IR (cm^{-1}): 3436 (NH), 1579 (CO).

3.1.3. Preparation of 3-arylaminopropanoic acid, 2a–c. To a 10% aqueous solution of NaOH (60 ml) was added 5 g of 3-aminoaryl propionitrile[11] and the mixture was heated under reflux for 6 h. The reaction was then cooled and acidified cautiously by dropwise addition of glacial acetic acid. The acidified solution was then extracted with ethyl acetate; the extract was dried and concentrated under vacuum to afford scales of product which were crystallized from petroleum ether-ether to afford.

3-Phenylaminopropanoic acid, **2a**. Greenish crystals, mp 70.5 °C. ^{1}H NMR (acetone-d^6): δ 2.62 (t, J=6.8 Hz, 2H,

CH_2–CO), 3.43 (t, J=6.8 Hz, 2H, CH_2–NH), 6.61 (d, J=7.6 Hz, 2H, ArH), 6.67 (t, J=7.6 Hz, 1H, ArH), 7.12 (t, J=7.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 34.0, 39.8, 113.8, 118.6, 129.8, 147.6, 177.8. Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.45; H, 6.6; N, 8.48. Found: C, 65.09; H, 6.55; N 8.6%. MS: m/z 165 (M^+). IR (cm^{-1}) 3407 (NH), 1682 (CO).

3-(p-Chloroanilino)propanoic acid, **2b**. Light brown crystals, mp 125 °C, ^{1}H NMR (acetone-d^6): δ 2.62 (t, J=6.8 Hz, 2H, CH_2), 3.41 (t, J=6.8 Hz, 2H, CH_2), 6.67 (d, J=6.8 Hz, 2H, Ar H), 7.11 (d, J=6.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 34.1, 40.0, 114.9, 123.3, 129.8, 146.4, 177.8. Anal. Calcd. for $C_9H_{10}NO_2$: C, 54.13; H, 5.01; N, 7.01. Found: C, 54.5; H, 5.07; N, 7.07%. MS: m/z=199 (M^+), IR (cm^{-1}): 3424 (NH), 1708 (CO).

3-(p-Methylphenylmino)propanoic acid, **2c**. Brown crystals, mp 85.5 °C, ^{1}H NMR (acetone-d^6): 2.18 (s, 3H, CH_3), 2.59 (t, J=6.8 Hz, 2H, CH_2), 3.38 (t, J=6.8 Hz, 2H, CH_2), 6.57 (d, J=8.4 Hz, 2H, Ar H), 6.93 (d, J=8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 21.0, 34.1, 40.5, 114.4, 128.4, 130.4, 145.3, 177.8. Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 66.75; H, 7.24; N, 7.99%. MS: m/z 179.1 (M^+). IR (cm^{-1}): 3364 (NH), 1684 (CO).

3.2. Kinetic runs and data analysis

Stock solution (7 ml) is prepared by dissolving 6–10 mg of the substrate in acetonitrile as solvent to give a concentration of 1000–2000 ppm. Internal standard is then added, the amount of which is adjusted to give the desired peak area ratio of substrate to standard (2.5:1). The solvent (acetonitrile) and the internal standard (chlorobenzene) were selected because both are stable under the conditions of pyrolysis, and because they do not react with either substrate or product. Each reaction mixture is filtered to ensure that a homogeneous solution is obtained.

The weight ratio of the substrate with respect to the internal standard is calculated from the ratio of the substrate peak area to the peak area of the internal standard. The kinetic rate was obtained by tracing the rate of disappearance of the substrate with respect to the internal standard as follows.

An aliquot (0.2 ml) of each solution containing the substrate and the internal standard was pipetted into the reaction tube which was then placed in the pyrolyzer for 6 min under non-thermal conditions. A sample was then analyzed using the HPLC probe with the UV detector at wavelength of 256 nm, and the standardization value (A_0) was calculated. Several HPLC measurements were obtained with an accuracy of ≥2%. The temperature of the pyrolysis block was then raised until approximately 10% pyrolysis was deemed to occur over 900 s. This process was repeated after each 10–15 °C rise in the temperature of the pyrolyzer until ≥90% pyrolysis occurred. The relative ratios of the integration values of the sample and the internal standard (A) at the pyrolysis temperature was then calculated. A minimum of three kinetic runs were carried out at each 10–15 °C rise in the temperature of the pyrolyzer to ensure reproducible values of (A). Treatment of the kinetic data has been detailed elsewhere.[12–14]

3.3. General procedure for product analysis

The apparatus used for this purpose was the same pyrolysis unit used for kinetic studies. Each of the substraters (0.2 g) was introduced in the reaction tube, cooled in liquid nitrogen, sealed under vacuum and placed in the pyrolyzer for 900 s at a temperature comparable to that used for complete pyrolysis in the kinetic studies. The contents of the tube were then analysed by NMR and LC/MS and the yield was determined by HPLC with reference sample (Table 4). The spectral data of the pyrolysates were compared with their reference spectra.

Table 4. Product analysis of compounds **1a–c** and **2a–c**

Cpd	T (K)	Pyrolysates and yields (%)	
1a	630	Aniline (52%)	Acetaldehyde (42%)
1b	620	*p*-Chloroaniline (33.7%)	Acetaldehyde (38.3%)
1c	600	*p*-Tolylaniline (26.4%)	Acetaldehyde (12%)
2a	630	Aniline (18.6%)	Acrylic acid (25.9%)
2b	620	*p*-Chloroaniline (49.9%)	Acrylic acid (30.6%)
2c	600	*p*-Tolylaniline (33.6%)	Acrylic acid (35.6%)

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References and notes

1. Al-Awadi, N.; Kaul, K.; El-Dusouqui, O. *J. Phys. Org. Chem.* **2000**, *13*, 499–504.
2. Al-Awadi, N.; El-Dusouqui, O.; Int, *J. Chem. Kinet.* **1997**, *29*, 295–298.
3. Al-Awadi, N.; Al-Bashir, R.; El-Dusouqui, O. *J. Chem Soc., Perkin Trans. 2* **1989**, 579–581.
4. Chuchani, G.; Rotinov, A. *Int. J. Chem. Kinet.* **1989**, *21*, 367–371.
5. Chuchani, G.; Martin, I.; Rotinov, A.; Dominiguzz, R. M. *Int. J. Chem. Kinet.* **1991**, *23*, 779–783.
6. Chuchani, G.; Martin, I.; Rotinov, A.; Dominguzz, R. M. *J. Phys. Org. Chem.* **1993**, *6*, 54–58.
7. Chuchani, G.; Martin, I.; Rotinov, A.; Dominguzz, R. M. *Int. J. Chem. Kinet.* **1995**, *27*, 849–853.
8. *Titan, Tutorial and User's Guide*, Wavefunction, Inc.: 18401 Von Karman Avenue, USA, 1999..
9. Scott, A.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
10. Szulc, Z.; Mlochowski, J.; Pauls, J. *J. Prakt. Chem.* **1988**, *330*, 1023–1029.
11. *Organic Synth.*; Rabjohn, E., Ed.; Wiley: London, 1963; Collect. Vol. 4, p 205.
12. Al-Awadi, N. A.; Elnagdi, M. H.; Kaul, K.; Ilingovan, S.; El-Dusouqui, O. M. E. *J. Phys. Org. Chem.* **1999**, *12*, 654–656.
13. Al-Awadi, N. A.; El-Dusouqui, O. M. E.; Kaul, K.; Dib, H. H. *Int. J. Chem. Kinet.* **2000**, *32*, 403–407.
14. Al-Awadi, N. A.; Kaul, K.; El-Dusouqui, O. M. E. *J. Phys. Org. Chem.* **2000**, *13*, 499–504.

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Synthesis and tautomeric structure of 2-[*N*-aryl-2-oxo-2-arylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinones

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Abstract—Two series of 2-(*N*-aryl-2-oxo-2-arylethanehydrazonoyl)-6-methyl-4(3*H*)-pyrimidinones **11** (**12**) were prepared by coupling of diazotized anilines with 2-(aroylmethylene)-1,2-dihydro-6-methyl-4(3*H*)-pyrimidinones **2** (**3**). The spectral data of such compounds together with their 3-methyl analogs **13** (**14**) indicated that they exist predominantly in the hydrazone tautomeric form.

1. Introduction

Our group has recently been interested in the azo-hydrazone tautomerism of arylazo heterocycles in both ground and excited states as many of them are useful in the field of material sciences and theoretical chemistry.[1] Also, there have been diverse studies on various reactions of 1,2-cyclic ketene aminals **1** such as nucleophilic additions[2] and substitutions[3] with a variety of electrophiles and 1,3-dipoles.[4] The results of such studies proved **1** to be powerful and useful building blocks for synthesis of compounds that are difficult to access by other synthetic methods.[5] However, a literature survey revealed that the chemistry of 2-(aroylmethyl)-6-methyl-4(3*H*)-pyrimidinones **2**-**5** (Chart 1) has received little, if any, attention although **2** (**3**) were reported in 1988 and shown to exist in the ketene aminal form **2B** (**3B**) (Chart 1).[6] As a consequence of this, and in continuation of our previous studies of azo-hydrazone tautomerism of diazonium coupling products of active methylene compounds,[1] we studied the reactions of each of the ketene aminals **2** and **3** together with their *N*-methyl analogs **4** and **5** with diazonium salts in an attempt to synthesize the respective azo derivatives **11**-**14** (Scheme 1) and to elucidate their tautomeric structures. Theoretically five tautomeric structures **A**-**E** can be written for such compounds (Chart 2). This study of compounds **11**-**14** was also thought necessary prior to the intended exploration of their nonlinear optical properties, use as synthons for other heterocycles and a study of their biological activity. This is because numerous derivatives of pyrimidinone ring system have been prepared over the past years and their pharmacology evaluated.[7]

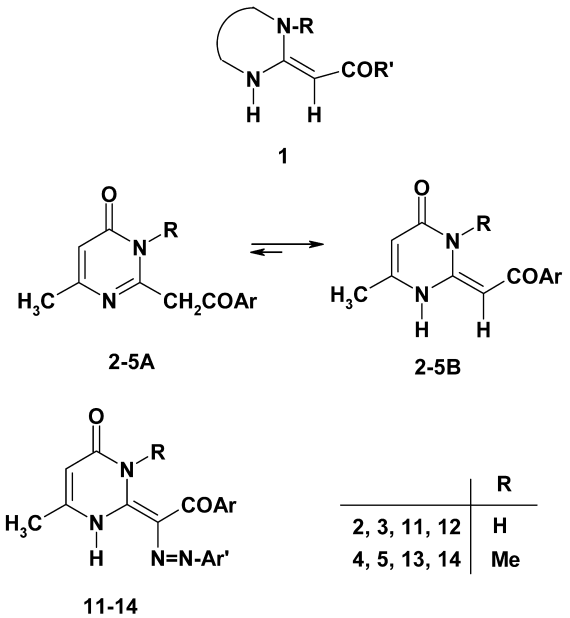

Chart 1.

2. Results and discussion

The starting ketene aminals **2** and **3** were prepared from 6-methyl-2-thiouracil **6** as previously described.[6] The other two ketene aminals **4** and **5**, which have not been previously reported, were synthesized in this work as outlined in Scheme 1. Thus, treatment of **6** with the appropriate phenacyl bromide in aqueous ethanolic sodium hydroxide afforded the respective 2-[(aroylmethyl)thio]-4(3*H*)-pyrimidinones **7** and **8**. Methylation of both **7** and **8** with methyl iodide in dimethylformamide in the presence of sodium carbonate afforded **9** and **10**. The structures of the novel derivatives **9** and **10** were confirmed by their spectra (MS,

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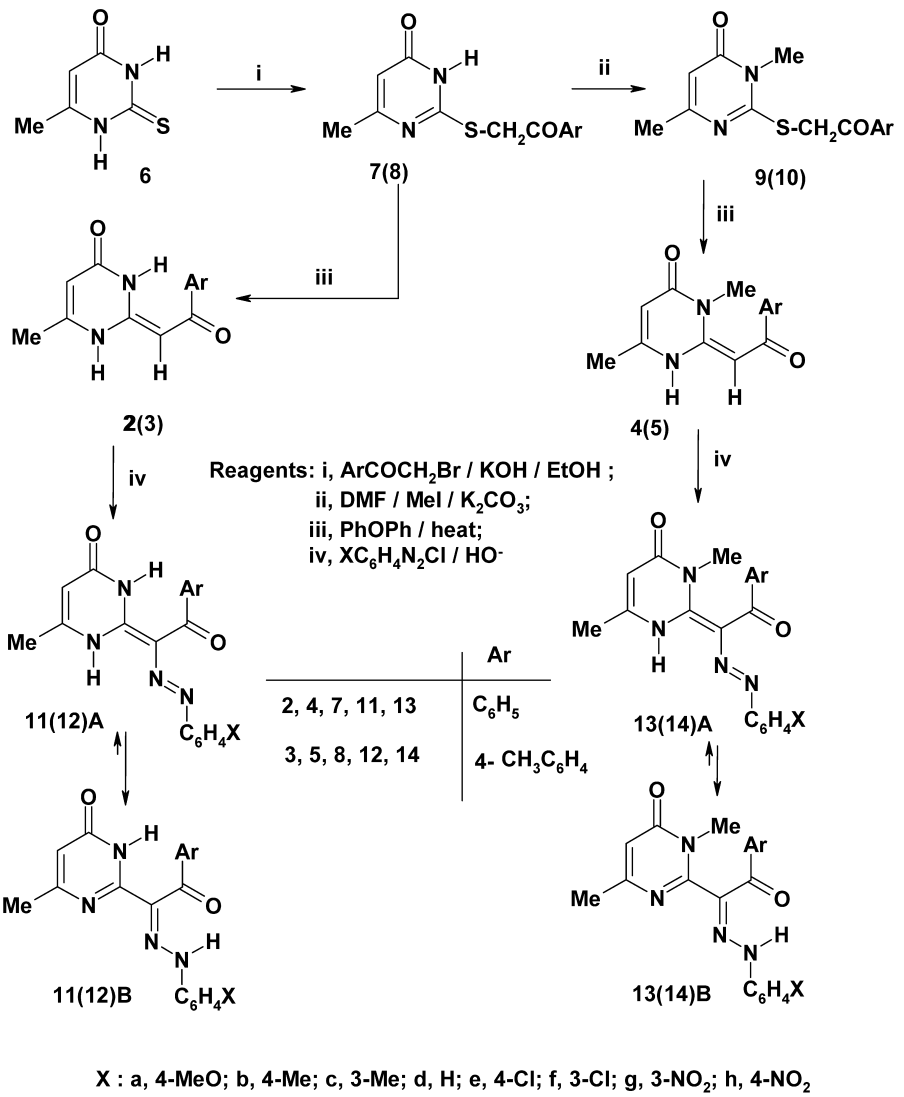

Scheme 1.

^{1}H NMR and IR) together with their elemental analyses. The ^{1}H NMR spectra revealed, in each case, four characteristic signals near δ 1.96, 3.53, 4.61 and 5.99 assignable to 6-CH_3, N–CH_3, –CH_2– and ring 5-CH protons, respectively.

Heating each of **9** and **10** in diphenyl ether at 200–210 °C gave the respective ketene aminals **4** and **5** in good yields (Scheme 1) via extrusion of sulfur. The structures of the new ketene aminals **4** and **5** were established by their analytical and spectroscopic data. The ^{1}H NMR spectra of **4** and **5** revealed in each case an NH proton signal near δ 15.20 which is lost on shaking the solution of each in chloroform-*d* with D_2O. In addition, the ^{1}H NMR spectra showed four characteristic singlet signals near δ 2.20, 3.38, 5.60, and 5.70 assignable to the pyrimidine 6-CH_3, N–CH_3, 5-CH and methine =CH– protons, respectively. This indicates that compounds **4** and **5**, like **2** and **3** exist predominantly in the enamine form (**B**).[6]

In aqueous ethanol in the presence of sodium hydroxide, each of compounds **2**-**5** reacted with diazotized anilines and afforded the respective arylazo derivatives **11**-**14**, respectively (Scheme 1). The mass spectra of the latter products revealed the molecular ion peaks at the expected *m*/*z* values with relative intensities varying from 40 to 100% and their elemental analysis data were consistent with their assigned structures. Their infrared spectral data (see Section 3) seem to be consistent more with the hydrazone structure (**B** or **C**) rather than the hydroxyazo tautomeric forms (**D** and **E**) (Chart 2). For example, all compounds exhibit two carbonyl bands in the regions 1689–1666 and 1640–1620 cm^{-1} corresponding to the stretching vibrations of the pyrimidinone and the benzoyl carbonyl groups, respectively. The observed wavenumber of the latter CO stretching band in the compounds **11**-**14** seems to result from strong chelation with the hydrazone NH and conjugation with the C=N double bond as required by both hydrazone forms **B** and **C** (Chart 2).[8] The fact that compounds **11**-**14** show evidence for strong intramolecular hydrogen bonding also excludes the azo form **A** (Chart 2).

To elucidate the actual tautomeric form of the studied compounds **11**-**14**, the electronic absorption spectra were measured. The data are summarized in Table 1. As shown, each of compounds **11**-**14** in dioxane exhibits two

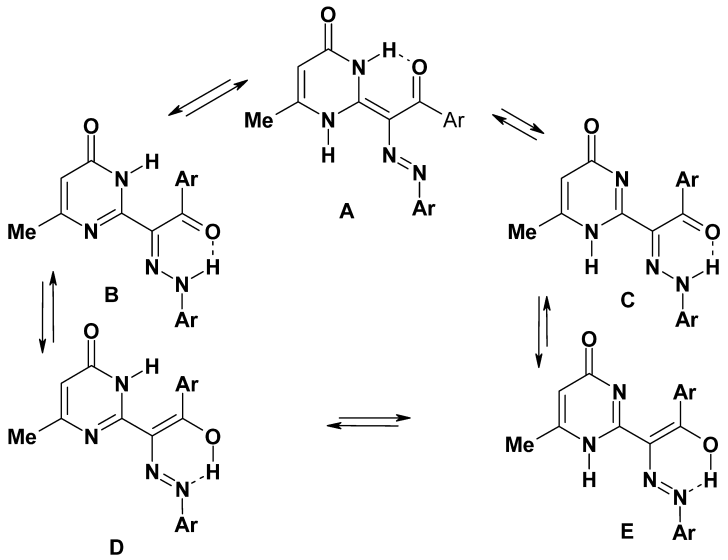

Chart 2.

Table 1. UV spectra of coupling products

Compound No.	λ_{max} (log ε)	Compound No.	λ_{max} (log ε)
11a	409 (4.49), 312 (4.10)	**12a**	410 (4.32), 312 (4.04)
11b	391 (4.13), 299 (3.73)	**12b**	396 (4.27), 306 (3.95)
11c	392 (4.20), 304 (3.83)	**12c**	392 (4.34), 303 (4.06)
11d[a]	389 (4.27), 301 (3.91)	**12d**[b]	390 (4.34), 302 (4.09)
11e	392 (4.21), 299 (3.85)	**12e**	393 (4.29), 306 (4.02)
11f	383 (4.27), 297 (3.93)	**12f**	383 (4.38), 298 (4.13)
11g	384 (4.30), 260 (3.86)	**12g**	384 (4.29), 262 (4.00)
11h	399 (4.17), 294 (3.70)	**12h**	400 (4.64), 296 (4.26)
13d	360 (5.20), 280 (5.00)	**14d**	357 (5.26), 286 (5.10)

[a] Solvent: λ_{max} (log ε): acetic acid 391 (4.29), 286 (4.15); chloroform 392 (4.37), 304 (4.01); ethanol 391 (4.36), 303 (4.01); cyclohexane 389 (3.98), 305 (3.60).

[b] Solvent: λ_{max} (log ε): acetic acid 391 (4.26), 299 (4.06); chloroform 393 (4.22), 306 (3.96); ethanol 392 (4.25), 304 (3.99); cyclohexane 389 (3.96), 305 (3.70).

characteristic absorption bands in the regions 400–380 and 304–290 nm. Such an absorption pattern is similar to that of typical hydrazone chromophore.[1b,9] Furthermore, the spectrum of **11d**, taken as a typical example of the two series studied was recorded in solvents of different polarities. The spectra obtained showed little, if any, shift (Table 1). The small shifts in λ_{max} of **11d** in different solvents are due to solute–solvent interaction. In agreement with this conclusion is the observation that the spectra of arylhydrazones derived from the reaction of quinones with *N*-alkyl-*N*-phenylhydrazine, unlike those of *o*- and *p*-hydroxyazo compounds are largely independent of the solvent polarity.[8]

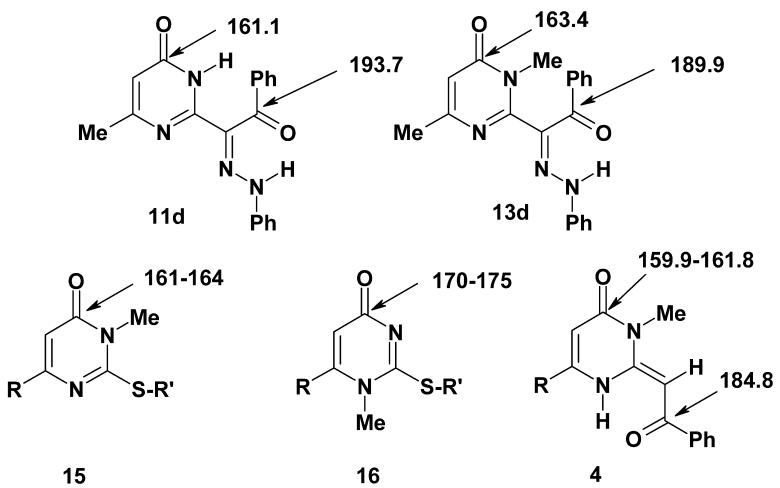

Chart 3.

This finding, while it excludes the azo tautomeric forms **A**, **D** and **E**, indicates that each of compounds **11**-**14** exists in one tautomeric form, namely **B** or **C** (Chart 1).

Finally, in order to distinguish between the two forms **B** and **C** (Chart 1), the ^{13}C NMR spectra of **11d** and **13d** were recorded and compared with those of compounds **4**, **15** and **16** (Chart 3). This is because literature reports[10,11] indicate that the chemical shift of the carbonyl group in pyrimidin-4(1*H*)-ones is markedly affected by the nature of the adjacent nitrogen, that is, N(3), pyridine type or pyrrole type, being larger for the former type (Chart 3). The ^{13}C NMR spectra of **11d** and **13d** revealed the signals for the ring carbonyl carbon at δ 161.1 and 163.4, respectively. These δ values suggest that N(3) is an sp3-hybridized nitrogen atom, that is, of pyrrole type, as it is similar to that found for the methyl derivatives **4** (δ 159.9) and **15** (δ 161–164) and different to that found for the pyrimidinones **16** (δ 170–175).[11] This finding indicates that the studied compounds **11**-**14** exist predominantly in the hydrazone tautomeric form **B** (Chart 2).

In conclusion, we have encountered two novel series of 2-(*N*-aryl-2-oxo-2-arylethanehydrazonoyl)-6-methyl-4(3*H*)-pyrimidinones **11** (**12**) and their spectral data presented here indicate collectively that such compounds exist predominantly in the hydrazone tautomeric form **B**.

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Perkin Elmer FTIR 1650 and Pye-Unicam SP300 infrared spectrophotometers. ^1H NMR spectra were recorded in deuterated chloroform using a Varian Gemini 200 NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu and GCMS 5988-A HP spectrometers. Electronic absorption spectra were recorded on Perkin–Elmer Lambada 40 spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt. 2-Mercapto-6-methyl-4(3*H*)-pyrimidinone **6**, 2-(Aroylmethylthio)-6-methyl-4(3*H*)-pyrimidinones **7** and **8** and the respective 2-(aroylmethylene)-1,2-dihydro-6-methyl-4(3*H*)-pyrimidinones **2** and **3** were prepared as previously described.[6]

3.2. 2-(Aroylmethylthio)-3,6-dimethyl-4(3*H*)-pyrimidinones (9 and 10)

To a stirred solution of **7** (0.05 mol) in dimethylformamide (100 ml) was added anhydrous potassium carbonate (3.0 g, 0.02 mol) and methyl iodide (7.5 g, 0.05 mol). The reaction was then left overnight while being stirred at room temperature, then was poured onto water. The crude solid that precipitated was collected by filtration and crystallized from methanol to give the respective **9** as white solid. Use of **8** in lieu in the above method afforded **10**.

3.2.1. 2-Benzoylmethylthio-3,6-dimethyl-4(3*H*)-pyrimidinone (9). (9.6 g, 70%) as white crystals, mp 102–104 °C. (Found: C, 61.3; H, 5.4; N, 10.5. $C_{14}H_{14}N_2O_2S$ (274.4) requires: C, 61.29; H, 5.14; N, 10.21%). δ_H ($CDCl_3$) 1.96 (s, 3H, 6-CH_3), 3.53 (s, 3H, N–CH_3), 4.61 (s, 2H, –CH_2–), 5.99 (s, 1H, 5-CH), 7.26–8.07 (m, 5H, ArH); ν_{max} (KBr) 1681 cm^{-1}. MS *m*/*z* (%) 274 (M^+, 2), 241 (12), 134 (23), 105 (100), 83 (16), 77 (28).

3.2.2. 2-(4-Methylbenzoylmethylthio)-3,6-dimethyl-4(3*H*)-pyrimidinone (10). (10.95 g, 76%) as white crystals, mp 105 °C. (Found: C, 62.5; H, 5.3; N, 9.5. $C_{15}H_{16}N_2O_2S$ (288.37) requires: C, 62.48; H, 5.59; N, 9.71%). δ_H ($CDCl_3$) 1.96 (s, 3H, 6-CH_3), 2.44 (s, 3H, ArCH_3), 3.53 (s, 3H, N–CH_3), 4.60 (s, 2H, –CH_2–), 5.99 (s, 1H, 5-CH), 7.52 (d, *J*=7 Hz, 2H, ArH), 7.77 (d, *J*=7 Hz,2H, ArH). ν_{max} (KBr) 1681 cm^{-1}. MS *m*/*z* (%) 288 (M^+, 1.9), 255 (9), 148 (18), 119 (100), 105 (2), 91 (26), 77 (2.6).

3.3. 2-(Aroylmethylene)-1,2-dihydro-6-methyl-4(3*H*)-pyrimidinones (2-5)

A solution of the appropriate compound **7** or **8** (2 mmol) in diphenyl ether (10 ml) was heated in an oil bath at 200–210 °C for 10 min, then cooled. To the cold mixture was added ether where a yellow solid product precipitated. After complete prcepitation, the solid product was collected, washed with ether and crystallized from ethanol to give **2** and **3**, respectively.

When this procedure was repeated using **9** and **10** each in place of **7** or **8**, 2-(aroylmethylene)-1,2-dihydro-3,6-dimethylpyrimidin-4(3*H*)-ones **4** and **5**, respectively, were produced.

3.3.1. 2-(Benzoylmethylene)-1,2-dihydro-6-methyl-4(3*H*)-pyrimidinone (2). (0.31 g, 69%), as pale yellow solid, mp 247–249 °C (lit. mp 247–250 °C).[6]

3.3.2. 2-(4-Methylbenzoylmethylene)-1,2-dihydro-6-methyl-4(3*H*)-pyrimidinone (3). (0.33 g, 69%) as pale yellow solid, mp 265 °C (lit. mp 267 °C).[6]

3.3.3. 2-(Benzoylmethylene)-1,2-dihydro-3,6-dimethyl-4(3*H*)-pyrimidinone (4). (0.34 g, 70%) as yellow solid, mp 138 °C. (Found: C, 69.3; H, 5.5; N, 11.4. $C_{14}H_{14}N_2O_2$ (242.28) requires: C, 69.41; H, 5.82; N, 11.56%). δ_H ($CDCl_3$) 2.25 (s, 3H, 6-CH_3), 3.39 (s, 3H, N–CH_3), 5.67 (s, 1H, 5-CH), 5.72 (s, 1H, =CH–), 7.26–7.90 (m, 5H, ArH), 15.23 (s, 1H, NH). δ_C (DMSO-d_6) 18.9, 28.3, 78.7, 101.6, 126.6, 128.3, 131.1, 139.1, 150.8, 155.6, 159.9, 184.6. ν_{max} (KBr) 3425, 1674 cm^{-1}. MS *m*/*z* (%) 243 (M^++1, 6), 242 (M^+, 37), 225 (14), 213 (14), 165 (25), 137 (21), 105 (100), 84 (29), 77 (67).

3.3.4. 2-(4-Methylbenzoylmethylene)-1,2-dihydro-3,6-dimethyl-4(3*H*)-pyrimidin-one (5). (0.39 g, 75%) as yellow solid, mp 170 °C. (Found: C, 70.3; H, 6.2; N, 10.5. $C_{15}H_{16}N_2O_2$ (256.31) requires: C, 70.29; H, 6.29; N, 10.93%. δ_H ($CDCl_3$) 2.25 (s, 3H, 6-CH_3), 2.40 (s, 3H, ArCH_3), 3.38 (s, 3H, N–CH_3), 5.66 (s, 1H, 5-CH), 5.71 (s, 1H, =CH–), 7.23 (d, *J*=8 Hz, 2H, ArH), 7.77 (d, *J*=8 Hz, 2H, ArH), 15.20 (s, 1H, NH). δ_C (DMSO-d_6) 21.2, 22.7, 29.9, 75.1, 106.7, 128.3, 129.3, 133.9, 143.9, 160.7, 160.9, 161.4, 192.8. ν_{max} (KBr) 3417, 1681 cm^{-1}. MS *m*/*z* (%) 257

(M^++1, 6), 256 (M^+, 33), 239 (15), 213 (14), 165 (18), 137 (18), 119 (100), 91 (49), 77 (3).

3.4. 2-[*N*,2-Diaryl-2-oxo-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11)

To a stirred solution of the appropriate **2**-**5** (10 mmol) in ethanol (50 ml) was added sodium hydroxide (0.4 g, 10 mmol) and the mixture was cooled in an ice bath to 0–5 °C. To the resulting solution, while being stirred, was added dropwise over a period of 20 min a solution of the appropriate arenediazonium chloride, prepared as usual by diazotizing the respective aniline (10 mmol) in hydrochloric acid (6 M, 6 ml) with sodium nitrite (1 M, 10 ml). The whole mixture was then left a refrigerator overnight. The precipitated solid was collected, washed with water and finally crystallized from ethanol to give the respective hydrazone **11**-**14**, respectively.

3.4.1. 2-[*N*-(4-Methoxyphenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11a). (Yield 2.54 g, 70%) as yellow crystals, mp 210 °C. (Found: C, 66.3; H, 5.2; N, 15.5. $C_{20}H_{18}N_4O_3$ (362.39) requires: C, 66.29; H, 5.01; N, 15.46%). δ_H ($CDCl_3$) 2.34 (s, 3H, 6-CH_3), 3.81 (s, 3H, OCH_3), 6.24 (s, 1H, 5-CH), 6.89 (d, *J*=8 Hz, 2H, ArH), 6.9–7.4 (m, 5H, ArH), 7.7 (d, *J*=8 Hz, 2H, ArH), 12.85 (s, 1H, NH), 16.20 (s, 1H, NH); δ_C (DMSO-d_6) 21.2, 23.1, 109.5, 113.2, 116.5, 125.9, 127.7, 129.6, 130.2, 131.8, 138.5, 139.3, 142.0, 152.4, 162.5, 191.5. ν_{max} (KBr) 3120, 1689, 1612 cm^{-1}. MS *m*/*z* (%) 363 (M^++1, 11.7), 362 (M^+, 56), 361 (100), 212 (11), 199 (15), 136 (27), 122 (30), 107 (14), 105 (65), 84 (16), 77 (84).

3.4.2. 2-[*N*-(4-Methylphenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11b). (2.60 g, 75%) as yellow needles, mp 208 °C. (Found: C, 69.5; H, 5.4; N, 15.9. $C_{20}H_{18}N_4O_2$ (346.39) requires: C, 69.35; H, 5.24; N, 16.12%). δ_H ($CDCl_3$) 2.40 (s, 3H, Ar-CH_3), 2.45 (s, 3H, 6-CH_3), 6.25 (s, 1H, 5-CH), 6.89 (d, *J*=8 Hz, 2H, ArH), 6.9–7.4 (m, 5H, ArH), 7.73 (d, *J*=7 Hz, 2H, ArH), 12.80 (s, 1H, NH), 16.0 (s, 1H, NH). δ_C ($CDCl_3$) 21.7, 23.6, 113.3, 114.4, 116.4, 125.5, 128.4, 130.7, 135.5, 135.7, 142.8, 143.1, 153.1, 160.5, 161.3, 194.1. ν_{max} (KBr) 3159, 1666, 1616 cm^{-1}. MS *m*/*z* (%) 346 (M^+, 40), 345 (100), 226 (12), 183 (13), 136 (27), 119 (24), 91 (47), 84 (19), 77 (24).

3.4.3. 2-[*N*-(3-Methylphenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11c). (2.39 g, 69%) as yellow crystals, mp 174 °C. (Found: C, 69.1; H, 5.4; N, 16.0. $C_{20}H_{18}N_4O_2$ (346.39) requires: C, 69.35; H, 5.24; N, 16.17%). δ_H ($CDCl_3$) 2.33 (s, 3H, Ar-CH_3), 2.42 (s, 3H, 6-CH_3), 6.26 (s, 1H, 5-CH), 6.89–7.81 (m, 9H, ArH), 12.80 (s, 1H, NH), 16.0 (s, 1H, NH); δ_C (DMSO-d_6) 21.8, 23.8, 110.0, 112.6, 113.7, 117.1, 126.5, 128.3, 129.4, 130.2, 130.7, 132.3, 139.0, 139.8, 142.6, 152.9, 164.0, 192.1. ν_{max} (KBr) 3179, 3059, 1682, 1620 cm^{-1}. MS *m*/*z* (%) 347 (M^++1, 42), 346 (M^+, 37), 345 (100), 212 (15), 183 (17), 136 (28), 119 (27), 105 (27), 91 (43), 84 (23), 77 (45).

3.4.4. 2-[*N*,2-Diphenyl-2-oxo-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidin-one (11d). (2.66 g, 80%) as pale yellow solid, mp 204 °C. (Found: C, 68.3; H, 5.1; N, 16.6. $C_{19}H_{16}N_4O_2$ (332.36) requires: C, 68.66; H, 4.85; N, 16.86%). δ_H ($CDCl_3$) 2.41 (s, 3H, 6-CH_3), 6.25 (s, 1H, 5-CH), 7.15–7.80 (m, 10H, ArH), 12.80 (s, 1H, NH), 16.05 (s, 1H, NH), δ_C (DMSO-d_6) 23.6, 112.6, 116.5, 128.4, 129.4, 129.5, 129.6, 130.3, 130.7, 134.6, 139.0, 142.7, 152.8, 161.1, 193.7. ν_{max} (KBr) 3140, 1666, 1608 cm^{-1}. MS *m*/*z* (%) 332 (M^+, 38), 331 (100), 303 (10), 169 (12), 136 (33), 105 (29), 84 (21), 77 (74).

3.4.5. 2-[*N*-(4-Chlorophenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11e). (2.86 g, 78%) as red crystals, mp 200 °C. (Found: C, 62.5; H, 4.0; N, 15.5. $C_{19}H_{15}ClN_4O_2$ (366.81) requires: C, 62.22; H, 4.12; N, 15.27%). δ_H ($CDCl_3$) 2.41 (s, 3H, 6-CH_3), 6.27 (s, 1H, 5-CH), 7.10 (d, *J*=7 Hz, 2H, ArH), 7.13–7.75 (m, 5H, ArH), 7.76 (d, *J*=7 Hz, 2H, ArH), 12.75 (s, 1H, NH), 16.1 (s, 1H, NH). ν_{max} (KBr) 3180, 3030, 1666, 1616 cm^{-1}. MS *m*/*z* (%) 369 (M^++2, 1), 368 (M^++1, 5), 367 (M^+, 14), 366 (14), 365 (36), 212 (11), 136 (50), 111 (17), 105 (66), 99 (12), 84 (18), 77 (100).

3.4.6. 2-[*N*-(3-Chlorophenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11f). (2.57 g, 70%) as red solid, mp 222 °C. (Found: C, 62.0; H, 3.9; N, 15.1. $C_{19}H_{15}ClN_4O_2$ (366.81) requires: C, 62.22; H, 4.12; N, 15.27%). δ_H ($CDCl_3$) 2.42 (s, 3H, 6-CH_3), 6.28 (s, 1H, 5-CH), 7.04–7.80 (m, 9H, ArH), 12.69 (s, 1H, NH), 15.97 (s, 1H, NH); ν_{max} (KBr) 3067, 1686, 1620 cm^{-1}. MS *m*/*z* (%) 369 (M^++2, 4), 368 (M^++1, 13), 367 (M^+, 40), 366 (39), 365 (99), 337 (11), 212 (14), 203 (13), 136 (64), 116 (16), 105 (48), 89 (12), 84 (38), 77 (100).

3.4.7. 2-[*N*-(3-Nitrophenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11g). (2.98 g, 79%) as orange crystals, mp 238 °C. (Found: C, 60.6; H, 4.2; N, 18.8. $C_{19}H_{15}N_5O_4$ (377.36) requires: C, 60.48; H, 4.01; N, 18.56%). δ_H ($CDCl_3$) 2.45 (s, 3H, 6-CH_3), 6.31 (s, 1H, 5-CH), 7.26–8.05 (m, 9H, ArH), 12.7 (s, 1H, NH), 16.10 (s, 1H, NH). δ_C (DMSO-d_6) 22.9, 109.7, 117.9, 121.6, 127.9, 128.9, 129.1, 130.0, 130.2, 130.9, 132.1, 134.4, 137.7, 143.8, 148.8, 164.1, 191.9. ν_{max} (KBr) 3030, 3059, 1681, 1625 cm^{-1}. MS *m*/*z* (%) 377 (M^+, 18), 376 (53), 212 (10), 136 (78), 116 (10), 105 (56), 84 (32), 78 (12), 77 (100).

3.4.8. 2-[*N*-(4-Nitrophenyl)-2-oxo-2-phenylethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (11h). (3.80 g, 80%) as deep red crystals, mp 280 °C. (Found: C, 60.2; H, 3.9; N, 18.7. $C_{19}H_{15}N_5O_4$ (377.36) requires: C, 60.48; H, 4.01; N, 18.56%). δ_H ($CDCl_3$) 2.48 (s, 3H, 6-CH_3), 6.31 (s, 1H, 5-CH), 7.67–7.54 (5H, m, ArH), 7.96 (d, *J*=9 Hz, 2H, ArH), 8.16 (d, *J*=7 Hz, 2H, ArH), 12.9 (s, 1H, NH), 18.2 (s, 1H, NH). ν_{max} (KBr) 3402, 3070, 1681, 1635 cm^{-1}. MS *m*/*z* (%) 377 (M^+, 33), 376 (100), 348 (14), 212 (13), 136 (58), 105 (43), 84 (20), 77 (75).

3.4.9. 2-[*N*-(4-Methoxyphenyl)-2-oxo-2-(4-methylphenyl)-ethane-hydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12a). (2.97 g, 79%) as orange solid, mp 182 °C. (Found: C, 67.2; H, 5.5; N, 14.9. $C_{21}H_{20}N_4O_3$ (376.42) requires: C, 67.01; H, 5.36; N, 14.88%). δ_H ($CDCl_3$) 2.39 (s, 3H, $ArCH_3$), 2.45 (s, 3H, 6-CH_3), 3.81 (s, 3H, OCH_3), 6.23 (s, 1H, 5-CH), 6. 9 (d, *J*=9 Hz, 2H, ArH), 7.15 (d, *J*=9 Hz, 2H,

ArH), 7.25 (d, J=8 Hz, 2H, ArH), 7.70 (d, J=8 Hz, 2H, ArH), 12.89 (s, 1H, NH), 16.15 (s, 1H, NH). ν_{max} (KBr) 3147, 3074, 1685, 1608 cm^{-1}. MS m/z (%) 377 (M^++1, 15), 376 (M^+, 63), 375 (100), 226 (15), 213 (12), 198 (11), 136 (19), 122 (22), 119 (54), 107 (16), 91 (53), 84 (11), 77 (12).

3.4.10. 2-[*N*-2-Di(4-methylphenyl)-2-oxo-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12b). (3.06 g, 85%) as orange plates, mp 238 °C. (Found: C, 70.2; H, 5.4; N, 15.6. $C_{21}H_{20}N_4O_2$ (360.42) requires: C, 69.98; H, 5.59; N, 15.54%). δ_H ($CDCl_3$) 2.35 (s, 3H, Ar-CH_3), 2.40 (s, 3H, 6-CH_3), 2.45 (s, 3H, 6-CH_3), 6.24 (s, 1H, 5-CH–), 7.10 (d, J=8 Hz, 2H, ArH), 7.16 (d, J=8 Hz, 2H, ArH), 7.25 (d, J=8 Hz, 2H, ArH), 7.71 (d, J=8 Hz, 2H, ArH), 12.82 (s, 1H, NH), 16.1 (s, 1H, NH); ν_{max} (KBr) 3143, 1666, 1616 cm^{-1}. MS m/z (%) 360 (M^+, 42), 359 (100), 226 (12), 197 (17), 136 (29), 119 (40), 91 (75), 84 (18), 77 (16).

3.4.11. 2-[*N*-(3-Methylphenyl)-2-oxo-2-(4-methylphenyl)-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12c). (2.63 g, 73%) as orange solid, mp 190 °C. (Found: C, 70.3; H, 5.4; N, 15.6. $C_{21}H_{20}N_4O_2$ (360.42) requires: C, 69.98; H, 5.59; N, 15.54%). δ_H ($CDCl_3$) 2.33 (s, 3H, Ar-CH_3), 2.41 (s, 3H, ArCH_3), 2.45 (s, 3H, 6-CH_3), 6.24 (s, 1H, 5-CH), 6.98 (d, J=8 Hz, 2H, ArH), 7.00–7.28 (m, 4H, ArH), 7.72 (d, J=8 Hz, 2H, ArH), 12.82 (s, 1H, NH), 15.95 (s, 1H, NH). ν_{max} (KBr) 3170, 1681, 1620 cm^{-1}. MS m/z (%) 360 (M^+, 40), 359 (100), 226 (10), 197 (13), 136 (24), 119 (27), 91 (56), 84 (14), 77 (10).

3.4.12. 2-[*N*-Phenyl-2-oxo-2-(4-methylphenyl)ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12d). (2.79 g, 80%) as orange crystals, mp 260 °C. (Found: C, 69.2; H, 5.5; N, 16.1. $C_{20}H_{18}N_4O_2$ (346.39) requires: C, 69.35; H, 5.24; N, 16.17%). δ_H ($CDCl_3$) 2.41 (s, 3H, Ar-CH_3), 2.46 (s, 3H, 6-CH_3), 6.25 (s, 1H, 5-CH), 7.15 (d, J=8 Hz, 2H, ArH), 7.2–7.4 (m, 5H, ArH), 7.72 (2H, J=8 Hz, ArH), 12.80 (s, 1H, NH), 16.01 (s, 1H, NH). ν_{max} (KBr) 3150, 3050, 1666, 1608 cm^{-1}. MS m/z (%) 346 (M^+, 40), 345 (100), 226 (12), 183 (13), 136 (27), 119 (24), 92 (10), 91 (47), 84 (18), 77 (24).

3.4.13. 2-[*N*-(4-Chlorophenyl)-2-oxo-2-(4-methylphenyl)-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12e). (2.86 g, 75%) as orange plates, mp 236 °C. (Found: C, 63.2; H, 4.9; N, 14.5. $C_{20}H_{17}ClN_4O_2$ (380.84) requires: C, 63.08; H, 4.50; N, 14.71%). δ_H ($CDCl_3$) 2.40 (s, 3H, ArCH_3), 2.46 (s, 3H, 6-CH_3), 6.26 (s, 1H, 5-CH), 7.12 (d, J=8 Hz, 2H, ArH), 7.25 (d, J=7 Hz, 2H, ArH), 7.32 (d, J=8 Hz, 2H, ArH), 7.70 (d, J=7 Hz, 2H, ArH), 12.74 (s, 1H, NH), 16.01 (s, 1H, NH). δ_C (DMSO-d_6) 21.7, 23.4, 111.9, 117.3, 118.1, 128.9, 129.3, 129.5, 130.1, 130.9, 136.1, 142.1, 142.8, 156.6, 162.8, 193.1; ν_{max} (KBr) 3182, 1666, 1616 cm^{-1}. MS m/z (%) 382 (M^++1, 3), 381 (M^+, 10), 380 (10), 379 (28), 136 (36), 119 (72), 99 (11), 91 (100), 89 (16), 84 (34), 76 (11).

3.4.14. 2-[*N*-(3-Chlorophenyl)-2-oxo-2-(4-methylphenyl)-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12f). (2.67 g, 70%) as orange crystals, mp 246 °C. (Found: C, 63.2; H, 4.9; N, 14.4. $C_{20}H_{17}ClN_4O_2$ (380.84) requires: C, 63.08; H, 4.50; N, 14.71%). δ_H ($CDCl_3$) 2.41 (s, 3H, Ar-CH_3), 2.46 (s, 3H, 6-CH_3), 6.27 (s, 1H, 5-CH), 7.10 (d, J=8 Hz, 2H, ArH), 7.14–7.31 (m, 4H, ArH), 7.72 (d, J=8 Hz, 2H, ArH), 12.73 (s, 1H, NH), 15.93 (s, 1H, NH). ν_{max} (KBr) 3150, 1685, 1620 cm^{-1}. MS m/z (%) 382 (M^++1, 12), 381 (M^+, 43), 379 (100), 226 (13), 217 (12), 136 (51), 119 (30), 91 (48), 84 (22).

3.4.15. 2-[*N*-(3-Nitrophenyl)-2-oxo-2-(4-methylphenyl)-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12g). (3.13 g, 80%) as orange solid, mp 244 °C. (Found: C, 61.1; H, 4.5; N, 17.6. $C_{20}H_{17}N_5O_4$ (391.39) requires: C, 61.38; H, 4.38; N, 17.89%). δ_H ($CDCl_3$) 2.44 (s, 3H, ArCH_3), 2.48 (s, 3H, 6-CH_3), 6.29 (s, 1H, 5-CH), 7.31 (d, J=8 Hz, 2H, ArH), 7.73 (d, J=8 Hz, 2H, ArH), 7.46–7.57 and 7.91–8.06 (m, 4H, ArH), 12.7 (s, 1H, NH), 16.00 (s, 1H, NH). ν_{max} (KBr) 3425, 3093, 1689, 1620 cm^{-1}. MS m/z (%) 392 (M^++1, 5), 391 (M^+, 24), 390 (73), 228 (11), 226 (17), 136 (87), 130 (10), 119 (62), 91 (100), 84 (34).

3.4.16. 2-[*N*-(4-Nitrophenyl)-2-oxo-2-(4-methylphenyl)-ethanehydrazonoyl]-6-methyl-4(3*H*)-pyrimidinone (12h). (3.13 g, 80%) as yellow solid, mp 296 °C. (Found: C, 60.3; H, 4.1; N, 17.7. $C_{20}H_{17}N_5O_4$ (391.39) requires: C, 61.38; H, 4.38; N, 17.89%). δ_H ($CDCl_3$) 2.44 (s, 3H, ArCH_3), 2.48 (s, 3H, 6-CH_3), 6.31 (s, 1H, 5-CH), 7.26 (d, J=8 Hz, 2H, ArH), 7.29 (d, J=8 Hz, 2H, ArH), 7.73 (d, J=9 Hz, 2H, ArH), 8.27 (d, J=9 Hz, 2H, ArH), 12.6 (s, 1H, NH), 16.05 (s, 1H, NH). ν_{max} (KBr) 3417, 3086, 1689, 1631 cm^{-1}. MS m/z (%) 392 (M^++1, 7), 391 (M^+, 35), 390 (100), 362 (11), 226 (16), 136 (52), 119 (36), 91 (55), 84 (16).

3.4.17. 2-(*N*-Phenyl-2-oxo-2-phenylethanehydrazonoyl)-3,6-dimethyl-4(3*H*)-pyrimidinone (13d). (2.58 g, 75%) as yellow solid, mp 195 °C. (Found: C, 69.15; H, 5.1; N, 16.0. $C_{20}H_{18}N_4O_2$ (346.39) requires: C, 69.35; H, 5.24; N, 16.17%). δ_H ($CDCl_3$) 2.38 (s, 3H, 6-CH_3), 3.36 (s, 3H, N–CH_3), 6.38 (s, 1H, 5-CH), 7.1–8.1 (m, 10H, ArH), 11.10 (s, 1H, NH). δ_C (DMSO-d_6) 23.6, 31.5, 112.4, 115.6, 123.8, 128.7, 130.0, 130.6, 132.7, 134.1, 137.9, 143.6, 153.6, 162.2, 163.4, 190.0; ν_{max} (KBr) 3440, 1666, 1627 cm^{-1}. MS m/z (%) 348 (M^++1, 0.3), 347 (M^+, 2), 226 (12), 169 (18), 158 (18), 150 (66), 136 (13), 105 (63), 89 (16), 77 (100).

3.4.18. 2-[*N*-Phenyl-2-oxo-2-(4-methylphenyl)ethanehydrazonoyl]-3,6-dimethyl-4(3*H*)-pyrimidinone (14d). (2.88 g, 80%) as yellow crystals, mp 170 °C. (Found: C, 69.5; H, 5.3; N, 15.6. $C_{21}H_{20}N_4O_2$ (360.4) requires: C, 69.98; H, 5.59; N, 15.54%). δ_H ($CDCl_3$) 2.24 (s, 3H, Ar-CH_3), 2.42 (s, 3H, 6-CH_3), 3.27 (s, 3H, N–CH_3), 6.38 (s, 1H, 5-CH), 7.2 (d, J=8 Hz, 2H, ArH), 7.3–7.5 (m, 5H, ArH), 7.91 (d, J=8 Hz, 2H, ArH), 10.98 (s, 1H, NH). δ_C (DMSO-d_6) 21.8, 23.6, 31.5, 112.4, 115.6, 123.7, 129.3, 130.0, 130.8, 134.2, 135.1, 143.1, 143.7, 153.7, 162.2, 163.4, 189.2. ν_{max} (KBr) 3417, 1651, 1627 cm^{-1}. MS m/z (%) 361 (M^++1, 5), 360 (M^+, 24.7), 359 (52), 240 (20), 183 (34), 158 (13), 150 (100), 119 (77), 106 (40), 91 (91), 77 (40).

References and notes

1. (a) Shawali, A. S.; Abdelkader, M. H.; Eltalbawy, F. M. A. *Tetrahedron* **2002**, *58*, 2875–2880. (b) Shawali, A. S.;

Abdallah, M. A.; Mosselhi, M. A. N.; Mohamed, Y. F. *Z. Naturforsch.* **2002**, *57b*, 552–556. (c) Mosselhi, M. N.; Abdallah, M. A.; Mohamed, Y. F.; Shawali, A. S. *Phosphorus, Sulfur Silicon* **2002**, *177*, 487–496. (d) Shawali, A. S.; Zeid, I. F.; Abdelkader, M. H.; Eltalbawy, F. M. A. *J. Chin. Chem. Soc.* **2001**, *48*, 65–72. (e) Mosselhi, M. A. N.; Abdallah, M. A.; Riyadh, S. M.; Harhash, A. E.; Shawali, A. S. *J. Prakt. Chem.* **1998**, *340*, 160–164. (f) Shawali, A. S.; Harb, N. M. S.; Badahdah, K. O. *J. Heterocycl. Chem.* **1985**, *22*, 1397–1403.

2. (a) Huang, Z. T.; Tzai, L. H. *Chem. Ber.* **1986**, *119*, 2208–2219. (b) Huang, Z. T.; Liu, Z. R. *Heterocycles* **1986**, *24*, 2247–2254. (c) Huang, Z. T.; Wang, M. X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1085–1094. (d) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998**, *54*, 6191–6200.
3. (a) Huang, Z. T.; Liu, Z. R. *Chem. Ber.* **1989**, *122*, 95–100. (b) Wang, L. B.; Yu, C. Y.; Huang, Z. T. *Synthesis* **1994**, 1441–1444. (c) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Turne, I. *Tetrahedron* **1997**, *53*, 11781–11790.
4. (a) Huang, Z. T.; Wang, M. X. *J. Org. Chem.* **1992**, *57*, 184–190. (b) Huang, Z. T.; Wang, M. X. *Synth. Commun.* **1991**, *21*, 1909–1916. (c) Liu, Z. R.; Huang, Z. T.; Wang, M. X. *Tetrahedron Lett.* **1999**, *40*, 7399–7402.
5. For a review, see: Huang, Z. T.; Wang, M. X. *Heterocycles* **1994**, *37*, 1233–1262.
6. Hurst, D. T.; Beaumont, C.; Jones, D. T. E.; Kingsley, D. A.; Pertridge, J. D.; Rutherford, T. J. *Aust. J. Chem.* **1988**, *41*, 1209–1219.
7. (a) Skulnick, H. I.; Ludens, J. H.; Wendling, M. G.; Glenn, E. M.; Rohloff, N. A.; Smith, R. J. *J. Med. Chem.* **1986**, *29*, 1499–1504. (b) De Melo, S. J.; Luu-Duc, C. *J. Chem. Res. (S)* **1992**, 286–287, and the references cited therein.
8. Jones, R.; Ryan, A. J.; Sternhell, S.; Wright, S. E. *Tetrahedron* **1963**, *19*, 1497–1507.
9. Shawali, A. S.; Khattab, S. A.; Farag, A. M. *J. Chem. Engng. Data* **1977**, *22*, 104–110.
10. (a) Shawali, A. S.; Elghandour, A. H.; Sayed, A. R. *Synth. Commun.* **2001**, *31*, 731–740. (b) Bedford, G. R.; Taylor, P. J.; Webb, G. A. *Magn. Res. Chem.* **1995**, *33*, 389–394. (c) Elguero, J.; Goya, P.; Martinez, A.; Rozas, I. *Chem. Ber.* **1989**, *122*, 919–924.
11. (a) Greenhill, J. V.; Ismail, M. J.; Bedford, G. R.; Edwards, P. N.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1265–1274. (b) Reiter, J.; Bongo, L.; Dyortsok, P. *Tetrahedron* **1987**, *43*, 2497–2504.

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Modular and stereoselective formal synthesis of MeBmt, an unusual amino acid constituent of cyclosporin A☆

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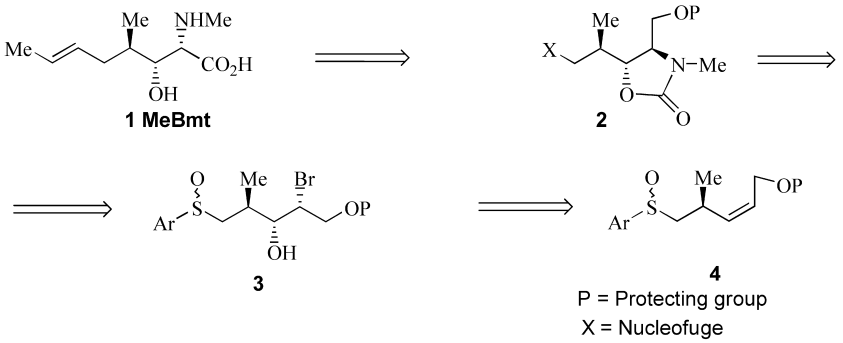
Abstract—A convergent, flexible and stereoselective formal synthesis of MeBmt, the nonproteinogenic amino acid constituent of cyclosporin A is disclosed. The sulfinyl moiety has been exploited as the internal nucleophile to stereo- and regioselectively functionalize an allylic carbamate.

1. Introduction

Cyclosporin A is a cyclic undecapeptide isolated from the fungus *Tolypocladium inflatium* Gams.,[1] possessing immunosuppressive activity, thus preventing organ rejection after transplantation. The structure of cyclosporin A is characterized by the presence of many *N*-methylated α-amino acids and a unique γ-alkyl-β-hydroxy-α-amino acid, MeBmt (**1**). MeBmt itself does not show any bioactivity, however modification of the MeBmt moiety in cyclosporin greatly affects its immunosuppressive activity. Many routes have been reported for the synthesis of MeBmt, employing starting materials from the chiral pool,[2] chiral epoxides[3] and the aldol reaction[4] in the key step of the reaction sequence. The syntheses employing the aldol reaction as the key step require chiral α-alkyl branched aldehyde and a chiral glycine synthon for good diastereoselection. The other syntheses require expensive catalysts or additional steps for the *N*-methylation of the final amino acid, thereby limiting their potential for the large scale preparation of MeBmt. As part of our interest in employing the sulfinyl moiety as an internal nucleophile[5] to stereo- and regioselectively functionalize allylic olefins and use of the resulting bromohydrins as intermediates for the synthesis of bioactive target molecules,[6] we detail herein a stereoselective and modular synthesis of MeBmt.

2. Results and discussion

MeBmt has three contiguous chiral centers, an *N*-Me group and a *trans* double bond. By retrosynthetic analysis (Scheme 1), MeBmt can be derived from the retron **2**, the forward sequence would require chain extension by a propenyl cuprate followed by oxidation of the primary hydroxy group and hydrolysis of the oxazolidinone. The oxazolidinone **2**



Scheme 1.

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Keywords: MeBmt; Sulfoxide; Neighbouring group participation; Bromohydrin.
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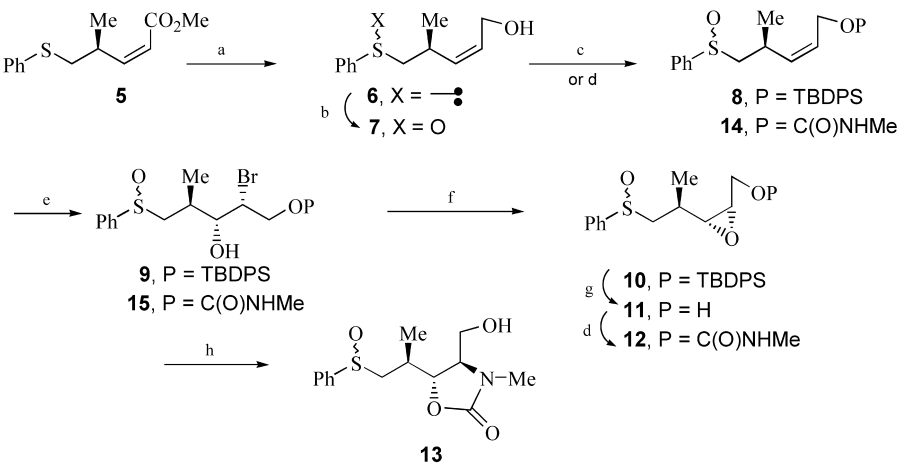
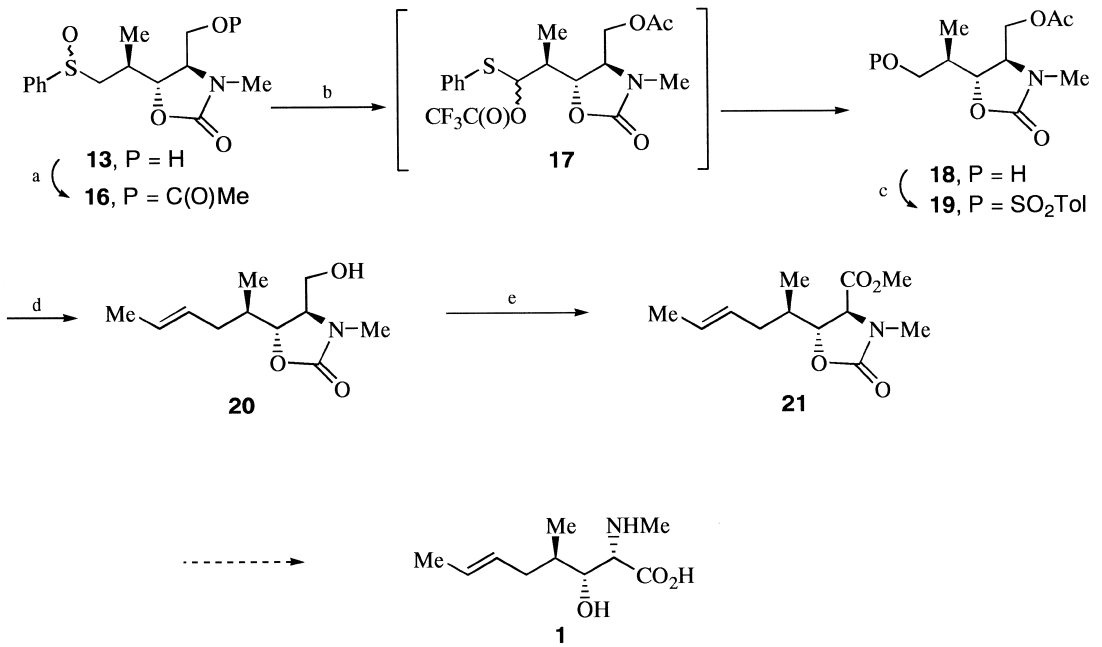


Scheme 2. (a) $LiAlH_4/AlCl_3$, THF/ether 0 °C, 1 h, 93%; (b) $NaIO_4$, CH_3OH/H_2O, rt, 16 h, 95%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h, 95%; (d) CH_3NCO, Et_3N, CH_2Cl_2, rt, 6 h, **14**, 90%, **12**, 95%; (e) NBS, H_2O, toluene, rt, 30 min, **9**, 80% **15**, 80%; (f) K_2CO_3, CH_3OH, rt, 1 h, **10**, 95%, **12**, 95%; (g) TBAF/AcOH, THF, rt, 2 h, 85%; (h) NaHMDS, THF, 0 °C, 30 min, 95%.

can itself be derived from bromohydrin **3** which in turn can be readily obtained from the olefinic substrate **4**. In the proposed strategy, the methyl group would serve to introduce the other two chiral centers stereoselectively by asymmetric induction.

The synthesis began with the unsaturated ester **5**,[6b] which was reduced with alane, generated in situ, to afford the primary alcohol **6**. Oxidation of the sulfide with $NaIO_4$ afforded an inseparable equimolar mixture of sulfoxides **7**, which was transformed into the silyl ether **8** by treatment with *t*-butyldiphenylchloro silane. No efforts were made to separate the epimeric sulfoxides **8**, since the sulfur chirality was of no consequence in the subsequent steps of the synthesis.[5b] Treatment of the sulfoxide **8** with NBS in toluene in the presence of water afforded bromohydrin **9**, the structure of which has been rigorously established.[5b] The product **9** has three stereocenters other than the sulfoxide, that are disposed both in a relative and an absolute sense as in MeBmt; the *N*-Me group therefore needed to be introduced by a double inversion procedure. Toward that direction, subjecting a methanolic solution of **9** to treatment with K_2CO_3 in methanol afforded the epoxide **10**. Deprotection of the silyl group by treatment with buffered TBAF[7] in anhydrous THF afforded epoxy alcohol **11**. Reaction of the epoxy alcohol **11** with methyl isocyanate afforded the carbamate **12**, which when subjected to treatment with NaHMDS in anhydrous THF afforded the rearranged oxazolidinone[8] **13** exclusively (Scheme 2).

It occurred to us that if the bromohydration could be done on the allylic carbamate **14**, two steps could be reduced in the overall synthetic sequence. Homoallylic carbamates have been reported to function as internal nucleophiles and afford



Scheme 3. (a) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, 30 min, 95%; (b) TFAA, Et_3N, CH_3CN, rt, 30 min, then aq. $NaHCO_3$, $NaBH_4$, at 0 °C, 30 min, 65%; (c) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 1 h, 85%; (d) 1-(*E*)-propenylmagnesium bromide, CuI, THF, −78 °C to rt, 2 h, 70%; (e) $PhI(OAc)_2$, TEMPO, CH_3CN/H_2O, rt, 2 h, then ethereal CH_2N_2, rt, 10 min, 80% for 2 steps.

iodocarbonates upon treatment with iodine in a biphasic system after a prolonged reaction period. A single example of a carbamate derived from an allyl alcohol was reported to yield the iodocarbonate in moderate yield under similar reaction conditions.[9] We were therefore not certain if the carbamate or the sulfinyl moiety would function as the intramolecular nucleophile in the reaction of **14** with NBS. Gratifyingly, reaction of **14**, prepared from alcohol **7** by treatment with methyl isocyanate, with NBS in toluene afforded exclusively, the bromohydrin **15**, as an epimeric mixture, within a period of 30 min. Subjecting bromohydrin **15** to treatment with K_2CO_3 in methanol afforded epoxy carbamate **12** identical to that prepared from the allyl silylether **8**. The cyclization of epoxycarbamate **12** to yield **13** not only served to introduce the *N*-methyl substituent but also served to simultaneously protect the hydroxy and amino groups. Having access to the oxazolidinone **13**, the next step of the synthesis called for the introduction of the olefinic side chain and oxidation of the primary hydroxy group. Acetylation of the hydroxy group in **13** afforded compound **16** which was more conveniently obtained in a one pot operation from **12** by quenching the reaction with Ac_2O. Subjecting **16** to Pummerer rearrangement[10] conditions followed by treatment of the resulting intermediate **17** with sat. aq. $NaHCO_3$ and $NaBH_4$ afforded alcohol **18** in an one pot operation. Tosylation of the hydroxy group yielded product **19** which upon treatment with excess (*E*)-propenyl magnesium bromide in the presence of cat. amount of CuI afforded olefinic alcohol[2a] **20** by concomitant deprotection of the acetyl group. The primary hydroxy group was oxidized by treatment with $PhI(OAc)_2$/TEMPO[11] to yield the acid which was esterified by treatment with excess of diazomethane to afford the ester **21**. Compound **21** had physical and spectroscopic properties similar to that reported in the literature.[2a] Oxazolidinone **21** has been transformed to MeBmt[2a,4a,g] and thus we have completed a formal synthesis of the unusual amino acid, MeBmt (Scheme 3).

In summary, we have disclosed a novel, modular and stereoselective synthesis of MeBmt. The key steps in the reaction sequence include regio- and stereoselective bromohydration of a double bond utilizing the sulfinyl group as an internal nucleophile, the use of a carbamate as an internal nucleophile to open the epoxide to yield the required *trans* oxazolidinone and the use of the sulfoxide as a masked hydroxyl group.

3. Experimental

3.1. General

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled freshly over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM and over P_2O_5 for toluene. Commercially available reagents were used without further purification except NBS, which was freshly recrystallized from hot water before use. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^1H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Insufficient resonances in the ^{13}C NMR data of the diastereomeric mixture of compounds is due to resonance overlap. Melting points are uncorrected.

3.1.1. 4-Methyl-5-phenylsulfanyl-(*Z*,4*S*)-2-pentene-1-ol 6. To the suspension of $LiAlH_4$ (0.91 g, 24 mmol) in dry ether (20 mL) maintained at 0 °C was added the solution of $AlCl_3$ (1.07 g, 8 mmol) in anhydrous ether (37 mL) and the reaction mixture stirred at the same temperature for 30 min. The solution of the ester **5**[6b] (3.78 g, 16 mmol) in anhydrous ether (37 mL) was then added to reaction mixture and the stirring continued at 0 °C for a further 30 min. The reaction mixture was diluted with ether and quenched by adding ice pieces. The reaction mixture was passed through a small pad of celite and the filtrate evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to yield allyl alcohol **6** (3.1 g, 14.9 mmol) in 93% yield. Viscous oil. R_f 0.3 (10% EtOAc/petroleum ether). $[\alpha]_D^{25}=-21.0$ (*c* 1.0, $CHCl_3$). *ms* LSIMS 209 $[M+H]^+$. IR (neat) 3554, 2889, 1087, 954, 690. ^1H NMR (200 MHz, $CDCl_3$) δ 7.38–7.10 (m, 5H), 5.68 (m, 1H), 5.35 (t, J=8.3 Hz, 1H), 4.20–3.95 (m, 2H), 3.0–2.70 (m, 3H), 1.13 (d, J=6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 32.1, 40.8, 58.3, 126.0, 128.9, 129.2, 136.1, 136.6. Anal. calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.35; H, 7.56; S, 15.25.

3.1.2. 4-Methyl-5(S_S)-phenylsulfinyl-(*Z*,4*S*)-2-pentene-1-ol and 4-methyl-5(R_S)-phenylsulfinyl-(*Z*,4*S*)-2-pentene-1-ol 7. To the solution of the sulfide **6** (3.0 g, 14.5 mmol), in 1:1 MeOH/THF (146 mL) was added the solution of $NaIO_4$ (3.4 g, 15.9 mmol) in water (73 mL) and the reaction mixture stirred at rt for 16 h. The precipitated solid was removed by filtration and the filtrate evaporated under reduced pressure. The aq. layer was extracted with ethyl acetate and the combined organic layers washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 50% EtOAc/petroleum ether (v/v) as the eluent to yield sulfoxide **7** (3.08 g, 13.77 mmol) as a 1:1 diastereomeric mixture in 95% yield. Viscous oil. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 225 $[M+H]^+$. IR (neat) 3327, 2953, 1651, 1598, 1047, 968 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.48 (m, 10H), 5.90 (m, 1H), 5.75 (m, 1H), 5.39 (t, J=10.4 Hz, 1H), 5.25 (t, J=10.4 Hz, 1H), 4.40–3.90 (m, 4H), 3.42–3.0 (m, 2H), 2.95–2.75 (m, 2H), 2.61–2.40 (m, 2H), 1.20 (d, J=7.8 Hz, 3H), 1.10 (d, J=7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.8, 27.4, 27.7, 57.8, 57.9, 64.3, 64.6, 123.8, 123.9, 129.1, 129.2, 129.3, 131.0, 131.1, 133.7, 134.6, 143.5, 143.7. Anal. calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.16; H, 7.04; S, 14.12.

3.1.3. 1(S_S)-[5-*tert*-Butyldiphenylsiloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene and 1(R_S)-[5-*tert*-butyldiphenylsiloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene 8. To the solution of the alcohol **7** (0.45 g, 2 mmol) in dry DCM (3.8 mL) was added imidazole (204 mg, 3 mmol) followed by the addition of TBDPS-Cl (0.56 mL,

2.2 mmol). The reaction mixture was stirred at rt for 3 h under an atmosphere of nitrogen. The reaction mixture was diluted with DCM (30 mL) and washed successively with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 10% EtOAc/pet. ether (v/v) as the eluent to yield **8** (0.71 g, 1.54 mmol) in 78% yield. A small amount of the epimeric sulfoxide was separated for characterization purposes into **8a** and **8b**.

Compound **8a**. Liquid. R_f 0.3 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=-38.6$ (*c* 1.0, $CHCl_3$). *ms* (EI) 405 ($M^+-C_4H_9$). IR (neat) 2953, 1655, 1595, 1032, 968, 854, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.68–7.30 (m, 15H), 5.56 (m, 1H), 5.23 (m, 1H), 4.19 (d, *J*=6.38 Hz, 2H), 2.77 (m, 1H), 2.73 (dd, *J*=12.7, 5.1 Hz, 1H), 2.50 (dd, *J*=12.7, 8.9 Hz, 1H), 1.13 (d, *J*=6.3 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 20.3, 26.9, 27.9, 60.2, 65.1, 124.1, 127.7, 129.2, 129.6, 130.9, 133.7, 135.6, 144.0. Anal. calcd for $C_{28}H_{34}O_2SSi$: C, 72.68; H, 7.41; S, 6.93. Found: C, 72.52; H, 7.73; S, 7.28.

Compound **8b**. Liquid. R_f 0.25 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=+135.8$ (*c* 1.0, $CHCl_3$). *ms* (EI) 405 [$M^+-C_4H_9$]. IR (neat) 2953, 1655, 1595, 1032, 968, 854, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.30 (m, 15H), 5.70 (m, 1H), 5.25 (m, 1H), 4.30 (d, *J*=6.3 Hz, 2H), 2.92 (m, 1H), 2.73 (dd, *J*=13.2, 5.1 Hz, 1H), 2.40 (dd, *J*=13.2, 9.1 Hz, 1H), 1.04 (bs, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 20.9, 26.8, 28.3, 60.3, 65.7, 123.8, 127.5, 127.6, 129.1, 129.5, 130.9, 133.8, 135.5, 144.8. Anal. calcd for $C_{28}H_{34}O_2SSi$: C, 72.68; H, 7.41; S, 6.93. Found: C, 72.84; H, 7.65; S, 7.30.

3.1.4. 2-Bromo-1-*tert*-butyldiphenylsilyloxy-4-methyl-5(S_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol and 2-bromo-1-*tert*-butyldiphenylsilyloxy-4-methyl-5(R_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol 9. To the solution of the sulfoxide **8** (0.56 g, 1.2 mmol) in dry toluene (4.8 mL) was added water (32 μL, 1.8 mmol), followed by NBS (256 mg, 1.44 mmol) and the reaction mixture stirred at rt for 1 h. The reaction was quenched by the addition of an aq. saturated $NaHCO_3$ solution. The layers were separated and the aq. layer extracted with EtOAc (2×25 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 20% EtOAc/pet. ether (v/v) as the eluent to yield bromohydrin **9** (0.5 g, 0.9 mmol) in 75% yield. Viscous oil. A small sample of the epimeric mixture of bromohydrins was separated into the individual isomers for the purpose of characterization.

Compound **9a**. Viscous oil. R_f 0.25 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=+49.1$ (*c* 1.0, $CHCl_3$). *ms* (FAB) 559, 501. IR (neat) 3326, 2943, 1554, 1043, 972, 698, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.58 (m, 6H), 7.52–7.33 (m, 9H), 4.15–3.94 (m, 3H), 3.66 (d, *J*=8.6 Hz, 1H), 3.10 (dd, *J*=13.1, 3.8 Hz, 1H), 2.92 (dd, *J*=13.1, 3.8 Hz, 1H), 2.39 (m, 1H) 1.06 (s, 9H), 1.02 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3, 19.8, 26.9, 34.7, 57.9, 61.2, 65.5, 72.4, 124.2, 127.9, 129.3, 129.9, 131.1, 133.7, 135.6, 144.0. Anal. calcd for $C_{28}H_{35}BrO_3SSi$: C, 60.09; H, 6.30; S, 5.73. Found: C, 60.18; H, 6.46; S, 5.98.

Compound **9b**. Viscous oil. R_f 0.2 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=-63.6$ (*c* 0.5, $CHCl_3$). *ms* (FAB) 559, 501. IR (neat) 3326, 2943, 1554, 1043, 972, 698, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.63 (m, 6H), 7.58–7.40 (m, 9H), 4.12–3.86 (m, 3H), 3.57 (d, *J*=8.8 Hz, 1H), 3.22 (dd, *J*=12.6, 4.0 Hz, 1H), 2.61 (dd, *J*=12.6, 7.0 Hz, 1H), 2.41 (m, 1H), 1.55 (d, *J*=6.3 Hz, 3H) 1.06 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.6, 19.2, 26.8, 34.7, 57.9, 62.4, 65.6, 73.2, 124.1, 127.9, 129.3, 130.0, 131.0, 133.2, 135.5, 135.6, 144.3. Anal. calcd for $C_{28}H_{35}BrO_3SSi$: C, 60.09; H, 6.30; S, 5.73. Found: C, 60.26; H, 6.43; S, 5.87.

3.1.5. 2-*tert*-Butyldiphenylsilyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane and 2-*tert*-butyldiphenylsilyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane 10. To the solution of bromohydrin **9** (0.44 g, 0.8 mmol) in methanol (4 mL) was added K_2CO_3 (0.22 g, 1.6 mmol) at 0 °C and stirred for 2 h at rt The reaction mixture was diluted with ether and filtered through a small pad of celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as the eluent to afford **10** (0.38 g, 0.8 mmol) as a 1:1 epimeric mixture in quantitative yield. Gummy liquid. R_f 0.3 (30% EtOAc/petroleum ether). *ms* LSIMS 479 $[M+H]^+$. IR (neat) 2961, 2932, 1588, 1471, 1428, 1062, 823, 698, 625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.35 (m, 30H), 3.90–3.60 (m, 4H), 3.20–3.0 (m, 4H), 2.85–2.55 (m, 4H), 2.0 (m, 1H), 1.75 (m, 1H), 1.25 (d, *J*=7.0 Hz, 3H), 1.20 (d, *J*=7.0 Hz, 3H), 1.05 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 19.2, 26.8, 28.6, 57.4, 59.9, 60.3, 61.8, 63.1, 124.2, 127.8, 129.2, 129.9, 131.0, 133.0, 135.5, 144.0. Anal. calcd for $C_{28}H_{34}O_3SSi$: C, 70.25; H, 7.16; S, 6.7. Found: C, 70.12; H, 7.24; S, 6.43.

3.1.6. 3-[1-Methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxiran-2-ylmethanol and 3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxiran-2-ylmethanol 11. To the solution of compound **10** (0.34 g, 0.71 mmol) in dry tetrahydrofuran (1.4 mL) was added acetic acid (0.13 mL, 2.13 mmol) and tetrabutylammonium fluoride (1.0 mL, 1 M in THF 1.0 mmol) at 0 °C and stirred for 2 h. The reaction mixture was then diluted with ether, washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) as the eluent to afford **11** (0.154 g, 0.64 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* (EI) 208 $[M^+]$. IR (Neat) 3354, 2964, 2932, 1586, 1462, 1425, 1047, 862, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.40 (m, 10H), 3.95–3.6 (m, 4H), 3.25–3.05 (m, 4H), 2.95–2.75 (m, 4H), 2.65–2.50 (m, 2H), 2.35–2.15 (m, 1H) 2.10–1.90 (m, 1H), 1.30 (d, *J*=7.0 Hz, 3H), 1.15 (d, *J*=7.0 Hz, 3H).

3.1.7. 2-*N*-Methylcarbonyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxirane and 2-*N*-methylcarbonyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxirane 12. To the solution of

compound **11** (0.12 g, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.2 mL, 1.5 mmol) and CH_3NCO (0.1 mL, 1.6 mmol) at rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, quenched by adding 10% aq. $NaHCO_3$ solution and diluted with ether. The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **12** (0.13 g, 0.45 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 298 $[M+H]^+$. IR (Neat) 3330, 2964, 1798, 1714, 1538, 1142, 1086, 1016, 750, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.50 (m, 10H), 5.50 (bs, 2H), 4.43–4.30 (m, 2H), 4.16–3.98 (m, 2H), 3.31–3.20 (m, 2H), 2.96–2.86 (m, 4H), 2.80 (d, J=5.2 Hz, 6H), 2.70–2.55 (m, 2H), 2.20–1.90 (m, 2H), 1.30 (d, J=6.7 Hz, 3H), 1.17 (d, J=6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 16.6, 28.4, 29.0, 54.2, 54.9, 59.4, 59.9, 61.9, 62.9, 63.5, 123.6, 123.9, 129.1, 131.0, 143.7, 144.4, 156.4. Anal. calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.47; H, 6.21; N, 4.62; S, 10.63.

3.1.8. 1(S_S)-[5-*N*-Methylcarbonyloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene and 1(R_S)-[5-*N*-methylcarbonyloxy-2-methyl-(2*S*, 3*Z*)-3-pentenylsulfinyl]-benzene 14. To the solution of compound **7** (1.9 g, 8.48 mmol) in dry CH_2Cl_2 (34 mL) was added Et_3N (3.5 mL, 25.4 mmol) and CH_3NCO (1.5 mL, 25.4 mmol) at rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, quenched by adding 10% aq. $NaHCO_3$ solution and diluted with ether. The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **14** (2.14 g, 7.63 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.3 (50% EtOAc/petroleum ether). *ms* LSIMS 282 $[M+H]^+$. IR (Neat) 3321, 2963, 1712, 1537, 1446, 1263, 1037, 821 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.40 (m, 10H), 5.80–5.60 (m, 2H), 5.50–5.30 (m, 2H), 4.70–4.50 (m, 4H), 3.30 (m, 2H), 3.0–2.40 (m, 10H), 1.30 (d, J=6.7 Hz, 3H), 1.10 (d, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 21.3, 27.4, 28.5, 28.9, 60.3, 61.3, 65.7, 66.2, 123.8, 124.7, 125.9, 129.2, 129.9, 130.9, 135.8, 136.5, 144.3, 144.8, 156.7. Anal. calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.39. Found: C, 59.87; H, 6.68; N, 4.73; S, 11.19.

3.1.9. 2-Bromo-1-*N*-methylcarbonyloxy-4-methyl-5(S_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol and 2-bromo-1-*N*-methylcarbonyloxy-4-methyl-5(R_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol 15. To the solution of compound **14** (2.1 g, 7.47 mmol) in toluene (30 mL) at rt was added water (0.23 mL, 12.7 mmol), *N*-bromosuccinimide (1.6 g, 8.96 mmol) and stirred for 30 min. When TLC examination revealed completion of the reaction. The reaction mixture was taken into ethyl acetate (70 mL) and washed successively with 10% aq. $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **15** (2.26 g, 5.98 mmol) as a 1:1 epimeric mixture in 80% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 378 $[M+H]^+$. IR (Neat) 3319, 2969, 1798, 1714, 1538, 1086, 1016, 750, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.50 (m, 10H), 5.50 (bs, 1H), 4.90 (bs, 1H), 4.60–4.10 (m, 8H), 3.50 (bs, 2H), 3.20–2.90 (m, 4H), 2.80 (d, J=4.5 Hz, 6H), 2.63 (m, 1H), 2.45 (m, 1H), 1.30 (d, J=7.4 Hz, 3H), 1.10 (d, J=7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8, 17.2, 27.5, 29.2, 34.2, 34.8, 54.9, 61.1, 62.0, 65.1, 65.5, 72.1, 74.2, 123.9, 124.0, 129.3, 131.2, 143.9, 156.8. Anal. calcd for $C_{14}H_{20}BrNO_4S$: C, 44.45; H, 5.33; N, 3.70; S, 8.48. Found: C, 44.26; H, 5.30; N, 3.56; S, 8.29.

3.1.10. *N*-Methylcarbonyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane and 2-*N*-methylcarbonyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane 12. To the solution of compound **15** (2.2 g, 5.82 mmol) in methanol (58 mL) was added K_2CO_3 (0.88 g, 6.4 mmol) and the mixture stirred at rt for 1 h. The reaction mixture was diluted with ether, filtered through a small pad of celite and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **12** (1.64 g, 5.53 mmol) as a 1:1 epimeric mixture in 95% yield which was identical to the sample obtained from **11**.

3.1.11. 4-Hydroxymethyl-3-methyl-5-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(4*R*,5*R*)1,3-oxazolan-2-one and 4-hydroxymethyl-3-methyl-5-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(4*R*,5*R*)1,3-oxazolan-2-one 13. To the solution of compound **12** (1.6 g, 5.39 mmol) in dry THF (108 mL) at 0 °C was added NaHMDS (3 mL, 2 M/THF, 6 mmol) and stirred for 30 min. The reaction mixture was quenched by adding saturated aq. NH_4Cl solution and diluted with ether (60 mL). The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford a residue which was purified by column chromatography using 70% EtOAc/petroleum ether (v/v) as the eluent to afford **13** (1.52 g, 5.12 mmol) as a 1:1 epimeric mixture in 95% yield. Viscous oil. R_f 0.1 (80% EtOAc/petroleum ether). *ms* LSIMS 298 $[M+H]^+$. IR (Neat) 3331, 2922, 1744, 1520, 1443, 1255, 1087, 1033, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.50 (m, 10H), 4.40–4.30 (m, 2H), 3.80–3.60 (m, 4H), 3.50–3.40 (m, 2H), 3.05–2.90 (m, 2H), 2.85 (s, 3H), 2.80 (s, 3H), 2.70–2.50 (m, 2H), 2.32 (m, 2H), 1.30 (d, J=6.8 Hz, 3H), 1.0 (d, J=6.8 Hz, 3H). Anal. calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.37; H, 6.53; N, 4.79; S, 10.89.

3.1.12. 3-Methyl-5-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate and 3-methyl-5-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 16. To the solution of compound **13** (1.48 g, 4.98 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (1.04 mL, 7.47 mmol) followed by acetic anhydride (0.52 mL, 5.48 mmol) and stirred at rt for 30 min. The reaction mixture was diluted with EtOAc (20 mL) and washed successively with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a

residue which was purified by column chromatography using 50% EtOAc/petroleum ether (v/v) as the eluent to afford **16** (1.6 g, 4.73 mmol) as a 1:1 epimeric mixture in 95% yield. Viscous oil. R_f 0.4 (80% EtOAc/petroleum ether). *ms* LSIMS 340 $[M+H]^+$. IR (Neat) 2918, 1747, 1444, 1230, 1088, 1037, 755, 692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.50 (m, 10H), 4.40–4.02 (m, 6H), 3.73–3.54 (m, 2H), 3.05–2.45 (m, 4H), 2.90 (s, 3H), 2.80 (s, 3H), 2.50–2.30 (m, 2H), 2.10 (s, 6H), 1.40 (d, J=6.7 Hz, 3H), 1.0 (d, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 15.9, 20.4, 20.5, 29.0, 29.1, 33.1, 33.2, 58.7, 58.9, 59.0, 59.6, 62.1, 62.3, 77.2, 78.4, 123.6, 123.8, 129.2, 129.3, 131.2, 143.2, 143.3, 156.8, 156.9, 170.2. Anal. calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13; S, 9.45. Found: C, 56.47; H, 6.14; N, 4.05; S, 9.36.

3.1.13. 5-[2-Hydroxy-1-methyl-(1*R*)-ethyl]-3-methyl-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 18. To the solution of compound **16** (1.50 g, 4.42 mmol) in acetonitrile (24 mL) at rt was added triethylamine (6.15 mL, 44.2 mmol) followed by trifluoroacetic anhydride (6.2 mL, 44.2 mmol) and stirred for 30 min. A solution of $NaHCO_3$ (7.40 g, 88.4 mmol) in water (24 mL) was added at 0 °C followed by solid $NaBH_4$ (1.68 g, 44.2 mmol) and the reaction mixture stirred for another 30 min. The reaction mixture was then extracted into ethyl acetate and washed successively with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **18** (0.66 g, 2.87 mmol) in 65% yield. Viscous oil. R_f 0.3 (80% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+24.6 (*c* 0.66, $CHCl_3$). *ms* LSIMS 232 $[M+H]^+$. IR (Neat) 3327, 2925, 1741, 1442, 1233, 1141, 1038 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.35 (dd, J=11.8, 4.1 Hz, 1H), 4.23 (t, J=5.9 Hz, 1H), 4.06 (dd, J=11.8, 4.1 Hz, 1H), 3.70–3.60 (m, 3H), 2.90 (s, 3H), 2.10 (s, 3H), 2.05–1.95 (m, 1H), 1.0 (d, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 20.7, 29.4, 39.2, 59.0, 62.8, 63.8, 77.5, 157.5, 170.2. Anal. calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.74; H, 7.32; N, 6.12.

3.1.14. 3-Methyl-5-[1-methyl-2-(4-methylphenylsulfonyl-oxy)-(1*R*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 19. To the solution of compound **18** (0.6 g, 2.6 mmol) in dry DCM (11 mL), was added catalytic amounts of DMAP, Et_3N (0.54 mL, 3.9 mmol), *p*-toluenesulfonyl chloride (0.55 g, 2.86 mmol) and the mixture stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (20 mL) and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) as the eluent to yield **19** (0.85 g, 2.21 mmol) in 85% yield and used immediately in the next step. Viscous oil. R_f 0.2 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+17.7 (*c* 0.23, $CHCl_3$). *ms* LSIMS 386 $[M+H]^+$. IR (Neat) 2987, 1747, 1651, 1633, 1435, 1036, 969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J=7.0 Hz, 2H), 7.38 (d, J=7.0 Hz, 2H), 4.32 (dd, J=12.7, 3.2 Hz, 1H), 4.12 (dd, J=12.7, 2.0 Hz, 1H), 4.05–3.95 (m, 3H), 3.70–3.60 (m, 1H), 2.85 (s, 3H), 2.46 (s, 3H), 2.20–2.05 (m, 4H), 1.0 (d, J=6.8 Hz, 3H).

3.1.15. (4*R*,5*R*)-4-Hydroxymethyl-3-methyl-5-[(*E*,1*R*)-1-methyl-3-pentenyl)-oxazolidin-2-one 20. To the suspension of CuI (0.2 g, 1.04 mmol) in dry THF (2 mL) at −78 °C was added compound **19** (0.4 g, 1.04 mmol) in dry THF (2 mL) and stirred for 30 min. 1-(*E*)-propenylmagnesium bromide (prepared from 0.49 g of Mg and 2.42 g of 1-(*E*)-propenyl bromide in 40 mL of THF) was added dropwise and the reaction mixture gradually allowed to attain rt and stirred further for 2 h. The reaction mixture was cooled to 0 °C and decomposed with sat. aq NH_4Cl solution. The reaction mixture was diluted with EtOAc and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to yield **20** (155 mg, 0.73 mmol) in 70% yield. White solid. Mp 82–83 °C. R_f 0.25 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+76.0 (*c* 0.85, CH_2Cl_2). (Lit.[2a] $[\alpha]_D^{25}$=+76.9 (*c* 0.92, CH_2Cl_2). *ms* LSIMS 214 $[M+H]^+$. IR (Neat) 3445, 1767, 1717, 1472, 980, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.60–5.30 (m, 2H), 4.20 (t, J=6.2 Hz, 1H), 3.83–3.78 (dd, J=12.2, 3.1 Hz, 1H), 3.56–3.50 (dd, J=12.2, 3.4 Hz, 1H), 3.39 (m, 1H), 2.87 (s, 3H), 2.20 (m, 1H), 1.91–1.76 (m, 2H), 1.70 (d, J=5.0 Hz, 3H), 0.90 (d, J=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 17.9, 29.3, 34.5, 37.4, 61.2, 61.6, 78.8, 127.7, 158.3. Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.78; H, 8.85; N, 6.53.

3.1.16. Methyl-(4*S*,5*R*)-3-methyl-5-[(*E*,1*R*)-1-methyl-3-pentenyl)-oxazolidin-2-one-4-carboxylate 21. To the solution of the compound **20** (100 mg, 0.47 mmol) in 1:1 acetonitrile/H_2O (3.0 mL) was added TEMPO (16 mg, 0.08 mmol) followed by $PhI(OAc)_2$ (314 mg, 0.98 mmol). The reaction mixture was stirred at rt for 2 h and the solvent was evaporated under reduced pressure. The reaction mixture was then extracted into ethyl acetate and washed with water. The organic layer was washed with 10% aq. $NaHCO_3$. The bicarbonate layer was acidified to pH 2 with 5 N HCl and extracted with ethyl acetate. To the ethyl acetate layer was added cold (0 °C) ethereal CH_2N_2, generated in situ from *N*-methyl *N*-nitroso urea (0.28 g, 2.59 mmol) in ether (10 mL) and 50% aq. KOH (4 mL) at 0 °C, and stirred at rt for 10 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **21** (90 mg, 0.38 mmol) in 80% overall yield for two steps. Clean oil. R_f. 0.5 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+37.0 (*c* 0.80, CH_2Cl_2). (Lit.[2a] $[\alpha]_D^{25}$=+39.2 (*c* 1.67, CH_2Cl_2). *ms* LSIMS 242 $[M+H]^+$. IR (neat) 1753, 1442, 1402, 1235, 1046, 986, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.55–5.31 (m, 2H), 4.28 (dd, J=6.2, 4.8 Hz, 1H), 3.97 (d, J=4.8 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.25–2.17 (m, 1H), 2.0–1.83 (m, 2H), 1.66 (d, J=6.0 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H). Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.74; H, 7.94; N, 5.81. Found: C, 59.70; H, 7.80; N, 5.70.

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References and notes

1. Wenger, R. M. In *Cyclosporin A*. White, D. J. G., Ed.; Biomedical: Amsterdam, 1992.
2. (a) Cook, G. R.; Sathya Shanker, P. *J. Org. Chem.* **2001**, *66*, 6818. (b) For a radical based approach refer: Matsunaga, H.; Ohta, H.; Ishizuka, T.; Kunieda, T. *Heterocycles* **1998**, *49*, 34. (c) Tuch, A.; Saniere, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1997**, *8*, 1649. (d) Lee, S. G.; Kim, Y. K.; Kim, S. K.; Yoon, Y.-J.; Park, K. H. *J. Korean. Chem. Soc.* **1995**, *39*, 123. (e) Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Hosoya, K. *Chem. Express* **1992**, *7*, 477. (f) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (g) Ogoroniidchuk, A. S.; Dybenko, A. G.; Romanova, V. P.; Shilin, V. V. *Ukr. Khim. Zh.* **1990**, *56*, 1203. (h) Rama Rao, A. V.; Yadav, J. S.; Chandrasekhar, S.; Srinivasa Rao, C. *Tetrahedron Lett.* **1989**, *30*, 6769. (i) Wenger, R. M. *Helv. Chim. Acta* **1983**, *66*, 2308.
3. (a) Savignac, M.; Durand, J. O.; Genet, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717. (b) Rama Rao, A. V.; Muralidhar, T. G.; Subhas Bose, D.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron* **1989**, *45*, 7361. (c) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139.
4. (a) Blaser, D.; Ko, S. Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230. (b) Rich, D. H.; Sun, C.-Q.; Guillaume, D.; Dunlap, B.; Evans, D. A.; Weber, A. E. *J. Med. Chem.* **1989**, *32*, 1982. (c) Togni, A.; Pastor, S. D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471. (d) Schmidt, U.; Siegel, W. *Tetrahedron Lett.* **1987**, *28*, 2849. (e) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (f) Aebi, J. D.; Dhaon, M. K.; Rich, D. H. *J. Org. Chem.* **1987**, *52*, 2881. (g) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757.
5. (a) Raghavan, S.; Rasheed, M. A.; Joseph, S. C.; Rajender, A. *J. Chem. Soc., Chem. Commun.* **1999**, 1845. (b) Raghavan, S.; Ramakrishna Reddy, S.; Tony, K. A.; Naveen Kumar, Ch.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838.
6. (a) Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101. (b) Raghavan, S.; Tony, K. A. *J. Org. Chem.* **2003**, *68*, 5002. (c) Raghavan, S.; Ramakrishna Reddy, S. *J. Org. Chem.* **2003**, *68*, 5754. (d) Raghavan, S.; Rasheed, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1371. (e) Raghavan, S.; Rajender, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2093. (f) Raghavan, S.; Rajender, A. *J. Org. Chem.* **2003**, *68*, 7094. (g) Raghavan, S.; Joseph, S. C. *Tetrahedron Lett.* **2003**, *44*, 6713. (h) Raghavan, S.; Ramakrishna Reddy, S. *Tetrahedron Lett.* **2003**, *44*, 7459. (i) Raghavan, S.; Joseph, S. C. *Tetrahedron Lett.* **2003**, *44*, 8237. (j) Raghavan, S.; Rasheed, M. A. *Tetrahedron* **2003**, *59*, 10307.
7. Yang, H.; Sheng, X. C.; Harrington, E. M.; Ackermann, K.; Garcia, A. M.; Lewis, M. D. *J. Org. Chem.* **1999**, *64*, 246.
8. Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752.
9. Hirama, M.; Mitsuko, U. *Tetrahedron Lett.* **1982**, *23*, 5307. Also refer Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 4963.
10. (a) Padwa, A.; Gunn, Jr. D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353. (b) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881. (c) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282.
11. De Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

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α-Alkyl(aryl)sulfenyl substituted β-ketophosphonates: synthesis, properties and reactivity

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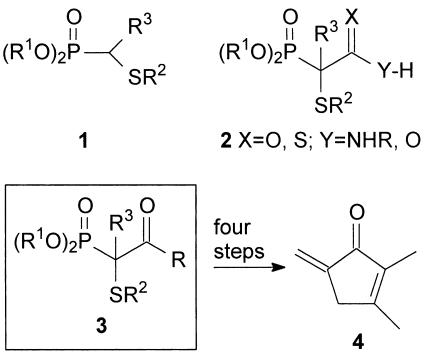
This paper is dedicated to Professor Reinhard Schmutzler on the occasion of his 70th birthday

Abstract—A new synthesis of the title compounds via acylation of α-lithio-α-phosphorylalkyl sulfides is described. Two additional approaches to these compounds, although less efficient, involve: (a) sulfenylation of O-silylated dialkyl β-ketophosphonates and (b) the Arbuzov reaction of triethyl phosphite with α-chloro-α-methylthiomethyl phenyl ketone. The keto–enol tautomerism of the title compounds and reactivity of the anions derived from them with electrophilic reagents were investigated. The P(O)-olefination products obtained from electron rich aromatic aldehydes were found to undergo the acid-catalyzed desulfenylation reaction affording α,β-unsaturated ketones.

1. Introduction

α-Phosphoryl sulfides **1** are an important class of heteroatom compounds useful in organic synthesis, medicine and technics.[1] Therefore, for the past two decades their synthesis, chemistry and applications have been intensively investigated in our laboratory.[2] Especially attractive was the Horner–Wittig reaction of **1** since vinyl sulfides produced in this reaction could be transformed into carbonyl compounds.[3] Thus, starting from the properly substituted α-phosphoryl sulfides **1**, we were able to elaborate the synthesis of aromatic ketones,[4] α-alkylsulfenyl ketones[5] and 1,4-diketones.[6] The latter were applied by us in the synthesis of cyclopentenone natural products like dihydrojasmone and methylenomycin B.[2] Moreover, nucleophilic (1,2 vs 1,4-addition)[7] and radical approaches[8] to the synthesis of highly functionalized phosphonates starting from **1** were also devised in our laboratory.

In addition to the above applications of **1**, their reactions with bifunctional reagents of the X=C=Y type (CO_2, RNCO, RNCS) allowed the synthesis of α-phosphoryl acetic acids **2** (X=Y=O),[9] acetamides **2** (X=O, Y=NHR)[10] and thioacetamides **2** (X=S, Y=NHR)[10] (Scheme 1) from which 1,2-dicarbonyl compounds, unsaturated γ- and δ-lactones as well as α-thioethene-thioamides were obtained. An alternative approach to **2** involved sulfenylation of α-phosphoryl acetic acid and α-phosphoryl propionic acid with Me_2S_2,[9] PhSCl[11] and ClSCN.[11]



1 **2** X=O, S; Y=NHR, O **3** **4**

Scheme 1.

A closely related class of α-sulfenylated β-ketophosphonates **3** was first synthesized by Lee and Oh[12] via sulfenylation of the α-phosphoryl enamine anions followed by hydrolysis of the resulting products. According to this method, the sulfenylation reaction was carried out using Ph_2S_2, PhSCl and $MeSO_2SMe$ as sulfenylation reagents. Dimethyl disulfide turned out to be unreactive towards the enamine anions. The above authors also reported that acylation of the α-phosphonate carbanions derived from **1** was an unsatisfactory approach to **3**. However, according to our experience acylation of the lithium salts of α-phosphoryl sulfides **1** with carboxylic acid esters can be successfully carried out to give **3** in moderate to high yields, thus becoming an alternative approach to these

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compounds. They were later applied by us as precursors of the corresponding α-phosphonate radicals in the synthesis of highly functionalized phosphonates[7] and in the first radical approach[13] to methylenomycin B **4**—a cyclopentanoid antibiotic. A recent paper by Olivato and his co-workers[14] on the synthesis of some aromatic β-ketophosphonates **3** prepared by the reaction of diethyl methylthio-1-lithiomethylphosphonate with substituted benzoyl chlorides prompted us to disclose herein full details of our synthetic approaches to **3** as well as investigation of the keto–enol tautomerism in this interesting class of compounds. We report also the behaviour of the ambident anion derived from **3** towards electrophilic reagents (alkyl halides, acyl halides and carbonyl compounds).

2. Results and discussion

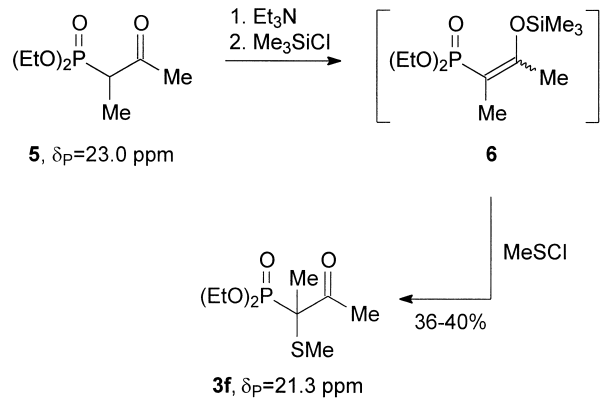
2.1. Synthesis

Searching for a convenient protocol for preparing the desired sulfenylated β-ketophosphonates **3**, three methods were selected and tested: (A)-acylation of **1**-Li with carboxylic acids esters, (B)-sulfenylation of O-silylated diethyl 2-oxoalkylphosphonates **6** and (C)-simultaneous introduction of the keto and sulfenyl groups via the Arbuzov reaction of triethyl phosphite with α-chloro-α-methylthiomethyl phenyl ketone **7**.

In the first place, method A was checked using differently substituted α-phosphoryl sulfides **1**. Generation of the lithium derivatives from **1** with *n*-butylithium in dry THF occurred smoothly at −78 °C under an argon atmosphere. The reversible acylation of the resulting lithium derivatives **1**-Li was carried out with ethyl acetate, ethyl propionate, and methyl benzoate. Due to a greater acidity of the product **3** as compared with the substrate **1**, the reaction required two fold excess of **1**-Li to convert **3** into **3**-Li (Scheme 2).

As a consequence, the purification step required separation of **3** from the starting material **1** by high vacuum distillation or silica gel chromatography. In this way, the acylation products **3a**-**e** were obtained in 44–78% yields, The regenerated sulfides **1** could be reused in further reactions. The stability of diethyl phosphonates **3b**-**e** was remarkable. For instance, **3b** was for the first time synthesized in our laboratory in 1978 and after 25 years its purity was still above 90%. The methyl ester analogues were much less stable.

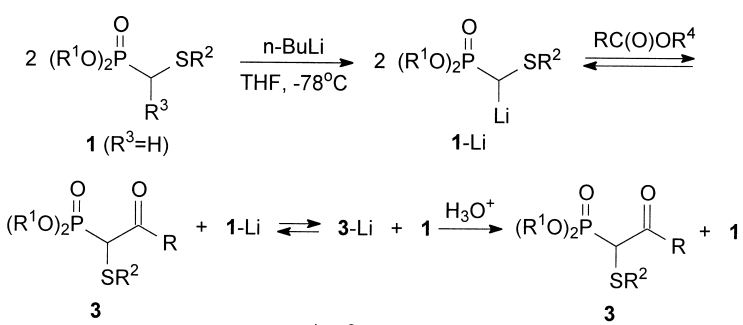
Next, the second possible synthesis of **3** in the reaction of O-silylated β-ketophosphonates with sulfenyl chlorides was examined. Thus, diethyl 1-methyl-2-oxopropylphosphonate **5** was treated with trimethylsilyl chloride in the presence of triethylamine and the O-silylated derivative **6** formed was reacted, without isolation, with methylsulfenyl chloride. The corresponding sulfenylated product **3f** was obtained in 36–40% yields. (Scheme 3).



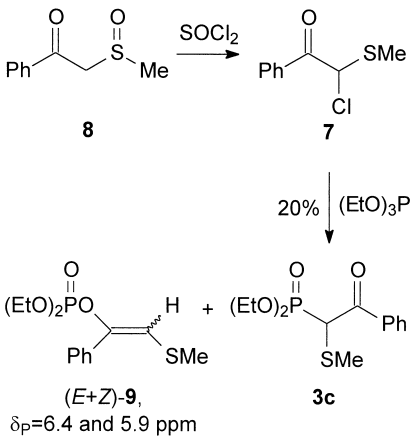
Scheme 3.

Due to lower yields of **3f** and some inconveniences connected with the synthesis and storage of methylsulfenyl chloride this synthetic approach to **3** was not further developed.

Finally, although we were aware that the reaction of trialkyl phosphites with α-halogenoketones affords mainly, if not exclusively, enol phosphates (Perkov reaction),[15] we attempted to find experimental conditions for the formation of a β-ketophosphonate (Arbuzov reaction) in the reaction between triethyl phosphite and a reactive 1-chloro-1-methylthiomethyl phenyl ketone **7**. The latter was quantitatively obtained in the Pummerer reaction of the β-ketosulfoxide **8** with thionyl chloride (Scheme 4).



Scheme 2.



Scheme 4.

Unfortunately, only in one case (see Table 1), when $(EtO)_3P$ was added to hot **7** at 140 °C without any solvent, the Arbuzov reaction product **3c** was obtained in 20% yield together with the Perkov reaction product **9** which was a mixture of the geometrical *E* and *Z* isomers in a ca. 2:1 ratio as revealed by the ^{31}P NMR spectra. A further structural assignment was based on the ^{1}H NMR spectra in which vinyl protons in the *E* and *Z* isomers of **9** appeared as two doublets at δ_H=6.05 ppm ($^3J_{H-P(cis)}$=2.2 Hz) and δ_H=6.24 ppm ($^3J_{H-P(trans)}$=3.2 Hz).

Table 1. Ratio of the Perkow (**9**) and Arbuzov (**3c**) reaction products under different experimental conditions

Entry	Procedure	**9** (*E*:*Z*)/**3c**[a]
1	$(EtO)_3P$ is added to **7** at 140 °C without solvent	75 (1.8:1)/25
2	**7** is added to $(EtO)_3P$ at 140 °C without solvent	100 (2.1:1)/0
3	**7** in benzene (1:1) is added to hot $(EtO)_3P$ in benzene (1:1)	100/0
4	**7** in hot benzene (1:1) is added to $(EtO)_3P$ in benzene (1:1) at 25 °C	100 (1.8:1)/0

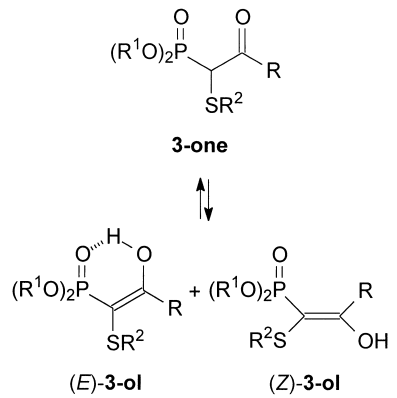
[a] Based on ^{31}P NMR spectra.

Summing up, the most convenient method for the synthesis of the β-ketophosphonates **3** involves the acylation reaction of the lithio derivatives of α-phosphoryl sulfides **1** with carboxylic acid esters, due to easy access to both substrates in large quantities and satisfactory yields of the desired products.

2.2. Keto–enol tautomerism

The ^{31}P NMR spectra of all the isolated products **3a-e** revealed two well separated signals which were ascribed to the keto-form, **3**-one, and the enol-form, **3**-ol, being in equilibrium as shown in Scheme 5. In a few cases additional signals of equal intensity due to the *E* and *Z* geometrical isomers of the enol-form of **3** were observed. The results of these measurements are collected in Table 2.

A further spectral analysis confirmed unequivocally the presence and structures of the tautomeric forms of **3**. Thus, the ^{1}H NMR spectra showed characteristic signals due to PCH and P–C=C–CH_3 protons as well as different signals due to MeS and OH groups. Similarly, in the ^{13}C NMR



Scheme 5.

Table 2. ^{31}P NMR chemical shifts and ratio of tautomeric forms of **3** in deuterated solvents

Phosphonate **3**	Solvent	Keto-form, **3**-one δ_P (%)	Enol-form, **3**-ol δ_P (%)
3b	DMSO-d_6	18.9 (92)	26.4 (8)
	$CDCl_3$	18.3 (92)	24.4 (8)
	Benzene-d_6	18.2 (66)	26.6 (33)
3c	DMSO-d_6	19.9 (83.5)	21.6 (16.5)
	$CDCl_3$	19.5 (83.5)	20.7 (16.5)
	Benzene-d_6	19.6 (77)	20.7 (23)
3e	DMSO-d_6	19.3 (96)	26.7 (4)
	Methanol-d_4	20.3 (95)	27.1, 26.5 (5)[a]
	$CDCl_3$	18.3 (92)	26.4, 25.1 (8)[a]
	Acetone-d_6	18.9 (89)	27.2 (11)
	Benzene-d_6	18.5 (81)	26.9 (19)

[a] Two signals correspond to *E* and *Z* forms of enol.

spectra typical signals for the P–CH and C=C carbons were observed. Accordingly, characteristic C=O and C=C frequencies in the IR spectra for both forms **3**-one and **3**-ol were visible. Moreover, in solvents of extreme polarity an increase in the intensity of absorption bands was observed for C=O in acetonitrile and for C=C in carbon tetrachloride.

The results mentioned above indicated that polar solvents favoured keto-forms having bigger dipole moments while nonpolar ones like CCl_4 favoured enol-forms, which were stabilized by intramolecular hydrogen bonds (Scheme 5). To further confirm this observation and to measure the **3**-one/**3**-ol ratios in various nondeuterated solvents, a series of ^{31}P NMR measurements was carried out (see Table 3).

An inspection of Table 3 revealed that in all the phosphonates **3** the keto-form prevailed (>70%). In protic solvents (MeOH) which are able to form hydrogen bonds with the carbonyl group the amount of the keto-form, **3**-one, increased even to 90%. The opposite bias was observed for the PhS containing **3d** for which the enol-form, **3**-ol, predominated, especially in low polar solvents (85% of **3**-ol in C_6H_6). The increase of the solvent polarity caused a decrease of the amount of the enol-form up to 64% in $CHCl_3$. Again in MeOH, due to stronger C=O···HOMe hydrogen bonds, the amount of the enol form of **3d** further decreased to 46.5% favouring the keto-form while the neat **3d** revealed high contents of the enol-form (83%) due to

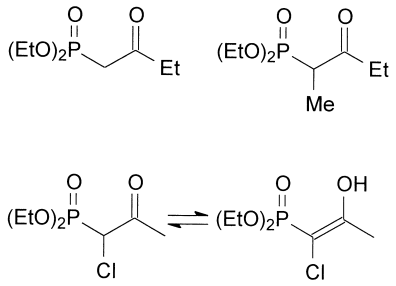
Table 3. Solvent effect on keto–enol equilibria

Phosphonate **3**	Solvent[a]									
	C_6H_6 δ_P [ppm] (%)		$CH_3C(O)CH_3$ δ_P [ppm] (%)		$CHCl_3$ δ_P [ppm] (%)		MeOH δ_P [ppm] (%)		Neat δ_P [ppm] (%)	
	Enol	Ketone	Enol	Ketone	Enol	Ketone	Enol	Ketone	Enol	Ketone
3a	28.0 (26.5)	19.4 (73.5)	27.55 (17.0)	19.25 (83.0)	28.20 (16.0)	20.0 (84.0)	27.23 (6.0)	20.86 (94.0)	28.0 (15.5)	20.2 (84.5)
3b	25.5 (29.5)	17.1 (70.5)	25.0 (19.7)	16.8 (80.3)	25.7 (13.5)	17.6 (86.5)	25.0 (9.4)	18.4 (90.6)	25.3 (22.0)	17.4 (78.0)
3c	20.9 (16.0)	18.3 (84.0)	19.8 (14.0)	17.9 (86.0)	20.7 (13.5)	18.7 (86.5)	22.9 (19.5)	21.1 (79.5)	21.5 (22.0)	19.8 (78.0)
3d	23.9 (85.0)	16.2 (15.0)	22.9 (72.0)	18.2 (28.0)	23.2 (64.0)	16.0 (36.0)	22.8 (46.5)	16.4 (53.5)	23.1 (83.0)	16.0 (17.0)

[a] The spectra were recorded at 25 °C and c=2 mol/L.

inter- and intramolecular hydrogen bonds of the P═O···H–O type.

The existence of **3** in tautomeric forms demonstrates a strong effect of the RS group on the acidity of the PCH hydrogen. In this context, it is interesting to point out that the ^{31}P NMR spectra of the β-ketophosphonates without sulfenyl substituents shown in Scheme 6 did not reveal even traces of enol forms. They are present, however, in α-chloro substituted β-ketophosphonates as reported by Savignac.[16]



Scheme 6.

2.3. Reactions with electrophilic reagents

Deprotonation of α-sulfenyl-β-ketophosphonate **3** leads to the formation of the corresponding enolate anion which should exhibit ambident reactivity. Moreover, the carbanionic center of the enolate anion derived from **3** should be well stabilized by the presence of three electron withdrawing groups: phosphoryl, carbonyl and sulfenyl. Therefore, its lower reactivity could be expected. For these reasons we decided to examine briefly the reactions of **3** with electrophilic reagents under basic conditions (Fig. 1).

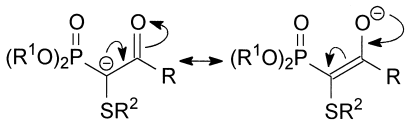
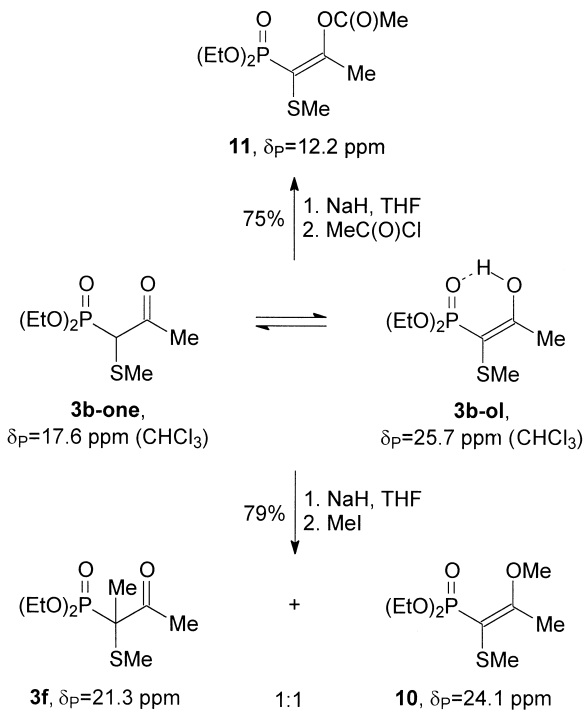


Figure 1.

As expected, the reaction of methyl iodide with the anion generated from **3b** with sodium hydride gave ca. 1:1.2 mixture of the C-methylated product **3f** and the O-methylated derivative **10** which were easily separated by column chromatography. Acetylation of the ambident anion of **3b** with acetyl chloride occurred exclusively at oxygen to give the corresponding *O*-acetyl vinylphosphonate **11** (Scheme 7).

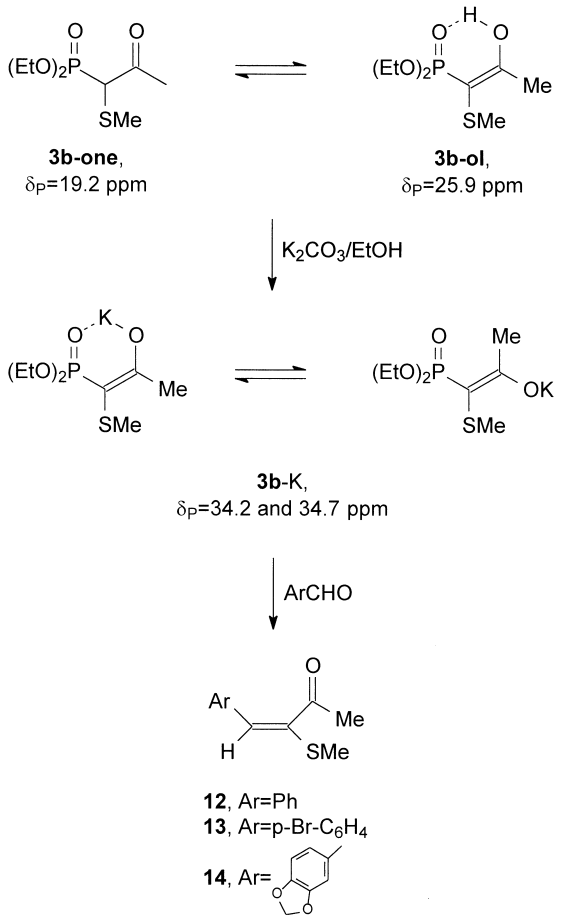


Scheme 7.

Just as other phosphonates,[17] the phosphonates **3** should react with carbonyl compounds in terms of the Horner–Wittig reaction to give the corresponding olefination products. Taking into account a relatively high acidity of the α-methine hydrogen, we used for the Horner–Wittig reaction with aromatic aldehydes weak bases for deprotonation as the first reaction step. However, in the presence of sodium bicarbonate in ethanol the reaction of **3b** with benzaldehyde did not occur within 18 h at room temperature. On the other hand, solid potassium carbonate in the same solvent was much more effective although the reaction was found to be sluggish.[†] Thus, when all three reaction components (K_2CO_3, PhCHO, **3b**) were used in equimolar

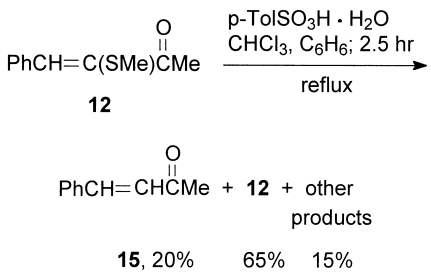
[†] Two signals observed in the ^{31}P NMR spectra of the potassium salt of **3b** were tentatively ascribed to *E* and *Z* geometrical forms of this salt.

amounts, the yield of the olefinic product **12** was only 16% after 7 h at room temperature (^{31}P NMR assay). It was increased to 50% after 72 h. When molar ratio of the reagents was 1.5:1:1, the product **12** was formed in 35% yield after 18 h at room temperature. Two hours at reflux in ethanol leads to **12** in 64% yield. Finally, it was found that the formation of **12** was almost complete after 72 h at 1.5:1.6:1 molar ratio of the reagents. It was found that the reaction afforded only one geometrical isomer of **12**. Its geometry was assigned as *Z* by using the additive increments method,[18] that is, comparison of the calculated chemical shifts of the β-proton for *E*-**12** (δ_H=7.21 ppm) and *Z*-**12** (δ_H=7.62 ppm) with the experimental value δ_H=7.61 ppm. The reaction of **3b** with *p*-bromobenzaldehyde in the presence of potassium carbonate used in equimolar ratio gave after 72 h at room temperature the corresponding enone **13** in 60% yield. However, in the Horner–Wittig reaction of **3b** with piperonal, carried out under the optimum reaction conditions determined for benzaldehyde (1.5:1.6:1 molar ratio of K_2CO_3, piperonal, **3b**, 72 h, rt), the corresponding enone **14** was formed in 17% yield only. A much lower reactivity of piperonal in this reaction as compared with benzaldehyde is undoubtedly connected with a lesser electrophilicity of the aldehyde carbon atom due to resonance effect involving the oxygen lone electron pairs of the dioxymethylene moiety (Scheme 8).



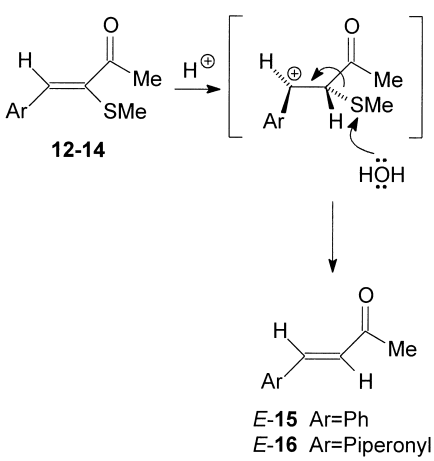
Scheme 8.

The resonance effect of the lone electron pairs of two oxygen atoms of the piperonyl moiety was also responsible for a greater sensitivity of the enone **14** than **12** towards acids. During routine work up involving quenching the reaction mixture with a saturated aqueous solution of ammonium chloride followed by extraction with chloroform (acidic conditions) and final purification by column chromatography on silica gel, the crude enone **14** was completely converted into the sulfur free α,β-unsaturated ketone **16**. Under these conditions the enone **13** was completely stable while only small amounts of benzylideneacetone **15** as the desulfenylation product from **12** were observed. The acid-catalyzed desulfenylation of the enone **12** was independently confirmed by the reaction of the isolated **12** with *p*-toluenesulfonic acid monohydrate carried out under reflux for 2.5 h in a mixture of chloroform and benzene (Scheme 9). It was found that benzylideneacetone **15** was formed in 20% yield in addition to 65% of the unreacted substrate **12** and 15% of unidentified higher boiling products.



Scheme 9.

The observed differences in acid sensitivity of the enones **12**, **13** and **14** may be easily rationalized by assuming the following mechanistic pathway for their desulfenylation process (Scheme 10). The first step is the addition of a proton to the carbon–carbon double bond according to anti-Markovnikov rule to form the intermediate benzyl carbocation. Then, nucleophilic attack of water on sulfur causes desulfenylation and the formation of a sulfur-free enone. Since the piperonyl moiety better stabilizes the benzyl carbocationic intermediate than the unsubstituted phenyl group the desulfenylation reaction occurs in this case much faster.



Scheme 10.

Although it was found that aliphatic aldehydes (formaldehyde, acetaldehyde) react with **3b** in the presence of K_2CO_3 much faster than aromatic ones (75–100% of the conversion of **3b** after 18 h at 25 °C as indicated by ^{31}P NMR), the instability of the olefination products formed precluded their isolation as pure compounds. Thus, our results provide additional evidence that α-sulfenylated enones are not stable and their synthesis and transformations demand care.[19] New conditions for the Horner–Wittig reaction of **3** with carbonyl compounds are under current studies.

3. Experimental

3.1. General

The ^1H NMR (60, 200 and 300 MHz), ^{13}C NMR (15.1, 50.3 and 75.4 MHz) and ^{31}P NMR (24.3, 81 and 121.5 MHz) spectra were recorded using R12B Perkin–Elmer, Jeol JNM-FX 60, Bruker AC-200, Bruker MSL-300 spectrometers. Chemical shifts in ^1H NMR spectra are reported relative to TMS. ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external standard. Mass spectra were obtained using a LKB 2091 and a Finnigan Mat 95 spectrometers. Column chromatography was carried out using a Merck silica gel (60, 70–230 and 230–400 mesh) using a gradient of indicated solvents which were distilled before use. Deuterated solvents for NMR-measurements were of commercial grade. All other commercial solvents were purified according to standard procedures and finally distilled before use. Melting and boiling points were uncorrected. HMDSO denotes hexamethyldisiloxane.

3.2. General procedure for synthesis of dialkyl 1-alkyk(aryl)sulfenyl 2-oxoalkylphosphonates (3)

To a stirred solution of dialkyl 1-alkyl(aryl)sulfenylmethylphosphonate **1** (0.07 mol) in dry tetrahydrofuran (70 mL), a solution *n*-butyllithium (0.07 mol+10% excess) in diethyl ether was added dropwise at −78 °C under argon atmosphere. After 45 min. a solution of the corresponding carboxylic ester (ethyl acetate, ethyl propionate or methyl benzoate; 0.035 mol) in tetrahydrofuran (35 mL) was added at this temperature. The resulting solution was stirred for 1 h, then temperature was raised to 0–5 °C and the solution was acidified with 10% aqueous hydrochloric acid. The solvent was evaporated and the residue was extracted with chloroform (100 mL). The chloroform solution was washed with 10% aqueous sodium hydroxide (3×50 mL) to remove the starting material. The basic aqueous solution containing mainly the product **3** in the form of sodium enolate was washed with chloroform (40 mL) then acidified with 10% aqueous solution of HCl and again extracted with chloroform (3×50 mL). The combined chloroform solutions (150 mL) were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was further purified by distillation or by column chromatography over silica gel using benzene/acetone in a gradient as the eluent.

3.2.1. Dimethyl 1-methylthio-2-oxopropylphosphonate (3a). Yellow oil, bp 47–48 °C/0.05 mm Hg, n_D^{24}=1.4795; yield 72% (crude); [Found: C, 34.30; H, 6.22; P, 14.87. $C_6H_{13}O_4PS$ requires C, 33.96; H, 6.17; P, 14.59]; ν_{max} (CCl_4) 2980, 2950, 2910, 2840, 1710, 1580 cm^{-1}; δ_H (CCl_4) 2.08 (3H, s, =C–CH_3, enol), 2.15 (3H, s, (O)C–CH_3, ketone); 2.30 (3H, s, SCH_3, ketone+enol); 3.67 (7H, d, *J*=12.0 Hz, CH_3OP, P(O)CH); 3.75 and 3.78 (3H, 2×d, *J*=10.6 Hz, CH_3O–P); δ_C ($CDCl_3$) 13.5 (d, *J*=4.5 Hz, SCH_3, ketone), 17.5, 24.6 (two brs, =CCH_3, SCH_3, enol), 25.9 (s, C(O)*C*H_3), 50.1 (d, *J*=138.7 Hz, P–C, ketone), 51.8, 52.4 (d, *J*=9 Hz, $POCH_3$, ketone), 197.3 (s, C=O).

3.2.2. Diethyl 1-methylthio-2-oxopropylphosphonate (3b). Yellow oil, bp 54–56 °C/0.05 mm Hg, n_D^{24}=1.4697; yield 78% (crude); [Found C, 39.96; H, 7.13; P, 12.92; S, 13.53. $C_8H_{17}O_4PS$ requires C, 39.99; H, 7.13; P, 12.89; S, 13.34]; ν_{max} (CCl_4) 1580, 1710 cm^{-1}; δ_H (C_6D_6) 1.01 (6H, t, *J*=7.1 Hz, $POCH_2CH_3$), 1.04 (6H, t, *J*=7.1 Hz, $POCH_2$-CH_3, enol), 1.87 (3H, d, *J*=1.0 Hz, SCH_3, ketone), 1.90 (3H, d, *J*=1.0 Hz, SCH_3, enol), 2.19 (3H, s, (O)CCH_3, ketone), 2.20 (3H, d, *J*=1.4 Hz, =C–CH_3, enol), 3.50 (1H, d, *J*=19.4 Hz, PCH, ketone), 3.71–4.03 (4H, m, $POCH_2CH_3$, enol), 3.98 (4H, 2×dq, *J*=7.1, 10.4 Hz, $POCH_2CH_3$, ketone), 12.93 (1H, brs, OH, enol); δ_C ($CDCl_3$) 15.31 (d, *J*=6.3 Hz, SCH_3, ketone), 15.56 (distd.d, SCH_3+$POCH_2$-CH_3, enol), 15.57 (d, *J*=5.4 Hz, $POCH_2CH_3$, ketone), 19.09, 18.82 (2×s, CH_3–C=C, *E*/*Z*of enol form); 27.23 (s, $C(O)CH_3$, ketone), 57.27 (d, *J*=138.0 Hz, P–C, ketone), 61.95 (d, *J*=4.8 Hz, $POCH_2CH_3$, enol), 63.03 (d, *J*=5.3 Hz, $POCH_2CH_3$, ketone); no visible signal from the enol C=C (8% of the enolic form only based on ^{31}P NMR); 198.99 (s, C=O); *m*/*z* (EI) 240 (M^+ (31)); 198 (100); 183 (31); 170 (27), 169 (43), 155 (38), 142 (42), 141 (20), 127 (45), 124 (24), 123 (21), 86 (60), 81 (23), 65 (32), 61 (36), 45 (35), 43 (82), 25 (41), 27 (37%).

3.2.3. Diethyl 1-methylthio-2-oxo-2-phenylethylphosphonate (3c). White crystals, mp 57 °C, yield 67% (crude); [Found: C, 51.70; H, 6.43; P, 10.22; S, 10.78. $C_{13}H_{19}O_4PS$ requires C, 51.64; H, 6.33; P,10.24; S, 10.60]; ν_{max} (film) 3440, 3050, 2970, 2905, 1670, 1570, 1585 cm^{-1}; δ_H ($CDCl_3$) 1.30 (6H, dt, *J*=7.1 0.6 Hz, $POCH_2CH_3$, ketone+enol), 2.25 (3H, ds, *J*=1.0 Hz, SCH_3, ketone); 3.57, 3.69, (3H, 2×s, SCH_3, enol-*E*/*Z*=1:1), 4.15–4.34 (4H, m, $POCH_2CH_3$, ketone+enol), 4.54 (1H, d, *J*=18.2 Hz, P–CH, ketone); 6.55 (1H, vbrs, OH, enol), 7.42–8.03 (5H, m, C_6H_5, ketone+enol); δ_C ($CDCl_3$) (major ketone form), 14.42 (s, $POCH_2CH_3$), 15.90 (d, *J*=5.7 Hz, SCH_3), 44.75 (d, *J*=117.7 Hz, P–C), 63.23 (m, $POCH_2$-CH_3), 128.42, 128.22, 133.26 (3xs, CH in C_6H_5); 134.81 (d, *J*=5.2 Hz, C in C_6H_5), 190.96 (s, C=O); *m*/*z* (EI) 105 (100), 77 (26%).

3.2.4. Diethyl 1-phenylthio-2-oxopropylphosphonate (3d). Yellow oil, n_D^{24}=1.5310; yield 48–50%; [Found: C, 52.17; H, 6.60; P, 10.16; S, 11.17. $C_{13}H_{19}O_4PS$ requires C, 51.64; H, 6.33; P, 10.24; S, 10.60]; ν_{max} (CCl_4) 1589, 1710 cm^{-1}; δ_H (CCl_4) 1.12 (6H, t, *J*=7.2 Hz, $POCH_2CH_3$, enol), 1.30 (6H, t, *J*=7.2 Hz, $POCH_2CH_3$, ketone), 2.20, 2.21 (3H, d, *J*=1.3 Hz, P–C=C–CH_3, enol), 2.26 (3H, s, $C(O)CH_3$), 3.45–4.31 (5H, m, PCH+$POCH_2CH_3$, ketone+enol), 6.70–7.50 (5H, m, C_6H_5), 14.20 (1H, vbrs, OH, enol); δ_C (C_6D_6/HMDSO) (major enol form) 13.98 (d, *J*=5.9 Hz, $POCH_2CH_3$), 17.93 (d, *J*=5.4 Hz, P–C=C–CH_3), 60.74

(d, J=5.8 Hz, POCH_2CH_3), 123.45, 126.95 (m, C_6H_5), 132.34 (d, J=115.2 Hz, P–C=), 182.57 (s, P–C=C); m/z (EI) 148 (95), 147 (27), 123 (44), 121 (100), 109 (21), 91 (25), 77 (29), 65 (23), 45 (26), 43 (59), 29 (41), 27 (24%); HRMS (EI): M^+ found 302.0741. $C_{13}H_{19}O_4PS$ requires 302.0754.

3.2.5. Diethyl 1-methylthio-2-oxobutylphosphonate (3e). Yellow oil, bp 105 °C/0.1 mm Hg (Kugelrohr), n_D^{24}=1.4725; yield 44%, [Found: C, 42.45; H, 7.44. $C_9H_{19}O_4PS$ requires C, 42.51; H, 7.53]; δ_H ($CDCl_3$) 1.09 (3H, t, J=7.2 Hz, C(O)CH_2CH_3, ketone), 1.18 (3H, dt, J=7.5, 0.4 Hz, =CCH_2CH_3, enol), 1.33 (6H, 2×dt, J=7.1, 1.6 Hz, POCH$_2$-CH_3, ketone), 2.15 (3H, d, J=1.0 Hz, SCH_3, enol), 2.20 (3H, d, J=1.0 Hz, SCH_3, ketone), 2.63–2.87 (2H, m, C–CH_2CH_3. enol+ketone), 3.62 (1H, d, J=19.4 Hz, PCH, ketone), 4.09–4.28 (4H, m, $POCH_2CH_3$, ketone+enol), 12.03 (1H, m, OH, enol); δ_C ($CDCl_3$) 6.94 (s, (O)CCH_2CH_3, ketone), 10.60 (s, =CCH_2CH_3, enol), 14.72 (d, J=5.8 Hz, POCH$_2$$CH_3$, ketone) 16.14 (s, POCH$_2$$CH_3$, enol), 19.1 (s, SCH_3, enol), 25.18(d, J=10.9 Hz, =CCH_2, enol), 32.95 (s, (O)CCH_2, ketone), 50.77 (d, J=137.9 Hz, PCH, ketone), 61.42 (d, J=4.7 Hz, POCH_2CH_3, enol), 62.39 (d, J=4.1 Hz, POCH_2CH_3, ketone), 201.33 (s, C=O); no visible signal from C=C.

3.2.6. Acetylation of diethyl 1-methylthio-2-oxopropylphosphonate (3b). To a stirred solution of **3b** (0.01 mol, 2.40 g) in dry THF (15 mL), sodium hydride (0.022 mol, 50% dispersion in oil, oil removed by washing with n-pentane) was added at room temperature under argon atmosphere. After stirring for 1.5 h, a solution of acetyl chloride (0.01 mol, 0.785 g) in THF (15 mL) was added dropwise and stirring was continued for further 1 h. The THF was evaporated and the residue was partitioned between chloroform and water. The chloroform solution was dried over $MgSO_4$, evaporated and the residue (79% yield) was distilled to give pure **11** as a yellow oil; bp 62–63 °C/0.05 mm Hg; n_D^{25}=1.4775.

[Found: C, 42.45; H, 6.83; P, 11.37; S, 11.45. $C_{10}H_{19}O_5PS$ requires C, 42.54; H, 6.78; P, 10.97; S, 11.35]; ν_{max} (film) 1760 (C=O); 1600 (C=C) cm^{-1}; δ_H (CCl_4) 1.30 (6H, t, J=7 Hz, CH_3CH_2OP), 2.10 (3H, s, C=C–CH_3), 2.23 (3H, s, OC(O)CH_3); 2.25 (3H, s, SCH_3), 3.95 (4H, m, CH_3CH_2-OP); δ_P (CCl_4) 12.2; m/z (EI) 282 M^+ (0.5), 240 (72), 225 (29), 169 (39), 155 (40), 86 (100), 43 (75%).

3.3. Methylation of diethyl 1-methylthio-2-oxopropylphosphonate (3b)

To a stirred solution of **3b** (2.4 g, 0.01 mol) in dry tetrahydrofuran (15 mL), sodium hydride (0.022 mol, 50% dispersion in oil) was added in portions at room temperature under argon atmosphere. The resulting solution was stirred for 2 h and then a solution of methyl iodide (0.01 mol, 1.42 g+25% excess) in THF (10 mL) was added dropwise. After 1 h, the solvent was evaporated and the crude product was partitioned between chloroform (70 mL) and water (50 mL). The chloroform solution was washed with water (40 mL) and dried over anhydrous $MgSO_4$ then filtered and evaporated to give the crude material in 79% yield (**3f**:**10**=1:1) which was further purified using column chromatography over silica gel. For separation of the C-methylated derivative **3f**, benzene/carbon tetrachloride in a 1:1 ratio was used. For separation of the O-methylated derivative **10**, benzene/acetone in a 2:1 ratio or CCl_4/benzene in a 1:1 ratio were employed.

3.3.1. Diethyl 1-methyl-1-methylthio-2-oxopropylphosphonate (3f). Yellow oil, n_D^{20}=1.4728; [Found: C, 42.51; H, 7.58; P, 12.45; S, 12.33. $C_9H_{19}O_4PS$ requires C, 42.51; H, 7.53; P, 12.18; S, 12.61]; ν_{max} (film) 1700 (C=O), 1250 (P=O) cm^{-1}; δ_H (CCl_4) 1.30 (6H, t, J=6.7 Hz, POCH$_2$-CH_3), 1.46 (3H, d, J=14.7 Hz, PCCH_3), 2.02 (3H, s, C(O)CH_3); 2.3 (3H, s, SCH_3); 4.1 (4H, m, POCH_2CH_3); δ_C ($CDCl_3$) 10.71 (d, J=5.86 Hz, P–C–CH_3), 14.49 (d, J=5.85 Hz, POCH$_2$$CH_3$), 16.11 (d, J=3.9 Hz, P–C–S–CH_3), 24.11 (s, C(O)CH_3); 61.46 (d, J=3.9 Hz, POCH_2-CH_3), 199.3 (brs, C=O); δ_P (CCl_4) 21.3; m/z (EI) M^+ (3), 212 (100), 208 (19), 197 (87), 183 (15), 169 (37), 155 (55), 73 (28), 59 (49), 43 (47), 29 (26%).

3.3.2. Diethyl 2-methoxy-1-methylthio-2-propenylphosphonate (10). White crystals, mp 70–71 °C (benzene/acetone=1:2). [Found: C, 42.33, H, 7.58; P, 11.89; S, 12.73. $C_9H_{19}O_4PS$ requires C, 42.51, H, 7.53; P, 12.18; S, 12.61]; ν_{max} (film) 1565 (C=C) cm^{-1}; δ_H ($CDCl_3$) 1.3 (6H, t, J=7.2, POCH$_2$CH_3), 2.12 (3H, s, C=C–CH_3), 3.00 (6H, s, SCH_3,OCH_3), 3.98 (4H, m, POCH_2CH_3); δ_P (CCl_4) 24.1; m/z (EI) 254 M^+ (37), 239 (45), 193 (25), 183 (76), 165 (40), 155 (55), 141 (22), 103 (27), 101 (17), 87 (23), 81 (21), 73 (22), 65 (32), 61 (50), 59 (20), 47 (25), 45 (23), 43 (100), 29 (61), 28 (18), 27 (42%).

3.4. Diethyl 1-methyl-1-methylthio-2-oxopropylphosphonate (3f) from sulfenylation of diethyl 1-methyl-2-oxopropylphosphonate (5) with methylsulfenyl chloride

To a stirred solution of **5** (2.08 g, 0.01 mol) in dry diethyl ether (15 mL), triethyl amine (1.06 g, 0.01 mol+5% excess) was added dropwise at 0 °C followed by trimethylsilyl chloride (1.19 g, 0.01 mol+10% excess). After 1 h, freshly distilled (at −40 °C) methylsulfenyl chloride was added dropwise to the resulting O-silylated phosphonate **6** and the mixture was stirred for additional 0.5 h. Then it was allowed to warm to room temperature. After 1 h, the precipitated triethyl ammonium chloride was partitioned between water (40 mL) and chloroform (60 mL). The chloroform solution was washed with water (40 mL) and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified using column chromatography over silica gel with a gradient of benzene/acetone as eluent to give the title compound **3f**; 36–40% yield, yellow oil; n_D^{20}=1.4735; δ_P (CCl_4)=21.3 ppm.

3.4.1. 1-Chloro-1-methylthiomethyl phenyl ketone (7). To a stirred solution of the sulfoxide **15** (1.78 g, 9.78 mmol) in DCM, thionyl chloride (9.7 mmol, 1.16 g, 0.7 mL) was added at −10 °C and the resulting mixture was stirred for 15 min at this temperature. Then, the cooling bath was removed and the mixture was stirred at room temperature for additional 1 h to give, after evaporation of the solvent, the crude product as the yellow liquid (1.514 g, 77%) which was used for further transformations without purification

(purity 97%); δ_H (CCl_4) 2.12 (3H, s SCH_3); 6.33 (1H, s, CH–Cl); 7.15–8.10 (5H, m, C_6H_5).

3.5. General procedure for reaction of diethyl 1-methylthio-2-oxopropylphosphonate (3b) with aldehydes

To a stirred solution of **3b** (120 mg, 0.5 mmol) and K_2CO_3 in EtOH (4 mL) a solution of the relevant aldehyde in ethanol (2 mL) was added at room temperature under argon atmosphere. The resulting mixture was stirred for 72 h. Then, saturated aqueous ammonium chloride was added, the solvent evaporated and the residue extracted with chloroform (3×10 mL). The combined chloroform solutions were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was further purified by column chromatography over silica gel using petroleum ether/acetone in a gradient as the eluent.

3.5.1. 3-Methylthio 4-phenyl-but-3-en-2-one (12). Yellow oil, 69% yield (based on the converted **3b** as 100%); ν_{max} (film) 2956, 2929, 1724, 1506, 1450, 1315, 812, 756 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3H, s, SCH_3); 2.55 (3H, s, $-C(O)CH_3$); 7.35–7.43 (3H, m, H_{arom}-7, 7′, 9); 7.61 (1H, s, H–C=); 7.79 (2H, m, H_{arom}-8, 8′); δ_C ($CDCl_3$) 17.29 (C-5); 27.49 (C-1); 128.22 (C-7, 7′); 128.98 (C-9); 130.54 (C-8, 8′); 134.63 (C-3); 137.82 (C-6); 140.69 (C-4); 200.36 (C-2). *m/z* (CI) MH^+ 193. HRMS (CI): MH^+, found 193.0687. $C_{11}H_{13}SO$ requires 193.0682.

3.5.2. 4-(4-Bromophenyl)-3-methylthiobut-3-en-2-one (13). Yellow oil, 67% yield (based on the converted **3b** as 100%). ν_{max} (film) 2962, 1716, 1603, 1446, 1261, 762 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3H, s, SCH_3); 2.54 (3H, s, $C(O)CH_3$); 7.50 (1H, s, H–C=); 7.54 (2H, d, J=8.68 Hz, H_{arom}); 7.67(2H, d, J=8.50 Hz, H_{arom}). δ_C ($CDCl_3$) 17.26 (C-5); 27.51 (C-1); 123.74 (C-9); 131.57 (C-7, 7′); 132.14 (C-8, 8′); 133.51 (C-3-); 138.51 (C-6); 138.99 (C-4); 197.84 (C-2); *m/z* (CI) MH^+ 271. HRMS (CI): MH^+, found: 270.9792. $C_{11}H_{12}OBrS$ requires 270.9791.

3.5.3. 4-(3,4-Methylenedioxyphenyl)but-3-en-2-one (14). Yellow oil, 59% yield (based on the converted **3b** as 100%); ν_{max} (film) 3018, 2962, 1732, 1689, 1603, 1504, 1259, 1217, 754 cm^{-1}; δ_H ($CDCl_3$) 2.35 (3H, s, $-C(O)CH_3$); 6.01 (2H, s, $O-CH_2-O$); 6.54 (1H, d, J=16.1 Hz; $=CH(C(O)CH_3)$); 6.81 (1H, d, J=7.56 Hz; H_{arom}-9); 7.02 (1H, d, J=7.67 Hz; H_{arom}-10); 7.04 (1H, s, H_{arom}-6); 7.42 (1H, d, J=16.1 Hz; $=CH$–Ph); δ_C ($CDCl_3$) 27.56 (C-1); 101.67 (C-11); 106.53 (C-6); 108.66 (C-9); 124.88 (C-10); 125.31 (C-3); 128.83 (C-5); 143.26 (C-4); 148.45 (C-8); 149.88 (C-7); 206.70 (C-2). *m/z* (CI) MH^+ 191. HRMS (CI) MH^+, found: 191.0708. $C_{11}H_{11}O_3$ requires 191.0708.

References and notes

1. Mikołajczyk, M.; Bałczewski, P. In *Advances in sulfur chemistry. α-Phosphoryl substituted organosulfur compounds*; Block, E., Ed.; JAI: Greenwich, Connecticut, 1994; Vol. 1, pp 41–96.
2. (a) Mikołajczyk, M. Current trends in organic synthesis. In *A new synthetic approach to 1,4-dicarbonyl systems and functionalized cyclopentenones based on the Horner–Wittig reaction of phosphonates containing sulfur*; Nozaki, H., Ed.; Pergamon: New York, 1983; pp 347–358. (b) Mikołajczyk, M. *Rev. Heteroat. Chem.* **1989**, *2*, 19–39. (c) Mikołajczyk, M. *S. Afr. J. Chem.* **1994**, *47*, 103–111.
3. Corey, E. J.; Shulman, J. T. *J. Org. Chem.* **1970**, *35*, 777–780.
4. Mikołajczyk, M.; Grzejszczak, S.; Chefczyńska, H.; Zatorski, A. *J. Org. Chem.* **1979**, *44*, 2967–2972.
5. Mikołajczyk, M.; Kiełbasiński, P.; Grzejszczak, S. *Synthesis* **1983**, 332–334.
6. Mikołajczyk, M.; Grzejszczak, S.; Łyzwa, P. *Tetrahedron Lett.* **1982**, *23*, 2237–2240.
7. Mikołajczyk, M.; Bałczewski, P. *Tetrahedron* **1992**, *40*, 8697–8710.
8. Bałczewski, P. *Tetrahedron* **1997**, *53*, 2199–2212.
9. Mikołajczyk, M.; Midura, W. H. *Synlett* **1991**, 245–247.
10. Bałczewski, P.; Graczyk, P.; Perlikowska, W.; Mikołajczyk, M. *Tetrahedron* **1993**, *49*, 10111–10122.
11. Kashemirov, B. A.; Khokhlov, P. S.; Polenov, E. A. *Reactions of phosphorus-containing CH-acids with some electrophilic Agents*, XIIth International Conference on Phosphorus Chemistry July 6–10, 1992, Toulouse, France; Abstract of Posters, p I-130.
12. Lee, K.; Oh, D. Y. *Synth. Commun.* **1991**, *21*, 279–284.
13. Bałczewski, P. *Heteroat. Chem.* **1997**, *8*, 67–69.
14. Rodrigues, A.; Vinhato, E.; Rittner, R.; Olivato, P. R. *Synthesis* **2003**, 1248–1252.
15. Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607–616.
16. Teulade, M. P.; Savignac, P.; Aboujaoude, E. E.; Collignon, N. *J. Organomet. Chem.* **1985**, *287*, 145–156.
17. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
18. Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691–697.
19. Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200–1205.

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Tandem reactions catalyzed by lanthanide iodides. Part 1: Tandem Mukaiyama–Michael iminoaldol reactions

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Abstract—Samarium diiodide, as well as lanthanide triiodides catalyze a one-pot procedure allowing to perform sequentially the Mukaiyama–Michael addition of a ketene silyl acetal on a cyclic α,β-unsaturated ketone, followed by the addition of a glyoxylic, aromatic or heteroaromatic imine. According to the nature of the silyl group the adducts resulting from this tandem process are isolated as ketones or as enoxysilanes. The presence of a coordinating group on the imine increases the rate of the reaction.

1. Introduction

Tandem or cascade reactions allowing the formation of several bonds by one-pot procedures afford useful methodologies for the preparation of complex molecules as they allow the reduction of the number of steps, but also the diminution of costs and of waste production. They are thus the focus of growing interest and the concern of several reviews.[1] Amongst the panel of tandem reactions reported in the literature, a large part is devoted to radical or anionic reactions and/or to intramolecular reactions allowing the rapid formation of cyclic or polycyclic molecules.[2] The use of metal catalysts which afford the possibility to modulate stereo and/or enantioselectivities has been more recently developed in sequences of tandem reactions.[3] Lewis acids catalyze a variety of three-component reactions, which involve the successive formation of two bonds with one catalyst.[4] Lanthanide and scandium triflates are useful catalysts for three-component reactions involving the in situ preparation of an imine followed by a carbon–carbon bond formation.[5] Michael–aldol sequences leading to the consecutive formation of two carbon–carbon bonds in three-component reactions are well known.[6] Michael additions of an organometallic on α,β-unsaturated ketones followed by aldolisation of the intermediate have been widely employed for the synthesis of prostaglandins. Lewis acids, especially $Cu(OTf)_2$ associated to chiral ligands are highly enantioselective catalysts for 1,4-additions of alkyl zinc on α,β-unsaturated ketones and the stereochemistry of the tandem adducts is thus controlled, while heterobimetallic ALB complex $[Li_3Al(binol)_3]$ is an effective catalyst for asymmetric tandem Michael–aldol reactions.[7] An alternative method for creating two carbon–carbon bonds by a one-pot procedure is to realize a Michael addition of silylated derivatives on α,β-unsaturated ketones leading to an enoxysilane as the intermediate which reacts in an aldol or a second Michael reaction.[8] These tandem reactions require the use of a Lewis acid as catalyst which is a trityl salt in most cases, while the second step involves an aldehyde or an α,β-unsaturated ketone. To the best of our knowledge, imino aldol reaction consecutive to a Michael reaction in tandem sequences has not been much studied.[9] Three-component reaction via tandem Michael iminoaldol reaction has been reported, but it involves the use of different Lewis acids for the two steps of the sequence, $SbCl_5–Sn(OTf)_2$ for the Michael addition and $Sc(OTf)_3$ for the iminoaldol reaction.[10] Double nucleophilic addition of ketene silyl acetals on α,β-unsaturated aldimines promoted by aluminium chloride has been also reported.[11]

The use of samarium diiodide as a precatalyst for a variety of Lewis acid-catalyzed reactions has been the topic of our previous investigations.[12] We have first described Mukaiyama aldol or Michael reactions,[13] cycloaddition reactions,[14] or enolization of ketones,[15] performed with catalytic amounts of samarium diiodide or other lanthanide iodides. We have further found that samarium diiodide can catalyze successively two reactions in a one-pot procedure, a Michael reaction on cyclic α,β-unsaturated ketones followed by an aldol reaction.[16] In all these reactions, an aldehyde or a ketone was used as the electrophile. Recently, we studied the reactivity of imines in similar reactions and reported on aza Diels–Alder as well as Mannich reactions catalyzed by samarium diiodide.[17] Especially imines react with acyclic or cyclic enoxysilanes to yield β-aminoketones

Keywords: Samarium diiodide; Catalysis; Imines; Michael reaction; Mannich reaction; Tandem reaction.
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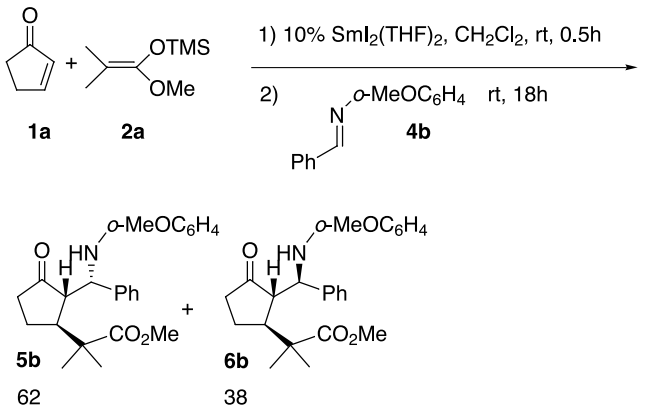
under mild conditions. This prompted us to examine the possibility to realize successively a Michael addition of ketene silyl acetal on α,β-unsaturated ketones leading to enoxysilanes followed by a Mannich reaction in a one-pot procedure. We have already reported our first results concerning tandem Michael–Mannich reactions using samarium diiodide as the sole catalyst.[18] We describe now our extensive study and especially the influence of the nature of ketene silyl acetal and imine on the Mannich step and on the structure of tandem adducts.

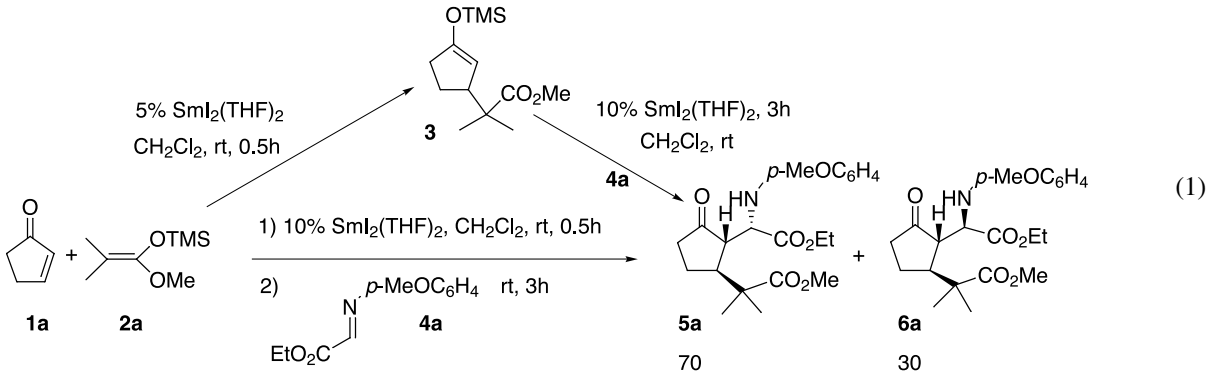
2. Results and discussion

We examined first the influence of various parameters on two tandem sequences considered as test reactions for optimizing the experimental procedure. We selected for Michael reaction cyclopenten-2-one **1a** and the commercially available ketene silyl acetal **2a**, which yield readily the enoxysilane **3** in the presence of catalytic amounts of samarium diiodide as was formerly shown.[13] For the Mannich step, *N-para*-anisyl ethyl glyoxylic imine **4a** and *N-ortho*-anisyl benzyl imine **4b** were chosen as we have already found their reactivity towards cyclic enoxysilanes to give β-aminoketones in the presence of catalytic amounts of samarium diiodide.[17] As was previously reported, in the reaction involving imine **4a** either the two consecutive reactions, or the tandem one-pot reaction afforded similar results (Eq. 1).[18] In the former procedure, the enoxysilane **3** resulting of the Michael addition was isolated, and its reaction with imine **4a** in the presence of 10% equiv. $SmI_2(THF)_2$, at room temperature, led to a product isolated in 44% yield as a diastereomeric mixture of **5a** and **6a**. The structure and configurational assignments and ratio were done after column chromatography separation on basis of NMR experiments (see below) as **5a** and **6a**, (**5a/6a**: 71/29). The one-pot reaction was realized by successive additions of ketene silyl acetal **2a** and cyclopenten-2-one **1a** on a suspension of samarium diiodide (10 mol%), in methylene chloride and after half-hour reaction time, at room temperature, the glyoxylic imine **4a** was added. Tandem adducts **5a** and **6a** were isolated in 50% yield and 70/30 diastereomeric ratio **5a/6a**, close to that obtained for the two steps procedure (Table 1, entry 1). We similarly realized a tandem sequence using **1**, **2**, *N-ortho*-anisyl benzyl imine **4b** and samarium diiodide (10 mol%) in methylene chloride, at room temperature, and isolated the adducts as a mixture of diastereoisomers **5b** and **6b** which could not be separated, in 45% yield (**5b/6b**: 62/38), (Eq. 2, entry 7).



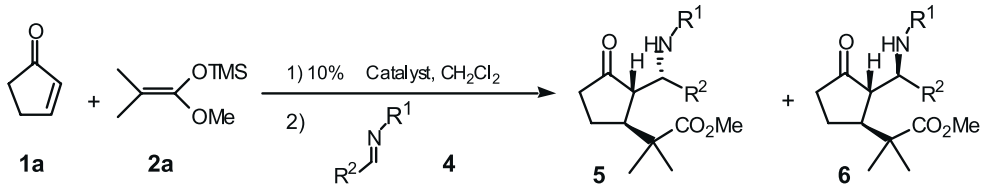
(2)

In the course of previous studies concerning the tandem Mukaiyama–Michael aldol reactions, we found that a decrease of temperature resulted in an increase of both yield, by suppression of by-products, and of stereoselectivity. Effect of temperature was thus examined on the two tandem sequences described in Eqs. 1 and 2. For the reactions with glyoxylic imine **4a** leading to adducts **5a** and **6a**, a decrease of temperature afforded a slight increase in diastereoselectivity (entries 1–4) together with an increase in yield down to −55 °C (81%, entry 3) which gave the best result. At lower temperature (−78 °C, entry 4) the yield decreased in spite of a longer reaction time. For reactions involving imine **4b**, from room temperature to −40 °C, no significant change in stereoselectivity could be detected (entries 7–9), while lower temperature resulted in the highest stereoselectivity (**5b/6b**: 80/20) albeit with a lower yield as with imine **4a** (entry 10). For this reaction, optimal temperature appears to be 0 °C (entry 8). As we precedently noticed for other reactions involving the use of samarium diiodide in catalytic amounts, the change of colour of the reaction mixtures from blue to yellow after the addition of substrates indicates that the actual catalytic species is trivalent. A comparative study of a variety of divalent and trivalent lanthanides as catalysts for aldol reaction did not allow to detect any difference in the rate of the reaction,[13] whereas for Mukaiyama Michael–aldol tandem reactions only $YbI_3(THF)_3$ and $LaI_3(DME)_2$ have exhibited an activity and selectivity similar to that of $SmI_2(THF)_2$.[16] Ytterbium and lanthanum triiodides were thus compared to



(1)

Table 1. Tandem Michael imino–aldol reactions, influence of reaction temperature and of catalyst

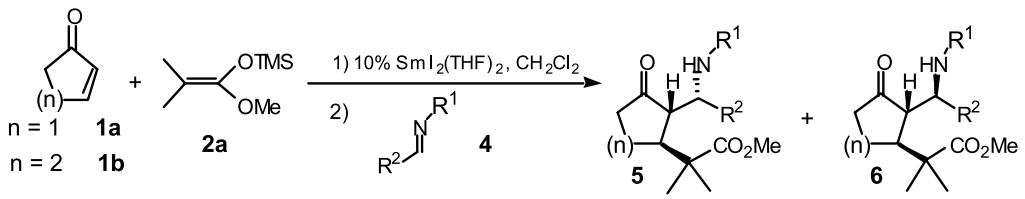


Entry	Catalyst	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield (%)[a,b]	**5/6**[c]
1	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	rt	3	**5a+6a**	50	70/30
2	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	3	**5a+6a**	76	70/30
3	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−55	18	**5a+6a**	81	78/22
4	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−78	46	**5a+6a**	70[d]	85/15
5	$YbI_3(THF)_3$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	4	**5a+6a**	60[d]	66/34
6	$LaI_3(DME)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	4	**5a+6a**	45[d]	60/40
7	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	rt	18	**5b+6b**	45	62/38
8	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	0	24	**5b+6b**	53	65/35
9	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−40	24	**5b+6b**	54	62/38
10	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−78	46	**5b+6b**	30	80/20
11	$YbI_3(THF)_3$	**4b**	Ph	*o*-$MeOC_6H_4$	−30	24	**5b+6b**	45	60/40
12	$LaI_3(DME)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−30	24	**5b+6b**	50	70/30

[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratio measured by ^1H NMR in crude product.
[d] Yield in crude product.

samarium diiodide for both test tandem Michael–iminoaldol reactions. For the tandem sequence leading to **5a** and **6a**, at −30 °C, yield and selectivity were higher with samarium diiodide than with both trivalent lanthanide iodides (entries 2, 5, 6). In the case of reactions leading to **5b** and **6b**, the three catalysts led to similar results, with close values for the stereomer ratios **5b/6b** and a slighty higher yield given by samarium diiodide at −40 °C (entries, 9, 11, 12). Scandium triflate which is known to display a high activity as a Lewis acid catalyst,[19] has been tested for the tandem Michael–iminoaldol reaction involving glyoxylic imine **4a**. Its catalytic activity was similar to that of samarium diiodide, but the adducts **5a** and **6a** were formed together with decomposition products which could not be separated by purification. Similar trend has been observed upon attempts to catalyze Mukaiyama Michael–aldol reactions by scandium

Table 2. Tandem Michael imino–aldol reactions catalyzed by samarium diiodide



Entry	Ketone	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield[a,b] (%)	**5/6**[c]
1	**1a**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−55	18	**5a+6a**	81	78/22
2	**1a**	**4b**	*o*-$MeOC_6H_4$	Ph	−40	24	**5b+6b**	54	62/38
3	**1a**	**4c**	Ph	Ph	0	24	**5c+6c**	47	71/29
4	**1a**	**4c**	Ph	Ph	−50	36	**5c+6c**	47	74/26
5	**1a**	**4d**	Ph	*p*-$CF_3C_6H_4$	0	24	**5d+6d**	42	50/50
6	**1a**	**4d**	Ph	*p*-$CF_3C_6H_4$	−50	24	**5d+6d**	50	59/41
7	**1a**	**4e**	Ph	*p*-$MeOC_6H_4$	rt	48		0	
8	**1a**	**4f**	*o*-$MeOC_6H_4$	*p*-$CF_3C_6H_4$	−40	24	**5f+6f**	66	83/17
9	**1a**	**4g**	*o*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	0	41	**5g+6g**	37	62/38
10	**1a**	**4h**	*o*-$MeOC_6H_4$	2-Furfuryl	0	68	**5h+6h**	36	75/25
11	**1b**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	0	24	**5i+6i**	46	86/14
12	**1b**	**4b**	*o*-$MeOC_6H_4$	Ph	rt	48		0	

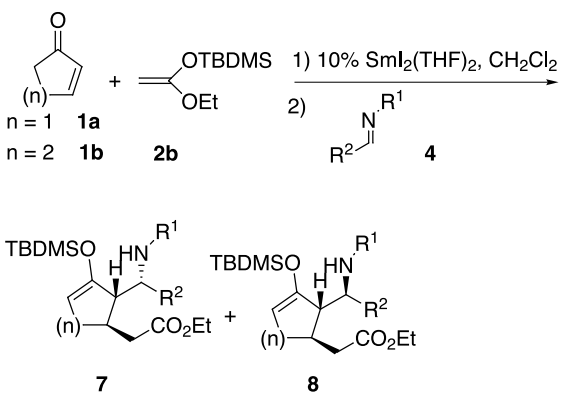
[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratios measured by ^1H NMR in the crude product.

triflate.[16] Samarium diiodide will be used in the following of this study since it is commercially available or easy to prepare,[20] and furnishes higher yields than the other lanthanide iodides.

The scope of the reaction was next examined aiming at the determination of the nature of imines that can be employed in the second step of the tandem sequence, the Mannich reaction. The results are gathered in Table 2. As indicated above, we first tested the imines **4a** and **4b**, which contain a coordinating group either on the carbon, or on the nitrogen group of the imine. This choice was dictated by our precedent results indicating that other imines such as *N*-phenyl benzylidene imine were unreactive towards enoxysilanes in the presence of samarium diiodide.[18] After having established the possibility to realize the tandem Michael–Mannich sequence with coordinating imines, we tried to extend the reaction to the non-coordinating *N*-phenyl benzylidene imine **4c**. Contrary to our expectations, this imine afforded the tandem adducts **5c** and **6c** (entry 3). A decrease in the temperature of the reaction did not bring any benefit on yield or selectivity (entry 4). The use of imine **4d** with an attracting group on the substituent of the carbon led to the adducts **5d** and **6d** in similar yield than with **4c** but lower selectivity (entries 3–6), while, with an electron donor group (imine **4e**), reaction did not afford the tandem adducts (entry 7). We compared the two latter imines with imines **4f** and **4g** which bear the coordinating *o*-anisyl group as substituent of the nitrogen atom. Comparison of **4d** and **4f** (entries 6 and 8) indicates that the presence of the coordinating group brings an increase in yield and selectivity. Tandem adducts were obtained from imine **4g** (entry 9) while **4e** was unreactive, which also reveals beneficial effect of the *o*-anisyl substituent on the imine. Furfuryl imine **4h** allowed isolation of tandem adducts albeit in low yield (entry 10). Influence of the size of the cycle was then examined and a low reactivity for the Mannich reaction was found in the case of cyclohexen-2-one (entries 11 and 12). The use of glyoxylic imine **4a** led to the mixture of tandem adducts **5i** and **6i** in moderate yield and high selectivity while no tandem product was obtained with the aromatic coordinating imine **4b**. This result can be explained by the lower reactivity of the six-membered ring enoxysilane resulting of the Michael addition towards imines compared to the similar five-membered ring enoxysilane.

Tandem products resulting of reaction of **1a**, **2a** and **4a** have been isolated after chromatography on silica gel as a mixture of two stereoisomers which have been separated after a second chromatography on alumina. 2D NMR experiments COSY and NOESY analysis of the major stereoisomer revealed a *trans* stereochemistry for the two lateral chains and *syn* situation for the iminoaldolisation products, as shown for **5a**. The other stereoisomer **6a** was assigned as the *anti* iminoaldolisation product. For the other tandem products assignments of stereomers have been done by comparison with **5a** and **6a**. Isomer **5** and **6** observed in all cases in the absence of other stereomers, are the result of the *anti* approach of imine on the cycle. Obtention of structure **5** with *syn* configuration as the major one is similar to the results reported in the case of the tandem Michael iminoaldol reaction.[16]

Our next aim was to extend these tandem reactions to another ketene silyl acetal. We thus studied the reaction of glyoxylic imine **4a** on enoxysilane formed by reaction of **2b** with cyclopenten-2-one in a one-pot procedure. To our surprise, we observed that Mannich reaction took place but the adducts did not had a similar structure than in reactions described above. Instead of ketones, the tandem adducts were isolated as the corresponding enoxysilanes (Eq. 3, Table 3). On the basis of ^{1}H, ^{13}C and 2D NMR analyses, the compounds isolated after purification on alumina have been identified as regioisomers **7** and **8** showing the less substituted double bond and the two chains in *trans* stereochemical situation. The major isomer was identified as **7**, with configuration *syn* for the carbons of the bond formed in the iminoaldolisation step, like in tandem reactions described above leading to β-aminoketones. The diastereoisomeric ratio **7/8** was evaluated by integration of ^{1}H NMR spectra. The enoxysilane obtained by reaction of ketene silyl acetal **2b** on cyclopenten-2-one was more reactive towards imine than the corresponding six-membered ring enoxysilane: reactions were performed at 0 °C with imines **4a** and **4h** for cyclopenten-2-one (entries 1 and 2) while only imine **4a** afforded the tandem products with cyclohexen-2-one (entries 3 and 4). Enolization of ketones catalyzed by lanthanide iodides was already observed. We had described that ketones could be transformed in the corresponding trimethylsilyl enoxysilanes by reaction with ketene silyl acetal **2a** in the presence of samarium diiodide or other lanthanide iodides.[15] In the reactions reported here, the transformation of the ketones into enoxysilanes seems to be related to the presence of a *tert*-butyldimethylsilyl group. We tested then the ketene silyl acetal **2c** derived from phenyl acetate substituted with a trimethylsilyl group. The tandem reaction involving **1a**, **2c** and **4a** was realized by the usual one-pot procedure at 0 °C and furnished the adducts as ketones **5j** and/or **6j** in moderate yield (Eq. 4). However we could not assign the stereomers and thus the selectivity of the reaction was not evaluated. The dependence of the structures of reaction products with the nature of the silyl group prompted us to investigate the samarium diiodide Mannich reaction of enoxysilanes bearing a *tert*-butyldimethylsilyl group with imines. We have indeed found that in this case also reactions products are isolated as enoxysilanes and not as ketones. These results as well as mechanistic pathways will be presented in the following paper.[21]

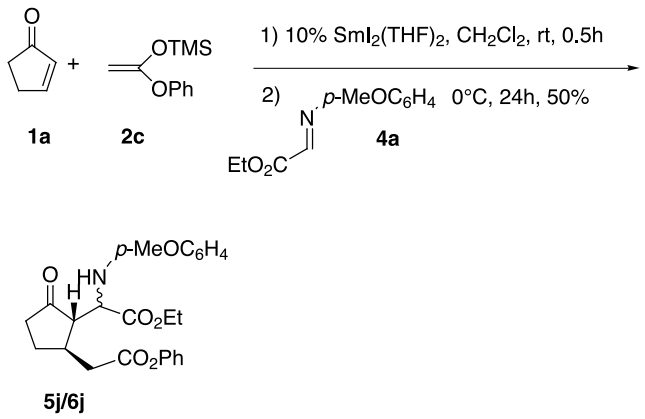


(3)

Table 3. Tandem Michael imino–aldol reactions catalyzed by samarium diiodide involving **2b**

Entry	Ketone	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield[a,b] (%)	**7/8**[c]
1	**1a**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	0	24	**7a+8a**	82	69/31
2	**1a**	**4h**	*o*-$MeOC_6H_4$	2-Furfuryl	0	68	**7b+8b**	60	82/18
3	**1b**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	20	24	**7c+8c**	58	75/25
4	**1b**	**4h**	*o*-$MeOC_6H_4$	2-furfuryl	20	24		0	

[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; Ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratios measured by ^1H NMR in the crude product.



(4)

In summary we have shown that samarium diiodide catalyzes the formation of two carbon–carbon bonds by successive Michael and Mannich reactions on α,β-unsaturated cyclic ketones to afford β-aminoketones or β-aminoenoxysilanes, depending upon the nature of the silyl group used as substituent of nucleophile in the Michael reaction. The rates and the yields of the tandem Michael–Mannich reactions are increased by the presence of a chelating group, either on the carbon, or on the nitrogen of imine. To the best of our knowledge, no other catalyst has been described for such sequences of tandem reactions. Since the removal of *N*-*o*-anisyl or *N*-*p*-anisyl groups on Mannich products has been already described,[22] samarium diiodide-catalyzed tandem Michael–Mannich reactions should give access to different β-aminoketones or lactams. Recently, we reported that iodo samarium binaphthoxides are enantioselective catalysts for Diels–Alder reactions[23] and moreover for Mannich reactions.[24] We are currently investigating the use of these catalysts for asymmetric tandem reactions.

3. Experimental

3.1. General

All manipulations were carried out under an argon atmosphere using standard Schlenk or glovebox techniques. CH_2Cl_2 was distilled from CaH_2 and degassed immediately prior to use. The method for preparing $SmI_2(THF)_2$ has been previously described,[25] as well as $LaI_3(DME)_2$ and $YbI_3(THF)_3$ prepared from La or Yb powder and iodine.[26] Silyl ketene acetal **2a** was purchased from Aldrich, **2b** and **2c** were prepared according to literature procedure.[27] Bruker AM 250 and AM 400 spectrometers, operating at 250 and 400 MHz for ^1H, 62.5 and 100.8 MHz for ^{13}C, were used for the NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra in $CDCl_3$. Infrared spectra were recorded as Nujol mulls using NaCl plates on a Perkin–Elmer 1000 FT-IR spectrometer and are reported in cm^{-1}. HRMS were measured with a Perkin–Elmer Finnigan-Mat 955 spectrometer. Flash chromatography was realized using 230–400 mesh silica gel desactivated by Et_3N or neutral alumina using heptane/ethyl acetate mixtures as eluents.

3.2. Typical procedure for the synthesis of tandem products 5 and 6

In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). Then CH_2Cl_2 (4 mL), 1-methoxy-2-methyl-1-trimethylsilyloxy-propene **2a** (203 μL, 1 mmol) and cyclopenten-2-one **1a** (125 μL, 1.5 mmol) were successively added under argon. The resulting yellow solution was then stirred for 0.5 h at room temperature, while the formation of enoxysilane **3** was monitored by GC and reaction mixture was cooled at −55 °C. A solution of imine **4a** (270 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) was then added. After 18 h stirring at the same temperature, the reaction mixture was hydrolyzed and extracted by CH_2Cl_2. The crude product was purified on silica gel desactivated by Et_3N (heptane/AcOEt: 85/15) to give a mixture of **5a+6a**, (317 mg, 81%, **5a/6a**, 78/22). Column chromatography on neutral alumina allowed to separate each of diastereoisomers **5a** and **6a** pure.

3.2.1. 2-Methyl-2-[3-oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclopentyl] propanoic acid methyl ester (*syn* 5a) and *anti* 6a. *syn* **5a**. ^1H NMR (250 MHz, $CDCl_3$, δ (ppm)): 6.73 (d, 2H, J=7.5 Hz), 6.66 (d, 2H, J=7.5 Hz), 4.59 (d, 1H, J=10 Hz), 4.35 (dd, 1H, J=10, 3.4 Hz), 4.10 (q, 2H, J=7.3 Hz), 3.70 (s, 3H), 3.65 (s, 3H), 2.64 (q, 1H, J=7.8 Hz), 2.52 (dd, 1H, J=7.5, 3.4 Hz), 2.26 (m, 2H), 2.09 (m, 1H), 1.64 (m, 1H), 1.23 (t, 3H, J=7.3 Hz), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 219.56, 177.64, 172.36, 153.16, 140.73, 116.43, 114.66, 61.39, 60.02, 55.61, 52.09, 51.65, 44.82, 44.64, 37.75, 24.16, 22.86, 21.12, 14.05. FTIR (NaCl) (cm^{-1}): 3374, 1731. HRMS: calcd for $C_{21}H_{29}NNaO_6$ (M^++Na): 414.1892, found: 414.1892.

anti **6a**. ^1H NMR (250 MHz, $CDCl_3$, δ (ppm)): 6.75 (d, 2H, J=8.7 Hz), 6.62 (d, 2H, J=8.7 Hz), 4.59 (d, 1H, J=10 Hz),

4.28 (dd, 1H, J=10, 2.9 Hz), 4.18 (q, 2H, J=7.3 Hz), 3.71 (s, 3H), 3.59 (s, 3H), 2.77 (dd, 1H, J=7.5, 2.9 Hz), 2.64 (q, 1H, J=7.5 Hz), 2.26 (m, 2H), 2.09 (m, 1H), 1.64 (m, 1H), 1.24 (t, 3H, J=7.3 Hz), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 218.21, 177.58, 171.79, 152.93, 140.66, 115.43, 114.79, 61.55, 58.45, 55.59, 52.49, 51.96, 45.27, 44.80, 37.75, 23.83, 22.72, 21.62, 14.06. HRMS: calcd for $C_{21}H_{29}NNaO_6$ (M^++Na): 414.1892, found: 414.1895.

3.2.2. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5b+*anti* 6b). *syn* **5b**+*anti* **6b**. ^{1}H NMR (200 MHz, $CDCl_3$, δ (ppm)): 7.35–7.16 (m, 5H), 6.72 (m, 1H), 6.57 (m, 2H), 6.29 (m, 1H), 5.98 (l, 0.62H, *syn* **5b**), 5.29 (l, 0.38H, *anti* **6b**), 4.61 (l, 1H), 3.90 (s, 1.86H, *syn* **5b**), 3.87 (s, 1.14H, *anti* **6b**), 3.63 (s, 1.86H, *syn* **5b**), 3.56 (s, 1.14H, *anti* **6b**), 2.69 (m, 1H), 2.52 (m, 1H), 2.10 (m, 1H), 1.65 (m, 3H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.05, 177.32, 146.82, 139.61, 136.07, 128.42, 127.44, 127.01, 120.83, 116.40, 110.65, 109.27, 58.96, 55.48, 54.63, 51.84, 45.33, 45.01, 38.82, 23.23, 22.41, 22.31. FTIR (NaCl) (cm^{-1}): 3410, 1726. HRMS: calcd for $C_{24}H_{29}NNaO_4$ (M^++Na): 418.1994, found: 418.1995.

3.2.3. 2-Methyl-2-[3-oxo-2-{α-(*N*-phenylamino)-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5c+*anti* 6c). *syn* **5c**+*anti* **6c**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.27 (m, 5H), 7.03 (m, 2H), 6.58 (m, 1H), 6.49 (m, 2H), 5.67 (l, 0.74H, *syn* **5c**), 5.05 (l, 0.26H, *anti* **6c**), 4.52 (l, 1H), 3.65 (s, 2.22H, *syn* **5c**), 3.57 (s, 0.78H, *anti* **6c**), 2.57 (m, 1H), 2.07 (m, 2H), 1.54 (m, 3H), 1.18 (s, 2.22H, *syn* **5c**), 1.13 (s, 2.22H, *syn* **5c**), 1.01 (s, 0.78H, *anti* **6c**), 0.96 (s, 0.78H, *anti* **6c**). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.64, 220.39, 177.90, 177.49, 146.81, 146.28, 140.71, 139.49, 129.03, 128.99, 128.61, 128.54, 127.72, 127.59, 127.21, 117.24, 117.46, 113.49, 113.37, 59.28, 58.30, 57.07, 54.24, 52.04, 52.00, 45.66, 45.39, 45.32, 44.98, 39.21, 37.26, 23.98 23.79, 22.18, 22.03, 21.82, 21.62. FTIR (NaCl) (cm^{-1}): 3386, 1728. HRMS: calcd for $C_{23}H_{27}NNaO_3$ (M^++Na): 388.1889, found: 388.1889.

3.2.4. 2-Methyl-2-[3-oxo-2-{α-(*N*-phenylamino)-4-trifluoromethyl-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5d+*anti* 6d). *syn* **5d**+*anti* **6d**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.47 (m, 4H), 7.05 (m, 2H), 6.63 (m, 1H), 6.47 (m, 2H), 5.75 (l, 0.59H, *syn* **5d**), 5.04 (l, 0.41H, *anti* **6d**), 4.61 (l, 1H), 3.68 (s, 1.77H, *syn* **5d**), 3.59 (s, 1.23H, *anti* **6d**), 2.68 (m, 1H), 2.52 (m, 1H), 2.14 (m, 1H), 1.59 (m, 3H), 1.22 (s, 1.77H, *syn* **5d**), 1.15 (s, 1.77H, *syn* **5d**), 1.09 (s, 1.23H, *anti* **6d**), 1.03 (s, 1.23H, *anti* **6d**). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 220.48, 192.33, 177.57, 145.88, 129.19, 128.23, 127.64, 125.53, 117.69, 113.30, 58.54, 54.19, 52.14, 45.20, 45.19, 39.17, 24.15, 22.16, 21.55. ^{19}F NMR: (235 MHz, $CDCl_3$, δ (ppm)): −63.74 (*syn* **5d**), −63.66 (*anti* **6d**). FTIR (NaCl) (cm^{-1}): 3383, 1727. HRMS: calcd for $C_{24}H_{26}F_3NNaO_3$ (M^++Na): 456.1762, found: 456.1761.

3.2.5. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-4-trifluoromethyl-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5f+*anti* 6f). *syn* **5f**+*anti* **6f**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.53 (d, 2H, J=8.3 Hz), 7.40 (d, 2H, J=8.3 Hz), 6.74 (m, 1H), 6.61 (m, 2H), 6.20 (m, 1H), 6.01 (l, 1H), 4.69 (l, 1H), 3.91 (s, 2.49H, *syn* **5f**), 3.88 (s, 0.51H, *anti* **6f**), 3.65 (s, 2.49H, *syn* **5f**), 3.58 (s, 0.51H, *anti* **6f**), 2.71 (m, 1H), 2.53 (m, 1H), 2.18 (m, 1H), 1.67 (m, 3H), 1.14 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 220.48, 177.42, 146.96, 144.18, 135.66, 128.04, 127.48, 125.49, 120.93, 117.06, 110.68, 109.49, 58.47, 55.60, 54.56, 52.05, 45.31, 44.92, 38.86, 23.57, 22.50, 22.03. ^{19}F NMR: (235 MHz, $CDCl_3$, δ (ppm)): −63.63 (*anti* **6f**), −63.69 (*syn* **5f**). FTIR (NaCl) (cm^{-1}): 3396, 1727. HRMS: calcd for $C_{25}H_{28}F_3NNaO_4$ (M^++Na): 486.1869, found 486.1868.

3.2.6. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-4-methoxy-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5g+*anti* 6g). *syn* **5g**+*anti* **6g**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.20 (m, 2H), 6.76 (m, 3H), 6.56 (m, 2H), 6.27 (m, 1H), 6.00 (d, 0.62H, J=8.8 Hz, *syn* **5g**), 5.26 (d, 0.38H, J=5.4 Hz, *anti* **6g**), 4.53 (m, 1H), 3.89 (s, 1.86H, *syn* **5g**), 3.87 (s, 1.14H, *anti* **6g**), 3.74 (s, 1.14H, *anti* **6g**), 3.72 (s, 1.86H, *syn* **5g**), 3.65 (s, 1.86H, *syn* **5g**), 3.58 (s, 1.14H, *anti* **6g**), 2.66 (m, 1H), 2.52 (m, 1H), 2.30–1.95 (m, 2H), 1.78–1.52 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.24, 220.23, 177.35, 177.08, 158.70, 146.84, 136.59, 136.12, 132.46, 131.41, 128.53, 128.04, 120.87, 120.81, 116.60, 116.29, 113.80, 113.74, 110.87, 110.65, 109.27, 58.40, 56.69, 55.48, 55.43, 55.02, 54.98, 54.60, 51.82, 51.68, 45.42, 45.30, 45.22, 45.13, 40.31, 38.94, 38.72, 37.18, 23.28, 23.15, 22.54, 22.46. FTIR (NaCl) (cm^{-1}): 3396, 1727. HRMS: calcd for $C_{25}H_{31}NNaO_5$: (M^++Na) 448.2100, found: 448.2100.

3.2.7. 2-Methyl-2-[3-oxo-2-{(*N*-2-methoxyphenylamino)-(2-furfuryl)-methyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5h+*anti* 6h). (*syn* **5h**+*anti* **6h**). ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.32 (m, 0.25H, *anti* **6h**), 7.28 (m, 0.75H, *syn* **5h**), 6.77 (m, 2H, *syn*+*anti*), 6.65 (m, 1H, *syn*+*anti*), 6.51 (m, 1H, *syn*+*anti*), 6.28 (m, 0.25H, *anti* **6h**), 6.23 (m, 0.75H, *syn* **5h**), 6.17 (m, 0.25H, *anti* **6h**), 6.14 (m, 0.75H, *syn* **5h**), 5.75 (d, J=10.3 Hz, 1H, *syn*+*anti*), 4.95–4.88 (m, 0.25H, *anti* **6h**), 4.81 (dd, J_1=10.3 Hz, J_2=4.3 Hz, 0.75H, *syn* **5h**), 3.87 (s, 2.25H, *syn* **5h**), 3.85 (s, 0.75H, *anti* **6h**), 3.66 (s, 2.25H, *syn* **5h**), 3.57 (s, 0.75H, *anti* **6h**), 2.83–2.79 (m, 0.25H, *anti* **6h**), 2.71–2.67 (m, 0.75H, *syn* **5h**), 2.57–2.49 (m, 1H, *syn*+*anti*), 2.30–1.94 (m, 3H, *syn*+*anti*), 1.78–1.62 (m, 1H, *syn*+*anti*), 1.19 (s, 0.75H, *anti* **6h**), 1.18 (s, 0.75H, *anti* **6h**), 1.17 (s, 2.25H, *syn* **5h**), 1.14 (s, 2.25H, *syn* **5h**). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 220.35, 177.43, 153.34, 147.31, 141.48, 136.11, 120.94, 117.26, 110.93, 110.36, 109.73, 107.78, 55.58, 55.14, 52.88, 51.78, 45.64, 45.18, 40.40, 38.80, 38.31, 37.61, 30.87, 29.61, 24.38, 23.42, 22.63, 21.19. FTIR (CCl_4,) (cm^{-1}): 3392, 1733. HRMS: calcd for $C_{22}H_{27}NNaO_5$ (M^++Na): 408.1787, found: 408.1788.

3.2.8. 2-Methyl-2-[3-oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclohexyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5i+*anti* 6i). *syn* **5i**+*anti* **6i**. ^{1}H NMR: (250 MHz, $CDCl_3$, δ (ppm)): 6.73

(m, 2H), 6.60 (m, 2H), 4.07 (m, 3H), 3.71 (s, 2.58, *syn* **5i**), 3.70 (s, 0.42H, *anti* **6i**), 3.61 (s, 2.58H, *syn* **5i**), 3.47 (s, 0.42H, *anti* **6i**), 2.66 (m, 2H), 2.53 (m, 1H), 2.27 (m, 1H), 1.88 (m, 3H), 1.52 (m, 1H), 1.19–1.13 (m, 9H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 212.12, 177.81, 172.48, 152.95, 140.74, 115.67, 114.66, 61.18, 60.42, 55.49, 55.00, 51.70, 45.85, 43.79, 39.48, 24.11, 23.88, 22.54, 21.39, 13.88. FTIR (NaCl) (cm^{-1}): 3360, 1728. HRMS: calcd for $C_{22}H_{31}NNaO_6$ (M^++Na): 428.2049, found: 428.2045.

3.2.9. [3-Oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclopentyl] acetic acid phenyl ester (*syn* 5j+*anti* 6j). *syn* **5j**+*anti* **6j**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.36 (m, 2H), 7.07 (m, 2H), 6.73 (s, 5H), 4.52 (l, 1H), 4.39 (l, 1H), 4.12 (q, 2H, J=7.32 Hz), 3.71 (s, 3H), 2.90–2.19 (m, 6H), 1.73–1.58 (m, 2H), 1.18 (t, 3H, J=7.32 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 216.77, 173.12, 170.57, 153.28, 150.34, 140.87, 129.41, 125.96, 121.41, 116.70, 114.60, 61.49, 57.85, 56.20, 55.54, 38.60, 37.79, 34.32, 27.27, 14.01. FTIR (film, NaCl) (cm^{-1}): 3373, 1749. HRMS calcd for $C_{24}H_{27}NNaO_6$ (M^++Na): 448.1735, found: 448.1736.

3.3. Typical procedure for the synthesis of tandem products 7 and 8

In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). Then 1-ethoxy-1-*tert*-butyldimethylsilyloxyethene **2b** (202 mg, 1 mmol) in solution in CH_2Cl_2 (4 mL), and cyclopenten-2-one **1a** (125 μL, 1.5 mmol) were successively added under argon. The resulting yellow solution was then stirred for 0.5 h at room temperature, while the formation of enoxysilane was monitored by GC and reaction mixture was cooled at 0 °C. A solution of imine **4a** (270 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) was then added. After 24 h stirring at the same temperature, the reaction mixture was hydrolyzed and extracted by CH_2Cl_2. The crude product was purified on alumina (heptane/AcOEt: 90/10) to give a mixture of **7a**+**8a**, (403 mg, 82%, **7a/8a**, 69/31). Diastereoisomer **7a** was then isolated form the mixture **7a**+**8a** by chromatography on alumina plate.

3.3.1. (5-Ethoxycarbonylmethyl-2-*tert*-butyldimethylsilyloxy-cyclopent-2-enyl)-(4-methoxyphenylamino) acetic acid ethyl ester (mixture of diastereomers, *syn* 7a+*anti* 8a). *syn* **7a**. ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 6.71 (d, J=8.8 Hz, 2H), 6.57 (d, J=8.8 Hz, 2H), 4.88 (bs, 1H), 4.59 (bs, 1H), 4.24 (bs, 1H), 4.13 (m, 4H), 3.70 (s, 3H), 2.70 (m, 2H), 2.56 (m, 1H), 2.56 (m, 2H), 1.88 (m, 1H), 1.22 (m, 6H), 0.91 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 173.32, 172.48, 152.48, 151.95, 141.58, 115.14, 114.62, 102.08, 60.93, 60.35, 59.42, 55.67, 54.10, 41.10, 34.17, 33.00, 25.67, 18.04, 14.23, −4.86, −4.97. FTIR (NaCl) (cm^{-1}): 3396, 1736, 1645. HRMS: calcd for $C_{26}H_{41}NNaO_6Si$: 514.2597, found: 514.2600.

syn **7a**+*anti* **8a**. ^{1}H NMR (200 MHz, $CDCl_3$, δ (ppm)): 6.73 (m, 2H, *syn*+*anti*), 6.57 (m, 2H, *syn*+*anti*), 4.88 (l, 0.31H, *anti* **8a**), 4.59 (l, 0.69H, *syn* **7a**), 4.24–4.06 (m, 5H, *syn*+*anti*), 3.71 (s, 0.93H, *anti* **8a**), 3.70 (s, 2.07H, *syn* **7a**), 2.76–1.59 (m, 8H, *syn*+*anti*), 1.27–1.18 (m, 6H, *syn*+*anti*), 0.92 (s, 2.79H, *anti* **8a**), 0.91 (s, 6.21H, *syn* **7a**), 0.18 (s, 0.93H, *anti* **8a**), 0.02 (s, 0.93H, *anti* **8a**), 0.15 (s, 2.07H, *syn* **7a**), 0.12 (s, 2.07H, *syn* **7a**).

3.3.2. [2-{(*N*-2-Methoxyphenylamino)-(2-furfuryl)-methyl}-3-*tert*-butyldimethylsilyloxy-cyclopent-3-enyl] acetic acid ethyl ester (mixture of diastereomers, *syn* 7b+*anti* 8b). *syn* **7b**+*anti* **8b**. ^{1}H NMR (250 MHz, $CDCl_3$ δ (ppm)): 7.32 (m, 0.82H, *syn* **7b**), 7.28 (m, 0.18H, *anti* **8b**), 6.71 (m, 2H, *syn*+*anti*), 6.59 (m, 1H, *syn*+*anti*), 6.44 (m, 1H, *syn*+*anti*), 6.25 (m, 1H, *syn*+*anti*), 6.17 (m, 1H, *syn*+*anti*), 4.95 (d, J=6.0 Hz, 0.18H, *anti* **8b**), 4.66 (m, 1H, *syn*+*anti*), 4.55 (d, J=1.5 Hz, 0.82H, *syn* **7b**), 4.07 (q, J=7.3 Hz, 2H, *syn*+*anti*), 3.85 (s, 0.54H, *anti* **8b**), 3.80 (s, 2.46H, *syn* **7b**), 2.85 (m, 1H, *syn*+*anti*), 2.65–2.37 (m, 2H, *syn*+*anti*), 2.19–2.03 (m, 2H, *syn*+*anti*), 1.89–1.79 (m, 1H, *syn*+*anti*), 1.21 (t, J=7.3 Hz, 3H, *syn*+*anti*), 0.88 (s, 1.62H, *anti* **8b**), 0.84 (s, 7.38H, *syn* **7b**), 0.14 (s, 3H, *syn*+*anti*), 0.01 (s, 3H, *syn*+*anti*). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 172.61, 155.13, 152.25, 146.75, 141.20, 137.32, 120.98, 116.41, 110.65, 110.32, 109.04, 106.76, 101.86, 60.18, 55.33, 55.12, 53.12, 40.82, 33.96, 33.23, 25.31, 18.00, 14.19, −4.89, −5.49. FTIR (CCl_4) (cm^{-1}): 3432, 1736, 1648. HRMS calcd for $C_{27}H_{39}NNaO_5Si$ (M^++Na): 508.2495, found: 508.2496.

3.3.3. (6-Ethoxycarbonylmethyl-2-*tert*-butyldimethylsilyloxy-cyclohex-2-enyl)-(4-methoxyphenylamino) acetic acid ethyl ester (mixture of diastereomers, *syn* 7c+*anti* 8c). *syn* **7c**+*anti* **8c**. ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 6.72 (m, 2H, *syn*+*anti*), 6.60 (m, 2H, *syn*+*anti*), 5.24 (m, 1H, *syn*+*anti*), 4.99 (t, J=3.7 Hz, 0.75H, *syn* **7c**), 4.95 (t, J=3.7 Hz, 0.25H, *anti* **8c**), 4.24 (bs, 1H, *syn*+*anti*), 4.19–4.03 (m, 4H, *syn*+*anti*), 3.70 (s, 3H, *syn*+*anti*), 2.53–2.42 (m, 1H, *syn*+*anti*), 2.41–2.30 (m, 1H, *syn*+*anti*), 2.30–2.17 (m, 3H, *syn*+*anti*), 2.07–1.99 (m, 1H, *syn*+*anti*), 1.90–1.84 (m, 1H, *syn*+*anti*), 1.40–1.34 (m, 1H, *syn*+*anti*), 1.25–1.18 (m, 6H, *syn*+*anti*), 0.98–0.94 (m, 9H, *syn*+*anti*), 0.22–0.14 (m, 6H, *syn*+*anti*). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 173.76, 172.69, 152.54, 147.43, 142.02, 115.54, 114.60, 106.40, 104.83, 61.04, 60.34, 55.67, 47.08, 38.21, 31.15, 25.74, 24.01, 21.00, 20.32, 14.21, −4.18, −4.86. FTIR (NaCl) (cm^{-1}): 3392, 1732, 1669. HRMS calcd for $C_{27}H_{43}NaO_6Si$ (M^++Na): 528.2764, found: 528.2757.

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References and notes

1. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–312. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) Denmark, S. E.; Thorarensen, A. *Chem. Rev.*

1996, *96*, 137–165. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (e) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194. (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159. (g) Poli, G.; Giambastani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (h) Ho, T. L. *Tandem organic reactions*; Wiley: New York, 1992.

2. (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207–222. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176. (c) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418–4427. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (e) Neuschütz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227–255.
3. (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393. (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269. (d) Molander, G. A.; Dowdy, E. D.; Schumann, H. *J. Org. Chem.* **1998**, *63*, 3386–3396. (e) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983–8988. (f) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757–1771. (g) Widenhoefer, R. A.; Stengone, C. N. *J. Org. Chem.* **1999**, *64*, 8681–8692. (h) Mikami, K.; Matsukawa, S.; Nagashima, M.; Funabashi, H.; Morishima, H. *Tetrahedron Lett.* **1997**, *38*, 579–582. (i) Mikami, K.; Yajima, T.; Sirre, N.; Terada, M.; Suzuki, Y.; Takanishi, Y.; Takezoe, H. *Synlett* **1999**, 1895–1898. (j) Sasai, H.; Hiroi, M.; Yamada, Y. M. A.; Shibazaki, M. *Tetrahedron Lett.* **1997**, *38*, 6031–6034. (k) Delas, C.; Moïse, C. *Synthesis* **2000**, 251–254. (l) Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *63*, 1344–1347. (m) Hollman, C.; Eilbracht, P. *Tetrahedron* **2000**, *56*, 1685–1692. (n) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984–10985.
4. (a) Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310–9313. (b) Ikeda, S.; Cui, D. M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712–4713. (c) Ikeda, I.; Kondo, K.; Sato, Y. *Chem. Lett.* **1999**, 1227–1228. (d) Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 4703–4706. (e) Mascarenhas, C. M.; Duffey, M. O.; Liu, S. Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427–1429. (f) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083–1086. (g) Ghosh, A. K.; Kawahama, R.; Wink, D. *Tetrahedron Lett.* **2000**, *41*, 8425–8429. (h) Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* **2001**, *42*, 3905–3907. (i) Loh, T. P.; Feng, L. C.; Yang, J. Y. *Synthesis* **2002**, 937–940. (j) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704.
5. (a) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379. (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773–5776. (c) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem Lett.* **1997**, 1039–1040. (d) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115–116. (e) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 19–20. (f) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125–4128. (g) Akiyama, T.; Iwai, J. *Synlett* **1998**, 273–274. (h) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293–8296. (i) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *J. Chem. Soc., Chem. Commun.* **1999**, *651*, 652. (j) Heaney, H.; Simcox, M. T.; Slawin, A. M. Z.; Giles, R. G. *Synlett* **1998**, 640–642. (k) Cozzi, P. G.; Di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691–1695. (l) Yu, L.; Li, J.; Ramirez, J.; Chen, D.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903–907. (m) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. L. *Tetrahedron Lett.* **2002**, *43*, 323–325. (n) Loh, T. P.; Wei, L. W. *Tetrahedron Lett.* **1998**, *39*, 323–326.
6. (a) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11389–11702. (b) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876. (c) Saito, S.; Yamazaki, S.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3613–3617.
7. (a) Alexakis, A.; March, S. *J. Org. Chem.* **2002**, *67*, 8753–8757. (b) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358–4359. (c) Feringa, B. L.; Pineshi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623. (d) Arnold, L. A.; Naaz, R.; Minnard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244–7254. (e) Shibazaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256. (f) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666–3672.
8. (a) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 221–224. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 1805–1808. (c) Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1986**, 1821–1824. (d) Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *114*, 8349–8362. (e) Danishefsky, S. J.; Audia, J. L. *Tetrahedron Lett.* **1988**, *29*, 1371–1374. (f) Marzcak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218–2223. (g) Klimko, P. G.; Singleton, D. A. *J. Org. Chem.* **1992**, *57*, 1733–1740. (h) Matsuda, I.; Makino, T.; Hasegawa, Y.; Itoh, K. *Tetrahedron Lett.* **2000**, *41*, 1409–1412.
9. Yang, X.; Hou, X.; Dai, L. *Tetrahedron Lett.* **2000**, *41*, 4431–4434.
10. Kobayashi, S.; Akiyama, R.; Morikawi, M. *Tetrahedron Lett.* **1997**, *38*, 4819–4822.
11. Shimizu, M.; Ogawa, T.; Nishi, T. *Tetrahedron Lett.* **2001**, *42*, 5463–5466.
12. Collin, J.; Giuseppone, N.; Van de Weghe, P. *Coord. Chem. Rev.* **1998**, *178–180*, 117–144.
13. Giuseppone, N.; Van de Weghe, P.; Mellah, M.; Collin, J. *Tetrahedron* **1998**, *54*, 13129–13148.
14. Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1994**, *35*, 2545–2548.
15. Hydrio, J.; Van de Weghe, P.; Collin, J. *Synthesis* **1997**, 68–72.
16. (a) Giuseppone, N.; Courtaux, Y.; Collin, J. *Tetrahedron Lett.* **1998**, *39*, 7845–7848. (b) Giuseppone, N.; Collin, J. *Tetrahedron* **2001**, *57*, 8989–8998.
17. Lannou, M. I.; Jaber, N.; Collin, J. *Tetrahedron Lett.* **2001**, *42*, 7405–7407.
18. Jaber, N.; Fiaud, J. C.; Collin, J. *Tetrahedron Lett.* **2001**, *42*, 9157–9159.
19. (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27. (b) Kobayashi, S.; Sugiara, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227–2302.
20. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
21. Gil, R.; Eternot, M.; Guillerez, M. G.; Collin, J. *Tetrahedron*, **2004**, *60*, 3085–3090.
22. (a) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431–432. (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984–985.
23. Collin, J.; Carrée, F.; Giuseppone, N.; Santos, I. *J. Mol. Catal. A* **2003**, *200/1–2*, 185–189.

24. Jaber, N.; Carrée, F.; Fiaud, J. C.; Collin, J. *Tetrahedron: Asymmetry* **2003**, 2067–2071.
25. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
26. Qian, C.; Zheng, P.; Wang, B.; Deng, D.; Sun, J. *J. Organomet. Chem.* **1994**, *466*, 101–105.
27. Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099–1104.

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Tandem reactions catalyzed by lanthanide iodides. Part 2: Tandem iminoaldol–enolisation reactions

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Abstract—Samarium diiodide is a catalyst for the reaction of cyclic and acyclic *tert*-butyldimethylsilyl enoxysilanes with chelating imines. Reaction products are isolated as β-aminoenoxysilanes instead of β-aminoketones as previously observed with the corresponding trimethylsilyl enoxysilanes. Several mechanistic pathways are discussed.

1. Introduction

Reactions allowing the formation of carbon–carbon bonds from imines have been widely studied due to their important synthetic applications.[1] During recent years, Lewis acids catalyzed Mannich-type reactions have been developed. They involve either preformed or in situ prepared imines and silyl enolates to afford β-aminoesters or β-aminoketones, respectively. The initial work reported by Ojima described the reaction of imines with ketene silyl acetals promoted by $TiCl_4$ yielding β-aminoesters.[2] Later, a variety of efficient catalysts for iminoaldol type reactions involving ketene silyl acetals have been studied, such as metal halides, $TiBr_4$, TiI_4,[3] SmI_3,[4] trimethylsilyl triflate,[5] tris pentafluorophenyl borate,[6] or trityl or phosphonium salts.[7,8] The interest of ytterbium and scandium triflates as Lewis acids for a wide range of reactions has been demonstrated by Kobayashi.[9] These triflates catalyze Mannich-type reactions of preformed imines,[10] as well as three-component reactions involving aldehydes, amines and enoxysilanes or silyl ketene acetals,[11] since the preferential reactivity of aldimines over aldehydes in the presence of lanthanide triflates in catalytic amount has been demonstrated.[12] Mannich reactions can be performed in aqueous media using Lewis acids such as $Yb(OTf)_3$, $InCl_3$, $BF_3{\cdot}OEt_2$ or $Zn(BF_4)_2$,[13] or Brönsted acids such as HBF_4.[14]

In the course of our previous works, we have studied the catalytic activity of $SmI_2(THF)_2$ as a Lewis acid in a variety of reactions,[15] including Mukaiyama aldol and Michael reactions.[16] Samarium diiodide allows to isolate products as silyl ethers in the former case or enoxysilanes in the latter. This has allowed to carry out tandem Michael–aldol reactions through a one-pot procedure.[17] Besides, reaction of methyl trimethylsilyl dimethylketene acetal with bulky carbonyl compounds, ketones or aldehydes, catalyzed by samarium diiodide, led readily to enoxysilanes.[18] We examined next the reactivity of imines in cycloaddition or Mannich-type reactions catalyzed by samarium diiodide,[19] as well as in the second step of tandem Michael–iminoaldol reactions.[20] The influence of the nature of substrates in these tandem Michael–iminoaldol reactions is described in the preceding article,[20b] and we have found that the use of a ketene silyl acetal bearing a *tert*-butyldimethylsilyl group led to β-amino enoxysilanes instead of β-aminoketones as reaction products. The intermediate in these tandem reaction is a *tert*-butyldimethylsilyl enoxysilane as previously shown.[16] This led us to study iminoaldol reactions involving *tert*-dimethylsilyl enoxysilane and to evaluate these reactions as a new method of preparation of enoxysilanes.

2. Results and discussion

We have previously examined iminoaldol reactions catalyzed by samarium diiodide and found that glyoxylic and aromatic imines react with a ketene silyl acetal to give β-aminoesters and with cyclic or acyclic trimethylsilyl enoxysilanes to give β-aminoketones.[19] However, the presence of a coordinating group in aromatic imines was necessary to isolate reaction products in good yields.

The following work will thus be focused on iminoaldol reactions using chelating imines **1a** and **1b**. We first examined the reaction of cyclic *tert*-butyldimethylsilyl enoxysilanes **2** with glyoxylic imine **1a** in the presence of

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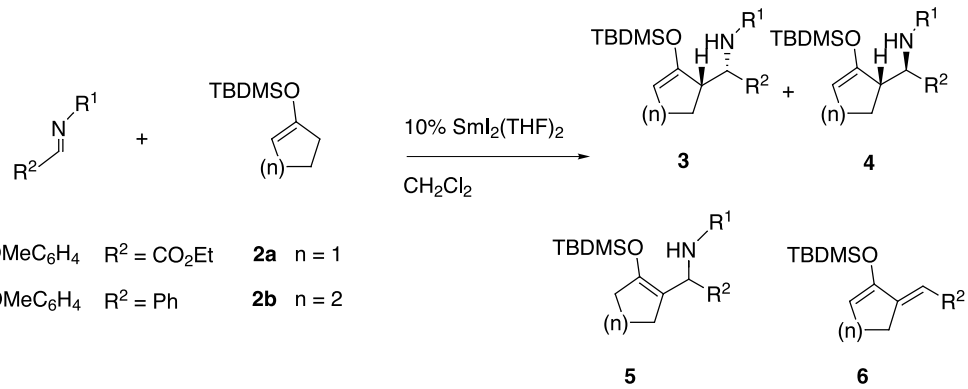


(1)

catalytic amounts of samarium diiodide, in methylene chloride. At room temperature, enoxysilane **2a** reacts with imine **1a** yielding a mixture of enoxysilanes **3aa**, **4aa**, **5aa** as reaction products, instead of the expected β-aminoketone (Table 1, entry 1). The regioisomers **3aa**+**4aa** (mixture of stereomers) and **5aa** were obtained in equal amounts in the crude product and could not be separated. For a longer reaction time, these enoxysilanes were converted into diene **6aa** which was then the sole compound in the crude product (entry 2). We studied the influence of the temperature on the selectivity of the reaction and observed only small effects on the regioselectivity and no effect on the ratio of stereomers **3aa/4aa** (entries 1, 3, 4). The six-membered ring enoxysilane **2b** reacted with the same imine **1a** at room temperature providing also the addition product as an enoxysilane. Surprisingly the reaction was regioselective, leading to sole isomer **5ab**. The reactions of chelating imine **1b** with enoxysilanes **2a** and **2b** were regioselective and led only to the mixture of diastereomers **3ba**+**4ba** for the five-membered ring enoxysilane (entries 6–8) and to the sole stereoisomer **3bb** for the six-membered ring enoxysilane (entry 9). A decrease in temperature for the reaction involving the five-membered ring enoxysilane had no effect on regioselectivity but resulted in a small increase in the diastereoselectivity of the reaction. Since stereoisomers **3** and **4** could not be separated, structure **3** was assigned to the major isomer by comparison with the tandem adducts of similar structure.[20b]

Formation of diene **6** from the reaction products took place readily either from the crude products or during the purification. This behavior is different from that of the tandem products obtained from Mukaiyama–Michael iminoaldol reactions. These were more stable towards decomposition and could be prepared without formation of by-product and easily purified. Total transformation into the corresponding diene **6**, from **3**, **4**, and **5** was observed during chromatography on silica gel and this degradation occurred also, but in a lesser extent, on alumina and explains the low yields in purificated products. The ratio in isomers **3**, **4** and **5** has thus been evaluated by integration of ^{1}H NMR spectra of crude products whenever possible.

In most cases, formation of enoxysilanes with the less substituted double bond is observed. In reactions involving imine **1b**, regioselectivity was similar to that observed in the case of tandem Michael–iminoaldol reactions, only stereoisomers **3** and **4** were formed in the absence of regioisomer **5**. Imine **1a** afforded the mixture of regioisomers for the five-membered enoxysilane **2a**, but led regioselectively to isomer **5** for the six-membered enoxysilane **2b**.

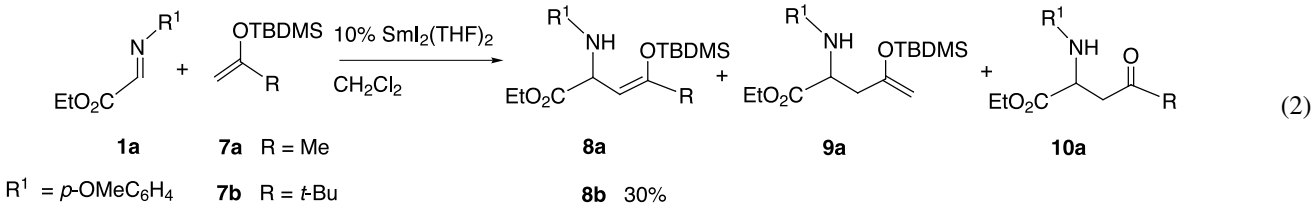
These iminoaldol reactions involving cyclic *tert*-butyldimethylsilyl enoxysilanes allow the preparation of new enoxysilanes substituted by an amino group and we have tried to extend these reactions to acyclic enoxysilanes. The glyoxylic imine **1a** reacted at room temperature or 0 °C with enoxysilane **7a** (Eq. 2) with total conversion after 12 h, providing iminoaldol products as a mixture of enoxysilanes **8a** and **9a** and β-aminoketone **10a**. Due to the complexity of NMR spectra, analysis of crude or purified products did not permit to evaluate the ratio of the different compounds. In

Table 1. Tandem iminoaldol–enolisation reactions catalyzed by samarium diiodide

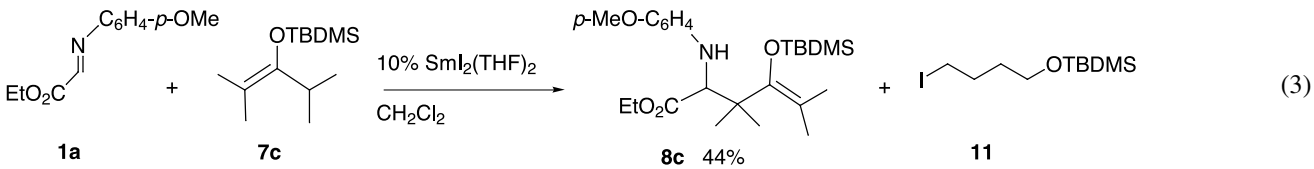
Entry	Imine	Enoxysilane	*T* (°C)	*t* (h)	**3**+**4**+**5** Yield[a,b] %	**3**+**4**/**5**[c]	**3**/**4**[c]	**6**[b]
1	**1a**	**2a**	20	2	88	48/52	50/50	5
2	**1a**	**2a**	20	18				100 (24)
3	**1a**	**2a**	0	18	80	54/46	50/50	7
4	**1a**	**2a**	−30	96	74 (40)	60/40	50/50	0
5	**1a**	**2b**	20	5	65 (25)	0/100		0
6	**1b**	**2a**	20	2	46 (14)	100/0	62/38	44
7	**1b**	**2a**	0	18	64 (19)	100/0	78/22	26
8	**1b**	**2a**	−40	18	57 (21)	100/0	85/15	45
9	**1b**	**2b**	12	72	(25)	100/0	100/0[d]	28[e]

[a] 10% $SmI_2(THF)_2$ in 8 mL CH_2Cl_2; ratio **1**/**2**: 1/1.
[b] Yield in crude product (isolated yield).
[c] Ratio measured by ^{1}H NMR on crude product.
[d] Only one isomer can be detected by ^{1}H and ^{13}C NMR after purification.
[e] Isolated yield.

order to prepare selectively a β-aminoenoxysilane, we tested substrates **7b** and **7c** (Eqs. 2 and 3) which could lead to a sole isomer after reaction. In both cases, we observed low rates and small conversions probably due to the bulkiness of substrates. 4-Iodo-*t*-butyldimethylsilyloxybutane **11** was obtained as a by-product. This compound resulted from the ring opening of the tetrahydrofuran coordinated to samarium, by *t*-butyldimethylsilyl iodide formed in situ. The opening of tetrahydrofuran has been already observed in iminoaldolisation reactions catalyzed by samarium diiodide,[21] and explains the deactivation of the catalyst.



(2)

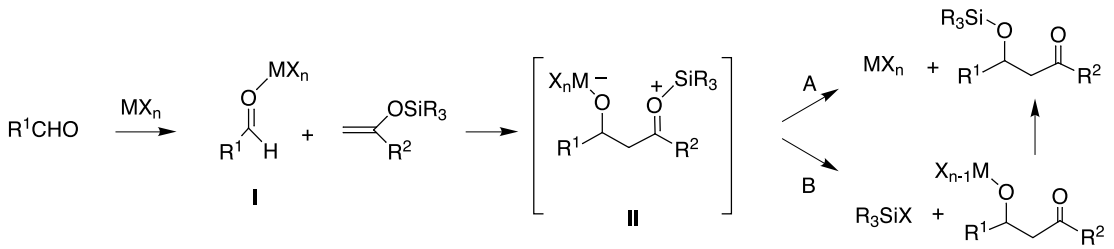


(3)

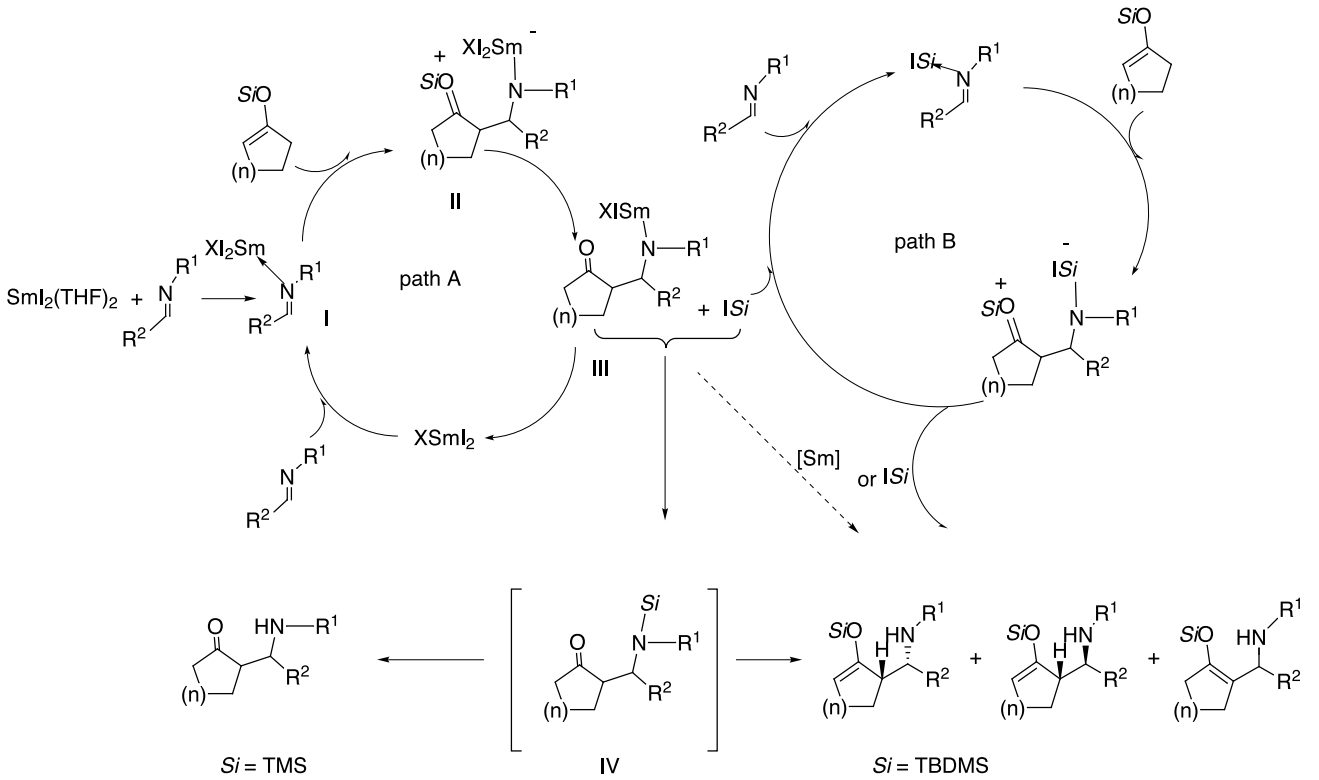
Reactions of the glyoxylic imine **1a** and chelating aromatic imine **1b** with *tert*-butyldimethylsilyl enoxysilanes catalyzed by samarium diiodide afforded Mannich-type products as was observed with trimethylsilyl enoxysilanes.[19] This reactivity differs from that of other Lewis acids such as $Yb(OTf)_3$, $InCl_3$, or $In(OTf)_3$ which catalyze cycloaddition reaction of *N*-phenylsubstituted imines and trimethylsilylenoxysilanes to give tetrahydroquinoline derivatives.[22]

2.1. Proposed mechanistic scheme for iminoaldolisation reaction

Several mechanisms have been proposed for Lewis acids catalyzed Mukaiyama aldol and Michael reactions, and the main different pathways proposed for the aldolisation reaction are depicted in Scheme 1.[23] In a first step the Lewis acid coordinates the carbonyl compound to form an intermediate I which reacts with the silyl derivative to afford the adduct II. The next step can be a concerted path A, or a non-concerted process B. The first one involves an intramolecular transfer of the silyl group, while, in the non-concerted process B, there is formation of an aldolate intermediate followed by intermolecular silylation reaction. In the latter process, the release of a silyl species R_3SiX allows a silicon-catalyzed competing process if the silylation of the aldolate is slow. In the course of our investigations concerning Mukaiyama aldol and Michael reactions catalyzed by lanthanide iodides, we had established, by performing crossover experiments, that intramolecular transfer of silicon does not occur.[16] We thus concluded that our aldolisation reactions should follow a process such as described in path B, in either a samarium-catalyzed, or a silicon-catalyzed process, or with both species as the actual catalysts. For iminoaldol reactions, a similar mechanism can be proposed, as depicted in Scheme 2. The first step is the coordination of the imine on a trivalent samarium species formed in situ. In all cases, reaction mixture turns from blue to yellow after the addition of the imine, indicating the trivalent state of samarium. Yet we have never detected reduction products such as amine or diamine and we have no information concerning the structure of the samarium species thus formed. The second step is the reaction of enoxysilane to form a samarium amide II, followed by liberation of silyl iodide and of the samarium amide III. Several reaction paths can then explain the formation of the reaction products. In presence of the silyl iodide the intermediate III can be transformed in a silylated β-aminoketone IV. This latter species either forms a β-aminoketone by cleavage of the nitrogen–silicon bond, or is transformed into enoxysilanes in the reactions involving *tert*-butyldimethylsilyl derivatives. The *tert*-butyldimethylsilyl enoxysilanes can alternatively be obtained directly from intermediates III by samarium catalyzed reactions, in a similar way to the transformation of ketones and aldehydes by reaction with ketene trimethylsilyl acetal catalyzed by samarium diiodide.[18] A silyl iodide-catalyzed process as indicated in path B can



Scheme 1.



Scheme 2.

alternatively occur, if the silylation of intermediate III is a slow step and explain the formation of the β-amino-enoxysilanes. In fact, silyl iodides prepared in situ can be used for the transformation of ketones in enoxysilanes.[24] However, we have obtained high enantiomeric excess for Mannich-type reactions of glyoxylic imines catalyzed by samarium iodo binaphtoxide, which indicates that in this latter case, catalysis by a samarium species was faster than with silyl iodide.[25] In the imino aldol reactions described above as well as in tandem Michael iminoaldol reactions,[20b] we have observed that the structures of reaction products are related to the silyl groups of the enoxysilanes or of the ketene silyl acetals for tandem reactions. Trimethylsilyl derivatives allow the isolation of ketones while *tert*-butyldimethylsilyl derivatives afford enoxysilanes. This may be explained by the transformation of β-amino trimethylsilylenoxysilanes in β-amino ketones during the treatment of reaction mixtures. However, in other samarium diiodide-catalyzed reactions, we have isolated trimethylsilyl enoxysilanes.[16,18] In iminoaldol reactions as well as in tandem Michael iminoaldol reactions, all our attempts to isolate trimethylsilyl substituted products, after filtration of samarium salts without hydrolysis of the reaction mixtures have been unsuccessful. If intermediates IV are formed after a silylation step, the difference of the nature of the products could be better explained by a difference in the strength of the nitrogen–silicon bond according to the nature of the silyl group. The weaker bond of trimethylsilyl group should be easily broken before the transfer of silicon on oxygen could occur.

In summary, we have shown that enoxysilanes substituted by a *tert*-butyldimethylsilyl group can be used in samarium diiodide catalyzed iminoaldol reactions as well as trimethylsilyl enoxysilanes. Thanks to the substitution of the silyl group, the nature of reaction products can be controlled, β-aminoketones are isolated with trimethylsilyl derivatives and β-aminoenoxysilanes with *tert*-butyldimethylsilyl derivatives. This confirms our previous results obtained for tandem Michael–iminoaldol reactions. Iminoaldol reactions using *tert*-butyldimethylsilyl enoxysilanes thus result in the functionalisation of the enoxysilanes by an amino group. This opens the route to new sequences of tandem reactions using samarium diiodide as a catalyst that we are currently investigating.

3. Experimental

3.1. General

All manipulations were carried out under an argon atmosphere using standard Schlenk or glovebox techniques. CH_2Cl_2 was distilled from CaH_2 and degassed immediately prior to use. $SmI_2(THF)_2$ was prepared as previously described.[26] Enoxysilanes **2a**, **2b**, **7a**, **7b**, **7c** were prepared according to literature procedures.[24] Bruker AM 250 and AM 400 spectrometers, operating at 250 and 400 MHz for ^1H, 62.5 and 100.8 MHz for ^{13}C, were used for the NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra in $CDCl_3$. Infrared spectra were recorded as Nujol mulls using NaCl plates on a Perkin–Elmer 1000 FTIR spectrometer and are reported in cm^{-1}. HRMS were measured with a Perkin–Elmer Finnigan-Mat 955 spectrometer. Mass spectra (MS) (70 eV) data were determined on a Ribermag R-10 GC/MS. Flash chromatography were realized on

neutral alumina, using heptane/ethyl acetate mixtures as eluents.

3.2. Typical procedure for the synthesis of tandem products

In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox) and suspended in CH_2Cl_2 (4 mL). Then a solution of 1-*tert*-butyldimethylsilyloxycyclopentene **2a** (198 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was cooled at −30 °C. A solution of glyoxylic imine **1a** (207 mg, 1 mmol) in CH_2Cl_2 (2 mL) was cooled at the same temperature and rapidly added on the reaction mixture to give an orange solution. After one night stirring at the same temperature, reaction mixture was then hydrolyzed (10 mL H_2O) and extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on alumina (heptane/AcOEt: 85/15) to afford the mixture of **3aa**+**4aa**+**5aa** (162 mg, 40%).

3.2.1. [(2-*tert*-Butyldimethylsilyloxy-cyclopent-2-enyl]-(4-methoxyphenylamino)-acetic acid ethyl ester (mixture of diastereomers, *syn* 3aa+*anti* 4aa)+[(2-*tert*-butyldimethylsilyloxy-cyclopent-1-enyl]-(4-methoxy-phenylamino)-acetic acid ethyl ester (5aa): (*syn* 3aa+*anti* 4aa+5aa). ^{1}H NMR ($CDCl_3$, 400 MHz, δ (ppm)): **3aa**+**4aa**+**5aa**: 6.76 (m, 2H), 6.60 (m, 2H), 4.96 (s, 0.4H, H, **5aa**), 4.70 (d, 0.6H, H_a, J=9 Hz, **3aa**+**4aa**), 4.20 (m, 2H), 4.10 (m, 0.6H, **3aa**+**4aa**), 3.75 (s, 3H), 3.20 (m, 0.6H, **3aa**+**4aa**), 2.40–1.80 (m, 4.8H), 1.3 (m, 3H), 0.99 (s, 3.6H, **5aa**), [0.94 (s, 2.7H,) 0.89 (s, 2.7H) **3aa**+**4aa**], 0.195 (s, 2.4H, **5aa**), [0.19 (s, 0.9 H), 0.18 (s, 0.9H), 0.17 (s, 0.9H), 0.11 (s, 0.9H), **3aa**+**4aa**]. ^{13}C NMR (62.5 MHz, $CDCl_3$, δ (ppm)): 172.95, 172.85, 172.36, 153.61, 152.42, 152.13, 151.84, 141.72, 141.55, 140.74, 116.04, 115.18, 114.94, 114.64, 112.89, 111.57, [103.42, 102.92, (**3aa**+**4aa**)], 61.09, 61.02, 60.79, 60.71, 59.45, 59.17, 55.71, 53.84 (**5aa**), 52.55, 48.02, 47.89, 47.74, 40.67, 33.60, 27.26, 27.16, 26.75, 25.70, 25.63, 24.52, 22.48, 20.21, 19.50, 18.10, 18.01, 14.20, −2.62, −2.96, −3.76, −4.02, −4.79, −4.95. FTIR (NaCl) (cm^{-1}): 3397, 1735, 1677, 1646. HRMS: calcd for $C_{22}H_{35}NO_4SiNa$ (M^++Na): 428.2229, found: 428.2233.

3.2.2. (2-*tert*-Butyldimethylsilyloxy-cyclopent-2-enyl-idene)-acetic acid ethyl ester, 6aa. ^{1}H NMR ($CDCl_3$, 250 MHz, δ (ppm)): 5.78 (s, 1H), 5.54 (s, 1H), 4.15 (q, 2H, J=6.8 Hz), 2.98 (m, 2H), 2.41 (m, 2H), 1.27 (t, 3H, J=6.8 Hz), 0.95 (s, 9H), 0.16 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ (ppm)): 206.50, 165.76, 147.38, 121.79, 75.68 61.00, 27.81, 25.63, 24.68, 18.07, 14.11, −3.00. GC-MS (EI) m/z (intensity): 283.1 (MH^+), 241.1 (100%). FTIR (NaCl) (cm^{-1}): 1713, 1644, 1521.

3.2.3. [(2-*tert*-Butyldimethylsilyloxy-cyclohex-1-enyl]-(4-methoxyphenylamino)-acetic acid ethyl ester, 5ab. ^{1}H NMR ($CDCl_3$, 400 MHz, δ (ppm)): 6.71 (d, 2H, J=12 Hz), 6.62 (d, 2H, J=12 Hz), 5.27 (s, 1H), 4.35 (s, 1H, NH), 4.18 (q, 2H, J=7.3 Hz), 3.71 (s, 3H), 2.09 (m, 2H), 1.98 (m, 2H), 1.75–1.40 (m, 4H), 1.23 (t, 3H, J=7.3 Hz), 1.01 (s, 9H), 0.21 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ (ppm)): 172.82, 151.87, 147.85, 140.70, 114.58, 110.77, 60.93, 55.66, 54.87, 30.31, 25.78, 23.06, 22.32, 22.20, 18.22, 14.20, −3.21, −3.81. FTIR (NaCl) (cm^{-1}): 3406, 1731, 1672, 1514. HRMS: calcd for $C_{23}H_{37}NO_4SiNa$ (M^++Na): 442.2387, found 442.2389.

3.2.4. [(2-*tert*-Butyldimethylsilyloxy-cyclopent-2-enyl)-phenyl-methyl]-(2-methoxy-phenyl)-amine (mixture of diastereomers, *syn* 3ba+*anti* 4ba). ^{1}H NMR ($CDCl_3$, 250 MHz, δ (ppm)) **3ba**+**4ba**: 7.35–7.10 (m, 5H), 6.70–6.47 (m, 3H), 6.14 (d, 0.15H, J=1.5 Hz, **4ba**), 6.11 (d, 0.85H, J=1.9 Hz, **3ba**), 4.63 (s, 0.85H, **3ba**), 4.54 (s, 0.15H, **4ba**), 4.45 (s, 1H), 3.78 (s, 0.45H, **4ba**), 3.72 (s, 2.55H, **3ba**), 3.05 (m, 0.85H, **3ba**), 2.90 (m, 0.15H, **4ba**), 2.11–1.62 (m, 4H), 0.87 (s, 1.35H, **4ba**), 0.78 (s, 7.65H, **3ba**), 0.12 (s, 0.45H, **4ba**), 0.08 (s, 2.55H, **3ba**), 0.01 (s, 0.45H, **4ba**), −0.03 (s, 2.55H, **3ba**). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ (ppm)): 128.17, 127.78, 126.93, 126.51, 121.09, 121.03, 116.41, 115.88, 111.92, 111.08, 109.09, 108.88, 104.42, 103.50, 58.96, 58.34, 52.17, 51.70, 55.36, 55.23, 31.90, 29.68, 25.73, 25.53, 24.26, 22.28, 17.99, −4.84, −5.65. FTIR (NaCl) (cm^{-1}): 3338, 1646. HRMS ($C_{25}H_{35}SiNO_2$-Na): calcd 432.2333, found 432.2335.

3.2.5. [(2-*tert*-Butyldimethylsilyloxy-cyclohex-2-enyl)-phenyl-methyl]-(2-methoxy-phenyl)-amine, *syn* 3bb. ^{1}H NMR ($CDCl_3$, 400 MHz, δ (ppm)): 7.20 (m, 5H), 6.71 (m 1H,), 6.55 (m, 2H), 6.14 (m, 1H), 5.02 (s, 1H), 4.81 (s, 1H), 4.77 (s, 1H), 3.85 (s, 3H), 2.66 (m, 1H), 2.20–2.00 (m, 2H), 1.70–1.50 (m, 2H), 1.30 (m, 2H), 0.79 (s, 9H), 0.16 (s, 3H), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ (ppm)): 150.05, 146.86, 142.64, 138.14, 128.21, 126.89, 126.42, 121.06, 116.00, 111.61, 109.06, 106.10, 57.59, 55.50, 46.21, 25.68, 24.20, 23.15, 21.93, 17.98, −5.30. FTIR (NaCl) (cm^{-1}): 3400, 1659. HRMS: calcd for $C_{26}H_{37}NO_2SiNa$ (M^++Na): calcd 446.2491, found 446.2491.

3.2.6. (6-Benzylidene-cyclohex-1-enyloxy)-*tert*-butyl-dimethyl-silane, 6bb. ^{1}H NMR ($CDCl_3$, 250 MHz, δ (ppm)): 7.17 (m, 5H), 6.76 (s, 1H), 5.13 (t, 1H, J=4.4 Hz), 2.55 (td, 2H, J=4.4 Hz, J=1.9 Hz), 2.12 (m, 2H), 1.55 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, δ (ppm)): 148.79, 137.94, 130.31, 129.28, 127.99, 126.16, 122.29, 110.15, 27.37, 25.96, 24.70, 23.08, 18.35, 1.02. MS (ESI POS): 339 (MK^+, 100%), 301 (MH^+).

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References and notes

1. Kleinman, E. F. *Comprehensive organic chemistry*; Trost, B. M., Ed.;, 1991; Vol. 2, pp 893–950.
2. (a) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, *18*, 3643–3646. (b) Ojima, I.; Inaba, S. *Tetrahedron Lett.*

1980, *21*, 2077–2080. (c) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2081–2084. (d) Ojima, I.; Inaba, S. *Synthesis* **1981**, 545–547.
3. Shimizu, M.; Kume, K.; Fujisawa, T. *Chem. Lett.* **1996**, 545–546.
4. Hayakawa, R.; Shimizu, M. *Chem. Lett.* **1999**, 591–592.
5. (a) Ikeda, K.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 4707–4710. (b) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331–4334.
6. (a) Ishihara, K.; Funahashi, M.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1996**, 963–964. (b) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, 527–538.
7. Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem. Lett.* **1990**, 889–892.
8. Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397–1400.
9. (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27. (b) Kobayashi, S.; Sugiara, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227–2302.
10. (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233–234. (b) Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099–1101. (c) Kobayashi, S.; Hachiya, I.; Suzuki, S. *Tetrahedron Lett.* **1996**, *37*, 2809–2812.
11. (a) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773–5776. (b) Cozzi, P. G.; Di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691–1694. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293–8296. (d) Dudot, B.; Chiaroni, A.; Royer, J. *Tetrahedron Lett.* **2000**, *41*, 6355–6359.
12. Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049–10053.
13. (a) Kobayashi, S.; Ishitani, H. *J. Chem. Soc. Chem. Commun.* **1995**, 1379. (b) Kobayashi, S.; Busijima, T.; Nagayama, S. *Synlett* **1999**, 545–546. (c) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L.; Yoshida, K. *Tetrahedron* **2000**, *56*, 3227–3237. (d) Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* **1999**, 947–948. (e) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983–988.
14. (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1045–1048. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426–1428. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Synlett* **2002**, 1269–1272. (d) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537–2544. (e) Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *J. Chem. Soc. Chem. Commun.* **2003**, 1644–1645.
15. Collin, J.; Giuseppone, N.; Van de Weghe, P. *Coord. Chem. Rev.* **1998**, 178–180, see also pp 117–144.
16. Giuseppone, N.; Van de Weghe, P.; Mellah, M.; Collin, J. *Tetrahedron* **1998**, *54*, 13129–13148.
17. (a) Giuseppone, N.; Collin, J. *Tetrahedron* **2001**, *57*, 8989–8998. (b) Giuseppone, N.; Courtaux, Y.; Collin, J. *Tetrahedron Lett.* **1998**, *39*, 7845–7848.
18. Hydrio, J.; Van de Weghe, P.; Collin, J. *Synthesis* **1997**, 68–72.
19. Lannou, M. I.; Jaber, N.; Collin, J. *Tetrahedron Lett.* **2001**, *42*, 7405–7407.
20. (a) Jaber, N.; Fiaud, J. C.; Collin, J. *Tetrahedron Lett.* **2001**, *42*, 9157–9159. (b) Jaber, N.; Assié, M.; Fiaud, J. C.; Collin J. *Tetrahedron*, **2004**, *60*, 3075–3083.
21. Jaber, G. M. Thesis. Orsay, 2002.
22. (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, *119*, 1195–1202. (b) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801–804. (c) Laurent-Robert, H.; Garrigues, B.; Dubac, J. *Synlett* **2000**, 1160–1161.
23. (a) Carreira, E. M.; Singer, R. *Tetrahedron Lett.* **1994**, *35*, 4323–4326. (b) Denmark, S. C.; Chen, C. T. *Tetrahedron Lett.* **1994**, *35*, 4327–4330. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570–4581.
24. (a) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Travel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777–4786. (b) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075–2088.
25. Jaber, N.; Carrée, F.; Fiaud, J. C.; Collin, J. *Tetrahedron: Asymmetry* **2003**, *142*, 2067–2071.
26. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

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Biotransformation of (+)-(1*R*,2*S*)-fenchol by the larvae of common cutworm (*Spodoptera litura*)

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Abstract—Biotransformation of (+)-(1*R*,2*S*)-fenchol by the larvae of *Spodoptera litura* was carried out. Substrate was converted to three new terpenoids, (+)-(1*R*,2*S*)-10-hydroxyfenchol, (+)-(1*R*,2*R*,3*S*)-8-hydroxyfenchol and (−)-(1*S*,2*S*,6*S*)-6-*exo*-hydroxyfenchol, and one known terpenoid, (−)-(1*R*,2*R*,3*R*)-9-hydroxyfenchol. These structures were established by NMR, IR, specific rotation and mass spectral studies.

1. Introduction

Terpenoids are known as not only raw materials for flavor and fragrance but also biologically active substances. A great majority of biologically active terpenoids are produced as plant secondary metabolites, and these terpenoids have been shown to have biological activity against plants, microorganisms and insects. Various attempts have been made to search for new biologically active terpenoids. However, it is difficult that these active compounds were produced by organic synthesis. Biotransformation is the biologically synthetic process that using enzymes in the living body as biocatalysts. The characters of biotransformation are as follows: regio- and stereo-selective reaction under mild condition and produced optical active compounds. These points suggested that the biotransformation is easy method for produce the new organic compounds. We have reported the biotransformation of various compounds, including monoterpenoids, by the larvae of *Spodoptera litura* as biocatalyst.[1–5] The reasons for using the larvae of common cutworm (*S. litura*) as a biological catalyst are as followed: lepidopteran larvae feed on plants contained terpenoids as their diet and therefore, possess a high level of enzymatic activity against terpenoids; the worm consumes a large amount of plants, making it possible to obtain more metabolites; and the worm is easy to rear on a laboratory scale. In our previous paper, terpenoids have been used to regio-selective hydroxylation.[1–5] Fenchol is bicyclic monoterpenoid with a fenchane skeleton. The structure modification of fenchol by organic synthesis has been few reported.[6–10] However, biotransformation of (+)-fenchol has not been reported previously.

In the present paper, we report for the first time the biotransformation of (+)-(1*R*,2*S*)-fenchol by the larvae of *Spodoptera litura* and structural elucidation of the biotransformation products.

2. Results and discussion

Biotransformation by the larvae of *S. litura* was observed as follows: substrate was administered to the larvae through their diet (4 mg/g of diet); metabolite was then detected and isolated from the frass of larvae. The larvae were fed the artificial diet without substrate were used as control, and the extract of frass was analyzed by GC. Substrate and metabolites were observed in the frass of biotransformed extracts. Consume of substrate in the diet observed by the internal standard method in GC. The result was that consumption of (+)-(1*R*,2*S*)-fenchol (**1**) was 93.3%.

In the biotransformation of **1**, the four metabolites isolated from the frass were identified as (+)-(1*R*,2*S*)-10-hydroxyfenchol (**2**), (+)-(1*R*,2*R*,3*S*)-8-hydroxyfenchol (**3**), (−)-(1*S*,2*S*,6*S*)-6-*exo*-hydroxyfenchol (**4**) and (−)-(1*R*,2*R*,3*R*)-9-hydroxyfenchol (**5**) (**2**, **3** and **4** are new compounds). Percentage of recovered substrate and metabolites **2**, **3**, **4** and **5** in the frass extract were 6.7, 52.4, 18.6, 15.5 and 4.0%, respectively. Percentage was calculated from the peak area in the GC chromatogram of the extract of frass (Table 1).

Keywords: *Spodoptera litura*; Biotransformation; Regioselective; Hydroxylation; (+)-(1*R*,2*S*)-10-Hydroxyfenchol; (+)-(1*R*,2*R*,3*S*)-8-Hydroxyfenchol; (−)-(1*S*,2*S*,6*S*)-6-*exo*-Hydroxyfenchol; (−)-(1*R*,2*R*,3*R*)-9-Hydroxyfenchol.
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Table 1. The biotransformation of (+)-fenchol (**1**) by the *S. litura* larvae[a]

Substrate	**1**[b]	**2**	**3**	**4**	**5**
(+)-Fenchol (**1**)	6.7%	52.4%	18.6%	15.5%	4.0%

[a] Metabolites were obtained from the frass of *S. litura*. Percentage was calculated from the peak area in the gas chromatogram of the extract of frass.
[b] Recovered substrate.

Metabolite **2** showed a widely hydroxyl band (ν_{max} 3385 cm^{-1}) relatively compared with substrate in the IR spectrum. FABMS (neg.) had a fragmentation at *m/z* 151 which was assigned to $[M-H-H_2O]^+$, however parent ion has not indicate. As the conformation, metabolite **2** was acetylated at room temperature and subsequently examined by TLC. The formation of only one reaction product was confirmed (R_f 0.5) by TLC and obtained acetylated compound **2a**. Acetylated **2a**, the IR spectrum still had hydroxyl band (ν_{max} 3497 cm^{-1}) and the high resolution FABMS (pos.) had a peak at *m/z* 213.1509 which was assigned to $[M+H]^+$, characterized its monoacetate. These results indicate metabolite **2** had a primary alcohol. Therefore, metabolite **2** was contained two hydroxyl groups. The proton and carbon NMR spectra were similar to that of the substrate, except for the existence of new methylene group and the disappearance of a methyl group. About the proton NMR, H_B-7 (1.09 ppm) has characteristic coupling constant (J=10.3 Hz) with H_A-7 (1.48 ppm). This was confirmed by assignment of the NMR spectra using two-dimensional techniques (COSY, HMQC, HMBC and NOESY). COSY spectrum indicates correlation cross-peaks were observed between H-4 (1.77–1.74 ppm) and δ 1.48, 1.44 and 1.09 ppm (H_A-7, H-5$_{exo}$ and H_B-7, respectively), H-2$_{exo}$ (3.62 ppm) and δ 1.15 ppm (H-6$_{exo}$; a long distance *W*-coupling J=1.8 Hz). Then, the proton NMR spectrum showed two methyl groups located at δ 1.01 and 0.87 ppm and the two doublets located at δ 3.82 and 3.74 ppm (J=10.6 Hz), latter spectra are characteristic of the new methylene group. In the characteristic HMBC spectrum correlation were observed of two methyl groups (1.01 and 0.87 ppm) with one nonprotonated carbon (39.4 ppm; C-3), of new methylene group (3.82 and 3.74 ppm) with the other nonprotonated carbon (54.1 ppm; C-1). Therefore, metabolite **2** was produced by hydroxylation at the C-10 position of **1**. Furthermore, to determine the complete assignment of metabolite **2**, NOESY was measured. The spectrum indicates correlation cross-peaks were observed between H-5$_{endo}$,6$_{endo}$ (1.73 and 1.87 ppm, respectively) and one methyl signal at δ 0.87 ppm (H-9), H_A-7 (1.48 ppm) and other methyl signal at δ 1.01 ppm (H-8), so that was established. The specific rotation shows the (+)-form. From these data it was concluded that the structure of **2** is (+)-(1*R*,2*S*)-10-hydroxyfenchol, which is a new compound.

It assigned the structure of **2a**, which was confirmed by study of its 2D NMR spectra (COSY, HMQC, HMBC and NOESY).

The second metabolite **3**, the IR spectrum had a widely hydroxyl band (ν_{max} 3339 cm^{-1}) relatively compared with substrate. FABMS (neg.) had a fragmentation at *m/z* 151 which was assigned to $[M-H-H_2O]^+$, however parent ion has not indicate. As the conformation, metabolite **3** was acetylated at room temperature and subsequently examined by TLC. The formation of only one reaction product was confirmed (R_f 0.5) by TLC and obtained acetylated compound **3a**. Acetylated **3a**, the IR spectrum still had hydroxyl band (ν_{max} 3495 cm^{-1}) and the high resolution FABMS (pos.) had a peak at *m/z* 213.1483 which was assigned to $[M+H]^+$, characterized its monoacetate. These results indicate metabolite **3** had a primary alcohol. Therefore, metabolite **3** was contained two hydroxyl groups. The proton and carbon NMR spectra were similar to that of the substrate, except for the existence of new methylene group and the disappearance of a methyl group. About the proton NMR, H_B-7 (1.15 ppm) has characteristic coupling constant (J=10.3 Hz) with H_A-7 (1.40 ppm). This was confirmed by assignment of the NMR spectra using two-dimensional techniques (COSY, HMQC, HMBC and NOESY). COSY spectrum indicates correlation cross-peaks were observed between H-4 (1.80–1.77 ppm) and δ 1.40, 1.44 and 1.15 ppm (H_A-7, H-5$_{exo}$ and H_B-7, respectively), H-2$_{exo}$ (3.37 ppm) and δ 1.19 ppm (H-6$_{exo}$; a long distance *W*-coupling J=1.8 Hz). Then, the proton NMR spectrum showed two methyl groups located at δ 1.11 and 0.93 ppm and the two doublets located at δ 3.40 and 3.37 ppm (J=10.5 Hz), latter spectra are characteristic of the new methylene group. In the characteristic HMBC spectrum correlation were observed of C-7 (41.0 ppm) with one methyl group (1.11 ppm; H-10), of C-6 (25.7 ppm) with nonprotonated carbon (48.7 ppm; C-1), of new methylene group with the other nonprotonated carbon (44.6 ppm; C-3). NOESY spectrum indicates correlation cross-peaks were observed between H-5$_{endo}$,6$_{endo}$ (1.73–1.64 ppm, both of them) and one methyl signal at δ 0.93 ppm (H-9), H_A-7 (1.40 ppm) and new methylene group at δ 3.40 and 3.37 ppm (H-8), so that was established. Therefore, metabolite **3** was produced by hydroxylation at the C-8 position of **1**. The specific rotation shows the (+)-form. From the above data, it was concluded that the structure of **3** is (+)-(1*R*,2*R*,3*S*)-8-hydroxyfenchol, which is also a new compound.

It assigned the structure of **3a**, which was confirmed by study of its 2D NMR spectra (COSY, HMQC, HMBC and NOESY).

The third metabolite **4**, the IR spectrum had a widely hydroxyl band (ν_{max} 3343 cm^{-1}) relatively compared with substrate. FABMS (neg.) had a fragmentation at *m/z* 151 which was assigned to $[M-H-H_2O]^+$, however parent ion has not indicate. As the conformation, metabolite **4** was acetylated at room temperature and subsequently examined by TLC. However, reaction was not progress at all (no reaction). Therefore, metabolite **4** was acetylated in the usual manner and obtained acetylated compound **4a**. EIMS data for **4a** had a molecular formula of $C_{14}H_{22}O_4$ ($[M]^+$=254) and the high resolution FABMS (pos.) had a peak at *m/z* 255.1596 which was assigned to $[M+H]^+$, characterized its diacetate. The proton and carbon NMR spectra of **4** were similar to that of the substrate, except for the existence of new methine group and the disappearance of a methylene group. About the proton NMR, evidence for the presence of three methyl groups. As the conformation, assignment of the three methyl signals were achieved by

HMBC and NOESY. In the characteristic HMBC spectrum correlation were observed of C-7 (36.8 ppm) with one methyl group (1.15 ppm; H-10), of C-6 (68.8 ppm) with nonprotonated carbon (53.5 ppm; C-1), of two methyl groups with the other nonprotonated carbon (39.3 ppm; C-3). NOESY spectrum indicates correlation cross-peaks were observed between H-5$_{endo}$,6$_{endo}$ (2.32 and 4.01 ppm, respectively) and one methyl signal at δ 0.85 ppm (H-9), H_A-7 (1.36–1.32 ppm) and the other methyl signal at δ 1.12 ppm (H-8), so that was established. Further, a coupling between H-2$_{exo}$ and H-6$_{exo}$ was disappearance (a long distance *W*-coupling). The above and confirmed by COSY and HMQC, so that configuration of the hydroxyl group at C-6 was *exo*. The specific rotation shows the (−)-form. From these data it was concluded that the structure of **4** is (−)-(1*S*,2*S*,6*S*)-6-*exo*-hydroxyfenchol, which is also a new compound.

It assigned the structure of **4a**, which was confirmed by study of its 2D NMR spectra (COSY, HMQC, HMBC and NOESY).

About metabolite **5**, the IR spectrum had a widely hydroxyl band (ν_{max} 3390 cm^{-1}) relatively compared with substrate. FABMS (neg.) had a fragmentation at *m/z* 151 which was assigned to $[M-H-H_2O]^+$, however parent ion has not indicate. As the conformation, metabolite **5** was acetylated at room temperature and subsequently examined by TLC. The formation of only one reaction product was confirmed (R_f 0.5) by TLC and obtained acetylated compound **5a**. Acetylated **5a**, the IR spectrum still had hydroxyl band (ν_{max} 3484 cm^{-1}) and the high resolution FABMS (pos.) had a peak at *m/z* 213.1479 which was assigned to $[M+H]^+$, characterized its monoacetate. These results indicate metabolite **5** had a primary alcohol. Therefore, metabolite **5** was contained two hydroxyl groups. The proton and carbon NMR spectra were similar to that of the substrate, except for the existence of new methylene group and the disappearance of a methyl group. About the proton NMR, H_B-7 (1.16 ppm) has characteristic coupling constant (J=10.3 Hz) with H_A-7 (1.50 ppm). This was confirmed by assignment of the NMR spectra using two-dimensional techniques (COSY, HMQC, HMBC and NOESY). COSY spectrum indicates correlation cross-peaks were observed between H-4 (1.74–1.72 ppm) and δ 1.50, 1.40 and 1.16 ppm (H_A-7, H-5$_{exo}$ and H_B-7, respectively), H-2$_{exo}$ (3.42 ppm) and δ 1.07 ppm (H-6$_{exo}$; a long distance *W*-coupling J=1.7 Hz). Then, the proton NMR spectrum showed two methyl groups located at δ 1.10 and 1.09 ppm and the two doublets located at δ 3.93 and 3.34 ppm (J=10.6 Hz), latter spectra are characteristic of the new methylene group. In the characteristic HMBC spectrum correlation were observed of C-7 (41.9 ppm) with one methyl group (1.09 ppm; H-10), of C-6 (25.2 ppm) with nonprotonated carbon (49.5 ppm; C-1), of new methylene group with the other nonprotonated carbon (43.4 ppm; C-3). NOESY spectrum indicates correlation cross-peaks were observed between H-5$_{endo}$, 6$_{endo}$ (1.62 and 1.80 ppm, respectively) and new methylene group at δ 3.93 and 3.34 ppm (H-9), H_A-7 (1.50 ppm) and one methyl signal at δ 1.10 ppm (H-8), so that was established. Therefore, metabolite **5** was produced by hydroxylation at the C-9 position of **1**. The specific rotation shows the (−)-form. From the above date, it was concluded that the structure of **5** is (−)-(1*R*,2*R*,3*R*)-9-hydroxyfenchol, which are reported in the literature,[6–8] however, they have not been published about completion assigned of structure and absolute stereochemistry.

It assigned the structure of **5a**, which was confirmed by study of its 2D NMR spectra (COSY, HMQC, HMBC and NOESY).

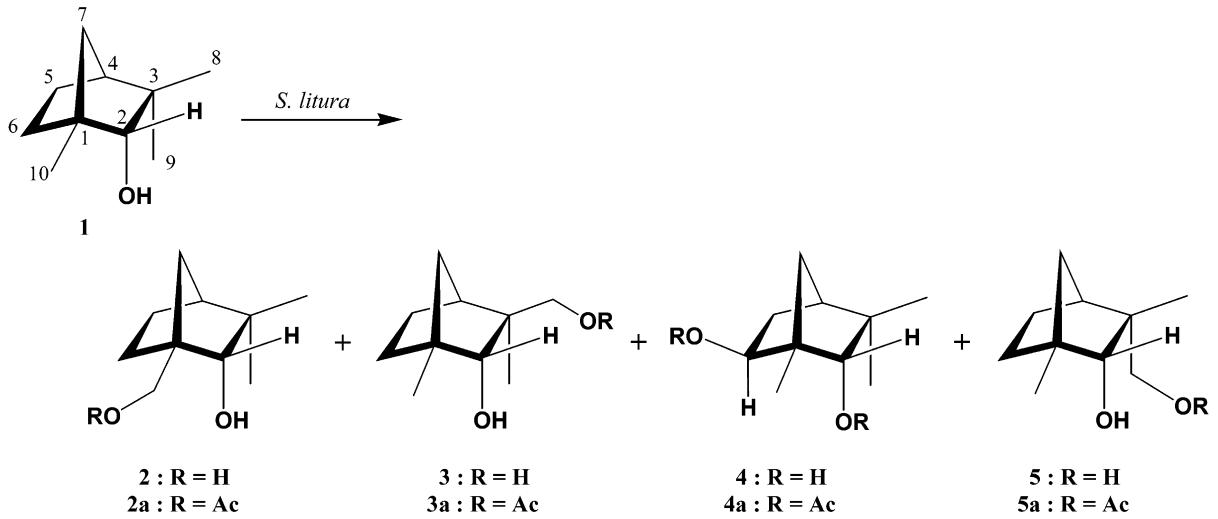
A previous paper described the participation of aerobically and anaerobically active intestinal bacteria in the metabolism of α-terpinene.[1] In the present study, the in vitro metabolism of **1** by intestinal bacteria was also examined in a manner similar to that of the previous paper.[1–3] However, substrate **1** was not metabolized at all (no reaction) both aerobic and anaerobic condition. These results suggested that the intestinal bacteria did not participate in the metabolism of **1**. The difference of reaction between **1** and α-terpinene was suggested to be due to the difference of substrate.

In the present study of biotransformation of **1**, the reaction was used the enzymatic activity which the larvae of *S. litura* possess. There are no reports on the biotransformation of **1** by biocatalysts, which is the new reaction. The larvae transformed **1** to mainly **2** (52.4%), **3** (18.6%), **4** (15.5%) and **5** (4.0%) (Scheme 1, Table 1). These results suggested that regioselective hydroxylation was progress in the metabolism of **1** by the larvae of *S. litura*. In this case, compound **1** is hydroxylated at C-6-*exo* position and methyl group of geminal dimethyl and C-10 position. These results indicate that the larvae of *S. litura* recognized the methyl groups and C-10 position of compound **1** being high degree of efficiency.

3. Experimental

3.1. General procedures

Thin-layer chromatography (TLC) was performed on precoated plates [silica gel 60 F_{254}, 0.25 mm (Merck)]. The solvent system was hexane–ethylacetate (1:1). Compounds were visualized by spraying plates with 1% vanillin in 96% sulfuric acid followed by brief heating. GC was performed on a Hewlett–Packard 5890A gas chromatograph equipped with a flame ionization detector (FID). The column was a fused silica capillary column (DB-5, 30 m length, 0.25 mm i.d.). Chromatographic conditions were as follows: oven temperature was programmed from 80 to 240 °C at 4 °C/min; injector and detector temperatures were 270 and 280 °C, respectively; split injection of 25:1; carrier gas, Helium at a flow rate of 30.0 cm/s. The peak area was integrated with a Hewlett–Packard HP3396 series II integrator. EIMS measurements were obtained using gas chromatography-mass spectrometry (GC–MS). GC–MS was performed on a Hewlett–Packard 5972A mass selective detector interfaced with a Hewlett–Packard 5890A gas chromatograph fitted with a capillary column (HP-5MS, 30 m length, 0.25 mm i.d.). Chromatographic condition were the same as described above. The temperature of the ion source was 230 °C, and the electron energy was 70 eV.



Scheme 1. The biotransformation of (+)-fenchol (**1**) by the larvae of *S. litura*.

FABMS was obtained on a JEOL the Tanden MStation JMS-700TKM. The IR spectra were obtained with a JASCO FT/IR-470 plus Fourier transform infrared spectrometer. $CHCl_3$ was used as a solvent. The NMR spectra were obtained with a JEOL FX-500 (500.00 MHz, ^1H; 125.65 MHz, ^{13}C) spectrometer. Tetramethylsilane (TMS) was used as the internal standard (δ 0.00) for ^1H NMR spectra measured in $CDCl_3$. Residual $CHCl_3$ was used as internal reference (δ 77.00) for ^{13}C NMR spectra measured in $CDCl_3$. Multiplicities were determined by the DEPT pulse sequence. The specific rotations were measured on a JASCO DIP-1000 digital polarimeter.

3.2. Rearing of larvae

Spodoptera litura used in this study were obtained from Nissan Kagaku. It is getting to change the generation every biotransformation. The larvae of *S. litura* were reared in plastic cases (200×300 mm wide, 100 mm high, 200 larvae/case) covered with a nylon mesh screen. The rearing conditions were as follows: 25 °C, 70% relative humidity, and 16:8 L:D (light:dark) photoperiod. A commercial diet (Insecta LFS; Nihon Nosan Kogyo) was given to the larvae from the first instar. From the fourth instar, the diet was changed to an artificial diet composed of kidney beans (100 g), agar (12 g), and water (600 mL).[11]

3.3. Chemical compounds

(+)-(1*R*,2*S*)-Fenchol **1** was purchased from Fluka. It structure was characterized by ^1H NMR, ^{13}C NMR, specific rotation and MS spectra. The purity of this compound was judged to be >99% on analysis with GC–MS.

3.4. Administration of substrate

The artificial diet without the agar was mixed with a blender. Substrate **1** (3000 mg) was then added directly into the blender. Agar was dissolved in water and boiled and then added into the blender. The diet was then mixed and cooled in a stainless steel tray (220×310 mm wide, 30 mm high). The diet containing **1** was stored in a refrigerator until the time of administration. The fourth to fifth instar larvae (average weight=0.5 g) were moved into new cases (100 larvae/case), and the diet was fed to the larvae in limited amounts. Groups of 800 larvae were fed the diet containing **1** (actually 1.4 g, about 1.75 mg for a body) for 2 days, and then the artificial diet not containing **1** was fed to the larvae for an additional 2 days. Frass was collected every five hours (total of 4 days) and stored in a solution of diethylether (300 mL). For diet and frass separation, the fresh frass was extracted as soon as the fourth to fifth instar larvae excreted.

3.5. Isolation and identification of metabolites from frass

The frass were extracted by diethylether (300 mL×2) and then ethylacetate (300 mL×2). Diethylether and ethylacetate extracts were mixed, the solvent was evaporated under reduced pressure, and 2992 mg of extract was obtained. The extract was dissolved in ethylacetate, and then was added to the 5% $NaHCO_3$ solution. After shaking, neutral fraction (1684 mg) was obtained from the ethylacetate layer. The aqueous layer (acidic fraction) was separated, then acidified with 1 N HCl, and extracted with ethylacetate. After shaking, acidic fraction (939 mg) was obtained from the aqueous layer. The neutral fraction was analyzed by GC–MS; metabolites **2**, **3**, **4** and **5** occurred in this fraction. The acidic fraction was reacted with ethereal CH_2N_2 overnight and subsequently examined by GC–MS, but methylated metabolites did not exist. The neutral fraction was subjected to silica gel open-column chromatography (silica gel 60, 230–400 mesh, Merck) with a 9:1 hexane/ethylacetate solvent system, and four major metabolites **2** (502 mg), **3** (178 mg), **4** (148 mg) and **5** (38 mg) was isolated.

3.5.1. (1*R*,2*S*)-10-Hydroxyfenchol (2). (+)-(1*R*,2*S*)-1-Hydroxymethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol; colorless viscous oil; $[\alpha]_D^{24.4}$ +15.5° ($CHCl_3$, *c* 0.66); FABMS (neg.), *m/z* 151 $[M-H-H_2O]^+$; EI-MS, *m/z* (rel. intensity) 137 $[M-H_2O-CH_3]^+$ (2), 134 $[M-2H_2O]^+$ (0.5), 127 (0.5), 121 (6), 115 (0.5), 109 (11), 105 (2), 103 (0.5), 95 (7), 93 (7), 87 (9), 81 (100), 80 (36), 79 (20), 77 (7), 72 (33), 69 (26), 67 (20), 57 (15), 55 (18), 43 (22), 41 (34); IR (KBr, ν_{max}, cm^{-1}) 3385, 2956, 1073; ^1H NMR ($CDCl_3$) δ

0.87 (3H, s, H-9), 1.01 (3H, s, H-8), 1.09 (1H, dd, J=1.8, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.15 (1H, dddd, J=1.8, 3.3, 12.3, 12.5 Hz, H-6$_{exo}$), 1.44 (1H, dddd, J=4.0, 6.0, 12.3, 12.5 Hz, H-5$_{exo}$), 1.48 (1H, dddd, J=2.0, 2.2, 2.8, 10.3 Hz, H_A-7; nearly C-2,3 position), 1.73 (1H, dddd, J=2.8, 3.3, 9.1, 12.3 Hz, H-5$_{endo}$), 1.74–1.77 (1H, m, H-4), 1.87 (1H, dddd, J=2.2, 6.0, 9.1, 12.3 Hz, H-6$_{endo}$), 3.62 (1H, d, J=1.8 Hz, H-2$_{exo}$), 3.74 (1H, d, J=10.6 Hz, H-10), 3.82 (1H, d, J=10.6 Hz, H-10′); ^{13}C NMR see Table 2.

Acetylation of **2**. Pyridine (1.0 mL) was added to a solution of **2** (8 mg) in acetic anhydride (18 mL), and the solution was stirred for 4 h at room temp (25 °C). The products were isolated in the usual manner and separated by silica gel column chromatography with a hexane–ethylacetate solvent system. The monoacetate **2a** (7 mg) was obtained.

(1*R*,2*S*)-10-Acetoxyfenchol (**2a**). (−)-(1*R*,2*S*)-1-Acetoxymethyl-3,3-dimethylbicyclo [2.2.1]heptan-2-ol; colorless viscous oil; $[\alpha]_D^{25.3}$ −4.1° ($CHCl_3$, *c* 1.54); HRFAB-MS (pos.), *m*/*z* 213.1509 $[M+H]^+$, calcd for $C_{12}H_{21}O_3$, 213.1491; EI-MS, *m*/*z* (rel. intensity) 212 $[M]^+$ (0.5), 194 $[M-H_2O]^+$ (0.5), 170 $[M-CH_2CO]^+$ (2), 169 (17), 152 $[M-CH_3COOH]^+$ (20), 137 (7), 134 (18), 129 (4), 123 (14), 121 (16), 109 (38), 95 (16), 91 (17), 81 (100), 80 (43), 79 (38) 77 (15), 72 (58), 69 (27), 67 (32), 55 (20); IR (KBr, ν_{max}, cm^{-1}) 3497, 2959, 1722, 1462, 1364, 1259, 1034; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, s, H-9), 1.01 (3H, s, H-8), 1.09–1.15 (1H, m, H-6$_{exo}$), 1.14 (1H, dd, J=2.0, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.39–1.48 (1H, m, H-5$_{exo}$), 1.58 (1H, dddd, J=1.9, 2.0, 2.5, 10.3 Hz, H_A-7; nearly C-2,3 position), 1.70–1.79 (2H, m, H-5$_{endo}$, 6$_{endo}$), 1.78–1.80 (1H, m, H-4), 2.08 (3H, s, 10-OCO*Me*), 3.46 (1H, dd, J=1.6, 3.8 Hz, H-2$_{exo}$), 4.04 (1H, d, J=11.4 Hz, H-10), 4.29 (1H, d, J=11.4 Hz, H-10′); ^{13}C NMR see Table 2.

3.5.2. (1*R*,2*R*,3*S*)-8-Hydroxyfenchol (3). (+)-(1*R*,2*R*,3*S*)-3-Hydroxymethyl-1,3-dimethylbicyclo[2.2.1]heptan-2-ol; colorless amorphous crystals; $[\alpha]_D^{24.2}$ +9.7° ($CHCl_3$, *c* 1.21); FABMS (neg.), *m*/*z* 151 $[M-H-H_2O]^+$; EI-MS, *m*/*z* (rel. intensity) 152 $[M-H_2O]^+$ (2), 139 (2), 137 [152-CH_3]$^+$ (5), 123 (4), 121 [139-H_2O]$^+$ (7), 109 (7), 108 (4), 95 (9), 93 (6), 81 (100), 80 (21), 79 (13), 71 (6), 69 (17), 55 (16), 43 (20), 41 (21); IR (KBr, ν_{max}, cm^{-1}) 3339, 2950, 1025; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, s, H-9), 1.08 (1H, dddd, J=1.8, 5.1, 7.6, 12.0 Hz, H-6$_{exo}$), 1.11 (3H, s, H-10), 1.15 (1H, dd, J=1.7, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.39 (1H, dddd, J=2.1, 2.2, 2.7, 10.3 Hz, H_A-7; nearly C-2,3 position), 1.41–1.50 (1H, m, H-5$_{exo}$), 1.64–1.73 (2H, m, H-5$_{endo}$, 6$_{endo}$), 1.77–1.80 (1H, m, H-4), 3.37 (1H, d, J=1.8 Hz, H-2$_{exo}$), 3.37 (1H, d, J=10.5 Hz, H-8), 3.40 (1H, d, J=10.5 Hz, H-8′); ^{13}C NMR see Table 2.

Acetylation of **3**. Pyridine (1.0 mL) was added to a solution of **3** (10 mg) in acetic anhydride (18 mL), and the solution was stirred for 4 h at room temp (25 °C). The products were isolated in the usual manner and separated by silica gel column chromatography with a hexane–ethylacetate solvent system. The monoacetate **3a** (9 mg) was obtained.

(1*R*,2*R*,3*S*)-8-Acetoxyfenchol (**3a**). (−)-(1*R*,2*R*,3*S*)-3-Acetoxymethyl-1,3-dimethylbicyclo [2.2.1]heptan-2-ol; colorless viscous oil; $[\alpha]_D^{25.8}$ −4.3° ($CHCl_3$, *c* 0.52); HRFAB-MS (pos.), *m*/*z* 213.1483 $[M+H]^+$, calcd for $C_{12}H_{21}O_3$, 213.1491; EI-MS, *m*/*z* (rel. intensity) 152 $[M-CH_3COOH]^+$ (4), 137 [152-CH_3]$^+$ (15), 123 (6), 121 (6), 109 (9), 95 (7), 93 (6), 81 (100), 80 (9), 79 (9), 69 (13), 67 (13), 55 (10); IR (KBr, ν_{max}, cm^{-1}) 3495, 2952, 1740, 1465, 1375, 1246, 1033; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, s, H-9), 1.04–1.12 (1H, m, H-6$_{exo}$), 1.11 (3H, s, H-10), 1.19 (1H, dd, J=1.6, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.43 (1H, dddd, J=1.4, 2.2, 2.4, 10.3 Hz, H_A-7; nearly C-2,3 position), 1.43–1.52 (1H, m, H-5$_{exo}$), 1.63–1.72 (2H, m, H-5$_{endo}$, 6$_{endo}$), 1.96–1.99 (1H, m, H-4), 2.08 (3H, s, 8-OCO*Me*), 3.33 (1H, d, J=1.8 Hz, H-2$_{exo}$), 3.83 (1H, d, J=10.9 Hz, H-8), 3.86 (1H, d, J=10.9 Hz, H-8′); ^{13}C NMR see Table 2.

3.5.3. (1*S*,2*S*,6*S*)-6-*exo*-Hydroxyfenchol (4). (+)-(1*S*,2*S*,6*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2,6-diol; white amorphous crystals; $[\alpha]_D^{25.0}$ −4.4° ($CHCl_3$, *c* 0.42); FABMS (neg.), *m*/*z* 151 $[M-H-H_2O]^+$; EI-MS, *m*/*z* (rel. intensity) 155 $[M-CH_3]^+$ (18), 152 $[M-H_2O]^+$ (15), 137 (20), 126

Table 2. ^{13}C NMR spectral data for (+)-fenchol (**1**) and their metabolites (**2**-**5**) and derivatives (**2a**-**5a**) (125.65 MHz, $CDCl_3$)

Carbon	Compounds							
	2	**2a**	**3**	**3a**	**4**	**4a**	**5**	**5a**
1	54.1 (s)	52.7 (s)	48.7 (s)	48.8 (s)	53.5 (s)	51.6 (s)	49.5 (s)	49.1 (s)
2	83.4 (d)	80.5 (d)	80.3 (d)	80.3 (d)	84.9 (d)	85.1 (d)	85.8 (d)	85.0 (d)
3	39.4 (s)	38.9 (s)	44.6 (s)	42.9 (s)	39.3 (s)	39.4 (s)	43.4 (s)	42.1 (s)
4	48.1 (d)	47.8 (d)	43.4 (d)	43.5 (d)	46.9 (d)	47.2 (d)	46.1 (d)	45.8 (d)
5	25.6 (t)	25.3 (t)	26.0 (t)	25.8 (t)	38.6 (t)	36.5 (t)	25.4 (t)	25.6 (t)
6	21.7 (t)	21.3 (t)	25.7 (t)	25.5 (t)	68.8 (d)	72.8 (d)	25.2 (t)[a]	25.1 (t)
7	36.6 (t)	36.9 (t)	41.0 (t)	40.8 (t)	36.8 (t)	38.0 (t)	41.9 (t)	41.3 (t)
8	30.6 (q)	30.6 (q)	71.8 (t)	72.1 (t)	30.6 (q)	29.5 (q)	25.2 (q)[b]	25.2 (q)
9	20.0 (q)	20.0 (q)	15.1 (q)	15.6 (q)	20.0 (q)	19.8 (q)	66.7 (t)	67.8 (t)
10	68.2 (t)	67.0 (t)	19.3 (q)	19.2 (q)	14.8 (q)	14.7 (q)	19.1 (q)	19.0 (q)
CO*Me*		20.9 (q)		21.0 (q)		20.8 (q)[c]		21.0 (q)
*C*OMe		171.5 (s)		171.6 (s)		171.3 (s)[c]		171.4 (s)
CO*Me*						21.2[d]		
*C*OMe						170.8 (s)[d]		

[a] 25.20 ppm.
[b] 25.23 ppm.
[c] C-2 position.
[d] C-6 position.

(14), 121 (52), 119 (6), 111 (29), 109 (35), 97 (41), 95 (23), 81 (93), 80 (76), 72 (51), 69 (40), 65 (9), 57 (41), 55 (53), 43 (100), 41 (86); IR (KBr, ν_{max}, cm^{-1}) 3343, 2948, 1054; ^1H NMR ($CDCl_3$) δ 0.85 (3H, s, H-9), 1.02 (3H, s, H-8), 1.15 (3H, s, H-10), 1.21 (1H, ddd, J=3.8, 4.0, 13.5 Hz, H-5_{exo}), 1.32–1.36 (1H, m, H_A-7; nearly C-2,3 position), 1.38 (1H, dd, J=1.5, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.68–1.73 (1H, m, H-4), 2.32 (1H, ddd, J=2.3, 7.2, 13.5 Hz, H-5_{endo}), 3.37 (1H, s, H-2_{exo}), 4.01 (1H, ddd, J=0.9, 3.8, 7.2 Hz, H-6_{endo}); ^{13}C NMR see Table 2.

Acetylation of **4**. Pyridine (2.0 mL) was added to a solution of **4** (5 mg) in acetic anhydride (30 mL), and the solution was refluxed for 5 h. The products were isolated in the usual manner and separated by silica gel column chromatography with a hexane–ethylacetate solvent system. The diacetate **4a** (4 mg) was obtained.

(1*S*,2*S*,6*S*)-2,6-Diacetoxyfenchol (**4a**). (−)-(1*S*,2*S*,6*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2,6-diacetate; colorless viscous oil; $[\alpha]_D^{25.3}$ −15.6° ($CHCl_3$, *c* 0.18); HRFAB-MS (pos.), *m/z* 255.1596 $[M+H]^+$, calcd for $C_{14}H_{23}O_4$, 255.1597; EI-MS, *m/z* (rel. intensity) 254 $[M]^+$ (0.5), 212 $[M-CH_2CO]^+$ (7), 194 $[M-CH_3COOH]^+$ (4), 179 (0.5), 170 $[212-CH_2CO]^+$ (0.5), 152 (18), 137 (10), 123 (18), 114 (31), 109 (24), 108 (26), 97 (13), 93 (13), 81 (93), 80 (100), 72 (26), 69 (27), 55 (13); IR (KBr, ν_{max}, cm^{-1}) 2961, 1740, 1463, 1375, 1238; ^1H NMR ($CDCl_3$) δ 0.78 (3H, s, H-9), 1.05 (3H, s, H-10), 1.14 (3H, s, H-8), 1.30 (1H, ddd, J=3.8, 4.1, 13.8 Hz, H-5_{exo}), 1.50 (1H, ddd, J=1.5, 10.6 Hz, H_B-7; nearly C-5,6 position), 1.56 (1H, dddd, J=1.2, 1.5, 2.9, 10.6 Hz, H_A-7; nearly C-2,3 position), 1.76–1.78 (1H, m, H-4), 2.04 (3H, s, 6-OCO*Me*), 2.08 (3H, s, 2-OCO*Me*), 2.41 (1H, ddd, J=2.9, 7.2, 13.8 Hz, H-5_{endo}), 4.46 (1H, s, H-2_{exo}), 5.02 (1H, ddd, J=1.2, 3.8, 7.2 Hz, H-6_{endo}); ^{13}C NMR see Table 2.

3.5.4. (1*R*,2*R*,3*R*)-9-Hydroxyfenchol (5). (−)-(1*R*,2*R*,3*R*)-3-Hydroxymethyl-1,3-dimethylbicyclo[2.2.1]heptan-2-ol; colorless amorphous crystals; $[\alpha]_D^{26.1}$ −19.0° ($CHCl_3$, *c* 0.40), [$[\alpha]_D^{28.5}$ −21.2° $CHCl_3$, *c* 2.8[6,7]; $[\alpha]_D^{20}$ −23° $CHCl_3$, *c* 3.0[8]]; FABMS (neg.), *m/z* 151 $[M-H-H_2O]^+$; EI-MS, *m/z* (rel. intensity) 152 $[M-H_2O]^+$ (0.5), 137 $[152-CH_3]^+$ (5), 123 (4), 121 (5), 109 (6), 108 (5), 95 (6), 93 (6), 81 (100), 80 (18), 79 (11), 71 (6), 69 (16), 67 (15), 55 (13), 53 (6), 43 (16), 41 (18); IR (KBr, ν_{max}, cm^{-1}) 3390, 2926, 1067; ^1H NMR ($CDCl_3$) δ 1.07 (1H, dddd, J=1.7, 3.2, 12.6, 12.6 Hz, H-6_{exo}), 1.09 (3H, s, H-10), 1.10 (3H, s, H-8), 1.16 (1H, dd, J=1.6, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.40 (1H, dddd, J=4.1, 6.3, 12.6, 12.6 Hz, H-5_{exo}), 1.50 (1H, dddd, J=2.0, 2.2, 2.9, 10.3 Hz, H_A-7; nearly C-2,3 position), 1.62 (1H, dddd, J=2.9, 3.2, 8.6, 12.6 Hz, H-5_{endo}), 1.72–1.74 (1H, m, H-4), 1.80 (1H, dddd, J=2.0, 6.3, 8.6, 12.6 Hz, H-6_{endo}), 3.34 (1H, d, J=10.6 Hz, H-9), 3.42 (1H, d, J=1.7 Hz, H-2_{exo}), 3.93 (1H, d, J=10.6 Hz, H-9′); ^{13}C NMR see Table 2.

Acetylation of **5**. Pyridine (1.0 mL) was added to a solution of **5** (5 mg) in acetic anhydride (18 mL), and the solution was stirred for 4 h at room temp (25 °C). The products were isolated in the usual manner and separated by silica gel column chromatography with a hexane–ethylacetate solvent system. The monoacetate **5a** (4 mg) was obtained.

(1*R*,2*R*,3*R*)-9-Acetoxyfenchol (**5a**). (+)-(1*R*,2*R*,3*R*)-3-Acetoxymethyl-1,3-dimethylbicyclo [2.2.1]heptan-2-ol; colorless amorphous crystals; $[\alpha]_D^{26.1}$ +6.4° ($CHCl_3$, *c* 0.19); HRFAB-MS (pos.), *m/z* 213.1479 $[M+H]^+$, calcd for $C_{12}H_{21}O_3$, 213.1491; EI-MS, *m/z* (rel. intensity) 152 $[M-CH_3COOH]^+$ (4), 137 $[152-CH_3]^+$ (6), 123 (6), 121 (5), 109 (6), 95 (6), 93 (6), 81 (100), 80 (17), 79 (8), 69 (13), 67 (13), 55 (9); IR (KBr, ν_{max}, cm^{-1}) 3484, 2954, 1720, 1460, 1373, 1248, 1034; ^1H NMR ($CDCl_3$) δ 1.04 (3H, s, H-8), 1.07 (1H, dddd, J=1.7, 3.4, 12.5, 12.6 Hz, H-6_{exo}), 1.10 (3H, s, H-10), 1.19 (1H, dd, J=1.7, 10.3 Hz, H_B-7; nearly C-5,6 position), 1.46 (1H, dddd, J=4.0, 6.1, 12.5, 12.6 Hz, H-5_{exo}), 1.47–1.51 (1H, m, H_A-7; nearly C-2,3 position), 1.57 (1H, dddd, J=2.9, 3.4, 8.9, 12.6 Hz, H-5_{endo}), 1.77 (1H, dddd, J=2.3, 6.1, 8.9, 12.6 Hz, H-6_{endo}), 1.83–1.85 (1H, m, H-4), 2.06 (3H, s, 9-OCO*Me*), 3.39–3.41 (1H, m, H-2_{exo}), 4.05 (1H, d, J=11.3 Hz, H-9), 4.10 (1H, d, J=11.3 Hz, H-9′); ^{13}C NMR see Table 2.

3.6. Incubation of intestinal bacteria

This experiment was intentionally carried out under sterile conditions. Petri dishes, pipets, and solutions were autoclaved. A GAM Broth (Nissui Pharmaceutical) was adjusted to pH 8.9 and placed in Petri dishes at 10 mL/Petri dish. The fresh frass (5 g) of the fourth to fifth instar larvae were suspended in physiological saline (100 mL), and the suspension (1 mL) was pipetted in the medium. The medium without frass was also prepared for a blank experiment. These media were incubated (20 °C, darkness, 2 days) under aerobic and anaerobic conditions. After growth of bacteria, substrate **1** (0.3 mg/mL) was added to the medium and the incubation was continued. The medium was distributed between ethylacetate and saturated solution of salt. The ethylacetate layer was evaporated under reduced pressure, and the extract was obtained. For the quantitative analysis of metabolites, the GC analysis was used as an internal standard with **1**.

References and notes

1. Miyazawa, M.; Wada, T.; Kameoka, H. *J. Agric. Food Chem.* **1996**, *44*, 2889–2893.
2. Miyazawa, M.; Murata, T. *J. Agric. Food Chem.* **2000**, *48*, 123–125.
3. Miyazawa, M.; Ohsawa, M. *J. Agric. Food Chem.* **2002**, *50*, 4916–4918.
4. Miyazawa, M.; Kasahara, H. *Phytochemistry* **1995**, *39*, 1027–1030.
5. Miyazawa, M.; Kasahara, H. *Nat. Prod. Lett.* **1996**, *8*, 87–88.
6. Bosworth, N.; Magnus, P. D. *Chem. Commun.* **1971**, *12*, 618–619.
7. Bosworth, N.; Magnus, P. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, *7*, 943–948.
8. Grison, C.; Bessiere-Chretion, Y. *Bull. Soc. Chim.* **1972**, *12*, 4570–4575.
9. Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Ruiz, P. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1737–1745.
10. Cocker, W.; Gordon, R. L.; Shannon, P. V. R. *J. Chem. Res. (S)* **1985**, *6*, 172–173.
11. Yushima, K.; Kamano, S.; Tamaki, Y. *Rearing methods of insects*. Japan Plant Protection Association: Tokyo, 1991; pp 214–218.

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Synthesis of a complementary dimer from mono(imidazolyl)-substituted cobalt(II) porphyrin as a new artificial T-form hemoglobin

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Abstract—Mono(imidazolyl)-substituted Co(II) porphyrin dimer with a 'picket fence' structure was synthesized as a new artificial hemoglobin model containing two binding sites. The dimer was confirmed by UV–vis, resonance Raman and ESR spectral measurements to bind two dioxygen molecules reversibly. The dioxygen binding affinity of the dimer was lower than that of the corresponding monomer. The decrease in this affinity is discussed in terms of steric hindrance and orientational effect of the axial ligand.

1. Introduction

We have reported previously that zincporphyrin having an imidazolyl group at the *meso* position could form a complementary dimer, where each imidazolyl group was coordinated to the Zn(II) ion of the other porphyrin in a slipped cofacial arrangement.[1] This coordination organization was sufficiently strong that the stability constant was estimated to be $10^{10}\,M^{-1}$ in $CHCl_3$, and the dimer was the structural and functional mimic of the special pair in the reaction center of bacterial photosynthesis.[1,2] The aim of this research is to use the complementary dimer of mono(imidazolyl)-substituted Co(II) porphyrin as a dioxygen carrier with two binding sites in a molecule that mimics the multi-binding sites of hemoglobin. The creation of a 'picket fence' Co(II) porphyrin, *meso*-tetrakis(α,α,α,α-*o*-pivalamidophenyl)porphyrinatocobalt(II), $Co^{II}Piv_4P$, has opened an ingenious approach to reversible dioxygen binding even at room temperature by sterically blocking the formation of the μ-oxo dimer and stabilizing the dioxygen adduct through hydrogen bonding in the picket fence cavity.[3–8]

In this report, complementary dimer formation was combined with the picket fence strategy to prepare a *meso*-[mono(2-imidazolyl)-tris(α,α,α-*o*-pivalamidophenyl)]porphyrinatocobalt(II) dimer, **5D**, $(Co^{II}Piv_3ImP)_2$ (Scheme 1). Some dioxygen carrier models, which provided two binding sites from a porphyrin dimer, have been reported in the literature. Examples include gable porphyrin,[9] dimeric picket fence porphyrin,[10] Traylor's porphyrin system,[11] and 'looping-over' porphyrin systems.[12] The new model described in this report is different from these dimeric models with regard to two structural points. Gable porphyrin and dimeric picket fence porphyrin systems require the addition of excess bidentate bases as axial ligands. On the other hand, dimer **5D** does not need the addition of external axial ligands in a similar way to looping-over porphyrin systems. Axial ligands are provided from another imidazolyl-substituted porphyrin component of the complementary dimer, and dioxygen binding sites can be constructed solely from the porphyrin component. The addition of excess external axial ligand frequently causes oxidation of Co(II) porphyrin. This factor also favors the model reported in this report. Secondly, the distance between the two porphyrin components of dimer **5D** is shorter than that of looping-over porphyrin systems, and is the shortest among the various dimer models reported. Based on these considerations, dimer **5D** was expected to be a new dioxygen carrier model with two binding sites in immediate proximity to the molecule.

In this paper, the reversible binding of two dioxygen molecules to two binding sites of dimer **5D** at low temperature is reported. Although the oxygen affinity of dimer **5D** was significantly decreased compared with the monomer, this novel dimer **5D** could be regarded as a T-form model of hemoglobin.

Keywords: Artificial hemoglobin; Porphyrin dimer; Picket fence cobalt porphyrin; Dioxygen binding; Oxygen affinity.
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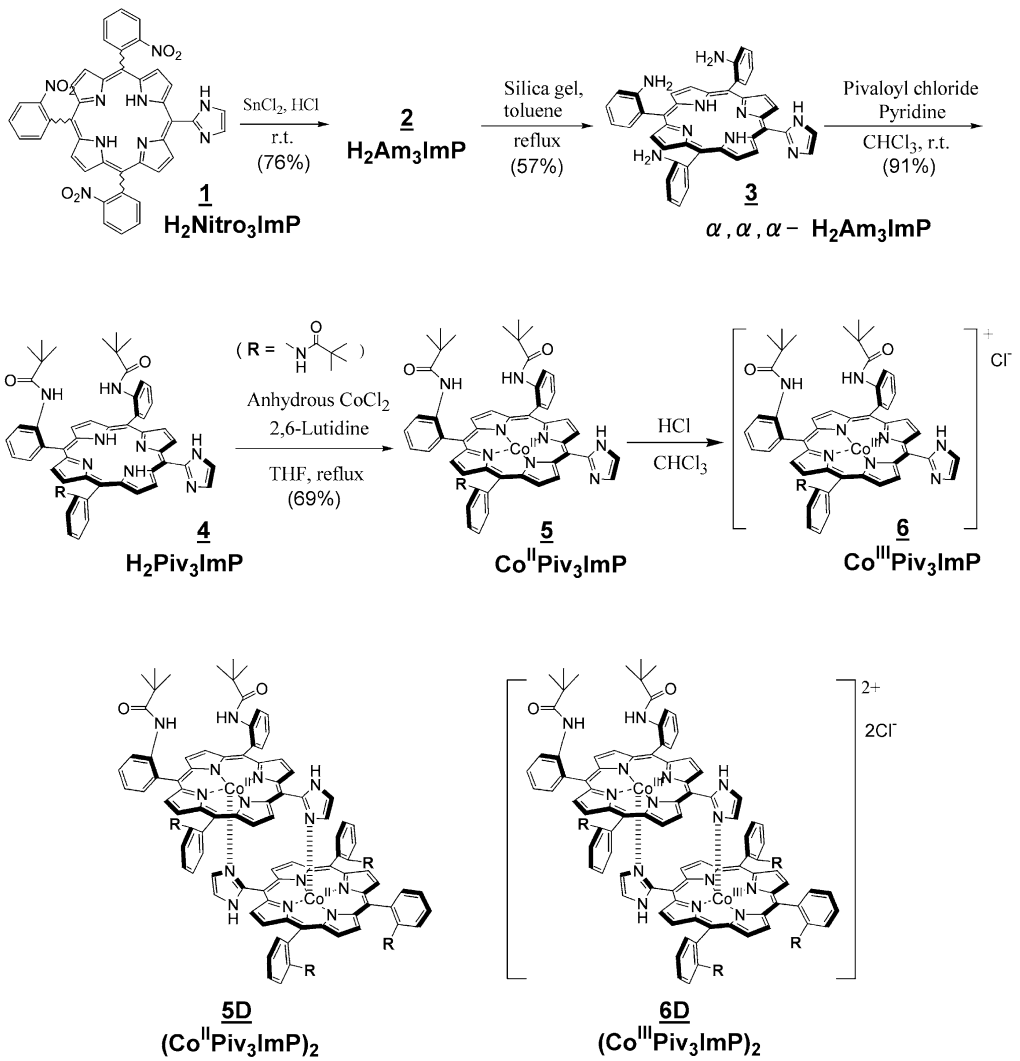


Scheme 1. Synthetic route to mono(imidazolyl)-substituted Co(II) porphyrin with a picket fence structure.

2. Results and discussion

2.1. Synthesis

Synthetic routes to mono(imidazolyl)-substituted picket fence Co(II) porphyrin **5**, $Co^{II}Piv_3ImP$, were referenced to the synthesis of picket fence porphyrins,[5,6] as is shown in Scheme 1. The starting porphyrin, 5-(2-imidazolyl)-10,15,20-tris(*o*-nitrophenyl)porphyrin, **1**, H_2Nitro_3ImP was obtained by the annelation reaction from pyrrole, 2-nitorobenzaldehyde, and imidazole-2-carboxaldehyde[13] (in a ratio of 3:2:1), in 8% yield. H_2Nitro_3ImP was reduced to aminophenylporphyrin, **2**, H_2Am_3ImP, by $SnCl_2{\cdot}2H_2O$ in conc. HCl at room temperature. The reduction of *meso*-tetrakis(*o*-nitrophenyl)porphyrin, H_2Nitro_4P, to *meso*-tetrakis(*o*-aminophenyl)porphyrin, H_2Am_4P, was effected by heating at 65–70 °C, following literature methods.[5] However, the same approach could not be applied to the reduction of H_2Nitro_3ImP, **1**. MALDI-TOF mass spectroscopy of the product obtained at 65–70 °C suggested over-reduction, and the UV–vis spectrum did not show the expected pattern of Soret and Q bands. Accordingly, the adduct was kept at room temperature for 30 min and the resulting product gave the mass $(M+H)^+$ in the MALDI-TOF mass spectrum, and the Soret and Q bands of the UV–vis spectrum were those expected of H_2Am_4P. H_2Am_3ImP, **2**, was obtained in 56% yield as a mixture of three atropisomers assigned tentatively as α,α,β-, α,β,α- and α,α,α-isomers. The mixture of atropisomers was isomerized to α,α,α-H_2Am_3ImP, **3**, by refluxing with silica gel in toluene under Ar.[14] The conversion of atropisomers was monitored by thin-layer chromatography on silica gel (TLC) (eluent $CHCl_3$/MeOH, 9:1) and reversed-phase high performance liquid chromatography (HPLC) (column TSK-gel Octadecyl-4PW (TOSHO); eluent MeOH/H_2O, 9:1, 0.8 mL/min). Before the reaction, one spot appeared at R_f=0.55 in TLC, and three peaks were detected in HPLC at 3.6, 3.9 and 6.2 min (in a ratio of about 5:5:1). After the reaction, the spot at R_f=0.55 disappeared almost completely and a new spot at R_f=0.50 appeared on the TLC, and in the HPLC, the two peaks at 3.6 and 3.9 min decreased and the peak at 6.2 min increased notably (in a ratio of about 1:4:20). The new compound, which appeared as a spot at R_f=0.50 in TLC with a retention time of 6.2 min in HPLC, was assigned as the α,α,α-isomer. The TLC spot at R_f=0.50 was the most polar product among three atropisomers, as expected from molecular dipole considerations by analogy with α,α,αα-H_2Am_4P.[5] The reason for the polarity reversal

in the reversed-phase HPLC against the TLC is not known. α,α,α-H_2Am_3ImP, **3**, was purified by silica gel column chromatography to give the product in 57% yield, and then this was reacted with pivaloyl chloride according to established methods.[5] As a result, monoimidazolyl picket fence porphyrin, H_2Piv_3ImP, **4**, was obtained in 88% yield, and treated with anhydrous $CoCl_2$ and 2,6-lutidine[6] to afford $Co^{II}Piv_3ImP$, **5**. $Co^{II}Piv_3ImP$ was oxidized to $Co^{III}Piv_3ImP$, **6**, by treatment with dilute HCl for the purpose of examining in detail the structure by NMR spectroscopy.

2.2. Structural elucidation of $Co^{III}Piv_3ImP$

We examined first the structure of *meso*-[mono(2-imidazolyl)-tris(α,α,α-*o*-pivalamidophenyl)]porphyrinatocobalt(III), $Co^{III}Piv_3ImP$, **6**. Liquid chromatography/high-resolution electrospray ionization mass spectra (LC/HRESI(+)MS) of the $CHCl_3$ solution of $Co^{III}Piv_3ImP$, **6**, gave two peaks corresponding to a monomer and a dimer with a relative intensity of 1:0.16, respectively. This mass spectroscopic data suggested that dimeric porphyrin **6D** was formed by complementary coordination of imidazolyl to Co(III) in $CHCl_3$. The UV–vis absorption spectrum of $Co^{III}Piv_3ImP$ in $CHCl_3$ showed a broad Soret band at 434 nm (half peak width of 45 nm) and a Q band at 554 nm, as shown in Figure 1. The broad Soret band may have arisen from the exciton interaction of the slipped cofacial dimeric structure of **6D**, $(Co^{III}Piv_3ImP)_2$, in nonpolar media, by analogy, had split bands for the imidazolyl-substituted Zn porphyrin dimer.[1]

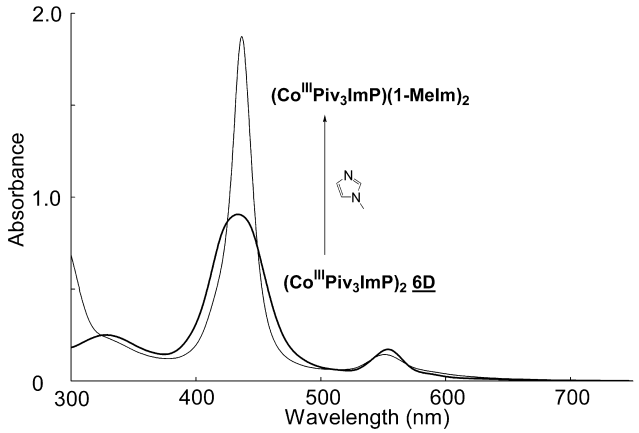


Figure 1. UV–vis spectra of $(Co^{III}Piv_3ImP)_2$ **5D** (bold line) and $(Co^{III}Piv_3ImP)(1\text{-MeIm})_2$ (narrow line) in $CHCl_3$.

The ^1H NMR spectrum (600 MHz, $CDCl_3$) of $Co^{III}Piv_3ImP$ was assigned carefully with help of H–H COSY spectra, with reference to the spectra of free-base porphyrin, H_2Piv_3ImP (Figs. 2 and 3). The protons of the phenyl and pivaloyl groups were readily assigned because the chemical shifts of these peaks resembled those of H_2Piv_3ImP and H_2Piv_4P. Distinctive differences between $Co^{III}Piv_3ImP$ and H_2Piv_3ImP were observed at the chemical shifts of the β-pyrrole and imidazole protons. All β-pyrrole protons of H_2Piv_3ImP were observed at 8.80 (4H, C12-, C18–H and C13-, C17–H), 8.83 (2H, C2-, C8–H) and 9.03 ppm (2H, C3-, C7–H; integral values are based on the monomer structure). In $Co^{III}Piv_3ImP$, on the other hand, the doublet peaks at 5.36–5.41, 8.43, 9.11 and 9.22 ppm were assigned as β-pyrrole protons. If $Co^{III}Piv_3ImP$ forms a slipped cofacial dimer, C3-, C7–H and C2-, C8–H should be considerably influenced by ring current effects from another porphyrin and appear at higher magnetic field.[1,2] The peaks at 5.36–5.41 and 8.43 ppm were correlated to each other in COSY, and the peaks at 5.36–5.41 and 8.43 ppm were assigned to C3-, C7–H's and C2-, C8–H's, respectively. Especially, C3-, C7–H's at 5.36–5.41 ppm were located above another porphyrin ring, receiving the ring current effect more efficiently than C2- and C8–H at 8.43 ppm. However, the peak integration at 5.36–5.41 ppm corresponded not to 2H but to 3H, and these peaks were correlated with two peaks at 0.66 (d, 1H) and 8.79 ppm (s, 1H) in COSY. It was thought that the peaks at 5.36–5.41 ppm might be overlapped with C22–H (imidazole). A doublet peak at 0.66 ppm, which correlated with a peak at 5.36–5.41 ppm in COSY, was assigned as C23–H, which was in the closest contact with another porphyrin. A broad singlet peak at 8.79 ppm was assigned as N5–H, because this peak correlated to the peak at 5.36–5.41 ppm in COSY and did not correlate to any other peaks of the ^{13}C NMR in HMQC. These shifts of β-pyrrole and imidazole protons to higher magnetic fields indicated the formation of the slipped cofacial dimer $(Co^{III}Piv_3ImP)_2$, **6D**, since the shielding by the second porphyrin ring current (a 'dimerization-induced shift'[1,15]) should be maximized. Imidazole protons (C22–H and C23–H) of H_2Piv_3ImP were observed at ~7.8 ppm as a broad single peak, because the imidazolyl group could rotate freely. In the case of $Co^{III}Piv_3ImP$, the imidazole protons were observed as two peaks. This differences also proved the formation of the dimeric structure, because the rotation was inhibited in $(Co^{III}Piv_3ImP)_2$, **6D**, by coordination of N6 to the cobalt of another porphyrin. These assignments are summarized in Figure 3.

Addition of excess 1-methylimidazole (1-MeIm) to dimer **6D** was expected to generate the monomeric species by competitive coordination. However, when $(Co^{III}Piv_3ImP)_2$ was dissolved in $CHCl_3$/1-MeIm=3:1, the UV–vis spectrum changed only very slowly. Even after a day, the spectrum continued to change. Therefore, this solution, Co^{III} complex in $CHCl_3$/1-MeIm, was concentrated once slowly, and redissolved in $CHCl_3$/1-MeIm=3:1. This time, the spectral change came to completion. The broad Soret band of $(Co^{III}Piv_3ImP)_2$ at 434 nm (half peak width of 45 nm) became sharp and shifted to 437 nm (half peak width of 21 nm), accompanied with shifts of the Q-bands to 551 from 554 nm (Fig. 1). The final sharp Soret band should have corresponded to that of the monomer by dissociation of the dimeric structure. The fact of the monomeric structure was confirmed by analyzing the ^1H NMR spectrum. The characteristic overlap of β-pyrrole (C3, C7–H) and imidazole (C22–H) protons at 5.36–5.41 ppm observed for $(Co^{III}Piv_3ImP)_2$, **6D**, disappeared completely. Therefore, $(Co^{III}Piv_3ImP)_2$, **6D**, was dissociated to the monomer by the addition of excess 1-MeIm to form the bis(1-MeIm) complex, $(Co^{III}Piv_3ImP)(1\text{-MeIm})_2$.

In order to obtain further evidence of the formation of the dimeric structure, the elution behavior in gel-permeation

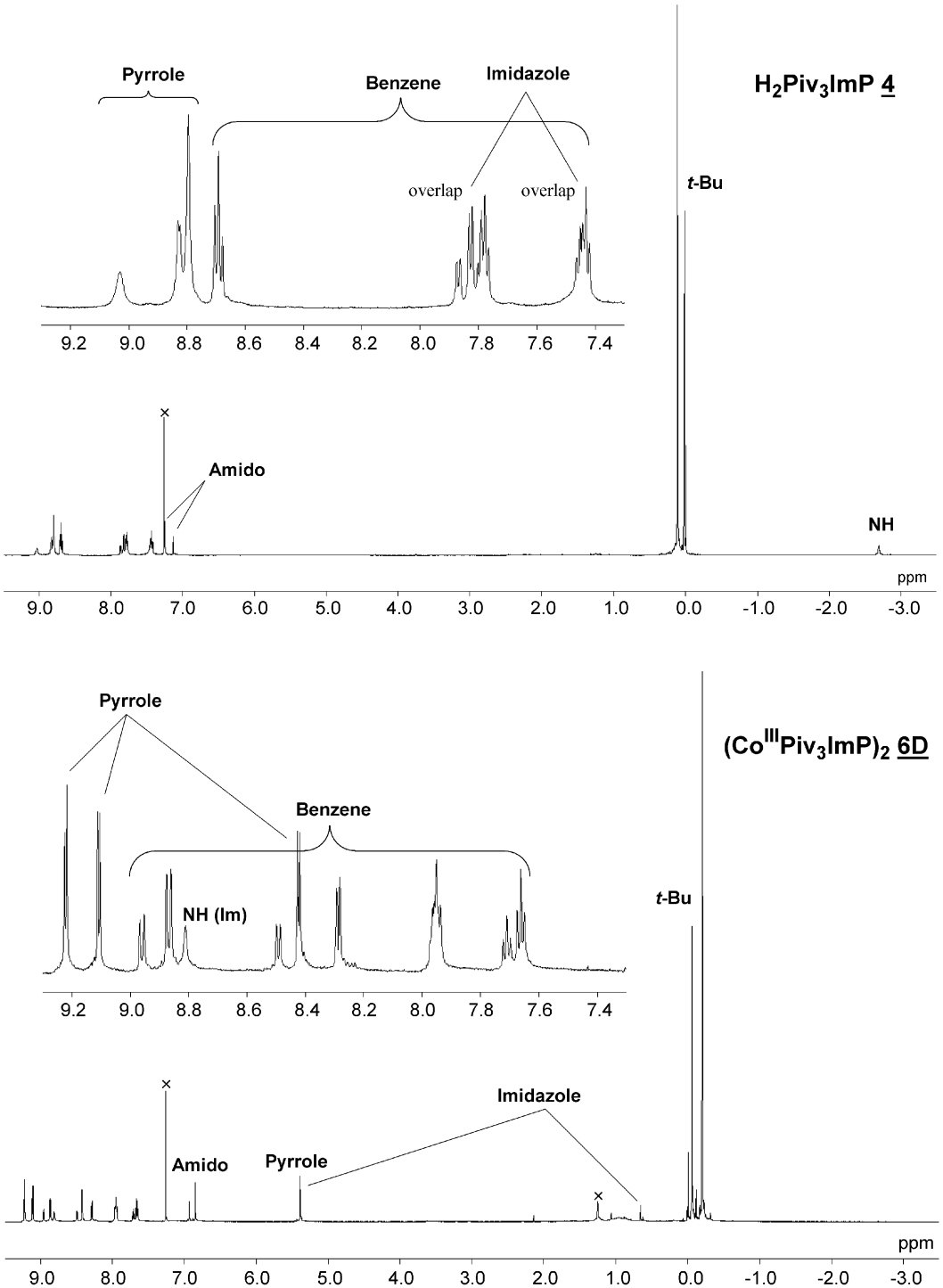


Figure 2. ^{1}H NMR spectra (600 MHz, $CDCl_3$) of H_2Piv_3ImP **4** and $(Co^{III}Piv_3ImP)_2$ **6D**.

chromatography (GPC) using a column with an exclusion limit of 2×10^4 Da was studied. This technique has been successfully applied to differentiating imidazolyl-substituted zincporphyrin oligomers.[2] For $(Co^{III}Piv_3ImP)_2$, **6D**, a sharp elution peak, with the same UV–vis spectrum shown in Figure 1, appeared at 10.7 min, which was a shorter retention time than that of $(Co^{III}Piv_3ImP)(1\text{-}MeIm)_2$, at 13.1 min (Fig. 4). This result supported the notion that $Co^{III}Piv_3ImP$, **6**, existed predominantly as a dimer, $(Co^{III}Piv_3ImP)_2$, **6D**.

2.3. Structural elucidation of $Co^{II}Piv_3ImP$

LC/HRESI(+)MS of the $CHCl_3$ solution of $Co^{II}Piv_3ImP$, **5**, gave two peaks corresponding to a monomer and a dimer, the latter with an intensity of 13% relative to that of the monomer. This mass spectral data also suggested that the dimeric porphyrin existed in $CHCl_3$, analogous to $Co^{III}Piv_3ImP$. The ^{1}H NMR spectrum of $Co^{II}Piv_3ImP$ in CD_2Cl_2 showed four broad peaks ascribable to the β-pyrrole protons at 7.5, 9.2, 12.2, and 13.8 ppm. In the case of

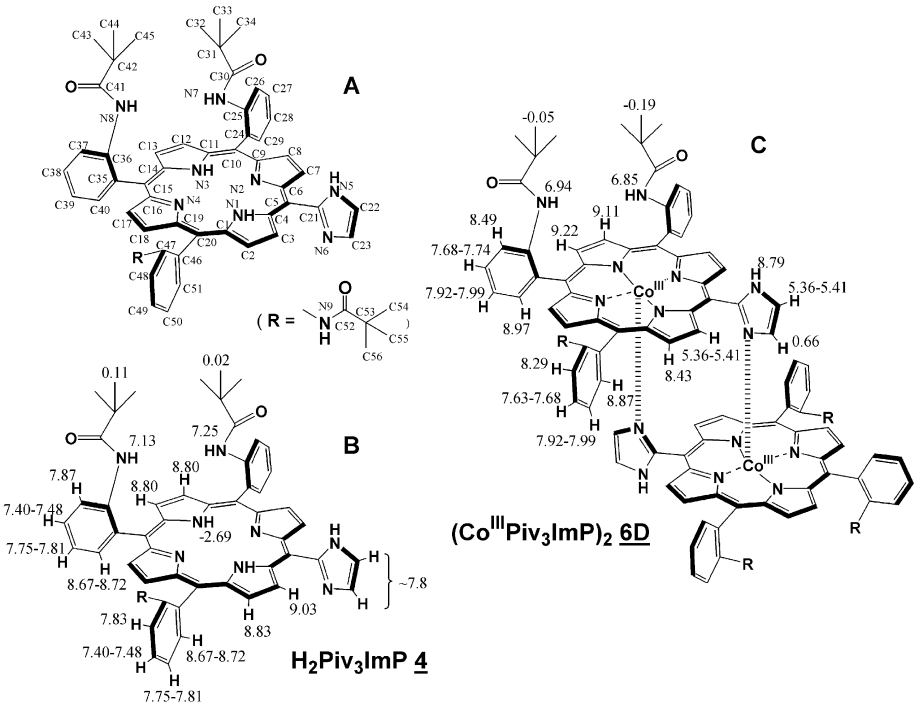


Figure 3. Chemical shifts data of H_2Piv_3ImP **4** and $(Co^{III}Piv_3ImP)_2$ **6D** in ^1H NMR (600 MHz, $CDCl_3$). Numerical values in **B** and **C** show the assignment of chemical shifts (ppm).

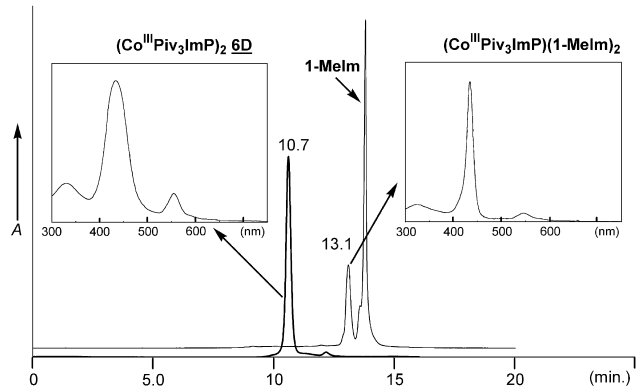


Figure 4. GPC analysis of $(Co^{III}Piv_3ImP)_2$ **6D** (bold line) and $(Co^{III}Piv_3ImP)(1\text{-MeIm})_2$ (narrow line) using a column (JAIGEL-2.5 HA) with an exclusion limit of 2×10^4 Da (eluent; $CHCl_3$, flow rate; 1.2 mL/min, detection; absorption at 420 nm). The UV–vis spectra of peaks at 10.7 and 13.1 min are shown as insets.

Co^{II}TPP-(pyridine-d_5), the β-pyrrole protons' signal appeared at 12.5 ppm as a single broad peak.[16] Therefore, the four broad peaks of $Co^{II}Piv_3ImP$ may be influenced anisotropically by a 'dimerization-induced shift'. However, we could not assign definitely these four peaks and imidazolyl protons because no correlation peaks were observed in H–H COSY and HMQC because of peak broadening.

Formation of the dimeric structure of $(Co^{II}Piv_3ImP)_2$, **5D**, was also suggested from 1-MeIm titration in CH_2Cl_2 (Fig. 5). The UV–vis absorption spectrum of $Co^{II}Piv_3ImP$ in CH_2Cl_2 under N_2, Figure 5A-a, showed a broad Soret band at 409 nm (half peak width of 42 nm) with a shoulder at 389 nm and a Q band at 534 nm. With the addition of 1-MeIm, this broad Soret band became sharp and shifted to 412 nm (half peak width of 25 nm), accompanied by shifts of the Q-bands from 534 to 531 nm. The final spectrum resembled that of $Co^{II}Piv_4P$ with axial coordination from 1-MeIm with respect to the half band width and the peak maxima. The resultant species was assigned as monomer **7** with an axial ligation by 1-MeIm, $(Co^{II}Piv_3ImP)(1\text{-MeIm})$. The initial mono(imidazolyl)-substituted Co(II) complex corresponded to the slipped cofacial dimer **5D** in CH_2Cl_2. This corresponds to Eq. 1 and the other related coordination equilibria, which are expressed as follows:

$$(CoPiv_3ImP)_2 + 2Im \overset{K_a}{\rightleftharpoons} 2(CoPiv_3ImP)Im \quad (1)$$

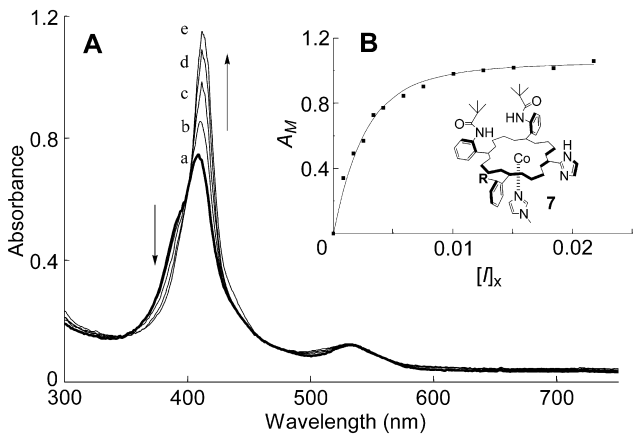


Figure 5. A: UV–vis spectral changes of dimer **5D** to monomer **7** on adding1-MeIm under N_2 in CH_2Cl_2 (**5D**: 4.0×10^{-6} M, $[1\text{-MeIm}]\times10^{-2}$: (a) 0, (b) 0.08, (c) 0.25, (d) 0.59, and (e) 2.18 M). B: Titration of absorbance of monomer **7** (A_M) at 409 nm versus $[I]_x$ (the concentration of titrated 1-MeIm). Line is a theoretical curve using K_0=2.0 for the imidazole coordination equilibrium.

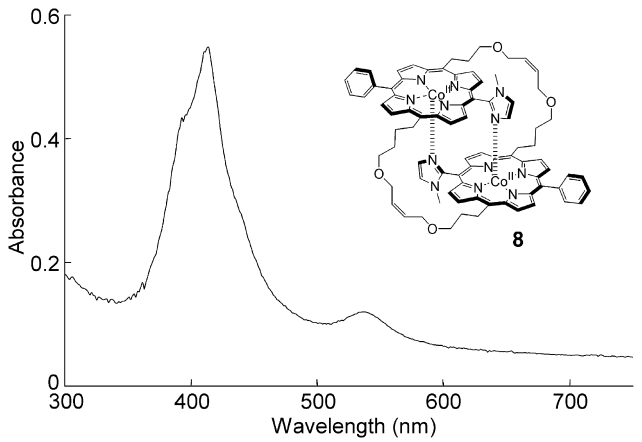


Figure 6. UV–vis spectrum of **8** in $CHCl_3$ under N_2.

$$CoPiv_3ImP + Im \overset{K_b}{\rightleftharpoons} (CoPiv_3ImP)Im \quad (2)$$

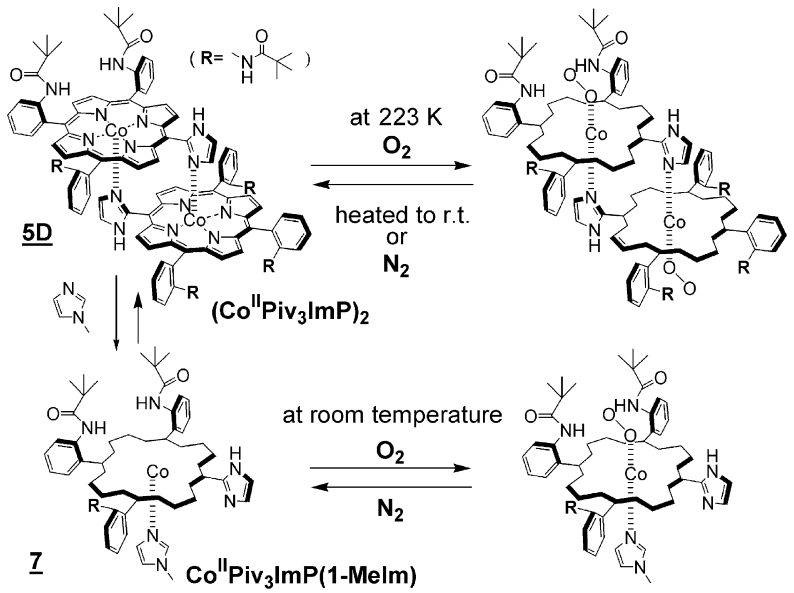
$$CoPiv_3ImP + Copiv_3ImP \overset{K_c}{\rightleftharpoons} (CoPiv_3ImP)_2 \quad (3)$$

The 1-MeIm titration curve for the peak at 409 nm was best fitted by the theoretical curve from Eq. 1 using K_a=2.0 M^{-1} (Fig. 5B).[17] Based on this value and the stability constant of K_b=1.9×10^4 M^{-1} for 1-MeIm coordination to $Co^{II}Piv_4P$,[18] the binding constant K_c (=K_b^2/K_a) for the dimer formation was evaluated as ca. 1.8×10^8 M^{-1}. This large stability constant was entirely consistent with the observation that the species exist predominantly as the dimer, 98% at 1×10^{-5} M and 95% at 1×10^{-6} M. The enhancement factor (K_c/K_b) of ca. 9.5×10^3 with the presence of porphyrin can be accounted for by the complementary nature of the coordination and the additional π stacking interaction between two porphyrins, in a similar way to the Zn complex.[1,2]

Further confirmation of the dimeric structure of ($Co^{II}Piv_3$-ImP)$_2$, **5D**, was obtained by comparing the UV–vis spectrum with that of the covalently linked imidazolyl-substituted Co(II) porphyrin dimer **8** (Fig. 6). The covalently linked imidazolyl-substituted Zn(II) porphyrin dimer, where two porphyrin components were connected by covalent bonding at the *meso* position, was previously reported.[19] Because the complementary coordination structure was frozen by covalent bonding, the structure was maintained even in the presence of a large excess of highly coordinating pyridine. Application of the same principle to Co (II) points conclusively to the dimeric structure of **8**. The UV–vis absorption spectrum of **8** in CH_2Cl_2 under N_2, presented in Figure 6, showed a broad Soret band at 414 nm (half peak width of 52 nm) with a shoulder at 395 nm and a Q band at 538 nm. The shape of this spectrum was in excellent agreement with that of $Co^{II}Piv_3ImP$. Therefore, these results suggested that $Co^{II}Piv_3ImP$, **5**, in CH_2Cl_2 formed the slipped cofacial dimeric structure ($Co^{II}Piv_3ImP)_2$, **5D**.

2.4. O_2 binding to ($Co^{II}Piv_3ImP)_2$ in UV–vis, resonance Raman, and ESR spectroscopy

The binding behavior of dioxygen was examined by introducing O_2 or N_2 gas in CH_2Cl_2 with monitoring by UV–vis spectroscopy. The spectral changes of monomer **7** generated by the addition of 1-MeIm to dimer **5D** were normal at room temperature, since the Q band at 531 nm under N_2 shifted to 542 nm under 1 atm O_2, similar to $Co^{II}Piv_4P$(1-MeIm) (530 nm under N_2, 547 nm under O_2).[6] These spectral changes were reversible. Compared to the monomer, the UV–vis spectrum of deoxy dimer **5D** did not change with introduction of O_2 at room temperature. When the temperature was lowered to 223 K under 1 atm O_2, the Soret and Q bands shifted to 412 and 547 nm, respectively. In either case, when N_2 was bubbled into the solution at 223 K or the temperature was raised up to 298 K under 1 atm O_2, the original spectrum of the deoxy state was regenerated. Therefore, the dimer showed reversible binding of dioxygen only at low temperature (223 K) (Scheme 2).



Scheme 2. Reversible dioxygen binding to dimer **5D** and monomer **7**.

In order to confirm the dioxygen binding to **5D**, resonance Raman (RR) spectroscopy was used to monitor the ν(O–O) band of the O_2 adducts.[20,21] A new band appeared at 1153 cm^{-1} under $^{16}O_2$ at 223 K, but neither at room temperature under O_2 nor at 223 K under N_2 (Fig. 7A). This band disappeared completely when the temperature was raised to 298 K, regenerating the deoxy spectrum under N_2. Under $^{18}O_2$ at 223 K, the 1153 cm^{-1} band disappeared and the intensity at 1085 cm^{-1} increased significantly (Fig. 7B). Although the 1085 cm^{-1} band was overlapped with another band, the difference in spectra under $^{16}O_2$ and under $^{18}O_2$ demonstrated clearly that the 1153 cm^{-1} band shifted to 1085 cm^{-1} (Fig. 7C), to give an isotope shift of $\Delta\nu_{obs}(^{16}O_2/^{18}O_2)$=68 cm^{-1}. This shift was nearly identical to the value calculated from the harmonic oscillator approximation for the O–O stretching vibration $\Delta\nu_{calc}(^{16}O_2/^{18}O_2)$=66 cm^{-1}, and the 1153 cm^{-1} band was assigned to $\nu(^{16}O-^{16}O)$. This value was almost the same as that observed for $\nu(^{16}O-^{16}O)$ of $Co^{II}Piv_4P$(1-MeIm), 1148 cm^{-1} in toluene at 298 K.[21]

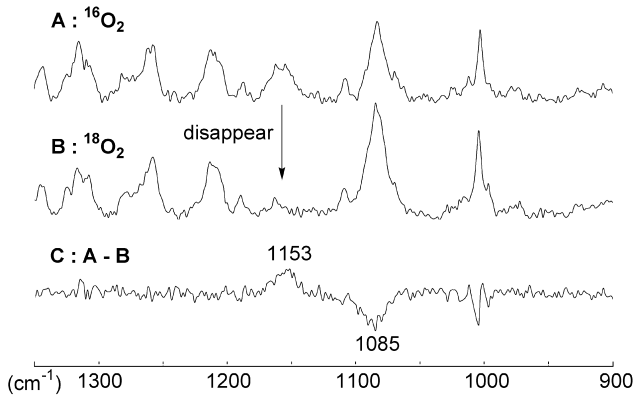


Figure 7. Resonance Raman spectra of dimer **5D** excited at 413 nm under O_2 in CH_2Cl_2 at 223 K. A: $^{16}O_2$. B: $^{18}O_2$. C: a difference spectrum of A−B.

Various dioxygen Co(II) porphyrin adducts with axial ligands have been analyzed by ESR measurements.[4,8,22] Dioxygen binding to dimer **5D** was also examined by ESR spectroscopy (Fig. 8). The ESR spectrum of dimer **5D** in toluene under N_2 at 223 K showed a single broad signal (g=2.30) analogous to that found in the spectra of Co(II) porphyrins with fifth axial ligands, for example $Co^{II}Piv_4P$(1-MeIm).[4] When dioxygen was introduced to dimer **5D** in toluene at 223 K, a new sharp peak appeared at g=2.02, which was ascribed to Co–O_2, and was accompanied by complete disappearance of the peak at g=2.30 under 1 atm O_2 (Fig. 8). The intensity changes of these two peaks at g=2.02 and 2.30 were completely correlated with each other. These results are compatible with the observations from UV–vis and RR spectra that dimer **5D** can bind dioxygen at low temperature. The complete disappearance of the peak at g=2.30 under 1 atm O_2 at 223 K indicates that the deoxy state, corresponding to a penta-coordinating Co(II) species, does not exist at all, and that the oxy state was formed 100% under these conditions. Therefore, two molecules of dioxygen can bind reversibly to the two binding sites of dimer **5D**.

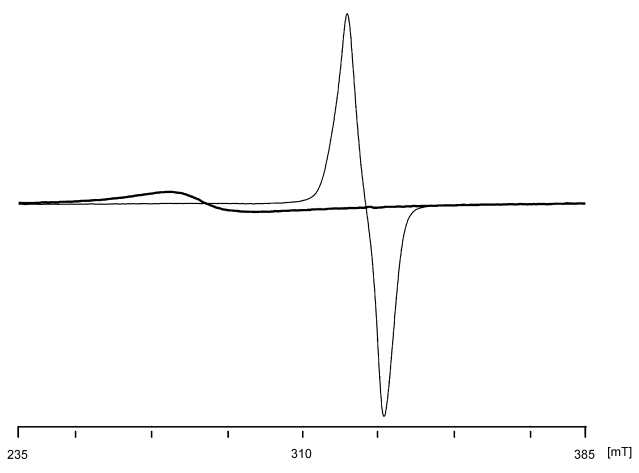


Figure 8. ESR spectral change of dimer **5D** on the addition of one atom O_2 at 223 K (narrow line) to the deoxy state (bold line) in toluene.

2.5. O_2 affinity of $(Co^{II}Piv_3ImP)_2$

The dioxygen binding equilibria of dimer **5D** are expressed as follows:

$$(CoPiv_3ImP)_2 + O_2 \overset{K_1}{\rightleftharpoons} (CoPiv_3ImP)_2O_2 \quad \text{(i)}$$

$$(CoPiv_3ImP)_2O_2 + O_2 \overset{K_2}{\rightleftharpoons} (CoPiv_3ImP)_2(O_2)_2 \quad \text{(ii)}$$

In order to determine the binding constants, K_1 and K_2, and the oxygen binding affinity $P_{1/2}$ (half-saturation oxygen pressures of O_2 binding) of dimer **5D**, UV–vis spectra were recorded at 223 K over a wide range of oxygen partial pressures using the apparatus described in Section 4. UV–vis spectra in toluene at 223 K are shown in Figure 9. From these spectra, Hill's coefficient n and $P_{1/2}$ were estimated by plotting log $Y/(1-Y)$ against log P (Y and P represent the ratio of oxy state and oxygen partial pressure, respectively). From the Hill plot, n and $P_{1/2}$ were obtained as 1.1 and 20 Torr, respectively. At first, we have expected that the dioxygen affinity of the second binding, K_2, would be different from that of the first binding, K_1. However, Hill's coefficient (n=1.1) indicates that O_2 binding to dimer **5D** is not cooperative, and K_1 is equal to K_2. From these $P_{1/2}$ values, the O_2 binding affinity of dimer **5D** is lower than those of monomeric models, for example monomer **7**, $Co^{II}Piv_4P$(1-MeIm), $Co^{II}Piv_4P$(1,2-dimethylimidazole,

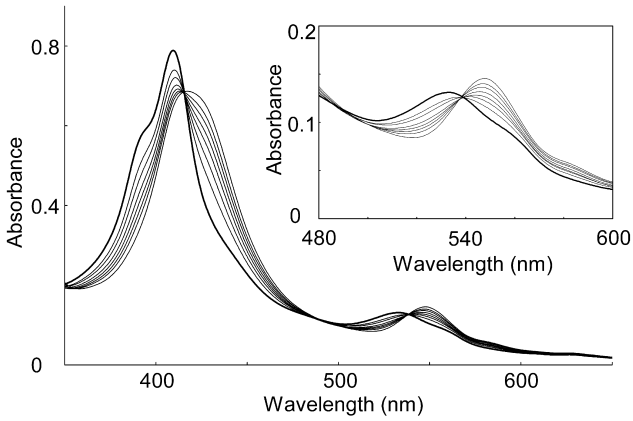


Figure 9. UV–vis spectral change of dimer **5D** on the addition of O_2 at 223 K to the deoxy state (bold line) to the oxy state (narrow line. partial pressure of O_2: 0, 7.6, 15, 23, 38, 61, 122, 760 mm Hg) in toluene. The inset is an enlarged spectral change of the Q band region.

Table 1. $P_{1/2}$ for O_2 binding to cobalt(II) porphyrins

Compound	Physical state	$P_{1/2}$ (223 K), Torr	$\Delta H°$ (kcal/mol)	$\Delta S°$ (eu)[a]	Reference
CoMb (Sperm whale)	0.1 M phosphate pH 7	0.04[b]	−13.3	−40	25
$CoPiv_4P$(1-MeIm)	Solid	0.04[b]	−13.3±0.9	−40±3	6
$CoPiv_4P$(1-MeIm)	Toluene	0.17[b]	−12.2±0.3	−38±1	6
$CoPiv_4P$(1,2-Me_2Im)	Toluene	1.1[b]	−11.8±0.4	−40±2	6
$CoPiv_3P$(1-MeIm)	Toluene	1.0[b]	−12.2	−41.6	8
($CoPiv_3$ImP)(1-MeIm) **7**	Toluene	'Very small'[c]	—	—	This work
($CoPiv_3$ImP)$_2$ **5D**	Toluene	20	—	—	This work
CoT(*p*-OCH_3)PP(1-MeIm)[d]	Toluene	106[b]	−8.9	−36	26

[a] Standard state, 1 atm O_2.
[b] Calculated from reported $\Delta H°$ and $\Delta S°$ by using equations, $\Delta H°-T\Delta S°=-RT\ln K_{eq}$, and $1/K_{eq}=P_{1/2}$.
[c] When the temperature was lowered to 223 K under N_2, a spectrum of the oxy state was obtained because a very small amount of dioxygen mingled with a cell.
[d] *meso*-Tetrakis(*p*-methoxyphenyl)porphyrinatocobalt(II)+1-MeIm.

1,2-Me_2Im), and *meso*-tetrakis(α,α,α,β-*o*-pivalamidophenyl)porphyrinatocobalt(II) with 1-MeIm, $Co^{II}Piv_3P$(1-MeIm) (see Table 1).

The decreased oxygen binding affinity of dimer **5D** compared with monomer **7** should be discussed in light of two factors. First, the axial ligand forming the complementary dimer **5D** is regarded as a 2-porphyrinyl-substituted imidazole. The steric hindrance from the 2-porphyrinyl substituent is large enough to decrease the oxygen affinity of dimer **5D**[6,7] On the other hand, the axial ligand of monomer **7** is 1-methylimidazole, which has no steric hindrance toward the porphyrin component. Hence, monomer **7** and dimer **5D** can be regarded as models for R and T forms of CoHb, respectively.This is similar to the relation between $Co^{II}Piv_4P$(1-MeIm) and $Co^{II}Piv_4P$(1,2-Me_2Im).

Secondly, the coordinating angle of the *meso*-imidazolyl groups were constrained to 45° relative to the N–Co–N axis (θ in Fig. 10) owing to the slipped cofacial complementary coordination, as shown in Figure 10A. At this orientation, the overlap between the π orbital (dπ or pπ) of Co and the pπ orbital of N on the axial base is claimed to be at a minimum,[23] and therefore the π-electron donation from the axial base to dioxygen via Co-porphyrin is reduced, decreasing the dioxygen affinity. This effect is invoked to explain the 'jellyfish' type Co(II) porphyrins.[24] On the other hand, the exogenous 1-MeIm in monomer **7** can rotate freely (Fig. 10B) and assume an angle that maximizes the π-electron donation. These two factors may explain the decreased oxygen affinity of dimer **5D** compared with monomeric models with picket fence structures, ($Co^{II}Piv_3$ImP)(1-MeIm) **7**, $Co^{II}Piv_4P$(1-MeIm), $Co^{II}Piv_4P$(1,2-Me_2Im), and $Co^{II}Piv_3P$(1-MeIm).

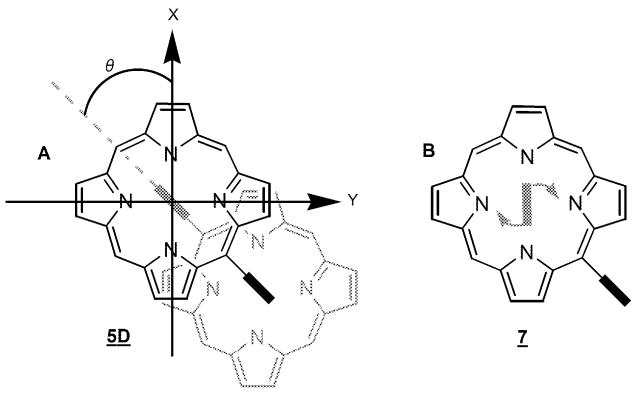


Figure 10. Schematic representation of the dihihedral angle between ligand and porphyrin axis in ($Co^{II}Piv_3ImP)_2$ **5D** and $Co^{II}Piv_3$ImP(1-MeIm) **7**. A solid bar indicates 1-MeIm.

3. Conclusion

The complementary coordination dimer of imidazolyl-substituted porphyrins was successfully and for the first time constructed into a new dioxygen carrier model, which could bind two dioxygen molecules to two binding sites of dimer **5D**. The oxygen affinity of dimer **5D** was significantly decreased compared with monomer **7**, which was obtained by adding external 1-MeIm to dimer **5D**. The relation between **5D** and **7** resembles that of hemoglobin working at lung with decreased oxygen affinity and myoglobin at terminal tissues with much higher affinity for oxygen. The significant decrease in O_2 affinity of dimer **5D** originates from the steric hindrance of the bulky 2-porphyrinyl substituent of the imidazolyl ligand and fixation at 45° of the dihedral angle between *meso*-imidazolyl ligand and the N–Co–N axis. In this way, the dioxygen affinity could readily be controlled using $Co^{II}Piv_3$ImP with the formation and dissociation of the dimeric structure.

4. Experimental

4.1. General

4.1.1. Apparatuses. ^{1}H NMR spectra were recorded on either a JEOL JNM EX 270, or a JEOL JNM-ECP 600 spectrometer. Chemical shifts are reported on a δ scale with respect to TMS as an internal standard. Coupling constants (J) are reported in Hertz (Hz). UV–vis spectra were measured by a Shimadzu UV-3100 PC spectrometer and an OXFORD OptistatDN for measurements at low temperatures with a liquid nitrogen cryostat and an OXFORD ITC502 as a temperature controller. Fluorescence spectra were recorded on a Hitachi F-4500 spectrometer. MALDI-TOF mass spectra were obtained with a PE-Biosystems Voyager-DE STR spectrometer with dithranol as a matrix. LC/HRESI(+) mass spectra were obtained with a JEOL JMS-700 (MStation) spectrometer. TLC was performed on analytical glass TLC plates coated with 60 F_{254} (E. Merck) silica gel. Column chromatography was performed using a

column packed with silica gel 60 N (Kanto Chemical, spherical, neutral, 63–210 μm). HPLC analyses of aminoporphyrins were carried out on a SHIMADZU LC-10A Series with a TOSHO TSK-gel Octadecyl-4PW column, monitored with a SHIMADZU SPD-10A UV–vis detector at 420 nm. GPC analyses were carried out on a HEWLETT–PACKARD HP 1100 Series with a JAIGEL-2.5 HA column (an exclusion limit of 2×10^4 Da), monitored by a UV–vis detector at 418 nm. Resonance Raman spectra were measured by a JASCO NRS-2100 with a COHERENT INNOVA 90C-K Kr ion laser (at 413 nm), and the temperature was controlled by a liquid nitrogen cooler system made by Daiwa Giken Co., Ltd and ourselves, and a digital thermometer (NIHON SHINTECH CT-700SD with LK-300). ESR spectra were measured on a JEOL JES-FA 100 with a temperature control unit ES-DVT4. Deoxy ($Co^{II}Piv3ImP)_2$, **5D**, and deoxy ($Co^{II}Piv3ImP$)(1-MeIm), **7**, were handled in a glove box (Miwa Seisakusho) equipped with a recycling oxygen removal system (Miwa MM3-P60S) under highly purified N_2 containing less than 0.1 ppm O_2. UV–vis titration with 1-MeIm was performed in a glove box on an Otsuka Electronics UV–vis spectrometer (MCPD-50S and MC-2530).

4.1.2. Preparation of reagents. All chemicals used in the study were of reagent grade. All dry solvents were distilled and stored under N_2. Dry THF was distilled after drying with Na metal, and CH_2Cl_2 dried with CaH_2. Dry DMF was stirred with anhydrous $CuSO_4$ for 2 days and distilled under reduced pressure from CaH_2. 1-MeIm was vacuum distilled from KOH, and 2,6-lutidine was purified by passing through an alumina column, followed by distillation from $BF_3{\cdot}Et_2O$. Anhydrous $CoCl_2$ powder was heated at 100 °C under vacuum for 30 min before use. N_2, Ar and O_2 gases were of high-quality grades (Taiyo Toyo Sanso).

4.2. Synthesis

4.2.1. 5-(2-Imidazolyl)-10,15,20-tris(*o*-nitrophenyl)-porphyrin, H_2Nitro_3ImP, (1). 2-Nitrobenzaldehyde (3.74 g, 24.8 mmol, 2 equiv.) and imidazole-2-carboxaldehyde (1.19 g, 12.4 mmol, 1 equiv.)[13] were dissolved in refluxing propionic acid (110 mL). Pyrrole (2.50 g, 37.2 mmol, 3 equiv.) was then added slowly to the boiling solution. The solution was heated under reflux for 20 min. After standing at room temperature, $CHCl_3$ (100 mL) was added to the solution, and stirred. The resulting mixture was filtered to remove *meso*-tetrakis(*o*-nitrophenyl)porphyrin and washed with $CHCl_3$. The filtrate was concentrated and purified by silica gel column chromatography, eluting with 8:1, $CHCl_3$/acetone. A purple solid of **1** was obtained, with a yield of 713 mg (0.963 mmol, 7.8%). MALDI-TOF MS *m/z* 740.4 ($M+H^+$), Calcd 740.2; UV–vis λ_{max} ($CHCl_3$) 423, 518, 555, 595, 654 nm; fluorescence λ_{Em} ($CHCl_3$) 658, 716 nm (λ_{Ex} 420 nm).

4.2.2. 5-(2-Imidazolyl)-10,15,20-tris(*o*-aminophenyl)-porphyrin, H_2Am_3ImP, (2). H_2Nitro_3ImP (**1**) (300 mg, 0.406 mmol) was dissolved in concentrated HCl (40 mL), followed by addition of excess $SnCl_2{\cdot}2H_2O$ (1.3 g). The resulting green mixture was stirred at room temperature for 30 min, and neutralized cautiously with $NaHCO_3$. Ethyl acetate was added to the suspension and the mixture was stirred. The resulting mixture was filtered under suction with addition of celite, and the residue was washed with ethyl acetate until the washings were essentially colorless. The ethyl acetate layer of the filtrate was separated, the aqueous layer extracted several times with ethyl acetate, and the extracts were combined. The ethyl acetate solution was concentrated to a smaller volume on a rotary evaporator, washed first with saturated $NaHCO_3$ solution, then twice with water and dried over anhydrous sodium sulfate. The solution was brought to dryness by a rotary evaporator and oil pump vacuum. A purple solid of the mixture of atropisomers of H_2Am_3ImP was obtained, yield 201 mg (0.309 mmol, 76%). TLC (silica gel, $CHCl_3$/MeOH, 9:1) R_f=0.55. MALDI-TOF MS *m/z* 650.4 ($M+H^+$), Calcd 650.3; UV–vis λ_{max} ($CHCl_3$) 422, 515, 556, 586, 644 nm; fluorescence λ_{Em} ($CHCl_3$) 657, 718 nm (λ_{Ex} 420 nm).

4.2.3. 5-(2-Imidazolyl)-10,15,20-tris(α,α,α-*o*-aminophenyl)porphyrin, α,α,α-H_2Am_3-ImP, (3). A mixture of atropisomers of H_2Am_3ImP (**2**) (175 mg) and 6.30 g of Kanto Chemical silica gel 60 N (63–210 μm, 600–700 m^2/g) were added to a 50 mL round-bottom flask fitted with a three-way stop-cock. The flask was evacuated with a vacuum pump for 1 h, then charged with argon gas. Toluene (15 mL) was added to the flask under a steady flow of argon gas, and argon gas was bubbled into the mixture for 10 min. The flask was attached with a reflux condenser, and immersed in an oil bath maintained at 110–120 °C, and the content was stirred under argon gas.[14] After 30 min, the slurry was cooled to room temperature and applied to the top of a silica gel chromatography column. The undesired atropisomers were eluted first with 3:1 $CHCl_3$/acetone, yield 58 mg, and then 1:1 $CHCl_3$/acetone was used to elute the α,α,α-atropisomer, yield 100 mg (57% conversion, 90% recovery). TLC (silica gel, $CHCl_3$/MeOH, 9:1) R_f=0.50. MALDI-TOF MS *m/z* 650.2 ($M+H^+$), Calcd 650.3; UV–vis λ_{max} ($CHCl_3$) 421, 517, 555, 588, 647 nm; fluorescence λ_{Em} ($CHCl_3$) 657, 716 nm (λ_{Ex} 421 nm).

4.2.4. 5-(2-Imidazolyl)-10,15,20-tris(α,α,α-*o*-pivalamidophenyl)porphyrin, H_2Piv_3ImP, (4). α,α,α-H_2Am_3-ImP (**3**) (21 mg, 0.032 mmol) was dissolved in $CHCl_3$ (2 mL), followed by addition of pyridine (10 μL) and pivaloyl chloride (10 μL, 0.112 mmol). The mixture was stirred for 1 h at room temperature, then brought to dryness on a rotary evaporator. The resulting solid was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed first with saturated $NaHCO_3$ solution, then twice with water. After drying over anhydrous sodium sulfate and reducing the volume by a rotary evaporator, the product was purified by chromatography on a silica gel column, eluting with 9:1 $CHCl_3$/acetone, yield 26 mg (0.029 mmol, 91%). MALDI-TOF MS *m/z* 902.5 ($M+H^+$), Calcd 902.4; UV–vis λ_{max} ($CHCl_3$) 421, 515, 552, 589, 649 nm; fluorescence λ_{Em} ($CHCl_3$) 655, 715 nm (λ_{Ex} 421 nm); ^1H NMR (600 MHz, $CDCl_3$) δ −2.69 (s, 2H, NH), 0.02 (s, 9H, *t*-Bu), 0.11 (s, 18H, *t*-Bu), 7.13 (s, 1H, amido), 7.25 (s, 2H, amido), 7.44 (m, 3H, benzene), 7.78 (q, 3H, benzene), 7.83 (d, *J*=6.6 Hz, 2H, benzene), 7.87 (d, *J*=6.6 Hz, 1H, benzene), 8.69 (t, 3H, benzene), 8.80 (s, 4H, pyrrole), 8.83 (d, *J*=4.4 Hz, 2H, pyrrole), 9.03 (s, 2H, pyrrole); ^{13}C NMR (600 MHz, $CDCl_3$) δ 26.44 (C43–45), 26.53 (C32–34, 54–56), 38.94 (C42), 39.05 (C31, 53), 108.47 (C5), 115.12 (C10, 20), 115.30

(C15), 120.83 (C40), 121.03 (C29, 51), 122.98 (C27, 38, 49), 130.01 (C39), 130.07 (C28, 50), 130.80 (C36), 130.92 (C25, 47), 134.23 (C37), 134.53 (C26, 48), 138.45 (C24, 46), 138.47 (C35), 146.59 (C21), 175.72 (C41), 176.11 (C30, 52).

4.2.5. 5-(2-Imidazolyl)-10,15,20-tris(α,α,α-*o*-pivalamidophenyl)porphyrinatocobalt(II) dimer, ($Co^{II}Piv_3ImP)_2$, (5D). H_2Piv_3ImP (**4**) (14 mg, 0.016 mmol) was dissolved in anhydrous THF (5 mL), followed by addition of 2,6-lutidine (30 mg, 0.310 mmol) and anhydrous $CoCl_2$ (20 mg, 0.155 mmol).[6] The mixture was stirred at 50 °C for 1 h, then brought to dryness on a rotary evaporator. The product was purified by neutral alumina (activity IV) column chromatography under N_2, eluting with 9:1 benzene/acetone, yield 11 mg (0.011 mmol, 69%). LC/HRESI(+)MS ($CHCl_3$) *m/z* 959.3692 (monomer, $M+H^+$, $C_{56}H_{54}O_3N_9Co$, Δ +1.1 ppm/+1.0 mmu), 1916.7195 (dimer, M^+, with 13% intensity relative to the monomeric peak, $C_{112}H_{106}O_6N_{18}Co_2$, Δ −0.6 ppm/+1.1 mmu); UV–vis λ_{max} (CH_2Cl_2) 389 (shoulder), 409 (ε, 1.60×10^5), 534 (1.9×10^4) nm.

4.2.6. 5-(2-Imidazolyl)-10,15,20-tris(α,α,α-*o*-pivalamidophenyl)porphyrinatocobalt(III) dimer, ($Co^{III}Piv_3ImP)_2$, (11D). ($Co^{II}Piv_3ImP)_2$ (**6D**) was dissolved in $CHCl_3$ and the solution was washed first with dilute hydrochloric acid, and then twice with water. After drying over anhydrous sodium sulfate, the solution was brought to dryness by a rotary evaporator and oil pump vacuum. The resulting solid was dissolved in a small amount of $CHCl_3$, and hexane was added dropwise to the $CHCl_3$ solution until it yielded black precipitates, and then the solution was settled over night. The resulting black precipitates were isolated by suction filtration and washed well with hexane. The product was brought to dryness on an oil pump vacuum for several hours. LC/HRESI(+)MS ($CHCl_3$) *m/z* 958.3615 (monomer, M^+, $C_{56}H_{53}O_3N_9Co$, Δ +1.2 ppm/+1.2 mmu), 1915.7109 (dimer, $M-H^+$, with intensity relative to the monomer of 16%, $C_{112}H_{105}O_6N_{18}Co_2$, Δ −1.0 ppm/−1.9 mmu); UV–vis λ_{max} (CH_2Cl_2) 328, 435, 554 nm; ^1H NMR (600 MHz, $CDCl_3$) δ −0.19 (36H, s, *t*-Bu), −0.05 (18H, s, *t*-Bu), 0.66 (2H, d, *J*=2.2 Hz, Im), 5.39 (6H, d, *J*=4.4 Hz, Im, pyrrole), 6.85 (4H, s, amido), 6.94 (2H, s, amido), 7.66 (4H, t, benzene), 7.71 (2H, t, benzene), 7.96 (6H, m, benzene), 8.29 (4H, d, *J*=7.3 Hz), 8.43 (4H, d, *J*=5.1 Hz, pyrrole), 8.49 (2H, d, *J*=7.3 Hz, benzene), 8.79 (2H, s, Im), 8.87 (4H, d, *J*=8.8 Hz, benzene), 8.97 (2H, d, *J*=8.8 Hz, benzene), 9.11 (4H, d, *J*=4.4 Hz, pyrrole), 9.22 (4H, d, *J*=4.4 Hz, pyrrole); ^{13}C NMR (600 MHz, $CDCl_3$) δ 26.59 (C32–34, 54–56, *t*-Bu), 26.72 (C43–45, *t*-Bu), 38.83 (C31, 53, *t*-Bu), 38.96 (C42, *t*-Bu), 98.79 (C5, *meso*), 113.28 (C22, Im), 115.44 (C10, 20, *meso*), 115.81 (C15, *meso*), 120.49 (C29, 40, 51, benzene), 122.50 (C38, benzene), 122.80 (C27, 49, benzene), 124.52 (C23, Im), 129.73 (C3, 7, pyrrole-β), 129.96 (C36, benzene), 130.21 (C39, benzene), 130.28 (C25, 47, benzene), 130.31 (C28, 50, benzene), 133.76 and 133.82 (C26, 48, benzene, or H12, 18, pyrrole-β), 134.71 (C37, benzene), 134.80 (C13, 17, pyrrole-β), 134.99 (C2, 8, pyrrole-β), 138.62 (C24, 46, benzene), 138.94 (C35, benzene), 143.94, 144.18, 144.96 (pyrrole-α), 145.25 (C21, Im), 145.52 (pyrrole-α), 176.59 (C30, 53, C═O), 176.64 (C41, C═O).

4.2.7. Covalently linked imidazolyl-substituted Co(II) porphyrin dimer, (8). Covalently linked imidazolyl-substituted Zn(II) porphyrin dimer[19] (9 mg, 6.45 μmol) was dissolved in $CHCl_3$ (3 mL). The solution was added to a MeOH/HCl (1:1) mixture (0.5 mL), stirred for 30 min and washed, first with saturated $NaHCO_3$ solution and then twice with water and subsequently dried over anhydrous sodium sulfate. The solution was dried completely on a rotary evaporator and then oil pump vacuum. A purple solid of covalently linked freebase porphyrin dimer was obtained, with a yield of 11 mg. The product (11 mg) was dissolved in anhydrous THF (3 mL), followed by addition of 2,6-lutidine (30 mg) and anhydrous $CoCl_2$ (20 mg). The mixture was stirred at 70 °C for 1 h under N_2, then dried on a rotary evaporator. The product was purified by neutral alumina (activity IV) column chromatography under N_2, eluted with 3:1 benzene/MeOH, yield 7 mg (5.06 μmol, 78%). MALDI-TOF MS *m/z* 1383.5 ($M+H^+$), Calcd 1382.5; UV–vis λ_{max} (CH_2Cl_2) 395, 414, 538 nm.

4.3. Measurement techniques

4.3.1. UV–vis titration of ($Co^{II}Piv_3ImP)_2$ with 1-MeIm. All operations were conducted in a glove box. A solution of ($Co^{II}Piv_3ImP)_2$ **5D** in CH_2Cl_2 (4.2×10^{-6} M, 3 mL) was injected into a cell having a plug (cell path length was 10 mm). The solution of 1-MeIm in CH_2Cl_2 (2.5 M) was titrated into the cell by micro syringe, and the resulting solution was stirred for 3 min and its UV–vis absorbance was measured. When, A, ε, M, and D represent absorbance, molar absorption coefficient, monomer **7**, and dimer **5D**, respectively, the following equations hold.

$$A = A_M + A_D = \varepsilon_M[M] + \varepsilon_D[D] \tag{4}$$

$$[D] = [D]_0 - \frac{[M]}{2} = [D]_0 - \frac{A_M}{2\varepsilon_M} \tag{5}$$

Since the initial solution is considered to contain dimer only, we assume Eq. 6.

$$A_0 = \varepsilon_D[D]_0 \tag{6}$$

These relations lead to Eq. 7:

$$A_M = \frac{2\varepsilon_M(A - A_0)}{2\varepsilon_M - \varepsilon_D} \tag{7}$$

The value of ε_M was evaluated from the absorption at the final titration point.

Eq. 8 is obtained by the definition of Eq. 1, where [I] is the concentration of 1-MeIm and rewritten in the form of Eq. 9.

$$K_a = \frac{[M]^2}{[D]\times[I]^2} = \frac{[M]^2}{([D]_0 - [M]/2)([I]_x - [M])^2} \tag{8}$$

$$K_a = \frac{(A_M/\varepsilon_M)^2}{(A_0/\varepsilon_D - A_M/2\varepsilon_M)([I]_x - A_M/\varepsilon_M)^2} \tag{9}$$

In Figure 6B, A_M at 409 nm was plotted as a function of $[I]_x$, the concentration of titrated 1-MeIm. The best fit K_0 value was evaluated as 2.0 M^{-1}.

4.3.2. Oxygen equilibria. A solution of ($Co^{II}Piv_3ImP)_2$, **5D**, in toluene (4.9×10^{-6} M) was injected into a cell (cell path

length 10 mm) and sealed by a rubber septum in a glove box. The cell was inserted into a liquid nitrogen cryostat, and the UV–vis absorption spectrum was measured at 223 K. Gas mixtures of N_2 and O_2 of various compositions were prepared by a KOFLOC GASCON GM-3B, and their oxygen partial pressures were monitored by a TORAY OXYGEN ANALYZER LC-850 KS. The gas mixture was bubbled into the sample solution through a needle for 5 min before measurements. From the spectra (Fig. 9), Hill's coefficient n and $P_{1/2}$ were estimated by plotting $\log Y/(1-Y)$ versus $\log P$.

$$\log\frac{Y}{1-Y} = \log\frac{A_{oxy}/A_{100\%}}{1-(A_{oxy}/A_{100\%})} = \log\frac{A_{oxy}}{A_{100\%}-A_{oxy}} \quad (10)$$

Y is the oxy state composition calculated by $A_{oxy}/A_{100\%}$, where A_{oxy} and $A_{100\%}$ represent the absorbance of the oxy state at 537 nm and that under 760 Torr O_2, respectively. A_{oxy} was calculated by using the equations shown below.

$$A = A_{oxy} + A_{deoxy} = \varepsilon_{oxy}[oxy] + \varepsilon_{deoxy}[deoxy] \quad (11)$$

$$[deoxy] = [deoxy]_0 - [oxy] = [deoxy]_0 - \frac{A_{oxy}}{\varepsilon_{oxy}} \quad (12)$$

where oxy and deoxy represent oxy and deoxy states, respectively. Since the initial solution is considered to contain only the deoxy state, Eq. 13 holds.

$$A_0 = \varepsilon_{deoxy}[deoxy]_0 \quad (13)$$

These relations (11)–(13) lead Eq. 14:

$$A_{oxy} = \frac{\varepsilon_{oxy}(A-A_0)}{\Delta\varepsilon} \quad (14)$$

where $\Delta\varepsilon$ is the difference between molar absorption coefficients of the oxy and the deoxy states. Finally, Eq. 15 is obtained by substitution of Eq. 14 into Eq. 10.

$$\log\frac{Y}{1-Y} = \log\frac{\varepsilon_{oxy}(A-A_0)}{\Delta\varepsilon A_{100\%} - \varepsilon_{oxy}(A-A_0)} \quad (15)$$

Hill's coefficient n was estimated by a slope of the straight line, which was obtained by using a linear least-squares program of the Hill's plot. $P_{1/2}$ was determined from the intercept at the x-axis.

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References and notes

1. (a) Kobuke, Y.; Miyaji, H. *J. Am. Chem. Soc.* **1994**, *116*, 4111–4112. (b) Ozeki, H.; Kobuke, Y. *Tetrahedron Lett.* **2003**, *44*, 2287–2291.
2. Kobuke, Y.; Ogawa, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 689–708.
3. (a) Collman, J. P.; Fu, L. *Acc. Chem. Res.* **1999**, *32*, 455–463. (b) Suzuki, Y.; Nishide, H.; Tsuchida, E. *Macromolecules* **2000**, *33*, 2530–2534.
4. Collman, J. P.; Gagne, R. R.; Kouba, J.; Ljusberg-Wahren, H. *J. Am. Chem. Soc.* **1974**, *96*, 6800–6802.
5. Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427–1439.
6. Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Hayes, S. E.; Suslick, K. S. *J. Am. Chem. Soc.* **1978**, *100*, 2761–2766.
7. Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Suslick, K. S. *Proc. Natl Acad. Sci. U.S.A.* **1978**, *75*, 564–568.
8. Imai, H.; Nakata, K.; Nakatsubo, A.; Nakagawa, S.; Uemori, Y.; Kyuno, E. *Synth. React. Inorg. Met.-Org. Chem.* **1983**, *13*, 761–780.
9. (a) Tabushi, I.; Sasaki, T. *J. Am. Chem. Soc.* **1983**, *105*, 2901–2902. (b) Tabushi, I.; Kugimiya, S.; Kinnaird, M. G.; Sasaki, T. *J. Am. Chem. Soc.* **1985**, *107*, 4192–4199.
10. (a) Uemori, Y.; Nakatsubo, A.; Imai, H.; Nakagawa, S.; Kyuno, E. *Inorg. Chim. Acta* **1986**, *124*, 153–160. (b) Uemori, Y.; Munakata, H.; Shimizu, K.; Nakatsumo, A.; Imai, H.; Nakagawa, S.; Kyuno, E. *Inorg. Chim. Acta* **1986**, *113*, 31–36.
11. (a) Traylor, T. G.; Tatsuno, Y.; Powell, D. W.; Cannon, J. B. *J. C. S. Chem. Commun.* **1977**, 732–734. (b) Traylor, T. G.; Mitchell, M. J.; Ciccone, J. P.; Nelson, S. *J. Am. Chem. Soc.* **1982**, *104*, 4986–4989.
12. Salmon, L.; Bied-Charreton, C.; Gaudemer, A.; Moisy, P.; Bedioui, F.; Devynck, J. *Inorg. Chem.* **1990**, *29*, 2734–2740.
13. (a) Iverson, P. E.; Lund, H. *Acta Chem. Scand.* **1966**, 2649. (b) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038–4040.
14. Lindsey, J. *J. Org. Chem.* **1980**, *45*, 5215.
15. (a) Smith, K. M.; Bobe, F. W.; Goff, D. A.; Abraham, R. J. *J. Am. Chem. Soc.* **1986**, *108*, 1111–1120. (b) Stibrany, R. T.; Vasudevan, J.; Knapp, S.; Poterza, J. A.; Emge, T.; Schugar, H. J. *J. Am. Chem. Soc.* **1996**, *118*, 3980–3981.
16. Shirazi, A.; Goff, H. M. *Inorg. Chem.* **1982**, *21*, 3420–3425.
17. If the initial species before 1-MeIm titration exists as monomer **10** in CH_2Cl_2, the coordination equilibria are expressed as Eq. (2). The theoretical curve using various K cannot fit the experimental values at all. Therefore, the initial species must correspond to dimer **10D**.
18. Imai, H.; Kyuno, E. *Inorg. Chem. Acta* **1988**, *153*, 175–182.
19. Ohashi, A.; Satake, A.; Kobuke, Y. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 365–374.
20. (a) Mackin, H. C.; Tsubaki, M.; Yu, N. T. *Biophys. J.* **1983**, *41*, 349–357. (b) Nakayama, S.; Tani, F.; Matsu-ura, M.; Naruta, Y. *Chem. Lett.* **2002**, *31*, 496.
21. Odo, J.; Imai, H.; Kyuno, E.; Nakamoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 742–748.
22. (a) Walker, F. A. *J. Am. Chem. Soc.* **1970**, *92*, 4235–4244. (b) Däges, G. P.; Hüttermann, J. *J. Phys. Chem.* **1992**, *96*, 4787–4794. (c) Bowen, J. H.; Shokhirev, N. V.; Raitsimring, A. M.; Buttlaire, D. H.; Walker, F. A. *J. Phys. Chem. B* **1997**, *101*, 8683–8691.
23. Scheidt, W. R.; Chipman, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 1163–1167.
24. Uemori, Y.; Miyakawa, H.; Kyuno, E. *Inorg. Chem.* **1988**, *27*, 377–382.
25. (a) Hoffman, B. M.; Petering, D. H. *Proc. Natl Acad. Sci. U.S.A.* **1970**, *67*, 637–643. (b) Spilburg, C. A.; Hoffman, B. M.; Petering, D. H. *J. Biol. Chem.* **1972**, *247*, 4219–4223.
26. (a) Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 1150–1153. (b) Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 1154–1159.

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Potent lipid peroxidation inhibitors from *Withania somnifera* fruits

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Abstract—A bioassay-guided purification of the methanolic extract of *Withania somnifera* fruits yielded novel withanamides A–I (**1**–**9**) and withanolides (**10**–**13**). Among the withanolides, compound **10** is novel. The structures of these compounds were determined by using FABMS, HRFABMS, 1D and 2D NMR spectral and chemical methods. The withanamides possess novel chemical structures and consisted of serotonin, glucose and long-chain hydroxyl fatty acid moieties. The stereochemistry of the hydroxyl group in the long-chain fatty acid moiety in compound **1** was determined by the modified Mosher's ester method. Compounds **1**–**13** were tested for their ability to inhibit lipid peroxidation in a model system using large unilamellar vesicles. Withanamides **1**–**5** and **9** inhibited lipid peroxidation by 98, 93, 79, 94, 81 and 86%, respectively, at 1 μg/mL. However, compounds **6**–**8** inhibited the lipid peroxidation by 85, 82 and 90%, respectively, at 0.5 μg/mL. Withanolides **10**–**13** were also tested and only compound **12** inhibited the lipid peroxidation by 82% at 10 μg/mL. To evaluate the structure activity relationships of withanamides A–I, compounds **14**–**16** were purchased and their lipid peroxidation activity determined as in the case of compounds **1**–**9**. Commercial antioxidants, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert-butylhydroquinone (TBHQ), were also tested in this assay at 1 μg/mL and showed 80, 81 and 85% of inhibition, respectively. Our results suggest that the potent antioxidant activity exhibited by novel withanamides is probably due to the hydroxylated long-chain acyl group. This is the first report of withanamides, unique serotonin conjugates, from *W. somnifera* fruits.

1. Introduction

The life-supporting oxygen becomes toxic to most aerobic organisms when exposed to greater concentrations. Reasons for this toxicity are due to the formation of superoxide (O_2^-), hydrogen peroxide (H_2O_2) and the hydroxyl radical (–OH·) during the conversion of oxygen to water in the mitochondria. The free radicals generated from environmental contaminants and by exogenous factors such as drugs, toxins and stress cause oxidative damage to biological macromolecular structure and function.[1] It results in the progression of many disease processes including atherosclerosis, cardiovascular diseases and cancer. Several studies linked the aging process to the generation of reactive oxygen and nitrogen.[2] The oxidative stress also damages the function of pancreatic β-cells function and results in diabetes.[3] The singlet oxygen reacts with unsaturated fatty acids to form lipid peroxides which in turn decompose to initiate the formation of mutagens. Therefore, natural products or chemicals with the potential to scavenge singlet species could reduce biological disorders that limit the progression of various aging related diseases. Many epidemiological studies show that diets rich in antioxidants play a major role in the prevention of heart disease, cancer, diabetes, and Alzheimers's disease.[4]

Some of the pharmaceuticals prescribed for depression or anxiety contain natural antioxidants. Mixtures of ascorbic acid, pyridoxine, carotene, vitamin E, Zn, nicotinamide, and Se are used to treat depression or anxiety. Also, natural antioxidants are used as food additives to inhibit lipid peroxidation and to maintain the nutritional qualities of food. It is also reported that antioxidants decrease the side effects of chemotherapy during cancer treatment.[5] The commonly used synthetic antioxidants to prevent the lipid peroxidation in food are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), and tert-butylhydroquinone (TBHQ). However, these antioxidants are considered to be potential carcinogens[6] and hence, there is considerable interest in developing safe and natural antioxidants.

Withania somnifera L Dunal, a member of the Solanaceae family and is well known for its medicinal uses. It is an annual herb, and the major constituents reported from its

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roots are withanolides and alkaloids.[7] In Ayurvedic medicine, commonly practiced in India, the fruits of *W. somnifera* are used as an emetic, sedative, diuretic and for the treatment of asthma, atherosclerosis, intestinal and liver disorders.[8] Our recent study on the leaves of this plant yielded several withanolides with cyclooxygenase enzyme inhibitory activity.[9] Also, unsaturated fatty acids[10–12] and withanolides[13,14] were reported from the seeds of *W. somnifera*. However, the components of *W. somnifera* fruits were not investigated for biological activities. In this study, we report the bioassay guided extraction and purification of withanamides, novel serotonin conjugates, and a novel withanolide with potent antioxidant activity from *W. somnifera* fruits.

2. Results and discussion

The fruits were collected from *W. somnifera* plants grown in the greenhouses of the Bioactive Natural Products and Phytoceutical Laboratory at Michigan State University. Dried fruits were ground and extracted at room temperature sequentially with hexane, EtOAc, MeOH and ammoniacal MeOH. Hexane and EtOAc extracts were analyzed by TLC and GCMS and found to contain mainly β-carotene and fatty acids. These extracts did not exhibit antioxidant activities and were not further investigated. Fractionation of the MeOH extract by MPLC yielded five fractions, and all inhibited lipid peroxidation at 10 ppm. Purifications of these active fractions by CC, reverse phase HPLC and prep. TLC yielded compounds **1**–**9**, the withanamides, and **10**–**13**, the withanolides.

Withanamide A (**1**) was obtained as a pale brown amorphous powder. The HRFABMS of **1** displayed an $[M+H]^+$ ion at *m/z* 779.4329 (calcd 779.4330) and indicated its molecular formula as $C_{40}H_{62}N_2O_{13}$. The IR spectrum gave bands at 1633, 3413 cm^{-1} and suggested the presence of amide carbonyl and hydroxyl groups in the molecule. The ^1H NMR spectrum displayed three doublets of doublets at δ 7.15, 6.92, and 6.66, respectively, and a singlet at δ 6.99. Also, it showed two triplets at δ 2.84 and 3.42, respectively. These signals clearly indicated the presence of a substituted tryptamine[15] moiety in the molecule. Two doublets at δ 4.38 and 4.30, integrated for one proton each, were assigned to two anomeric protons, respectively, and indicated that compound **1** contained a disaccharide moiety. A broad singlet at δ 1.27, a triplet at δ 2.12 and a multiplet, integrated for four protons, at δ 5.31 were assigned to the presence of an unsaturated fatty acid moiety in compound **1**. A methyl signal at δ 1.19 appeared as a doublet was indicative of a methine carbon in the fatty acid moiety and was assigned to H-18‴. Also, a one-proton multiplet at δ 3.79 confirmed the presence of a hydroxyl moiety at C-17. Three signals observed at δ 2.04 and 2.75 were typical of allylic methylene protons, and the corresponding carbon signals were at δ 28.2, 28.1 and 26.5, respectively. The ^{13}C NMR shift values indicated that the geometry of double bonds in compound **1** as *Z* since the allylic carbons in the *E* isomer would appear at around 32 ppm.[16,17]

The ^{13}C NMR signals observed in compound **1** at δ 112.4, 112.6, 112.5, 151.0 and 133.0 were assigned to C-6, C-7, C-3, C-5 and C-9, respectively. The signal at δ 176.2 indicated an amide linkage in the molecule. The signals at δ 77.7 and 22.1 were attributable to hydroxyl and methyl carbons, respectively, of the fatty acid moiety in **1**.

Acid hydrolysis of compound **1** gave glucose as the only sugar in addition to serotonin and a fatty acid as products. The identity of glucose was confirmed by NMR spectral data and was further supported by the TLC comparison of the sugar resulting from the hydrolysis with an authentic sample of glucose. The downfield shifts observed for C-6′ (δ 69.7) by 7 ppm as compared to the C-6″ (δ 62.7) in the ^{13}C NMR spectrum of compound **1** suggested a 1″→6′ linkage of the two glucose moieties. The ^1H and ^{13}C NMR data confirmed that the sugar unit in compound **1** was a diglucoside and was also in agreement with published spectral data of diglucosides.[9]

Additional evidence for the structural assignment of compound **1** was obtained from its MS fragmentation, NOESY, HMBC and COSY studies. The ion at *m/z* 617 observed in its MS confirmed the loss of one of the glucose units from the molecular ion. The fragment at *m/z* 455 was assigned to the aglycone moiety and showed that the hydroxyl fatty acid side chain contained 18-carbons. The diglucoside unit was placed at C-5 based on the NOESY correlation of H-1′ to H-4. Also, the HMBC correlations between the H-1″ at δ 4.30 and C-6′ at δ 69.7 confirmed a 1″→6′ linkage of glucose moieties (Fig. 1). The COSY and TOCSY spectral data of compound **1** confirmed the positions of double bonds at C-6‴ and C-9‴, respectively (Fig. 1). The methine proton of the oxygenated carbon at δ 3.79 in the side chain was correlated to the terminal methyl group in the molecule as indicated by its COSY spectrum. It was also supported by HMBC correlations (Fig. 1) and confirmed the −OH group at C-17‴.

The absolute configuration of the −OH group at C-17‴ in compound **1** was determined by Mosher ester method.[18] Compound **1** was reacted separately with *R* (−) and *S* (+) α-methoxytrifluorophenylacetyl chlorides (MTPA) in anhydrous pyridine. Purification of the reaction mixtures yielded the *R* and *S*-MTPA esters. The ^1H NMR analyses of the resulting esters revealed that the terminal methyl in the *S*-MTPA ester appeared at a lower field than in the *R*-MTPA ester. Similarly, H-16‴ in *S*-MTPA ester appeared at higher field than the corresponding proton in the *R*-MTPA ester. The $\Delta\delta$ ($\delta_S-\delta_R$) value for H-18‴ and H-16‴ were+0.03 and −0.02, respectively, and confirmed the configuration at C-17‴ as *R*.[18]

Withanamide B (**2**), a colorless amorphous powder with an $[\alpha]_D$ of −34°, gave the $[M+H]^+$ at *m/z* 755.4330 and confirmed its molecular formula as $C_{38}H_{63}N_2O_{13}$ (calcd 755.4331). The ^1H and ^{13}C NMR spectra of **2** were very similar to those of compound **1** except that it lacked olefinic protons signals. Molecular ion of **2** was 24 amu less than that of compound **1**. This showed that side chain in **2** was saturated and contained only sixteen carbons. The linkage of the glucose moieties was evidenced as 1″→6′ by the downfield shift of C-6′ to δ 69.7 and HMBC correlations observed between C-1″ and H-6′ (Fig. 2). The methyl

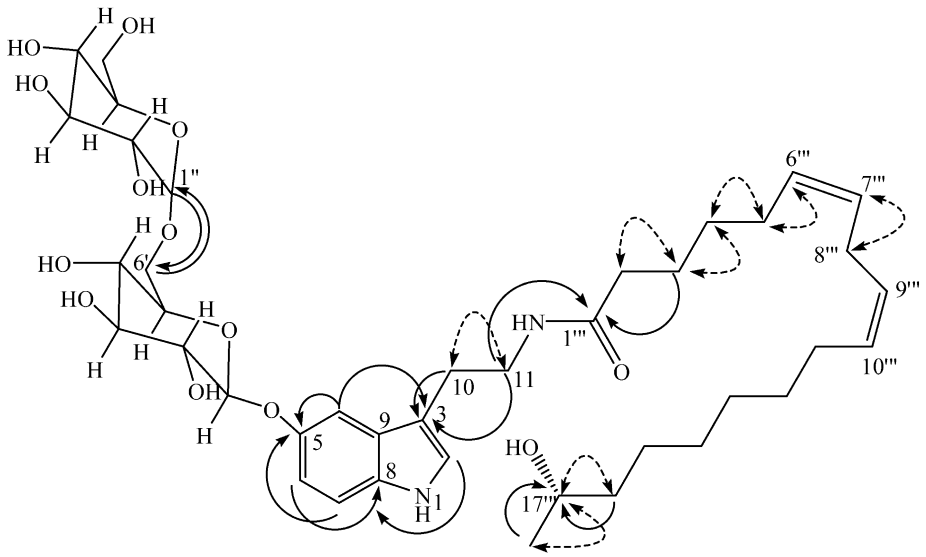


Figure 1. Selected HMBC (→) and COSY (↔) correlations observed in compound **1**.

protons (3H, d, J=6.5 Hz, H-16‴) were correlated to the carbon at δ 77.7 in its HMBC spectrum and confirmed the −OH substitution at C-15‴ (Fig. 2). The proposed structure of **2** was confirmed by HMQC, HMBC, DEPT and NOESY experiments.

The ^{1}H NMR of withanamide C (**3**) was similar to compound **2** except for the presence of a methyl triplet at δ 0.91 instead of a doublet at δ 1.20. In addition, it gave the molecular formula as $C_{38}H_{63}N_2O_{13}$ similar to that of compound **2**. The major difference in the ^{13}C NMR spectrum of **3** was the up-field shift of one of the methylene groups and appeared at δ 26.3. The appearance of a methyl carbon at δ 10.1, as compared to those of the regular fatty acids (14.0 ppm) and the downfield shift of a long chain hydroxyl carbon (δ 82.0) suggested the position of an −OH group at C-14‴. The triplet at δ 0.91 showed a COSY correlation to the methylene protons at δ 1.56, which in turn

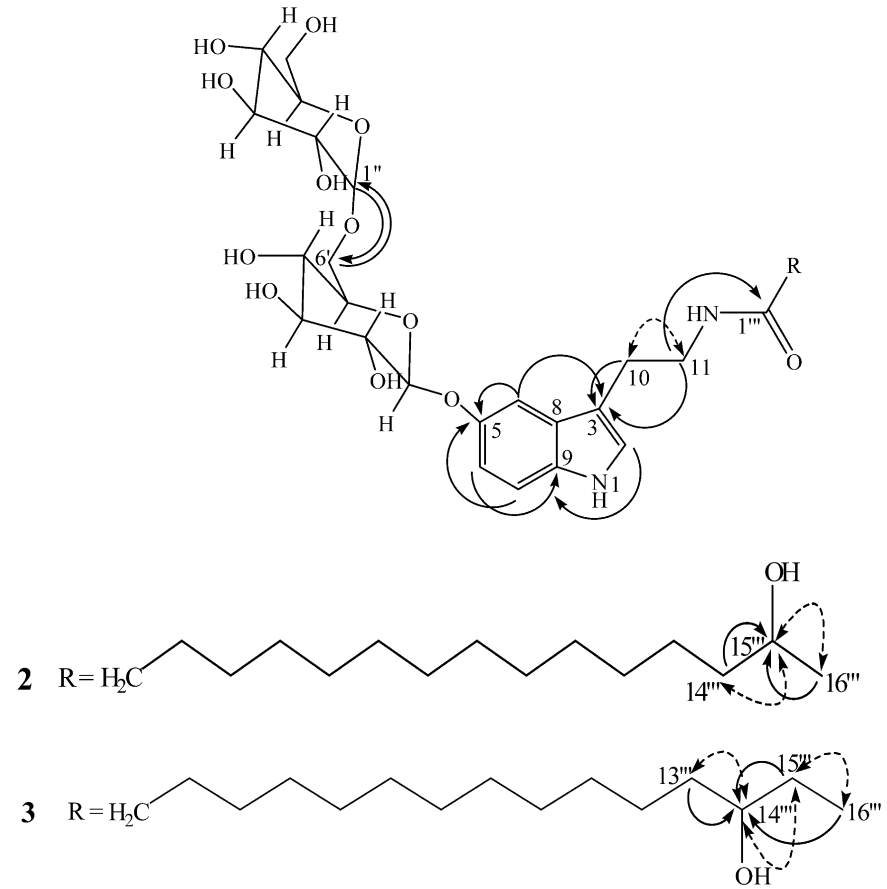


Figure 2. Significant HMBC (→) and COSY (↔) correlations of **2** and **3**.

correlated to the proton at δ 3.63, further confirming the $-$OH moiety at C-14‴ (Fig. 2). The presence of $-$OH at C-14‴ was also substantiated by HMBC correlations of the methyl triplet at δ 0.91 to the hydroxyl carbon at δ 82.0 (Fig. 2). Therefore, compound **3** was confirmed as a positional isomer of **2**.

The HRMS of withanamide D (**4**) gave an $[M+Na]^+$ ion at *m*/*z* 805.4462 that indicated its molecular formula as $C_{40}H_{66}O_{13}N_2$. The ^1H and ^{13}C NMR spectral data of **4** were similar to those of compound **2** and indicated that it contained a saturated side chain with hydroxyl group. Since the methyl signal appeared as a doublet at δ 1.12, the position of the hydroxyl in 4 was assigned at C-17‴. In addition, the MS data confirmed that the side chain in compound **4** consisted of eighteen carbons.

Withanamide E (**5**), a pale brown solid, gave the $[M+H]^+$ ion at *m*/*z* 783.4645 that indicated its molecular formula as $C_{40}H_{66}N_2O_{13}$. The ^1H NMR spectral data of **5** was similar to those of withanamide C (**3**) and indicated the presence of a saturated side chain in the molecule. The methyl triplet at δ 0.91 suggested that the terminal carbons in compound **5** had a similar substitution pattern as in **3**. The difference in the molecular weight by 28 amu, as compared to **3**, indicated the presence of two additional $-CH_2$ groups in **5**. This confirmed that compound **5** contained an 18-carbon side chain with the $-$OH group at C-16‴. Therefore, compound **5** was characterized as a positional isomer of **4**.

The ^1H NMR data of compound **6** were similar to those of withanamide A (**1**), with the exception that it gave a 2H multiplet at δ 5.33 assigned to the olefinic protons in the molecule. The corresponding carbons signals appeared at δ 130.9 and 130.8, respectively. The appearance of a methyl triplet at δ 0.91 together with the signal for a carbon at δ 82.0 in compound **6** indicated that the terminal carbon in the fatty acid moiety had a similar substitution pattern as in compounds **3** and **5**. Therefore, the olefinic moiety was assigned to C-9‴ since the chemical shift of these two olefinic carbons differed by 0.2 ppm.[17] The geometry of the double bond was deduced as *Z* since C-8‴ and C-11‴ appeared at δ 28.1 and 28.2, respectively.[17] The HRFABMS of **6** gave a molecular ion at *m*/*z* 803.4304 $[M+Na]^+$ and further supported a C-18 fatty acid moiety in its structure.

Withanamide G (**7**) gave a molecular ion at *m*/*z* 753.4173, $[M+H]^+$, which was two mass units less than the molecular weight of compound **2** (755.4331). Therefore, it suggested that the fatty acid moiety present in it contained 16-carbons with one olefinic moiety. A 2H multiplet at δ 5.34 supported this assignment. The doublet appeared at δ 1.21, assigned to methyl protons, indicated that the $-$OH moiety present in the side chain had similar substitution to that of compounds **1** and **2**. The ^{13}C NMR displayed signals for serotonin diglucoside and unsaturated hydroxy fatty acid side chain moieties. The olefinic carbon signals in **7** appeared at δ 130.9 and 130.8, similar to that of compound **6**, were assigned to C-9‴ and 10‴, respectively.[17] The geometry of the double bond in compound **7** was therefore deduced as *Z* based on the chemical shifts of the allylic carbons C-8‴ and C-11‴ at δ 28.0 and 28.1, respectively.

Withanamide I (**8**) gave a molecular ion at *m*/*z* 775.4013. The ^1H and ^{13}C NMR spectra of compound **8** were similar to those of withanamide A (**1**) except for the 8H multiplet at δ 5.34. The corresponding carbon signals appeared at δ 132.6, 132.2, 131.4, 130.1, 128.7 and 128.5, respectively, and indicated the presence of four double bonds in the hydroxyl fatty acid moiety. One of the double bonds was assigned at C-15‴ based on correlations observed in its TOCSY spectrum (Fig. 3). A signal at δ 2.82, integrated for 6H, was assigned to three methylene groups adjacent to the double bonds at C-9‴, C-12‴ and C-15‴. As in withanamide A, the geometry of the double bonds was deduced to be *Z* based on the chemical shifts of allylic carbons at δ 26.6, 27.0 and 28.2, respectively, in its ^{13}C NMR spectrum.[17]

Withanamide I (**9**) also gave a similar ^1H NMR spectral data to that of withanamide A (**1**) as indicated by the chemical shifts for the serotonin and hydroxyl-fatty acid moieties in it. The $[M+H]^+$ ion at *m*/*z* 941.4857 confirmed that the molecular formula of compound **9** was $C_{46}H_{72}O_{18}N_2$. The presence of two double bonds in the fatty acid moiety was confirmed by 4H multiplet at 5.33 ppm. In addition, the presence of three anomeric protons at δ 4.32, 4.36 and 4.39

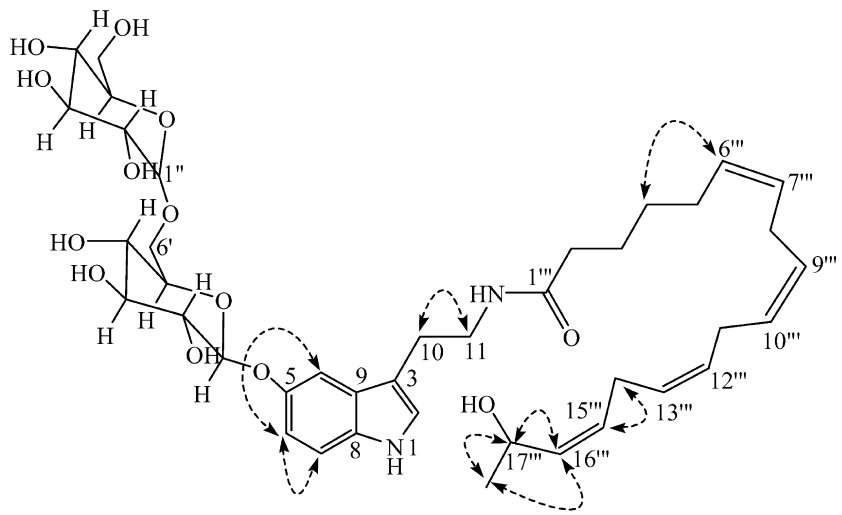
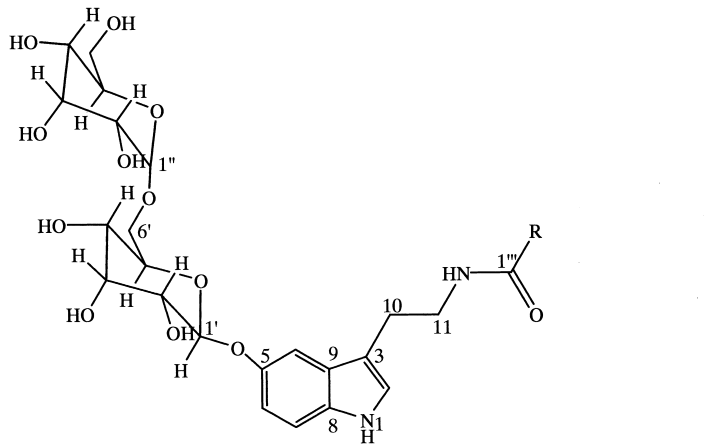
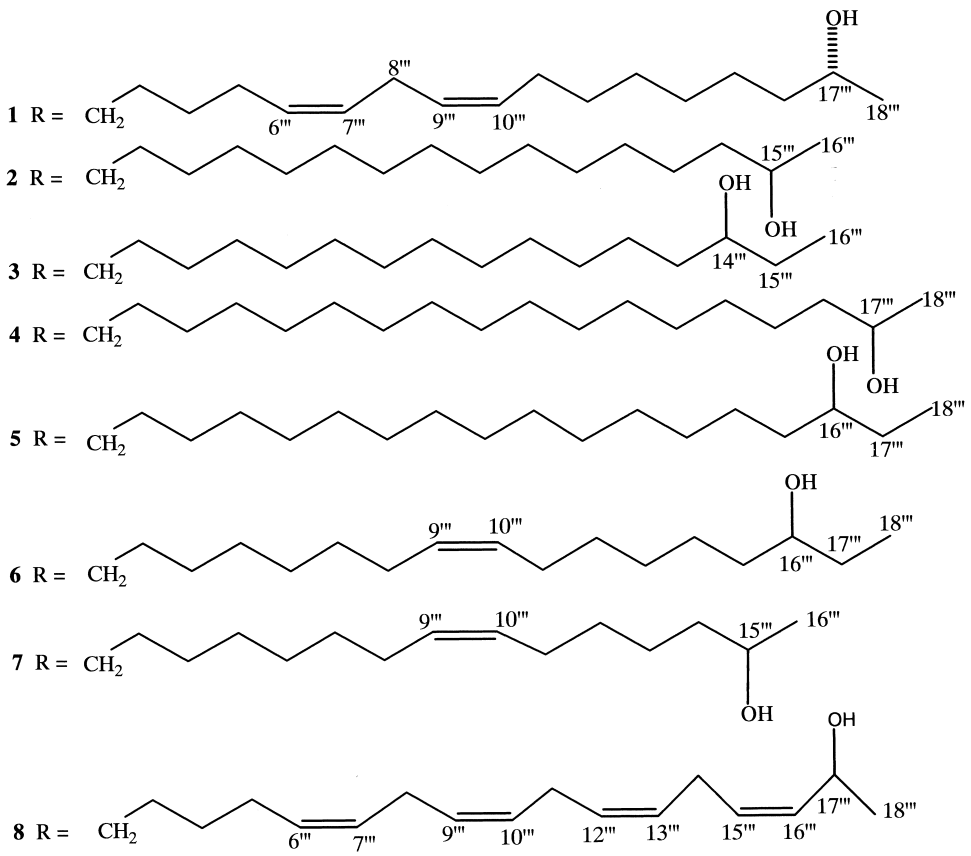


Figure 3. Selected TOCSY (→) correlations of **8**.

indicated that withanamide I (**9**) was a triglucoside. The linkage of two glucose units, as in the case of withanamide A (**1**), was established as C-1″→C-6′as indicated by the downfield shift of H-6′ protons. A third glucose unit present in **9** was also assigned a linkage of 1‴→6″, as confirmed by the downfield shift of H-6″. Therefore, the polysaccharide unit in compound **9** was established as β-D-glucopyranosyl (1″→6′)-β-D-glucopyranosyl (1‴→6″)-β-D-glucopyranoside. The spectral data of compound **1** and **9** were very similar except that compound **9** showed signals for an additional glucose moiety. Also, the appearance of the methyl group as a doublet in the ^{1}H NMR of compound **9** was identical to that of the terminal substitution of long chain fatty acid moiety present in withanamide A (**1**).

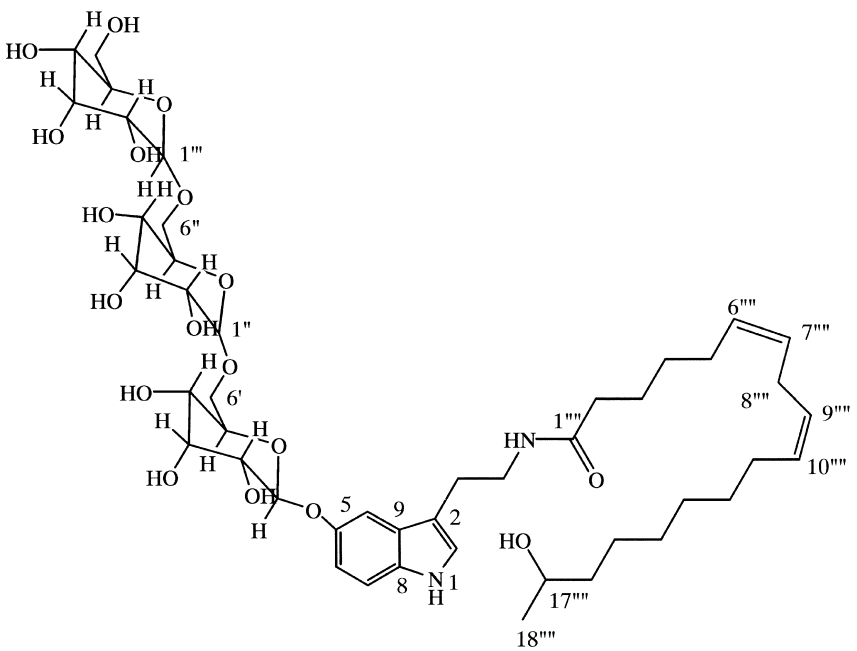
Compound **10** was isolated as a colorless amorphous powder and displayed a molecular ion at *m*/*z* 785 in its FABMS spectrum. The IR absorption bands at 3421, 1724 and 1663 cm^{-1} in **10** suggested the presence of an −OH and a saturated lactone in the molecule. The HRFABMS confirmed its molecular formula as $C_{40}H_{65}O_{15}$ (M+H$^+$ 785.4325; calcd 785.4323). Three singlets at δ 0.89, 1.01, 1.25 and two doublets at δ 1.17 and 1.15 observed in its ^{1}H NMR spectrum were assigned to the methyl groups at 18, 19, 21, 27 and 28, respectively. The broad doublet at δ 5.52 and doublets at δ 4.39 and 4.36, which integrated for one proton each, were assigned to olefinic and anomeric protons, respectively. The doublet of doublets at δ 4.24 and a multiplet at δ 4.00 were assigned to H-22 and H-3, respectively. Although compounds **10** and withanoside VI (**11**) showed similar ^{1}H NMR chemical shifts,[19] the appearance of two methyl doublets in **10** indicated that a





double bond in the α,β-unsaturated δ-lactone ring was absent. In addition, the signal at δ 178.9, assigned to C=O, confirmed a saturated lactone moiety in compound **10**. Two signals at δ 104.8 and 103.1, assigned to anomeric carbons, supported a diglucosidic moiety in the molecule. The downfield shift of H-6′ protons as compared to H-6″ indicated a 1″→6′ linkage of the two glucose moieties in compound **10**. Also, the downfield shift of C-6 (δ 69.7) of one of the glucose units further confirmed the linkage as 1″→6′ similar to the results in withanamides. The carbon signals at δ 81.9, 58.1, 56.1, 139.1, 125.5, 75.1 and 73.6 were assigned to C-22, C-14, C-17, C-5, C-6, C-1 and C-3, respectively. Other carbon signals, which appeared at δ 14.2, 14.4, 19.9, 20.5 and 21.2, were assigned to methyls at C-18, C-28, C-19, C-27 and C-21, respectively. The position of the diglucoside moiety was assigned at C-3 by comparison of its spectral data to the spectral data of withanolides **11**–**13**. The molecular ion at *m*/*z* 784 indicated that it is two mass units higher than the withanoside VI and further supported the proposed structure for compound **10**. From the spectral data, the structure of compound **10** was derived as 24, 25-dihydrowithanolide VI.

Serotonin, a neurotransmitter, is the aglycone moiety in all the withanamides A–I (**1**–**9**) characterized from *W. somnifera* fruits. Therefore, to compare the structure and activity of these compounds, tryptamine (**14**), 5-methoxy-serotonin (**15**) and serotonin (**16**) were assayed along with the withanamides. Compounds **1**–**16** and commercial antioxidants BHT, BHA and TBHQ were tested for the inhibition of lipid peroxidation by using large unilamellar vesicles (LUVs) model system.[20] A dose response study was performed for all compounds and Fig. 4 represents the activity profiles of withanamides compared to the commercial antioxidants evaluated at 1 ppm concentration. BHA, BHT and TBHQ inhibited lipid peroxidation by 80, 81 and



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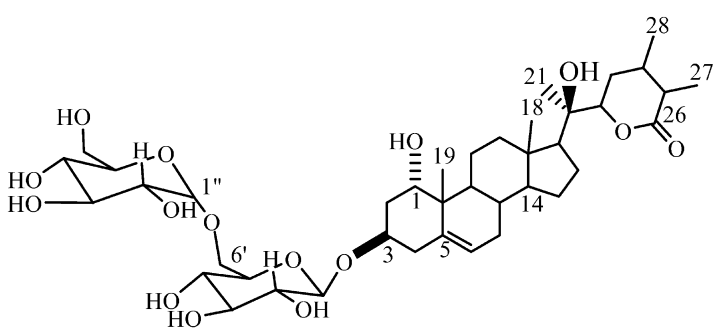

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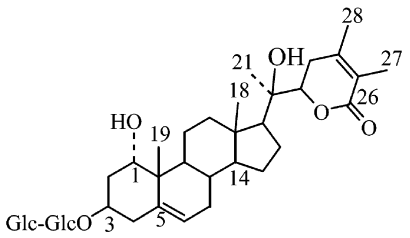

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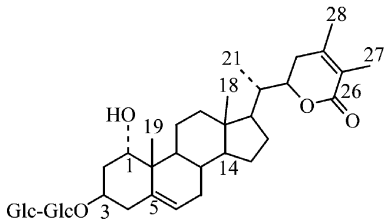

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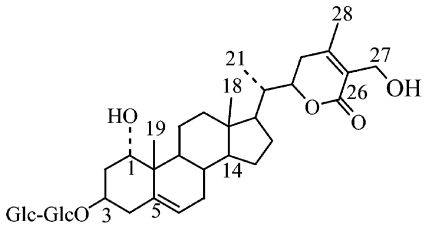

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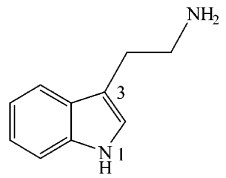

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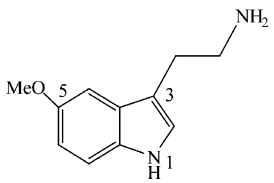

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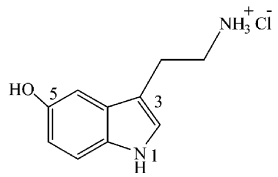

16

85%, respectively, at 1 μg/mL (Fig. 4). Withanamide B (**2**) contained a saturated side chain and inhibited lipid peroxidation by 93% at 1 μg/mL (Fig. 4) whereas withanamide C (**3**), a positional isomer of **2**, showed 79% inhibition. Similarly, the inhibitions observed with withanamide D (**4**) and E (**5**) were 94 and 81%, respectively, at 1 μg/mL. Interestingly, compounds **6** and **7** with one double bond in the acyl moiety showed 85 and 82% inhibition, respectively, at 0.5 μg/mL. Similarly, withanamide H (**8**) with four double bonds in its fatty acid moiety exhibited 90% inhibition at 0.5 μg/mL. However, Withanamide A (**1**), a digluoside with two double bonds in its fatty acid moiety, inhibited lipid peroxidation by 98% whereas withanamide I (**9**), a triglucoside, gave 86% inhibition at 1 μg/mL (Fig. 4).

Tryptamine (**14**) inhibited lipid peroxidation by 40% at 100 μg/mL. However, 5-methoxytryptamine or 5-methylserotonin, compound **15**, inhibited lipid peroxidation by 30% at 50 μg/mL compared to serotonin (5-hydroxy tryptamine) hydrochloride which inhibited by 44% at 10 μg/mL. 5-Methoxytryptamine (**15**) gave a higher activity than tryptamine (**7**) and indicated that 5-oxygenation contributed to the increased lipid peroxidation activity. Increased peroxidation inhibition was observed for serotonin hydrochloride when compared to its 5-methoxyl derivative and suggested that the free hydroxyl at the 5-position was significant to account for the increased lipid peroxidation activity. Withanamides A–I, (**1**–**9**), exhibited excellent lipid peroxidation inhibitory activity equal to or better than the commercial antioxidants and far better than serotonin (Fig. 4). The serotonin and hydroxyl fatty acid moieties were therefore contributing to the strong lipid peroxidation inhibitory activity displayed by these compounds. Among withanamides, the unsaturation in the acyl moiety further contributed to higher lipid peroxidation inhibitory activity. Compounds **2** and **4**, with hydroxyl groups at C-15‴ and C-17‴, respectively, were more active than their isomers **3** and **5**. This indicated that the position of the hydroxyl groups in the acyl moieties also played an important role in the antioxidant activity.

Withanolides isolated from the fruits *W. somnifera* in our study also inhibited lipid peroxidation (Fig. 5). Withanoside V (**12**), one of the major compounds isolated from *W. somnifera* fruits, showed 82.5% inhibition of lipid peroxidation at 10 ppm whereas the inhibition of withanoside IV (**13**) was only 25% at 100 μg/mL. Withanolide VI (**11**) gave 86% lipid peroxidation inhibitory activity at 50 ppm and its 24, 25-dihydroderivative (**10**) showed similar activity at 100 ppm (Fig. 5). The saturation of the lactone moiety in compound **10** decreased the activity as compared to its dehydroderivative **11** and indicated that the α,β-unsaturated δ-lactone moiety was significant for the

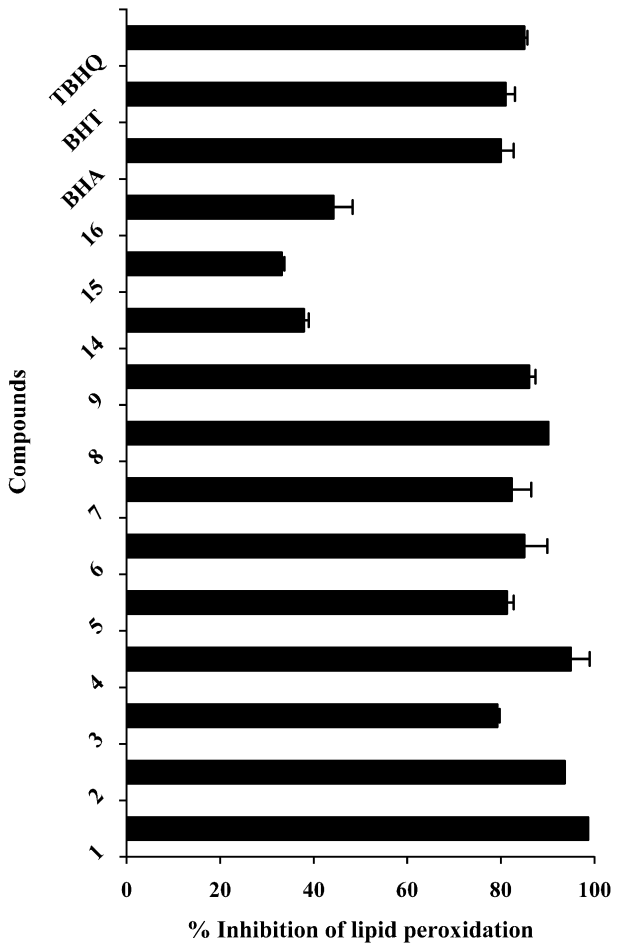

Figure 4. Inhibition of lipid peroxidation by compounds **1**–**9** and **14**–**16**. Fluorescence intensity was monitored for 21 min at intervals of 3 min. The percentage of inhibition represented was calculated with respect to DMSO control at 21 min. Fe^{2+} was used to induce the peroxidation. The concentrations of compounds tested were **1**–**5** and **9** at 1 μg/mL; **6**–**8** at 0.5 μg/mL; **15** at 100 μg/mL; **16** at 50 μg/mL; **17** at 10 μg/mL. Commercial antioxidants BHA, BHT and TBHQ were tested at 1 μg/mL. Data represented indicates the mean±one standard deviation (n=2).

lipid peroxidation inhibitory activity of withanolides. Hydroxylation at C-27 in compound **13** decreased the activity than the hydroxylation at C-20 in compound **11**. This may be due to hydrogen bonding between the C-27 hydroxyl and the carbonyl group of the lactone moiety in compound **13**.

Withanamides A–C (**1**–**3**) were also tested in the 2,2-azobis-(2-amidinopropane) dihydrochloride (AAPH) induced lipid peroxidation (Fig. 6) assay[20] using LUVs under identical conditions with LUVs and Fe^{2+}. Withanamides **1**–**3** and TBHQ exhibited 71, 60, 63 and 67% of inhibition at 1 μg/mL, respectively. This confirmed that the lipid peroxidation inhibitory activity observed for withanamides was not due to the chelation effect with Fe^{2+}.

Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes inhibitory activities of withanamides A–C (**1**–**3**) and withanoside V (**12**) were found to be inactive when assayed at 100 μg/mL.[9] Compounds **1**–**3** were also tested for the inhibition of tumor cell proliferation on NCI-H460 (Lung), HCT-116 (colon), SF-268 (Central Nervous System; CNS) and MCF-7 (breast) human tumor cell lines using MTT assay[21] and found to be inactive. This implied that withanamides possessed little or no cytotoxicity. These compounds were not tested against corresponding normal cells due to the unavailability of normal cells.

The lipid peroxidation inhibition by these withanamides at 0.5–1 μg/mL was similar to or better than that of BHA, BHT and TBHQ, suggesting that these compounds could be used as natural antioxidants and a potential substitute for BHA, BHT and TBHQ. It is important to note that these compounds did not exhibit cellular toxicity in our human tumor cell assays. Therefore, *W. somnifera* fruits or the withanamides are potential candidates for the development of natural antioxidants for food and health applications.

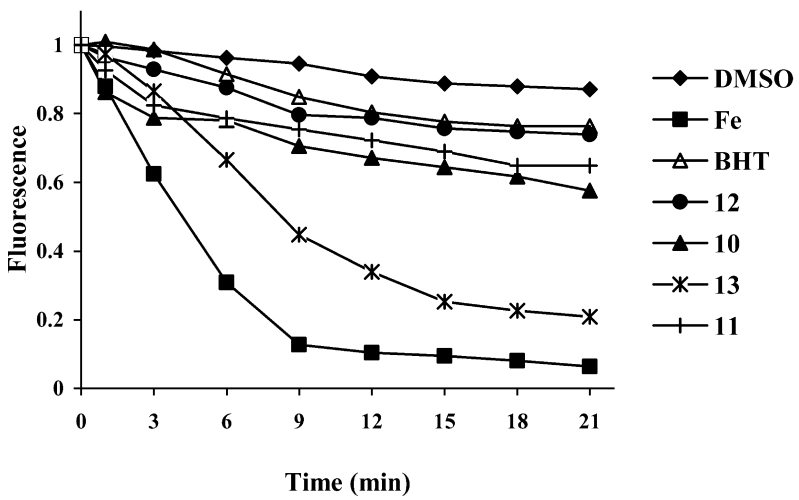

Figure 5. The fluorescence intensity was monitored over 21 min of Fe^{2+} induced lipid peroxidation by withanolides **10**–**13** at intervals of 3 min. BHT was used as positive control in this assay at 1 ppm. Compounds tested were **10** and **13** at 100 μg/mL; **12** and **11** were at 10 and 50 μg/mL, respectively. Data represented indicates the mean±one standard deviation (n=2).

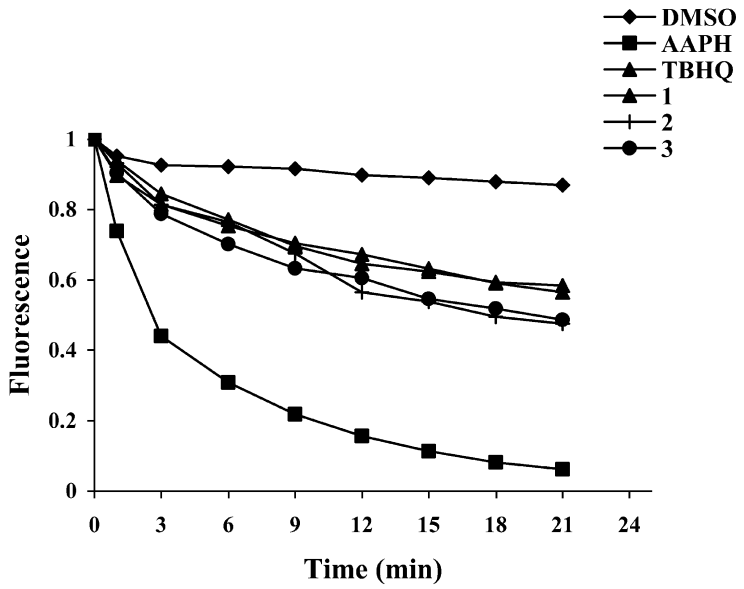

Figure 6. Effect of withanamides **1**–**3** on AAPH induced lipid peroxidation at 1 ppm. Fluorescence intensity was monitored for 21 min at intervals of 3 min. The percentage of inhibition was with respect to control (DMSO). TBHQ was used as positive control in this assay at 1 ppm. The concentration of AAPH was 2.5 mM at 37 °C.

3. Experimental

3.1. General

The HRFAB and FAB (positive ion mode) mass spectra were measured on JEOL MX 110 mass spectrometer at the Mass Spectrometry Facility Center, Michigan State University. ^{1}H (500 MHz) and ^{13}C (125 MHz) and 2D NMR experiments were carried out on an INOVA VARIAN VRX 500 instrument using standard pulse sequences. The chemical shifts were measured in CD_3OD and expressed in δ (ppm). HMBC was optimized for J=8 Hz. IR spectra were recorded on Mattson Galaxy Series FTIR 300 using WinFIRST software (Thermo Nicoloet, Madison, WI) spectrometer. $[\alpha]_D$ was measured in MeOH at 20 °C using a Polarimeter (Perkin Elmer Model 341, Shelton, CT). ACS grade solvents were used for the isolation and purification. The silica gel used for MPLC was Merck Silica gel 60 (35–70 μm particle size). Si gel PTLC plates (20×20, 500 μm) were purchased from Analtech, Inc. (Newark, DE). Recycling preparative HPLC (Japan Analytical Industry Co. model LC-20) was used with JAIGEL-ODS-C_{18} Column for separation of compounds. Positive controls butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tert-butylhdroquinone (TBHQ), serotonine, 5-methoxyserotonine, and tryptamine were purchased from sigma-aldrich Co (St Louis, MO). The lipid, 1-stearoyl 2-linoleoyl *sn*-glycerol 3-phosphocholine (SLPC), was purchased from Avanti Polar Lipids (Alabaster, AL). The fluorescent probe, 3-[*p*-(6-phenyl)-1,3,5-hexatrienyl]-phenylpropionic acid was purchased from Molecular Probes (Eugene, OR) and *R*- and *S*-methoxy-(trifluoromethyl)-phenylacetyl (MTPA) chlorides from Sigma-Aldrich Co.

3.2. Plant material

The *W. somnifera* plants were grown in the greenhouses of Bioactive Natural Products and Phytoceutical Laboratory at Michigan State University. Plants were grown under 12 h photoperiod at 75 °F in 1:1 mixture of loamy sand and bacto mix in 6″-plastic pots. The plants were watered and fertilized daily using 20:20:20 (N–P–K). The fully ripened fruits were collected, dried at room temperature and extracted immediately.

3.3. Extraction and isolation

The dried and ground fruits (100 g) of *W. somnifera* were sequentially extracted with *n*-hexane (3×500 mL), EtOAc (3×500 mL), MeOH (5×500 mL) and ammoniacal MeOH (3×500 mL). Evaporation of the solvent under reduced pressure yielded *n*-hexane (8 g), EtOAc (2 g), MeOH (8 g) and ammoniacal MeOH (2 g) crude extracts. The MeOH extract (7 g) was defatted (1.5 g) with *n*-hexane (5×150 mL) and fractionated by silica gel medium pressure liquid chromatography under gradient conditions with 70% $CHCl_3$ to 80% MeOH. The 70% $CHCl_3$ eluates were collected in 10 fractions of each 40 mL, similar on TLC, pooled and concentrated to yield fractions I (300 mg). The similar fractions (8 fractions, 50 mL each) obtained from $CHCl_3$–MeOH (1:1) elution were combined and concentrated to give fraction II (100 mg). The $CHCl_3$–MeOH (40:60) eluates gave 15 fractions (50 mL each) were similar, pooled, evaporated to afford fraction III (2 g). Concentration of six similar fractions (each 45 mL) from $CHCl_3$–MeOH (30:70) elution gave fraction IV (1.8 g). The 80% MeOH eluates were pooled and evaporated to afford V (200 mg).

The fractions I and II contained predominantly fatty acids as indicated by TLC. Fraction III (1.8 g) was purified by prep. HPLC using JAIGEL-ODS-C_{18} column and MeOH–H_2O (75:25, v/v) as mobile phase at 3 mL/min. Fractions collected were A (15–30 min, 500 mg), B (31–41 min, 200 mg), C (42–56 min, 500 mg), D (58–70 min, 200 mg) and E (71–95 min, 50 mg). Fraction C was further purified by prep. HPLC using MeCN–H_2O (62.5:37.5, v/v) and yielded pure compounds **1** (81.95 min, 62 mg), **2** (92.0 min, 71 mg) and a fraction (104 min, 35 mg). Compounds **1** and

2 were purified again by prep. HPLC using MeCN–H_2O (1:1, v/v) and yielded pure compounds **1** (35 min, 50 mg) and **2** (38.0, 70 mg). The fraction at 104 min was further purified on prep. TLC using EtOAc–MeOH (9:1, v/v) and developed three times in the same mobile phase yielded pure compound **3** (R_f=0.5, 12 mg). Fraction D was purified by HPLC using MeOH–H_2O (76:24, v/v) and gave pure compound **12** (67.3 min, 150 mg). Fraction E was purified by HPLC using MeOH–H_2O (75:25) and yielded three fractions F (71 min, 14 mg), G (101 min, 5 mg), H (112 min, 4.0 mg).

The fraction G was purified by preparative TLC (PTLC) ($CHCl_3$–MeOH, 4:1) and gave compound **4** (R_f=0.6, 2.5 mg). Purification of fractions F and H on PTLC using $CHCl_3$–MeOH (5:1) on the mobile phase gave **5** (R_f=0.65, 8 mg) and **6** (R_f=0.58, 3.0 mg). Fraction II was subjected to HPLC using ACN–H_2O (34:66, v/v) to yield five fractions fr.1 (37.0 min, 38.1 mg), fr.2 (45–70 min, 68.8 mg), fr.3 (84.4 min, 19.8 mg) and fr.4 (94.9 min, 11.4 mg).

Fr.1 was purified by prep.TLC using the mobile phase ($CHCl_3$–MeOH, 1:1, v/v) and afforded a pure withanolide **13** (R_f=0.40, 7.0 mg). Repeated purification of fr.4 by PTLC ($CHCl_3$–MeOH; 75:25, v/v) yielded pure compound **8** (R_f=0.72, 2 mg). Similarly, fr.3 was purified by PTLC ($CHCl_3$–MeOH, 70:30, v/v) yielded compounds **7** (R_f=0.61, 1.0 mg) and **9** (R_f=0.8, 0.7 mg). Purification of fr.2 by PTLC ($CHCl_3$–MeOH, 1:1, v/v) gave band of R_f=0.5 (25.0 mg) and further purified by prep. HPLC using MeCN–H_2O (33:67) as mobile phase to yield withanolides **10** (62.4 min, 6.0 mg) and **11** (70.8 min, 4.0 mg).

3.3.1. Withanamide A (1). Amorphous powder; $[\alpha]_D$=−35° (C 0.0125); UV (MeOH) λ_{max} nm (log ε) 276 (3.50), 300 sh (3.40); IR ν_{max} (KBr) 3413 (–OH), 2926, 2854, 1633 (–CONH), 1458, 1071, 1033, 626. ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (1H, dd, J=8.5, 1.0 Hz, H-7), 6.99 (1H, s, H-2), 6.92 (1H, dd, J=2.5, 0.5 Hz, H-4), 6.66 (1H, ddd, J=9.0, 2.0, 0.5 Hz, H-6), 5.31 (4H, m, H-6‴, 7‴, 9‴, 10‴), 4.38 (1H, d, J=8.0 Hz, H-1′), 4.30 (1H, d, J=7.5 Hz, H-1″), 4.10 (1H, dd, J=11.5, 2.0 Hz, H-6′b), 3.85 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.79 (1H, m, H-17‴), 3.77 (1H, dd, J=11.5, 5.0 Hz, H-6′a), 3.65 (1H, dd, J=12.0, 5.5 Hz, H-6″a), 3.42 (2H, t, J=7.5 Hz, H-11), 3.40 (1H, m, H-5′), 3.39 (2H, m, H-4′, 4″), 3.27–3.38 (3H, m, H-5″, 3″, 3′), 3.20 (1H, d, J=9.0, 8.0 Hz, H-2″), 3.15 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.84 (2H, t, J=7.0 Hz, H-10), 2.75 (2H, t, J=6.5 Hz, H-8‴), 2.12 (2H, t, J=7.5 Hz, H-2‴), 2.04 (4H, m, H-5‴, 11‴), 1.54 (2H, m, H-3‴), 1.42 (2H, m, H-4‴), 1.32 (2H, m, H-16‴), 1.27 (8H, br. s, H-12‴-H-15‴), 1.19 (3H, d, J=6.0 Hz, H-18‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.2 (C-1‴), 151.0 (C-5), 133.0 (C-8), 130.9 (C-10‴), 130.8 (C-7‴), 129.4 (C-9), 129.2 (C-9‴), 129.0 (C-6‴), 124.2 (C-2), 112.6 (C-7), 112.5 (C-3), 112.4 (C-6), 104.7 (C-1″), 104.0 (C-1′), 103.5 (C-4), 77.9 (C-3′, 3″, 5″), 77.7 (C-17‴), 76.8 (C-5′), 75.2 (C-2″), 75.0 (C-2′), 71.6 (C-4″), 71.4 (C-4′), 69.7 (C-6′), 62.7 (C-6″), 41.2 (C-11), 37.3 (C-16‴), 37.2 (C-2‴), 30.6-30.1 (C-12‴-15‴), 30.0 (C-4‴), 28.2 (C-11‴), 28.1 (C-5‴), 27.0 (C-3‴), 26.5 (C-8‴), 26.3 (C-10), 22.1 (C-18‴). HRFABMS 779.4329 (calcd for $C_{40}H_{63}N_2O_{13}$ $(M+H)^+$, 779.4330). FABMS (m/z) 779 $[M+H]^+$, 778 $[M]^+$, 617, 455, 437, 175, 160, 159, 146.

3.3.2. Withanamide B (2). Amorphous powder; $[\alpha]_D$=−34° (C 0.0125); UV (MeOH) λ_{max} nm (log ε) 277 (3.32), 300 sh (3.22); IR ν_{max} (KBr) 3372 (–OH), 2924, 2853, 1632 (–CONH), 1463, 1371, 1071, 1031, 631. ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (1H, dd, J=8.5, 0.5 Hz, H-7), 7.0 (1H, s, H-2), 6.94 (1H, dd, J=2.5, 0.5 Hz, H-4), 6.66 (1H, dd, J=9.0, 2.5 Hz, H-6), 4.40 (1H, d, J=8.0 Hz, H-1″), 4.32 (1H, d, J=7.5 Hz, H-1′), 4.11 (1H, dd, J=12.0, 2.0 Hz, H-6′b), 3.87 (1H, dd, J=12.0, 2.0 Hz, H-6″b), 3.79 (1H, m, H-15‴), 3.78 (1H, dd, J=12.0, 5.5 Hz, H-6′a), 3.67 (1H, dd, J=12.0, 5.5 Hz, H-6″a), 3.44 (2H, t, J=7.0 Hz, H-11), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.38 (3H, m, H-5″, 3″, 3′), 3.24 (1H, dd, J=9.0, 8.0 Hz, H-2″), 3.17 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.85 (2H, t, J=8.0 Hz, H-10), 2.13 (2H, t, J=7.0 Hz, H-2‴), 1.55 (2H, m, H-3‴), 1.39 (4H, m, H-4‴, H-14‴), 1.26 (18H, br. s, H-5‴-H-13‴), 1.20 (3H, d, J=6.5 Hz, H-16‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.2 (C-1‴), 151.0 (C-5), 133.0 (C-8), 129.4 (C-9), 124.2 (C-2), 112.6 (C-7), 112.4 (C-3), 112.3 (C-6), 104.7 (C-1″), 103.9 (C-1′), 103.5 (C-4), 77.9 (3″, 5″), 77.8 (C-3′), 77.7 (C-15‴), 76.8 (C-5′), 75.2 (C-2″), 75.0 (C-2′), 71.5 (C-4″), 71.4 (C-4′), 69.7 (C-6′), 62.7 (C-6″), 41.2 (C-11), 37.6 (C-14‴), 37.2 (C-2‴), 30.8-30.2 (C-4‴-13‴), 27.0 (C-3‴), 26.3 (C-10), 22.0 (C-16‴). HRFABMS 755.4331 (calcd for $C_{38}H_{63}N_2O_{13}$ $(M+H)^+$, 755.4330). FABMS (m/z) 777 $[M+Na]^+$, 755 $[M+H]^+$, 754 $[M]^+$, 593, 431, 413, 396, 160, 146.

3.3.3. Withanamide C (3). Amorphous powder; $[\alpha]_D$=−34° (C 0.01); UV (MeOH) λ_{max} nm (log ε) 276 (3.53), 300 sh (3.42); IR ν_{max} (KBr) 3422 (–OH), 2924, 2853, 1633 (–CONH), 1459, 1071, 1032, 631. ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (1H, dd, J=8.5, 0.5 Hz, H-7), 6.99 (1H, s, H-2), 6.92 (1H, dd, J=2.0, 0.5 Hz, H-4), 6.65 (1H, dd, J=8.5, 2.0 Hz, H-6), 4.40 (1H, d, J=8.0 Hz, H-1″), 4.30 (1H, d, J=8.0 Hz, H-1′), 4.10 (1H, dd, J=12.0, 2.0 Hz, H-6′b), 3.86 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.79 (1H, dd, J=12.0, 6.0 Hz, H-6′a), 3.66 (1H, dd, J=12.0, 5.5 Hz, H-6″a), 3.63 (1H, m, H-14‴), 3.44 (2H, t, J=7.0 Hz, H-11), 3.40 (1H, m, H-4′), 3.39 (1H, t, J=7.5 Hz, H-5′), 3.25–3.37 (4H, m, H-5″, 4″, 3′, 4′), 3.20 (1H, dd, J=9.0, 7.5 Hz, H-2″), 3.16 (1H, dd, J=9.0, 7.5 Hz, H-2′), 2.85 (2H, t, J=7.5 Hz, H-10), 2.14 (2H, t, J=7.5 Hz, H-2‴), 1.56 (4H, m, H-3‴, 15‴), 1.52 (2H, m, H-13‴), 1.27 (18H, br. s, H-4‴-H-12‴), 0.91 (3H, t, J=7.5 Hz, H-16‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.3 (C-1‴), 151.1 (C-5), 133.1 (C-8), 129.5 (C-9), 124.2 (C-2), 112.6 (C-7), 112.5 (C-3), 112.4 (C-6), 104.9 (C-1″), 103.6 (C-1′), 103.5 (C-4), 82.0 (C-14‴), 78.1 (C-5″), 78.0 (C-3′, 3″), 77.0 (C-5′), 75.3 (C-2″), 75.2 (C-2′), 71.7 (C-4″), 71.6 (C-4′), 69.9 (C-6′), 62.8 (C-6″), 41.2 (C-11), 37.2 (C-2‴), 34.5 (C-13‴), 31.0-28.6 (C-4‴-12‴), 27.0 (C-3‴), 26.3 (C-15‴), 26.0 (C-10), 10.1 (C-16‴). HRFABMS 755.4331 (calcd for $C_{38}H_{63}N_2O_{13}$ $(M+H)^+$, 755.4330). FABMS (m/z) 777 $[M+Na]^+$, 755 $[M+H]^+$, 754 $[M]^+$, 431, 413, 396, 160, 159, 146.

3.3.4. Withanamide D (4). Amorphous powder; UV (MeOH) λ_{max} nm (log ϵ) 277 (3.43), 301 sh (3.30); IR ν_{max} (KBr) 3402 (–OH), 2923, 2852, 1636 (–CONH), 1464, 1381, 1071, 1040, 630. ^{1}H NMR (500 MHz, CD_3OD)

δ 7.14 (1H, dd, J=9.0, 0.5 Hz, H-7), 6.99 (1H, s, H-2), 6.93 (1H, dd, J=2.5, 0.5 Hz, H-4), 6.65 (1H, dd, J=9.0, 2.5 Hz, H-6), 4.39 (1H, d, J=8.0 Hz, H-1″), 4.32 (1H, d, J=8.0 Hz, H-1′), 4.10 (1H, dd, J=11.5, 2.0 Hz, H-6′b), 3.86 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.79 (1H, m, H-17‴), 3.79 (1H, dd, J=12.0, 5.5 Hz, H-6′a), 3.66 (1H, dd, J=12.0, 5.5 Hz, H-6″a), 3.44 (2H, t, J=7.0 Hz, H-11), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.36 (4H, m, H-3′, 3″, 5′, 5″), 3.20 (1H, dd, J=9.0, 8.0 Hz, H-2″), 3.15 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.86 (2H, t, J=7.0 Hz, H-10), 2.14 (2H, t, J=7.0 Hz, H-2‴), 1.57 (2H, m, H-3‴), 1.40 (2H, m, H-16‴), 1.28 (24H, br. s, H-4‴-H-15‴), 1.21 (3H, d, J=6.0 Hz, H-18‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.3 (C-1‴), 151.1 (C-5), 133.1 (C-8), 129.5 (C-9), 124.2 (C-2), 112.6 (C-7), 112.5 (C-3), 112.4 (C-6), 104.8 (C-1″), 104.0 (C-1′), 103.5 (C-4), 78.0 (C-3′, 3″, 5″), 77.8 (C-17‴), 77.0 (C-5′), 75.3 (C-2″), 75.1 (C-2′), 71.6 (C-4′), 71.5 (C-4″), 69.8 (C-6′), 62.8 (C-6″), 41.2 (C-11), 37.8 (C-16‴), 37.2 (C-2‴), 30.9-30.2 (C-4‴-15‴), 27.0 (C-3‴), 26.3 (C-10), 22.1 (C-18‴). HRFABMS 805.4462 (calcd for $C_{40}H_{67}N_2O_{13}Na$, 805.4463). FABMS (m/z) 805 $[M+Na]^+$, 783 $[M+H]^+$, 643, 459, 441, 371, 363, 347, 160, 159.

3.3.5. Withanamide E (5). Amorphous powder; UV (MeOH) λ_{max} nm (log ε) 275 (3.30), 300 sh (3.20). ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (1H, dd, J=8.5, 1.0 Hz, H-7), 7.0 (1H, s, H-2), 6.93 (1H, dd, J=2.0, 0.5 Hz, H-4), 6.65 (1H, dd, J=8.5, 2.0 Hz, H-6), 4.40 (1H, d, J=8.0 Hz, H-1″), 4.30 (1H, d, J=8.0 Hz, H-1′), 4.10 (1H, dd, J=12.0, 2.0 Hz, H-6′b), 3.86 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.78 (1H, dd, J=12.0, 6.0 Hz, H-6′a), 3.66 (1H, dd, J=12.0, 5.5 Hz, H-6″a), 3.63 (1H, t, J=6.0, H-16‴), 3.44 (2H, t, J=7.5 Hz, H-11), 3.40 (1H, m, H-4′), 3.39 (1H, t, J=7.5 Hz, H-5′), 3.25–3.37 (4H, m, H-5″, 4″, 3′, 4′), 3.20 (1H, dd, J=9.0, 7.5 Hz, H-2″), 3.16 (1H, dd, J=9.0, 7.5 Hz, H-2′), 2.85 (2H, t, J=7.5 Hz, H-10), 2.14 (2H, t, J=7.5 Hz, H-2‴), 1.56 (4H, m, H-3‴, 17‴), 1.52 (2H, m, H-15‴), 1.27 (22H, br. s, H-4‴-H-14‴), 0.91 (3H, t, J=7.5 Hz, H-18‴). HRFABMS 783.4645 (calcd for $C_{40}H_{67}O_{13}N_2$ 783.4644). FABMS (m/z) 805 $[M+Na]^+$, 783 $[M+H]^+$, 765, 621, 459, 441, 282, 202, 175, 160, 159, 146.

3.3.6. Withanamide F (6). Amorphous powder; UV (MeOH) λ_{max} nm (log ε) 276 (3.31), 301 sh (3.21); IR ν_{max} (KBr) 3402 (–OH), 2926, 2853, 1635 (–CONH), 1456, 1368, 1069, 1036, 615. ^{1}H NMR (500 MHz, CD_3OD) δ 7.14 (1H, dd, J=8.5, 0.5 Hz, H-7), 6.99 (1H, s, H-2), 6.92 (1H, dd, J=2.5, 0.5 Hz, H-4), 6.65 (1H, dd, J=8.5, 2.5 Hz, H-6), 5.33 (2H, m, H-9‴, 10‴), 4.39 (1H, d, J=7.0 Hz, H-1″), 4.30 (1H, d, J=7.5 Hz, H-1′), 4.09 (1H, dd, J=11.5, 2.0 Hz, H-6′b), 3.86 (1H, dd, J=11.5, 2.0 Hz, H-6″b), 3.78 (1H, dd, J=11.5, 5.5 Hz, H-6′a), 3.66 (1H, dd, J=11.5, 5.5 Hz, H-6″a), 3.62 (1H, t, J=6.0 Hz, H-16‴), 3.44 (2H, t, J=7.5 Hz, H-11), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.36 (4H, m, H-3′, 3″, 5′, 5″), 3.20 (1H, dd, J=9.0, 8.0 Hz, H-2″), 3.15 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.85 (2H, t, J=7.0 Hz, H-10), 2.14 (2H, t, J=7.5 Hz, H-2‴), 2.02 (4H, m, H-8‴, 11‴), 1.55 (8H, m, H-3‴, 17‴, 7‴, 12‴), 1.28 (12H, br. s, H-4‴-6‴, H-13‴-15‴), 0.91 (3H, t, J=7.5 Hz, H-18‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.3 (C-1‴), 151.2 (C-5), 133.1 (C-8), 130.9 (C-10‴), 130.8 (C-9‴), 129.5 (C-9), 124.2 (C-2), 112.6 (C-7), 112.5 (C-3), 112.4 (C-6), 104.9 (C-1″), 103.6 (C-1′), 103.5 (C-4), 82.0 (C-16‴), 78.0 (C-3′, 3″, 5″), 77.0 (C-5′), 75.3 (C-2″), 75.1 (C-2′), 71.7 (C-4″), 71.6 (C-4′), 69.9 (C-6′), 62.8 (C-6″), 41.2 (C-11), 37.2 (C-2‴), 30.8-30.1 (C-5‴-7‴, C-12‴-C15‴), 30.2 (C-4‴), 28.2 (C-11‴), 28.1 (C-8‴), 27.0 (C-3‴), 26.5 (C-17‴) 26.3 (C-10), 10.2 (C-18‴). HRFABMS 803.4304 (calcd for $C_{40}H_{64}O_{13}N_2Na$, 803.4306). FABMS (m/z) 803 $[M+Na]^+$, 781 $[M+H]^+$, 641, 619, 457, 439, 393, 347, 160, 159, 146.

3.3.7. Withanamide G (7). Amorphous powder; UV (MeOH) λ_{max} nm (log ε) 277 (3.34), 301 sh (3.23). ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (1H, d, J=9.0 Hz, H-7), 7.0 (1H, s, H-2), 6.92 (1H, d, J=2.0 Hz, H-4), 6.65 (1H, dd, J=9.0, 2.0 Hz, H-6), 5.34 (2H, m, H-9‴, 10‴), 4.39 (1H, d, J=7.5 Hz, H-1″), 4.31 (1H, d, J=7.5 Hz, H-1′), 4.10 (1H, dd, J=12.0, 2.0 Hz, H-6′b), 3.85 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.79 (1H, m, H-15‴), 3.78 (1H, dd, J=12.0, 5.0 Hz, H-6′a), 3.66 (1H, dd, J=12.0, 5.0 Hz, H-6″a), 3.44 (2H, t, J=7.5 Hz, H-11), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.38 (4H, m, H-5″, H-3″, H-3′), 3.24 (1H, dd, J=9.0, 8.0 Hz, H-2″), 3.16 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.85 (2H, t, J=7.0 Hz, H-10), 2.14 (2H, t, J=7.5 Hz, H-2‴), 1.55 (2H, m, H-3‴, H-14‴), 2.03 (4H, m, H-8‴, 11‴), 1.55 (4H, m, H-3‴, H-14‴), 1.39 (2H, m, H-4‴), 1.28 (16H, br. s, H-5‴-7‴, 12‴, 13‴), 1.21 (3H, d, J=6.5 Hz, H-16‴). ^{13}C NMR[†] (125 MHz, CD_3OD) δ 151.3 (C-5), 130.9 (C-10‴), 130.8 (C-9‴), 129.5 (C-9), 124.2 (C-2), 112.7 (C-7), 112.5 (C-3), 112.3 (C-6), 104.9 (C-1″), 104.0 (C-1′), 103.5 (C-4), 77.9 (C-15‴), 78.0 (C-3′, 3″, 5″), 77.0 (C-5′), 75.3 (C-2″), 75.1 (C-2′), 71.6 (C-4″), 71.5 (C-4′), 69.9 (C-6′), 62.8 (C-6″), 41.2 (C-11), 37.2 (C-2‴), 30.9-30.1 (C-5‴-7‴, 12‴-13‴), 30.2 (C-4‴), 28.1 (C-11‴), 28.0 (C-8‴), 27.0 (C-3‴), 26.3 (C-10), 22.1 (C-16‴). HRFABMS 753.4173 (calcd for $C_{38}H_{61}O_{13}N_2$, 753.4174). FABMS (m/z) 775 $[M+Na]^+$, 753 $[M+H]^+$, 596, 155, 114.

3.3.8. Withanamide H (8). Amorphous powder; UV (MeOH) λ_{max} nm (log ε) 276 (3.53), 301 sh (3.38), 330 sh (3.20). ^{1}H NMR (500 MHz, CD_3OD) δ 7.14 (1H, d, J=8.5 Hz, H-7), 6.99 (1H, s, H-2), 6.92 (1H, d, J=2.5 Hz, H-4), 6.65 (1H, dd, J=8.5, 2.5 Hz, H-6), 5.34 (8H, m, H-6‴, 7‴, 9‴, 10‴, 12‴, 13‴, 15‴, 16‴), 4.33 (1H, d, J=8.0 Hz, H-1″), 4.27 (1H, d, J=8.0 Hz, H-1′), 4.10 (1H, dd, J=12.0, 2.0 Hz, H-6′b), 3.85 (1H, dd, J=12.0, 2.5 Hz, H-6″b), 3.79 (1H, m, H-15‴), 3.78 (1H, dd, J=12.0, 5.0 Hz, H-6′a), 3.66 (1H, dd, J=12.0, 5.0 Hz, H-6″a), 3.44 (2H, t, J=7.5 Hz, H-11), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.38 (3H, m, H-5″, H-3″, H-3′), 3.24 (1H, dd, J=9.0, 8.0 Hz, H-2″), 3.16 (1H, dd, J=9.0, 8.0 Hz, H-2′), 2.85 (2H, t, J=7.0 Hz, H-10), 2.82 (6H, m, H-8‴, 11‴, 14‴), 2.14 (2H, t, J=7.5 Hz, H-2‴), 2.07 (2H, m, 5‴), 1.55 (2H, m, H-3‴), 1.28 (2H, br. s, H-4‴), 1.24 (3H, d, J=6.5 Hz, H-18‴). ^{13}C NMR (125 MHz, CD_3OD) δ 176.3 (C-1‴), 151.2 (C-5), 133.2 (C-8), 132.6 (C-9‴), 132.2 (C-6‴), 131.4 (C-7‴, 10‴), 130.1 (C-15‴), 129.5 (C-9), 128.7 (C-12‴, 13‴), 128.5 (C-15‴, 16‴), 124.2 (C-2), 112.6 (C-7), 112.5 (C-3), 112.4 (C-6), 104.9 (C-1″), 100.9 (C-1′), 103.5 (C-4), 78.0 (C-3′, 3″, 5″), 77.7 (C-17‴), 76.8 (C-5′), 75.0 (C-2″), 74.9 (C-2′), 71.6 (C-4″), 71.3 (C-4′), 69.6 (C-6′), 62.8 (C-6″), 41.2 (C-11), 37.2 (C-2‴), 30.7 (C-4‴), 28.2 (C-5‴), 27.0 (C-3‴),

[†] ^{13}C NMR signals for C-8 and C-1‴ were not observed due to insufficient quantity of sample.

26.6 (C-8‴, 11‴, 14‴), 26.3 (C-10), 21.9 (C-18‴). HRFABMS 775.4013 (calcd for $C_{40}H_{59}O_{13}N_2$, 775.4017). FABMS (*m/z*) 799 $[M+Na]^+$, 775 $[M+H]^+$, 591, 435, 411, 160, 159, 146.

3.3.9. Withanamide I (9). Amorphous powder; UV (MeOH) λ_{max} nm (log ε) 278 (3.43), 302 sh (3.30). ^1H NMR (500 MHz, CD_3OD) δ 7.14 (1H, dd, *J*=8.5, 0.5 Hz, H-7), 6.99 (1H, s, H-2), 6.93 (1H, dd, *J*=2.5, 0.5 Hz, H-4), 6.65 (1H, dd, *J*=8.5, 2.0 Hz, H-6), 5.33 (4H, m, H-6‴, 7‴, 9‴, 10‴), 4.39 (1H, d, *J*=7.5 Hz, H-1″), 4.36 (1H, d, *J*=8.0 Hz, H-1‴), 4.32 (1H, d, *J*=8.0 Hz, H-1′), 4.15 (1H, bd, *J*=12.0 Hz, H-6″b), 4.09 (1H, br. d, *J*=12.0 Hz, H-6′b), 3.86 (1H, dd, *J*=12.0, 2.0 Hz, H-6‴b), 3.79 (1H, m, H-17‴), 3.78 (1H, dd, *J*=12.0, 5.5 Hz, H-6″a), 3.75 (1H, dd, *J*=11.0, 6.0 Hz, H-6′a), 3.66 (1H, dd, *J*=12.0, 5.0 Hz, H-6‴a), 3.44 (2H, t, *J*=7.5 Hz, H-11), 3.41 (3H, m, H-4″, 4‴, 5′), 3.40 (1H, m, H-4′), 3.25-3.38 (5H, m, H-5″, 5‴, 3‴, 3″, 3′), 3.24 (1H, dd, *J*=9.0, 8.0 Hz, H-2″, 2‴), 3.16 (1H, dd, *J*=9.0, 8.0 Hz, H-2′), 2.85 (2H, t, *J*=7.0 Hz, H-10), 2.77 (2H, t, *J*=6.0 Hz, H-8⁗), 2.15 (2H, t, *J*=7.5 Hz, H-2⁗), 2.04 (4H, m, H-5⁗, 11⁗), 1.42 (2H, m, H-4⁗), 1.28 (8H, br s, H-12⁗-H-15⁗), 1.56 (2H, m, H-3⁗), 1.21 (3H, d, *J*=6.5 Hz, H-18⁗). HRFABMS 941.4857 (calcd for $C_{46}H_{73}O_{18}N_2$, 941.4859). FABMS (*m/z*) 963 $[M+Na]^+$, 941 $[M+H]^+$, 617, 455, 437, 316, 160, 159, 146.

3.3.10. 23,24-Dihydrowithanolide VI (10). Colorless, amorphous powder; IR ν_{max} (KBr) 3421 (–OH), 2936, 1724, 1663, 1460, 1384, 1073, 1043. ^1H NMR (500 MHz, CD_3OD) δ 5.52 (1H, br d, *J*=5.0 Hz, H-6), 4.39 (1H, d, *J*=8.0 Hz, H-1″), 4.36 (1H, d, *J*=8.0 Hz, H-1′), 4.24 (1H, dd, *J*=11.5, 2.5 Hz, H-22), 4.12 (1H, dd, *J*=11.5, 2.5 Hz, H-6′b), 4.0 (1H, m, H-3), 3.86 (1H, dd, *J*=11.5, 2.0 Hz, H-6″b), 3.80 (1H, m, H-1), 3.76 (1H, dd, *J*=11.5, 6.0 Hz, H-6′a), 3.66 (1H, dd, *J*=12.0, 6.0 Hz, H-6″a), 3.41 (2H, m, H-4″, 5′), 3.40 (1H, m, H-4′), 3.25–3.38 (3H, m, H-5″, H-3″, H-3′), 3.24 (1H, dd, *J*=9.0, 8.0 Hz, H-2″), 3.16 (1H, dd, *J*=9.0, 8.0 Hz, H-2′), 1.24 (3H, s, Me-21), 1.17 (3H, d, *J*=6.5 Hz, Me-27), 1.15 (3H, d, *J*=6.5 Hz, Me-28), 1.01 (3H, s, Me-19), 0.89 (3H, s, Me-18). ^{13}C NMR (125 MHz, CD_3OD) δ 178.9 (C-26), 139.2 (C-5), 125.5 (C-6), 104.8 (C-1″), 103.1 (C-1′), 81.9 (C-22), 78.0 (C-3′, 3″), 77.9 (C-5″), 77.0 (C-5′), 76.5 (C-20), 75.5 (C-2″), 75.2 (C-2′), 75.1 (C-1), 73.6 (C-3), 71.7 (C-4″), 71.6 (C-4′), 69.7 (C-6′), 62.8 (C-6″), 58.1 (C-14), 56.1 (C-17), 44.0 (C-24), 42.7 (C-13), 42.5 (C-10), 41.4 (C-9), 41.1 (C-12), 39.2 (C-4), 37.8 (C-2), 32.8 (C-25), 32.7 (C-23), 32.6 (C-7), 32.0 (C-8), 25.0 (C-15), 23.0 (C-16), 21.3 (C-11), 21.2 (C-21), 20.5 (C-27), 19.9 (C-19), 14.4 (C-28), 14.2 (C-18). HRFABMS 785.4325 (calcd for $C_{40}H_{65}O_{15}$, 785.4323). FABMS *m/z* 807 $[M+Na]^+$, 785, 623, 605, 587, 443, 425, 407, 255.

3.3.11. Compounds 11–13. The structures of compounds **11–13** were elucidated by ^1H and ^{13}C NMR experiments and their identity was confirmed by comparing the spectral data with the published results.[9,19]

3.4. Preparation of *R*- and *S*-MTPA esters of compound 1

A mixture of compound **1** (1.5 mg) and *R*-(−)-Methoxy trifluorophenyl acetyl chyloride (*R*-MTPA) in pyridine was stirred with dimethylaminopyridine (DMAP) (5 h) at room temperature. The solvent was evaporated and residue obtained was purified over PTLC using $CHCl_3$–MeOH (9:1, v/v) to yield *R*-MTPA ester (1.0 mg). Similarly, compound **1** (1.2 mg) was treated with *S*-(+)-methoxytrifluorophenyl acetyl chloride and the purification of the resulting product gave *S*-MTPA ester (0.9 mg).

3.5. Fe^{2+} induced lipid peroxidation assay

Compounds **1–16** were tested for their inhibition of lipid peroxidation using LUVs (Liposome suspension) according to the published procedure.[20] The liposome suspension was prepared by mixing the phospholipid 1-stearoyl-2-linoleoyl-*sn*-glycero-3-phosphocoline (SLPC) and a fluorescence probe [3-[*p*-(6-phenyl)-1,3,5-hexatrienyl]phenylpropionic acid (DPH-PA). The final assay volume was 2 mL and consisted HEPES (100 μL), 1 M NaCl (200 μL), N_2-sparged water (1.64 mL), test sample or DMSO (20 μL) and liposome suspension (20 μL). The peroxidation was initiated by the addition of 20 μL of $FeCl_2$. $4H_2O$ (0.5 mM). The decrease in fluorescence intensity over time (21 min) indicated the rate of peroxidation. The percentage of lipid peroxidation was calculated with respect to DMSO solvent control. Stock solutions of the samples were prepared at 100 μg/mL and diluted further for the assay. Commercial standards BHA, BHT and TBHQ were tested at 1 μg/mL.

3.6. AAPH $^+$ induced lipid peroxidation assay

The AAPH (2,2-azobis (2-amidinopropane) dihydrochloride) induced lipid peroxidation was carried out using LUVs[20] at 37 °C. The HEPES (100 μL), 1 M NaCl (200 μL), N_2-sparged water (1.64 mL) and test sample or DMSO (20 μL) were mixed and 20 μL of liposome added. The peroxidation was initiated by the addition of 2.5 mM APPH. The flourescence was monitored for 21 min for every three minutes and percentage inhibition was calculated as in the case of Fe^{+2} induced lipid peroxidation assay.

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References and notes

1. Wickens, A. P. *Respir Physiol* **2001**, *128*, 371–391.
2. Vaya, J.; Aviram, M. *Curr. Med. Chem. Immunol., Endocrinol. Metab. Agents* **2001**, *1*, 99–117.
3. West, I. C. *Diabet. Med.* **2000**, *17*, 171–180.
4. Temple, N. J. *Nutr. Res.* **2000**, *20*, 449–459, and references cited therein.
5. Conclin, K. A. *Nut. Canc.* **2000**, *37*, 1–18.

6. Marchant, C. A. *Environ. Health Perspect. Supp.* **1996**, *104*, 1065–1073.
7. Anjaneyulu, A. S. R.; Rao, D. S.; Le Quesne, P. W. *Studies in natural products chemistry: structure and chemistry (Part F)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1998; Vol. 20, pp 135–261.
8. Thakur, R. S.; Puri, H. S.; Husain, A. Major medicinal plants of India; CIMAP: Lucknow, India, 1989; pp 531–534.
9. Jayaprakasam, B.; Nair, M. G. *Tetrahedron* **2003**, *59*, 841–849.
10. Stoller, E. W.; Stohs, S. J.; El-Olemy, M. M.; Yu, P. C.; Tarng, C. S. *Lloydia* **1974**, *37*, 309–312.
11. Pachori, M.; Rathee, P. S.; Mishra, S. N. *Asian J. Chem.* **1994**, *6*, 442–444.
12. Pachori, M.; Rathee, P. S.; Mishra, S. N. *Sci. Phys. Sci.* **1993**, *5*, 81–83.
13. Kundu, A. B.; Mukherjee, A.; Dey, A. K. *Ind. J. Chem.* **1976**, *14B*, 434–435.
14. Abou-Douh, A. M. *Archiv der Pharmazie* **2002**, *335*, 267–276.
15. Watanabe, M. *J. Agric. Food. Chem.* **1999**, *47*, 4500–4505.
16. Spinell, A.; Zubia, E.; Martinez, E.; Ortea, J.; Cimino, G. *J. Org. Chem.* **1997**, *62*, 5471–5475.
17. Wenkert, E.; Buckwalter, B. L.; Burfitt, I. R.; Gasic, M. J.; Gottlieb, H. E.; Hagaman, E. W.; Schell, F. M.; Wovkulich, P. M. In *Topics in ^{13}C NMR spectroscopy*; Levy, G. C., Ed.; Wiley: New York, Vol. 2, pp 81–117.
18. Reznaka, T.; Guschina, I. A. *Phytochemistry* **2000**, *54*, 635–645.
19. Matsuda, M.; Murakami, T.; Kishi, A.; Yoshikawa, M. *Bioorg. Med. Chem.* **2001**, *9*, 1499–1507.
20. Arora, A.; Nair, M. G.; Strasburg, G. M. *Arch. Biochem. Biophys.* **1998**, *356*, 133–141.
21. Jayaprakasam, B.; Zhang, Y.; Seeram, N. P.; Nair, M. G. *Life Sci.* **2003**, *74*, 125–132.