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Tetrahedron

Tetrahedron Vol. 62, No. 14, 2006

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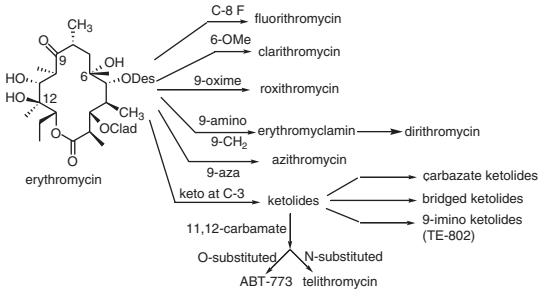
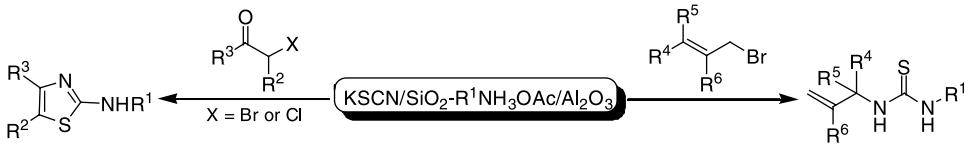
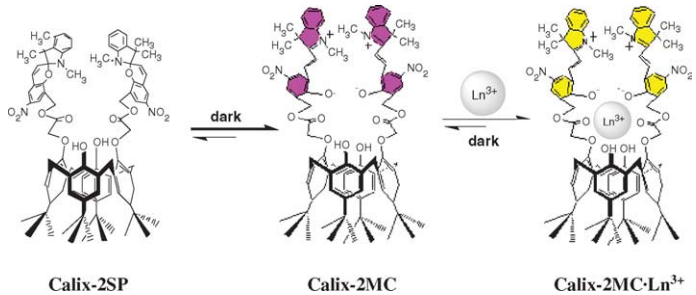
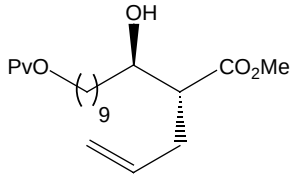


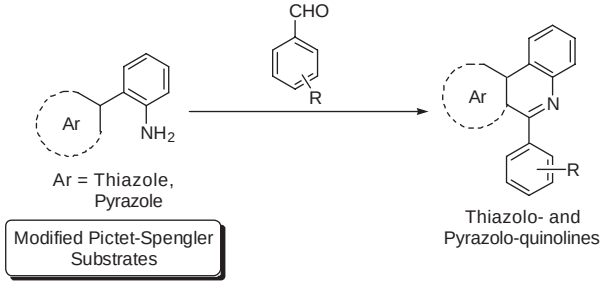
ARTICLES

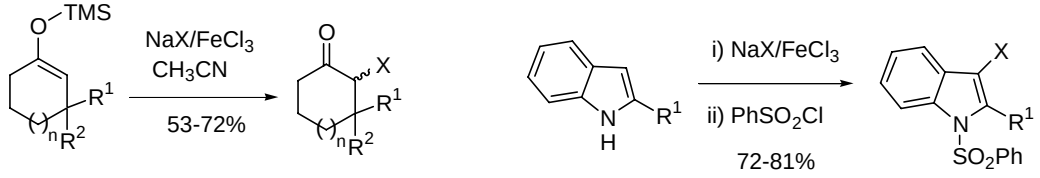


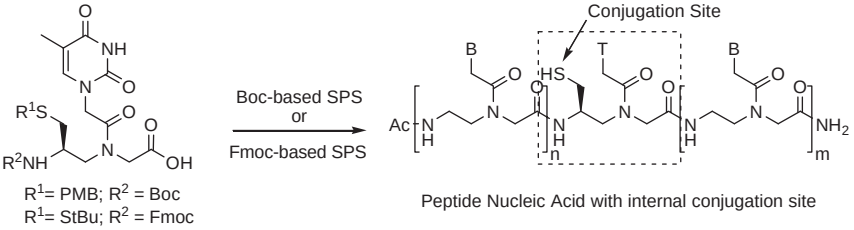


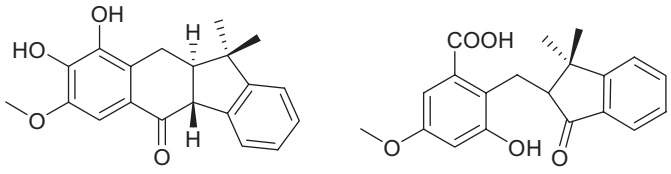


We report the synthesis of a single enantiomer of a functionalised β-hydroxy acid as a synthon for a wide range of mycolic acids

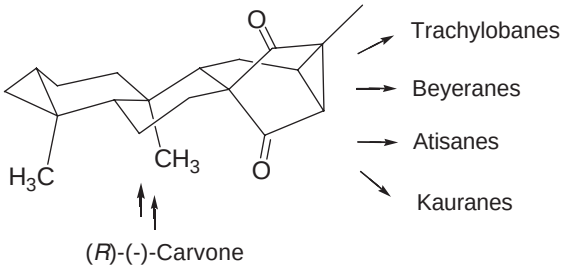


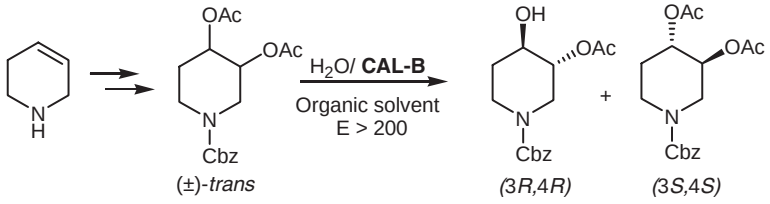


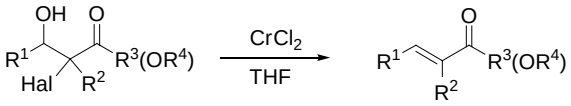


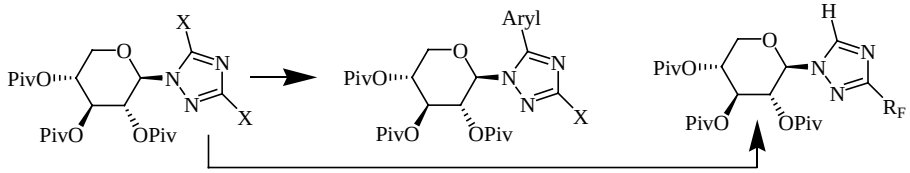


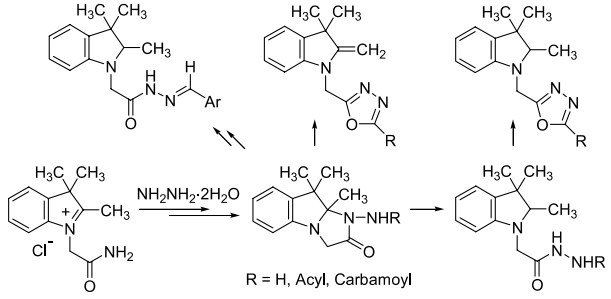
A stereoselective general synthetic approach to trachylobane-, beyerane-, atisane- and kaurane-type diterpenoids in both enantiomeric series, starting from (*S*)- or (*R*)-carvone, is described.

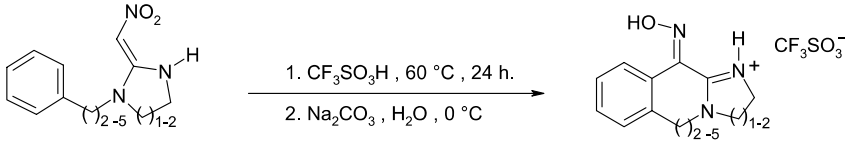


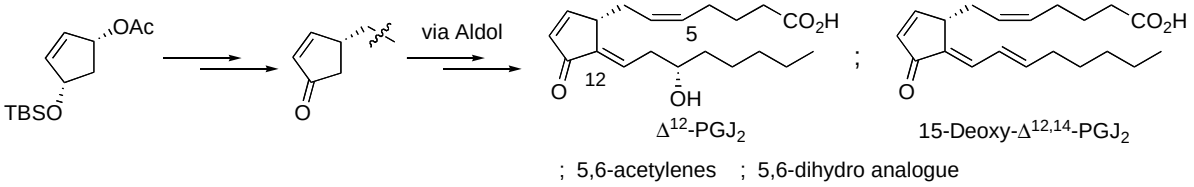


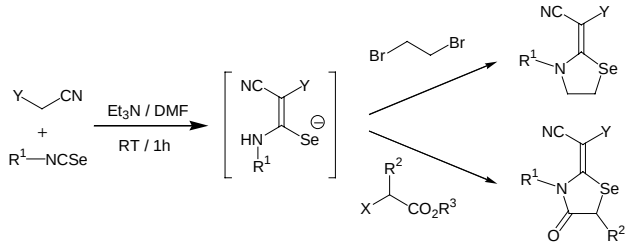


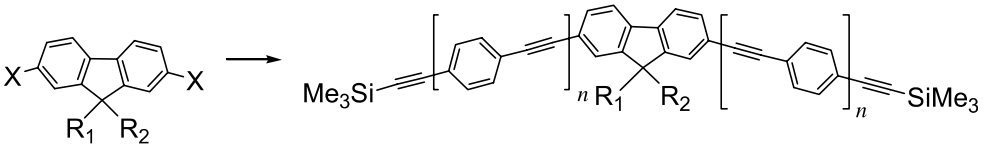








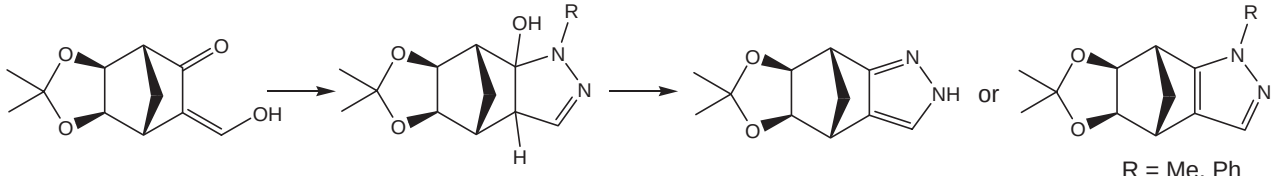




X = Br, I

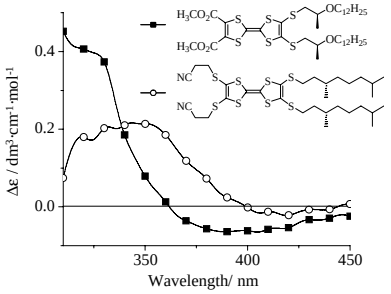
$R_1 = R_2 = O$;
R_1 = Me; R_2 = *p*-MeO-Ph

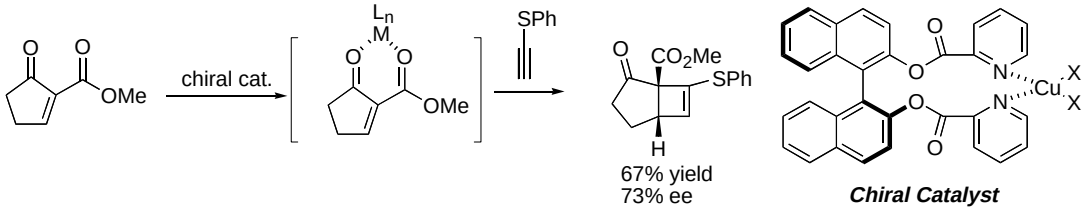
n = 0, 1, 2

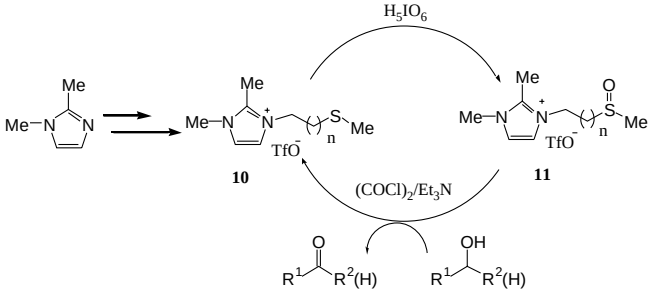


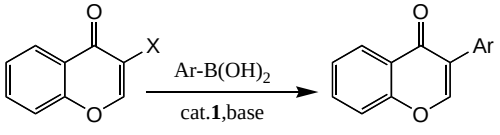
R = H, Me, Ph

R = Me, Ph

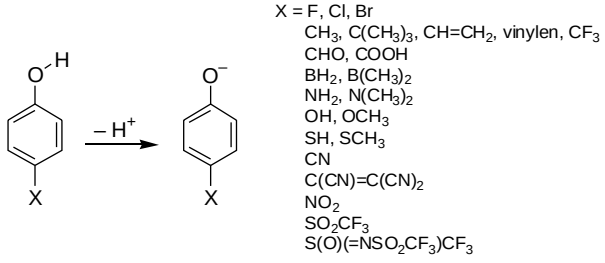


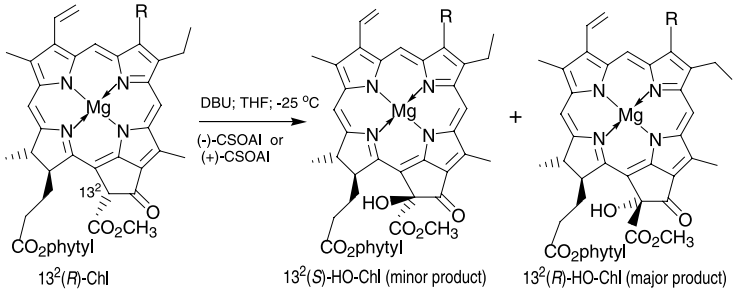


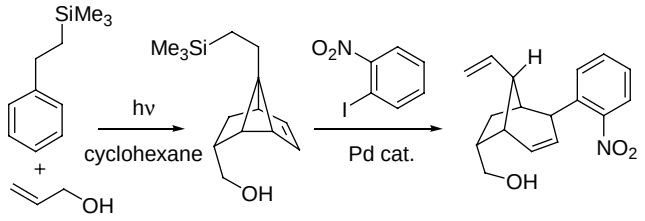


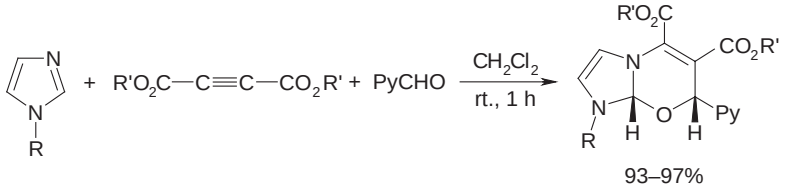


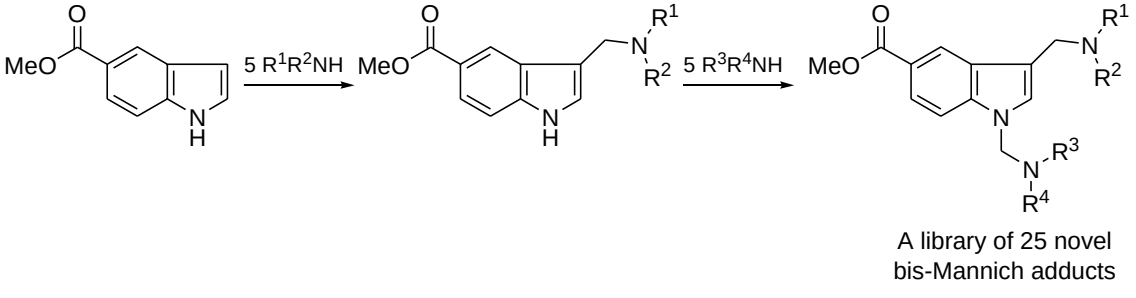
The use of an air stable Pd–oxazoline catalyst (**1**) as mediator of selective C–C bond formation reactions is described. The methodolgy is then applied to the syntheses of a number of biologically relevant stilbene and isoflavone derivatives.

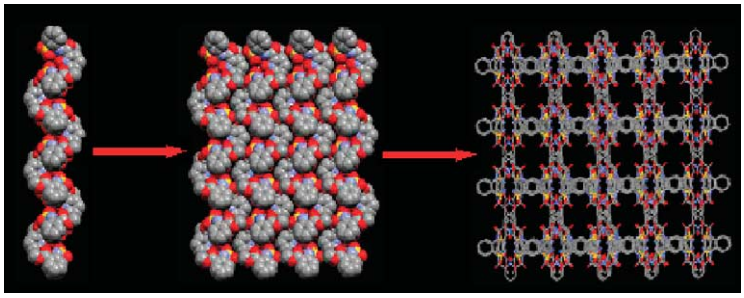












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The cover figure shows the preparation of biogenetically related atisane, kaurane and beyerane tetracyclic diterpenes through the regioselective cleavage of the cyclopropane ring of a key trachylobane-type intermediate, which can be prepared in both enantiomeric forms starting from (*S*)- or (*R*)-carvone. *Tetrahedron*, **2006**, *62*, 3266–3283.
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ELSEVIER

ISSN 0040-4020

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SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 3171–3200

Tetrahedron report number 755

A journey across the sequential development of macrolides and ketolides related to erythromycin

Sarbani Pal*

Department of Chemistry, MNR Post Graduate College, Kukatpally, Hyderabad, India

Received 17 November 2005

Available online 20 December 2005

Contents

Keywords: Erythromycin; Macrolides; Carbamate ketolides; Carbazate ketolides; Acylides.

Abbreviations: Ac, acetyl; Bn, benzyl; Bz, benzoyl; Clad, cladinose; CBZ, carbobenzyloxy; CDI, carbonyldiimidazole; DBU, 1,5-diazabicyclo[5.4.0]-undec-5-ene; DEAD, diethyl azadicarboxylate; Des, desosamine; DMAP, *N*,*N*-dimethyl-4-pyridinamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DPPA, diphenylphosphoryl azide; EDC, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide; HMDS, hexamethyldisilazane; MEM, 2-methoxyethoxymethyl; THF, tetrahydrofuran; TMS, trimethylsilyl; TFA, trifluoroacetic acid; *p*-Ts, *p*-toluenesulfonyl; SAR, Structure–activity relationship; TABF, tetra-*n*-butylammonium fluoride.

* Tel.: +91 40 23041488; e-mail: sarbani277@yahoo.com

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.064

1. Introduction: the family of macrolides

The macrolides belong to the polyketide class of natural products. They are a group of drugs, the activity of which stems from the presence of a macrolide ring, a large lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, are attached. The macrocyclic lactone ring can either be fourteen 14-, fifteen 15- or sixteen 16-membered and, depending on the size of the ring, macrolides can be classified as follows:

Fourteen 14-membered ring	Fifteen 15-membered ring	Sixteen 16-membered ring
Erythromycin	Azithromycin	Josamycin
Roxithromycin		Spiramycin
Clarithromycin		Miocamycin
Dirithromycin		

2. Erythromycin—the origin of all 14-membered macrolide antibiotics

One of the most successful drugs of all time, erythromycin, characterized by a 14-membered lactone ring, is a mixture of macrolides produced by the fermentation of the fungus, *Streptomyces erythreus*. Macrolide antibiotics are usually safe and effective for the treatment of upper and lower respiratory tract infections, as well as genital infections.[1a–d] Erythromycin A (**1**) (Fig. 1), the main component of the mixture, has been in clinical use for about 50 years[2] and was first isolated by McGuire et al.[3] in 1952.

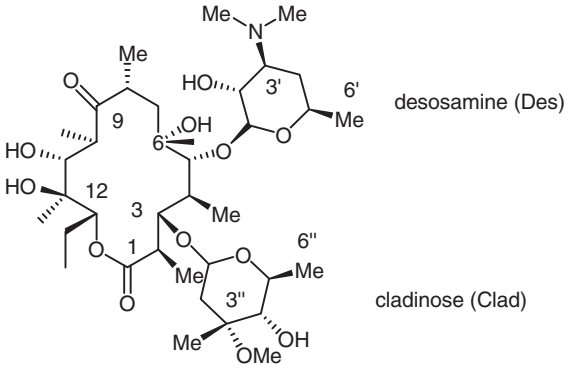


Figure 1. Erythromycin.

Erythromycin, a unique antibiotic, is effective against many gram-positive bacteria, although *Staphylococci* are often resistant. Among the gram-negative agents, *Bordetella pertussis* and *Legionella pneumophila,* are worthy of mention. Erythromycin has a similar activity spectrum to penicillin. Like tetracyclines, erythromycin is also active against bacteria such as *Chlamydia trachomatis*, *Mycoplasma pneumoniae* and *Ureaplasma urealyticum*. The specific antibacterial action of erythromycin, however, involves the blockade of protein synthesis on ribosomes.[4]

2.1. Synthesis of erythromycin—a brief overview

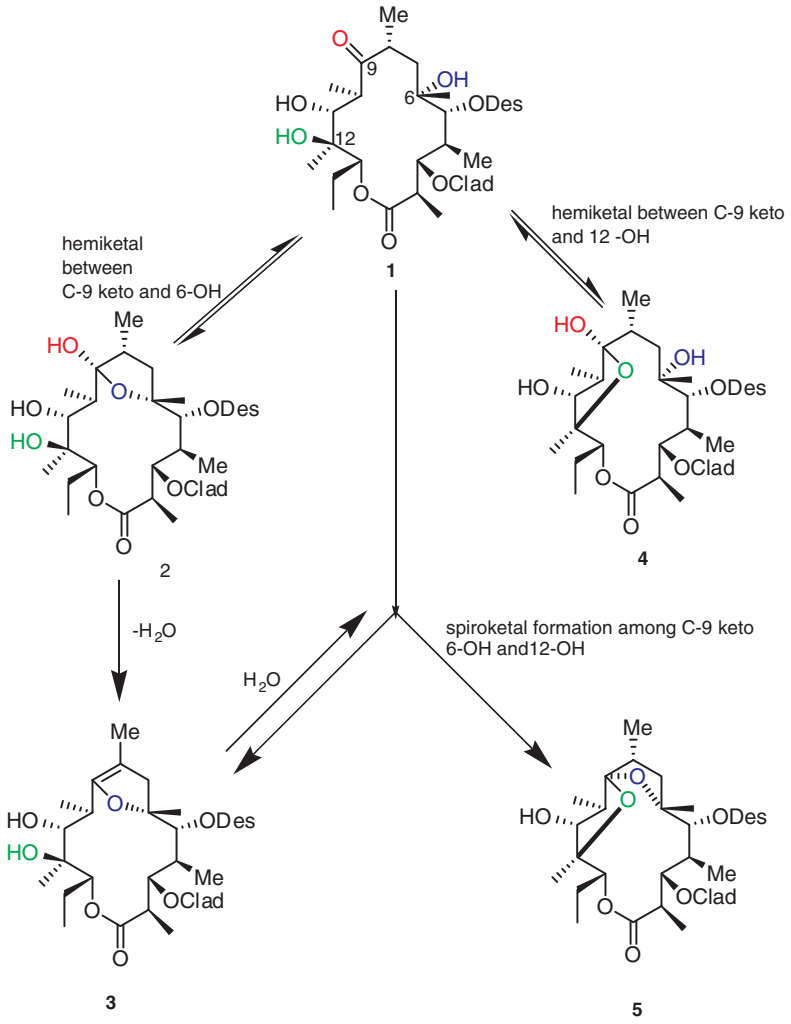
Although erythromycin can be obtained on an industrial scale by a fermentation method, the chemical synthesis of erythromycin and related compounds offers a formidable synthetic challenge, due to (i) its apparently complex structure containing ten asymmetric carbon atoms (five of which are consecutive) and (ii) the lack of an efficient methodology for the crucial lactonisation process. Inspired and challenged by the complexity of its macrocyclic structure, different research groups were involved for more than a decade in order to achieve its chemical synthesis. Nevertheless, all the total syntheses of erythromycin follow the same synthetic strategy, the formation of aglycons from the seco acids followed by glycosidation.[5a–c,6,7] The seco acids can be assembled in a convergent manner from two major components (Eastern and Western zones) or can be obtained in a linear fashion.[8] Usually, seco acids are subjected to lactonization, which can be achieved either by a Corey–Nicolaou double-activation method[9a,b] or by Yamaguchi lactonisation.[10] The aglycon is then subjected to glycosidation with properly activated and suitably protected desosamine and cladinose, respectively, to synthesize erythromycin. The syntheses of erythromycin via the reverse protocol, that is, glycosidation followed by lactonisation, are relatively few.[11]

2.2. Use of erythromycin as an antibacterial agent: its limitations—a chemist's view

The antibacterial activity of erythromycin stems from its ability to inhibit protein biosynthesis. In other words, macrolides inhibit protein biosynthesis by binding to 2058–2062 region of 23S ribosomal RNA of the 50S ribosomal subunit. They act by stimulating the dissociation of peptidyl *t*-RNA from ribosomes during the translocation process, thereby inhibiting protein synthesis.[12] Although allergic reactions to erythromycin are unusual, the use of erythromycin suffers from a few limitations such as hepatotoxicity and degradability in acid.

The hepatotoxicity of erythromycin is a limiting factor, to which very little attention has been paid. It has been shown that the *N*,*N*-dimethylamino group of the cladinose moiety plays a vital role in inducing inactivity into erythromycin.[13a,b] As this tertiary amine is essential for the binding of macrolide antibiotics to their ribosomal target within the bacteria,[14] the hepatotoxicity can be decreased by several factors: (i) increasing protonation, leading to the protonated form at physiological pH,[15] (ii) conformational changes,[16] (iii) introducing steric crowding around the *N*,*N*-dimethylamino group[17] and (iv) diminishing the hydrophobicity by introducing extra hydroxy groups on to erythromycin A (**1**).[18]

Erythromycin degrades in acidic conditions found in the stomach and produces inactive byproducts,[19]which are responsible for its poor bioavailability and gastrointestinal side effects. This degradation involves reactions of four sites, for example, C-9 ketone, 6-OH, 12-OH and C-8, as they are in close proximity. Under non-aqueous acidic conditions, erythromycin gives enol ether **3**[20] via **2** and, in aqueous acidic conditions, it gets converted into a 6,9:9, 12-spiroketal, anhydroerythromycin A (**5**).[21] Both **3** and **5** can, however, formed simultaneously.[22] In an aqueous medium, neither **3** nor **5** is present in significant amounts, but the predominant tautomer is **4** (Scheme 1).



Scheme 1. Formation of hemiketal and spiroketal from **1** in acid medium.

2.3. Strategies to overcome the limitations of erythromycin via modifications of its basic skeleton

In order to prevent its degradation in the presence of acid, modifications to the basic skeleton of erythromycin A were carried out at the four active sites such as C-9 ketone, 6-OH, 12-OH and 8-H. These gave rise to several analogues with an expanded gram-negative antibacterial activity spectrum and a wider tolerance for oral administration (Fig. 2). Among these analogues, clarithromycin (**6**), azithromycin (**7**) and roxithromycin (**8**) are the most popular in current use. These drugs are relatively more stable towards acids and can be given in lower doses for a shorter period of time, compared to erythromycin.

Other compounds of potential clinical interest are the 8-fluoro analog, flurithromycin (**9**), and the 9,11-oxazine, dirithromycin (**10**), both of which have shown promising results in animal models.

2.3.1. Synthesis of 6-*O*-alkylerythromycins via chemoselective alkylation. Although the structure of 6-*O*-methylerythromycin is deceptively simple, its synthesis was not trivial. Since erythromycin A (**1**) has five hydroxyl groups, it was difficult to alkylate the C-6 hydroxyl group selectively without affecting the other OH groups. The first regioselective alkylation was achieved by Watanabe and co-workers[23] via 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin (**11**) (Scheme 2). The process involved chromatographic separation of the desired product from a mixture of methylated products obtained after the methylation reaction. The main disadvantage of this process was the regioselective methylation that preferentially occurred at the undesired secondary 11-OH position more effectively than the desired tertiary 6-OH position. Methylation with a protected 11-OH group also failed, since it gave exclusively the 9-*O*-methyl derivative of the 6,9-hemiacetal. Finally, Watanabe and co-workers solved[24a,b] this problem by methylating 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-oxime derivatives, obtained from **11** (Scheme 3) via an oximation reaction.

The reactivity and selectivity of 6-OH were studied extensively by varying several parameters such as (a) protective groups of oxime, (b) solvents, (c) bases and (d) methylating agents. It was observed that, among the various protective groups examined, that is, trityl, benzyl, 2-chlorobenzyl, allyl, methyl etc., the selectivity improved with an increase in bulkiness of the group. By considering the slow reactivity caused by the bulky groups, however, the

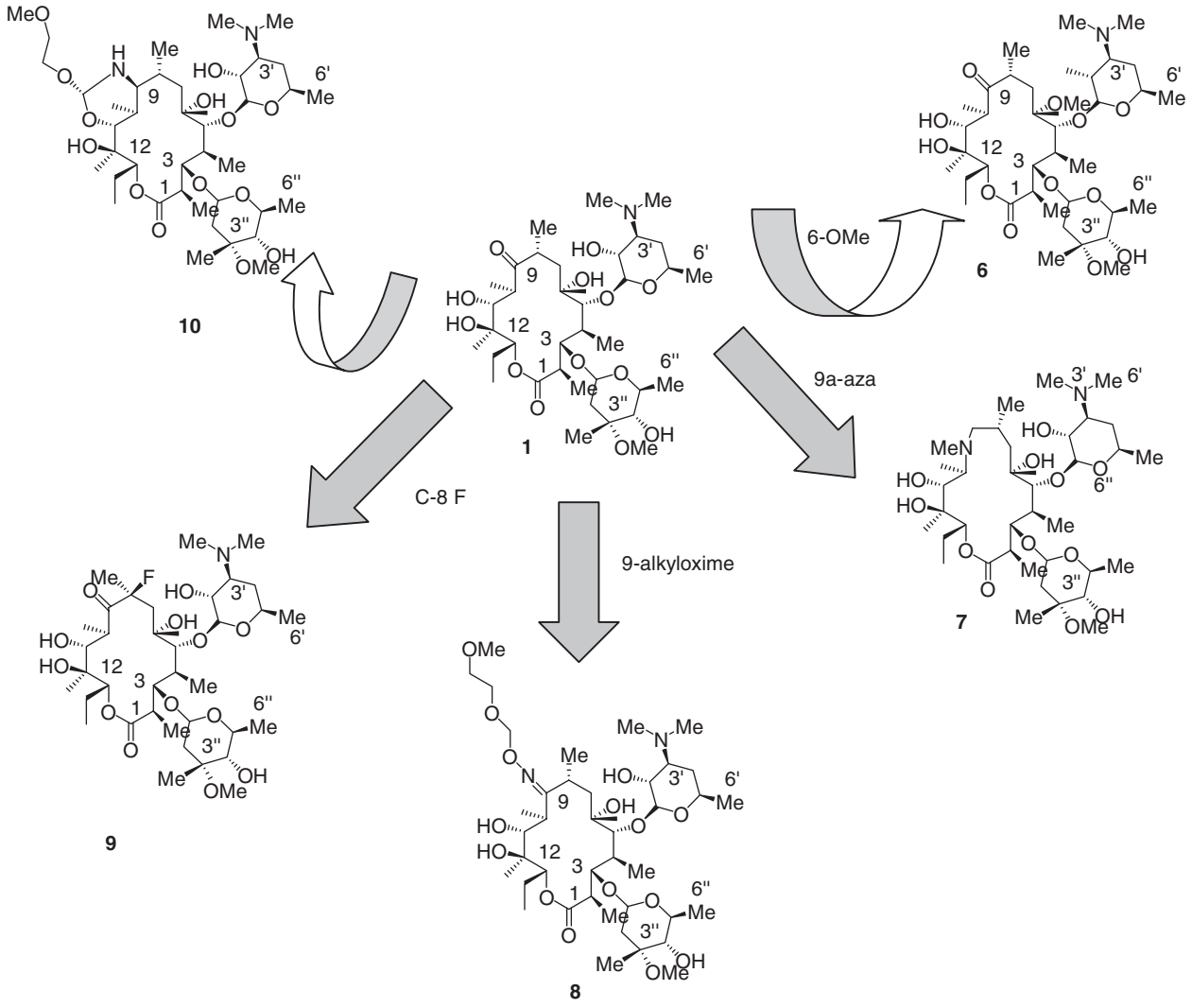


Figure 2. Modifications to basic skeleton of erythromycin.

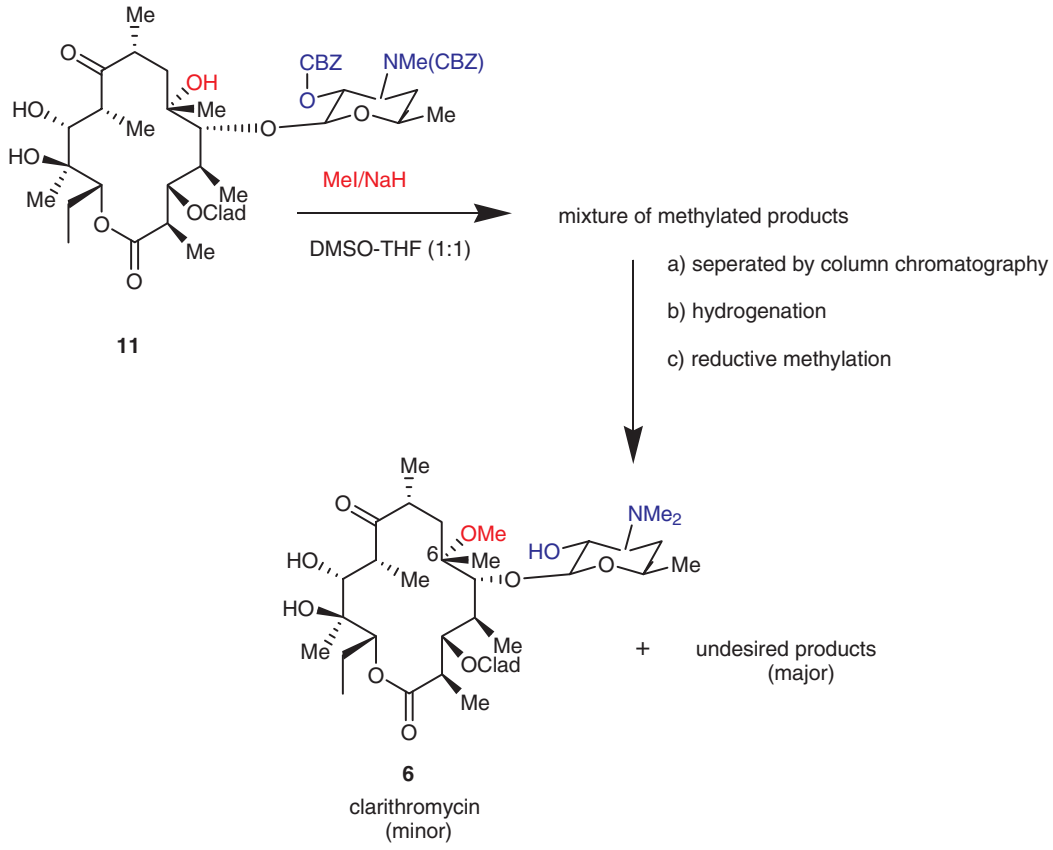
2-chlorobenzyl group was selected as the most suitable. Polar aprotic solvents were better than nonpolar solvents, but the optimum choice was a 1:1 mixture of DMSO–THF. Methyl iodide was found to be superior to dimethyl sulphate as a methylating agent.

Although the expected reactivity and selectivity were achieved elegantly in the previous synthesis (Scheme 3), in order to avoid the use of the irritant and toxic benzyl chloroformate, 6-*O*-methylerythromycin (**6**) was synthesized via methylation of a quaternery ammonium derivative of erythromycin A (Scheme 4).[25] This method was superior, because all the protections were carried out efficiently in one pot by treating erythromycin A 9-oxime (**12**) with benzyl bromide and sodium hydride, when deprotection was performed by a transfer hydrogenation method. Moreover, the maximum selectivity was achieved by using this reaction sequence.

Despite its advantages over previous methods in terms of the yield and selectivity, this protocol suffered from a few practical shortcomings. Elimination of all three benzyl groups by hydrogenation in one pot, especially in a large-scale preparation, was often inconsistent and difficult to accomplish. One of the most impressive studies concerning **6** was carried out by Watanabe and co-workers.[26] They prepared 6-*O*-methylerythromycin A (**6**) from erythromycin A 9-oxime (**12**) without purifying the intermediates (Scheme 5), but the reported yield was found to be less than that in the previous synthesis.

6-*O*-Methylerythromycin A (**6**) (clarithromycin, biaxin), a second-generation macrolide, was expected to show strong antibacterial activity and more acid resistance[19,20] than **1**. Apparently, it showed better activity against *Mycoplasma pneumoniae* and *Chlamydia trachomatis*[27–31a,b] and exhibited improved pharmacokinetic profiles and gastrointestinal tolerability over erythromycin. Additionally, clarithromycin exhibited good activity against *Helicobacter pylori* and has been approved in a combination regiment for the treatment of peptic ulcer disease.[32]

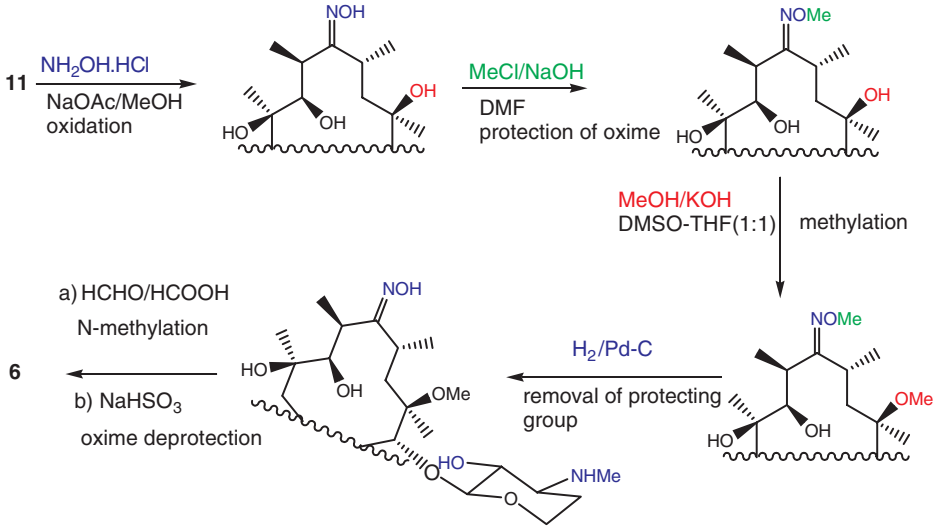
Inspired by the improved biological profile of **6**, different groups of scientists became interested in the synthesis of 6-*O*-substituted macrolides. The immense steric crowding around the C-6 hydroxy group was, however, a major synthetic problem in attempting the introduction of higher alkyl chains on this oxygen. Clark and co-workers reported



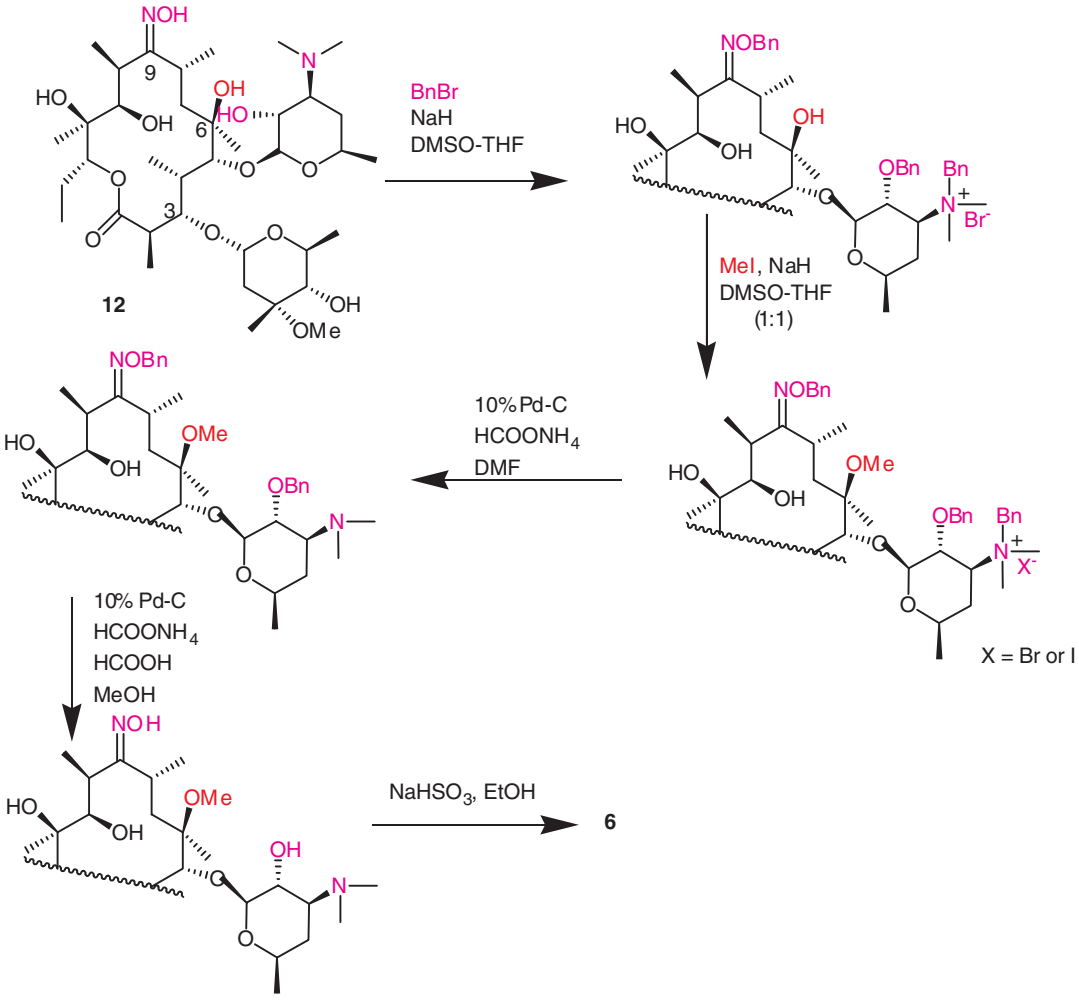
Scheme 2. Attempted synthesis of clarithromycin (**6**).

a facile method[33] to prepare 6-*O*-substituted erythromycins, which are highly active against erythromycin resistant respiratory pathogens, using suitably protected erythromycin derivatives. Thus, 2′,4″-bis-*O*-trimethylsilylerythromycin A 9-*O*-(1-isopropoxycyclohexyl)oxime (**13**) was reacted with active electrophilic reagents, in order to generate the corresponding 6-*O*-substituted derivatives. Removal of the protecting groups provided the 6-*O*-alkylerythromycin A 9-oxime, which, on subsequent deoximation, afforded the 6-*O*-alkylerythromycin A (**14a–f**) (Scheme 6).

6-*O*-Allylerythromycin A (**14a**) was identified as a versatile synthetic equivalent, which was converted into an array of diversified derivatives (**14g–p**), as shown in Figure 3. These derivatives were screened for in vitro antibacterial activity against erythromycin susceptible and resistant *Staphylococci*, *Streptococci* and *Pneumococci*. In particular,



Scheme 3. Synthesis of clarithromycin (**6**) with improved yield.



Scheme 4. Synthesis of clarithromycin (**6**) with excellent selectivity.

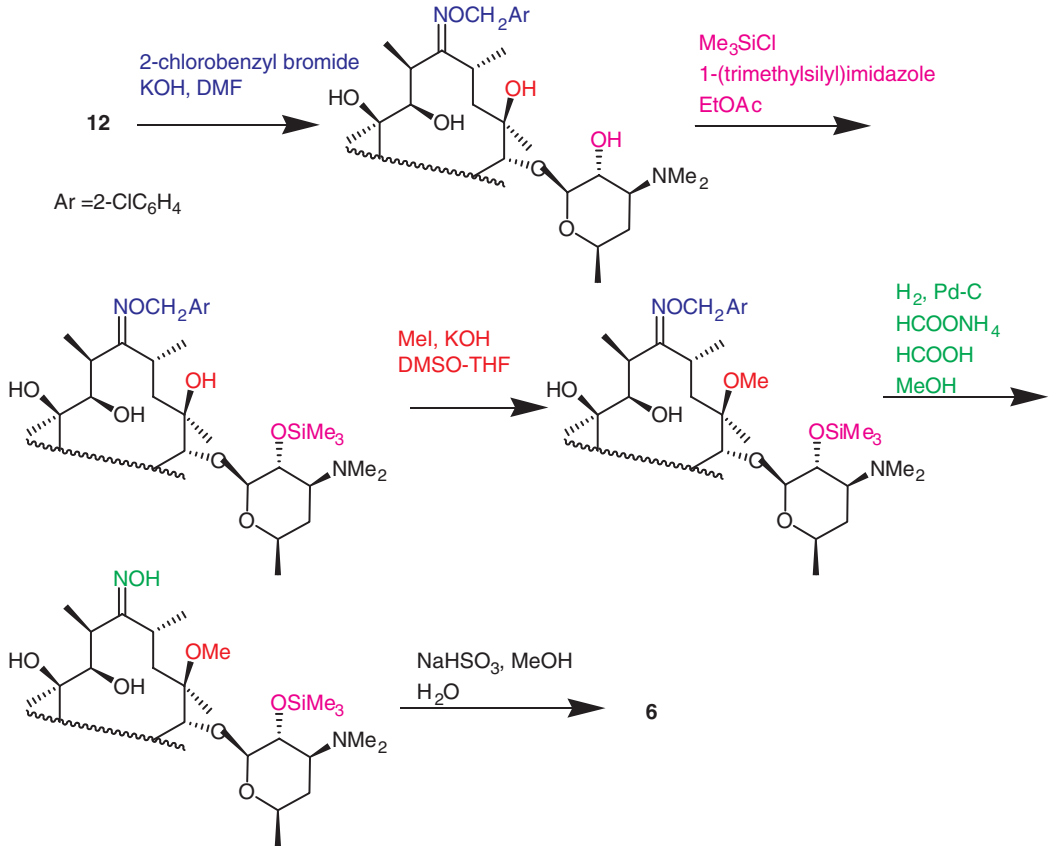
the introduction of multiple bonds (**14h**), heteroatoms (**14m**) or a conjugated aromatic system (**14f**, **14n**) showed activities over much of the bacterial spectrum. 6-*O*-Fluorobenzyl-erythromycin A (**14d**) and 6-*O*-naphthylallylerythromycin A (**14n**), having aromatic substituents tethered to the macrolide by a hydrocarbon linkage, showed a 16-fold improved activity against both *S. pyogenes* 930 and *S. pneumoniae* 5737.

2.3.2. Synthesis of azalides by functional group interconversion (FGI) and ring expansion. Djokic and coworkers[34] exploited the stereospecific Beckmann rearrangement to introduce a nitrogen atom into the 14-membered aglycon ring of erythromycin A. In order to achieve this, the *E* isomer of **12** was treated with *p*-toluenesulphonyl chloride (*p*-TsCl) (Scheme 7). The expected normal rearranged product **17** and abnormal product **16** were formed via a common intermediate **15** and were isolated in two different solvents. Both **16** and **17** were, however, converted separately into another important semisynthetic macrolide antibiotic, the first member in the series of azalides, azithromycin (**7**) (marketed as Zithromax)[35,36] (Scheme 7).

From the early trials, azithromycin (**7**) proved to be an extremely efficient antibiotic with expanded and enhanced antibacterial activity (especially against gram-negative pathogens), along with a low incidence of gastrointestinal side effects. It was found to be more acid stable and therefore better absorbed and distributed to tissues.

2.3.3. Oximation followed by oximinoether formation. Due to the acid-labile nature of the keto oxime **12**, alkylation of the oxime hydroxy group was investigated and was found to be effective in enhancing the stability. Thus, alkylation of erythromycin oxime (**12**), using 2-methoxyethoxymethyl chloride (MEM chloride) in the presence of $NaHCO_3$ in refluxing acetone[37,38] (Scheme 8), led to the generation of another useful antibiotic, roxithromycin (**8**).

Roxithromycin has a similar antibacterial spectrum to erythromycin, but a longer half life and absorption. It can often be prescribed for upper and lower respiratory tract infection, asthma, gum infections like gingivitis and bacterial infections associated with stomach and intestinal ulcers. It might be useful in treating toxoplasmosis (which usually affects the brain, sometimes leading to coma and seizures) and cryptosporidiosis (a parasitic infection, which often leads to severe diarrhea and weight loss).

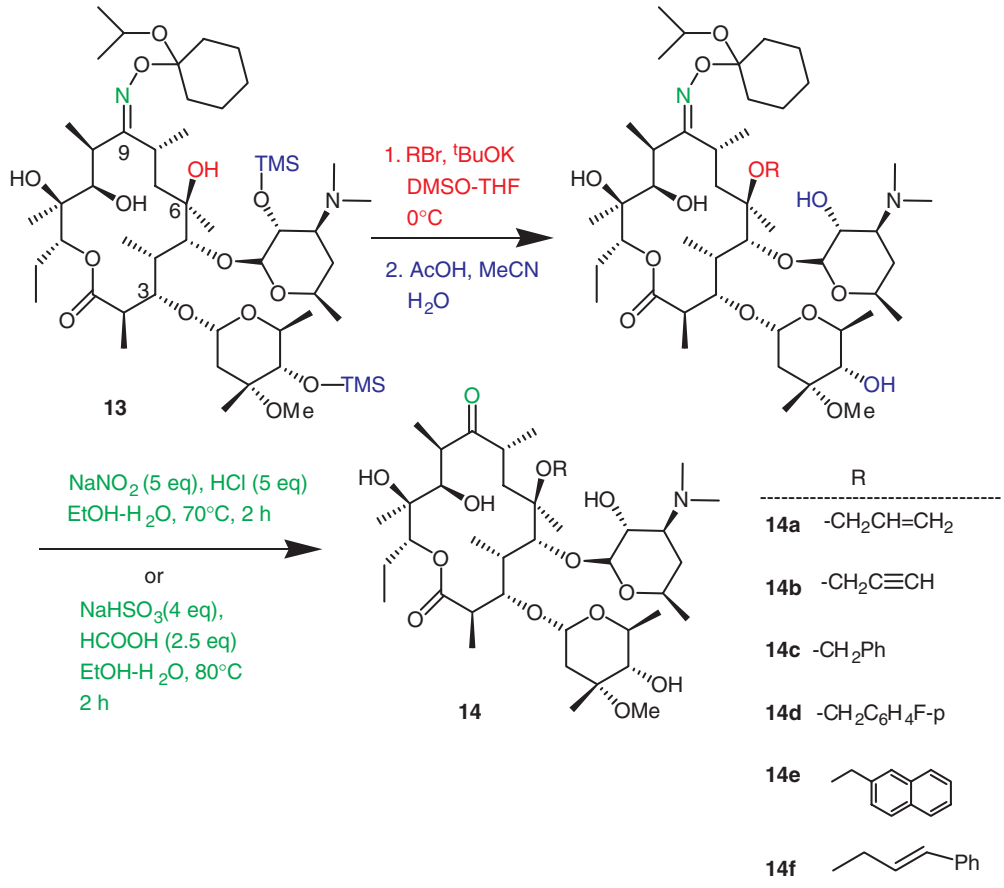


Scheme 5. Synthesis of clarithromycin (**6**) from erythromycin A 9-oxime (**12**) by Watanabe's method.

3. Bacterial resistance to erythromycin and its congeners: an emergency call

3.1. What does it mean and how does it work? A biologist's view

Although the macrolides including erythromycin enjoy a wide spectrum of antibacterial activity, their extensive clinical application has resulted in an increasing emergence of bacterial resistance. This increasing bacterial resistance to antibiotic treatment has turned out to be a major concern in global health.[39a–c] A surveillance study indicated that, among 1601 clinical isolates of *S. pneumonae* collected in 34 US medical centers, 19% were erythromycin resistant. This bacterial resistance to erythromycin and its congeners has increased dramatically over the past several years, and, therefore, the development of alternative antibacterial agents became essential. Thus, different research groups initiated investigation in several directions: (1) a search for new compounds that retain the favorable safety profile, along with a spectrum of activity confined to respiratory pathogens, (2) a search for new naturally occurring macrolide antibiotics and (3) an exploration of new targets from bacterial genomics that could be carried out by inserting the genes (by hijacking the biosynthetic machinery of bacteria) into *Escherichia coli* bacterium, thereby transforming this into an organism that can turn out new precursors of erythromycin (which can kill the bacteria). While designing new macrolide drugs that could overcome the bacterial resistance and at the same time, maintain identical pharmacokinetic profiles, gastrointestinal tolerability and other activity of this class of compounds, an understanding of their mode of action, along with the mechanism of resistance, became desirable. Three different mechanisms were assumed to be responsible for the majority of examples of macrolide resistance.[32] The first, known as 'high level resistance', results from mono and dimethylation of the amino group of adenine residue of A 2058 (this site is located in the peptidyl transferase loop of the RNA that catalyses polypeptide chain growth and is one of the erythromycin binding sites on the 23S ribosomal RNA of the 50S ribosomal subunit) by an enzyme called enzyme-ribosomal methylase, a product of a family of genes called erm and is involved in modification of the target.[40a–c] This resistance is also referred to as 'MLS_B phenotype', since these organisms are not only resistant to macrolide (M), but also to lincosamide (L lincomycin, clindamycin, celesticetin) and type B streptogramin (SB vernamycin B, pristinomycin I, staphylomycins). In the second mechanism, known as 'low level resistance', an efflux transporter, a product of the mef gene pumps macrolides out of the bacterial cell and has been reported in a number of *Streptococci* species.[41] As the strains of *Staphylococci* are inducibly resistant to macrolides and type B streptogramin, but not to the lincosamides, it is referred as MS_B resistance. The third possibility is the modification of the macrolide itself, where a number of mechanisms have been discovered to account for this structural modification of erythromycin, among which hydrolysis of the lactone ring and/or possible phosphorylation is of particular importance. Hence,



Scheme 6. Synthesis of 6-*O*-alkyl substituted erythromycins.

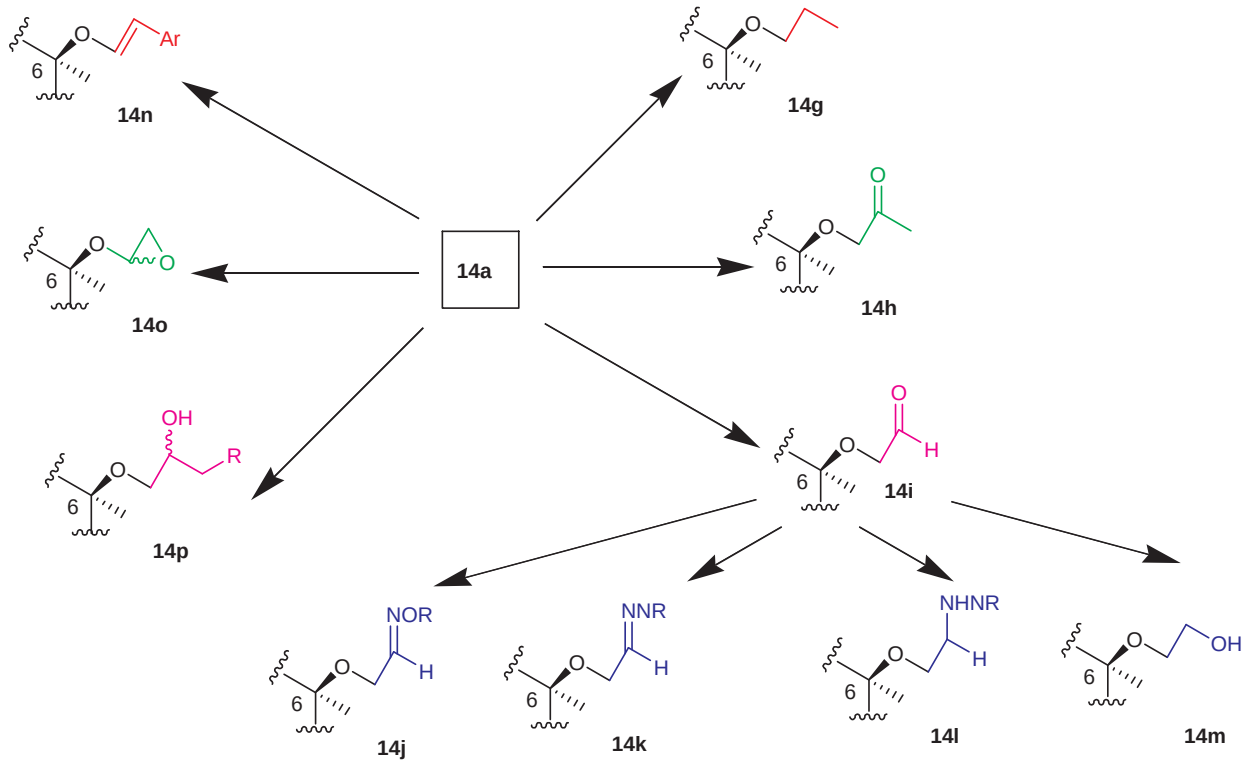
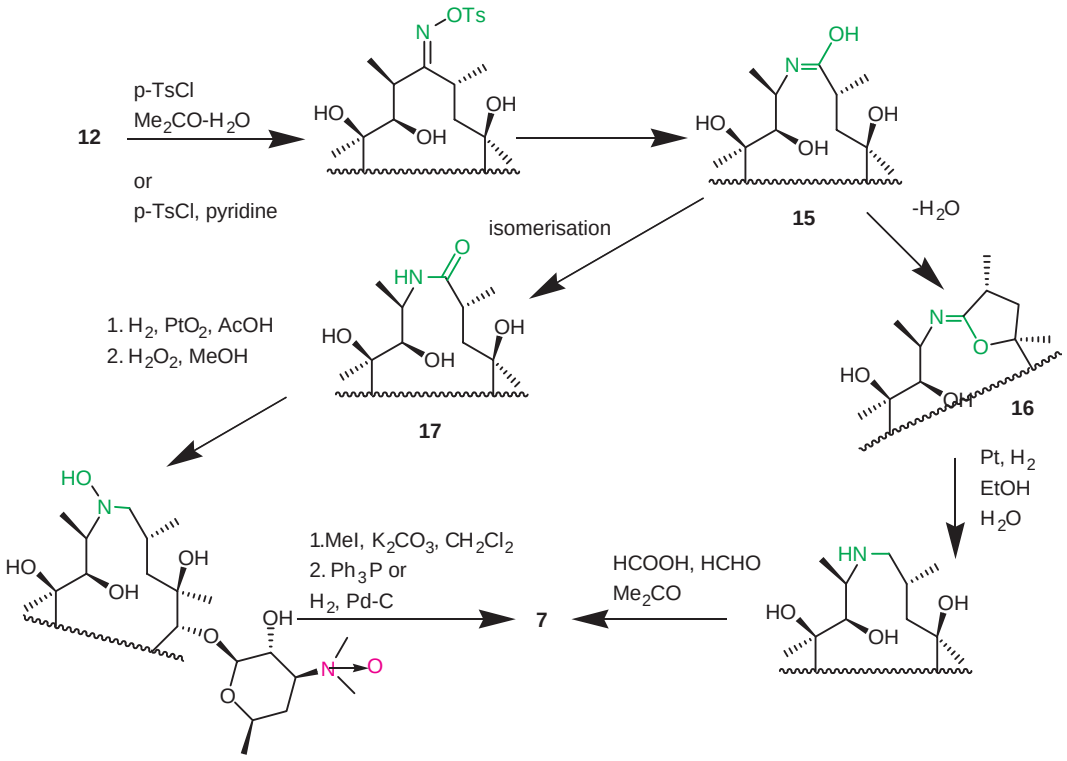


Figure 3. Compounds obtained from 6-*O*-allylerythromycin (**14a**).



Scheme 7. Synthesis of azithromycin (**7**) via Beckmann rearrangement.

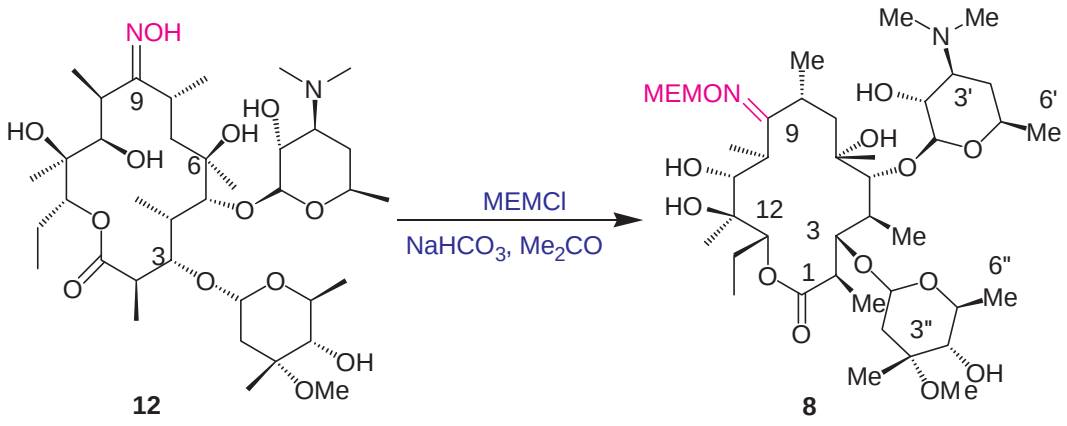
the identification of a new macrolide structure was essential that could bind to methylated ribosome and avoid the efflux protein recognition.

3.2. Chemist's approach to enhance antibacterial activity via chemical modification: the first breakthrough on the synthesis of 3-ketoerythromycin (ketolide)

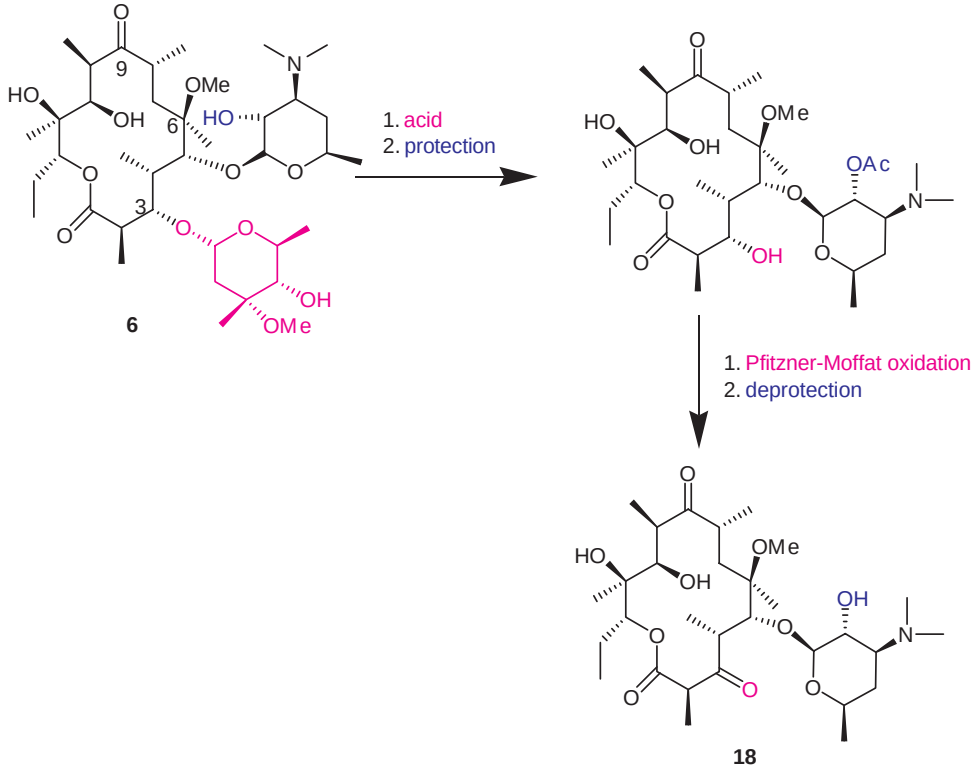
The neutral sugar ring, L-cladinose attached at the C-3 position of the macrolide, plays a vital role in the efflux mechanism, which has been, wrongly, long thought to be essential for the antibiotic activity of erythromycin A. Therefore, the effect on the antibiotic activity of 14-membered macrolides after removal of this moiety was investigated. Recent research has led to the discovery of a new distinct class, the ketolides, characterized by a 3-keto group in place of the cladinose moiety. The first attempt to prepare a ketolide from a protected erythromycin 9-oxime was unsuccessful,[42] as the hemiketal of the corresponding ketolide was isolated, due to the close proximity of the C-6 hydroxy group to the C-3 ketone. The first successful preparation of a semisynthetic ketolide **18** from 6-*O*-methoxyerythromycin (**6**) was accomplished by Agouridas et al.,[43] where blocking of the C-6 OH (by converting it into OMe) eliminated any possibility of ketal formation (Scheme 9).

3.3. Improvement of antibacterial activity via proper modifications of ketolide skeleton

The ketolides showed good activity against erythromycin susceptible bacteria, along with weak, but remarkable, activity against erythromycin resistant bacteria. Thus,



Scheme 8. Synthesis of roxithromycin (**8**).



Scheme 9. First successful preparation of semisynthetic ketolide.

the discovery of ketolides proved uniquely that it was the cladinose ring that needed to be removed to separate the resistance inducibility from the antibacterial activity of erythromycin. These results subsequently attracted immense interest in ketolide research, but the ketolide skeleton alone remained less attractive, as it showed modest activity against MLS_B resistance. The results of SAR studies, however, an area of outstanding importance, suggested that the 11,12-carbamate ketolides possess better antibacterial activities than the ketolide itself. The antibacterial activity of this new class of ketolides was dependent on a few structural features such as (i) a four atom side chain with an aromatic ring as substituent, mainly on either the nitrogen atom of the 11,12-carbamate ring or on the C-6 oxygen to overcome MLS_B resistance as well as efflux resistance (Fig. 4) and (ii) the aryl group, the selection of which was crucial. It has been shown that neither the ketolide nor the aryl-substituted carbamate ring alone could account for the activity against both erythromycin susceptible, as well as resistant, bacteria. This is exemplified by the carbamate macrolide, A-66321 (**19**) (Fig. 5), a nonketolide candidate prepared by Abbott Labs[44] in 1989, which showed increased in vitro activity against both inducibly and constitutively resistant strains of *Streptococcus pyogenes*, but poor activity against efflux resistance. On the other hand, RU-708 (**20**) (Fig. 5), a ketolide version of (**19**), showed very encouraging overall activity. Similarly, HMR-3004 (RU-004) (**21**), HMR-3647 (RU-66647) (**22**) and ABT-773 (**23**) (Fig. 5) were also found to be very potent.[45–49] Ketolide (**24**) (Fig. 5) is discussed in the following section.

3.4. Achievements: a tough job, but executed well with remarkable accuracy

3.4.1. Synthesis of suitably substituted 11,12-carbamate and carbazate ketolides. Both the carbamate and the 11,12-hydrazono carbamate (also known as the carbazate

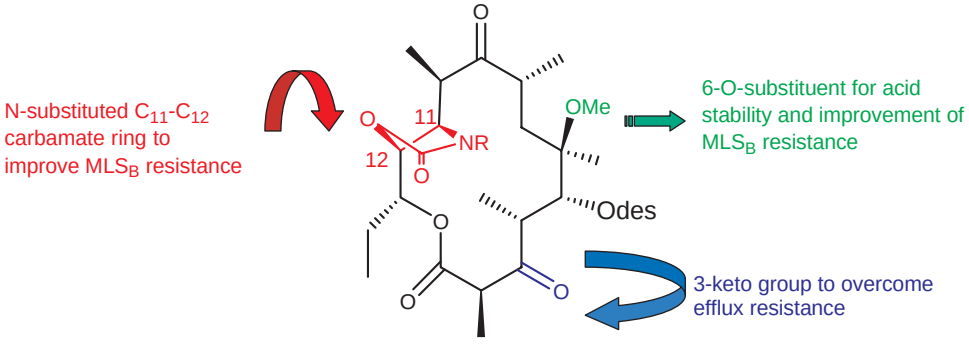


Figure 4. Structural features required for higher antibacterial activity of ketolides.

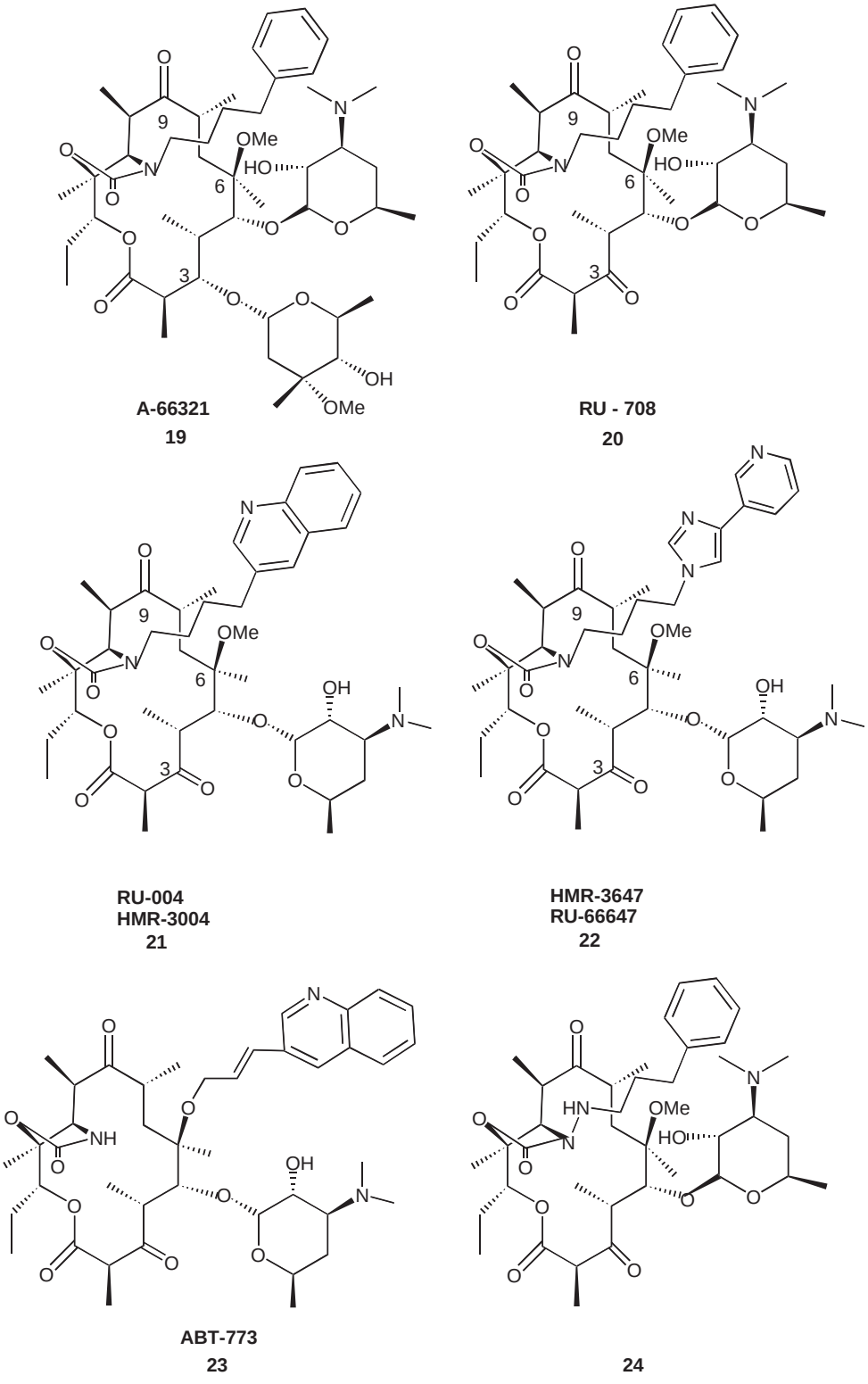
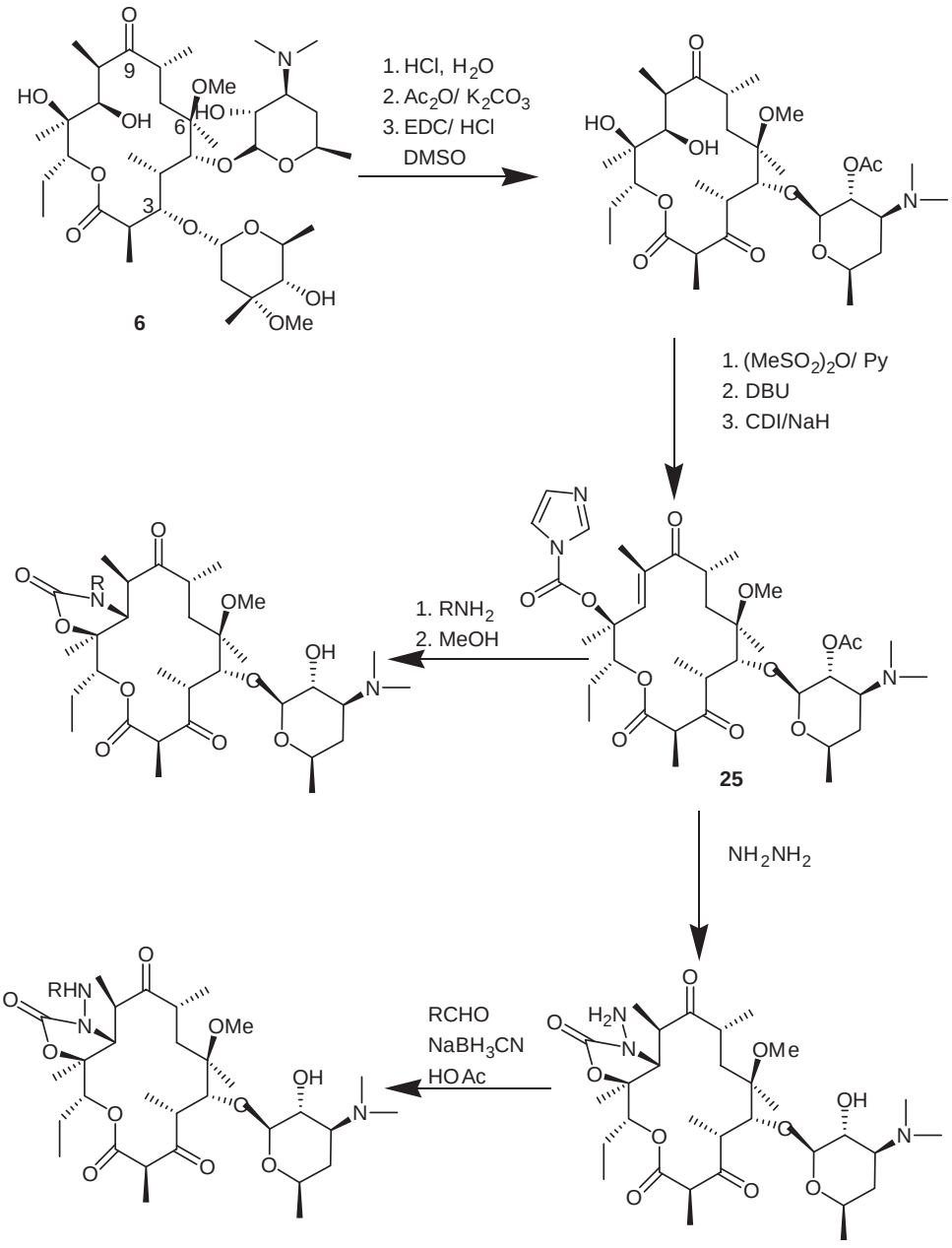


Figure 5. Macrolides with promising antibacterial activity.

ketolide) were prepared from clarithromycin (**6**) via its 12-acylimidazolyl ketolide derivative **25**[50,51] (Scheme 10). Among the 11,12-carbamate ketolides and the carbazate ketolides tested, the most active compound was found to be **24**, (Fig. 5), an analogue of RU-708 **20**. This was not only effective against the erythromycin susceptible organisms, but also approximately 300-fold more potent than erythromycin against the inducibly resistant *S. aureus* 2548.

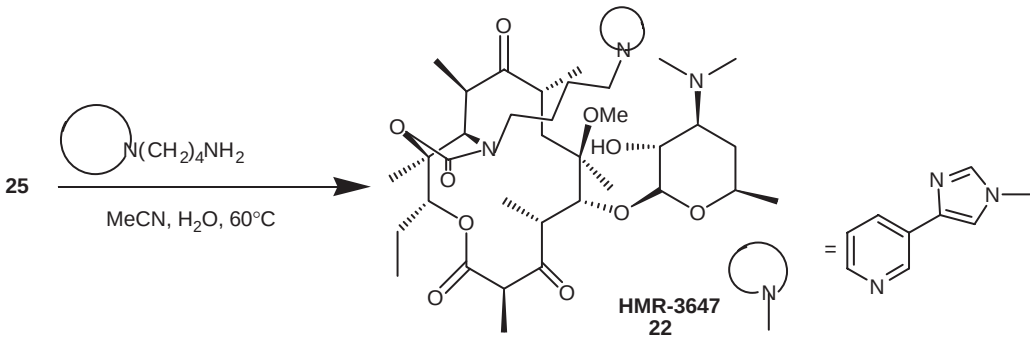
3.4.2. Synthesis of appropriately functionalized 11, 12-hydrazonocarbamate ketolides. Boosted by the discovery of some highly potent 11,12-carbazate ketolides, Agouridas et al.[52] re-investigated the role of the heterocyclic moiety in



Scheme 10. Synthesis of carbamate and carbazate ketolides from clarithromycin (**6**).

the carbamate series. Their speculation on the advantages of the additional heterocyclic nitrogen for antibacterial activity led them to synthesize ketolides with the introduction of arylimidazoles, benzimidazoles and triazoles at C-4 position of the butyl chain. The desired 11,12-cyclocarbamate ketolides were all synthesized according to Scheme 11 by the treatment of 12-acylimidazolyl ketolide **25** in aqueous acetonitrile with the appropriate amines.[53] Extensive lead optimization and introduction of an imidazolyl–pyridyl group in the side chain, for example, HMR-3647 (**22**) (commercially known as telithromycin, Ketek, Aventis Pharmaceuticals), resulted in the desired profile of antibacterial activity (Table 1). HMR-3647 is an innovative and promising new antibacterial agent.

Recently, Denis and co-workers have reported the synthesis of 2-fluoro telithromycins, HMR-3562 (**27**) and HMR-3787 (**28**). Direct comparison of HMR-3562 and telithromycin showed that the 2-fluoro derivative was relatively more active[54] (Table 1) against constitutively resistant *S. pneumoniae*, as well as inducibly resistant *S. aureus* and *S. pneumoniae*. It showed a higher activity than azithromycin against *H. influenzae*. Both **27** and **28** demonstrated good efficacy against infections caused by various susceptible and resistant bacterial strains in murine septicemia. These macrolides also showed good in vivo and in vitro activity against macrolide resistant strains of *S. pneumoniae* and *H. influenzae*. The compounds were synthesized by two different methods, one of which involved the formation of the carbamate ring, followed by fluorination of **26** (Scheme 12), and the other the reverse protocol, that is, fluorination of **29**, followed by carbamate ring formation (Scheme 13). Other analogues of telithromycin such as 2-chloro and 2-methyl derivatives were also



Scheme 11. Synthesis of carbamate ketolides with substitution at the C-4 position of the butyl chain.

Table 1. Comparision of antibacterial activities of HMR-3647 with other macrolides

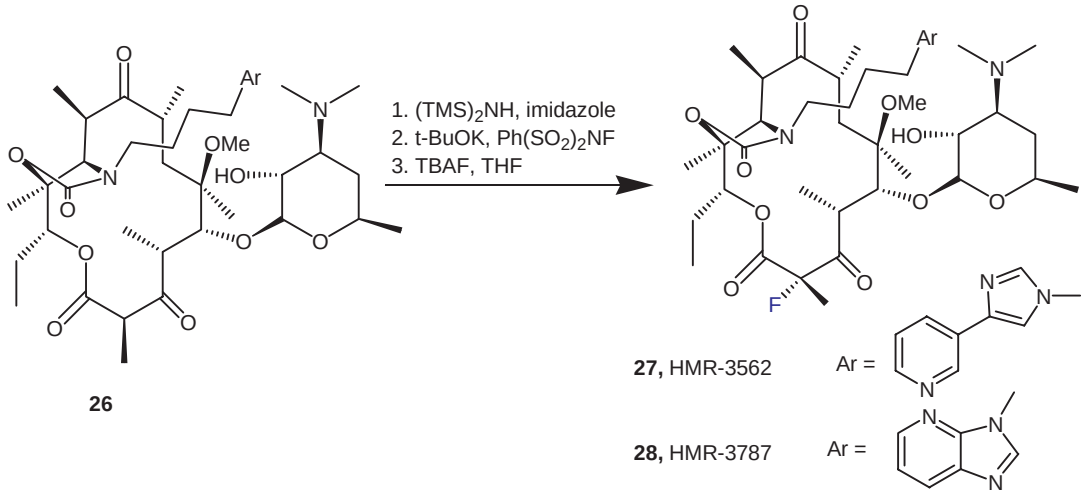
Macrolide	Sa[a] Ery S[b]	Sa Ery Ri	Sa Ery Rc	S_{pyo} Ery S	Sp Ery S	Sp Ery Rc	Sp Ery Ri
CLA[c]	0.3	40	40	0.8	0.04	40	40
AZI[d]	0.3	40	40	0.60	0.15	40	40
HMR-3562 (**27**)	0.04	0.08	40	0.02	0.02	0.08	0.02
HMR-3647 (**22**) (telithromycin)	0.04	0.08	>40	0.02	<0.02	<0.02	<0.02

[a] Sa, *Staphylococcus aureus*; Sp, *Streptococcus pneumoniae*; S^{pyo}, *Streptococcus pyogenes*.
[b] Ery S, erythromycin susceptible; Ery Rc, constitutively erythromycin resistant; Ery Ri, inducibly erythromycin resistant.
[c] Clarithromycin.
[d] Azithromycin.

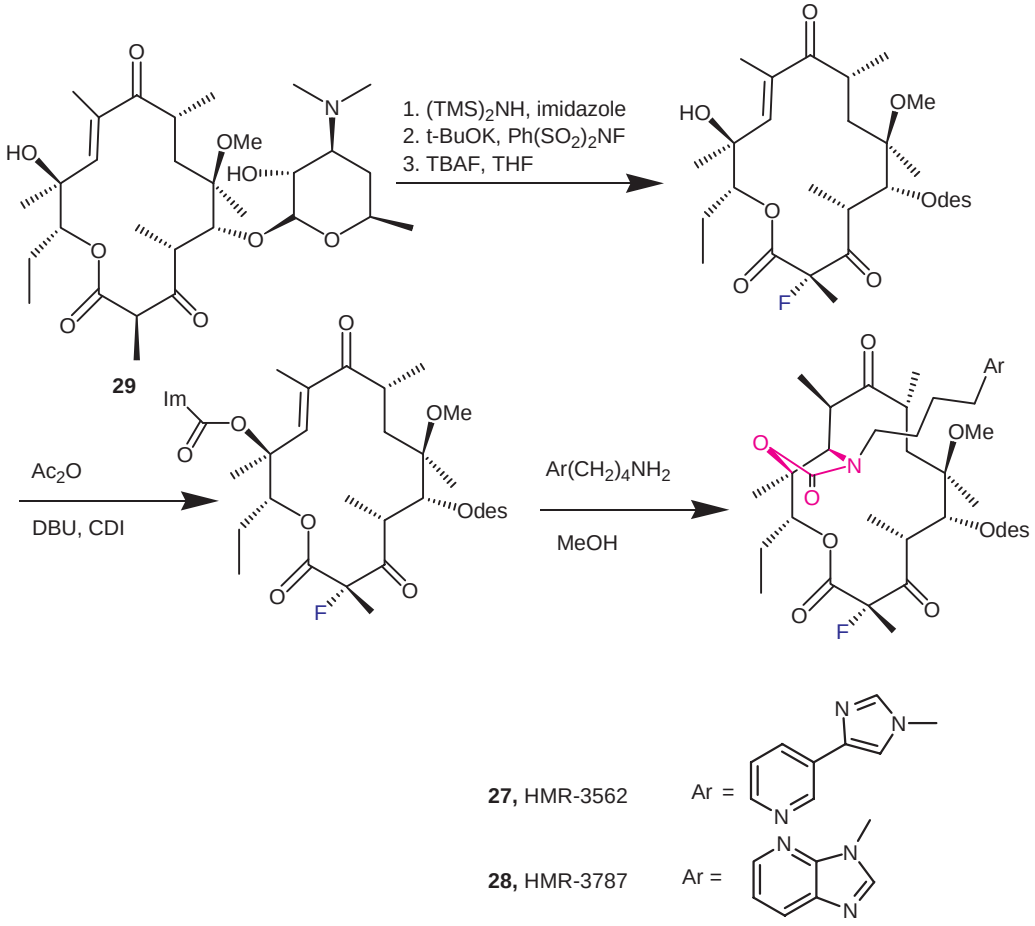
generated,[54] but the introduction of these larger substituents resulted in loss of activity, indicating the importance of steric factors at C-2, which could only tolerate the presence of small substituents.

3.4.3. Synthesis of few non-carbamate ketolides: 9-oxime ketolides and 6-*O*-alkylketolides. A variety of 9-oxime ketolides were prepared from 3-ketoclarithromycin (**30**). Thus, **31** was obtained from **30** via oximation followed by hydrogenation (Scheme 14).[55a–d,56] Initially, compound **31** showed significant activity against *H. influenzae* as well as macrolide resistant organisms, with the 3(*R*) piperidinyl isomer being more active than the 3(*S*) isomer. Replacement of the active hydrogen on nitrogen by an arylalkyl group did not improve the overall activity. Therefore, further effort was initiated in order to introduce substituents at the C-2 position and this resulted in the development of a new series, that is, 2-substituted ketolides having a 9-oxime functionality, reported by Kaneko and co-workers.[57] Among several C-2 substituents, the 2-fluoro derivative CP-654743 (**33**) showed the best activity against both erythromycin susceptible and resistant organisms. It was relatively more active than CP-605006 (**32**), its non-fluoro derivative and telithromycin against key respiratory-tract pathogens.

3.4.4. Synthesis of 6-*O*-substituted ketolides having 11,12-carbamate pharmacophores—a new class of promising antibacterial agents. Synthesis of **33** involves oximation of a suitably protected 6-*O*-methylcarbazate ketolide followed by the introduction of an arylalkyl chain at $-NH_2$ of the cyclic 11,12-carbazate and, finally, fluorination at the C-2 position (Scheme 15).



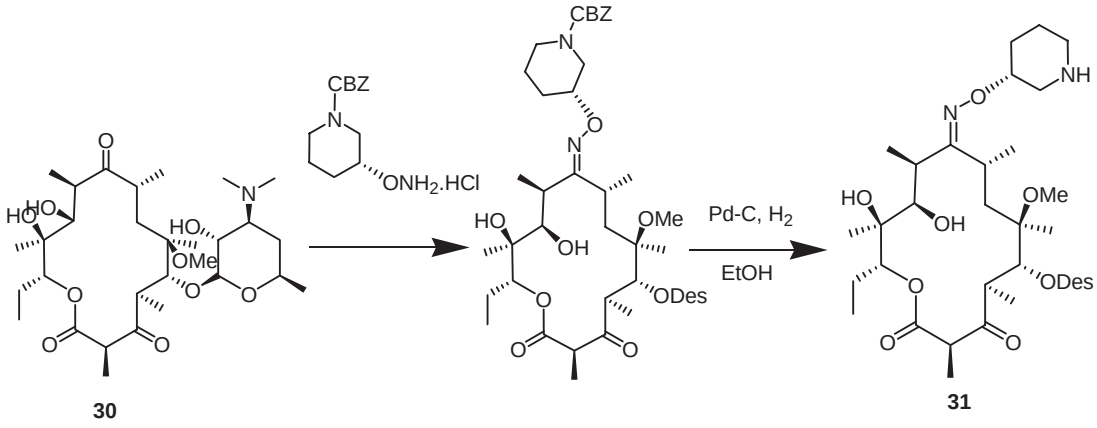
Scheme 12. Synthesis of 2-flourocarbamate ketolides.



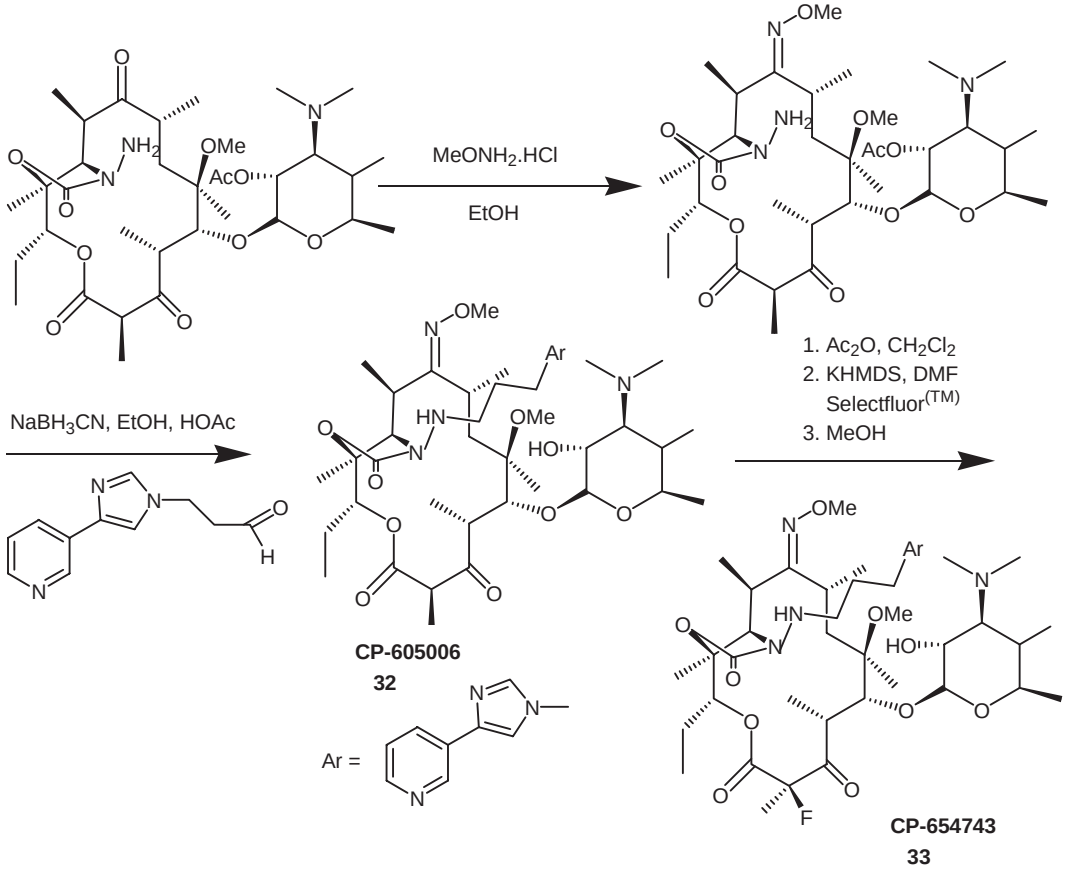
Scheme 13. Alternative synthesis of 2-fluorocarbamate ketolides.

Since the C-6 hydroxy group is also directed near the center of the hydrophilic face hence it was planned to incorporate an arylalkyl chain to 6-*O*-position. Thus, linking an aryl group to this position would provide a minimized conformation where the aryl group occupies a spatial region similar to the aryl group attached to telithromycin. Based on this SAR, a series of ketolides were synthesized.[58a,b]

In 1998, Clark et al. revealed a general strategy for the introduction of an alkyl group at the C-6 position through the formation of 6-*O*-allylerythromycin (**14a**). The keto group at the 3-position was then introduced through further three steps: removal of the cladinose sugar by acidic hydrolysis, protection of 2′-OH as an acetyl ester and, finally, Corey–Kim oxidation of the 3-hydroxy group to provide the 6-*O*-allylketolide (**34**) (Scheme 16). This compound served as the key intermediate for the preparation of other analogs. Thus, reaction of **34** with aryl halides, under Heck conditions, provides a series of (3-aryl)prop-2-enyl ketolides (**35a–e**) (Scheme 17). Conversion of the allyl group into aldehyde (**36**) followed by reductive ammination provided a series of amino analogs **37a–e** (Scheme 17).



Scheme 14. Synthesis of 9-oxime ketolides.

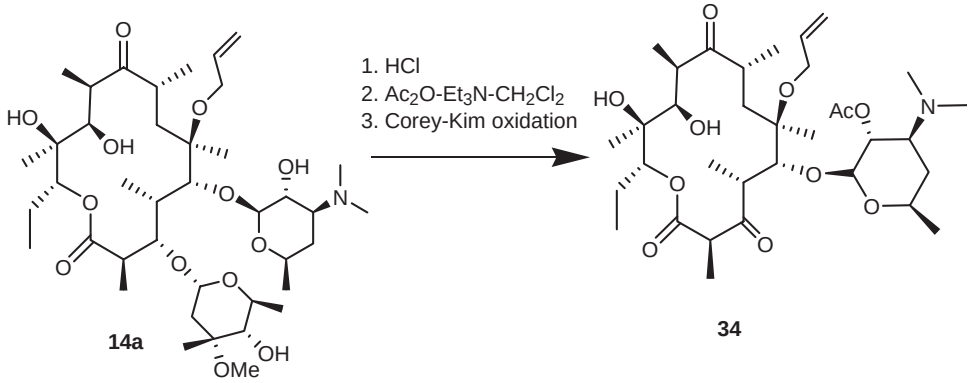


Scheme 15. Synthesis of amino- substituted 2-fluoro-9-oxime-11,12-carbazate derivatives.

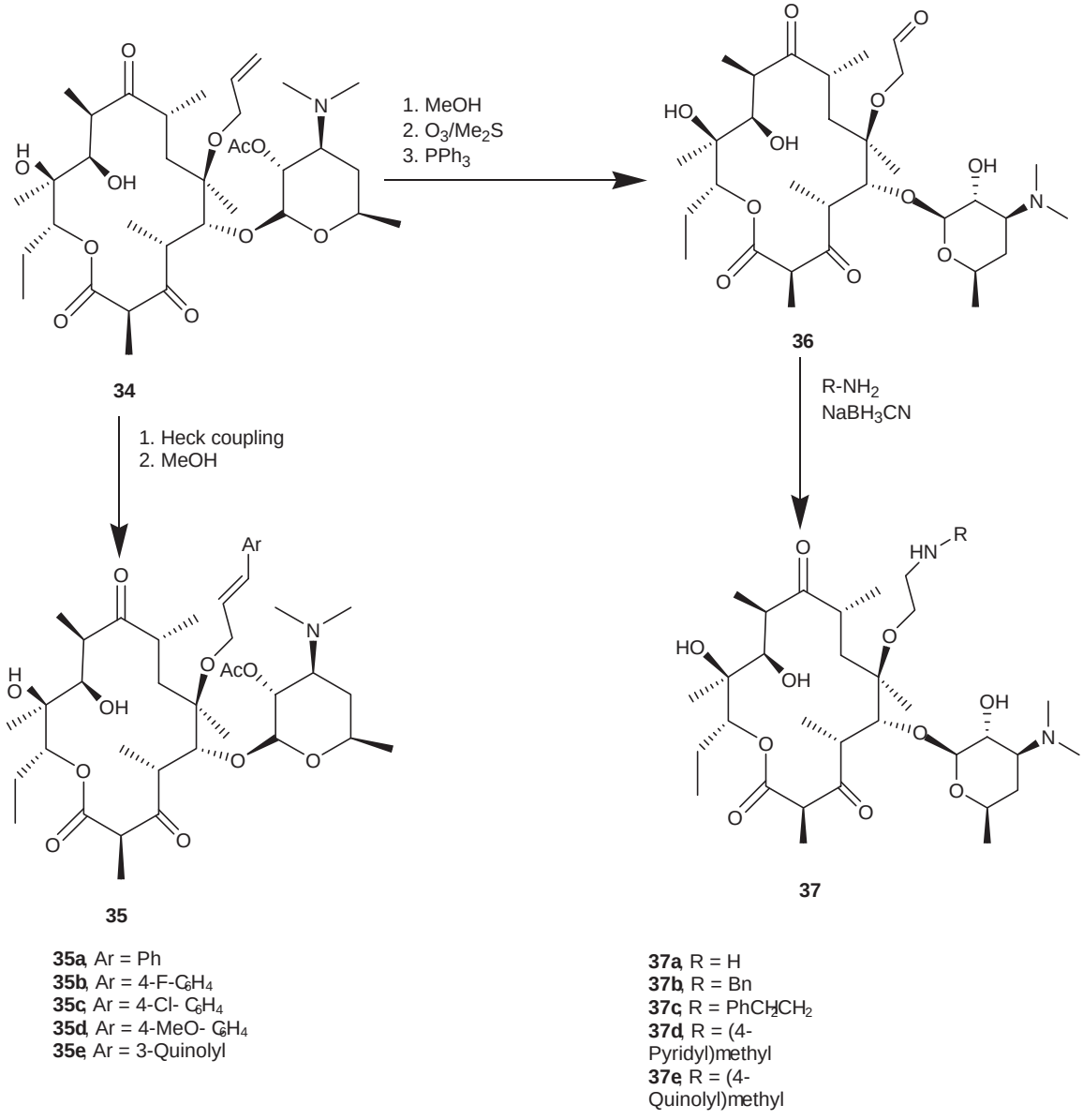
Only **35e**, the (3-quinolyl)prop-2-enyl analog, was found to be as active as erythromycin against erythromycin susceptible strains, whereas both series **35** and **37** exhibited improved activity against various erythromycin resistant bacteria. The most active compound **35e**, however, exhibited MICs of 0.2 and 0.25 μg/ml against inducibly MLS_B resistant *S. aureus* and efflux resistance, as compared to 6.2 and 16 μg/ml for erythromycin, but showed weak activity against *H. influenzae* and constitutively MLS_B resistant strains.

In an alternative strategy, it has been shown that the introduction of an 11,12-carbamate pharmacophore into the 6-*O*-substituted ketolide improved the antibacterial activity, mainly against *H. influenza* and constitutively MLS_B resistant strains. The necessary key intermediate, 6-*O*-allyl-11,12-carbamate ketolide **38**,[40] was prepared by one of two routes, starting from 6-*O*-allylerythromycin **14a** (Scheme 18).[59,60] Heck coupling reactions of various aryl halides with the intermediate **38** led to a series of 6-*O*-arylprop-2′-enyl-11,12-carbamate ketolides (**23**, **39a**–**h**) (Fig. 6).

Compound **23** (ABT-773),[61] the carbamate derivative of **35d**, showed an excellent and well-balanced antibacterial profile against both susceptible and resistant organisms. ABT-773 also exhibited remarkably enhanced activity against MLS_B resistant *S. pyogenes* and *S. pneumoniae*,



Scheme 16. Synthesis of 6-*O*-allylketolide.

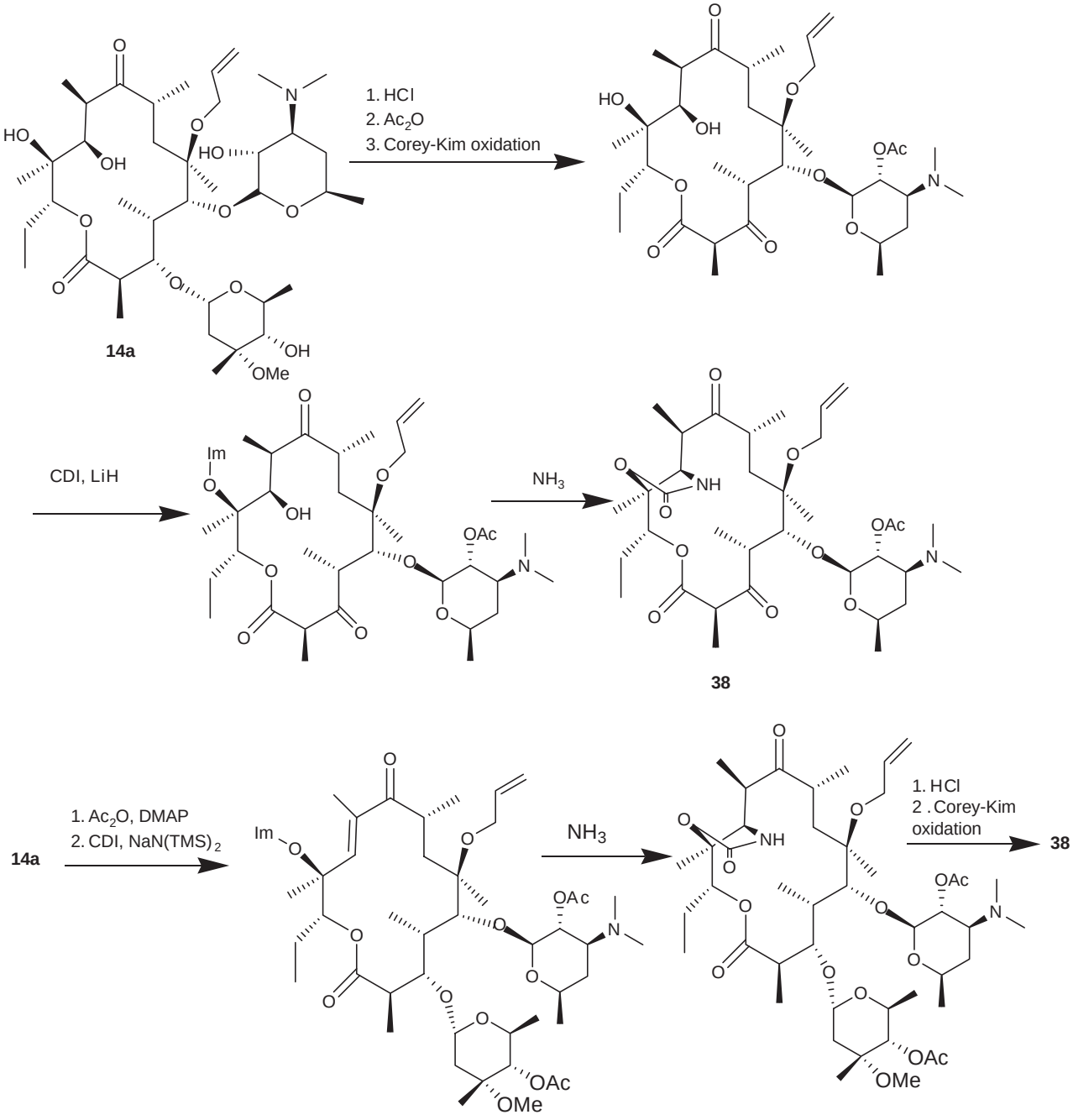


Scheme 17. Conversion of 6-*O*-allylketolide (**34**) into **35** and **37**.

with MICs of 1.0 and 0.25 μg/ml as compared to 100 and 128 μg/ml for **35d**. Further modification of **39** provided three other analogs, **40**, **41** and **42**, which possessed different types of linkages between the lactone skeleton and aryl group. The effect of a linker between the lactone ring and 3-quinolyl group on the in vitro antibacterial activity is presented in Table 2. The olefin linkage in ABT-773 appeared to be optimal. Interestingly, the alkyne linkage in **42** provided a comparable activity to ABT-773, except against *H. influenzae*.

All the different regioisomers of ABT-773 were prepared (**39d–h**) for evaluating their antibacterial activity. It was observed that the point of attachment to the quinoline ring was important for optimal antibacterial activity especially against MLS_B resistant organisms. In addition to the 3-quinolyl analog **23**, the 6-quinolyl isomer **39f** also exhibited excellent overall antibacterial activity (Table 2). The enhanced antibacterial activity of 2-fluoro substitution was observed in the 6-*O*-substituted ketolide. A 4- and 16-fold increase in the in vivo activity against macrolide resistant *S. pyogenes* and *S. pneumoniae* was observed in the case of the 2-fluoro derivative of ABT-773, that is, **43** (A-20316, Fig. 6). This compound also demonstrated a 5-fold improved efficacy over ABT-773 when evaluated against macrolide susceptible *S. pneumoniae* ATCC 6303.

Recently, the 6-*O*-propenylaryl side chain of erythromycin derivatives was also constructed by olefin cross metathesis.[62] Undoubtedly, these intermolecular reactions are often complicated by competition between the desired intermolecular cross metathesis (CM) and undesired intermolecular self metathesis (SM), but a logical selection of the two olefins by Hsu and co-workers as the starting compounds eliminated all possibilities of self metathesis (Scheme 19). In most of the cases the major product isolated



Scheme 18. Synthesis of 6-*O*-substituted 11,12-carbamate ketolide.

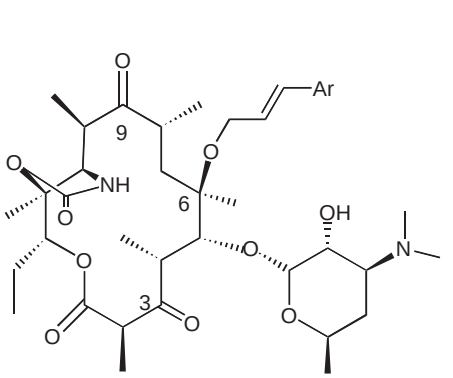
had >95:5 *E*-selectivity. These reactions were, however, complicated by the formation of some side products.

3.4.5. Synthesis of cyclic ketolides. In order to study the potential of other ketolides as potent antibacterial agents, some cyclic ketolide systems and their substituted derivatives were synthesized, in the hope that these analogues could be used as scaffolds to probe secondary ribosomal binding sites. Based on the literature available, they can be categorized into two types:

(a) Tricyclic ketolides
(b) Tetracyclic ketolides.

Type a: tricyclic ketolides. In 1995, Asaka et al. reported a novel tricyclic ketolide series by fusing one additional ring to the North–Western hemisphere of the 11,12-carbamate ketolide to enhance the stability, bioavailability and antimicrobial activity. Actually, three types of tricyclic ketolides are available in the literature, depending on the size of the newly formed ring: (a) tricyclo[14.5.5] ketolides **44** are exemplified by a cyclized version of Ru-004[63a] (Fig. 7), (b) tricyclo[14.5.6] ketolides **45** (Fig. 7)[63b] and (c) tricyclo[14.5.7]ketolides (**46**) (Fig. 7).[64a]

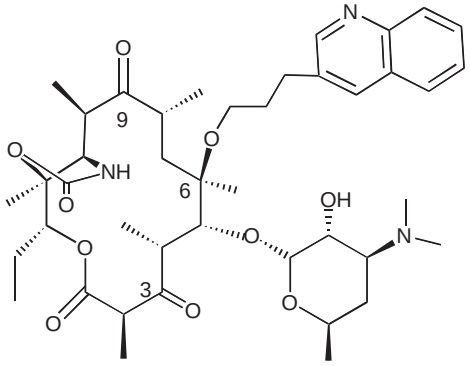
TE-802 (**46a**) (Scheme 20) was the first member of this 9-iminoketolide family discovered by Asaka et al. at



39

Ar =

39a Ph
39b H
39c 2-Quinolyl
23 3-Quinolyl (ABT-773)
39d 4-Quinolyl
39e 5-Quinolyl
39f 6-Quinolyl
39g 7-Quinolyl
39h 8-Quinolyl



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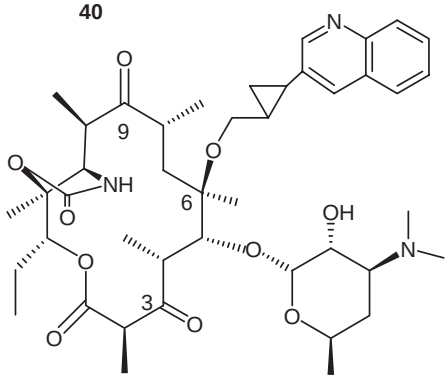

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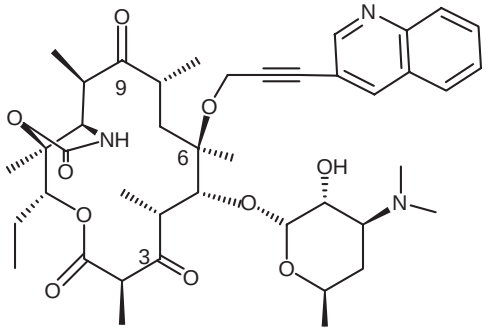

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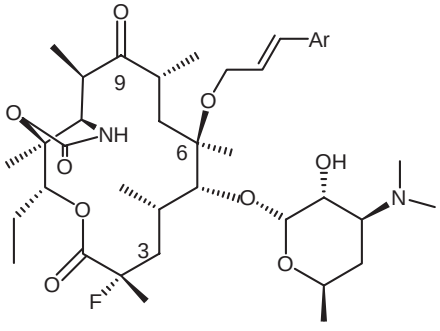


A-20316
43

Ar = 3-Quinolyl

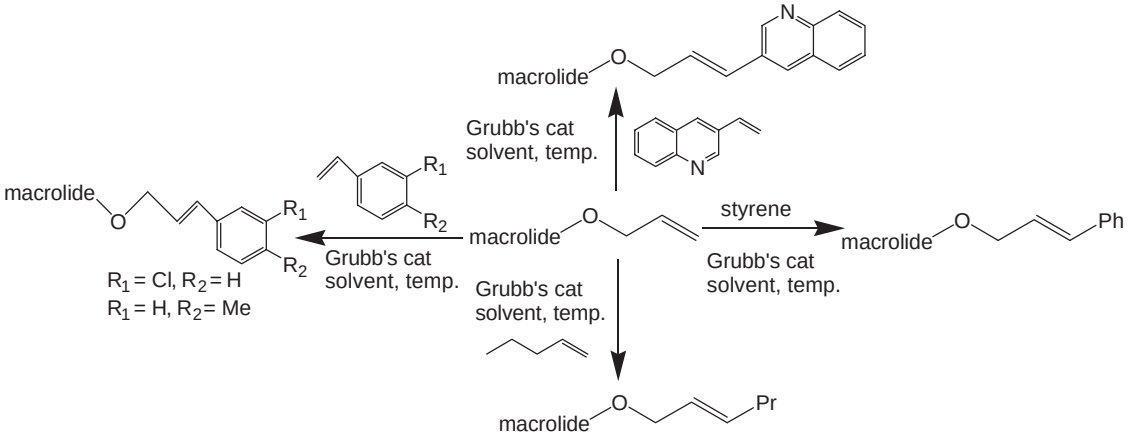
Figure 6. Examples of 6-*O*-arylprop-2′-enyl-11,12-carbamate ketolides.

Taisho.[64b,c] These tricyclic ketolides were prepared by treating 12-*O*-acylimidazolyl intermediate **47** with ethylenediamine and substituted ethylenediamine. Carbamate formation followed by an intramolecular imine formation led to the tricyclic skeleton. Acid hydrolysis of the cladinose ring followed by a modified Pfitzner–Moffatt oxidation afforded the tricyclic ketolides **46a–d** (Scheme 20).

Table 2. Comparison of antibacterial activities of ABT-773 (**23**), its 6-quinonyl derivative (**39f**) and **42** with erythromycin A

		23	**39f**	**42**	Ery-A
Sa[a] ATCC 6538	Ery S	0.05	0.05	0.05	0.39
Sa[a] A5177	erm	0.05	0.05	0.05	6.2
Sa[a] A5278	erm	>100	>100	>100	>100
S_{pyo}[b] EE561	Ery S	0.004	0.004	0.01	0.03
S_{pyo}[b] 930	erm	1	1	0.39	>128
S_{pyo}[b] PIU 2548	mef	0.125	0.25	0.10	32
Sp[c] ATCC 6303	Ery S	0.004	0.004	0.004	0.06
Sp[c] 5737	erm	0.25	1	0.08	>128
Sp[c] 5979	erm	4	—	4	>128
Sp[c] 5639	mef	0.25	0.25	0.25	16

[a] Sa, *Staphylococcus aureus*.
[b] S_{pyo}, *Streptococcus pyogenes*.
[c] Sp, *Streptococcus pneumoniae*.



Scheme 19. Synthesis of 6-*O*-3-aryl-propenyl macrolides via olefin cross metathesis reaction.

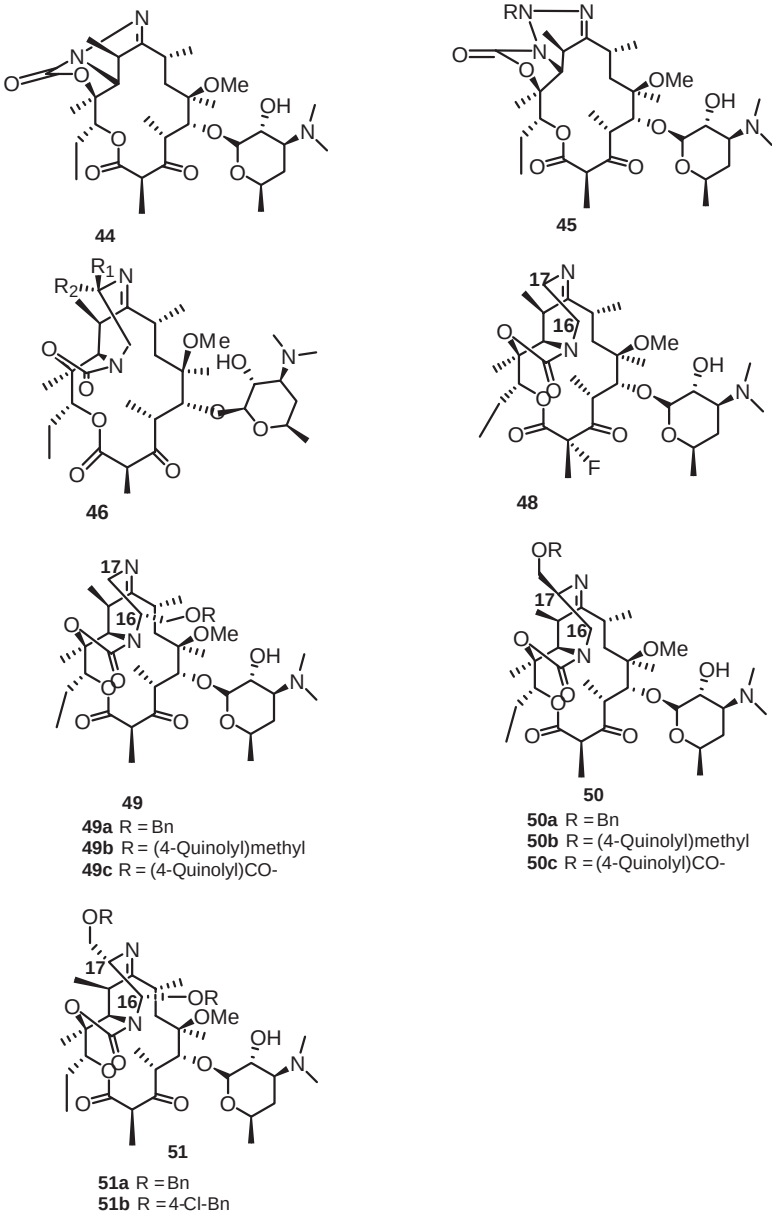
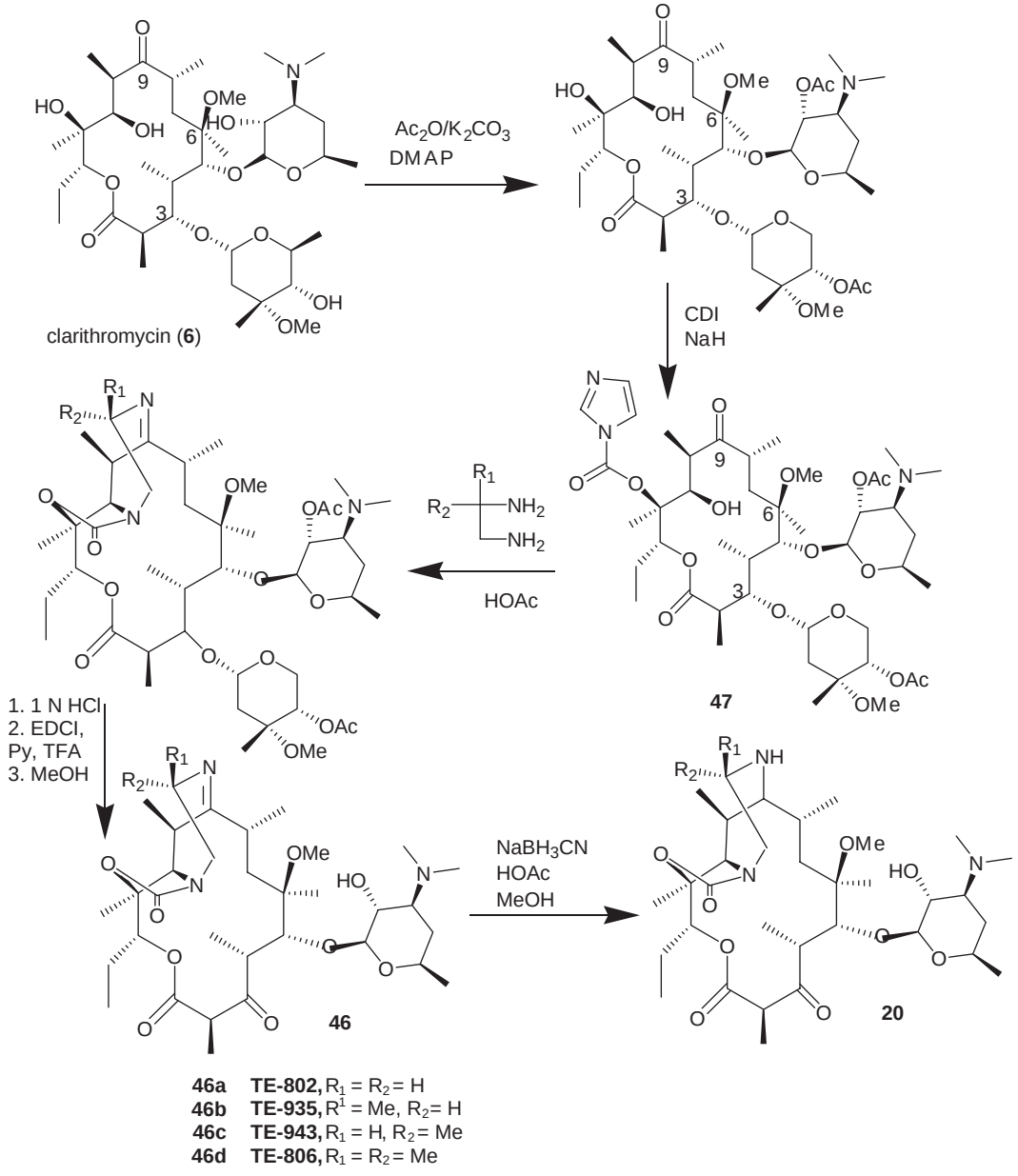


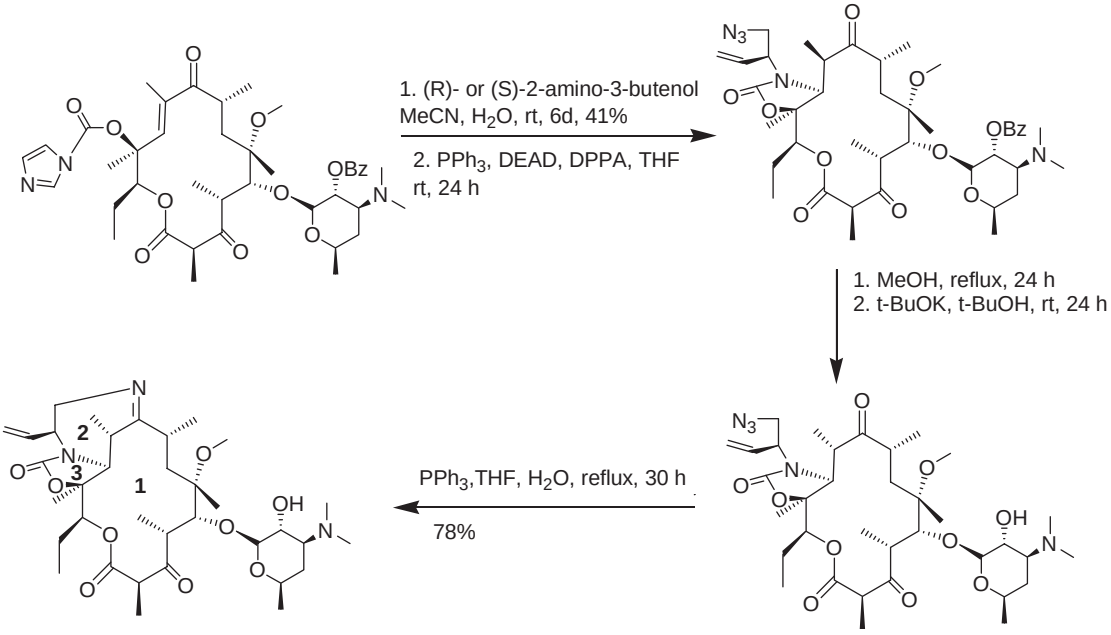
Figure 7. Examples of tricyclic ketolides.



Scheme 20. Synthesis of tricyclic ketolides.

TE-802 (**46a**) showed promising activity. In order to enhance its antibacterial activity, mainly against erythromycin resistant gram-positive organisms and *H. influenzae*, a series of C-2-substituted tricyclic ketolides were prepared by Phan et al.[65,66] The 2-fluoro derivative of TE-802 (**46a**),[50] that is, **48** (Fig. 7), showed enhanced in vivo efficacy, particularly against *H. influenzae*, in mouse pulmonary infections (ED_{50} of **48**: 36 mg/kg; ED_{50} of **46**: >60 mg/kg). All other C-2 substituents examined, for example, hydroxyl, chlorine, bromine and alkyl groups, resulted in a significant loss of activity. These results clearly demonstrated that only small substituents such as fluorine and hydrogen could be tolerated at C-2. To improve the relatively weak activity against MLS_B resistant *S. pneumoniae* and *H. influenzae*, aryl-containing substituents were introduced into the ethylene bridge of TE-802 (**46a**),[67a] based on earlier SAR information. In general, aryl-substituted TE-802 derivatives exhibited a higher activity than TE-802 (**46a**). Derivatives with aryl substitution at position C-16, that is, **49a–c** (Fig. 7), showed higher activity, particularly against MLS_B resistant *Streptococci* and *H. influenzae*. Substitution at C-17, that is, **50a–c** (Fig. 7), however, resulted in a 2- to 3-fold improvement in in vivo efficacy when compared to clarithromycin (**6**) and exhibited the same efficacy as TE-802. Among these compounds, quinolyl derivatives such as **49b** and **49c** provided the highest activity against MLS_B resistant *Streptococci* and *H. influenzae*. The C-16 and C-17 disubstituted analogue **51** (Fig. 7) was less active against *H. influenzae*, but showed enhanced activity against MLS_B constitutively resistant *S. aureus* (MIC 6.2 μg/ml vs >100 μg/ml for erythromycin).

Or and co-workers synthesized[67b] a novel vinyl-substituted bridged tricyclic ketolide, which can be further used as building blocks for the synthesis of new generation ketolides to overcome macrolide resistance (Scheme 21).

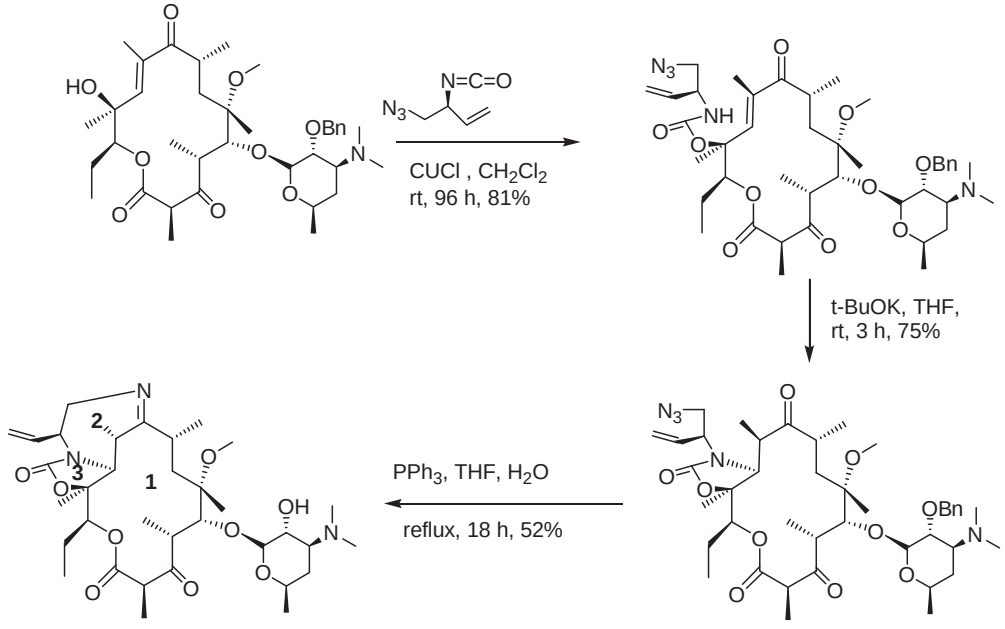


Scheme 21. Synthesis of vinyl-substituted tricyclic ketolide.

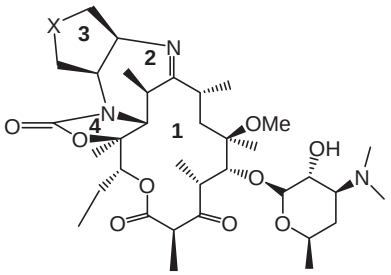
This original synthesis of a vinyl-substituted cyclic ketolide had some major drawbacks, for example, low yield due to the formation of a mixture of products and difficulty in purifying the final product. Very recently, Keyes and co-workers[67c] reported a short, efficient and improved synthesis of the same macrolide by utilizing the unwanted side product of the previous method as the starting compound and azido isocyanate (Scheme 22).

Type b: tetracyclic ketolides. Phan et al. reported a series of tetracyclic ketolides with one fused carbocycle or heterocycle ring to the diazapene ring of TE-802.[68] The synthesis, which employed *meso-cis*-diamines in the cyclization, generated two possible diastereomers, **52a–d** and **53a–d** (Fig. 8), where **52a–d** was found to be the major isomer. Or and co-workers also reported a novel cyclic ketolide **55**. It was prepared by reducing the nitro group of compound **54**, followed by intramolecular condensation (Scheme 23)[69] of the resulting amine with the nearby carbonyl group. Further reduction of **55** provided **56**. None of these tetracyclic ketolides exhibited significant in vitro activity against constitutively macrolide resistant *S. pneumoniae* and none showed azithromycin-like MICs against *H. influenzae*.

3.4.6. Synthesis of bridged ketolides. The synthesis and activity of two novel series of bridged ketolides reported by Or et al. are now described.

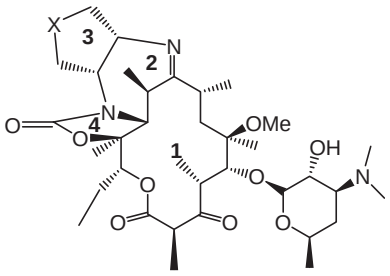


Scheme 22. Improved synthesis of tricyclic erythromycin analogue.



52

52a,X = -CH_2CH_2-
52b,X = -CH_2-
52c,X = -O-
52d,X = -NR-



53

53a, X = -CH_2CH_2-
53b, X = -CH_2-
53c, X = -O-
53d, X = -NR-

Figure 8. Tetracyclic ketolides.

(a) The first series, 6,9-bridged ketolides, is exemplified by **57** and **58**.[70a] Compound **57** was prepared from the protected erythromycin derivative **13** according to the procedure outlined in Scheme 24. Thus, fluoromethylation of **13** with fluoromethyl bromide followed by deprotection provided the bridged erythromycin derivative **57**. Compound **57** was converted into the corresponding 11,12-cyclic carbonate, that is, **58**. Sequential hydrolysis of cladinose, protection of the 2′-hydroxy group and Corey–Kim oxidation of the 3-hydroxy group followed by final deprotection provided the 6,9-bridged ketolide **59**. It was slightly less active than erythromycin A against macrolide susceptible organisms, including *H. influenzae*, it was very active against erythromycin resistant organisms harboring an efflux mechanism, but it failed to show activity against resistant organisms with a ribosome methylation mechanism.[70b]

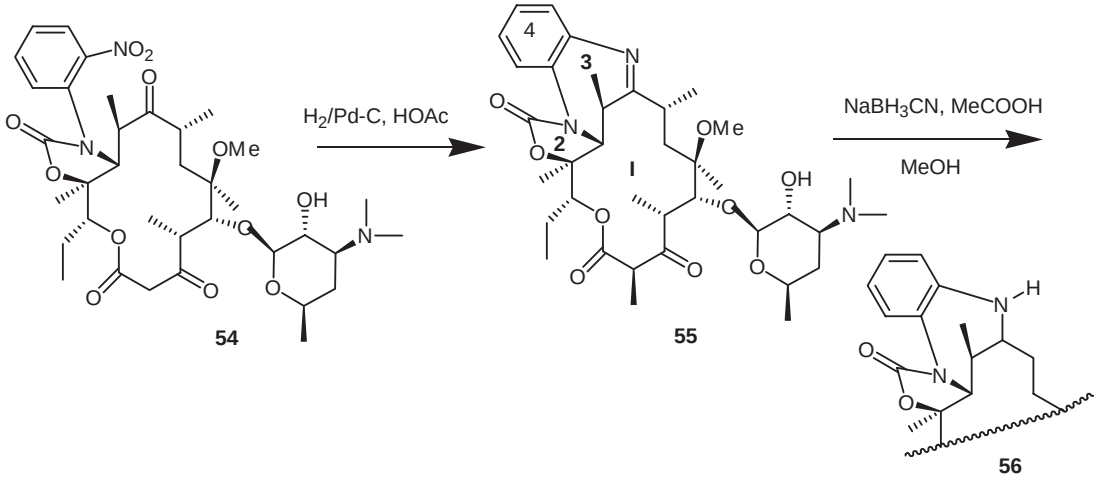
(b) The other series reported by Or et al. comprising structurally unique 6,11-bridged ketolides[71a] was generated by the intramolecular Heck reaction of **60** and **61** to form 17- and 18-membered macrolides (**62** and **63**) followed by their conversion into the desired ketolides, that is, **64** and **65**. In a similar manner, the Heck reaction was also performed on an *N*-substituted carbamate ketolide **66** in order to generate the 18-membered ketolide, that is, **67** (Scheme 25).

Apart from these derivatives, two other 6,11-bridged ketolides **69a** and **69b** were prepared via an alternative synthetic strategy, that is, a ring-closing olefin metathesis of compound **68** (Scheme 26).[71b]

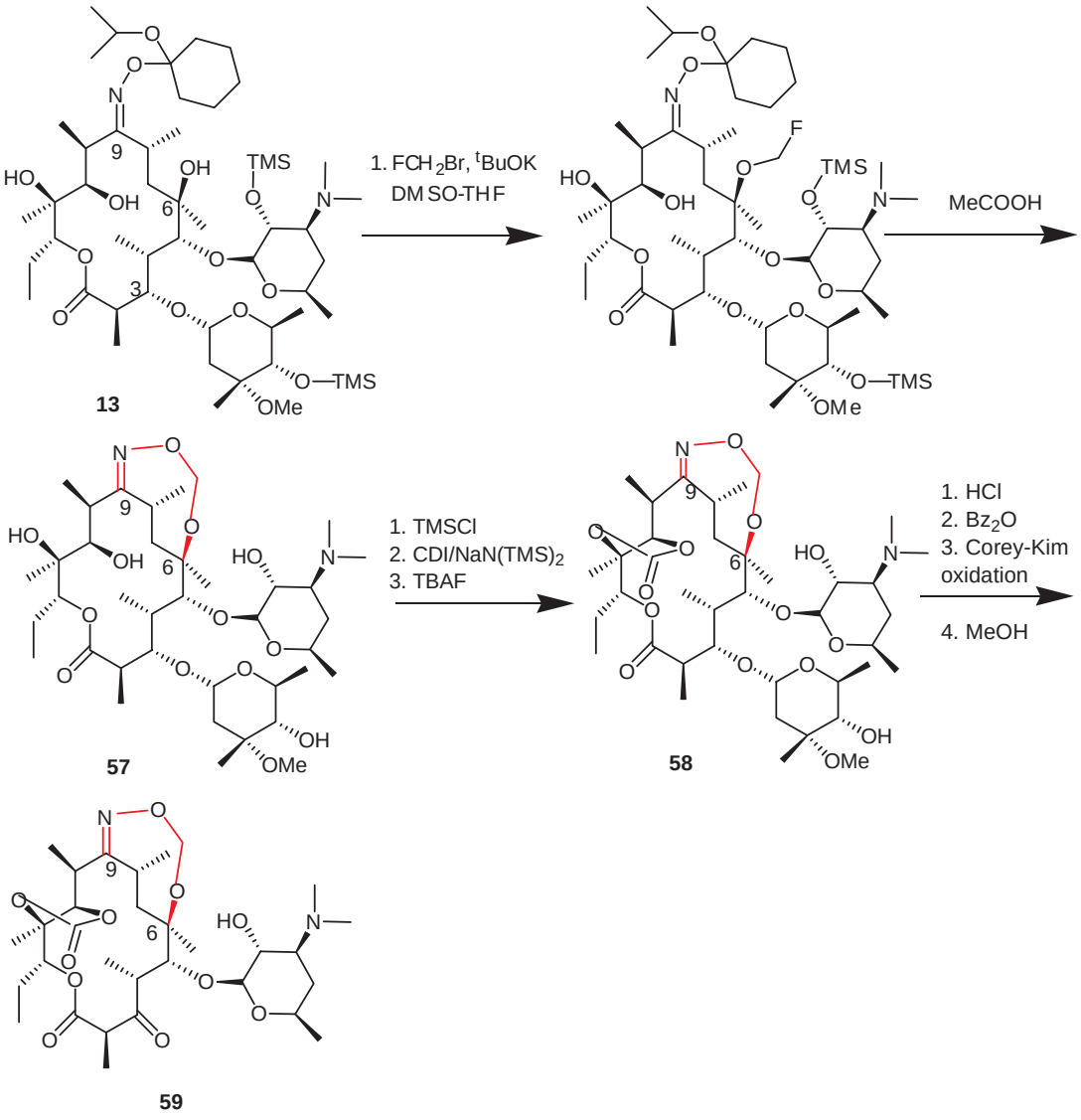
Another novel series of 6,11-bridged ketolides were prepared by Li et al.[72a] Compounds **70** and **71** (Fig. 9) can be considered as hybrids of the 6-*O*-substituted ketolide series developed by Abbott and the 11,12-carbamate ketolide series developed by Aventis. Denis and Renou achieved the *N*-demethylation of ketolides by using solution-phase parallel synthesis of *N*-desosaminyl-substituted ketolides.[72b]

Among the various types of ketolides reported, ABT-773 (**23**, Fig. 6) has been identified as a highly potent, broad-spectrum ketolide effective against drug resistant *Streptococcus pneumoniae*.[73–75]

3.4.7. Synthesis of promising macrolides other than ketolides. The ketolide series is not necessarily the only



Scheme 23. Synthesis of tetracyclic ketolide.



Scheme 24. Synthesis of 6,9-bridged ketolides.

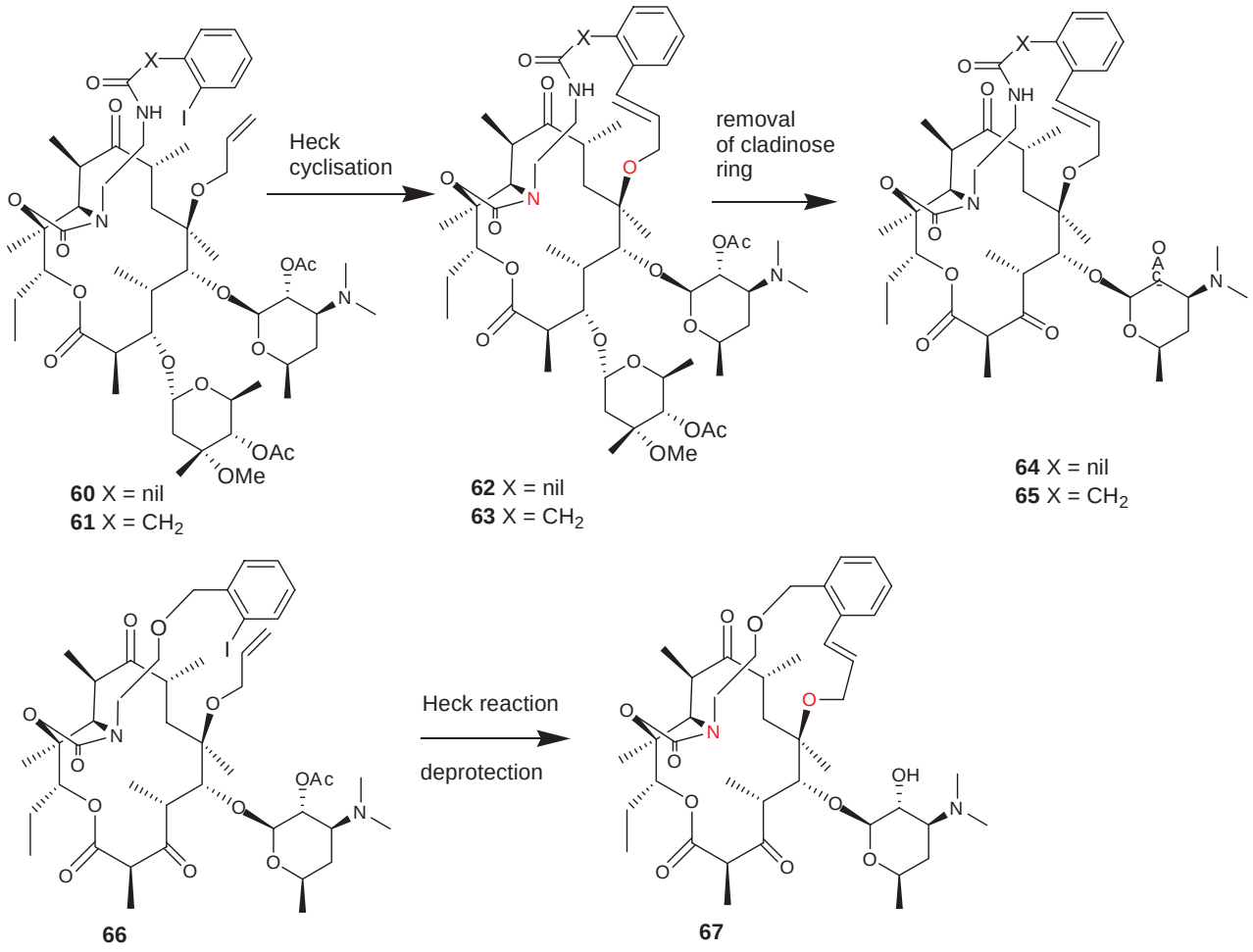
class of macrolides to achieve this goal. Some modifications to the C-3 cladinose sugar have been reported. These modifications include:

(i) 3-Deoxymacrolides exemplified by 3-deoxy-3-descladinosyl-6-*O*-methylerythromycin analogues[76] (**72**, Fig. 10). These had moderate antibacterial activity against gram-positive organisms.

(ii) 2,3-Anhydro macrolides, which contain a planar (non-keto) sp^2 carbon at the C-2 and C-3 positions of the macrolactone ring. A series of 3-descladinosyl-2,3-anhydro-6-*O*-methylerythromycin A 11,12-cyclic carbazates exemplified by A-179461 (**73**, Fig. 10) was prepared by Griesgraber et al.[77,78] and evaluated for antibacterial activity. They were found to be potent antibacterial agents in vitro against macrolide susceptible organisms including *Staphylococcus aureus* 6538P, *Streptococcus pyogenes* EES61 and *Streptococcus pneumoniae* ATCC 6303. These compounds were also highly active against some organisms that showed macrolide resistance (*S. aureus* A5177, *S. pyogenes* P1U2584 and *S. pneumoniae* 5649). The compounds generally showed poor activity against organisms with constitutive MLS_B resistance. They were less active than erythromycin A against *H. influenzae*.

(iii) 3-Acylides. The synthesis and antibacterial activity of 3-*O*-acylerythromycin derivatives (3-acylides) were first reported by Asaka et al.[79] This class of macrolide contains an ester functional group at the C-3 position instead of a ketone in the ketolides. Both FMA-199 (**74**) and FMA-481 (**75**) (Fig. 10) have in vitro activity against *S. pneumoniae*, comparable to HMR-3647, but they did not show activity against constitutively MLS resistant *S. aureus* strains like HMR-3647 and ABT-773. FMA-481 was more active in vitro, even though FMA-199 was more active in vivo. The lower in vivo potency of FMA-481 may be due to lower absorption of FMA-481.

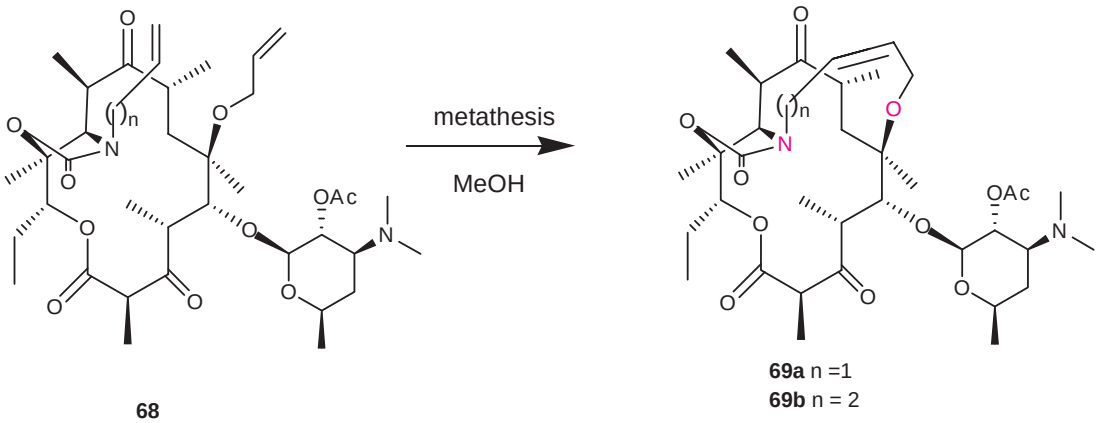
Tanikawa et al.[80] reported another class of 3-acylide, exemplified by 3-*O*-(4-nitrophenyl)acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide (TEA-0777, **76**, Scheme 27),



Scheme 25. Synthesis of 6,11-bridged ketolides.

which showed 250-fold greater activity against the erythromycin susceptible strain than the 3-*O*-acetyl derivative. This acylide demonstrated potent activity against the erythromycin susceptible strain of *Streptococcus pneumoniae*, like other macrolides. It was highly effective against *Enterococcus* strains and the efflux resistant strain of *S. pneumoniae*. In the case of in vitro evaluation, acylide TEA-0777 was significantly more active than erythromycin A and comparable to clarithromycin. It has the potential to be one of the next generation macrolide antibiotics.

Very recently, Randolph and co-workers in Abbott Laboratories synthesized[81] a series of novel acylides **77** (Fig. 11), which are potent nonpeptide luteinizing hormone—releasing hormone (LHRH) antagonist and may be useful for the treament of endometriosis, uterine fibroids, precocious puberty and certain malignancies.[82,83] Extensive optimization of the lead gave **78** (Fig. 11), which is a potent inhibitor of LH release in vitro. In vivo, it was found to produce a dose-dependent suppression of LH in male castrated rats.



Scheme 26. Synthesis of 6,11-bridged ketolides by olefin metathesis.

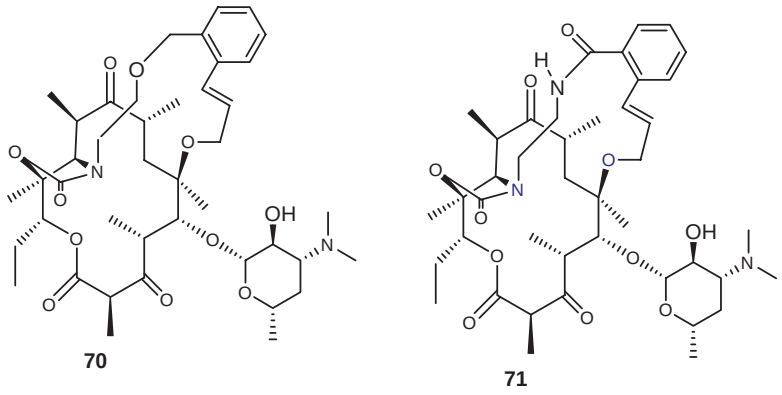


Figure 9. Further examples of 6,11-bridged ketolides.

4. Promising natural products

Some of the recent studies show that the search for promising new structures from natural products can be fruitful in supplying novel compounds having potential for clinical use. The discovery of 6-deoxyerythromycin A (**79**, Fig. 11) by systematic gene disruptions in of *Saccharopolyspora erythraea*[84] provided an understanding of the role of 6-OH on the pharmacokinetics and antibacterial activity. It has a weaker activity in vitro than **1**, but 6-deoxy derivative is more acid stable than **1**. It is hoped that modification may lead to a better efficacy. Sporeamicin A (**80**, Fig. 11), which represents another promising class,[85–87] has good antibacterial activity and attains higher blood and tissue levels than **1** in mice. Barber and co-workers[88] pointed out that erythromycin B (which lacks a C-12 hydroxy group) (**81**, Fig. 11) may be useful as a natural product sharing the relative acid stability of the second-generation erythromycin A derivatives, clarithromycin and azithromycin, and the therapeutic profile of erythromycin A.

5. Conclusions: an evergreen field of new drug discovery

Finally, this review is concluded by looking back over the past 53 years (2005–1952). An attempt has been made in this article to review the development of all of the significant synthetic modifications of erythromycin such as clarithromycin, azithromycin, roxithromycin, telithromycin and ABT-773, which address the serious problem of antibiotic resistance among the major respiratory pathogens. As described in this review, however, the strategy and tactics for the synthesis of new classes of compounds are still under development. Substantial strides have been made in the last few years to overcome the challenge posed by microorganisms and the information in this area has grown rapidly, which has allowed some important conclusions to be deduced regarding structure–activity relationships. The removal of the cladinose sugar at C-3 and the introduction of a keto group at the same position gave rise to a new class of macrolides called ketolides that can effectively solve the efflux resistance. The MLS_B resistance caused by the methylation of ribosome cannot, however, be addressed by the ketolides. In order to overcome such resistance, further structural modifications were carried out by medicinal chemists. 11,12-Carbamate and -carbazate ketolides were better than ketolides to tackle MLS_B resistance. In addition, an anchor of a four-carbon butyl chain with specific aryl groups must be present either at the nitrogen atom of the carbamate and carbazate rings or at the oxygen of C-6. Telithromycin and ABT-773 are the two successful representative molecules of this family, which have elicited a great deal of interest. They have spurred a new wave of interest in macrolide and ketolide classes of antibiotics. The availability of several novel series represents a significant conceptual advance in therapy and may afford new treatment options in the near future. It is worthy of note that the ketolide series is not the only class

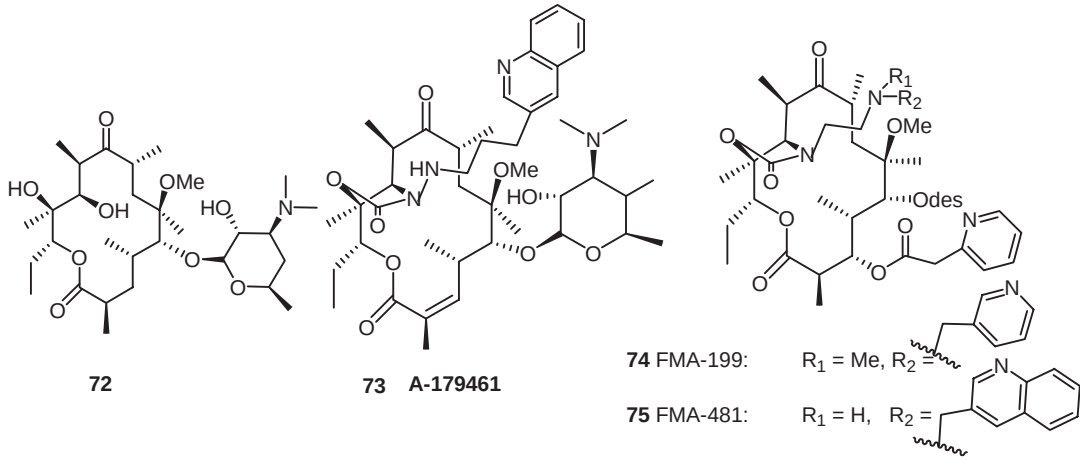
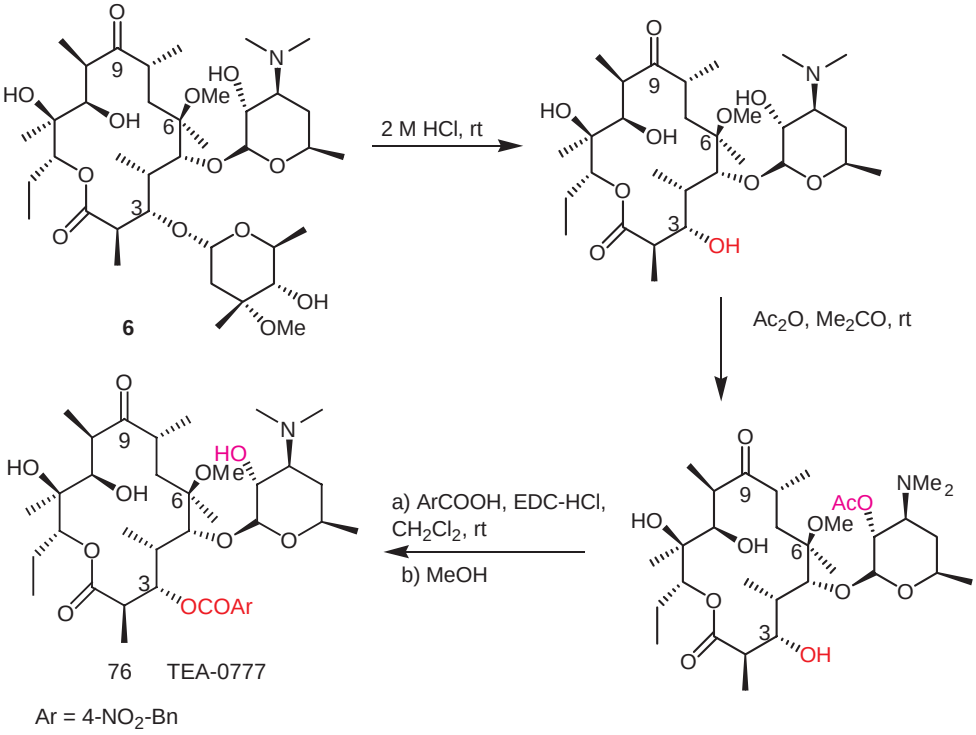


Figure 10. Some modified macrolides (apart from ketolides).



Scheme 27. Synthesis of 3-*O*-(4-nitrophenyl)-acetyl erythromycin A derivative (TEA-0777).

for the effective management of respiratory tract infections. Medicinal chemists have synthesized some derivatives of a nonketolide family. These modifications include derivatives of A-179461, FMA-199 and TEA-0777, which are undergoing clinical trial so their biological activities are yet to be unveiled. As more imaginative chemistry in this field continues, further synthetic work is aimed at extensive modifications, and it is hoped that progressive applications of the knowledge of enzyme mechanisms and their interactions with inhibitors will yield analogs with better activity profiles. Although the last few years have witnessed stunning breakthroughs in the clinical development of carbamate and carbazate ketolides, there is still much to be learned about the complex mechanism of bacterial

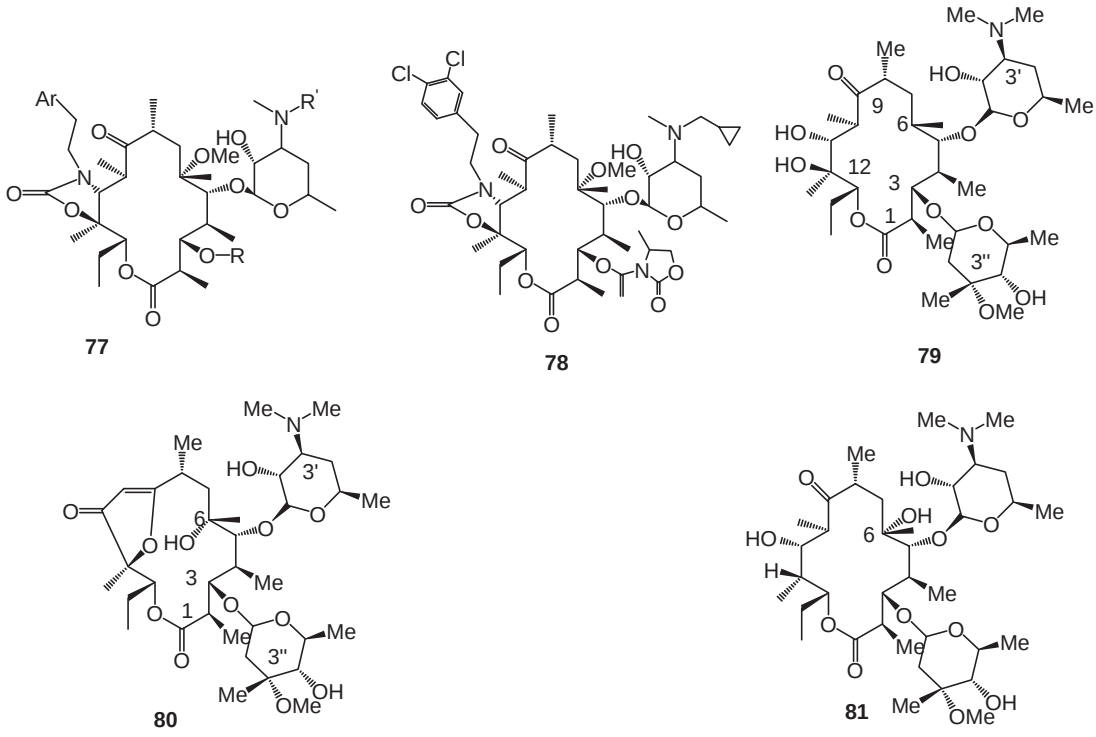


Figure 11.

resistance, due to both the anatomical and physiological diversity of microorganisms. As a result, a better understanding of the drugs is expected to emerge in the near future. The search for new compounds from natural products could, however, be fruitful. To address increasing antibacterial resistance, the search for new compounds from natural products could present a significant opportunity in the development of new macrolide antibiotics.

Last, but not the least, the author would like to apologize to those whose contributions in this field she may have inadvertently overlooked.

Acknowledgements

The author thanks Mr. M. N. Raju, the chairman of M.N.R. Educational Trust, for his constant support and encouragement.

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Biographical sketch

Sarbani Pal (nee Das) is a Lecturer at the Department of Chemistry of M.N.R. Post-Graduate College in Hyderabad (India). Born in Kolkata (India), Dr. Pal began her university training at the University of Calcutta (India), where she obtained her M.Sc degree in Chemistry with specialization in Organic Chemistry in 1990. She subsequently moved to the Indian Association for the Cultivation of Science, Kolkata (India), where she worked under the guidance of Professor D. Mukherjee with a research fellowship (1991–1996) awarded by Council of Scientific and Industrial Research, New Delhi, India. She was awarded her Ph.D. degree by Jadavpur University, Kolkata (India) in 1996. She then moved to the Department of Chemistry, M.S. University, Gujarat (India), where she worked as a Lecturer in Chemistry (1996–1997). Subsequently, she moved to Hyderabad (India), where she joined the M.N.R. Post-Graduate College (affiliated to Osmania University, Hyderabad) as a Lecturer in Organic Chemistry. Her research interests include the total synthesis of bicyclic and tricyclic sesquiterpenes, synthesis of organo–ruthenium complexes, design and synthesis of anti-inflammatory agents and macrolide antibiotics.

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Tetrahedron 62 (2006) 3201–3213

One pot synthesis using supported reagents system $KSCN/SiO_2$–RNH_3OAc/Al_2O_3: synthesis of 2-aminothiazoles and *N*-allylthioureas

Tadashi Aoyama,[a,*] Sumiko Murata,[a] Izumi Arai,[a] Natsumi Araki,[a] Toshio Takido,[a] Yoshitada Suzuki[b] and Mitsuo Kodomari[b]

[a]*Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan*
[b]*Department of Applied Chemistry, Shibaura Institute of Technology, Shibaura, Minato-ku, Tokyo 108-8548, Japan*

Received 24 November 2005; revised 20 January 2006; accepted 20 January 2006

Available online 13 February 2006

Abstract—A simple and efficient method has been developed for the synthesis of 2-aminothiazoles and *N*-allylthioureas from commercially available materials in one pot by using a supported reagents system, $KSCN/SiO_2$–RNH_3OAc/Al_2O_3, in which α-halo ketone reacts first $KSCN/SiO_2$ and the product, α-thiocyanatoketone, reacts with RNH_3OAc/Al_2O_3 to give the final product, 2-aminothiazoles, in good yield and allyl bromide reacts with $KSCN/SiO_2$ and the product, allyl isothiocyanate, reacts with RNH_3OAc/Al_2O_3 to give *N*-allylthiourea.
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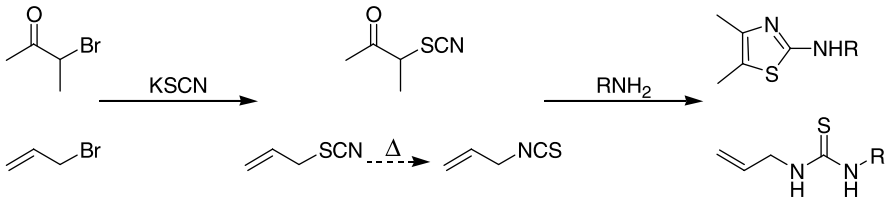
1. Introduction

Thiazoles and thioureas are very useful compounds in medicinal, drug and agricultural chemistry. For example, the aminothiazole ring system is a useful structural element in medicinal chemistry and has found broad application in drug development for the treatment of allergies,[1] hypertension,[2] inflammation,[3] bacterial infection[4] and HIV.[5] Symmetrical and unsymmetrical thioureas are an important class of compounds in agricultural and medicinal chemistry[6] and are also used as building blocks for the synthesis of both five and six membered heterocycles.[7] 2-Aminothiazoles are usually synthesized either by the condensation of α-halo ketones with monosubstituted thioureas or by the reaction of α-thiocyanatoketones with aromatic or aliphatic amine hydrochloride.[8] α-Thiocyanatoketones are prepared from the reaction of α-halo ketones with potassium thiocyanate. There are many procedures for the synthesis of symmetrical and unsymmetrical thioureas.[9–14] The most common method is the condensation of primary or secondary amines with isothiocyanates.[6,15] *N*-Allylthioureas are prepared from the reaction of allylisothiocyanate with amines. Allylic isothiocyanates are easily prepared from the reaction of potassium thiocyanate and allylic halides.[16] Thus, both 2-aminothiazoles and allylthioureas could be able to synthesize by using a same reaction process, thiocyanation and amination process (Scheme 1).



Scheme 1. Stepwise synthesis of aminothiazole and allylthiourea.

Keywords: Thiazoles; Thioureas; One pot process.
* Corresponding author. Tel./fax: +81 3 3259 0818; e-mail: aoyama@chem.cst.nihon-u.ac.jp

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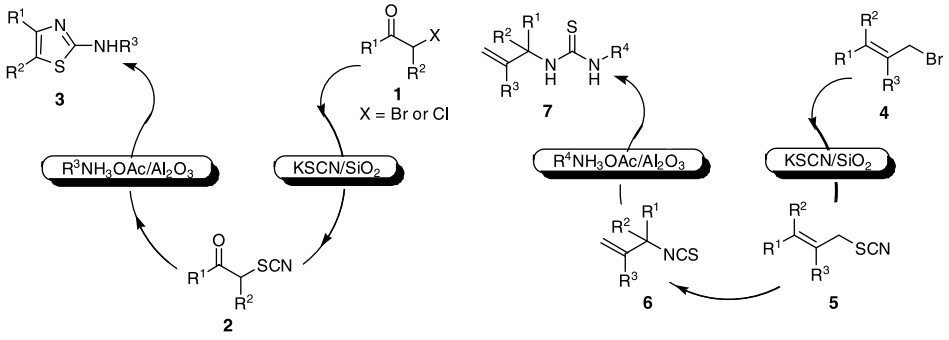
doi:10.1016/j.tet.2006.01.075



Scheme 2. One-pot synthesis of thiazoles and thioureas using supported reagents.

One-pot synthesis, which can carry out multi-step reactions or multiple reactions in one pot, is very attractive in organic synthesis. In traditional process, the reaction and the isolation of products have to be carried out more than once to synthesize the target compounds. One-pot process, however, can provide the target compounds in not only a single operation and with low cost but also in high total yield. Much effort has been devoted to the development of one-pot reaction process. One-pot synthesis using polymer or inorganic solid supported reagents is unique. Three different reaction stages are able to exist separately in the same vessel when three kinds of inorganic solid supported reagents are used.[17] Thus, synthesis of a compound, which is prepared stepwise in homogeneous solution could be possible in one-pot if each step in the multi-step reaction can be achieved using inorganic solid supported reagents. We have demonstrated the possibility of multi-step reactions in one-pot by using a couple of supported reagents, for example, $ZnCl_2/SiO_2$–K_2CO_3/Al_2O_3,[18a] $CuBr_2/Al_2O_3$–$KSCN/SiO_2$,[18b] $KSCN/SiO_2$–RNH_3OAc/Al_2O_3[18c,d] $CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3[17] and Na_2CO_3/SiO_2–PPA/SiO_2.[18e] We described recently the highly efficient method for the one-pot synthesis of 2-aminothiazoles and *N*-allylthioureas from α-halo ketones and allylic halides by using a supported reagents system, silica gel-supported potassium thiocyanate ($KSCN/SiO_2$)-alumina-supported ammonium acetates (RNH_3OAc/Al_2O_3). In this paper, we report on the one-pot synthesis using the supported reagents system, $KSCN/SiO_2$–RNH_3OAc/Al_2O_3, in detail (Scheme 2).

2. Results and discussion

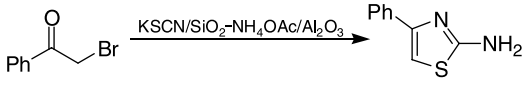
2.1. Determination of the optimum conditions

First, we optimized molar ratios of the reagents by using the reaction of phenacyl bromide (**1a**) as a model reaction (Table 1). A mixture of **1a** (1 mmol), $KSCN/SiO_2$ (1 mmol) and NH_4OAc/Al_2O_3 (2 mmol) in benzene was stirred at 80 °C for 6 h to gave the desired product **3a** in 44% yield along with large amount of **1a** (entry 1). Although twice amount of $KSCN/SiO_2$ was used under the same reaction conditions, the yield of **3a** did not increase. α-Thiocyanatoketone (**2a**) was formed as a main product (entry 2). The use of large amount of NH_4OAc/SiO_2 (6 mmol) gave **3a** in 75% yield along with acetic acid phenacyl ester, which was formed from the reaction of **1a** with NH_4OAc/Al_2O_3 (entry 3). When 5 mmol of $KSCN/SiO_2$ and 6 mmol of NH_4OAc/Al_2O_3 was used against 1 mmol of **1a**, **3a** was obtained in 83% yield (entry 4).

Next, various inorganic solids were tested to decide the most effective inorganic support for NH_4OAc. The results obtained were summarized in Table 2. Neutral alumina was the most effective inorganic support for NH_4OAc. The other inorganic solids tested gave a moderate yield of **3a**. When using magnesium oxide (MgO) as a support, **3a** was formed in a very low yield, and **2a** was obtained as a main product in 72% yield. Thus, we decided to use neutral alumina as a support for NH_4OAc.

The optimum amount of NH_4OAc loaded on Al_2O_3 was investigated (Table 3). When the loading ratio of

Table 1. Preparation of **3a** using $KSCN/SiO_2$–NH_4OAc/Al_2O_3



Entry	$KSCN/SiO_2$ (mmol)	NH_4OAc/Al_2O_3 (mmol)	Yield (%)[a]
1	1	2	44
2	2	2	46
3	3	6	75
4	5	6	83

[a] Isolated yield.

Table 2. Preparation of **3a** using various inorganic supported NH_4OAc

Support	SSA (m^2/g)[a]	pH	Yield (%)[b]
Neutral alumina	200	7.5	83
Acidic alumina	200	4.5	72
Basic alumina	200	10.0	58
Silica gel	450	5.5–7.0	47
MS-5A	400	11.0	67 (24)[c]
Magnesium oxide	70	11.1	17 (72)[c]

[a] Specific surface area.
[b] Isolated yield.
[c] Yield **2a**.

Table 3. Effect of loading ratio NH_4OAc/Al_2O_3

Entry	Loading ratio (mmol/g)	Yield of **3a** (%)[a]
1	0.5	32
2	1.0	83
3	2.0	45 (46)[b]
4	4.0	34 (60)[b]
5	6.0	40 (63)[b]

[a] Isolated yield.
[b] Yield of **2a**.

NH_4OAc/Al_2O_3 was over 2.0 mmol/g, the yield of **3a** was low and **2a** was formed. In these cases NH_4OAc/Al_2O_3 worked as well as NH_4OAc. The reaction using NH_4OAc/Al_2O_3 with a loading of 0.5 mmol/g also gave **3a** in low yield but **2a** was not detected. In this case, the reaction proceeded completely but **3a** was strongly adsorbed on the surface of alumina. When a mixture of **3a** (1 mmol) and alumina (12 g) was stirred in benzene for 6 h, trace amount of **3a** was in solution. When **3a** adsorbed on alumina was extracted with ethyl acetate, **3a** was recovered in 93% yield. NH_4OAc/Al_2O_3 with a loading of 1.0 mmol/g was the most effective for the reaction and was used in the subsequent reactions.

Previously, we have reported that silica gel is effective support for KSCN and $KSCN/SiO_2$ is a useful reagent for transformation of alkyl halides to alkyl thiocyanates.[19]

This supported reagents system, $KSCN/SiO_2$–NH_4OAc/Al_2O_3, worked well for the thiocyanation and the amination in one pot, whereas in the case of the reaction using the unsupported reagents system or using the reagents system in which one reagent is supported on inorganic solid and the other is unsupported, the yields of products were lower than that in the reaction using the supported reagents system. **3a** was also synthesized by using stepwise reaction process, thiocyanation and amination process, and the total yield of **3a** was lower than that from the reaction using $KSCN/SiO_2$–NH_4OAc/Al_2O_3. The reaction of **1a** with $KSCN/SiO_2$ in benzene proceeded at 80 °C to give **2a** in quantitatively after 1.5 h. The reaction of **2a** with NH_4OAc/Al_2O_3 also occurred in benzene under similar conditions and afforded **3a** in 54% yield after 6 h. When the reaction using 0.1 mmol of **2a** and 6 mmol of NH_4OAc/Al_2O_3 was carried out under the similar conditions, **3a** was formed in 78% yield. This result suggests that the amination process successfully proceeds in the presence of a large excess of NH_4OAc. In one-pot process, **2a** formed from the reaction of **1a** and $KSCN/SiO_2$ reacts immediately with NH_4OAc/Al_2O_3, in which a large excess of NH_4OAc to **2a** is always present. Therefore the yield in one-pot synthesis is higher than that in stepwise process (see Table 4).

Table 4. Reaction of **1a** with various reagents systems[a]

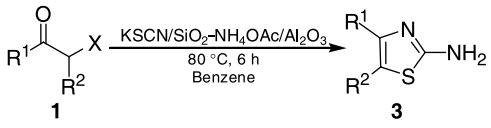
Reagents system	Yield of **3a** (%)[b]
KSCN–NH_4OAc	14
KSCN–NH_4OAc/SiO_2	31
$KSCN/SiO_2$–NH_4OAc	32
$KSCN/SiO_2$–NH_4OAc/Al_2O_3	83

[a] All reactions were carried out using **1a** (1 mmol), KSCN/(SiO_2) (5 mmol) and $NH_4OAc/(Al_2O_3)$ (6 mmol).
[b] Isolated yield.

2.2. Preparation of 2-aminothiazoles

As shown in Table 5, various α-halo ketones react with $KSCN/SiO_2$ and NH_4OAc/Al_2O_3 in one pot to afford the desired 2-aminothiazoles in moderate to high yields. When phenacyl chloride was used instead of phenacyl bromide, **3a** was obtained in 80% yield (Table 1, entry 4 vs Table 5, entry 1). The halo ketones in which, halogen is attached to the primary carbon and the benzylic carbon, afforded the corresponding 2-aminothiazoles in high yield (entries 1–5). On the other hand, in the reactions with the halo ketones having a halogen attached on the secondary carbon, the yields were low (entries 6–8). 2-Bromopropiophenone (**1g**) gave bis[2-(4-phenyl-5-methyl)thiazoyl] amine (**8g**) as a main product in 54% yield and expected **3g** in 46% yield (Scheme 3). Compound **8g** was resulted from the reaction of **2g** with **3g**.

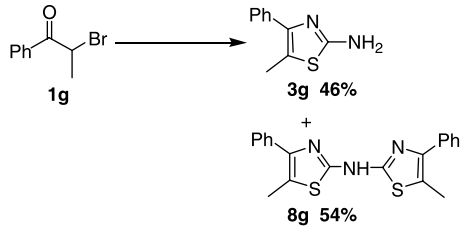
Table 5. One-pot synthesis of 2-aminothiazoles[a]



1 **3**

Entry	X	R^1	R^2	Product	Yield (%)[b]
1	Cl	C_6H_5	H	**3a**	80
2	Br	C_6H_5	C_6H_5	**3b**	87
3	Br	4-Me–C_6H_4	C_6H_5	**3c**	90
4	Br	4-Cl–C_6H_4	C_6H_5	**3d**	92
5	Cl	CH_3	H	**3e**	83
6	Cl	CH_3	CH_3	**3f**	58
7	Br	C_6H_5	CH_3	**3g**	46
8	Br	4-Cl–C_6H_4	CH_3	**3h**	74

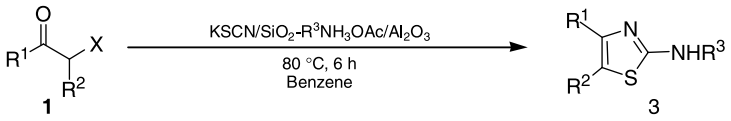
[a] All reactions were carried out using **1** (1 mmol), $KSCN/SiO_2$ (5 mmol) and NH_4OAc/Al_2O_3 (6 mmol).
[b] Isolated yield.



Scheme 3. Formation of **8g** from **1g**.

The reaction of various combinations of α-halo ketones and alkylammonium acetate were carried out. The results were shown in Table 6. The reaction of α-bromo propiophenone with various alkylammonium acetates gave the corresponding 2-alkylaminothiazoles in good to excellent yields. The yields of the products were not affected by the length of alkyl chain attached on an amine. When alicyclic ammonium acetate was used the yields were increased. The successful use of ethanolamine, 2-hydroxypropylamine and allylamine indicates that this procedure is unaffected by the presence of a functional group such as a C–C double bond and a hydroxyl group in an amine part. The reaction of 3-chloro-2-butanone with 2-hydroxyethylamino acetate and 2-hydroxypropylamino acetate gave unexpected compounds, 4,5-dimethyl-3-(2-hydroxyethyl)-1,3-thiazole-2(3*H*)-imine (**3′ao**) and 4,5-dimethyl-3-(2-hydroxypropyl)-1,3-thiazole-2(3*H*)-imine (**3′ap**), along with desired **3ao** and **3ap** (entries 33 and 34). We examined whether **3′** was formed from isomerization reaction of **3**. When **3ao** was stirred in benzene in the presence of $KSCN/SiO_2$ and RNH_3OAc/Al_2O_3 at 80 °C for 6 h, isomerization reaction

Table 6. One-pot synthesis of 2-alkylamino thiazoles from haloketones and various alkylammonium acetates[a]



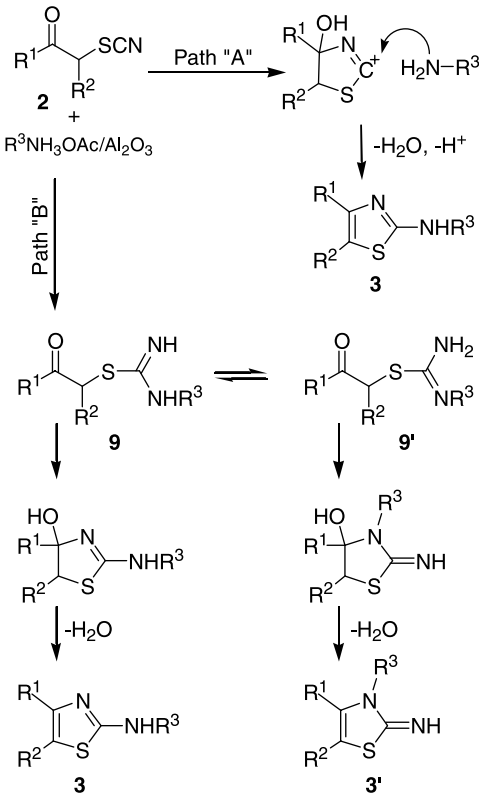
Entry	X	R^1	R^2	R^3	Product	Yield (%)[b]
1	Br	C_6H_5	CH_3	*n*-C_4H_9	**3i**	85
2	Br	C_6H_5	CH_3	*iso*-C_4H_9	**3j**	83
3	Br	C_6H_5	CH_3	*sec*-C_4H_9	**3k**	88
4	Br	C_6H_5	CH_3	$C_{10}H_{21}$	**3l**	87
5	Br	C_6H_5	CH_3	*cyclo*-C_5H_9	**3m**	92
6	Br	C_6H_5	CH_3	*cyclo*-C_6H_{11}	**3n**	88
7	Br	C_6H_5	CH_3	$CH_2C_6H_5$	**3o**	79
8	Br	C_6H_5	CH_3	$C_2H_4C_6H_5$	**3p**	83
9	Br	C_6H_5	CH_3	CH_2CHCH_2	**3q**	99
10	Br	C_6H_5	CH_3	C_2H_4OH	**3r**	60
11	Br	C_6H_5	CH_3	$CH_2CH(OH)CH_3$	**3s**	99
12	Br	C_6H_5	C_6H_5	*n*-C_4H_9	**3t**	65
13	Br	C_6H_5	C_6H_5	*iso*-C_4H_9	**3u**	80
14	Br	C_6H_5	C_6H_5	*sec*-C_4H_9	**3v**	69
15	Br	C_6H_5	C_6H_5	$C_{10}H_{21}$	**3w**	60
16	Br	C_6H_5	C_6H_5	*cyclo*-C_5H_9	**3x**	97
17	Br	C_6H_5	C_6H_5	*cyclo*-C_6H_{11}	**3y**	95
18	Br	C_6H_5	C_6H_5	$CH_2C_6H_5$	**3z**	88
19	Br	C_6H_5	C_6H_5	$C_2H_4C_6H_5$	**3aa**	86
20	Br	C_6H_5	C_6H_5	CH_2CHCH_2	**3ab**	94
21	Br	C_6H_5	C_6H_5	C_2H_4OH	**3ac**	62
22	Br	C_6H_5	C_6H_5	$CH_2CH(OH)CH_3$	**3ad**	96
23	Cl	CH_3	H	$CH_2C_6H_5$	**3ae**	80
24	Cl	CH_3	H	CH_2CHCH_2	**3af**	73
25	Cl	CH_3	H	C_2H_4OH	**3ag**	45
26	Cl	CH_3	H	$CH_2CH(OH)CH_3$	**3ah**	54
27	Br	C_6H_5	H	$CH_2C_6H_5$	**3ai**	82
28	Br	C_6H_5	H	CH_2CHCH_2	**3aj**	72
29	Br	C_6H_5	H	C_2H_4OH	**3ak**	39
30	Br	C_6H_5	H	$CH_2CH(OH)CH_3$	**3al**	53
31	Cl	CH_3	CH_3	$CH_2C_6H_5$	**3am**	46
32	Cl	CH_3	CH_3	CH_2CHCH_2	**3an**	55
33	Cl	CH_3	CH_3	C_2H_4OH	**3ao**	17 (7)[c]
34	Cl	CH_3	CH_3	$CH_2CH(OH)CH_3$	**3ap**	17 (4)[d]

[a] All reactions were carried out using **1** (1 mmol), $KSCN/SiO_2$ (5 mmol) and R^3NH_3OAc/Al_2O_3 (6 mmol).
[b] Isolated yield.
[c] Yield of 4,5-dimethyl-3-(2-hydroxyethyl)-1,3-thiazole-2(3*H*)-imine (**3′ao**).
[d] Yield of 4,5-dimethyl-3-(2-hydroxypropyl)-1,3-thiazole-2(3*H*)-imine (**3′ap**).

was not observed. Considerable mechanism was proposed in Scheme 4. The reaction between an intermediate, α-thiocyanatoketones, and RNH_3OAc/Al_2O_3 proceeds through two pathways. When the reaction proceeds with path A, only 2-aminated thiazoles are formed. If nucleophilic attack of an amine to the thiocyanato group occurs faster than cyclization of α-thiocyanatoketones (path B), an intermediate (**9**) are produced. In principle, both nitrogen atoms can attack the carbonyl carbon. It is known that the sp^2 nitrogen atom is a better base and nucleophile than the sp^3 nitrogen atom.[20] The ring closure provably occurs in a fast step, therefore 2-aminothiazoles are mainly produced in many cases.

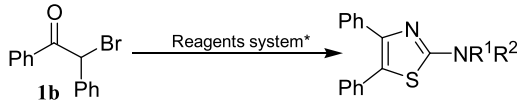
Schantl et al. have reported one-pot synthesis of 2-aminothiazoles in methanol.[21] However, the synthesis of *N*,*N*-disubstituted-2-aminothioureas by this method is sluggish and the yields are low. In contrast, our procedure gave *N*,*N*-disubstituted-2-aminothioureas in high yields. The results were summarized in Table 7. For instance the reaction of 2-bromo-2-phenyl benzophenone (**1b**) with $KSCN/SiO_2$ and alumina supported pyrrolidino acetate gave 4,5-diphenyl-2-pyrrolidino thiazole (**3aq**) in 89% yield. All of the *sec*-alicyclic ammonium acetate afforded the corresponding *N*,*N*-disubstituted-2-aminothiazoles in good yields. The reaction of **1b** with 2-hydroxy-*N*-methylethylamine salt gave **3at** in moderate yield. Dibutyl ammonium and di-*iso*-butyl ammonium acetate are soluble in benzene, thus, in the case of these amines an ammonium trifluoroacetate were used. **3au** and **3av** were also obtained in good yields from **1b**.

Kurz et al. have reported the synthesis of the aminothiazole derivatives from the reaction of α-thiocyanato malonic acid derivatives and hydroxylamines (Scheme 5).[22] We carried out the synthesis of similar compounds from α-bromo-α-methyl malonic acid diethyl ester by using a couple of supported reagents $KSCN/SiO_2$ and NH_4OAc/Al_2O_3. However, the expected compounds were not observed, and a small amount of thiocyanated compounds were detected. α-Bromo-α-methyl malonic acid diethyl ester did not react with $KSCN/SiO_2$ under similar conditions. Therefore our method could not be applicable for the halo



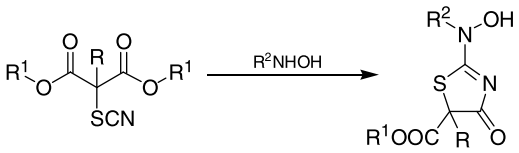
Scheme 4. Reaction path of 2-aminothiazoles.

Table 7. Preparation of 2-dialkylamino-4,5-diphenylthiazoles[a]



Product	Yield (%)[b]
3aq	89
3ar	94
3as	84
3at	65
3au	72[c]
3av	67[c]

[a] All reactions were carried out using **1b** (1 mmol), $KSCN/SiO_2$ (5 mmol) and $R^1R^2NH_2OAc/Al_2O_3$ (6 mmol).
[b] Isolated yield.
[c] Using a salt of trifluoroacetic acid.



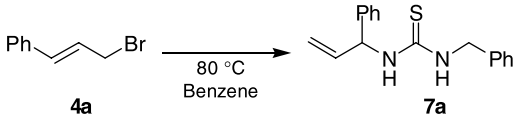
Scheme 5. Reaction of thiocyanato malonic acid derivatives and hydroxylamines.

ketone containing a halogen attached on the tertiary carbon.

2.3. Preparation of *N*-allylthioureas

The synthesis of *N*-allylthioureas using $KSCN/SiO_2$–NH_4OAc/Al_2O_3 system was also tried. In order to determine the optimum conditions for the synthesis of *N*-allylthioureas in fast and efficient way, molar ratios of the supported reagents and the reaction time were investigated (see Table 8). The reaction of cinnamyl bromide with $KSCN/SiO_2$ (5 mmol) and $BnNH_3OAc/Al_2O_3$ (6 mmol) in benzene at 80 °C for 3 h gave **7a** in 68% yield along with a small amount of dibenzylthiourea as a byproduct (entry 1). This dibenzylthiourea is presumed to result from the transamination of **7a** with benzylamine, which released from benzyl ammonium acetate. Transamination of *N*-benzoyl-*N′*-alkylthioureas with amines has been reported.[23] When 3 mmol of $BnNH_3OAc/Al_2O_3$ was used for the reaction, **7a** was yielded without dibenzylthiourea, and the reaction intermediate **5a** was observed in the reaction mixture (entry 2). When the reaction time was prolonged to 6 h, the yield of **7a** increased to 78% (entry 3). Using 1.5 mmol of $BnNH_3OAc/Al_2O_3$, the yield of **7a** decreased (entry 4). Thus, we decided to use 5 mmol of $KSCN/SiO_2$ and 3 mmol of $BnNH_3OAc/Al_2O_3$ against 1 mmol of allylic bromide for subsequent reactions.

Table 8. Preparation of **7a** using $KSCN/SiO_2$–$BnNH_3OAc/Al_2O_3$



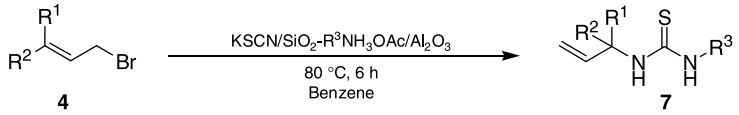
4a **7a**

Entry	$KSCN/SiO_2$ (mmol)	$BnNH_3OAc/Al_2O_3$ (mmol)	Time (h)	Yield (%)[a]
1	5	6	3	68
2	5	3	3	68
3	5	3	6	78
4	5	1.5	6	67

[a] Isolated yield.

Various combination of ammonium acetates and allylic bromides were used for the synthesis of *N*-allylthioureas. The results were summarized in Table 9. Various allylic bromides reacted with $KSCN/SiO_2$ and $BnNH_3OAc/Al_2O_3$ in one pot to afford the corresponding thioureas (entries 1–3). The reaction of crotyl bromide and of 1-bromo-3-methyl-2-butene gave the desired products **7c** and **7d** in excellent

Table 9. One-pot synthesis of *N*-allylthioureas from allylic bromides and various alkylammonium acetates[a]



Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	H	$CH_2C_6H_5$	**7b**	59
2	H	CH_3	$CH_2C_6H_5$	**7c**	92
3	CH_3	CH_3	$CH_2C_6H_5$	**7d**	94
4	H	C_6H_5	*n*-C_4H_9	**7e**	74
5	H	C_6H_5	*iso*-C_4H_9	**7f**	65
6	H	C_6H_5	*sec*-C_4H_9	**7g**	51
7	H	C_6H_5	CH_2CHCH_2	**7h**	60
8	H	C_6H_5	*cyclo*-C_5H_9	**7i**	50
9	H	C_6H_5	*cyclo*-C_6H_{11}	**7j**	70
10	H	C_6H_5	$C_2H_4C_6H_5$	**7k**	51
11	H	CH_3	*n*-C_4H_9	**7l**	89
12	H	CH_3	*iso*-C_4H_9	**7m**	82
13	H	CH_3	*sec*-C_4H_9	**7n**	88
14	H	CH_3	CH_2CHCH_2	**7o**	88
15	H	CH_3	*cyclo*-C_5H_9	**7p**	92
16	H	CH_3	*cyclo*-C_6H_{11}	**7q**	90
17	H	CH_3	$C_2H_4C_6H_5$	**7r**	89
18	CH_3	CH_3	*n*-C_4H_9	**7s**	79
19	CH_3	CH_3	*iso*-C_4H_9	**7t**	73
20	CH_3	CH_3	*sec*-C_4H_9	**7u**	62
21	CH_3	CH_3	CH_2CHCH_2	**7v**	71
22	CH_3	CH_3	*cyclo*-C_5H_9	**7w**	82
23	CH_3	CH_3	*cyclo*-C_6H_{11}	**7x**	85
24	CH_3	CH_3	$C_2H_4C_6H_5$	**7y**	92

[a] All reaction were carried out using **4** (1 mmol), KSCN/SiO_2 (5 mmol) and R^3NH_3OAc/Al_2O_3 (3 mmol).
[b] Isolated yield.

yields, respectively. Cinnamyl bromide and 1-bromo-2-methyl-2-butene were also converted into the corresponding *N*-allylthioureas in good yields under the same conditions. Allyl bromide was the most inactive among the allylic bromides used for the transformations. When cinnamyl chloride was used instead of cinnamyl bromide for the reaction, the yield of **7a** was lower than that of cinnamyl bromide. The reactions of allylic bromides and a series of alkylammonium acetate gave the corresponding thioureas, however, *tert*-butylammonium acetate did not give the desired thiourea. The yields of *N*-allylthioureas depended on the allylic bromides used. For instance, cinnamyl bromide gave the products in moderate yields, whereas, 2-bromo-3-methyl-2-butene gave the product in good to excellent yields. The yields seem to depend on the rate of the rearrangement from the thiocyanate into the isothiocyanate. A mixture of allylic bromides and KSCN/SiO_2 was stirred in benzene at 80 °C for 6 h, and then the ratio of the thiocyanate to the isothiocyanate in the solution was measured by ^{1}H NMR. The correlation, however, between the yield and the rate of the rearrangement was not observed. Further investigation is now in progress. Although Bergmann et al.[24] has reported that cinnamyl thiocyanate isomerizes without allyl rearrangement and cinnamyl isothiocyanate is formed instead of the anticipated α-phenyl isothiocyanate, in our reaction process cinnamyl thiocyanate rearranged into α-phenyl isothiocyanate, resulting thioureas (**7e–7k**) were 1-phenylallyl type compound.

In conclusion, various α-halo ketones and allylic bromides were converted into 2-aminothiazoles and *N*-allylthioureas in the presence of KSCN/SiO_2–RNH_4OAc/Al_2O_3. It is particularly noteworthy that this method does not need to handle of the isolation of reaction intermediate and this method may be applicable to laboratory scale and combinatorial synthesis of 2-aminothiazoles and *N*-allylthioureas.

3. Experimental

3.1. General

Melting points were determined on a Yanako Micro melting point apparatus or on a Büchi 535 or were uncorrected. Elemental analysis were performed on a Yanako CHN corder MT-5. NMR spectra were recorded on a JEOL JNM-GX400 or on a JEOL JNM-LA300 spectrometer. Tetramethylsilane ($\delta=0$) was used as an internal standard for ^{1}H NMR. Mass analysis were performed on an Agilent G1969 LC/MDS TOF. IR spectra were recorded on a HORIBA FT-710 or on a Thermo Electron Nicolet 380 spectrometer.

Preparation of KSCN/SiO_2. Silica gel [Wakogel C-200 (Wako Pure Chemical Ind. LTD), 25.70 g] was added to a solution of potassium thiocyanate (250 mmol, 24.30 g) in distilled water, and the mixture was stirred at room temperature for 0.5 h. The water was removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 150 °C for 2 h.

Preparation of NH_4OAc/Al_2O_3. Alumina (ICN Biomedical N-Super 1, 9.23 g) was added to a solution of ammonium acetate (10 mmol. 0.77 g) in methanol, and the mixture was stirred at room temperature for 0.5 h. The methanol was

removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at room temperature for 2 h.

3.2. Typical procedure for the preparation of 2-aminothiazoles

A mixture of α-halo ketones (1 mmol), $KSCN/SiO_2$ (5 mmol, 1 g) and RNH_3OAc/Al_2O_3 (6 mmol, 6 g) was stirred in benzene (10 mL) at 80 °C for 6 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column chromatography.

3.2.1. 2-Amino-4-phenylthiazole (3a). Yellow needles. Mp 150–151 °C (hexane/ethyl acetate) (lit.[25] 150 °C). HR-MS (TOF-CI) Calcd for $C_9H_9N_2S$ (MH^+): 177.0486. Found: 177.0494. IR (KBr): 3436, 3115, 1598, 1518, 1342, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.33 (2H, s), 6.71 (1H, s), 7.25–7.31 (1H, m), 7.35–7.40 (2H, m), 7.74–7.78 (2H, m).

3.2.2. 2-Amino-4,5-diphenylthiazole (3b). White solid. Mp 189–190 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{15}H_{13}N_2S$ (MH^+): 253.0799. Found: 253.0805. IR (KBr): 3423, 3273, 3060, 1631, 1543, 1529, 1336, 764, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.25 (2H, s), 7.23–7.28 (8H, m), 7.44–7.47 (2H, m).

3.2.3. 2-Amino-4-(*p*-methylphenyl)-5-phenylthiazole (3c). Yellow solid. Mp 181–182 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{16}H_{15}N_2S$ (MH^+): 267.0955. Found: 267.0961. IR (KBr): 3433, 3255, 3059, 1622, 1525, 1504, 1331, 829, 760, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 2.27 (3H, s), 7.06 (2H, d, $J=8.3$ Hz), 7.19 (2H, s), 7.20–7.32 (7H, m).

3.2.4. 2-Amino-4-(*p*-chlorophenyl)-5-phenylthiazole (3d). Yellow powder. Mp 188–189 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{15}H_{12}ClN_2S$ (MH^+): 287.0409. Found: 287.0408. IR (KBr): 3429, 3251, 3076, 1618, 1525, 1493, 1331, 841, 762, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.24 (2H, s), 7.19–7.28 (7H, m), 7.37–7.41 (2H, m).

3.2.5. 2-Amino-4-methylthiazole (3e). Yellow oil. HR-MS (TOF-CI) Calcd for $C_4H_7N_2S$ (MH^+): 115.0329. Found: 115.0336. IR (neat): 3444, 3290, 1620, 1545, 1520, 1442, 1331, 787 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.13 (3H, s), 5.61 (2H, s), 5.96 (1H, s).

3.2.6. 2-Amino-4,5-dimethylthiazole (3f). Yellow solid. Mp 83–84 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_5H_9N_2S$ (MH^+): 129.0486. Found: 129.0485. IR (KBr): 3423, 3296, 1612, 1520, 1317, 877 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.17 (3H, s), 4.92 (2H, s).

3.2.7. 2-Amino-5-methyl-4-phenylthiazole (3g). Brown crystals. Mp 115–116 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{10}H_{11}N_2S$ (MH^+): 191.0642. Found: 191.0635. IR (KBr): 3419, 3276, 3080, 1635, 1597, 1537, 1333, 773, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (3H, s), 4.95 (2H, s), 7.27–7.32 (1H, m), 7.37–7.42 (2H, m), 7.55–7.57 (2H, m).

3.2.8. Bis[2-(4-phenyl-5-methyl)thiazoyl] amine (8g). Yellow solid. Mp 128–129 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{20}H_{18}N_3S_2$ (MH^+): 364.0942. Found: 364.0945. IR (neat): 3199, 3055, 2932, 2857, 1587, 1533, 1445, 1311, 770, 697 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 2.45 (6H, s), 7.32–7.36 (2H, m), 7.44–7.48 (4H, m), 7.68–7.70 (4H, m), 12.04 (1H, s).

3.2.9. 2-Amino-4-(*p*-chlorophenyl)-5-methylthiazole (3h). Yellow needles. Mp 144–145 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{10}H_{10}ClN_2S$ (MH^+): 225.0253. Found: 225.0258. IR (KBr): 3437, 3261, 3107, 1624, 1541, 1487, 1335, 1092, 835 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (3H, s), 5.22 (2H, s), 7.35 (2H, d, $J=8.4$ Hz), 7.49 (2H, d, $J=8.4$ Hz).

3.2.10. 2-Butylamino-5-methyl-4-phenylthiazole (3i). Brown oil. HR-MS (TOF-CI) Calcd for $C_{14}H_{19}N_2S$ (MH^+): 247.1268. Found: 247.1274. IR (neat): 3203, 3100, 2957, 2930, 1585, 1332, 773, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, $J=7.3$ Hz), 1.41 (2H, sext, $J=7.3$ Hz), 1.63 (2H, quint, $J=7.3$ Hz), 2.40 (3H, s), 3.22 (2H, t, $J=7.3$ Hz), 5.47 (1H, s), 7.25–7.31 (1H, m), 7.36–7.40 (2H, m), 7.55–7.58 (2H, m).

3.2.11. 2-*iso*-Butylamino-5-methyl-4-phenylthiazole (3j). White crystals. Mp 123–124 °C (hexane/ethyl acetate). Anal. Calcd for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.24; H, 7.40; N, 11.49. HR-MS (TOF-CI) Calcd for $C_{14}H_{19}N_2S$ (MH^+): 247.1268. Found: 247.1275. IR (neat): 3199, 3106, 2951, 2865, 1590, 1464, 1432, 1330, 774, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (6H, d, $J=6.8$ Hz), 1.85–1.97 (1H, m), 2.40 (3H, s), 3.02 (2H, t, $J=6.3$ Hz), 5.30 (1H, s), 7.26–7.30 (1H, m), 7.37–7.40 (2H, m), 7.56–7.58 (2H, m).

3.2.12. 2-*sec*-Butylamino-5-methyl-4-phenylthiazole (3k). Brown oil. HR-MS (TOF-CI) Calcd for $C_{14}H_{19}N_2S$ (MH^+): 247.1268. Found: 247.1261. IR (neat): 3199, 3081, 2966, 2930, 2874, 1626, 1449, 1334, 770, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, $J=7.3$ Hz), 1.23 (3H, d, $J=6.3$ Hz), 1.55–1.66 (2H, m), 2.38 (3H, s), 3.30–3.39 (1H, m), 5.76 (1H, s), 7.26–7.30 (1H, m), 7.35–7.39 (2H, m), 7.55–7.57 (2H, m).

3.2.13. 2-Decylamino-5-methyl-4-phenylthiazole (3l). Brown oil. HR-MS (TOF-CI) Calcd for $C_{20}H_{31}N_2S$ (MH^+): 331.2207. Found: 331.2212. IR (neat): 3205, 3101, 3058, 2925, 2854, 1587, 1466, 1333, 773, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $J=7.1$ Hz), 1.24–1.33 (14H, m), 1.53–1.60 (2H, m), 2.38 (3H, s), 3.14 (2H, t, $J=7.1$ Hz), 5.82 (1H, s), 7.26–7.30 (1H, m), 7.35–7.40 (2H, m), 7.54–7.57 (2H, m).

3.2.14. 2-*cyclo*-Pentylamino-5-methyl-4-phenylthiazole (3m). Yellow solid. Mp 99–100 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{15}H_{19}N_2S$ (MH^+): 259.1268. Found: 259.1271. IR (neat): 3184, 3056, 2953, 2868, 1622, 1447, 1353, 769, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.46–1.70 (6H, m), 1.96–2.04 (2H, m), 2.39 (3H, s),

3.71–3.76 (1H, m), 5.68 (1H, s), 7.25–7.28 (1H, m), 7.35–7.39 (2H, m), 7.55–7.57 (2H, m).

3.2.15. 2-*cyclo*-Hexylamino-5-methyl-4-phenylthiazole (3n). Yellow crystals. Mp 97–99 °C (hexane/ethyl acetate). Anal. Calcd for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28. Found: C, 70.71; H, 7.29; N, 10.49. HR-MS (TOF-CI) Calcd for $C_{16}H_{21}N_2S$ (MH^+): 273.1425. Found: 273.1433. IR (neat): 3171, 3079, 2925, 2851, 1577, 1447, 1333, 770, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.18–1.44 (5H, m), 1.60–1.62 (1H, m), 1.73–1.78 (2H, m), 2.07–2.11 (2H, m), 2.40 (3H, s), 3.23–3.32 (1H, m), 4.92 (1H, d, J= 7.3 Hz), 7.26–7.30 (1H, m), 7.36–7.40 (2H, m), 7.56–7.59 (2H, m).

3.2.16. 2-Benzylamino-5-methyl-4-phenylthiazole (3o). White solid. Mp 152–153 °C (hexane/ethyl acetate) (lit.[26] 151–153 °C). HR-MS (TOF-CI) Calcd for $C_{17}H_{17}N_2S$ (MH^+): 281.1112. Found: 281.1107. IR (KBr): 3186, 1600, 1576, 1452, 1331, 777, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (3H, s), 4.33 (2H, s), 6.42 (1H, s), 7.22–7.36 (8H, m), 7.53–7.57 (2H, m).

3.2.17. 2-(2-Phenylethylamino)-5-methyl-4-phenylthiazole (3p). White crystals. Mp 118–119 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{18}H_{19}N_2S$ (MH^+): 295.1268. Found: 295.1278. IR (neat): 3186, 3085, 1581, 1493, 1433, 772, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (3H, s), 2.95 (2H, t, J=7.1 Hz), 3.51 (2H, dt, J=7.1, 5.9 Hz), 5.10 (1H, s), 7.22–7.34 (6H, m), 7.37–7.41 (2H, m), 7.56–7.59 (2H, m).

3.2.18. 2-Allylamino-5-methyl-4-phenylthiazole (3q). Crystals. Mp 102–103 °C (hexane/ethyl acetate). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.69; H, 6.05; N, 12.18. HR-MS (TOF-CI) Calcd for $C_{13}H_{15}N_2S$ (MH^+): 231.0955. Found: 231.0957. IR (KBr): 3194, 1645, 1589, 1421, 1331, 966, 914, 773, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s), 3.76 (2H, d, J= 4.4 Hz), 5.12–5.17 (1H, m), 5.22–5.29 (1H, m), 5.78–5.91 (1H, m), 6.05 (1H, s), 7.25–7.31 (1H, m), 7.38 (2H, t, J= 7.5 Hz), 7.56 (2H, d, J=7.5 Hz).

3.2.19. 2-(2-Hydroxyethylamino)-5-methyl-4-phenylthiazole (3r). Brown oil. HR-MS (TOF-CI) Calcd for $C_{12}H_{15}N_2OS$ (MH^+): 235.0905. Found: 235.0908. IR (neat): 3277, 3082, 2917, 2859, 1564, 1539, 1490, 1441, 1330, 1070, 773, 699 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 2.32 (3H, s), 3.28 (2H, q, J=5.9 Hz), 3.55 (2H, t, J= 5.9 Hz), 4.79 (1H, s), 7.26–7.30 (1H, m), 7.36–7.41 (3H, m), 7.55–7.58 (2H, m).

3.2.20. 2-(2-Hydroxypropylamino)-5-methyl-4-phenylthiazole (3s). White powder. Mp 92–93 °C (hexane/ethyl acetate). Anal. Calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.67; H, 6.47; N, 11.26. HR-MS (TOF-CI) Calcd for $C_{13}H_{17}N_2OS$ (MH^+): 249.1061. Found: 249.1059. IR (KBr): 3345, 3319, 3205, 1600, 1560, 1443, 1134, 1078, 771, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, d, J=6.2 Hz), 2.31 (3H, s), 3.15 (2H, t, J=5.7 Hz), 3.75–3.87 (1H, m), 4.82 (1H, d, J=4.6 Hz), 7.27 (1H, t, J=7.3 Hz), 7.35–7.41 (3H, m), 7.55 (2H, d, J=7.2 Hz).

3.2.21. 2-Butylamino-4,5-diphenylthiazole (3t). White crystals. Mp 117–118 °C (hexane/ethyl acetate) (lit.[27] 117–118 °C). HR-MS (TOF-CI) Calcd for $C_{19}H_{21}N_2S$ (MH^+): 309.1425. Found: 309.1428. IR (KBr): 3203, 3097, 2983, 2954, 1585, 1436, 1334, 756, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.90 (3H, t, J=7.2 Hz), 1.36 (2H, s, J=7.2 Hz), 1.56 (2H, q, J=7.2 Hz), 3.24 (2H, q, J= 6.8 Hz), 7.18–7.30 (8H, m), 7.37–7.40 (2H, m), 7.72 (1H, t, J=5.3 Hz).

3.2.22. 2-(*iso*-Butylamino)-4,5-diphenylthiazole (3u). White powder. Mp 115 °C (hexane/ethyl acetate). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.41; N, 9.14. HR-MS (TOF-CI) Calcd for $C_{19}H_{21}N_2S$ (MH^+): 309.1425. Found: 309.1429. IR (KBr): 3199, 3093, 2960, 2866, 1570, 1462, 1427, 1335, 758, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.92 (6H, d, J= 6.6 Hz), 1.89 (1H, m), 3.07 (2H, t, J=5.7 Hz), 7.17–7.30 (8H, m), 7.36–7.40 (2H, m), 7.78 (1H, t, J=5.7 Hz).

3.2.23. 2-(*sec*-Butylamino)-4,5-diphenylthiazole (3v). White powder. Mp 93–94 °C (hexane/ethyl acetate). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.43; N, 9.17. HR-MS (TOF-CI) Calcd for $C_{19}H_{21}N_2S$ (MH^+): 309.1425. Found: 309.1434. IR (KBr): 3157, 3080, 2968, 2927, 2879, 1618, 1442, 1335, 756, 688 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.92 (3H, t, J= 7.3 Hz), 1.19 (3H, d, J=6.4 Hz), 1.45–1.66 (2H, m), 3.58–3.71 (1H, m), 7.20–7.31 (8H, m), 7.39–7.42 (2H, m), 7.63 (1H, d, J=7.7 Hz).

3.2.24. 2-Decylamino-4,5-diphenylthiazole (3w). White solid. Mp 57 °C (hexane/ethyl acetate). Anal. Calcd for $C_{25}H_{32}N_2S$: C, 76.48; H, 8.22; N, 7.14. Found: C, 76.58; H, 8.22; N, 7.17. HR-MS (TOF-CI) Calcd for $C_{25}H_{33}N_2S$ (MH^+): 393.2364. Found: 393.2368. IR (KBr): 3192, 3080, 3060, 2918, 2850, 1581, 1433, 1338, 758, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.83 (3H, t, J=7.0 Hz), 1.23–1.30 (14H, m), 1.57 (2H, quint, J=6.8 Hz), 3.22 (2H, q, J= 6.8 Hz), 7.17–7.31 (8H, m), 7.35–7.39 (2H, m), 7.71 (1H, t, J=5.5 Hz).

3.2.25. 2-*cyclo*-Pentylamino-4,5-diphenylthiazole (3x). White powder. Mp 144 °C (hexane/ethyl acetate). Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 75.07; H, 6.32; N, 8.80. HR-MS (TOF-CI) Calcd for $C_{20}H_{21}N_2S$ (MH^+): 321.1425. Found: 321.1430. IR (KBr): 3192, 3080, 2947, 2868, 1562, 1441, 1338, 756, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.51–1.61 (4H, m), 1.63–1.67 (2H, m), 1.89–1.94 (2H, m), 3.94 (1H, m), 7.17–7.30 (8H, m), 7.36–7.40 (2H, m), 7.76 (1H, d, J=6.5 Hz).

3.2.26. 2-*cyclo*-Hexylamino-4,5-diphenylthiazole (3y). White powder. Mp 154 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{21}H_{23}N_2S$ (MH^+): 335.1581. Found: 335.1581. IR (KBr): 3205, 3078, 2929, 2856, 1558, 1439, 1338, 756, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.14–1.36 (5H, m), 1.54–1.57 (1H, m), 1.69 (2H, m), 1.96–1.99 (2H, m), 3.48 (1H, m), 7.16–7.29 (8H, m), 7.35–7.38 (2H, m), 7.67 (1H, d, J=7.5 Hz).

3.2.27. 2-Benzylamino-4,5-diphenylthiazole (3z). White powder. Mp 142 °C (hexane/ethyl acetate). Anal. Calcd for

$C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.18; H, 5.11; N, 8.21. HR-MS (TOF-CI) Calcd for $C_{22}H_{19}N_2S$ (MH^+): 343.1268. Found: 343.1271. IR (KBr): 3199, 3099, 2972, 2887, 1581, 1448, 760, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 4.49 (2H, d, J=5.8 Hz), 7.12–7.41 (15H, m), 8.26 (1H, t, J=5.8 Hz).

3.2.28. 4,5-Diphenyl-2-(2phenethylamino)thiazole (3aa). White powder. Mp 137–138 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{23}H_{21}N_2S$ (MH^+): 357.1425. Found: 357.1427. IR (KBr): 3195, 3086, 1583, 1495, 1335, 758, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 2.91 (2H, t, J=7.3 Hz), 3.49 (2H, q, J=6.8 Hz), 7.17–7.33 (13H, m), 7.39–7.42 (2H, m), 7.85 (1H, t, J=5.5 Hz).

3.2.29. 2-Allylamino-4,5-diphenylthiazole (3ab). White powder. Mp 131–132 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{18}H_{17}N_2S$ (MH^+): 293.1112. Found: 293.1122. IR (KBr): 3188, 3078, 2972, 2925, 1581, 1439, 1425, 1338, 1309, 964, 910, 760, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 3.91 (2H, t, J=5.5 Hz), 5.13 (1H, dd, J=10.3, 1.5 Hz), 5.27 (1H, dd, J=17.0, 1.5 Hz), 5.86–5.99 (1H, m), 7.18–7.31 (8H, m), 7.36–7.39 (2H, m), 7.88 (1H, t, J=5.5 Hz).

3.2.30. 4,5-Diphenyl-2-(2-hydroxyethylamino)thiazole (3ac). White solid. Mp 91 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{17}H_{17}N_2OS$ (MH^+): 297.1061. Found: 297.1057. IR (KBr): 3311, 3199, 3107, 3016, 2924, 1572, 1444, 1336, 1068, 756, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 3.36 (2H, q, J=5.7 Hz), 3.60 (2H, q, J=5.7 Hz), 4.83 (1H, t, J=5.4 Hz), 7.18–7.32 (8H, m), 7.37–7.41 (2H, m), 7.77 (1H, t, J=5.7 Hz).

3.2.31. 4,5-Diphenyl-2-(2-hydroxypropylamino)thiazole (3ad). White powder. Mp 111–112 °C (hexane/ethyl acetate). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.71; H, 5.72; N, 9.02. HR-MS (TOF-CI) Calcd for $C_{18}H_{19}N_2OS$ (MH^+): 311.1218. Found: 311.1215. IR (KBr): 3357, 3209, 3082, 2972, 1558, 1442, 1336, 1124, 1072, 758, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.11 (3H, d, J=6.2 Hz), 3.21 (2H, t, J=5.7 Hz), 3.85 (1H, m), 4.83 (1H, d, J=4.8 Hz), 7.16–7.31 (8H, m), 7.35–7.39 (2H, m), 7.74 (1H, t, J=5.7 Hz).

3.2.32. 2-Benzylamino-4-methylthiazole[28] (3ae). White solid. Mp 95–96 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{11}H_{13}N_2S$ (MH^+): 205.0799. Found: 205.0802. IR (KBr): 3201, 1589, 1468, 1450, 1360, 980, 731, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (3H, s), 4.44 (2H, s), 6.02 (1H, s), 6.39 (1H, s), 7.25–7.38 (5H, m).

3.2.33. 2-Allylamino-4-methylthiazole (3af). Brown oil. HR-MS (TOF-CI) Calcd for $C_7H_{11}N_2S$ (MH^+): 155.0642. Found: 155.0649. IR (neat): 3205, 1583, 1547, 1427, 1417, 922, 688 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 2.05 (3H, s), 3.83 (2H, d, J=5.0 Hz), 5.07–5.12 (1H, m), 5.18–5.25 (1H, m), 5.82–5.94 (1H, m), 6.14 (1H, s), 7.58 (1H, m).

3.2.34. 2-(2-Hydroxyethylamino)-4-methylthiazole (3ag). Brown oil. HR-MS (TOF-CI) Calcd for $C_6H_{11}N_2OS$ (MH^+): 159.0592. Found: 159.0590. IR (neat): 3280, 2947, 2918, 1562, 1541, 1067 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 2.01 (3H, s), 3.18 (2H, q, J=5.6 Hz), 3.44 (2H, t, J=5.6 Hz), 4.69 (1H, s), 6.05 (1H, s), 7.33 (1H, t, J=5.6 Hz).

3.2.35. 2-(2-Hydroxypropylamino)-4-methylthiazole (3ah). Yellow solid. Mp 71 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_7H_{13}N_2OS$ (MH^+): 173.0748. Found: 173.0748. IR (KBr): 3240, 1558, 1543, 1442, 1321, 1146, 1066, 690 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.04 (3H, d, J=6.2 Hz), 2.06 (3H, s), 3.10 (2H, t, J=5.7 Hz), 3.71–3.82 (1H, m), 4.77 (1H, d, J=4.7 Hz), 6.09 (1H, s), 7.38 (1H, t, J=5.7 Hz).

3.2.36. 2-Benzylamino-4-phenylthiazole (3ai). Yellow solid. Mp 98–99 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{16}H_{15}N_2S$ (MH^+): 267.0955. Found: 267.0956. IR (KBr): 3234, 2972, 1591, 1481, 1448, 1334, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (2H, s), 6.35 (1H, s), 6.66 (1H, s), 7.22–7.35 (8H, m), 7.77–7.80 (2H, m).

3.2.37. 2-Allylamino-4-phenylthiazole (3aj). Yellow crystals. Mp 73 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{12}H_{13}N_2S$ (MH^+): 217.0799. Found: 217.0797. IR (KBr): 3192, 1601, 1585, 1483, 1442, 1423, 926, 702, 671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (2H, m), 5.14–5.19 (1H, m), 5.25–5.32 (1H, m), 5.82–5.94 (1H, m), 6.26 (1H, s), 6.68 (1H, s), 7.24–7.30 (1H, m), 7.34–7.39 (2H, m), 7.56–7.80 (2H, m).

3.2.38. 2-(2-Hydroxyethylamino)-4-phenylthiazole (3ak). Brown oil. HR-MS (TOF-CI) Calcd for $C_{11}H_{13}N_2OS$ (MH^+): 221.0748. Found: 221.0749. IR (neat): 3282, 3116, 1556, 1051, 773, 706 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 3.35 (2H, q, J=5.6 Hz), 3.58 (2H, q, J=5.6 Hz), 4.78 (1H, t, J=5.6 Hz), 7.02 (1H, s), 7.23–7.26 (1H, m), 7.33–7.37 (2H, m), 7.64 (1H, t, J=5.6 Hz), 7.79–7.81 (2H, m).

3.2.39. 2-(2-Hydroxypropylamino)-4-phenylthiazole (3al). Yellow powder. Mp 104–105 °C (hexane/ethyl acetate). Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.57; H, 5.94; N, 11.93. HR-MS (TOF-CI) Calcd for $C_{12}H_{15}N_2OS$ (MH^+): 235.0905. Found: 235.0905. IR (KBr): 3359, 3113, 1560, 1483, 1340, 1119, 943, 704 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.11 (3H, d, J=6.2 Hz), 3.24 (2H, t, J=5.6 Hz), 3.81–3.93 (1H, m), 4.85 (1H, d, J=4.6 Hz), 7.03 (1H, s), 7.26 (1H, t, J=7.2 Hz), 7.37 (2H, t, J=7.2 Hz), 7.65 (3H, t, J=5.6 Hz), 7.82 (2H, d, J=7.2 Hz).

3.2.40. 2-Benzylamino-4,5-dimethylthiazole[28] (3am). Brown powder. Mp 114–115 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{12}H_{15}N_2S$ (MH^+): 219.0955. Found: 219.0958. IR (KBr): 3199, 1593, 1468, 1454, 1354, 712 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.97 (3H, s), 2.08 (3H, s), 4.35 (2H, d, J=5.5 Hz), 7.18–7.39 (5H, m), 7.68 (1H, t, J=5.5 Hz).

3.2.41. 2-Allylamino-4,5-dimethylthiazole (3an). Brown needles. Mp 69 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_8H_{13}N_2S$ (MH^+): 169.0799. Found:

169.0797. IR (KBr): 3203, 3103, 1593, 1427, 1344, 1306, 1228, 966, 912, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.18 (3H, s), 3.83 (2H, d, $J=5.3$ Hz), 5.15–5.20 (1H, m), 5.26–5.33 (1H, m), 5.60 (1H, s), 5.84–5.98 (1H, m).

3.2.42. 2-(2-Hydroxyethylamino)-4,5-dimethylthiazole (3ao). Brown oil. HR-MS (TOF-CI) Calcd for $C_7H_{13}N_2OS$ (MH^+): 173.0748. Found: 173.0747. IR (neat): 3270, 2923, 2854, 1542, 1058, 822 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 1.96 (3H, s), 2.08 (3H, s), 3.19 (2H, q, $J=5.9$ Hz), 3.48 (2H, t, $J=5.9$ Hz), 4.74–4.92 (1H, m), 7.12 (1H, t, $J=5.1$ Hz).

3.2.43. 4,5-Dimethyl-3-(2-hydroxyethyl)-1,3-thiazole-2(3*H*)-imine (3′ao). White solid. Mp 176–177 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_7H_{13}N_2OS$ (MH^+): 173.0748. Found: 173.0742. IR (neat): 3170, 3092, 2961, 2925, 2878, 1655, 1502, 1444, 1402, 1057 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 1.94 (3H, s), 2.04 (3H, s), 3.58 (2H, q, $J=5.8$ Hz), 3.88 (2H, t, $J=5.8$ Hz), 4.85 (1H, t, $J=5.8$ Hz), 11.81 (1H, s).

3.2.44. 2-(2-Hydroxypropylamino)-4,5-dimethylthiazole (3ap). Brown oil. HR-MS (TOF-CI) Calcd for $C_8H_{15}N_2OS$ (MH^+): 187.0905. Found: 187.0897. IR (neat): 3250, 2961, 2923, 2857, 1562, 1454, 1410, 1375, 1085 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 1.03 (3H, d, $J=6.6$ Hz), 1.96 (3H, s), 2.07 (3H, s), 3.00–3.11 (2H, m), 3.70–3.78 (1H, m), 4.77 (1H, s), 7.13 (1H, t, $J=5.4$ Hz)

3.2.45. 4,5-Dimethyl-3-(2-hydroxypropyl)-1,3-thiazole-2(3*H*)-imine (3′ap). White powder. Mp 160–161 °C (hexane/ethyl acetate). Anal. Calcd for $C_8H_{14}N_2OS$: C, 51.58; H, 7.58; N, 15.04. Found: C, 51.49; H, 7.62; N, 14.98. HR-MS (TOF-CI) Calcd for $C_8H_{15}N_2OS$ (MH^+): 187.0905. Found: 187.0897. IR (neat): 3374, 3103, 2962, 2947, 2926, 2892, 1660, 1493, 1438, 1401, 1369, 1134, 936 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 1.05 (3H, d, $J=6.3$ Hz), 1.94 (3H, s), 2.03 (3H, s), 3.55 (1H, dd, $J=13.5$, 8.2 Hz), 3.89 (1H, dd, $J=13.5$, 4.0 Hz), 4.00–4.06 (1H, m), 4.79 (1H, d, $J=5.1$ Hz), 11.79 (1H, s).

3.2.46. 4,5-Diphenyl-2-pyrrolidinothiazole (3aq). Yellow solid. Mp 116–117 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{19}H_{19}N_2S$ (MH^+): 307.1268. Found: 307.1277. IR (KBr): 2914, 2852, 1599, 1560, 1495, 1331, 762, 700 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.94–2.00 (4H, m), 3.39 (4H, t, $J=6.5$ Hz), 7.17–7.30 (8H, m), 7.39–7.42 (2H, m).

3.2.47. 4,5-Diphenyl-2-piperidinothiazole (3ar). Yellow crystals. Mp 152–153 °C (hexane/ethyl acetate) (lit.[27] 152–153 °C). HR-MS (TOF-CI) Calcd for $C_{20}H_{21}N_2S$ (MH^+): 321.1425. Found: 321.1432. IR (KBr): 2933, 2852, 1600, 1541, 1495, 1444, 1329, 761, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 1.61 (6H, m), 3.45 (4H, m), 7.20–7.33 (8H, m), 7.36–7.41 (2H, m).

3.2.48. 4,5-Diphenyl-2-morpholinothiazole (3as). White crystals. Mp 116–117 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{19}H_{19}N_2OS$ (MH^+): 323.1218. Found: 323.1226. IR (KBr): 2960, 2845, 1599, 1572, 1444, 1336, 1120, 762, 702 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 3.41 (4H, t, $J=4.8$ Hz), 3.72 (4H, t, $J=4.8$ Hz), 7.22–7.30 (8H, m), 7.39–7.42 (2H, m).

3.2.49. 4,5-Diphenyl-2-(*N*-methyl-2-hydroxyethylamino)thiazole (3at). White powder. Mp 69 °C (hexane/ethyl acetate). HR-MS (TOF-CI) Calcd for $C_{18}H_{19}N_2OS$ (MH^+): 311.1218. Found: 311.1215. IR (KBr): 3367, 2924, 2862, 1599, 1552, 1415, 1333, 754, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 3.10 (3H, s), 3.53 (2H, t, $J=5.7$ Hz), 3.67 (2H, q, $J=5.7$ Hz), 4.86 (1H, t, $J=5.7$ Hz), 7.19–7.31 (8H, m), 7.39–7.42 (2H, m).

3.2.50. 2-(*N*,*N*-Dibutylamino)-4,5-diphenylthiazole (3au). Yellow oil. HR-MS (TOF-CI) Calcd for $C_{23}H_{29}N_2S$ (MH^+): 365.2051. Found: 365.2051. IR (KBr): 1600, 1545, 1495, 1444, 1336, 756, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.98 (6H, t, $J=7.4$ Hz), 1.39 (4H, m), 1.69 (4H, m), 3.45 (4H, t, $J=7.4$ Hz), 7.15–7.30 (8H, m), 7.51–7.55 (2H, m).

3.2.51. 2-(*N*,*N*-Di-*iso*-butylamino)-4,5-diphenylthiazole (3av). Yellow oil. HR-MS (TOF-CI) Calcd for $C_{23}H_{29}N_2S$ (MH^+): 365.2051. Found: 365.2056. IR (KBr): 1601, 1541, 1495, 1442, 1336, 756, 696 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.96 (12H, d, $J=6.6$ Hz), 2.24 (2H, m), 3.34 (4H, d, $J=7.5$ Hz), 7.25–7.37 (8H, m), 7.40–7.47 (2H, m).

3.3. Typical procedure for the preparation of *N*-allylthioureas

A mixture of allyl bromides (1 mmol), $KSCN/SiO_2$ (5 mmol, 1 g) and RNH_3OAc/Al_2O_3 (3 mmol, 3 g) was stirred in benzene (10 mL) at 80 °C for 6 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column chromatography.

3.3.1. 1-Benzyl-3-(1-phenylallyl)-thiourea (7a). White powder. Mp 80–81 °C (hexane/ethyl acetate). Anal. Calcd for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.21; H, 6.53; N, 10.10. HR-MS (TOF-CI) Calcd for $C_{17}H_{19}N_2S$ (MH^+): 283.1268. Found: 283.1273. IR (neat): 3266, 1549 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (2H, s), 5.06–5.18 (2H, m), 5.54 (1H, s), 5.83–5.93 (1H, m), 6.30 (1H, s), 6.40 (1H, s), 7.08–7.26 (10H, m).

3.3.2. 1-Allyl-3-benzyl thiourea (7b). White solid. Mp 93 °C (hexane/ethyl acetate). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.10; H, 6.94; N, 13.83. HR-MS (TOF-CI) Calcd for $C_{11}H_{15}N_2S$ (MH^+): 207.0955. Found: 207.0962. IR (neat): 3237, 1558 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.03 (2H, s), 4.65 (2H, s), 5.14–5.19 (2H, m), 5.76–5.86 (1H, m), 6.19 (1H, s), 6.37 (1H, s), 7.27–7.37 (5H, m).

3.3.3. 1-Benzyl-3-(1-methylallyl)-thiourea (7c). White solid. Mp 68–69 °C (hexane/ethyl acetate). Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.44; H, 7.44; N, 12.70. HR-MS (TOF-CI) Calcd for $C_{12}H_{17}N_2S$ (MH^+): 221.1112. Found: 221.1108. IR (neat): 3221, 1558 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, d, $J=6.8$ Hz), 4.42 (1H, s), 4.62 (2H, s), 5.02–5.10 (2H, m),

5.67–5.78 (1H, m), 6.08 (1H, s), 6.29 (1H, s), 7.23–7.30 (5H, m).

3.3.4. 1-Benzyl-3-(1,1-dimethylallyl)-thiourea (7d). White crystals. Mp 58–59 °C (hexane/ethyl acetate). Anal. Calcd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.76; H, 7.85; N, 12.04. HR-MS (TOF-CI) Calcd for $C_{13}H_{19}N_2S$ (MH^+): 235.1268. Found: 235.1268. IR (KBr): 3267, 1545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (6H, s), 4.77 (2H, d, $J=5.1$ Hz), 5.13–5.22 (2H, m), 5.94 (1H, dd, $J=17.9$, 10.6 Hz), 6.26 (1H, s), 6.29 (1H, s), 7.22–7.29 (5H, m).

3.3.5. 1-Butyl-3-(1-phenylallyl)-thiourea (7e). White powder. Mp 77–78 °C (hexane/ethyl acetate). Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.60; H, 8.28; N, 11.26. HR-MS (TOF-CI) Calcd for $C_{14}H_{21}N_2S$ (MH^+): 249.1425. Found: 249.1425. IR (neat): 3264, 1545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J=7.3$ Hz), 1.25 (2H, sext, $J=7.3$ Hz), 1.47 (2H, quint, $J=7.3$ Hz), 3.44 (2H, s), 5.24–5.31 (2H, m), 5.49 (1H, s), 5.88 (1H, s), 5.97–6.05 (1H, m), 6.30 (1H, s), 7.28–7.39 (5H, m).

3.3.6. 1-*iso*-Butyl-3-(1-phenylallyl)-thiourea (7f). White powder. Mp 92–93 °C (hexane/ethyl acetate). Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.40; H, 8.21; N, 11.49. HR-MS (TOF-CI) Calcd for $C_{14}H_{21}N_2S$ (MH^+): 249.1425. Found: 249.1421. IR (neat): 3266, 1552 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–0.84 (6H, m), 1.73–1.86 (1H, m), 3.29 (2H, s), 5.25–5.32 (2H, m), 5.42 (1H, s), 5.89 (1H, s), 5.97–6.05 (1H, m), 6.34 (1H, s), 7.29–7.39 (5H, m).

3.3.7. 1-*sec*-Butyl-3-(1-phenylallyl)-thiourea (7g). White powder. Mp 112–113 °C (hexane/ethyl acetate). Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.72; H, 8.27; N, 11.16. HR-MS (TOF-CI) Calcd for $C_{14}H_{21}N_2S$ (MH^+): 249.1425. Found: 249.1430. IR (neat): 3266, 1536 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.72 (1.5H, t, $J=7.4$ Hz), 0.90 (1.5H, t, $J=7.4$ Hz), 1.06 (1.5H, d, $J=6.3$ Hz), 1.15 (1.5H, d, $J=6.3$ Hz), 1.36–1.43 (1H, m), 1.44–1.57 (1H, m), 4.18 (1H, s), 5.24–5.34 (2H, m), 5.38 (1H, s), 5.59 (1H, s), 5.96–6.06 (1H, m), 6.20 (1H, s), 7.30–7.40 (5H, m).

3.3.8. 1-Allyl-3-(1-phenylallyl)-thiourea (7h). White powder. Mp 56–57 °C (hexane/ethyl acetate). Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.35; H, 6.91; N, 11.95. HR-MS (TOF-CI) Calcd for $C_{13}H_{17}N_2S$ (MH^+): 233.1112. Found: 233.1113. IR (neat): 3251, 1540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.09 (2H, s), 5.09–5.14 (2H, m), 5.24–5.31 (2H, m), 5.61 (1H, s), 5.76–5.85 (1H, m), 5.96–6.05 (1H, m), 6.09 (1H, s), 6.40 (1H, s), 7.29–7.38 (5H, m).

3.3.9. 1-*cyclo*-Pentyl-3-(1-phenylallyl)-thiourea (7i). White powder. Mp 137–138 °C (hexane/ethyl acetate). Anal. Calcd for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76. Found: C, 69.12; H, 7.89; N, 10.99. HR-MS (TOF-CI) Calcd for $C_{15}H_{21}N_2S$ (MH^+): 261.1425. Found: 261.1430. IR (neat): 3263, 1539 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31–1.47 (2H, m), 1.54–1.63 (4H, m), 1.89–2.04 (2H, m), 4.31 (1H, s), 5.25–5.33 (2H, m), 5.58 (1H, s), 5.88 (1H, s), 5.98–6.07 (1H, m), 6.12 (1H, s), 7.30–7.40 (5H, m).

3.3.10. 1-*cyclo*-Hexyl-3-(1-phenylallyl)-thiourea (7j). White powder. Mp 136–137 °C (hexane/ethyl acetate). Anal. Calcd for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21. Found: C, 69.78; H, 8.19; N, 10.28. HR-MS (TOF-CI) Calcd for $C_{16}H_{23}N_2S$ (MH^+): 275.1581. Found: 275.1578. IR (neat): 3250, 1541 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01–1.18 (3H, m), 1.27–1.40 (2H, m), 1.54–1.63 (3H, m), 1.84–1.87 (1H, m), 1.97–1.99 (1H, m), 4.03 (1H, s), 5.25–5.32 (2H, m), 5.42 (1H, s), 5.77 (1H, s), 5.96–6.04 (1H, m), 6.25 (1H, s), 7.28–7.39 (5H, m).

3.3.11. 1-Phenetyl-3-(1-phenylallyl)-thiourea (7k). Yellow oil. HR-MS (TOF-CI) Calcd for $C_{18}H_{21}N_2S$ (MH^+): 297.1425. Found: 297.1429. IR (neat): 3260, 1545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.70–2.82 (2H, m), 3.69 (2H, s), 5.07–5.14 (2H, m), 5.45 (1H, s), 5.82–5.90 (1H, m), 6.13 (1H, s), 6.59 (1H, s), 7.07 (2H, d, $J=6.8$ Hz), 7.15–7.29 (8H, m).

3.3.12. 1-Butyl-3-(1-methylallyl)-thiourea (7l). Yellow oil. HR-MS (TOF-CI) Calcd for $C_9H_{19}N_2S$ (MH^+): 187.1268. Found: 187.1276. IR (neat): 3263, 1549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, $J=7.5$ Hz), 1.32 (3H, d, $J=6.8$ Hz), 1.37 (2H, sext, $J=7.5$ Hz), 1.58 (2H, quint, $J=7.5$ Hz), 3.48 (2H, s), 4.55 (1H, s), 5.15–5.27 (2H, m), 5.81–5.89 (1H, m), 6.15 (2H, s).

3.3.13. 1-*iso*-Butyl-3-(1-methylallyl)-thiourea (7m). Colorless oil. HR-MS (TOF-CI) Calcd for $C_9H_{19}N_2S$ (MH^+): 187.1268. Found: 187.1269. IR (neat): 3264, 1549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (6H, d, $J=6.8$ Hz), 1.31 (3H, d, $J=6.8$ Hz), 1.90 (1H, m), 3.31 (2H, s), 4.66 (1H, s), 5.13–5.25 (2H, m), 5.81–5.90 (1H, m), 6.55 (2H, s).

3.3.14. 1-*sec*-Butyl-3-(1-methylallyl)-thiourea (7n). White powder. Mp 72–73 °C (hexane/ethyl acetate). Anal. Calcd for $C_9H_{18}N_2S$: C, 58.02; H, 9.74; N, 15.04. Found: C, 57.99; H, 10.04; N, 14.92. HR-MS (TOF-CI) Calcd for $C_9H_{19}N_2S$ (MH^+): 187.1268. Found: 187.1262. IR (neat): 3236, 1553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90–0.96 (3H, m), 1.17–1.20 (3H, m), 1.32 (3H, d, $J=6.6$ Hz), 1.50–1.62 (2H, m), 4.21 (1H, s), 4.42 (1H, s), 5.18–5.28 (2H, m), 5.80–5.89 (2H, m), 6.07 (1H, s).

3.3.15. 1-Allyl-3-(1-methylallyl)-thiourea (7o). Yellow oil. HR-MS (TOF-CI) Calcd for $C_8H_{15}N_2S$ (MH^+): 171.0955. Found: 171.0960. IR (neat): 3261, 1549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, d, $J=6.8$ Hz), 4.13 (2H, s), 4.52 (1H, s), 5.17–5.27 (4H, m), 5.80–5.93 (2H, m), 6.09 (2H, s).

3.3.16. 1-*cyclo*-Pentyl-3-(1-methylallyl)-thiourea (7p). White powder. Mp 72–73 °C (hexane/ethyl acetate). Anal. Calcd for $C_{10}H_{18}N_2S$: C, 60.56; H, 9.15; N, 14.12. Found: C, 60.33; H, 9.18; N, 14.32. HR-MS (TOF-CI) Calcd for $C_{10}H_{19}N_2S$ (MH^+): 199.1268. Found: 199.1264. IR (neat): 3240, 1549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, d, $J=6.6$ Hz), 1.45–1.52 (2H, m), 1.59–1.72 (4H, m), 2.00–2.05 (2H, m), 4.34 (1H, s), 4.60 (1H, s), 5.16–5.26 (2H, m), 5.82–5.90 (1H, m), 5.99 (1H, s), 6.13 (1H, s).

3.3.17. 1-*cyclo*-Hexyl-3-(1-methylallyl)-thiourea (7q). White powder. Mp 107–108 °C (hexane/ethyl acetate). Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22; H, 9.49; N, 13.19. Found: C, 62.10; H, 9.77; N, 13.35. HR-MS (TOF-CI) Calcd for $C_{11}H_{21}N_2S$ (MH^+): 213.1425. Found: 213.1423. IR (neat): 3240, 1552 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15–1.24 (3H, m), 1.32 (3H, d, $J=6.8$ Hz), 1.34–1.43 (2H, m), 1.59–1.71 (3H, m), 1.99–2.04 (2H, m), 4.03 (1H, s), 4.40 (1H, s), 5.18–5.28 (2H, m), 5.79–5.88 (1H, m), 5.86 (1H, s), 5.95 (1H, s).

3.3.18. 1-(1-Methylallyl)-3-phenetyl thiourea (7r). White powder. Mp 54–55 °C (hexane/ethyl acetate). Anal. Calcd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.60; H, 7.87; N, 11.74. HR-MS (TOF-CI) Calcd for $C_{13}H_{19}N_2S$ (MH^+): 235.1268. Found: 235.1275. IR (neat): 3224, 1550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, d, $J=6.8$ Hz), 2.88–2.92 (2H, m), 3.81 (2H, s), 4.20 (1H, s), 4.98–5.04 (2H, m), 5.64–5.72 (1H, m), 5.92 (1H, s), 6.09 (1H, s), 7.19–7.25 (3H, m), 7.28–7.33 (2H, m).

3.3.19. 1-Butyl-3-(1,1-dimethylallyl)-thiourea (7s). Yellow oil. HR-MS (TOF-CI) Calcd for $C_{10}H_{21}N_2S$ (MH^+): 201.1425. Found: 201.1425. IR (neat): 3258, 1545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, $J=7.5$ Hz), 1.34 (2H, sext, $J=7.5$ Hz), 1.40 (6H, s), 1.54 (2H, quint, $J=7.5$ Hz), 3.56–3.61 (2H, m), 5.29–5.36 (2H, m), 6.02 (1H, s), 6.02 (1H, dd, $J=17.6$, 10.7 Hz), 6.14 (1H, s).

3.3.20. 1-(1,1-Dimethylallyl)-3-*iso*-butylthiourea (7t). White solid. Mp 48–49 °C (hexane/ethyl acetate). Anal. Calcd for $C_{10}H_{20}N_2S$: C, 59.95; H, 10.06; N, 13.98. Found: C, 59.94; H, 10.31; N, 13.89. HR-MS (TOF-CI) Calcd for $C_{10}H_{21}N_2S$ (MH^+): 201.1425. Found: 201.1418. IR (neat): 3234, 1533 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (6H, d, $J=6.7$ Hz), 1.41 (6H, s), 1.89 (1H, m), 3.43 (1H, d, $J=6.7$ Hz), 3.44 (1H, d, $J=6.7$ Hz), 5.31–5.38 (2H, m), 6.04 (1H, dd, $J=17.7$, 10.6 Hz), 6.09 (1H, s), 6.14 (1H, s).

3.3.21. 1-*sec*-Butyl-3-(1,1-dimethylallyl)-thiourea (7u). Colorless oil. HR-MS (TOF-CI) Calcd for $C_{10}H_{21}N_2S$ (MH^+): 201.1425. Found: 201.1428. IR (neat): 3258, 1542 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, $J=7.3$ Hz), 1.17 (3H, d, $J=6.6$ Hz), 1.40 (3H, s), 1.40 (3H, s), 1.53 (2H, quint, $J=7.3$ Hz), 4.31–4.42 (1H, m), 5.29–5.37 (2H, m), 5.91 (1H, s), 6.03 (1H, dd, $J=17.7$, 10.6 Hz), 6.04 (1H, s).

3.3.22. 1-Allyl-3-(1,1-dimethylallyl)-thiourea (7v). White solid. Mp 55–57 °C (hexane/ethyl acetate). Anal. Calcd for $C_9H_{16}N_2S$: C, 58.65; H, 8.75; N, 15.20. Found: C, 58.59; H, 8.99; N, 15.11. HR-MS (TOF-CI) Calcd for $C_9H_{17}N_2S$ (MH^+): 185.1112. Found: 185.1118. IR (neat): 3246, 1545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (6H, s), 4.24–4.27 (2H, m), 5.14–5.21 (2H, m), 5.29–5.37 (2H, m), 5.83–5.93 (1H, m), 6.03 (1H, dd, $J=17.6$, 10.7 Hz), 6.10 (1H, s), 6.33 (1H, s).

3.3.23. 1-*cyclo*-Pentyl-3-(1,1-dimethylallyl)-thiourea (7w). White solid. Mp 66–67 °C (hexane/ethyl acetate). Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22; H, 9.49; N, 13.19. Found: C, 62.24; H, 9.86; N, 13.03. HR-MS (TOF-CI) Calcd for $C_{11}H_{21}N_2S$ (MH^+): 213.1425. Found: 213.1429. IR (KBr): 3246, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (6H, s), 1.44–1.49 (2H, m), 1.56–1.67 (4H, m), 1.97–2.05 (2H, m), 4.56–4.64 (1H, m), 5.29–5.36 (2H, m), 6.04 (1H, dd, $J=17.7$, 10.6 Hz), 6.12 (1H, s), 6.36 (1H, s).

3.3.24. 1-*cyclo*-Hexyl-3-(1,1-dimethylallyl)-thiourea (7x). White solid. Mp 97–99 °C (hexane/ethyl acetate). Anal. Calcd for $C_{12}H_{22}N_2S$: C, 63.67; H, 9.80; N, 12.37. Found: C, 63.39; H, 10.11; N, 12.21. HR-MS (TOF-CI) Calcd for $C_{12}H_{23}N_2S$ (MH^+): 227.1581. Found: 227.1575. IR (KBr): 3220, 1540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.28 (2H, m), 1.36–1.47 (2H, m), 1.40 (6H, s), 1.54–1.65 (4H, m), 1.98–2.02 (2H, m), 4.18–4.27 (1H, m), 5.29–5.36 (2H, m), 6.02 (1H, dd, $J=17.7$, 10.6 Hz), 6.02 (1H, s), 6.04 (1H, s).

3.3.25. 1-(1,1-Dimethylallyl)-3-phenetyl thiourea (7y). White needles. Mp 70–71 °C (hexane/ethyl acetate). Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.52; H, 8.34; N, 11.35. HR-MS (TOF-CI) Calcd for $C_{14}H_{21}N_2S$ (MH^+): 249.1425. Found: 249.1417. IR (neat): 3254, 1551 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (6H, s), 2.91 (2H, t, $J=6.6$ Hz), 3.91 (2H, dt, $J=6.6$, 5.4 Hz), 4.90–4.98 (2H, m), 5.76 (1H, dd, $J=17.7$, 10.6 Hz), 5.93 (1H, s), 6.22 (1H, s), 7.20–7.25 (3H, m), 7.29–7.33 (2H, m).

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A selective colorimetric chemosensor for lanthanide ions

Zhilian Liu,[a,b] Lin Jiang,[a,b] Zhi Liang[a,b] and Yunhua Gao[a,*]

[a]*Technical Institute of Physics and Chemistry, Chinese Academy of Sciences (CAS), Box 5131, Beijing 100101, People's Republic of China*
[b]*Graduate School of Chinese Academy of Sciences (GSCAS), Beijing 100039, People's Republic of China*

Received 10 August 2005; revised 18 January 2006; accepted 20 January 2006

Abstract—The synthesis and complexing properties of a calix[4]arene derivate (**6**) carrying two spirobenzopyran moieties are described. The addition of lanthanide ions resulted in significant UV–vis spectral shifts (68–84 nm) in visible region. It indicates that the synthetic receptor can recognize lanthanide ions by naked eyes over other cations including Na^+, K^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, Cu^{2+} and Zn^{2+}. The mechanism of recognition was studied with ^1H NMR, UV–vis spectra and emission spectra. The receptor may be applied to sense lanthanide ions.
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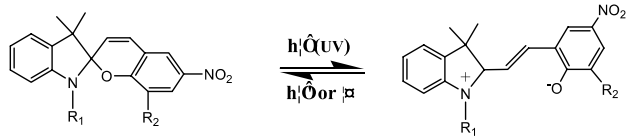
1. Introduction

Lanthanide ions have been widely applied in many fields, for example, as probes and labels in chemical and biological applications.[1] In order to overcome the weak absorption coefficients of the lanthanide ions and sensitize their luminescence, many lanthanide (III) chelates have been designed containing 'antenna effect'.[2] The macrocyclic chelating agents including cryptands,[3] calixarene,[4] cyclodextrins[5] and crown-ether derivatives,[6] are commonly used to sensitize luminescence of Eu (III) and Tb (III) ion.

Spirobenzopyran derivatives have been extensively investigated for their photochromism[7] and applications in photoswitchable molecular devices.[8] Under the irradiation of ultraviolet light (or in dark conditions), the colorless, neutral spiropyran (**SP**) forms are isomerized to the colored, zwitterionic merocyanine forms (**MC**) while the s–p hybridization of a single C atom becomes p-conjugation over the whole molecule (Scheme 1). The zwitter-ionic merocyanine forms may have stronger affinity for lanthanide ions than the neutral host for their electrostatic interaction.[9]



closed forms (colorless, **SP**) open forms (colored, **MC**)

Scheme 1. Photochromic reactions of spirobenzopyran derivatives.

In the present work, we report the synthesis of receptor **6** by incorporating two 1′,3′,3′-trimethyl-6-nitro-8-hydromethyl-spiro-(2-*H*-1-benzopyran-2,2′-indoline) (**5**) groups to a 5,11,17,23-tetra-*tert*-butyl-25,27-bis(chloroformylmethoxy)-26,28-dihydroxycalix[4]arene (**4**) (Scheme 2). The structure of compound **6** was identified by IR, ^1H, ^{13}C NMR, elemental analysis and MALDI-TOF MS. Two doublets of the CH_2 bridging groups (at 3.26 and 4.35 ppm) in the ^1H NMR data revealed that **6** is in the cone conformation. The host compound **6** can selectively recognize lanthanide ions with significant hypsochromic shifts and enhancement of maximum absorption intensity in visible region. Meanwhile, the color of the solution changed from purple to yellow. Whereas, addition of alkali metal cations (such as Na^+, K^+), alkali earth metal cations (such as Mg^{2+}, Ca^{2+}) or transition metal cations (such as Fe^{3+}, Cu^{2+}, Zn^{2+}) resulted in no visible changes in the UV–vis absorption spectra. Thus, compound **6** may be applied as a lanthanide sensor with naked eye. The model compound **8** (Scheme 2) without calix[4]arene cavity had poorer selective ability for lanthanide ions than compound **6**. Compound **5** (Scheme 2) is of the least selectivity for the investigated ions among these three receptors. In this paper, we studied the mechanism of recognition by means of ^1H NMR, UV–vis spectra and emission spectra of the **6**-Eu^{3+} complexes.

2. Results and discussion

2.1. Metal cations recognition

We investigated the recognition ability of receptor **6** for metal ions such as alkali metal cations (Na^+, K^+), alkali earth metal cations (Mg^{2+}, Ca^{2+}), transition metal cations (Fe^{3+}, Cu^{2+}, Zn^{2+}) and lanthanide cations (La^{3+}, Pr^{3+}, Eu^{3+}, Gd^{3+},

Keywords: Calix[4]arene derivatives; Spirobenzopyrans; Recognition; Lanthanide ions; Sensors.
* Corresponding author. Tel.: +86 10 64859580; fax: +86 10 64879375; e-mail: yhgao@mail.ipc.ac.cn

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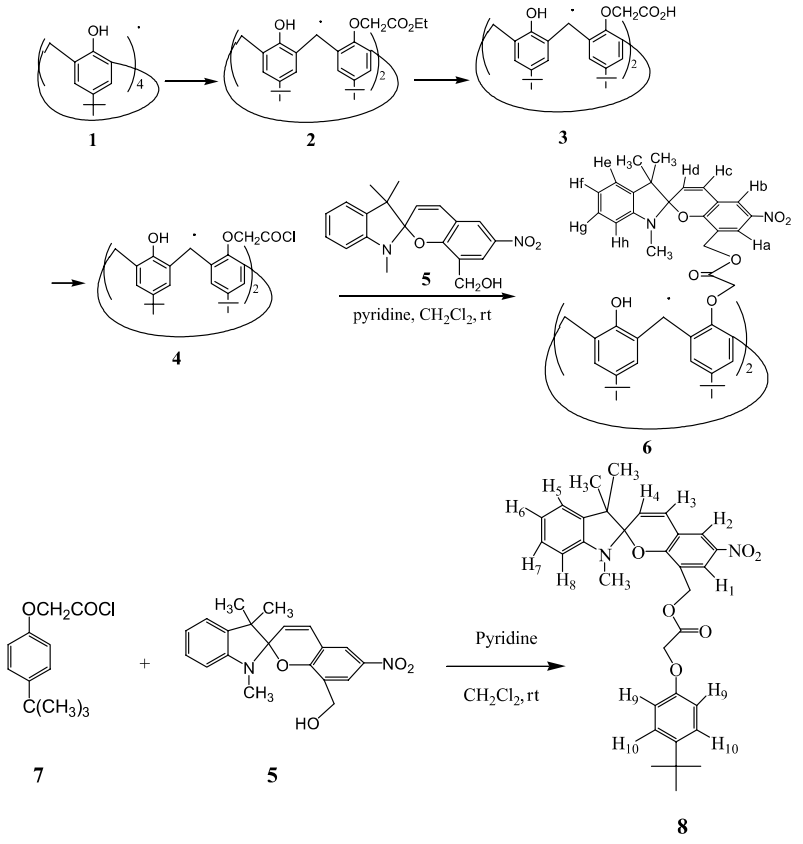
doi:10.1016/j.tet.2006.01.073



Scheme 2. Synthesis of receptor **6** and model compound **8**.

Dy^{3+}, Er^{3+}, Yb^{3+}). When the colorless lanthanide solutions in acetonitrile were added to the purple solution of receptor **6** in acetonitrile, the color changed to yellow immediately. However, there was no remarkable color change upon the addition of Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Fe^{3+}, Cu^{2+} and Zn^{2+}. As shown in Figure 1, the color change of **6** upon the addition of lanthanide ions is visible to the naked eye. Figure 2 shows the absorbance at the maximum absorption wavelength of the mixed solution of receptor **6** with equally molar metal cations, which were allowed to stand for 48 h under dark conditions for complete complexation. The addition of lanthanide ions caused significant hypsochromic shifts (68–84 nm) and enhancement of maximum absorption intensity (5.5–9.0 folds, Table 1) in visible region. The hypsochromic shifts can be explained by the location of electron cloud of the open merocyanine forms (**Calix-2MC**) attributed to electrostatic interaction between the phenolate anions of merocyanine groups (**MC**) and trivalent lanthanide ions under dark conditions. These changes suggest **6** coordinated with lanthanide ions. The complexing process was described in Scheme 3 (**Calix-2SP** and **Calix-2MC** denote the closed forms and the open forms of receptor **6**, respectively. **Calix-2MC**·$\mathbf{Ln^{3+}}$ means the complexes of the open **6** and lanthanide ions). According to hard soft acid base principle, lanthanide ions belong to hard acid, which have strong affinity for hard alkali (such as oxygen). In the lower rim of the receptor **6**, there are 10 oxygen atoms, which are not only able to coordinate with lanthanide ions but also meet their large coordination number. What is interesting is that the trend of spectral changes is $Yb^{3+} > Er^{3+} > Gd^{3+} > Dy^{3+} > Eu^{3+} > Pr^{3+} > La^{3+}$ opposite to that of the lanthanide ions' radii. This implies that the recognition process is relative to the size-fit effect. Hence upon the addition of lanthanide ions, the receptor changes color due to strong electrostatic interaction, hard acid–hard alkali interaction and size-fit effect between **Calix-2MC** and lanthanide ions.

Figure 1. Color change of compound **6** (50 μM) in acetonitrile induced by addition of 2 equiv of metal nitrate (from left to right: compound **6** without metal ion; addition of Na^{+}; Ca^{2+}; Zn^{2+}; La^{3+}; Pr^{3+}; Eu^{3+}; Gd^{3+}; Er^{3+}).

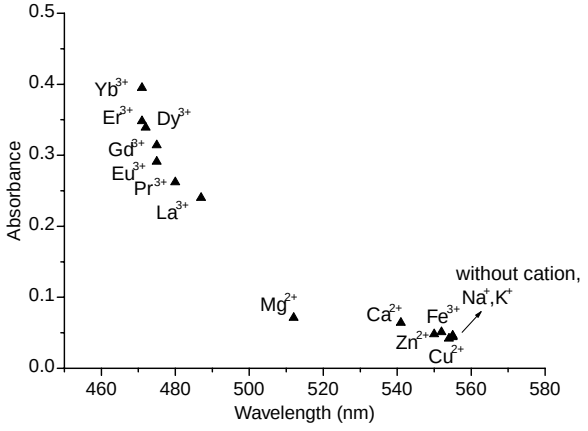
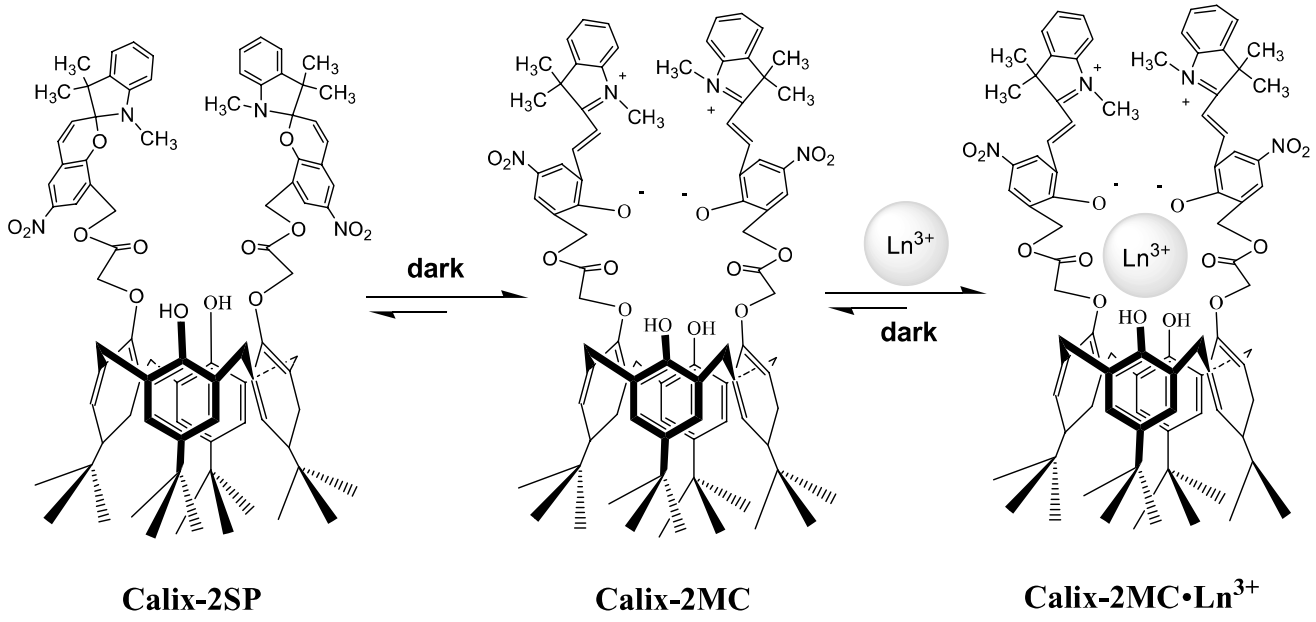


Figure 2. UV–vis spectra of compound **6** (20 μM) in the presence of and without metal ions (20 μM) in acetonitrile under dark conditions for 48 h.

Table 1. Spectral changes of compound **6**, compound **8** and compound **5** on addition of metal ions[a]

Metal ion	r (nm)[b]	Compound **6**		Compound **8**		Compound **5**	
		λ_{max} (nm) ($\Delta\lambda$)[c]	$A(\Delta A)$[d]	λ_{max} (nm) ($\Delta\lambda$)[c]	$A(\Delta A)$[d]	λ_{max} (nm) ($\Delta\lambda$)[c]	$A(\Delta A)$[d]
None		555	0.044 (1)	550	0.054 (1.0)	550	0.030 (1.0)
Na^+	0.095	555 (0)	0.046 (1)	550 (0)	0.052 (1.0)	547 (−3)	0.025 (0.8)
K^+	0.133	555 (0)	0.045 (1)	550 (0)	0.053 (1.0)	547 (−3)	0.026 (0.8)
Mg^{2+}	0.065	512 (−43)	0.071 (1.6)	550 (0)	0.053 (1.0)	485 (−65)	0.119 (3.9)
Ca^{2+}	0.099	541 (−14)	0.064 (1.5)	550 (0)	0.051 (0.9)	538 (−12)	0.034 (1.1)
Fe^{3+}	0.064	552 (−3)	0.051 (1.2)	550 (0)	0.052 (1.0)	469 (−81)	0.048 (1.6)
Cu^{2+}	0.069	554 (−1)	0.042 (0.9)	549 (−1)	0.051 (0.9)	540 (−10)	0.030 (1.0)
Zn^{2+}	0.074	550 (−5)	0.048 (1.1)	550 (0)	0.052 (1.0)	470 (−80)	0.056 (1.9)
La^{3+}	0.120	487 (−68)	0.240 (5.5)	548 (−2)	0.048 (0.9)	478 (−72)	0.262 (8.7)
Pr^{3+}	0.115	480 (−75)	0.262 (6.0)	499 (−51)	0.051 (0.9)	477 (−73)	0.410 (13.7)
Eu^{3+}	0.109	475 (−80)	0.291 (6.6)	478 (−72)	0.063 (1.2)	471 (−79)	0.392 (13.1)
Gd^{3+}	0.108	475 (−80)	0.314 (7.1)	477 (−73)	0.047 (0.9)	469 (−81)	0.328 (10.9)
Dy^{3+}	0.105	472 (−83)	0.339 (7.7)	467 (−83)	0.124 (2.3)	467 (−83)	0.390 (13)
Er^{3+}	0.102	471 (−84)	0.348 (7.9)	468 (−82)	0.114 (2.1)	466 (−84)	0.402 (13.4)
Yb^{3+}	0.100	471 (−84)	0.395 (9.0)	468 (−82)	0.092 (1.7)	465 (−85)	0.374 (12.5)

[a] [Compound **6**]=[metal ions]=20 μM, [compound **8**]=[compound **5**]=40 μM in acetonitrile.
[b] Pauling radius of the investigated ions.
[c] Shifts of the λ_{max} (minus denotes hypsochromic shift).
[d] The increased folds of the absorbance of compound **6**, **8** and **5**.



Scheme 3. Sketches of equilibrium reactions of compound **6** in the presence of and without lanthanide ions.

In order to investigate the contribution of the calix[4]arene cavity to the selectivity, we designed a model compound **8** without cavity (Scheme 2). As shown in Figure 3, the compound **8** have selectivity for Pr^{3+}, Eu^{3+}, Gd^{3+}, Dy^{3+}, Er^{3+}, Yb^{3+} with significant blue shifts. In these experiments, the concentration of compound **8** and **5** (40 μM) is double of that of compound **6** (20 μM) so that the concentration of spirobenzopyran groups is consistent. However, the addition of these ions to a solution of compound **8** caused less visible color changes than those of compound **6**. It may be explained that the concentration of the complexes in the mixture of the compound **6** and Ln^{3+} is higher than that of the compound **8** and lanthanide ions systems. Figure 4 shows the recognition ability of the compound **5** to the investigated ions. It has poor selectivity for lanthanide ions for the interference of Fe^{3+}, Zn^{2+} and Mg^{2+}. Data of spectral changes are listed in Table 1. These data shows compound **6** and **8** have better selectivity for

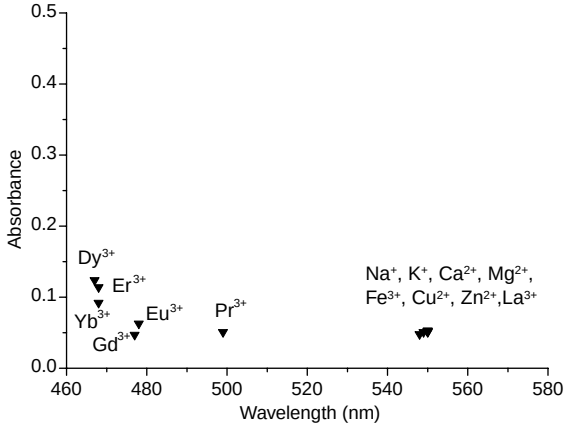


Figure 3. UV–vis spectra of compound **8** (40 μM) in the presence of and without metal ions (20 μM) in acetonitrile under dark conditions for 48 h.

lanthanide ions than compound **5**. Nevertheless, the addition of lanthanide ions caused larger enhancement of absorbance for compound **6** and **5** than that of compound **8**, which indicates compound **6** and **5** have higher sensitivity for lanthanide ions than compound **8**. Hence, compound **6** has high sensitivity and high selectivity for lanthanide ions. Compared with compound **5**, compound **8** bearing a *p-tert*-buytlphenoxyacetyl substitute have an increasing spatial hindrance for the formation of complexes it has lower affinity but higher selectivity for the investigated ions than compound **5**. Especially in the presence of Fe^{3+} and Zn^{2+}, the absorption spectral differences between compound **5** and **8** is a good example for different binding ability caused by different structure. The introduction of calix[4]arene blocks increases selectivity of compound **6** likewise. However, it enhances coordinative ability simultaneously for the calix[4]arene cavity playing an important role for the stability of the complexes. We studied the ^{1}H NMR spectra, UV–vis spectra and luminescence spectra of the receptor **6** with and without Eu^{3+} for illustrating the coordinating process.

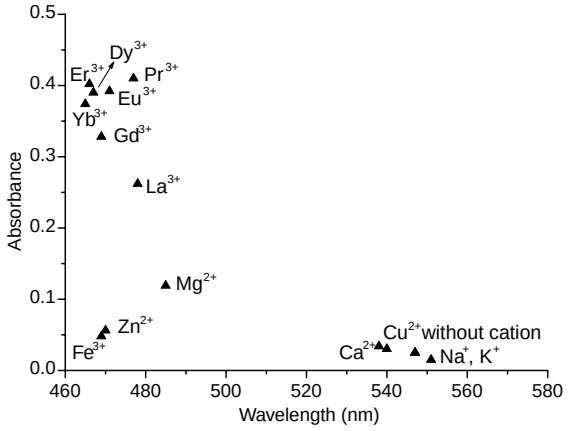


Figure 4. UV–vis spectra of compound **5** (40 μM) in the presence of and without metal ions (20 μM) in acetonitrile under dark conditions for 48 h.

2.2. ^{1}H NMR spectra studies

The spectrum **a** (Fig. 5) is a partial ^{1}H NMR spectra of compound **6** in CD_3CN. Two equivalents of europium (III) nitrate were added to the solution of **6** and then the mixture was kept in dark. Two hours later, the ^{1}H NMR spectrum was measured (spectrum **b** in Fig. 5). There are no remarkable differences between spectrum **a** and **b** except two small peaks at 7.72 and 7.94 ppm in spectrum **b**, which was assigned to signals of receptor **6**'s merocyanine structure (**Calix-2MC**). It means that the isomerization of the closed forms to the open forms occurred in the presence of Eu^{3+}. Significant spectral changes were observed after the mixture had been kept under dark conditions for 18 h. Spectrum **c** (Fig. 5) shows the concentration of the spiropyran forms (**Calix-2SP**) had decreased, meanwhile that of the merocyanine forms (**Calix-2MC**) increased. It suggests that the equilibrium of the first reaction in Scheme 3 was broken by addition of Eu^{3+}.

The changes of ^{1}H NMR spectra disclosed the complexing process was that the formation of the **Calix-2MC**·Eu^{3+}

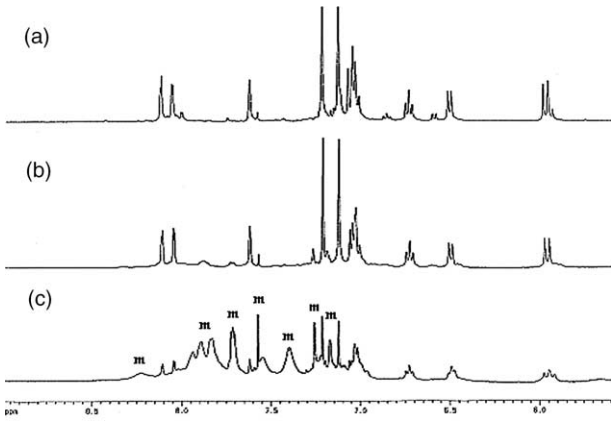


Figure 5. ^{1}H NMR spectra (400 MHz) of compound **6** in CD_3CN (a) before the addition of Eu^{3+}, (b) 2 h after the addition in dark, and (c) 18 h after the addition in dark. The signals marked with 'm' are for the merocyanine structure **Calix-2MC**.

caused the concentration of **Calix-2MC** to decrease and the equilibrium between **Calix-2SP** and **Calix-2MC** was broke and then **Calix-2SP** was isomerized to **Calix-2MC** gradually. Subsequently, **Calix-2MC** produced newly coordinated with Eu^{3+} again (Scheme 3). The process was repeated until a new equilibrium was established.

2.3. UV–vis spectra

The receptor **6** showed absorption band centered at 555 nm in visible region (shown in Fig. 6). We added different equivalents of Eu^{3+}(0, 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4 equiv) to the solution of receptor **6** (20 μM) in acetonitrile. Then these mixtures had been kept in dark for 48 h for a complete complexation. On the concentration of the Eu^{3+} increasing, the absorbance at 555 and 269 nm decreased and meanwhile that at 475 nm (a new ligand-centred absorption band) and 358 nm increased. Three isosbestic points were observed at 543, 293 and 227 nm. These results confirmed the formation of the complexes.

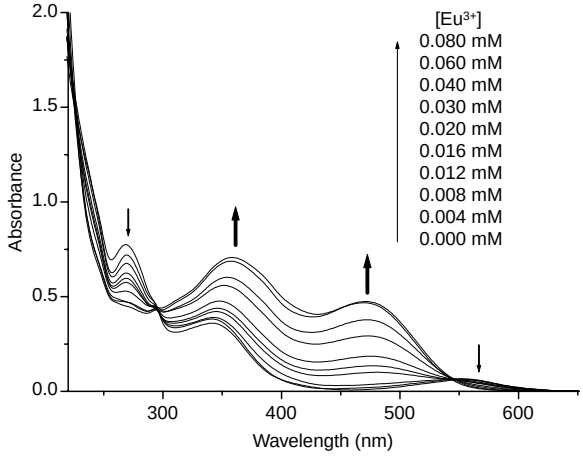


Figure 6. Changes in the UV–vis spectra of **6** (20 μM) upon titration by $Eu(NO_3)_3$ in a acetonitrile solution, where the concentration of the $Eu(NO_3)_3$ varies from 0 to 80 μM.

2.4. Fluorescence spectra

It has been reported that spirobenzopyran derivatives can emit red fluorescence.[10] The formation of complexes gave rise to the changes of emission spectra.[11] Therefore, the changes of luminescence spectra can be a witness of the interaction between hosts and guests. We studied the fluorescence spectra of the receptor **6** with and without the presence of the Eu^{3+} ([**6**]=20 μM, $[Eu^{3+}]/[\mathbf{6}]$=0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 3.0, 4.0). As shown in Figure 8, the relative fluorescence intensity of these mixed solutions was enhanced with the increasing concentration of Eu^{3+} when they were excited at 475 nm. Compared with the fluorescence spectrum of the compound **6**, that of the mixed solutions showed a blue shift of 42 nm (from 637 to 595 nm).

The broad-band emission is neither similar to that of Eu^{3+} whose emission is narrow and line-like nor to that of Eu^{2+} (a broad emission at about 430 nm). Therefore, the emission can be assigned to the π–π* emission of the conjugated system of the open forms of compound **6** (**Calix-2MC**). The blue shifts were caused by **6**'s coordination with Eu^{3+}, which is in accordance with the blue shifts in the absorption spectra. These results further favor the fore conclusion of the formation of the **Calix-2MC·Eu^{3+}**.

2.5. Determination of stoichiometry and stability constant of the complexes

The equilibrium of complexation in the mixture of compound **6** and $Eu(NO_3)_3$ is

$$\text{Calix}-2\text{MC}+n\text{Eu}^{3+}\leftrightarrow\text{Calix}-2\text{MC}\cdot n\text{Eu}^{3+}$$

The stability constant of the complex is defined as

$$K_n=\frac{[\text{M}_n\text{L}]}{[\text{L}][\text{M}]^n} \tag{1}$$

where M_nL, L and M stand for Calix-2MC·nEu^{3+}, Calix-2MC and Eu^{3+}. Calix-2SP and Eu^{3+} have no absorption above 400 nm, so the absorbance at visible region is the absorbance sum of Calix-2MC and Calix-2MC·nEu^{3+}. We select 440 and 555 nm as investigated wavelength because the ligand has minimum and maximum absorbance at these two wavelength. Thus, we have

$$A_{440}=\varepsilon_{\text{M}_n\text{L }440}l[\text{M}_n\text{L}]+\varepsilon_{\text{L }440}l[\text{L}] \tag{2}$$

$$A_{555}=\varepsilon_{\text{M}_n\text{L }555}l[\text{M}_n\text{L}]+\varepsilon_{\text{L }555}l[\text{L}] \tag{3}$$

In Eqs. 2 and 3, $\varepsilon_{M_nL\ 440}$ and $\varepsilon_{M_nL_555}$ is the molar extinction coefficient of Calix-2MC·nEu^{3+} at 440 and 555 nm, respectively. $\varepsilon_{L\ 440}$ and $\varepsilon_{L\ 555}$ is the molar extinction coefficient of Calix-2MC at 440 and 555 nm, respectively. And l is the optical path length (cm). The Eqs. 1–3 lead to

$$\frac{A_{440}}{A_{555}}=\frac{(K_n\varepsilon_{\text{M}_n\text{L }440}[\text{M}]^n+\varepsilon_{\text{L }440})}{(K_n\varepsilon_{\text{M}_n\text{L }555}[\text{M}]^n+\varepsilon_{\text{L }555})} \tag{4}$$

The overall concentration in cation is

$$C_{\text{M}}=[\text{M}]+n[\text{M}_n\text{L}] \tag{5}$$

Thus,

$$[\text{M}]=C_{\text{M}}-n[\text{M}_n\text{L}]=\frac{C_{\text{M}}-nA_{440}}{\varepsilon_{\text{M}_n\text{L }440}l} \tag{6}$$

The absorbance data were analyzed by using a nonlinear least-squares method[14] for n and K_n. The analysis provided the stoichiometry of the complex formed from compound **6** and $Eu(NO_3)_3$ (Fig. 7a) was 1:1 (**6**: Eu^{3+}) and the association constant log $K=5.14\pm0.02$ with the correlation coefficient 0.9996. For the complex of compound **5** and $Eu(NO_3)_3$ (Fig. 7b), the stoichiometry was 2:1 (**5**: Eu^{3+}) and the association constant log $K=4.31\pm0.05$ with the correlation coefficient 0.9981. These results of compound **5** and **6** are consistent and therefore verify the proposed coordinating process (as shown in Scheme 3) further (Fig. 8).

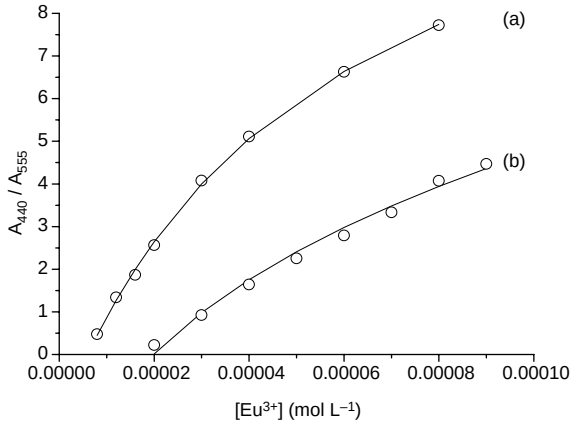


Figure 7. Variations in absorbance of A_{440}/A_{555} (○) of a solution of compounds **6** (a) and **5** (b) in acetonitrile (2×10^{-5} M) as a function of the concentration of europium nitrate. The solid line represents the best fit with Eqs. 4 and 6.

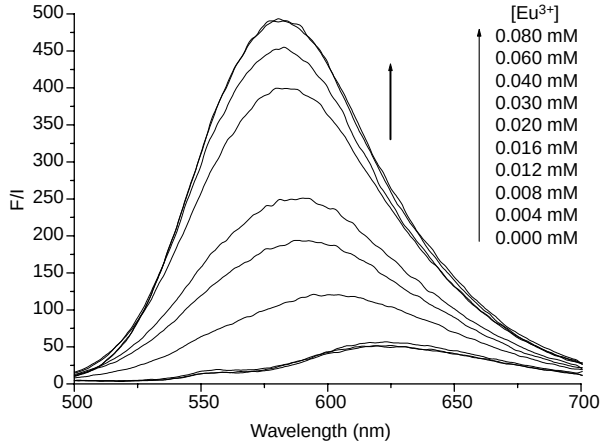


Figure 8. Changes in the emission spectra of **6** (20 μM) upon titration by $Eu(NO_3)_3$ in a acetonitrile solution, where the concentration of the $Eu(NO_3)_3$ varies from 0 to 80 μM.

3. Conclusion

We synthesized a novel receptor **6** containing two photochromic spirobenzopyran groups, which can used to recognize lanthanide ions with naked eye. The addition of lanthanide

ions to the solution of receptor **6** resulted in remarkable shifts of the UV–vis spectra (68–84 nm) and the emission spectra (42 nm for Eu^{3+}), which suggested the formation of complexes. The ^1H NMR explained the microcosmic changes during the coordination of the receptor **6** with Eu^{3+}. When Eu^{3+} were added to the solution of the receptor **6**, some of the Eu^{3+} coordinated with **Calix-2MC** at first, which resulted in the decrease of concentration of **Calix-2MC** and the breakage of original equilibrium of **Calix-2SP** and **Calix-2MC**. The system then tended to establish a new equilibrium among **Calix-2SP**, **Calix-2MC** and **Calix-2MC**·Eu^{3+}. The calix[4]-arene cavity contributed to the stability of the complex **Calix-2MC**·$\mathbf{Ln^{3+}}$. The selectivity of **6** for lanthanide ions is relative to the strong electrostatic interaction, hard acid–hard alkali interaction and size-fit effect. These spectroscopic properties might be applied to sense lanthanide ions by light.

4. Experimental

4.1. General remarks

^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 400 (CD_3CN and $CDCl_3$, TMS as internal standard, chemical shifts in ppm). Mass spectra (MALDI-TOF MS) were recorded with BIFLEXIII MALDI-TOF. UV–vis spectra were recorded with Hitachi U3010. Emission spectra were performed with PERKIN ELMER Luminescence Spectrometer LS 50 B. Elemental analyses were performed with FLASH EA1112 Elemental Analysis Apparatus.

4.2. Synthesis

Compound **1**, **2**,[12] **3**,[12] **4**[12] and **5**[13] were synthesized according to literatures.

4.2.1. 5,11,17,23-Tetra-*tert*-butyl-25,27-bis(1′,3′,3′-trimethyl-6-nitrospiro-[2-*H*-1-benzopyran-2,2′-indoline]-8-methoxycarbonylmethoxy)-26,28-dihydroxycalix[4]-arene, 6. To a solution of **4** (1.36 g, 1.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of 1,3,3-trimethyl-6′-nitro-8′-hydromethyl-spiro-(2′-*H*,1′-benzopyran-2,2′-indoline) (**5**, 1.232 g, 3.5 mmol) in CH_2Cl_2 (15 mL) with stirring. The color of the mixed solution changed from colorless to dark brown. Then, the CH_2Cl_2 solution (5 mL) of pyridine (0.26 g, 3.3 mmol) was added dropwise to the mixture. The color changed to purple quickly. The mixture was stirred for 36 h at room temperature. Then the solvent was evaporated to dryness. The residue was dissolved in chloroform and washed with water 3 times. After chloroform was evaporated, the purple residue was purified by column chromatography with petroleum ether and ethyl acetate as an eluent and gave compound **6** as a purple powder in 15% yield. Mp 143–144 °C; ^1H NMR (400 MHz, [D_1]chloroform, 25 °C): δ 0.93 (s, 18H; Bu^t), 1.19 (s, 6H; SP-CH_3), 1.28 (s, 18H; Bu^t), 1.31 (s, 6H; SP-CH_3), 2.68 (s, 6H; SP-NCH_3), 3.26 (d, J=13.2 Hz, 4H; ArCH_2Ar), 4.35 (d, J=13.2 Hz, 4H; ArCH_2Ar), 4.56 (s, 4H; ArOCH_2CO$_2$–), 4.96 (d, J=12.9 Hz, 2H; ArCH_2O–), 5.05 (d, J=12.9 Hz, 2H; ArCH_2O–), 5.89 (d, J=10.3 Hz, 2H; SP-H_d), 6.49 (d, J=7.5 Hz, 2H; SP-H_h), 6.72 (s, 2H; Ar-OH), 6.75 (s, 4H; Ar-H), 6.80 (t, J=7.5 Hz, 2H; SP-H_f), 6.92 (d, J=10.3 Hz, 2H; SP-H_c), 7.01 (s, 4H; Ar-H), 7.02 (d, J=7.5 Hz, 2H; SP-H_e), 7.09 (t, J=7.5 Hz, 2H; SP-H_g), 7.97 (s, 2H; SP-H_b), 8.07 (s, 2H; SP-H_a); ^{13}C NMR (100 MHz, [D_1]chloroform, 25 °C): δ 168.5, 157.3, 150.6, 150.3, 147.3, 147.1, 141.5, 140.5, 135.8, 132.2, 128.1, 127.9, 126.0, 125.7, 125.6, 125.3, 125.1, 122.6, 122.5, 121.6, 121.4, 120.1, 118.8, 107.1, 107.0, 71.9, 60.8, 52.0, 33.9, 33.8, 32.8, 32.1, 31.7, 31.5, 31.3, 31.0, 28.8, 26.0, 20.0; IR (Nujol): ν=3430 cm^{-1} (C=O), 1762 cm^{-1} (O–H); MALDI-TOF MS: m/z 1431.8 $[M]^+$, 1454.8 $[M+Na]^+$, 1470.9 $[M+K]^+$; elemental analysis calcd (%) for $C_{88}H_{96}N_4O_{14}$ (1433.72): C, 73.45; H, 7.02; N, 3.89; found: C, 73.18; H, 7.20; N, 3.64.

4.2.2. 1′,3′,3′-Trimethyl-6-nitro-8-(4-*tert*-butylphenoxy-acetylmethyl)spiro[2-*H*-1-benzopyran-2,2′-indoline], 8. To a solution of **7** (Alfa Aesar, 0.45 g, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of **5** (0.704 g, 2 mmol) in CH_2Cl_2 (10 mL) with stirring. The color of the mixed solution changed from colorless to dark brown. Then, the CH_2Cl_2 solution (5 mL) of pyridine (0.16 g, 2 mmol) was added dropwise to the mixture. The color changed to purple quickly. The mixture was stirred for 10 h at room temperature. Then the solvent was evaporated to dryness. The purple residue was purified by column chromatography with petrol ether and acetic ester as an eluent and gave compound **8** in 20% yield. Mp 59–61 °C; ^1H NMR (400 MHz, [D_1]chloroform, 25 °C): δ 1.20 (s, 3H; SP-CH_3), 1.29 (s, 12H; Bu^t and SP-CH_3), 2.71 (s, 3H; SP-NCH_3), 4.49 (s, 2H; ArOCH_2CO$_2$–), 4.98 (d, J=11.8 Hz, 1H; ArCH_2O–), 5.05 (d, J=11.8 Hz, 1H; ArCH_2O–), 5.91 (d, J=10.4 Hz, 1H; SP-H_4), 6.53 (d, J=7.3 Hz, 1H; SP-H_8), 6.78 (d, J=8.8 Hz, 2H; H_9), 6.87 (t, J=7.3 Hz, 1H; SP-H_6), 6.96 (d, J=10.4 Hz, 1H; SP-H_3), 7.06 (d, J=7.3 Hz, 1H; SP-H_5), 7.17 (t, J=7.3 Hz, 1H; SP-H_7), 7.29 (d, J=8.8 Hz, 2H; H_{10}), 8.01 (s, 1H; SP-H_2), 8.07 (s, 1H; SP-H_1); ^{13}C NMR (100 MHz, [D_1]chloroform, 25 °C): δ 168.6, 157.3, 155.4, 147.4, 144.5, 140.5, 135.9, 128.1, 127.9, 126.4, 125.3, 122.7, 122.4, 121.7, 121.5, 120.1, 118.8, 114.1, 107.1, 65.2, 60.9, 52.1, 34.1, 31.5, 28.8, 26.0, 20.0; MS (70 eV, EI): m/z (%) 542 (28) $[M]^+$, 335 (100) $[C_{20}H_{19}N_2O_3^+]$; elemental analysis calcd (%) for $C_{32}H_{34}N_2O_6$ (542.62): C, 70.83; H, 6.32; N, 5.16; found: C, 70.91; H, 6.39; N, 5.29.

Acknowledgements

We would like to thank the National Natural Sciences Foundation of China (NSFC, Grant No. 20275042) for their financial support.

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An improved procedure for the preparation of the β-hydroxy-α-alkyl fatty acid fragment of mycolic acids

Gianna Toschi† and Mark S. Baird*

Department of Chemistry, University of Wales, Bangor, Gwynedd LL 57 2 UW, UK

Received 25 November 2005; revised 29 December 2005; accepted 19 January 2006

Abstract—An approach to a β-hydroxy-α-alkyl fatty acid intermediate that can be applied in the synthesis of a range of mycolic acids is described.
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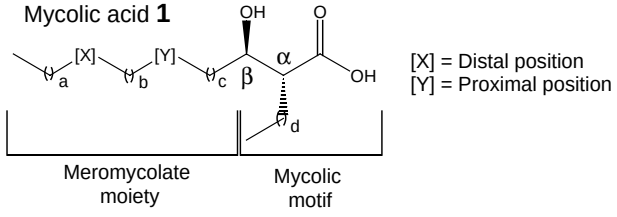
1. Introduction

Mycolic acids (**1**) (Scheme 1), are major constituents of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, some of which are pathogenic to animals and humans.[1,2] Their presence is thought to be linked to the characteristic resistance of these organisms to most current antibiotics and other chemotherapeutic agents.[3] In every mycolic acid two moieties can be distinguished: the meromycolate and the mycolic motif. The structure of the mycolic motif is common to each mycobacterial mycolic acid, except for minor variations in the length of the chain in the α-position (d). The meromycolate moiety, however, is much more variable.[4,5]



Scheme 1.

The two stereocentres in the α and β-positions relative to the carboxylic group have both been found to be in the *R*-configuration for all the mycolic acids examined, irrespective of the other functional groups contained in the meromycolate moiety.[6–10]

The presence of the hydroxyl group and the relative configuration between it and the alkyl chain has been demonstrated to be capable of altering the film molecular packing. The formation of a hydrogen bond between the hydroxyl group and the carboxylic group has a stabilising effect for the aligned conformation between the two long chains.[11,12] Minnikin first proposed that, for the same reasons, the mycolic motif allows the formation of a closely packed structure among the mycolic acids in the cell wall of mycobacteria.[1,2] Moreover, the absolute configuration of these two chiral centres is necessary for efficient recognition by T cells and the generation of an immune response by the host organism against pathogenic mycobacteria;[13] the same is also true for the antitumour properties of mycolic acid derivatives.[14] This motif is therefore critical in defining some physical and biological properties of these particular fatty acids.

While different methods for the synthesis of single enantiomers of corynomycolic acids (**2**) have been proposed,[15–20] the preparation of the functionalised analogue (**3**) has only recently been reported (Scheme 2).[21] The potential of this compound in the preparation of enantiomerically pure mycolic acids (**1**) has also been illustrated. [21] However, the C-24 chain of (**3**) is not readily available in large quantities and had first to be prepared by coupling two smaller units.

2. Results and discussion

This paper proposes a new method for the synthesis of an alternative intermediate (**11**) for the preparation of any mycolic acid (Scheme 4) which allows any alkyl chain or labelled alkyl chain to be introduces at the β-position.

The β-hydroxy ester (**10**) was prepared following a similar method to that described for the preparation of *R*-α-lipoic acid (Scheme 3).[22] The *E*-α,β-unsaturated ester (**7**),

Keywords: Mycolic acid synthesis.
* Corresponding author. Tel.: +44 1248382374; fax: +44 1248370528; e-mail: chs028@bangor.ac.uk
† Current address: Department of Biochemistry, University of Pretoria, South Africa

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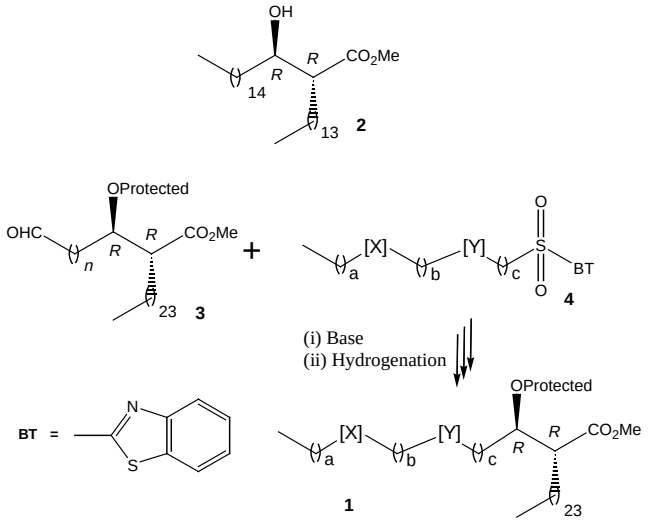
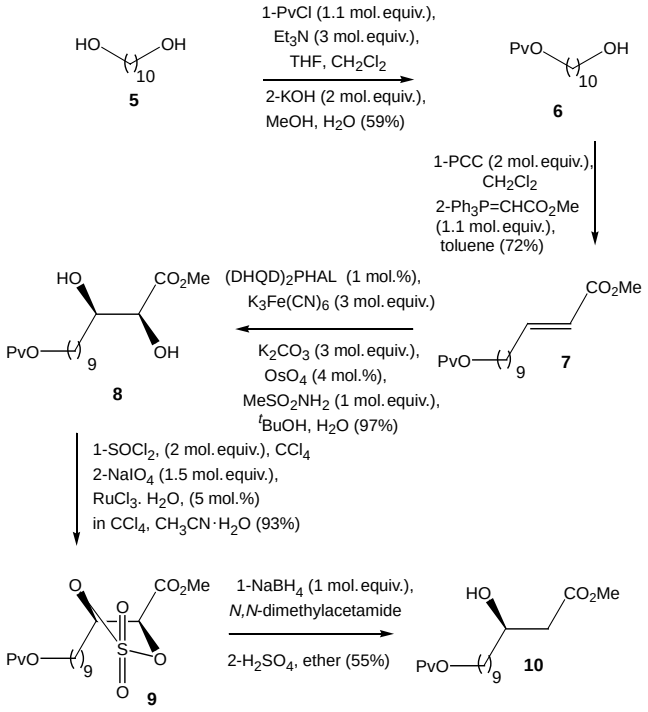
doi:10.1016/j.tet.2006.01.070



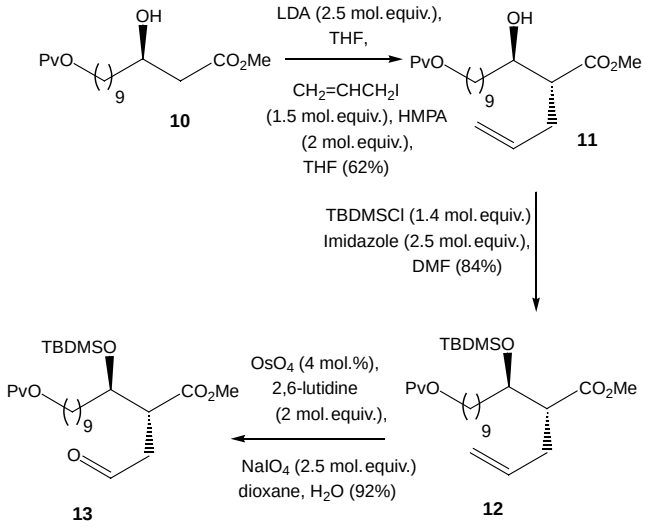
Scheme 2.



Scheme 3.

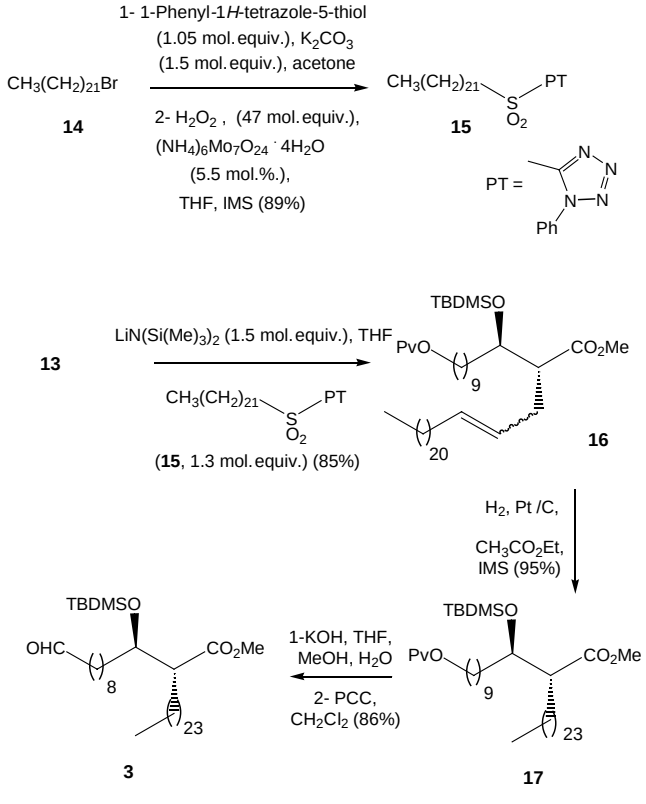
prepared from the diol (**5**), was transformed into the diol (**8**) using a Sharpless dihydroxylation.[23] The diol was then converted into the cyclic sulfate (**9**) via cyclic sulfite.[24] The sulfate (**9**) was regioselectively reduced and hydrolysed to give the (3*R*)-3-hydroxy ester (**10**).

Subsequently, a Fräter alkylation with allyl iodide introduced an allyl chain at the α-position to give (2*R*,3*R*)-2-allyl-3-hydroxy ester (**11**) (Scheme 4).[25,26] The use of such a reactive electrophile resulted in a much more reliable reaction than that previously described,[21] which used a very long chain alkyl iodide. It also gave twice the best yield achieved with a long chain.[21] Nonetheless, it was still very sensitive to the precise conditions and sometimes produced a minor isomer apparently derived by allylation on oxygen.[27]



Scheme 4.

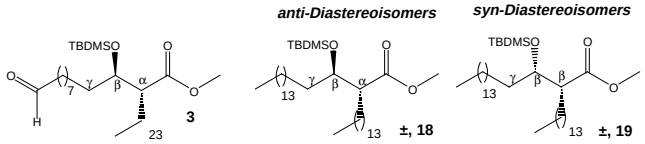
After having protected the secondary alcohol (**11**), an OsO_4–$NaIO_4$ oxidation transformed the alkene (**12**) into the corresponding aldehyde (**13**). The reaction was carried out in the presence of 2,6-lutidine, since it has been reported that this base suppresses side reactions, improving the cleavage of the olefin.[28] A Julia reaction with the 1*H*-tetrazole (**15**) (Scheme 5), followed by reduction of the unsaturated intermediate (**16**), allowed the formation of the desired long chain at the β-position.[29] Finally, deprotection of the terminal alcohol in the diol (**17**) and its oxidation gave the required compound (**3**).



Scheme 5.

Through NMR comparison of compound (**3**) with the *anti*- and *syn*-corynomycolate derivatives (**18** and **19**), prepared as described by Datta et al.,[30] it was possible to show that the α-alkyl-β-hydroxy groups were still in *anti*-configuration to each other (Table 1). Thus, the use of different bases in the process for the elongation of the α-branch did not produce epimerisation at the α-position via enol-formation, as has been described when other basic conditions were employed.[12,31]

Table 1.



Atom	β-Hydroxy-α-alkyl acid (**3**) (ppm)	*anti*-Diastereoisomer (**18**) (ppm)	*syn*-Diastereoisomer (**19**) (ppm)
C=O	175.0	175.1	175.2
Cα	51.6	51.6	51.5
Cβ	73.2	73.2	73.4
Cγ	33.7	33.7	34.8
Hα	2.53 (ddd, J=10.9, 7.0, 3.8 Hz)	2.53 (ddd, J=10.7, 7.0, 3.8 Hz)	2.48 (dt, J=9.8, 5.7 Hz)

This method was based on the formation of alkene (**12**), which was obtained with a good yield and could be readily transformed into any desired α-alkyl-β-hydroxy ester. Through formation of aldehydes (**13**) and (**3**) and their subsequent coupling with heterocyclic sulfones, every α-branch or meromycolate chain, including labelled compounds, can easily be introduced at different points of the synthesis. Therefore, this method could be used for the production not only of any natural mycolic acid as a single enantiomer, but also of intermediates useful for studies of the biosynthesis of these fatty acids.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich Chemical Co. Ltd, Lancaster Synthesis Ltd, or Avocado Chemical Co. Ltd. THF was distilled over sodium and benzophenone under nitrogen, while dichloromethane was distilled over calcium hydride. Petrol refers to the fraction bp 40–60 °C. Organic solutions were dried over anhydrous magnesium sulfate and solvents were removed at 14 mmHg; residual traces of solvent were finally removed at 0.1 mmHg. All glassware used in anhydrous reactions was dried for not less than 5 h in a 250 °C oven.

Column chromatography was conducted under medium pressure using silica gel (BDH, particle size 33–70 μm); TLC was carried out on pre-coated Kieselgel 60 F254 (Art. 5554; Merck) plates. Optical rotations were measured as solutions in chloroform of known concentration using a Polar 2001 automatic polarimeter. Infra-red spectra were recorded as KBr discs (solids) or thin films on NaCl windows or using a Perkin Elmer 1600 series FT-IR spectrometer. NMR spectra were recorded on a Bruker Advance 500 spectrometer as solutions in deuterated chloroform ($CDCl_3$) if not differently indicated. Chemical shifts are quoted in δ relative to chloroform (δ 7.27 ppm), and $CDCl_3$ (δ 77.0 ppm). Mass spectra were obtained using a Bruker MicroTOF time of flight mass spectrometer with ESI source. The accurate mass of compound (**3**) was obtained using a Bruker APEX IV FT ICR mass spectrometer with a 4.7 T magnet with ESI source.

3.1.1. 2,2-Dimethylpropionic acid 10-hydroxydecyl ester. Trimethylacetyl chloride (13.2 g, 110 mmol) was added to a solution of 1,10-decanediol (**5**, 17.4 g, 100 mmol) and triethylamine (30 g, 300 mmol) in dry THF (300 ml) and CH_2Cl_2 (400 ml) at 5 °C. The mixture was monitored by TLC and quenched with dil HCl (2 N, 200 ml) after 3 h. The product was extracted with dichloromethane (3×500 ml) and the combined organic layers were washed with water (100 ml), dried and the solvent evaporated. The product was then purified by chromatography eluting with petrol–ether (1/1) to give 2,2-dimethylpropionic acid 10-hydroxydecyl ester (**6**, 12.6 g, 49%), which has been partly described,[32] which showed δ_H: 4.01 (2H, t, J=6.6 Hz, CH_2OCO), 3.60 (2H, br t, J=6.6 Hz, CH_2OH), 2.2–2.0 (1H, m, OH), 1.7–1.6 (2H, m), 1.6–1.5 (2H, m), 1.4–1.2 (13H, m), 1.16 (9H, s (CH_3)$_3$); δ_C: 178.63 (C=O), 64.39 (CH$_2$OC=O), 62.80 (CH$_2$OH), 38.65 (C(CH$_3$)$_3$), 29.19 (CH$_2$), 28.96 (CH$_2$), 28.52 (CH$_2$), 27.24 (CH$_2$), 27.12 (C(CH$_3$)$_3$), 26.97 (CH$_2$); ν_{max}/cm^{-1}: 3393, 2929, 1732, 1458, 1285, 1158, 1056 (Found (M+H)$^+$: 259.2258; $C_{15}H_{31}O_3$ requires: 259.2268). The diprotected compound, 2,2-dimethylpropionic acid 10-(2,2-dimethylpropionyloxy)decyl ester (**20**, 6 g, 18%) was also obtained as an oil, which showed δ_H: 4.00 (4H, t, J=6.7 Hz, CH$_2$OCO), 1.7–1.5 (4H, m), 1.4–1.2 (12H, m), 1.14 (18H, s (CH_3)$_3$); δ_C: 178.50 (C=O), 64.33 (CH$_2$OC=O), 38.65 (C(CH$_3$)$_3$), 29.19 (CH$_2$), 28.96 (CH$_2$), 28.52 (CH$_2$), 27.24 (CH$_2$), 27.12 (C(CH$_3$)$_3$), 26.97 (CH$_2$); ν_{max}/cm^{-1}: 2930, 1730, 1480, 1284, 1155 (Found (M+H)$^+$: 343.2844; $C_{20}H_{39}O_4$ requires: 343.2843). This was added to a solution of KOH (1.9 g, 34 mmol) in methanol (100 ml) and water (5 ml). The mixture was refluxed for 1.5 h, monitoring by TLC, then evaporated. The residue was dissolved in water (50 ml) and extracted with dichloromethane (3×75 ml). The combined organic layers were dried and evaporated to give the crude product; chromatography eluting with 1:1 petrol and ether gave 2,2-dimethylpropionic acid 10-hydroxydecyl ester (**6**, 2.5 g, 57%) which showed the same NMR spectra as those above. Combining the two reactions, gave (**6**) (59%).

3.1.2. (*E*)-12-(2,2-Dimethylpropionyloxy)dodec-2-enoic acid methyl ester (7). The alcohol (**6**, 15 g, 58 mmol) in dichloromethane (40 ml) was added to PCC (25 g, 116 mmol) in dichloromethane (800 ml) and vigorously stirred for 2 h when TLC showed no starting material, then quenched by diluting with ether (500 ml) and filtered on a pad of Celite and silica. Evaporation and chromatography using petrol and ether (10:1) to give 2,2-dimethylpropionic acid 10-oxodecyl ester (**21**, 12.4 g, 84%) as an oil, δ_H: 9.73 (1H, br t, J=1.6 Hz, CHO), 4.04 (2H, t, J=6.4 Hz, CH_2OCO), 2.39 (2H, br td, J_1=1.6 Hz, J_2=ca. 7.3 Hz, CH_2CHO), 1.59 (2H, m), 1.4–1.2 (12H, m), 1.16 (9H, s (CH_3)$_3$); δ_C: 202.67 (CH=O), 178.52 (C=O), 64.31

(CH_2OCO), 43.80 ($CH_2CH{=}O$), 38.65 ($C(CH_3)_3$), 29.19 (CH_2), 29.17 (CH_2), 29.03 (CH_2), 28.52 (CH_2), 27.24 (CH_2), 27.12 ($C(CH_3)_3$), 25.78 (CH_2), 21.97 (CH_2); ν_{max}/cm^{-1}: 2928, 1728, 1458, 1285, 1155.

The aldehyde (**21**, 12.2 g, 48 mmol) was dissolved in toluene (20 ml) and then added to a suspension of (methoxycarbonylmethylene)triphenylphosphorane (18 g, 54 mmol) in toluene (100 ml). The mixture was stirred overnight, then the solvent was evaporated to give a white solid. This was refluxed for 1 h with petrol and ether (1:1, 300 ml) then filtered and the precipitate washed with the same solution (150 ml). The combined organic layers were dried and evaporated. Chromatography eluting with petrol and ether (10:1) gave (*E*)-12-(2,2-dimethylpropionyloxy)-dodec-2-enoic acid methyl ester (**7**, 12.8 g, 86%) as a pale yellow oil, which showed δ_H: 6.97 (1H, dt, $J_1=15.5$ Hz, $J_2=6.9$ Hz, C*H*=$CHCO_2Me$), 5.81 (1H, d, $J=15.5$ Hz, CH=C*H*CO_2Me), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.72 (3H, s, OCH_3), 2.25–2.15 (2H, m), 1.7–1.6 (2H, m), 1.5–1.4 (2H, m), 1.4–1.2 (10H, m), 1.19 (9H, s $(CH_3)_3$); δ_C: 178.61 (*C*=O), 167.16 (*C*=O), 149.71 (*C*H=$CHCO_2Me$), 120.83 (CH=*C*HCO_2Me), 64.39 (CH_2OCO), 51.33 (OCH3), 38.70 ($C(CH_3)_3$), 32.16 (CH_2), 29.34 (CH_2), 29.25 (CH_2), 29.14 (CH_2), 29.05 (CH_2), 28.58 (CH_2), 27.97 (CH_2), 27.18 ($C(CH_3)_3$), 25.86 (CH_2); ν_{max}/cm^{-1}: 2928, 2856, 1728, 1658, 1284, 1157 (Found $(M+H)^+$: 313.2369; $C_{18}H_{33}O_4$ requires: 313.2373).

3.1.3. (2*S*,3*R*)-12-(2,2-Dimethylpropionyloxy)-2,3-dihydroxydodecanoic acid methyl ester (8). The $(DHQD)_2PHAL$ ligand (313 mg, 0.4 mmol), $K_3Fe(CN)_6$ (39.6 g, 120 mmol), K_2CO_3 (16.8 g, 120 mmol) and a solution 2.5% of OsO_4 in *tert*-butanol (2.0 ml, 1.6 mmol) were dissolved in 1:1 water and *tert*-butanol (380 ml) at room temperature. $MeSO_2NH_2$ (3.8 g, 40 mmol) was added and the mixture, vigorously stirred, was cooled to 2.5 °C when the alkene (**7**, 12.5 g, 40 mmol) was added. The reaction was maintained at this temperature and monitored by TLC. After 8 h, it was worked up by addition of sodium sulfite (60 g, 48 mmol), then warmed to room temperature for 45 min and extracted with dichloromethane (3×500 ml); the organic layers were washed with 2 N KOH (100 ml), dried and concentrated to give an oil. Chromatography using 7:3 petrol and ether gave (2*S*,3*R*)-12-(2,2-dimethylpropionyloxy)-2,3-dihydroxydodecanoic acid methyl ester (**8**, 13.4 g, 97%) as an oil; δ_H: 4.10 (1H, dd, $J_1=5.3$ Hz, $J_2=1.9$ Hz, C*H*OH), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.95–3.85 (1H, m, C*H*OH), 3.83 (3H, s, OCH_3), 3.3–3.2 (1H, br s, O*H*), 2.1–2.0 (1H, br s, O*H*), 1.6–1.5 (4H, m), 1.5–1.2 (12H, m), 1.12 (9H, s $(CH_3)_3$); δ_C: 178.67 (*C*=O), 174.07 (*C*=O), 73.07 (*C*HOH), 72.45 (*C*HOH), 64.42 (CH_2OCO), 52.78 (OCH_3), 38.71 ($C(CH_3)_3$), 33.71 (CH_2), 29.38 (CH_2), 29.14 (CH_2), 28.57 (CH_2), 27.18 ($C(CH_3)_3$), 25.85 (CH_2), 25.65 (CH_2); ν_{max}/cm^{-1}: 3493, 2932, 2858, 1728, 1285, 1157; $[\alpha]_D^{19}$ +11.5 (*c* 1.0, $CHCl_3$), (lit. $[\alpha]_D^{24}$ +11.4 (*c* 0.57, $CHCl_3$) for (2*S*,3*R*)-2,3-dihydroxydecanoic acid ethyl ester)[33] (Found $(M+H)^+$: 347.2425; $C_{18}H_{35}O_6$ requires: 347.2428).

3.1.4. (4*S*,5*R*)-5-[9-(2,2-Dimethylpropionyloxy)nonyl]-2,2-dioxo-2λ^6-[1,3,2]dioxathiolane-4-carboxylic acid methyl ester (9). The dihydroxy ester (**8**, 5 g, 14.4 mmol) was dissolved in CCl_4 (20 ml). Thionyl chloride (2.0 ml, 27.4 mmol) was added and the mixture was vigorously refluxed for 2 h. After cooling, the solution was diluted with CH_3CN (20 ml) and ruthenium trichloride hydrate (150 mg, 0.72 mmol) and $NaIO_4$ (4.7 g, 21.7 mmol) were added followed by water (30 ml). The mixture was stirred at room temperature for 1 h then diluted with ether (400 ml). The water layer was extracted with ether (2×50 ml). The combined organic layers were washed with water (30 ml), satd aq sodium bicarbonate (30 ml) and brine (30 ml) and dried. Evaporation and chromatography (7:3 petrol and ether) gave (4*S*,5*R*)-5-[9-(2,2-dimethylpropionyloxy)nonyl]-2,2-dioxo-2λ^6-[1,3,2]-dioxathiolane-4-carboxylic acid methyl ester (**9**, 5.5 g, 93%) as an oil; δ_H: 5.0–4.8 (2H, m, C*H*OSO_2OCH, including br d, 4.88, $J=7.2$ Hz), 4.02 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.87 (3H, s, OCH_3), 2.0–1.9 (2H, m), 1.65–1.4 (4H, m), 1.4–1.2 (10H, m), 1.17 (9H, s, $(CH_3)_3$); δ_C: 178.51 (*C*=O), 165.25 (C=O), 84.05 (*C*HOCO), 79.76 (*C*HOCO), 64.25 (CH_2OCO), 53.57 (OCH_3), 38.61 ($C(CH_3)_3$), 32.84 (CH_2), 29.14 (CH_2), 29.01 (CH_2), 28.98 (CH_2), 28.69 (CH_2), 28.46 (CH_2), 27.09 ($C(CH_3)_3$), 25.73 (CH_2), 24.66 (CH_2); ν_{max}/cm^{-1}: 2932, 2858, 1775, 1725, 1399, 1287, 1211, 1160, 1034; $[\alpha]_D^{19}$ +33.7 (*c* 1.3, $CHCl_3$) (Found $(M+H)^+$: 409.1889; $C_{18}H_{33}O_8S$ requires: 409.1891).

3.1.5. (*R*)-12-(2,2-Dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (10). The cyclic sulfate (**9**, 2.04 g, 5 mmol) was dissolved in *N*,*N*-dimethylacetamide (25 ml) and $NaBH_4$ (190 mg, 5 mmol) was slowly added at 0 °C, stirred at 25 °C for 1 h, then concentrated by distillation under high vacuum. Ether (25 ml) and 10% aq H_2SO_4 (25 ml) were slowly added to the residue and stirred vigorously for 8 h. The water layer was extracted with ether (4×75 ml). The combined organic layers were washed with water and brine, dried and concentrated. Chromatography (7:3 petrol and ether) gave (*R*)-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (**10**, 900 mg, 55%) as an oil; δ_H: 4.00 (2H, t, $J=6.7$ Hz, CH_2OCO), 3.96 (1H, m, C*H*OH), 3.67 (3H, s, $COOCH_3$), 3.1–2.9 (1H, br s, O*H*), 2.47 (1H, dd, $J_1=16.1$ Hz, $J_2=3.2$ Hz, $COCH_2CHOH$), 2.38 (1H, dd, $J_1=16.1$ Hz, $J_2=9.1$ Hz, $COCH_2CHOH$), 1.65–1.55 (2H, m), 1.55–1.35 (3H, m), 1.4–1.2 (11H, m) 1.15 (9H, s, $(CH_3)_3$); δ_C: 178.58 (*C*=O), 173.36 (*C*=O), 67.92 (*C*HOH), 64.36 (CH_2OCO), 51.62 (OCH_3), 41.10 ($CHOHCH_2CO$), 38.63 ($C(CH_3)_3$), 36.46 (CH_2), 30.22 (CH_2), 29.37 (CH_2), 29.35 (CH_2), 29.32 (CH_2), 29.09 (CH_2), 28.50 (CH_2), 27.11 ($C(CH_3)_3$), 25.79 (CH_2), 25.36 (CH_2); ν_{max}/cm^{-1}: 3509, 2930, 2856, 1729, 1725, 1286, 1160; $[\alpha]_D^{19}$ −11.6 (*c* 1.1 in $CHCl_3$) (lit. $[\alpha]_D^{20}$ −13.8 (*c* 1.48 in $CHCl_3$) for (*R*)-3-hydroxyhexadecanoic acid methyl ester)[34] (Found $(M+H)^+$: 331.2472; $C_{18}H_{35}O_5$ requires: 331.2479).

3.1.6. (2*R*,3*R*)-2-Allyl-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (11). The ester (**10**, 330 mg, 1 mmol) in THF (5 ml) was added to a stirred solution of LDA (2.3 ml, 2.5 mmol, 1.1 M in hexanes) in THF (5 ml) at −55 °C. The temperature was slowly increased to −15 °C for 3.5 h, then reduced to −25 °C and 1-iodopropene (252 mg; 1.5 mmol) and HMPA (360 mg; 2 mmol) in THF (6 ml) was added dropwise at below −20 ° C, stirred at room temperature for 18 h, then

quenched with satd aq ammonium chloride (10 ml) and extracted with dichloromethane (3×25 ml). The combined organic layers were washed with water (10 ml), dried and evaporated. Chromatography (9:1 petrol and ethyl acetate) gave (2*R*,3*R*)-2-allyl-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (**11**, 230 mg; 62%)[27] as an oil, which showed δ_H: 5.72 (1H, m, C*H*=CH$_2$), 5.05 (2H, m, CH=C*H*$_2$), 4.03 (2H, t, J=6.6 Hz, C*H*$_2$OCO), 3.69 (4H, m, including s for COOC*H*$_3$), 2.6–2.5 (2H, m), 2.5–2.4 (2H, m), 1.4–1.2 (16H, m) 1.18 (9H, s, (C*H*$_3$)$_3$); δ_C: 178.44 (*C*=O), 175.10 (*C*=O), 134.85 (*C*H$_2$=CH), 116.93 (CH$_2$=*C*H), 71.61 (*C*HOH), 64.28 (*C*H$_2$OCO), 51.36 (O*C*H$_3$), 50.59 (CHOH*C*HCO), 38.58 (*C*(CH$_3$)$_3$), 35.32 (*C*H$_2$), 33.56 (*C*H$_2$), 29.34 (*C*H$_2$), 29.31 (*C*H$_2$), 29.28 (*C*H$_2$), 29.05 (*C*H$_2$), 28.47 (*C*H$_2$), 27.07 (C(*C*H$_3$)$_3$), 25.76 (*C*H$_2$), 25.56 (*C*H$_2$); ν_{max}/cm^{-1}: 3518, 2929, 2855, 1728, 1642, 1285, 1162; $[\alpha]_D^{19}$ +3.1 (*c* 1.1 in CHCl$_3$) (lit. $[\alpha]_D^{19}$ −11.5 (*c* 3.3 in CHCl$_3$) for (2*S*,3*S*)-2-allyl-3-hydroxypentanedioic acid dimethyl ester)[35] (Found (M+K)$^+$: 409.2368; $C_{21}H_{38}KO_5$ requires: 409.2351).

3.1.7. (2*R*,3*R*)-2-Allyl-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)dodecanoic acid methyl ester (12). Imidazole (465 mg, 6.8 mmol) was added to the alcohol (**11**, 1 g; 2.7 mmol) in dry DMF (9 ml), followed by *tert*-butyldimethylsilylchloride (530 mg, 3.5 mmol), then stirred at 40 °C overnight, when TLC showed no starting material. After concentrating, water was added and the product was extracted with dichloromethane (3× 50 ml). The combined organic layers were washed with water (2×15 ml), dried and evaporated. Chromatography eluting with 9:1 petrol and ether gave (2*R*,3*R*)-2-allyl-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)dodecanoic acid methyl ester (**12**, 1.1 g, 84%) as an oil; δ_H: 5.72 (1H, ddt, J_1=17.0 Hz, J_2=10.0 Hz, J_3=7.0 Hz, C*H*=CH$_2$), 5.03 (1H, dd, J_1=17.0 Hz, J_2=1.6 Hz, CH=C*H*$_2$), 4.98 (1H, m, CH=C*H*$_2$), 4.04 (2H, t, J=6.6 Hz, C*H*$_2$OCO), 3.93 (1H, m, C*H*OSi), 3.65 (3H, s, COOC*H*$_3$), 2.61 (1H, m, CHOH*C*HCO), 2.37 (2H, m, C*H*$_2$CH=CH$_2$), 1.7–1.2 (16H, m), 1.19 (9H, s, (COC*H*$_3$)$_3$), 0.87 (9H, s, (CC*H*$_3$)$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$); δ_C: 178.60 (*C*=O), 175.02 (*C*=O), 135.95 (*C*H$_2$=CH), 116.29 (CH$_2$=*C*H), 72.78 (*C*HOSi), 64.40 (*C*H$_2$OCO), 51.35 (*C*HCO), 51.26 (O*C*H$_3$), 38.71 (*C*(CH$_3$)$_3$), 33.64 (*C*H$_2$), 31.57 (*C*H$_2$), 29.70 (*C*H$_2$), 29.43 (*C*H$_2$), 29.41 (*C*H$_2$), 29.18 (*C*H$_2$), 28.61 (*C*H$_2$), 27.19 (C(*C*H$_3$)$_3$), 25.81 (C(*C*H$_3$)$_3$), 25.73 (*C*H$_2$), 25.68 (*C*H$_2$), 24.13 (*C*H$_2$), 17.97 (Si*C*(CH$_3$)$_3$), −4.41 (Si*C*H$_3$), −4.90 (Si*C*H$_3$); ν_{max}/cm^{-1}: 3078, 2929, 2856, 1731, 1642, 1156; $[\alpha]_D^{20}$ −13.3 (*c* 1.3 in CHCl$_3$) (Found (M+K)$^+$: 523.3229; $C_{27}H_{52}KO_5Si$ requires: 523.3216).

3.1.8. 5-Docosylsulfanyl-1-phenyl-1*H*-tetrazole (22). Potassium carbonate (3 g, 21.2 mmol) was added to a solution of 1-bromodocosane (**14**, 5.5 g, 14.1 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.6 g, 14.8 mmol) in acetone (500 ml). The mixture was vigorously stirred and refluxed at 60 °C overnight. The solvent was evaporated and the residue was dissolved in water (300 ml) and extracted with dichloromethane (3×300 ml). The combined organic layers were dried and evaporated. Recrystallisation from acetone (100 ml) and methanol (200 ml) gave 5-docosylsulfanyl-1-phenyl-1*H*-tetrazole (**22**, 6.5 g, 96%) as a colourless solid, mp 70–72 °C, which showed δ_H: 7.55–7.45 (5H, m, aromatic), 3.40 (2H, t, J=7.2 Hz, C*H*$_2$S), 1.82 (2H, m), 1.6 (4H, m), 1.45 (2H, m), 1.35–1.25 (32H, br m), 0.89 (3H, t, J=6.6 Hz, C*H*$_3$); δ_C: 154.33 (C=N heterocyclic), 133.79 (C–N aromatic), 130.05 (CH aromatic), 129.75 (CH aromatic), 123.87 (CH aromatic), 33.40 (*C*H$_2$S), 31.92 (*C*H$_2$), 29.69 (*C*H$_2$), 29.65 (*C*H$_2$), 29.61 (*C*H$_2$), 29.54 (*C*H$_2$), 29.43 (*C*H$_2$), 29.35 (*C*H$_2$), 29.08 (*C*H$_2$), 29.02 (*C*H$_2$), 28.64 (*C*H$_2$), 22.68 (*C*H$_2$), 14.10 (*C*H$_3$); ν_{max}/cm^{-1}; 3017, 2925, 2853, 1598, 1500 (Found (M+H)$^+$: 487.3837; $C_{29}H_{51}N_4S^+$ requires: 487.3829).

3.1.9. 5-(Docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (15). Ammonium molybdate tetrahydrate (8 g, 0.70 mmol) was dissolved in stages in aq H_2O_2 (31 ml, 300 mmol, 35% w/w) and added slowly the sulfide (**22**, 6.2 g, 12.7 mmol) in IMS and THF (3:5, 400 ml). After stirring at room temperature for 2 h, ammonium molybdate tetrahydrate (8 g, 0.70 mmol) in aq H_2O_2 (31 ml, 300 mmol, 35% w/w) was added and stirred overnight. After partial concentration, the reaction was quenched with water (150 ml) and extracted with dichloromethane (3×150 ml). The combined organic layers were dried and evaporated. Chromatography eluting with 8:1 petrol and ether gave 5-(docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**15**, 6.1 g, 93%) as a colourless solid, mp 56–59 °C, which showed δ_H: 7.70 (2H, m, aromatic), 7.61 (3H, m, aromatic), 3.72 (2H, m, C*H*$_2$S), 1.95 (2H, m, C*H*$_2$CH$_2$S), 1.50 (2H, m), 1.4–1.2 (36H, m), 0.89 (3H, t, J=7.2 Hz, C*H*$_3$); δ_C: 153.50 (C=N heterocyclic), 133.06 (C–N aromatic), 131.39 (CH aromatic), 129.67 (CH aromatic), 125.06 (CH aromatic), 56.01 (*C*H$_2$S), 31.90 (*C*H$_2$), 29.68 (*C*H$_2$), 29.64 (*C*H$_2$), 29.61 (*C*H$_2$), 29.54 (*C*H$_2$), 29.44 (*C*H$_2$), 29.33 (*C*H$_2$), 29.17 (*C*H$_2$), 28.87 (*C*H$_2$), 28.12 (*C*H$_2$), 22.667 (*C*H$_2$), 21.91 (*C*H$_2$), 14.08 (*C*H$_3$); ν_{max}/cm^{-1}: 3018, 2926, 2854, 1498, 1342, 1152 (Found (M+H)$^+$: 519.3706; $C_{29}H_{51}N_4O_2S$ requires: 519.3727).

3.1.10. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)decyl]-hexacos-4-enoic acid methyl ester (16). To a solution of alkene (**12**, 150 mg, 0.3 mmol) in dioxane–water (3/1, 8 ml) were added 2,6-lutidine (66 mg, 0.6 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 62 mg, 75 μl, 0.006 mmol), and $NaIO_4$ (260 mg, 1.2 mmol). After 2 h stirring at 25 °C, the reaction was complete by TLC; water (10 ml) and dichloromethane (20 ml) were added. The water layer was extracted by dichloromethane (3×10 ml). The combined organic layers were washed with brine (10 ml), dried and concentrated. Chromatography eluting with 9:1 ether/ petrol gave (2*R*,3*R*)-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)-2-(2-oxoethyl)dodecanoic acid methyl ester (**13**, 130 mg, 92%) as a colourless oil, which was immediately used without complete characterization (δ_H: 9.79 (1H, m, C*H*=O), 4.05–4.00 (3H, including 4.02, t, J=6.7 Hz, C*H*$_2$OCO), 3.65 (3H, s, COOC*H*$_3$), 3.18 (1H, dt, J_1=10.4 Hz, J_2=3.7 Hz, *C*HCO), 2.94 (1H, dd, J_1=18 Hz, J_2=10.4 Hz, C*H*$_2$CH=O), 2.65 (1H, dd, J_1=18 Hz, J_2=3.4 Hz, C*H*$_2$CH=O), 1.7–1.2 (16H, m), 1.17 (9H, s, (COC*H*$_3$)$_3$), 0.85 (9H, s, (CC*H*$_3$)$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$)).

Lithium bis(trimethylsilyl)amide (0.4 mmol, 0.4 ml, 1 M, in hexanes) was added at −10 °C to a solution of the aldehyde

(**13**, 130 mg, 0.28 mmol) and the sulfone (**14**, 180 mg, 0.36 mmol) in dry THF (10 ml) under nitrogen. The reaction was stirred at room temperature for 24 h then quenched with satd aq ammonium chloride (10 ml) and extracted with dichloromethane (3×40 ml). The combined organic layers were dried and concentrated. Chromatography eluting with 10:0.5 petrol and ether gave (*E*,*Z*)-(*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)-decyl]hexacos-4-enoic acid methyl ester ((*E*)/(*Z*), 2.7:1) (**16**, 185 mg, 85%) as an oil, which showed δ_H: 5.42 (1H, m, C*H*=CH), 5.30 (1H, m, C*H*=CH), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.92 (1H, m, C*H*OSi), 3.64 (3H, s, OCH_3), 2.57 (1H, m, *C*HCO), 2.4–2.1 (2H, m), 2.1–1.9 (2H, m), 1.8–1.6 (2H, m), 1.8–1.3 (55H, m), 1.19 (9H, s, (COCH_3)$_3$), 0.87 (9H, s, (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 178.68 (*C*=O), 174.44 (*C*=O, Z), 174.37 (*C*=O, E), 132.80 (*C*H=CH, E), 131.92 (*C*H=CH, Z), 126.88 (CH=*C*H, E), 126.25 (*C*H=CH, Z), 72.96 (*C*HOSi, Z), 72.83 (*C*HOSi, E), 64.46 (*C*H_2OCO), 51.85 (*C*HCO, E), 51.75 (*C*HCO, Z), 51.32 (O*C*H$_3$, Z), 51.21 (O*C*H$_3$, E), 38.74 (*C*(CH$_3$)$_3$), 33.69 (*C*H$_2$), 32.55 (*C*H$_2$), 31.94 (*C*H$_2$), 30.71 (*C*H$_2$), 29.72 (*C*H$_2$), 29.67 (*C*H$_2$), 29.55 (*C*H$_2$), 29.51 (*C*H$_2$), 29.50 (*C*H$_2$), 29.47 (*C*H$_2$), 29.38 (*C*H$_2$), 29.23 (*C*H$_2$), 29.12 (*C*H$_2$), 27.22 (C(*C*H$_3$)$_3$), 25.91 (*C*H$_2$), 25.75 (C(*C*H$_3$)$_3$), 23.92 (*C*H$_2$), 22.69 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.11 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.91 (Si*C*H$_3$); ν_{max}/cm^{-1}: 2922, 2853, 1732, 1464, 1157; $[\alpha]_D^{20}$ −5.9 (*c* 1.1 in CHCl$_3$) (Found (M+K)$^+$: 817.6502; $C_{48}H_{94}KO_5Si$ requires: 817.6502).

3.1.11. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)-decyl]-hexacosanoic acid methyl ester (17). The alkene (**16**, 550 mg, 0.7 mmol) was dissolved IMS and ethyl acetate (1:3, 32 ml) then Pd on C (10%, 100 mg) was added. The mixture was stirred under hydrogen, until no more was absorbed, then diluted with diethyl ether (150 ml) and filtered on a pad of Celite. The filtrate was evaporated; chromatography eluting with petrol and ether (9:1) gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)decyl]hexacosanoic acid methyl ester (**17**, 520 mg, 95%) as an oil, which showed δ_H: 4.05 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.90 (1H, m, C*H*OSi), 3.66 (3H, s, OCH_3), 2.53 (1H, ddd, $J_1=11$ Hz, $J_2=7.0$ Hz, $J_3=3.5$ Hz, *C*HCO), 1.6–1.2 (62H, m), 1.21 (9H, s, (COCH_3)$_3$), 0.87 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 178.64 (*C*=O), 174.10 (*C*=O), 73.20 (*C*HOSi), 64.44 (*C*H$_2$OCO), 51.60 (*C*HCO), 51.21 (O*C*H$_3$), 38.72 (*C*(CH$_3$)$_3$), 33.67 (*C*H$_2$), 31.92 (*C*H$_2$), 29.80 (*C*H$_2$), 29.70 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.48 (*C*H$_2$), 29.45 (*C*H$_2$), 29.35 (*C*H$_2$), 29.20 (*C*H$_2$), 29.05 (*C*H$_2$), 28.61 (*C*H$_2$), 27.85 (*C*H$_2$), 27.65 (*C*H$_2$), 27.21 (C(*C*H$_3$)$_3$), 25.91 (*C*H$_2$), 25.76 (C(*C*H$_3$)$_3$), 23.92 (*C*H$_2$), 22.69 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.11 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.93 (Si*C*H$_3$); ν_{max}/cm^{-1}: 2923, 2852, 1732, 1458, 1155; $[\alpha]_D^{23}$ −4.7 (*c* 1.1 in CHCl$_3$) (lit. $[\alpha]_D^{20}$ −35.1 (*c* 1.34 in CHCl$_3$) for methyl (3*R*)-*tert*-butyldimethylsilyloxy-(2*R*)-methylpentanoate)[36] (Found (M+K)$^+$: 819.6649; $C_{48}H_{96}KO_5Si$ requires: 819.6659).

3.1.12. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-hydroxydecyl]hexacosanoic acid methyl ester (23). The pivaloyl-protected alcohol (**17**, 200 mg, 0.26 mmol) was added to potassium hydroxide (215 mg, 3.8 mmol) in THF, MeOH and H_2O (21 ml, 10:10:1). The mixture was refluxed at 70 °C and monitored by TLC. After 4 h, TLC showed no starting material and the reaction was quenched with water and extracted with ethyl acetate (3×100 ml), dried and concentrated. Chromatography eluting with 1:1 petrol and ether gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-hydroxydecyl]hexacosanoic acid methyl ester (**23**, 170 mg, 94%) as an oil, which showed δ_H: 3.90 (1H, m, C*H*OSi), 3.66 (5H, m, HOCH_2 and OCH_3), 2.53 (1H, ddd, $J_1=10.7$ Hz, $J_2=7.0$ Hz, $J_3=3.8$ Hz, *C*HCO), 1.6–1.2 (63H, m), 0.88 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 175.18 (*C*=O), 73.25 (*C*HOSi), 63.09 (*C*H$_2$OH), 51.66 (*C*HCO), 51.18 (O*C*H$_3$), 33.73 (*C*H$_2$), 32.83 (*C*H$_2$), 31.92 (*C*H$_2$), 29.81 (*C*H$_2$), 29.70 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.52 (*C*H$_2$), 29.49 (*C*H$_2$), 29.45 (*C*H$_2$), 29.39 (*C*H$_2$), 29.35 (*C*H$_2$), 27.86 (*C*H$_2$), 27.47 (*C*H$_2$), 25.78 (C(*C*H$_3$)$_3$), 23.87 (*C*H$_2$), 22.67 (*C*H$_2$), 22.67 (*C*H$_2$), 17.99 (Si*C*(CH$_3$)$_3$), 14.07 (*C*H$_3$), −4.37 (Si*C*H$_3$), −4.90 (Si*C*H$_3$). ν_{max}/cm^{-1}: 3358, 2923, 2859, 1738, 1465; $[\alpha]_D^{22}$ −4.0 (*c* 1.2 in CHCl$_3$) (Found (M+H)$^+$: 697.6542; $C_{43}H_{89}O_4Si$ requires: 697.6525).

3.1.13. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-oxodecyl]hexacosanoic acid methyl ester (3). The alcohol (**23**, 100 mg, 0.14 mmol) in dichloromethane (5 ml) was added to PCC (80 mg, 0.36 mmol) in dichloromethane (30 ml). The mixture was vigorously stirred for 2 h when TLC showed no starting material, then diluted with ether (50 ml) and filtered on a pad of Celite and silica. The solvent was evaporated; chromatography (1:1 petrol/ether) gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-oxo-decyl]-hexacosanoic acid methyl ester (**3**, 90 mg, 91%) as an oil, δ_H: 9.77 (1H, t, $J=1.9$ Hz, C*H*O), 3.9 (1H, m, C*H*OSi), 3.66 (3H, s, OCH_3), 2.53 (1H, ddd, $J_1=10.9$ Hz, $J_2=7.0$ Hz, $J_3=3.8$ Hz, *C*HCO), 2.39 (2H, br dt, $J_1=7.5$ Hz, $J_2=1.9$ Hz, CH_2CHO), 1.7–1.2 (60H, m), 0.88 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 202.64 (*C*H=O), 175.00 (*C*=O), 73.23 (*C*HOSi), 51.65 (*C*HCO), 51.17 (O*C*H$_3$), 43.89 (*C*H$_2$CH=O), 33.71 (*C*H$_2$), 31.92 (*C*H$_2$), 29.75 (*C*H$_2$), 29.69 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.44 (*C*H$_2$), 29.34 (*C*H$_2$), 29.28 (*C*H$_2$), 29.14 (*C*H$_2$), 27.86 (*C*H$_2$), 27.46 (*C*H$_2$), 25.76 (C(*C*H$_3$)$_3$), 23.85 (*C*H$_2$), 22.67 (*C*H$_2$), 22.10 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.07 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.90 (Si*C*H$_3$). ν_{max}/cm^{-1}: 2924, 2953, 2710, 1738, 1464; $[\alpha]_D^{25}$ −6.4 (*c* 1.4 in CHCl$_3$) (Found (M+H)$^+$: 695.63651; $C_{43}H_{87}O_4Si$ requires: 695.63681).

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Application of modified Pictet–Spengler reaction for the synthesis of thiazolo- and pyrazolo-quinolines☆

Srinivas Duggineni, Devesh Sawant, Biswajit Saha and Bijoy Kundu*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received 11 November 2005; revised 27 December 2005; accepted 19 January 2006

Available online 17 February 2006

Abstract—Two new thiazole and pyrazole-based arylamine substrate have been used for the Pictet–Spengler reaction. This is in contrast to the traditionally used indole/imidazole-based aliphatic amine substrates that has remained in use for the last ~100 years. The condensation of both the substrates with a variety of aldehydes in the presence of 2% TFA–DCM at 0° for 30 min or *p*TsOH in toluene at reflux led to the synthesis of thiazoloquinolines and pyrazoloquinolines, respectively. Unlike aliphatic amine substrates, our substrates readily underwent Pictet–Spengler cyclization even with aldehydes having electron donating group. The studies are based on a new concept proposed by us that arylamines linked to an activated heterocyclic ring can lead to a variety of second-generation substrates for the Pictet–Spengler cyclization. Our studies open up new avenues for the application of Pictet–Spengler reaction beyond syntheses of the tetrahydroisoquinolines and tetrahydro-β-carbolines.
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1. Introduction

For the last ~100 years, the Pictet–Spengler reaction[1] has remained as one of the most widely used methods for the syntheses of isoquinolines and β-carbolines via C–C bond formation.[2] In general, it is a two-step method and involves acid catalyzed condensation of an aliphatic amine attached to a sufficiently reactive aromatic nucleus with aldehydes.[3] In the first step an imine is formed, which may be activated by acids and in the second step *endo* cyclization is affected between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion resulting in a *N*-heterocyclic ring via a new C–C bond. Over the years, several groups have studied the detail mechanistic aspects of this reaction and have developed a number of diastereo- and enantio-selective methods for the Pictet–Spengler cyclization.[4] It is interesting to note that the method continues to be a significant focus of research as chemists continue to improve upon the methodology by applying new reaction conditions including asymmetric catalysis of the *N*-acyliminium Pictet–Spengler reaction.[5] However, despite being one of the most powerful method, the strategy has remained unchanged ever since its inception and its use has been limited to only three amine substrates: Trp/tryptamine, His/histamine or dopamine/tyramine, thereby invariably resulting in the formation of heterocycles based on either tetrahydro-β-carbolines/tetrahydroimidazopyridines or tetrahydroisoquinolines.[4] Therefore, the challenge of applying the Pictet–Spengler reaction beyond syntheses of isoquinolines and β-carbolines appears to be associated with the limited availability of amine substrates.

Recently, we described[6] a new strategy for the Pictet–Spengler reaction by using arylamines linked to the *N*-1 of the imidazole (**1** and **2**; Fig. 1) as an alternative substrates instead of traditionally used aliphatic amines linked to the C-3 of the imidazole. We argued that the iminium ion derived from an arylamine would facilitate C–C bond formation better than an aliphatic amine since enhancement of the electrophilic nature of the iminium intermediate is known to be the driving force for the cyclization.[7]

Though the use of substrates **1** and **2** led to the synthesis of *N*-rich heterocycles: imidazoquinoxalines and an unusual seven membered ring triazabenzoazulenes, both of them were derived from the imidazole, an activated aromatic nucleus used traditionally in the Pictet–Spengler reaction. We envisaged that by applying our new concept of 'arylamines linked to an activated heterocyclic ring', a variety of structurally diverse substrates can be designed for the Pictet–Spengler reaction, which in turn may lead to novel benzoannelated heterosystems devoid of any stereochemical issues traditionally associated with a typical

☆ CDRI communication no. 6785.

Keywords: Thiazoloquinoline; Pyrazoloquinoline; Pictet–Spengler reaction; C–C bond formation.
* Corresponding author. Tel.: +91 522 2262411 18x4383; fax: +91 522 2623405; e-mail: bijoy_kundu@yahoo.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.063

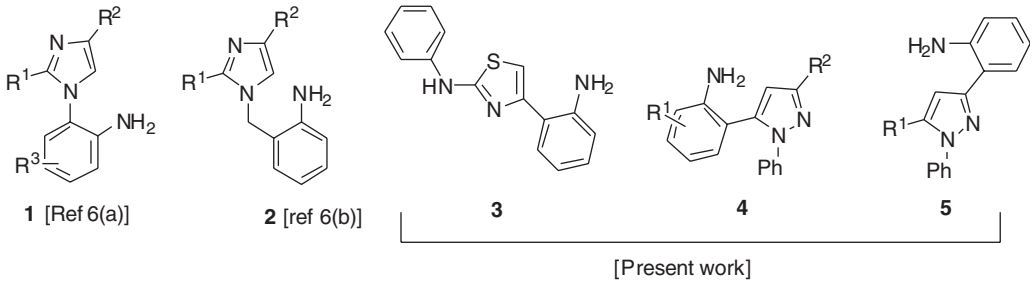


Figure 1. Second generation substrates for the Pictet–Spengler reaction.

Pictet–Spengler reaction (Fig. 2). While the manuscript was under preparation, Pictet–Spengler reaction was recently demonstrated on heteroaryl amines linked to an activated aromatic ring as substrates, which is also in accordance to our modified strategy.[8] In order to test the viability and generality of our concept, we searched for an entirely new generation of substrates having aryl amines linked to the C of an activated heterocyclic ring other than the traditionally used indoles and imidazoles. In the first instance, we directed our efforts towards the activated heterocycles analogous to imidazole. We envisaged that since imidazole falls under the class of azoles, an arylamine originating from the azoles other than the imidazole could be equally active to facilitate the Pictet–Spengler cyclization. After screening various azoles, our choice ultimately fell for thiazoles and pyrazoles as an activated heterocyclic rings, which are common substructures present in many natural and medicinal compounds. We proposed to link the arylamine through one of the C in the thiazole and pyrazole ring instead of the nitrogen (as in substrates **1** and **2**) in a manner to facilitate the Pictet–Spengler cyclization. In order to select the carbon in both the rings for linking the arylamine, we analyzed the electrophilic substitution patterns in azoles.

The multiply bonded nitrogen atom present in azoles, is generally known to have differential deactivating affects on the carbon atoms in the ring.[9] The α- and γ-positions to the multiply bonded *N*-atom are deactivated towards electrophilic attack whereas the β-carbon is the least deactivated and is therefore prone towards electrophilic substitution. Thus, the C-4 position in the pyrazole while the C-5 position in the thiazole being β to the multiply bonded nitrogen atom are the positions prone to electrophilic substitution (Fig. 3).

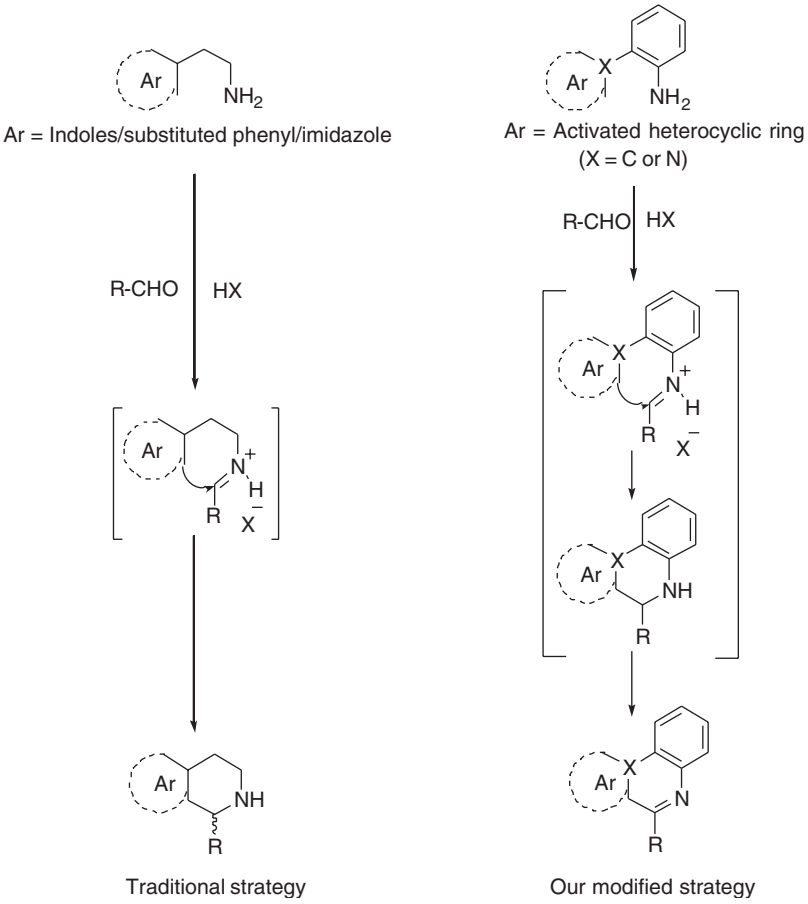


Figure 2. Traditional and modified strategies for the Pictet–Spengler reaction.

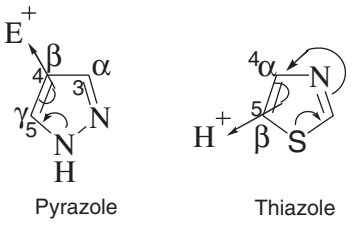


Figure 3. Pattern of electrophilic substitution in pyrazole and thiazole.

Based on these facts, we envisaged that an aryl amine originating from the γ-carbon (C-5) in the pyrazole and α-carbon (C-4) in the thiazole, which are adjacent to the β-carbon in both the azoles, might act as novel substrates for the Pictet–Spengler cyclization. Keeping these structural requirements in mind, we next analyzed the structures and synthetic feasibilities of a variety of thiazole and pyrazole based compounds from the literature, which led to the identification of [4-(2-amino-phenyl)-thiazol-2-yl]-phenyl-amine (**3**) and 2-(2,5-diphenyl-2*H*-pyrazol-3-yl)-phenyl-amine (**4**) as probable substrates for the Pictet–Spengler reaction (Fig. 1). In the thiazole-based substrate **3**, an aryl amine has been allowed to originate from the C-4 position; the C-2 position has been derivatized for introducing diversity while the C-5 has been kept devoid of any substitution so as to facilitate *endo* cyclization. Similarly in the pyrazole-based substrate **4**, an aryl amine has been allowed to originate from the C-5 position, the C-3 has been derivatized for introducing diversity while the C-4 has been kept free to facilitate *endo* cyclization. Interestingly, for pyrazoles, we had two options available for the attachment of aryl amine since the C-4 involved in the cyclization is flanked between the C-5 and C-3. The arylamine can be linked to either of these two (Fig. 1) positions resulting in substrates **4** with two-point diversity and **5** with single diversity, respectively. However, in view of the higher chemical diversity, we restricted ourself to the substrate **4** since the synthesis for substrate **5** involves use of *o*-nitroacetophenone for which only a limited commercial diversity is available. In contrast, the synthesis of **4** involves use of *o*-nitrobenzaldehydes for which a plenty of diversity is available commercially. A careful survey of the literature for substrates **3** and **4** revealed, a single reference wherein an unsuccessful attempt[10] was made to synthesize thiazoloquinolines from the thiazole-based substrate **3** using Bischler–Napieralski reaction.

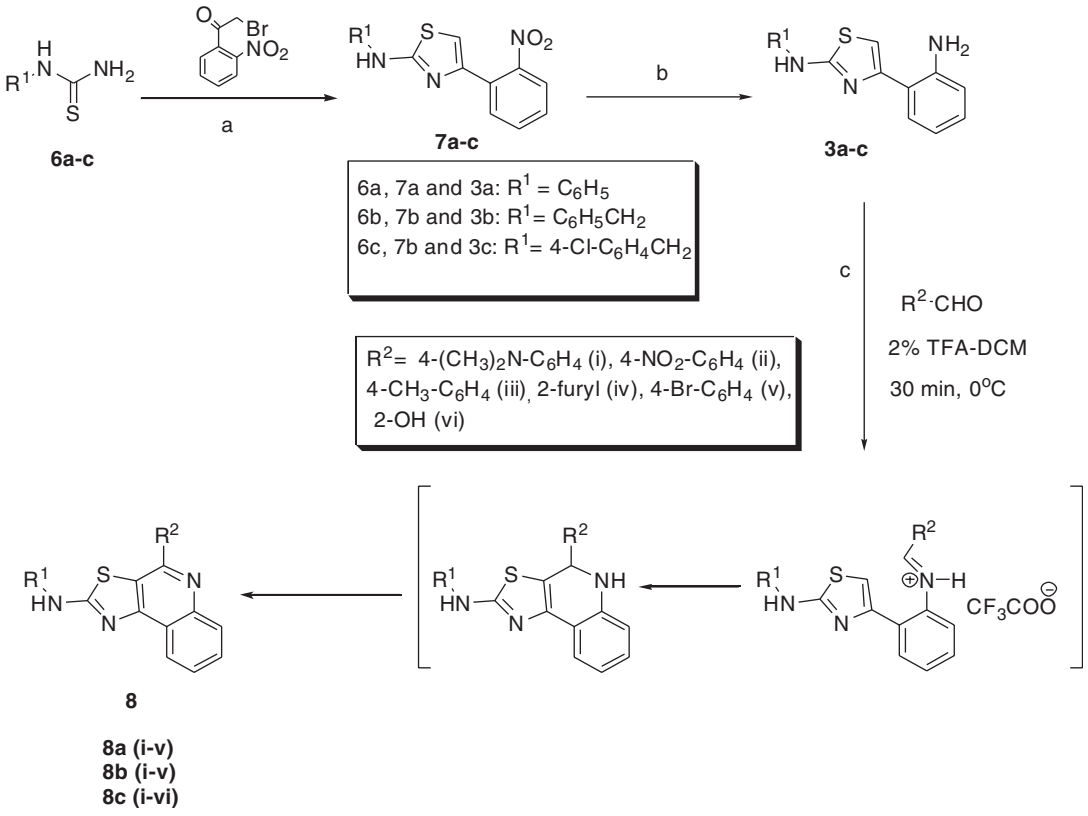
In this communication, we report application of **3** and **4** as novel substrates for the Pictet–Spengler reaction leading to the synthesis of heterocycles beyond isoquinolines and β-carbolines. Though, substrates **3** and **4** with an arylamine originating from the C-4 and C-5, respectively, differs from our previously reported imidazole based substrates **1** and **2** with arylamines originating from the *N*-1, all four of them are based on our new concept wherein arylamines are linked to an activated heterocyclic ring via carbon or nitrogen and therefore can be collectively grouped under second-generation substrates for the Pictet–Spengler reaction (Fig. 1).

Pictet–Spengler reaction on substrates **3** and **4** in the presence of aldehydes led to the synthesis of thiazolo[5,4-*c*]-quinolines (**8**) and pyrazolo[4,3-*c*]quinolines (**12**), respectively. Both of them are completely aromatized compounds and devoid of any stereochemical centers. This is in contrast to the traditional Pictet–Spengler reaction involving substrates based on aliphatic amines linked to an activated heterocyclic ring, which invariably furnishes tetrahydro-derivatives with new stereochemical centre. However, prolonged heating at reflux for 48 h under acidic conditions has been reported to produce fully aromatic compounds such as β-carboline.[2c] Literature survey for thiazolo- and pyrazolo-quinolines revealed a single reference for the synthesis of thiazolo[5,4-*c*]quinoline-2-yl-amines analogous to our compounds **8** using disubstituted thioureas and bromine.[11] Indeed, a variety of structural variants such as thiazolo[5,4-*b*]-,[12] thiazolo[4,5-*g*]-, -[5,4-*g*]-, -[4,5-*h*]-, -[5,4-*h*]-, -[4,5-*f*]- and -[5,4-*f*]-quinolines have been reported in the literature with antibacterial,[13] antispasmodics,[14] antiinflammatory[15] and antitumor activities.[16] Similarly a single reference for pyrazolo[4,3-*c*]quinoline (CGS 9896), which is analogous to our compounds **12** have been reported to exhibit nonsedating anxiolytic activity.[17] Synthesis of pyrazolo[4,3-*c*]quinolines have been generally carried out by treating *o*-chloro-derivatives of cyano quinolines with hydrazine hydrate.[18] This is in contrast to our method that involves generation of quinoline ring onto the pyrazole using the Pictet–Spengler reaction. Structural variant in the form of pyrazolo[3,4-*c*]quinoline ring systems has been reported to exhibit significant biological activities such as good affinity and selectivity for adenosine A3 receptors, benzodiazepine receptor activity and NMDA receptor inhibition.[19] Another variant, pyrazolo[3,4-*b*]quinolines has been identified as a potential candidate for the blue light electroluminescent materials.[20]

2. Results and discussion

The synthetic strategy dealing with the application of substrate **3** for the Pictet–Spengler reaction is depicted in Scheme 1. Substrate **3** can be readily obtained using Hantzsch-thiazole synthesis[21] by first treating 2-nitrophenacyl bromide with thioureas **6** followed by the reduction of the resulting [4-(2-nitro-phenyl)-thiazol-2-yl]-phenyl-amine **7** with $SnCl_2 \cdot 2H_2O$. Diversity in thioureas was introduced by derivatizing one of the NH_2' and this has been accomplished by treating aryl isothiocyanates with ammonia. For the Pictet–Spengler cyclization, the substrate **3a** was treated with *p*-*N*,*N*-dimethylbenzaldehyde under a variety of traditional Pictet–Spengler protocols involving *p*TsOH in toluene at reflux, 2% TFA in DCM at 0 °C, AcOH in ethanol at reflux, neat toluene at 80 °C and with $Yb(OTF)_3$. Interestingly, *endo* cyclization resulting in thiazoloquinoline **8a**(**i**) occurred under all conditions and it took from 30 min (in 2% TFA) to 6 h (toluene) for the completion of the reaction (Table 1). The crude product (>85% based on HPLC) obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluent and characterized by LC–MS and NMR.

It is interesting to note that the Pictet–Spengler reaction on **3** occurred under both protic and nonacidic aprotic media, and, the C–C bond formation was found to be comparatively faster than tryptamine and Trp-OMe (generally used as substrate in the traditional Pictet–Spengler reaction) under



Scheme 1. Pictet–Spengler reaction using (2-amino-phenyl)-thiazolo-phenyl-amine (**3**); conditions: (a) MeOH, rt, 2 h; (b) $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 2 h; (c) 2% TFA in DCM, 0 °C, 15 min.

similar protocols. Indeed, the rate of cyclization was found to be at par with the protocol involving highly reactive cyclic *N*-acyliminium ion strategy.[22] The elegant *N*-acyliminium strategy is known to enhance the reactivity of iminium intermediates; the only limitation is that the acyl group invariably becomes part of the final compound and needs to be removed. Cook et al. attributed electrophilicity of the imine double bond resulting from the condensation of amines with aldehydes as the limiting factor for Pictet–Spengler cyclization and applied pK_a values of amines to compare the electrophilicities of the 'imines'.[23] Thus, comparing the pK_a values of tryptamine 10.2 and Trp-OMe 7.29 with the aniline (in the absence of pK_a value available for **3**, aniline's pK_a value was taken into account) 4.2, clearly suggests that the carbon–nitrogen double bond derived from substrate **3** is highly electrophilic, for the nitrogen carries a less electron density than that found for the imines derived from Trp-OMe and tryptamine, respectively (Fig. 4).

Table 1. Optimization of reaction involving conversion of **3a** to **8a**(**i**) using *p*-*N*,*N*-dimethylbenzaldehyde under different Pictet–Spengler protocols

Entry	Conditions	Time	Product (%)[a]
1	2% TFA, DCM, 0 °C	30 min	98
2	*p*TsOH (0.1 equiv), toluene, reflux	45 min	95
3	5% AcOH in EtOH, reflux	45 min	95
4	$Yb(OTf)_3$, DCM, rt	1 h	92
5	Toluene, reflux	6 h	92

[a] Based on HPLC of crude products.

These findings suggest that the aryl amine derived substrates are likely to undergo the Pictet–Spengler reaction relatively faster than the substrate derived from aliphatic amines. The scope and limitation of our strategy was established by synthesizing 15 compounds based on thiazoloquinolines **8** by using three thiazole substrates based on **3** and five aromatic aldehydes. For the Pictet–Spengler cyclization 2% TFA–DCM protocol was used. Purities of the crude products were typically in the excess of 85% based on HPLC analysis and substitutions on either **3** or aldehydes had no affect on the rate and yield of the *endo* cyclized product. We were especially pleased to see that aldehydes with electron-donating group had no adverse effect on the rate of cyclization. This is in contrast to the typical Pictet–Spengler reaction where aldehydes with electron withdrawing group had favorable affects on *endo* cyclization while aldehydes with electron donating substituent such as salicylaldehyde produced imine as the only product when treated with Trp-OMe. Cook et al. circumvented this problem by using N_b-benzyl Trp-OMe that furnished an iminium ion intermediate with enhanced electrophilicity than the imine obtained from the Trp-OMe and in turn facilitated *endo* cyclization. Condensation of substrate **3c** with salicylaldehyde furnished thiazoloquinoline **8c**(**vi**) in 78% isolated yield. We believe that in the substrate **3**, the imine intermediate derived from the aldehydes with electron donating group is relatively more electrophilic than the imine derived from the Trp-OMe using the same aldehyde since the pK_a value of aryl amine (4.2 for aniline) is significantly less than that of Trp-OMe (7.29).

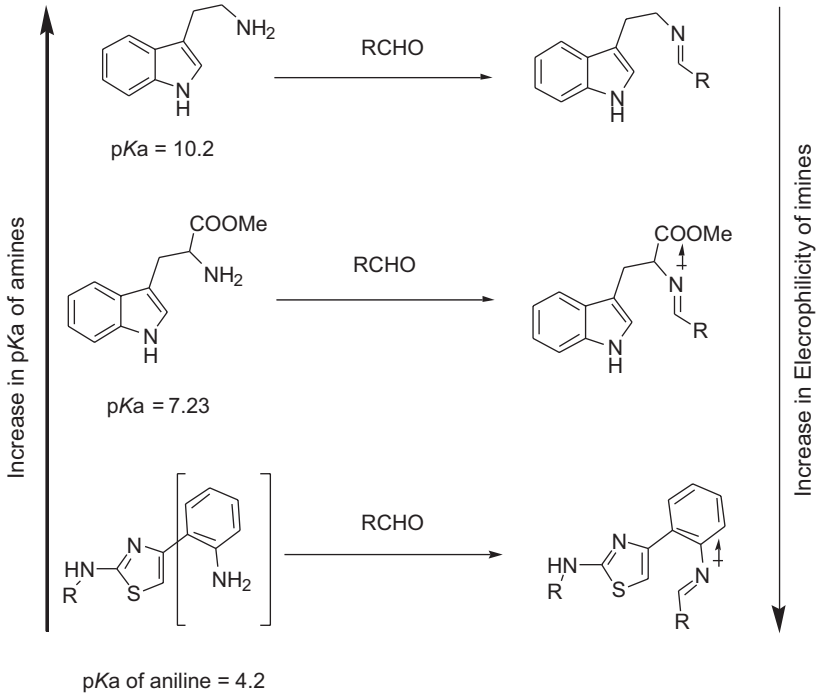


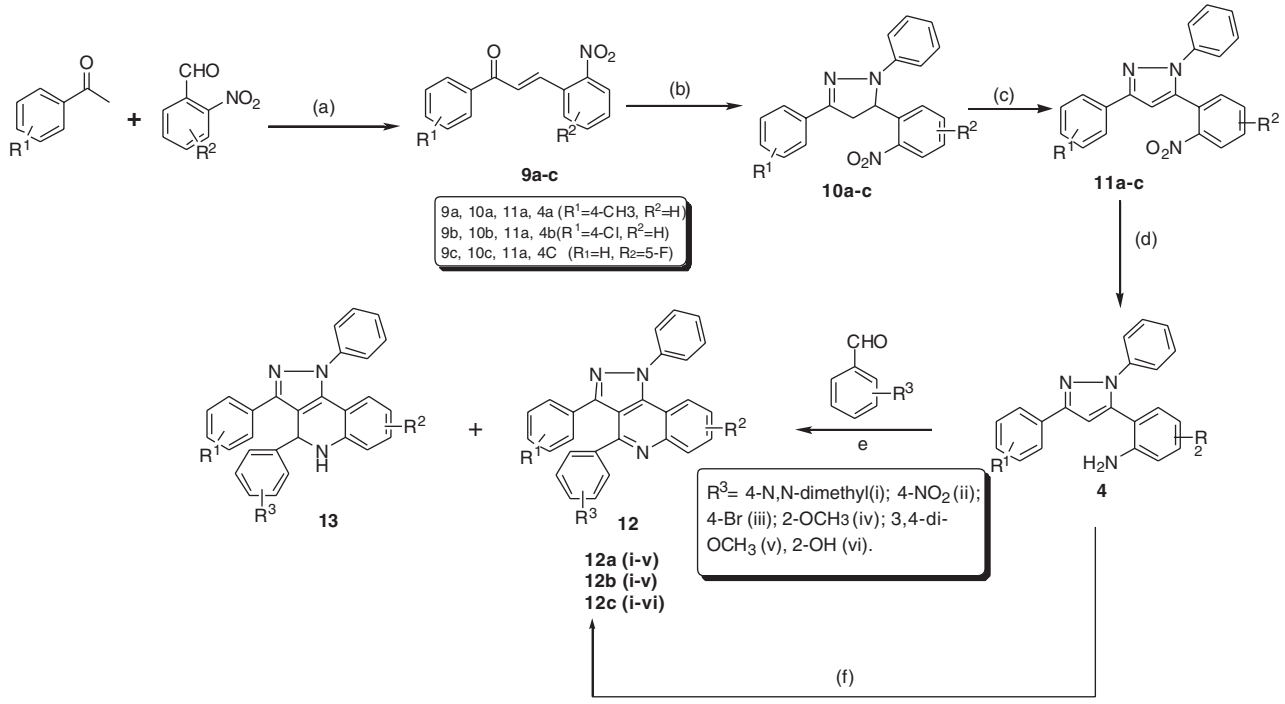
Figure 4. pK_a of amines versus electrophilicity of imines.

Results of the analytical data of thiazoloquinoline derivatives **8** are summarized in Table 2.

The synthetic strategy for pyrazoloquinolines from substrate **4** is depicted in Scheme 2. Out of the variety of regioselective methods reported for dihydropyrazoles (pyrazolines) or pyrazoles, we decided to synthesize dihydropyrazoles from enones in the first instance followed by oxidation to give the desired pyrazole substrate **4**. Surprisingly, our initial attempts to prepare chalcones from *o*-nitrobenzaldehyde and acetophenones using KOH/EtOH as general procedure were not successful. Though, $BF_3\cdot$ AcOH has been reported for the synthesis of chalcones from *o*-nitrobenzaldehyde by stirring it with acetophenone for 5 days,[24] we decided to use ammonium acetate instead and were pleased to see the formation of chalcones in 60% yield after being refluxed in toluene for only 7 h. For the synthesis of regioselective dihydropyrazoles, we treated chalcones (enones) with *N*-phenylhydrazine as described earlier by Powers et al.[25] The authors established the regioselectivity by X-ray analysis of the dihydropyrazoles. Chalcones (enones) **9** derived from acetophenone and *o*-nitrobenzaldehydes were reacted with *N*-phenylhydrazine to give dihydropyrazoles **10**. As expected, the reaction furnished a single pyrazolines regiomer; no product of the alternative regiochemistry of addition was detected. The structure was confirmed by ^{1}H NMR, which showed the presence of three alkyl protons with appropriate geminal and vicinal constants. Next, dihydropyrazoles **10**, which are quite stable and do not suffer from aerial oxidation upon storage, were oxidized to pyrazoles **11** using DDQ. The resulting C-5 linked aryl nitro in **11** was then reduced to NH_2 functionality via catalytic hydrogenation to give substrate **4**. Finally, **4** was subjected to Pictet–Spengler reaction by treating it with *2*-methoxybenzaldehyde in the presence *p*TsOH in toluene at reflux for 18–20 h. As evident by both

Table 2. Syntheses of thiazoloquinolines **8**

Product	R^1	R^2	Isolated yield (%)
8a(i)	C_6H_5	4-$(CH_3)_2NC_6H_4$	83
8a(ii)	C_6H_5	4-$NO_2C_6H_4$	80
8a(iii)	C_6H_5	4-$CH_3C_6H_4$	82
8a(iv)	C_6H_5	2-C_4H_3O	85
8a(v)	C_6H_5	4-BrC_6H_4	76
8b(i)	C_6H_5–CH_2	4-$(CH_3)_2NC_6H_4$	81
8b(ii)	C_6H_5–CH_2	4-$NO_2C_6H_4$	79
8b(iii)	C_6H_5–CH_2	4-$CH_3C_6H_4$	85
8b(iv)	C_6H_5–CH_2	2-C_4H_3O	83
8b(v)	C_6H_5–CH_2	4-BrC_6H_4	78
8c(i)	4-Cl–$C_6H_4CH_2$	4-$(CH_3)_2NC_6H_4$	80
8c(ii)	4-Cl–$C_6H_4CH_2$	4-$NO_2C_6H_4$	77
8c(iii)	4-Cl–$C_6H_4CH_2$	4-$CH_3C_6H_4$	81
8c(iv)	4-Cl–$C_6H_4CH_2$	2-C_4H_3O	83
8c(v)	4-Cl–$C_6H_4CH_2$	4-BrC_6H_4	75
8c(vi)	4-Cl–$C_6H_4CH_2$	2-OH	78



Scheme 2. Pictet–Spengler reaction using 2-(2,5-diphenyl-2*H*-pyrazol-3-yl)-phenylamine (**4**); conditions: (a) NH_4OAc, toluene, reflux, 7 h; (b) phenyl hydrazine, EtOH, reflux 7 h; (c) DDQ, DCM–THF (1/1), rt, 4 h; (d) $SnCl_2 \cdot 2H_2O$, EtOH, reflux, 1.5 h; (e) *p*-TsOH, toluene, reflux, 4 h; (f) *p*-TsOH, toluene reflux 4 h and DDQ, DCM–THF (1/1), rt, 2 h.

HPLC and TLC, the crude product was found to be a mixture of two components with a major spot ~85% and minor <10%. The two spots were separated by column chromatography using 10–30% EtOAc–hexane as mobile phase and characterized by ESMS and NMR. One of the components with lower R_f on TLC was found to be the dihydropyrazoloquinolines **13** and the second component with higher R_f was pyrazoloquinolines **12**, an oxidized product of the first component. The former had a moderate stability, as even after purification it had a tendency to undergo slow oxidation to **12**. Such an oxidation for dihydroimidazoquinoxaline to imine has been reported earlier by us and TenBrink et al.[26]

In order to synthesize **12** as the only product, we treated **4a** with 2-methoxybenzaldehyde by applying other traditionally used Pictet–Spengler protocols involving 2% TFA in DCM at 0 °C, AcOH in ethanol at reflux, and toluene at 80 °C (Table 3). All protocols except toluene at 80 °C, where schiff base was the only isolated product (Table 3), were accompanied with the formation of the **13**. This led us to add an oxidizing agent after the Pictet–Spengler reaction so as to convert the remaining **13** into **12**. Thus, after the Pictet–Spengler reaction of the substrate **4** with an aldehyde, the resulting crude product was treated with DDQ to give **12** as the only product. The scope and limitation of our strategy was examined by utilizing three 3,5 disubstituted pyrazoles and five aldehydes. In all cases, the title compounds were obtained in excellent yields (75–82%) and aldehydes with electron-donating group had no adverse effect on the rate of cyclization. Condensation of salicylaldehyde having electron donating substituent with **4c** furnished pyrazoloquinoline **12c**(**vi**) (Table 5) in 75% yield. A comparative profile of the Pictet–Spengler reaction of aliphatic and aryl amine based substrates with salicylaldehyde has been depicted in Table 4. It is thus clear that substrates with aryl amine attached directly to either C or N of the heterocyclic ring readily underwent Pictet–Spengler cyclization with aldehydes bearing electron donating groups whereas substrates derived either from aliphatic amine (Trp-OMe) or even from aryl amine not directly linked to the heterocycle (**2**) failed to undergo cyclization. The structure of 16 compounds based on **12** has been summarized in Table 5.

Table 3. Ratio of pyrazoloquinoline **12** and its dihydro-derivative **13** formed during the Pictet–Spengler reaction of **4a** with *2*-methoxybenzaldehyde

Entry	Conditions	**12** (%)[a]	**13** (%)[a]	Time
1	2% TFA, DCM, 0°	20	80	2 h
2	*p*TsOH (0.1 equiv), toluene, reflux	80	8	5 h
3	5% AcOH in EtOH, reflux	40	60	8 h
4	Toluene, reflux[b]	—	—	20 h
5	(i) *p*TsOH (0.1 equiv), toluene, reflux, (ii) DDQ	89	—	4 and 2 h

[a] Based on HPLC of crude reaction product.
[b] Schiff base was isolated as the only product.

Though both the substrates **3** and **4** successfully underwent Pictet–Spengler cyclization, however, when compared with the *N*-linked aryl amine substrates **1** and **2** described earlier, we observed that C-linked aryl amine substrates **3** and **4** underwent Pictet–Spengler cyclization faster than **1** and **2**. This may be attributed to the relative decrease in the pK_a value of the aryl amine linked to the C-4 and C-5 in **3** and **4**, respectively, which are the already deactivated positions due to the multiply bonded *N*-atom than the pK_a value of aryl amine linked to the nitrogen, which behaves as an electron donor.

Table 4. Comparative profile of substrates undergoing Pictet–Spengler cyclization with salicylaldehyde

Substrate	Reaction condition	Cyclized product	Yield (%)	Ref.
1	Toluene, 80 °C, 48 h	Imidazoquinoxalines	73	6a
2	*p*-TsOH, toluene, 125 °C, 18 h	No product[a]	—	6b
3	2% TFA–DCM	Thiazoloquinoline	78	—
4	*p*-TsOH, toluene, reflux, 5 h	Pyrazoloquinoline	75	—
Trp-OMe	*p*-TsOH, toluene, reflux	Tetrahydro-β-carboline	5	22
Trp-OMe	Toluene, reflux	No product[a]	—	22

[a] Imine was isolated as the only product.

Table 5. Synthesis of pyrazoloquinolines **12**

Product	R^1	R^2	R^3	Isolated yield (%)
12a(i)	4-CH_3	H	4-$(CH_3)_2N$	79
12a(ii)	4-CH_3	H	4-NO_2	75
12a(iii)	4-CH_3	H	4-Br	76
12a(iv)	4-CH_3	H	2-OCH_3	82
12a(v)	4-CH_3	H	3,4-Di-OCH_3	80
12b(i)	4-Cl	H	4-$(CH_3)_2N$	82
12b(ii)	4-Cl	H	4-NO_2	80
12b(iii)	4-Cl	H	4-Br	76
12b(iv)	4-Cl	H	2-OCH_3	79
12b(v)	4-Cl	H	3,4-Di-OCH_3	82
12c(i)	H	5-F	4-$(CH_3)_2N$	80
12c(ii)	H	5-F	4-NO_2	75
12c(iii)	H	5-F	4-Br	77
12c(iv)	H	5-F	2-OCH_3	79
12c(v)	H	5-F	3,4-Di-OCH_3	80
12c(vi)	4-CH_3	H	2-OH	75

3. Conclusion

In summary, we have identified new thiazole and pyrazole derived substrates for the Pictet–Spengler reaction, which is based on our concept of 'arylamine attached to an activated heterocyclic ring'. This in turn will set the stage for a wide application of this powerful reaction and can be used for the synthesis of novel polyheterocyclic skeletons based on privileged structures. Currently work is in progress in our lab with several second-generation substrates designed on the basis of our new concept for the Pictet–Spengler reaction and will be reported soon.

4. Experimental

All solvents were commercially available and used without purification. All products were characterized by ^{1}H NMR. ^{13}C NMR, ESMS, IR and HPLC. Analytical TLC was performed using 2.5×5 cm plated coated with a 0.25 mm thickness of silica gel. 60F-254 Merck and visualization was accomplished with UV light and iodine. Column chromatography was performed using silica gel 60 Thomas Baker (100–200 mesh). ^{1}H NMR spectra (300 MHz) are reported as follows: chemical shifts in parts per million downfield from TMS as internal standard (δ scale), multiplicity [br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, o=overlapped, integration and coupling constant (Hz)]. All ^{13}C NMR spectra (50/75 MHz) are determined with complete proton decoupling and reported in ppm. All spectra were recorded at 25 °C Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. Analytical HPLC were performed on C-18 reverse-phase column (250 mm×4.6 mm). Mass spectra were recorded on a Merck MS-8000 spectrometer. Phenylisothiocyanates, aldehydes, and *o*-nitrophenacylbromide, tin chloride dihydrate etc were purchased from Aldrich and Lancaster. The LC–Ms profile of selected compounds were generated using High Throughput LC–MS (Lachrom MS- 8000) using a 5 μ, 10×50 mm C-18 Reverse Phase Column with a Linear gradient 10–100% methanol–water v/v with 0.1% formic acid over 12 min with a flow rate of 6 mL/min. Melting points reported were uncorrected.

4.1. General method for the preparation of (2-nitro-phenyl)-thiazolo-phenyl-amine (7)

2-Nitro phenacyl bromide (0.50 g, 2.05 mmol) was added to a solution of **6a** (0.31 g, 2.05 mmol) in methanol (5 mL). The reaction mixture was stirred for 2 h. The reaction mixture was evaporated and digested with water and then extracted with ethyl acetate. The organic phase was washed with a saturated solution of sodium bicarbonate (100 mL) followed by brine (50 mL), dried over sodium sulfate and evaporated to dryness under reduced pressure to obtained a crude solid, which was further purified by recrystallization in ethanol to afford **7a** as a yellow solid.

4.1.1. [4-(2-Nitro-phenyl)-thiazol-2-yl]-phenyl-amine (7a). Yield 95%; yellow solid; mp 162–164 °C; IR (KBr) ν_{max} 1599, 1528, 1334, ^{1}H NMR (300 MHz, DMSO) δ=10.27 (s, 1H, NH), 7.86 (t, 2H, ArH), 7.76 (t, 1H, ArH), 7.56 (t, 3H, ArH), 7.34 (s, 1H, thiazole H), 7.28 (t, 2H, J=8.1 Hz, ArH), 6.95 (t, 1H, J=7.2 Hz, ArH); ^{13}C NMR (50 MHz, DMSO) δ=170.6, 163.4, 149.2, 146.1, 141.2, 132.3, 130.2, 129.2, 128.1, 124.7, 123.9, 122.3, 121.7, 117.1, 107.3; mass (ES^+) m/z 298 (M^++1). Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.69; H, 3.53; N, 14.50.

4.1.2. Benzyl-[4-(2-nitro-phenyl)-thiazol-2-yl]-amine (7b). Yield 98%; solid, mp 152–154 °C; IR (KBr) ν_{max} 3382, 2832, 2719, 1589, 1366; ^{1}H NMR (300 MHz, DMSO) δ=8.18 (t, 1H, J=5.7 Hz, NH), 7.76 (d, 2H, J=8.1 Hz, ArH), 7.64 (t, 1H, J=7.65 Hz, ArH), 7.52 (t, 1H, J=7.8 Hz, ArH), 7.29 (m, 5H, ArH), 7.01 (s, 1H, thiazole H), 4.38 (d, 2H, J=5.7 Hz, CH_2); ^{13}C NMR (75 MHz, DMSO) δ=168.2, 148.8, 145.6, 139.1, 131.9, 129.9, 128.6, 128.3, 128.2, 127.7, 127.0, 123.5, 105.0, 47.7; mass (ES^+) m/z 312 (M^++1). Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.68; H, 4.35; N, 13.45.

4.1.3. (4-Chloro-benzyl)-[4-(2-nitro-phenyl)-thiazol-2-yl]-amine (7c). Yield 96%; oil; IR (neat) ν_{max} 3377, 2928, 2853, 1590, 1363; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.21

(t, 1H, $J=5.25$ Hz, NH), 7.74 (d, 2H, $J=7.8$ Hz, ArH), 7.64 (t, 1H, $J=7.5$ Hz, ArH), 7.51 (t, 1H, $J=7.65$ Hz, ArH), 7.35 (m, 4H, ArH), 7.02 (s, 1H, thiazole H), 4.36 (d, 2H, $J=5.4$ Hz, CH_2); ^{13}C NMR (75 MHz, DMSO) $\delta=168.4$, 149.2, 145.2, 138.6, 132.2, 131.9, 130.26, 129.8, 129.0, 128.6, 123.8, 105.5, 47.3; mass (ES^+) m/z 346 (M^++1). Anal. Calcd for $C_{16}H_{12}ClN_3O_2S$: C, 55.57; H, 3.50; N, 12.15. Found: C, 55.79; H, 3.53; N, 12.20.

4.2. General method for the preparation of (2-amino-phenyl)-thiazolo-phenyl-amine (3)

Tin (II) chloride dihydrate (2.28 g, 10.13 mmol) was added to a solution of **7a** (0.60 g, 2.03 mmol) in ethanol (15 mL) at 80 °C. The reaction mixture was stirred for 2 h and then poured in cold water and basified with 5% sodium bicarbonate (pH 8). The mixture was extracted with ethyl acetate, washed with brine (100 mL), dried over sodium sulfate, and evaporated to dryness under reduced pressure to afford a crude material, which was purified on a silica gel column using hexane–ethyl acetate (70/30, v/v) as eluent to afford **3a** as an oil.

4.2.1. (Amino-phenyl)-thiazol-2-yl]-phenyl-amine (3a). Yield 96%; oil; IR (neat) ν_{max} 3450 (br, NH), 1593; ^1H NMR (300 MHz, DMSO) $\delta=10.26$ (s, 1H, NH), 7.56 (d, 2H, $J=7.8$ Hz, ArH), 7.45 (d, 1H, $J=7.5$ Hz, ArH), 7.32 (t, 2H, $J=7.5$ Hz, ArH), 6.98 (m, 2H, ArH), 6.71 (d, 1H, $J=8.1$ Hz, ArH), 6.57 (t, 1H, $J=7.5$ Hz, ArH), 5.92 (s, 2H, CH_2), ^{13}C NMR (50 MHz, DMSO) $\delta=163.3$, 150.7, 146.3, 141.4, 130.1, 129.4, 128.9, 128.6, 121.8, 118.3, 117.3, 116.5, 108.8, 103.1; mass (ES^+) m/z 268.32 (M^++1). Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.49; H, 4.73; N, 15.53.

4.2.2. [4-(2-Amino-phenyl)-thiazol-2-yl]-benzyl-amine (3b). Yield 95%; oil; IR (neat) ν_{max} 3450 (br, NH), 2836, 2700, 1592; ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.41$–7.33 (m (o), 6H, ArH), 7.09 (t, 1H, $J=7.8$ Hz, ArH), 6.69 (t, 1H, $J=8.25$ Hz, ArH), 6.58 (s, 1H, thiazole H), 5.47 (br s, 1H, NH), 4.52 (d, 2H, $J=6.0$ Hz, CH_2); mass (ES^+) m/z 282 (M^++1). Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.32; H, 5.51; N, 14.84.

4.2.3. [4-(2-Amino-phenyl)-thiazol-2-yl]-(4-chloro-benzyl)-amine (3c). Yield 96%; white solid; mp 182–184 °C; IR (KBr) ν_{max} 3420 (br, NH), 2920, 2860, 1598; ^1H NMR (300 MHz, DMSO) $\delta=8.27$ (t, 1H, $J=5.4$ Hz, NH), 7.36 (m, 5H, ArH), 6.96 (t, 1H, $J=7.35$ Hz, ArH), 6.75 (s, 1H, thiazole H), 6.64 (d, 1H, $J=7.8$ Hz, ArH), 6.51 (t, 1H, $J=7.35$ Hz, ArH), 5.86 (br s, 2H, NH_2), 4.45 (d, 2H, $J=5.7$ Hz, CH_2); ^{13}C NMR (50 MHz, DMSO) $\delta=168.7$, 150.8, 146.3, 138.7, 131.8, 129.5, 128.67, 128.2, 118.3, 116.3, 116.1, 101.1, 101.2, 47.4; mass (ES^+) m/z 316 (M^++1). Anal. Calcd for $C_{16}H_{14}ClN_3S$: C, 60.85; H, 4.47; N, 13.31. Found: C, 60.77; H, 4.51; N, 13.50.

4.3. General procedure for the Pictet–Spengler reaction on substrate 3

A mixture of **3a** (0.10 g, 0.39 mmol) and *p*-*N*,*N*-dimethyl-aminobenzaldehyde (0.058 g, 0.39 mmol) in DCM (2 mL) was treated with 2% TFA in DCM. The completion of Pictet–Spengler cyclization was monitored by TLC. After 30 min, the reaction mixture was evaporated, and the residue so obtained was triturated with 5% $NaHCO_3$. It was then extracted with EtOAc, washed with brine (10 mL), and dried over sodium sulfate. EtOAC was evaporated to dryness under reduced pressure and the crude obtained was purified by column chromatography to afford **8a(i)** as a white solid.

4.3.1. [4-(4-Dimethylamino-phenyl)-thiazolo [5,4-*c*] quinolin-2-yl]-phenyl-amine [8a(i)]. Yield 83%; white solid, mp 218–220 °C; IR (KBr) ν_{max} 3246 (br, NH), 2923, 2830, 1478, 1400, 1355 cm^{-1}; ^1H NMR (300 MHz, DMSO): $\delta=11.05$ (s, NH), 8.48 (d, $J=7.8$ Hz, 1H), 8.04 (d, $J=8.4$ Hz, 1H), 7.99 (d, $J=7.8$ Hz, 2H), 7.91 (d, $J=7.8$ Hz, 2H), 7.73 (t, $J=7.35$ Hz, 1H), 7.61 (t, $J=7.5$ Hz, 1H), 7.47 (t, $J=7.2$ Hz, 2H), 7.13 (t, $J=7.23$ Hz, 1H), 6.90 (t, $J=8.1$ Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (75 MHz, DMSO) $\delta=166.0$, 154.8, 150.9, 150.8, 146.2, 139.9, 129.0, 128.6, 126.4, 125.1, 123.1, 122.7, 120.1, 118.2, 112.3, 111.4, 39.8; mass (ES^+) m/z 397 (M^++1). Anal. Calcd for $C_{24}H_{20}N_4S$: C, 72.70; H, 5.08; N, 14.33. Found: C, 72.68; H, 5.10; N, 14.30.

4.3.2. [4-(4-Nitro-phenyl)-thiazolo [5,4-*c*]quinolin-2-yl]-phenyl-amine [8a(ii)]. Yield 80%; yellow solid, mp 234–236 °C; IR (KBr) ν_{max} 3366 (br, NH), 1602, 1454, 1402, 1344; ^1H NMR (300 MHz, DMSO), $\delta=11.20$ (s, 1H, NH), 8.53 (d, 1H, $J=7.8$ Hz, ArH), 8.46 (d, 2H, $J=8.4$ Hz, ArH), 8.32 (d, 2H, $J=8.4$ Hz, ArH), 8.13 (d, 1H, $J=8.1$ Hz, ArH), 7.89 (d, 2H, $J=7.8$ Hz, ArH), 7.80 (t, 1H, $J=7.35$ Hz, ArH), 7.72 (t, 1H, $J=7.35$ Hz, ArH), 7.47 (t, 2H, $J=7.80$ Hz, ArH), 7.15 (t, 1H, $J=7.35$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO d_6), $\delta=166.3$, 155.8, 148.4, 147.8, 146.2, 145.4, 139.9, 129.3, 129.0, 126.8, 123.9, 123.6, 123.3, 120.7, 119.6, 118.6; mass (ES^+) m/z 399 (M^++1). Anal. Calcd for $C_{22}H_{14}N_4O_2S$: C, 66.32; H, 3.54; N, 14.06. Found: C, 66.31; H, 3.55; N, 14.10.

4.3.3. Phenyl-(4-*p*-tolyl-thiazolo [5,4-*c*]quinolin-2-yl)-amine [8a(iii)]. Yield 82%; white solid, mp 128–130 °C; IR (KBr) ν_{max} 3196 (br, NH), 2931, 2835, 1591, 1493, 1363; ^1H NMR (300 MHz, $CDCl_3$), $\delta=8.5$ (d, 1H, $J=8.1$ Hz, ArH), 8.20 (d, 1H, $J=8.4$ Hz, ArH), 7.95 (d, 3H, $J=7.8$ Hz, overlapped with NH, ArH), 7.72 (t, 1H, $J=7.65$ Hz, ArH), 7.58 (m, 3H, ArH), 7.44 (t, 2H, $J=7.8$ Hz, ArH), 7.35 (d, 2H, $J=7.8$ Hz, ArH), 7.22 (t, 1H, $J=7.5$ Hz, ArH), 2.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ 155.3, 152.4, 147.0, 139.6, 139.4, 137.3, 129.6, 129.6, 129.0, 128.0, 125.9, 124.7, 123.7, 121.2, 120.2, 21.4; mass (ES^+) m/z 368 (M^++1). Anal. Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.44. Found: C, 75.15; H, 4.65; N, 11.45.

4.3.4. (4-Furan-2-yl-thiazolo [5,4-*c*]quinolin-2-yl)-phenyl-amine [8a(iv)]. Yield 85%; white solid, >250 °C; IR (KBr) ν_{max} 3264 (br, NH), 1607, 1472, 1406, 1347. Anal. ^1H NMR (300 MHz, DMSO), $\delta=11.13$ (s, NH), 8.51 (d, 1H, $J=8.1$ Hz, ArH), 8.04 (d, 2H, $J=8.4$ Hz, ArH), 7.92 (d, 2H, $J=8.1$ Hz, ArH), 7.75 (t, 1H, $J=7.5$ Hz, ArH), 7.64 (t, 1H, $J=7.5$ Hz, ArH), 7.48 (t, 2H, $J=7.5$ Hz, ArH), 7.41 (d, 1H, $J=3$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO), $\delta=$ 167.9, 155.9, 152.7, 146.3, 145.3, 147.0, 140.4, 129.6,

128.9, 126.3, 123.8, 123.5, 121.0, 119.0, 116.8, 113.2, 111.1; mass (ES^+) m/z 344 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.94; H, 3.81; N, 12.25.

4.3.5. [4-(4-Bromo-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-phenyl-amine [8a(v)]. Yield 76%; yellow solid, mp 184–186 °C; IR (KBr) ν_{max} 3288 (br, NH), 1601, 1476, 1406, 1361; ^1H NMR (300 MHz, DMSO), $\delta = 11.16$ (br s, 1H, NH), 8.52 (d, 1H, $J = 7.8$ Hz, ArH), 8.13 (d, 1H, $J = 8.4$ Hz, ArH), 8.03 (d, 2H, $J = 7.2$ Hz, ArH), 7.83 (m, 5H, ArH), 7.70 (t, 1H, $J = 7.2$ Hz, ArH), 7.468 (t, 2H, $J = 7.05$ Hz, ArH), 7.14 (t, 1H, $J = 7.05$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO), δ 166.3, 155.5, 149.7, 146.3, 140.0, 138.8, 131.8, 129.8, 129.0, 126.6, 123.3, 123.2, 120.6, 119.4, 118.6; mass (ES^+) m/z 433 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{14}BrN_3S$: C, 61.12; H, 3.26; N, 9.72. Found: C, 61.10; H, 3.25; N, 9.73.

4.3.6. Benzyl-[4-(4-dimethylamino-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8b(i)]. Yield 81%; pink solid, mp 160–162 °C; IR (KBr) ν_{max} 3209 (br, NH), 2929, 2831, 1599, 1365; ^1H NMR (300 MHz, DMSO), $\delta = 10.20$ (s, NH), 8.48 (d, 1H, $J = 7.8$ Hz, ArH), 8.16 (d, 1H, $J = 8.4$ Hz, ArH), 7.94 (t, 1H, $J = 7.5$ Hz, ArH), 7.85 (d, 2H, $J = 8.4$ Hz, ArH), 7.76 (t, 1H, $J = 7.35$ Hz, ArH), 7.39 (m, 5H, ArH), 6.97 (d, 2H, $J = 8.4$ Hz, ArH), 4.84 (s, 2H, CH_2), 3.08 (s, 6H, $2CH_3$); ^{13}C NMR (50 MHz, DMSO), $\delta = 167.0$, 161.3, 153.6, 148.2, 138.4, 133.2, 130.8, 129.4, 128.6, 128.5, 127.8, 125.2, 120.4, 119.0, 117.8, 112.4, 47.8; mass (ES^+) m/z 411 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{22}N_4S$: C, 73.14; H, 5.40; N, 13.65. Found: C, 73.16; H, 5.38; N, 13.59.

4.3.7. Benzyl-[4-(4-nitro-phenyl)-thiazolo[5,4-*c*]-quinolin-2-yl]-amine [8b(ii)]. Yield 79%; white solid, mp 205–207 °C; IR (KBr) ν_{max} 3403 (br, NH), 2924, 2834, 1630, 1569, 1532, 1475, 1403, 1349; ^1H NMR (300 MHz, DMSO), 9.41 (br s, 1H, NH), 8.43 (t, 3H, $J = 7.5$ Hz, ArH), 8.28 (d, 1H, $J = 8.7$ Hz, ArH), 8.08 (d, 1H, $J = 8.4$ Hz, ArH), 7.75 (t, 1H, $J = 7.5$ Hz, ArH) 7.64 (t, 1H, $J = 7.4$ Hz, ArH), 7.47 (d, 2H, $J = 7.2$ Hz, ArH), 7.38 (t, 2H, $J = 7.4$ Hz, ArH), 7.28 (d, 1H, $J = 7.2$ Hz, ArH), 4.77 (d, 2H, $J = 5.1$ Hz, CH_2); ^{13}C NMR (50 MHz, DMSO), δ 170.8, 156.3, 153.3, 148.5, 147.7, 146.3, 145.6, 138.1, 129.1, 129.0, 128.5, 127.7, 127.4, 126.4, 124.0, 123.6, 120.6, 119.8, 47.8; mass (ES^+) m/z 413 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{16}N_4O_2S$: C, 66.97; H, 3.91; N, 13.58. Found: C, 66.98; H, 3.90; N, 13.59.

4.3.8. Benzyl-(4-*p*-tolyl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8b(iii)]. Yield 85%; white solid, mp 162–164 °C; IR (KBr) ν_{max} 3202, (br, NH), 2925, 2834, 1629, 1585, 1405, 1355; ^1H NMR (300 MHz, DMSO), $\delta = 9.30$ (br s, 1H, NH), 8.38 (d, 1H, $J = 7.8$ Hz, ArH), 8.03 (d, 1H, $J = 8.1$ Hz, ArH), 7.92 (d, 2H, $J = 7.2$ Hz, ArH), 7.69 (t, 1H, ArH), 7.59 (t, 1H, ArH), 7.36 (m, 7H, ArH), 4.75 (s, 2H, CH_2), 2.41 (s, 3H, CH_3; ^{13}C NMR (50 MHz, DMSO), $\delta =$ 167.2, 160.0, 144.6, 142.6, 141.2, 134.0, 133.2, 131.9, 130.5, 129.8, 129.4, 129.0, 128.6, 127.9, 127.5, 127.4, 125.7, 122.4, 118.6, 117.7, 117.0, 114.6, 55.4, 51.6, 48.4, 34.0; mass (ES^+) m/z 382 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{19}N_3S$: C, 75.56; H, 5.02; N, 11.01. Found: C, 75.56; H, 5.03; N, 11.00.

4.3.9. Benzyl-(4-furan-2-yl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8b(iv)]. Yield 83%; solid, mp 180–182 °C; IR (KBr) ν_{max} 3202 (br, NH), 2930, 2832, 1592, 1489, 1364; ^1H NMR (300 MHz, DMSO), $\delta = 7.67$ (d, 1H, $J = 8.1$ Hz, ArH), 7.23 (d, 2H, $J = 8.4$ Hz, ArH), 7.02 (s, 1H, ArH), 6.88 (t, 1H, $J =$ 7.2 Hz, ArH), 6.72 (m, 3H, ArH), 6.57–6.48 [m (o), 5H, ArH), 5.92 (s, 2H, CH_2); mass (ES^+) m/z 358 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.55; N, 11.45.

4.3.10. Benzyl-[4-(4-bromo-phenyl)-thiazolo[5,4-*c*]-quinolin-2-yl]-amine [8b(v)]. Yield 78%; white solid, mp 175–178 °C; IR (KBr) ν_{max} 3170 (br, NH), 2963, 2833, 1629, 1590, 1352; ^1H NMR (300 MHz, DMSO), $\delta = 7.67$ (d, 1H, $J = 7.8$ Hz, ArH), 7.24 (d, 1H, $J = 8.7$ Hz, ArH), 7.05 (d, 2H, $J = 8.4$ Hz, ArH), 6.91 (t, 3H, $J = 8.4$ Hz, ArH), 6.77 (t, 1H, $J = 7.5$ Hz, ArH), 6.66 (d, 2H, $J = 7.2$ Hz, ArH), 6.55 (t, 2H, $J = 7.2$ Hz, ArH), 6.48 (d, 1H, $J = 7.2$ Hz, ArH), 3.97 (s, 2H,CH_2); ^{13}C NMR (50 MHz, DMSO), $\delta = 156.4$, 146.5, 138.2, 131.7, 129.8, 128.9, 128.6, 128.5, 127.7, 127.3, 125.9, 123.7, 123.2, 120.8, 119.9, 47.6; mass (ES^+) m/z 447 ($M^+ + 1$). Anal. Calcd for. $C_{23}H_{16}BrN_3S$. C, 61.89; H, 3.61; N, 9.41. Found: C, 61.90; H, 3.69; N, 9.42.

4.3.11. (4-Chloro-benzyl)-[4-(4-dimethylamino-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8c(i)]. Yield 80%; white solid, mp 134–136 °C; IR (KBr) ν_{max} 3383 (br, NH), 2925, 2833, 1629, 1589, 1360; ^1H NMR (300 MHz, DMSO), $\delta = 10.26$ (br s, 1H, NH), 8.44 (d, 1H, $J = 9$ Hz, ArH), 8.16 (d, 1H, $J = 9$ Hz, ArH), 7.92 (t, 1H, $J = 7.35$ Hz, ArH), 7.84 (d, 2H, $J = 8.7$ Hz, ArH), 7.73 (t, 1H, $J =$ 7.35 Hz, ArH), 7.47 (q, 4H, ArH), 6.95 (d, 2H, $J = 8.7$ Hz, ArH), 4.82 (s, 2H, CH_2), 3.07 (s, 6H, $2 \times CH_3$); ^{13}C NMR (50 MHz, DMSO), $\delta = 160.0$, 152.9, 148.3, 139.1, 136.7, 132.5, 130.4, 130.08, 128.9, 127.3, 124.7, 121.4, 120.0, 118.7, 112.1, 47.7, 40.0; mass (ES^+) m/z 445 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{21}ClN_4S$: C, 67.48; H, 4.76; N, 12.59. Found: C, 67.49; H, 4.74; N, 12.58.

4.3.12. (4-Chloro-benzyl)-[4-(4-nitro-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8c(ii)]. Yield 77%; white solid, mp 220–222 °C; IR (KBr) ν_{max} 3320 (br, NH), 2963, 2833, 1629, 1590, 1352; ^1H NMR (300 MHz, DMSO), $\delta = 9.44$ (s, 1H, NH), 8.43 (t, 3H, ArH), 8.28 (d, 2H, $J = 8.1$ Hz, ArH), 8.08 (d, 1H, $J = 8.1$ Hz, ArH), 7.76 (t, 1H, $J = 7.35$ Hz, ArH), 7.64 (t, 1H, $J = 7.05$ Hz, ArH), 7.61 (t, 1H, $J = 7.2$ Hz, ArH), 7.49 (d, 2H, $J = 8.4$ Hz, ArH), 7.43 (d, 2H, $J = 8.4$ Hz, ArH), 4.75 (d, 2H, $J = 5.1$ Hz, CH_2); ^{13}C NMR (75 MHz, DMSO), $\delta = 171.2$, 156.6, 148.2, 148.1, 146.6, 145.9, 137.5, 131.3, 129.9, 129.4, 128.8, 126.8, 124.3, 123.9, 120.9, 120.2, 47.4; mass (ES^+) m/z 447 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}ClN_4O_2S$: C, 61.81; H, 3.38; N, 12.54. Found: C, 61.82; H, 3.36; N, 12.56.

4.3.13. (4-Chloro-benzyl)-(4-*p*-tolyl-thiazolo[5,4-*c*]-quinolin-2-yl)-amine [8c(iii)]. Yield 81%; white solid, mp 90–92 °C; IR (KBr) ν_{max} 3313 (br, NH), 2922, 2830, 1583, 1484, 1402, 1351, ^1H NMR (300 MHz, DMSO), $\delta = 9.31$ (s, 1H, NH), 8.37 (d, 1H, $J = 8.1$ Hz, ArH), 8.03 (d, H, $J = 8.4$ Hz, ArH), 7.92 (d, 2H, $J = 7.8$ Hz, ArH), 7.71 (t, 1H, $J = 7.65$ Hz, ArH), 7.58 (t, 1H, $J = 7.5$ Hz, ArH), 7.44 (m, 6H, ArH), 4.74 (d, 2H, $J = 4.8$ Hz, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO d_6), $\delta = 171.2$, 156.1,

151.3, 146.8, 139.5, 137.7, 137.5, 132.3, 129.6, 129.0, 128.7, 128.0, 125.9, 123.9, 120.8, 120.0, 47.4, 21.3; mass (ES^+) *m/z* 416 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}ClN_3S$: C, 69.30; H, 4.36; N, 10.10. Found: C, 69.28; H, 4.35; N, 10.13.

4.3.14. (4-Chloro-benzyl)-(4-furan-2-yl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8c(iv)]. Yield 83%; white solid, mp 164–166 °C; IR (KBr) ν_{max} 3225 (br, NH), 2928, 2833, 1585, 1488, 1401, 1360; ^1H NMR (300 MHz, DMSO), δ= 9.35 (s, 1H, NH), 8.386 (d, 1H, *J*=8.1 Hz, ArH), 8.04 (s, 1H, furan H), 7.97 (d, 1H, *J*=8.4 Hz, ArH), 7.69 (t, 2H, *J*= 7.8 Hz, ArH), 7.56 (d, 1H, *J*=7.8 Hz, ArH), 7.50 (d, 2H, *J*=8.4 Hz, ArH), 7.44 (d, 2H, *J*=8.4 Hz, ArH), 7.34 (d, 1H, *J*=3 Hz, furan H), 6.79 (t, 1H, *J*=1.65 Hz, furan H), 4.76 (d, 2H, *J*=5.4 Hz, CH_2); ^{13}C NMR (75 MHz, DMSO), δ= 172.2, 156.4, 152.8, 146.4, 145.2, 141.9, 137.7, 132.3, 129.9, 129.3, 128.8, 125.9, 123.9, 120.9, 116.9, 113.1, 110.9, 47.4; mass (ES^+) *m/z* 392 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}ClN_3OS$: C, 64.36; H, 3.60; N, 10.72. Found: C, 64.35; H, 3.60; N, 10.75.

4.3.15. [4-(4-Bromo-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-(4-chloro-benzyl)-amine [8c(v)]. Yield 75%; white solid, mp 156–158 °C; IR (KBr) ν_{max} 3219 (br, NH), 2930, 2832, 1599, 1482, 1355; ^1H NMR (300 MHz, DMSO), δ 9.37 (s, 1H, NH), 8.38 (d, 1H, *J*=7.8 Hz, ArH), 8.05 (d, H, *J*=8.4 Hz, ArH), 7.97 (d, 2H, *J*=8.4 Hz, ArH), 7.80 (d, 2H, *J*=8.4 Hz, ArH), 7.73 (t, 1H, *J*= 7.05 Hz, ArH), 7.61 (t, 1H, *J*=7.2 Hz, ArH), 7.49 (d, 2H, *J*=8.4 Hz, ArH), 7.43 (d, 2H, *J*=8.4 Hz, ArH), 4.75 (d, 2H, *J*=5.1 Hz, CH_2); ^{13}C NMR (75 MHz, CD_3COCD_3), δ= 150.0, 146.9, 139.5, 137.4, 132.7, 131.7, 129.8, 129.6, 129.2, 128.7, 128.5, 125.8, 123.8, 123.1, 121.2, 47.4; mass (ES^+) *m/z* 481 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}BrClN_3S$: C, 57.45; H, 3.14; N, 8.74. Found: C, 57.43; H, 3.15; N, 8.75.

4.4. General procedure for the synthesis of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-4,5-dihydro-1*H*-pyrazole (10)

A mixture of 3-(2-nitro-phenyl)-1-*p*-tolyl-propenone **9a** (1.00 g, 3.74 mmol), and phenyl hydrazine (0.808 mL, 7.48 mmol) was refluxed in ethanol for 7 h. Ethanol was evaporated in vacuo and the residue so obtained was purified on a silica gel column using hexane: ethyl acetate (70:30, v/v) as eluent to afford **10a** as a red solid.

4.4.1. 5-(2-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole (10a). Yield 82%; red solid; mp 142–144 °C; IR (KBr) ν_{max} 1521, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.23 (d, *J*=7.8 Hz, 1H, ArH), 7.63 (d, *J*=8.1 Hz, 2H, ArH), 7.53–7.44 (m, 3H, ArH), 7.19 (t, *J*=7.8 Hz, 4H, ArH), 6.94 (d, *J*=8.1 Hz, 2H, ArH), 6.80 (t, *J*=7.5 Hz, 1H, ArH), 5.88–5.82 (m, 1H, –CHPh), 4.11 (dd, *J*=17.5, 12.4 Hz, 1H, $-CH_2-$), 3.14 (dd, *J*=17.5, 6.6 Hz, 1H, $-CH_2-$), 2.38 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=147.85, 144.68, 139.49, 138.12, 134.92, 130.91, 130.01, 129.75, 129.55, 128.95, 128.69, 126.25, 125.86, 124.99, 123.50, 119.73, 113.36, 61.05, 43.66, 21.86; mass *m/z* 358.25 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{19}N_3O_2$. C, 73.93; H, 5.36; N, 11.76. Found: C, 73.71; H, 5.42; N, 11.64.

4.4.2. 3-(4-Chloro-phenyl)-5-(2-nitro-phenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (10b). Yield 87%; red solid; mp 150–152 °C; IR (KBr) ν_{max} 1516, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.13 (d, *J*=8.1 Hz, 1H, ArH), 7.66 (d, *J*=8.1 Hz, 2H, ArH), 7.55–7.51 (m, 1H, ArH), 7.46–7.42 (m, 2H, ArH), 7.35 (d, *J*=8.1 Hz, 2H, ArH), 7.19 (t, *J*=7.5 Hz, 2H, ArH), 6.94 (d, *J*=7.8 Hz, 2H, ArH), 6.82 (t, *J*=7.2 Hz, 1H, ArH), 5.91–5.85 (m, 1H, –CHPh), 4.09 (dd, *J*=18.0, 12.3 Hz, 1H, $-CH_2-$), 3.13 (dd, *J*=18.0, 6.6 Hz, 1H, $-CH_2-$); mass *m/z* 378.20 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}ClN_3O_2$ C, 66.76; H, 4.27; N, 11.12. Found: C, 66.62; H, 4.22; N, 11.43.

4.4.3. 5-(5-Fluoro-2-nitro-phenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (10c). Yield 85%; red solid; mp 132–134 °C; IR ν_{max} (KBr) 1524, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28–8.24 (m, 1H, ArH), 7.74 (d, *J*=7.2 Hz, 2H, ArH), 7.43–7.36 (m, 3H, ArH), 7.25–7.17 (m, 3H, ArH), 7.13 (t, *J*=7.5 Hz, 1H, ArH), 6.95 (d, *J*= 8.1 Hz, 2H, ArH), 6.85 (t, *J*=7.2 Hz, 1H, ArH), 5.94–5.87 (m, 1H, –CHPh), 4.15 (dd, *J*=18.0, 12.6 Hz, 1H, $-CH_2-$), 3.16 (dd, *J*=17.5, 6.6 Hz, 1H, $-CH_2-$); mass *m/z* 362.40 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}FN_3O_2$: C, 69.80; H, 4.46; N, 11.63. Found: C, 69.74; H, 4.32; N, 11.74.

4.5. General procedure for the synthesis of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-1*H*-pyrazole (11)

A solution of 5-(2-nitro-phenyl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole **10a** (0.80 g, 2.25 mmol) in DCM–THF (1/1, 7 mL) was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1.02 g, 4.50 mmol) at rt. The reaction mixture was stirred for 4 h. The solvent was removed under reduced pressure and the crude red residue was chromatographed on silica gel (5:1 hexane/ethyl acetate) to afford **11a** as a yellow solid.

4.5.1. 5-(2-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazole (11a). Yield 87%; yellow solid; mp 90–92 °C; IR (KBr) ν_{max} 1521, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.90 (d, 1H, *J*=7.8 Hz, ArH), 7.79 (d, *J*=7.8 Hz, 2H, ArH), 7.60 (t, *J*=6.9 Hz, 1H, ArH), 7.52 (t, *J*=6.9 Hz, 1H, ArH), 7.45 (d, *J*=7.5 Hz, 1H, ArH), 7.28–7.22 (m, 7H, ArH), 6.75 (s, 1H, =CH), 2.38 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=152.66, 149.18, 139.85, 139.58, 138.35, 133.29, 133.12, 130.29, 129.77, 129.44, 127.92, 126.18, 124.93, 106.07, 21.70; mass *m/z* 356.13 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.54; H, 4.72; N, 11.74.

4.5.2. 3-(4-Chloro-phenyl)-5-(2-nitro-phenyl)-1-phenyl-1*H*-pyrazole (11b). Yield 88%; yellow solid; mp 102–104 °C; IR (KBr) ν_{max} 1530, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.93 (d, *J*=8.1 Hz, 1H, ArH), 7.84 (d, *J*=8.4 Hz, 2H, ArH), 7.64–7.52 (m, 2H, ArH), 7.45 (d, *J*=7.2 Hz, 1H, ArH), 7.39 (d, *J*=8.4 Hz, 2H, ArH), 7.28 (s, 5H, ArH), 6.75 (s, 1H, =CH); mass *m/z* 376.20 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 67.22; H, 3.82; N, 11.70.

4.5.3. 5-(5-Fluoro-2-nitro-phenyl)-1,3-diphenyl-1*H*-pyrazo (11c). Yield 83%; yellow solid; mp 165–167 °C; IR (KBr) ν_{max} 1529, 1596 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ=8.01–7.97 (m, 1H, ArH), 7.91 (d, J=7.5 Hz, 2H, ArH), 7.44 (t, J=7.5 Hz, 2H, ArH), 7.36 (d, J=7.5 Hz, 1H, ArH), 7.30 (s, 5H, ArH), 7.20 (d, J=8.1 Hz, 2H, ArH), 6.79 (s, 1H, =CH), mass m/z 360.43 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69. Found: C, 70.22; H, 3.80; N, 11.79.

4.6. General procedure for the reduction of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-1*H*-pyrazole to get 4

Tin (II) chloride dihydrate (2.28 g, 9.25 mmol) was added to a solution of 5-(2-nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazole **11a** (0.65 g, 1.84 mmol) in ethanol (15 mL) at 80 °C. The reaction mixture was stirred for 1.5 h. After that the reaction mixture was poured in cold water and basified with 5% aqueous sodium bicarbonate solution (pH 8). The mixture was extracted with ethyl acetate, washed with brine (100 mL), dried over sodium sulfate, and evaporated to dryness under reduced pressure to afford **4a**

4.6.1. 2-(2-Phenyl-5-*p*-tolyl-2*H*-pyrazol-3-yl)-phenyl-amine (4a). Yield 92%; yellow oil; IR (neat) ν_{max}, 1596, 3473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.82 (d, J=7.8 Hz, 2H, ArH), 7.41 (d, J=7.5 Hz, 2H, ArH), 7.33–7.23 (m, 5H, ArH), 7.17 (t, J=7.5 Hz, 1H, ArH), 6.98 (d, J=7.5 Hz, 1H, ArH), 6.81 (s, 1H, =CH), 6.72 (t, J=6.9 Hz, 2H, ArH), 3.84 (br s, 2H, NH_2), 2.40 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=152.57, 145.19, 141.40, 140.49, 138.30, 131.56, 130.53, 129.84, 129.25, 127.43, 126.13, 124.25, 118.62, 116.48, 115.96, 106.23, 21.78; mass m/z 326.80 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.37; H, 5.62; N, 12.78.

4.6.2. 2-[5-(4-Chloro-phenyl)-2-phenyl-2*H*-pyrazol-3-yl]-phenylamine (4b). Yield 88%; yellow oil; IR (neat) ν_{max} 1600, 3464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.86 (d, J=8.4 Hz, 2H, ArH), 7.40 (d, J=8.1 Hz, 3H, ArH), 7.34–7.23 (m, 4H, ArH), 7.18 (t, J=7.5 Hz, 1H, ArH), 6.97 (d, J=7.5 Hz, 1H, ArH), 6.81 (s, 1H, =CH), 6.74–6.67 (m, 2H, ArH), 3.82 (br s, 2H, NH_2); mass m/z 346.40 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.82; H, 4.82; N, 12.31.

4.6.3. 2-(2,5-Diphenyl-2*H*-pyrazol-3-yl)-4-fluoro-phenyl-amine (4c). Yield 86%; yellow oil; IR (neat) ν_{max} 1595, 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.92 (d, J=7.2 Hz, 2H, ArH), 7.50–7.16 (m, 8H, ArH), 6.88 (t, J=8.1 Hz, 1H, ArH), 6.83 (s, 1H, =CH–), 6.73 (d, J=8.7 Hz, 1H, ArH), 6.71–6.63 (m, 1H, ArH), 3.67 (br s, 2H, NH_2); mass m/z 330.32 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}FN_3$: C, 76.58; H, 4.90; N, 12.76. Found: C, 76.42; H, 4.86; N, 12.88.

4.7. General procedure for the Pictet–Spengler reaction on substrate 4

A mixture of 2-(2-phenyl-5-*p*-tolyl-2*H*-pyrazol-3-yl)-phenylamine **4a** (0.10 g, 0.32 mmol), 4-N, *N*-dimethyl-benzaldehyde (0.048 g, 0.32 mmol) and *p*-tolylsulphonic acid (6.08 mg, 0.032 mmol) was refluxed in toluene for 4 h. Toluene was evaporated in vacuo and residue so obtained was dissolved in ethyl acetate (25 mL). The organic layer was washed with 5% aqueous sodium bicarbonate, water (2×10 mL) and brine solution (1×10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated to obtain a residue. The residue was dissolved in DCM–THF (1/1) 10 mL and DDQ (18 mg, 0.08 mmol) was added. The resulting mixture was stirred at rt for 2 h. Then solvent was evaporated in vacuo and the residue so obtained was purified on column chromatography on silica gel with hexane: ethyl acetate (80:20, v/v) as eluent to afford **12a(i)** as a white solid.

4.7.1. Dimethyl-[4-(1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl)-phenyl]-amine [12a(i)]. Yield 79%; off white solid; mp 190–192 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.27 (d, J=8.4 Hz, 1H, ArH), 7.70–7.56 (m, 7H, ArH), 7.36 (d, J=8.4 Hz, 2H, ArH), 7.30 (d, J=7.5 Hz, 1H, ArH), 7.17 (d, J=7.5 Hz, 2H, ArH), 6.96 (d, J=7.8 Hz, 2H, ArH), 6.49 (d, J=8.7 Hz, 2H, ArH), 2.92 [s, 6H, –$N(CH_3)_2$], 2.31 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.90, 151.31, 149.00, 146.32, 141.81, 141.23, 137.31, 130.90, 130.21, 129.90, 129.72, 129.01, 128.42, 127.60, 127.31, 125.41, 121.75, 115.34, 111.93, 40.80, 21.40; mass m/z 455.40 ($M^+ + 1$). Anal. Calcd for $C_{31}H_{26}N_4$: C, 81.91; H, 5.77; N, 12.33. Found: C, 81.81; H, 5.84; N, 12.43.

4.7.2. 4-(4-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(ii)]. Yield 75%; yellow solid; mp 235–237 °C; IR (KBr) ν_{max} 1524, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.4 Hz, 1H, ArH), 8.02 (d, J=8.4 Hz, 2H, ArH), 7.71–7.63 (m, 9H, ArH), 7.42 (t, J=7.5 Hz, 1H, ArH), 7.09 (d, J=7.8 Hz, 2H, ArH), 6.94 (d, J=7.8 Hz, 2H, ArH), 2.29 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=154.15, 148.56, 148.07, 146.13, 145.42, 141.92, 141.04, 138.96, 130.96, 130.27, 129.95, 129.80, 129.65, 128.93, 127.74, 127.15, 123.12, 122.06, 116.03, 114.47, 21.59; mass m/z 457.30 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}N_4O_2$: C, 76.30; H, 4.42; N, 12.27. Found: C, 76.42; H, 4.22; N, 12.43.

4.7.3. 4-(4-Bromo-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(iii)]. Yield 76%; off white solid; mp 210–212 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28 (d, J=8.1 Hz, 1H, ArH), 7.73–7.60 (m, 7H, ArH), 7.39–7.30 (m, 5H, ArH), 7.09 (d, J=7.8 Hz, 2H, ArH), 6.97 (d, J=7.8 Hz, 2H, ArH), 2.35 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.58, 148.88, 146.27, 141.86, 141.21, 138.47, 138.19, 131.57, 131.14, 130.79, 130.21, 129.98, 129.84, 129.56, 128.84, 127.78, 126.56, 123.42, 122.00, 115.8, 114.57, 21.69; mass m/z 490.78 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}BrN_3$: C, 71.03; H, 4.11; N, 8.57. Found: C, 71.42; H, 4.22; N, 8.43.

4.7.4. 4-(2-Methoxy-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(iv)]. Yield 82%; off white; mp 216–218 °C; IR (KBr) ν_{max} 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.4 Hz, 1H, ArH), 7.71–7.61 (m, 8H, ArH), 7.36–7.26 (m, 2H, ArH), 7.09 (d, J=7.2 Hz, 3H, ArH), 6.88 (d, J=7.5 Hz, 2H, ArH), 6.40 (d, J=8.1 Hz, 1H, ArH), 3.18 (s, 3H, –OCH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.35, 154.73, 149.72, 146.51, 141.40, 141.02, 137.70, 130.90, 130.83, 130.66, 130.17, 129.92, 129.44, 129.31, 129.17, 128.25, 127.85, 126.31, 122.04, 121.14, 116.29, 115.95, 110.57, 55.10, 21.67; mass

m/z 442.20 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}N_3O$: C, 81.61; H, 5.25; N, 9.52. Found: C, 81.47; H, 5.22; N, 9.43.

4.7.5. 4-(3,4-Dimethoxy-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(v)]. Yield 80%; yellow solid; mp 158–160 °C; IR (KBr) ν_{max} 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.29 (d, J=8.4 Hz, 1H, ArH), 7.71–7.65 (m, 6H, ArH), 7.58 (d, J=8.1 Hz, 1H, ArH), 7.34 (t, J=7.5 Hz, 1H, ArH), 7.25 (d, J=6.9 Hz, 1H, ArH), 7.19 (d, J=8.4 Hz, 2H, ArH), 7.00 (s, 1H, ArH), 6.96 (d, J=6.9 Hz, 2H, ArH), 6.77 (d, J=8.4 Hz, 1H, ArH), 3.89 (s, 3H, –OCH_3), 3.55 (s, 3H, –OCH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.34, 150.09, 148.86, 148.60, 146.27, 142.09, 141.30, 138.20, 132.25, 130.60, 130.41, 130.19, 130.10, 129.42, 128.75, 127.81, 126.77, 126.15, 122.95, 121.92, 115.68, 114.28, 113.77, 111.28, 56.51, 55.86, 21.65; mass *m/z* 472.33 ($M^+ + 1$). Anal. Calcd for $C_{31}H_{25}N_3O_2$: C, 78.96; H, 5.34; N, 8.91. Found: C, 78.49; H, 5.62; N, 8.54.

4.7.6. {4-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl]-phenyl}-dimethyl-amine [12b(i)]. Yield 82%; pale yellow solid; mp 244–246 °C; IR (KBr) ν_{max} 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.27 (d, J=8.1 Hz, 1H, ArH), 7.69–7.63 (m, 5H, ArH), 7.56 (d, J=8.1 Hz, 1H, ArH), 7.39–7.20 (m, 6H, ArH), 7.12 (d, J=8.1 Hz, 2H, ArH), 6.50 (d, J=8.4 Hz, 2H, ArH), 2.95 [s, 6H, –$N(CH_3)_2$]. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.87, 151.60, 147.99, 146.60, 142.07, 141.25, 134.04, 132.01, 131.51, 131.07, 130.53, 130.22, 130.16, 129.45, 128.13, 127.77, 127.08, 125.79, 121.88, 115.49, 114.62, 112.06, 41.00; mass *m/z* 475.33 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}ClN_4$: C, 75.86; H, 4.88; N, 11.80. Found: C, 75.77; H, 4.99; N, 11.54.

4.7.7. 3-(4-Chloro-phenyl)-4-(4-nitro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(ii)]. Yield 80%; yellow solid; mp 231–233 °C; IR (KBr) ν_{max} 1520, 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.31 (d, J=8.4 Hz, 1H, ArH), 8.09 (d, J=8.6 Hz, 2H, ArH), 7.76–7.61 (m, 9H, ArH), 7.48–7.38 (m, 2H, ArH), 7.15 (d, J=4.2 Hz, 3H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.27, 153.71, 148.24, 145.33, 140.85, 131.98, 131.33, 131.02, 130.54, 130.39, 130.25, 130.03, 129.65, 129.31, 129.06, 128.98, 128.52, 128.01, 127.68, 127.41, 123.37, 122.05, 115.89; mass *m/z* 477.18 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}ClN_4O_2$: C, 70.52; H, 3.59; N, 11.75. Found: C, 70.42; H, 3.75; N, 11.53.

4.7.8. 4-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(iii)]. Yield 76%; white solid; mp 242–244 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28 (d, J=8.4 Hz, 1H, ArH), 7.74–7.67 (m, 6H, ArH), 7.60 (d, J=8.1 Hz, 1H, ArH), 7.40–7.34 (m, 5H, ArH), 7.16 (s, 4H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.18, 147.50, 146.25, 142.05, 141.00, 138.06, 134.83, 131.55, 131.41, 131.37, 131.36, 130.80, 130.39, 130.33, 129.80, 128.38, 127.72, 126.79, 123.79, 121.98, 115.75, 114.32; mass *m/z* 510.33 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}BrClN_3$: C, 65.84; H, 3.35; N, 8.23. Found: C, 65.73; H, 3.39; N, 8.54.

4.7.9. 3-(4-Chloro-phenyl)-4-(2-methoxy-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(iv)]. Yield 79%; pale yellow solid; mp 242–244 °C; IR (KBr) ν_{max} 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.31 (d, J=8.2 Hz, 1H, ArH), 7.72–7.59 (m, 9H, ArH), 7.39–7.29 (m, 1H, ArH), 7.17–7.03 (m, 5H, ArH), 6.46 (d, J=8.2 Hz, 1H, ArH), 3.22 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.21, 154.33, 148.40, 146.52, 141.22, 134.15, 131.99, 131.42, 130.99, 130.91, 130.85, 130.68, 130.19, 130.12, 129.36, 129.18, 128.96, 127.73, 126.50, 122.00, 121.31, 116.17, 115.81, 110.61, 55.06; mass *m/z* 462.15 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}ClN_3O$: C, 75.40; H, 4.36; N, 9.10. Found: C, 75.42; H, 3.55; N, 9.31.

4.7.10. 3-(4-Chloro-phenyl)-4-(3,4-dimethoxy-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(v)]. Yield 82%; pale yellow solid; mp 212–214 °C; IR (KBr) ν_{max} 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.1 Hz, 1H, ArH), 7.73–7.67 (m, 5H, ArH), 7.53 (d, J=7.2 Hz, 1H, ArH), 7.35 (t, J=7.8 Hz, 1H, ArH), 7.28–7.22 (overlapped, 2H, ArH), 7.16 (m, 2H, ArH), 7.05 (m, 2H, ArH), 6.67 (m, 2H, ArH), 3.89 (s, 3H, –OCH_3), 3.68 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.15, 150.36, 148.99, 146.34, 141.14, 134.52, 131.98, 131.88, 131.40, 130.68, 130.27, 129.78, 129.61, 129.32, 129.02, 128.22, 127.74, 126.71, 126.34, 123.29, 121.90, 115.60, 113.36, 111.21, 56.59, 56.05; mass *m/z* 492.20 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{22}ClN_3O_2$: C, 73.24; H, 4.51; N, 8.54. Found: C, 73.57; H, 5.89; N, 8.59.

4.7.11. [4-(8-Fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]-quinolin-4-yl)-phenyl]-dimethyl-amine [12c(i)]. Yield 80%; pale yellow solid; mp 193–195 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.26 (m, 1H, ArH), 7.68–7.67 (overlapped, 5H, ArH), 7.56–7.26 (m, 5H, ArH), 7.23–7.16 (m, 4H, ArH), 6.48 (d, J=8.1 Hz, 2H, ArH), 2.92 [s, 6H, –$N(CH_3)_2$]. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.36, 156.28, 151.53, 149.17, 143.46, 141.73, 140.79, 133.31, 132.79, 132.62, 131.07, 130.29, 128.07, 127.77, 127.14, 118.66, 118.72, 115.90, 114.58, 112.11, 106.95, 106.44, 40.96; mass *m/z* 459.33 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}FN_4$: C, 78.58; H, 5.06; N, 12.22. Found: C, 78.87; H, 5.25; N, 12.45.

4.7.12. 8-Fluoro-4-(4-nitro-phenyl)-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(ii)]. Yield 75%; brown solid; mp 196–198 °C; IR (KBr) ν_{max} 1513, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.34–8.26 (m, 1H, ArH), 8.03 (d, J=8.8 Hz, 2H, ArH), 7.70 (s, 5H, ArH), 7.62 (d, J=8.8 Hz, 2H, ArH), 7.48 (td, J=8.4, 2.8 Hz, 1H, ArH), 7.29–7.10 (overlapped, 6H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=163.24, 158.31, 153.32, 148.44, 148.13, 143.01, 141.62, 140.36, 133.41, 133.23, 132.42, 130.92, 130.69, 130.45, 130.08, 129.01, 128.34, 127.66, 123.20, 119.38, 118.89, 116.70, 114.47, 107.21, 106.71; mass *m/z* 461.23 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}FN_4O_2$: C, 73.04; H, 3.72; N, 12.17. Found: C, 73.42; H, 3.85; N, 12.01.

4.7.13. 4-(4-Bromo-phenyl)-8-fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(iii)]. Yield 77%; off white solid; mp 194–196 °C; IR (KBr) ν_{max} 1592 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ=8.28 (m, 1H, ArH), 7.68 (s, 5H, ArH), 7.46 (td, J=8.1, 2.7 Hz, 1H, ArH), 7.34–7.26 (overlapped, 6H, ArH), 7.23–7.15 (m, 4H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.89, 157.98, 154.70, 148.76, 143.13, 140.52, 137.89, 133.19, 133.00, 132.61, 131.51, 131.25, 130.56, 130.39, 130.13, 128.64, 128.22, 127.70, 123.56, 119.09, 118.60, 116.42, 114.52, 107.10, 106.60; mass m/z 494.33 (M^++1). Anal. Calcd for $C_{28}H_{17}BrFN_3$: C, 68.03; H, 3.47; N, 8.50. Found: C, 68.41; H, 3.25; N, 8.67.

4.7.14. 8-Fluoro-4-(2-methoxy-phenyl)-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(iv)]. Yield 79%; off white solid; mp 212–214 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=8.33–8.26 (m, 1H, ArH), 7.72–7.58 (m, 6H, ArH), 7.42 (td, J=8.0, 2.8 Hz, 1H, ArH), 7.28–7.18 (overlapped, 6H, ArH), 7.09 (d, J=6 Hz, 2H, ArH), 6.39 (d, J=8.2 Hz, 1H, ArH), 3.17 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.81, 157.91, 157.27, 153.90, 149.62, 143.41, 140.74, 133.24, 133.06, 132.65, 130.86, 130.28, 129.43, 128.71, 128.11, 127.76, 127.62, 121.19, 118.62, 118.13, 116.85, 115.98, 110.58, 107.08, 106.59, 55.01; mass m/z 446.26 (M^++1). Anal. Calcd for $C_{29}H_{20}FN_3O$: C, 78.19; H, 4.53; N, 9.43. Found: C, 78.47; H, 4.25; N, 9.58.

4.7.15. 4-(3,4-Dimethoxy-phenyl)-8-fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(v)]. Yield 80%; yellow solid; mp 185–187 °C; IR (KBr) ν_{max} 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.29 (m, 1H, ArH), 7.68 (m, 5H, ArH), 7.44 (td, J=8.1, 5.4 Hz, 1H, ArH), 7.31–7.24 (overlapped, 4H, ArH), 7.20–7.12 (m, 3H, ArH), 6.87 (s, 1H, ArH), 6.82 (d, J=8.4 Hz, 1H, ArH), 3.88 (s, 3H, –OCH_3), 3.52 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.77, 155.52, 150.14, 148.80, 148.59, 143.14, 140.62, 133.08, 132.79, 131.91, 130.49, 130.37, 130.18, 128.56, 128.11, 127.73, 122.76, 118.92, 118.34, 116.31, 114.37, 113.63, 111.31, 107.00, 106.50, 56.47, 55.85; mass m/z 476.20 (M^++1). Anal. Calcd for $C_{30}H_{22}FN_3O_2$: C, 75.78; H, 4.66; N, 8.84. Found: C, 75.57; H, 4.95; N, 8.67.

4.7.16. 2-(1-Phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl)-phenol [12c(vi)]. Yield 75%; off white solid; mp 201–203 °C; IR (KBr) ν_{max} 1597, 3425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=8.15 (d, J=8.4 Hz, 1H, ArH), 7.68–7.57 (overlapped, 6H, ArH), 7.55 (d, J=8.2 Hz, 1H, ArH), 7.38–7.27 (m, 3H, ArH), 7.20–7.03 (m, 5H, ArH), 6.26 (t, J=7.4 Hz, 1H, ArH), 2.35 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=158.47, 156.13, 149.27, 143.79, 142.69, 141.13, 138.58, 133.60, 131.50, 130.65, 130.29, 130.11, 129.89, 129.12, 127.84. 127.29, 126.64, 122.04, 120.12, 118.22, 117.45, 115.69, 113.10, 21.72; mass m/z 427.18 (M^++1). Anal. Calcd for $C_{29}H_{21}N_3O$: C, 81.48; H, 4.95; N, 9.83. Found: C, 81.76; H, 4.55; N, 9.53.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.063.

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Tetrahedron 62 (2006) 3242–3247
Tetrahedron

A simple iodination protocol via in situ generated ICl using NaI/$FeCl_3$

Arasambattu K. Mohanakrishnan,* Chandran Prakash and Neelamegam Ramesh

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, Tamil Nadu, India

Received 4 November 2005; revised 27 December 2005; accepted 19 January 2006

Available online 14 February 2006

Abstract—A novel iodination of silyl-enol ethers using hitherto unexplored NaI/$FeCl_3$ system is reported. The procedure has been extended to the iodination of aromatic and hetero aromatic compounds.
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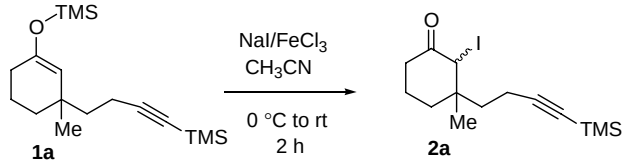
1. Inroduction

In general iodination is a relatively difficult process compared to bromination and hence several additives have been used to enhance the rate of iodination reaction.[1] Olah and co-workers reported an iodination of electron-deficient aromatic compounds using *N*-iodosuccinimide in trifluoromethanesulfonic acid.[2] Tour and Kosynkin reported[3] a facile preparation of iodoanilines using a combination of benzyltriethylammonium dichloroiodate and sodium bicarbonate. A novel synthesis of heterocyclic iodo compounds are reported using potassium dichloroiodate under aqueous condition.[4] Colobert and co-workers reported a mild and regioselective iodination of electron-rich aromatics using *N*-iodosuccinimide in the presence of a catalytic amount of TFA,[5] wherein the iodination was proceeded through the formation of iodotrifluroacetate. Bedekar and co-workers reported[6] an environmentally benign halogenation of aromatic amines, hydrocarbons and naphthols. Recently, Krishnan Mohan et al. reported a regioselective oxiiodination of aromatic compounds using ammonium iodide and oxone.[7] A regioselective bromination of aromatic compounds using LiBr-tetrabutylammonim peroxydisulfate has been observed.[8] Braddock and co-workers reported a similar bromination using LiBr-(diacetoxyiodo)-benzene.[9] Sha and co-workers reported a facile iodination of silyl-enol ether using NaI and *m*-CPBA.[10]

2. Results and discussion

In an ongoing project we required a wide variety of α-bromo/iodo ketones for our work on the synthesis of carbocyclic natural products involving a tandem cyclization of a α-carbonyl radical. The required silyl-enol ethers were smoothly prepared via a CuI promoted 1,4-addition of various Grignards to enones. Initially the iodination/bromination of silyl-enol ether **1a** was tried using NIS/NBS without any success. The existing procedure for iodination using NaI/*m*-CPBA requires the preparation of dry *m*-CPBA, which is somewhat difficult and also problematic. Additionally we had a lot of problems with the reproducibility of this iodination reaction using NaI/*m*-CPBA protocol. Considering the synthetic utility of α-iodo ketones we sought to develop a simple procedure, which can iodinate silyl-enol ether in a reasonable yield. We envisioned that $FeCl_3$[11] could be used for oxidation of the iodide under a mild condition. Our method is based on the generation of electrophilic iodonium ion in situ via the interaction of NaI with $FeCl_3$ in acetonitrile.

As a model reaction silyl-enol ether **1a**[12] was reacted with NaI and $FeCl_3$ (1:2 molar ratio) in acetonitrile at 0 °C to room temperature for 2 h followed by usual workup and column chromatographic purification afforded iodo compound **2a** in 72% yield, Scheme 1. It should be mentioned that when the iodination was performed with 1 mol equiv of NaI/$FeCl_3$ (1:1 molar ratio) it was found to be incomplete.



Scheme 1. Preparation of iodoketone **2a**.

Keywords: Iodination; Silyl-enol ether; Iodo cycloalkanones; Iodoindoles.
* Corresponding author. Tel.: +91 44 24451108; fax: +91 44 22352494; e-mail: mohan_67@hotmail.com

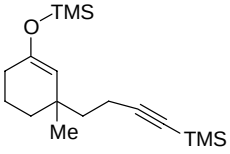
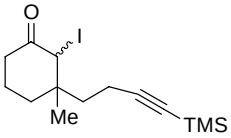
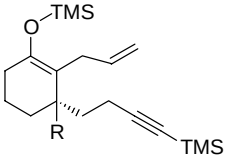
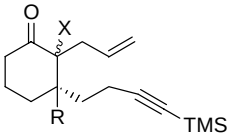
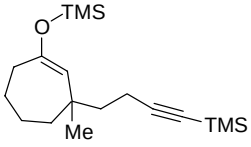
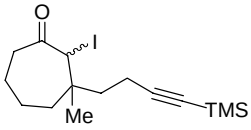
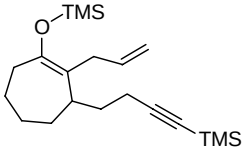
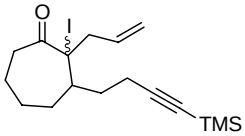
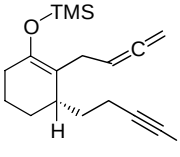
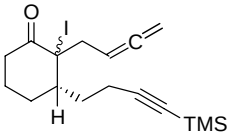
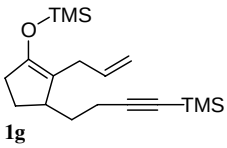
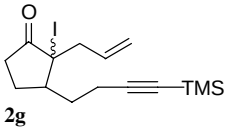
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.067

TLC analysis of the pure iodo compound **2a** indicated as a diastereomeric mixture. The ^{1}H NMR spectrum of **2a** confirmed the presence of two diastereomers in the ratio of 1:1, in which the methyl protons appeared as two singlets at δ 0.91 and 0.98 with equal intensity. The ^{13}C NMR spectrum further evidenced the existence of two diastereomers in which twenty-four carbon signals were observed for **2a**. The electron impact mass spectrum of **2a** exhibited $[M-15]^+$ peak at *m*/*z* 347 probably due to the loss of one methyl radical.

Under identical conditions several silyl-enol ethers **1b–g** also underwent a smooth iodination/bromination to afford the respective 2-iodo/bromo cycloalkanones **2b–g** in moderate to good yields. The iodination/bromination details of the silyl-enol ethers and the yield of the respective iodo/bromo compounds are presented in Table 1. The silyl-enol ethers **1b** and **1c** could also be converted into the corresponding α-bromo compounds **2b** and **2c** in 58 and 56% yields under identical conditions using NaBr/$FeCl_3$ (entry 2). Relatively the bromination of silyl-enol ethers **1b** and **1c** are found to be slower than the iodination, and also the yield of α-bromo compounds are almost 5% less than the corresponding iodo compounds (entry 2). The formation of tertiary α-iodo/bromo compounds **2b**, **2c**, **2c′**, **2e**, **2f** and **2g** are found to proceed with somewhat diminished yields (entries 2–6). The ^{1}H NMR spectrum of **2c**, **2c′** and **2d** confirmed the existence of diastereomers in the ratio of 1:1 based on the methyl protons, which appeared as two singlets with equal intensity. The ^{13}C NMR signals for compounds **2b**, **2c**, **2c′** and **2d** were found to be doubled due to the existence of two diastereomers. Surprisingly the compounds **2e**, **2f** and **2g** exhibited only 14, 16 and 14 C-13 signals, respectively. The bromo compound **2b**, **2c** and iodo compound **2c′** exhibited M^+ion peaks at *m*/*z* 340, 354 and 402, respectively. The iodo compound **2d** exhibited $[M-15]^+$ ion peak at *m*/*z* 361.

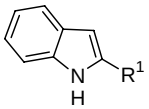
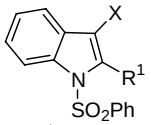
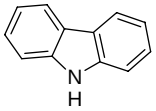
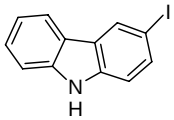
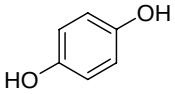
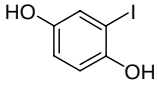
We have extended the mild iodination procedure to the synthesis of various iodoindoles,[13] Table 2. Since the *N*-free iodoindoles are somewhat less stable, the iodination yield

Table 1. Synthesis of halo compounds using NaX/$FeCl_3$

Entry	Substrates	Condition[a]	Iodo/bromo compounds	Yield (%)[b]
1	 **1a**	NaI/$FeCl_3$, 2 h	 **2a**	72
2	 **1b** R=H; **1c** R=Me	NaBr/$FeCl_3$, 4 h NaI/$FeCl_3$, 3 h	 **2b** R=H, X=Br; **2c** R=Me, X=Br; **2c′** R=Me, X=I	58; 56; 60
3	 **1d**	NaI/$FeCl_3$, 3 h	 **2d**	63
4	 **1e**	NaI/$FeCl_3$, 3 h	 **2e**	53
5	 **1f**	NaI/$FeCl_3$, 3 h	 **2f**	55
6	 **1g**	NaI/$FeCl_3$, 3 h	 **2g**	58

[a] CH_3CN used as a solvent.
[b] Isolated yield after column chromatography.

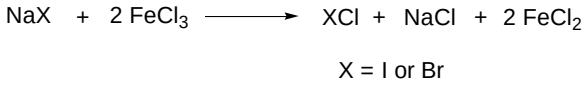
Table 2. Synthesis of halo aromatics using NaX/$FeCl_3$

Entry	Substrates	Condition[a]	Iodo/bromo compounds	Yield (%)[b]
1	 **3** R^1=H; **4** R^1=Me	NaI/$FeCl_3$, 6 h NaBr/$FeCl_3$, 7 h	 **5a** R^1=H, X=I; **5b** R^1=Me, X=I; **6a** R^1=H, X=Br; **6b** R^1=Me, X=Br	72; 81; 74; 76
2	 **7**	NaI/$FeCl_3$, 8 h	 **8**	68
3	 **9**	NaI/$FeCl_3$, 5 h	 **10**	75

[a] CH_3CN used as a solvent.
[b] Isolated yield after column chromatography.

was calculated based on *N*-phenylsufonylated derivative. It should be mentioned that many iodoindoles are utilized as crucial intermediates towards the synthesis of several indole alkaloids.[14] The iodination methodology has been further generalized with the synthesis of iodocarbazole[15] (entry 2) and 2-iodohydroquinone[16] (entry 3).

The observed iodination/bromination may proceed through the intermediacy of ICl/BrCl generated in situ via the oxidation of NaX by the 2 equiv of anhydrous $FeCl_3$ (Scheme 2).



Scheme 2. Mechanism of iodination protocol.

3. Conclusions

In conclusion, we have described a simple and efficient halogenation protocol using NaX/$FeCl_3$ system. Using the procedure several α-iodoketones are prepared in good yields. The α-iodo cycloalkanones **2a–g** could be used as crucial intermediates to the synthesis of angular tricyclic framework of carbocyclic natural products such as dankasterone,[17] laurenene,[18] and guanacastepene.[19] The iodination procedure has been successfully applied to the synthesis of 3-iodoindoles, 3-iodocarbazole and 2-iodohydroquinone. Hopefully this procedure will find wide application since it is mild and environmentally benign. Further application of this methodology and also the synthetic utility of α-iodo cycloalkanones will be explored in due course.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL 400 spectrometer at 400 and 100 MHz and Varian Gemini-300, respectively. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. Elemental analysis were carried out on a Perkin-Elmer 240 B instrument.

4.2. Representative procedure for iodination of silyl-enol ether 2a–g

To a solution of $FeCl_3$ (525 mg, 3.2 mmol) in acetonitrile (20 mL), NaI (243 mg, 1.6 mmol) was added and stirred at 0 °C for 15 min. To this, a solution of silyl-enol ether **1a** (500 mg, 1.6 mmol) in acetonitrile (5 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. It was then quenched (consumption of starting material indicated by TLC) with saturated NH_4Cl solution and reaction mixture was extracted with Et_2O (2×20 mL). The organic layer was separated and washed with saturated $Na_2S_2O_3$ (2×10 mL) solution, water (20 mL) and dried (Na_2SO_4). Removal of solvent followed by flash column chromatographic purification (silica gel, 1% ethyl acetate in hexane) afforded moderately stable iodo compound **2a** as a pale yellow liquid (425 mg, 72%).

4.2.1. 2-Iodo-3-methyl-3-(4-trimethylsilyl-3-butynyl)-1-cyclohexanone 2a. Following the general procedure, compound **2a** was obtained as a pale yellow liquid in 72% yield; (Found: C, 46.32; H, 6.47. $C_{14}H_{23}IOSi$ requires C, 46.41; H, 6.40%); IR (liquid) ν_{max}: 2175, 1710, 844, 763 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.32 and 4.10 (1H, 2s, COC*H*I), 2.13–2.02 (4H, m, CH_2CH_2), 1.77–1.69 (2H, m, CH_2), 1.61–1.48 (4H, m, CH_2CH_2), 0.98 and 0.91 (3H, 2s, *Me*), 0.10 and 0.09 (9H, 2s, Si*Me*$_3$); δ_C (100 MHz, $CDCl_3$) 205.2, 204.7, 106.3, 106.0, 85.4, 84.9, 53.4, 48.6, 46.4, 41.6, 40.9, 35.7, 35.1, 32.2, 31.2, 26.8, 24.5, 21.0, 20.9, 19.7, 14.5, 14.1, 0.1, 0.05; MS (EI) *m/z* (%): 347 $[M-15]^+$, (25%), 221 (41), 179 (21), 149 (26), 128 (54), 82 (100).

4.2.2. 2-Bromo-2-(2-allyl)-3-(4-trimethylsilyl-3-butynyl)-1-cyclohexanone 2b. Following the general procedure, compound **2b** was obtained as a pale yellow liquid in 58% yield; (Found: C, 56.42; H, 7.29. $C_{16}H_{25}BrOSi$ requires C, 56.30; H, 7.38%); IR (liquid) ν_{max}: 2171, 1712, 1610, 845, 759 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.71–5.66 (1H, m, $CH_2CH{=}CH_2$), 5.20–5.08 (2H, m, $CH_2CH{=}CH_2$), 3.32 (1H, dd, $J=5.6$, 5.6 Hz, $CHCH{=}CH_2$), 3.18 (1H, m, CH_2CHCH_2), 2.78 (1H, dd, $J=8.4$, 8.4 Hz, $CHCH{=}CH_2$), 2.42–2.21 (2H, m, CH_2CH_2), 2.02–1.89 (4H, m, CH_2CH_2-CH_2), 1.68–1.51 (4H, m, $CH_2CH_2CH_2$), 0.15 and 0.12 (9H, 2s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 203.2, 202.9, 133.4, 132.3, 119.8, 119.3, 107.1, 106.1, 76.71, 75.0, 46.4, 43.3, 41.1, 39.9, 37.1, 36.6, 29.8, 27.7, 26.5, 25.9, 24.4, 24.2, 22.0, 19.4, 17.9, 17.3, 0.16, 0.07; MS (EI) *m/z* (%): 342 $[M+2]^+$, (15%), 340 (M^+, 15), 308 (12), 261 (78), 170 (65), 129 (82), 73 (100).

4.2.3. 2-Bromo-2-(2-allyl)-3-methyl-3-(4-trimethylsilyl-3-butynyl)-1-cyclohexanone 2c. Following the general procedure, compound **2c** was obtained as a pale yellow liquid in 56% yield; (Found: C, 57.56; H, 7.74. $C_{17}H_{27}$-BrOSi requires C, 57.45; H, 7.66%); IR (liquid) ν_{max}: 2173, 1712, 1613, 848, 762 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.58–5.52 (1H, m, $CH_2CH{=}CH_2$), 5.09–5.00 (2H, m, CH_2-$CH{=}CH_2$), 3.89 (1H, d, $J=15.0$ Hz, $CHCH{=}CH_2$), 2.41 (1H, dd, $J=8.3$, 5.4 Hz, $CHCH{=}CH_2$), 2.39–2.07 (2H, m, $CH_2CH_2CH_2$), 1.96–1.60 (4H, m, $CH_2CH_2CH_2$), 1.32–1.19 (4H, m, $CH_2CH_2CH_2$), 1.01 and 0.77 (3H, 2s, *Me*), 0.13 and 0.11 (9H, 2s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 204.6, 203.1, 132.1, 131.9, 118.5, 118.0, 107.8, 107.1, 84.3, 84.1, 61.3, 58.3, 45.1, 38.9, 38.5, 37.4, 37.3, 36.4, 33.7, 31.4, 31.2, 25.0, 21.8, 21.6, 19.4, 17.7, 15.0, 14.4, 0.16, 0.07; MS (EI) *m/z* 356 $[M+2]^+$, (18), 354 (M^+, 18), 341 (14), 278 (23), 253 (65), 190 (35), 116 (76), 82 (100%).

4.2.4. 2-Iodo-2-(2-allyl)-3-methyl-3-(4-trimethylsilyl-3-butynyl)-1-cyclohexanone 2c′. Following the general procedure, compound **2c′** was obtained as a pale yellow liquid in 60% yield; (Found: C, 50.87; H, 6.68. $C_{17}H_{27}IOSi$ requires C, 50.74; H, 6.76%); IR (liquid) ν_{max}: 2175, 1710, 1610, 844, 760 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.78–5.66 (1H, m, $CH_2CH{=}CH_2$), 5.46–5.32 (2H, m, $CH_2CH{=}CH_2$), 4.08 (1H, d, $J=13.5$ Hz, $CHCH{=}CH_2$), 2.58 (1H, dd, $J=$ 8.4, 5.6 Hz, $CHCH{=}CH_2$), 2.48–2.16 (2H, m, CH_2CH_2-CH_2), 2.03–1.68 (4H, m, $CH_2CH_2CH_2$), 1.43–1.24 (4H, m, $CH_2CH_2CH_2$), 1.16 and 0.98 (3H, 2s, *Me*), 0.13 and 0.11 (9H, 2s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 204.7, 203.4, 132.2, 131.9, 118.4, 118.1, 108.0, 107.3, 84.5, 84.1, 62.8, 59.3, 46.2, 39.2, 38.6, 37.9, 37.4, 36.8, 33.8, 32.5, 32.2, 25.6, 22.4, 21.3, 19.9, 17.3, 15.7, 15.5, 0.19, 0.09; MS (EI) *m/z* 402 (M^+, 13), 277 (31), 261 (6), 234 (4), 127 (95), 82 (100%).

4.2.5. 2-Iodo-3-methyl-3-(4-trimethylsilyl-3-butynyl)-1-cycloheptanone 2d. Following the general procedure, compound **2d** was obtained as a pale yellow liquid in 63% yield; (Found: C, 48.05; H, 6.77. $C_{15}H_{25}IOSi$ requires C, 47.87; H, 6.70%); IR (liquid) ν_{max}: 2173, 1706, 840, 758 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.33 and 4.24 (1H, 2s, $COCHI$), 2.47–2.23 (3H, m, CH_2CHCH_2), 2.16–2.03 (3H, m, CH_2CHCH_2), 1.86–1.71 (2H, m, $CH_2CH_2CH_2$), 1.69–1.24 (4H, m, $CH_2CH_2CH_2$), 0.96 and 0.89 (3H, 2s, *Me*), 0.14 and 0.10 (9H, 2s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 205.6, 204.9, 108.3, 107.4, 86.3, 85.7, 65.3, 64.9, 62.4, 61.2, 57.6, 53.4, 49.4, 42.2, 37.8, 30.3, 29.3, 27.8, 24.4, 22.9, 19.6, 19.1, 18.1, 17.4, 0.13, 0.08; MS (EI) *m/z* 361 $[M-15]^+$, (23), 347 (10), 235 (20), 221 (12), 127 (35), 82 (100%).

4.2.6. 2-Iodo-2-(2-allyl)-3-(4-trimethylsilyl-3-butynyl)-1-cycloheptanone 2e. Following the general procedure, compound **2e** was obtained as a pale yellow liquid in 53% yield; IR (liquid) ν_{max}: 2174, 1704, 1610, 842, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.86–5.76 (1H, m, $CH_2CH{=}CH_2$), 5.08–4.96 (2H, m, $CH_2CH{=}CH_2$), 3.30 (1H, dt, $J=2.4$, 11.4 Hz, $CHCH{=}CH_2$), 3.09 (1H, dd, $J=6.1$, 14.4 Hz, CH_2CHCH_2), 2.72 (1H, dd, $J=7.8$, 14.1 Hz, $CHCH{=}CH_2$), 2.58–2.34 (3H, m, CH_2CHCH_2), 2.28–2.08 (3H, m, CH_2CHCH_2), 1.94–1.72 (2H, m, $CH_2CH_2CH_2$), 1.58–1.26 (4H, m, $CH_2CH_2CH_2$), 0.13 and 0.10 (9H, 2s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 205.8, 136.8, 117.4, 105.7, 86.0, 64.9, 42.1, 37.9, 30.4, 30.3, 27.3, 18.3, 0.16, 0.09; HRMS (EI): M^+ found 402.0867. $C_{17}H_{27}IOSi$ requires 402.0876.

4.2.7. 2-Iodo-2-(2,3-butadienyl)-3-(4-trimethylsilyl-3-butynyl)-1-cyclohexanone 2f. Following the general procedure, compound **2f** was obtained as a pale yellow liquid in 55% yield; IR (liquid) ν_{max}: 2174, 1950, 1704, 1610, 842, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.02–4.97 (1H, m, $CH{=}C{=}CH_2$), 4.68–4.63 (2H, m, $CH{=}C{=}CH_2$), 3.48–3.36 (2H, m, $CH_2CH{=}C{=}CH_2$), 2.89–2.80 (1H, m, CH_2CHCH_2), 2.38–2.15 (4H, m, $CH_2CH_2CH_2$), 1.98–1.82 (2H, m, $CH_2CH_2CH_2$), 1.55–1.31 (4H, m, $CH_2CH_2CH_2$), 0.12 and 0.06 (9H, 2s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 209.3, 203.5, 125.1, 106.0, 87.1, 85.5, 75.2, 43.5, 38.9, 35.8, 32.6, 27.5, 24.3, 17.2, 0.16, 0.09; HRMS (EI): M^+ found 400.0711. $C_{17}H_{27}IOSi$ requires 400.0719.

4.2.8. 2-Iodo-2-(2-allyl)-3-(4-trimethylsilyl-3-butynyl)-1-cyclopentanone 2g. Following the general procedure, compound **2g** was obtained as a pale yellow liquid in 58% yield; (Found: C, 48.27; H, 6.25. $C_{15}H_{23}IOSi$ requires C, 48.13; H, 6.19%); IR (liquid) ν_{max}: 2174, 1704, 1610, 842, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.64–5.57 (1H, m, $CH_2CH{=}CH_2$), 5.12–5.02 (2H, m, $CH_2CH{=}CH_2$), 3.08 (1H, dd, $J=6.7$, 14.5 Hz, $CHCH{=}CH_2$), 2.67 (1H, dd, $J=$ 7.8, 13.8 Hz, CH_2CHCH_2), 2.43 (1H, dd, $J=7.8$, 17.3 Hz, $CHCH{=}CH_2$), 2.38–2.15 (2H, m, CH_2CH_2), 2.14–2.03 (1H, m, CH_2CH), 1.98–1.82 (2H, m, CH_2CH_2), 1.47–1.33 (2H, m, CH_2CH_2), 0.89–0.82 (1H, m, $CHCH_2$), 0.14 and 0.07 (9H, 2s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 210.9, 133.9, 119.8, 107.1, 85.6, 63.7, 43.9, 42.8, 34.3, 34.2, 25.2, 16.9, 0.14, 0.08; MS (EI) *m/z* 374 (M^+, 15), 247 (100), 206 (43), 148 (23%).

4.3. Representative procedure for iodination of indole 5a–10

4.3.1. 1-Phenylsulfonyl-3-iodoindole 5a. To a solution of $FeCl_3$ (1.39 g, 8.5 mmol) in acetonitrile (20 mL), NaI (0.64 g, 4.3 mmol) was added and stirred at 0 °C for 15 min. To this, indole **3** (0.5 g, 4.3 mmol) was added and the stirring was continued for an additional 6 h. The reaction mixture was then poured into saturated NH_4Cl solution, extracted with ethyl acetate (2×20 mL). The organic layer

was washed with saturated $Na_2S_2O_3$ solution (20 mL), water (20 mL), dried (Na_2SO_4) and the solvent was removed under vacuo. (0.94 g, 90%). The crude product used as such for next step without any further purification. The crude 3-iodoindole (0.84 g, 3.5 mmol) and phenylsulfonyl chloride (0.5 mL, 3.9 mmol) were dissolved in benzene (20 mL). To this 60% NaOH solution (10 mL) was added along with tetrabutylammonium hydrogensulfate (50 mg). The two-phase system was stirred for 1 h at room temperature. Then the reaction mixture was diluted with water (20 mL), the organic layer separated and dried (Na_2SO_4). Removal of solvent followed by crystallization from MeOH afforded **5a** (0.95 g, 72%) as brown crystals, mp 124 °C; [Found: C, 43.97; H, 2.71; N, 3.59; S, 8.34. $C_{14}H_{10}INO_2S$ requires C, 43.88; H, 2.63; N, 3.66; S, 8.37%]; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, d, $J=8.3$ Hz), 8.14 (2H, d, $J=8.3$ Hz), 7.81 (1H, s), 7.71–7.76 (1H, m), 7.61–7.65 (3H, m), 7.50–7.52 (2H, m); δ_C (100 MHz, $CDCl_3$) 137.8, 134.9, 134.4, 130.2, 129.3, 126.9, 125.9, 125.3, 124.1, 121.2, 113.4, 101.1; MS (EI) *m/z* 383 (M^+, 22), 256 (42), 115 (73), 77 (100%).

4.3.2. 1-Phenylsulfonyl-3-iodo-2-methyindole 5b. Following the general procedure, compound **5b** was obtained as a brown solid in 81% yield; mp 130 °C; [Found: C, 45.41; H, 3.09; N, 3.57; S, 8.13. $C_{15}H_{12}INO_2S$ requires C, 45.35; H, 3.04; N, 3.53; S, 8.07%]; δ_H (300 MHz, $CDCl_3$) 8.16 (1H, d, $J=7.8$ Hz), 7.78 (2H, d, $J=7.5$ Hz), 7.24–7.56 (6H, m), 2.71 (3H, s); δ_C (75 MHz, $CDCl_3$) 138.9, 137.2, 136.5, 134.3, 130.3, 129.5, 126.9, 126.2, 125.3, 119.7, 115.1, 101.7, 14.2; MS (EI) *m/z* 397 (M^+, 15), 256 (48), 129 (46), 77 (100%).

4.3.3. 1-Phenylsulfonyl-3-bromoindole 6a. Following the general procedure, compound **6a** was obtained as a pale yellow solid in 74% yield; mp 120 °C; [Found: C, 50.08; H, 2.94; N, 4.11; S, 9.61. $C_{14}H_{10}BrNO_2S$ requires C, 50.01; H, 3.00; N, 4.17; S, 9.54%]; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, d, $J=8.3$ Hz), 8.12 (2H, d, $J=8.3$ Hz), 7.87 (1H, s), 7.70–7.76 (1H, m), 7.61–7.67 (3H, m), 7.52–7.55 (2H, m); δ_C (100 MHz, $CDCl_3$) 137.7, 134.2, 134.1, 129.3, 126.8, 125.8, 124.7, 123.9, 120.0, 113.5, 99.8; MS (EI) *m/z* 338 $[M+2]^+$, (47%), 336 (M^+, 47), 195 (73), 115 (47), 77 (100%).

4.3.4. 1-Phenylsulfonyl-3-bromo-2-methylindole 6b. Following the general procedure, compound **6b** was obtained as a pale yellow solid in 76% yield; mp 125 °C; [Found: C, 51.38; H, 3.51; N, 3.96; S, 9.11. $C_{15}H_{12}BrNO_2S$ requires C, 51.44; H, 3.45; N, 4.00; S, 9.16%]; IR (KBr) ν_{max}: 1368, 1180 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.19 (1H, d, $J=$ 8.3 Hz), 7.77 (2H, d, $J=7.3$ Hz), 7.49–7.53 (1H, s), 7.38–7.42 (2H, m), 7.24–7.35 (3H, m), 2.63 (3H, s); δ_C (100 MHz, $CDCl_3$) 138.6, 136.9, 135.6, 133.9, 129.3, 128.9, 126.3, 125.2, 124.1, 119.2, 114.5, 101.5, 13.9; MS (EI) *m/z* 352 $[M+2]^+$, (46), 350 (M^+, 46), 209 (100), 129 (44), 77 (49%).

4.3.5. 3-Iodocarbazole 8.[15] Following the general procedure, compound **8** was obtained as a white solid in 68% yield; mp 190 °C (lit.[15] mp 191 °C); [Found: C, 49.28; H, 2.79; N, 4.72. $C_{12}H_8IN$ requires C, 49.17; H, 2.75; N, 4.78%]; δ_H (400 MHz, $CDCl_3$) 10.23 (1H, s), 8.25 (1H, s), 7.96 (1H, d, $J=8.3$ Hz), 7.90 (1H, d, $J=7.8$ Hz), 7.52 (1H, d, $J=8.3$ Hz), 7.29 (1H, t, $J=8.3$ Hz), 7.19 (1H, d, $J=$ 8.3 Hz), 7.09 (1H, t, $J=7.3$ Hz); δ_C (100 MHz, $CDCl_3$) 139.3, 132.8, 124.9, 124.8, 122.2, 119.5, 119.3, 118.4, 117.9, 112.4, 110.4, 80.3; MS (EI) *m/z* 293 (M^+, 42), 272 (24), 209 (15), 164 (100%).

4.3.6. 2-Iodohydroquinone 10.[16] Following the general procedure, compound **10** was obtained as a white solid in 75% yield; mp 115 °C (lit.[16] mp 115–117 °C); [Found: C, 30.67; H, 2.21. $C_6H_5IO_2$ requires C, 30.53; H, 2.14%]; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, s), 8.01 (1H, d, $J=7.6$ Hz), 7.58 (1H, d, $J=8.4$ Hz), 7.43 (1H, d, $J=8.4$ Hz); δ_C (100 MHz, $CDCl_3$) 134.7, 133.9, 131.0, 130.3, 129.9, 128.3; MS (EI) *m/z* 236 (M^+, 46), 167 (26), 158 (38), 139 (48), 117 (66), 109 (53), 101 (57), 97 (47), 68 (100%).

Acknowledgements

We thank CSIR (01/1765/02/EMR-II), New Delhi for the financial support. C.P. thanks CSIR for fellowship. Financial support to the Department by DST-FIST is also acknowledged.

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Tetrahedron 62 (2006) 3248–3258
Tetrahedron

Synthesis of thiol-modified peptide nucleic acids designed for post-assembly conjugation reactions

Martijn C. de Koning, Lene Petersen, Jimmy J. Weterings, Mark Overhand, Gijsbert A. van der Marel and Dmitri V. Filippov*

Leiden Institute of Chemistry, Leiden University, PO Box 9502, 2300 RA Leiden, The Netherlands

Received 28 October 2005; revised 23 December 2005; accepted 19 January 2006

Available online 14 February 2006

Abstract—Two orthogonally protected PNA monomers were prepared having the mercaptomethyl moiety attached to the PNA backbone. These building blocks were employed in solid-phase PNA synthesis and it was shown that Boc/S-*p*-methoxybenzyl protection scheme was only satisfactory for the introduction of N-terminal thiol modification while the Fmoc/S-butylthio protected monomer proved to be amenable to elongation. The mercaptomethyl modification did not influence the thermal stability of a PNA/RNA duplex. The feasibility of PNA–PNA native ligation was demonstrated.
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1. Introduction

Peptide nucleic acids (PNAs) are achiral, uncharged DNA mimics that bind strongly to DNA and RNA in a sequence-specific manner.[1–3] PNAs are composed of repeating 2-aminoethylglycine units of which the secondary amine is connected to a nucleobase via a methylene–carbonyl linker (Fig. 1, **1**). PNAs are both chemically and biologically stable, which makes them attractive as leads for the development of gene therapeutics and as biomolecular tools.[1,4]

PNAs have been conjugated to a wide variety of ligands, such as artificial nucleases,[5] peptides,[6] intercalators[7,8] or fluorescent reporter groups[9] in order to combine the favorable properties of both entities in a single construct. In most of these conjugates the ligand is attached to either the C- or N-terminal end of the PNA. Current strategies to link ligands at various points along the PNA chain rely on replacement of a nucleobase by the desired ligand.[8,10]

We reasoned that the development of a PNA monomer in which the backbone is provided with a suitable handle would give the opportunity to connect various ligands at a predetermined position in the PNA sequence.

Over the years, a number of backbone-modified PNAs have been prepared[11] to study the effect of introducing chirality, charge or steric bulk on their physicochemical properties such as hybridization or solubility. In a very recent article, Englund and Appella[12] describe an amine-modified PNA backbone for linkage to a fluorophore. Alternatively, the application of a suitably protected thiol-modified PNA monomer (**2**) would give access to a PNA oligomer (**3**) containing a sulfhydryl group suitable for post-assembly conjugation employing well-established conjugation methods[6] (Fig. 1, **4**). Moreover, the installation of a thiol-modified PNA monomer at the N-terminus of a PNA sequence leads to a PNA with the N-terminal 1,2-aminothiol motive (**5**), which may be exploited in a chemical ligation reaction[13] with a PNA thioester (**6**)[14] to give the full length PNA (**3**) having the modified PNA monomer at the ligation site.

In this paper, we focus on the synthesis of two suitably protected thiol-modified PNA monomers (**12** and **23**, Fig. 2) and their incorporation into PNA oligomers. The position and stereochemistry (*R*-isomer and substitution at the γ-position) seemed favorable in terms of accommodation of a substituent on the basis of the NMR-structures of a PNA/R(D)NA duplex.[15] While many PNA backbone modifications have shown a deleterious effect on PNA hybridization,[16] we show that the thiol modification in **3**

Keywords: Peptide nucleic acid; Conjugation; Solid-phase synthesis.
Abbreviations: Boc, *t*-butyloxycarbonyl; Bhoc, benzhydryloxycarbonyl; DTT, dithiothreitol; Fmoc, 9-fluorenylmethyloxycarbonyl; PMB, *para*-methoxybenzyl; EDC, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride; HATU, 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole hydrate; TFA, trifluoroacetic acid; NMM, *N*-methylmorpholine; TEA, triethylamine; Cbz, benzyloxycarbonyl; DIC, diisopropylcarbodiimide; DiPEA, diisopropylethylamine; TIS, triisopropylsilane; TFMSA, trifluoromethanesulfonic acid; MBHA, methylbenzhydrylamine; ma, major; mi, minor.
* Corresponding author. Tel.: +31 71 5274353; fax: +31 71 5274307; e-mail: filippov@chem.leidenuniv.nl

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doi:10.1016/j.tet.2006.01.065

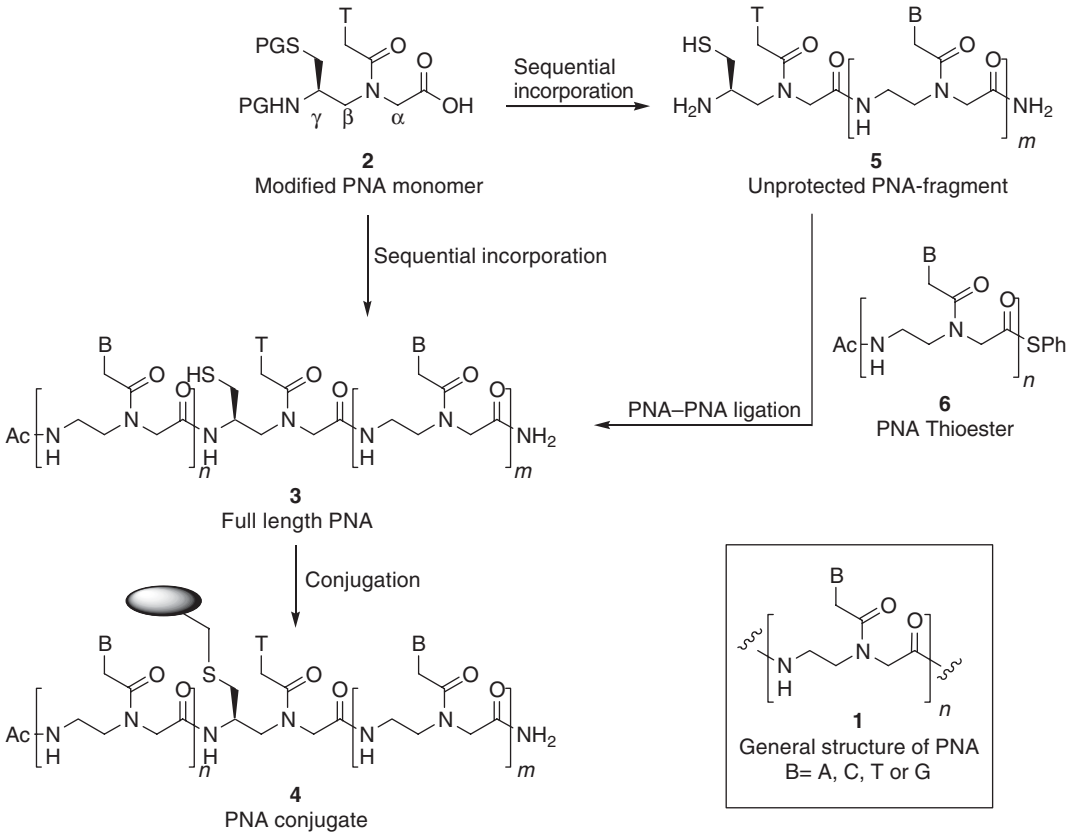


Figure 1. Synthetic strategies towards thiol-modified PNA oligomers.

hardly influences the stability of a PNA/RNA duplex. Finally, we provide data that support the assumption that the PNA–PNA ligation approach is feasible with N-terminal thymine monomers.[17]

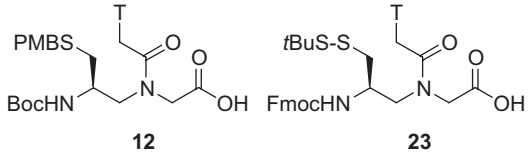
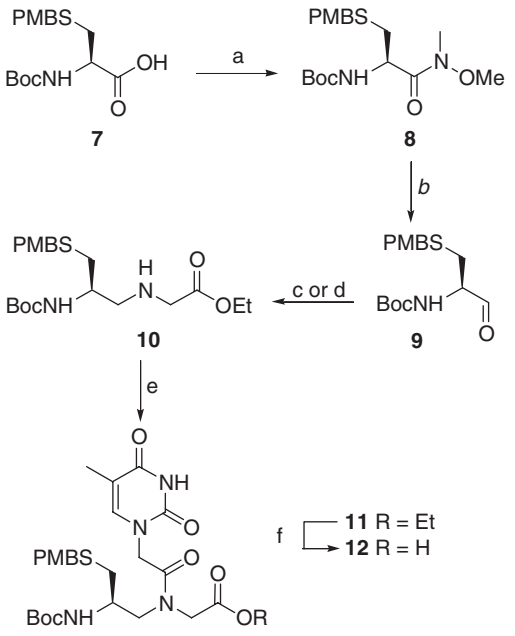


Figure 2. Target backbone-modified thymine PNA monomers.

2. Results and discussion

The protecting group pattern in PNA monomers **12** and **23** (i.e., Boc/PMB and Fmoc/S*t*Bu, respectively) facilitates the use of the two standard elongation protocols for solid-supported PNA synthesis.[18,19] The S*t*Bu group in Fmoc-protected **23** is compatible with release of the PNA oligomer from the resin and deprotection of the nucleobases (Bhoc-groups). The stability of this protecting group precludes oxidation or dimerization of the PNAs by the formation of disulfide bonds. On the other hand, the S*t*Bu group can be elegantly cleaved in situ using a water-soluble phosphine, for example during the conjugation reaction. The PMB group in **12** is stable to the conditions used for Boc-chemistry (TFA) but can be cleaved in concert with the Cbz groups on the nucleobases and concomitant cleavage from the resin.

The preparation of the Boc/PMB monomer **12** started with commercially available *N-tert*-butyloxycarbonyl-S-*p*-methoxybenzyl-protected L-cysteine **7**, which was converted into the Weinreb amide **8** in good yield (Scheme 1). Reduction of **8** with $LiAlH_4$ to give intermediate aldehyde **9** and subsequent reductive amination with glycine ethylester gave, after column chromatography, the modified PNA backbone **10** in 45% yield over the two steps. The chiral purity of **10** was ascertained (>95% ee) using chiral HPLC by comparison with the independently prepared *S*-isomer of **10**. In an attempt to increase the somewhat disappointing yield of the reductive amination by executing an aza-Wittig reaction between aldehyde **9** and readily available[20] azidoglycine ethylester was executed. However, trimethylphosphine mediated imine formation and in situ reduction with $NaCNBH_3$ afforded the modified PNA backbone **10** in a comparable yield. The final steps to the target PNA building block **12** comprised the EDC-mediated installation of the thymine nucleobase (→**11**) in 83% yield and saponification of the ethylester in **11**, which was effected quantitatively using LiOH in a mixture of methanol and water. The identity and purity of the modified PNA monomer **12** were confirmed by NMR, HPLC and mass spectrometry.

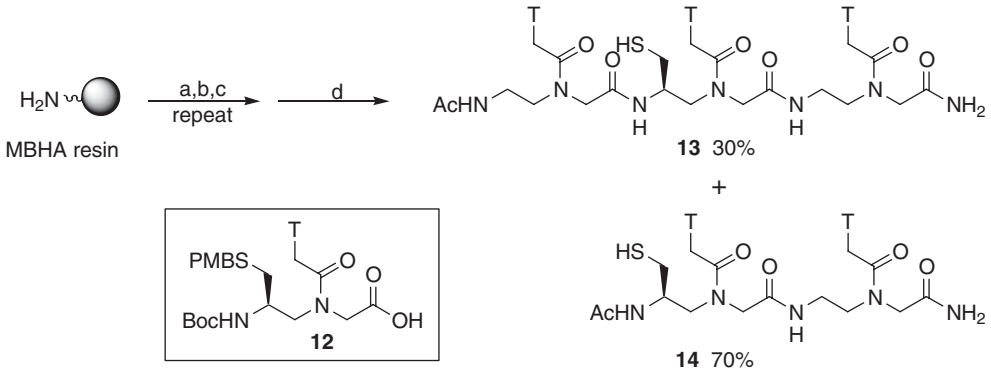


Scheme 1. Reagents and conditions: (a) MeONHMe·HCl, DIC (78%); (b) $LiAlH_4/Et_2O$; (c) glycine ethylester·hydrochloride, $NaCNBH_3$, AcOH, MeOH (45%, two steps); (d) azidoglycine ethylester and Me_3P in THF, then **9**, $NaCNBH_3$, (43%, two steps); (e) thymine-1-yl-acetic acid, EDC, DMF (85%); (f) LiOH, $MeOH/H_2O$, then Dowex-H^+ (quant.)

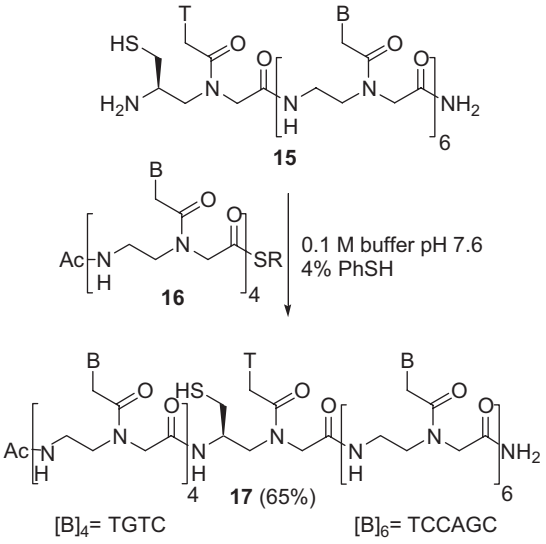
Next, the viability of the Boc/PMB-protected modified PNA monomer **12** in standard in situ neutralization protocols[19] for Boc-based PNA synthesis on the methylbenzhydrylamine (MBHA) resin was investigated (Scheme 2). Thus, after partial loading (0.25 mmol/g) of the commercially available resin with Boc-PNA(T) monomer using a HATU-mediated reaction two elongation cycles involving Boc group removal (TFA), coupling of the monomer (5 equiv) and capping were carried out. Finally, the Boc group was removed and the N-terminus was acetylated. Cleavage from the solid-support and deprotection was effected by subjection of the resin to trifluoromethanesulfonic acid in TFA and triisopropylsilane as the scavenger for 2 h. After filtration and precipitation with cold ether, the crude product was dissolved in water. LC–MS-analysis of this sample revealed the presence of two major products (30/70), which were identified by mass spectrometry to be the target trimer **13** and dimer **14**, respectively. The latter compound evidently resulted from an inefficient coupling of the third PNA monomer. Attempts to increase the trimer/dimer ratio by increasing the excess of reactants and reaction times failed.

However, the successful coupling of **12** to the N-terminus of a PNA oligomer allowed us to investigate the feasibility of the chemical ligation approach depicted in Figure 1. Reaction of the separately prepared hexameric PNA derivative **15**[14] (Scheme 3) with a slight excess of PNA thioester **16**[15] in a phosphate buffer pH 7.6 containing 4% thiophenol resulted, as judged by LC–MS (see Fig. 3), in complete[22] conversion of **15** into PNA undecamer **17**.

At this stage, the preparation of the Fmoc/S*t*Bu-monomer **23** (Scheme 4) was undertaken, following a strategy involving reductive amination of the aldehyde obtained by $LiAlH_4$ reduction of Weinreb amide **19**, with glycine-*t*-butyl ester. A similar strategy was reported[12h] to be effective in the preparation of an *N*-Fmoc-PNA backbone having a methyl substituent at the γ-carbon. Since the thio-*tert*-butyl function would not survive $LiAlH_4$ reduction, it was decided to use *N*-Fmoc-S-Trt-cysteine as the starting compound and replace the Trt-group with the S*t*Bu group in a later stage. Thus, *N*-Fmoc-S-Trt-protected L-cysteine **18** was converted to the corresponding Weinreb amide **19** in 97% yield by treatment with isobutyl chloroformate and *N*,*O*-dimethylhydroxylamine. Lithium aluminium hydride reduction gave the corresponding aldehyde, which was directly used in the next step to suppress racemization. Reductive amination with glycine *tert*-butyl ester and $NaBH_3CN$ gave, after rather tedious column chromatography, the PNA backbone **20** in 42% yield over the two steps. It is of interest to note that **20** was not stable on prolonged storage probably due to intramolecular Fmoc cleavage by the secondary amine as previously reported for the corresponding unmodified PNA backbone.[20] Reaction of the backbone **20** with thymine-1-yl-acetic acid and EDC as the coupling reagent gave the fully protected monomer **21** in 70% yield. Preferably, crude **20** was directly condensed with thymine-1-yl-acetic acid to give monomer **21** in 36% overall yield for three steps. Column chromatography purification was easier at this stage and the overall yields for the two routes were comparable.



Scheme 2. Reagents and conditions: (a) Boc-T-OH or **12**, HATU, DiPEA, DMF; (b) Ac_2O, DiPEA, DMF; (c) 50% TFA/DCM; (d) TFMSA/TFA/TIS, 10:80:10, v/v/v.



Scheme 3. Chemical ligation of two PNA oligomers. R= $[CH_2CH_2CONH]_2H$.

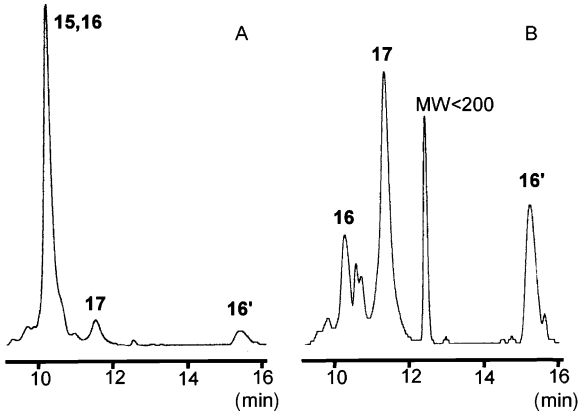
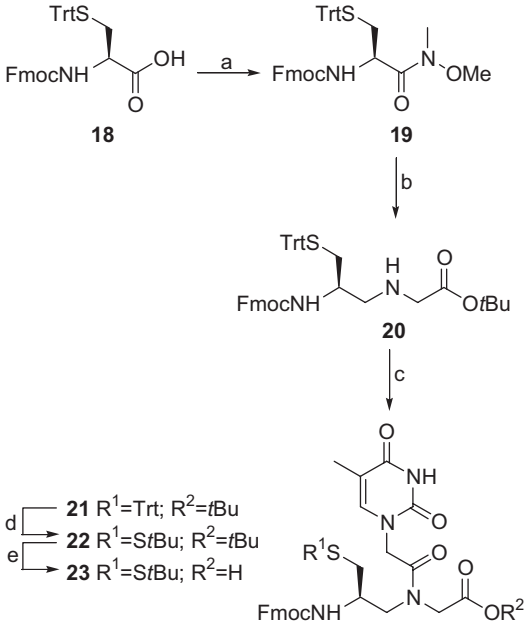


Figure 3. Parts of the HPLC traces of the ligation mixtures. A: $t=15$ min; B: $t=20$ h. **16′** is the thiophenylester of **16**; the unidentified peak (MW < 200) disappears after the addition of dithiothreitol (DTT).

Comparison of **21** with its enantiomer (independently prepared starting from *N*-Fmoc-S-Trt-D-cysteine) by chiral HPLC revealed an enantiomeric purity >95% for both enantiomers.

With the fully protected monomer **21** in hand, attempts were made to exchange the trityl protecting group for the thio-*tert*-butyl function. Initially, TFA-mediated removal of the trityl group and concomitant cleavage of the *t*-butyl ester was followed by direct reaction of the resulting intermediate with different disulfides (either the symmetrical dimer of *t*-butylthiol or the mixed dimer of *t*-butylthiol and 2-pyridyl-thiol). However, these reactions gave complex mixtures (according to LC–MS analysis) and the products were not separable by column chromatography. Fortunately, exchange of the trityl group for the thio-*tert*-butyl function could be effected in a single step by treatment of **21** with an excess of iodine and *t*-butylthiol in DCM in the presence of pyridine in 86% yield. The pyridine was added to prevent the

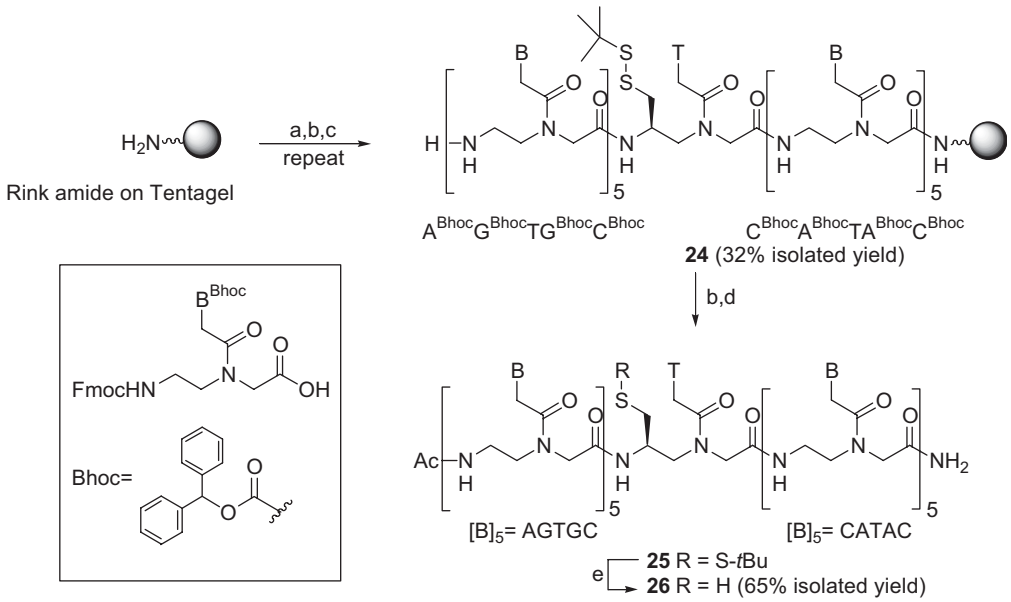


Scheme 4. Reagents and conditions: (a) 1. isobutyl chloroformate, NMM, THF, −20 °C; 2. *N*,*O*-dimethylhydroxylamine hydrochloride, TEA, DMF, −20 °C, 97%; (b) 1. $LiAlH_4$, Et_2O, 0 °C; 2. Gly-O*t*Bu·HCl, $NaBH_3CN$, MeOH, 3 Å sieves, 42% (two steps); (c) thymine-1-acetic acid, EDC·HCl, 36% (three steps); (d) 2-methyl-2-propanethiol, I_2, pyridine, DCM, 86%; (e) 90% TFA/DCM, quant.

otherwise observed premature cleavage of the *t*-butyl ester. Finally, cleavage of the ester in **22** with TFA afforded the desired monomer **23** in quantitative yield.

The incorporation of PNA monomer **23** into a PNA oligomer (AGTGCT*CATAC where T* represents the modified monomer) was carried out with an automated synthesizer using TentaGel® resin loaded with the Rink amide linker (Scheme 5). Elongation (→**24**) was effected by applying the standard Fmoc-synthesis protocols supplied by the manufacturer (using commercially available Fmoc-PNA(B^{Bhoc})-OH monomers, **23** and HATU/DiPEA-lutidine as the coupling reagents). After standard deprotection and release from the resin (95% TFA, TIS, water), the S*t*Bu protected PNA **25** was precipitated from ether. LC–MS analysis of the crude mixture revealed the presence of a single major product having the expected mass, thus indicating that coupling and subsequent elongation of the modified monomer could be accomplished using standard Fmoc-based PNA chemistry. The S*t*Bu group in crude **25** could be removed efficiently by treatment with a solution of tris(2-carboxyethyl)phosphine (TCEP) in buffer (pH 6). PNAs **25** and **26** were readily purified by HPLC and used to investigate the effect of the thiol-modification on the duplex formation.

The hybridization properties of the modified PNAs **25** and **26** with complementary, antiparallel RNA were examined using variable-temperature UV. Comparison of the melting temperatures showed that the backbone modification (i.e., CH_2SH or CH_2SStBu) did not significantly affect the stability of the duplex (Table 1).



Scheme 5. Reagents and conditions: (a) Fmoc/Bhoc-PNA monomer or **23**, HATU, DiPEA, lutidine, DMF/NMP; (b) Ac_2O, lutidine, NMP; (c) 20% piperidine, DMF; (d) TFA/water/TIS 95:2.5:2.5, 2 h; (e) 50 mM tris-(2-carboxyethyl)phosphine, pH 6.

Table 1. Melting temperatures of the (un)modified PNAs with complementary, antiparallel RNA

	T_m value (°C)
RNA/Ref PNA	67.2
RNA/**25**	68.2
RNA/**26**	67.1

The given T_m value is the average of three independent measurements. RNA (5′→3′): AUU UAA GAG UAU GAG CAC UAU CGAA; Ref PNA (N→C): AGTGCTCATAC.

3. Conclusion

Orthogonally protected thiol-modified PNA monomers **12** and **23** were prepared and applied in standard PNA synthesis protocols using Boc (**12**) and Fmoc (**23**) chemistry, respectively. The latter compound proved to be superior in terms of the yield of chain elongation after coupling of the modified monomer. It was demonstrated that the thiol-modification in synthesized undecamer PNAs **25** and **26** did not notably affect the hybridization properties with complementary RNA. The here presented methodology is a valuable asset for future conjugation of PNAs with a variety of ligands such as artificial RNA-nucleases for the sequence-selective degradation of the target RNA.[5b] Finally, pilot experiments suggested that a PNA having a modified thymine monomer at the N-terminus can be used for the ligation with PNA thioesters. This procedure[17] may be implemented in the preparation of cyclic PNAs[14b,23] as well as PNAs of unprecedented lengths.

4. Experimental

4.1. General

All reagents were used as received.

Analytical LC–MS was conducted on a JASCO system using an Alltima C_{18} analytical column (5 μ particle size, flow: 1.0 mL/min). Absorbance was measured at 214 and 254 nm. Solvent system: A: 100% water, B: 100% acetonitrile, C: 0.5% TFA. Gradients of B in 10% C were applied over 15 min unless otherwise stated. Mass spectra were recorded on a Perkin Elmer Sciex API 165 equipped with a custom-made Electrospray Interface (ESI) or for HR-MS on a LTQ-FT (Thermo Electron). Purifications were conducted on a BioCAD 'Vision' automated HPLC system (PerSeptive Biosystems, Inc.), equipped with a semi-preparative Alltima C_{18} column (5 μ particle size, running at 4 mL/min). Solvent system: A: 100% water, B: 100% acetonitrile, C: 1% TFA. Gradients of B in 10% C were applied over 3CV unless otherwise stated. A TitroLine alpha machine or Merck Universal indikator pH 1–10 pH paper was used to measure the pH of buffers.

NMR spectra were measured on Bruker AC200, AC300, AV400 or AV600 spectrometers. Chemical shifts are given in ppm, relative to the signal of the internal standard tetramethylsilane.

IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer, $[\alpha]_D$ values were determined using a Propol Automatic Polarimeter and melting points were determined using a Buchi Schmeltzpunkt Bestimmungsapparat.

4.1.1. Boc-L-Cys(PMB)-N(Me)OMe (8). *N-tert*-Butyloxycarbonyl-S-*p*-methoxybenzyl-L-cysteine (17.07 g, 50 mmol) was dissolved in dry DMF (200 mL). To this solution were added subsequently molecular sieves, 1.6 equiv of HOBt (10.8 g), 1.6 equiv of *N*,*O*-dimethylhydroxylamine·HCl (7.76 g), 1.6 equiv of DiPEA (13.6 mL) and 2 equiv of DIC (15.5 mL). The mixture was stirred for 1 h at room temperature. TLC (eluent: EtOAc/PE, 1:1, v/v, containing 0.5% triethylamine) indicated the nearly complete conversion of the starting compound into a higher running product (R_f=0.55). The solution was filtered and evaporated to dryness. The residue was redissolved in EtOAc and

transferred into a separatory funnel. The organic layer was washed with 10% $KHSO_4$, 10% $NaHCO_3$, water and finally with brine. The organic layer was dried with $MgSO_4$, filtered and evaporated to a small volume. Silica was added and the mixture was evaporated to dryness. The solid residue was applied onto a silica column and eluted with a mixture of EtOAc/PE, 1:1, v/v, containing 0.5% Et_3N. The fractions containing the target compound were collected and evaporated to yield 15 g (39 mmol, 78%) of the product as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25, 7.22 (2×2H, CH arom.), 5.38 (1H, d, J=8.7 Hz, NH Boc), 4.88 (1H, br s, CH_α), 3.78, 3.74, 3.70 (8H, 3×s, MeO PMB, CH_2 PMB, MeO–N), 3.2 (3H, s, CH_3–N), 2.85–2.56 (2H, m, CH_2 Cys), 1.45 (9H, s, *t*Bu). ^{13}C NMR ($CDCl_3$): δ 171.0 (C=O amide), 158.1 (Cq. PMB), 154.8 (C=O Boc), 129.6 (CH arom.), 129.3 (Cq. PMB), 113.4 (CH arom.), 79.0 (Cq. *t*Bu), 61.0 (MeO), 54.7 (MeO), 49.0 (CH), 35.1, 32.8 (2×CH_2), 31.6 (CH_3), 27.8 (*t*Bu). ES MS (found/calculated): 385.4/385.5 $(M+H)^+$. $[\alpha]_D^{23}$ −19.2 (*c* 1 in $CHCl_3$) (L-isomer). IR (cm^{-1}): 1705.0, 1654.8, 1508.2, 1245.9, 1164.9, 729.0.

4.1.2. (*R*) Boc-Cys(PMB) backbone ethyl ester (10).

By reductive amination:

Compound **8** (1.85 g, 4.8 mmol) was weighed in a dried 50 mL round bottom flask, co-evaporated with DCE (2×), dissolved in freshly distilled diethylether (12 mL) and put under a nitrogen gas atmosphere. Next, the solution was cooled to −30 °C. A suspension of 1.2 equiv $LiAlH_4$ (219 mg) in freshly distilled diethylether (12 mL) was added dropwise under streaming nitrogen gas. The reaction mixture was allowed to warm to 0 °C over 20 min and analyzed with TLC, which revealed complete conversion of the starting compound (the starting compound colors blue when the TLC is charred with molybdenum, whereas the product gives a yellow coloring). The mixture was then cooled to −30 °C and a 10% solution of $KHSO_4$ (20 mL) was carefully added to quench the excess of $LiAlH_4$. The acidic mixture was allowed to warm to room temperature and transferred into a separatory funnel. The organic layer was washed three times with 10% $KHSO_4$, and one time with brine, dried ($MgSO_4$), filtered and evaporated to yield a white foam (1.56 g, 4.8 mmol) of the crude aldehyde **9**. The aldehyde was co-evaporated (2×) with DCE and dissolved in dry methanol (20 mL). 1 equiv (672 mg, 4.8 mmol) of glycine ethyl ester hydrochloride and molecular sieves were added and the reaction was stirred under a nitrogen atmosphere. 2 Equiv of $NaCNBH_3$ (605 mg, 9.6 mmol) were added and the mixture was stirred overnight at room temperature. TLC analysis (eluent: EtOAc/PE, 2:1, v/v containing AcOH (0.5%)) indicated (besides several byproducts) one major spot (R_f=0.2). The reaction mixture was filtered and evaporated to dryness. The residue was taken up in EtOAc, washed with water and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was applied onto a silica gel column and was eluted with a gradient of EtOAc in PE (1/1→3/1, v/v) to yield the title compound as a colorless oil. (852 mg, 2.1 mmol, 45%).

By aza-Wittig-reaction:

To a cooled (0 °C) solution of azidoacetic acid ethyl ester[21] (1.66 mmol, 214 mg) in freshly distilled THF (6 mL) was added under an argon atmosphere trimethylphosphine (2 mL, 1 M in toluene). The reaction mixture was allowed to warm to room temperature and molecular sieves (3 Å) were added. Crude aldehyde **9** (1.99 mmol, 647 mg) was co-evaporated with DCE (2×) and dissolved in freshly distilled THF (6 mL). The two solutions were combined and stirred for 30 min. Next, 1.5 equiv $NaCNBH_3$ (2.99 mmol, 186 mg) in MeOH (2 mL) was added. TLC analysis (eluent: EtOAc/PE 2:1, v/v containing AcOH (0.5%)), after 20 h, indicated the formation of a main product. The reaction mixture was filtered and concentrated in vacuo. The residue was taken up in EtOAc, washed with 10% $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was applied onto a silica column, which was eluted with a gradient of EtOAc in PE 1/1→3/1, v/v) to yield the title compound as a colorless oil in 35% (354 mg, 0.86 mmol).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (2H, d, J=8.8 Hz, 2× CH arom. PMB), 6.84 (2H d, J=8.8 Hz, 2×CH arom. PMB), 5.22 (1H, br s, NH Boc), 4.18 (2H, q. J=7.3 Hz, CH_2 Et), 3.76 (3H, s, MeO PMB), 3.68 (2H, s, CH_2 PMB), 3.37 (2H, CH_2), 2.76–2.47 (5H, m, 2×CH_2, CH), 1.94 (1H, s, NH), 1.45 (9H, s, *t*Bu), 1.26 (3H, t, J=7.3 Hz, CH_3 Et). ^{13}C NMR ($CDCl_3$): δ 172.0 (C=O ester), 158.1 (C=O Boc), 155.2, 129.7 (2×Cq. PMB), 129.6, 113.5 (2×CH arom. PMB), 78.9 (Cq. *t*Bu), 60.3 (CH_2 Gly), 54.8 (MeO, PMB), 51.0, 50.5 (2×CH_2), 49.4 (CH), 35.6, 33.6 (2×CH_2), 28.1 (CH_3 *t*Bu), 13.9 (CH_3 Et). HR-MS (found/calculated) $(M+H)^+$: 413.2089/413.2105. $[\alpha]_D^{23}$ +12.6 (*c* 1 in $CHCl_3$) (*R*-isomer). IR (cm^{-1}): 1735.8, 1701.1, 1512.1, 1242.1, 1164.9, 1029.9, 732.9.

The synthesis of the *S*-isomer of **10** was carried out in an identical manner to that described above starting from the D-isomer of cysteine. Spectroscopic data (NMR) were identical. $[\alpha]_D^{23}$ −10.8 (*c* 1 in $CHCl_3$) (*S*-isomer).

4.1.3. (*R*) Boc-Cys(PMB) thymine monomer ethyl ester (11).

Compound **10** (284 mg, 0.69 mmol) was dissolved in dry DMF (3.5 mL). 1.5 Equiv of thymin-1-yl-acetic acid (188 mg) and 1.5 equiv of EDC (199 mg) were added and the mixture was stirred for 30 min. TLC (EtOAc/PE, 3:1, v/v) indicated complete conversion of the starting compound into a lower running product (R_f=0.6). The mixture was evaporated and the residue was taken up in EtOAc. The EtOAc-layer was washed subsequently with 10% $KHSO_4$, 10% $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified further by column chromatography using silica gel and a gradient of EtOAc in PE (75→100%, v/v), which afforded the title compound as a white powder (0.59 mmol, 340 mg) in 85% yield.

^{1}H NMR (200 MHz, two rotamers, $CDCl_3$): δ 7.28 (2H, d, J=8.8 Hz, 2×CH arom. PMB), 7.01 (1H, s, CH thymine), 6.86 (2H, d, J=8.8 Hz, 2×CH arom. PMB), 4.30–4.07 (4H, m, CH_2 Et, CH_2), 3.78 (3H, s, MeO PMB), 3.73–3.62 (5H, m, CH, 2×CH_2), 3.51 (2H, br s, CH_2 Gly), 2.79–2.54 (2H, m, CH_2 Cys), 1.90 (mi), 1.91 (ma) (3H, 2×s, CH_3 thymine), 1.43 (mi), 1.41 (ma) (9H, 2×s, *t*Bu), 1.31 (mi), 1.28 (ma) (3H, 2×t, J=7.1 Hz, CH_3 Et). ^{13}C NMR ($CDCl_3$): δ 168.8 (C=O ester), 167.3 (C=O amide), 164.4 (C4 thymine),

158.4 (C=O Boc), 155.3 (Cq. PMB), 151.0 (C2 thymine), 141.1 (C6 thymine), 129.7 (CH arom. PMB), 129.5 (Cq. PMB), 113.7 (CH arom. PMB), 110.2 (C5 thymine), 79.5 (Cq. *t*Bu), 61.8 (mi), 61.0 (ma) (CH$_2$COOEt), 54.9 (MeO PMB, 50.3 (CH$_2$), 49.0 (CH), 48.4, 47.4, 35.7, 33.0 (4×CH$_2$), 28.0 (CH$_3$ *t*Bu), 13.8 (CH$_3$ Et), 12.0 (CH$_3$ thymine). HR-MS (found/calculated) $(M+H)^+$: 579.2521/579.2483. $[\alpha]_D^{23}$ −8.0 (*c* 1 in CHCl$_3$). Mp: 74–78 °C. HPLC: 50–90% B, t_R=3.7 min (single peak). IR (cm^{-1}): 1666.4, 1512.1, 1465.8, 1242.1, 1164.9, 910.3, 725.2.

4.1.4. (*R*) Boc-Cys(PMB)-thymine-monomer (12). Compound **11** (652 mg, 1.13 mmol) was suspended in a 2/1 (v/v) mixture of MeOH and water (8 mL) LiOH (3 equiv, 68 mg) was added and the reaction mixture was stirred for 15 min, during which the compound dissolved. TLC analysis (3:1 EtOAc/PE, v/v) indicated the disappearance of the starting compound and the formation of a product running near the baseline. The mixture was acidified (to pH 5) by the addition of Dowex-H$^+$ and filtered. The resin was washed with a mixture of water–MeOH (1/1, v/v). The combined filtrates were evaporated to afford the pure title compound as a white foam in near quantitative yield (606 mg, 1.1 mmol).

^{1}H NMR (200 MHz, two rotamers, CD$_3$OD): δ 7.19 (2H, d, J=8.8 Hz, 2×CH arom. PMB), 7.12 (1H, s, C6 thymine), 4.1–3.4 (10H, m, 3×CH$_2$, CH, MeO (3.66)), 3.21 (2H, s, CH$_2$) 2.49–2.35 (2H, m, CH$_2$ Cys), 1.78 (3H, s, CH$_3$ thymine), 1.36 (mi), 1.35 (ma) (9H, 2×s, *t*Bu). ^{13}C NMR (methanol-d_4, 75 MHz): δ 172.0 (C=O acid), 170.0, 169.5 (C=O amide), 166.7 (C4 thymine), 159.9, 159.8 (C=O Boc), 157.5 (Cq. PMB), 152.6 (C2 thymine), 143.3, 143.2 (C6 thymine), 131.3 (Cq. PMB), 131.0, 114.8 (2×CH arom. PMB), 110.9, 110.8 (C5 thymine), 80.5, 80.2 (Cq. *t*Bu), 55.6 (MeO PMB), 51.9, 50.8 (2×CH$_2$), 50.5, 50.2 (CH), 49.1, 36.6, 28.7 (3×CH$_2$), 28.7 (CH$_3$ *t*Bu), 12.3 (CH$_3$ thymine). ES MS (found/calculated) $(M+H)^+$: 551.6 (551.2). HPLC: 5–70% B, t_R=15.9 min (single peak). IR (cm^{-1}): 3355.9 (broad), 1658.7, 1242.1, 1164.9. $[\alpha]_D^{23}$ −80 (*c* 1 in CHCl$_3$). Mp=120–122 °C.

4.1.5. Modified PNA oligomer 13. PNA-synthesis was carried out manually on a 10 μmol scale (15 mg of MBHA resin 0.66 mmol/g). The Boc-protected PNA thymine monomer was pre-acivated for 1 min with HATU (4.9 equiv) and DiPEA (10 equiv) in DMF (0.5 mL) and added to the resin. The resin was shaken for 30 min, drained and washed with DMF, followed by a 1 min capping step (cap-solution: Ac$_2$O/2,6-lutidine/NMP, 5:6:89, 2 mL). The resin was washed with DMF and DCM. Boc deprotection was effected by a 15 min treatment with 50% TFA/DCM (2 mL). After thorough washing with DCM and DMF, the coupling procedure was repeated using monomer **12**. The resulting resin was used in the third coupling step (i.e., Boc deprotection and coupling with the Boc-protected thymine monomer to give the immobilized trimer).

The Boc group in the immobilized trimeric compound was removed by treatment with 50% TFA/DCM (2 mL) for 15 min, followed by extensive washing with DCM and DMF. After capping (see above) the resin was washed with DMF and DCM and dried.

Deprotection/cleavage: the resin was transferred into a glass tube and suspended in TFA (3.2 mL) and TIS (400 μL). The resulting mixture was cooled in an ice-bath followed by dropwise addition of TFMSA (400 μL) under streaming argon. The mixture was kept at 0 °C for 5 more minutes and was then allowed to warm to room temperature and shaken for 1.5–2 h. The suspension was filtered into cold diethylether (30 mL) and the resin was washed with neat TFA (2×1 mL). The resulting suspension was centrifuged and the diethylether layer was decanted. The precipitate was washed with diethylether and after centrifugation, the ether was removed and the precipitate was dissolved in water and purified by semi-preparative HPLC.

Compound **13**: LC–MS: 5–35% B, t_R=10.0 min. ES MS (found/calculated) $(M+H)^+$: 904.2 (904.3).

4.1.6. PNA derivative 15. The synthesis was performed manually on a 10 μmol scale using the Rinkamide-TentaGel® resin (loading capacity 0.22 mmol/g). A single elongation cycle consisted of the following three steps: Fmoc deprotection: wash with NMP, 20% piperidine in DMF (5 min), NMP washes; elongation: DMF washes, 5 equiv of monomer (Fmoc/Bhoc-protected PNA monomers or **12** in the final coupling), 4.9 equiv of HATU, 10 equiv of DiPEA, in DMF (~0.1 M monomer concentration), 1 min preactivation, 30 min coupling time, DMF washes; capping: 5/6/89 Ac$_2$O/lutidine/DMF, 2 min. Deprotection/release from the resin was effected in a two-step procedure, to prevent capture of the released benzhydryl cation by the free thiol group.[24] The resin was suspended in a mixture of TFA (1.6 mL) and TIS (0.2 mL) and shaken for 1.5 h. The mixture was then cooled to 0 °C and TFMSA (0.2 mL) was added slowly and kept at 0 °C for another 5 min. The mixture was removed from the ice-bath and shaken for 1 h at room temperature. After filtration, the filtrate was precipitated from cold diethylether (~35 mL) and centrifuged. The residue was washed again with cold diethylether and centrifuged. The remaining crude product was dissolved in 1 mL of 0.1 M NaOAc in water–acetonitrile (1/1, v/v) and the pH was adjusted to 6. PEGA-aldehyde resin[25] (250 mg, 0.1 mmol, 10 equiv) was added and the mixture was shaken for 15 h. The resin was collected by filtration and thoroughly washed with acetonitrile–water (1/1, v/v). The resin was then suspended in a 0.2 M solution of methoxylamine·hydrochloride (1 mL, pH 3) and left for 8 h at room temperature. The resin was removed by filtration and washed with 1% TFA (1 mL total). The collected filtrates were applied to a ready desalting step using semi-preparative HPLC column chromatography (6–40% over 3 CV).

Compound **15**: LC–MS: 5–35% B, t_R=10.3 min. ES MS (found/calculated) $(M+H)^+$: 1917.6 (1916.9), $(M+2H)^{2+}$: 958.8 (959.0), $(M+3H)^{3+}$: 639.6 (639.6).

4.1.7. PNA thioester 16. PNA thioesters were prepared manually on 10 μmol scale on the TrtSCH$_2$CH$_2$CO-βAla-MBHA-resin[26] using slightly modified protocols as described previously.[14c] In brief, PNA elongation was accomplished as follows: Boc-deprotection: 15 min treatment with 50% TFA/DCM; elongation: 5 equiv monomer, 4.9 equiv HATU, 10 equiv DiPEA, 0.1 M in DMF, 1 min

preactivation, 30 min coupling time; cap: 5/6/89 Ac_2O/lutidine/DMF, 2 min. Cleavage/deprotection: 2 mL TFMSA–TIS–TFA (10/10/80, v:v), 1.5 h. Precipitation in cold diethylether (~30 mL) and centrifuging gave the crude thioester, which was purified by ready RP-HPLC.

Compound **16**: LC–MS: 5–35% B, t_R 10.1 min. ES MS (found/calculated) $(M+H)^{+}$: 1293.8 (1293.5), $(M+2H)^{2+}$: 647.6 (647.3).

4.1.8. PNA–PNA ligation→17. A stock solution of (120 μL) **15** (2 mM, determined by measuring A_{260} units) in ligation buffer containing 6 M guanidine HCl, 0.1 M Na_2HPO_4, 0.1 M TCEP, pH 7.6 was mixed with 120 μL of a solution of **16** (4.6 mg/mL; 1.8 equiv) in the same ligation buffer. Thiophenol (10 μL, 4%, V) was added and the mixture was vortexed for a few seconds and shaken for 20 h at ambient temperature. 5 mg of DTT was added and after 15 min the mixture was diluted with 1% TFA to a total volume of 1 mL and purified by RP-HPLC (6–29% B over 3 CV).

Compound **17**: Yield 0.5 mg (65%, determined by A_{260} units) LC–MS: 5–35% B, t_R 11.5 min. ES MS (found/calculated): $(M+2H)^{2+}$: 1517.6 (1517.5), $(M+3H)^{3+}$: 1011.8 (1012.0), $(M+4H)^{4+}$: 759.4 (759.2).

4.1.9. Fmoc-L-Cys(Trt)-N(CH_3)OCH_3 (19). *N*-Fmoc-L-Cys(Trt)-OH (5.86 g, 10 mmol) was dissolved in THF (60 mL), *N*-methylmorpholine (1.21 mL, 11 mmol) was added and the solution was cooled to −20 °C. Isobutylchloroformate (1.30 mL, 10 mmol) was added and the solution was stirred 30 min at the same temperature. Triethylamine (1.53 mL, 11 mmol) was added and then a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) in DMF (25 mL). The solution was stirred for 30 min at −20 °C and then 1 h at room temperature Then the solvent was removed in vacuo, the residue was taken up in EtOAc (200 mL), which was washed with 0.5 M HCl (100 mL). The aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Compound **19** was isolated after column chromatography (PE/EtOAc, 1:1, R_f=0.58) as a white foam. Yield: 97%; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (1H, dd, *J*=8.1, 12.2 Hz, C*H*HS), 2.62 (1H, dd, *J*=4.5, 12.3 Hz, CH*H*S), 3.16 (3H, s, NCH_3), 3.63 (3H, s, OCH_3), 4.22 (1H, t, *J*=7.2 Hz, C*H*CH_2O), 4.31–4.44 (2H, m, CHCH_2), 4.78–4.82 (1H, m, CHCO), 5.40 (1H, d, *J*=9.0 Hz, NH), 7.18–7.77 (23H, m, H_{ar}). ^{13}C NMR ($CDCl_3$): δ 32.06 (NCH_3), 33.94 (CH_2S), 47.02 (*C*HCH_2O), 50.13 (*C*HCH_2N), 61.54 (OCH_3), 66.84 (*C*($Ph)_3$), 67.03 (CH*C*H_2N), 119.89, 125.16, 126.74, 127.03, 127.64, 127.91, 129.53 (CH_{ar}), 141.19, 143.71, 143.85, 144.36, 155.74, 170.59 (C_{ar}, CO). HR-MS (found/calculated): 646.2756/646.2740 $(M+Na)^{+}$. $[\alpha]_D^{23}$ −13.6 (*c* 1 in $CHCl_3$). IR (cm^{-1}): 2360.7, 2350.4, 1716.5, 1654.8, 1245.9, 1033.8.

D-Isomer of **19**:

The synthesis was carried out in an identical manner to that described above. Spectroscopic data were identical. Yield: 92%. $[\alpha]_D^{23}$ +13.0 (*c* 1 in $CHCl_3$)

4.1.10. (*R*) Fmoc-Cys(Trt)-thymine monomer *t*Bu ester (21). Weinreb amide (**19**, 2.00 g, 2.93 mmol) was dissolved in dry Et_2O (25 mL) and the solution was cooled to 0 °C. $LiAlH_4$ (0.139 g, 3.66 mmol) was added in one portion and the reaction mixture was stirred for 10 min at 0 °C. The reaction was quenched by careful addition of 0.5 M HCl (50 mL) and the mixture was allowed to warm to room temperature The organic phase was diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2×50 mL). The combined Et_2O layers were washed with 0.5 M HCl (2×50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a foam, which was re-dissolved in MeOH (35 mL). Glycine *tert*-butyl ester HCl (0.982 g, 5.86 mmol) was dissolved in MeOH (15 mL) and added. 3 Å sieves and $NaBH_3CN$ (0.552 g, 8.79 mmol) were added and pH was checked (pH 6). The reaction mixture was stirred overnight before the solvent was evaporated and the residue was re-dissolved in EtOAc (150 mL). The organic phase was washed with $NaHCO_3$ (2×50 mL), dried ($MgSO_4$) and evaporated in vacuo to give crude **20** as a foam, which was used directly in the next reaction.

Compound **20** could be isolated with column chromatography (PE/EtOAc, gradient 2:1→1:1), but proved to be unstable. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (9H, s, C($CH_3)_3$), 2.31–2.73 (4H, m, CH_2S, CHCH_2N), 3.18 (1H, d, *J*=2.2 Hz, $NHCH_2CO$), 3.42–3.70 (1H, m, C*H*CH_2N), 4.20–4.24 (1H, m, C*H*CH_2O), 4.34–4.41 (2H, m, CHCH_2O), 5.13 (1H, d, *J*=8.0 Hz, NH), 7.19–7.39 (23H, m, H_{ar}). ^{13}C NMR ($CDCl_3$): δ 27.90 (C(*C*$H_3)_3$), 34.24 (CH_2S), 47.04 (*C*HCH_2O), 50.10 (*C*HCH_2N), 51.31 (CH*C*H_2N), 66.30, 66.63 (*C*($Ph)_3$, CH*C*H_2O), 81.00 (*C*($CH_3)_3$), 119.73, 124.97, 126.55, 126.85, 127.46, 127.76, 129.40 (CH_{ar}), 141.08, 143.75, 144.41, 155.69, 171.40 (C_{ar}, CO).

Crude PNA backbone **20** obtained in the previous step, was dissolved in DMF (20 mL). Thymine-1-acetic acid (0.567 g, 3.08 mmol) was added and the mixture was stirred until the acid was dissolved. Then EDC (0.562 g, 2.93 mmol) was added and the reaction mixture was stirred overnight at room temperature Then the solvent was evaporated under reduced pressure and the residue was re-dissolved in EtOAc (150 mL). The organic layer was washed with 0.5 M HCl (2×50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated in vacuo. The product **21** was isolated after column chromatography (PE/EtOAc, gradient 1:1→1:3) as a white foam (R_f=0.33 with PE/EtOAc 1:2). Yield: 36% (over three steps based on **19**). ^{1}H NMR (600 MHz, $CDCl_3$, two rotamers): δ 1.44, 1.48 (9H, 2×s, C($CH_3)_3$), 1.81, 1.84 (3H, 2×s, CH_3-T), 2.33–2.46, 2.65–2.75 (2H, 2×m, CH_2S), 3.01–3.13, 3.43–4.55 (10H, 2×m, $CHCH_2O$, $CHCH_2N$, NCH_2CO, $NCOCH_2N$), 5.13 (0.5H, d, *J*=6.5 Hz, NH), 5.50 (0.5H, br s, NH), 6.81 (0.5H, s, H6), 6.85 (0.5H, d, *J*=1.0 Hz, H6), 7.18–7.75 (23H, m, H_{ar}), 9.00, 9.02 (1H, 2×br s, NH). ^{13}C NMR ($CDCl_3$, two rotamers): 12.23 (CH_3-T), 27.99 (C($CH_3)_3$), 33.41, 34.22 (CH_2S), 47.07, 47.17 ($CHCH_2O$), 47.25, 47.53, 49.49, 50.34, 50.47, 50 79 (CH_2), 49.43, 49.71 ($CHCH_2N$), 66.53, 66.67 ($CHCH_2N$), 67.03, 67.45 (C($Ph)_3$), 82.17, 83.36 (C($CH_3)_3$), 110.36, 110.46 (C5), 119.85, 119.92, 125.05, 125.19, 126.77, 126.95, 127.07, 127.61, 127.69, 127.94,

128.05, 129.47, 129.51 (CH_{ar}), 140.81, 141.12 (C6), 141.12, 141.23, 143.71, 144.07, 144.36, 144.48, 150.79, 150.85, 155.86, 155.93, 164.07, 164.12, 167.33, 167.86, 167.99, 168.30 (C_{ar}, CO).

LC–MS: 70–90% B, $t_R=13.9$ min. ES MS (found/calculated): 873.6/873.3 $(M+Na)^+$, HR-MS (found/calculated): 868.3699/868.3744 $(M+NH_4)^+$. $[\alpha]_D^{23}$ +17.6 (*c* 1 in $CHCl_3$). IR (cm^{-1}): 2360.7, 2351.2, 1670.2, 1222.8, 1149.5.

S-Isomer of **21**:

The synthesis was carried out in an identical manner to that described above. Spectroscopic data were identical. Yield: 32% (over three steps based on **19** (D)). $[\alpha]_D^{23}$ −17.0 (*c* 1 in $CHCl_3$).

4.1.11. (*R*) Fmoc-Cys(S*t*Bu)-thymine monomer *t*Bu ester (22). Iodine (12.07 g, 47.55 mmol) was dissolved in DCM (50 mL) and pyridine (5.38 mL, 66.57 mmol) was added. To this mixture was added a solution of compound **21** (2.7 g, 3.17 mmol) and 2-methyl-2-propanethiol (1.79 mL, 15.85 mmol) in DCM (50 mL). The reaction mixture was stirred at room temperature for 40 min and then the reaction was quenched by the addition of 0.5 M $Na_2S_2O_3$ (200 mL). The phases were separated and the organic layer was additionally washed with 0.5 M $Na_2S_2O_3$ (50 mL). The combined aqueous layers were extracted with EtOAc (3× 100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Compound **22** was purified by column chromatography (PE/EtOAc, gradient 1:1→1:3) to yield a white foam.

Yield: 86%; ^{1}H NMR (600 MHz, $CDCl_3$, two rotamers): δ 1.33, 1.35 (9H, 2×s, $SC(CH_3)_3$), 1.46, 1.50 (9H, 2×s, $OC(CH_3)_3$), 1.86, 1.88 (3H, 2×s, CH_3-T), 2.79–2.84, 2.95–3.04 (2H, 2×m, CH_2S), 3.48–4.69 (10H, m, $CHCH_2O$, $CHCH_2N$, NCH_2CO, $NCOCH_2N$), 5.64 (0.5H, d, J= 7.1 Hz, NH), 6.10 (0.5H, d, J=6.9 Hz, NH), 6.93 (0.5H, s, H6), 6.95 (0.5H, d, J=1.1 Hz, H6), 7.28–7.76 (8H, m, H_{ar}), 8.94 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, two rotamers): δ 12.29 (CH_3-T), 27.99 ($OC(CH_3)_3$), 29.84 ($SC(CH_3)_3$), 41.76, 42.22 (CH_2S), 47.11, 47.19 ($CHCH_2O$), 47.58, 47.65, 48.32, 48.63, 49.73, 49.83, 50.64, 50.98 (CH_2, $SC(CH_3)_3$), 50.33, 50.59 ($CHCH_2N$), 66.77, 66.90 ($CHCH_2N$), 82.44, 83.60 ($OC(CH_3)_3$), 110.58, 110.71 (C5), 119.91, 119.97, 125.16, 125.26, 127.02, 127.66, 127.72 (CH_{ar}), 140.87, 141.18 (C6), 141.21, 141.26, 143.72, 143.78, 144.00, 150.90, 156.02, 164.05, 168.09, 168.23, 168.70 (C_{ar}, CO).

LC–MS: 50–90% B, $t_R=15.6$ min. ES MS (found/calculated): 697.3/697.3 $(M+H)^+$. HR-MS (found/calculated): 714.3022/714.2995 $(M+NH_4)^+$. $[\alpha]_D^{23}$ +9.6 (*c* 1 in $CHCl_3$). IR (cm^{-1}): 2358.7, 2340.4, 1666.8, 1222.5, 1149.4.

S-Isomer of **22**:

The synthesis was carried out in an identical manner to that described above. Spectroscopic data were identical. Yield: 71%. $[\alpha]_D^{23}$ −10.2 (*c* 1 in $CHCl_3$).

4.1.12. (*R*) Fmoc-Cys(S*t*Bu)-thymine monomer (23). Compound **22** (0.255 g, 0.366 mmol) was dissolved in DCM (0.5 mL) and TFA (4.5 mL) was added. The reaction mixture was stirred for 2 h and then the solvents were coevaporated under reduced pressure with toluene to give a white solid.

Yield: quantitative ^{1}H NMR (400 MHz, CD_3OD, two rotamers): δ 1.30, 1.33 (9H, 2×s, $SC(CH_3)_3$), 1.81 (3H, s, CH_3-T), 2.80–2.93 (2H, m, CH_2S), 3.30–3.36, 3.50–3.55, 3.63–3.71, 4.00–4.86 (10H, 4×m, $CHCH_2O$, $CHCH_2N$, NCH_2CO, $NCOCH_2N$), 7.09–7.81 (9H, m, H6, H_{ar}). ^{13}C NMR (CD_3OD, two rotamers): δ 12.24 (CH_3-T), 30.26 ($SC(CH_3)_3$), 43.19, 43.95 (CH_2S), 48.36, 50.73, 51.81, 52.06 (CH_2, $SC(CH_3)_3$), 48.47, 48.52 ($CHCH_2O$), 51.22, 51.47 ($CHCH_2N$), 67.74, 67.92 ($CHCH_2N$), 110.90, 110.99 (C5), 120.92, 126.30, 128.18, 128.78 (CH_{ar}), 142.60 (C_{ar}), 143.48 (C6), 145.29, 152.91, 158.39, 166.97, 169.94, 170.50, 172.01, 172.21 (C_{ar}, CO).

LC–MS: 20–90% B, $t_R=15.4$ min. ES MS (found/calculated): 641.2/641.2 $(M+H)^+$. HR-MS (found/calculated): 641.2073/641.2104 $(M+H)^+$. $[\alpha]_D^{23}$ −10.0 (*c* 1 in CH_3OH). IR (cm^{-1}): 2360.7, 2341.4, 1670.2, 1222.8, 1149.5.

4.1.13. Modified PNAs 25 and 26 and the reference PNA. The synthesis was performed on 10 μmol scale on an automated synthesizer (Applied Biosystems) using the Rink-Tentagel resin (loading capacity 0.22 mmol/g) and protocols supplied by the manufacturer. Deprotection/release from the resin was effected by suspension of the resin in a mixture of TFA/TIS/H_2O 90:5:5 (V, 5 mL) and filtered into Et_2O (40 mL). The precipitate was washed 1× with Et_2O, redissolved in H_2O–CH_3CN (3/1, 2 mL), and purified using the BIOCAD: 10–28% B over 5 CV.

Compound **25**: LC–MS: 5–35% B, $t_R=14.5$ min. Yield: 32% (estimated by A_{260} units). ES MS (found/calculated): $(M+2H)^{2+}$: 1578.0 (1577.6), $(M+3H)^{3+}$: 1052.6 (1052.1), $(M+4H)^{4+}$: 789.6 (798.3). MALDI-TOF MS (found/calculated) $(M+H)^+$: 3153.6 (3154.2).

PNA **26**: PNA **25** (1.59 mg, 0.5 μmol) was dissolved in 400 μL buffer (0.1 M Na_2HPO_4, 0.1 M TCEP) and the pH was adjusted to 6 with 1 M NaOH. After 4 h of agitation, 1% TFA/H_2O (400 μL) as well as 2 drops of neat TFA were added to dissolve all materials completely. Purification was performed on the BIOCAD VISION system.

Compound **26**: LC–MS: 5–35% B, $t_R=11.5$ min. Yield: 65% (estimated by A_{260} units). ES MS $(M+2H)^{2+}$: 1533.9 (1534.0), $(M+3H)^{3+}$: 1023.2 (1023.0), $(M+4H)^{4+}$: 767.6 (767.5), $(M+5H)^{5+}$: 614.2 (614.2). MALDI-TOF MS (found/calculated) $(M+H)^+$: 3068.2 (3067.0).

The reference PNA was synthesized as described for **25** (2 μmol scale, 9 mg of resin). Purification (10–25% B over 3 CV) gave the pure compound. LC–MS: 5–30% B, $t_R=11.9$ min, ES MS $(M+2H)^{2+}$: 1511.0 (1511.0), $(M+3H)^{3+}$: 1007.8 (1007.6), $(M+4H)^{4+}$: 756.9 (756.0). MALDI-TOF MS (found/calculated) $(M+H)^+$: 3021.5 (3020.9).

4.2. Chiral HPLC

Chiral HPLC experiments were executed using a Chiralcel OD column at 1 mL/min. A mixture of hexane–*i*-propyl-alcohol (92/8, V) containing 0.2% diethylamine was used as the eluent. The absorption was monitored at 254 nm. *R*-Enantiomer of **10**: $t_R = 10.4$ min, *S*-enantiomer of **10**: $t_R = 7.8$ min.

For compounds **21** a Chiralpak AD column together with the eluent isopropanol/hexane 1:1 (1 mL/min) was used: *R*-enantiomer of **21**: $t_R = 8.4$ min, *S*-enantiomer of **21**: $t_R = 15.5$ min.

4.3. Thermal denaturation studies

The melting temperature experiments were performed on a Perkin-Elmer lambda 20 spectrometer using a 1.0 mL cuvette with 1.0 μM of the two complementary strands in a phosphate buffered solution. Buffer A was prepared by mixing appropriate volumes of buffer 1 (200 mm sodium chloride, 20 mm NaH_2PO_4 and 0.2 mm EDTA) and buffer 2 (200 mm sodium chloride, 10 mm Na_2HPO_4 and 0.2 mm EDTA) until a pH value of 7.0 was obtained (using a pH-meter for determination of the pH value). The two complementary strands (dissolved in distilled H_2O) were added to 500 μL of buffer A. Distilled H_2O was added to a total volume of 1000 μL.

The samples were heated to 70 °C and cooled to 5 °C before initiating the experiment with a ramp of 1 °C/min. The melting temperature T_m was determined as the local maximum of the first derivative of the melting curve (A_{260} vs temperature).

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Tetrahedron 62 (2006) 3259–3265

Structural elucidation and bioactivity of novel secondary metabolites from *Carex distachya*

Antonio Fiorentino,* Brigida D'Abrosca, Angelina Izzo, Severina Pacifico and Pietro Monaco

Dipartimento di Scienze della Vita, Seconda Università di Napoli, via Vivaldi 43, I-81100 Caserta, Italy

Received 25 October 2005; revised 2 January 2006; accepted 19 January 2006

Abstract—Four new carexanes and a new seco-derivative metabolite have been isolated and characterized from the herbaceous plant *Carex distachya* Desf. All of the structures have been elucidated on the basis of spectroscopic data. These compounds derive from the cyclization of prenylate stylbenoid precursors. The seco-carexane is formed by a further oxidative cleavage of the C-7–C-8 bond. The absolute configurations have been determined by Mosher's method using appropriate chemical correlations. All of the carexanes A–H have been tested for their phytotoxicity against *Lactuca sativa*. The bioassays showed an inhibitory effect on seed germination for all compounds described in this report.
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1. Introduction

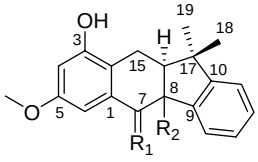
The organization of ecosystems is based on complex interactions among life forms living in close union. The search for food, the struggle for the reproduction, and defense from predators have induced organisms to develop suitable strategies to assure their survival, and the plant organisms interact no less aggressively than animals. In fact, on account of their stillness, plants have developed physical and chemical mechanisms to make contact with other plants and/or with animals living in the same ecosystem. Amongst such chemical strategies, the development of natural products is the most sophisticated mode to insure their existence. A variety of secondary plant metabolites are released into the soil, either as exudates from living plant tissues or by decomposition of plant residues.[1,2] Some of these chemicals play an important role in chemical interactions in natural plant communities and are known as allelochemicals.

Although allelopathic science is a relatively new field of study, there is convincing evidence that allelopathic interactions between plants play a crucial role in both natural and manipulated ecosystems.[1,3] These interactions are an important factor in determining species distribution and abundance within some ecosystems and for the success of many invasive plants.

In the search for allelochemicals from plants found near the Mediterranean area,[4,5] we recently reported the isolation and characterization of three new secondary metabolites, named carexanes A–C (**1**–**3**), from the leaves of *Carex distachya*,[6] a herbaceous plant growing in a Mediterranean bushland. These compounds showed a new tetracyclic molecular skeleton and should derive from the prenylation and successive cyclization of stilbene precursors, and are believed to be structurally interesting.[7]

Literature data suggested that other *Carex* species produce oligostilbenes,[8,9] constituted by two to four monomers of resveratrol (3,5,4′-trihydroxystilbene), most of them showing antimicrobial activity.

In further investigations on the same source we isolated five new compounds. In this paper, we report the elucidation of five new metabolites, named carexane D–H, and the phytotoxicity evaluation of these metabolites against *Lactuca sativa*, the test organism currently used for phytotoxic assays.



carexane A (**1**)	R_1 = βOH,αH	R_2 = βH
carexane B (**2**)	R_2 = O	R_2 = αOH
carexane C (**3**)	R_1 = O	R_2 = βOH
carexane D (**4**)	R_1 = O	R_2 = βH
9	R_1 = αOH,βH	R_2 = βH

Keywords: *Carex distachya* Desf; Carexanes; Prenyl stilbenes; NMR analysis; Phytotoxicity; *Lactuca sativa*.
* Corresponding author. Tel.: +39 0823 274576; fax: +39 0823 274571; e-mail: antonio.fiorentino@unina2.it

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doi:10.1016/j.tet.2006.01.066

2. Results and discussion

Compound **4** has been isolated as an amorphous powder and named carexane D. The elemental analysis and the presence of 20 carbons in the ^{13}C NMR spectrum justified the molecular formula $C_{20}H_{20}O_3$. The EIMS spectrum showed the molecular ion at *m/z* 308 confirming the presence of 11 unsuturations. The ^{1}H NMR spectrum (Table 1) showed six aromatic protons, two of them appear as doublets at δ 7.02 and 6.60, a doublet at δ 4.13, a methoxyl at δ 3.76, two methylene protons as double doublets at δ 3.07 and 2.33, a doublet of double of doublets at δ 2.72 and two singlet methyls at δ 1.16 and 1.27.

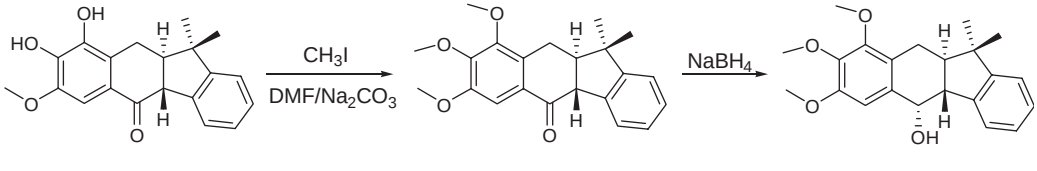
A DQ-COSY experiment showed cross-peaks of the two methylene protons with each other and with the methine at δ 2.72, which was, in turn, correlated with the doublet at δ 4.13. The ^{13}C NMR spectrum, on the basis of a DEPT experiment, identified three methyls, a methylene, eight methines, seven tetrasubstituted carbons and a carbonyl carbon. The NMR values of the signals confirmed the presence of two aromatic rings in the molecule.[6] The doublet at δ 4.13, bonded to the carbon at δ 53.7, was heterocorrelated, in an HMBC experiment, to the carbons at δ 20.9, 47.2, 50.8, 138.7, 152.5, and 199.5. The carbonyl showed correlations with the aromatic proton at δ 7.02 and with the doublet of double of doublet at δ 2.72. The signal at δ 7.02 showed interactions with the carbons at δ 108.6, 160.1 and with the tetrasubstituted carbons at δ 135.0 and 125.7, which were both correlated with the methylene protons. These data confirm the presence of a carexane skeleton possessing a C-7 carbonyl group, a methoxyl on the C-5 carbon, and a hydroxyl bonded to the C-3 carbon. The constant coupling (Table 1) of the H-8 and H-16 protons indicated their trans-orientation on the basis of the generalized Karplus equation.[10] To establish the absolute configurations to the chiral carbons, the carexane D was reduced in MeOH with $NaBH_4$. The products of the reaction were purified by HPLC and identified, by NMR spectroscopic analysis, as the known carexane A[6] and its epimer **9**, confirming an *R* configuration for both C-8 and C-16 carbons and also for the compound **4**.

Compound **5**, named carexane E, showed 20 signals in the ^{13}C NMR spectrum and a molecular peak, in the EIMS spectrum, in accordance with the molecular formula $C_{20}H_{20}O_4$. The ^{1}H NMR spectrum (Table 1) showed five aromatic protons as a doublet at δ 7.36 and four signals ranging from δ 7.12 to 7.19 ppm. In the aliphatic region of the spectrum a doublet at δ 4.06, a doublet of double of doublets at δ 2.68, a methylene as doublet of doublets at δ 3.08 and 2.35 were evident, besides a methoxyl at δ 3.85 and two methyls at δ 1.18 and 1.23. The ^{13}C NMR spectrum showed five methines and seven tetrasubstituted carbons, in the aromatic region. In the aliphatic region, a methylene, two aliphatic methines, three methyls, a quaternary carbon, besides a carbonyl carbon at δ 198.5, were present. The latter carbon showed correlations, in the HMBC experiment, with

Table 1. ^{1}H and ^{13}C NMR data of carexane D–G in CD_3OD

Position	Carexane D (**4**)		Carexane E (**5**)		Carexane F (**6**)		Carexane G (**7**)	
	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C
1	—	135.0	—	127.5	—	127.6	—	127.6
2	—	125.7	—	124.7	—	123.9	—	123.9
3	—	157.0	—	143.0	—	142.9	—	143.9
4	6.60d (2.4)	108.6	—	141.6	—	142.3	—	140.9
5	—	160.1	—	148.0	—	148.4	—	148.2
6	7.02d (2.4)	101.6	7.15s	101.9	7.08s	102.5	7.24s	103.8
7	—	199.5	—	198.5	—	197.4	—	196.5
8	4.13d (6.9)	53.7	4.06d (6.6)	53.4	—	82.0	—	80.3
9	—	138.7	—	138.8	—	143.5	—	142.4
10	—	152.5	—	152.4	—	153.2	—	155.5
11	7.17m	123.3	7.15m	123.3	7.17m	123.0	7.32m	123.5
12	7.20m	128.8	7.19m	128.7	7.28m	129.8	7.35m	130.0
13	7.18m	127.8	7.16m	127.8	7.25m	127.8	7.25m	127.5
14	7.38m	126.0	7.36d (6.9)	125.8	7.67m	127.0	7.94d (6.9)	127.5
15	3.07dd (6.0, 16.8) 2.33dd (8.4, 16.8)	20.9	3.08dd (6.0, 16.5)	21.3 2.35dd (9.0, 16.5)	3.08d (4.8)	19.7	3.09dd (10.9, 16.5) 2.95dd (5.4, 16.5)	20.9
16	2.72ddd (6.0, 6.9, 8.4)	50.8	2.68ddd (6.0, 6.6, 9.0)	51.0	2.71t (4.8)	57.3	2.22dd (10.9, 5.4)	58.7
17	—	47.2	—	47.2	—	46.1	—	44.8
18	1.16s	24.0	1.18s	23.9	0.75	26.6	1.39	27.8
19	1.27s	28.3	1.23s	28.2	1.43	29.4	1.41	26.9
OMe	3.76	55.7	3.85	56.4	3.83	56.4	3.89	56.5

s=singlet, d=doublet, dd=double doublet, ddd=double double doublet, m=multiplet, t=triplet; *J* values (Hz) are reported in brackets.



5 **10** **11**

Scheme 1. Chemical modifications used to determinate the absolute configurations of carexane E.

Table 2. NMR data of carexane H (**8**) in CD_3OD

Position	^1H (δ)	J (Hz)	DQ-COSY	^{13}C (δ)	DEPT	HMBC
1	—	—	—	135.2	C	—
2	—	—	—	121.3	C	—
3	—	—	—	158.3	C	—
4	6.51d	2.7	H-6	105.5	CH	C-2, C-3, C-5, C-6
5	—	—	—	159.7	C	—
6	6.83d	2.7	H-4	107.6	CH	C-2, C-4, C-5, C-7
7	—	—	—	172.4	C	—
8	—	—	—	210.1	C	—
9	—	—	—	135.6	C	—
10	—	—	—	164.4	C	—
11	7.56d	7.8	H-12	124.1	CH	C-9, C-10, C-12, C-13, C-17
12	7.63t	7.8	H-11, H-13	136.1	CH	C-10, C-11, C-13, C-14
13	7.37t	7.8	H-12, H-14	128.5	CH	C-9, C-12, C-14
14	7.62d	7.8	H-13	124.4	CH	C-8, C-9, C-10, C-12
15	3.38dd	7.5, 13.8	H-16	23.6	CH_2	C-1, C-2, C-3, C-8, C-16, C-17
	3.24dd	6.6, 13.8				C-1, C-2, C-3, C-8, C-16, C-17
16	2.97dd	6.6, 7.5	H-15	61.2	CH	C-2, C-8, C-10, C-15, C-17
17	—	—	—	43.6	C	—
18	1.28s	—	—	27.0	CH_3	C-10, C-16, C-17, C-19
19	1.31s	—	—	28.6	CH_3	C-10, C-16, C-17, C-18
OMe	3.77s	—	—	55.7	CH_3	C-5

s=singlet, d=doublet, dd=double doublet, ddd=double double doublet, m=multiplet, t=triplet; J values (Hz) are reported in brackets.

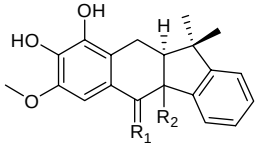
Table 3. Bioactivity of carexanes A–F and H on the germination, root elongation and shoot elongation of *L. sativa*

Carexanes	Germination						Root elongation						Shoot elongation					
	10^{-4} M	10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M	10^{-4} M	10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M	10^{-4} M	10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M
A	−2.0	−7.0	−5.0	−7.0	−3.0	−5.0	+11.5	+12.6	+9.1	+9.0	+5.1	−1.7	+2.5	+2.0	−4.3	+1.9	+2.8	+22.1
B	−25.0	−24.0	−36.0[a]	−39.0[a]	−35.0[a]	−28.0[b]	+1.9	+18.1[b]	+13.3[b]	+18.7[a]	+8.2	+7.4	+1.7	+14.5[b]	+11.8	+12.6	+10.4	−3.8
C	−4.0	−9.0	−10.0	−17.0[b]	−12.0[b]	−21.0[a]	+17.5[b]	+12.0	+12.8	+8.3	+2.1	+4.8	−4.4	+11.4	+11.0	+9.8	+8.4	+9.5
D	−46.0[a]	−34.0[a]	−15.0	−7.0	−6.0	−3.0	−43.5[a]	+1.2	+39.5[a]	+28.8[b]	+23.8	+32.7[b]	−36.5[b]	−14.5[b]	+16.3	+19.8[b]	+14.5	+19.9
E	−10.0	−6.0	−6.0	−3.0	−8.0	−7.0	+15.5[b]	+0.8	−2.0	+0.9	+5.0	−3.3	−24.5[a]	−7.9	+7.2	−7.1	−2.0	−10.3
F	−8.0	−7.0	−8.0	−11.0	−7.0	−8.0	+0.2	+14.3	+20.1[b]	+49.4[a]	+34.1[b]	+37.5[a]	−0.1	+5.1	+10.1	+29.4[a]	+34.8[a]	+37.9[b]
H	−24.0[a]	−20.0[a]	−11.0	−7.0	−6.0	+2.0	−22.3[b]	+0.2	+31.6[b]	+18.2[b]	+28.6	+52.1[a]	−29.4	−28.4	+1.2	+6.7	+12.0	+32.9[a]

Value are presented as percentage differences from control and are significantly different with $P>0.05$ for Student's t-test.
[a] $P<0.01$.
[b] $0.01<P<0.05$.

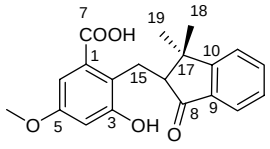
an aromatic proton at δ 7.15 and with both the methines at δ 4.06 and 2.68, suggesting a 7-oxocarexane skeleton. The NMR spectroscopic data indicated the presence of a further hydroxyl group in the A ring. In fact, heterocorrelation between the methylene protons and the carbon at δ 143.0 was evident; between the H-6 aromatic proton with the carbons at δ 141.6 and 148.0 and between this latter with the methoxyl protons at δ 3.85. These data were in good agreement with the proposed structure for carexane E. The absolute configurations to the carbons C-8 and C-16 were determined in this way: the coupling constant of the H-8 and H-16 protons indicated their trans-orientation. The reduction of compound **5** with $NaBH_4$ failed, probably due to the presence of a hydrochinon moiety in the molecule. Therefore, the compound was first methylated with CH_3I, and then reduced with $NaBH_4$ to produce the carexane **11**. The coupling constant (4.0 Hz) of the H-7 proton, geminal to the hydroxyl group, was in accordance with a cis-orientation in respect to the H-8 proton, which is trans in respect to the H-16 proton. The absolute configuration of the C-7 carbon was established by using a modified Mosher method.[11] The negative and positive $\Delta\delta_{R-S}$ values the H-8, and the H-6 protons were found, respectively, on the right and left sides of the MTPA plane, indicated an *S* configuration for C-7 and, consequently, an *R* configuration for the C-8 and C-16 carbons (Scheme 1).

Carexanes F and G (compounds **6** and **7**) were identified as two isomers on the basis of their ^{13}C NMR and EIMS spectra. The molecular formula found $C_{20}H_{20}O_5$, and the spectroscopic data, indicated that these compounds were 4-hydroxy derivatives of carexanes B and C, respectively. In fact the differences in chemical shifts (Table 1) were attributed to the presence of a further hydroxyl group at the C-4 carbon. The hypothesised structures were confirmed by two-dimensional NMR (HSQC, HMBC, NOESY) and EIMS data.



carexane E (**5**)	R_1 = O	R_2 = βH
carexane F (**6**)	R_1 = O	R_2 = αOH
carexane G (**7**)	R_1 = O	R_2 = βOH

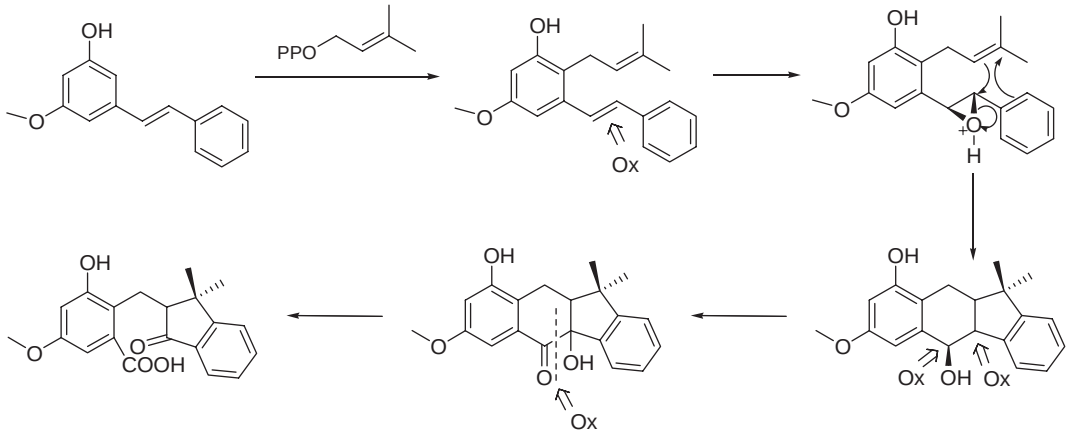
Compound **8** has been isolated as a colourless oil and named carexane H. The elemental analysis and the ^{13}C NMR spectroscopic data were in accordance with a molecular formula $C_{20}H_{20}O_5$. The EIMS spectrum showed a molecular peak at *m/z* 340, confirming the presence of 11 unsaturations in the molecule.



carexane H (**8**)

In the aromatic region of the ^1H NMR spectrum (Table 2), six protons were present: three protons were overlapped in the range from 7.70 to 7.50 ppm besides a triplet at δ 7.31 and two *meta* coupled doublets at δ 6.83 and 6.51. In the aliphatic region of the spectrum, a methoxyl at δ 3.77, two doublet of doublets at δ 3.38 and 3.24, a methine at δ 2.97 and two methyls at δ 1.28 and 1.31 were observed. The DQ-COSY experiment showed correlations between the methylene protons and the methine at δ 2.97, between the aromatic doublets at δ 6.51 and 6.83 and between the remaining four aromatic protons. The ^{13}C NMR spectrum exhibited 20 signals, which were identified on the basis of a DEPT experiment as three methyls, a methylene, seven methines, and nine quaternary carbons. In particular, a carbonyl carbon at δ 210.1 and a carboxyl at δ 172.4 were present.

The HMBC experiment (Table 2) showed heterocorrelations with the aromatic protons and the carbons at δ 159.7, 158.3, 121.3 and 107.6. The latter signal showed a correlation, in the HSQC spectrum, with the proton at δ 6.83. This latter showed correlations with the carbons at δ 159.2, 135.2, 121.3 and the carboxyl group. These data confirmed the presence of the A ring with an hydroxyl and methoxyl groups bonded at the C-3 and C-5 carbons. The C-2 carbon at δ 121.3 were correlated to the methylene protons and to the methine at δ 2.97 bonded to the carbon at δ 61.2. The latter proton resulted correlated to both the methyls, to the carbons at δ 43.6 and 164.2 and to the carbonyl at δ 210.1, which was in turn, correlated with the methylene protons. These data suggested, for the compound **8**,



Scheme 2. Biosynthetic pathway proposed for the carexanes.

a 7,8-*seco*-carexane structure derived by a oxidative cleavage of the C-7–C-8 bond. In fact the C-7 and C-8 carbon were oxidized at carboxyl and carbonyl groups, respectively.

All of the compounds, with exception of the less abundant carexane G, have been tested on the dicotyledonous *L. sativa* L.[12,13] and the results are reported in Table 3. The inhibitory effect on germination, on the contrary, a stimulating effect was shown against plant growth. The most active compounds on the germination were carexanes B and D. This latter and the carexane H showed a similar behaviour: on the seed germination showed a good dose-response relationship, while on the plant growth they were active at the highest concentration used and became stimulating at the lower doses.

No many articles report the isolation of prenylated stilbenes from natural sources.[14] These compounds are identified as cytotoxic against ovarian cancer cell lines.[15] The tetracyclic prenylated structures of the carexanes A–G and the derivative carexane H have been reported for the first time. They could originate by the prenylation of a stilbene precursors, cyclization and successive modifications, as hypothesised in the Scheme 2.

3. Experimental

3.1. General procedures

NMR spectra were recorded at 300 MHz (for ^{1}H) and 75 MHz (for ^{13}C) on a Varian 300 spectrometer Fourier transform NMR spectrometer in CD_3OD at 25 °C. Proton-detected heteronuclear correlations were measured using a gradient heteronuclear single-quantum coherence (HSQC), optimised for $^{1}J_{HC}=140$ Hz, and a gradient heteronuclear multiple bond coherence (HMBC), optimised for $^{n}J_{HC}=8$ Hz. UV spectra were performed in MeOH solution on UV-1601 Shimadzu spectrophotometer. Optical rotations were measured in MeOH solution on a Perkin-Elmer 141. Electron ionization mass spectra (EIMS) were obtained with a HP 6890 instrument equipped with a MS 5973 N detector.

The preparative HPLC apparatus consisted of a pump (Shimadzu LC-10AD), a refractive index detector (Shimadzu RID-10A) and a Shimadzu Chromatopac C-R6A recorder. Preparative HPLC was performed using RP-8 (Luna 10 μm, 250×10 mm i.d., Phenomenex) column. Analytical TLC was performed on Merck Kieselgel 60 F_{254} or RP-8 F_{254} plates with 0.2 mm layer thickness. Spots were visualized by UV light or by spraying with H_2SO_4–AcOH–H_2O (1/20/4). The plates were then heated for 5 min at 110 °C. Preparative TLC was performed on Merck Kieselgel 60 F_{254} plates, with 0.5 or 1 mm film thickness. Flash column chromatography (FCC) was performed on Merck Kieselgel 60 (230–400 mesh) at medium pressure. Column chromatography (CC) was performed on Merck Kieselgel 60 (70–240 mesh).

3.2. Plant material, extraction and isolation of the metabolites

Plants of *C. distachya* Desf (Cyperaceae) were collected in June 2004, in the vegetative state, in Castelvolturno, near Caserta (Italy), and identified by Dr. Assunta Esposito of the Second University of Naples. A voucher specimen (CE278) has been deposited at the Herbarium of the Dipartimento di Scienze della Vita of Second University of Naples.

Fresh leaves of *C. distachya* (6 kg) were extracted with hexane for 5 days at 4 °C in the dark. The organic solution was distilled under reduced pressure by a Rotavapor® to obtain 30.0 g of crude extract. The hexane extract was chromatographed on SiO_2, with hexane and EtOAc solutions, to give three fractions I–III.

Fraction I, eluted with hexane–EtOAc (5/1), was rechromatographed by Sephadex LH-20® eluting with hexane–$CHCl_3$–MeOH (3/1/1) to obtain a fraction, which was purified by TLC eluting with hexane–EtOAc (4/1) to give pure carexane D (12.4 mg).

Fraction II, eluted with hexane–EtOAc (4/1), was rechromatographed by Sephadex LH-20® eluting with hexane–$CHCl_3$–MeOH (3/1/1) to obtain the carexane E (40.2 mg) and two further fractions. The first one was purified by preparative RP-8 HPLC eluting with MeOH–MeCN–H_2O (2/2/1) to give pure carexanes A (3.2 mg), B (5.0 mg) and C (4.3 mg). The second fraction was chromatographed by TLC with $CHCl_3$–Me_2CO (9/1) to have pure carexane H (2.1 mg).

Fraction III, eluted with hexane–EtOAc (3/2), was rechromatographed by Sephadex LH-20 eluting with hexane–$CHCl_3$–MeOH (3/1/1) to obtain a fraction, which was purified by preparative RP-8 HPLC eluting with MeOH–MeCN–H_2O (2/2/1) to give pure carexanes F (2.0 mg) and G (1.0 mg).

3.2.1. Characterization of the carexanes D–H. *Carexane D* (**4**). Amorphous white powder; UV (MeOH) λ_{max} nm (log ε): 334.4 (2.86), 273.4 (3.39), 213.0 (3.84); ^{1}H NMR (300 MHz, CD_3OD) and ^{13}C NMR (75 MHz, CD_3OD): Table 1; EIMS *m/z* 308 $[M]^+$, 293 $[M-CH_3]^+$, 291 $[M-OH]^+$; $[\alpha]_D^{25}$ +136.5 (*c* 0.14, MeOH). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.54; H, 6.91.

Carexane E (**5**). Amorphous white powder; UV (MeOH) λ_{max} nm (log ε): 308.0 (3.84), 213.2 (4.19); ^{1}H NMR (300 MHz, CD_3OD) and ^{13}C NMR (75 MHz, CD_3OD): Table 1; EIMS *m/z* 324 $[M]^+$, 309 $[M-CH_3]^+$, 307 $[M-OH]^+$; $[\alpha]_D^{25}$ +80.2 (*c* 0.41, MeOH). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.32; H, 6.51.

Carexane F (**6**). Amorphous white powder; UV (MeOH) λ_{max} nm (log ε): 314.4 (3.48), 203.2 (3.92); ^{1}H NMR (300 MHz, CD_3OD) and ^{13}C NMR (75 MHz, CD_3OD): Table 1; EIMS *m/z* 416 $[M]^+$, 401 $[M-CH_3]^+$; $[\alpha]_D^{25}$ −64.3 (*c* 0.06, MeOH). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.78; H, 5.84.

Carexane G (**7**). Amorphous white powder; UV (MeOH) λ_{max} nm (log ε): 301.8 (3.69), 204.4 (4.12); ^{1}H NMR

(300 MHz, CD_3OD) and ^{13}C NMR (75 MHz, CD_3OD): Table 1; EIMS *m/z* 340 $[M]^+$, 325 $[M-CH_3]^+$, 323 $[M-OH]^+$; $[\alpha]_D^{25}$ +203.8 (*c* 0.13, MeOH). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.67; H, 6.01.

Carexane H (**8**). Colourless oil; UV (MeOH) λ_{max} nm (log ε): 287.6 (3.11), 240.4 (3.53), 205.4 (4.16); ^1H NMR (300 MHz, CD_3OD) and ^{13}C NMR (75 MHz, CD_3OD): Table 1; EIMS *m/z* 340 $[M]^+$, 325 $[M-CH_3]^+$, 295 $[M-CO_2H]^+$; $[\alpha]_D^{25}$ 0 (*c* 0.10, MeOH). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.76; H, 5.89.

3.2.2. Reduction of carexanes D. To a solution of compound **4** (6 mg, 0.019 mmol) in MeOH (0.5 ml) 2 mg of $NaBH_4$ (0.053 mmol) were added. The solution was kept under magnetic stirring for 1 h and then treated with AcOH (1 drop) and dried under nitrogen flow. The mixture were purified by TLC [EtOAc–$CHCl_3$ (1/4)] to give carexane A (1 mg) and product **9** (4 mg). Compound **9**: ^1H NMR (300 MHz, CD_3OD) δ: 7.38 (1H, m, H-14), 7.06 (3H, m, H-11–H-13), 6.48 (1H, d, J=2.1 Hz, H-6), 6.22 (1H, d, J=2.1 Hz, H-4), 4.99 (1H, d, J=4.2 Hz, H-7), 3.70 (3H, s, OMe), 3.65 (1H, dd, J=4.2, 9.3 Hz, H-8), 2.81 (1H, dd, J=8.1, 15.0 Hz, H-15), 2.74 (1H, dd, J=7.8, 15.0 Hz, H-15), 2.55 (1H, ddd, J=7.8, 8.1, 9.3 Hz, H-16), 1.29 (3H, s, H-18), 1.27 (3H, s, H-19); ^{13}C NMR (300 MHz, CD_3OD) δ: 159.6 (C-5), 155.4 (C-10), 155.1 (C-3), 144.0 (C-1), 142.2 (C-9), 127.8 (C-12), 127.2 (C-13), 126.3 (C-14), 117.7 (C-2), 104.3 (C-4), 101.1 (C-6), 72.8 (C-9), 55.6 (OMe), 51.8 (C-8), 48.0 (C-16), 46.7 (C-17), 33.5 (C-19), 25.8 (C-18), 21.0 (C-15); EIMS *m/z* 310 $[M]^+$, 295 $[M-CH_3]^+$. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.56; H, 7.64.

3.2.3. Methylation and reduction of carexane E. To 1 ml of dry DMF, saturated with anhydrous Na_2CO_3, 15 mg of carexane E (0.046 mmol) were added. After 5 min 10 µl of CH_3I were added and the mixture was kept under magnetic stirring for 1 h (Scheme 1). The mixture was then treated with H_2O (15 ml) and extracted with EtOAc (2×15 ml). The organic extract was dried with anhydrous Na_2SO_4 and evaporated in vacuo to afford the methyl derivative **10** (10 mg): ^1H NMR (300 MHz, CD_3OD) δ: 7.38 (1H, m, H-14), 7.23–7.18 (3H, m, H-11–H-13), 7.15 (1H, s, H-6), 4.14 (1H, d, J=6.9 Hz, H-8), 3.86 (9H, s, OMe), 3.11 (1H, d, J=6.3, 16.8 Hz, H-15), 2.74 (1H, ddd, J=6.3, 6.9, 7.8 Hz, H-16), 2.38 (1H, dd, J=8.7, 16.8 Hz, H-15), 1.28 (3H, s, H-18), 1.20 (3H, s, H-19); EIMS *m/z* 352 $[M]^+$, 337 $[M-CH_3]^+$. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.98; H, 6.86. Found: C, 75.11; H, 6.95. To a solution of compound **10** (10 mg, 0.028 mmol) in MeOH (0.5 ml) 3 mg of $NaBH_4$ (0.080 mmol) were added. The solution was kept under magnetic stirring for 1 h and then treated with AcOH (1 drop) and dried under nitrogen flow. The mixture was purified by TLC EtOAc–$CHCl_3$–hexane (2/8/1) to give **11** (6 mg) as the main product. ^1H NMR (300 MHz, CD_3OD) δ: 7.38 (1H, m, H-14), 7.22–7.04 (3H, m, H-11–H-13), 6.58 (1H, s, H-6), 5.00 (1H, d, J=4.0 Hz, H-7), 3.82 (9H, s, OMe), 3.63 (1H, dd, J=4.0, 9.9 Hz, H-8), 2.85 (1H, dd, J=5.7, 16.0 Hz, H-15), 2.76 (1H, dd, J=8.1, 16.0 Hz, H-15), 2.55 (1H, ddd, J=5.7, 8.1, 9.9 Hz, H-16), 1.29 (6H, s, H-18 and H-19); EIMS *m/z* 354 $[M]^+$, 339 $[M-CH_3]^+$. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.61; H, 7.64.

3.2.4. Preparation of (*S*) and (*R*)-MTPA esters of compound 11. (*R*)-(−)-MTPA chloride (5 µl, 26 µmol) was added to a solution of pure compound **11** (1.5 mg, 4.2 µmol) in dry pyridine (50 µl). After 6 h under magnetic stirring at room temperature, EtOAc (5 ml) and H_2O (5 ml) were added to the reaction mixture. The organic layer, separated by centrifugation at 4000 rpm for 10 min, gave a crude extract, which was purified by preparative TLC eluting with hexane–EtOAc (7/3). The (*S*)-MTPA ester had the ^1H NMR spectral data (300 MHz, CD_3OD) δ: 6.77 (1H, s, H-6), 6.34 (1H, d, J=3.9 Hz, H-7), 4.21 (1H, m, H-8), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.73 (3H, s, OMe). The (*R*)-MTPA ester had the ^1H NMR spectral data (300 MHz, CD_3OD) δ: 6.73 (1H, s, H-6), 6.31 (1H, d, J=3.8 Hz, H-7), 3.93 (1H, m, H-8), 3.76 (3H, s, OMe), 3.72 (3H, s, OMe), 3.69 (3H, s, OMe).

3.3. Phytotoxicity test

Seeds of *L. sativa* L. (cv Napoli V.F.), collected during 2003, were obtained from Ingegnoli S.p.a. All undersized or damaged seeds were discarded and the assay seeds were selected for uniformity. Bioassays used Petri dishes (50 mm diameter) with one sheet of Whatman No. 1 filter paper as support. In four replicate experiments, germination and growth were conducted in aqueous solutions at controlled pH. Test solutions (10^{-4} M) were prepared using (2-[*N*-morpholino]ethanesulfonic acid (MES; 10 mm, pH 6) and the rest (10^{-5}–10^{-9} M) were obtained by dilution. Parallel controls were performed. After the addition of 25 seeds and 2.5 ml test solns, Petri dishes were sealed with Parafilm® to ensure closed-system models. Seeds were placed in a growth chamber KBW Binder 240 at 25 °C in the dark. Germination percentage was determined daily for 5 days (no more germination occurred after this time). After growth, plants were frozen at −20 °C to avoid subsequent growth until the measurement process. Data are reported as percentage differences from control in the graphics. Thus, zero represents the control, positive values represent stimulation of the parameter studied and negative values represent inhibition.

Statistical treatment. The statistical significance of differences between groups was determined by a Student's *t*-test, calculating mean values for every parameter (germination average, shoot and root elongation) and their population variance within a Petri dish. The level of significance was set at $P<0.05$.

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Tetrahedron 62 (2006) 3266–3283
Tetrahedron

A unified synthetic approach to trachylobane-, beyerane-, atisane- and kaurane-type diterpenes

Antonio Abad,* Consuelo Agulló, Ana C. Cuñat, Ignacio de Alfonso Marzal, Ismael Navarro and Antonio Gris

Departamento de Química Orgánica, Universitat de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

Received 1 December 2005; revised 17 January 2006; accepted 18 January 2006

Abstract—A general synthetic approach to the polycyclic carbon skeleton of biogenetically related trachylobane, beyerane, atisane, and kaurane diterpenes from carvone is described. The skeleton of these diterpenes is prepared from a common intermediate, that is, **25**, readily prepared from carvone using an IMDA reaction and an intramolecular diazo ketone cyclopropanation of an unsaturated ketone as key steps. The tetracyclic diterpene ring systems are obtained from this key trachylobane-type intermediate through the regioselective reductive cleavage of the cyclopropane ring, after adequate modification of the functionalization around the tricyclo[3.2.1.0^{2,7}]octane moiety.
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1. Introduction

Trachylobanes, beyeranes, atisanes, and kaurane represent an important group of closely biosynthetically related polycyclic diterpenes,[1] many of which display a wide range of biological activities.[2–5] The usual mechanism proposed for the formation of the carbon skeleton of these diterpenes is based upon the original Wenkert biogenetic pathway to polycyclic diterpenes and implies the initial formation of the tetracyclic cation **2** from copalyl pyrophosphate, via the pymaranyl cation **1** (Scheme 1).[6,7] Closure of this intermediate takes place by either formation of a protonated cyclopropane or by loss of a proton forming the trachylobane skeleton **3**. The three different cleavage modes of the cyclopropane ring lead to the skeletons of kaurane **4** (path a), beyerane **5** (path b) or atisane **6** (path c).[†]

A large number of synthetic routes have been developed for the construction of the carbon framework of these diterpenes,[8] as well as for the elaboration of the tricyclo[3.2.1.0^{2,7}]-, bicyclo[3.2.1]-, and bicyclo[2.2.2]-octane moieties, characteristic of trachylobanes, beyeranes/kauranes, and atisanes, respectively.[9]

In connection with our continued interest for the synthesis of biologically active polycyclic terpenes from carvone,[10] we describe in this paper a unified approach for the construction of the carbocyclic skeleton of these diterpenes, which implies the initial preparation of a common key intermediate with a trachylobane-like skeleton that, in a way conceptually similar to that of the proposed biogenetic pathway, is regioselectively transformed into the atisane-, beyerane- or kaurane-framework. A preliminary communication of part of this work has appeared previously.[11‡]

2. Results and discussion

As illustrated in the retrosynthetic analysis in Scheme 2, we considered that a compound such as **7**, which contains all the carbon atoms of the diterpenoid framework and the tricyclo[3.2.1.0^{2,7}]octane moiety incorporated into the ring C, would be a versatile common key intermediate for the

Keywords: Terpenoids; Diels–Alder reaction; Diazo compounds; Ring opening; Cyclopropane.
* Corresponding author. Tel.: +34 6 3864509; fax: +34 6 3864328; e-mail: antonio.abad@uv.es
† All the diterpenes and related compounds described in this paper belong to the enantiomeric series having the 10α-methyl configuration (diterpene numbering), as shown in the structures of Scheme 1. However, the *ent* descriptor is omitted from the names of the diterpenes in the Section 2 for convenience (see heading in the Section 4 for complete systematic names, conforming to the IUPAC recommendations for systematic nomenclature of cyclic diterpenes). It should be noted that although most of the natural tetracyclic diterpenes isolated so far belong to the *ent*-series, some of them, for example, kauranes, are known in both antipodal forms. As will be seen, the approach described in this paper allows the preparation of compounds of both enantiomeric series.

‡ It must be noted that the synthesis described in this initial account starts with (*S*)-(+)-carvone, and therefore all the compounds described there belong to the opposite enantiomeric series of that of the compounds described herein.

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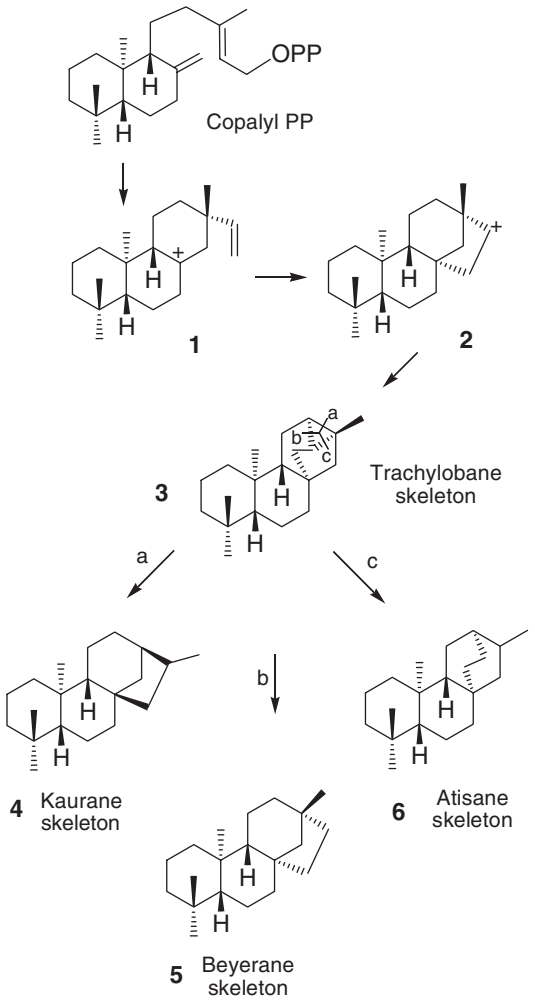
doi:10.1016/j.tet.2006.01.062



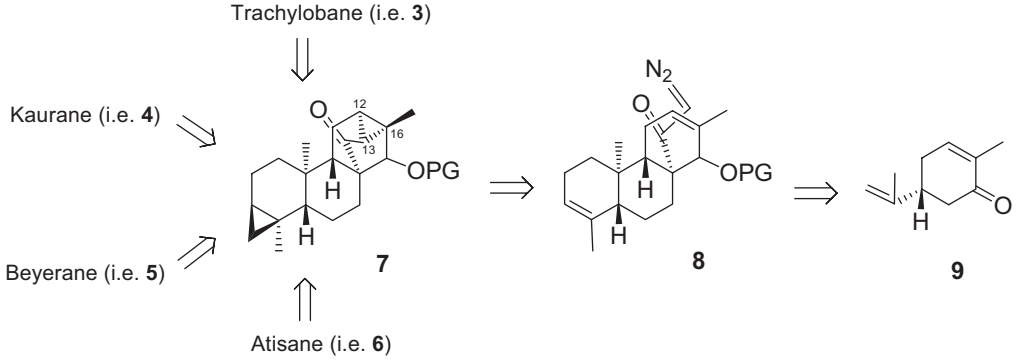
Scheme 1. Structural-biogenetic relationship of tetracyclic diterpenes.

construction of the carbocyclic skeleton of these diterpenes. The tricyclooctane moiety of **7** could be prepared by the intramolecular addition of an α-diazo carbonyl group to the double bond of a homochiral tricyclic system,[12] such as, for example, in **8**, which could conceivably be prepared from (*R*)-(−)-carvone (**9**) using a well-established methodology.[13] Transformation of the key intermediate **7** into the trachylobane skeleton should only require the completion of the gem-dimethyl group at C-4 (e.g., by hydrogenation of the cyclopropane moiety), while its transformation into the beyerane-, kaurane-, and atisane-frameworks should require additional regioselective fragmentation of the C12–C13, C12–C16 or C13–C16 cyclopropane bonds, respectively. This could be achieved, for example, via a reductive process after adequate modification of the functionalization around the cyclopropane ring.

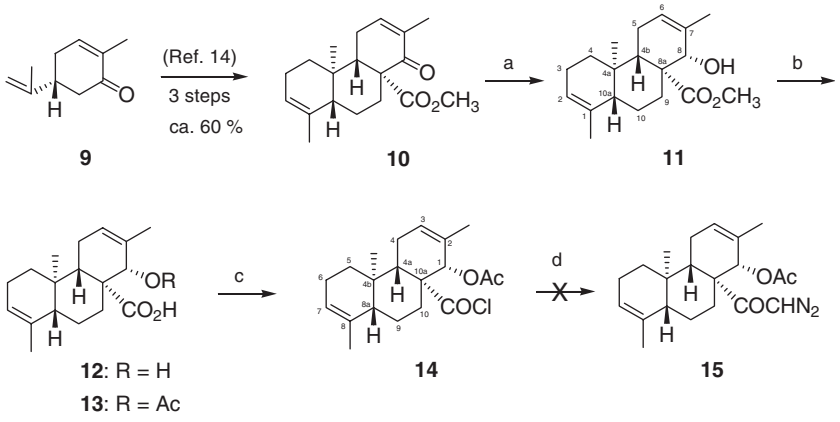
2.1. Preparation of the key intermediate. Construction of the tricyclo[3.2.1.0^{2,7}]octane moiety

A first approach to the required intermediate tricyclic α-diazoketone (Scheme 3), was based on the initial preparation of a carboxylic acid such as **13**, which, in principle, we expected could be easily converted into the required diazoketone by reaction of the corresponding acyl chloride with diazomethane. Accordingly, the (*R*)-(−)-carvone (**9**) was transformed into the known β-ketoester **10**, in three steps, with a 55–60% overall yield.[14] Luche reduction of the carbonyl function of **10** took place stereoselectively, affording the allylic alcohol **11** in 88% yield. The stereochemistry of the new stereogenic centre was determined by NOE measurement. Particularly relevant is the NOESY cross-peak observed between the axially oriented H-8 at δ 3.93 ppm and H-4b at δ 1.53 ppm that unequivocally determines the α-disposition of the hydroxyl function. It must be noted that the above ketone-to-alcohol reduction was necessary since the direct saponification of the methoxycarbonyl moiety of β-ketoester **10** gives rise the retro-Claisen fragmentation of the ring C. Thiolate nucleophile-catalysed hydrolysis of the hindered methyl ester functionality of **11** afforded the expected carboxylic acid **12**, which was transformed into the acetate **13** by acetylation of the alcohol function under standard conditions, in 75% overall yield for the two steps. Conversion of the carboxylic acid moiety of **13** to the corresponding acyl chloride **14** was readily accomplished in 85% yield by reaction of **13** with thionyl chloride and catalytic DMF in benzene.

Unfortunately, all attempts to transform the acyl chloride **14** into the α-diazoketone **15** met with disappointing results; treatment of **14** with diazomethane under a set of different reaction conditions always afforded starting material rather than the desired diazoketone. Although the acyl chloride **14** appeared to be relatively stable (e.g., it could be purified without substantial decomposition by rapid filtration through a short column of silica gel), its lack of reactivity with diazomethane was somewhat unexpected since it reacts smoothly with other weak nucleophiles, for example, MeOH, at rt.



Scheme 2. Retrosynthetic route to tetracyclic diterpenes.

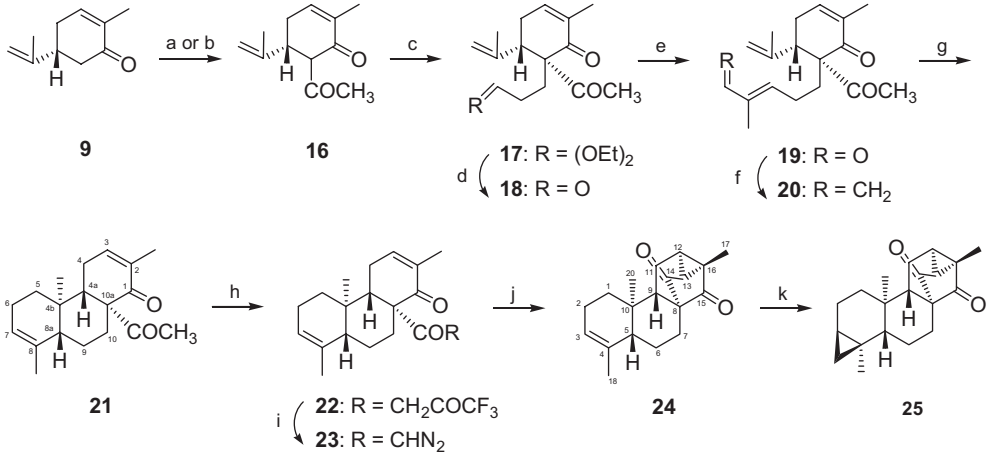


Scheme 3. Failed attempted approach to tricyclic α-diazoketone intermediate. Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 1 h, 88%; (b) NaSPr, DMF, 85 °C, 2 h; (c) Ac_2O–DMAP-Py, rt, 2 h, 75% from **11**; $SOCl_2$, DMF–C_6H_6, rt, 3 h, 85%; (d) see text.

We also failed in all attempts to prepare the desired diazoketone using the conditions developed by Nicolaou for highly hindered carboxylic acids.[15] Thus, treatment of carboxylic acid **13** with mesyl chloride and Et_3N and then with diazomethane resulted, after aqueous work-up, in the recovery of the starting material. The same disappointing results were obtained using other protecting group of the hydroxyl function instead of the acetate, such as the methoxy methyl ether group, for example.

The resistance of the hindered carboxylic acid group of **13** to conversion into the corresponding α-diazoketone, prompted us to consider other possibilities. A very convenient alternative was found in the initial preparation of methyl-ketone **21** (Scheme 4), which was readily converted into the diazoketone **23** through a diazo-transfer reaction.[16] The synthesis of methyl-ketone **21** commences with the preparation of β-diketone **16** from (*R*)-(−)-carvone (**9**). This was done either by reaction of the kinetic enolate of carvone with acetaldehyde, followed by Swern oxidation of the resulting β-hydroxy-ketone or, more conveniently, in a single synthetic step, by reaction of the same enolate with acetyl cyanide (pyruvonitrile). In both cases, the β-diketone **16** was obtained in excellent yield as a mixture of epimers at C-6, as inferred through ^1H NMR analysis of the mixture. Alkylation of the β-diketone **16** with 6-bromo or 6-iodo-3-methyl-1,3-hexadiene, in order to directly obtain the compound **20** in a similar process to that used for the preparation of β-keto ester **10** (see Ref. 14), afforded a very low yield of the alkylation product, so a stepwise approach was followed for introduction of the 4-methyl-hexa-3,5-dienyl moiety. First, the tetrabutylammonium enolate of **16**, readily obtained by sequential treatment of **16** with 2 equiv of NaH and 1 equiv of $BuNHSO_4$ in THF–DMF,[17] was alkylated with 3-iodopropanaldehyde diethyl acetal in high yield and with very good diastereoselectivity. The diethyl acetal protecting groups of the alkylated product **17** was removed by acid hydrolysis with pyridinium *p*-toluenesulfonate (PPTS) in aq acetone, followed by chemoselective homologation of the aldehyde group by Wittig reaction with (α-formylethylidene)triphenyl phosphorane to give the α,β-unsaturated aldehyde **19** in 80% overall yield for the two steps.

The hexadienyl moiety was completed by Wittig methylenation of the unsaturated aldehyde **19**, which afforded the 1,3,9-decatriene **20** in 92% yield. Finally, the ABC-ring system was completed by intramolecular Diels–Alder reaction (IMDA) of **20**, which was conducted in toluene containing a small amount



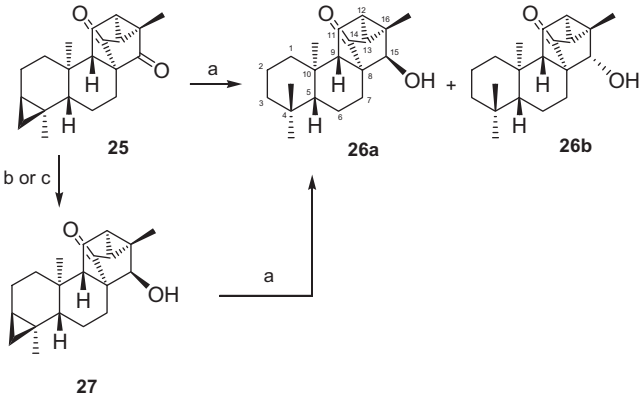
Scheme 4. Preparation of α-diazoketone intermediate and key polycyclic compound **25**. Reagents and conditions: (a) (i) LDA, THF, −78 °C then CH_3CHO, 92%; (ii): $(ClCO)_2$–DMSO, CH_2Cl_2, −30 °C then Et_3N, 90%; (b) LiHMDS, THF, −78 °C then $CNCOCH_3$, 93%; (c) NaH (2 equiv), THF, 0 °C then Bu_4NHSO_4–DMF and $ICH_2CH_2CH(EtO)_2$, 93%; (d) PPTS, H_2O–CH_3COCH_3, ref, 1 h, 93%; (e) $Ph_3P{=}C(Me)CHO$, C_6H_6, ref, 48 h, 86%; (f) Ph_3PCH_3Br–KHMDS, $PhCH_3$, −20 °C to rt, 1 h, 92%; (g) PhMe, propylene oxide, 190–200 °C; 6 days, 90%; (h) LiHMDS, THF, −78 °C then $CF_3CO_2CH_2CF_3$; (i) MsN_3, CH_3CN, H_2O–Et_3N, rt, 80% from **21**; (j) bis(*N-tert*-butylsalicylaldiminate)Cu(II), toluene, ref, 4 h, 95%; (k) CH_2I_2, $ZnEt_2$, toluene, 0 °C to rt, 3 h, 94%.

of propylene oxide as acid scavenger at 190–200 °C in a sealed ampoule for 6 days, affording stereoselectively the desired tricyclic methyl-ketone **21** in 90% yield. Although expected on the basis of previous IMDA reactions of related 1,3,9-decatrienes,[18] the stereochemistry of the Diels–Alder adduct **21** was confirmed through a detailed spectroscopic study, including HSQC and NOESY experiments, and comparison of the data with those of related systems (e.g., **10**).

In order to undertake the above mentioned diazo-transfer reaction, the methyl-ketone **21** was first transformed into the trifluoromethyl β-diketone **22** by reaction of its lithium enolate with 2,2,2-trifluoroethyltrifluoroacetate at low temperature. Further diazo-transfer reaction and subsequent in situ retro-Claisen reaction on treatment with mesyl azide or *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and Et_3N in CH_3CN in the presence of 1 equiv of water, afforded the α-diazoketone **23** in 80% overall yield for the two steps. It was gratifying to find, in contrast with the poor results obtained in the few examples of this reaction described so far,[19] that intramolecular addition of the α-diazoketone to the enone double bond took place very efficiently when **23** was slowly added to boiling toluene containing a catalytic amount of bis(*N-tert*-butyl salicylaldiminate)copper(II), thus completing the construction of the tricyclo[3.2.1.$0^{2,7}$]octane moiety. The carbon atom required for further elaboration of the characteristic diterpene C-4 gem-dimethyl group was introduced by cyclopropanation of the A-ring double bond of **24**, using standard Simmons–Smith cyclopropanation conditions. This reaction takes place stereoselectively from the less hindered β-side of the double bond, affording the key intermediate **25** in an excellent 94% yield.[§]

2.2. Completion of the trachylobane framework

The next objective after preparation of this key intermediate was its transformation into each of the target diterpenic systems. Transformation into a trachylobane-type compound was readily achieved by selective hydrogenolysis of the cyclopropane ring fused to the A ring. The hydrogenation of **25** was complete after 48 h at 35–40 °C under a hydrogen pressure of 65 psi using AcOH as the solvent and PtO_2 as the catalyst (Scheme 5). This treatment not only produces the hydrogenolysis of the cyclopropane bond, with formation of the C-4 geminal dimethyl group, but also regioselective reduction of the C-15 carbonyl group affording a ca. 2:1 mixture of C-15 epimeric trachylobanols **26a** and **26b** in 95% combined yield. The structure and stereochemistry of the major trachylobanol was established by detailed spectral analysis and comparisons with the data reported for related compounds.[20] In particular, the stereochemistry at the C-15 carbinolic centre was assigned on the basis of 2D NOESY experiments in which H-15 at δ 3.61 ppm clearly shows NOE with both H-7 at δ 1.78 and 1.20 ppm and Me-16 at δ 1.34 ppm, which, together with the remarkable shielding experienced by C-9 (7–8 ppm) in the ^{13}C NMR spectrum,



Scheme 5. Synthesis of trachylobane framework from **25**. Reagents and conditions: (a) H_2, PtO_2, AcOH, 4 atm, 35 °C, 48 h, 95% overall yield for **26a**/**26b** from **25** and 96% of **26a** from **27**; (b) $NaBH_4$, MeOH–CH_2Cl_2, 0 °C, 30 min, 96%; (c) H_2, 10% Pt/C, AcOEt, 4 atm, 24 h, 95%.

clearly establish a β disposition for the hydroxyl group at C-15. Alternatively, a highly chemo- and stereoselective reduction of the C-15 carbonyl group of **25** was effected by hydrogenation at ambient temperature in AcOEt with 10% Pt on carbon as the catalyst and also by sodium borohydride reduction in MeOH–CH_2Cl_2 at 0 °C. In both cases a very high yield of the alcohol **27** was obtained, which was converted to the trachylobanol **26a** in 95% yield by hydrogenolysis of the cyclopropane ring as described above for **25**.

2.3. Regioselective cleavage of the cyclopropane ring: completion of the beyerane, atisane, and kaurane frameworks

Having completed the elaboration of the trachylobane system, we focussed on our goal of regioselective cleavage of the cyclopropane bonds[21] in order to access to the atisane, beyerane, and kaurane carbocyclic systems. In spite of the previously reported results on electrophile-initiated selective ring cleavage of cyclopropyl-ketones, all attempts to open the cyclopropane ring of the cyclopropyl-diketone moiety of **25** under different electrophilic/acid reaction conditions were unsuccessful. Thus, reaction of this compound under relatively smooth acidic conditions, for example, cat. PTSA–LiBr–DMF,[22] $BF_3{\cdot}Et_2O$–Ac_2O–CH_2Cl_2,[23] led to the recovery of the starting material, while more severe conditions, for example, hydrogen chloride–CH_2Cl_2,[24] aq HBr–AcOH,[25] TMSI–$CHCl_3$,[26] led only to the opening of the cyclopropane ring fused to the A ring. Only the treatment with 48% HBr in AcOH apparently led to the cyclopropane-ring opening, yielding a complex mixture of non-identified products. A brief exploration of the reactivity of hydroxy-cyclopropyl-ketone **27** towards some of this electrophilic reaction conditions was also undertaken. In general, complex reaction mixtures were obtained, probably due to the initial formation of a cyclopropyl carbocation.[¶]

However, when the 15-hydroxyl group was protected, for example, as acetate, the cyclopropyl-ketone moiety was not

[§] As described in the previous communication, the structure of this key intermediate, but of the antipodal series, has been firmly established by X-ray analysis. The crystallographic data has been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 172270.

[¶] The easy formation of a carbocation of this type is illustrated by the result obtained in the solvolitic reaction of trachylobanol **26a** with HCOOH–0.5% Na_2CO_3 at 50 °C, which cleanly afforded an equimolecular mixture of C-15 epimeric formates.

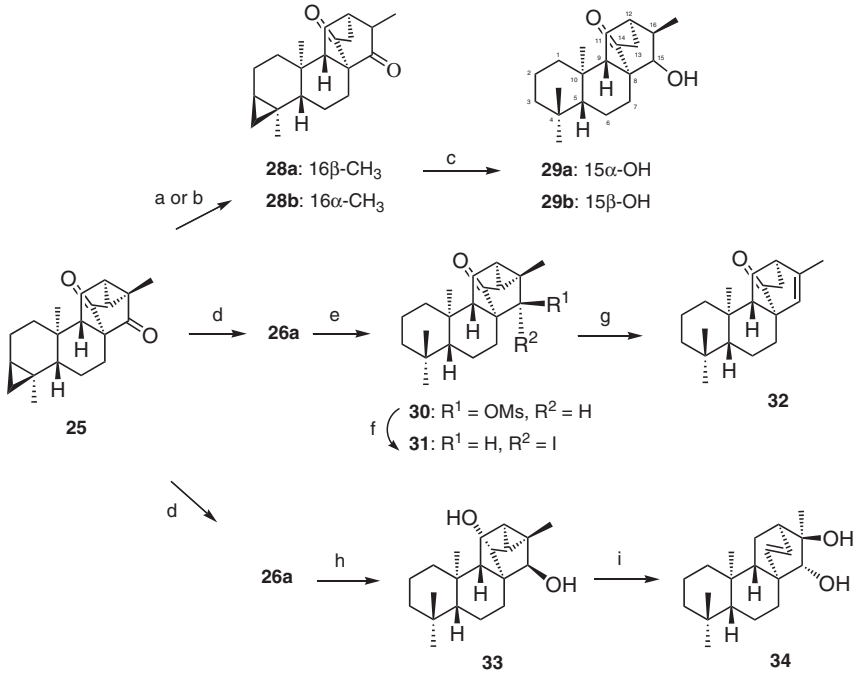
affected by these treatments. For example, the cyclopropyl-ketone moiety of the acetate derivative of **27** remained unaltered after treatment with hydrogen chloride in CH_2Cl_2 or aq HBr in acetic acid.

Highly satisfactory results were obtained via reductive cleavage of the cyclopropane ring. For example, a regioselective reductive cleavage of the C13–C16 cyclopropane bond took place when the cyclopropyl-diketone **25** was treated with lithium in liquid ammonia at low temperature or SmI_2 in THF–MeOH at rt, to give the cyclo-atisane-type diketone **28** as a ca. 2:1 mixture of epimers at C-16 in 83 and 89% yield, respectively (Scheme 6). Both isomers were readily separated by column chromatography and the stereochemistry at C-16 of each epimer was deduced from comparison of their carbon chemical shifts. The most salient feature is the shielding of C-11 in the major epimer **28a** and C-13 in the minor one **28b**, ca. 6 ppm, which is due to the γ-interaction with the, respectively, β- and α-oriented methyl group at C-16. The regioselectivity observed in the above reductive cyclopropane ring cleavage can be rationalized on the basis of the mechanism involved, which implies a two-electron reduction of the cyclopropyl-diketone to a dienolate. Obviously, the regioselective cleavage of the C13–C16 cyclopropane bond is controlled by the stabilization of the negative charge developed at C-13 by the adjacent carbonyl group.[27] Once the bicyclo[2.2.2]octane moiety that constitutes the CD-ring system had been elaborated, completion of the atisane framework was effected by cyclopropane ring hydrogenolysis. Hydrogenation of the major epimeric diketone obtained above, **28a**, under similar conditions to those used for **25** produces a 2:1 mixture of hydroxy-ketones **29a** and **29b**, as result of the hydrogenolysis of the cyclopropane ring and selective reduction of the C-15 carbonyl group. Both epimeric atisanols were also readily separated by chromatography and their stereochemistry was easily established by NMR. Thus, the stereochemistry (α-orientation) of the hydroxyl group at C-15 in the major epimer **29a** was established by the NOE observed between H-15 (δ 3.18) and H-7β (δ 0.86), H-9 (δ 1.34) and Me-16 (δ 1.16). In the same way, the correlation of H-16 (δ 1.65) with H-13 (δ 2.27) in the NOE spectrum confirmed the β-orientation of the methyl attached to C-16.

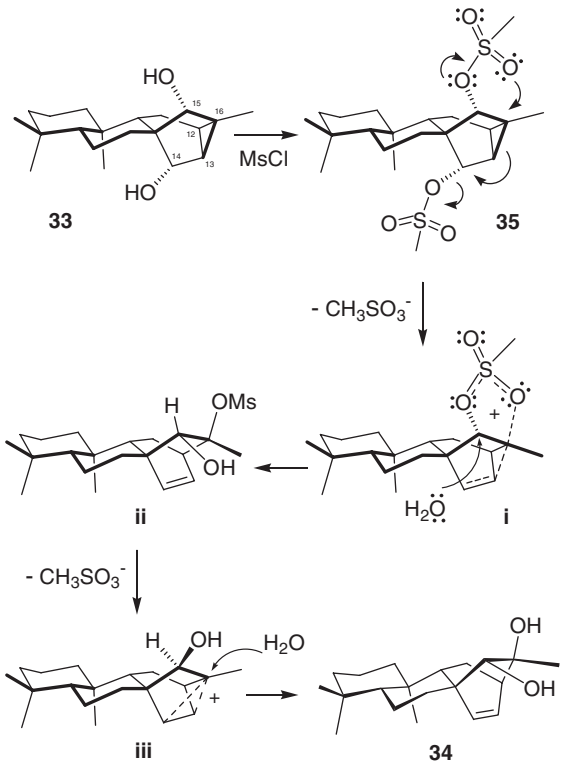
We also investigated alternative modes of regioselective fragmentation of the C13–C16 cyclopropane bond that could afford atisane-type compounds with a functionalization in the surroundings of the CD-rings complementary to that of the atisane system described above. Two additional procedures to complete the trachylobane-to-atisane transformation are described in the following paragraphs.

The first procedure is based on a radical-ring opening of the cyclopropane ring. First, the trachylobanol **26a** is transformed into the α-iodoketone **31** via the corresponding mesylate, in an overall yield for the two steps of 85% (Scheme 6). Treatment of **31** with samarium iodide in THF–MeOH produces the corresponding C15-centered cyclopropylcarbinyl radical, which then undergoes cleavage of the endocyclic cyclopropane bond to give the atisenone **32** in 85% yield.

In the second procedure, **25** is first converted to the trachylobanol **26a**, as described in Scheme 5, and this to the 1,3-diol **33** by stereoselective reduction of the C-14 ketone (Scheme 6). This transformation is effected in 88% yield by



Scheme 6. Synthesis of atisane framework from **25**. Reagents and conditions: (a) Li, NH_3(liq)–THF, −78 °C, 10 min, 57% of **28a** and 26% of **28b**; (b) SmI_2, THF–MeOH, rt, 1 h, 61% of **28a** and 28% of **28b**; (c) H_2, PtO_2, AcOH, 4 atm, 35 °C, 48 h, 45% of **29a** and 23% of **29b**; (d) as in Scheme 5; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) NaI, acetone, 40 °C, 2 h, 85% from **27**; (g) SmI_2, THF–MeOH, rt, 1 h, 85%; (h) $LiAlH_4 \cdot 2THF$, Toluene–THF, 0 °C, 30 min, 88%; (i) MsCl, Et_3N, H_2O, CH_2Cl_2, 0 °C, 1 h, 66%.



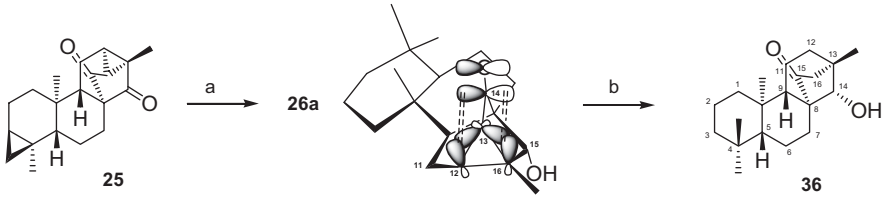
Scheme 7. Tentative mechanistic proposal for the formation of atisenediol **34**.

treatment of **26a** with $LiAlH_4$ in a 1:1 mixture of toluene and THF at 0 °C. The use of this solvent mixture is crucial for the success of the reduction reaction; no reaction is observed in toluene alone, probably due to precipitation of the initially formed aluminium alkoxide, and a complex mixture of products is obtained when THF is used as the only solvent. The stereochemistry at the new carbinolic centre was assigned on the basis of the strong NOESY cross-peak observed between both carbinolic protons at δ 3.75 ppm (H-14) and 3.32 ppm (H-15). Treatment of trachylobanediol **33** under the usual mesylation conditions but in the presence of water gives rise to a very rapid opening of the cyclopropane ring that leads to the atisenediol **34** in 66% yield, after chromatographic purification. The structure and stereochemistry of this compound were elucidated by means of detailed spectroscopic analysis involving comparison with data from literature of related atisane systems.[28] Particularly important for the assignment of the stereochemistry around the bicyclo[2.2.2]octane moiety was the NOESY correlation seen from H-15 (δ 3.15) to H-7β (δ 1.96) and H-9 (δ 1.34) which indicates an α-orientation of the hydroxyl group at C-15, as well as the cross-peak of Me-16 (δ 1.13) with H-13 (δ 6.18) that establishes the β-configuration of the other hydroxyl group at C-16.

At first sight, the transformation of trachylobanediol **33** into atisenediol **34** seems rather surprising, particularly because of the inversion of the configuration at the C15-carbinolic centre. Nevertheless, it can be mechanistically rationalized by considering the initial formation of a dimesylate intermediate. This assumption seems quite reasonable since control experiments showed that a very low yield of **34** is obtained when less than 2 equiv of mesyl chloride are used in this reaction. As shown in the proposed mechanism in Scheme 7, the initially formed dimesylate **35** may experience a rapid elimination of the methylsulfonyloxy group at C-14, probably propitiated by the steric acceleration[29] originated by the sterically congested nature of this position and the anchimeric assistance[30] provided by the neighbouring C-15 methylsulfonyloxy group. The cationic intermediate formed (**i**) should react with H_2O at C-15 with concomitant migration of the C-15 methylsulfonyloxy group to the neighbour C-16, affording the atisane-type intermediate **ii**. Nevertheless, since the assistance provide by the sulfonyloxy group is generally weak,[31] it seems quite reasonable to suppose that the formation of the latter intermediate could take place concertedly from dimesylate **35**. In any case, this intermediate should easily experience a unimolecular substitution of the C-16 methylsulfonyloxy group by H_2O, via the non-classical carbocation **iii**,[32] to give the isolated atisenediol **34**.

The trachylobane-to-beyerane interconversion was also effected with great efficacy via reductive cleavage of the cyclopropane ring of trachylobanol **26a** (Scheme 8). Thus, regioselective fragmentation of the C12–C13 cyclopropane bond of **26a** by lithium–liquid ammonia reduction furnished the beyerane diterpene **36** in 85% yield. In this case, and in contrast with the previous result obtained with the cyclopropyl-diketone **25**, the use of the milder electron-transfer reagent samarium diiodide was unsatisfactory, and the cyclopropyl ketone unit remained intact after treatment of **26a** with this reductor system. The structure of the beyerane **36** was confirmed by detailed spectroscopic analysis and comparison with the data reported for this compound by Fetizon, who prepared it during the synthesis of (−)-hibaene.[33]

It must be noted that the bond cleaved in the above reductive cleavage of the hydroxy-cyclopropyl-ketone **26a** is the one that gives rise to the carbanion intermediate at the least substituted carbon atom, that is, C-12, a result that can be rationalized in terms of the previously reported mechanistic model. It is well established that the bond that breaks in a fused bicyclic cyclopropyl-ketone upon reduction by alkali



Scheme 8. Synthesis of beyerane framework from **25**. Reagents and conditions: (a) as in Scheme 5; (b) Li, NH_3(liq)–THF, −78 °C, 15 min, 85%.

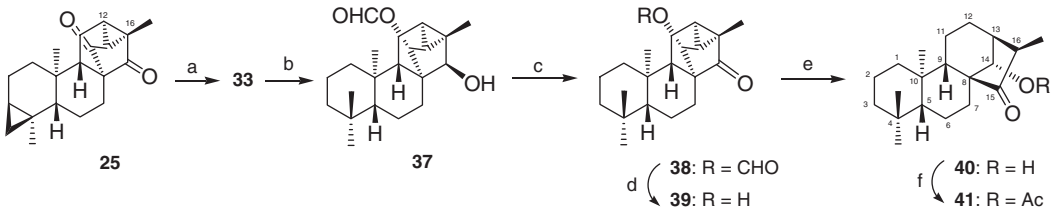
metals in liquid ammonia is governed by stereoelectronic effects, specifically the magnitude of overlap between the cyclopropane C–C bond and the π-orbital of the carbonyl group (geometrical control).[34] However, when equal π-orbital overlap to either cyclopropane bond exists, the principal factor that controls the cyclopropane ring opening is the relative thermodynamic stability of the carbanionic intermediates generated (electronic control). The optimized geometry of **26a** (see structure in Scheme 8) shows that the C-14 carbonyl group is situated in a bisected orientation with respect to the two contiguous cyclopropane bonds, such that a very similar π-orbital overlap to the C12–C13 and C13–C16 cyclopropane bonds exists, and thus the formation of the more stable secondary carbanion at C-12 versus the destabilized α-hydroxy tertiary carbanion at C-16 is the predominant factor controlling the course of the cyclopropane ring opening.

It was estimated, on the basis of the above mechanistic considerations, that an interchange of the carbonyl and hydroxyl functional groups at C-14 and C-15, respectively, of hydroxy-trachylobanone **26a** could lead to a preferred reductive cleavage of the C12–C16 cyclopropane bond, thus completing the desired trachylobane-to-kaurane skeletal interconversion. With this objective in mind, we investigated possible ways of effecting this functional group interconversion in a limited number of steps with good yield. After some experimentation, this transformation was achieved quite satisfactorily in four steps from **26a** via the previously prepared 1,3-diol **33**, through a sequence involving mono-protection of the C14–OH, oxidation of the C15–OH to the corresponding ketone and regeneration of the C14–hydroxyl group (Scheme 9). Initial attempts to selectively protect the C14–OH with various usual hydroxyl-protecting groups were unsuccessful, fundamentally due to the lack of selectivity in the reaction of both hydroxyl groups of diol **33** with the different reagents used. For example, attempted regioselective silylation of diol **33** using 1 equiv of the silylating reagent (e.g., TMSOTf, TBDMSTf or TMSCl) afforded a mixture of C14-and C15-mono-silyl ethers, di-silylated product and unreacted diol. Fortunately, it was found that the required mono-protection of the C14–OH of **33** as the corresponding formate ester could be accomplished indirectly under solvolytic conditions. Thus, treatment of this compound with buffered formic acid in THF at 0–5 °C overnight smoothly afforded the hydroxy-formate ester **37** in 80% yield. It must be mentioned that the control of the temperature was fundamental for the success of this formolysis reaction; an extremely slow reaction took place at lower temperatures, while a complex mixture of products was obtained at higher temperatures. The spectroscopic data of **37** are very similar to those of the diol precursor, with the exception of the expected changes due to the different substituent at C-14. As for the diol **33**, the stereochemistry at C-14 was confirmed by the strong NOESY cross-peak observed between H-14 at δ 4.92 ppm and H-15 at δ 3.44 ppm.

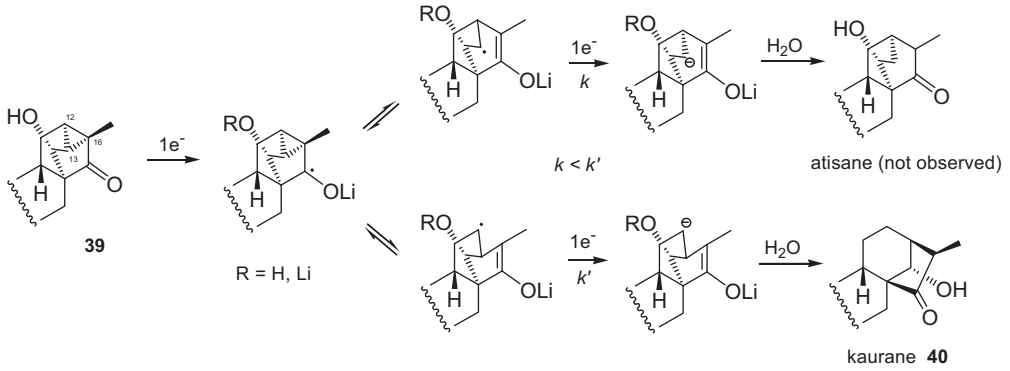
Some interesting observations can be made about the result obtained in the above formolysis of diol **33**, which leads to the formal protection of the C14–OH as the corresponding formate ester. Firstly, the preferential solvolysis at the more crowded C-14 position is remarkable, particularly considering that, as previously mentioned, formolysis at the C-15 position of the trachylobane system can also take place. Probably, as in the conversion of **33** to **34**, the higher reactivity of the C-14 position can be attributed to the higher relief of steric strain in the transition state relative to the ground state that takes place upon ionization at this position (steric acceleration). Secondly, the solvolytic reaction proceeds with retention of configuration at C-14. This stereochemical result is a consequence of the structural characteristics of the non-classical carbonium ion intermediate formed, which requires that the addition of formic acid take place from the same face as the OH group departs, and which, in this case, corresponds to the most hindered face of the cyclopropylcarbinyl cation.[32]

The synthesis of the desired hydroxy-ketone **39** was readily completed from the hydroxy-formate **37** by Dess–Martin oxidation of the hydroxyl group followed by smooth hydrolysis of the formate ester moiety with potassium carbonate in MeOH at rt. This transformation was accomplished, without the need of purification of the intermediate ketone-formate **38**, in 78% overall yield.

As initially estimated, reduction of the cyclopropyl-ketone **39** with lithium in liquid ammonia, under similar conditions to those previously used with **25**, led exclusively to the product resulting from reductive cleavage of the C12–C16 exocyclic cyclopropane bond, the kaurane-type compound **40**. The structure of this compound was initially assigned on the basis of its spectroscopic properties and by comparison of the spectral data with those of known closely related kaurane-type compounds.[35] Further unequivocal confirmation of the structure and stereochemistry of **40** was obtained from a detailed spectroscopic analysis of the corresponding acetate derivative, that is, **41**, which was based on a combination of HMQC, HMBC, and NOESY 2D experiments. Particularly important was the NOESY correlation seen from H-14 (δ 4.79) to H-16 (δ 2.37) which placed these two protons in a cis configuration



Scheme 9. Synthesis of kaurane framework from **25**. Reagents and conditions: (a) as in Scheme 5; (b) HCO_2H, 0.5% Na_2CO_3, THF, 0–5 °C 14 h, 80%. (c) Dess–Martin periodinane, Py, CH_2Cl_2, rt, 2 h, 86%; (d) K_2CO_3, MeOH, rt, 1 h, 90%; (e) Li, NH_3(liq)–THF, −78 °C, 15 min, 86%.; (f) Ac_2O–DMAP-Py, rt, 3 h, 93%.



Scheme 10.

relationship, thus establishing the stereochemistry at C-16 and C-14 positions. Additional cross-peaks between the signals for H-14 and the equatorially disposed (α-orientated) H-7 (δ 1.47) and for the angular methyl group at C-10 (δ 1.04) and the methyl acetyl group (δ 2.18) strongly support the stereochemistry assigned to **41** and therefore to the hydroxy-kauranone **40**.

The regioselectivity observed in the above reductive cleavage of cyclopropyl-ketone **39** contrasts with that obtained in the opening of a related, although structurally simpler, tricyclo[3.2.1.0^{2,7}]octane system that has a hydrogen atom in place of the C-14 hydroxyl group.[36] As shown in Scheme 10, the direction of the cyclopropane ring opening of **39** seems also to be controlled by the electronic factors. In this case, presumably, the destabilizing effect originated by the hydroxyl group at C-14 (or the lithium alkoxide generated from it) on the carbanionic intermediate that is originated upon cleavage of the C12–C16 cyclopropane bond seems to be the main factor favouring the regioselective fragmentation that leads to the kaurane framework.

3. Conclusion

In summary, we have developed a general unified protocol for the efficient preparation of four biogenetically related polycyclic diterpenes. The skeleton of these diterpenes can be obtained in both enantiomeric forms starting from (*R*)-(−) or (S)-(+)-carvone, via a common intermediate that possesses a tricyclo[3.2.1.0^{2,7}]octane moiety characteristic of the trachylobane framework, which is regioselectively cleaved to obtain the bicyclo[3.2.1]- and bicyclo[2.2.2]octane moieties, characteristic of beyeranes/kauranes and atisanes, respectively. The type of functionalization obtained around the CD-rings of these diterpenic skeletons and the possibility of easily introducing additional functionalization around the AB-rings and the C-20 angular position, by adequate modification of the synthetic route that gives access to the key trachylobane-like intermediate, enhances the versatility of this approach for the preparation of both non-natural and naturally occurring highly functionalised tetracyclic diterpenes.

4. Experimental

4.1. General information

All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz, and NMR ^{13}C spectra at 75 or 100 MHz. ^{1}H spectra were referenced to residual $CHCl_3$ (δ 7.26) and ^{13}C spectra to the central component of the $CDCl_3$ triplet at δ 77.0. Carbon substitution degrees were established by DEPT pulse sequences. A combination of COSY, HMQC, and NOE experiments was utilized when necessary for the assignment of ^{1}H and ^{13}C chemical shifts. IR spectra were measured as KBr pellets or liquid films; peak intensities are specified as strong (s), medium (m) or weak (w). Elemental analyses were performed by servicio de semimicroanálisis of S.C.S.I.E. (Valencia); final purification of all products for microanalysis was done by preparative HPLC on a μ-Porasil column. Mass spectra were obtained by electron impact (EI) at 70 eV or chemical ionization (CI). Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All operations requiring anhydrous conditions and/or involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringes, oven-dried glassware, and freshly distilled and dried solvents. Sodium hydride was thoroughly washed with pentane and dried under vacuum prior to use.

4.2. Synthesis of tricyclic acyl chloride 14

4.2.1. (4a*R*,4b*S*,8a*R*,10a*R*)-Methyl 1,4a,7-trimethyl-8-oxo-3,4,4a,4b,5,8,8a,9,10,10a-decahydrophenanthrene-8a-carboxylate (10). β-Keto ester **10** was prepared from (*R*)-(−)-carvone (**9**) in three steps and 60% overall yield as we described previously in Ref. 14.

4.2.2. (4a*R*,4b*S*,8*S*,8a*R*,10a*R*)-Methyl 8-hydroxy-1,4a,7-trimethyl-3,4,4a,4b,5,8,8a,9,10,10a-decahydrophenanthrene-8a-carboxylate (11). To a solution of tricyclic enone **10** (859 mg, 2.86 mmol) in MeOH (106 mL) was added $CeCl_3 \cdot 7H_2O$ (1.6 g, 4.24 mmol). The mixture was

stirred at rt until complete dissolution of the cerium salt and then cooled to 0 °C. $NaBH_4$ was then slowly added in small portions (318 mg, 5.72 mmol) while the reaction was monitored by TLC (hexane/AcOEt, 7:3). Upon the completion of the reduction (ca. 1 h), the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography, using hexane/AcOEt 8:2 as eluent, affording hydroxy ester **11** (747 mg, 88%) as a solid. Mp 150–154 °C (from cold MeOH); $[\alpha]_D^{23}$ +19 (1.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3458s, 2939s, 2894s, 1720s, 1440s, 1380m, 1225s, 1155m, 1110m, 1075m, 1045m; ^1H NMR (300 MHz) δ 5.64 (1H, m, H-6), 5.28 (1H, br s, H-2), 3.93 (1H, br s, H-8), 3.65 (3H, s, OMe), 2.85 (1H, ddd, J=13.0, 6.0, 3.0 Hz, H-9α), 2.33 (1H, ddd, J=8.0, 5.0, 3.0 Hz, H-5α), 1.82 (1H, ddd, J=10.0, 7.0, 4.0 Hz, H-4), 1.71 (3H, s, Me-C_7), 1.61 (3H, s, Me-C_1), 1.53 (1H, dd, J=12.5, 5.0 Hz, H-4b), 1.22–1.09 (2H, m, H-9β and H′-4), 0.62 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) m/z (%) 286 (M^+-H_2O, 16), 241 (12), 225 (18), 197 (9), 127 (18), 111 (24), 105 (11), 85 (42); 69 (100); HRMS m/z calcd for $C_{19}H_{26}O_2$ [M^+-H_2O] 286.1933, found 286.1927. Anal. Calcd for $C_{19}H_{28}O_3$: C 74.96, H 9.27; found C 75.10, H 9.18.

4.2.3. (4a*R*,4b*S*,8*S*,8a*R*,10a*R*)-8-Acetoxy-1,4a,7-trimethyl-3,4,4a,4b,5,8,8a,9,10,10a-decahydro phenanthrene-8a-carboxylic acid (13). A solution of **11** (501 mg, 1.67 mmol) in DMF (11 mL) was added to a solution of *n*-PrSNa in DMF, prepared by treating a suspension of NaH (400 mg, 16.7 mmol) in DMF (25 mL) with *n*-PrSH (1.41 mL, 15.6 mmol) at rt for 30 min. The reaction mixture was heated at 85 °C for 2 h. After cooling to rt, the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 and acidified to pH 4 with 1 N aq HCl solution. The organic phase was separated, washed with brine and dried over $MgSO_4$. After solvent removal, the crude hydroxy-acid **12** was used in the next step without further purification. A sample was purified by chromatography (CH_2Cl_2–MeOH 9.3:0.7) for analysis.

Data for **12**. A foam solid. $[\alpha]_D^{22}$ +22 (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3409s, 2941m, 2911w, 2850w, 1695s, 1436s, 1212m, 1049m, 1008m, 759m; ^1H NMR (300 MHz) δ 5.63 (1H, m, H-6), 5.28 (1H, br s, H-2), 3.96 (1H, s, H-8), 2.84 (1H, ddd, J=13.0, 6.0, 3.0 Hz, H-9α), 2.34 (1H, m, H-5α), 2.1–1.5 (8H, m), 1.72 (3H, s, Me-C_7), 1.61 (3H, s, Me-C_1), 1–25–0.9 (3H, m), 0.72 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) m/z (%) 290 (M^+, 4), 272 (6), 244 (24), 228 (19), 157 (23), 145 (47), 131 (38), 119 (54), 105 (100), 91 (96); HRMS m/z calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1885.

The above obtained crude hydroxy-acid **12** (495 mg) was dissolved in dry pyridine (30 mL) and treated with 4-(dimethylamino)pyridine (DMAP) (55 mg, 0.41 mmol) and Ac_2O (850 μL, 8.96 mmol). The mixture was stirred at rt for 2 h and then treated with MeOH (1.2 mL) and stirred for 30 min. The reaction mixture was concentrated under vacuum and the residue obtained was purified by chromatography, using hexane/AcOEt 7:3 as eluent, to give the carboxylic acid–acetate **13** (388 mg, 75% from **11**) as a very viscous oil that solidified in the freezer. $[\alpha]_D^{24}$ 12 (0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3350m, 2929s, 2849s, 1740s, 1445m, 1370m, 1235s, 1025m; ^1H NMR (300 MHz) δ 5.70 (1H, br s, H-6), 5.45 (1H, br s, H-8), 5.25 (1H, br s, H-2), 2.49 (1H, ddd, J=13.5, 1.5, 1.5 Hz, H-9), 2.44 (1H, m, H-5), 2.14 (1H, m, H′-5), 2.077 (3H, s, OCOMe), 2.01 (1H,

Table 1. ^{13}C NMR chemical shifts (δ) in ppm for compounds **11–14**, **21** and **23**[a]

Compound	**11**	**12**	**13**	**14**	**21**	**23**
C-1	134.44	134.44	134.25	80.80	197.98	198.22
C-2	120.30	120.26	120.28	128.61	131.18	131.88
C-3	22.69	22.67	22.68	126.42	148.22	148.75
C-4	33.93	33.95	33.84	23.45	25.61	25.52
C-4a	35.72	36.48	35.95	51.39	53.17	53.42
C-4b	49.84†	49.79†	49.85	36.13	36.63	36.74
C-5	23.72	21.79	23.48	33.21	33.60	33.73
C-6	125.31	125.89	126.59	21.93	22.70	22.66
C-7	132.06	132.14	129.55	120.51	120.15	120.79
C-8	79.85	80.73	80.31	133.71	133.76	133.68
C-8a	49.74†	49.84†	48.08	48.32	48.32	48.49
C-9	36.57	35.89	36.00	22.70	21.93	21.47
C-10	21.97	23.63	22.51	37.76	32.42	32.10
C-10a	48.70	48.69	48.58	56.82	64.04	60.83
C-*C*O	174.71	179.45	178.36	170.77	207.73	193.23
Me-C_1	21.08	21.22	21.13	—	—	—
Me-C_2	—	—	—	18.44	16.62	16.97
Me-C_{4a}	11.60	11.19	11.34	—	—	—
Me-C_{4b}	—	—	—	12.69	13.84	13.65
Me-C_7	19.49	19.11	18.68	—	—	—
Me-C_8	—	—	—	21.03	21.05	21.34
Others	[b]	—	[c]	[d]	[e]	[f]

[a] The signals with the same superscript may be interchanged within the same column.
[b] CO_2*Me* at C_{8a} at 51.29 ppm.
[c] O*C*OMe at 170.99 and OCO*Me* at 20.80 ppm.
[d] O*C*OMe and OCO*Me* at C_1 at 174.40 and 20.75 ppm, respectively.
[e] CO*Me* at C_{10a} at 28.46 ppm.
[f] CO*C*HN$_2$ at C_{10a} at 54.94 ppm.

m, H-3), 1.92 (1H, m, H-10a), 1.75 (1H, ddd, J=13.8, 10.0, 3.6 Hz, H-10), 1.79 (1H, m, H′-10), 1.71 (1H, m, H-4), 1.67 (1H, m, H-4b), 1.59 (3H, s, Me-C_7), 1.55 (3H, s, Me-C_1), 1.18 (1H, m, H′-9), 1.14 (1H, m, H′-4), 0.72 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; FAB-HRMS m/z calcd for $C_{20}H_{29}O_4$ [M+H$^+$] 333.2065, found 333.2041. Anal. Calcd for $C_{20}H_{28}O_4$: C 72.26, H 8.49; found C 72.35, H 8.54.

4.2.4. (1*S*,4a*S*,4b*R*,8a*R*,10a*R*)-10a-(Chlorocarbonyl)-2,4b,8-trimethyl-1,4,4a,4b,5,6,8a,9,10,10a-decahydrophenanthren-1-yl acetate (14). DMF (280 μL, 3.6 mmol) and $SOCl_2$ 42 μL, 1.2 mmol) were successively added to a solution of the acid **13** (190 mg, 0.60 mmol) in benzene (6 mL) and the solution was stirred at rt for 3 h. Removal of excess $SOCl_2$ and solvents under reduced pressure gave the acid chloride **14** as a yellowish solid (200 mg), which was shown to be practically pure by NMR spectrum and could be used without further purification or filtered through a short pad of silica gel, which was washed with a mixture of hexane/AcOEt 1:1, to give pure acid chloride **14** as a foam solid (170 mg, 85%); ^{1}H NMR (300 MHz) δ 5.65 (1H, m, H-3), 5.57 (1H, s, H-1), 5.28 (1H, br s, H-7), 2.16 (3H, s, COMe), 2.82 (1H, m, H-10α), 2.33 (1H, m, H-4α), 2.15–1.62 (7H, m), 1.62 (3H, s, Me-C_2), 1.56 (3H, s, Me-C_8), 1.40 (1H, ddd, J=13.2, 13.2, 3.1 Hz), 1.18 (2H, m), 0.75 (3H, s, Me-C_{4b}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) m/z (%) 352 (M+2, 2), 350 (M$^+$, 6), 308 (15), 286 (18), 273 (35), 245 (17), 228 (100), 189 (12), 171 (22), 157 (24), 145 (46), 105 (56); HRMS m/z calcd for $C_{20}H_{27}{}^{35}ClO_3$ 350.1648, found 350.1645.

4.3. Synthesis of key intermediate 25 via α-diazoketone 23

4.3.1. (5*R*)-6-Acetyl-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (16). *Method A*. A solution of commercial (*R*)-(−)-carvone (0.70 mL, 670 mg, 4.47 mmol) in THF (5 mL) was added dropwise over 30 min to a solution of LHMDS in THF–hexane [prepared by addition of BuLi (4.2 mL of a 1.6 M solution in hexane, 6.7 mmol) to a solution of hexamethyldisylazane (1.45 mL, 6.70 mmol) in THF (2 mL)] at −78 °C and the reaction mixture was stirred at the same temperature for 45 min. Pyruvonitrile (0.45 mL, 6.35 mmol) was added at once to the mixture and the stirring was continued for 10–15 min, and then quenched by the addition of saturated aq NH_4Cl solution and extracted with a 1:1 mixture of hexane/ether. The combined organic layers were washed with 5% aq HCl and brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using hexane as eluent, to give β-diketone **16** (801 mg, 93%) as an oil, which was shown to be a mixture of mainly two epimers at C-6 on the basis of ^{1}H NMR spectroscopic data. Partial separation of the slightly more polar epimer, with the acyl group at C-6 equatorially oriented, was able to be achieved in some cases. This epimer has the following spectral data: $[\alpha]_D^{22}$ −63.5 (1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2972m, 2922m, 2636w, 1716s, 1663s, 1439m, 1361m, 1225m, 899m; ^{1}H NMR (300 MHz,) δ 6.72 (1H, m, H-3), 4.78 (1H, s, H-2″), 4.74 (1H, s, H′-2″), 3.48 (1H, d, J=12.2 Hz, H-6), 3.09 (1H, ddd, J=11.1, 10.1, 5.1 Hz, H-5), 2.4 (2H, m, H_2-4), 2.13 (3H, s, CO*Me*), 1.72 (3H, s, Me-C_2), 1.68 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 205.60 (C_1), 196.31 (*CO*Me), 144.83 ($C_{1''}$), 144.73 (C_3), 134.97 (C_2), 113.09 ($C_{2''}$), 64.64 (C_6), 45.06 (C_5), 30.70 (C_4), 29.87 (CO*Me*), 19.55 (Me-$C_{1''}$), 15.40 (Me-C_2); MS (EI) m/z (%) 193 (M$^+$1, 6), 192 (M$^+$, 46), 177 (17), 159 (15), 149 (100), 135 (30), 121 (22), 109 (40); HRMS m/z calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149.

Method B. A solution of (*R*)-(−)-carvone (4.17 mL, 3.90 g, 26 mmol) in THF (28 mL) was added dropwise over a period of 2 h to a solution of LDA in THF [prepared from BuLi (21 mL of a 1.6 M solution in hexane, 33.8 mmol), diisopropylamine (4.72 mL, 33.8 mmol) and THF (42 mL)] at −15 °C. The reaction mixture was allowed to warm to 0 °C (ca. 2.5 h) and stirred at this temperature for 30 min, cooled to −78 °C, and treated with acetaldehyde (3 mL, 52 mmol). After 30 min the reaction mixture was quenched by the addition of saturated aq NH_4Cl solution, poured into 5% aq $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using hexane–AcOEt (from 9/1 to 1/1) as eluent, to give a mixture of diastereoisomeric β-hydroxy-ketones (4.97 g, 92%) as an oil. ^{1}H NMR spectra of this product showed that it was a mixture of four diastereoisomers in the ratio 4:3:1:1.

A solution of DMSO (4.16 mL, 53 mmol) in CH_2Cl_2 (14 mL) was slowly added to a solution of oxalyl chloride (2.45 mL, 27.2 mL) in CH_2Cl_2 (70 mL) at −60 °C, and the resulting solution was stirred for 30 min. A solution of the above obtained mixture of β-hydroxy-ketones (4.60 g, 23.3 mmol) in CH_2C1_2 (34 mL) was added via cannula over 30 min, and the mixture was stirred for an additional 15 min; Et_3N (16.6 mL, 118.5 mmol) was added, and the resulting mixture was stirred for 15 min at −60 °C and then warmed slowly to rt (ca. 2 h). The reaction was quenched with water and extracted with CH_2C1_2. The combined organic extracts were washed successively with 5% aq HCl solution, 10% aq Na_2CO_3 solution and brine, filtered and dried over $MgSO_4$. Purification of the residue left after evaporation of the solvent by chromatography, using hexane/AcOEt 9:1 as eluent, gave diketone **16** (4.10 g, 90%) as an oil.

4.3.2. (5*S*,6*S*)-6-Acetyl-6-(3,3-diethoxypropyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (17). A solution of β-diketone **16** (1.30 g, 6.76 mmol) in THF (2 mL) was added dropwise to a stirring suspension of NaH (340 mg, 14.2 mmol, 2.1 equiv) in THF (8 mL) at 0 °C. When the evolution of hydrogen had ceased, a solution of Bu_4NHSO_4 (2.37 g, 6.76 mmol) in DMF (3 mL) was carefully added at the same temperature. After the evolution of hydrogen has ceased, the reaction mixture was warmed to rt and sonicated in a water bath for 15–20 min at 20 °C. The resulting white slurry was cooled to 0 °C and 3-iodopropanaldehyde diethylacetal[37] (2.61 g, 10.14 mmol) was added. The mixture was stirred at 5 °C for 12 h, then poured into water and extracted with hexane. The organic layer was washed with 5% aq sodium thiosulphate solution and brine, dried over Na_2SO_4 and then concentrated under vacuum. The crude oil was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to yield compound **17**

(1.76 g, 93%) as a yellowish oil. $[\alpha]_D^{23}$ +48 (2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2973s, 2926m, 2887m, 1700s, 1660s, 1443m, 1364m, 1189m, 1130m, 1130s, 1064s; ^1H NMR (300 MHz) δ 6.70 (1H, m, H-3), 4.83 (1H, s, H-2″), 4.71 (1H, s, H′-2″), 4.42 (1H, dd, J=5.6, 5.6 Hz, H-3′), 3.57 and 3.43 (4H, two m, 2×O*CH*$_2$), 2.91 (1H, dd, J=6.3, 6.2 Hz, H-5), 2.5 (2H, m, H_2-4), 2.16 (3H, s, CO*Me*) 1.78 (3H, m, Me-C_2), 1.68 (3H, s, Me-$C_{1''}$), 1.17 (6H, two t, J=7.0 Hz, 2×OCH$_2$*Me*); ^{13}C NMR (75 MHz) δ 208.37 (C_1), 198.04 (*CO*Me), 144.70 ($C_{1''}$), 143.92 (C_3), 134.64 (C_2), 115.21 ($C_{2''}$), 102.58 ($C_{3'}$), 61.02 and 60.62 (2×OCH$_2$), 65.13 (C_6), 48.31 (C_5), 28.34 (C_4), 30.34 (CO*Me*), 28.81 ($C_{2'}$), 28.36 ($C_{1'}$), 22.50 (Me-$C_{1''}$), 16.30 (Me-C_2), 15.21 (2×OCH$_2$*CH*$_3$); MS (EI) m/z (%) 323 (M^++1, 6), 322 (M^+, 1), 277 (90), 265 (19), 248 (11), 234 (20), 209 (15); HRMS m/z calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2136.

4.3.3. 3-((1*S*,6*S*)-1-Acetyl-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enyl)propanal (18). A solution of ketal **17** (794 mg, 2.46 mmol) and PPTS (306 mg, 1.5 mmol) in 4% aq acetone (50 mL) was heated at reflux for 1 h. The mixture was cooled down to rt, then poured into water and extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent left a residue that was purified by column chromatography, using hexane/AcOEt 8:2 as eluent, to give aldehyde **18** (573 mg, 93%) as a colourless oil. $[\alpha]_D^{21}$ +63 (1.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2923m, 1723s, 1701s, 1657s, 1439m, 1355m, 1187m, 1044w, 904w; ^1H NMR (300 MHz) δ 9.68 (1H, s, H-3), 6.73 (1H, m, H-4′), 4.84 (1H, s, H-2″), 4.72 (1H, s, H′-2″), 2.83 (1H, dd, J=5.9, 5.9 Hz, H-6′), 2.5 (1H, ddd, J=13.4, 8.5, 6.4 Hz, H-5′), 2.14 (3H, s, CO*Me*), 1.78 (3H, m, Me-$C_{3'}$), 1.66 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 207.86 ($C_{2'}$), 200.91 (C_1), 197.86 (*CO*Me), 144.45 ($C_{1''}$), 144.08 ($C_{4'}$), 134.78 ($C_{3'}$), 116.04 ($C_{2''}$), 64.71 ($C_{1'}$), 49.63 ($C_{6'}$), 39.23 (C_2), 30.45 (*CH*$_3$CO), 28.87 ($C_{5'}$), 25.64 (C_3), 22.32 (Me-$C_{1''}$), 16.25 (Me-$C_{3'}$); MS (EI) m/z (%) 249 (M^++1, 2), 248 (M^+, 5), 236 (33), 221 (15), 161 (54), 149 (13), 135 (24), 121 (100), 109 (17); HRMS m/z calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1408.

4.3.4. (*E*)-5-((1*S*,6*S*)-1-Acetyl-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enyl)-2-methylpent-2-enal (19). A solution of aldehyde **18** (1.00 g, 4.05 mmol) and commercial (α-formylethylidene)triphenyl phosphorane (1.70 g, 5.33 mmol) in benzene (32 mL) was stirred at reflux for 48 h. The mixture was allowed to cool to rt and then treated with saturated aq NH_4Cl solution. The aqueous phase was separated and extracted with ethyl ether. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to afford the α,β-unsaturated aldehyde **19** (1.00 g, 86%) as a colourless oil: $[\alpha]_D^{23}$ +147 (1.9, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2921w, 1684s, 1654s, 1644s, 1438m, 1360m, 1179w, 904w; ^1H NMR (300 MHz) δ 9.34 (1H, s, H-1), 6.74 (1H, m, H-4′), 6.38 (1H, ddd, J=7.3, 7.3, 1.2 Hz, H-3), 4.84 (1H, s, H-2″), 4.74 (1H, s, H′-2″), 2.90 (1H, dd, J=7.0, 7.0 Hz, H-6′), 2.65 (1H, br d, J=19.8 Hz, H-4), 2.50 (1H, br d, J=19.8 Hz, H′-4), 2.4 (1H, ddd, J=13.0, 11.1, 5.3 Hz, H-5′), 2.14 (3H, s, CO*Me*), 1.83 (3H, m, Me-$C_{3'}$), 1.79 (3H, s, Me-C_2), 1.79 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 207.68 ($C_{2'}$), 197.70 (*CO*Me), 195.06 (C_1), 153.05 (C_3), 144.38 ($C_{4'}$), 144.38 ($C_{1''}$), 139.72 (C_2), 134.72 ($C_{3'}$), 115.82 ($C_{2''}$), 65.36 ($C_{1'}$), 49.04 ($C_{6'}$), 30.32 (*Me*CO), 31.85 (C_4), 29.03 ($C_{5'}$), 24.12 (C_5), 22.24 (Me-$C_{1''}$), 16.33 (Me-$C_{3'}$), 9.11 (Me-C_2); MS (EI) m/z (%) 289 (M^++1, 1), 288 (M^+, 2), 260 (43), 245 (9), 220 (12), 205 (27), 192 (91), 177 (50), 163 (100), 149 (58), 135 (31), 121 (98), 105 (30), 91 (51); HRMS m/z calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1726.

4.3.5. (5*S*,6*S*)-6-Acetyl-2-methyl-6-((E)-4-methylhexa-3,5-dienyl)-5-(prop-1-en-2-yl)cyclohex-2-enone (20). Methyltriphenylphosphonium bromide (1.38 g, 3.9 mmol) was suspended in toluene (45 mL) and the mixture was cooled to −20 °C. A solution of KHMDS in toluene (1 M, 3.9 mL, 3.9 mmol) was added dropwise and the solution was allowed to warm to rt and then stirred for 15 min. After cooling to −20 °C, compound **19** (930 mg, 3.3 mmol) in toluene (45 mL) was added slowly and the mixture stirred while it was allowed to warm to rt. After 1 h, the mixture was treated with saturated aq NH_4Cl, poured into water and extracted with a 1:1 mixture of hexane/ethyl ether. The combined organic layers were washed sequentially with diluted hydrochloric acid, 5% aq $NaHCO_3$, and brine and dried over Na_2SO_4. Evaporation of the solvent and chromatography, using hexane/AcOEt 9:1 as eluent, provided compound **20** (849 mg, 92%) as an oil. $[\alpha]_D^{23}$ +81 (3.2, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2925m, 2353w, 1700m, 1660s, 1441w, 1361w, 1180w, 899w; ^1H NMR (300 MHz) δ 6.74 (1H, m, H-3), 6.30 (1H, dd, J=17.5, 10.7 Hz, H-5′), 5.40 (1H, dd, J=7.3, 7.3 Hz, H-3′) 5.07 (1H, d, J=17.4 Hz, H-6′), 4.92 (1H, d, J=10.7 Hz, H′-6), 4.85 (1H, s, H-2″), 4.72 (1H, s, H′-2″), 2.93 (1H, dd, J=6.4, 6.4 Hz, H-5), 2.60 (1H, br d, J=19.4 Hz, H-2′), 2.50 (1H, br d, J=19.4 Hz, H′-2′), 2.27 (1H, ddd, J=12.6, 11.4, 4.5 Hz, H-4), 2.15 (3H, s, CO*Me*), 1.81 (3H, br s, Me-C_2), 1.68 (3H, s, Me-$C_{4'}$), 1.68 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 208.30 (C_1), 198.00 (*CO*Me), 144.80 ($C_{1''}$), 143.83 (C_3), 141.25 ($C_{3'}$), 134.83 (C_2), 134.83 ($C_{4'}$), 131.61 ($C_{5'}$), 115.26 ($C_{2''}$), 110.97 ($C_{6'}$), 65.44 (C_6), 48.58 (C_5), 33.26 ($C_{2'}$), 30.38 (*Me*CO), 28.96 (C_4), 22.48 ($C_{1'}$), 22.24 (Me-$C_{1''}$), 16.38 (Me-C_2), 11.56 (Me-$C_{4'}$); MS (CI) m/z 287 (M^++1, 50), 219 (23), 205 (12), 192 (100), 177 (27), 163 (5), 151 (21); HRMS m/z calcd for $C_{19}H_{27}O_2$ [M+H$^+$] 287.2011, found 287.2002.

4.3.6. (4a*S*,4b*R*,8a*R*,10a*S*)-10a-Acetyl-2,4b,8-trimethyl-4,4a,5,6,8a,9,10,10a-octahydrophenanthren-1(4*bH*)-one (21). A solution of triene **20** (510 mg, 1.8 mmol) in toluene (20 mL) was transferred to a previously silylated ampoule and rigorously degassed by the freeze–thaw-cycle. The ampoule was cooled down under argon, a drop of propylene oxide was added and it was then sealed under vacuum. After heating at 195 °C for 120 h, the solvent was eliminated on a rotary evaporator and the residue was chromatographed, using 9:1 hexane/AcOEt as eluent, to give the Diels–Alder adduct **21** as a solid (460 mg, 90%). Mp 83–84 °C (MeOH); $[\alpha]_D^{21}$ −104 (0.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2963s, 1703m, 1660s, 1437m, 1379m, 1147w; ^1H NMR (400 MHz) δ 6.90 (1H, m, H-3), 5.30 (1H, br s, H-7), 3.06 (1H, dddd, J=19.1, 11.5, 2.5, 2.5 Hz, H-4α), 2.85 (1H, ddd, J=14.5, 2.6, 2.7 Hz, H-10), 2.33 (1H, m, H-4β), 2.17 (3H, s, CO*Me*), 2.10 (1H, m, H-6), 1.97 (1H, m, H′-6), 1.86 (1H, m, H-9), 1.85 (1H, m, H-8a), 1.79 (1H, dd, J=13.0, 5.0 Hz,

H-4a), 1.73 (1H, m, H-5), 1.70 (3H, m, Me-C_2), 1.60 (3H, s, Me-C_8), 1.49 (1H, ddd, J=14.5, 14.0, 3.0 Hz, H′-10), 1.32 (1H, ddd, J=15.0, 13.0, 3.0 Hz, H′-9), 1.15 (1H, m, H′-5), 0.70 (3H, s, Me-C_{4b}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) m/z (%) 287 (M^++1, 3), 286 (M^+, 10), 268 (9), 243 (100), 229 (8), 165 (20), 147 (26), 135 (24), 121 (94), 109 (41); HRMS m/z calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1934. Anal. Calcd for $C_{19}H_{26}O_2$: C 79.68, H 9.15; found: C 79.54, H 9.19.

4.3.7. (4a*S*,4b*R*,8a*R*,10a*R*)-10a-(2-Diazoacetyl)-2,4b,8-trimethyl-4,4a,5,6,8a,9,10,10a-octahydrophenanthren-1(4*bH*)-one (23). A solution of methyl-ketone **21** (1.50 g, 5.2 mmol) in THF (7 mL) was added dropwise over a period of 30 min to a THF solution of LHMDS [prepared from 1.6 M BuLi in hexanes (3.72 mL, 6 mmol), hexamethyldisilazane (1.30 mL, 6 mmol), and THF (4.5 mL)] at −78 °C. The solution was stirred for an additional 30 min at −78 °C and then treated with 2,2,2-trifluoroethyltrifluoroacetate (1.7 mL, 12 mmol). The reaction mixture was stirred for 10 min and then poured into 5% aq HCl solution, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give crude β-diketone **22**, which was used in the next step without further purification.

Triethylamine (1.25 mL, 9 mmol), H_2O (122 μL, 6.7 mmol), and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (4.5 g, 18.6 mmol) were added to a solution of the above obtained β-diketone **22** in CH_3CN (14 mL) at rt. Although the reaction is usually complete in 3 h under these conditions, in this case, the mixture was allowed to stir overnight (12 h). Then, the reaction mixture was diluted with ether and washed with 10% aq NaOH solution and brine, and dried over Na_2SO_4. The solvent was removed under vacuum, leaving a brown oil that was chromatographed, using hexane/AcOEt 9:1, to afford α-diazoketone **23** (1.30 g, 80% from **21**) as a colourless oil. $[\alpha]_D^{25}$ −42 (2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2938m, 2104s, 1665s, 1620m, 1334s, 1148w; ^{1}H NMR (300 MHz) δ 6.92 (1H, m, H-3), 5.59 (1H, s, CHN_2), 5.27 (1H, br s, H-7), 3.09 (1H, dddd, J=19.2, 11.7, 2.5, 2.5 Hz, H-4α), 2.47 (1H, m, H-10), 2.33 (1H, ddd, J=19.2, 5.8, 5.8 Hz, H-4β), 2.09–1.96 (2H, m), 1.92 (2H, m), 1.85 (1H, dd, J=11.0, 4.0 Hz, H-8a), 1.75 (3H, m, Me-C_2), 1.73 (1H, m), 1.60 (3H, s, Me-C_8), 1.57–1.38 (2H, m), 1.12 (1H, J=12.0, 12.0, 8.0 Hz, H-1β), 0.81 (3H, s, Me-C_{4b}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) m/z (%) 313 (M^++1, 5), 312 (M^+, 15), 284 (28), 259 (10), 256 (14), 243 (21), 147 (36), 135 (20), 121 (100), 109 (35), 91 (54); HRMS m/z calcd for $C_{19}H_{24}N_2O_2$ 312.1838, found 312.1832.

4.3.8. 19-Nor-*ent*-trachylob-3-en-14,15-dione (24). A solution of α-diazoketone **23** (930 mg, 3 mmol) in toluene (90 mL) was added dropwise over a period of 4 h over a solution of bis(*N*-*tert*-butylsalicylaldiminate)Cu(II) (70 mg, 0.15 mmol) in refluxing toluene (90 mL). When the addition was complete, the solvent was evaporated under vacuum and the residue was purified by chromatography, using hexane/AcOEt 8:2 as eluent, to give compound **24** (803 mg, 95%) as a white solid. Mp 127–128.5 °C (from MeOH); $[\alpha]_D^{21}$ −26 (3.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2926m, 1757m, 1703s, 1454w, 1379w, 1297w, 1216w; ^{1}H NMR (400 MHz) δ 5.27 (1H, br s, H-3), 2.58 (1H, d, J=7.8 Hz, H-13), 2.49 (1H, ddd, J=8.0, 3.0, 1.8 Hz, H-12), 2.18 (1H, ddd, J=13.0, 9.0, 3.0 Hz, H-11), 2.02 (1H, dd, J=17.0, 5.0 Hz, H-9), 1.98 (1H, m, H′-11), 1.94 (1H, m, H-6), 1.92 (2H, m, H_2-2), 1.79 (1H, m, H′-6), 1.72 (2H, m, H_2-7), 1.58 (3H, s, Me-C_4), 1.49 (1H, m, H-5), 1.41 (1H, m, H-1), 1.39 (3H, s, Me-C_{16}), 1.07 (1H, J=12.0, 12.0, 8.0 Hz, H-1β), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) m/z (%) 285 (M^++1, 18), 284 (M^+, 100), 269 (10), 255 (9), 241 (5), 122 (31), 107 (21), 91 (24), 77 (15); HRMS m/z calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1770. Anal. Calcd for $C_{19}H_{24}O_2$: C 80.24, H 8.51; found: C 80.06, H 8.46.

4.3.9. 3β,18-Cyclo-*ent*-trachylobane-14,15-dione (25). Diethyl zinc (1.0 M solution in hexane, 35.8 mL, 35.8 mmol) and diiodomethane (5.5 mL, 54 mmol) were added to a solution of **24** (807 mg, 4.5 mmol) in toluene (72 mL) at 0 °C. The reaction mixture was allowed to slowly warm to rt (ca. 1 h) and then stirred at this temperature for 2 h. The mixture was quenched by the addition of saturated aq NH_4Cl solution and extracted with hexane. The organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to give a solid. Chromatography, using hexane/AcOEt 8:2 as eluent, yielded the diketone **25** (802 mg, 94%) as a white solid. Mp 142–143 °C (from MeOH); $[\alpha]_D^{27}$ −73 (2.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2926m, 2856m, 1754m, 1704s, 1444m, 1360m, 1297w, 1177w, 1016w, 918w; ^{1}H NMR (400 MHz) δ 2.55 (1H, d, J=8.0 Hz, H-13), 2.44 (1H, ddd, J=8.0, 5.0, 2.2 Hz, H-12), 2.12 (1H, ddd, J=13.6, 9.6, 3.1 Hz, H-11), 1.90 (1H, ddd, J=7.3, 7.3, 1.8 Hz, H′-11), 1.95–1.75 (2H, m, H-6 and H-7), 1.85 (1H, m, H-9), 1.72 (1H, m, H-2), 1.66 (1H, m, H′-7), 1.64 (1H, m, H-3), 1.60 (1H, m, H′-2), 1.39 (3H, s, Me-C_{16}), 1.20 (1H, ddd, J=13.1, 6.2, 6.2 Hz, H-1), 0.97 (1H, m, H-5), 0.94 (3H, s, Meα-C_4), 0.71 (3H, s, Me-C_{10}), 0.62–0.50 (2H, m, H′-6 and H′-1), 0.43 (1H, dd, J=9.3, 4.0 Hz, H-18α), −0.03 (1H, dd, J=5.7, 4.3 Hz, H-18β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) m/z (%) 299 (M^++1, 18), 298 (M^+, 58), 256 (100), 201 (21), 187 (21), 159 (15), 107 (22), 91 (43); HRMS m/z calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1932.

4.4. Completion of trachylobane, atisane, beyerane and kaurane frameworks from key intermediate 25

4.4.1. 15β-Hydroxy-*ent*-trachyloban-14-one (26a) and 15α-hydroxy-*ent*-trachyloban-14-one (26b). A solution of diketone **25** (72 mg, 0.24 mmol) and PtO_2 (15 mg) in AcOH (2 mL) was stirred under a hydrogen atmosphere (4 atm) at 35–40 °C for 48 h. The reaction mixture was then filtered through a Celite pad eluting with AcOEt and concentrated. The crude product was purified by chromatography, using hexane/AcOEt 7:3 as eluent, to afford hydroxy-ketone **26a** (46.5 mg, 64%) as a solid, followed by epimeric **26b** (26 mg, 31%) as a white solid.

Data for **26a**. Mp 155–156 °C (from pentane) $[\alpha]_D^{21}$ −48 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3389s, 2921s, 2842m, 1692s, 1416m, 1442m, 1114m, 1080m; ^{1}H NMR (400 MHz) δ 3.61 (1H, s, H-15), 2.00 (1H, m, H-11), 1.95 (1H, dd, J=8.0, 5.0 Hz, H-9), 1.90 (1H, m, H-12), 1.78 (3H, m, H-13, H′-11 and H-7α), 1.71 (1H, m, H-6), 1.51 (3H, m,

Table 2. ^{13}C NMR chemical shifts (δ) in ppm for compounds **25–29**, **31–34** and **36–41**[a]

Compound	**24**	**25**	**26a**	**26b**	**27**	**28a**	**28b**	**29a**	**29b**	**31**	**32**	**33**	**34**	**36**	**37**	**38**	**39**	**40**	**41**
C-1	34.74	33.45	38.91	39.09	33.93	33.10	32.93	38.87	38.71	38.92	39.64	40.67	39.11	39.88	40.76	40.59	40.69	40.13	40.17
C-2	22.07	21.49	18.14	19.00	22.25	21.60	21.55	18.82	18.82	18.56	18.35†	18.79	18.03	18.51	17.41	18.56	18.63†	19.98†	18.80†
C-3	120.79	19.16	42.06	42.03	19.30	19.22	19.26	41.92	41.99	41.90	42.04	41.83	42.02	41.94	41.85	41.62	41.67	41.92	41.84
C-4	134.32	15.64	32.98	32.93	15.84	15.84	15.85	32.93	32.95	32.97	32.99	32.95	34.20	33.14	32.96	32.81	32.84	33.23	33.21
C-5	57.73	49.68	54.82	54.94	50.40	50.39	50.36	55.42	55.16	52.07	55.79	56.09	55.17	55.06	55.86	54.59	54.82	55.76	55.58
C-6	19.76	18.58	18.14	18.01	19.09	18.81	18.79	21.24	20.91	18.03	19.05†	19.90	19.11	19.41‡	19.59	18.56	19.03†	19.03†	18.62†
C-7	21.42	19.85	28.11	26.24	27.94	22.65	23.09	28.71	26.24	28.64	26.83	35.46	32.93	30.80§	34.88	28.73	29.22	33.42	32.85
C-8	55.92	55.62	50.26	51.58	49.81	66.06	66.78	52.73	53.00	50.22	66.55	43.48	44.62	55.16	42.73	48.74	49.70	54.72	53.80
C-9	47.24	57.36	49.66	57.08	45.83	46.24	45.26	49.23	41.89	54.82	55.07	43.11	50.47	46.93	43.00	56.56	56.47	52.66	52.68
C-10	37.26	37.22	37.18†	37.99†	35.85†	37.903	38.78	37.93	37.83	37.99	37.54	36.33	37.71	37.51†	36.65	37.70	37.32	38.49	38.75
C-11	19.73	21.23	18.76	19.22	19.43	22.68	28.61	18.23	18.28	17.08	29.98	18.79	22.38	19.31‡	18.75	17.59	17.79	16.61	16.55
C-12	43.09	43.15	34.94	35.34	34.85	32.17	31.71	32.88	33.53	38.37	37.14	20.53	44.26	30.60§	20.94	32.67	33.48	18.18	18.86
C-13	47.14	47.09	39.96	36.69	40.14	46.03	40.14	45.50	46.42	42.89	41.77	27.22	132.55	37.72†	24.30	33.97	35.68	39.87	36.76
C-14	207.41†	206.70†	212.11	214.10	212.42	210.35†	210.84†	215.78	217.93	206.95	214.57	79.50	133.20	81.07	79.99	77.30	76.55	79.32	79.43
C-15	206.40†	207.40†	77.22	82.01	77.12	209.42†	209.14†	85.68	71.10	56.94	128.91	79.32	87.76	220.03	78.66	209.89	211.85	221.95	218.8
C-16	49.20	49.01	37.54†	36.89†	38.63†	46.14	45.19	41.45	35.83	37.88	146.15	25.75	77.20	49.05	26.59	37.70	37.32	45.78	45.60
C-17	12.90	12.83	17.95	16.39	17.95	14.85	14.50	19.24	13.41	20.98	20.02	17.87	25.64	24.20	17.78	12.77	12.92	9.72	9.58
C-18	21.34	21.91	21.2	21.59	23.71	21.34	21.44	33.49	33.55	21.42	21.67	33.47	33.65	33.60	33.39	33.33	34.03	33.40	33.31
C-19		21.19	33.22	33.27	21.57	23.67	23.72	21.71	21.71	33.09	33.57	21.92	21.95	21.93	21.87	21.80	21.89	21.53	21.45
C-20	11.26	11.28	14.01	13.52	11.31	11.54	11.59	13.60	13.67	13.76	13.11	15.81	15.65	13.63	15.67	15.52	15.75	16.54	16.46
Others		—	—	—	—	—	—	—	—	—	—	—	—	—	[b]	[c]	—	—	[d]

[a] The signals with the same superscript may be interchanged within the same column.
[b] OCH at C-14 at 161.21 ppm.
[c] OCH at C-14 at 160.68 ppm.
[d] OCO*Me* and O*CO*Me at C-14 at 21.56 and 170.41 ppm, respectively.

H′-6, H-2 and H-1), 1.35 (1H, m, H-3), 1.34 (3H, s, Me-C_{16}), 1.34 (1H, m, H′-2), 1.20 (1H, ddd, J=12.9, 12.9, 4.2 Hz, H′-7β), 1.09 (1H, m, H′-3), 0.87 (3H, s, Meβ-C_4), 0.81 (3H, s, Meα-C_4), 0.80 (1H, m, H′-1), 0.74 (1H, m, H-5), 0.75 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 303 (M^++1, 25), 302 (M^+, 100), 284 (65), 269 (50), 245 (54), 199 (14), 165 (62), 147 (36), 137 (43), 123 (66); HRMS *m/z* calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2244. Anal. Calcd for $C_{20}H_{30}O_2$: C 79.42, H 10.00; found: C 79.61, H 9.86.

Data for **26b**. Mp 180–183 °C (from cold pentane); $[\alpha]_D^{21}$ −44 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3393s, 2914s, 2837m, 1690s, 1450m, 1388m, 1082m, 970w; ^{1}H NMR (400 MHz) δ 3.75 (1H, s, H-8), 2.10 (1H, ddd, J=12.8, 3.2, 3.2 Hz, H-7α), 1.99 (1H, m, H-11), 1.78 (1H, m, H′-11), 1.72 (1H, m, H-12), 1.68 (1H, m, H-13), 1.61 (1H, m, H-9), 1.56 (2H, m, H_2-2), 1.41 (1H, m, H-6), 1.40 (1H, m, H-1), 1.31 (1H, m, H-3), 1.29 (1H, m, H′-6), 1.14 (3H, s, Me-C_{16}), 1.05 (1H, m, H′-3), 0.98 (1H, m, H′-7), 0.84 (3H, s, Meβ-C_4), 0.78 (3H, s, Meα-C_4), 0.71 (1H, m, H′-1), 0.69 (3H, s, Me-C_{10}), 0.68 (1H, m, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 303 (M^++1, 14), 302 (M^+, 51), 287 (20), 242 (42), 227 (13), 178 (21), 165 (60), 137 (100), 119 (67), 91 (55); HRMS *m/z* calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2234.

4.4.2. 15β-Hydroxy-3β,18-cyclo-*ent*-trachyloban-14-one (27). (A) *By catalytic hydrogenation of* **25**. A heterogeneous mixture of ketone **25** (75 mg, 0.25 mmol), 10% Pt/C (15 mg) and AcOEt (2 mL) was stirred under a hydrogen atmosphere (4 atm) at rt for 24 h. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification of the residue by column chromatography, using hexane/AcOEt 7:3 as eluent, afforded **27** (72 mg, 95%) as a white solid.

(B) *By $NaBH_4$ reduction of* **25**. A solution of ketone **25** (433.2 mg, 1.44 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (20 mL) was cooled to 0 °C and $NaBH_4$ (106 mg, 2.88 mmol) was added in small portions over a period of 45 min. Stirring was continued for 30 min at the same temperature, and then the reaction mixture was quenched with water and stirred for a few minutes until the evolution of hydrogen ceased. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent left a residue that was purified as above to give hydroxy-ketone **27** (420.2 mg, 96%) as a solid. Mp 174–175 °C (from MeOH); $[\alpha]_D^{27}$ +40 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3393m, 2929s, 1694s, 1465m, 1377w, 1071m; ^{1}H NMR (400 MHz) δ 3.58 (1H, s, H-15), 2.05 (1H, ddd, J=12.8, 10.0, 2.6 Hz, H-11β), 1.92 (3H, m, H-9, H-12 and H-2), 1.86 (2H, m, H-13 and H-11α), 1.82 (1H, m, H-7), 1.75 (1H, m, H′-2), 1.66 (2H, m, H_2-6), 1.34 (3H, s, Me-C_{16}), 1.32 (1H, m, H-1), 1.23 (1H, m, H′-7), 0.96 (1H, m, H-5), 0.93 (3H, s, Meβ-C_4), 0.72 (3H, s, Me-C_{10}), 0.61 (1H, m, H′-1), 0.58 (1H, m, H′-3), 0.39 (1H, dd, J=9.2, 4.0 Hz, H-18α), −0.03 (1H, dd, J=5.8, 4.0 Hz, H-18β); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 300 (M^+, 1), 282 (4); 258 (11), 240 (6), 227 (6), 185 (5), 145 (9), 119 (20), 105 (29), 83 (100); HRMS *m/z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2093.

4.4.3. 3β,18-Cyclo-16αH-*ent*-atisane-14,15-dione (28a) and 3β,18-cyclo-16βH-*ent*-atisane-14,15-dione (28b). Cyclopropyl diketone **25** (31 mg, 0.10 mmol) was dissolved in a 3:1 mixture of THF/MeOH (2 mL) and a 0.1 M solution of SmI_2 in THF was added dropwise until persistence of the blue colour. The reaction mixture was stirred at rt for 1 h and then treated with a saturated aq NH_4Cl solution and extracted with ether. The organic layer was washed with water, 5% aq $Na_2S_2O_4$ solution and brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed, using 9.5:0.5 hexane/AcOEt as eluent, to give atisane–dione **28a** (19 mg, 61%) followed by the C-16 epimer **28b** (9 mg, 28%).

Data for **28a**. Mp 190–191 °C (MeOH); $[\alpha]_D^{29}$ −52 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2935s, 2862m, 1728s, 1696s, 1444m, 1060m, 1032m, 705m, 649m; ^{1}H NMR (400 MHz) δ 2.55 (1H, dd, J=19.9, 3.8 Hz, H-13), 2.41 (1H, m, H′-13), 2.38 (1H, m, H-12), 2.30 (1H, m, H-11), 2.25 (1H, m, H-16), 2.08 (1H, m, H′-11), 1.82 (1H, m, H-7), 1.67 (2H, m, H_2-6), 1.61–1.49 (3H, m, H′-7 and H_2-2), 1.45 (1H, m, H-9), 1.38 (1H, m, H-1), 1.24 (3H, d, J=7.0 Hz, Me-C_{16}), 0.95 (1H, m, H-5), 0.94 (3H, s, Me-C_4), 0.73 (3H, s, Me-C_{10}), 0.55 (2H, m, H-3 and H′-1), 0.42 (1H, dd, J=9.2, 4.0 Hz, H-18α), −0.05 (1H, dd, J=5.8, 4.0 Hz, H-19β); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 301 (M^++1, 10), 300 (M^+, 25), 272 (39), 258 (100), 243 (35), 230 (31), 217 (20), 176 (30), 162 (34), 121 (29), 197 (27), 91 (26); HRMS *m/z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2099.

Data for **28b**. Mp 126–127 °C (cold MeOH); $[\alpha]_D^{29}$ −36 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2979s, 2853m, 1731s, 1700s, 1419m, 1378m, 1040m, 968w; ^{1}H NMR (400 MHz) δ 2.54 (1H, dd, J=19.8, 3.9 Hz, H-13), 2.38 (1H, m, H′-13), 2.32 (1H, m, H-12), 2.40–2.20 (3H, m, H-16 and H_2-11), 2.10–1.20 (8H, m, H-9, H_2-7, H_2-6, H_2-2 and H-1), 1.10 (3H, d, J=7.0 Hz, Me-C_{16}), 0.95 (1H, m, H-5), 0.93 (3H, s, Me-C_4), 0.72 (3H, s, Me-C_{10}), 0.62 (2H, H-3, H′-1), 0.42 (1H, dd, J=9.0, 4.0 Hz, H-18α), −0.05 (1H, dd, J=5.8, 4.0 Hz, H-18β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 301 (M^++1, 4), 300 (M^+, 21), 286 (14), 272 (40), 258 (100), 243 (40), 230 (44), 217 (35), 176 (38), 162 (44), 121 (72), 107 (75), 91 (94); HRMS *m/z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2088.

4.4.4. 15β-Hydroxy-16αH-*ent*-atisan-14-one (29a) and 15α-hydroxy-16αH-*ent*-atisan-14-one (29b). Hydrogenation of diketone **28a** (35 mg, 0.12 mmol) as described above for **25** (4.4.1) gave a mixture of epimeric hydroxy-atisanones **29a** and **29b**, which were separated by chromatography using hexane/AcOEt 7:3, to afford, in order of elution, atisanone **29b** (8.2 mg, 23%) and C-15 epimeric **29a** (16 mg, 45%).

Data for **29a**. Mp 164–166 °C (cold pentane); $[\alpha]_D^{22}$ +16 (0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3512m, 2939s, 2842m, 1716s, 1692s, 1459m, 1386m, 1367m, 1016m; ^{1}H NMR (400 MHz) δ 3.18 (1H, d, J=3.0 Hz, H-15), 2.54 (1H, ddd, J=12.8, 3.8, 2.8 Hz, H-7α), 2.27 (1H, dd, J=19.0, 3.2 Hz, H-13), 2.20 (1H, ddd, J=19.0, 5.3, 2.6 Hz, H′-13), 1.95 (1H, m, H-12), 1.84 (1H, m, H-6), 1.65 (1H, m, H-16), 1.58 (1H, m, H-1), 1.57 (2H, m, H_2-2), 1.39 (3H, m, H_2-11, H′-6 and H-3), 1.34 (1H, m, H-9), 1.16 (3H, d, J=7.1 Hz, Me-

C_{16}), 1.12 (1H, m, H′-3), 0.86 (2H, m, H-1 and H-7β), 0.85 (3H, s, Meβ-C_4), 0.78 (1H, m, H-5), 0.78 (3H, s, Meα-C_4), 0.69 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 305 (M^++1, 15), 304 (M^+, 75), 289 (22.4), 245 (100), 148 (66), 123 (36); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2399.

Data for **29b**. Mp 145–147 °C (cold MeOH); $[\alpha]_D^{29}$ +20 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3493s, 2914s, 2863m, 1705s, 1465m, 1393m, 1055m, 1009m; ^{1}H NMR (400 MHz) δ 3.45 (1H, dd, *J*=9.6, 2.1 Hz, H-15), 2.29 (1H, dd, *J*=19.0, 2.8 Hz, H-13), 2.15 (1H, ddd, *J*=19.0, 4.5, 2.3 Hz, H′-13), 2.02 (1H, m, H-7), 2.01 (1H, m, H-16), 1.92 (3H, m, H-12, H-9 and H-6), 1.55 (1H, m, H-1), 1.52 (2H, m, H_2-2), 1.39 (3H, M, H_2-11, H′-7 and H-3), 1.36 (1H, m, H′-6), 1.12 (1H, m, H′-3), 1.09 (3H, d, *J*=7.3 Hz, Me-C_{16}), 0.86 (1H, m, H′-1), 0.85 (3H, s, Meβ-C_4), 0.79 (1H, m, H-5), 0.78 (3H, s, Meα-C_4), 0.69 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 305 (M^++1, 8), 304 (M^+; 39), 289 (10), 271 (14), 245 (57), 178 (40), 149 (92), 137 (50), 123 (85), 109 (60), 95 (52), 69 (72); 57 (100); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2396.

4.4.5. 15α-Iodo-*ent*-trachyloban-14-one (31). Et_3N (140 μL, 0.99 mmol) and mesyl chloride (65 μL, 0.73 mmol) were added to a solution of hydroxy-ketone **26a** (65 mg, 0.22 mmol) in CH_2Cl_2 (2.3 mL) at 0 °C. After stirring at rt for 2 h, the mixture was diluted with ether and washed successively with diluted hydrochloric acid, 5% aq $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure at rt afforded a yellowish residue of crude mesylate **30** (70 mg) that was used in the subsequent step without further purification.

The above obtained mesylate was dissolved in a 10% solution of NaI in dry acetone (2 mL) and the mixture was heated at 40 °C for 2 h. The reaction mixture was cooled down to rt, poured into water and extracted with hexane. The combined organic phases were washed with dilute $Na_2S_2O_3$ and H_2O, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by column chromatography, using hexane/AcOEt 9:1 as eluent, afforded iodo-ketone **31** (73 mg, 85% for the two steps) as a white solid. Mp 151–153 °C (with decomposition) (from cold ethyl ether); $[\alpha]_D^{29}$ +8 (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2866m, 1727s, 1462m, 1439m, 1389m, 1367m; ^{1}H NMR (400 MHz) δ 4.28 (1H, s, H-15), 2.14 (1H, ddd, *J*=10.5, 2.2, 2.2 Hz, H-11α), 2.06 (1H, d, *J*=7.2 Hz, H-13), 1.94 (1H, m, H-9), 1.89 (1H, m, H-12), 1.69 (2H, m, H-7 and H-2), 1.67 (1H, m, H′-11), 1.52 (2H, m, H-6 and H′-2), 1.43 (1H, m, H-1), 1.32 (3H, s, Me-C_{16}), 1.33 (1H, m, H′-6), 1.31 (1H, m, H-3), 1.28 (1H, m, H′-7), 1.05 (1H, m, H′-3), 0.85 (3H, s, Meβ-C_4), 0.77 (3H, s, Meα-C_4), 0.75 (1H, m, H′-1), 0.69 (1H, m, H-5), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 413 (M^++1, 1), 412 (M^+, 0.1), 320 (9), 285 (100), 257 (25), 203 (6), 161 (10), 137 (44), 119 (32), 105 (37); HRMS *m/z* calcd for $C_{20}H_{30}IO$ [M+H^+] 413.1341, found 413.1338.

4.4.6. *ent*-Atis-15-en-14-one (32). Iodo-ketone **31** (35 mg, 0.085 mmol) in a mixture of THF (1.5 mL) and MeOH (0.5 mL) was treated dropwise with a 0.1 M solution of SmI_2 in THF at rt until persistence of the blue colour (ca. 1.5–2 mL). After being stirred for 1 h, saturated aq NH_4Cl solution was added and the mixture was poured into water and extracted with ether. The organic layer was washed with dilute $Na_2S_2O_3$ and brine, dried and evaporated under reduced pressure. Chromatography, using hexane/AcOEt 8:2 as eluent, yielded atisenone **32** (20 mg, 85%) as a solid. Mp 132–133 °C (from MeOH); $[\alpha]_D^{25}$ −142 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2858m, 1700s, 1427m, 1126m, 1071m; ^{1}H NMR (400 MHz) δ 5.32 (1H, s, H-15), 2.60 (1H, m, H-12), 2.46 (1H, ddd, *J*=13.2, 3.6, 3.6 Hz, H-11α), 2.13 (1H, ddd, *J*=18.0, 3.2, 3.2 Hz, H-13), 2.02 (1H, dd, *J*=18.0, 2.3 Hz, H′-13), 1.77 (3H, s, Me C_{16}), 1.65 (1H, m, H-7), 1.45 (2H, m, H_2-6), 1.42 (3H, m, H-9, H′-7, H-1), 1.29 (3H, m, H_2-2 and H-3), 1.15 (1H, m, H-11β), 1.10 (1H, m, H′-3), 0.86 (3H, s, Meβ-C_4), 0.85 (1H, m, H-5), 0.79 (3H, s, Meα-C_4), 0.78 (1H, m, H′-1), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 286 (M^+, 6), 244 (100), 230 (31), 137 (31), 120 (33), 106 (54), 91 (22); HRMS *m/z* calcd for $C_{20}H_{30}O$ 286.2297, found 286.2287. Anal. Calcd for $C_{20}H_{30}O$: C 83.86, H 10.56; found: C 83.99, H 10.47.

4.4.7. *ent*-Trachylobane-14α,15β-diol (33). A 1 M solution of $LiAlH_4$·2THF in toluene (2.5 mL, 2.5 mmol) was added dropwise to a solution of hydroxy-ketone **26a** (154 mg, 0.50 mmol) in THF (3.8 mL) and toluene (2.2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, AcOEt (3 mL) was slowly added to destroy excess hydride, followed by the dropwise addition of H_2O until the appearance of a milky white solid (ca. 0.75 mL). Anhydrous Na_2SO_4 was then added until a fine white precipitate separated from the solution, which was removed by filtration and washed with AcOEt. The residue left after concentration of the clear filtrate under reduced pressure was purified by chromatography, using dichloromethane/AcOEt 4:1 as eluent, to give diol **33** (100.8 mg, 88%) as a white solid. Mp 192–193 °C (from $CHCl_3$); $[\alpha]_D^{29}$ −33 (1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3301s, 2927m, 2863w, 1439m, 1316m, 1262m, 1075m, 1051s, 982m; ^{1}H NMR (400 MHz) δ 3.75 (1H, d, *J*=3.5 Hz, H-14), 3.32 (1H, s, H-15), 1.80 and 1.73 (1H each, two m, H_2-11), 1.54 (1H, m, H-2α), 1.48 (2H, m, H-1α), 1.37 (1H, m, H-3β), 1.35 (1H, m, H-2β), 1.29 (1H, m, H-9), 1.18 (3H, s, Me-C_{16}), 1.14 (1H, dd, *J*=3.5, 7.5 Hz, H-13), 1.11 (1H, m, H-3α), 1.00 (3H, s, Me-C_{10}), 1.00 (1H, m, H-6β), 0.91 (1H, m, H-12), 0.84 (3H, s, Meα-C_4), 0.83 (2H, m, H-1β), 0.81 (1H, m, H-6α), 0.80 (3H, s, Meβ-C_4), 0.76 (1H, m, H-5); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 304 (M^+, 2.5), 286 (100), 271 (43), 230 (23), 213 (18), 137 (60), 123 (47), 109 (35), 105 (64), 95 (50); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2400. Anal. Calcd for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 79.05, H 10.49.

4.4.8. *ent*-Atis-13-en-15α,16β-diol (34). Et_3N (55 μL, 0.4 mmol, 6 equiv), H_2O (6 μL, 0.33 mmol, 5 equiv), and methanesulfonyl chloride (16 μL, 0.2 mmol, 3 equiv) were successively added to a solution of diol **33** (20 mg, 0.066 mmol) in CH_2C1_2 (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, quenched with saturated aq solution of $NaHCO_3$, and diluted with CH_2C1_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$. Purification of the residue left after evaporation of the solvent by column chromatography, using hexane/AcOEt

from 4:1 to 2:3, afforded atisenediol **34** (13.2 mg, 66%) as an amorphous solid. $[\alpha]_D^{29}$ −20 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3409s, 2915s, 2847m, 2353m, 2336m, 1636m, 1456m, 1112m, 1052m, 910w; ^1H NMR (400 MHz) δ 6.18 (1H, dd, J=7.0, 8.0 Hz, H-13) 5.77 (1H, dd, J=8.0, 1.0 Hz, H-14), 3.15 (1H, s, H-15), 2.37 (1H, ddd, J=3.0, 3.0, 7.0 Hz, H-12), 2.24 (1H, ddd, J=13.0, 3.0, 3.0 Hz, H-7α), 2.00 (1H, ddd, J=13.0, 9.0, 3.0 Hz, H-11β), 1.96 (1H, m, H-7β), 1.62 (1H, m, H-6), 1.47 (1H, m, H-2), 1.43 (1H, m, H-1) 1.39 (1H, m, H-3), 1.35 (1H, m, H′-2), 1.34 (1H, m, H-9), 1.32 (1H, m, H′-6), 1.26 (1H, m, H-7α), 1.14 (1H, m, H′-3), 1.13 (3H, s, Me-C_{16}), 0.95 (1H, ddd, J=13.0, 7.0, 3.0 Hz, H-11α), 0.90 (1H, m, H′-1), 0.88 (3H, s, Meβ-C_4), 0.84 (1H, m, H-5), 0.80 (3H, s, Meα-C_4), 0.61 (3H, d, J=0.8 Hz, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 304 (M^+, 1), 286 (M^+-H_2O, 7), 230 (44), 145 (28), 131 (100), 119 (67), 106 (23), 100 (20), 91 (32); HRMS m/z calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2405.

4.4.9. 14α-Hydroxy-*ent*-beyeran-15-one (36). A solution of cyclopropyl-ketone **26a** (29.0 mg, 0.095 mmol) in THF (1 mL) was added dropwise to a solution of lithium (5 mg, 0.83 mmol) in liquid ammonia (1 mL) and THF (0.5 mL) at −78 °C. After stirring for 10–15 min, isoprene was added dropwise until disappearance of the blue colour. The ammonia was allowed to evaporate, saturated aq NH_4Cl solution was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue, using hexane/AcOEt 8:2 as eluent, afforded hydroxy-beyeranone **36** (24.9 mg, 85%) as a solid. Mp 165–166 °C (from pentane); $[\alpha]_D^{29}$ +42 (1.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3440m, 2949s, 2864m, 1713s, 1460m, 1150m, 1108m, 1038m; ^1H NMR (400 MHz) δ 3.17 (1H, s, H-14), 2.25 (1H, d, J=19.0 Hz, H-16), 1.85 (1H, d, J=19.0 Hz, H′-16), 1.55 (1H, br s, OH), 1.07 (3H, s, Me-C_{13}), 0.86 (3H, s, Meβ-C_4), 0.83 (3H, s, Meα-C_4), 0.80 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 305 (M^++1, 25), 304 (M^+, 100), 289 (46), 286 (62), 245 (40), 244 (56), 229 (47), 138 (39), 123 (91), 95 (34); HRMS m/z calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2397. Anal. Calcd for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 78.79, H 10.66.

4.4.10. 14α-Formyloxy-*ent*-trachyloban-15β-ol (37). A solution of diol **33** (48.1 mg, 0.15 mmol) in buffered formic acid (4.5 mL of a solution of 50 mg of anhydrous Na_2CO_3 in 10 mL of formic acid) and THF (1.5 mL) was stirred at 5 °C for 14 h. The mixture was diluted with cold ether and washed with saturated aq $NaHCO_3$ solution until basic, then with water until neutral and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield an oily residue, which was purified by chromatography, using hexane/Et_2O 1:1 as eluent, to afford formate **37** (41.3 mg, 80%) as a colourless oil. $[\alpha]_D^{29}$ −12 (0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3414m, 2923s, 2859m, 1716s, 1463m, 1439m, 1166s, 1092m, 983w, 745m; ^1H NMR (400 MHz) δ 8.17 (1H, d, J=0.8 Hz, OC*H*O), 4.92 (1H, d, J=3.5 Hz, H-14), 3.44 (1H, s, H-15), 1.76–1.95 (2H, m, H_2-11), 1.72 (1H, m, H-9), 1.56 (1H, m, H-2α), 1.53 (1H, m, H-1α), 1.44 (1H, m, H-6β), 1.38 (1H, m, H-2β), 1.37 (1H, m, H-3β), 1.30 (1H, dd, J=3.5, 7.5 Hz, H-13), 1.20 (3H, s, Me-C_{16}), 1.20 (1H, m, H-6α), 1.14 (1H, m, H-3α), 1.00 (3H, s, Me-C_{10}), 0.99 (1H, m, H-12), 0.86 (1H, m, H-1β), 0.83 (3H, s, Meβ-C_4), 0.785 (3H, s, Meα-C_4), 0.71 (1H, m, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 332 (M^+, 0.2), 314 (M^+-H_2O, 9), 286 (48), 257 (34), 230 (44), 137 (57), 131 (35), 131 (35), 105 (68), 100 (20), 91 (81); HRMS m/z calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2451.

4.4.11. 14α-Formyloxy-*ent*-trachyloban-15-one (38). Pyridine (30 μL, 0.37 mmol) was added to a solution of alcohol **37** (39.2 mg, 0.12 mmol) in CH_2Cl_2 (3 mL), followed by Dess–Martin periodinate reagent (78 mg, 0.18 mmol) in one portion. The resulting reaction mixture was stirred at rt for 2 h before being quenched with saturated aq $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by chromatography, using hexane/AcOEt 8:2 as eluent, to afford ketone **38** (33.6 mg, 86% yield) as an oil. $[\alpha]_D^{29}$ −4 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 2923m, 2858s, 1716s, 1465m, 1388m, 1164s, 984w; ^1H NMR (400 MHz) δ 8.19 (1H, d, J=0.8 Hz, OC*H*O), 5.19 (1H, d, J=3.5 Hz, H-14), 2.17 (1H, m, H-7), 2.15 (1H, m, H-12), 1.94 (2H, m, H_2-11), 1.91 (1H, m, H-13), 1.54 (1H, m, H-2), 1.37 (1H, m, H′-2), 1.49 (1H, m, H-9), 1.47 (1H, m, H-1), 1.39 (1H, m, H-7), 1.35 (1H, m, H-3), 1.26 (3H, s, Me-C_{13}), 1.23 (1H, m, H-6), 1.12 (1H, m, H′-6), 1.10 (1H, m, H′-3), 0.98 (3H, s, Me-C_{10}), 0.84 (3H, s, Meβ-C_4), 0.79 (3H, s, Meα-C_4) 0.79 (1H, m, H′-1), 0.72 (1H, dd, J=12.2, 2.1 Hz, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 330 (M^+, 2.4), 315 (2), 284 (15), 269 (7), 178 (12), 161 (7), 137 (11), 123 (13), 86 (62), 84 (100); HRMS m/z calcd for $C_{21}H_{30}O_3$ 330.2194, found 330.2191.

4.4.12. 14α-Hydroxy-*ent*-trachyloban-15-one (39). A solution of formate ester **38** (35 mg, 0.11 mmol) and Na_2CO_3 (50 mg, 0.46 mmol) in MeOH (1 mL) was stirred at rt for 1 h. After addition of H_2O, the solution was extracted with AcOEt. The organic layers were washed with H_2O, then brine and dried. Evaporation of the solvent and purification by chromatography, using hexane/AcOEt 7:3 as eluent, gave alcohol **39** (29 mg, 90%) as a white foam solid. $[\alpha]_D^{29}$ −19 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3420m, 2912s, 2874m, 1694s, 1448m, 1388m, 1099s; ^1H NMR (400 MHz) δ 4.09 (1H, m, H-14), 2.15 (1H, ddd, J=14.3, 14.3, 5.9 Hz, H-7β), 2.02 (1H, dd, J=7.2, 3.8 Hz, H-13), 1.93 (3H, m, H-12 and H_2-11), 1.51 (2H, m, H-6 and H-2), 1.42 (2H, m, H-1 and H-9), 1.32 (3H, m, H′-7, H′-6 and H′-2), 1.30 (1H, m, H-3), 1.24 (3H, s, Me-C_{16}), 1.12 (1H, m, H′-3), 1.04 (3H, s, Me-C_{10}), 0.84 (3H, s, Meβ-C_4), 0.80 (1H, m, H′-1), 0.69 (1H, dd, J=12.1, 1.3 Hz, H-5), 0.80 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 302 (M^+, 65), 287 (25), 269 (16), 165 (50), 137 (10), 123 (68), 105 (40), 84 (100), 69 (82); HRMS m/z calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2232.

4.4.13. 14α-Hydroxy-*ent*-kauran-15-one (40). A solution of cyclopropyl-ketone **39** (22.8 mg, 0.075 mmol) in THF (0.5 mL) was added dropwise to a solution of lithium (5 mg, 0.71 mmol) in liquid ammonia (1 mL) and THF (0.5 mL) at −78 °C. After stirring for 15–20 min, the reaction mixture was worked-up as described above for the preparation of **36**. The crude product was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to obtain kauranone **40** (19.6 mg,

86%) as a white solid. Mp 186–187 °C (from pentane); $[\alpha]_D^{29}$ −20 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3416s, 2919s, 2852m, 1716s, 1460m, 1449m, 1378m, 1209m, 1137w; ^1H NMR (400 MHz) δ 3.82 (1H, dd, J=4.7 Hz, H-14), 2.35 (2H, m, H-13 and H-16), 1.90 (1H, m, H-12), 1.87 (1H, m, H-7), 1.68 (1H, ddd, J=11.8, 11.8, 3.0 Hz, H-1β), 1.58 (2H, m, H-6 and H-2), 1.57 (1H, m, H-11), 1.52 (1H, m, H′-12), 1.44 (2H, m, H′-6 and H′-2), 1.43 (1H, m, H′-7), 1.36 (1H, m, H′-11), 1.35 (1H, m, H-3), 1.17 (1H, m, H-9), 1.16 (3H, d, J=7.0 Hz, Me-C_{16}), 1.12 (1H, m, H′-3), 1.06 (3H, s, Me-C_{10}), 0.91 (1H, dd, J=13.5, 3.5 Hz, H-5), 0.86 (3H, s, Meβ-C_4), 0.72 (1H, ddd, J=12.6, 12.6, 3.2 Hz, H-1), 0.80 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 304 (M^+,16), 289 (14), 246 (17), 167 (35), 137 (41), 123 (100), 109 (34), 83 (76); HRMS m/z calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2388.

4.4.14. 14α-Acetoxy-*ent*-kauran-15-one (41). A solution of alcohol **40** (11.3 mg, 0.037 mmol), Ac_2O (70 μL, 0.74 mmol), pyridine (30 μl, 0.36 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (2 mL) was stirred at rt for 3 h. The reaction was quenched by the addition of H_2O and extracted with AcOEt, the organic phase was washed successively with 5% aq HCl solution, 10% aq Na_2CO_3 solution and brine, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography, using hexane/AcOEt 9:1 as eluent, to give acetate **41** (11.6 mg, 93%) as a solid. Mp 125–127 °C (from cold MeOH); $[\alpha]_D^{29}$ −8 (0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2863s, 2852m, 1732s, 1454m, 1361m, 1241s, 1115w, 1055w; ^1H NMR (400 MHz) δ 4.79 (1H, d, J=4.8 Hz, H-14), 2.50 (1H, m, H-13), 2.37 (1H, quin, J=6.5 Hz, H-16), 2.18 (3H, s, *Me*COO), 1.94 (1H, ddd, J=13.6, 13.6, 4.3 Hz, H-7β), 1.75 (1H, m, H-12), 1.71 (1H, m, H-1α), 1.60 (1H, m, H-11), 1.56 (1H, m, H′-12), 1.47 (1H, m, H-7α), 1.45 (1H, m, H-6), 1.40 (1H, m, H-3), 1.32 (1H, m, H′-11), 1.23 (1H, m, H′-6), 1.22 (1H, m, H-9), 1.18 (1H, m, H′-3), 1.16 (3H, d, J=7.0 Hz, Me-C_{16}), 1.04 (3H, s, Me-C_{10}), 0.90 (1H, dd, J=12.3, 2.2 Hz, H-5), 0.85 (3H, s, Meβ-C_4), 0.80 (3H, s, Meβ-C_4), 0.77 (1H, ddd, J=12.8, 12.8, 3.5 Hz, H-1β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) m/z (%) 346 (M^+, 1), 303 (10), 286 (19), 258 (96), 230 (41), 137 (100), 121 (51), 81 (68); HRMS m/z calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2482. Anal. Calcd for $C_{22}H_{34}O_3$: C 76.26, H 9.89; found: C 76.39, H 9.78.

Acknowledgements

Financial support from the Dirección General de Enseñanza Superior e Investigación Científica (Grant BQU2002-00272) is gratefully acknowledged. We are grateful to the Conselleria d′Educació i Ciència de la Generalitat Valenciana and the Ministerio de Educación y Ciencia for providing research fellowships to I. Navarro and I. de Alfonso Marzal, respectively.

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Tetrahedron 62 (2006) 3284–3291
Tetrahedron

Biocatalytic preparation of enantioenriched 3,4-dihydroxypiperidines and theoretical study of *Candida antarctica* lipase B enantioselectivity

Laura F. Solares, Iván Lavandera, Vicente Gotor-Fernández, Rosario Brieva and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, 33006 Oviedo, Spain

Received 19 November 2005; revised 17 January 2006; accepted 18 January 2006

Available online 17 February 2006

Abstract—Enzymatic acetylations of *N*-substituted *cis*- and *trans*-3,4-dihydroxypiperidine and hydrolysis of their diacetylated derivatives have been studied. High enantioselectivities are obtained with *Pseudomonas cepacia* lipase and *Candida antarctica* lipase B for the hydrolysis of the trans-derivative, while the cis-derivatives are not adequate substrates in the same biocatalytic conditions. The enantiopreference of these processes can be rationalized by means of a molecular modelling study.
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1. Introduction

Polyhydroxylated piperidines have attracted great interest due to their biological properties. Some of them are inhibitors of glycosidases and glycoprotein-processing enzymes.[1] These inhibitors have shown a promising therapeutical potential for the treatment of various diseases related to metabolic disorders of carbohydrates such as diabetes,[2] and viral infections including AIDS[3] or cancer.[4] In this sense, optically pure 3,4-dihydroxypiperidine is an interesting structure since the (3*R*,4*R*)-*trans* isomer is an inhibitor of β-D-glucoronidase[5] and has been used as intermediate for the preparation of a xylanase inhibitor (Fig. 1).[6] Also, this structure is a suitable precursor of the gastroprokinetic agent cisapride.[7] On the other hand, the cis-isomer is an intermediate for the preparation of the antidepressant ifoxetine.[8]

The optically pure (3*R*,4*R*)-*trans*-isomer has been synthesized from either D-arabinose[5] or D-tartaric acid.[6]

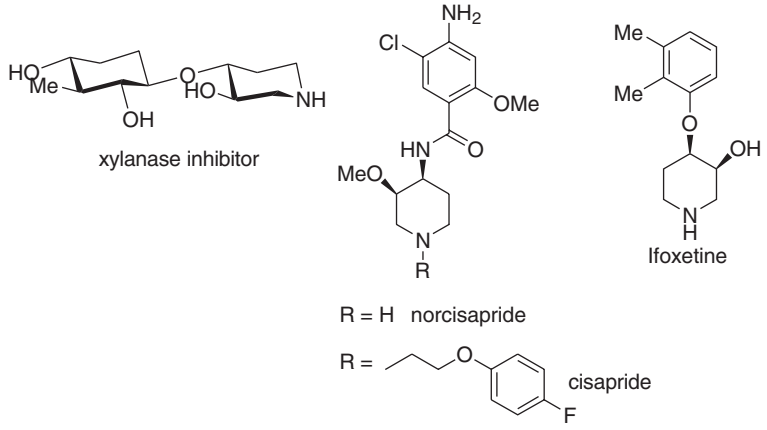

Figure 1. Examples of different chiral 3,4-dihydroxypiperidine derivatives.

Keywords: *Camdida antarctica* lipase B; *Dihydroxypiperidine*; Enzymatic hydrolysis and transesterification; Molecular modeling.
* Corresponding author. Tel./fax: +34 985 103 448; e-mail: vgs@fq.uniovi.es

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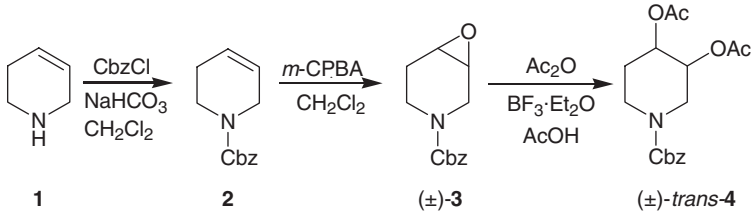
doi:10.1016/j.tet.2006.01.061



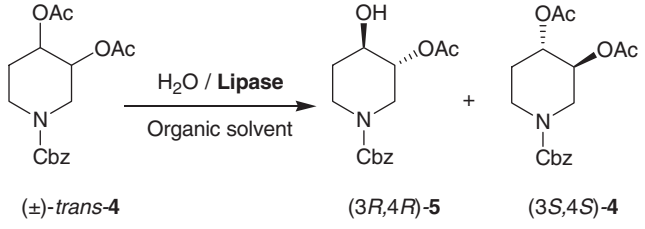
Scheme 1. Synthesis of (±)-*trans*-**4**.

Both routes require a large number of steps to afford the desired compound in low overall yields. Recently, Chang et al.[9] have reported the preparation of the optically pure trans-isomers using enantioselective *trans*-dihydroxylations or epoxidations of *N*-substituted 1,2,5,6-tetrahydropyridines, catalyzed by the bacterial strain *Sphingomonas* sp. HXN-200.

On the other hand, lipase-catalyzed processes in organic solvents are very advantageous alternatives to the conventional chemical reactions, that have been widely used for the preparation of optically pure cycloalkanediols[10] and carbosugars.[11] Nevertheless, to the best of our knowledge, the use of this methodology for the preparation of polyhydroxylated piperidines has not been studied until now. This paper describes the acetylation of *N*-protected *cis*- and *trans*-3,4-dihydroxypiperidine and the hydrolysis of their diacetylated derivatives catalyzed by lipases. Some of the results presented here have been rationalized using a computational approach.

2. Results and discussion

Our initial experiments were designed to find the most suitable lipase for catalyzing the hydrolysis of the diacetylated derivative (±)-*trans*-**4**. This substrate has been prepared almost in quantitative yield by treatment of 1-benzyloxycarbonyl-1,2,5,6-tetrahydropyridine (**2**) with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 and subsequent opening of the resulting epoxide (±)-**3** with acetic anhydride and $BF_3 \cdot Et_2O$ (Scheme 1).



Scheme 2. Enzymatic hydrolysis of (±)-*trans*-**4** in organic solvents.

First, we studied the hydrolysis of (±)-*trans*-**4**, in aqueous media (phosphate buffer, pH 7). In these conditions, the non-enzymatic hydrolysis occurred in competition with the enzymatic reaction. So, we decided to examine the process in organic solvents using a small amount of water as nucleophile (Scheme 2).

Since we had previously obtained good results in these hydrolytic conditions,[12] in a first set of experiments at 30 °C, acetonitrile was chosen as the reaction solvent and different lipases were used as biocatalysts: *Candida antarctica* A (CAL-A), *C. antarctica* B in two forms [Novozym 435 (CAL-B) and Chirazyme-L2 (CAL-B-L2)], *Candida rugosa* (CRL) and *Pseudomonas cepacia* (PSL-C). Three of the tested enzymes catalyzed the regioselective hydrolysis of (±)-*trans*-**4** affording only the 3-acetyl-4-hydroxy derivative (3*R*,4*R*)-**5** (Table 1, entries 1–3). In all cases, the enzymatic reactions were regioselective towards the acetyl group at *O*-4 position. This was confirmed by means of a two-dimensional ^1H–^1H COSY NMR analysis.

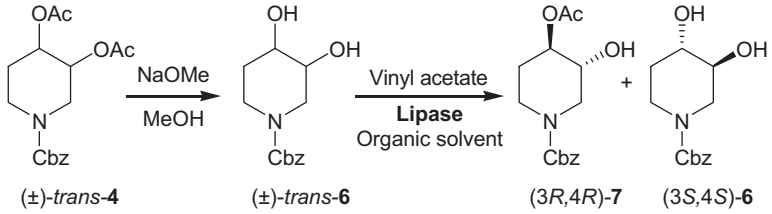
The enantioselectivity of the enzymatic hydrolysis was also very high. Both immobilized forms of lipase B from *C. antarctica*, CAL-B and CAL-B-L2, showed the highest enantioselectivities ($E>200$),[13] with excellent reaction rates, after 24 h a 49% conversion was achieved. The lipase PSL-C also showed a high enantioselectivity under these conditions, ($E=98$), but displayed a lower reaction rate. In these conditions, CAL-A and CRL did not show any activity.

The absolute configurations of the product and the remaining substrate were assigned as follows. Hydrolysis of (−)-*trans*-**5** using NaOMe in MeOH, afforded the dihydroxy derivative (+)-*trans*-**6**, whose specific rotation sign was in agreement with that reported for (3*R*,4*R*)-(+)-**6**, $[\alpha]_D^{20}$ +3.51 (*c* 0.76, $CHCl_3$).[9]

Table 1. Lipase catalyzed hydrolysis of (±)-*trans*-**4** in organic solvents at 30 °C

Entry	Lipase	Solvent	H_2O (equiv)	*t* (h)	*c* (%)[a]	ee_s (%)[b]	ee_p (%)[b]	*E*[c]
1	CAL-B	Acetonitrile	5	24	49	97	>99	>200
2	CAL-B-L2	Acetonitrile	5	24	49	96	>99	>200
3	PSL-C	Acetonitrile	5	24	8	9	98	98
4	CAL-B	1,4-Dioxane	5	48	47	89	>99	>200
5	CAL-B	Toluene	5	24	10	9	83	12
6	CAL-B	Acetonitrile	10	24	36	54	>99	>200

[a] Conversion, $c=ee_s/(ee_s+ee_p)$.
[b] Determined by chiral HPLC.
[c] Enantiomeric ratio, $E=\ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$.[13]



(±)-*trans*-**4** (±)-*trans*-**6** (3*R*,4*R*)-**7** (3*S*,4*S*)-**6**

Scheme 3. Enzymatic acetylation of (±)-*trans*-**6**.

Table 2. Lipase catalyzed acetylation of (±)-*trans*-**6** with vinyl acetate (VA) in organic solvents at 30 °C

Entry	Lipase	Solvent	VA (equiv)	*t* (h)	*c* (%)[a]	ee_s (%)[b]	ee_p (%)[b]	*E*[c]
1	CAL-B-L2	Acetonitrile	5	15	59	20	14	2
2	PSL-C	Acetonitrile	5	16	30	74	61	2
3	CAL-B	Acetonitrile	5	72	—	—	—	—
4	CAL-B	Acetonitrile	50	22	30	19	13	9
5	PSL-C	Toluene	5	15	62	39	24	2
6	PSL-C	^{t}BuOMe	5	15	68	25	11	2

[a] Conversion, $c=ee_s/(ee_s+ee_p)$.
[b] Determined by chiral HPLC.
[c] Enantiomeric ratio, $E=\ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$.[13]

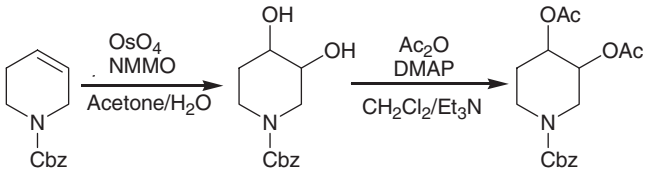
In order to improve the performance of the process, we studied the influence of the organic solvent on the enantioselectivity of the hydrolysis catalyzed by CAL-B. Thus, under the same reaction conditions, similar results were obtained in 1,4-dioxane than in acetonitrile (Table 1, entry 4), even though it is apparent that in acetonitrile were slightly higher. Lower reaction rate and enantioselectivity were achieved in toluene (Table 1, entry 5). Finally, an increase of the nucleophile concentration up to 10 equiv furnished lower conversion (Table 1, entry 6).

Another common approach for the resolution of racemic polyalcohols is the enzymatic transesterification reaction.[14] So, we decided to synthesize the dihydroxypiperidine (±)-*trans*-**6**, starting from the diacetate (±)-*trans*-**4** and using NaOMe in MeOH. Taking into account that the best enzymes for the hydrolysis are both CAL-B preparations and PSL-C, we examined the acetylation of the dihydroxy derivative (±)-*trans*-**6** catalyzed by these lipases (Scheme 3, Table 2).

First we carried out the process using 5 equiv of vinyl acetate as acyl donor and acetonitrile as solvent. In these conditions, CAL-B-L2 and PSL-C catalyzed the processes with good reaction rates (entries 1 and 2), however, both showed very low enantioselectivities. Surprisingly, in the process catalyzed by CAL-B, after 72 h of reaction only the unaltered substrate was recovered (entry 3). A 50-fold excess of the acylating agent was necessary to obtain a moderate reaction rate with this catalyst (entry 4). Also a slight improvement in the enantioselectivity was observed.

As expected according to the principle of microscopic reversibility, the regio- and stereochemical preferences of these lipases were the same as for the hydrolytic processes: the hydroxyl group at C-4 position of the piperidine ring was preferentially acetylated to afford the product (3*R*,4*R*)-**7**. In all cases, the formation of only one of the two possible regioisomers was observed. Unfortunately, the enantioselectivities of the enzymatic acylations were very low. Attempts to improve the results obtained in the reaction catalyzed by PSL-C, using different solvents such as toluene (entry 5) or *tert*-butyl methyl ether (entry 6) afforded also poor enantioselectivities, although these processes were faster.

In order to establish the scope of this enantiomer separation methodology, similar biocatalytic conditions were applied for the hydrolysis of (±)-*cis*-*N*-benzyloxycarbonyl-3,4-diacetoxypiperidine derivative. The substrate was synthesized according to the Scheme 4. Treatment of 1-benzyloxycarbonyl-1,2,5,6-tetrahydropyridine (**2**) with OsO_4 and *N*-methylmorpholine *N*-oxide (NMMO) yielded the diol (±)-*cis*-**8**, that was acetylated to the corresponding diacetate derivative (±)-*cis*-**9**.



2 (±)-*cis*-**8** (±)-*cis*-**9**

Scheme 4. Synthesis of (±)-*cis*-**8** and (±)-*cis*-**9**.

Unfortunately, the enzymatic hydrolysis carried out with this substrate showed, in all cases, very low reaction rates. For instance, the conversion of the reaction catalyzed by CAL-B in acetonitrile at 30 °C, using 5 equiv of water was less than 5% after 7 days of reaction. An increment of the temperature at 60 °C or an excess of the nucleophile up to 50-fold did not increase the reaction rate. Other lipases and different organic solvents were tested but no improvement on the reaction rate was obtained. Even more, when we analyzed the products using gas chromatography, we observed a mixture 1:1 of the two possible regioisomers.

Similar results were achieved in the acetylation of the dihydroxyderivative (±)-*cis*-**8**. Very low reactivities and

regioselectivities were found in all the tested conditions (data not shown).

Since all these lipase-catalyzed reactions were dramatically influenced by the stereochemistry of the chiral centres, we were very interested to rationalize the experimental facts observed in the hydrolysis of the *trans*-derivative (±)-**4** using a computational approach. Since the X-ray crystal structure of CAL-B was resolved,[15] several molecular modeling[16] and molecular dynamics studies[17] have been made in order to explain its excellent reactivity and selectivity with chiral alcohols and amines. These reports have been very useful to make rational design of this biocatalyst[18] with improved selectivities,[17b,19] or catalyzing through novel reaction pathways.[20] Thus, engineered CAL-B has been utilized to perform aldol,[21] Michael-type additions,[22] or Baeyer–Villiger reactions.[23]

The restricted volume of the active site of this lipase has been used to rationalize its special properties. So, viewed with the catalytic triad Asp187-His224-Ser105 oriented from left to right, CAL-B presents two well-differed subsites: (a) the large hydrophobic pocket (or acyl pocket) above the catalytic triad, which is lined by Leu140 and Leu144 at the top, Ile189 and Val190 on the left, as well as Val154 on the far right of the pocket. Deep in this subsite, Asp134 is on the left and Gln157 on the right; and (b) the medium-sized pocket (so called nucleophile or stereospecificity pocket) below it, which is crowded by Trp104 at the bottom and the Leu278-Ala287 helix to the right. The acyl chains lie in the large subsite, while nucleophiles bind to the medium-sized pocket. This smaller subsite has been found as the key factor to the enantioselectivity of secondary alcohols.[24]

Thus, the fast-reacting enantiomer (following Kazlauskas' rule,[25] usually the *R*), places the medium-sized substituent into this subsite and the big one into the acyl pocket, while the slow enantiomer has to introduce them in the opposite orientation, existing more unfavorable steric interactions. This general rule for acyclic alcohols, is not so clear for the cyclic one, although *R*-acylated or hydrolyzed enantiomers are usually obtained, in several cases it has been observed that for 1,2-*cis*-cyclohexanols, lipase-catalyzed processes are not achieved or are not selective, in spite of the excellent enantioselectivity for their trans counterparts.[26] There are no many examples of the use of molecular modeling to study CAL-B-catalyzed acylations or hydrolysis of cyclic alcohols.[16c,d,g] Here, we will use this tool to explain qualitatively the experimental results obtained for the hydrolysis at the 4-position in the cyclic diacetate (±)-**4**.

We have modeled the first tetrahedral intermediate (TI-1) since in the hydrolysis processes this is the structure where the ester is bound to the lipase, and is responsible for the enantioselection. Phosphonate analogues were used for mimicking this intermediate using the AMBER force field,[27] and several local energy minima were obtained for each enantiomer by means of a systematical search, as described elsewhere.[16g] The selection of the best structures was based in two main criteria: (a) those that presented the most possible of the six essential hydrogen-bonds [one between Asp187 and N_{δ}-His224; one between N_{ε}-His224 and O_{γ}-Ser105; one between N_{ε}-His224 and the proton-acceptor oxygen of the acetate; and three between the oxygen of the oxyanion formed with Gln106 (one) and Thr40 (two)]; and (b) those that minimized the steric clashes between the phosphonate and the amino acids, which surrounded the active site of CAL-B. In general, the nucleophile pocket restricted the binding of the substrate to such an extent that only a few conformations were obtained with the desired properties.

We started with the minimization of the intermediate for the hydrolysis in the 4-position of (3*R*,4*R*)-**4**. This enantiomer was experimentally the fast-reacting one. We used the X-ray structure 1LBS[16a] obtained from the Protein Data Bank (http://www.rcsb.org/pdb/), which presented an inhibitor phosphonate that was manually deleted, and then the substrate was built.[16g]

When the bulky benzyloxycarbonyl moiety was manually added to the phosphonate and minimized, two families of intermediates were usually acquired. In both cases, this group was accommodated into the narrow tunnel created by Ile189, Leu278, Ala281, Ala282, Ile285, and Val286, but with different orientations. Some of them (usually more stable), presented this moiety on the left, with the phenyl group close to Ile189 and Leu278, and the other one had the phenyl ring on the right side near Ala282, Ile285, and Val286 pointing to the solvent.

The best structure obtained for (3*R*,4*R*)-**4** is shown in Figure 2. As described previously,[16b,g] the cycle was placed into the stereospecificity pocket, with the acetyl group in the 3-position fitted into the acyl pocket, generating appropriate interactions between the methyl group with Val154 and the carbonyl moiety with the hydrophilic side chains of Gln157 and Thr40. The benzyloxycarbonyl group was on the left of the tunnel with the phenyl ring making stabilizing hydrophobic interactions with the side chains of Ile189,

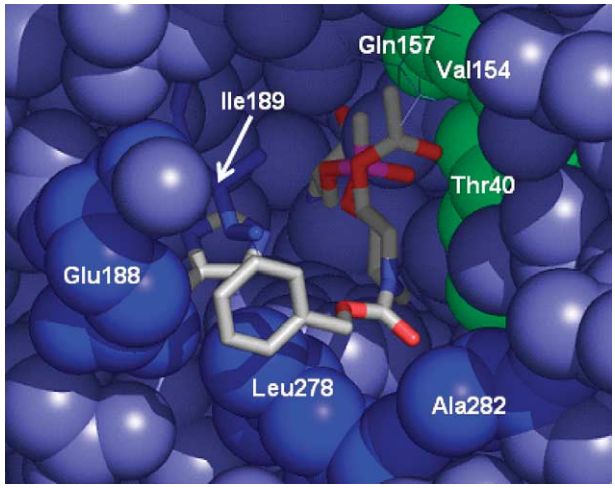


Figure 2. Best intermediate obtained for the CAL-B-catalyzed acylation of (3*R*,4*R*)-**4**. Amino acids, which make stabilizing interactions with the 3-*O*-acetyl group of the substrate are depicted in green, and those with the *N*-benzyloxycarbonyl moiety are shown in dark blue. The above image displays Leu144 in a line illustration and Ile189 in a stick representation to allow a better view of the large pocket of the lipase.

Glu188, and Leu278, with the carbonyl group making a H-bond with the NH-backbone of the Ala282 (3.03 Å), and the methylene moiety interacting with the hydrophobic side chain of Ala282. All key-hydrogen bonds were present in this structure.

When the intermediate for (3*S*,4*S*)-**4** was built and minimized, the best structure obtained presented several structural differences with regards to the (*R*,*R*)-enantiomer (Fig. 3). Although all essential-hydrogen bonds existed too, due to the acetyl moiety in 3-position bound into the medium nucleophile subsite, the carbocycle did not fit in this pocket, and the Cbz was not placed as stable as in the case of (3*R*,4*R*)-**4**. On the one hand, many destabilizing interactions appeared between the acetyl group and Trp104, Ala281 (both with the carbonyl), Gly39 (with the methyl), Leu278 and more importantly, with the catalytic His224 (both with the oxygen of the alcohol); on the other hand, the benzyloxycarbonyl moiety was placed at the top of the tunnel making unfavorable clashes between the carbonyl group and the hydrophobic chain of Ile285, and the phenyl ring with the carbonyl-backbone of Glu188.

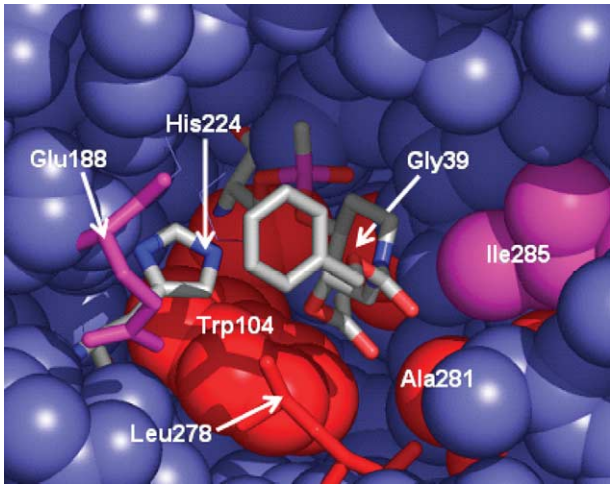


Figure 3. Best intermediate obtained for the CAL-B-catalyzed acylation of (3*S*,4*S*)-**4**. Amino acids, which make destabilizing interactions with the 3-*O*-acetyl group of the substrate are depicted in red and with the *N*-benzyloxycarbonyl moiety are shown in violet. The above image displays Ile189 in a line illustration and Glu188 and Leu278 in a stick representation to allow a better view of the phosphonate structure.

Molecular modeling studies agree with the experimental results, explaining the excellent enantioselectivity showed by CAL-B towards *trans*-diacetate **4**. Thus, although all essential hydrogen-bonds were present for both intermediates, better fitting of the (*R*,*R*)-enantiomer into the active site of the lipase, and more stabilizing interactions with the amino acids, which are surrounding it can be the key explanation for this resolution. Furthermore, in the (*S*,*S*)-structure, the acetyl in 3-position seemed to be very close from the catalytic His224, what might destabilize its position for the necessary transfer of the proton to the reactive carbonyl.

Looking at these structures, a plausible explanation for the bad enantioselectivity in the acetylation of the diol derivative *trans*-(±)-**6** could be established. Thus, the only difference between the first tetrahedral intermediate in the hydrolysis process, and the second tetrahedral intermediate in the acetylation reaction, is that in the first case at the 3-position there is an acetoxy group, and in the second one there is a hydroxyl moiety at this position. Some of the main structural differences obtained between both enantiomers were based on the altered interactions of the 3-*O*-acetyl group with the amino acids close to the lipase active-site. Thus, while for the (*R*,*R*) structure they were stabilizing (see green interactions in Fig. 2), in the (*S*,*S*) enantiomer they destabilized the intermediate (see red interactions in Fig. 3). Since this moiety is not present in the acetylation intermediates both structures would present less differences.

3. Conclusions

This paper describes an easy methodology for the preparation of both enantiomers of *trans*-1-benzyloxycarbonyl-3,4-dihydroxypiperidine and the (*R*,*R*)-3-*O*-monoacetylated derivative via a lipase catalyzed hydrolysis. Thus, among all the lipases tested, CAL-B presented the best results, allowing us to obtain one of the six possible products of this reaction (four monoalcohols and two diols) with high yield, showing this process total regio- and enantioselectivity at the same time. Attempts to acetylate the *trans*-diol (±)-**6** afforded good regioselectivity but lower reaction rates and enantioselectivities.

Molecular modeling has been used in order to rationalize these experimental facts. Thus, phosphonate analogues of both enantiomers of diacetate **4** were built and minimized, obtaining several structural divergences that can explain the excellent enantioselectivity obtained in the hydrolysis reaction with this substrate.

On the other hand, from the results shown in this paper, it is apparent that the cis-isomer is not a suitable substrate for the tested lipases, neither through hydrolysis nor acylation processes.

Taking into account the simplicity and easy scale-up of lipase catalyzed reactions,[28] it is noteworthy the applicability of this method for the preparation of the gastroprokinetic agent cisapride and other optically pure structures with highly interesting biological properties.

4. Experimental

4.1. General remarks

Enzymatic reactions were carried out in a Gallenkamp incubatory orbital shaker. Immobilized *C. antarctica* lipase B, CAL-B Novozym 435 (7300 PLU/g), was a gift from Novo Nordisk co. *C. antarctica* lipase B (CAL-B-L2, CHIRAZYME L-2, c-f, C3, ≥400 U/g), *Candida rugosa* lipase (CRL, CHIRAZYME L3, >250 U/mg) and *C. antarctica* lipase A (CAL-A, CHIRAZYME L5, 1 kU/g) were supplied by Roche Molecular Biochemicals. *P. cepacia* lipase lyophilized (PSL, 30000 U/g) and immobilized (PSL-C, 783 U/g) are commercialized by Amano Pharmaceuticals.

Chemical reagents were commercialized by Aldrich, Fluka, Lancaster or Prolabo. Solvents were distilled over an appropriate desiccant under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Optical rotations were measured using a Perkin-Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H, ^{13}C NMR and DEPT spectra were recorded in a Bruker AC-300, Bruker AC-300 DPX and Bruker NAV-400 spectrometer using $CDCl_3$ as solvent. The chemical shift values (δ) are given in parts per million. Positive electrospray ionisation (ESI^+) was used to record mass spectra on an Hewlett-Packard 110 LC/MSD Series spectrometers. The enantiomeric excesses were determined by chiral HPLC analysis on a Hewlett-Packard 1100, LC liquid chromatograph, using a CHIRALCEL OD for the diacetylated derivative **4**. The diol **6** and the monoacetylated products **5** and **7** were first acetylated to convert them into the diacetate derivative **4** and then analyzed.

Molecular modeling. The program Insight II, version 2000.1, was used for viewing the structures. The geometric optimizations were performed using Discover, version 2.9.7 (Accelrys, San Diego CA, USA), using the AMBER force field.[27] The distance dependent dielectric constant was set to 4.0 to mimic the electrostatic shielding of the solvent and the 1–4 van der Waals interactions were scaled to 50%. The crystal structure for the CAL-B (1LBS[16a]) was obtained from the Protein Data Bank (www.rcsb.org/pdb/). Protein structures in Figures 2 and 3 were generated using PyMOL 0.97.[29] The methodology followed for localization of energy minima structures by means of a systematically search has been described elsewhere.[16g]

4.1.1. Synthesis of 1-benzyloxycarbonyl-1,2,5,6-tetrahydropyridine, (2). Benzyl chloroformate (3.8 mL, 26.3 mmol) was added dropwise to a stirred mixture of 1,2,5,6-tetrahydropyridine **1** (2.0 g, 21.9 mmol) and $NaHCO_3$ (2.8 g, 26.3 mmol) in H_2O (50 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. After this time CH_2Cl_2 (50 mL) and 5% aqueous Na_2CO_3 (20 mL) were added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to afford the Cbz-protected product **2** as a yellow oil (4.4 g, 85%). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 7.36 (m, 5H), 5.81 (br s, 1H), 5.64 (br s, 1H), 5.16 (s, 2H), 3.96 (m, 2H), 3.57 (m, 2H), 2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.2 (CO), 136.6 (C), 128.2 (CH), 127.7 (CH), 127.6 (CH), 125.1 (CH), 124.8 (CH), 66.7 (CH_2), 43.1 (CH_2), 40.1 (CH_2), 24.7 (CH_2); IR (CH_2Cl_2): ν 1713, 1630, 1425 cm^{-1}; MS (ESI^+, *m*/*z*): 218 [$(M+H)^+$, 100%], 240 [$(M+Na)^+$, 30].

4.1.2. Synthesis of (±)-1-benzyloxycarbonyl-3,4-epoxypiperidine, [(±)-3]. A solution of *m*-CPBA (4.3 g, 25.0 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a stirred solution of **2** (3.9 g, 18.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h, then washed with 5% aqueous K_2CO_3 solution (20 mL), followed by a saturated aqueous NaCl solution (20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford the product (±)-**3** as a yellow oil (3.8 g, 90%). ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 7.36 (m, 5H), 5.10 (s, 2H), 3.85–3.72 (m, 2H), 3.44 (m, 2H), 3.23 (m, 2H), 2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.2 (CO), 136.3 (C), 128.4 (CH), 128.0 (CH), 127.8 (2 CH), 67.4 (CH_2), 55.3 (2 CH), 47.5 (CH_2), 41.3 (CH_2), 21.1 (CH_2); IR (CH_2Cl_2): ν 1715, 1428, 1212 cm^{-1}; MS (ESI^+, *m*/*z*): 234 [$(M+H)^+$, 10%], 256 [$(M+Na)^+$, 100%].

4.1.3. Preparation of (±)-*trans*-3,4-diacetoxy-1-benzyloxycarbonylpiperidine, [(±)-*trans*-4]. To a solution of (±)-**3** (0.95 g, 4.1 mmol) in acetic acid (35 mL), acetic anhydride was added (1.6 mL, 17 mmol). Boron trifluoride etherate (507 μL, 4.1 mmol) was slowly added, and the mixture was stirred at room temperature for 4 h. An aqueous saturated solution of $NaHCO_3$ (10 mL) was added, and the mixture extracted with EtOAc (20 mL). The organic phase was washed with saturated aqueous Na_2CO_3 solution (20 mL) followed by saturated aqueous NaCl solution (20 mL), and then was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford the product (±)-*trans*-**4** as a yellow oil (1.2 g, 90%). ^{1}H NMR ($CDCl_3$, 400.13 MHz, 40 °C): δ 7.38 (m, 5H), 5.18 (d, 2H), 4.98 (s, 1H), 4.83 (m, 1H), 3.84 (dd, 1H, $^3J_{HH}$=3.45, 13.80 Hz), 3.71–3.47 (m, 3H), 2.11–2.01 (m, 1H), 2.10 (s, 3H), 1.97 (s, 3H), 1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 40 °C): δ 169.7 (CO), 169.5 (CO), 155.1 (CO), 136.2 (C), 128.3 (CH), 127.8 (CH), 127.6 (CH), 68.0 (2 CH), 67.1 (CH_2), 44.1 (CH_2), 40.1 (CH_2), 26.1 (CH_2), 20.8 (CH_3); IR (CH_2Cl_2): ν 1737, 1712, 1425, 1210 cm^{-1}; MS (ESI^+, *m*/*z*): 358 [$(M+Na)^+$, 100%].

4.1.4. Enzymatic hydrolysis of (±)-*trans*-4. The reaction mixture containing (±)-*trans*-**4** (50 mg, 0.15 mmol), the appropriate amount of H_2O (see Table 1) and the lipase (50 mg) in the corresponding organic solvent (50 mL) was shaken at 30 °C and 250 rpm in an orbital shaker. The progress of the reaction was monitored by TLC (hexane/EtOAc 1:1) until the achievement of the required conversion. Then, the enzyme was removed by filtration and washed with the corresponding organic solvent. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford the monoacetylated product (3*R*,4*R*)-**5** and the remaining substrate (3*S*,4*S*)-**4**.

4.1.4.1. (3*S*,4*S*)-3,4-Diacetoxy-1-benzyloxycarbonylpiperidine, [(3*S*,4*S*)-4]. Yellow oil $[\alpha]_D^{25}$ +30.6 (*c* 1, $CHCl_3$), ee>99%.

4.1.4.2. (3*R*,4*R*)-3-Acetoxy-1-benzyloxycarbonyl-4-hydroxypiperidine, [(3*R*,4*R*)-5]. Yellow oil $[\alpha]_D^{25}$ −20.2 (*c* 1, $CHCl_3$), ee>99%. ^{1}H NMR ($CDCl_3$, 400.13 MHz, 40 °C): δ 7.38 (m, 5H), 5.16 (2s, 2H), 4.66 (m, 1H), 4.03 (dd, 1H, $^3J_{HH}$=3.32, 13.32 Hz), 3.88–3.80 (m, 3H), 3.25 (m, 1H), 2.22 (br s, 1H, OH), 2.06 (s, 3H), 2.04–2.00 (m, 1H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 40 °C): δ 170.6 (CO), 155.3 (CO), 136.6 (C), 128.5 (CH), 128.0 (CH), 127.9 (CH), 72.5 (CH), 69.4 (CH), 67.3 (CH_2), 44.4 (CH_2),

40.8 (CH_2), 30.8 (CH_2), 20.9 (CH_3); IR (CH_2Cl_2): ν 3621, 1728, 1715, 1430, 1213 cm^{-1}; MS (ESI^+, *m/z*): 316 [$(M+Na)^+$, 100%].

4.1.5. Preparation of (±)-*trans*-1-benzyloxycarbonyl-3,4-dihydroxypiperidine, [(±)-*trans*-6]. To a solution of (±)-*trans*-**4** (1.2 g, 3.7 mmol) in MeOH (35 mL), a solution of a catalytic amount of NaOMe in MeOH (1 mL) was added. The mixture was stirred for 2 h, and then the solvent was evaporated under reduced pressure and the product was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford the product (±)-*trans*-**6** as a yellow oil (0.85 g, 94%). ^1H NMR ($CDCl_3$, 400.13 MHz, 40 °C): δ 7.35 (m, 5H), 5.13 (s, 2H), 4.25 (dd, 1H, $^3J_{HH}=3.23$, 13.10 Hz), 4.11–4.08 (m, 3H), 3.55–3.47 (m, 2H), 1.98 (m, 1H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 40 °C): δ 155.3 (CO), 136.5 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 71.8 (2 CH), 67.4 (CH_2), 47.8 (CH_2), 42.1 (CH_2), 31.4 (CH_2); IR (CH_2Cl_2): ν 3618, 3447, 1710, 1425, 1204 cm^{-1}; MS (ESI^+, *m/z*): 252 [$(M+H)^+$, 30%], 274 [$(M+Na)^+$, 100%].

4.1.6. Enzymatic acetylation of (±)-*trans*-6. The reaction mixture containing (±)-*trans*-**6** (50 mg, 0.15 mmol), vinyl acetate (see Table 2) and the lipase (50 mg) in the corresponding organic solvent (50 mL) was shaken at 30 °C and 250 rpm in an orbital shaker. The progress of the reaction was monitored by TLC using the solvent system hexane/EtOAc 1:1 until the required conversion was achieved. Then, the enzyme was removed by filtration and washed with the corresponding organic solvent. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford the monoacetylated product (3*R*,4*R*)-**7** and the remaining substrate (3*S*,4*S*)-**6**.

4.1.6.1. (3*S*,4*S*)-1-Benzyloxycarbonyl-3,4-dihydroxypiperidine, [(3*S*,4*S*)-6]. Yellow oil $[\alpha]_D^{25}$ −3.7 (*c* 1, $CHCl_3$), ee>99%.

4.1.6.2. (3*R*,4*R*)-4-Acetoxy-1-benzyloxycarbonyl-3-hydroxypiperidine, [(3*R*,4*R*)-7]. Yellow oil $[\alpha]_D^{25}$ −12.2 (*c* 1, $CHCl_3$), ee>99%. ^1H NMR ($CDCl_3$, 400.13 MHz, 40 °C): δ 7.38 (m, 5H), 5.15 (2s, 2H), 4.77 (m, 1H), 4.13 (dd, 1H, $^3J_{HH}=3.16$, 13.52 Hz), 3.97–3.87 (m, 3H), 3.19–2.92 (m, 1H), 2.52 (br s, 1H, OH), 2.13 (s, 3H), 2.12–2.05 (m, 1H), 1.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 40 °C): δ 171.0 (CO), 155.4 (CO), 136.5 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 74.7 (CH), 68.8 (CH), 67.4 (CH_2), 47.7 (CH_2), 41.4 (CH_2), 28.2 (CH_2), 21.1 (CH_3); IR (CH_2Cl_2): ν 3520, 1717, 1432, 1218 cm^{-1}; MS (ESI^+, *m/z*): 294.1 [$(M+H)^+$, 40%], 316.1 [$(M+Na)^+$, 100%].

4.1.7. Preparation of (±)-*cis*-1-benzyloxycarbonyl-3,4-dihydroxypiperidine, [(±)-*cis*-8]. To a solution of **2** (1.0 g, 4.6 mmol) in acetone–H_2O (1/1, 8 mL), *N*-methylmorpholine *N*-oxide (0.8 g, 6.8 mmol) was added, followed by a solution of OsO_4 in *tert*-butanol (0.8 mL, 2.5% w/v), then the mixture was stirred for 5 days at room temperature. A saturated solution of $Na_2S_2O_5$ (60 mL) was added and the mixture was extracted with EtOAc (5×40 mL); the organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:2) to afford the product (±)-*cis*-**8** as a yellow oil (0.88 g, 76%). ^1H NMR ($CDCl_3$, 400.13 MHz, 0 °C): δ 7.35 (m, 5H), 5.12 (2s, 2H), 3.84–3.30 (m, 6H), 1.82 (m, 1H), 1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 0 °C): δ 155.8 (CO), 136.4 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 68.4 (CH), 67.8 (CH), 67.2 (CH_2), 46.1 (CH_2), 40.1 (CH_2), 29.6 (CH_2); IR (CH_2Cl_2): ν 3534, 3427, 1715, 1423, 1210 cm^{-1}; MS (ESI^+, *m/z*): 252 [$(M+H)^+$, 100%].

4.1.8. Synthesis of (±)-*cis*-3,4-diacetoxy-1-benzyloxycarbonylpiperidine, [(±)-*cis*-9]. To a solution at 0 °C of (±)-*cis*-**8** (0.9 g, 3.6 mmol) in CH_2Cl_2 (8 mL), Et_3N (2.0 mL, 14.3 mmol) and a catalytic amount of DMAP, acetic anhydride (1.4 mL, 14.3 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 8 h. Then the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:1) to afford the product (±)-*cis*-**9** as a yellow oil (1.1 g, 90%). ^1H NMR ($CDCl_3$, 400.13 MHz, 0 °C): δ 7.38 (m, 5H), 5.22–5.03 (m, 4H), 4.07–3.95 (m, 2H), 3.89–3.84 (m, 2H), 2.08 (s, 3H), 2.02–1.81 (m, 2H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, 0 °C): δ 170.5 (2CO), 155.5 (CO), 136.4 (C), 128.7 (CH), 128.3 (CH), 128.0 (CH), 69.5 (2CH), 67.5 (CH_2), 44.8 (CH_2), 41.2 (CH_2), 26.5 (CH_2), 21.1 (CH_3); IR (CH_2Cl_2): ν 1740, 1716, 1432, 1207 cm^{-1}; MS (ESI^+, *m/z*): 358 [$(M+Na)^+$, 100%].

4.1.9. Enzymatic hydrolysis and acetylation of (±)-*cis*-8 and (±)-*cis*-9. These reactions were carried out using the same procedures as described as for the trans derivatives.

Acknowledgements

This work was supported by the Ministerio de Ciencia y Tecnología (PTR1995-0775-OP). L.F.S. thanks MEC for a predoctoral fellowship. V.G.-F. thanks MEC for a personal grant (Juan de la Cierva Program). We express our appreciation to Novo Nordisk Co. for the generous gift of the lipase Novozym 435.

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An efficient synthesis of (*E*)-α,β-unsaturated ketones and esters with total stereoselectivity by using chromium dichloride

José M. Concellón,* Humberto Rodríguez-Solla and Carmen Méjica

Departamento de Química Orgánica e Inorgánica, Facultad de Químicas, Universidad de Oviedo, Julián Clavería, 8, 33071 Oviedo, Spain

Received 21 December 2005; accepted 17 January 2006

Available online 13 February 2006

Abstract—(*E*)-α,β-Unsaturated ketones **1** or esters **2** can be obtained with complete stereoselectivity by reaction of different 2-chloro-3-hydroxy ketones **3** or esters **4** and $CrCl_2$. A comparative study of the results of synthesis of ketones **1** with $CrCl_2$ or samarium is performed. A mechanism to explain both β-elimination reactions has been proposed.
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1. Introduction

The development of methodologies for the formation of carbon–carbon double bonds could be considered one of the most important challenges in organic synthesis.[1]

α,β-Unsaturated ketones are one of the most useful starting materials to prepare different polifunctionalized organic compounds and have been widely used in organic synthesis.[2] The stereoselective synthesis of α,β-unsaturated ketones[3] has been extensively developed and is generally achieved by condensation,[4] oxidation,[5] elimination,[6] acylation[7] reactions, and by insertion of carbon monoxide[8] among others. However, in most of these syntheses, the stereoselective control of the carbon–carbon double bond formation remains unsolved. The poor yields or the difficult preparation of the starting materials also limit other methodologies.

Respect to α,β-unsaturated esters, its preparation[9] is generally achieved by C=C bond formation by Wittig,[10] Horner–Emmons,[11] Heck[12] or Peterson[13] reactions. Another useful approach employs the Cope rearrangement,[14] utilising acetylenic compounds[15] or using α-mercaptoesters derivatives.[16] However, most of these methodologies, give a mixture of diastereoisomers, and poor yields are obtained. In other cases, poor generality is a major limitation. In addition, the preparations of α,β-unsaturated esters in which C=C bond is trisubstituted are scarce.[17]

The sum of all theses features would make a general and highly stereoselective method to prepare α,β-unsaturated ketones and esters from easily available starting material of great interest.

Recently, we describe the preliminary results of a new methodology to obtain α,β-unsaturated esters **2** with total diastereoselectivity by treatment of the easily available α-halo-β-hydroxyesters **4** with chromium dichloride.[18] A $CrCl_2$-promoted sequential condensation–elimination reaction of various aldehydes with ethyl dibromoacetate to afford α,β-unsaturated esters in high yield and with total selectivity has been also published.[19] In addition, we have also reported a synthesis of α,β-unsaturated ketones from 2-chloro-3-hydroxy ketones by using SmI_2 or SmI_3.[20]

In the present work, as part of our interest on developing new selective syntheses of functionalized alkenes, we wish to extend these previous results and to explore the possible use of chromium dichloride to carry out other β-elimination reactions. Concretely, here we report the preparation of (*E*)-α,β-unsaturated ketones **1** and esters **2** with total stereoselectivity promoted by $CrCl_2$.

2. Results and discussion

2.1. Synthesis of α,β-unsaturated ketones 1

The treatment of a solution of 2-chloro-3-hydroxy ketones **3** in refluxing THF with 3 equiv of $CrCl_2$ during 4 h afforded, after acid hydrolysis,[21] the corresponding α,β-unsaturated ketones **1** in high yields and with total (*E*)-selectivity (Scheme 1 and Table 1).

Keywords: Diastereoisomers; α-β-unsaturated ketones; Ketones; Stereoselectivity; α,β-unsaturated esters.
* Corresponding author. Tel.: +34 985103457; fax: +34 985103446; e-mail: jmcg@uniovi.es

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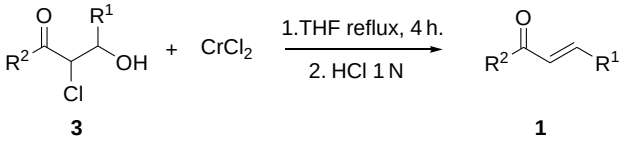
doi:10.1016/j.tet.2006.01.052



3 1

Scheme 1. Synthesis of (*E*)-α,β-unsaturated ketones **1**.

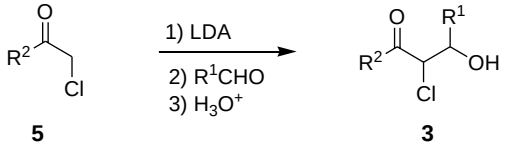
Table 1. Synthesis of (*E*)-α,β-unsaturated ketones **1**

Entry	1[a]	R^1	R^2	Yield		
				1 (%)[b]		**3** (%)[c]
				$CrCl_2$	SmI_2[d]	
1	**1a**	*n*-C_4H_9	Ph	81	96 (72)	82
2	**1b**	*n*-C_7H_{15}	Ph	84	98 (91)	85
3	**1c**	Cyclohexyl	Ph	91	67 (72)	93
4	**1d**	Ph	Ph	72	73 (80)	80
5	**1e**	*i*-Bu	Ph	85	—[e]	88
6	**1f**	$CH_3CH(Ph)$	Ph	68	—[e]	67
7	**1g**	*n*-C_4H_9	*n*-C_4H_9	77	—[e]	64
8	**1h**	Ph	*n*-C_4H_9	71	82 (70)	92
9	**1i**	*n*-C_4H_9	*t*-Bu	89	65 (58)	79
10	**1j**	4-MeO-Ph	Me	91	—[e]	61

[a] Three equivalents of $CrCl_2$ were used in all cases.
[b] Isolated yield based on the starting α-chloro-β-hydroxy ketones **3**.
[c] Isolated yield based on the starting α-chloroketones **5**.
[d] Isolated yield by using SmI_3, in parenthesis.
[e] This reaction was not performed by using SmI_2 or SmI_3.

The diastereoisomeric excess was determined on the crude products by ^{1}H NMR spectroscopy (300 MHz) and GC–MS, showing the presence of a single stereoisomer. The (*E*)-configuration of the C–C double bond in products **1** was assigned on the basis of ^{1}H NMR coupling constants observed for the olefinic protons.[22] These values are in agreement with those previously reported (**1a–d**).[20]

The starting ketones **3** were easily prepared by reaction of the corresponding lithium enolates of α-haloketones **5** with aldehydes at −78 °C[20] (Scheme 2 and Table 1).



5 3

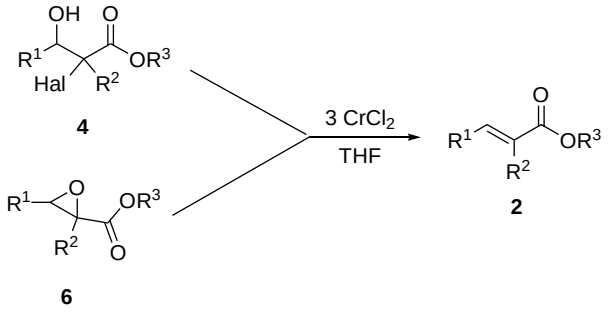
Scheme 2. Preparation of starting compounds **3**.

Several comments are worth of mention: (1) interestingly, although different mixtures of stereoisomers (ranging from 1:1 to 4:1) of starting materials **3** were used, the corresponding α,β-unsaturated ketones **1** were obtained with total (*E*)-stereoselectivity. (2) The method presents wide applicability. Both aromatic and aliphatic (linear, branched or cyclic) (*E*)-α,β-unsaturated ketones **1** can be obtained (Table 1). (3) In some cases (**1a–d**, **1i**) the crude reaction products were obtained with high purity and no purification by column chromatography was necessary.

As was previously described,[20] the same transformation (synthesis of (*E*)-α,β-unsaturated ketones **1** from the same α-chloro-β-hydroxy ketones **3**) can also accomplish by using SmI_3 or SmI_2. Results in Table 1 show that, in general, similar or slightly higher yields of α,β-unsturated ketones were obtained by using $CrCl_2$ instead of SmI_3 or SmI_2, the stereoselectivity being complete in both cases, the two proposed methods can be complementary and represent valuable methods for the preparation α,β-unsaturated ketones.

2.2. Synthesis of α,β-unsaturated esters 2

Our first attempts were carried out using α-chloro-β-hydroxyesters and α,β-epoxyesters in order to determine suitable starting materials. Thus, treatment of a solution of ethyl 2-chloro-3-hydroxy-2-methyldecanoate **4d** in THF with $CrCl_2$ at reflux during 4 h afforded ethyl 2-methyldecan-2-enoate **2d**, after hydrolysis, with total diastereoselectivity (de>98%) and 64% yield. The same treatment of 2,3-epoxy-2-methyl decanoate **6d**, gave **2d** with slightly lower diastereoselection (de 95%) and yield (51%). Based on these results, preparation of α,β-unsaturated esters was performed from compounds **4**. So, the treatment of different 2-halo-3-hydroxyesters **4** with $CrCl_2$ (3 equiv) at room temperature afforded (*E*)-α,β-unsaturated esters with total diastereoselectivity (Scheme 3). Table 2 summarizes the obtained results.



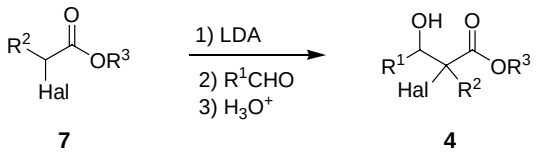
Scheme 3. Synthesis of (*E*)-α,β-unsaturated esters **2**.

Table 2. Synthesis of (*E*)-α,β-unsaturated esters **2**

Entry	2[a]	R^1	R^2	R^3	Hal	Yield	
						4 (%)[b]	**2** (%)[c]
1	**2a**	*n*-C_7H_{15}	H	Me	Cl	87	65
2	**2b**	*p*Cl–C_6H_4	H	Me	Cl	69	68
3	**2c**	MeCH(Ph)	H	Me	Cl	75	52
4	**2d**	*n*-C_7H_{15}	Me	Et	Cl	93	64
5	**2e**	Cyclohexyl	Me	Et	Cl	95	65
6	**2f**	Ph	Me	Et	Cl	97	60
7	**2g**	*p*MeO–C_6H_4	Me	Et	Cl	91	70
8	**2h**	Ph	*n*-C_6H_{13}	Et	Br	92	65
9	**2i**	Ph	*n*-C_5H_{11}	Et	Br	89	90
10	**2j**	Cyclohexyl	Me	*i*-Pr	Cl	84	70

[a] In all cases de was >98%. It was determinated on crude reaction products by ^{1}H NMR spectroscopy and GC–MS.
[b] Isolated yield after column chromatography based on compound **7**.
[c] Isolated yield after column chromatography based on compound **4**.

The starting materials **4** were easily prepared by reaction of the corresponding lithium enolates of α-haloesters **7** (generated by treatment of α-haloesters with LDA at −78 °C) with aldehydes at −78 °C (Scheme 4).



Scheme 4. Preparation of starting compounds **4**.

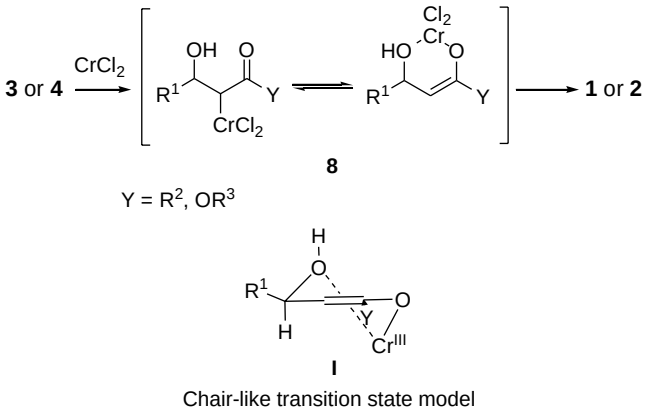
α,β-Unsaturated esters **2** were also obtained with total diastereoselectivity from mixtures of diastereoisomers (roughly 1:1) of the starting compounds **4**. ^{1}H NMR spectroscopy (300 MHz) and GC–MS of the crude reaction of products **2**, shown the presence of a single diastereoisomer.

The *E* stereochemistry in the C–C double bond of α,β-unsaturated esters **2** was assigned on the basis of the value of ^{1}H NMR coupling constants between the olefinic protons of compound **2a–c** (Table 2, entries 1–3);[23] by NOE experiments in the case of the trisubstituted compounds **2g**, and **2i** or by comparison with the ^{1}H and ^{13}C NMR spectra of authentic samples described in the literature (**2d–e**).[24]

This methodology for obtaining α,β-unsaturated esters is also general: R^1, R^2 and R^3 can be widely varied. R^1 can be aliphatic (linear, branched or cyclic) or aromatic, and substitution at the C2 position could also be changed using different esters to prepare the starting compounds **4** (Scheme 4). Interestingly, the diastereoselectivity was unaffected by changing the carboxyl ester (Table 2, entries 5 and 10) in opposition to the Wittig olefination reaction.[25]

2.3. Mechanism

The observed results and the *E*-configuration of products **1** or **2** can be explained (Scheme 5) assuming the initial metallation of the C–Cl bond of **3** or **4** by two consecutive single electron transfers from $CrCl_2$ to afford a chromium enolate like **8**. The Cr^{III} center would be coordinated to the oxygen atom of the alcohol to produce a six-membered ring. Tentatively, we assume the involvement of a chair-like transition state model **I**, with the R^1 group adopting an equatorial orientation to avoid 1,3-diaxial interactions. Elimination from **I** leads to α,β-unsaturated ketones **1** or esters **2** with total (*E*)-stereoselectivity.



Scheme 5. Proposed mechanism.

Synthesis of **1** or **2** with total stereoselection from a mixture of diastereoisomers of **3** or **4** could be also explained taking into account that after reaction of **3** or **4** with $CrCl_2$, the stereogenic C–Cl center suffers enolization. Therefore, the mixture of diastereoisomers **3** or **4** is transformed to a mixture of enantiomers **8**, which eliminates to afford a single (*E*)-stereoisomer **1** or **2**.

3. Conclusion

In conclusion, an easy, simple and general method has been developed to synthesise α,β-unsaturated ketones **1** or esters **2** in high yield and with total (*E*)-stereoselectity from readily available 2-halo-3-hydroxy ketones **3** or esters **4** and being promoted by chromium dichloride.

4. Experimental

4.1. General remarks

Reactions which required an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were commercially available and were used without further purification. Silica gel for flash chromatography was purchased from Merck (230–400 mesh), and compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded at 200, 300 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 75 or 100 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants *J* are reported in Hz. The diastereoisomeric excesses were obtained from ^{1}H NMR analysis and GC–MS of crude products. GC–MS and HRMS were measured at 70 eV. Only the most important IR absorptions (cm^{-1}) and the molecular ions and/or base peaks in MS are given.

4.2. General procedure for the synthesis of starting compounds 3

To a −78 °C stirred solution of the α-haloketone (9.7 mmol) in dry THF (8 mL) was added dropwise lithium diisopropylamide [prepared from MeLi (6.5 mL of 1.5 M solution in ether) and diisopropylamine (1.4 mL, 10 mmol) in THF (50 mL) at 0 °C]. After stirring for 10 min, a solution of the aldehyde (5 mmol) in dry THF (4.5 mL) was added dropwise at −78 °C and the mixture was stirred for 2 h. Then the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl (20 mL). Usual workup provided the corresponding α-halo-β-hydroxy ketone **3**, which was purified by flash column chromatography on silica gel (hexane/EtOAc 10:1).

4.2.1. 2-Chloro-3-hydroxy-1-phenylheptan-1-one (3a). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–7.23 (m, 10H), 5.11 (d, *J*=4.3 Hz, 1H), 4.93 (d, *J*=7.9 Hz, 1H), 4.22–4.14 (m, 2H), 2.95 (s, 2H), 1.92–1.86 (m, 12H), 0.96–0.89

(m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.4 (C), 194.3 (C), 134.5 (2×C), 134.0 (CH), 133.9 (2×CH), 128.9 (4×CH), 128.7 (2×CH), 128.6 (CH), 71.6 (CH), 70.8 (CH), 60.6 (CH), 57.6 (CH), 33.2 (CH_2), 32.3 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 22.3 (2×CH_2), 13.8 (CH_3), 13.7 (CH_3); MS (70 eV, EI) *m/z* (%) 205 $[M-Cl]^+$ (3), 154 (12), 123 (25), 105 (100), 78 (14), 77 (44), 51 (12), 41 (19); IR (neat): $\tilde{\nu}$=3476, 3086, 2956, 2870, 1688, 1596, 1448 cm^{-1}; R_f=0.36 (hexane/EtOAc 5:1).

4.2.2. 2-Chloro-3-hydroxy-1-phenyldecan-1-one (3b). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.45 (m, 10H), 5.09 (d, J=4.0 Hz, 1H), 4.94 (d, J=7.7 Hz, 1H), 4.25–4.18 (m, 2H), 3.32 (s, 2H), 2.01–1.15 (m, 24H), 0.89–0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.4 (C), 194.2 (C), 134.5 (C), 134.2 (C), 133.9 (2×CH), 133.8 (2×CH), 128.8 (4×CH), 128.6 (2×CH), 71.5 (CH), 70.9 (CH), 60.7 (CH), 57.6 (CH), 33.5 (2×CH_2), 31.6 (2×CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 22.4 (4×CH_2), 13.9 (2×CH_3); MS (70 eV, EI) *m/z* (%) 247 $[M-Cl]^+$ (5), 158 (5), 154 (16), 123 (20), 106 (8), 105 (100), 78 (13), 77 (38), 43 (21), 41 (22); IR (neat): $\tilde{\nu}$=3387, 3063, 2951, 2923, 2855, 1689, 1596, 1581, 1464, 1449 cm^{-1}; R_f=0.45 (hexane/EtOAc 5:1).

4.2.3. 2-Chloro-3-cyclohexyl-3-hydroxy-1-phenylpropan-1-one (3c). White solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00–7.26 (m, 5H), 5.32 (d, J=2.8 Hz, 1H), 3.89 (ddd, J=7.9, 4.8, 2.8 Hz, 1H), 3.06 (d, J=4.8 Hz, 1H), 2.10–2.04 (m, 1H), 1.85–1.53 (m, 5H), 1.48–0.84 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5 (C), 134.1 (C), 134.0 (CH), 128.8 (2×CH), 128.7 (2×CH), 75.0 (CH), 59.1 (CH), 40.1 (CH), 28.8 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.5 (CH_2); MS (70 eV, EI) *m/z* (%) 231 $[M-Cl]^+$ (9), 156 (7), 154 (20), 147 (19), 123 (9), 105 (100), 83 (12), 82 (13), 78 (25), 77 (72), 73 (28), 55 (41), 51 (20); IR (neat): $\tilde{\nu}$=3507, 3058, 2923, 2852, 1683, 1596, 1580, 1448, 1392, 1265, 1208, 1071 cm^{-1}; R_f=0.47 (hexane/EtOAc 5:1).

4.2.4. 2-Chloro-3-hydroxy-1,3-diphenylpropan-1-one (3d). Data on the 65:55 mixture of diastereoisomers. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05–7.28 (m, 20H), 5.37 (d, J=5.7 Hz, 1H), 5.31 (d, J=5.7 Hz, 1H), 5.30 (d, J=8.5 Hz, 1H), 5.20 (d, J=8.5 Hz, 1H), 3.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3 (C), 194.0 (C), 139.1 (C), 138.5 (C), 134.5 (2×C), 134.0 (CH), 128.9 (CH), 128.7 (4×CH), 128.1 (2×CH), 128.4 (4×CH), 128.3 (4×CH), 128.2 (2×CH), 127.1 (CH), 126.7 (CH), 74.5 (CH), 73.2 (CH), 61.3 (CH), 57.4 (CH); IR (neat): $\tilde{\nu}$=3504, 3087, 3032, 1964, 1903, 1695, 1595, 1580, 1453, 1307, 1062 cm^{-1}; R_f=0.34 (hexane/EtOAc 5:1).

4.2.5. 2-Chloro-3-hydroxy-5-methyl-1-phenylhexan-1-one (3e). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61–7.45 (m, 10H), 7.99 (d, J=7.9 Hz, 2H), 4.91 (d, J=7.9 Hz, 2H), 4.29 (s, 2H), 2.14–1.54 (m, 6H), 0.94 (d, J=6.9 Hz, 6H), 0.89 (d, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0 (C), 196.9 (C), 137.1 (2×C), 136.6 (2×CH), 131.5 (4×CH), 131.3 (4×CH), 72.7 (CH), 71.5 (CH), 63.5 (CH), 60.7 (CH), 45.0 (CH_2), 44.3 (CH_2), 26.8 (CH), 26.2 (CH), 25.8 (2×CH_3), 24.2 (CH_3), 23.8 (CH_3); R_f=0.37 (hexane/EtOAc 5:1).

4.2.6. 2-Chloro-3-hydroxy-1,4-diphenylpentan-1-one (3f). White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95–7.31 (m, 10H), 5.03 (s, 1H), 4.31 (dd, J=8.2, 5.9 Hz, 1H), 3.58 (d, J=5.9 Hz, 1H), 3.31–3.08 (m, 1H), 1.50 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3 (C), 142.7 (C), 133.9 (CH), 133.7 (C), 128.8 (CH), 128.7 (2×CH), 128.6 (2×CH), 128.1 (2×CH), 127.6 (CH), 127.2 (CH), 75.5 (CH), 60.1 (CH), 43.1 (CH), 17.9 (CH_3); R_f=0.42 (hexane/EtOAc 5:1).

4.2.7. 6-Chloro-7-hydroxyundec-5-one (3g). Data on the 60:40 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (d, J=3.4 Hz, 2H), 4.13–4.08 (m, 4H), 2.75–2.66 (m, 4H), 1.65–1.27 (m, 20H), 0.93 (t, J=7.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3 (C), 205.9 (C), 72.1 (CH), 71.4 (CH), 67.7 (CH), 64.1 (CH), 40.0 (CH_2), 39.9 (CH_2), 33.5 (2×CH_2), 32.6 (2×CH_2), 27.5 (CH_2), 27.2 (CH_2), 25.3 (2×CH_2), 22.3 (2×CH_2), 22.0 (2×CH_3), 13.7 (2×CH_3); IR (neat): $\tilde{\nu}$=3427, 2958, 2932, 2872, 1711, 1466, 1379 cm^{-1}; R_f=0.23 (hexane/EtOAc 10:1).

4.2.8. 2-Chloro-1-hydroxy-1-phenylheptan-3-one (3h). Data on the 50:50 mixture of diastereoisomers. Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.32 (m, 10H), 5.16 (d, J=5.3 Hz, 1H), 5.01 (d, J=8.2 Hz, 1H), 4.44 (d, J=5.3 Hz, 1H), 4.35 (d, J=8.2 Hz, 1H), 3.12 (s, 2H), 2.67–2.30 (m, 4H), 2.30–1.66 (m, 8H), 0.91 (t, J=6.9 Hz, 3H), 0.86 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (C), 205.2 (C), 139.0 (C), 138.7 (C), 128.4 (CH), 128.3 (2×CH), 128.2 (4×CH), 126.8 (2×CH), 126.4 (CH), 74.7 (CH), 73.6 (CH), 67.5 (CH), 63.4 (CH), 40.7 (CH_2), 40.1 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 21.8 (CH_2), 21.7 (CH_2), 13.6 (CH_3), 13.5 (CH_3); IR (neat): $\tilde{\nu}$=3460, 3088, 3033, 1714, 1604, 1495, 1454, 1380, 1267, 1050 cm^{-1}; R_f=0.30 (hexane/EtOAc 5:1).

4.2.9. (*R,*R**)-4-Chloro-5-hydroxy-2,2-dimethylnonan-3-one (3i).** Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.38 (d, J=8.5 Hz, 1H), 4.03 (dt, J=8.5, 2.3 Hz, 1H), 3.28 (s, 1H), 1.59–1.31 (m, 6H), 1.23 (s, 9H), 0.92 (t, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6 (C), 72.0 (CH), 55.0 (CH), 44.6 (C), 32.3 (CH_2), 27.2 (CH_2), 26.2 (3×CH_3), 22.4 (CH_2), 13.9 (CH_3); IR (neat): $\tilde{\nu}$=3512, 2986, 2913, 2857, 1715, 1478, 1369, 1096 cm^{-1}; R_f=0.37 (hexane/EtOAc 5:1).

4.2.10. 3-Chloro-4-hydroxy-4-(4-methoxyphenyl)butan-2-one (3j). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J=6.9 Hz, 2H), 7.01 (d, J=6.9 Hz, 2H), 5.99 (d, J=7.9 Hz, 2H), 3.89 (s, 3H), 3.28 (s, 1H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (C), 164.5 (C), 131.9 (2×CH), 129.6 (C), 114.1 (2×CH), 78.4 (CH), 70.0 (CH), 55.4 (CH_3), 22.7 (CH_3); R_f=0.44 (hexane/EtOAc 5:1).

4.3. General procedure for the synthesis of (*E*)-α,β-unsaturated ketones (1) by using $CrCl_2$

To a stirred suspension of $CrCl_2$ (3 equiv) in THF (10 mL) was added a solution of the corresponding 2-halo-3-hydroxy

ketone **3** (1 equiv). After stirring at reflux temperature for 4 h, the reaction was quenched with HCl 1 N (5 mL) and extracted with diethyl ether (3×10 mL). The combined extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. When it was necessary, purification by flash chromatography on silica gel (hexane/EtOAc 10:1) afforded the α,β-unsaturated ketones **1**.

4.4. General procedure for the synthesis of (*E*)-α,β-unsaturated ketones (1) by using SmI_2

Over a solution of the starting α-chloro-β-hydroxy ketone **3** (0.4 mmol) in dry THF (2 mL) a solution of samarium diiodide [prepared from 0.069 g of Sm (0.4 mmol), 5 mL of dry THF and 0.032 mL of CH_2I_2] was added dropwise at −25 °C. The reaction mixture was stirred at the same temperature over 2 h and then heated at reflux for one additional hour (the colour changed from yellow to orange). The reaction mixture was quenched with 5 mL of 0.1 M HCl and the usual workup gave the crude α,β-unsaturated ketone. Purification by flash column chromatography over silica or by distillation afforded the pure compound **1**.

4.5. General procedure for the synthesis of (*E*)-α,β-unsaturated ketones (1) by using SmI_3

0.4 mmol of the starting ketone were treated with a solution of 0.4 mmol of samarium triiodide (0.069 g of Sm, 5 mL of dry THF and 0.150 g of I_2) at −25 °C during 2 h and later heated at reflux by one additional hour. The reaction was quenched with 5 mL of 0.1 M HCl, extracted with dichloromethane and concentrated. Purification by flash column chromatography or by distillation yielded the pure enone **1**.

4.5.1. (*E*)-1-Phenylhept-2-en-1-one (1a). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93–7.41 (m, 5H), 7.06 (dt, *J*=15.4, 6.8 Hz, 1H), 6.86 (d, *J*=15.4 Hz, 1H), 2.29 (q, *J*=6.8 Hz, 2H), 1.70–1.19 (m, 4H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8 (C), 150.1 (CH), 137.9 (C), 132.5 (CH), 125.8 (CH), 128.4 (4×CH), 32.4 (CH_2), 30.1 (CH_2), 22.2 (CH_2), 13.7 (CH_3); MS (70 eV, EI) *m*/*z* (%) 188 $[M]^+$ (15), 159 (14), 145 (14), 131 (14), 115 (18), 105 (100), 91 (18), 77 (85), 55 (42), 51 (37), 43 (22), 41 (40); IR (neat): $\tilde{\nu}$=3085, 3059, 3028, 2957, 2930, 2871, 1725, 1670, 1620, 1597, 1447, 1344, 1282, 1003 cm^{-1}; R_f=0.34 (hexane/EtOAc 10:1). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.17; H, 8.46.

4.5.2. (*E*)-1-Phenyldec-2-en-1-one (1b). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.38 (m, 5H), 7.08 (dt, *J*=15.4, 6.7 Hz, 1H), 6.88 (d, *J*=15.4 Hz, 1H), 2.32 (q, *J*=6.7 Hz, 2H), 1.65–1.21 (m, 10H), 0.89 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.7 (C), 150.0 (CH), 137.8 (C), 132.4 (CH), 128.4 (4×CH), 125.6 (CH), 32.7 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 13.9 (CH_3); MS (70 eV, EI) *m*/*z* (%) 230 $[M]^+$ (3), 159 (15), 145 (13), 133 (19), 120 (3), 105 (100), 91 (16), 77 (69), 73 (28), 55 (33), 43 (51), 41 (65); HRMS (70 eV) calcd for $C_{16}H_{22}O$ 230.1671, found 230.1679; IR (neat): $\tilde{\nu}$=3059, 2956, 2927, 2855, 1672, 1622, 1463, 1448 cm^{-1}; R_f=0.34 (hexane/EtOAc 10:1). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.65; H, 9.75.

4.5.3. (*E*)-3-Cyclohexyl-1-phenylpropenone (1c). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93–7.26 (m, 5H), 7.01 (dd, *J*=15.4, 6.7 Hz, 1H), 6.82 (dd, *J*=15.4, 1.1 Hz, 1H), 2.26–2.22 (m, 1H), 1.85–1.70 (m, 5H), 1.36–1.19 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3 (C), 154.9 (CH), 138.0 (C), 132.5 (CH), 128.4 (4×CH), 123.2 (CH), 41.0 (CH), 31.7 (2×CH_2), 25.8 (CH_2), 25.7 (2×CH_2); MS (70 eV, EI) *m*/*z* (%) 214 $[M]^+$ (13), 157.2 (7), 120 (9), 115 (9), 105 (100), 91 (9), 79 (12), 77 (60), 67 (14), 55 (21), 51 (20); HRMS (70 eV) calcd for $C_{15}H_{18}O$ 214.1358, found 214.1368; IR (neat): $\tilde{\nu}$=3084, 3057, 3025, 2996, 2925, 2851, 1725, 1665, 1614, 1578, 1446, 1336, 1016, 984 cm^{-1}; R_f=0.40 (hexane/EtOAc 10:1). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.67; H, 8.39.

4.5.4. (*E*)-1,3-Diphenylpropenone (1d). White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–7.28 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3 (C), 144.6 (CH), 137.9 (C), 134.6 (C), 132.6 (CH), 130.4 (CH), 128.8 (2×CH), 128.4 (2×CH), 128.3 (4×CH), 121.7 (CH); MS (70 eV, EI) *m*/*z* (%) 208 $[M]^+$ (25), 207 (34), 179 (9), 165 (5), 131 (16), 103 (23), 102 (19), 77 (100), 51 (51), 50 (19). Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.62; H, 5.73.

4.5.5. (*E*)-5-Methyl-1-phenylhex-2-en-1-one (1e). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.11 (m, 5H), 7.06 (dt, *J*=15.1, 7.0 Hz, 1H), 6.88 (d, *J*=15.1 Hz, 1H), 2.23 (t, *J*=7.0 Hz, 2H), 2.18–1.80 (m, 1H), 0.98 (d, *J*=6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7 (C), 148.8 (CH), 137.9 (C), 132.5 (CH), 128.4 (4×CH), 126.9 (CH), 42.0 (CH_2), 27.9 (CH), 22.4 (2×CH_3); MS (70 eV, EI) *m*/*z* (%) 188 $[M]^+$ (5), 158 (120), 77 (30); IR (neat): $\tilde{\nu}$=3064, 2957, 2870, 1687, 1597, 1449, 1251 cm^{-1}; R_f=0.32 (hexane/EtOAc 10:1). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.01; H, 8.46.

4.5.6. (*E*)-1,4-Diphenylpent-2-en-1-one (1f). Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, *J*=6.9, 1.5 Hz, 2H), 7.58–7.24 (m, 9H), 6.91 (dd, *J*=15.5, 1.4 Hz, 1H), 3.79 (quint., *J*=7.0 Hz, 1H), 1.57 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9 (C), 152.9 (CH), 143.3 (C), 137.8 (C), 132.6 (CH), 128.6 (2×CH), 128.4 (4×CH), 127.3 (2×CH), 126.7 (CH), 124.4 (CH), 42.5 (CH), 20.4 (CH_3); MS (70 eV, EI) *m*/*z* (%) 236 $[M]^+$ (19), 221 (8), 131 (27), 105 (100), 77 (46); IR (neat): $\tilde{\nu}$=3027, 2968, 1669, 1619, 1448, 1290 cm^{-1}; R_f=0.57 (hexane/EtOAc 3:1). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.49; H, 6.73.

4.5.7. (*E*)-Undec-6-en-5-one (1g). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (dt, *J*=14.9, 6.9 Hz, 1H), 6.06 (d, *J*=14.9 Hz, 1H), 2.50 (t, *J*=7.1 Hz, 2H), 2.19 (q, *J*=7.1 Hz, 2H), 1.59–1.28 (m, 8H), 0.89 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9 (C), 147.2 (CH), 130.2 (CH), 39.7 (CH_2), 32.0 (CH_2), 30.1 (CH_2), 26.3 (CH_2), 22.3 (CH_2), 21.9 (CH_2), 13.8 (CH_3), 13.7 (CH_3); MS (70 eV, EI) *m*/*z* (%) 168 $[M]^+$ (<1), 126 (26), 111 (100), 83 (7), 55 (94), 29 (17); IR (neat): $\tilde{\nu}$=3024, 2961, 2869, 1700, 1676, 1633, 1465, 1261 cm^{-1}; R_f=0.49 (hexane/EtOAc 5:1).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.73; H, 11.86.

4.5.8. (*E*)-1-Phenylhept-1-en-3-one (1h). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70–7.37 (m, 6H), 6.76 (d, J=16.2 Hz, 1H), 2.68 (t, J=7.4 Hz, 2H), 1.76–1.27 (m, 4H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.6 (C), 142.2 (CH), 134.5 (C), 130.3 (CH), 128.8 (CH), 128.2 (2×CH), 126.2 (2×CH), 40.6 (CH_2), 26.4 (CH_2), 22.4 (CH_2), 13.8 (CH_3); MS (70 eV, EI) *m*/*z* (%) 188 $[M]^+$ (7), 146 (41), 131 (100), 103 (46), 77 (27), 51 (8); HRMS (70 eV) calcd for $C_{13}H_{16}O$ 188.1201, found 188.1198; IR (neat): $\tilde{\nu}$=3021, 2937, 2865, 1686, 1620, 1500, 1181, 1069 cm^{-1}; R_f=0.47 (hexane/EtOAc 5:1). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.03; H, 8.51.

4.5.9. (*E*)-2,2-Dimethylnon-4-en-3-one (1i). Pale orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (dt, J=15.2, 6.8 Hz, 1H), 6.47 (d, J=15.2 Hz, 1H), 2.18 (q, J=7.1 Hz, 2H), 1.47–1.21 (m, 4H), 1.15 (s, 9H), 0.91 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4 (C), 147.6 (CH), 124.0 (CH), 42.7 (C), 32.1 (CH_2), 30.2 (CH_2), 26.1 (3×CH_3), 22.2 (CH_2), 13.8 (CH_3); MS (70 eV, EI) *m*/*z* (%) 168 $[M]^+$ (5), 111 (100), 83 (8), 57 (30); IR (neat): $\tilde{\nu}$=2958, 2929, 2871, 1705, 1624, 1458, 1364, 1066, 1003, 720 cm^{-1}; R_f=0.47 (hexane/EtOAc 10:1). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.75; H, 11.86.

4.5.10. (*E*)-4-(4-Methoxyphenyl)but-3-en-2-one (1j). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J=11.5 Hz, 1H), 7.43 (d, J=11.2 Hz, 2H), 6.84 (d, J=11.2 Hz, 2H), 6.54 (d, J=11.5 Hz, 1H), 3.77 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6 (C), 161.6 (C), 143.4 (CH), 129.9 (2×CH), 126.9 (C), 124.9 (CH), 114.4 (2×CH), 55.3 (CH_3), 27.3 (CH_3); MS (70 eV, EI) *m*/*z* (%) 176 $[M]^+$ (52), 161 (100), 145 (8), 133 (48), 118 (16), 89 (17), 77 (14); IR (neat): $\tilde{\nu}$=2959, 2918, 2849, 1664, 1602, 1512, 1250 cm^{-1}; R_f=0.48 (hexane/EtOAc 1:1). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.09; H, 6.77.

4.6. General procedure for the synthesis of starting compounds 4

To a −78 °C stirred solution of the α-haloester (9.7 mmol) in dry THF (8 mL) was added dropwise lithium diisopropylamide [prepared from MeLi (6.5 mL of 1.5 M solution in ether) and diisopropylamine (1.4 mL, 10 mmol) in THF (50 mL) at 0 °C]. After stirring for 10 min, a solution of the aldehyde (5 mmol) in dry THF (4.5 mL) was added dropwise at −78 °C and the mixture was stirred for 2 h. Then the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl (20 mL). Usual workup provided the corresponding α-halo-β-hydroxyester **4**, which was purified by flash column chromatography on silica gel (hexane/EtOAc 10:1).

4.6.1. Methyl 2-chloro-3-hydroxydecanoate (4a). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (d, J=3.9 Hz, 1H), 4.14 (d, J=3.9 Hz, 1H), 4.12–3.90 (m, 2H), 3.88–3.75 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 1.66–1.21 (m, 24H), 0.80 (t, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (C), 168.9 (C), 72.4 (CH), 71.7 (CH), 61.9 (CH), 59.4 (CH), 52.9 (CH_3), 52.7 (CH_3), 31.9 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 24.9 (2×CH_2), 24.5 (2×CH_2), 22.4 (2×CH_2), 13.8 (2×CH_3); IR (neat): $\tilde{\nu}$=3452, 1754 cm^{-1}; R_f=0.30 (hexane/EtOAc 5:1).

4.6.2. Methyl 2-chloro-3-(4-chlorophenyl)-3-hydroxypropanoate (4b). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 8H), 5.07 (d, J=6.0 Hz, 1H), 4.95 (d, J=6.0 Hz, 1H), 4.46 (s, 2H), 4.42 (dd, J=6.0, 1.5 Hz, 1H), 4.33 (dd, J=6.0, 1.5 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (C), 168.1 (C), 137.1 (C), 136.7 (C), 134.0 (2×C), 128.3 (CH), 128.2 (2×CH), 128.1 (4×CH), 127.7 (CH), 74.1 (CH), 73.4 (CH), 62.2 (CH), 58.8 (CH), 53.0 (CH_3), 52.8 (CH_3); IR (neat): $\tilde{\nu}$=3468, 1744, 1493, 1285 cm^{-1}; R_f=0.40 (hexane/EtOAc 5:1).

4.6.3. Methyl 2-chloro-3-hydroxy-4-phenylpentanoate (4c). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.20 (m, 10H), 4.24 (dd, J=1.4 Hz, 2H), 4.14–4.02 (m, 4H), 3.78 (s, 3H), 3.58 (s, 3H), 2.851 (s, 2H), 1.45 (d, J=6.9 Hz, 3H), 1.36 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (C), 169.0 (C), 142.8 (C), 142.3 (C), 128.6 (CH), 128.5 (2×CH), 128.2 (2×CH), 128.0 (2×CH), 127.6 (2×CH), 127.3 (CH), 76.8 (CH), 76.3 (CH), 60.7 (CH), 57.1 (CH), 52.9 (CH_3), 52.7 (CH_3), 43.0 (CH), 40.9 (CH), 18.0 (CH_3), 14.5 (CH_3); IR (neat): $\tilde{\nu}$=2950, 1717, 1632, 1168, 1039 cm^{-1}; R_f=0.32 (hexane/EtOAc 5:1).

4.6.4. Ethyl 2-chloro-3-hydroxy-2-methyldecanoate (4d). Data on the 60:40 mixture of diastereoisomers. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (q, J=7.1 Hz, 2H), 4.24 (q, J=7.1 Hz, 2H), 3.98 (s, 1H), 3.96 (s, 1H), 2.61 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H), 1.67–1.27 (m, 30H), 0.86 (t, J=7.1 Hz, 3H), 0.79 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (C), 170.5 (C), 75.9 (CH), 75.6 (CH), 73.6 (C), 71.1 (C), 62.2 (2×CH_2), 31.6 (CH_2), 31.5 (CH_2), 31.0 (4×CH_2), 29.2 (4×CH_2), 29.1 (CH_2), 26.2 (CH_2), 22.5 (2×CH_3), 22.2 (2×CH_3), 13.9 (CH_3), 13.8 (CH_3); IR (neat): $\tilde{\nu}$=3425, 1741 cm^{-1}; R_f=0.26 (hexane/EtOAc 10:1).

4.6.5. Ethyl 2-chloro-3-cyclohexyl-3-hydroxy-2-methylpropanoate (4e). Data on the 50:50 mixture of diastereoisomers. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (q, J=7.2 Hz, 4H), 3.84–3.76 (m, 2H), 2.90 (s, 2H), 1.93–1.09 (m, 22H), 1.88 (s, 6H), 1.21 (t, J=7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9 (C), 170.5 (C), 79.3 (CH), 78.7 (CH), 73.6 (C), 71.9 (C), 62.0 (CH_2), 61.9 (CH_2), 40.7 (CH), 40.3 (CH), 31.0 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 28.4 (CH_2), 27.9 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 21.8 (CH_3), 21.2 (CH_3), 13.6 (CH_3), 13.3 (CH_3); R_f=0.31 (hexane/EtOAc 10:1).

4.6.6. Ethyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropanoate (4f). Pale yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46–7.34 (m, 5H), 5.22 (s, 1H), 4.29 (q, J=7.1 Hz, 2H), 3.22 (s, 1H), 1.66 (s, 3H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8 (C), 137.4 (C), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 77.6 (CH), 69.4 (C), 62.4 (CH_2), 21.6 (CH_3), 13.8

(CH_3); IR (neat): $\tilde{\nu}$=2994, 1724, 1454 cm^{-1}; R_f=0.43 (hexane/EtOAc 5:1).

4.6.7. Ethyl 2-chloro-3-hydroxy-2-methyl-3-(4-methoxyphenyl)propanoate (4g). Data on the 75:25 mixture of diastereoisomers. Pale orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.28 (m, 4H), 6.89–6.80 (m, 4H), 5.21 (s, 1H), 5.15 (s, 1H), 4.27 (q, J=7.2 Hz, 2H), 4.26 (q, J=7.2 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.29 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.31 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8 (C), 170.4 (C), 159.4 (C), 159.3 (C), 129.8 (C), 129.4 (2×CH), 129.2 (2×CH), 128.9 (C), 113.1 (2×CH), 112.9 (2×CH), 77.0 (2×CH), 73.5 (C), 69.8 (C), 62.3 (CH_2), 62.1 (CH_2), 55.0 (2×CH_3), 22.6 (CH_3), 21.4 (CH_3), 13.7 (2×CH_3); IR (neat): $\tilde{\nu}$=3490, 1737 cm^{-1}; R_f=0.33 (hexane/EtOAc 5:1).

4.6.8. Ethyl 2-bromo-3-hydroxy-2-hexyl-3-phenylpropanoate (4h). Data on the 50:50 mixture of diastereoisomers. Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.33 (m, 10H), 5.09 (s, 2H), 4.25 (q, J=7.1 Hz, 4H), 3.60 (s, 2H), 2.06–1.76 (m, 4H), 1.56–1.20 (m, 22H), 0.90 (t, J=7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (C), 169.2 (C), 138.3 (C), 137.8 (C), 127.8 (2×CH), 127.7 (2×CH), 127.6 (4×CH), 127.1 (2×CH), 78.1 (CH), 77.6 (CH), 75.6 (C), 73.8 (C), 62.0 (CH_2), 61.7 (CH_2), 37.6 (CH_2), 37.0 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 22.1 (CH_2), 13.6 (CH_3), 13.5 (CH_3), 13.4 (CH_3), 13.3 (CH_3); IR (neat): $\tilde{\nu}$=3503, 2956, 1734, 1717 cm^{-1}; R_f=0.32 (hexane/EtOAc 5:1).

4.6.9. Ethyl 2-bromo-3-hydroxy-2-pentyl-3-phenylpropanoate (4i). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.36 (m, 5H), 5.12 (s, 1H), 4.30 (q, J=7.1 Hz, 2H), 3.39 (s, 1H), 2.06–1.83 (m, 2H), 1.79–1.24 (m, 9H), 0.90 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (C), 137.8 (C), 128.3 (CH), 128.0 (CH), 127.9 (2×CH), 127.6 (CH), 77.6 (CH), 75.9 (C), 62.5 (CH_2), 37.3 (CH_2), 31.4 (CH_2), 25.5 (CH_2), 22.1 (CH_2), 13.8 (CH_3), 13.7 (CH_3); IR (neat): $\tilde{\nu}$=3503, 2931, 1734, 1455 cm^{-1}; R_f=0.31 (hexane/EtOAc 5:1).

4.6.10. Isopropyl 2-chloro-3-cyclohexyl-3-hydroxy-2-methylpropanoate (4j). Data on the 65:55 mixture of diastereoisomers. Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 5.07 (apparent quint., J=6.1 Hz, 2H), 3.81 (d, J=4.7 Hz, 1H), 3.75 (d, J=4.7 Hz, 1H), 2.58 (s, 2H), 1.75 (s, 3H), 1.71 (s, 3H), 1.91–1.18 (m, 22H), 1.30 (d, J=6.1 Hz, 6H), 1.27 (d, J=6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (C), 170.0 (C), 79.4 (CH), 78.8 (CH), 73.8 (C), 72.2 (C), 69.9 (CH), 69.7 (CH), 40.7 (CH), 40.3 (CH), 31.2 (CH_2), 30.8 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 26.3 (2×CH_2), 26.0 (2×CH_2), 25.9 (2×CH_2), 22.4 (2×CH_3), 21.9 (CH_3), 21.5 (CH_3), 21.2 (CH_3), 21.1 (CH_3); IR (neat): $\tilde{\nu}$=3499, 1732, 1450, 1376, 1266 cm^{-1}; R_f=0.37 (hexane/EtOAc 5:1).

4.7. General procedure for the synthesis of α,β-unsaturated esters 2

To a stirred solution of the corresponding β-hydroxyester α-halogenated **4** (0.4 mmol) in dry THF (5 mL) was added $CrCl_2$ (0.15 g, 1.2 mmol). After 4 h at reflux the reaction mixture was quenched with water. Usual workup and filtration through a pad of Celite provided α,β-unsaturated esters **2**, which were purified by flash column chromatography on silica gel (hexane/EtOAc 15:1).

4.7.1. (*E*)-Methyl dec-2-enoate (2a). Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 6.96 (dt, J=15.4, 7.0 Hz, 1H), 5.81 (dt, J=15.4, 1.3 Hz, 1H), 3.71 (s, 3H), 2.23–2.14 (m, 2H), 1.46–1.26 (m, 10H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.1 (C), 149.8 (CH), 120.7 (CH), 51.3 (CH_3), 32.1 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.9 (CH_2), 22.5 (CH_2), 14.0 (CH_3); MS (70 eV, EI) *m*/*z* (%) 184 $[M]^+$ (<1), 153 (28), 87 (100); IR (neat): $\tilde{\nu}$=2928, 1728, 1651 cm^{-1}; HRMS (70 eV) calcd for $C_{11}H_{20}O_2$ 184.2753, found 184.1463; R_f=0.50 (hexane/EtOAc 10:1). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.81; H, 10.85.

4.7.2. (*E*)-Methyl 3-(4-chlorophenyl)prop-2-enoate (2b). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J=16.1 Hz, 1H), 7.50–7.48 (AB system, J=6.5 Hz, 4H), 6.45 (d, J=16.1 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (C), 143.3 (CH), 136.1 (C), 132.8 (C), 129.1 (2×CH), 129.0 (2×CH), 118.3 (CH), 51.7 (CH_3); IR (neat): $\tilde{\nu}$=2283, 1728, 1168, 937, 821, 731 cm^{-1}; R_f=0.51 (hexane/EtOAc 3:1). Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.28; H, 4.49.

4.7.3. (*E*)-Methyl 4-phenylpent-2-enoate (2c). Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 7.50–7.17 (m, 5H), 7.13 (d, J=15.6 Hz, 1H), 5.83 (dd, J=15.6, 1.6 Hz, 1H), 3.78 (s, 3H), 3.67–3.57 (q, J=7.0 Hz, 1H), 1.44 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (C), 152.8 (CH), 143.1 (C), 129.0 (2×CH), 127.6 (2×CH), 127.2 (CH), 119.5 (CH), 52.8 (CH_3), 41.9 (CH), 20.0 (CH_3); MS (70 eV, EI) *m*/*z* (%) 190 $[M]^+$ (21), 175 (5), 131 (100), 115 (74), 91 (46), 77 (23); R_f=0.53 (hexane/EtOAc 5:1). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.87; H, 7.31.

4.7.4. (*E*)-Ethyl 2-methyldec-2-enoate (2d). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.81–6.72 (m, 1H), 4.20 (q, J=7.2 Hz, 2H), 2.21–2.11 (m, 2H), 1.84 (s, 3H), 1.75–1.25 (m, 13H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (C), 142.4 (CH), 127.5 (C), 60.3 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 14.2 (CH_3), 14.0 (CH_3), 12.2 (CH_3); MS (70 eV, EI) *m*/*z* (%) 212 $[M]^+$ (19), 167 (80), 113 (73); IR (neat): $\tilde{\nu}$=2928, 1728, 1651 cm^{-1}; R_f=0.50 (hexane/EtOAc 10:1). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.76; H, 11.24.

4.7.5. (*E*)-Ethyl 3-cyclohexyl-2-methylpropenoate (2e). White solid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (d, J=9.6 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 2.45–2.25 (m, 1H), 1.82 (s, 3H), 1.83–1.05 (m, 10H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5 (C), 147.2 (CH), 125.8 (C), 60.3 (CH_2), 37.6 (CH), 31.8 (2×CH_2), 25.8 (CH_2), 25.5 (2×CH_2), 14.2 (CH_3), 12.3 (CH_3); MS (70 eV, EI) *m*/*z* (%) 196 $[M]^+$ (30), 151 (34), 123 (10); IR (neat): $\tilde{\nu}$=2926, 1709, 1649, 1381 cm^{-1}; R_f=0.54 (hexane/EtOAc 10:1). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.15.

4.7.6. (*E*)-Ethyl 2-methyl-3-phenylprop-2-enoate (2f). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.69–7.26 (m, 5H), 4.23 (q, J=7.0 Hz, 2H), 2.14 (s, 3H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (C), 138.6 (CH), 135.9 (C), 129.5 (2×CH), 128.3 (C), 128.1 (3×CH), 60.8 (CH_2), 14.2 (CH_3), 14.0 (CH_3); MS (70 eV, EI) *m/z* (%) 190 $[M]^+$ (29), 115 (100), 145 (40), 91 (40); IR (neat): $\tilde{\nu}$=2927, 1708, 1638, 764 cm^{-1}; R_f=0.61 (hexane/EtOAc 3:1). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.87; H, 7.53.

4.7.7. (*E*)-Ethyl 2-methyl-3-(4-methoxyphenyl)propenoate (2g). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.37 (d, J=8.3 Hz, 2H), 6.89 (d, J=8.3 Hz, 2H), 4.25 (q, J=7.1 Hz, 2H), 3.80 (s, 3H), 2.12 (s, 3H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (C), 159.4 (C), 138.2 (CH), 131.2 (2×CH), 128.3 (C), 126.1 (C), 113.6 (2×CH), 60.6 (CH_2), 55.0 (CH_3), 14.2 (CH_3), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 220 $[M]^+$ (100), 191 (32), 175 (85), 147 (83), 131 (72), 91 (75), 77 (59); IR (neat): $\tilde{\nu}$= 2975, 1702, 1605 cm^{-1}; R_f=0.43 (hexane/EtOAc 5:1). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.02; H, 7.25.

4.7.8. (*E*)-Ethyl 2-hexyl-3-phenylprop-2-enoate (2h). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.41–7.36 (m, 5H), 4.33 (q, J=7.2 Hz, 2H), 2.54 (t, J= 7.2 Hz, 3H), 1.60–0.90 (m, 10H), 1.37 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.4 (C), 138.3 (CH), 135.8 (C), 133.9 (C), 129.0 (CH), 128.3 (3×CH), 128.0 (CH), 60.6 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 22.5 (CH_2), 14.2 (CH_3), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 260 $[M]^+$ (33), 144 (30), 172 (29), 77 (26); IR (neat): $\tilde{\nu}$= 2957, 2858, 1709, 1630 cm^{-1}; R_f=0.59 (hexane/EtOAc 5:1). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.60; H, 9.13.

4.7.9. (*E*)-Ethyl 2-penthyl-3-phenylprop-2-enoate (2i). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.37–7.26 (m, 5H), 4.33 (q, J=7.2 Hz, 2H), 1.72–1.37 (m, 8H), 1.33 (t, J=7.2 Hz, 3H), 0.91 (t, J=10.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (C), 138.3 (CH), 135.8 (C), 133.9 (C), 129.1 (2×CH), 128.3 (2×CH), 128.1 (CH), 60.4 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 22.3 (CH_2), 14.2 (CH_3), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 246 $[M]^+$ (35), 217 (17), 129 (32), 117 (17); IR (neat): $\tilde{\nu}$=2957, 2930, 1709, 765, 700 cm^{-1}; R_f=0.58 (hexane/EtOAc 5:1). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.25; H, 9.05.

4.7.10. (*E*)-Isopropyl 3-cyclohexyl-2-methylprop-2-enoate (2j). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, J=9.6 Hz, 1H), 5.06 (apparent quint., J=6.3 Hz, 1H), 1.84 (s, 3H), 1.68–1.27 (m, 11H), 1.28 (d, J=6.3 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.1 (C), 146.8 (CH), 136.4 (C), 67.5 (CH), 37.7 (CH), 31.9 (2×CH_2), 25.8 (2×CH_2), 25.6 (CH_2), 21.8 (2×CH_3), 12.3 (CH_3); MS (70 eV, EI) *m/z* (%) 210 $[M]^+$ (9), 168 (100), 151 (48), 82 (61), 43 (27); R_f=0.50 (hexane/EtOAc 5:1). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.33; H, 10.41.

Acknowledgements

We thank Ministerio de Educación y Cultura (CTQ2004-01191/BQU) for financial support and to Vicente del Amo for his revision of the English. C.M. thanks Ministerio de Educación y Cultura for a predoctoral fellowship. J.M.C. thanks Carmen Fernández-Flórez for her time.

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First cross-coupling reactions on halogenated 1*H*-1,2,4-triazole nucleosides

Susanne Wille, Martin Hein and Ralf Miethchen*

Institut für Chemie, Universität Rostock, Albert-Einstein-Straße 3a, D-18059 Rostock, Germany

Received 19 December 2005; revised 16 January 2006; accepted 17 January 2006

Available online 14 February 2006

Abstract—The halogenated 1*H*-1,2,4-triazole glycosides **6–10** were synthesized by BF_3-activated glycosylation of 3(5)-chloro-1,2,4-triazole (**2**), 3,5-dichloro-1,2,4-triazole (**3**), 3,5-dibromo-1,2,4-triazole (**4**), and 3(5)-bromo-5(3)-chloro-1,2,4-triazole (**5**) with 1,2,3,4-tetra-*O*-pivaloyl-β-D-xylopyranose (**1**). The β-anomeric major products 3-chloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**6**β), 3,5-dichloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**7**β), and 3,5-dibromo-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**8**β) were used as starting materials for transition metal catalyzed C–C-coupling reactions. Arylations of the triazole ring of **7**β, and **8**β were successful in 5-position with phenylboronic acid, 4-vinylphenylboronic acid, and 4-methoxyphenylboronic acid, respectively, under Suzuki cross-coupling conditions (products **11–17**). Moreover, a Cu-catalyzed perfluoroalkylation of **8**β is reported with 1-iodoperfluorohexane yielding 3-perfluorohexyl-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**18**). Compound **18** was depivaloylated to the trihydroxy derivative **19**. The copper-mediated reaction of **8**β with Rupert's reagent gave the bis(3-bromo-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazol-5-yl) (**20**).
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1. Introduction

Substituted 1,2,4-triazoles are of current interest because of their antiinflamatory, insecticide, antifungal, or antimicrobial activity.[1] Glycosylated triazole derivatives like 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide (Virazol)[2] belong to the highly potent drugs against DNA- and RNA-viruses.[3] Moreover, this compound shows antitumor activity,[4] just as the anomeric 1-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-5-nitro-1*H*-1,2,4-triazoles.[5]

In order to broaden the approach for 1,2,4-triazole nucleoside analogues and animated by a recent excellent review[6] on regioselective cross-coupling reactions of halogenated heterocycles, we investigated first examples of cross-coupling reactions with this heterocycle (arylation and perfluoroalkylation). We focused our efforts on selected methods which allow the regioselective formation of carbon–carbon bonds by selective displacement of halogen atoms of halogenated 1*H*-1,2,4-triazole glycosides. In previous publications[7,8] it could be shown that a halogen atom linked to C-atom 5 of 1-substituted 1,2,4-triazole derivatives allows regioselective nucleophilic substitutions quite easy compared to a halogen atom linked to C-atom 3. The reason is a better mesomeric stabilization of the intermediate formed by attack of the nucleophilic reagent to C-atom 5.[8] For the C–C-coupling experiments within the scope of this paper, three different transition metal catalyzed methods (Fürstner-type coupling, Suzuki-type couplings and Ullmann-type couplings) were selected. Fürstner[9,10] used $Fe(acac)_3$ as catalyst. Suzuki cross-couplings are Pd-catalyzed C–C-couplings of organoboron compounds with carbon electrophiles (especially, aryl halogenides)[6,11,12] and Ullmann-type reactions[13] are catalyzed by Cu-catalysts.

The starting materials, compounds **6–10**, were synthesized by BF_3-activated glycosylations of 3-chloro-1*H*-1,2,4-triazole (**2**),[14] 3,5-dichloro-1*H*-1,2,4-triazole (**3**),[15] 3,5-dibromo-1*H*-1,2,4-triazole (**4**),[16] and 3-bromo-5-chloro-1,2,4-triazole (**5**)[16] with 1,2,3,4-tetra-*O*-pivaloyl-β-D-xylopyranose (**1**)[17] in acetonitrile (Scheme 1); for an alternative strategy to synthesize halogenated 1,2,4-triazole nucleosides by addition of *N*-halo-1,2,4-triazole derivatives to the double bond of glycals see our recent report in synthesis.[8]

The BF_3-activated glycosylation procedures of β-D-xylopyranose **1** with the azoles **2–5** required relatively long reaction times (3–6 days). The glycosidic linkages of the reactants occurred at N-1/N-2 of the triazole ring but never at N-atom 4. The dihalogen triazoles **3** and **4** gave α/β-anomeric mixtures of the glycosyl triazoles **7**α/β and **8**α/β, respectively, in which the corresponding β-anomers were

Keywords: Cross-coupling; Glycosylation; Triazoles.
* Corresponding author. Tel.: +49 381 498 6420; fax: +49 381 498 6412; e-mail: ralf.miethchen@uni-rostock.de

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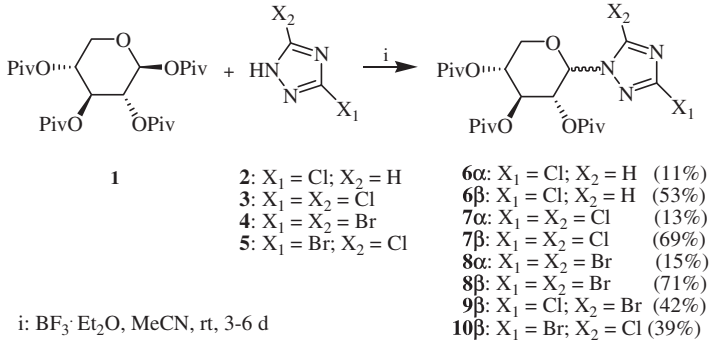
doi:10.1016/j.tet.2006.01.053



Scheme 1. Glycosylation of halogenated 1,2,4-triazoles with acylated sugars.

the major products (Scheme 1). When the reaction was carried out with 3-bromo-5-chloro-1,2,4-triazole (**5**), bearing different halogens at C-3 and C-5, only the regioisomeric β-glycosides (**9**β and **10**β) were formed, namely in similar amounts.

By contrast, 3-chloro-1*H*-1,2,4-triazole (**2**) likewise asymmetrically substituted in the positions 3 and 5, reacted regioselectively with 1,2,3,4-tetra-*O*-pivaloyl-β-D-xylopyranose (**1**), that is, the glycosyl donor attacked that N-atom of the triazole ring, which is 1,3-located to the Cl-substituted ring carbon. However, the product consisted of the two anomers **6**α and **6**β (Scheme 1).

There is abundant information about the tautomerism of azoles in solution. The knowledge on 1,2,4-triazoles indicates that only 1H tautomers are stable, that is, the NH-proton of the monochloro derivative **2** alternates between N1 and N2 of the triazole ring (Ref. 18 and papers cited therein). Moreover, Elguero et al.[18] postulate the preference of that tautomeric form of C-monohalogeno-1,2,4-triazoles in which the NH-proton and the halogen atom are 1,3-arranged.

The structures of the triazole nucleosides **6–10** are supported by their ^{1}H and ^{13}C NMR spectra. The assignment of signals was performed by recording DEPT, two-dimensional ^{1}H,^{1}H and ^{13}C,^{1}H correlation spectra. The ^{13}C NMR chemical shifts of the nucleosides **6**α/β were additionally compared to data from the literature.[7,8,19] Table 1 shows the chemical shifts of C-3 (triazole) and C-5 (triazole) for the nucleoside analogues **6–10**. For derivatives with identical substituents at the heteroaromatic C-atoms 3 and 5 is valid that the ^{13}C signal of C-atom 3 is shifted to lower field than that of C-atom 5. That is probably caused by the neighbourhood of two pyridine-type nitrogen atoms in the case of C-3, whereas C-atom 5 is linked to one pyridine- and one pyrrol-type nitrogen atom. Compared to triazole derivatives being unsubstituted at C-3 and C-5, the introduction of one or two chloro substituents does not significantly alter the chemical shifts of the C-atoms 3 and 5. By contrast, bromo substituents cause significant shifts (Table 1 and Refs. 7,8,19).

Table 1. ^{13}C-Chemical shifts of C-atom 3 and C-atom 5 of the xylosyl triazoles **6–10**

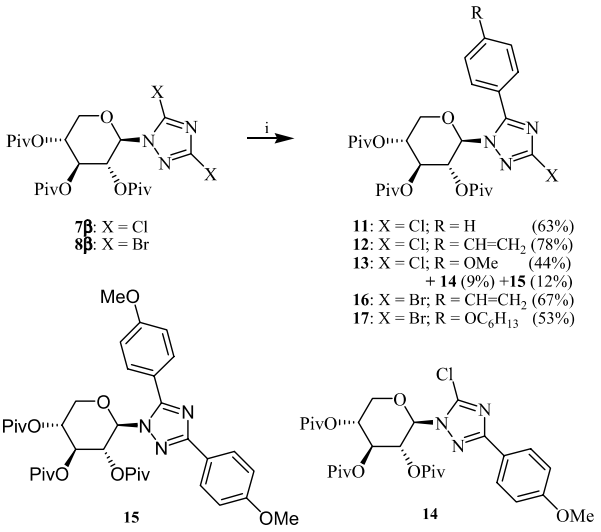
Compound	Triazole substituents (C-3, C-5)	δ (C-3) (ppm)	δ (C-5) (ppm)
6β	Cl, H	153.2	144.0
6α	Cl, H	153.6	146.2
7β	Cl, Cl	153.0	143.1
7α	Cl, Cl	152.5	143.9
8β	Br, Br	141.8	131.2
8α	Br, Br	141.3	132.0
9β	Cl, Br	154.4	131.0
10β	Br, Cl	140.5	143.5

The ^{13}C chemical shifts found for the C-atoms 5 of the anomeric monochloro derivatives **6**α and **6**β (146.2, 144.0 ppm) are similar to those of other 1-substituted 1,2,4-triazole derivatives with hydrogen in this position. As expected, the mixed halogenated glycoside **9**β shows one carbon atom with a shift similar to C-3 of dichloro derivative **7**β and another one with a shift similar to C-5 of dibromo derivative **8**β. Consequently, the mixed halogenated regioisomer **10**β shows one ^{13}C-signal matches with that of C-3 from **8**β and another one matches with that of C-5 from **7**β. This indicates, that **9**β is the 5-bromo-3-chloro- and **10**β the 3-bromo-5-chloro-derivative.

In the following, the behaviour of the glycosyl triazoles **6**β, **7**β, **8**β is described in different C–C-cross-coupling reactions. Firstly, we examined the Fürstner coupling reaction of **6**β and **7**β, respectively, with ethylmagnesium bromide in the presence of Fe(acac)$_3$. The 3-chloro derivative **6**β did not give any product,[9,10] whereas 3,5-dichloro derivative **7**β was hydrodechlorinated in 5-position under Fürstner conditions. However, a C–C-coupling product was likewise not found in this case. The product obtained from **7**β is identical with 3-chloro derivative **6**β.

In further cross-coupling experiments, we investigated reactions of the 3,5-dihalogeno-1,2,4-triazole glycosides **7**β and **8**β under Suzuki conditions. The compounds were reacted with different phenylboronic acids as shown in Scheme 2.

When diadamantyl-butylphosphine (pAd$_2$Bu), in situ prepared from the corresponding hydroiodide,[20] was used as ligand for the Pd-catalyst, compound 7β gave the desired product **11** in 63% yield. Further cross-couplings of the glycosides **7**β and **8**β were realized with differently substituted phenylboronic acids (Scheme 2). In all cases, the preferred position of arylation was C-atom 5 of the heteroaromatic ring. This position was also preferred in various nucleophilic substitution reactions of halogenated 1-alkyl, 1-aryl, and 1-glycosyl-1,2,4-triazoles.[7,8] It is known that also various transition metal catalysts can act as a

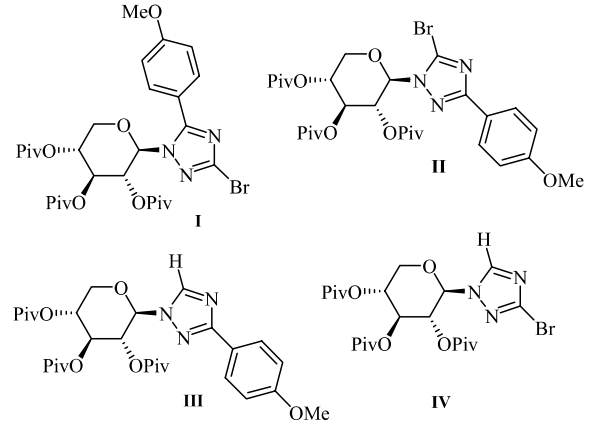


Scheme 2. Suzuki reactions of **7**β and **8**β with different phenylboronic acids. (i) Arylboronic acid, $Pd(OAc)_2$, $[HPAd_2Bu]^+I^-$, K_3PO_4, DMF, 100 °C, 20 h.

nucleophile and preferentially attack the most electron-deficient position of a substrate.[6]

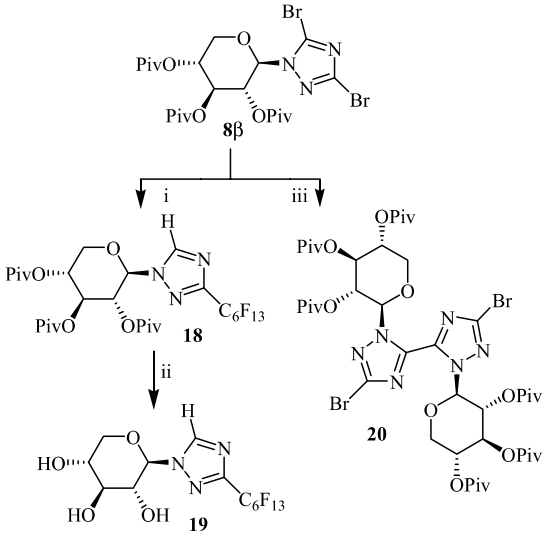
Some side products were found in the arylations of the nucleosides **7**β and **8**β with 4-methoxyphenylboronic acid. Thus, compound **7**β gave 9% yield of the 3-arylated product **14** and 12% yield of the 3,5-diarylated product **15** beside the major product **13** (44%) (Scheme 2). The analogous conversion of the bromo derivative **8**β proceeded still less selective. The result was 25% yield of the slightly contaminated 5-arylated 3-bromo derivative **I** beside mixtures containing the 3-arylated derivatives **II** and **III**, 3,5-diaryl compound **15**, and 3-bromo-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**IV**), respectively (Scheme 3). These products could not be fully characterized. On the other hand, the conversion of 4-hexyloxyphenylboronic acid did not work well with **7**β, whereas the bromo derivative **8**β yielded 53% of the desired product **17** (Scheme 2).

Besides coupling reactions with arylboronic acids, we were interested in the introduction of trifluoromethyl- and perfluoroalkyl groups into the heteroaromatic 5-position of glycosyl triazoles. Perfluoroalkylcopper reagents are the most studied perfluoroalkyl organometallic reagents, readily prepared from halogeno perfluoroalkanes by copper metal insertion using a coordinating solvent.[21]



Scheme 3. Products of the conversion of bromo derivative **8**β with 4-methoxyphenylboronic acid.

For the perfluoroalkylation of the glycosides **7**β and **8**β we used such a copper-mediated procedure.[22] No perfluoroalkylation was observed on heating of dichloro derivative **7**β with 1-iodo-perfluorohexane in the presence of copper powder at 110 °C in DMSO for 20 h. Under the same conditions, dibromo derivative **8**β reacted to 3-perfluorohexyl-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (**18**) in a yield of 37% (Scheme 4). In addition, traces of a compound were detected, which is probably the 3,5-di-perfluorohexylated derivative. This result indicates that the hydrodebromination, competing with the C–C-cross-coupling reaction for the more reactive 5-position of the triazole ring of **8**β, proceeded faster. Consequently, the cross-coupling can only occur in 3-position. Products reduced in 5-position were also formed from compound **8**β in the Suzuki coupling with 4-methoxyphenylboronic acid (Scheme 3). Compound **18** was deprotected by treatment with 1% methanolic potassium *tert*butoxide yielding **19** (yield 75%). Attempts to introduce a trifluoromethyl group into the 5-position of **8**β applying the reagent combination $(CH_3)_3SiCF_3$–KF–CuI as precursor of a trifluoromethylcopper(I) species,[23] were not successful in DMF. The only product observed was compound **20**, which can be discussed as a result of an Ullmann-type coupling reaction. Leave out of only one component of the reagent combination resulted in no conversion of **8**β.



Scheme 4. Conversion of **8**β with 'perfluorohexylcopper(I)' and 'trifluoromethylcopper(I)' and following deprotection of the perfluorohexylated compound. (i) $C_6F_{13}I$, Cu, DMSO, 110 °C, 20 h. (ii) $KOBu^t$, MeOH, rt, 4–5 days. (iii) $(CH_3)_3SiCF_3$, KF, CuI, DMF, 80 °C, 24 h.

The formation of bis-heterocycles was also observed in other organometal cross-couplings, for example, in a reaction of 2,4-dibromothiazole.[6]

In summary, halogenated 1-glycosyl-1,2,4-triazoles synthesized by a BF_3-activated glycosylation procedure with a relatively high β-selectivity are suitable substrates in transition metal catalyzed cross-coupling reactions. In Suzuki reactions with a modified Pd-catalyst, a preferred substitution at C-5 of the triazole ring was observed, which is in accordance with results of nucleophilic substitutions at similar substrates.[8] In perfluoroalkylations the brominated precursor **8**β proved to be more suitable than the corresponding chloro derivative, when the reaction was carried out with in situ formed perfluoroalkylcopper(I) reagent. The reaction proceeded to the 3-substituted derivative **18** accompanied by hydrodebromination at C-atom 5.

2. Experimental

2.1. General

Chemicals were obtained from Aldrich, Fluka and Merck KGaA and used without further purification. Solvents were dried according to standard procedures. Melting points were determined with a Leitz polarizing microscope (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90) and are uncorrected. Microanalyses were carried out with a C/H/N/S-analyzer Thermoquest Flash EA 1112. Standard ^{1}H, ^{13}C NMR and DEPT spectra were recorded on a Bruker spectrometer AC 250. For the correlation spectra (COSY, NOESY, HMBC) we used a Bruker Spectrometer AVANCE 500. ^{1}H and ^{13}C NMR chemical shifts are given in ppm, and refer to tetramethylsilane (^{1}H, 0 ppm) and $CDCl_3$ (^{13}C, 77.00 ppm), CD_3OD (^{13}C, 49.05 ppm), C_6D_6 (^{13}C, 128.02 ppm), respectively. Optical rotations were measured on a Polar LμP (IBZ Meßtechnik). Column chromatography was carried out with Merck Silica Gel 60 (63–200 μm) and TLC on Merck Silica Gel 60 F_{254} sheets. TLC was carried out on a silica gel 60 GF_{250} (Merck) by charring with 5% H_2SO_4 in methanol.

2.1.1. 3-Chloro-1-(2,3,4-tri-*O*-pivaloyl-α-D-xylopyranosyl)-1,2,4-triazole (6α) and 3-chloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (6β). To a solution of 1,2,3,4-tetra-*O*-pivaloyl-β-D-xylopyranose (**1**) (3.0 g, 6.2 mmol) and 3-chloro-1*H*-1,2,4-triazole (**2**)[14] (1.28 g, 12.4 mmol) in anhyd acetonitrile (50 mL), 3–5 equiv of $BF_3\cdot Et_2O$ were added. The mixture was stirred for about 6 days at room temperature (TLC control). Then, it was poured into a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted three times with chloroform. After washing of the chloroform phase with water and brine, the solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: heptane/diethyl ether, v:v=3:1; **6**α: R_f=0.12, **6**β: R_f=0.08) yielding 0.32 g (11%) of **6**α and 1.6 g (53%) of **6**β.

Compound **6**β: colorless crystals; mp 166–168 °C (cyclohexane); $[\alpha]_D^{20}$ −18.43 (*c* 1.09, $CHCl_3$). ^{1}H NMR (250 MHz, C_6D_6): δ=7.67 (s, 1H, H-triazole); 5.38–5.24 (m, 2H, H-2, H-3); 5.00 (ddd, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.1 Hz, $^3J_{4,5b}$=10.3 Hz, H-4); 4.71 (d, 1H, $^3J_{1,2}$=8.6 Hz, H-1); 3.68 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 2.65 (t, 1H, $^3J_{4,5b}$=11.0 Hz, H-5b); 1.15, 1.11, 1.01 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.1, 177.0, 176.8 (3s, 3C=O); 153.2 (C-3-triazole); 144.0 (C-5-triazole); 86.3 (C-1); 71.4, 69.9, 68.1 (C-2, C-3, C-4); 65.6 (C-5); 38.8, 38.7 (3*C*(CH_3)$_3$); 27.1, 27.0, 26.8 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{34}ClN_3O_7$ (487.98): C, 54.15; H, 7.02; N, 8.61. Found: C, 54.30; H, 7.13; N, 8.66.

Compound **6**α: colorless crystals; mp 142–146 °C (heptane); $[\alpha]_D^{21}$ +96.71 (*c* 1.18, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.06 (s, 1H, H-triazole); 6.16 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-3); 5.97 (d, 1H, $^3J_{1,2}$=5.9 Hz, H-1); 5.17–5.03 (m, 2H, $^3J_{4,5a}$=5.8 Hz, $^3J_{1,2}$=6.0 Hz, $^3J_{4,5b}$=10.2 Hz, H-2, H-4); 4.00 (t, 1H, $^3J_{4,5b}$=10.7 Hz, H-5b); 3.90 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.0 Hz, H-5a); 1.19, 1.15, 0.93 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.5, 176.6 (3s, 3C=O); 153.6 (C-3-triazole); 146.2 (C-5-triazole); 81.3 (C-1); 69.7, 68.8, 68.3 (C-2, C-3, C-4); 62.5 (C-5); 38.8, 38.7 (3*C*(CH_3)$_3$); 27.1, 27.0 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{34}ClN_3O_7$ (487.98): C, 54.15; H, 7.02; N, 8.61. Found: C, 54.37; H, 7.11; N, 8.26.

2.1.2. 3,5-Dichloro-1-(2,3,4-tri-*O*-pivaloyl-α-D-xylopyranosyl)-1,2,4-triazole (7α) and 3,5-dichloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (7β). 1.0 g (2.05 mmol) of **1**, 0.57 g (4.1 mmol) of 3,5-dichloro-1,2,4-triazole (**3**)[15] and 3–5 equiv of $BF_3\cdot Et_2O$ dissolved in 50 mL of anhyd acetonitrile were reacted for about 3 days at room temperature (TLC control). The work-up procedure was analogous to that for **6**α/**6**β. After column chromatographic purification (eluent: heptane/ethyl acetate, v:v=20:1; **7**α: R_f=0.10, **7**β: R_f=0.07), 0.14 g (13%) of **7**α and 0.74 g (69%) of compound **7**β were isolated.

Compound **7**β: colorless crystals; mp 125–126 °C (heptane); $[\alpha]_D^{20}$ −33.10 (*c* 1.28, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.65 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-2); 5.52 (d, 1H, $^3J_{1,2}$=9.1 Hz, H-1); 5.48 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-3); 5.23–5.10 (m, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.3 Hz, $^3J_{4,5b}$=10.5 Hz, H-4); 4.30 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.54 (t, 1H, $^3J_{4,5b}$=11.0 Hz, H-5b); 1.16, 1.14, 0.99 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.1, 177.0, 175.7, (3s, 3C=O); 153.0 (C-3-triazole); 143.1 (C-5-triazole); 84.2 (C-1); 71.7, 69.4, 68.1 (C-2, C-3, C-4); 65.6 (C-5); 38.8, 38.6 (3*C*(CH_3)$_3$); 27.1, 27.0, 26.7 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}Cl_2N_3O_7$ (522.42): C, 50.58; H, 6.37; N, 8.04. Found: C, 50.89; H, 6.46; N, 8.63.

Compound **7**α: colorless crystals; mp 120–124 °C (heptane); $[\alpha]_D^{21}$ +76.33 (*c* 0.96, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.31–6.20 (m, 2H, $^3J_{1,2}$=6.0 Hz, $^3J_{2,3}$=9.9 Hz, H-3, H-1); 5.22–5.08 (m, 2H, $^3J_{4,5a}$=5.8 Hz, $^3J_{1,2}$=6.3 Hz, $^3J_{3,4}$=9.3 Hz, $^3J_{2,3}$=9.9 Hz, $^3J_{4,5b}$=10.5 Hz, H-2, H-4); 4.02 (t, 1H, $^3J_{4,5b}$=11.0 Hz, H-5b); 3.89 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.0 Hz, H-5a); 1.19, 1.15, 0.96 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.5, 177.2, 176.7, (3s, 3C=O); 152.5 (C-3-triazole); 143.9 (C-5-triazole); 79.5 (C-1); 69.4, 68.5, 68.4 (C-2, C-3, C-4); 62.1 (C-5); 38.8, 38.7 (3*C*(CH_3)$_3$); 27.1, 27.0, 26.6 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}Cl_2N_3O_7$ (522.42): C, 50.58; H, 6.37; N, 8.04. Found: C, 50.79; H, 6.49; N, 7.78.

2.1.3. 3,5-Dibromo-1-(2,3,4-tri-*O*-pivaloyl-α-D-xylopyranosyl)-1,2,4-triazole (8α) and 3,5-dibromo-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (8β). 2.0 g (4.1 mmol) of **1**, 1.85 g (8.2 mmol) of 3,5-dibromo-1,2,4-triazole (**4**)[16] and 3–5 equiv of $BF_3 \cdot Et_2O$ dissolved in 50 mL of anhyd acetonitrile were reacted for about 3–4 days at room temperature (TLC control). The work-up procedure was analogous to that for **6α/6**β. After column chromatographic separation (eluent: heptane/ethyl acetate, v:v=8:1; **8**α: R_f=0.21, **8**β: R_f=0.13), 0.38 g (15%) of **8**α and 1.79 g (71%) of **8**β were isolated.

Compound **8**β: colorless crystals; mp 142–145 °C (cyclohexane); $[\alpha]_D^{20}$ −30.51 (*c* 1.11, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.70 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-2); 5.55 (d, 1H, $^3J_{1,2}$=9.2 Hz, H-1); 5.49 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-3); 5.17 (ddd, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.5 Hz, $^3J_{4,5b}$=10.3 Hz, H-4); 4.30 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5a); 3.54 (dd, 1H, $^3J_{4,5b}$=10.3 Hz; $^2J_{5a,5b}$=11.6 Hz, H-5b); 1.16, 1.14, 0.98 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.3, 177.2, 175.7, (3s, 3C=O); 141.8 (C-3-triazole); 131.2 (C-5-triazole); 85.0 (C-1); 72.0, 69.6, 68.3 (C-2, C-3, C-4); 65.8 (C-5); 38.9, 38.8 (3*C*(CH_3)$_3$); 27.2, 26.9 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}Br_2N_3O_7$ (611.32): C, 43.22; H, 5.44; N, 6.87. Found: C, 43.51; H, 5.46; N, 6.77.

Compound **8**α: colorless crystals; mp 124–125 °C (heptane); $[\alpha]_D^{24}$ +59.23 (*c* 1.48, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.28 (d, 1H, $^3J_{1,2}$=6.2 Hz, H-1); 6.25 (t, 1H, $^3J_{2,3}$=9.8 Hz, H-3); 5.20–5.02 (m, 2H, $^3J_{4,5a}$=6.0 Hz, $^3J_{1,2}$=6.4 Hz, $^3J_{2,3}$=9.8 Hz, H-2, H-4); 3.99 (t, 1H, $^3J_{4,5b}$=10.9 Hz, H-5b); 3.86 (dd, 1H, $^3J_{4,5a}$=6.0 Hz, $^2J_{5a,5b}$=11.1 Hz, H-5a); 1.17, 1.13, 0.93 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.6, 177.4, 176.8, (3s, 3C=O); 141.3 (C-3-triazole); 132.0 (C-5-triazole); 80.5 (C-1); 69.6, 68.7, 68.3 (C-2, C-3, C-4); 62.1 (C-5); 38.9, 38.8 (3*C*(CH_3)$_3$); 27.2, 26.7 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}Br_2N_3O_7$ (611.32): C, 43.22; H, 5.44; N, 6.87. Found: C, 43.86; H, 5.63; N, 6.55.

2.1.4. 5-Bromo-3-chloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (9β) and 3-bromo-5-chloro-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (10β). 2.0 g (4.1 mmol) of **1**, 1.5 g (8.2 mmol) of 3-bromo-5-chloro-1,2,4-triazole (**5**)[16] and 3–5 equiv of $BF_3 \cdot Et_2O$ dissolved in 50 mL of anhyd acetonitrile were reacted for about 3–4 days at room temperature (TLC control). The work-up procedure was analogous to that for **6α/6**β. After column chromatographic separation (eluent: heptane/ethyl acetate, v:v=10:1), 0.98 g (42%) of **9**β and 0.91 g (39%) of **10**β were isolated; (eluent: heptane/ethyl acetate, v:v=2:1; **9**β: R_f=0.37, **10**β: R_f=0.32).

Compound **9**β: colorless crystals; mp 134–136 °C (cyclohexane); $[\alpha]_D^{22}$ −25.23 (*c* 1.20, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.68 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-2); 5.54 (d, 1H, $^3J_{1,2}$=9.0 Hz, H-1); 5.48 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-3); 5.24–5.08 (m, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.5 Hz, $^3J_{4,5b}$=10.4 Hz, H-4); 4.29 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5a); 3.54 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5b); 1.16, 1.13, 0.97 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.3, 177.2, 175.8, (3s, 3C=O); 154.4 (C-3-triazole); 131.0 (C-5-triazole); 85.1 (C-1); 72.0, 69.6, 68.3 (C-2, C-3, C-4); 65.8 (C-5); 38.9, 38.8 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.9 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}BrClN_3O_7$ (566.87): C, 46.61; H, 5.87; N, 7.41. Found: C, 47.05; H, 5.94; N, 7.00.

Compound **10**β: colorless crystals; mp 128–131 °C (cyclohexane); $[\alpha]_D^{22}$ −21.08 (*c* 1.14, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.65 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-2); 5.51 (d, 1H, $^3J_{1,2}$=9.0 Hz, H-1); 5.46 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-3); 5.22–5.06 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{3,4}$=9.4 Hz, $^3J_{4,5b}$=10.3 Hz, H-4); 4.28 (dd, 1H, $^3J_{4,5a}$=5.7 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5a); 3.52 (dd, 1H, $^3J_{4,5b}$=10.4 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5b); 1.14, 1.12, 0.97 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.3, 175.8, (3s, 3C=O); 140.5 (C-3 triazole); 143.5 (C-5 triazole); 84.4 (C-1); 71.9, 69.5, 68.3 (C-2, C-3, C-4); 65.8 (C-5); 38.9, 38.8 (3*C*(CH_3)$_3$); 27.2, 27.1, 26.9 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{22}H_{33}BrClN_3O_7$ (566.87): C, 46.61; H, 5.87; N, 7.41. Found: C, 47.03; H, 6.00; N, 7.06.

2.1.5. 3-Chloro-5-phenyl-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (11). 0.3 g (0.57 mmol) of the β-glycoside **7**β dissolved in 10 mL of anhyd DMF were placed in an ACS pressure tube. After pass through of argon (10–15 min), phenylboronic acid (210 mg, 1.52 mmol), potassium phosphate (240 mg, 1.14 mmol), 0.01 equiv of $Pd(OAc)_2$ and 0.01 equiv of $[(Ad)_2PHBu]^+I^-$ were added (argon atmosphere). The mixture was stirred at 100 °C for 20 h. For work-up the reaction mixture was diluted with ethyl acetate (50 mL), washed twice with 1 N aqueous solution of NaOH (30 mL), and water (30 mL) After separation and drying (Na_2SO_4), the organic phase was concentrated under reduced pressure. Compound **11** (0.2 g, 63%) was isolated via column chromatographic purification (eluent: heptane/ethyl acetate, v:v=10:1; R_f=0.21). Small amounts of starting material **7**β were recovered.

Compound **11**: colorless crystals; mp 124–126 °C (heptane/ethyl acetate); $[\alpha]_D^{22}$ −1.05 (*c* 2.63, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.71–7.49 (m, 5H, Ph); 5.85 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-2); 5.40 (d, 1H, $^3J_{1,2}$=9.2 Hz, H-1); 5.33 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-3); 5.26–5.09 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{4,5b}$=10.3 Hz, H-4); 4.34 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.47 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.4 Hz, H-5b); 1.14, 1.12, 0.90 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.7, 177.4, 175.7, (3s, 3C=O); 158.9 (C-5 triazole); 153.4 (C-3 triazole); 132.0, 129.8, 129.2, 126.2 (Ph); 84.9 (C-1); 72.5, 69.9, 68.7 (C-2, C-3, C-4); 65.7 (C-5); 39.2, 39.0 (3*C*(CH_3)$_3$); 27.5, 27.4, 27.1 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{28}H_{38}ClN_3O_7$ (564.07): C, 59.62; H, 6.79; N, 7.45. Found: C, 59.24; H, 6.84; N, 7.32.

2.1.6. 3-Chloro-5-(4-vinylphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (12). Glycoside **7**β (0.25 g, 0.48 mmol), 4-vinylphenylboronic acid (190 mg, 1.28 mmol), K_3PO_4 (204 mg, 0.96 mmol), 0.01 equiv of $Pd(OAc)_2$, and 0.01 equiv of $[(Ad)_2PHBu]^+I^-$ were reacted as described for compound **11**. After column chromatographic purification (eluent: heptane/ethyl acetate, v:v=5:1; R_f=0.18), 0.22 g (78%) of **12** were isolated.

Compound **12**: colorless crystals; mp 124–125 °C (cyclohexane); $[\alpha]_D^{21}$ −1.72 (*c* 1.04, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.73–7.42 (m, 4H, Ph); 6.77 (dd, 1H, $^3J_{vinyl}$=11.0, 17.5 Hz, =CH); 5.90 (d, 1H, $^3J_{vinyl}$=17.5 Hz, =CH_2); 5.86 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-3); 5.43 (d, 1H, $^3J_{vinyl}$=11.0 Hz, =CH_2); 5.41 (d, 1H, $^3J_{1,2}$=9.2 Hz, H-1); 5.33 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-2); 5.26–5.12 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{4,5b}$=10.0 Hz, H-4); 4.35 (dd, 1H, $^3J_{4,5a}$=5.7 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.48 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5b); 1.14, 1.12, 0.90 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.4, 177.3, 175.4, (3s, 3C=O); 158.8 (C-5 triazole); 140.9 (C-3 triazole); 135.8 (=CH); 129.2, 127.2, 124.9 (Ph); 116.9 (=CH_2); 84.7 (C-1); 72.3, 69.6, 68.5 (C-2, C-3, C-4); 65.5 (C-5); 38.9, 38.7 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.8 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{30}H_{40}ClN_3O_7$ (590.11): C, 61.06; H, 6.83; N, 7.12. Found: C, 60.59; H, 6.90; N, 6.86.

2.1.7. 3-Chloro-5-(4-methoxyphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (13), 5-chloro-3-(4-methoxyphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (14), and 3,5-di-(4-methoxyphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (15). Glycoside **7**β (0.2 g, 0.38 mmol), 4-methoxyphenylboronic acid (150 mg, 1.01 mmol), K_3PO_4 (160 mg, 0.76 mmol), 0.01 equiv of $Pd(OAc)_2$, and 0.01 equiv of $[(Ad)_2PHBu]^+I^-$ were reacted as described for compound **11**. After column chromatographic purification (eluent: heptane/ethyl acetate, v:v=7:1), 0.1 g (44%) of **13**, 0.02 g (9%) of **14** and 0.03 g (12%) of **15**, were isolated (TLC: eluent: heptane/ethyl acetate, v:v=2:1; **15**: R_f=0.46, **13**: R_f=0.40, **14**: R_f=0.34).

Compound **13**: colorless crystals; mp 112–113 °C (heptane/ethyl acetate); $[\alpha]_D^{21}$ +5.29 (*c* 1.01, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.64–7.56 (m, 2H, Ph); 7.11–702 (m, 2H, Ph); 5.85 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-2); 5.40 (d, 1H, $^3J_{1,2}$=9.1 Hz, H-1); 5.35 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-3); 5.26–5.12 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{4,5b}$=10.1 Hz, H-4); 4.35 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5a); 3.91 (s, 3H, OCH_3); 3.49 (dd, 1H, $^3J_{4,5b}$=10.4 Hz, $^2J_{5a,5b}$=11.4 Hz, H-5b); 1.16, 1.14, 0.91 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.5, 177.3, 175.4 (3s, 3C=O); 162.3 ($C_{quart.}$-Ph) 158.6 (C-5 triazole); 153.0 (C-3 triazole); 130.5, 118.1 ($C_{quart.}$-Ph), 114.9 (Ph); 84.7 (C-1); 72.3, 69.6, 68.5 (C-2, C-3, C-4); 65.5 (C-5); 55.6 (s, OCH_3); 38.9, 38.7 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.8 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{29}H_{40}ClN_3O_8$ (594.10): C, 58.63; H, 6.79; N, 7.07. Found: C, 58.53; H, 6.80; N, 6.93.

Compound **14**: colorless crystals; mp 172–173 °C (heptane/ethyl acetate); $[\alpha]_D^{22}$ −34.62 (*c* 2.81, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=8.04–7.90 (m, 2H, Ph); 6.98–6.87 (m, 2H, Ph); 5.89 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-2); 5.57 (d, 1H, $^3J_{1,2}$=9.1 Hz, H-1); 5.52 (t, 1H, $^3J_{2,3}$=9.6 Hz, H-3); 5.32–5.15 (m, 1H, H-4); 4.33 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.6 Hz, H-5a); 3.85 (s, 3H, OCH_3); 3.49 (dd, 1H, $^3J_{4,5b}$=10.4 Hz, $^2J_{5a,5b}$=11.4 Hz, H-5b); 1.18, 1.17, 0.92 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.4, 177.3, 175.8 (3C=O); 162.8 ($C_{quart.}$-Ph), 162.4 (C-3 triazole); 143.2 (C-5 triazole); 121.1 ($C_{quart.}$-Ph), 128.1, 114.1 (Ph); 83.9 (C-1); 72.3, 69.4, 68.5 (C-2, C-3, C-4); 65.8 (C-5); 55.56 (s, OCH_3); 38.9, 38.7 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.8 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{29}H_{40}ClN_3O_8$ (594.10): C, 58.63; H, 6.79; N, 7.07. Found: C, 58.25; H, 6.59; N, 6.96.

Compound **15**: colorless crystals; mp 89–90 °C (ethyl acetate); $[\alpha]_D^{22}$ −23.95 (*c* 0.89, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=8.11–8.01 (m, 2H, Ph); 7.71–7.60 (m, 2H, Ph); 7.12–7.01 (m, 2H, Ph); 6.98–6.87 (m, 2H, Ph); 6.10 (t, 1H, $^3J_{2,3}$=9.4 Hz, H-2); 5.42–5.18 (m, 3H, $^3J_{4,5a}$=5.7 Hz, $^3J_{1,2}$=9.2 Hz, $^3J_{2,3}$=9.6 Hz, H-1, H-3, H-4); 4.37 (dd, 1H, $^3J_{4,5a}$=5.6 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.91, 3.84 (2s, 6H, 2OCH_3); 3.48 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.3 Hz, H-5b); 1.16, 1.14, 0.81 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.4, 177.3, 175.6 (3s, 3C=O); 161.9, 161.8 (2$C_{quart.}$-Ph) 160.9 (C-3 triazole); 157.9 (C-5 triazole); 130.5, 128.4, 114.8, 114.0 (Ph); 123.2, 119.5 (2$C_{quart.}$-Ph); 84.6 (C-1); 72.6, 69.5, 68.6 (C-2, C-3, C-4); 65.4 (C-5); 55.6, 55.4 (2OCH_3); 38.9, 38.6 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.7 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{26}H_{47}N_3O_9$ (665.78): C, 64.95; H, 7.12; N, 6.31. Found: C, 64.71; H, 7.10; N, 6.27.

2.1.8. 3-Bromo-5-(4-vinylphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (16). Glycoside **8**β (1.0 g, 1.6 mmol), 4-vinylphenylboronic acid (630 mg, 4.26 mmol), K_3PO_4 (680 mg, 3.2 mmol), 0.01 equiv of $Pd(OAc)_2$, and 0.01 equiv of $[(Ad)_2PHBu]^+I^-$ were reacted as described for compound **11**. After column chromatographic purification (eluent: heptane/diethyl ether, v:v=5:1; R_f=0.22), 0.7 g (67%) of **16** were isolated.

Compound **16**: colorless crystals; mp 94–95 °C (heptane); $[\alpha]_D^{21}$ +3.98 (*c* 1.09, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.73–7.42 (m, 4H, Ph); 6.77 (dd, 1H, $^3J_{vinyl}$=11.0, 17.5 Hz, =CH); 5.90 (d, 1H, $^3J_{vinyl}$=17.5 Hz, =CH_2); 5.86 (t, 1H, $^3J_{2,3}$=9.3 Hz, H-3); 5.43 (d, 1H, $^3J_{vinyl}$=11.0 Hz, =CH_2); 5.41 (d, 1H, $^3J_{1,2}$=9.2 Hz, H-1); 5.33 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-2); 5.26–5.12 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{4,5b}$=10.0 Hz, H-4); 4.35 (dd, 1H, $^3J_{4,5a}$=5.7 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.48 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5b); 1.14, 1.12, 0.90 (3s, 27H, 3C(CH_3)$_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.4, 177.3, 175.4, (3s, 3C=O); 158.8 (C-5 triazole); 140.9 (C-3 triazole); 135.8 (=CH); 129.2, 127.2, 124.9 (Ph); 116.9 (=CH_2); 84.7 (C-1); 72.3, 69.6, 68.5 (C-2, C-3, C-4); 65.5 (C-5); 38.9, 38.7 (3*C*(CH_3)$_3$); 27.3, 27.2, 26.8 (3C(*C*H_3)$_3$). Anal. Calcd for $C_{30}H_{40}BrN_3O_7$ (634.56): C, 56.78; H, 6.35; N, 6.62. Found: C, 56.66; H, 6.30; N, 6.31.

2.1.9. 3-Bromo-5-(4-hexyloxyphenyl)-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (17). Glycoside **8**β (0.47 g, 0.77 mmol), 4-hexyloxyphenylboronic acid (454 mg, 2.05 mmol), K_3PO_4 (330 mg, 1.54 mmol), 0.01 equiv of $Pd(OAc)_2$, and 0.01 equiv of $[(Ad)_2PHBu]^+I^-$ were reacted as described for compound **11**. After column chromatographic purification (eluent: heptane/ethyl acetate, v:v=10:1), 0.29 g (53%) of **17** were isolated (eluent: heptane/ethyl acetate, v:v=2:1; R_f=0.64) beside traces of the 3,5-diarylated product.

Compound **17**: colorless crystals; mp 113–115 °C (heptane/ethyl acetate); $[\alpha]_D^{21}$ +12.34 (*c* 0.50, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ=7.64–7.50 (m, 2H, Ph); 7.10–6.96 (m, 2H, Ph); 5.85 (t, 1H, $^3J_{2,3}$=9.2 Hz, H-2); 5.39 (d, 1H,

$^3J_{1,2}$=9.1 Hz, H-1); 5.33 (t, 1H, $^3J_{2,3}$=9.5 Hz, H-3); 5.25–5.12 (m, 1H, $^3J_{4,5a}$=5.7 Hz, $^3J_{4,5b}$=10.1 Hz, H-4); 4.34 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.4 Hz, H-5a); 4.04 (t, 2H, OCH_2); 3.47 (t, 1H, $^3J_{4,5b}$=10.8 Hz, H-5b); 1.91–1.74 (m, 2H, OCH_2CH_2); 1.57–1.29 (m, 6H, $3CH_2$); 1.15, 1.12, 0.90 (3s, 27H, $3C(CH_3)_3$); 0.89 (t, 3H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.5, 177.2, 175.4 (3C=O); 161.8 ($C_{quart.}$-Ph); 159.0 (C-5 triazole); 140.9 (C-3 triazole); 130.4, 115.3 (Ph); 117.6 ($C_{quart.}$-Ph); 84.6 (C-1); 72.5, 69.6, 68.7 (C-2, C-3, C-4); 67.5 (s, OCH_2); 65.4 (C-5); 38.9, 38.7 ($3C(CH_3)_3$); 31.7, 29.1, 25.7, 22.7 ($4CH_2$); 27.3, 27.2, 26.8 ($3C(CH_3)_3$); 14.2 (CH_3). Anal. Calcd for $C_{34}H_{50}BrN_3O_8$ (708.69): C, 57.62; H, 7.11; N, 5.93. Found: C, 57.22; H, 7.15; N, 5.68.

2.1.10. 3-Perfluorohexyl-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-1,2,4-triazole (18). To a suspension of copper powder (0.75 g, 11.8 mmol) in 10 mL anhyd DMSO, 50 mg of iodine were added under Argon. After the mixture was sonicated by ultrasound for 5 min, 1-iodo-perfluorohexane (1.30 mL, 6.0 mmol) was dropwise added with stirring. Stirring was continued for 30–40 min at 110 °C before the glycoside **8**β (0.45 g, 0.74 mmol) was added. Then stirring was continued at this temperature for 15–20 h. Finally, the mixture was diluted with ethyl acetate (20 mL), filtered through Celite, and concentrated under reduced pressure. The residue was column chromatographically purified (eluent: heptane/ethyl acetate, v:v=10:1; R_f=0.21) yielding 0.21 g (37%) of product **18**.

Compound **18**: colorless crystals; mp 130–133 °C (heptane/ethyl acetate); $[\alpha]_D^{21}$ −17.43 (*c* 0.95, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.44 (s, 1H, H-5 triazole); 5.66–5.43 (m, 3H, H-1, H-2, H-3); 5.28–5.12 (m, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.4 Hz, $^3J_{4,5b}$=10.4 Hz, H-4); 4.32 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.55 (dd, 1H, $^3J_{4,5b}$=10.6 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5b); 1.18, 1.14, 0.97 (3s, 27H, $3C(CH_3)_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.3, 177.1, 176.3 (3s, 3C=O); 155.6 (C-3 triazole); 144.7 (C-5 triazole); 87.0 (C-1); 71.6, 70.1, 68.3 (C-2, C-3, C-4); 65.9 (C-5); 39.0, 38.9, 38.8 ($3C(CH_3)_3$); 27.2, 26.8 ($3C(CH_3)_3$). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−80.5 (s, CF_3); −112.0, −121.3, −121.8, 122.5, −125.8 (5s, $5CF_2$). Anal. Calcd for $C_{28}H_{34}F_{13}N_3O_7$ (771.57): C, 43.59; H, 4.44; N, 5.45. Found: C, 43.81; H, 4.38; N, 5.35.

2.1.11. 3-Perfluorohexyl-1-(β-D-xylopyranosyl)-1,2,4-triazole (19). A solution of **18** (0.2 g, 0.26 mmol) in 1% methanolic KOBu^t was stirred for 4–5 days at room temperature (TLC-control). For work-up, the mixture was neutralized with cation exchange resin (IR 120), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (eluent: toluene/ethyl acetate/ethanol, v:v:v=7:2:1; R_f=0.16). Yield of **19**: 0.10 g (75%).

Compound **19**: colorless crystals; mp 126–131 °C (toluene/ethanol); $[\alpha]_D^{22}$ −18.81 (*c* 0.95, MeOH). ^{1}H NMR (250 MHz, CD_3OD): δ=8.87 (s, 1H, H-5 triazole); 5.43 (d, 1H, $^3J_{1,2}$=9.1 Hz, H-1); 4.03 (dd, 1H, $^3J_{4,5a}$=5.3 Hz, $^2J_{5a,5b}$=11.2 Hz, H-5a); 3.93 (t, 1H, $^3J_{2,3}$=9.1 Hz, H-2); 3.69 (ddd, 1H, $^3J_{4,5a}$=5.2 Hz, $^3J_{3,4}$=9.0 Hz, $^3J_{4,5b}$=10.4 Hz, H-4); 3.48 (t, 1H, $^3J_{3,4}$=9.0 Hz, H-3); 3.46 (t, 1H, $^2J_{5a,5b}$=10.9 Hz, H-5b). ^{13}C NMR (63 MHz, CD_3OD): δ=154.4 (C-3 triazole); 148.0 (C-5 triazole); 89.9 (C-1); 78.7, 73.3, 70.6 (C-2, C-3, C-4); 69.9 (C-5). ^{19}F NMR (235 MHz, CD_3OD): δ=−78.8 (s, CF_3); −109.8, −119.1, −119.9, 120.3, −123.7 (5s, $5CF_2$). Anal. Calcd for $C_{13}H_{10}F_{13}N_3O_4$ (519.21): C, 30.07; H, 1.94; N, 8.09. Found: C, 30.26; H, 2.01; N, 7.62.

2.1.12. Bis (3-bromo-1-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyrano-syl)-1,2,4-triazol-5-yl) (20). To a solution of glycoside **8**β (0.25 g, 0.41 mmol) in anhyd DMF (argon atmosphere), CuI (0.16 g, 0.84 mmol), KF (60 mg, 1.0 mmol), and $CF_3Si(CH_3)_3$ (0.15 mL, 1.0 mmol) were added. The mixture was stirred at 80 °C for 24 h. For work-up, the mixture was diluted with 50 mL of ethyl acetate and washed three times with 20 mL of water. After drying (Na_2SO_4), filtration and concentration of the organic layer under reduced pressure, the residue was purified by column chromatography (eluent: heptane/ethyl acetate, v:v=8:1; R_f=0.26) yielding 0.11 g (51%) of compound **20**.

Compound **20**: colorless crystals; mp 166–171 °C (heptane); $[\alpha]_D^{23}$ +0.75 (*c* 1.20, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.70 (d, 1H, $^3J_{1,2}$=9.2 Hz, H-1); 5.88 (t, 1H, $^3J_{1,2}$=9.3 Hz, H-2); 5.51 (t, 1H, $^3J_{3,4}$=9.5 Hz, H-3); 5.18 (sym. M, 1H, $^3J_{4,5a}$=5.8 Hz, $^3J_{3,4}$=9.9 Hz, H-4); 4.22 (dd, 1H, $^3J_{4,5a}$=5.8 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5a); 3.55 (dd, 1H, $^3J_{4,5b}$=10.3 Hz, $^2J_{5a,5b}$=11.5 Hz, H-5b); 1.16, 1.15, 0.90 (3s, 27H, $3C(CH_3)_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ=177.4, 177.3, 175.6 (3s, 3C=O); 144.1 (C-5 triazole); 140.6 (C-3 triazole); 84.9 (C-1); 72.4, 69.7, 68.5 (C-2, C-3, C-4); 65.7 (C-5); 38.9, 38.9, 38.7 ($3C(CH_3)_3$); 27.3, 27.2, 26.8 ($3C(CH_3)_3$). MS-FAB (pos. NBA): *m/z*=1066 $[M+2H]^{2+}$. MS-EI: *m/z*=677 $[M-385]^+$, 385 [2,3,4-tri-*O*-pivaloyl-D-xylopyranosyl $(C_{20}H_{33}O_7)]^+$. Anal. Calcd for $C_{44}H_{66}Br_2N_6O_{14}$ (1062.84): C, 49.72; H, 6.26; N, 7.91. Found: C, 49.64; H, 6.07; N, 7.66.

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Synthesis and ring transformations of 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones

Joana Dumčiūtė,[a] Vytas Martynaitis,[a] Wolfgang Holzer,[b] Sven Mangelinckx,[c] Norbert De Kimpe[c] and Algirdas Šačkus[a,*]

[a]*Department of Organic Chemistry, Kaunas University of Technology, LT-50270 Kaunas, Lithuania*
[b]*Department of Drug Synthesis, Faculty of Life Sciences, University of Vienna, Pharmaziezentrum, A-1090 Vienna, Austria*
[c]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Gent, Belgium*

Received 14 December 2005; revised 11 January 2006; accepted 17 January 2006

Available online 20 February 2006

Abstract—Heating 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolinium chloride in the presence of hydrazine bishydrate produces regioselectively the five-membered heterocycle 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one. The assignment of the structure is based on extensive ^{1}H, ^{13}C and ^{15}N NMR spectroscopic studies. No ring-chain tautomerism of the 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one was observed to open-chain hydrazides or the corresponding six-membered 1,2,10,10a-tetrahydro[1,2,4]triazino[4,3-*a*]indol-3(4*H*)-one. Further transformations of 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one were performed by treatment with aromatic aldehydes, acid chlorides and isocyanates giving access to 40 novel hydrazones, *N*,*N*′-diacylhydrazines, *N*-acyl-*N*′-carbamoylhydrazines and 1,3,4-oxadiazoles.
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1. Introduction

1-Carbamoylmethyl-3*H*-indolinium salts **1** are known to cyclize to 1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones upon treatment with base.[1] If, however, the 1-carbamoylmethyl-3*H*-indolinium salts **1** are transformed to the corresponding hydrazides **2**, further cyclization could either lead to 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones **3**, similar as to ring closure of the amides, or to the corresponding six-membered ring systems, that is, 1,2,10,10a-tetrahydro[1,2,4]triazino[4,3-*a*]indol-3(4*H*)-one **4**, if the terminal NH_2 group enters into reaction (Scheme 1). The objective of this work is to investigate the reaction of such hydrazides and, apart from the structural investigations, to study the reactivity of the novel cyclic products and route to novel heterocyclic compounds. The potential biological activity of the unknown 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones is also of interest, as these tricyclic derivatives contain both the 2,3-dihydro-1*H*-indole and imidazolidin-4-one nuclei. Via the reaction of an α-amino amide with a carbonyl compound followed by intramolecular cyclization, the conformationally rigid imidazolidin-4-one scaffold has already been introduced in some compounds to modify their physiological activities such as cognition enhancing activity,[2] nootropic activity,[3] antimalarial activity,[4] and analgesic activity.[5] Metabolic stable N-terminal imidazolidin-4-one prodrugs of Leu-enkephalin have also been prepared.[6] Compounds containing the indole-1-acetamide moiety also exhibit interesting physiological activities such as central muscle relaxation,[7] anticonvulsive activity,[8] and CNS depressant activity.[9]

2. Results and discussion

Heating 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolinium chloride **1** in the presence of hydrazine bishydrate, resulted in the isolation of a cyclized compound identified as the racemic five-membered heterocycle 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (**3**) (Scheme 2).

The main evidence for the assignment of structure **3**, containing the 3-aminoimidazolidin-4-one ring, follows from the ^{15}N NMR data. The ^{15}N,^{1}H HMBC spectrum shows three different N-atoms (δ −317.6, −299.1 and −224.6 ppm). In a ^{15}N DEPT experiment (optimized for $^{1}J_{NH}$=70 Hz) only the N-atom with the smallest chemical shift (δ −317.6) emerges, namely as a triplet (^{1}J=68.9 Hz)

Keywords: Hydrazides; Structural identification; 1,2,3,9a-Tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones; Hydrazines; Oxadiazoles.
* Corresponding author. Tel./fax: +370 37 451432; e-mail: algirdas.sackus@ktu.lt

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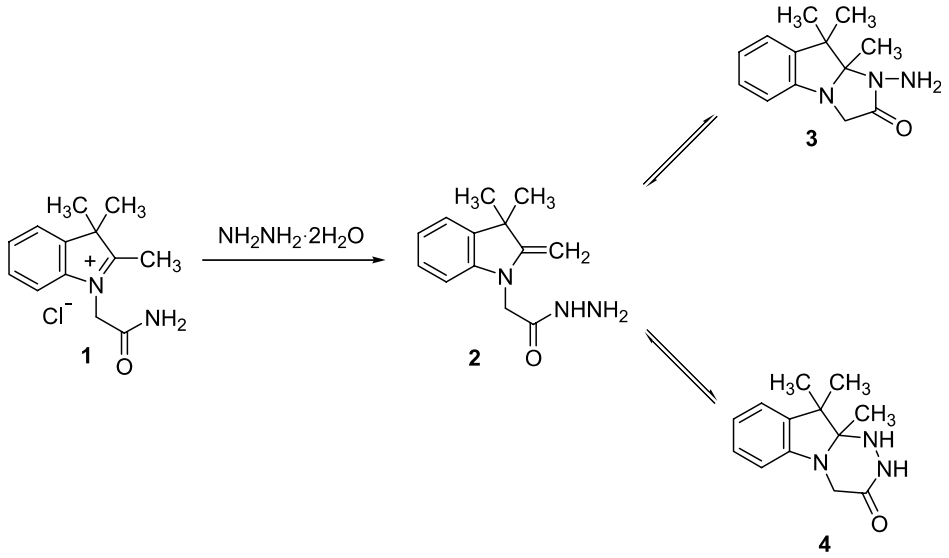
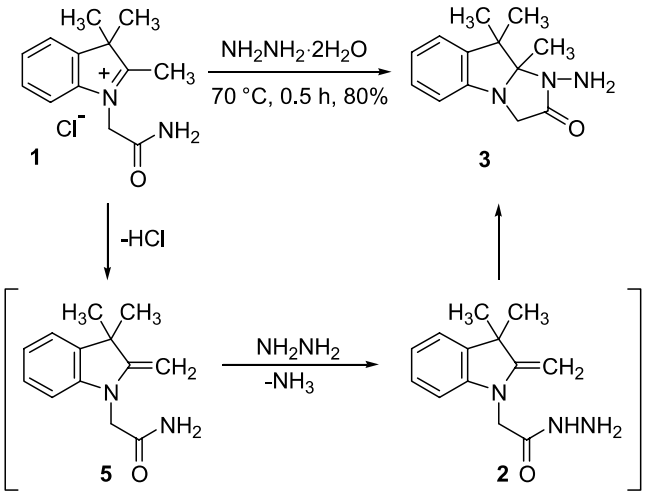
doi:10.1016/j.tet.2006.01.054



Scheme 1.



Scheme 2.

and thus proving to origin from an NH_2 moiety what definitely rules out structure **4**. Moreover, the ^{15}N, ^{1}H HMBC spectrum exhibits a correlation between the nitrogen atom with the largest chemical shift (N-1, δ −224.6) and the protons of 9a-CH_3 (δ 1.40 ppm), what seems improbable with structure **4** where the involved nuclei would be separated by four bonds and thus no correlation is expected. In addition, in the ^{1}H NMR spectrum there is only one sharp signal of relative intensity two for the NH-protons. For structure **4**, two different type of NH-signals have to be expected (CONH, N–NH). The assignments presented in Figure 1a are based on the combined application of standard NMR techniques such as NOE-difference (Fig. 1b), NOESY, APT, DEPT, HSQC, HMBC and long-range INEPT spectra with selective excitation.[10]

Although the amino nitrogen atom of the hydrazide moiety of **2** is more reactive[11] than the amide one, the condensation reaction involves the latter exclusively to give a five-membered ring. This observed reactivity is similar to addition reactions of phenylhydrazine in which it was proven that the N-1 of phenylhydrazine reacts as the nucleophilic site and not the NH_2-group.[12] The exclusive formation of the five-membered ring can be tentatively rationalized on the basis of the *E*/*Z* rotamerism of hydrazide **2** with respect to the nitrogen–carbon hydrazide bond with partial double bond character (Scheme 3). Studies concerning this hindered rotation of hydrazine derivatives have shown that steric effects of the substituents are driving the equilibrium towards the (*Z*) forms, augmented by intramolecular hydrogen bonding in the (*Z*) form.[13] It can be assumed that the large steric effect of the indolylmethyl carbonyl substituent of hydrazide **2** and the two possible intramolecular hydrogen bonds between the hydrogen atoms attached to the nitrogen and the oxygen atom, make the (*Z*) form much more favored. This (*Z*)-hydrazide is

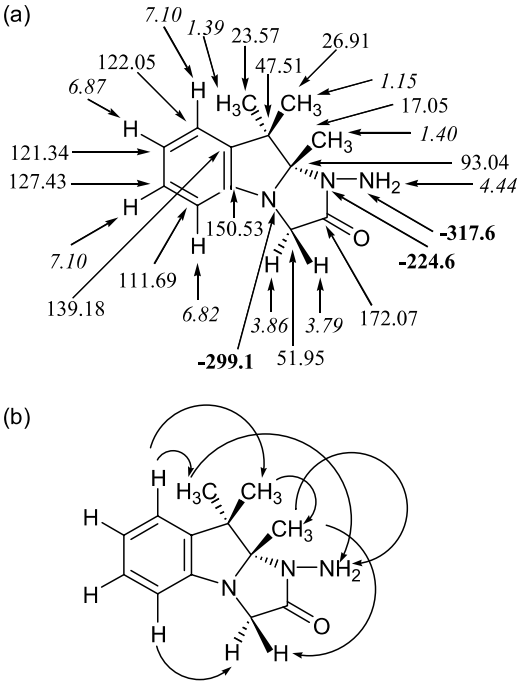
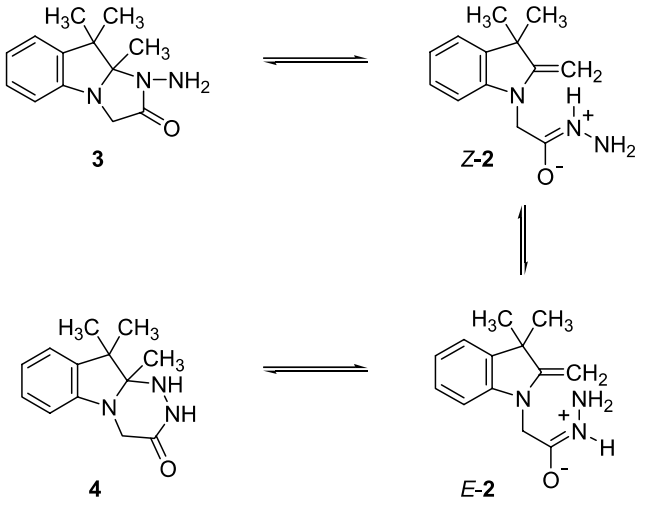


Figure 1. (a) ^{1}H (italics), ^{13}C and ^{15}N NMR (bold) chemical shifts [ppm; ref. TMS (^{1}H and ^{13}C) and CH_3NO_2 (^{15}N)] for **3** in DMSO-d_6. (b) Relevant NOE correlations.

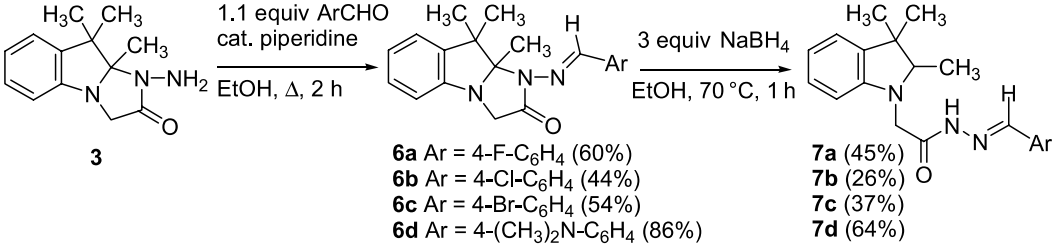


Scheme 3.

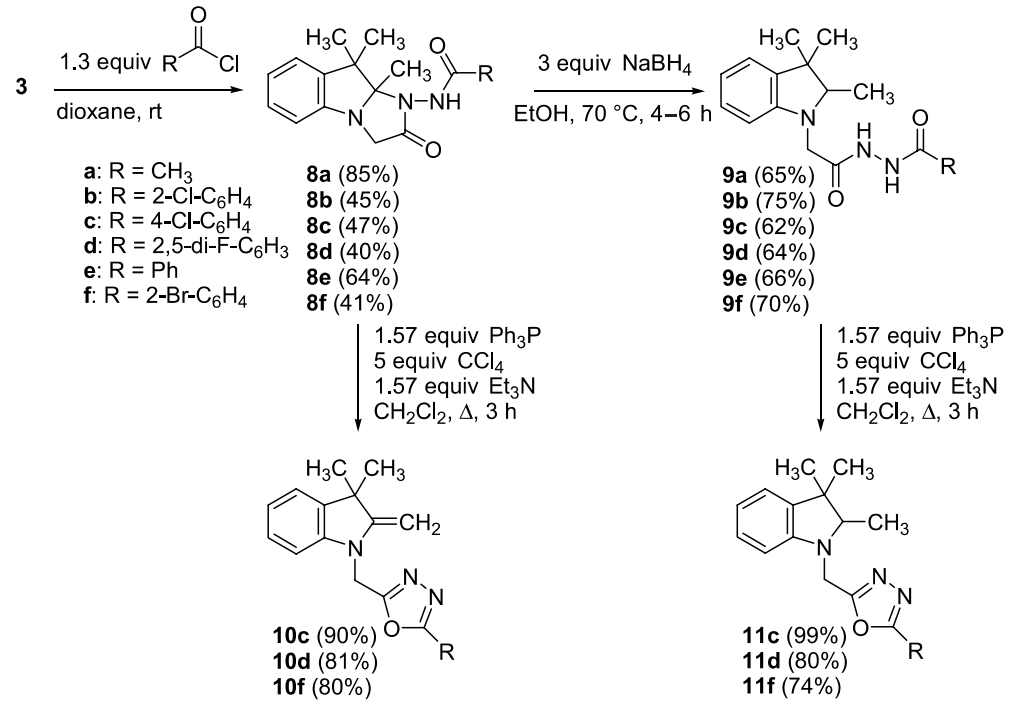
potentially capable of ring-chain tautomerism (*Z*)−**2**⇄**3**, while the unfavorable (*E*)-form would potentially be capable of ring-chain tautomerism (*E*)−**2**⇄**4**. No other ring-chain tautomeric forms of 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (**3**) were, however, visible by ^{1}H and ^{13}C NMR in $CDCl_3$ or DMSO-d_6, which can be explained by the annellation effect, that is, due to higher substitution and thereby higher conjugation the tricyclic compound **3** is expected to be more favored than the open-chain hydrazide **2**. These observations are in agreement with similar ring closures of α-amino acid hydrazides with aldehydes or ketones, which also resulted in 3-aminoimidazolidin-4-ones,[14] or the open-chain hydrazone tautomers in the case of low substituted compounds.[14c] Similarly, glycine hydroxamic acid condenses with benzaldehyde[15] and ketones,[16] leading to the formation of five-membered 3-hydroxyimidazolidin-4-ones. To the best of our knowledge, only few reports have been made on the synthesis of 1,2,4-triazin-6-ones from the reaction of α-amino acid hydrazides with aldehyde or ketone functions. Regarding a first report on the reaction of α-amino acid phenylhydrazides with formaldehyde,[17] it was stated by the same group in a later disclosure,[14a] that the proposed six-membered ring structures might be incorrect. A second report involved the intramolecular reaction of oxamic hydrazides with a ketone function giving 1,2,4-triazin-5,6-diones.[18] Also reported is the synthesis of pyrazolotriazines by reaction of pyrazolecarboxylic acid hydrazides and acetone.[19] Another special case involved reaction of aziridine-2-carboxylic acid hydrazides with acetone or cyclohexanone giving 1,3,4-triazabicyclo[4.1.0]-heptan-5-ones.[20] Moreover, reactions between α-amino acid hydrazides and carbonyl functions like imidoyl chlorides,[21] thioesters,[22] orthocarboxylates,[23] in which both five- and six-membered compounds could be formed, seem to give systematically the six-membered 1,2,4-triazin-6-ones. Therefore, it seems acceptable to assume that 3-amino-imidazolidin-4-ones are the preferred ring-chain tautomers with respect to 1,2,4-triazin-6-ones if imidazolidinone C-2 and C-5 are sp^3-hybridized, otherwise 1,2,4-triazin-6-ones seem to be favored. The only exception observed so far being the 1,3,4-triazabicyclo[4.1.0]heptan-5-ones,[20] in which, however, C-5 also has more double-bond character, being part of a three-membered ring. Interesting to mention also is the fact that acid-catalyzed rearrangement of substituted *N*-aminoimidazolidinones to 3-imino-hexahydro-1,2,4-triazine-6-ones has been reported.[24]

Further proof for the presence of the primary amino group in the cyclized compound was given by reacting the 3-aminoimidazolidin-4-one **3** with different types of electrophiles. Heating compound **3** with aromatic aldehydes in ethanol in the presence of catalytic amounts of piperidine afforded the corresponding hydrazones **6a–d** as single *E*-isomers in good to fair yield after crystallization (Scheme 4).[25] Further reduction of these 1-(arylidenamino)-imidazo[1,2-*a*]indolones **6a–d** with sodium borohydride in ethanol at 70 °C resulted in ring cleavage of the annelated imidazolidin-4-one ring,[26] to give acylated hydrazones **7a–d**. The lower yields can probably be explained by partial reduction of the hydrazone moiety.

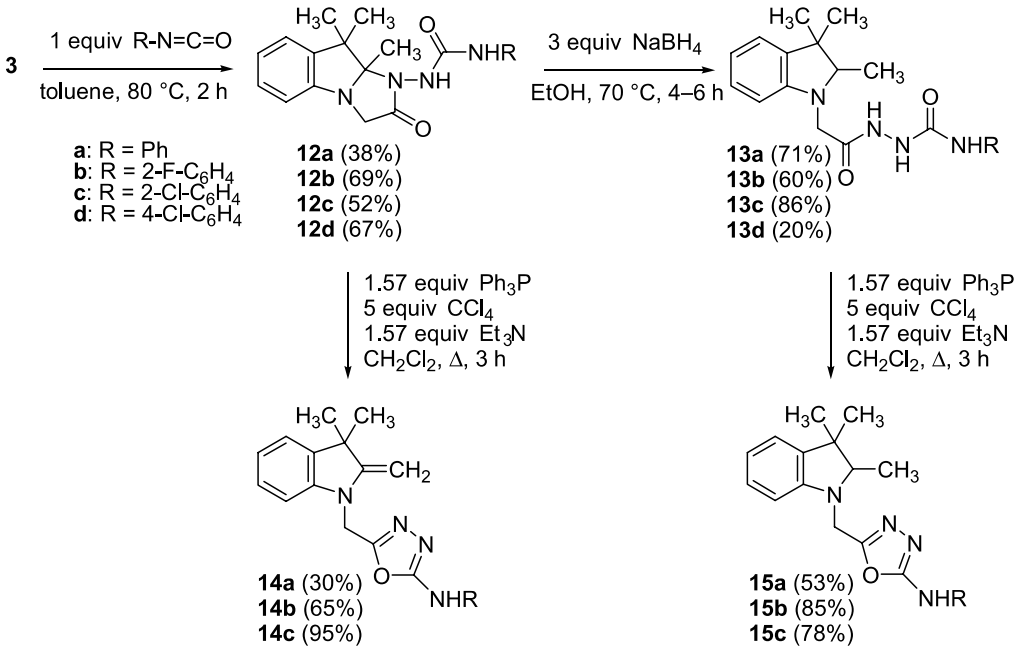
Acylation of 3-aminoimidazolidin-4-one **3** with acetyl chloride or benzoyl chlorides afforded *N*,*N*′-diacylhydrazines **8a–f**, which also could be reduced upon reaction with sodium borohydride to give ring cleaved *N*,*N*′-diacyl-hydrazines **9a–f** (Scheme 5). Both *N*,*N*′-diacylhydrazines **8c**,**d**,**f** and **9c**,**d**,**f** were cyclized to 1,3,4-oxadiazoles **10c**,**d**,**f** and **11c**,**d**,**f** under dehydration condition utilizing triphenyl-phosphine in carbon tetrachloride in the presence of triethylamine.[27] Similarly, *N*-acyl-*N*′-carbamoylhydrazines **12a–d** and **13a–d**, prepared by reaction of imidazolidinone **3** with isocyanates and further reduction, respectively, were cyclized to 2-amino-1,3,4-oxadiazoles **14a–c** and **15a–c** (Scheme 6). Substituted 1,3,4-oxadiazoles exhibit numerous pharmacological properties, including analgesic, antiinflammatory, anticonvulsive, diuretic, antiemetic, hypnotic and sedative activities.[28] More specific, 2-amino-1,3,4-oxadiazoles act as muscle relaxants[29] and possess antimitotic activity.[30]



Scheme 4.



Scheme 5.



Scheme 6.

3. Conclusion

1-Carbamoylmethyl-3*H*-indolinium salt **1** is regioselectively cyclized into a five-membered ring compound, that is, 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one **3**, via an intermediate hydrazide **2**. No indication of the presence of other ring chain tautomers was observed and 1-amino-1,2,3,9a-tetrahydro-9*H*-imidazo[1,2-*a*]indol-2-one **3** was readily transformed into novel hydrazones **6**, *N*,*N*′-diacylhydrazines **8** and **9** and *N*-acyl-*N*′-carbamoylhydrazines **12** and **13** upon treatment with aromatic aldehydes, acid chlorides and isocyanates, respectively. Further cyclizations to potentially active 1,3,4-oxadiazoles **10**, **11**, **14** and **15** were performed under dehydration conditions.

4. Experimental

4.1. General

The melting points were determined in open capillary tubes on a Büchi B-540 melting point apparatus and are

uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets. ^{1}H NMR spectra were recorded at 270 MHz on a Jeol-270 spectrometer, at 300 MHz on a Varian Unity Inova spectrometer and at 500 MHz on a Bruker Avance 500 spectrometer; ^{13}C NMR spectra were registered at 67.5, 75 and 125 MHz, respectively. Chemical shifts, expressed in parts per million, were relative to tetramethylsilane (TMS). ^{15}N NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Mass spectra were recorded on a Agilent 110 (series MS with VL) instrument. For thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used.

4.2. Synthetic procedures

4.2.1. Synthesis of 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one 3. A mixture of 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolinium chloride **1** (2.53 g, 10 mmol) and hydrazine hydrate (55%, 10 mL) was heated at 70 °C for 0.5 h. The reaction mixture was cooled to room temperature, the liquid layer was poured out from the resulting resinous substance, and the latter was crystallized from diethyl ether. The obtained crystalline material was recrystallized from ethanol to yield 1.85 g (80%) of **3**. Mp 100–101 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.15 (3H, s, 9-CH_3), 1.39 (3H, s, 9-CH_3), 1.40 (3H, s, 9a-CH_3), 3.75–3.90 (2H, AB-q, ^2J=16.5 Hz, NCH_2), 4.44 (2H, s, NH_2), 6.81–6.89 (2H, m, 5-H, 7-H), 7.01–7.12 (2H, m, 6-H, 8-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.1 (9a-CH_3), 23.6 (9-CH_3), 26.9 (9-CH_3), 47.5 (C-9), 52.0 (C-3), 93.0 (C-9a), 111.7 (C-5), 121.3 (C-7), 122.1 (C-8), 127.4 (C-6), 139.2 (C-8a), 150.5 (C-4a), 172.1 (C=O). ^{15}N NMR (50.69 MHz, DMSO-d_6): δ −224.6 (N-1), −299.1 (N-4), −317.6 (t, ^1J=68.9 Hz, NH_2). IR (KBr, cm^{-1}): ν_{N-H}=3330; ν_{N-H}=3210; $\nu_{C=O}$=1705. MS *m*/*z* (%): 232 (M+H$^+$, 100). Anal. Calcd for $C_{13}H_{17}N_3O$: C 67.51; H 7.41; N 18.17. Found: C 67.33; H 7.31; N 18.39.

4.3. General procedure for the condensation of 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (3) with aromatic aldehydes

To a solution of **3** (0.93 g, 4 mmol) and appropriate benzaldehyde (4.4 mmol) in absolute ethanol (20 mL) three drops of piperidine were added and the mixture was refluxed for 2 h, after which the mixture was cooled to room temperature. The reaction mixture was poured into water (40 mL) and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with water (20 mL), dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was crystallized from absolute ethanol to give the corresponding 1-arylidenamino-imidazo[1,2-*a*]indolones (**6a–d**).

4.3.1. 1-{[(1*E*)-(4-Fluorophenyl)methylene]amino}-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one 6a. Yield 60%. Mp 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, s, 9-CH_3), 1.34 (3H, s, 9-CH_3), 1.76 (3H, s, 9a-CH_3), 3.98 (1H, d, *J*=16.6 Hz, C*H*(H)), 4.04 (1H, d, *J*=16.6 Hz, CH(*H*)), 6.77–7.74 (8H, m, aromatic protons), 8.96 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4 (9a-CH_3), 24.5 (9-CH_3), 27.2 (9-CH_3), 48.7 (9-C), 53.5 (CH_2), 94.6 (9a-C), 111.9, 115.7 (d, *J*=22.0 Hz, 2×CH), 122.2, 122.3, 127.9, 129.3 (d, *J*=8.5 Hz, 2×CH), 130.8 (d, *J*=3.1 Hz, C), 139.2, 149.9 (Ar-C), 154.6 (C=N), 162.5 (d, *J*=251.4 Hz, C–F), 168.9 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$=1703; $\nu_{C=N}$=1607. MS *m*/*z* (%): 338 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}FN_3O$: C 71.20; H 5.97; N 12.45. Found: C 71.47; H 5.63; N 12.14.

4.3.2. 1-{[(1*E*)-(4-Chlorophenyl)methylene]amino}-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one 6b. Yield 44%. Mp 168–169 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.30 (3H, s, 9-CH_3), 1.31 (3H, s, 9-CH_3), 1.73 (3H, s, 9a-CH_3), 3.98 (1H, d, *J*=16.2 Hz, C*H*(H)), 3.99 (1H, d, *J*=16.2 Hz, CH(*H*)), 6.74–7.65 (8H, m, aromatic protons), 8.99 (1H, s, N=CH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 19.5 (9a-CH_3), 24.6 (9-CH_3), 27.1 (9-CH_3), 48.7 (9-C), 53.5 (CH_2), 94.6 (9a-C), 111.9, 122.19, 122.3, 127.9, 128.6 (2×C), 128.9 (2×C), 133.2, 136.5, 139.3, 149.9 (Ar-C), 154.2 (C=N), 169.6 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$=1700; $\nu_{C=N}$=1603. MS *m*/*z* (%): 356/54 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}ClN_3O$: C 67.89; H 5.70; N 11.88. Found: C 67.58; H 5.35; N 11.73.

4.3.3. 1-{[(1*E*)-(4-Bromophenyl)methylene]amino}-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one 6c. Yield 54%. Mp 170–171 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.30 (3H, s, 9-CH_3), 1.32 (3H, s, 9-CH_3), 1.74 (3H, s, 9a-CH_3), 3.98 (1H, d, *J*=16.5 Hz, C*H*(H)), 3.98 (1H, d, *J*=16.5 Hz, CH(*H*)), 6.75–7.66 (8H, m, aromatic protons), 8.98 (1H, s, N=CH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 19.5 (9a-CH_3), 24.6 (9-CH_3), 27.1 (9-CH_3), 48.8 (9-C), 53.6 (CH_2), 94.7 (9a-C), 112.0, 122.2, 122.3, 124.9, 127.9, 128.8 (2×C), 131.9 (2×C), 133.7, 139.3, 149.9 (Ar-C), 154.3 (C=N), 169.6 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$=1703; $\nu_{C=N}$=1595. MS *m*/*z* (%): 400/398 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}BrN_3O$: C 60.31; H 5.06; N 10.55. Found: C 59.98; H 5.35; N 10.78.

4.3.4. 1-{[(1*E*)-(4-[Dimethylamino]phenyl)methylene]-amino}-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one 6d. Yield 86%. Mp 205–206 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28 (3H, s, 9-CH_3), 1.31 (3H, s, 9-CH_3), 1.73 (3H, s, 9a-CH_3), 2.99 (6H, s, $N(CH_3)_2$), 3.96 (2H, s, CH_2), 6.66–7.60 (8H, m, aromatic protons), 8.78 (1H, s, N=CH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 19.6 (9a-CH_3), 24.9 (9-CH_3), 27.0 (9-CH_3), 40.1 ($N(CH_3)_2$), 48.7 (9-C), 53.7 (CH_2), 94.3 (9a-C), 111.6 (2×C), 111.9, 121.9, 122.2, 122.4, 127.8, 128.9 (2×C), 139.6, 150.1, 152.0 (Ar-C), 157.0 (C=N), 168.4 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$=1700; $\nu_{C=N}$=1602. MS *m*/*z* (%): 363 (M+H$^+$, 100). Anal. Calcd for $C_{22}H_{26}N_4O$: C 72.90; H 7.23; N 15.46. Found: C 72.64; H 6.99; N 15.70.

4.4. General procedure for the acylation of 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (3) with acetyl and benzoyl chlorides

To a stirred solution of **3** (1.16 g, 5 mmol) in dioxane (7.5 mL), a solution of acetyl chloride or the appropriate benzoyl chloride (6.5 mmol) in dioxane (10 mL) was added dropwise at room temperature. The formed crystals (**8a** and

8e) were separated by filtration, or the formed resinous substance (**8b–d**, **8f**) was separated by decantation of the solvent, and dissolved in water (25 mL). Solid $NaHCO_3$ was added in portions to basify the mixture to pH 8–9. The mixture was extracted with diethyl ether (3×25 mL), the combined extracts were washed with water (25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was crystallized from ethanol to give the corresponding 1-(*N'*-acylamino)-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-ones (**8a–f**).

4.4.1. *N*-(9,9,9a-Trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)acetamide 8a. Yield 85%. Mp 201–202 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.10 (3H, s, 9-CH_3), 1.28 (3H, s, 9-CH_3), 1.41 (3H, s, 9a-CH_3), 1.48 (3H, s, CH_3CO), 3.80 (1H, d, J=16.5 Hz, C*H*(H)), 3.93 (1H, d, J=16.5 Hz, CH(*H*)), 6.67–7.30 (4H, m, aromatic protons), 8.22 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 16.9 (9a-CH_3), 20.0 (9-CH_3), 23.4 (9-CH_3), 27.4 (C=OCH_3), 48.4 (9-C), 52.7 (CH_2), 95.3 (9a-C), 112.0, 122.3, 122.5, 127.9, 138.7, 149.6 (Ar-C), 168.4 (C=O), 172.5 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3250; $\nu_{C=O}$=1730; $\nu_{C=O}$=1680. MS *m/z* (%): 274 (M+H$^+$, 100). Anal. Calcd for $C_{15}H_{19}N_3O_2$: C 65.91; H 7.01; N 15.37. Found: C 65.54; H 7.39; N 15.12.

4.4.2. 2-Chloro-*N*-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)benzamide 8b. Yield 45%. Mp 177–178 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.24 (3H, s, 9-CH_3), 1.48 (3H, s, 9-CH_3), 1.67 (3H, s, 9a-CH_3), 3.85 (1H, d, J=16.7 Hz, C*H*(H)), 4.02 (1H, d, J=16.7 Hz, CH(*H*)), 6.72–7.73 (9H, m, aromatic protons and NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 17.7 (9a-CH_3), 24.0 (9-CH_3), 27.6 (9-CH_3), 48.5 (9-C), 52.4 (CH_2), 95.2 (9a-C), 112.1, 122.2, 122.3, 127.3, 128.0, 130.1, 130.5, 130.8, 132.0, 132.6, 138.5, 149.8 (Ar-C), 164.7 (C=O), 170.8 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3290; $\nu_{C=O}$=1730; $\nu_{C=O}$=1690. MS *m/z* (%): 372/70 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}ClN_3O_2$: C 64.95; H 5.45; N 11.36. Found: C 65.20; H 5.11; N 11.17.

4.4.3. 4-Chloro-*N*-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)benzamide 8c. Yield 47%. Mp 202–203 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17 (3H, s, 9-CH_3), 1.29 (3H, s, 9-CH_3), 1.47 (3H, s, 9a-CH_3), 3.66 (1H, d, J=16.6 Hz, C*H*(H)), 3.91 (1H, d, J=16.6 Hz, CH(*H*)), 6.64–7.26 (8H, m, aromatic protons), 8.93 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 18.0 (9a-CH_3), 23.8 (9-CH_3), 26.9 (9-CH_3), 48.4 (9-C), 52.5 (CH_2), 95.2 (9a-C), 112.2, 121.9, 122.4, 127.9, 128.6, 128.8 (2×C), 128.9 (2×C), 138.6, 138.9, 149.2 (Ar-C), 164.4 (C=O), 172.3 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3250; $\nu_{C=O}$=1730; $\nu_{C=O}$=1695. MS *m/z* (%): 372/70 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}ClN_3O_2$: C 64.95; H 5.45; N 11.36. Found: C 65.33; H 5.09; N 11.21.

4.4.4. 2,5-Difluoro-*N*-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)benzamide 8d. Yield 40%. Mp 203–204 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.24 (3H, s, 9-CH_3), 1.52 (3H, s, 9-CH_3), 1.64 (3H, s, 9a-CH_3), 3.92 (1H, d, J=16.3 Hz, C*H*(H)), 4.05 (1H, d, J=16.3 Hz, CH(*H*)), 6.73–7.77 (7H, m, aromatic protons), 8.16 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 17.4 (9a-CH_3), 23.6 (9-CH_3), 27.7 (9-CH_3), 48.6 (9-C), 52.4 (CH_2), 95.4 (9a-C), 112.2, 117.8, 118.8, 121.3, 121.4, 122.2, 125.8, 127.6, 138.4 (2×C), 149.8 (2×C) (Ar-C), 160.3 (C=O), 170.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3224; $\nu_{C=O}$=1737; $\nu_{C=O}$=1717. MS *m/z* (%): 372 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{19}F_2N_3O_2$: C 64.68; H 5.16; N 11.31. Found: C 64.33; H 5.37; N 11.52.

4.4.5. *N*-(9,9,9a-Trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)benzamide 8e. Yield 64%. Mp 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, s, 9-CH_3), 1.36 (3H, s, 9-CH_3), 1.52 (3H, s, 9a-CH_3), 3.70 (1H, d, J=16.5 Hz, C*H*(H)), 3.97 (1H, d, J=16.5 Hz, CH(*H*)), 6.67–7.67 (9H, m, aromatic protons), 8.92 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 (9a-CH_3), 23.8 (9-CH_3), 26.9 (9-CH_3), 48.4 (9-C), 52.4 (CH_2), 95.0 (9a-C), 112.1, 121.9, 122.3, 127.4 (2×C), 127.8, 128.3 (2×C), 130.8, 131.9, 138.9, 149.3 (Ar-C), 165.6 (C=O), 172.0 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3266; $\nu_{C=O}$=1724; $\nu_{C=O}$=1687. MS *m/z* (%): 336 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{21}N_3O_2$: C 71.62; H 6.31; N 12.53. Found: C 71.25; H 6.43; N 12.72.

4.4.6. 2-Bromo-*N*-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)benzamide 8f. Yield 41%. Mp 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, s, 9-CH_3), 1.49 (3H, s, 9-CH_3), 1.70 (3H, s, 9a-CH_3), 3.87 (1H, d, J=16.6 Hz, C*H*(H)), 4.04 (1H, d, J=16.6 Hz, CH(*H*)), 6.73–7.59 (9H, m, aromatic protons and NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8 (9a-CH_3), 24.1 (9-CH_3), 27.6 (9-CH_3), 48.6 (9-C), 52.3 (CH_2), 95.2 (9a-C), 112.1, 119.3, 122.2, 122.3, 127.6, 128.0, 129.9, 131.9, 133.3, 135.2, 138.5, 149.8 (Ar-C), 165.7 (C=O), 170.8 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3257; $\nu_{C=O}$=1726; $\nu_{C=O}$=1684. MS *m/z* (%): 416/14 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}BrN_3O_2$: C 57.98; H 4.87; N 10.14. Found: C 57.58; H 5.12; N 9.98.

4.5. General procedure for the reaction of 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (3) with isocyanates

To a solution of **3** (1.0 g, 4.32 mmol) in dry toluene (10 mL), the appropriate phenylisocyanate (4.32 mmol) was added and the mixture was heated at 80 °C for 2 h. Then the reaction mixture was cooled to room temperature, the precipitated solid was filtered off and recrystallized from ethanol to give the corresponding 1-(1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-on-1-yl)-3-phenylureas (**12a–d**).

4.5.1. 1-Phenyl-3-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)urea 12a. Yield 38%. Mp 182–183 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.15 (3H, s, 9-CH_3), 1.42 (3H, s, 9-CH_3), 1.51 (3H, s, 9a-CH_3), 3.92 (2H, s, NCH_2CO), 6.88–7.41 (9H, m, aromatic protons), 8.26 (1H, br s, NH), 8.79 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 17.3 (9a-CH_3), 23.0 (9-CH_3), 27.3 (9-CH_3), 47.8 (9-C), 51.7 (CH_2), 93.0 (9a-C), 112.0, 118.0 (2×C), 121.7, 121.9, 122.2, 127.6, 128.7 (2×C), 138.9, 139.3, 150.1 (Ar-C), 153.7 (C=O), 171.4 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3312; $\nu_{C=O}$=1711; $\nu_{C=O}$=1687. MS *m/z* (%): 351 (M+H$^+$, 100). Anal.

Calcd for $C_{20}H_{22}N_4O_2$: C 68.55; H 6.33; N 15.99. Found: C 68.32; H 6.65; N 15.97.

4.5.2. 1-(2-Fluorophenyl)-3-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)urea 12b. Yield 69%. Mp 194–196 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.15 (3H, s, 9-CH_3), 1.43 (3H, s, 9-CH_3), 1.51 (3H, s, 9a-CH_3), 3.94 (2H, s, NCH_2CO), 6.89–7.43 (8H, m, aromatic protons), 8.24 (1H, br s, NH), 8.79 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 17.8 (9a-CH_3), 25.6 (9-CH_3), 27.8 (9-CH_3), 48.8 (9-C), 52.2 (CH_2), 93.7 (9a-C), 112.7, 115.5, 115.7, 120.8, 122.4, 122.8, 123.2, 125.1, 127.8, 128.3, 139.5, 150.7 (Ar-C), 153.8 (C=O), 171.9 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3325; $\nu_{C=O}$=1712; $\nu_{C=O}$=1690. MS *m*/*z* (%): 369 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{21}FN_4O_2$: C 65.20; H 5.75; N 15.21. Found: C 65.03; H 5.92; N 15.52.

4.5.3. 1-(2-Chlorophenyl)-3-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)urea 12c. Yield 52%. Mp 199–200 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.17 (3H, s, 9-CH_3), 1.44 (3H, s, 9-CH_3), 1.55 (3H, s, 9a-CH_3), 3.98 (2H, s, NCH_2CO), 6.90–8.16 (8H, m, aromatic protons), 8.34 (1H, br s, NH), 8.93 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 17.1 (9a-CH_3), 23.7 (9-CH_3), 27.3 (9-CH_3), 47.7 (9-C), 51.5 (CH_2), 93.2 (9a-C), 112.0, 120.4, 121.4, 121.8, 122.2, 123.4, 127.6 (2×C), 129.2, 135.5, 138.8, 150.1 (Ar-C), 153.4 (C=O), 172.1 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3365; $\nu_{C=O}$=1749; $\nu_{C=O}$=1697. MS *m*/*z* (%): 387/85 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{21}ClN_4O_2$: C 62.42; H 5.50; N 14.56. Found: C 62.13; H 5.72; N 14.78.

4.5.4. 1-(4-Chlorophenyl)-3-(9,9,9a-trimethyl-2-oxo-2,3,9,9a-tetrahydro-1*H*-imidazo[1,2-*a*]indol-1-yl)urea 12d. Yield 67%. Mp 211–212 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.14 (3H, s, 9-CH_3), 1.41 (3H, s, 9-CH_3), 1.50 (3H, s, 9a-CH_3), 3.92 (2H, s, CH_2), 6.88–7.46 (8H, m, aromatic protons), 8.32 (1H, br s, NH), 8.96 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 17.3 (9a-CH_3), 22.8 (9-CH_3), 27.3 (9-CH_3), 47.8 (9-C), 51.6 (CH_2), 93.0 (9a-C), 112.0, 119.5, 119.6, 121.7, 121.8, 125.5, 127.6, 128.5 (2×C), 138.4, 138.9, 151.1 (Ar-C), 153.6 (C=O), 171.4 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3362; $\nu_{C=O}$=1723; $\nu_{C=O}$=1681. MS *m*/*z* (%): 387/85 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{21}ClN_4O_2$: C 62.42; H 5.50; N 14.56. Found: C 62.11; H 5.89; N 14.34.

4.6. General procedure for the reduction of 1-(*N*-substituted amino)-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-ones (6a–d, 8a–f, 12a–d) with sodium borohydride

To a solution of an appropriate *N*′-substituted 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one (**6a–d**, **8a–f**, **12a–d**) (1.35 mmol) in 20 mL of ethanol (**6a–d**, **8a–f**) or 20 mL of tetrahydrofuran (**12a–d**), sodium borohydride (0.153 g, 4.05 mmol) was added. The mixture was heated at 70 °C for the indicated period, then cooled to room temperature, poured into water (30 mL) and extracted with ether (3×20 mL). The combined extracts were washed with water (20 mL), dried over sodium sulfate, the solvent removed under reduced pressure, and the residue crystallized from ethanol to obtain the various *N*′-substituted 2,3-dihydro-2,3,3-trimethyl-1*H*-indole-1-acetic acid *N*′-substituted hydrazides (**7a–d**, **9a–f**, **13a–d**).

4.6.1. *N*′-[(1*E*)-(4-Fluorophenyl)methylene]-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetohydrazide 7a. Yield 45%. Mp 148–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3H, s, 3-CH_3), 1.25 (3H, d, J=6.6 Hz, 2-CH_3), 1.34 (3H, s, 3-CH_3), 3.17 (1H, q, J=6.6 Hz, 2-CH), 3.77 (2H, s, CH_2), 6.50–7.75 (8H, m, aromatic protons), 8.06 (1H, s, NH), 9.73 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.9 (2-CH_3), 23.6 (3-CH_3), 25.8 (3-CH_3), 43.1 (3-C), 53.1 (CH_2), 72.3 (CH), 108.7, 116.1 (d, J=22.1 Hz, 2×CH), 120.9, 122.5, 128.0, 129.8 (d, J=3.0 Hz, C), 129.9 (d, J=8.6 Hz, 2×CH), 139.5, 148.0 (Ar-C), 150.3 (C=N), 164.4 (d, J=251.4 Hz, C–F), 167.1 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3190; $\nu_{C=O}$=1685; $\nu_{C=N}$=1606. MS *m*/*z* (%): 340 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{22}FN_3O$: C 70.77; H 6.53; N 12.38. Found: C 70.43; H 6.67; N 12.01.

4.6.2. *N*′-[(1*E*)-(4-Chlorophenyl)methylene]-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetohydrazide 7b. Yield 26%. Mp 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (3H, s, 3-CH_3), 1.25 (3H, d, J=6.6 Hz, 2-CH_3), 1.34 (3H, s, 3-CH_3), 3.18 (1H, q, J=6.6 Hz, 2-CH), 3.77 (2H, s, CH_2), 6.50–7.66 (8H, m, aromatic protons), 8.06 (1H, s, NH), 9.80 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.2 (3-CH_3), 25.4 (3-CH_3), 42.8 (3-C), 52.7 (CH_2), 71.9 (CH), 108.3, 120.6, 122.1, 127.7, 128.8 (2×C), 128.9 (2×C), 131.7, 136.5, 139.2, 147.6 (Ar-C), 149.9 (C=N), 166.9 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3190; $\nu_{C=O}$=1680; $\nu_{C=N}$=1607. MS *m*/*z* (%): 358/56 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{22}ClN_3O$: C 67.50; H 6.23; N 11.81. Found: C 67.32; H 6.65; N 11.41.

4.6.3. *N*′-[(1*E*)-(4-Bromophenyl)methylene]-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetohydrazide 7c. Yield 37%. Mp 143–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3H, s, 3-CH_3), 1.25 (3H, d, J=6.6 Hz, 2-CH_3), 1.34 (3H, s, 3-CH_3), 3.17 (1H, q, J=6.6 Hz, 2-CH), 3.78 (2H, s, CH_2), 6.51–8.05 (9H, m, aromatic protons and NH), 9.76 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.3 (3-CH_3), 25.5 (3-CH_3), 42.8 (3-C), 52.8 (CH_2), 71.9 (CH), 108.3, 120.7, 122.2, 124.9, 127.7, 129.1 (2×C), 131.9 (2×C), 132.2, 139.2, 147.6 (Ar-C), 149.9 (C=N), 166.9 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3204; $\nu_{C=O}$=1677; $\nu_{C=N}$=1605. MS *m*/*z* (%): 402/00 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{22}BrN_3O$: C 60.01; H 5.54; N 10.50. Found: C 60.33; H 5.72; N 10.37.

4.6.4. *N*′-[(1*E*)-(4-[Dimethylamino]phenyl)methylene]-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetohydrazide 7d. Yield 64%. Mp 153–154 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 (3H, s, 3-CH_3), 1.25 (3H, d, J=6.6 Hz, 2-CH_3), 1.34 (3H, s, 3-CH_3), 3.00 (6H, s, $N(CH_3)_2$), 3.17 (1H, q, J=6.6 Hz, 2-CH), 3.76 (2H, s, CH_2), 6.52–7.86 (9H, m, aromatic protons and NH), 9.53 (1H, s, N=CH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.3 (3-CH_3), 25.4 (3-CH_3), 40.1 ($N(CH_3)_2$), 42.8 (3-C), 52.7 (CH_2), 71.9 (CH), 106.5, 111.5 (2×C), 120.4, 120.6, 122.0, 127.7, 129.3 (2×C), 139.2, 149.5, 150.0, 151.9, 166.0 (C=O). IR (KBr, cm^{-1}): ν_{N-H}=3195; $\nu_{C=O}$=1690; $\nu_{C=N}$=1609. MS

m/z (%): 365 ($M+H^+$, 100). Anal. Calcd for $C_{22}H_{28}N_4O$: C 72.50; H 7.74; N 15.37. Found: C 72.84; H 7.91; N 15.12.

4.6.5. *N′*-Acetyl-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetohydrazide 9a. Yield 65%. Mp 172–173 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09 (3H, s, CH_3), 1.24 (3H, d, $J=6.6$ Hz, CH_3), 1.31 (3H, s, CH_3), 2.03 (3H, s, $COCH_3$), 3.16 (1H, q, $J=6.6$ Hz, CH), 3.72 (1H, d, $J=17.8$ Hz, C*H*(H)CO), 3.76 (1H, d, $J=17.8$ Hz, CH(*H*)CO), 6.48–7.25 (4H, m, aromatic protons), 9.35 (1H, s, NH), 9.62 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.5 (2-CH_3), 20.4 (3-CH_3), 23.0 (3-CH_3), 25.4 (*C*H_3CO), 42.8 (3-C), 51.7 (CH_2), 71.9 (CH), 107.9, 120.2, 122.0, 127.5, 139.1, 149.8 (Ar-C), 167.2 (C=O), 167.6 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3280$; $\nu_{C=O}=1710$; $\nu_{C=O}=1675$. MS *m/z* (%): 276 ($M+H^+$, 100). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C 65.43; H 7.69; N 15.26. Found: C 65.11; H 7.82; N 15.54.

4.6.6. 2-Chloro-*N′*-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]benzohydrazide 9b. Yield 75%. Mp 169–170 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 (3H, s, CH_3), 1.30 (3H, d, $J=6.6$ Hz, CH_3), 1.34 (3H, s, CH_3), 3.18 (1H, q, $J=6.6$ Hz, CH), 3.76 (1H, d, $J=17.0$ Hz, C*H*(H)CO), 3.80 (1H, d, $J=17.0$ Hz, CH(*H*)CO), 6.53–7.78 (8H, m, aromatic protons), 9.23 (1H, d, $J=6.12$ Hz, NH), 9.46 (1H, d, $J=6.12$ Hz, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.7 (2-CH_3), 23.2 (3-CH_3), 25.5 (3-CH_3), 42.9 (3-C), 52.1 (CH_2), 72.1 (CH), 108.2, 120.4, 122.1, 127.1, 127.7, 130.5, 130.8, 131.3, 131.5, 132.3, 139.2, 149.9 (Ar-C), 162.4 (C=O), 167.3 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3350$; $\nu_{N-H}=3220$; $\nu_{C=O}=1703$; $\nu_{C=O}=1671$. MS *m/z* (%): 374/72 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{22}ClN_3O_2$: C 64.60; H 5.96; N 11.30. Found: C 64.91; H 6.13; N 11.05.

4.6.7. 4-Chloro-*N′*-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]benzohydrazide 9c. Yield 62%. Mp 174–175 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.13 (3H, s, CH_3), 1.27 (3H, d, $J=6.4$ Hz, CH_3), 1.34 (3H, s, CH_3), 3.19 (1H, q, $J=6.4$ Hz, CH), 3.78 (1H, d, $J=18.0$ Hz, C*H*(H)CO), 3.81 (1H, d, $J=18.0$ Hz, CH(*H*)CO), 6.52–7.75 (8H, m, aromatic protons), 9.35 (1H, d, $J=4.8$ Hz, NH), 9.89 (1H, d, $J=4.8$ Hz, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.2 (3-CH_3), 25.5 (3-CH_3), 42.9 (3-C), 52.2 (CH_2), 72.1 (CH), 108.0, 120.5, 122.5, 127.6, 128.7 (2×C), 128.9 (2×C), 129.5, 138.6, 139.2, 149.8 (Ar-C), 163.6 (C=O), 168.7 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3220$; $\nu_{C=O}=1696$; $\nu_{C=O}=1684$. MS *m/z* (%): 374/72 ($M+H^+$, 73), 160 (100). Anal. Calcd for $C_{20}H_{22}ClN_3O_2$: C 64.60; H 5.96; N 11.30. Found: C 64.93; H 5.79; N 11.12.

4.6.8. 2,5-Difluoro-*N′*-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]benzohydrazide 9d. Yield 64%. Mp 114–115 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 (3H, s, CH_3), 1.27 (3H, d, $J=6.8$ Hz, CH_3), 1.34 (3H, s, CH_3), 3.19 (1H, q, $J=6.8$ Hz, CH), 3.80 (1H, d, $J=17.8$ Hz, C*H*(H)), 3.83 (1H, d, $J=17.8$ Hz, CH(*H*)), 6.54–7.79 (7H, m, aromatic protons), 9.28 (1H, d, $J=6.0$ Hz, NH), 9.44 (1H, d, $J=6.0$ Hz, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.2 (3-CH_3), 25.4 (3-CH_3), 42.9 (3-C), 52.0 (CH_2), 72.1 (CH), 108.0, 117.5, 117.8, 118.2, 120.4, 120.9, 122.2, 127.6, 139.2, 149.9, 156.4, 158.4 (Ar-C), 160.8 (C=O), 167.2 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3205$; $\nu_{C=O}=1700$; $\nu_{C=O}=1684$. MS *m/z* (%): 374 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{21}F_2N_3O_2$: C 64.33; H 5.67; N 11.25. Found: C 64.05; H 5.81; N 11.42.

4.6.9. *N′*-[(2,3,3-Trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]benzohydrazide 9e. Yield 66%. Mp 125–126 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11 (3H, s, CH_3), 1.25 (3H, d, $J=6.8$ Hz, CH_3), 1.31 (3H, s, CH_3), 3.16 (1H, q, $J=6.8$ Hz, CH), 3.76 (1H, d, $J=17.8$ Hz, C*H*(H)), 3.83 (1H, d, $J=17.8$ Hz, CH(*H*)), 6.45–7.85 (9H, m, aromatic protons), 9.43 (1H, d, $J=6.0$ Hz, NH), 9.73 (1H, d, $J=6.0$ Hz, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.2 (3-CH_3), 25.5 (3-CH_3), 42.9 (3-C), 52.1 (CH_2), 72.1 (CH), 108.1, 120.4, 122.1, 127.3 (2×C), 127.6, 128.6 (2×C), 131.2, 132.3, 139.2, 149.9 (Ar-C), 164.3 (C=O), 167.9 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3257$; $\nu_{C=O}=1697$; $\nu_{C=O}=1684$. MS *m/z* (%): 338 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}N_3O_2$: C 71.19; H 6.87; N 12.45. Found: C 71.01; H 7.19; N 12.17.

4.6.10. 2-Bromo-*N′*-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]benzohydrazide 9f. Yield 70%. Mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3H, s, CH_3), 1.28 (3H, d, $J=6.6$ Hz, CH_3), 1.33 (3H, s, CH_3), 3.18 (1H, q, $J=6.6$ Hz, CH), 3.71 (1H, d, $J=17.8$ Hz, C*H*(H)), 3.79 (1H, d, $J=17.8$ Hz, CH(*H*)), 6.52–7.62 (8H, m, aromatic protons), 9.14 (1H, br s, NH), 9.43 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (2-CH_3), 23.2 (3-CH_3), 25.5 (3-CH_3), 42.8 (3-C), 52.0 (CH_2), 72.1 (CH), 108.2, 119.9, 120.4, 122.1, 127.5, 127.6, 130.2, 132.1, 133.6, 134.2, 139.2, 149.9 (Ar-C), 163.6 (C=O), 167.4 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3355$; $\nu_{N-H}=3213$; $\nu_{C=O}=1711$; $\nu_{C=O}=1671$. MS *m/z* (%): 418/16 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{22}BrN_3O_2$: C 57.70; H 5.33; N 10.09. Found: C 57.42; H 5.70; N 9.98.

4.6.11. *N*-Phenyl-2-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]hydrazinecarboxamide 13a. Yield 71%. Mp 189–190 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.98 (3H, s, 3-CH_3), 1.17 (3H, d, $J=6.3$ Hz, 2-CH_3), 1.24 (3H, s, 3-CH_3), 3.32 (1H, q, $J=6.3$ Hz, CH), 3.68 (1H, d, $J=16.8$ Hz, C*H*(H)), 3.88 (1H, d, $J=16.8$ Hz, CH(*H*)), 6.53–7.52 (9H, m, aromatic protons), 8.07 (1H, br s, NH), 8.66 (1H, br s, NH), 9.76 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 12.0 (2-CH_3), 22.9 (3-CH_3), 25.6 (3-CH_3), 42.1 (3-C), 47.8 (CH_2), 69.3 (CH), 107.3, 117.9, 118.3 (2×C), 121.4, 121.8, 126.9, 128.6 (2×C), 138.4, 139.5, 150.3 (Ar-C), 155.2 (C=O), 169.4 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3288$; $\nu_{C=O}=1725$; $\nu_{C=O}=1652$. MS *m/z* (%): 353 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{24}N_4O_2$: C 68.16; H 6.86; N 15.90. Found: C 68.45; H 7.11; N 15.56.

4.6.12. *N*-(2-Fluorophenyl)-2-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]hydrazinecarboxamide 13b. Yield 60%. Mp 178–179 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.98 (3H, s, 3-CH_3), 1.17 (3H, d, $J=6.6$ Hz, 2-CH_3), 1.24 (3H, s, 3-CH_3), 3.29 (1H, q, $J=6.6$ Hz, CH), 3.67 (1H, d, $J=16.9$ Hz, C*H*(H)), 3.87 (1H, d, $J=16.9$ Hz, CH(*H*)), 6.36–7.99 (8H, m, aromatic protons), 8.04 (1H, br s, NH), 8.51 (1H, br s, NH), 9.87 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.9 (2-CH_3), 22.9 (3-CH_3), 25.6 (3-CH_3), 42.1 (3-C), 47.9 (CH_2), 69.4 (CH), 107.2, 114.8, 115.1, 117.9, 120.9, 121.4, 124.4, 127.6, 129.1, 135.4,

138.7, 150.0 (Ar-C), 154.7 (C=O), 169.3 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3305$; $\nu_{C=O}=1727$; $\nu_{C=O}=1646$. MS *m/z* (%): 371 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}FN_4O_2$: C 64.85; H 6.26; N 15.13. Found: C 64.79; H 6.41; N 15.43.

4.6.13. *N*-(2-Chlorophenyl)-2-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]hydrazinecarboxamide 13c. Yield 86%. Mp 180–181 °C. ^1H NMR (270 MHz, DMSO-d_6): δ 0.98 (3H, s, 3-CH_3), 1.17 (3H, d, $J=6.6$ Hz, 2-CH_3), 1.24 (3H, s, 3-CH_3), 3.30 (1H, q, $J=6.6$ Hz, CH), 3.67 (1H, d, $J=16.6$ Hz, C*H*(H)), 3.89 (1H, d, $J=16.6$ Hz, CH(*H*)), 6.51–8.11 (8H, m, aromatic protons), 8.19 (1H, br s, NH), 9.14 (1H, br s, NH), 9.63 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 12.0 (2-CH_3), 23.0 (3-CH_3), 25.6 (3-CH_3), 42.1 (3-C), 48.0 (CH_2), 69.3 (CH), 107.3, 117.9, 120.9, 121.4, 121.8, 123.2, 126.9, 127.6, 129.1, 135.8, 138.4, 150.3 (Ar-C), 154.5 (C=O), 168.9 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3314$; $\nu_{C=O}=1724$; $\nu_{C=O}=1659$. MS *m/z* (%): 389/87 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}ClN_4O_2$: C 62.09; H 5.99; N 14.48. Found: C 61.78; H 5.75; N 14.59.

4.6.14. *N*-(4-Chlorophenyl)-2-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetyl]hydrazinecarboxamide 13d. Yield 20%. Mp 172–173 °C. ^1H NMR (270 MHz, DMSO-d_6): δ 0.97 (3H, s, 3-CH_3), 1.16 (3H, d, $J=6.6$ Hz, 2-CH_3), 1.23 (3H, s, 3-CH_3), 3.29 (1H, q, $J=6.6$ Hz, CH), 3.68 (1H, d, $J=16.8$ Hz, C*H*(H)), 3.87 (1H, d, $J=16.8$ Hz, CH(*H*)), 6.52–7.54 (8H, m, aromatic protons), 8.15 (1H, br s, NH), 8.84 (1H, br s, NH), 9.75 (1H, br s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.9 (2-CH_3), 22.9 (3-CH_3), 25.6 (3-CH_3), 47.8 (3-C), 64.9 (CH_2), 69.3 (CH), 107.3, 117.9, 119.8, 121.4, 125.3, 126.9, 128.2, 128.4 (2×C), 138.3, 138.6, 150.3 (Ar-C), 155.1 (C=O), 169.4 (C=O). IR (KBr, cm^{-1}): $\nu_{N-H}=3293$; $\nu_{C=O}=1700$; $\nu_{C=O}=1655$. MS *m/z* (%): 389/87 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}ClN_4O_2$: C 62.09; H 5.99; N 14.48. Found: C 62.13; H 6.18; N 14.72.

4.7. General procedure for the synthesis of 1-(1,3,4-oxadiazol-2-yl)methylindole derivatives (10c,d,f, 11c,d,f, 14a–c, 15a–c)

To a stirred suspension of appropriate hydrazide (**8c**,**d**,**f**, **9c**,**d**,**f**, **12a**–**c**, **13a**–**c**) (1 mmol) in dichloromethane (12 mL) were added triphenylphosphine (1.57 mmol), carbon tetrachloride (5 mmol), triethylamine (1.57 mmol), and the mixture was heated to reflux for 3 h. Then the mixture was cooled to room temperature, poured into water (15 mL) and extracted with dichloromethane (3×15 mL). Combined organic layers were dried over sodium sulfate, the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane/ethyl acetate 2:1 as eluent to yield 1,3,4-oxadiazoles (**10c**,**d**,**f**, **11c**,**d**,**f**, **14a**–**c**, **15a**–**c**).

4.7.1. 1-{[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-3,3-dimethyl-2-methyleneindoline 10c. Yield 90%. Mp 125–126 °C. ^1H NMR (270 MHz, DMSO-d_6): δ 1.21 (6H, s, 2×3-CH_3), 4.01 (1H, d, $J=2.2$ Hz, =C*H*(H)), 4.15 (1H, d, $J=2.2$ Hz, =CH(*H*)), 5.18 (2H, s, CH_2), 6.78–7.92 (8H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 30.4 (2×3-CH_3), 37.8 (CH_2), 44.5 (3-C), 76.8 (=CH_2), 106.8, 120.1, 122.7, 122.8, 128.3, 128.9 (2×C), 129.0, 130.4 (2×C), 137.5, 145.4 (Ar-C), 160.8 (2-C), 163.9, 164.3 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}=1655$. MS *m/z* (%): 354/52 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{18}N_3ClO$: C 68.28; H 5.16; N 11.94. Found: C 68.08; H 5.10; N 11.80.

4.7.2. 1-{[5-(2,5-Difluorophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-3,3-dimethyl-2-methyleneindoline 10d. Yield 81%. Oil. ^1H NMR (270 MHz, DMSO-d_6): δ 1.31 (6H, s, 2×3-CH_3), 4.00 (1H, d, $J=2.2$ Hz, =C*H*(H)), 4.13 (1H, d, $J=2.2$ Hz, =CH(*H*)), 5.21 (2H, s, CH_2), 6.78–7.75 (7H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 29.7 (2×3-CH_3), 36.9 (CH_2), 43.8 (3-C), 76.1 (=CH_2), 106.1, 112.8, 115.3, 115.7, 119.1, 119.4, 120.9, 122.1, 127.5, 136.8, 142.1, 144.7 (Ar-C), 160.1 (2-C), 163.6, 163.7 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}=1655$. MS *m/z* (%): 354 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{17}N_3F_2O$: C 67.98; H 4.85; N 11.89. Found: C 67.53; H 4.56; N 11.53.

4.7.3. 1-{[5-(2-Bromophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-3,3-dimethyl-2-methyleneindoline 10f. Yield 80%. Oil. ^1H NMR (270 MHz, DMSO-d_6): δ 1.31 (6H, s, 2×3-CH_3), 4.01 (1H, d, $J=2.2$ Hz, =C*H*(H)), 4.15 (1H, d, $J=2.2$ Hz, =CH(*H*)), 5.22 (2H, s, CH_2), 6.77–7.85 (8H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 29.7 (2×3-CH_3), 36.9 (CH_2), 43.7 (3-C), 76.2 (=CH_2), 106.2, 119.3, 120.7, 122.0, 124.5, 127.5, 128.3, 131.6, 133.4, 134.3, 136.8, 144.7 (Ar-C), 160.0 (2-C), 163.2, 163.4 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}=1652$. MS *m/z* (%): 398/96 ($M+H^+$, 50). Anal. Calcd for $C_{20}H_{18}N_3BrO$: C 60.62; H 4.58; N 10.60. Found: C 60.31; H 4.75; N 10.29.

4.7.4. 1-{[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2,3,3-trimethylindoline 11c. Yield 99%. Mp 121–122 °C. ^1H NMR (270 MHz, DMSO-d_6): δ 0.96 (3H, s, 3-CH_3), 1.24 (6H, m, 2-CH_3, 3-CH_3), 3.28 (1H, q, $J=6.5$ Hz, CH), 4.59 (1H, d, $J=16.8$ Hz, C*H*(H)), 4.87 (1H, d, $J=16.8$ Hz, CH(*H*)), 6.67–7.93 (8H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.8 (2-CH_3), 22.9 (3-CH_3), 25.3 (3-CH_3), 42.2 (3-C, CH_2), 68.5 (CH), 107.6, 118.7, 121.8, 122.1, 127.0, 128.2 (2×C), 129.7 (2×C), 136.7, 138.5, 148.9 (Ar-C), 163.4, 163.8 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}=1606$. MS *m/z* (%): 356/54 ($M+H^+$, 50). Anal. Calcd for $C_{20}H_{20}N_3ClO$: C 67.89; H 5.70; N 11.88. Found: C 67.55; H 5.35; N 11.69.

4.7.5. 1-{[5-(2,5-Difluorophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-2,3,3-trimethylindoline 11d. Yield 80%. Mp 104–105 °C. ^1H NMR (270 MHz, DMSO-d_6): δ 0.96 (3H, s, 3-CH_3), 1.25 (6H, m, 2-CH_3, 3-CH_3), 3.29 (1H, q, $J=6.5$ Hz, CH), 4.61 (1H, d, $J=16.8$ Hz, C*H*(H)), 4.90 (1H, d, $J=16.8$ Hz, CH(*H*)), 6.66–7.76 (7H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.7 (3-CH_3), 22.8 (2-CH_3), 25.3 (3-CH_3), 39.3 (3-C), 42.1 (CH_2), 68.4 (CH), 107.5, 112.5, 115.5, 118.6, 119.0, 120.7, 121.7, 126.9, 138.4, 148.7, 156.9, 159.4 (Ar-C), 160.0, 164.1 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}=1604$. MS *m/z* (%): 356 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{19}N_3F_2O$: C 67.59; H 5.39; N 11.82. Found: C 67.15; H 5.26; N 11.45.

4.7.6. 1-{[5-(2-Bromophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-2,3,3-trimethylindoline 11f. Yield 74%. Mp

124–125 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.95 (3H, s, 3-CH_3), 1.23 (6H, m, 2-CH_3, 3-CH_3), 3.34 (1H, q, J=6.5 Hz, CH), 4.61 (1H, d, J=16.8 Hz, C*H*(H)), 4.92 (1H, d, J=16.8 Hz, CH(*H*)), 6.66–7.84 (8H, m, aromatic protons). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.8 (2-CH_3), 22.9 (3-CH_3), 25.3 (3-CH_3), 42.2 (CH_2, 3-C), 68.3 (CH), 107.8, 118.7, 120.7, 121.7, 124.7, 127.1, 128.3, 131.7, 133.4, 134.2, 138.5, 148.2 (Ar-C), 163.2, 164.1 (C–O–C). IR (KBr, cm^{-1}): $\nu_{C=N}$=1602. MS *m*/*z* (%): 400/98 (M+H$^+$, 50). Anal. Calcd for $C_{20}H_{20}N_3BrO$: C 60.31; H 5.06; N 10.55. Found: C 60.80; H 5.51; N 10.35.

4.7.7. 5-[(3,3-Dimethyl-2-methylene-2,3-dihydro-1*H*-indol-1-yl)methyl]-*N*-phenyl-1,3,4-oxadiazol-2-amine 14a. Yield 30%. Oil. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.29 (6H, s, 2×3-CH_3), 3.98 (1H, d, J=2.0 Hz, =C*H*(H)), 4.11 (1H, d, J=2.0 Hz, =CH(*H*)), 4.99 (2H, s, CH_2), 6.77–7.53 (9H, m, aromatic protons), 10.46 (1H, s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 29.7 (2×3-CH_3), 36.9 (CH_2), 43.7 (3-C), 76.0 (=CH_2), 106.0, 116.9 (2×C), 119.2, 121.8, 122.1, 127.6, 129.0 (2×C), 136.8, 138.6, 144.8 (Ar-C), 156.0 (2-C), 160.0, 160.1 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3189; $\nu_{C=N}$=1655. MS *m*/*z* (%): 333 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{20}N_4O$: C 72.27; H 6.06; N 16.86. Found: C 71.93; H 5.87; N 16.59.

4.7.8. 5-[(3,3-Dimethyl-2-methylene-2,3-dihydro-1*H*-indol-1-yl)methyl]-*N*-(2-fluorophenyl)-1,3,4-oxadiazol-2-amine 14b. Yield 65%. Mp 141–142 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.30 (6H, s, 2×3-CH_3), 3.98 (1H, d, J=2.1 Hz, =C*H*(H)), 4.11 (1H, d, J=2.1 Hz, =C*H*(H)), 4.98 (2H, s, CH_2), 6.66–7.84 (8H, m, aromatic protons), 10.31 (1H, s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 29.7 (2×3-CH_3), 37.0 (CH_2), 43.7 (3-C), 75.9 (=CH_2), 106.0, 115.4, 115.6, 119.2, 120.6, 122.1, 123.6, 124.6, 126.5, 127.5, 136.8, 144.8 (Ar-C), 156.6 (2-C), 160.0, 160.4 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3160; $\nu_{C=N}$=1654. MS *m*/*z* (%): 351 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{19}N_4FO$: C 68.56; H 5.47; N 15.99. Found: C 68.09; H 5.90; N 15.59.

4.7.9. 5-[(3,3-Dimethyl-2-methylene-2,3-dihydro-1*H*-indol-1-yl)methyl]-*N*-(2-chlorophenyl)-1,3,4-oxadiazol-2-amine 14c. Yield 95%. Mp 125–126 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.29 (6H, s, 2×3-CH_3), 3.98 (1H, d, J=2.1 Hz, =C*H*(H)), 4.11 (1H, d, J=2.1 Hz, =CH(*H*)), 4.97 (2H, s, CH_2), 6.77–7.91 (8H, m, aromatic protons), 9.89 (1H, s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 29.7 (2×3-CH_3), 37.1 (CH_2), 43.7 (3-C), 75.9 (=CH_2), 106.0, 119.2, 122.1, 122.2, 124.1, 124.8, 127.5, 127.8, 129.8, 135.3, 136.8, 144.8 (Ar-C), 156.8 (2-C), 160.0, 160.7 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3201; $\nu_{C=N}$=1627. MS *m*/*z* (%): 369/67 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{19}N_4ClO$: C 65.48; H 5.22; N 15.27. Found: C 65.22; H 5.66; N 15.03.

4.7.10. *N*-Phenyl-5-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)methyl]-1,3,4-oxadiazol-2-amine 15a. Yield 53%. Mp 167–168 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.94 (3H, s, 3-CH_3), 1.21 (6H, m, 2×CH_3), 3.18 (1H, q, J=6.5 Hz, CH), 4.39 (1H, d, J=16.4 Hz, C*H*(H)), 4.68 (1H, d, J=16.5 Hz, CH(*H*)), 6.66–7.53 (9H, m, aromatic protons), 10.43 (1H, s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.8 (2-CH_3), 22.9 (3-CH_3), 25.3 (3-CH_3), 30.2 (CH_2), 42.2 (3-C), 68.5 (CH), 107.7, 116.8 (2×C), 118.6, 121.7, 121.8, 127.1, 128.9 (2×C), 138.5, 138.7, 149.1 (Ar-C), 156.8, 160.0 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3201; $\nu_{C=N}$=1627. MS *m*/*z* (%): 335 (M+H$^+$, 30). Anal. Calcd for $C_{20}H_{22}N_4O$: C 71.83; H 6.63; N 16.75. Found: C 72.16; H 7.03; N 16.25.

4.7.11. *N*-(2-Fluorophenyl)-5-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)methyl]-1,3,4-oxadiazol-2-amine 15b. Yield 85%. Mp 144–145 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.95 (3H, s, 3-CH_3), 1.21 (3H, d, J=6.5 Hz, 2-CH_3), 1.24 (3H, s, 3-CH_3), 3.23 (1H, q, J=6.5 Hz, CH), 4.39 (1H, d, J=16.5 Hz, C*H*(H)), 4.65 (1H, d, J=16.5 Hz, CH(*H*)), 6.66–7.97 (8H, m, aromatic protons), 10.26 (1H, s, NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 11.8 (2-CH_3), 22.9 (3-CH_3) 25.3 (3-CH_3), 30.2 (CH_2), 42.2 (3-C), 68.5 (CH), 107.7, 115.3, 115.6, 118.6, 120.5, 121.7, 124.6, 126.4, 126.6, 127.0, 138.5, 149.0 (Ar-C), 157.4, 160.3 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3165; $\nu_{C=N}$=1655. MS *m*/*z* (%): 353 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{21}N_4FO$: C 68.16; H 6.01; N 15.90. Found: C 68.58; H 5.99; N 15.53.

4.7.12. *N*-(2-Chlorophenyl)-5-[(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)methyl]-1,3,4-oxadiazol-2-amine 15c. Yield 78%. Mp 94–95 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.99 (3H, s, 3-CH_3), 1.25 (6H, m, 2-CH_3, 3-CH_3), 3.19 (1H, q, J=6.5 Hz, CH), 4.37 (1H, d, J=16.4 Hz, C*H*(H)), 4.55 (1H, d, J=16.4 Hz, C*H*(H)), 6.69–8.12 (9H, m, aromatic protons and NH). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 12.1 (2-CH_3), 22.9 (3-CH_3), 25.4 (3-CH_3), 40.1 (CH_2), 42.6 (3-C), 69.1 (CH), 107.6, 118.3, 119.2, 121.0, 121.9, 123.3, 127.3, 128.0, 129.1, 134.0, 138.8, 148.9 (Ar-C), 157.9, 171.0 (C–O–C). IR (KBr, cm^{-1}): ν_{N-H}=3208; $\nu_{C=N}$=1621. MS *m*/*z* (%): 371/69 (M+H$^+$, 50). Anal. Calcd for $C_{20}H_{21}N_4ClO$: C 65.12; H 5.74; N 15.19. Found: C 64.77; H 6.21; N 15.04.

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Tetrahedron 62 (2006) 3320–3328

Synthesis of 6- to 10-membered ring (*E*)-hydroxyiminohydroazaazoniabenzocycloalkenes derivative from cyclization of 2-nitromethylene-1-(ω-phenylalkyl)imidazolidine or 2-nitromethylene-1-(ω-phenylalkyl)hexahydropyrimidine in trifluoromethanesulfonic acid

Jean-Marie Coustard,[a,*] Yaya Soro,[b] Sorho Siaka,[b] Fanté Bamba[a] and Alain Cousson[c]

[a]*Laboratoire 'Synthèse et Réactivité des Substances Naturelles', UMR 6514 40, Avenue du Recteur Pineau, F-86022 Poitiers, France*
[b]*Laboratoire des Procédés Industriels de Synthèse et d'Environnement, Institut National Polytechnique Félix Houphouët-Boigny, BP 991 Yamoussoukro, Côte d'Ivoire*
[c]*Laboratoire Léon Brillouin-CEA Saclay, 91191 Gif-sur-Yvette Cedex, France*

Received 8 December 2005; revised 11 January 2006; accepted 17 January 2006

Available online 13 February 2006

Abstract—In trifluoromethanesulfonic acid, 2-nitromethylene-1-(ω-phenylalkyl)imidazolidine or 2-nitromethylene-1-(ω-phenylalkyl)hexahydropyrimidine derivatives undergo an intramolecular cyclization to afford (*E*)-hydroxyiminohydroazaazoniabenzocycloalkenes, in their trifluoromethanesulfonate salt form. The reaction probably occurres via the formation of an electrophilic transient hydroxynitrilium ion (or *O*-protonated nitrile oxide). The yields are generally good, except for the higher-membered ring derivatives.
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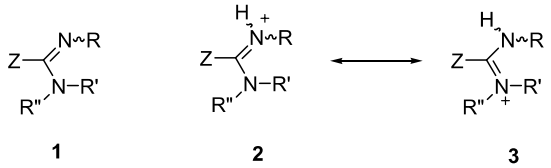
1. Introduction

Amidines have long been regarded as useful intermediates in the synthesis of heterocyclic compounds,[1] characteristic structural feature of many natural substances[2] and important pharmacophore in the active ingredients of drugs.[3,4] Because of these activities, substituted amidine-containing compounds have found frequent application in medicinal chemistry.[5,6]

From a structural point of view, amidines **1** have two nitrogen atoms in the 1,3-position of an allylic system (Fig. 1). This arrangement is particularly favorable for *n*-π heteroallylic nitrogen conjugation, which confers a highly basic character to the group. Because of this strong basic character, they are easily *N*-protonated to give resonance-stabilized amidinium cations with mesomeric formulas **2** and **3**[7] or they form strong interactions with proteins[8] and other biomolecules, particularly in regions bearing anionic and hydrogen bonding groups such as those found in DNA.[9] This kind of association plays a key role in their physiological activity[10] and explains why they are present in many drugs.



1 **2** **3**

Figure 1.

Numerous synthetic methods have been developed for the preparation of amidines, the first of which is the classical Pinner's reaction, dating back to the 1800's.[11] Amidine-containing compounds are generally prepared from nitriles, amides (with the help of PCl_5 or $Et_3O^+BF_4^-$ or P_2O_5) or thioamides involving highly acidic,[12] alkaline[13] or strongly reducing conditions.[14] For complex molecules with sensitive functions, a mild method starting from nitriles and *N*-acetylcysteine as a catalyst has also been described.[15]

Keywords: 2-Nitromethyleneimidazolidine derivatives; 2-Nitromethylene-hexahydropyrimidine derivatives; Trifluoromethanesulfonic acid; Cyclic hydroxyiminoamidines; Cyclization.
* Corresponding author. Tel.: +33 549 454 100; fax: +33 549 453 501; e-mail: jmcousta@univ-poitiers.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.057

In previous papers, we reported the behavior and reactivity of 1-arylamino-1-methylthio-2-nitroethene derivatives **4** (Fig. 2) and acyclic nitroketene *S*,*S*-acetals **5** in superacidic media in HF–SbF_5 and trifluoromethanesulfonic acid.[16,17]

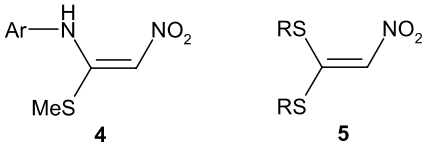


Figure 2.

In this paper, we present a new method for the synthesis of tricyclic (*E*)-hydroxyiminohydroazaazoniabenzocycloalkene derivatives in their triflate salt forms, starting from new cyclic nitroketene aminals, which were cyclized in trifluoromethanesulfonic acid.

2. Results and discussion

2.1. Starting material

Firstly, the appropriate linear monosubstituted diamines **9** and **10** bearing a tethered phenyl group were prepared, by reacting the corresponding 1-bromo-ω-phenyl derivatives **6** with excess 1,2-ethylenediamine **7** or 1,3-diaminopropane **8** (Scheme 1).

A potential synthon for the synthesis of nitroketene aminals derivatives is 1,1-bis(methylthio)-2-nitroethene **11**. In this compound, both methylthio groups are easily substituted by amino groups in mild conditions.[18,19] Reactions with aromatic[20] or non-aromatic amines[21] afford nitroketene *S*,*N*-acetals. Thus, nucleophilic substitution between one molar equivalent of diamine **9** or **10** and 1,1-bis(methylthio)-2-nitroethene **11** afforded the expected nitroketene aminals, either in the imidazolidine series **12** ($n=1$) or hexahydropyrimidine series **13** ($n=2$) with yields varying from 33 to 78% (Table 1).

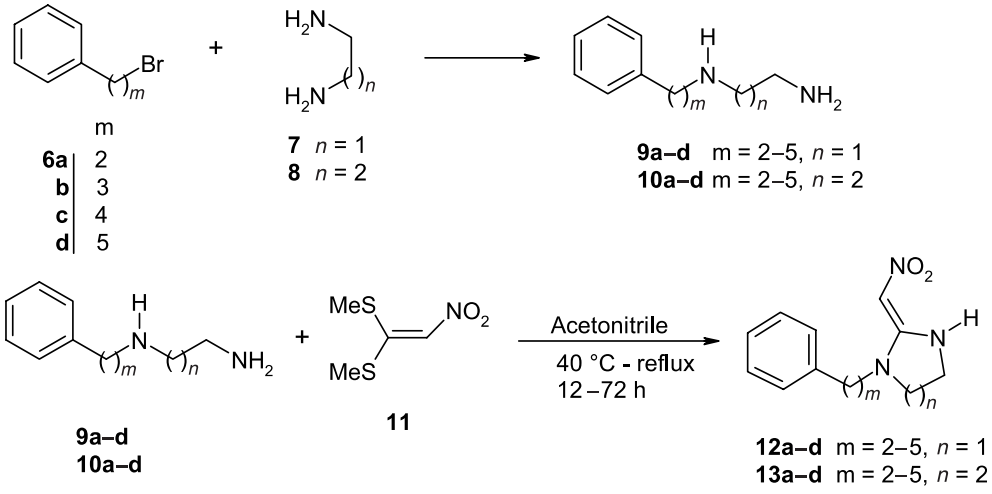
Compounds **12** and **13** were isolated by flash chromatography, followed by crystallization from a mixture of dichloromethane–petroleum ether. These compounds were characterized by NMR spectroscopy and HRMS.

For the imidazoline series **12**, a vinylic proton resonates in the range δ_H 6.48–6.52 ppm, the nitromethylene carbon $=CH–NO_2$ at δ_C 96.4–96.6 ppm and the $>C=C$ ethylene carbon at δ_C 159.0–159.3 ppm. In the hexahydropyrimidine series **13**, the observed chemical shifts are similar for the vinylic proton at δ_H 6.61–6.70 ppm and the nitromethylene carbon: δ_C 97.8–98.6 ppm but somewhat different for the ethylene carbon, which resonates at higher field due to a cycle effect: δ_C 153.8–154.5 ppm.[22]

In organic solvent solution, these compounds exist as sole isomers, as shown by a single set of signals in the ^{13}C NMR spectra. They are probably all (*E*)-isomers since this conformation allows the formation of an intramolecular hydrogen bond between the N–H and the $–NO_2$ groups, as previously reported for the 1-arylamino-1-methylthio-2-nitroethenes **4**.[20]

2.2. Reactions in trifluoromethanesulfonic acid

The reactions were carried out in trifluoromethanesulfonic acid at 60 °C under nitrogen atmosphere (Scheme 2).

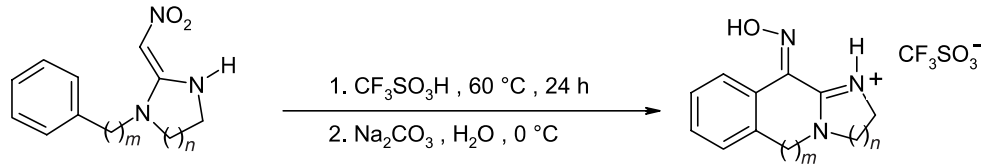


Scheme 1. Synthesis of imidazolidine and hexahydropyrimidine derivatives **12** and **13**.

Table 1. Yields of imidazolidine **12a–d** and hexahydropyrimidine **13a–d**

Starting diamine	**9a**	**9b**	**9c**	**9d**	**10a**	**10b**	**10c**	**10d**
Product	**12a**	**12b**	**12c**	**12d**	**13a**	**13b**	**13c**	**13d**
Yield (%)	78	62	33[a]	56	76	64	69	82

[a] With 25% of unreacted **11**.



12a–d m = 2-5, *n* = 1
13a–d m = 2-5, *n* = 2

14a–d m = 2-5, *n* = 1
15a–d m = 2-5, *n* = 2

Scheme 2. Preparation of cyclic hydroxyiminoamidine derivatives **14** and **15** from the corresponding imidazoline and hexahydropyrimidine **12** and **13**, respectively.

Table 2. Yields of triflate salts **14a–d** and **15a–d**

Starting compound	**12a**	**12b**	**12c**	**12d**	**13a**	**13b**	**13c**	**13d**
Triflate salt	**14a**	**14b**	**14c**	**14d**	**15a**	**15b**	**15c**	**15d**
Yield (%), isolated product	62	79	89	13	90	85	72	12

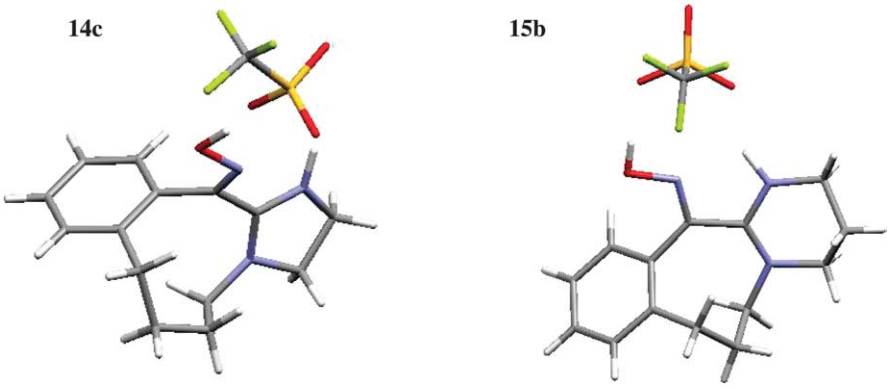


Figure 3. X-ray analysis of **14c** and **15b**.[23]

The molar ratio of trifluoromethanesulfonic acid/imidazolidine **12** or hexahydropyrimidine **13** molar was 50:1. At the end of the reaction, the acidic solution is poured into a mixture of ice (15 g) and anhydrous Na_2CO_3 (6 g) and the extraction is carried out promptly at approximately 0 °C with dichloromethane–methanol (95/5). The reactions were generally clean and the starting materials were fully transformed after 24 h reaction time, with yields varying from 12 to 90% (Table 2).

The structure of compounds **14** and **15** was determined by NMR and was corroborated by X-ray crystallographic analysis of **15b** and **15c** (Fig. 3).

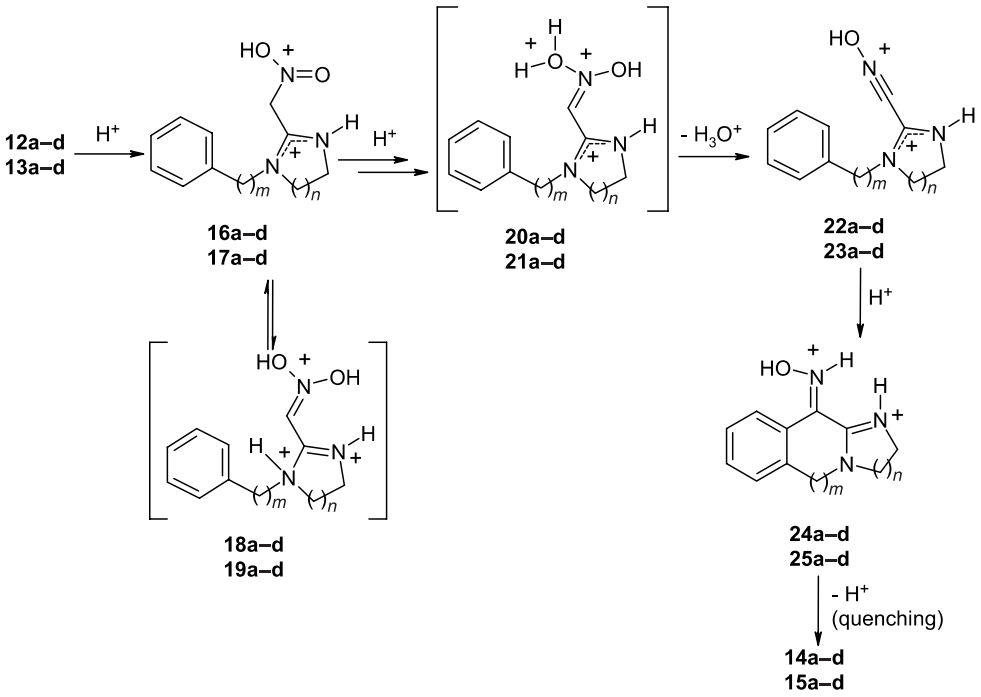
Crystal data for **14c** and **15d** were recorded at room temperature with a Nonius Kappa CDD difractometer equipped with a graphite monochromator and X-ray tube with a Mo anticathode (λ=0.71069 Å). The structure was solved using direct methods[24] and refined using least square calculation.[25]

The X-ray analysis indicated that the hydroxyl group of the formed hydroxyimino group adopts a cis configuration relative to the aromatic ring. This assignment is in agreement with previous observations[16,17,26] and is also as expected on a theoretical point of view[27] from an addition step on a triple bond. Another interesting feature is that in the amidine group, the CN bond distance between the central carbon and both nitrogen atoms are very similar (1.312/1.317 Å for **14c** and 1.335/1.325 for **15b**). This observation is in agreement with the delocalized character of the 'double bond'. These bonds are longer than in the localized CN double bond of the hydroxyimino group (1.291 and 1.289 Å for **14c** and **15b**, respectively).

The formation of compounds **14** and **15** may be explained by a similar mechanism as reported for acyclic nitroketene *S*,*S*-acetals **5** (Scheme 3).[17]

In this mechanism, compounds **12** and **13** undergo multiple protonation[16] and loss of a molecule of water, leading to the formation of transient conjugated hydroxynitrilium cations, **22** and **23**, which immediately react with the tethered phenyl ring by way of an electrophilic aromatic substitution mechanism, to afford the observed cationic compounds **24** and **25**.

The formation of cationic compounds **24** and **25** occurs through a rate-limiting step that requires heating at 60 °C. This may be explained by the fact that (poly)protonation of the starting molecule on both nitrogen atoms, slows down the water elimination step. In agreement with this assumption is the fact that with the less basic sulfur atom



Scheme 3. Suggested mechanism for the formation of **14** and **15**.

in series **4** or **5**, formation of the stable hydroxynitrilium ions occurs even at low temperature.[17,28]

At the end of the reaction, even when the acidity was quenched, compounds **14** and **15** were isolated as salts due to the strong basicity of the amidine group.[7]

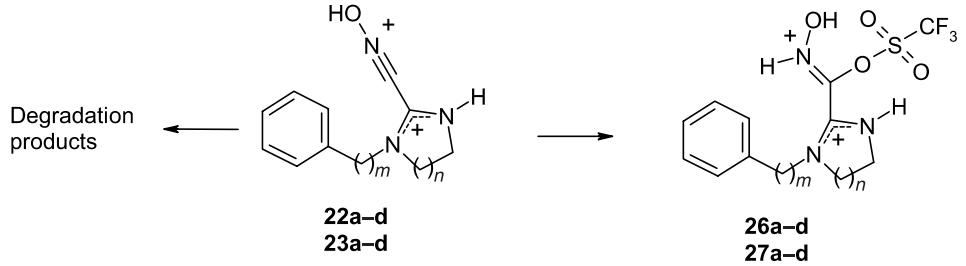
In the imidazoline series, the yields of isolated cyclization products **14a–c** varies, depending on the size of the formed ring; ranging from 62% for a seven-membered ring (**14a**) to 89% for the nine-membered ring (**14c**). As expected for reason of entropy, the yield in intramolecular cyclization drops to 13% for the 10-membered ring product **14d**.[29] The hexahydropyrimidine series **15a–c** follows the same pattern, with the yield decreasing regularly from 90% (seven-membered ring **15a**) to 72% (nine-membered ring **15c**) and dropping to 12% in the 10-membered ring product **15d**. In this case, the formed hydroxynitrilium ion can also either react (i) to afford degradation products or (ii) with triflate anion to form the nucleophilic addition compound, as previously observed in situ, with 1-amino-2-nitroethylene derivatives, affording ions **26** or **27** that easily decomposed during the hydrolysis step of the reaction medium (Scheme 4).[28]

The influence of the imidazoline ring or hexahydropyrimidine ring on the yield of this cyclization reaction is not very clear-cut.

NMR spectroscopy shows a sole (*E*)-isomer for the seven to nine-membered ring products **14a–c** and **15a–c**, but two sets of signals are observed for the 10-membered ring products **14d** and **15d**. These two sets of signals can be due to either (i) (*E*) and (*Z*) isomers or (ii) to a mixture of two conformers, formation of which would occur due to hampering of the flexing of the 10-membered ring by the presence of both the phenyl ring and the imidazoline, or hexahydropyrimidine, ring.[30]

3. Conclusion

The present study constitutes an extension of the use of acyclic 1-arylalkyl-substituted-2-nitroethylene diaminoacetals in the field of heterocyclic synthesis. Tricyclic hydroxyiminohydroazaazoniabenzocycloalkene trifluoromethanesulfonate derivatives can be easily prepared from 2-nitromethylene-1-(phenylalkyl)imidazolidine or 2-nitromethylene-1-(phenylalkyl)hexahydropyrimidine derivatives in trifluoromethanesulfonic acid. These derivatives



Scheme 4. Other suggested reactions for the formed hydroxynitrilium ions.

may be used in the field of natural products synthesis and work is in progress in this field.

4. Experimental

4.1. General remarks

Melting points were determined with a Büchi Melting point B545 apparatus using capillary tubes (temperature rate 2 °C/min) and were not corrected. A Brucker DPX 300 spectrometer, equipped with a low temperature probe, was used for ^{1}H, ^{9}F and ^{13}C NMR spectra recorded at 300.13, 282.37 and 75.47 MHz, respectively. NMR spectra were recorded at room temperature and chemical shifts reported relative to Me_4Si or $CFCl_3$ for fluorine. The reproducibility of ^{13}C NMR shift was about ± 0.05 ppm, depending on cell and concentration. Chemical assignments were made using DEPT135 technic and usual chemical shift assignments rules. Electron-impact ionization (70 eV) mass spectra were obtained with a Finnigan Incos 500 Instrument. High Resolution Mass Spectrometry was performed by the 'Centre Régional de Mesures Physiques de l'Ouest—Université de Rennes, France'. Flash chromatography was achieved on silica gel (20–45 μm particle size). HPLC was used to check the purity or to identify the various compounds described below. A Waters 600 pump equipped with a Rheodyne 7125 injector valve (20 μL loop) and an Applied Biosystem 785A programmable or Waters 486 UV detector at 254 nm, column 250×4 mm I.D., 5 μm Spherisorb silica or equivalent, were used with eluent CH_3CN:H_2O (with 1.5% AcOH) 70:30 and a 1 mL min^{-1} flow rate.

Trifluoromethanesulfonic acid was purchased from across and 1,1-bis(methylthio)-2-nitroethene from Lancaster and were used without further purification. No attempt was made to optimize the yields.

4.2. Starting material

4.2.1. 2-Nitromethylene-1-phenethylimidazolidine (12a). Typical procedure. *N′*-1′-Phenethylethane-1,2-diamine (1.75 g, 10.7 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.76 g, 10.7 mmol) were heated at 60 °C in acetonitrile (30 mL) for 14 h under N_2. The advancement of the reaction was checked by thin-layer chromatography on silica gel deposited on aluminum sheet. The solution was concentrated under vacuum and the resulting residue was separated by flash chromatography with CH_2Cl_2–EtOH (97/3) and then crystallized from CH_2Cl_2/petroleum ether to afford compound **12a** as white crystals (1.92 g, 78%). Mp 99–98 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): $\delta=2.87$ (t, $J=7.3$ Hz, 2H, –CH_2-Ph), 3.39 (t, $J=7.3$ Hz, 2H, –CH_2–N<), 3.46 (dd, $J=10.4$, 1.2 Hz, 1H, imidazolidine –CH_2–N<), 3.48 (br d, $J=9.5$ Hz, 1H, imidazolidine –CH_2–N<), 3.67 (d, $J=9.7$ Hz, 1H, imidazolidine –HN–CH_2–), 3.70 (br d, $J=11.1$ Hz, 1H, imidazolidine –HN–CH_2–), 6.54 (s, 1H, vinylic H), 7.10–7.25 (m, 3H, aromatic *o*-H and *p*-H), 7.30–7.39 (m, 2H, aromatic *m*-H), 8.60 (br s, 1H, N–H). ^{13}C NMR ($CDCl_3$): $\delta=33.7$ (*C*H_2-Ph), 42.4 (–*C*H_2–N<), 47.2 and 49.1 (imidazolidine CH_2), 96.4 (=*C*H–NO_2), 127.0, 128.6 and 128.8 (aromatic CH), 137.6 (*ipso*-C), 159.1 [>*C*=CH(NO_2)]. HRMS for $C_{12}H_{15}N_3O_2$ ([M^+]): calcd 233.1164, found 233.1155. HRMS for $C_{12}H_{15}N_2O$ ([M^+-NO]): calcd 203.1184, found 203.1181.

4.2.2. 2-Nitromethylene-1-(3-phenylpropyl)imidazolidine (12b). From *N′*-1′-(3-phenylpropyl)ethane-1,2-diamine (1.44 g, 8 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.76 g, 8 mmol) in refluxed acetonitrile (25 mL) for 12 h. The desired compound **12b** crystallized as white crystals (1.25 g, 62%). Mp 117–118 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): $\delta=1.90$ (q, $J=7.5$ Hz, 2H, –CH_2–CH_2–CH_2–), 2.63 (t, $J=7.5$ Hz, 2H, –CH_2-Ph), 3.12 (t, $J=7.4$ Hz, 2H, –CH_2–N<), 3.59 (m, 2H, imidazolidine –CH_2–N<), 3.70 (m, 2H, imidazolidine –HN–CH_2–), 6.48 (s, 1H, vinylic H), 7.16 (cd, $J=7.2$ Hz, 2H, aromatic *o*-H), 7.20 (ct, $J=7.3$ Hz, 1H, aromatic *p*-H), 7.29 (ct, $J=6.7$ Hz, 2H, aromatic *m*-H), 8.59 (br s, 1H, N–H). ^{13}C NMR ($CDCl_3$): $\delta=28.3$ (CH_2), 32.6 (*C*H_2-Ph), 42.1 (–*C*H_2–N<), 45.0 and 48.3 (imidazolidine CH_2), 96.4 (=*C*H–NO_2), 126.1, 128.0 and 128.4 (aromatic CH), 140.1 (*ipso*-C), 159.0 [>*C*=CH(NO_2)]. HRMS for $C_{13}H_{17}N_3O_2$ ([$M^{\cdot+}$]): calcd 247.13208, found 247.1334. HRMS for $C_{13}H_{17}N_2O$ ([$M-NO]^+$): calcd 217.1341, found 217.1335.

4.2.3. 2-Nitromethylene-1-(4-phenylbutyl)imidazolidine (12c). From *N′*-1′-(4-phenylbutyl)ethane-1,2-diamine (2.41 g, 12.5 mmol) and 1,1-bis(methylthio)-2-nitroethene (2.12 g, 12.8 mmol) in refluxed acetonitrile (25 mL) for 72 h. The resulting products were separated by flash chromatography: unreacted 1,1-bis(methylthio)-2-nitroethene (0.53 g, 25%) was first separated using CH_2Cl_2 as eluent, then compound **12c** (1.10 g, 33%) as white crystals. Mp 96–97 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): $\delta=1.60$ (m, 4H, –CH_2–CH_2–), 2.63 (t, $J=6.9$ Hz, –CH_2-Ph), 3.10 (t, $J=6.9$ Hz, –CH_2–N<), 3.58 (complex t, $J_{app}=9.0$ Hz, 2H, imidazolidine –CH_2–N<), 3.71 (ct, $J_{app}=9.0$ Hz, 2H, imidazolidine –HN–CH_2–), 6.52 (s, 1H, vinylic H), 7.12–7.22 (m, 3H, aromatic *o*-H and *p*-H), 7.30 (m, 2H, aromatic *m*-H), 8.60 (br s, H, N–H). ^{13}C NMR ($CDCl_3$): $\delta=26.6$ (CH_2), 28.4 (CH_2), 35.4 (*C*H_2-Ph), 42.3 (–*C*H_2–N<), 45.6 and 48.5 (imidazolidine CH_2), 96.6 (=*C*H–NO_2), 126.1, 128.3 and 128.5 (aromatic CH), 141.4 (*ipso*-C), 159.3 [>*C*=CH(NO_2)]. HRMS for $C_{14}H_{19}N_3O_2$ ([M^+]): calcd 261.1477, found 261.1482. HRMS for $C_{14}H_{19}N_2O$ ([M^+-NO]): calcd 231.1497, found 231.1507. HRMS for $C_{14}H_{19}N_2$ ([M^+-NO_2]): calcd 215.1548, found 215.1545.

4.2.4. 2-Nitromethylene-1-(5-phenylpentyl)imidazolidine (12d). From *N′*-1′-(4-phenylpentyl)ethane-1,2-diamine (2.21 g, 10.7 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.69 g, 10.2 mmol) at 50 °C in acetonitrile (30 mL) for 23 h was obtained on cooling compound **12d** (1.58 g, 56%) as light white crystals. Mp 115.8 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): $\delta=1.33$ (m, 2H, –CH_2–CH_2–CH_2–), 1.59–1.67 (m, 4H, –CH_2–CH_2–CH_2–CH_2–), 2.62 (ct, $J=7.64$, 7.49 Hz, 2H, –CH_2-Ph), 3.09 (ct, $J=7.49$, 7.33 Hz, 2H, –CH_2–N<), 3.61 (m, 2H, imidazolidine –CH_2–N<), 3.73 (m, 2H, imidazolidine –HN–CH_2–), 6.52 (s, 1H, vinylic H), 7.15–7.21 (m, 3H, aromatic *o*-H and *p*-H), 7.26–7.31 (m, 2H, aromatic *m*-H), 8.62 (br s, H, N–H). ^{13}C NMR ($CDCl_3$): $\delta=26.6$ (CH_2), 27.1 (CH_2), 30.9 (CH_2),

35.6 (CH_2-Ph), 42.3 (–CH_2–N<), 45.6 and 48.6 (imidazolidine CH_2), 96.6 (=CH–NO_2), 125.9 and 128.4 (aromatic CH), 141.9 (*ipso*-C), 159.3 [>C=CH(NO_2)]. $C_{15}H_{21}N_3O_2$ (275.35): calcd C 65.49, H 7.63, N 15.34, found C 65.43, H 7.69, N 15.26.

4.2.5. 2-Nitromethylene-1-phenethylhexahydropyrimidine (13a). Typical procedure. *N*′-1′-Phenethylpropane-1,3-diamine (1.27 g, 7.1 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.19 g, 7.2 mmol) were heated at 40 °C in acetonitrile (30 mL) for 18 h under N_2. The solution was concentrated under vacuum and the resulting product was purified by flash chromatography with CH_2Cl_2–EtOH (97/3) and then crystallized from CH_2Cl_2/petroleum ether to afford **13a** as light yellow crystals (1.33 g, 76%). Mp 113–114 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): δ=1.86 (q, J=8.8 Hz, 2H, hexahydropyrimidine –CH_2–), 2.89 (t, J=7.2 Hz, 2H, –CH_2-Ph), 3.13 (t, J=5.8 Hz, 2H, –CH_2–N<), 3.34 (dd, J=5.6, 3.1 Hz, 2H, hexahydropyrimidine –CH_2–N<), 3.43 (t, J=7.2 Hz, 2H, hexahydropyrimidine –HN–CH_2–), 6.70 (s, 1H, vinylic H), 7.16–7.23 (m, 2H, aromatic *o*-H and *p*-H), 7.25–7.36 (m, 3H, 2 aromatic *m*-H and aromatic *o*-H), 10.72 (br s, 1H, N–*H*). ^{13}C NMR ($CDCl_3$): δ=19.7 (CH_2), 33.7 (CH_2-Ph), 37.5 (–CH_2–N<), 47.4 and 52.5 (hexahydropyrimidine CH_2), 97.8 [=CH(NO_2)], 126.7, 128.4 and 128.5 (aromatic CH), 137.0 (*ipso*-C), 153.8 [>C=CH(NO_2)]. HRMS for $C_{13}H_{17}N_3O_2$ ([M^+]): calcd 247.1321, found 247.1309. HRMS for $C_{13}H_{17}N_2O$ ([M^+−NO]): calcd 217.1341, found 217.1356.

4.2.6. 2-Nitromethylene-1-(3-phenylpropyl)hexahydropyrimidine (13b). From *N*′-1′-(3-phenylpropyl)propane-1,3-diamine (2.23 g, 11.6 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.99 g, 12 mmol) at 40 °C in acetonitrile (30 mL) for 18 h. Compound **13b** (1.95 g, 64%) was obtained as light yellow crystals. Mp 126–127 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): δ=1.87 (m, 2H, hexahydropyrimidine –CH_2–), 2.00 (m, 2H, CH_2–CH_2–CH_2), 2.62 (t, J=7.6 Hz, 2H, –CH_2-Ph), 3.16 (d, J=8.0 Hz, 1H, –CH_2–N<), 3.19 (d, J=7.8 Hz, 1H, –CH_2–N<), 3.30–3.40 (m, 4H, hexahydropyrimidine –HN–CH_2– and –CH_2–N<), 6.61 (s, 1H, vinylic H), 7.12–7.24 (m, 3H, aromatic *o*-H and *p*-H), 7.26–7.32 (m, 2H, aromatic *m*-H), 10.70 (br s, 1H, N–H). ^{13}C NMR ($CDCl_3$): δ=20.6 (CH_2), 29.2 (CH_2), 33.1 (CH_2-Ph), 38.2 (–CH_2–N<), 47.3 and 51.2 (hexahydropyrimidine CH_2), 98.5 [=CH(NO_2)], 126.7, 128.5 and 129.0 (aromatic CH), 140.6 (*ipso*-C), 154.5 [>C=CH(NO_2)]. HRMS for $C_{14}H_{19}N_3O_2$ ([M^+]): calcd 261.1477, found 261.1480. HRMS for $C_{14}H_{19}N_2O$ ([M^+−NO]): calcd 231.1497, found 231.1496. HRMS for $C_{14}H_{19}N_2$ ([M^+−NO_2]): calcd 215.1548, found 215.1537.

4.2.7. 2-Nitromethylene-1-(4-phenylbutyl)hexahydropyrimidine (13c). From *N*′-1′-(4-phenylbutyl)propane-1,3-diamine (3.63 g, 17.8 mmol) and 1,1-bis(methylthio)-2-nitroethene (2.81 g, 17.0 mmol) at 52 °C in acetonitrile (30 mL) for 15 h. Compound **13c** (2.40 g, 69%) was obtained as light yellow crystals. Mp 127–128 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): δ=1.61 (m, 4H, –CH_2–CH_2–), 1.98 (q, J=5.9 Hz, 2H, hexahydropyrimidine –CH_2–), 2.63 (ct, J=6.9 Hz, 2H, –CH_2-Ph), 3.15 (ct, J=7.3 Hz, 2H, –CH_2–N<), 3.33 (t, J=5.8 Hz, 2H, hexahydropyrimidine –CH_2–N<), 3.38 (m, 2H, hexahydropyrimidine –HN–CH_2–), 6.62 (s, 1H, vinylic H), 7.13–7.23 (m, 3H, aromatic *o*-H and *p*-H), 7.25–7.34 (m, 2H, aromatic *m*-H), 10.70 (br s, 1H, N–*H*). ^{13}C NMR ($CDCl_3$): δ=20.0 (CH_2), 26.8 (CH_2), 28.2 (CH_2), 35.2 (CH_2-Ph), 37.6 (–CH_2–N<), 46.7 and 50.9 (hexahydropyrimidine CH_2), 97.9 (=CH–NO_2), 125.8, 128.1 and 128.2 (aromatic CH), 141.2 (*ipso*-C), 153.8 [>C=CH(NO_2)]. HRMS for $C_{15}H_{21}N_3O_2$ ([M^+]): calcd 275.1634, found 275.1636. HRMS for $C_{14}H_{19}N_2O$ ([M^+−NO]): calcd 245.1654, found 245.1652.

4.2.8. 2-Nitromethylene-1-(5-phenypentyl)hexahydropyrimidine (13d). From *N*′-1′-(5-phenylpentyl)propane-1,3-diamine (1.0 g, 4.5 mmol) and 1,1-bis(methylthio)-2-nitroethene (0.75 g, 4.5 mmol) at 55 °C in acetonitrile (15 mL) for 17 h. Compound **13d** (0.99 g, 82%) was obtained as yellow crystals. Mp 112.8 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR ($CDCl_3$): δ=1.30 (m, 2H, –CH_2–), 1.62 (m, 4H, –CH_2–CH_2–CH_2–CH_2–), 2.01 (q, J=5.95 Hz, 2H, hexahydropyrimidine –CH_2–), 2.62 (t, J=7.57 Hz, 2H, –CH_2-Ph), 3.13 (dd, J=7.87, 7.77 Hz, 2H, –CH_2–N<), 3.33 (ct, J_{app}=5.75 Hz, 2H, hexahydropyrimidine –CH_2–N<), 3.40 (m, 2H, hexahydropyrimidine –HN–CH_2–), 6.62 (s, 1H, vinylic-H), 7.15–7.22 (m, 3H, aromatic *o*-H and *p*-H), 7.29–7.61 (m, 2H, aromatic *m*-H), 10.75 (br s, 1H, N–H). ^{13}C NMR ($CDCl_3$): δ=20.6 (CH_2), 26.5 (CH_2), 27.8 (CH_2), 31.4 (CH_2), 36.1 (CH_2-Ph), 38.2 (–CH_2–N<), 47.4 and 51.7 (hexahydropyrimidine CH_2), 98.6 (=CH–NO_2), 126.2 and 128.7 (aromatic CH), 142.3 (*ipso*-C), 154.4 [>C=CH(NO_2)]. HRMS for $C_{16}H_{23}N_3O_2$ ([M^+]): calcd 289.1790, found 289.1797. HRMS for $C_{16}H_{23}N_2O$ ([M^+−NO]): calcd 259.1810, found 259.1802. HRMS for $C_{16}H_{23}N_2$ ([M^+−NO_2]): calcd 243.1861, found 243.1863.

4.3. Cyclic compounds. Typical procedure

4.3.1. 4-[(*E*)-Hydroxyimino]-2,4,9,10-tetrahydro-1*H*-10a-aza-3-azoniabenzo[*f*]azulene trifluoromethanesulfonate (14a). 2-Nitroethylene-1-(4-phenethyl)imidazolidine (233 mg, 1.0 mmol) was dissolved in trifluoromethanesulfonic acid (4.4 mL, 50 mmol). The solution was heated to 60 °C for 24 h. After cooling, the solution was poured over ice (15 g) and anhydrous Na_2CO_3 (6.0 g, 56.6 mmol). The aqueous phase was quickly extracted with CH_2Cl_2–MeOH (95/5) (4×50 mL). The organic phases were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting product was purified by flash chromatography with CH_2Cl_2–MeOH (95/5) and then crystallized from CH_2Cl_2/petroleum ether to afford **14a** (227 mg, 62%) as white crystals. Mp 191–192 °C (CH_2Cl_2/petroleum). ^{1}H NMR ($CDCl_3$-[d_6]DMSO): δ=3.13 (s, 2H, –CH_2-Ph), 3.59 (br s, 2H, –CH_2–N<), 3.83 (t, J=10.8 Hz, 2H, imidazolidine –CH_2–N<), 4.05 (t, J=10.5 Hz, 2H, imidazolidine –CH_2–N=), 7.41 (m, 3H, aromatic H), 7.52 (d, J=7.5 Hz, 1H, aromatic H), 9.87 (br s, 1H, =NH–), 13.03 (br s, 1H, >=N–OH). ^{13}C NMR ($CDCl_3$-[d_6]DMSO): δ=31.6 (CH_2-Ph), 42.4 (CH_2), 49.7 (CH_2), 54.3 (CH_2), 121.5 (q, J^1_{CF}=321 Hz, $CF_3SO_3^-$), 127.6 and 128.6 (aromatic CH), 129.9 and 130.9 (aromatic CH), 132.0 (*ipso*-C), 137.6 (*ipso*-C), 142.2 (>C=N–H), 160.1 (>C=N–OH). ^{19}F NMR (282.37 MHz, $CDCl_3$-[d_6]DMSO): δ=−78.40 ($CF_3SO_3^-$).

HRMS for $C_{12}H_{13}N_3O$ ([$M^+ - CF_3SO_3H$]): calcd 215.1057, found 215.1070.

4.3.2. 11-[(*E*)-Hydroxyimino]-2,3,4,5,6,11-hexahydro-3a-aza-1-azoniabenzo[*a*]cyclopenta[*d*]cyclooctene trifluoromethanesulfonate (14b). From 2-nitroethylene-1-(4-phenylpropyl)imidazolidine (247 mg, 1.0 mmol) was obtained cyclic compound as the triflate salt **14b** (299 mg, 79%), white crystals. Mp 160.7 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([d_6]acetone): δ=1.86 (m, 2H, –CH_2–CH_2–CH_2–), 2.68 (t, J=6.5 Hz, 2H, –CH_2-Ph), 3.18 (m, 2H, CH_2–N<), 3.88 (t, J=10.3 Hz, 2H, imidazolidine –CH_2–N<), 4.26 (t, J=11.0 Hz, imidazolidine –CH_2–N=), 7.26 (t, J=7.5 Hz, 2H, aromatic H), 7.40 (t, J=8.0 Hz, 2H, aromatic H), 9.11 (br s, 1H, =N–H), 12.40 (vbs, 1H, >=N–OH). ^{13}C NMR ([d_6]acetone): δ=29.9 (CH_2), 30.1 (*C*H_2-Ph), 43.5 (CH_2), 45.2 (CH_2), 55.4 (CH_2), 122.9 (q, J_{CF}=321 Hz, $CF_3SO_3^-$), 128.5 and 128.8 (aromatic CH), 130.9 and 132.9 (aromatic CH), 133.3 (*ipso*-C), 139.5 (*ipso*-C), 144.8 (>C=N–H), 162.9 (>C=N–OH). ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−77.29 ($CF_3SO_3^-$). MS (70 eV); *m*/*z* (%): 229 (50) [$M^+ - CF_3SO_3H$], 228 (70) [$M^+ - CF_3SO_3H$–H], 212 (25) [$M^+ - CF_3SO_3H$–OH], 184 (20), 69 (100). HRMS for $C_{13}H_{15}N_3O$ ([$M^+ - CF_3SO_3H$]): calcd 229.1215, found 229.1205.

4.3.3. 12-[(*E*)-Hydroxyimino]-2,4,5,6,7,12-hexahydro-3*H*-3a-aza-1-azoniabenzo[*a*]cyclopenta[*d*]cyclononene trifluoromethanesulfonate (14c). From 2-nitroethylene-1-(4-phenylbutyl)imidazolidine (261 mg, 1.0 mmol) was obtained compound **14c** (351 mg, 89%) as white crystals. Mp 197.5 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([d_6]acetone): δ=1.82 (m, 4H, –CH_2–CH_2–), 2.81 (br t, J=6.3 Hz, 2H, –CH_2-Ph), 3.40 (br t, J=5.5 Hz, 2H, CH_2–N<), 4.12 (ddd, J=12.5, 2.50, 1.56 Hz, 2H, imidazolidine –CH_2–N=), 4.30 (ddd, J=12.5, 2.50, 1.56 Hz, 2H, imidazolidine –CH_2–N<), 7.26–7.32 (m, 1H, aromatic H), 7.36–7.42 (m, 2H, aromatic H), 7.44–7.48 (m, 1H, aromatic H), 10.92 (br s, 2H, =N–H and >=N–OH). ^{13}C NMR ([d_6]acetone): δ=25.4 (CH_2), 27.6 (CH_2), 33.6 (*C*H_2-Ph), 44.7 (CH_2), 45.8 (CH_2), 53.4 (CH_2), 123.0 (q, J_{CF}=321 Hz, *C*$F_3SO_3^-$), 128.4 and 130.38 (aromatic CH), 130.41 and 132.1 (aromatic CH), 132.5 (*ipso*-C), 143.1 (*ipso*-C), 146.7 (>C=N–H), 163.7 (>C=N–OH). ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−79.28 ($CF_3SO_3^-$). MS (70 eV); *m*/*z* (%): 243 (42) [$M^+ - CF_3SO_3H$], 225 (98) [$M^+ - CF_3SO_3H$–OH], 197 (45), 116 (75) [$C_7H_6CN^+$], 56 (100). HRMS for $C_{14}H_{15}N_3$ ([$M^+ - CF_3SO_3H$–OH]): calcd 225.1266, found 225.1256.

4.3.4. 2-Hydroxyimino-7-aza-4-azoniatricyclo-[11.4.0.0.^{3,7}]heptadeca-1(17),3,13,15-tetraene trifluoromethanesulfonate (14d) From 2-nitromethylene-1-(5-phenylpentyl)imidazolidine (276 mg, 1 mmol) was obtained compound **14d** (54 mg, 13%) as white crystals. Mp 149.1 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([D_6]acetone): δ=1.16 (massif, 2H, –CH_2–CH_2–CH_2–), 1.64 (m, 2H, –CH_2–CH_2–N<), 1.73 (m, 2H, Ph-CH_2–CH_2–), 2.56 (dd, J=5.8 Hz, 2H, –CH_2-Ph), 3.40 (dd, J=5.9 Hz, 2H, CH_2–N<), 4.03 (m, 2H, imidazolidine –CH_2–N<), 4.10 (m, 2H, imidazolidine, –CH_2–N=), 7.23–7.32 (m, 2H, aromatic H), 7.34–7.40 (m, 1H, aromatic H), 7.53 (m, 1H, aromatic H). ^{13}C NMR ([d_6]acetone): δ=22.7*, 21.8 (CH_2), 27.9, 25.8* (CH_2), 30.6*, 30.4 (CH_2), 31.2*, 32.6 (*C*H_2-Ph), 34.7*, 34.2 (CH_2), 43.9, 43.4* (CH_2), 46.7*, 46.7 (CH_2), 51.8*, 50.7 (CH_2), 127.7 and 127.9* (aromatic CH), 131.0* and 131.5 (aromatic CH), 131.8, 131.7* (*ipso*-C), 144.2*, 142.6 (*ipso*-C), 145.0, 144.6* (>C=N–H), 162.5, 163.8* (>C=N–OH) {* signals from the second isomer}. ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−78.47 ($CF_3SO_3^-$). HRMS for $C_{15}H_{18}N_3$ ([$M^+ - CF_3SO_3H$–OH]): calcd 240.1501, found 240.1494.

4.3.5. 5-[(*E*)-Hydroxyimino]-1,2,3,5,10,11-hexahydro-11a-aza-4-azoniadibenzo[*a*,*d*]cycloheptene trifluoromethanesulfonate (15a). From 2-nitroethylene-1-(4-phenethyl) hexahydropyrimidine (247 mg, 1.0 mmol) was obtained compound **15a** (342 mg, 90%) as white crystals. Mp 193–195 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([d_6]-acetone): δ=2.23 (q, J=5.8 Hz, 2H, hexahydropyrimidine –CH_2–), 3.33 (t, J=5.6 Hz, 2H, CH_2-Ph), 3.62 (t, J=5.5 Hz, –CH_2–N<), 3.88 (t, J=5.7 Hz, 2H, hexahydropyrimidine CH_2–N<), 4.03 (t, J=5.6 Hz, 2H, hexahydropyrimidine CH_2–N=), 7.34 (dt, J=7.4, 1.5 Hz, 1H, aromatic H), 7.37 (dd, J=7.0, 1.4 Hz, 1H, aromatic H), 7.45 (dt, J=7.4, 1.4 Hz, 1H, aromatic H), 7.71 (dd, J=7.8, 1.4 Hz, 1H, aromatic H), 9.42 (br s, 1H, =N–H), 12.14 (br s, 1H, =N–OH). ^{13}C NMR ([d_6]acetone): δ=20.6 (CH_2), 32.6 (*C*H_2-Ph), 40.3 (CH_2), 48.8 (CH_2), 53.0 (CH_2), 122.8 (q, J^1_{CF}=321 Hz, C*F*$_3SO_3^-$), 127.7 and 127.7 (aromatic CH), 131.9 and 132.3 (aromatic CH), 132.5 (*ipso*-C), 138.3 (*ipso*-C), 148.0 (>C=N–H), 159.7 (>C=N–OH). ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−79.56 ($CF_3SO_3^-$). MS (70 eV); *m*/*z* (%): 229 (35) [$M^+ - CF_3SO_3H$], 228 (70) [$M^+ - CF_3SO_3H$–H], 213 (55), 212 (100) [$M^+ - CF_3SO_3$-H–OH], 184 (80). HRMS for $C_{13}H_{15}N_3O$ ([$M^+ - CF_3SO_3H$]): calcd 229.1215, found 229.1210.

4.3.6. 12-[(*E*)-Hydroxyimino]-3,4,5,6,7,12-hexahydro-2*H*-4a-aza-1-azoniadibenzo[*a*,*d*]cyclooctene trifluoromethanesulfonate (15b). From 2-nitroethylene-1-(4-phenylpropyl)hexahydropyrimidine (261 mg, 1.0 mmol) was obtained compound **15b** (334 mg, 85%) as white crystals. Mp 154–155 °C (acetone/petroleum ether). ^{1}H NMR ([d_6]acetone): δ=2.04 (m, 2H, hexahydropyrimidine –CH_2–), 2.19 (q, J=5.8 Hz, 2H, –CH_2–CH_2–CH_2–), 2.87 (t, J=6.1 Hz, –CH_2-Ph), 3.64 (t, J=5.6 Hz, –CH_2–N<), 3.69 (t, J=5.3 Hz, 2H, hexahydropyrimidine –CH_2–N<), 3.84 (t, J=5.6 Hz, 2H, hexahydropyrimidine –CH_2–N=), 7.34 (d, J=7.6 Hz, 1H, aromatic H), 7.35 (dt, J=7.6, 1.5 Hz, 1H, aromatic H), 7.45 (dt, J=7.4, 1.5 Hz, 1H, aromatic H), 7.59 (d, J=7.9 Hz, 1H, aromatic H), 9.54 (br s, 1H, =N–H), 12.10 (br s, 1H, =N–OH). ^{13}C NMR ([d_6]acetone): δ=20.7 (CH_2), 29.8 (CH_2), 33.5 (*C*H_2-Ph) (br and weak signal), 40.7 (CH_2), 50.9 (CH_2), 54.2 (CH_2) (br and weak signal), 123.0 (q, J_{CF}=321 Hz, *C*$F_3SO_3^-$), 127.4 and 130.5 (aromatic CH), 130.6 and 130.8 (aromatic CH), 131.7 (*ipso*-C), 139.6 (*ipso*-C), 147.9 (>C=N–H), 158.2 (>C=N–OH). ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−81.27 ($CF_3SO_3^-$). MS (70 eV); *m*/*z* (%): 243 (45) [$M^+ - CF_3SO_3H$], 242 (87) [$M^+ - CF_3SO_3H$–H], 226 (30) [$M^+ - CF_3SO_3$-H–OH], 98 (100). HRMS for $C_{14}H_{17}N_3O$ ([$M^+ - CF_3SO_3H$]): calcd 243.1372, found 243.1368. Analysis: $C_{15}H_{18}F_3N_3SO_4$ (393.38): calcd C 46.89, H 4.78, N 10.49, S 8.19; found C 45.80, H 4.58, N 10.7, S 8.14.

4.3.7. 13-[(*E*)-Hydroxyimino]-2,3,4,5,6,7,8,13-octahydro-4a-aza-1-azoniadibenzo[*a*,*d*]cyclononene trifluoromethanesulfonate (15c). From 2-nitroethylene-1-(4-phenylpropyl)hexahydropyrimidine (275 mg, 1.0 mmol) was obtained compound **15c** (294 mg, 72%) as white crystals. Mp 182.9 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([d_6]acetone): δ=1.77 (br s, 4H, –C*H*$_2$–C*H*$_2$–), 2.28 (quintuplet, J=6.0 Hz, 2H, hexahydropyrimidine –CH_2–), 2.87 (m, 2H, –C*H*$_2$-Ph), 3.72 (br t, J=4.5 Hz, 2H, CH_2–N<), 3.87 (m, 4H, hexahydropyrimidine CH_2–N< and –CH_2–N=), 7.35–7.45 (m, 2H, aromatic H), 7.45–7.55 (m, 2H, aromatic H), 8.56 (br s, 1H, =N–H), 10.57 (br s, 1H, =N–OH). ^{13}C NMR ([d_6]acetone): δ=19.6 (CH_2), 26.4 (CH_2), 27.6 (CH_2), 29.1 (*C*H$_2$-Ph), 39.8 (CH_2), 48.4 (CH_2), 50.4 (CH_2), 122.1 (q, J_{CF}=321 Hz, *C*$F_3SO_3^-$), 127.5 and 129.1 (aromatic CH), 130.6 and 130.9 (aromatic CH), 131.4 (*ipso*-C), 141.9 (*ipso*-C), 148.4 (>C=N–H), 158.2 (>C=N–OH). ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−74.14 ($CF_3SO_3^-$). MS (70 eV); *m*/*z* (%): 257 (8) [M^+−CF_3SO_3H], 240 (75) [M^+−CF_3SO_3H–OH], 116 (80), 98 (100). HRMS for $C_{15}H_{19}N_3O$ ([M^+−CF_3SO_3H]): calcd 257.1528, found 257.1547. HRMS for $C_{15}H_{18}N_3$ ([M^+−CF_3SO_3H–OH]): calcd 240.1501, found 240.1494.

4.3.8. 2-Hydroxyimino-8-aza-4-azoniatricyclo-[12.4.0.0.^{3,8}]octadeca-1(18),3,14,16-tetraene trifluoromethanesulfonate (15d) From 2-nitroethylene-1-(5-phenylpentyl)hexahydropyrimidine (289 mg, 1 mmol) was obtained compound **15d** (50 mg, 12%) as white crystals. Mp 201.2 °C (CH_2Cl_2/petroleum). ^{1}H NMR ([d_6]methanol): δ=1.17 (m, 2H, –CH_2–C*H*$_2$–CH_2–), 1.80–1.84 (massif, 4H, –C*H*$_2$–CH_2–C*H*$_2$–), 2.08–2.10 (ct, J=5.77 Hz, 2H, hexahydropyrimidine, –CH_2–), 2.70–2.75 (dd, J=6.5 Hz, 2H, –C*H*$_2$-Ph), 3.51–3.61 (m, 4H, –CH_2–N< and hexahydropyrimidine –CH_2–N<), 3.90 (dd, J=5.8 Hz, 2H, hexahydropyrimidine –C*H*$_2$–N=), 7.30–7.35 (m, 2H, aromatic H), 7.37–7.44 (m, 1H, aromatic H), 7.95 (m, 1H, aromatic H). ^{13}C NMR ([d_6]methanol) mixture of isomers: δ=19.89*, 19.71 (CH_2), 24.86, 24.86* (CH_2), 28.19, 26.38* (CH_2), 33.47, 33.38* (CH_2), 37.67, 37.67* (*C*H$_2$-Ph), 40.46, 40.11* (CH_2), 48.18*, 46.82 (CH_2), 54.64*, 53.65 (CH_2), 125.98, 123.93* and 127.83*, 127.64 (aromatic CH), 131.20, 130.92* and 131.47, 131.34* (aromatic CH), 132.84*, 131.83 (*ipso*-C), 145.95, 142.66* (*ipso*-C), 149.39*, 148.35 (>C=N–H), 159.26, 159.01* (>C=N–OH) {* signals from the second isomer}. ^{19}F NMR (282.37 MHz, [d_6]acetone): δ=−77.00 ($CF_3SO_3^-$). HRMS for $C_{16}H_{20}N_3$ ([M^+−CF_3SO_3H–OH]): calcd 254.1657, found 254.1672.

Acknowledgements

Thanks to CNRS for financial support and to 'Ministère des Affaires Étrangères' for fellowship fund for some of us.

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Highly efficient total synthesis of Δ^{12}-PGJ_2, 15-deoxy-$\Delta^{12,14}$-PGJ_2, and their analogues

Hukum P. Acharya and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

Received 26 November 2005; accepted 17 January 2006

Available online 13 February 2006

Abstract—Palladium-catalyzed reaction of TBS ether of 4-cyclopentene-1,3-diol monoacetate (>95% ee) with an anion derived from methyl malonate and a base such as *t*-BuOK and LDA proceeded highly efficiently and reproducibly. The product obtained in >90% isolated yield was transformed in five steps into the key cyclopentenone possessing the α-chain at the γ position. Aldol reaction of this enone with the ω-chain aldehyde afforded the aldol adduct, and exposure of the derived mesylate to Al_2O_3 furnished the cross-conjugated dienone of the full structure. Finally, functional group manipulation furnished Δ^{12}-PGJ_2 efficiently. Similarly, 15-deoxy-$\Delta^{12,14}$-PGJ_2, 5,6-acetylene analogues, and a 5,6-dihydro analogue were synthesized.
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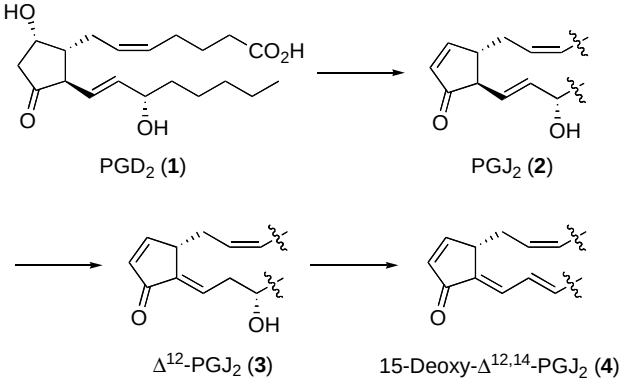
1. Introduction

In the 1980s, Fitzpatrick and Wyland reported[1] albumin-catalyzed metabolism of PGD_2 in vitro to afford Δ^{12}-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 (Scheme 1, Fig. 1). Later, Hayashi et al. extracted Δ^{12}-PGJ_2 from normal human urine to support the existence of albumin-catalyzed metabolism in vivo.[2] In contrast with other PGs, which elicit a biological response through binding to G-protein coupled receptors, these metabolites interact with other specific cellular targets such as signaling molecules and transcriptional factors directly.[3,4] For example, 15-deoxy-$\Delta^{12,14}$-PGJ_2 represents the most potent natural ligands reported to date for PPARγ, a receptor that has been linked to non-insulin dependent diabetes mellitus (NIDDM or type II diabetes), obesity, hypertension, and atherosclerosis.[5] Inhibition of the NF-κB-mediated transcription is another property of 15-deoxy-$\Delta^{12,14}$-PGJ_2, and is responsible for anti-inflammatory activity. On the other hand, Δ^{12}-PGJ_2 exhibits strong antitumor effects by incorporating into tumor cells and transferring into nuclei, activating the gadd45 promoter independently of p53[6] and inhibiting topoisomerase.[7]



Scheme 1. Biosynthesis of Δ^{12}-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2.

Although the fundamental profiles of these Δ^{12}-PGs **3** and **4** have been thus elucidated, more than 50 publications using these PGs have emerged every year in the last several years indicating importance of their property in life science. PGs **3** and **4** in those studies have been purchased from a company or gifted by another company. According to a recent review,[8] the former company produces PG **4**[9] by base-catalyzed decomposition of PGD_2 (**1**), while the method for synthesis of **3** is not disclosed. On the other hand, **3** and **4** are synthesized from a $PGF_{2\alpha}$ derivative in the latter company.[10] Consequently, we felt it important to establish a chemical method for synthesizing not only these PGs but also analogues thereof for further biological study (Fig. 1).

Keywords: Aldol reaction; Cyclopentenone; Palladium; PPARγ; Δ^{12}-PGJ_2; 15-Deoxy-$\Delta^{12,14}$-PGJ_2.
* Corresponding author. Tel./fax: +81 45 924 5789;
e-mail: ykobayas@bio.titech.ac.jp

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doi:10.1016/j.tet.2006.01.051

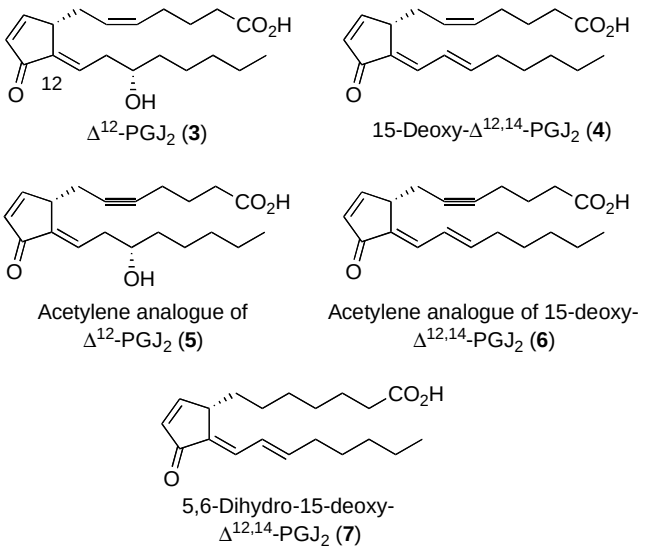


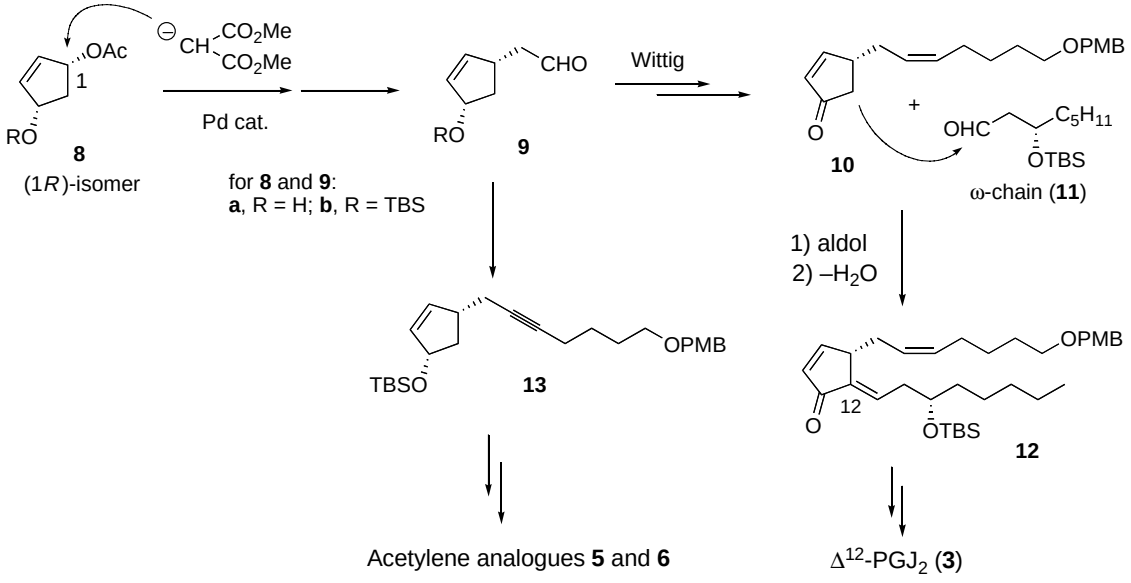
Figure 1. Δ^{12}-PGJ_2 and related PGs we have synthesized.

Among these targets, **4** was synthesized by Sutton in 2003, for the first time.[11] Meinwald rearrangement[12] of the norbornadiene was utilized to construct the core cyclopentenone structure, and was coupled with asymmetric acetylation using enzyme in two stages to accomplish resolutions at the stereocenters on the ω chain and on the cyclopentene ring. Later, **4** was again synthesized as a racemate by Brummond through a silicon-tethered allenic [2+2+1] cycloaddition.[13] At the same time we reported another approach to optically active PGs (**3** and **4**) and the acetylene analogue **5** as a communication.[14] The former two syntheses by Sutton and Brummond, however, seem to present little advantage over our method with respect to the product selectivity, efficiency, and, in particular, diastereoselectivity in the former rearrangement.[15] Furthermore, the reaction conditions would be hardly applicable to synthesis of **3**, the parent compound of this class. These limited syntheses prompted us to publish a full account of the synthesis of **3**–**5** as well as other analogues **6** and **7**. The acetylene analogues **5** and **6** would be precursors of radio labeled **3** and **4**. On the other hand, **5**–**7** would allow access to the structure–activity relation. In addition, **7** is formally the metabolite of PGD_1 derived from bishomo-γ-linolenic acid (5-dihydro derivative of arachidonic acid) though isolation of **7** is not yet reported.

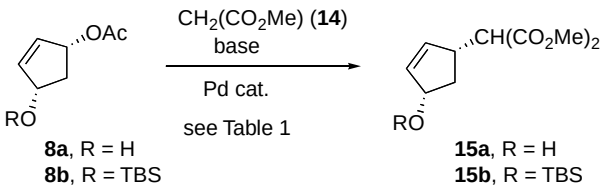
2. Results and discussion

We envisioned that the cross-conjugated dienone structure of **3**–**7** will be constructed by aldol condensation between cyclopentenone possessing the α chain and an aldehyde of the ω chain. For example, aldol reaction between cyclopentenone **10** and aldehyde **11** would furnish **12** with the Δ^{12}-PGJ_2 structure (Scheme 2). Likewise, simply changing the aldehyde partner would produce analogue **4**. It should be mentioned at this stage that γ-substituted cyclopentenones such as **10** were compounds for which an efficient method has not been established. In this investigation, we contemplated a sequence, which consists of palladium-catalyzed reaction[16] of cyclopentene monoacetate **8** with malonate anion and subsequent Wittig reaction of the derived aldehyde **9**. On the other hand, we envisaged that Corey–Fuchs[17] reaction of aldehyde **9** followed by alkylation of the derived acetylene would produce acetylene **13**, which would be transformed to 5,6-dehydro derivatives **5** and **6** by the aldol strategy. Concerning a synthesis of 5,6-dihydro analogue **7**, we decided to apply a copper-catalyzed S_N2 type reaction[18] of *ent*-**8** and RMgBr to construct the necessary enone intermediate (vide infra).

When 0.5–2 g of racemic monoacetate **8a** (R=H) was subjected several times to the reaction with methyl malonate (**14**) (2–2.5 equiv), NaH (2 equiv), and $Pd(PPh_3)_4$ (5 mol%) in THF at room temperature−50 °C according to the reported protocol[16] (Scheme 3), yields of product **15a** observed were among 50–70% (the best yield is shown in entry 1 of Table 1), which were lower than that (86%) reported for 100 mg-scale.[19] Since this step was strategically very important, this



Scheme 2. Our approach to Δ^{12}-PGJ_2 and the acetylene analogues through Aldol reaction.



Scheme 3. Palladium-catalyzed reaction of **8a**,**b** with malonate anion.

Table 1. Palladium-catalyzed reaction of **8a**,**b** with **14** (Scheme 3)[a]

Entry	Substrate	Base	Time (h)	Temperature (°C)	Yield (%)
1	**8a**	NaH	2	rt	69[b,c]
2	**8a**	MeONa	2	rt	71[b]
3	**8a**	LDA	1.5	rt	83[b]
4	**8a**	*t*-BuOK	2	rt	90
5	**8b**	NaH	4	50[d]	66
6	**8b**	MeONa	3	50[d]	87
7	**8b**	LDA	3	rt	91
8	**8b**	*t*-BuOK	3	50[d]	93

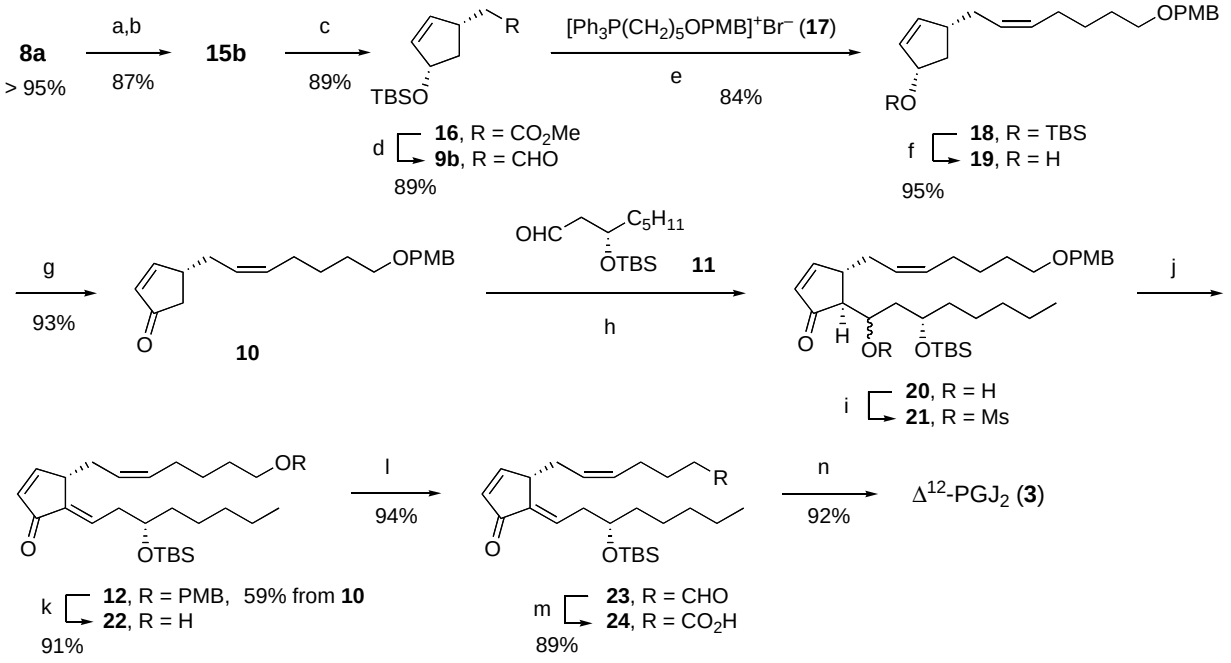
[a] Reactions were carried out with malonate anions (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol%) in THF.
[b] An unidentified by-product was also produced.
[c] The maximum yield among several runs is given. See the text for more information.
[d] No reaction at room temperature was monitored by TLC.

reaction was re-investigated under various conditions. We first focused on the loading of $Pd(PPh_3)_4$ (5–20%) and the PPh_3 ligand (2–6 equiv of Pd), use of polar solvents, etc. These changes, however, resulted in no improvement. Next, malonate anion generated from **14** (2.2 equiv) and a base (2.0 equiv) was subjected to the reaction with 5 mol% $Pd(PPh_3)_4$. Among the bases listed in Table 1, LDA and *t*-BuOK provided substantially higher yields of **15a** than NaH (entries 3 and 4).

Next, these bases were applied to TBS ether of **8a**, that is, **8b** (R=TBS). Reaction with LDA proceeded at room temperature, while *t*-BuOK required a higher temperature of 50 °C (entries 7 and 8). Except for the difference in the reaction temperatures, both entries produced **15b** in >90% yields (entries 7 and 8). Of the two bases, we have routinely used the latter base for the present investigation because of easy handling. In several 2–3 g-scale reactions, yields constantly exceeded 90% (see Section 4).

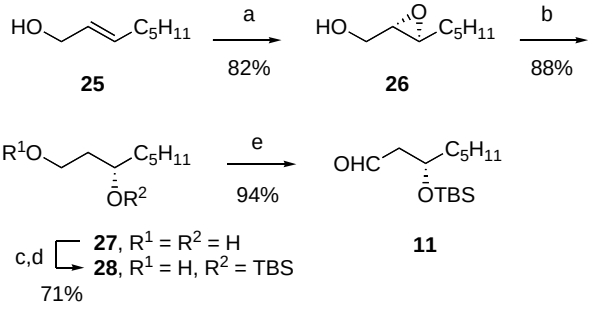
The above reaction was repeated with **8b** derived from **8a**[20] of >95% ee to obtain optically active **15b**. Transformation of **15b** to the key enone **10**, aldol reaction thereof, and further transformation to Δ^{12}-PGJ_2 (**3**) are delineated in Scheme 4. Decarboxylation of **15b** with KI in wet DMI proceeded well at 130 °C to afford ester **16** in 89% isolated yield after chromatography. Ester **16** was also synthesized from alcohol **15a** by decarboxylation using KI in wet DMF followed by silylation with TBSCl. Of the two routes to **16**, the former sequence had the advantage of easily purifying the crude TBS ether **16** containing DMI, because of the sufficiently different R_f values thereof. Aldehyde **9b** synthesized in 89% yield by DIBAL reduction of **16** was subjected to Wittig reaction with the ylide derived from $[Ph_3P(CH_2)_5OPMB]^+Br^-$ (**17**) and $NaN(TMS)_2$ first at −70 °C then at room temperature according to the literature procedure[21] to afford *cis* olefin **18** exclusively in 84% yield.[22] The TBS group was removed and the resulting alcohol **19** was oxidized to the key intermediate **10** in good yield.

Aldehyde **11**, the aldol partner of enone **10**, was synthesized from alcohol **25** through epoxy alcohol **26** in five steps in 48% overall yield (Scheme 5). Thus, epoxy alcohol **26** ($[\alpha]_D^{24}$ −43 (*c* 0.45, $CHCl_3$); lit.[23] $[\alpha]_D^{25}$ −42.7 (*c* 4.7, $CHCl_3$) for >98% ee), synthesized by the Sharpless asymmetric epoxidation[23,24] of **25**, was subjected to



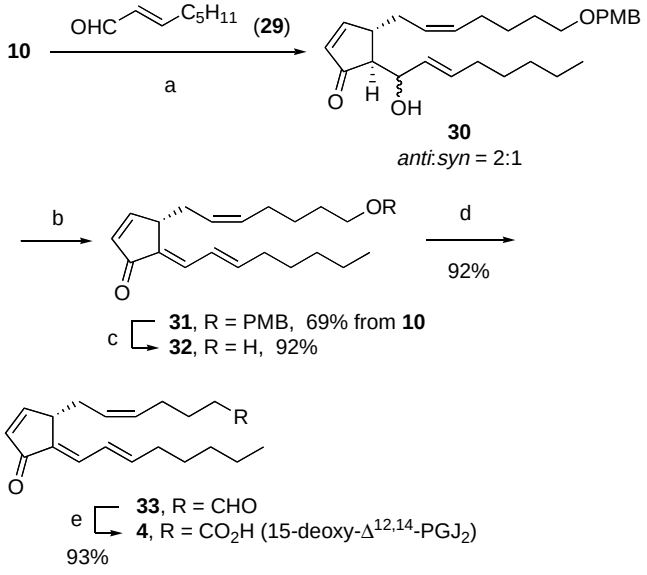
Scheme 4. Synthesis of Δ^{12}-PGJ_2: (a) TBSCl, imidazole; (b) $CH_2(CO_2Me)_2$, *t*-BuOK, $Pd(PPh_3)_4$ (cat.); (c) KI, DMI–H_2O (10:1), 130 °C; (d) DIBAL, CH_2Cl_2, −78 °C; (e) **17**, $NaN(TMS)_2$, −70 °C to rt; (f) TBAF; (g) PCC; (h) LDA (2.0 equiv), −78 °C, THF then **11** (1.2 equiv), −78 °C; (i) MsCl, Et_3N, 0 °C; (j) Al_2O_3; (k) DDQ, CH_2Cl_2–H_2O (19:1); (l) PCC; (m) $NaClO_2$, MeCH=C(Me)$_2$, *t*-BuOH, phosphate buffer (pH 3.6); (n) HF–MeCN (1:19).

reduction with Red-Al to produce 1,3-diol **27** in good yield with 22:1 regioselection over the 1,2-isomer by ^{1}H NMR spectroscopy. Diol **27** was converted to the bis-silyl ether, and exposed to PPTS (1.2 equiv) in EtOH–CH_2Cl_2 (1:1) to afford, after easy chromatography, mono alcohol **28** and unwanted diol **27** in 71 and 26% yield, respectively. Diol **27** was recycled. Finally, PCC oxidation of **28** afforded aldehyde **11** ($[\alpha]_D^{27}$ +6.7 (*c* 0.21, $CHCl_3$); lit.[25] $[\alpha]_D^{24}$ −5.0 (*c* 1.0, $CHCl_3$) for the enantiomer of >98% ee).[26]



Scheme 5. Preparation of aldehyde **11**: (a) *t*-BuOOH, L-(+)-DIPT (0.3 equiv), $Ti(i\text{-}PrO)_4$ (0.25 equiv), MS 4 Å; (b) Red-Al, THF; (c) TBSCl, imidazole; (d) PPTS, EtOH–CH_2Cl_2 (1:1); (e) PCC.

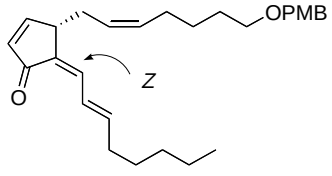
According to the protocol[27] for aldol reaction of cyclopentenone with aldehyde, the lithium enolate of enone **10** was prepared by using LDA at −78 °C for 20 min, and subjected to aldol reaction with aldehyde **11**. After 30 min at −78 °C, the reaction was quenched to afford aldol **20** as a 3:1 mixture of the *anti* and *syn* isomers by ^{1}H NMR spectroscopy.[28] Without separation, the aldol mixture was converted to mesylates with MsCl and Et_3N. During the mesylation, elimination of the derived mesylate to dienone **12** did not take place (cf. Scheme 6 for the aldol **30** derived from enal **29**). After filtration through a silica gel pad, the mesylate was exposed to Al_2O_3 at room temperature, which assisted stereoselective and exclusive formation of dienone **12** in 59% yield from enone **10**. The corresponding (*Z*)-olefin isomer of **12** (structure not shown) was not detected at the expected 0.5 ppm up field region in the ^{1}H NMR spectrum of the crude dienone **12**.[29] The selective formation of the (*E*)-olefin by using Al_2O_3 is consistent with the original dehydration of an aldol,[30] though the reason for the selectivity is still a matter of conjecture.[31]



Scheme 6. Synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2: (a) LDA (2.0 equiv), −78 °C, THF then **29** (1.2 equiv), −78 °C; (b) MsCl, Et_3N, −15 °C; (c) DDQ, CH_2Cl_2–H_2O (19:1); (d) PCC; (e) $NaClO_2$, $MeCH{=}C(Me)_2$, *t*-BuOH, phosphate buffer (pH 3.6).

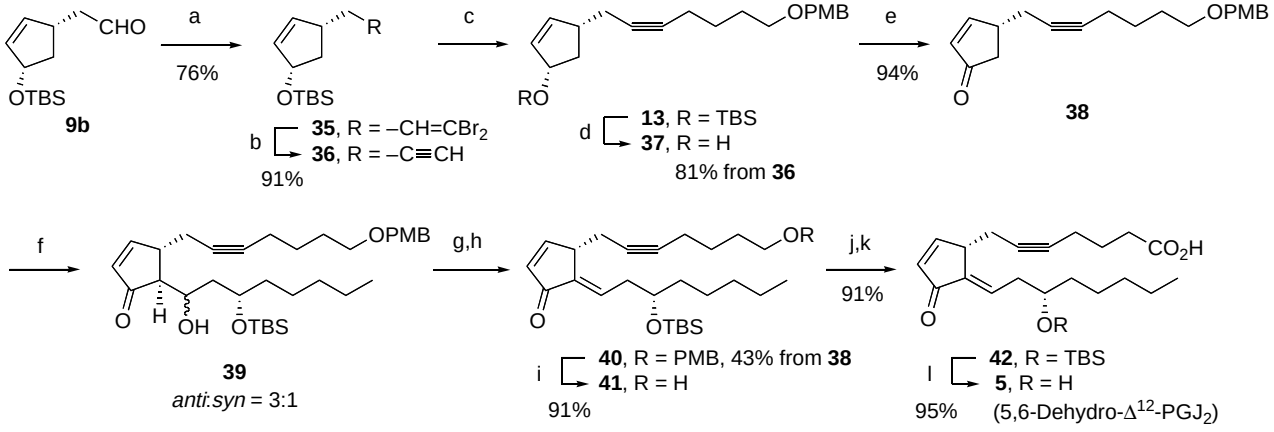
The remaining transformation of **12** to Δ^{12}-PGJ_2 (**3**) was accomplished efficiently as presented in Scheme 4. The PMB group of **12** was removed with DDQ in wet CH_2Cl_2 without affecting the dienone moiety. The resulting alcohol **22** was converted to acid **24** by two-step oxidation through aldehyde **23** in 84% yield. Direct oxidation of **22** with PDC in DMF produced a mixture of products. Finally, deprotection of the TBS group with HF in MeCN afforded Δ^{12}-PGJ_2 (**3**) in 92% yield.[32] The ^{1}H NMR spectrum of synthetic **3** was identical with that reported (δ 5–8 ppm)[1] and that provided by Ono Pharmaceutical Co., Ltd.

As illustrated in Scheme 6, the above enone **10** was next converted to 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**4**). Thus, aldol reaction between enone **10** and *trans*-2-octenal (**29**) afforded aldol **30** as a 2:1 mixture of the *anti* and *syn* isomers.[28] Without separation, the mixture was treated with MsCl at 0 °C. In contrast to the above case, elimination of the mesylate took place simultaneously to produce dienone **31** and its (*Z*)-isomer **34** in a 4:1 ratio.[33] Fortunately, this low product selectivity was improved to 14:1 by simply conducting the reaction at −15 °C to furnish dienone **31** in 69% from enone **10** after chromatography. Following the procedure described above in Scheme 4, the CH_2OPMB group of **31** was converted to the carboxylic acid moiety of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**4**) in 79% yield from the PMB ether **31**. The structure of **4** thus synthesized was confirmed by comparison of the ^{1}H NMR (500 MHz, δ 5–8 ppm)[1] and ^{13}C NMR (75 MHz, all peaks)[11] spectra with those reported. These spectra were also consistent with those reported by Brummond.[13]



34: (*Z*)-Isomer of **31**

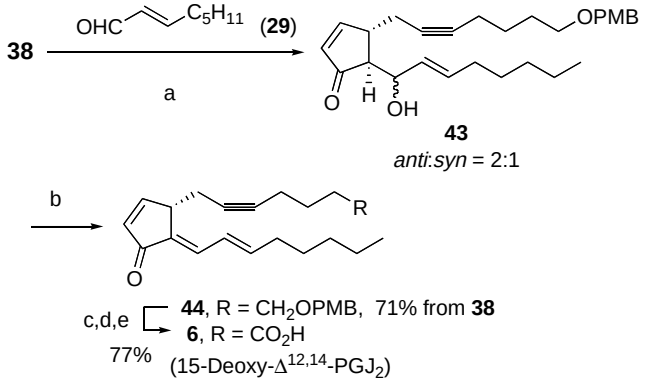
Synthesis of acetylene analogue **5** was accomplished through a sequence delineated in Scheme 7. Initially, aldehyde **9b** was converted to acetylene **36**[34] by the Corey–Fuchs method.[17] Alkylation of **36** with $Br(CH_2)_4$-OPMB proceeded in THF–DMPU (4:1), and the silyl group of **13** thus produced was removed by using TBAF to afford alcohol **37** in 81% yield from acetylene **36**. Oxidation of **37** to the key enone **38** followed by aldol reaction with aldehyde **11** furnished **39**, which upon mesylation and elimination with Al_2O_3 gave dienone **40** exclusively. Finally, the C(1) carbon was oxidized to the carboxylic



Scheme 7. Synthesis of acetylene analogue of Δ^{12}-PGJ$_2$: (a) PPh_3, CBr_4, 0 °C; (b) *n*-BuLi, −78 °C; (c) *n*-BuLi, $PMBO(CH_2)_4Br$, THF–DMPU (4:1), −78 °C to rt; (d) TBAF; (e) PCC; (f) LDA then **11**, −78 °C; (g) MsCl, Et_3N, 0 °C; (h) Al_2O_3; (i) DDQ; (j) PCC; (k) $NaClO_2$, $MeCH{=}C(Me)_2$, *t*-BuOH, phosphate buffer (pH 3.6); (l) HF–MeCN (1:19).

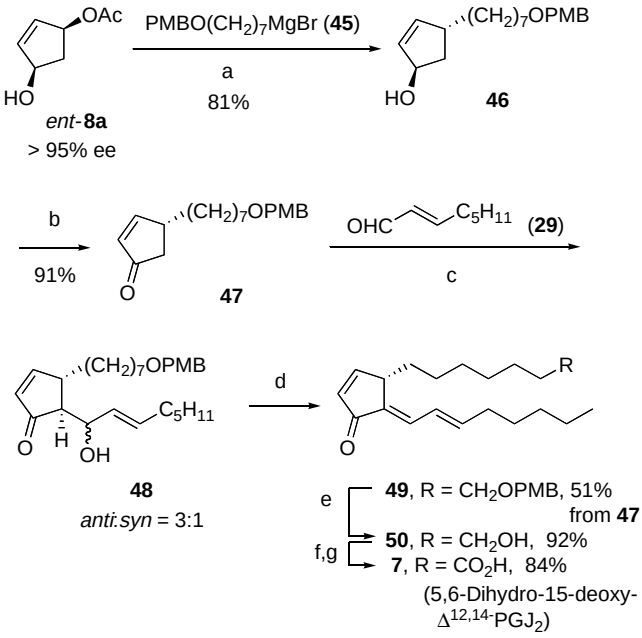
acid moiety, and the protective group of the C(15)–OH was removed to furnish 5,6-dehydro-Δ^{12}-PGJ$_2$ (**5**) in good yield.

Synthesis of another acetylene analogue **6** is summarized in Scheme 8. Aldol **43** was derived from enone **38** and aldehyde **29** with similar efficiency. Subsequently, mesylation with MsCl and Et_3N at −15 °C produced dienone **44** in good yield with high product selectivity (**44**:(*Z*)-isomer = 12:1).

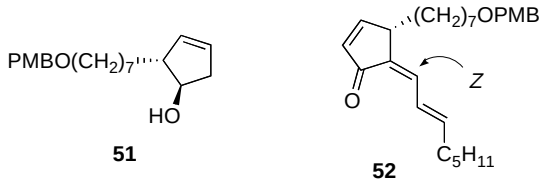


Scheme 8. Synthesis of 5,6-dehydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$: (a) LDA, −78 °C, THF then **29**, −78 °C; (b) MsCl, Et_3N, −15 °C; (c) DDQ, CH_2Cl_2–H_2O (19:1); (d) PCC; (e) $NaClO_2$, $MeCH{=}C(Me)_2$, *t*-BuOH, phosphate buffer (pH 3.6).

Recently, the S_N2 type reaction of 4-cyclopentene-1,3-diol monoacetate **8a** with RMgBr (R = aryl, alkenyl) was attained with the CuCN catalyst and the LiCl additive.[18] We envisioned that this reaction with an *alkyl* Grignard reagent of the α-chain would afford **46** and that transformation of **46** along the present strategy would produce 5,6-dihydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (**7**) (Scheme 9). To this end, the required *ent*-**8a** of >95% ee was prepared by the literature method[35] and subjected to the CuCN-catalyzed reaction with $PMBO(CH_2)_7MgBr$ (3 equiv) in the presence of LiCl (4 equiv) to afford S_N2 product **46** and *anti* S_N2' product **51** in a 92:8 ratio. The isomers were easily separated by chromatography and alcohol **46** thus isolated in 81% yield was oxidized to the key enone **47** with PCC.



Scheme 9. Synthesis of 5,6-dihydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$: (a) **45** (3 equiv), CuCN (0.3 equiv), LiCl (4.0 equiv), THF, −10 °C; (b) PCC; (c) LDA, −78 °C, THF then **29**, −78 °C; (d) MsCl, Et_3N, −20 °C; (e) DDQ, CH_2Cl_2–H_2O (19:1); (f) SO_3·pyridine, DMSO, Et_3N; (g) $NaClO_2$, $MeCH{=}C(Me)_2$, *t*-BuOH, phosphate buffer (pH 3.6).



Aldol reaction between the key enone **47** and *trans*-2-octenal (**29**) furnished aldol **48** as a mixture of *anti* and *syn* isomers in a 3:1 ratio.[28] Upon treatment with MsCl and Et_3N at −20 °C, aldol **48** underwent mesylation/elimination smoothly as in the above cases (see Schemes 6 and 8) to produce dienone **49** and the (*Z*)-isomer **52** in 51 and 5% yields, respectively, from enone **47**. Finally, dienone **49** was

converted into 5,6-dihydro-15-deoxy-$\Delta^{12,14}$-PGJ_2 (**7**) in good yield.

3. Conclusion

In summary, total synthesis of Δ^{12}-PGJ_2 (**3**) was accomplished through aldol reaction between cyclopentenone **10** and aldehyde **11** (Schemes 2 and 3). Cyclopentenone **10** was prepared from monoacetate **8b**, and the first step, that is, the palladium-catalyzed reaction of **8a** and malonate anion, was improved with *t*-BuOK, which was found to generate the highly reactive malonate anion. The synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**4**) and Δ^{12}-PGJ_2 analogues **5**–**7** was carried out with similar efficiency, thus demonstrating flexibility and reliability of the aldol strategy using γ-substituted cyclopentenones for construction of the cross-conjugated cyclopentadienone structures. We believe that the biological investigation of Δ^{12}-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 would be spurred by these analogues.

4. Experimental

4.1. General methods

Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 and 500 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta=0$ ppm) and the center line of $CDCl_3$ triplet ($\delta=77.1$ ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). Purity of the title compounds were confirmed by elemental analysis in most of cases or by the spectral method (^1H and ^{13}C NMR) in the case the satisfactory results were not recorded.

4.2. Synthesis of the key enone 10

4.2.1. (1*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopenten-1-yl acetate (8b). According to the literature method,[20] a solution of **8a** (1.52 g, 10.7 mmol, 96% ee by ^1H NMR spectroscopy of the derived MTPA ester), TBSCl (2.42 g, 16.1 mmol), and imidazole (1.46 g, 21.4 mmol) in DMF (22 mL) was stirred at room temperature for 2 h to afford silyl acetate **8b** (2.58 g, 94% yield) after chromatography (hexane/EtOAc). The ^1H and ^{13}C NMR spectra were identical with those reported.[36]

4.2.2. Dimethyl (1*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopenten-1-yl malonate (15b). To an ice-cold slurry of *t*-BuOK (2.19 g, 19.5 mmol) in THF (18 mL) was added methyl malonate (**14**) (2.46 mL, 21.4 mmol) in a dropwise manner. After being stirred vigorously at room temperature for 30 min, $Pd(PPh_3)_4$ (564 mg, 0.49 mmol) and a solution of **8b** (2.50 g, 9.76 mmol) in THF (2 mL) were added into the mixture. The resulting mixture was stirred vigorously at 50 °C for 3 h. The reaction was quenched by adding saturated NH_4Cl and hexane with vigorous stirring. The organic layer was separated and the aqueous layer was extracted by using hexane three times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford an yellow oily residue, which was purified by chromatography (hexane/EtOAc) to furnish **15b** (2.98 g, 93% yield): bp 130 °C (1 mmHg); IR (neat) 1738, 1252, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.40 (ddd, $J=14$, 7, 5 Hz, 1H), 2.44 (dt, $J=14$, 7 Hz, 1H), 3.15–3.26 (m, 1H), 3.37 (d, $J=10$ Hz, 1H), 3.74 (s, 6H), 4.77–4.84 (m, 1H), 5.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.61, −4.58, 18.2, 25.9, 39.0, 43.5, 52.52, 52.54, 57.3, 76.8, 133.6, 136.3, 168.98, 169.04. Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found: C, 58.49; H, 8.49.

4.2.3. Methyl (1*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-yl acetate (16). A slurry of **15b** (2.80 g, 8.52 mmol), KI (11.32 g, 68.2 mmol), DMI (30 mL), and water (3 mL) was vigorously stirred at 130 °C for 10 h and diluted with water and hexane. The organic layer was separated and the aqueous layer was extracted four times with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish an oily residue, which was purified by chromatography (hexane/EtOAc) to afford **16** (2.05 g, 89% yield): $[\alpha]_D^{31}$ −19 (*c* 0.56, $CHCl_3$); bp 115 °C (1 mmHg); IR (neat) 1742, 1252, 1085, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.30 (ddd, $J=13$, 6, 5 Hz, 1H), 2.38 (dd, $J=16$, 8 Hz, 1H), 2.46 (dt, $J=13$, 7.5 Hz, 1H), 2.48 (dd, $J=16$, 7 Hz, 1H), 2.86–3.00 (m, 1H), 3.68 (s, 3H), 4.78–4.86 (m, 1H), 5.74 (dt, $J=6$, 2 Hz, 1H), 5.80 (dt, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, 18.2, 26.0, 40.4, 40.6, 40.8, 51.5, 77.3, 135.0, 135.7, 173.1. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 61.86; H, 9.70.

4.2.4. (1*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopenten-1-yl ethanal (9b). To a stirred solution of **16** (1.80 g, 6.66 mmol) in CH_2Cl_2 (26 mL) at −78 °C was added $(i\text{-Bu})_2AlH$ (7.98 mL, 0.95 M in hexane, 7.59 mmol) dropwise. After 45 min the solution was poured into a flask containing water (2.5 mL, 140 mmol) and ether with vigorous stirring. The mixture was stirred with NaF (2.8 g, 67 mmol) at room temperature for 30 min, and filtered through a pad of Celite. The filtrate was concentrated and purified by chromatography (hexane/EtOAc) to afford aldehyde **9b** (1.42 g, 89% yield) and the corresponding alcohol (138 mg, 9% yield): $[\alpha]_D^{30}$ −23 (*c* 0.38, $CHCl_3$); IR (neat) 1726, 1251, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.29 (ddd, $J=13$, 6, 5 Hz, 1H), 2.41–2.68 (m, 3H), 2.92–3.04 (m, 1H), 4.78–4.85 (m, 1H), 5.71–5.80 (m, 2H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.44, −4.42, 18.3, 26.1, 38.1, 40.9, 50.6, 77.2, 135.0, 135.4, 201.6. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.96; H, 9.80.

4.2.5. (1*S*,4*R*,2′*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[7′-(4-methoxybenzyloxy)-2′-heptenyl]-2-cyclopentene (18). To an ice-cold slurry of $[PPh_3P(CH_2)_5OPMB]^+Br^-$ (**17**) (2.05 g, 3.73 mmol) in THF (25 mL) was added $NaN(TMS)_2$ (5.0 mL, 1.0 M in THF, 5.0 mmol) dropwise. After being stirred for 30 min at room temperature, the mixture was cooled to −70 °C and aldehyde **9b** (0.60 g, 2.50 mmol) was added to it. The temperature was kept at −70 °C for 1 h, and then allowed to increase gradually to room temperature over 2 h. The mixture was stirred overnight at ambient temperature and diluted with saturated

NH_4Cl and hexane. The organic layer was separated and the aqueous layer was extracted with hexane twice. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain an yellow oil, which was purified by chromatography (hexane/EtOAc) to afford **18** (0.90 g, 84% yield): IR (neat) 1612, 1513, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.22–1.32 (m, 1H), 1.35–1.48 (m, 2H), 1.54–1.66 (m, 2H), 1.98–2.25 (m, 4H), 2.36 (dt, $J=13$, 7 Hz, 1H), 2.46–2.58 (m, 1H), 3.43 (t, $J=7$ Hz, 2H), 3.78 (s, 3H), 4.42 (s, 2H), 4.78–4.86 (m, 1H), 5.33–5.46 (m, 2H), 5.70 (dt, $J=6$, 2 Hz, 1H), 5.78 (dt, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.26 (d, $J=9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.34, −4.31, 18.4, 26.2, 26.5, 27.3, 29.6, 34.0, 40.8, 44.5, 55.4, 70.1, 72.6, 77.7, 113.8, 128.1, 129.2, 130.5, 130.8, 134.1, 136.7, 159.0. Anal. Calcd for $C_{26}H_{42}O_3Si$: C, 72.51; H, 9.83. Found: C, 72.84; H, 9.86.

4.2.6. (1*S*,4*R*,2′*Z*)-4-[7′-(4-Methoxybenzyloxy)-2′-heptenyl]-2-cyclopenten-1-ol (19). To an ice-cold solution of silyl ether **18** (1.21 g, 2.81 mmol) in THF (28 mL) was added TBAF (3.36 mL, 1.0 M in THF, 3.36 mmol). The solution was stirred at room temperature for 5 h and diluted with saturated NH_4Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain an oily residue, which was purified by chromatography (hexane/EtOAc) to afford **19** (835 mg, 95% yield): $[\alpha]_D^{26}$ +51 (*c* 0.51, $CHCl_3$); IR (neat) 3409, 1613, 1513, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (dt, $J=14$, 5 Hz, 1H), 1.36–1.48 (m, 2H), 1.55–1.68 (m, 2H), 1.93 (br s, 1H), 1.98–2.25 (m, 4H), 2.43 (dt, $J=14$, 8 Hz, 1H), 2.56–2.68 (m, 1H), 3.43 (t, $J=6$ Hz, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 4.71–4.82 (m, 1H), 5.30–5.52 (m, 2H), 5.74–5.81 (m, 1H), 5.82–5.88 (m, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.26 (d, $J=9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.2, 29.4, 33.7, 39.8, 44.5, 55.3, 70.0, 72.5, 77.2, 113.7, 127.6, 129.2, 130.6, 131.1, 133.4, 138.1, 159.0. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.85; H, 9.12.

4.2.7. (4*R*,2′*Z*)-4-[7′-(4-Methoxybenzyloxy)-2′-heptenyl]-2-cyclopenten-1-one (10). A mixture of alcohol **19** (750 mg, 2.37 mmol) and PCC (1.02 g, 4.73 mmol) in CH_2Cl_2 (23 mL) was stirred vigorously at room temperature for 3 h and diluted with ether. The resulting mixture was filtered through a short pad of Celite. The filtrate was concentrated to furnish an yellow residue, which was purified by chromatography (hexane/EtOAc) to afford enone **10** (693 mg, 93% yield): $[\alpha]_D^{29}$ +106 (*c* 0.39, $CHCl_3$); IR (neat) 1711, 1612, 1586, 1512, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–1.49 (m, 2H), 1.54–1.67 (m, 2H), 1.95–2.08 (m, 3H), 2.12–2.34 (m, 2H), 2.50 (dd, $J=19$, 6 Hz, 1H), 2.93–3.03 (m, 1H), 3.43 (t, $J=6$ Hz, 2H), 3.79 (s, 3H), 4.42 (s, 3H), 5.28–5.40 (m, 1H), 5.43–5.56 (m, 1H), 6.15 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.26 (d, $J=9$ Hz, 2H), 7.61 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.2, 29.5, 32.0, 40.6, 41.5, 55.3, 69.9, 72.6, 113.7, 125.7, 129.2, 130.6, 132.4, 134.0, 159.0, 167.9, 209.6. Anal. Calcd for $C_{13}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.12; H, 8.30.

4.3. Synthesis of aldehyde 11

4.3.1. (2*S*,3*S*)-2,3-Epoxy-1-octanol (26). (*E*)-Octen-1-ol (**25**) (1.20 g, 9.36 mmol) was subjected to Sharpless epoxidation by using Ti(*i*-PrO)$_4$ (0.69 mL, 2.33 mmol), L-(+)-DIPT (0.59 mL, 2.78 mmol), *t*-BuOOH (2.3 mL, 5.71 M in CH_2Cl_2, 13.1 mmol) over activated 4 Å molecular sieves (600 mg) at −20 °C for 9 h. After the reaction, H_2O (1.7 mL) and NaF (4.0 g, 95 mmol) were added. The resulting mixture was stirred vigorously for 30 min at room temperature and filtered through a pad of Celite. The filtrate was concentrated to obtain an yellow residue, which was diluted with CH_2Cl_2 (10 mL). Brine and 30% NaOH (4 mL) were added to the solution, and the mixture was stirred at room temperature for 20 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 two times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oil, which was purified by chromatography (hexane/EtOAc) to furnish epoxy alcohol **26** (1.11 g, 82% yield): $[\alpha]_D^{24}$ −43 (*c* 0.45, $CHCl_3$); lit.[24] $[\alpha]_D^{25}$ −42.7 (*c* 4.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.24–1.66 (m, 8H), 1.73 (br t, $J=6$ Hz, 1H), 2.90–3.00 (m, 2H), 3.58–3.70 (m, 1H), 3.87–3.97 (m, 1H). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.85; H, 11.31.

4.3.2. (*S*)-1,3-Octanediol (27). To an ice-cold solution of epoxy alcohol **26** (150 mg, 1.04 mmol) in THF (4 mL) was added Red-Al (0.65 mL, 65% in toluene, 2.09 mmol) in a dropwise manner. After being stirred at 0 °C for 1 h and then at room temperature for 10 h, the solution was poured into a flask containing water (0.4 mL, 22 mmol) and ether (10 mL) at 0 °C with vigorous stirring. The mixture was stirred vigorously with NaF (350 mg, 8.3 mmol) for 30 min at ambient temperature, and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography (hexane/EtOAc) to afford 1,3-diol **27** (134 mg, 88% yield): IR (neat) 3350, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.22–1.54 (m, 8H), 1.58–1.78 (m, 2H), 2.61 (br s, 1H), 2.70 (br s, 1H), 3.76–3.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.3, 31.9, 37.8, 38.3, 61.9, 72.4. Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.95; H, 12.39.

4.3.3. (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-octan-1-ol (28). A solution of diol **27** (1.70 g, 11.6 mmol), TBSCl (5.25 g, 34.8 mmol), and imidazole (3.16 g, 46.4 mmol) in DMF (22 mL) was stirred at room temperature for 3 h, and diluted with saturated $NaHCO_3$ and hexane with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with hexane several times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtained an oily residue, which was purified by chromatography (hexane/EtOAc) to obtain the corresponding disilyl ether (3.64 g, 94% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 12H), 0.88 (s, 9H), 0.89 (s, 9H), 0.86–0.90 (m, 3H), 1.20–1.48 (m, 9H), 1.64 (q, $J=6$ Hz, 1H), 3.62–3.73 (m, 2H), 3.79 (quintet, $J=6$ Hz, 1H).

A solution of the above disilyl ether (380 mg, 1.14 mmol) and PPTS (342 mg, 1.36 mmol) in EtOH (6 mL) and CH_2Cl_2 (6 mL) was stirred for 14 h at room temperature,

and diluted with saturated NH_4Cl and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc twice. The combined organic portions were dried over $MgSO_4$ and concentrated under reduced pressure to obtained an oily residue, which was purified by chromatography (hexane/EtOAc) to afford alcohol **28** (226 mg, 76% yield) and diol **27** (26 mg, 16% yield). Diol **27** was recycled. Alcohol **28**: $[\alpha]_D^{27}$ +18 (*c* 0.62, $CHCl_3$); IR (neat) 3350, 1255, 1058, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (br s, 9H), 0.85–0.91 (m, 3H), 1.20–1.36 (m, 6H), 1.45–1.56 (m, 2H), 1.57–1.70 (m, 1H), 1.74–1.87 (m, 1H), 2.55 (br s, 1H), 3.65–3.76 (m, 1H), 3.77–3.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −4.2, 14.2, 18.2, 22.8, 25.2, 26.0, 32.1, 36.9, 37.8, 60.4, 72.1. Anal. Calcd for $C_{14}H_{32}O_2Si$: C, 64.55; H, 12.38. Found: C, 64.40; H, 12.27.

4.3.4. (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]octanal (11). A mixture of alcohol **28** (1.18 g, 4.53 mmol) and PCC (1.95 g, 9.05 mmol) in CH_2Cl_2 (45 mL) was stirred vigorously at room temperature for 3 h and diluted with ether. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. An yellow oil obtained was purified by chromatography (hexane/EtOAc) to afford aldehyde **11** (1.10 g, 94% yield): $[\alpha]_D^{27}$ +6.7 (*c* 0.21, $CHCl_3$); lit.[26] $[\alpha]_D^{24}$ −5.0 (*c* 1.0, $CHCl_3$) for the enantiomer of >98% ee; IR (neat) 1713, 1256, 1095, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (br s, 9H), 0.84–0.92 (m, 3H), 1.18–1.40 (m, 6H), 1.45–1.60 (m, 2H), 2.51 (dd, *J*=6, 2 Hz, 2H), 4.17 (quintet, *J*=6 Hz, 1H), 9.81 (t, *J*=2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −4.2, 14.2, 18.2, 22.8, 25.0, 31.9, 38.0, 51.0, 68.4, 202.3.

4.4. Synthesis of Δ^{12}-PGJ$_2$ (3)

4.4.1. Dienone 12. To an ice-cold solution of $(i\text{-Pr})_2NH$ (0.15 mL, 1.07 mmol) in THF (4 mL) was added *n*-BuLi (0.37 mL, 1.90 M in hexane, 0.703 mmol). The solution was stirred at 0 °C for 20 min to generate LDA and then cooled to −78 °C. A solution of enone **10** (109 mg, 0.347 mmol) in THF (2 mL) was added into the LDA solution. After 20 min of stirring at the same temperature, aldehyde **11** (108 mg, 0.418 mmol) dissolved in THF (1 mL) was added. The solution was stirred for 30 min at the same temperature, and poured into a flask containing saturated NH_4Cl and ether with vigorous stirring. After 15 min, the organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried over $MgSO_4$ and concentrated to afford aldol **20** as a mixture of *anti* and *syn* isomers. The ratio of the mixture was ca. 3:1 by ^1H NMR spectroscopy (δ 2.78–2.92 (m) and 3.00–3.11 (m) for *anti* and *syn* isomers, respectively) and TLC analysis. After being passed through a short column of silica gel (hexane/EtOAc), the crude aldol was used for the next reaction.

To an ice-cold solution of the above aldol **20** dissolved in CH_2Cl_2 (3.5 mL) were added Et_3N (0.24 mL, 1.72 mmol) and MsCl (0.053 mL, 0.685 mmol). The solution was stirred for 45 min at the same temperature, and diluted with saturated $NaHCO_3$. The product was extracted with EtOAc repeatedly. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish mesylate **21** as an yellow oil. After being passed through a short column of silica gel (hexane/EtOAc), the crude mesylate was subjected to the next reaction.

To a slurry of activated alumina (350 mg, ICN, N-Super I, activated by heating on a heater for 20 min under vacuum) in CH_2Cl_2 (5 mL) was added a solution of the crude mesylate **21** in CH_2Cl_2 (2 mL). The mixture was stirred vigorously at room temperature for 10 h and filtered through a pad of Celite with CH_2Cl_2. The filtrate was concentrated under reduced pressure to furnish an yellow oil, which was purified by chromatography (hexane/EtOAc) to afford dienone **12** (114 mg, 59% yield from enone **10**): $[\alpha]_D^{26}$ +96 (*c* 0.43, $CHCl_3$); IR (neat) 1705, 1657, 1513, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.80–0.96 (m, 12H), 1.20–1.64 (m, 12H), 2.00 (q, *J*=7 Hz, 2H), 2.17 (dt, *J*=15, 9 Hz, 1H), 2.39–2.46 (m, 2H), 2.55–2.67 (m, 1H), 3.43 (t, *J*=7 Hz, 3H), 3.80 (s, 3H), 3.78–3.88 (m, 1H), 4.42 (s, 2H), 5.28–5.40 (m, 1H), 5.42–5.56 (m, 1H), 6.32 (dd, *J*=6, 1.5 Hz, 1H), 6.60 (t, *J*=8 Hz, 1H), 6.87 (d, *J*=8 Hz, 2H), 7.25 (d, *J*=8 Hz, 2H), 7.49 (dd, *J*=6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, 14.2, 18.3, 22.8, 25.1, 26.0, 26.4, 27.3, 29.6, 30.7, 32.1, 37.4, 37.5, 43.6, 55.4, 70.0, 71.6, 72.6, 113.8, 125.1, 129.2, 130.7, 132.45, 132.51, 134.8, 138.7, 159.0, 161.5, 196.2.

4.4.2. Aldehyde 23. To an ice-cold solution of dienone **12** (108 mg, 0.195 mmol) in CH_2Cl_2 (3.8 mL) and water (0.2 mL) was added DDQ (66 mg, 0.29 mmol). The mixture was stirred at 0 °C for 45 min and filtered through a pad of Celite using ether. The filtrate was concentrated, and a reddish brown residue produced was purified by chromatography (hexane/EtOAc) to furnish alcohol **22** (77 mg, 91% yield): IR (neat) 3441, 1701, 1654, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.80 (br s, 12H), 1.2–1.7 (m, 12H), 1.95–2.30 (m, 3H), 2.39–2.46 (m, 2H), 2.55–2.67 (m, 1H), 3.43–3.48 (m, 1H), 3.65 (t, *J*=7 Hz, 2H), 3.78–3.90 (m, 1H), 5.28–5.40 (m, 1H), 5.42–5.56 (m, 1H), 6.32 (dd, *J*=6, 1.5 Hz, 1H), 6.60 (t, *J*=8 Hz, 1H), 7.49 (dd, *J*=6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, 14.2, 18.3, 22.8, 25.1, 25.9, 26.0, 27.3, 30.8, 32.1, 32.5, 37.5, 43.6, 62.8, 71.7, 125.3, 132.4, 132.6, 134.8, 138.7, 161.5, 196.2.

A mixture of alcohol **22** (45 mg, 0.104 mmol) and PCC (45 mg, 0.209 mmol) in CH_2Cl_2 (1 mL) was stirred for 2.5 h at room temperature, diluted with ether, and filtered through a short pad of Celite. The filtrate was concentrated, and an yellow residue obtained was purified by chromatography (hexane/EtOAc) to afford aldehyde **23** (42 mg, 94% yield): $[\alpha]_D^{29}$ +57 (*c* 0.14, $CHCl_3$); IR (neat) 1709, 1649, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.83–0.91 (m, 3H), 1.16–1.52 (m, 8H), 1.60–1.76 (m, 2H), 2.04 (q, *J*=7 Hz, 2H), 2.12–2.26 (m, 1H), 2.30–2.54 (m, 4H), 2.56–2.68 (m, 1H), 3.40–3.52 (m, 1H), 3.78–3.90 (m, 1H), 5.30–5.53 (m, 2H), 6.33 (dd, *J*=6, 2 Hz, 1H), 6.60 (t, *J*=8 Hz, 1H), 7.48 (dd, *J*=6, 2.5 Hz, 1H), 9.76 (t, *J*=1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, 14.2, 18.3, 22.0, 22.8, 25.1, 26.0, 26.8, 30.7, 32.1, 37.4, 37.5, 43.40, 43.44, 71.6, 126.2, 131.2, 132.7, 135.0, 138.5, 161.2, 196.1, 201.9.

4.4.3. Acid 24. To a slurry of aldehyde **23** (42 mg, 0.097 mmol) in *t*-BuOH (1.3 mL), phosphate buffer of pH 3.6 (0.61 mL), and 2-methyl-2-butene (0.105 mL, 0.99 mmol) was added $NaClO_2$ (17 mg, 0.15 mmol, purity 80%) in water (0.5 mL) and the resulting mixture was stirred at room temperature. After 3 h, *t*-BuOH was removed by using a vacuum pump and the phosphate buffer (pH 3.6) was added to the residue. The product was extracted with EtOAc several times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oily residue, which was purified by chromatography (CH_2Cl_2/EtOH) to furnish acid **24** (39 mg, 89% yield): IR (neat) 3100, 1710, 1652, 1252, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.84–0.92 (m, 12H), 1.18–1.52 (m, 8H), 1.69 (quintet, $J=7$ Hz, 2H), 2.00–2.22 (m, 3H), 2.34 (t, $J=7$ Hz, 2H), 2.40–2.48 (m, 2H), 2.60–2.70 (m, 1H), 3.41–3.50 (m, 1H), 3.78–3.90 (m, 1H), 5.32–5.56 (m, 2H), 6.33 (dd, $J=6$, 1 Hz, 1H), 6.60 (t, $J=8$ Hz, 1H), 7.50 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, 14.2, 18.3, 22.8, 24.6, 25.1, 26.0, 26.8, 30.7, 32.0, 33.3, 37.4, 37.5, 43.6, 71.8, 126.2, 131.3, 132.7, 134.9, 138.6, 161.5, 178.1, 196.3.

4.4.4. Δ^{12}-PGJ$_2$ (3). To an ice-cold flask containing acid **24** (9 mg, 0.020 mmol) was added a solution of HF in MeCN (0.2 mL), which had been prepared by mixing 55% HF and MeCN in a 1:19 ratio. The solution was stirred at 0 °C for 15 min and poured into brine. The product was extracted with EtOAc several times. The combined extracts were dried over $MgSO_4$ and concentrated to leave an oil, which was purified by chromatography (CH_2Cl_2/EtOH) to furnish Δ^{12}-PGJ$_2$ (**3**) (6.2 mg, 92% yield): IR (neat) 3409, 1699, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t $J=7$ Hz, 3H), 1.20–1.80 (m, 10H), 2.06–2.18 (m, 3H), 2.26–2.63 (m, 4H), 2.66–2.78 (m, 1H), 3.42–3.54 (m, 1H), 3.78–3.92 (m, 1H), 5.1–5.9 (br s, 4H), 6.35 (dd, $J=6$, 2 Hz, 1H), 6.59 (t, $J=8$ Hz, 1H), 7.56 (dd, $J=6$, 2 Hz, 1H). The ^1H NMR spectrum was identical with that provided by Ono Pharmaceutical Co., Ltd.

4.5. Synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (4)

4.5.1. Dienone 31 through aldol 30. To a solution of *i*-Pr_2NH (0.22 mL, 1.57 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (0.58 mL, 2.20 M in hexane, 1.28 mmol). The solution was stirred at the same temperature for 20 min to prepare LDA, and cooled to −78 °C. A solution of enone **10** (200 mg, 0.636 mmol) in THF (3 mL) was added into the LDA solution dropwise, and the solution was stirred for 20 min. (*E*)-2-Octenal (**29**) (0.115 mL, 0.771 mmol) was added to the solution. After 20 min at the same temperature, the solution was poured into a flask containing saturated NH_4Cl and ether with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford aldol **30** as a mixture of the *anti* and *syn* isomers in a 2:1 ratio by ^1H NMR spectroscopy (*anti* isomer, δ 4.14 (t, $J=$ 8 Hz); *syn* isomer, δ 4.49–4.58 (m)). The aldol product **30** was subjected to the next reaction after filtration through a short column of silica gel (hexane/EtOAc).

The aldol reaction was repeated, and the stereoisomers were separated by chromatography on silica gel (hexane/EtOAc). *anti* Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.16–1.48 (m, 8H), 1.52–1.66 (m, 2H), 1.94–2.14 (m, 5H), 2.15–2.37 (m, 2H), 2.64–2.72 (m, 1H), 3.43 (t, $J=7$ Hz, 2H), 3.80 (s, 3H), 3.95 (br s, 1H), 4.14 (t, $J=8$ Hz, 1H), 4.42 (s, 2H), 5.26–5.37 (m, 1H), 5.39–5.58 (m, 2H), 5.73 (dt, $J=15$, 7 Hz, 1H), 6.14 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.25 (d, $J=9$ Hz, 2H), 7.62 (dd, $J=6$, 2 Hz, 1H). *syn* Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.16–1.50 (m, 7H), 1.53–1.76 (m, 3H), 1.94–2.14 (m, 4H), 2.15–2.38 (m, 3H), 2.59 (d, $J=6$ Hz, 1H), 2.82–2.94 (m, 1H), 3.43 (t, $J=7$ Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 4.49–4.59 (m, 1H), 5.28–5.57 (m, 3H), 5.73 (dt, $J=15$, 7 Hz, 1H), 6.15 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.25 (d, $J=9$ Hz, 2H), 7.63 (dd, $J=6$, 2 Hz, 1H).

To a solution of the above aldol **30** in CH_2Cl_2 (6 mL) and Et_3N (0.88 mL, 6.31 mmol) at −15 °C was added MsCl (0.20 mL, 2.58 mmol) dropwise. After 45 min at the same temperature, the reaction was quenched by addition of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish an yellow residue, which was subjected to chromatography (hexane/EtOAc) to afford dienone **31** (185 mg, 69% yield from enone **10**) and its (*Z*)-isomer **34** (14 mg, 5%). Dienone **31**: IR (neat) 1685, 1631, 1512, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=$ 7 Hz, 3H), 1.1–1.6 (m, 10H), 2.01 (q, $J=7$ Hz, 2H), 2.16–2.35 (m, 3H), 2.58 (dt, $J=14$, 6 Hz, 1H), 3.42 (t, $J=6$ Hz, 2H), 3.51–3.60 (m, 1H), 3.80 (s, 3H), 4.42 (s, 2H), 5.27–5.39 (m, 1H), 5.41–5.53 (m, 1H), 6.15–6.39 (m, 3H), 6.87 (d, $J=8$ Hz, 2H), 6.94 (d, $J=11$ Hz, 1H), 7.25 (d, $J=8$ Hz, 2H), 7.46 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.6, 26.4, 27.3, 28.6, 29.6, 31.0, 31.5, 33.6, 43.7, 55.4, 70.0, 72.6, 113.8, 125.1, 125.7, 129.2, 130.6, 131.6, 132.5, 135.1, 135.2, 146.7, 159.0, 160.7, 197.2. (*Z*)-Isomer **34**: IR (neat) 1684, 1634, 1512, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.20–1.66 (m, 10H), 2.01 (q, $J=7$ Hz, 2H), 2.16–2.36 (m, 3H), 2.44 (dt, $J=14$, 7 Hz, 1H), 3.29–3.38 (m, 1H), 3.42 (t, $J=6$ Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 5.28–5.56 (m, 2H), 6.06 (dt, $J=$ 15, 7 Hz, 1H), 6.28 (dd, $J=6$, 2 Hz, 1H), 6.43 (d, $J=11$ Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.25 (d, $J=9$ Hz, 2H), 7.37 (dd, $J=6$, 2 Hz, 1H), 7.66 (ddt, $J=15$, 11, 2 Hz, 1H).

4.5.2. Aldehyde 33 through alcohol 32. To an ice-cold solution of PMB ether **31** (53 mg, 0.125 mmol) in CH_2Cl_2 (1.2 mL) and water (0.1 mL) was added DDQ (43 mg, 0.19 mmol). After 45 min, the reaction was quenched by addition of saturated $NaHCO_3$ and ether. The organic layer was separated and the aqueous layer was extracted with ether twice. The combined organic fractions were dried over $MgSO_4$ and concentrated to obtained an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish alcohol **32** (35 mg, 92% yield): IR (neat) 3421, 1685, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.1–1.7 (m, 11H), 2.02 (q, $J=7$ Hz, 2H), 2.16–2.38 (m, 3H), 2.54–2.66 (m, 1H), 3.50–3.70 (m, 3H), 5.25–5.60 (m, 2H), 6.16–6.31 (m, 2H), 6.32–6.40 (m, 1H), 6.95 (d, $J=11$ Hz, 1H), 7.48 (dd, $J=6$, 2 Hz, 1H).

To an ice-cold solution of alcohol **32** (35 mg, 0.116 mmol) in CH_2Cl_2 (1.2 mL) was added PCC (37 mg, 0.17 mmol).

The mixture was stirred vigorously at room temperature for 2.5 h, and diluted with Et_2O. The resulting mixture was filtered through a short pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography (hexane/EtOAc) to afford aldehyde **33** (32 mg, 92% yield): IR (neat) 1727, 1695, 1632, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.20–1.72 (m, 8H), 2.02 (q, $J=7$ Hz, 2H), 2.16–2.44 (m, 5H), 2.58 (dt, $J=15$, 5 Hz, 1H), 3.54–3.62 (m, 1H), 5.28–5.52 (m, 2H), 6.14–6.40 (m, 3H), 6.94 (d, $J=11$ Hz, 1H), 7.45 (dd, $J=6$, 3 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.0, 22.7, 26.8, 28.7, 30.9, 31.6, 33.6, 43.4, 43.6, 125.6, 126.1, 131.3, 131.6, 135.0, 135.3, 146.9, 160.4, 197.1, 202.0.

4.5.3. 15-Deoxy-$\Delta^{12,14}$-PGJ_2 (4). To a slurry of aldehyde **33** (32 mg, 0.106 mmol) in *t*-BuOH (1.4 mL), phosphate buffer of pH 3.6 (0.66 mL), and 2-methyl-2-butene (0.11 mL, 1.04 mmol) was added $NaClO_2$ (18 mg, 0.16 mmol, 80% purity) in water (0.53 mL). The mixture was stirred at ambient temperature for 3 h, and concentrated by using a vacuum pump. Phosphate buffer of pH 3.6 was added to the residue, and the mixture was extracted with EtOAc several times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oily residue, which was purified by chromatography (CH_2Cl_2/EtOH) to furnish 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**4**) (31 mg, 93% yield): $[\alpha]_D^{26}$ +193 (*c* 0.17, $CHCl_3$) (lit.[13] $[\alpha]_D$ +194.3 (*c* 0.7, $CHCl_3$)); IR (neat) 3303, 1707, 1628, 1209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.15–1.54 (m, 6H), 1.67 (quintet, $J=7$ Hz, 2H), 2.05 (q, $J=7$ Hz, 2H), 2.16–2.40 (m, 5H), 2.54–2.66 (m, 1H), 3.54–3.62 (m, 1H), 3.6–5.0 (br s, 2H), 5.28–5.56 (m, 2H), 6.16–6.42 (m, 3H), 6.96 (d, $J=11$ Hz, 1H), 7.47 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.6, 24.6, 26.7, 28.6, 30.9, 31.6, 33.4, 33.6, 43.6, 125.6, 126.1, 131.3, 131.9, 135.0, 135.3, 147.0, 160.7, 178.5, 197.5.

The following ^1H NMR spectrum, measured at 500 MHz, unambiguously indicated the trans olefin geometry at C(14)–C(15): ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.22–1.36 (m, 4H), 1.39–1.49 (m, 2H), 1.62–1.72 (m, 2H), 2.04 (q, $J=7$ Hz, 2H), 2.22 (q, $J=7$ Hz, 2H), 2.26–2.37 (m, 3H), 2.56–2.62 (m, 1H), 3.56–3.61 (m, 1H), 5.33–5.40 (m, 1H), 5.42–5.49 (m, 1H), 6.23 (dt, $J=15$, 7 Hz, 1H), 6.31 (ddt, $J=15$, 11, 1 Hz, 1H), 6.36 (dd, $J=6$, 2 Hz, 1H), 6.95 (d, $J=11$ Hz, 1H), 7.47 (ddd, $J=6$, 2.5, 1 Hz, 1H).

These spectra were in good agreement with the reported IR,[13] ^1H NMR (600 MHz),[13] and ^{13}C NMR (150, 75 MHz) spectra.[11,13]

4.6. Synthesis of 5,6-dehydro-Δ^{12}-PGJ_2 (5)

4.6.1. (1*S*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[3′,3′-dibromo-2′-propenyl]-2-cyclopentene (35). To an ice-cold solution of PPh_3 (436 mg, 1.66 mmol) in CH_2Cl_2 (3 mL) was added CBr_4 (276 mg, 0.832 mmol) portionwise. After vigorous stirring for 10 min, aldehyde **9b** (100 mg, 0.416 mmol) dissolved in CH_2Cl_2 (1.5 mL) was added slowly. The solution was stirred at 0 °C for 30 min and diluted with hexane. The resulting mixture was filtered through a pad of Celite with hexane and the filtrate was concentrated under reduced pressure to leave an oil, which was purified by chromatography (hexane) to afford dibromide **35** (125 mg, 76% yield): IR (neat) 3058, 1256, 1086, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 1.31 (dt, $J=13$, 5 Hz, 1H), 2.08–2.32 (m, 2H), 2.39 (dt, $J=13$, 8 Hz, 1H), 2.66 (quintet, $J=7$ Hz, 1H), 4.78–4.85 (m, 1H), 5.75 (s, 2H), 6.45 (t, $J=7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.3, 18.4, 26.1, 39.2, 40.3, 42.8, 77.3, 89.3, 135.1, 135.5, 137.0. Anal. Calcd for $C_{14}H_{24}Br_2OSi$: C, 42.44; H, 6.11. Found: C, 42.93; H, 6.52.

4.6.2. (1*S*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-(2′-propynyl)-2-cyclopentene (36). To a solution of **35** (115 mg, 0.290 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (0.32 mL, 2.25 M in hexane, 0.72 mmol) dropwise. After being stirred at −78 °C for 30 min, the reaction flask was immersed into an ice-water bath (0 °C). The reaction was continued for 30 min and quenched by addition of saturated NH_4Cl and hexane. The phases were separated and the aqueous layer was extracted with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil, which was purified by chromatography (hexane/EtOAc) to furnish acetylene **36** (62 mg, 91% yield): IR (neat) 3313, 1256, 1079, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.37 (ddd, $J=13$, 6, 5 Hz, 1H), 1.96 (t, $J=2.5$ Hz, 1H), 2.26 (d, $J=2.5$ Hz, 1H), 2.28 (d, $J=2.5$ Hz, 1H), 2.44 (dt, $J=13$, 8 Hz, 1H), 2.66–2.78 (m, 1H), 4.79–4.87 (m, 1H), 5.76 (dt, $J=6$, 2 Hz, 1H), 5.87 (dt, $J=6$, 2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 18.3, 25.3, 26.0, 40.4, 43.4, 68.8, 77.4, 83.3, 135.2, 135.5. Anal. Calcd for $C_{14}H_{24}OSi$: C, 71.12; H, 10.23. Found: C, 71.22; H, 10.51.

4.6.3. (1*S*,4*R*)-4-[7′-(4-Methoxybenzyloxy)-2′-heptynyl]-2-cyclopenten-1-ol (37). To a solution of acetylene **36** (180 mg, 0.761 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (0.76 mL, 1.90 M in hexane, 1.44 mmol) dropwise. After 20 min of stirring at the same temperature, DMPU (1.5 mL) and $PMBO(CH_2)_4Br$ (250 mg, 0.915 mmol) were added. The reaction was conducted at −78 °C for 1 h, and then gradually warmed to room temperature over 10 h. The mixture was diluted with saturated NH_4Cl and hexane. The organic layer was separated and the aqueous layer was extracted with hexane twice. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain an oil containing acetylene **13** and $PMBO(CH_2)_4Br$. This residue was passed through a short pad of silica gel for the next reaction: ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks only) δ 3.40–3.52 (m, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 4.78–4.87 (m, 1H), 5.73 (dt, $J=6$, 2 Hz, 1H), 5.86 (dt, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.26 (d, $J=9$ Hz, 2H).

To an ice-cold solution of the above product dissolved in THF (8 mL) was added *n*-Bu_4NF (1.14 mL, 1.0 M in THF, 1.14 mmol). The solution was stirred at room temperature for 3 h and diluted with saturated NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil, which was purified by chromatography (hexane/EtOAc) to afford alcohol **37** (193 mg, 81% yield in two steps): $[\alpha]_D^{28}$ +50 (*c* 0.31, $CHCl_3$); IR (neat) 3420, 1612, 1513, 1248 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 1.42 (dt, $J=14$, 4 Hz, 1H), 1.50–1.75 (m, 4H), 1.89–1.97 (m, 1H), 2.12–2.22 (m, 2H), 2.28–2.36 (m, 2H), 2.45 (dt, $J=14$, 8 Hz, 1H), 2.74–2.84 (m, 1H), 3.44 (t, $J=6$ Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 4.73 (br s, 1H), 5.83 (dd, $J=6$, 2 Hz, 1H), 5.88 (dt, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.26 (d, $J=9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 25.1, 25.9, 29.0, 39.1, 43.5, 55.3, 69.6, 72.6, 76.9, 79.2, 81.7, 113.7, 129.2, 130.6, 134.3, 137.0, 159.0. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.25; H, 8.12.

4.6.4. (*R*)-4-[7′-(4-Methoxybenzyloxy)-2′-heptynyl]-2-cyclopenten-1-one (38). A mixture of alcohol **37** (190 mg, 0.604 mmol) and PCC (195 mg, 0.905 mmol) in CH_2Cl_2 (6 mL) was stirred for 1 h, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to obtain an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish enone **38** (177 mg, 94% yield): $[\alpha]_D^{28}$ +107 (*c* 0.62, $CHCl_3$); IR (neat) 1714, 1612, 1512, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.72 (m, 4H), 2.08–2.21 (m, 3H), 2.34–2.44 (m, 2H), 2.52 (dd, $J=19$, 7 Hz, 1H), 3.06–3.16 (m, 1H), 3.45 (t, $J=6$ Hz, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 6.20 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=8$ Hz, 2H), 7.26 (d, $J=8$ Hz, 2H), 7.63 (dd, $J=6$, 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 24.0, 25.8, 29.0, 40.2, 40.6, 55.4, 69.6, 72.6, 76.4, 82.4, 113.7, 129.2, 130.6, 134.6, 159.0, 166.7, 209.2. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.52; H, 8.99.

4.6.5. Dienone 40. According to the aldol reaction of enone **10** and aldehyde **11**, a solution of LDA was prepared (0 °C, 20 min) from *i*-Pr_2NH (0.23 mL, 1.64 mmol) and *n*-BuLi (0.67 mL, 1.90 M in hexane, 1.27 mmol) in THF (9 mL) and used for preparation of the anion from enone **38** (200 mg, 0.64 mmol) in THF (2 mL) at −78 °C for 20 min. Aldehyde **11** (199 mg, 0.77 mmol) in THF (2 mL) was added to the solution, and, after 20 min, the solution was poured into a flask containing saturated NH_4Cl and ether with vigorous stirring. Aldol **39**, thus synthesized as a mixture of the *anti* and *syn* isomers (ca. 3:1 by TLC), was subjected to the next reaction after filtration through a short column of silica gel (hexane/EtOAc).

According to the conversion of aldol **20** to dienone **12**, the above aldol **39** in CH_2Cl_2 (6.5 mL) was converted into the mesylate with MsCl (0.10 mL, 1.29 mmol) and Et_3N (0.45 mL, 3.23 mmol) at 0 °C for 45 min. This mesylate, after being passed through a short column of silica gel (hexane/EtOAc), was dissolved in CH_2Cl_2 (2 mL) and the solution was added to a slurry of alumina (496 mg, ICN Alumina N-Super I, activated by heating on a heater for 20 min under vacuum) in CH_2Cl_2 (7 mL). After 13 h at room temperature, the mixture was filtered through a pad of Celite, and the filtrate was concentrated to furnish an yellow residue, which was purified by chromatography (hexane/EtOAc) to afford dienone **40** (151 mg, 43% yield from enone **38**): $[\alpha]_D^{28}$ +98 (*c* 0.38, $CHCl_3$); IR (neat) 1708, 1662, 1515, 1246 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.84–0.92 (m, 3H), 1.16–1.74 (m, 12H), 2.10–2.28 (m, 3H), 2.35–2.44 (m, 2H), 2.70–2.82 (m, 1H), 3.45 (t, $J=6$ Hz, 2H), 3.48–3.58 (m, 1H), 3.80 (s, 3H), 3.70–3.92 (m, 1H), 4.42 (s, 2H), 6.37 (dd, $J=6$, 1.5 Hz, 1H), 6.61 (t, $J=8$ Hz, 1H), 6.87 (d, $J=8$ Hz, 2H), 7.26 (d, $J=8$ Hz, 2H), 7.65 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.1, 14.2, 18.3, 18.7, 22.8, 23.2, 25.1, 25.8, 26.0, 29.1, 32.1, 37.4, 37.5, 43.0, 55.4, 69.7, 71.6, 72.7, 76.5, 82.8, 113.8, 129.2, 130.6, 133.0, 135.3, 137.9, 159.0, 161.0, 195.8.

4.6.6. Alcohol 41. A solution of dienone **40** (102 mg, 0.184 mmol) in CH_2Cl_2 (2 mL) and water (0.1 mL) was treated with DDQ (63 mg, 0.278 mmol) at 0 °C for 45 min, and diluted with saturated $NaHCO_3$ and ether to obtain an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish alcohol **41** (73 mg, 91% yield): $[\alpha]_D^{29}$ +158 (*c* 0.61, $CHCl_3$); IR (neat) 3441, 1703, 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 0.82–0.90 (m, 3H), 1.1–1.7 (m, 12H), 1.87 (br s, 1H), 2.10–2.20 (m, 2H), 2.28–2.48 (m, 3H), 2.72 (ddt, $J=17$, 4, 2 Hz, 1H), 3.50–3.59 (m, 1H), 3.61 (t, $J=6$ Hz, 2H), 3.82 (quintet, $J=6$ Hz, 1H), 6.39 (dd, $J=6$, 2 Hz, 1H), 6.61 (t, $J=8$ Hz, 1H), 6.59 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, 14.2, 18.2, 18.6, 22.8, 22.9, 25.1, 25.2, 26.0, 31.9, 32.0, 37.3, 37.4, 42.8, 62.5, 71.5, 76.3, 82.9, 133.1, 135.4, 137.8, 160.9, 196.2.

4.6.7. Acid 42. A mixture of alcohol **41** (20 mg, 0.046 mmol) and PCC (15 mg, 0.069 mmol) in CH_2Cl_2 (1 mL) was stirred vigorously at room temperature for 2 h, and diluted with ether to afford the corresponding aldehyde (18 mg, 90% yield) after chromatography (hexane/EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.84–0.92 (m, 3H), 1.16–1.50 (m, 8H), 1.72–1.84 (m, 2H), 2.16–2.50 (m, 5H), 2.53 (dt, $J=1.5$, 7 Hz, 2H), 2.75 (ddt, $J=17$, 4.5, 3 Hz, 1H), 2.68–2.82 (m, 1H), 3.50–3.60 (m, 1H), 3.83 (quintet, $J=6$ Hz, 1H), 6.39 (dd, $J=6$, 1.5 Hz, 1H), 6.61 (t, $J=8$ Hz, 1H), 7.60 (dd, $J=6$, 2 Hz, 1H), 9.79 (t, $J=1.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.1, 14.2, 18.26, 18.32, 21.5, 22.8, 23.0, 25.1, 26.0, 32.1, 37.4, 37.5, 42.7, 42.9, 71.6, 77.4, 81.8, 133.1, 135.4, 137.8, 160.6, 195.7, 201.7.

A mixture of the above aldehyde (18 mg, 0.042 mmol) in *t*-BuOH (0.55 mL), phosphate buffer of pH 3.6 (0.26 mL), and 2-methyl-2-butene (0.045 mL, 0.42 mmol) was treated with $NaClO_2$ (8 mg, 0.071 mmol, 80% purity) in water (0.21 mL) at ambient temperature for 3 h to afford acid **42** (17.5 mg, 91% yield) after chromatography (CH_2Cl_2/EtOH): IR (neat) 3100, 1707, 1653, 813, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.84–0.92 (m, 3H), 1.16–1.54 (m, 8H), 1.79 (quintet, $J=7$ Hz, 2H), 2.12–2.60 (m, 7H), 2.76 (dm, $J=17$ Hz, 1H), 3.52–3.62 (m, 1H), 3.84 (quintet, $J=6$ Hz, 1H), 4.4–5.6 (br s, 1H), 6.41 (dd, $J=6$, 2 Hz, 1H), 6.62 (t, $J=8$ Hz, 1H), 7.63 (dd, $J=6$, 2 Hz, 1H).

4.6.8. 5,6-Dehydro-Δ^{12}-PGJ_2 (5). To a flask containing acid **42** (17 mg, 0.039 mmol) was added a solution (0.39 mL) of 55% HF and MeCN in a ratio of 1:19. The solution was stirred at 0 °C for 15 min and diluted with brine to furnish 5-dehydro-Δ^{12}-PGJ_2 (**5**) (12 mg, 95% yield) after chromatography (CH_2Cl_2/EtOH): $[\alpha]_D^{26}$ +199 (*c* 0.14, $CHCl_3$); IR (neat) 3417, 1699, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.20–1.60

(m, 8 H), 1.77 (quintet, $J=7$ Hz, 2H), 2.16–2.28 (m, 2H), 2.38–2.56 (m, 5H), 2.68–2.82 (m, 1H), 3.56–3.64 (m, 1H), 3.83 (quintet, $J=6$ Hz, 1H), 3.2–4.2 (br s, 2H), 6.43 (dd, $J=6$, 2 Hz, 1H), 6.66 (t, $J=8$ Hz, 1H), 7.59 (dd, $J=6$, 2 Hz, 1H).

4.7. Synthesis of 5,6-dehydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (6)

4.7.1. Dienone 44 through aldol 43. To a solution of *i*-Pr_2NH (0.17 mL, 1.21 mmol) in THF (8 mL) at 0 °C was added *n*-BuLi (0.44 mL, 2.20 M in hexane, 0.97 mmol). The solution was stirred at the same temperature for 20 min to prepare LDA, and cooled to −78 °C. Enone **38** (150 mg, 0.48 mmol) dissolved in THF (2 mL) was added into the LDA solution dropwise, and the solution was stirred for 20 min. (*E*)-2-Octenal (**29**) (0.086 mL, 0.58 mmol) was added to the solution. After being stirred for further 20 min at the same temperature, the solution was poured into a flask containing saturated NH_4Cl and ether with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford aldol **43** as the *anti* and *syn* isomers in a 2:1 ratio by ^{1}H NMR spectroscopy (*anti* isomer, δ 4.19 (q, $J=8$ Hz); *syn* isomer, δ 4.55–4.62 (m)). The aldol **43** was subjected to the next reaction after being passed through a short column of silica gel. The aldol reaction was repeated, and the stereoisomers were separated by chromatography (hexane/EtOAc). *anti* Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.1–1.8 (m, 11H), 1.96–2.56 (m, 7H), 2.72–2.80 (m, 1H), 3.44 (t, $J=7$ Hz, 2H), 3.80 (s, 3H), 4.19 (q, $J=8$ Hz, 1H), 4.42 (s, 2H), 5.44 (ddt, $J=16$, 8, 1 Hz, 1H), 5.74 (dt, $J=16$, 8 Hz, 1H), 6.18 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.25 (d, $J=9$ Hz, 2H), 7.66 (dd, $J=6$, 2 Hz, 1H). *syn* Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=7$ Hz, 3H), 1.1–1.8 (m, 11H), 2.03 (q, $J=7$ Hz, 2H), 2.08–2.22 (m, 2H), 2.28–2.40 (m, 2H), 2.44–2.52 (m, 1H), 2.95–3.04 (m, 1H), 3.44 (t, $J=7$ Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 4.55–4.62 (m, 1H), 5.46 (ddt, $J=16$, 7, 1.5 Hz, 1H), 5.74 (dt, $J=16$, 7 Hz, 1H), 6.19 (dd, $J=6$, 2 Hz, 1H), 6.87 (d, $J=9$ Hz, 2H), 7.25 (d, $J=9$ Hz, 2H), 7.66 (dd, $J=6$, 2 Hz, 1H).

To a solution of the crude aldol **43** in CH_2Cl_2 (5 mL) and Et_3N (0.67 mL, 4.8 mmol) at −15 °C was added MsCl (0.15 mL, 1.94 mmol) dropwise. After 45 min at the same temperature, the reaction was quenched by addition of saturated $NaHCO_3$. The mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish an yellow residue, which was purified by chromatography (hexane/EtOAc) to afford dienone **44** (143 mg, 71% yield from enone **38**) and (*Z*)-isomer (12 mg, 6% yield). Dienone **44**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.22–1.75 (m, 10H), 2.10–2. 28 (m, 5H), 2.70–2.82 (m, 1H), 3.46 (t, $J=6$ Hz, 2H), 3.58–3.67 (m, 1H), 3.80 (s, 3H), 4.43 (s, 2H), 6.16–6.35 (m, 2H), 6.40 (dd, $J=7$, 2 Hz, 1H), 6.88 (d, $J=8$ Hz, 2H), 6.95 (d, $J=11$ Hz, 1H), 7.26 (d, $J=8$ Hz, 2H), 7.64 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.7, 22.6, 23.6, 25.8, 28.7, 29.1, 31.6, 33.6, 43.2, 55.4, 69.7, 72.7, 77.2, 82.9, 113.8, 125.4, 129.2, 130.7, 132.0, 134.3, 135.6, 147.3, 159.1, 160.2, 196.8. (*Z*)-Isomer of **44**: ^{1}H NMR (300 MHz, $CDCl_3$) (characteristic signals) δ 6.06 (dt, $J=15$, 8 Hz, 1H), 6.33 (dd, $J=6$. 2 Hz, 1H), 6.49 (d, $J=11$ Hz, 1H), 7.49 (dd, $J=6$, 2 Hz, 1H), 7.26–7.68 (m, 1H).

4.7.2. 5,6-Dehydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (6). To an ice-cold solution of dienone **44** (55 mg, 0.13 mmol) in CH_2Cl_2 (1.2 mL) and water (0.1 mL) was added DDQ (45 mg, 0.198 mmol). After 45 min, the reaction was quenched by addition of saturated $NaHCO_3$ and ether. The organic layer was separated and the aqueous layer was extracted with ether twice. The combined organic fractions were dried over $MgSO_4$ and concentrated to obtained an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish the corresponding alcohol (36 mg, 92% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.20–1.83 (m, 11H), 2.10–2.30 (m, 5H), 2.37 (ddt, $J=16$, 9, 2 Hz, 1H), 2.74 (ddt, $J=16$, 4, 3 Hz, 1H), 3.64, (t, $J=7$ Hz, 2H), 3.58–3.72 (m, 1H), 6.22–6.32 (m, 2H), 6.42 (dd, $J=6$, 1.5 Hz, 1H), 6.72 (d, $J=11$ Hz, 1H), 7.59 (dd, $J=6$, 3 Hz, 1H).

To an ice-cold solution of the above alcohol (35 mg, 0.116 mmol) in CH_2Cl_2 (1 mL) was added PCC (38 mg, 0.176 mmol). The mixture was stirred vigorously at room temperature for 2 h and diluted with ether. The resulting mixture was filtered through a short pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography (hexane/EtOAc) to afford the corresponding aldehyde (32 mg, 92% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.16–1.52 (m, 6H), 1.80 (quintet, $J=7$ Hz, 2H), 2.10–2.40 (m, 5H), 2.53 (t, $J=7$ Hz, 2H), 2.75 (ddt, $J=17$, 4.5, 2 Hz, 1H), 3.60–3.69 (m, 1H), 6.17–6.34 (m, 2H), 6.41 (dd, $J=6$, 1.5 Hz, 1H), 6.96 (d, $J=11$ Hz, 1H), 7.59 (dd, $J=6$, 3 Hz, 1H), 9.79 (t, $J=2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.3, 21.5, 22.6, 23.4, 28.6, 31.6, 33.6, 42.8, 42.9, 77.3, 81.8, 125.3, 132.0, 134.2, 135.8, 147.4, 159.8, 196.7, 201.8.

To a slurry of the above aldehyde (25 mg, 0.084 mmol) in *t*-BuOH (1.1 mL), phosphate buffer of pH 3.6 (0.53 mL), and 2-methyl-2-butene (0.09 mL, 0.85 mmol) was added $NaClO_2$ (14 mg, 0.12 mmol, 80% purity) in water (0.42 mL). The mixture was stirred at ambient temperature for 3 h, and concentrated by using a vacuum pump. Phosphate buffer of pH 3.6 was added to the residue, and the mixture was extracted with EtOAc several times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oily residue, which was purified by chromatography (CH_2Cl_2/EtOH) to furnish the title acid **6** (24 mg, 91% yield): $[\alpha]_D^{27}$ +157 (*c* 0.22, $CHCl_3$); IR (neat) 3100, 1699, 1630, 1209 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.20–1.56 (m, 6H), 1.79 (quintet, $J=7$ Hz, 2H), 2.14–2.38 (m, 5H), 2.45 (t, $J=7$ Hz, 2H), 2.70–2.84 (m, 1H), 3.60–3.70 (m, 1H), 6.15–6.36 (m, 2H), 6.42 (dd, $J=6$, 2 Hz, 1H), 6.96 (d, $J=11$ Hz, 1H), 7.61 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.3, 22.6, 23.4, 23.9, 28.6, 31.6, 32.8, 33.7, 43.0, 77.4, 81.7, 125.3, 132.3, 134.2, 135.7, 147.6, 160.2, 178.1, 197.1.

4.8. Synthesis of 5,6-dihydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (7)

4.8.1. (1*R*,4*R*)-4-[7′-(4-Methoxybenzyloxy)heptyl]-2-cyclopenten-1-ol (46). To an ice-cold slurry of LiCl (180 mg, 4.25 mmol) and $PMBO(CH_2)_7MgBr$ (**45**) (9.10 mL, 0.35 M in THF, 3.19 mmol) was added CuCN

(29 mg, 0.323 mmol). After 30 min at −10 °C, monoacetate *ent*-**8a** (150 mg, 1.06 mmol, >95% ee) in THF (2 mL) was added. The mixture was stirred at the same temperature for 3 h, and the solution was diluted with saturated NH_4Cl, few drops of 28% NH_3, and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic fractions were dried over $MgSO_4$ and concentrated to obtain an yellow oil, which was a mixture of 1,4-isomer **46** and 1,2-isomer **51** in a 92:8 ratio by ^1H NMR spectroscopy. The mixture was separated by chromatography (hexane/EtOAc). Alcohol **46** (272 mg, 81% yield): IR (neat) 3398, 1613, 1513, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16–1.48 (m, 8H), 1.52–1.70 (m, 5H), 1.75 (ddd, J=14, 7, 5 Hz, 1H), 1.89 (ddd, J=14, 7, 3 Hz, 1H), 2.78–2.90 (m, 1H), 3.43 (t, J=7 Hz, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 4.79–4.87 (m, 1H), 5.80 (dt, J=5, 2 Hz, 1H), 5.93 (dd, J=5, 2 Hz, 1H), 6.87 (d, J=9 Hz, 2H), 7.26 (d, J=9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 27.9, 29.4, 29.70, 29.75, 35.9, 40.6, 44.1, 55.3, 70.2, 72.5, 77.1, 113.7, 129.2, 130.8, 132.4, 140.2, 159.1. Regioisomer **51**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.10–1.46 (m, 8H), 1.50–1.65 (m, 5H), 2.25 (dm, J=18 Hz, 1H), 2.46–2.56 (m, 1H), 2.70 (dd, J=18, 7 Hz, 1H), 3.43 (t, J=7 Hz, 2H), 3.79 (s, 3H), 4.04–4.12 (m, 1H), 4.42 (s, 2H), 5.61–5.73 (m, 2H), 6.87 (d, J=9 Hz, 2H), 7.26 (d, J=9 Hz, 2H).

4.8.2. (*R*)-4-[7′-(4-Methoxybenzyloxy)heptyl]-2-cyclopenten-1-one (47). To a solution of alcohol **46** (250 mg, 0.79 mmol) in CH_2Cl_2 (8 mL) was added PCC (254 mg, 1.18 mmol). After being stirred vigorously for 1 h, the mixture was diluted with ether and filtered through a pad of Celite. The filtrate was concentrated to obtain an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish enone **47** (226 mg, 91% yield) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.1–1.7 (m, 12H), 1.99 (dd, J=19, 2 Hz, 1H), 2.52 (dd, J=19, 7 Hz, 1H), 2.84–2.96 (m, 1H), 3.42 (t, J=7 Hz, 2H), 3.79 (s, 3H), 4.42 (s, 2H), 6.13 (dd, J=6, 2 Hz, 1H), 6.87 (d, J=9 Hz, 2H), 7.25 (d, J=9 Hz, 2H), 7.62 (dd, J=6, 2 Hz, 1H).

4.8.3. Dienone 49. To an ice-cold solution of *i*-Pr_2NH (0.27 mL, 1.93 mmol) in THF (9 mL) was added *n*-BuLi (0.67 mL, 1.90 M in hexane, 1.27 mmol). The solution was stirred at the same temperature for 20 min to prepare LDA and cooled to −78 °C. To this solution were added enone **47** (200 mg, 0.63 mmol) dissolved in THF (3 mL) and, after 20 min, *trans*-2-octenal (**29**) (0.14 mL, 0.94 mmol). The solution was stirred for further 30 min at the same temperature, and poured into a flask containing saturated NH_4Cl and ether with vigorous stirring. After 30 min, the organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford aldol **48** as the *anti* and *syn* isomers in a 3:1 ratio by TLC analysis, which was used for the next reaction after filtration through a short column of silica gel: ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks only) δ 5.38–5.50 (m, 1H), 5.64–5.78 (m, 1H), 6.12 (dd, J=6, 2 Hz, 1H), 6.87 (d, J=9 Hz, 2H), 7.25 (d, J=9 Hz, 2H), 7.65–7.72 (m, 1H).

To a solution of the above aldol **48** in CH_2Cl_2 (6 mL) and Et_3N (0.88 mL, 6.31 mmol) at −20 °C was added MsCl (0.195 mL, 2.52 mmol) dropwise. After 45 min at the same temperature, the reaction was quenched by addition of saturated $NaHCO_3$. The mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish an yellow residue, which was subjected to chromatography (hexane/EtOAc) to afford dienone **49** (136 mg, 51% yield from enone **47**) and (*Z*)-isomer **52** (14 mg, 5% yield). Dienone **49**: IR (neat) 1694, 1633, 1513, 1248, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=7 Hz, 3H), 1.2–1.7 (m, 17H), 1.75–1.95 (m, 1H), 2.22 (q, J=7 Hz, 2H), 3.41 (t, J=7 Hz, 2H), 3.49–3.56 (m, 1H), 3.79 (s, 3H), 4.42 (s, 2H), 6.14–6.30 (m, 2H), 6.34 (dd, J=6, 2 Hz, 1H), 6.87 (d, J=9 Hz, 2H), 6.92 (d, J=10 Hz, 1H), 7.25 (d, J=9 Hz, 2H), 7.51 (dd, J=6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 26.0, 26.2, 28.5, 29.4, 29.76, 29.78, 31.4, 33.0, 33.5, 43.6, 55.3, 70.2, 72.6, 113.8, 125.7, 129.3, 130.8, 131.3, 135.2, 135.7, 146.6, 159.1, 161.2, 197.7. (*Z*)-Isomer **52**: ^1H NMR (300 MHz, $CDCl_3$) (characteristic signals) δ 6.07 (dt, J=15, 8 Hz, 1H), 6.28 (dd, J=6, 2 Hz, 1H), 6.38 (d, J=11 Hz, 1H), 7.42 (dd, J=6, 2 Hz, 1H), 7.60–7.74 (m, 1H).

4.8.4. Alcohol 50. To an ice-cold solution of dienone **49** (135 mg, 0.317 mmol) in CH_2Cl_2 (3 mL) and water (0.2 mL) was added DDQ (108 mg, 0.476 mmol). After 45 min, the reaction was quenched by addition of saturated $NaHCO_3$ and ether. The organic layer was separated and the aqueous layer was extracted with ether twice. The combined organic fractions were dried over $MgSO_4$ and concentrated to obtained an yellow residue, which was purified by chromatography (hexane/EtOAc) to furnish alcohol **50** as an oil (90 mg, 92% yield): IR (neat) 3417, 1695, 1630, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7 Hz, 3H), 1.1–1.7 (m, 18H), 1.80–1.94 (m, 1H), 2.22 (q, J=7 Hz, 2H), 3.50–3.59 (m, 1H), 3.63 (t, J=7 Hz, 2H), 6.15–6.31 (m, 2H), 6.35 (dd, J=6, 2 Hz, 1H), 6.92 (d, J=11 Hz, 1H), 7.51 (dd, J=6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.7, 26.0, 28.5, 29.4, 29.8, 31.5, 32.8, 33.0, 33.5, 43.6, 63.1, 125.7, 131.4, 135.2, 135.7, 146.7, 161.2, 197.8.

4.8.5. 5,6-Dihydro-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (7). To an ice-cold solution of alcohol **50** (90 mg, 0.296 mmol) in CH_2Cl_2 (5 mL), DMSO (1.5 mL), and Et_3N (0.29 mL, 2.1 mmol) was added SO_3·pyridine (141 mg, 0.89 mmol). The solution was stirred vigorously at the same temperature for 1.5 h, and diluted with ether and cold water. The resulting mixture was stirred vigorously at room temperature for 20 min. The phases were separated and the aqueous layer was extracted with ether twice. The combined organic layers were dried over $MgSO_4$ and concentrated to obtain an yellow residue, which was purified by column chromatography (hexane/EtOAc) to afford the corresponding aldehyde (83 mg, 93% yield): IR (neat) 1725, 1694, 1634, 1205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7 Hz, 3H), 1.1–1.7 (m, 17H), 1.78–1.92 (m, 1H), 2.22 (q, J=7 Hz, 2H), 2.41 (dt, J=1.5, 7 Hz, 2H), 3.50–3.58 (m, 1H), 6.14–6.30 (m, 2H), 6.35 (dd, J=6, 2 Hz, 1H), 6.92 (d, J=10 Hz, 1H), 7.51 (dd, J=6, 2 Hz, 1H), 9.76 (t, J=1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.5, 25.8, 28.5, 29.0, 29.6, 31.4, 32.9, 33.5, 43.5, 43.9, 125.7, 131.4, 135.3, 135.6, 146.7, 161.1, 197.8, 202.7.

To a slurry of the above aldehyde (80 mg, 0.264 mmol) in *t*-BuOH (3.5 mL), phosphate buffer of pH 3.6 (1.7 mL), and 2-methyl-2-butene (0.26 mL, 2.45 mmol) was added $NaClO_2$ (45 mg, 0.398 mmol, purity 80%) in water

(1.3 mL). The resulting mixture was stirred at room temperature for 1 h, and connected to a vacuum pump to remove volatile compounds (*t*-BuOH). The phosphate buffer of pH 3.6 was added to the residue, and the mixture was extracted with EtOAc several times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oily residue, which was purified by chromatography (CH_2Cl_2/EtOH) to furnish acid **7** (76 mg, 90% yield): IR (neat) 3000, 1708, 1697, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.1–1.7 (m, 17H), 1.78–1.94 (m, 1H), 2.22 (q, $J=7$ Hz, 2H), 2.33 (t, $J=7.5$ Hz, 2H), 3.50–3.58 (m, 1H), 6.15–6.34 (m, 2H), 6.35 (dd, $J=6$, 2 Hz, 1H), 6.93 (d, $J=11$ Hz, 1H), 7.51 (dd, $J=6$, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 24.6, 25.8, 28.5, 29.0, 29.5. 31.4, 32.9, 33.5, 33.9, 43.6, 125.7, 131.5, 135.3, 135.6, 146.8, 161.2, 179.1, 197.8.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. We thank Ono Pharmaceutical Co., Ltd for providing us ^1H NMR spectrum of Δ^{12}-PGJ_2.

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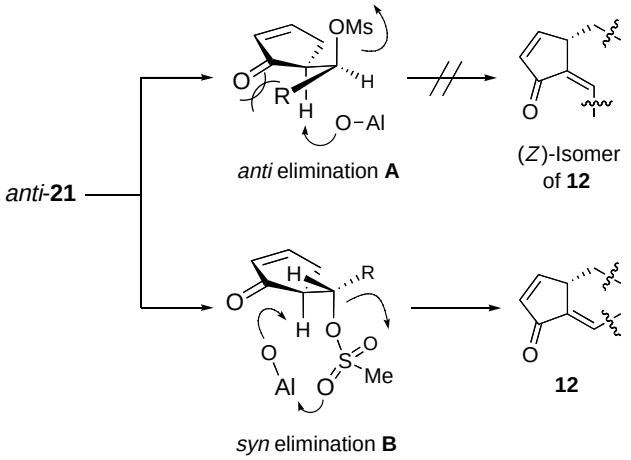
31. The result indicates that (1) among the transition states **A** and **B** for the *anti* and *syn* eliminations of the mesyloxy group and the hydrogen at C(12), the steric congestion between the carbonyl oxygen and the C(14) methylene (shown as R) changes **A** less favorably than **B**, and that (2) the participation of Al_2O_3 in the transition state (**B**) assisted the *syn* elimination effectively.



32. Deprotection of the TBS group with TBAF in THF and with NBS in wet DMSO was unsuccessful.
33. The stereochemistry of the newly formed olefin at C(13) was assigned by the chemical shift of the C(13)–H: (*E*)-isomer **31**, δ 6.87 (d, $J=11$ Hz); (*Z*)-isomer **34**, δ 6.43 (d, $J=11$ Hz).
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Tetrahedron 62 (2006) 3344–3354
Tetrahedron

Selenium-containing heterocycles from isoselenocyanates: synthesis of 2-methylidene-1,3-selenazolidine derivatives

Geoffroy L. Sommen,☆ Anthony Linden and Heinz Heimgartner*

Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Received 16 November 2005; revised 16 January 2006; accepted 17 January 2006

Abstract—A convenient and unequivocal synthesis of the title compounds from isoselenocyanates, malononitrile or 2-cyanoacetate, and 1,2-dibromoethane or α-halogenated carboxylic acid derivatives is reported. The proposed reaction mechanism involves in situ cyclization of different halogenated compounds with an intermediate keten-N,Se-acetal, generated by the base promoted nucleophilic addition of the acidic cyanomethylenes to aliphatic and aromatic isoselenocyanates. Chemical and spectroscopic evidence for the structures of the new compounds is presented.
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1. Introduction

The explosive growth of the interest in organoselenium chemistry over the past 25 years can be attributed to the specific properties of organic selenium compounds, which fit into the requirements of modern organic synthesis. Most of them are well adapted to chemo-, regio-, and stereoselective reactions.[1] In particular, selenium-containing heterocyclic compounds have been well recognized not only because of their remarkable reactivities and chemical properties,[2] but also because of their diverse pharmaceutical applications.[3] For this reason we are interested in the use of isoselenocyanates **1** in heterocyclic synthesis.[4] They are useful starting materials, since they are easy to prepare[5] and are safe to handle and store. In addition, they typically react under mild conditions, which are compatible with the low stability of substrates and products in the preparation of complex molecules.

Several reviews[6] have described the preparation and pharmaceutical potential of 1,3-selenazoles.[7] They have been studied in diverse areas of interest, for example as antitumor[8] and antiradiation agents,[9] enzyme inhibitors,[10] antifilarial[11] and antiviral compounds,[12] delivery agents,[13] and prodrugs of selenocysteine,[14] and are also well recognized in the chemistry of dyes.[15]

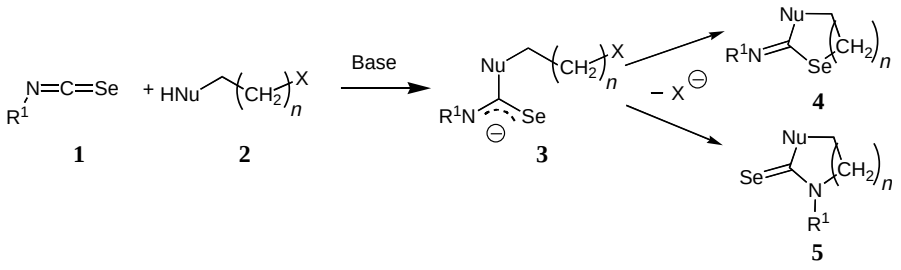
For the reaction of isoselenocyanates with nucleophiles it is known that nitrogen, oxygen, sulfur, and selenium nucleophiles add to the central carbon atom,[16] whereas phosphorus nucleophiles attack either the central carbon atom or the selenium atom.[17] Although only a few examples of the reaction of isoselenocyanates with carbon nucleophiles have been described, it was recently reported that suitable carbanions and isoselenocyanates can produce selenium-containing compounds.[18] To the best of our knowledge, only one paper describes such a reaction being used for the synthesis of 1,3-selenazoles.[19] On the other hand, 1,3-selenazolidinones have been prepared from different starting materials, such as isothiocyanates,[20] selenazadienes,[21] and widely from selenoureas,[22] but never with isoselenocyanates. For this reason, we have investigated the use of isoselenocyanates **1**, which are conveniently prepared by Barton's procedure,[5] as building blocks in the synthesis of selenaheterocycles and heterocyclic selones.[23–34] For example, it has been shown that the reactions of bifunctional nucleophiles **2** with **1** yield five to seven-membered heterocycles of type **4** and **5** (Scheme 1). A likely intermediate is the adduct **3**, which undergoes the ring closure by nucleophilic substitution of the leaving group X either by the Se or the N-atom. As a continuation of previous work, we decided to investigate the addition of carbon nucleophiles with **1** and to trap the intermediate by a suitably substituted electrophilic reagent.

2. Results and discussion

After several unsuccessful attempts at reactions of isoselenocyanates with β-diketons like acetylacetone and

Keywords: Isoselenocyanates; Selenaheterocycles; 1,3-Selenazolidines.
* Corresponding author. Tel.: +41 44 6354282; fax: +41 44 6356812; e-mail: heimgart@oci.unizh.ch
☆ Postdoctoral stay at the University of Zürich (8.2004-8.2005).

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.077



Scheme 1.

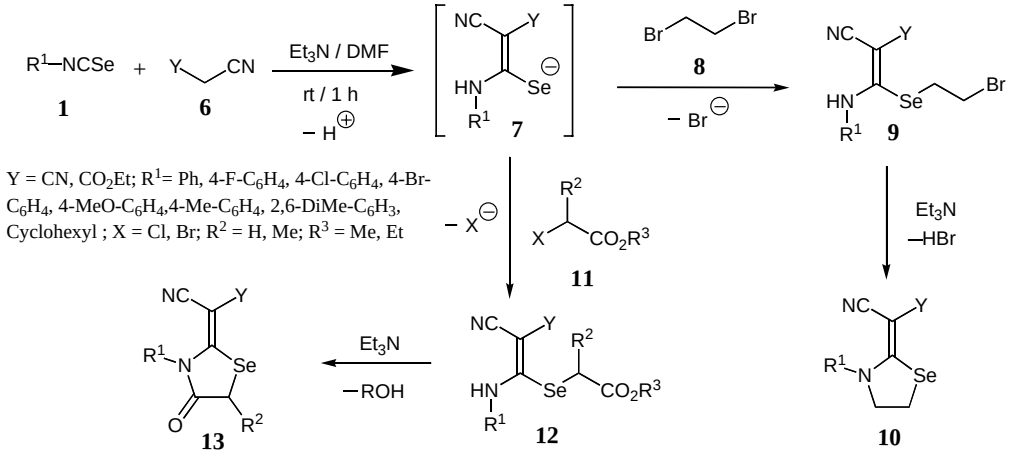
dibenzoylmethane, we were successful by using cyanomethylene derivatives. Malononitrile and ethyl cyanoacetate react at rt with aryl and alkyl isoselenocyanates in the presence of a base to afford an intermediate keten-N,Se-acetal **7**, which subsequently can react with different halogenated compounds (Scheme 2).

For example, the carbanion obtained from malononitrile (**6a**) and triethylamine in DMF added to isoselenocyanates **1** to give an intermediate of type **7**. The latter reacted with 1,2-dibromoethane (**8**) to give another intermediate **9**, which cyclized to yield 1,3-selenazolidine derivatives of type **10**. After stirring for 4 h, the reaction mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel and recrystallization from ethyl acetate (Table 1). Similar reactions were performed starting with ethyl cyanoacetate (**6b**). It is worth mentioning that only one isomer was obtained in the case of the cyanoacetates **10e–g** (Table 1).

The structures of the products were established on the basis of their spectroscopic data and, in the cases of **10a** and **10c**, by X-ray crystallography (Fig. 1). The 2-(1,3-selenazolidin-2-ylidene)malononitriles **10a–d** show two different CN absorptions in the IR spectra (KBr; ca. 2203 and 2190 cm^{-1}) and ^{13}C NMR spectra (DMSO; ca. 112 and 118 ppm). For the 2-cyano-2-(1,3-selenazolidin-2-yliden)acetates **10e–g**, the CN absorption appears at ca. 2195 cm^{-1} and 114 ppm.

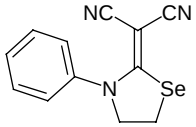
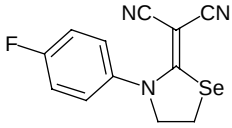
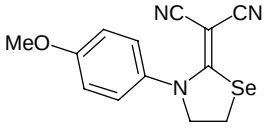
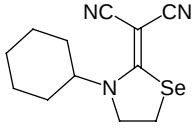
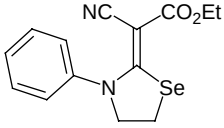
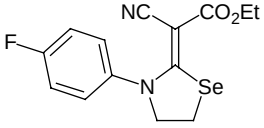
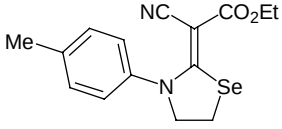
In the crystal structure of **10a**, the two CH_2 groups in the five-membered ring are disordered over two approximately equally occupied positions, which result from alternate half-chair puckering of the ring conformation. The two cyano groups are coplanar with the atoms Se(1), C(2), N(3), and C(6), but the bond angles at the dicyanomethylidene C-atom are significantly different: whereas the angles C(2)–C(6)–C(7) and C(7)–C(6)–C(8) are small (118.2(1) and 115.7(1)°, respectively), the angle C(2)–C(6)–C(8) is widened (126.1(2)°), that is, the CN group is tilted away from the phenyl residue. In turn, the latter is twisted out of the above mentioned plane by ca. 86°. Furthermore, the CN group pointing toward the phenyl residue is slightly bent away from the phenyl ring (N(8)–C(8)–C(6)=175.2(2)°) whereas the other one is linear (N(7)–C(7)–C(6)=179.3(2)°). In the case of **10c**, the five-membered ring has a half-chair conformation twisted on C(4)–C(5). The other structure parameters of **10c** are very similar to those of **10a**. In both compounds, the C(2), C(6) bond longer (1.392(2) and 1.399(3) Å, respectively) than a normal C=C bond. On the other hand, the formal single bonds C(6), C(7) and C(6), C(8) are short (1.421(2), 1.428(2) and 1.424(2), 1.418(3) Å, respectively) as well as the N(3), C(2) and the Se(1), C(2) bonds (1.332(2), 1.900(2) and 1.328(2), 1.898(2) Å, respectively). Together with the remarkable chemical shifts of C(2) and C(6) (ca. 172 and 51 ppm, respectively), dipolar structures containing the unit $–CH_2(Ar)N^+–C^-(CN)_2$ are most likely.

The analogous reaction of **1**, **6a**, and methyl 2-chloroacetate (**11a**) gave the 2-(4-oxo-1,3-selenazolidin-2-ylidene)malononitriles of type **13** (Scheme 2, Table 2). We propose that **12** is the intermediate, which is the product of the reaction of the initially formed **7** with the halogenated compound. A subsequent condensation by elimination of methanol then yields **13**. In the case of **13a** and **13d**, the same products were obtained in increased yield by using ethyl



Scheme 2.

Table 1. Preparation of 1,3-selenazolidines **10** from isoselenocyanates **1**

Entry	R^1	Y	1,3-Selenazolidines **10**	Yield (%)
a	Phenyl	CN		62
b	4-F–C_6H_4	CN		54
c	4-MeO–C_6H_4	CN		61
d	Cyclohexyl	CN		42
e	Phenyl	CO_2Et		31
f	4-F–C_6H_4	CO_2Et		36
g	4-Me–C_6H_4	CO_2Et		31

bromoacetate (**11b**). Furthermore, the reaction with methyl 2-chloropropionate **11c** led to the 5-methyl derivatives **13h** and **13i** (Table 2).

As in the case of the malononitriles **10a–d**, the 4-oxo derivatives of type **13** show two CN absorptions in the IR (ca. 2220 and 2210 cm^{-1}) and in the ^{13}C NMR spectrum (ca. 110 and 115 ppm). In addition, the CO group appears at 1733–1743 cm^{-1} and 160–173 ppm. The structure of **13a** was established by X-ray crystallography (Fig. 2). Although the compound is achiral, it has crystallized in a polar space group and the absolute structure has been determined by the diffraction experiment. The five-membered ring is almost planar, but is puckered slightly towards an envelope conformation where atom C(5) lies 0.149(2) Å from the mean plane defined by the other four ring atoms. The adjacent atoms O(4) and C(9), as well as the dicyanomethylidene group, are also lying in this ring plane.

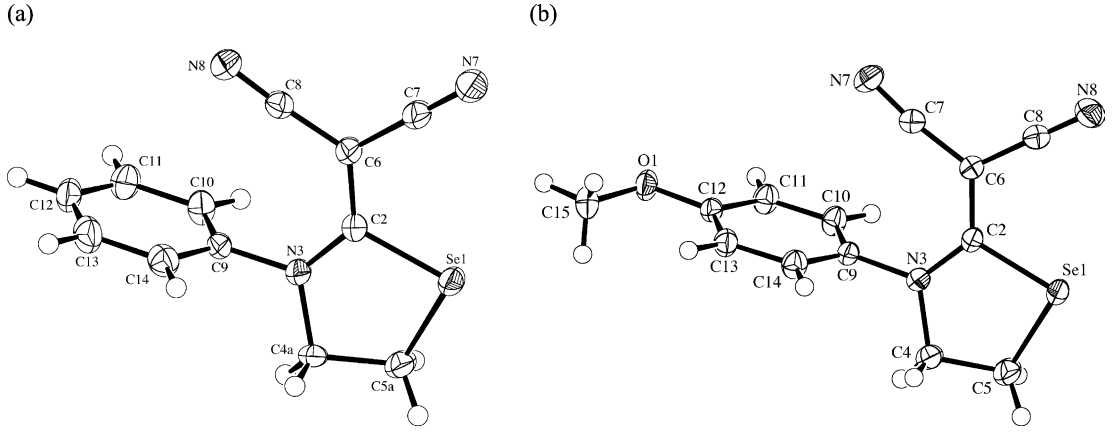
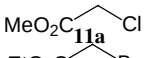
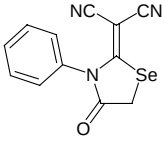
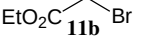
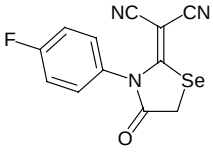
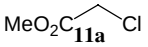
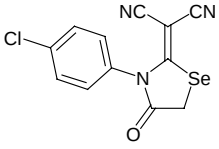
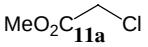
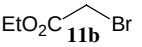
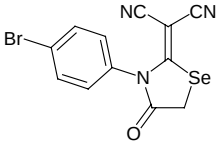
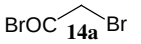
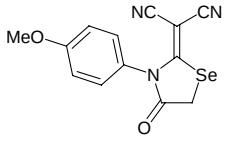
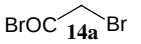
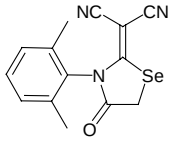
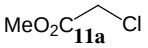
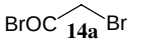
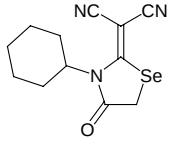
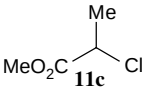
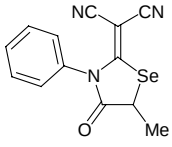
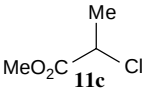
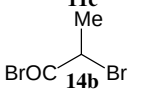
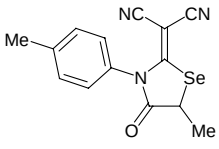
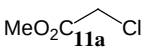
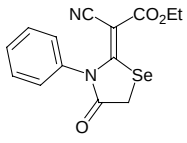
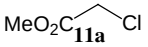
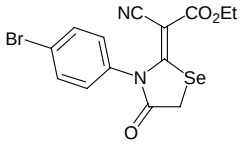
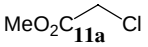
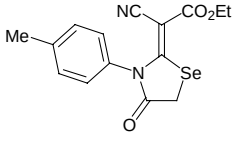


Figure 1. ORTEP plot[35] of the molecular structure of (a) the major conformation of **10a** and (b) of **10c** (arbitrary numbering of atoms; 50% probability ellipsoids).

Table 2. Preparation of 1,3-selenazolidin-4-ones **13** from isoselenocyanates **1**

Entry	R^1	Acetate	1,3-Selenazolidin-4-ones **13**	Yield (%)
a	Phenyl			74 81 85
b	4-F–C_6H_4			83
c	4-Cl–C_6H_4			68
d	4-Br–C_6H_4	 		87 95
e	4-MeO–C_6H_4			74
f	2,6-DiMe–C_6H_3			83
g	Cyclohexyl	 		34 33
h	Phenyl			63
i	4-Me–C_6H_4	 		89 63
k	Phenyl			64
l	4-Br–C_6H_4			86
m	4-Me–C_6H_4			78

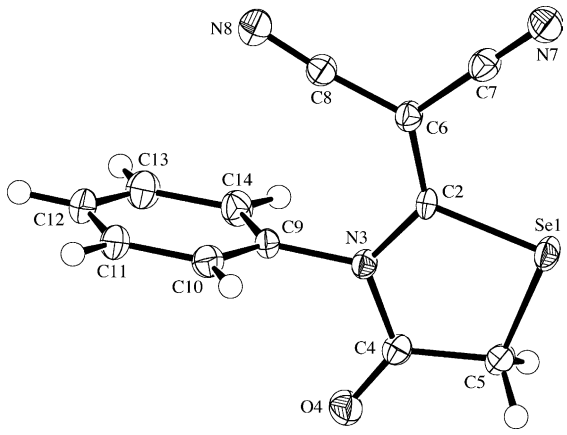


Figure 2. ORTEP plot[35] of the molecular structure of **13a** (arbitrary numbering of atoms; 50% probability ellipsoids).

The phenyl group is oriented almost orthogonal to the above defined heterocyclic ring plane (dihedral angle ca. 86°). The other structure parameters are very similar to those of **10a** and **10c**, and the chemical shifts of C(2) and C(6) in the ^{13}C NMR spectra (173.3 and 56.7 ppm, respectively) show that again a dipolar structure has to be considered.

The corresponding ethyl 2-cyano-2-(4-oxo-1,3-selenazolidin-2-yliden)acetates **13k–m** were prepared in a similar manner from **1**, **6b**, and **11a** (Scheme 2, Table 2). Again, only one isomer was obtained (TLC, NMR). In the case of **13k**, the molecular structure was established by X-ray crystallography (Fig. 3). The exocyclic C, C-double bond is (*Z*)-configured, that is, the sterically more demanding ester group is pointing away from the *N*-phenyl group. There are two symmetry-independent molecules in the asymmetric unit. One of these molecules (A) has disorder in the terminal ethyl group of the ester substituent, with the major conformation being present in ca. 58% of the molecules. Molecules A and B have almost identical conformations with the only significant conformational difference being a small rotation in the orientation of the terminal ethyl group. The five-membered heterocyclic rings deviate only slightly from perfect planarity with the maximum deviation from the mean plane of the ring in molecule B being 0.032(2) Å for atom C(22). The ring in molecule A has a flattened envelope conformation puckered on atom Se(1), where Se(1) lies 0.204(1) Å from the mean plane defined by the other four ring atoms. As in the cases of **10a**, **10c**, and **13a**, the bond lengths and the ^{13}C NMR data indicate a significant dipolar character of the molecule.

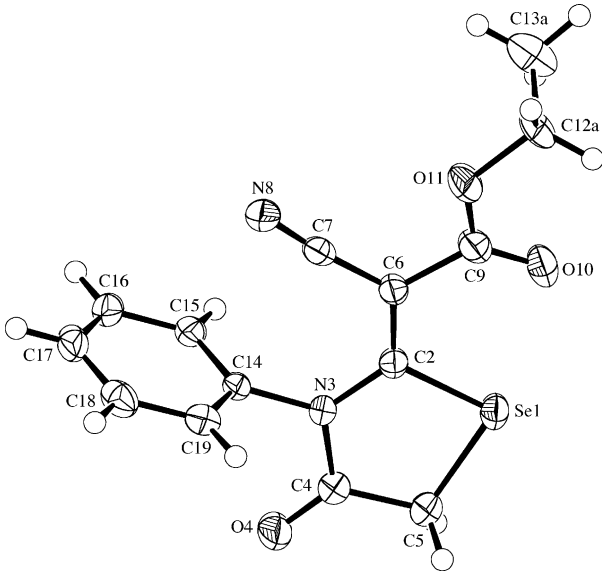


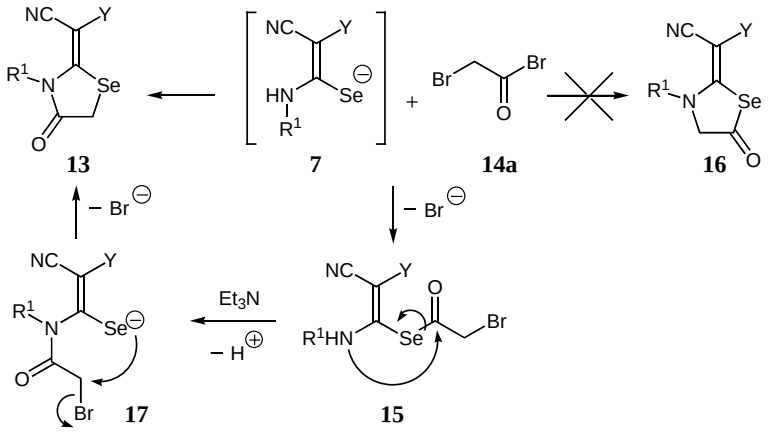
Figure 3. ORTEP plot[35] of the molecular structure of the major conformation of molecule A of **13k** (arbitrary numbering of atoms; 50% probability ellipsoids).

Treatment of the intermediates **7** with bromoacetyl bromide (**14a**) led to a surprising result. As the reaction between thioureas and acyl halides is known to give *S*-acylated isothioureas,[36] we expected that **7** and **14a** would give **15** by the reaction of the more nucleophilic Se-atom with the more electrophilic acyl C-atom (Scheme 3). Under the basic reaction conditions, the subsequent cyclization via nucleophilic substitution of bromide by the N-atom could lead to the 5-oxo-1,3-selenazolidine derivatives **16**, which are isomers of **13**. Mohareb,[37] Bukowski,[38] and more recently Metwally and coworkers,[39] described analogous reactions with isothiocyanates, which led to 1,3-thiazolidin-5-ones. On the other hand, Koketsu et al.[40] reported the synthesis of 1,3-selenazolidine-4-ones from selenourea and α-haloacyl halides. Although NMR analysis should differentiate clearly between the two isomeric structures, some doubts about the structures remain.

The reaction of **1a** with **6a** and **14a** under the usual conditions led to a single product in 85% yield, which was identified as **13a** by direct comparison with the product obtained from the reaction with **11a**. Analogously, only one product was formed in all the other reactions of **1** with **6a**,**b** and **14a**. By comparison of their ^{1}H and ^{13}C NMR spectra with those of **13a**, we attributed the structures **13b**, **13e**, **13f**, and **13g** to these products (Table 2). Furthermore, the product **13g** obtained from cyclohexyl isoselenocyanate, malononitrile (**6a**), and 2-bromoacetyl bromide (**14a**) was in all respects identical with **13g** formed in the reaction with methyl 2-chloroacetate. With 4-methylphenyl isoselenocyanate, **6a**, and 2-bromopropanoyl bromide (**14b**), **13i** was obtained in 63% yield (Table 2).

The unexpected formation of the 4-oxo-1,3-selenazolidine derivatives **13** in the reactions with 2-bromoacetyl bromide **14a** can be explained by the reaction mechanism shown in Scheme 3. The intermediate **15**, which is formed by the nucleophilic substitution of the acyl bromide of **14a** by the Se-atom of **7** undergoes a base catalyzed 1,3-acyl shift to give the rearranged intermediate **17**. Similar S→N migrations of the acetyl group are known and have been studied in depth kinetically[41] and described recently by Pihlaja and coworkers.[42] Finally, the Se-atom attacks the α-carbon atom of the amide group and forms the 1,3-selenazolidinone ring by displacing the bromide ion to give **13**.

Another goal of the present study was the synthesis of analogous 1,3-selenazolidin-4,5-diones. In the first instance, we tried to trap **7** with oxalyl chloride, but we did not succeed in obtaining the dioxo derivatives. Furthermore, all attempts to use diethyl oxalate or the recently described ethyl 2-chloro-oxoacetate[43] were also unsuccessful. In



Scheme 3.

addition, the oxidation of **13a** by selenium dioxide[44] failed to give the corresponding 1,3-selenazolidine-4,5-dione.

3. Conclusion

In conclusion, we have shown that malononitrile (**6a**) and alkyl 2-cyanoacetates (**6b**,**c**) react with isoselenocyanates **1** in DMF in the presence of excess triethylamine to give intermediates **7**, which react with 1,2-dibromoethane or α-halogenated acyl derivatives to give 1,3-selenazolidines **10** and 1,3-selenazolidin-4-ones **13**, respectively, in moderate to good yields. This one-pot reaction offers a convenient access to these selenium-containing five-membered heterocycles by starting with isoselenocyanates **1** as building blocks.

4. Experimental

4.1. General

Thin-layer chromatography (TLC): silica gel 60 F_{254} plates (0.25 mm; Merck). Column chromatography (CC): silica gel 60 (0.040–0.063 mm; Merck). Mp: Büchi B-540 apparatus in capillary tubes; uncorrected. IR Spectra: Perkin-Elmer-1600 FT-IR spectrophotometer; in KBr; absorptions in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) Spectra: Bruker ARX-300 instrument; in (D_6)DMSO unless otherwise stated; chemical shifts (δ) in ppm; couplig constants J in Hz. CI-MS: Finnigan SSQ-700 or MAT-90 instrument; NH_3 as carrier gas.

Starting materials. Malononitrile (**6a**) and all halogenated compounds are commercially available (Fluka). Isoselenocyanates (**1**) were prepared according to Barton's procedure[5] by starting from formamides. Formanilide and *N*-cyclohexylformamide were purchased (Fluka and Aldrich), *N*-(4-chlorophenyl)-, *N*-(4-bromophenyl)-, *N*-(4-fluorophenyl)-, and *N*-(4-methoxyphenyl)formamide were prepared from the respective anilines and 95% formic acid (Ref. 45). The solution was heated to reflux for 30 min and then evaporated to dryness in vacuo. The residue was dissolved in ether and washed with diluted acetic acid (5%), water, and aqueous $NaHCO_3$ (5%). The aqueous layer was extracted with ether, the combined organic extracts were dried over $MgSO_4$, and evaporated under reduced pressure. The crude products were purified by recrystallization in water.

General procedure for the preparation of 1,3-selenazolidine derivatives. A 25 mL round-bottom flask equipped with a magnetic stirrer and condenser was charged with a solution of malononitrile (**6a**; 73 mg, 1.1 mmol) in DMF (10 mL). Triethylamine (0.15 mL, 1.1 mmol) was added and the mixture was stirred for 30 min at rt. Isoselenocyanate (**1**; 1.1 mmol) was added and the mixture was stirred for 1 h at rt. Then, the α-halogenated compound (1.1 mmol) was added dropwise and the mixture was stirred for 4 h before being evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane–ethyl acetate (100/0–50/50) as eluant and recrystallized from ethyl acetate.

4.2. Preparation of 2-methylene-1,3-selenazolidines 10

4.2.1. 2-(3-Phenyl-1,3-selenazolidin-2-ylidene)malononitrile (10a). Yield: 187 mg (62%). Yellowish crystals. Mp 295–297 °C. IR: 2935w, 2205s, 2191s, 1594w, 1527s, 1492m, 1453w, 1432w, 1388m, 1310m, 1238w, 1220w, 1064w, 1057w, 759w, 691m. ^1H NMR: 3.49 (t, $J=7.1$ Hz, CH_2), 4.46 (t, $J=7.1$ Hz, CH_2), 7.31 (d-like, $J=8.2$ Hz, 2 arom. H), 7.46–7.51 (m, 3 arom. H). ^{13}C NMR: 22.2 (CH_2), 51.8 ($C(CN)_2$), 64.6 (CH_2), 112.0 (CN), 117.7 (CN), 126.4 (2CH), 129.8 (CH), 129.9 (2CH), 138.9 (C_{ar}), 171.9 (CNSe). ESI-MS: 298 (100, $[M(^{80}Se)+Na]^+$), 276 (22, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{12}H_9N_3Se$ (274.19): C 52.57, H 3.31, N 15.33; found: C 52.54, H 3.49, N 15.41.

Suitable crystals for the X-ray crystal structure determination were grown from CH_2Cl_2 by slow evaporation of the solvent.

4.2.2. 2-[3-(4-Fluorophenyl)-1,3-selenazolidin-2-ylidene]malononitrile (10b). Yield: 174 mg (54%). White crystals. Mp 193–195 °C. IR: 2985w, 2202s, 2191s, 1535s, 1505s, 1453w, 1394w, 1319w, 1236w, 1214m, 1054w, 846w. ^1H NMR: 3.54 (t, $J=7.1$ Hz, CH_2), 4.42 (t, $J=7.1$ Hz, CH_2), 7.27 (t-like, $J=8.9$ Hz, 2 arom. H), 7.50 (dd-like, $J=9.0, 4.9$ Hz, 2 arom. H). ^{13}C NMR: 23.6 (CH_2), 51.1 ($C(CN)_2$), 65.5 (CH_2), 113.1 (CN), 117.4 (d, $^2J_{CF}=22$ Hz,

2CH), 118.7 (CN), 129.7 (d, $^3J_{CF}$=9 Hz, 2CH), 141.9 (C_{ar}), 167.4 (d, $^1J_{CF}$=248 Hz, CF), 173.7 (CNSe). CI-MS: 311 (100, $[M(^{80}Se)+NH_4]^+$), 294 (7, $[M(^{80}Se)+1]^+$).

4.2.3. 2-[3-(4-Methoxyphenyl)-1,3-selenazolidin-2-ylidene]malononitrile (10c). Yield: 205 mg (61%). Yellowish crystals. Mp 187–189 °C. IR: 2939w, 2839w, 2203s, 2190s, 1607w, 1587w, 1539s, 1509w, 1474m, 1443w, 1391s, 1319m, 1299m, 1246s, 1171w, 1109w, 1056w, 1026m, 985w, 864w, 831m, 803w. ^{1}H NMR: 3.47 (t, J=7.1 Hz, CH_2), 3.83 (s, CH_3), 4.40 (t, J=7.1 Hz, CH_2), 6.96, 7.21 (AA′BB′, J_{AB}=8.2 Hz, 4 arom. H). ^{13}C NMR: 22.0 (CH_2), 51.2 (C(CN)$_2$), 55.5 (CH_3O), 64.8 (CH_2), 112.2 (CN), 115.0 (2CH), 118.0 (CN), 127.8 (2CH), 131.4 (C_{ar}), 160.5 (C_{ar}), 172.2 (CNSe). CI-MS: 323 (100, $[M(^{80}Se)+NH_4]^+$), 306 (8, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{13}H_{11}N_3OSe$ (304.21): C 51.33, H 3.64, N 13.81; found: C 51.22, H 3.62, N 13.77.

Suitable crystals for the X-ray crystal structure determination were grown from CH_2Cl_2 by slow evaporation of the solvent.

4.2.4. 2-(3-Cyclohexyl-1,3-selenazolidin-2-ylidene)malononitrile (10d). Yield: 130 mg (42%). Yellowish crystals. Mp 187–189 °C. IR: 2937s, 2850m, 2202s, 2188s, 1527s, 1457m, 1396w, 1372m, 1350w, 1308w, 1241w, 1192w, 1124w, 1010w, 982w, 893w, 879w, 823w. ^{1}H NMR: 1.40–1.52 (m, 4H), 1.60–1.70 (m, 2H), 1.75–1.98 (m, 4H), 3.26 (t, J=7.1 Hz, CH_2), 4.13 (t, J=7.1 Hz, CH_2) 4.35–4.45 (m, CH). ^{13}C NMR: 21.7 (CH_2), 24.8 (2CH_2), 24.9 (CH_2), 31.4 (2CH_2), 48.0 (C(CN)$_2$), 55.6 (CH), 59.4 (CH_2), 115.1 (CN), 118.3 (CN), 171.4 (CNSe). CI-MS: 299 (100, $[M(^{80}Se)+NH_4]^+$), 282 (7, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{12}H_{15}N_3Se$ (280.23): C 51.43, H 5.40, N 15.00; found: C 51.33, H 5.45, N 14.88.

4.2.5. Ethyl 2-cyano-2-(3-phenyl-1,3-selenazolidin-2-ylidene)acetate (10e). Yield: 110 mg (31%). Yellowish crystals. Mp 151–153 °C. IR: 2969w, 2195s, 1668s, 1595w, 1512s, 1458m, 1431w, 1392m, 1367w, 1283s, 1254w, 1187w, 1172m, 1023w, 921w, 763m, 695m. ^{1}H NMR: 1.27 (t, J=7.1 Hz, CH_3), 3.10 (t, J=7.2 Hz, CH_2), 4.21 (q, J=7.2 Hz, CH_2), 4.28 (t, J=7.1 Hz, CH_2), 7.26 (d-like, J=8.2 Hz, 2 arom. H), 7.40–7.49 (m, 3 arom. H). ^{13}C NMR: 14.3 (CH_3), 20.0 (CH_2), 61.1 (CH_2), 62.5 (CH_2), 73.3 (C(CN)), 114.6 (CN), 126.5 (2CH), 128.9 (CH), 129.6 (2CH), 141.3 (C_{ar}), 167.6 (CO_2), 171.6 (CNSe). CI-MS: 340 (100, $[M(^{80}Se)+NH_4]^+$), 323 (53, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{14}H_{14}N_2O_2Se$ (321.24): C 52.35, H 4.39, N 8.72; found: C 51.98, H 4.46, N 8.70.

4.2.6. Ethyl 2-cyano-2-[3-(4-fluorophenyl)-1,3-selenazolidin-2-ylidene]acetate (10f). Yield: 135 mg (36%). Yellowish crystals. Mp 162–164 °C. IR: 3048w, 2976m, 2878w, 2190s, 1671s, 1603m, 1510s, 1454s, 1432m, 1387s, 1365m, 1288s, 1234m, 1221m, 1191w, 1171w, 1117s, 1057w, 1029w, 995m, 918m, 845s, 767s, 735w, 717w. ^{1}H NMR: 1.28 (t, J=7.1 Hz, CH_3), 3.11 (t, J=7.2 Hz, CH_2), 4.19–4.27 (m, 2CH_2), 7.11–7.17 (m, 2 arom. H), 7.23–7.29 (m, 2 arom. H). ^{13}C NMR: 14.3 (CH_3), 19.9 (CH_2), 61.2 (CH_2), 62.5 (CH_2), 73.1 (C(CN)), 114.5 (CN), 116.7 (d, $^2J_{CF}$=23 Hz, 2CH), 128.4 (d, $^3J_{CF}$=9 Hz, 2CH), 137.2 (C_{ar}), 163.4 (d, $^1J_{CF}$=256 Hz, CF), 167.5 (CO_2), 171.9 (CNSe). CI-MS: 358 (100, $[M(^{80}Se)+NH_4]^+$), 341 (33, $[M(^{80}Se)+1]^+$).

4.2.7. Ethyl 2-cyano-2-[3-(4-methylphenyl)-1,3-selenazolidin-2-ylidene)acetate (10g). Yield: 115 mg (31%). Yellowish crystals. Mp 144–146 °C. IR: 2982w, 2918w, 2198s, 1669s, 1511s, 1392m, 1370w, 1287s, 1192w, 1170m, 1129s, 1058w, 1029w, 921w, 766m. ^{1}H NMR: 1.27 (t, J=7.1 Hz, CH_3), 2.39 (s, CH_3), 3.09 (t, J=7.2 Hz, CH_2), 4.18–4.28 (m, 2CH_2), 7.15, 7.25 (AA′BB′, J_{AB}=8.1 Hz, 4 arom. H). ^{13}C NMR: 14.3 (CH_3), 19.9 (CH_2), 21.2 (CH_3), 61.1 (CH_2), 62.6 (CH_2), 73.1 (C(CN)), 114.6 (CN), 126.2 (2CH), 130.2 (2CH), 138.8 (C_{ar}), 139.0 (C_{ar}), 167.7 (CO_2), 171.6 (CNSe). CI-MS: 354 (100, $[M(^{80}Se)+NH_4]^+$), 337 (43, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{15}H_{16}N_2O_2Se$ (335.26): C 53.74, H 4.81, N 8.36; found: C 53.60, H 5.01, N 8.43.

4.3. Preparation of 2-methylene-1,3-selenazolidin-4-ones 13

4.3.1. 2-(4-Oxo-3-phenyl-1,3-selenazolidin-2-ylidene)-malononitrile (13a). Yield: 235–270 mg (74–85%). Colorless crystals. Mp 265–267 °C. IR: 2985w, 2216s, 1733s, 1596w, 1522s, 1493m, 1368m, 1223s, 851w, 758w, 698m. ^{1}H NMR: 4.39 (s, CH_2), 7.43 (d-like, J=7.9 Hz, 2 arom. H), 7.50–7.60 (m, 3 arom. H). ^{13}C NMR: 29.1 (CH_2), 56.7 (C(CN)$_2$), 110.1 (CN), 115.1 (CN), 128.9 (2CH), 129.4 (2CH), 130.8 (CH), 134.8 (C_{ar}), 173.3, 173.9 (CO, CNSe). CI-MS: 307 (100, $[M(^{80}Se)+NH_4]^+$); CI-MS (*i*-butane): 290 (100, $[M(^{80}Se)+1]^+$). Anal. Calcd for $C_{12}H_7N_3OSe$ (288.16): C 50.02, H 2.45, N 14.58; found: C 49.98, H 2.60, N 14.34.

Suitable crystals for the X-ray crystal structure determination were grown from CH_2Cl_2 by slow evaporation of the solvent.

4.3.2. 2-[3-(4-Fluorophenyl)-4-oxo-1,3-selenazolidin-2-ylidene]malononitrile (13b). Yield: 280 mg (83%). Colorless crystals. Mp 244–246 °C. IR: 2995w, 2982w, 2219s, 2210s, 1737s, 1600w, 1528s, 1516s, 1507s, 1373m, 1222s, 1208s, 1161w, 858w, 826w, 791w. ^{1}H NMR: 4.65 (s, CH_2), 7.67 (t-like, J=9 Hz, 2 arom. H), 7.49–7.59 (m, 2 arom. H). ^{13}C NMR: 29.0 (CH_2), 56.7 (C(CN)$_2$), 110.2 (CN), 114.9 (CN), 116.4 (d, $^2J_{CF}$=23 Hz, 2CH), 131.1 (C_{ar}), 131.5 (d, $^3J_{CF}$=9 Hz, 2CH), 163.2 (d, $^1J_{CF}$=248 Hz, CF), 173.7, 173.9 (CO, CNSe). CI-MS: 325 (100, $[M(^{80}Se)+NH_4]^+$). Anal. Calcd for $C_{12}H_6N_3OSeF$ (306.16): C 47.08, H 1.98, N 13.73; found: C 47.01, H 2.21, N 14.02.

4.3.3. 2-[3-(4-Chlorophenyl)-4-oxo-1,3-selenazolidin-2-ylidene]malononitrile (13c). Yield: 242 mg (68%). Colorless crystals. Mp 245–247 °C. IR: 2947w, 2223m, 2213m, 1733s, 1529s, 1485m, 1404w, 1370m, 1219s, 1172w, 1084w, 1015w, 845w, 813w, 722w. ^{1}H NMR: 4.33 (s, CH_2), 7.45, 7.58 (AA′BB′, J_{AB}=8.7 Hz, 4 arom. H). ^{13}C NMR: 29.1 (CH_2), 56.7 (C(CN)$_2$), 110.3 (CN), 114.9 (CN), 129.5 (2CH), 131.0 (2CH), 133.7 (C_{ar}), 135.5 (C_{ar}), 173.4, 173.8 (CO, CNSe). CI-MS: 341 (100, $[M(^{80}Se, ^{35}Cl)+NH_4]^+$). Anal. Calcd for $C_{12}H_6N_3OSeCl$ (322.61): C 44.68, H 1.87, N 13.03; found: C 44.75, H 2.10, N 12.92.

4.3.4. 2-[3-(4-Bromophenyl)-4-oxo-1,3-selenazolidin-2-ylidene]malononitrile (13d). Yield: 351–383 mg (87–95%). Colorless crystals. Mp 247–249 °C. IR: 2947w, 2222s, 2211s, 1736s, 1585w, 1526s, 1481s, 1399w, 1371m, 1218s, 1171m, 1066w, 1012m, 842m, 809m, 711w. ^{1}H NMR: 4.67 (s, CH_2), 7.71, 8.05 (AA′BB′, J_{AB}=8.7 Hz, 4 arom. H). ^{13}C NMR: 29.1 (CH_2), 56.8 ($C(CN)_2$), 110.3 (CN), 114.9 (CN), 129.5 (2CH), 131.0 (2CH), 133.7 (C_{ar}), 135.6 (C_{ar}), 173.4, 173.8 (CO, CNSe). CI-MS: 387 (79, [M(^{80}Se, ^{81}Br)+NH_4]$^+$), 385 (100, [M(^{80}Se, ^{79}Br)+NH_4]$^+$). Anal. Calcd for $C_{12}H_6N_3OSeBr$ (367.07): C 39.27, H 1.65, N 11.45; found: C 39.44, H 1.86, N 11.49.

4.3.5. 2-[3-(4-Methoxyphenyl)-4-oxo-1,3-selenazolidin-2-ylidene]malononitrile (13e). Yield: 259 mg (74%). Orange crystals. Mp 193–195 °C. IR: 2945w, 2216m, 2210m, 1752m, 1606w, 1523s, 1508s, 1369m, 1303w, 1255m, 1212m, 1015w, 822w. ^{1}H NMR: 3.83 (s, CH_3O), 4.38 (s, CH_2), 7.07, 7.35 (AA′BB′, J_{AB}=8.0 Hz, 4 arom. H). ^{13}C NMR: 28.9 (CH_2), 55.4 (CH_3), 56.6 ($C(CN)_2$), 110.2 (CN), 114.6 (2CH), 115.1 (CN), 127.3 (C_{ar}), 130.2 (2CH), 132.4 (C_{ar}), 160.8 (CO), 173.9 (CNSe). CI-MS: 337 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{13}H_9N_3O_2Se$ (318.20): C 49.07, H 2.85, N 13.21; found: C 48.84, H 3.01, N 13.57.

4.3.6. 2-[3-(2,6-Dimethylphenyl)-4-oxo-1,3-selenazolidin-2-ylidene]malononitrile (13f). Yield: 289 mg (83%). Colorless crystals. Mp 296–298 °C. IR: 3000w, 2944w, 2217s, 2206s, 1742s, 1517s, 1474m, 1392w, 1352s, 1217m, 1205s, 1183m, 1151m, 1035w, 837w, 785m, 736w. ^{1}H NMR: 2.16 (s, $2CH_3$), 4.72 (s, CH_2), 7.28 (d, J=7.8 Hz, 2 arom. H), 7.44 (t, J=7.9 Hz, 1 arom. H). ^{13}C NMR: 16.7 ($2CH_3$), 28.7 (CH_2), 57.1 ($C(CN)_2$), 109.3 (CN), 114.7 (CN), 128.3 (2CH), 130.9 (CH), 132.4 (C_{ar}), 136.5 ($2C_{ar}$), 171.5, 173.3 (CO, CNSe). CI-MS: 335 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{14}H_{11}N_3OSe$ (316.22): C 53.18, H 3.51, N 13.29; found: C 53.18, H 3.58, N 13.03.

4.3.7. 2-(3-Cyclohexyl-4-oxo-1,3-selenazolidin-2-ylidene)-malononitrile (13g). Yield: 107–110 mg (33–34%). Brownish crystals. Mp 123–125 °C. IR: 2996w, 2942s, 2855m, 2217m, 2206m, 1738s, 1701w, 1573m, 1507s, 1448m, 1400w, 1335m, 1254w, 1202m, 1193m, 1179m, 1141m, 1052w, 980w, 895w, 696m. ^{1}H NMR: 1.23–1.54 (m, 4H), 1.71–1.90 (m, 4H), 2.27–2.40 (m, 2H), 3.98 (s, CH_2), 4.51–4.61 (m, CH). ^{13}C NMR: 24.4 (CH_2), 24.8 ($2CH_2$), 28.7 ($2CH_2$), 32.2 (CH), 59.4 ($C(CN)_2$), 61.7 (CH), 112.0 (CN), 114.3 (CN), 170.1 (CO), 173.5 (CNSe). CI-MS: 313 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{12}H_{13}N_3OSe$ (294.21): C 48.99, H 4.45, N 14.28; found: C 50.23, H 4.54, N 14.40.

4.3.8. 2-(5-Methyl-4-oxo-3-phenyl-1,3-selenazolidin-2-ylidene)malononitrile (13h). Yield: 210 mg (63%). White crystals. Mp 173–175 °C. IR: 2961w, 2217m, 2202m, 1735s, 1593w, 1518s, 1493m, 1363m, 1266w, 1222s, 1069w, 996w, 940w, 763w, 728w, 697w. ^{1}H NMR: 1.94 (d, J=7.3 Hz, CH_3), 4.55 (q, J=7.3 Hz, CH), 7.26 (d, J=8.1 Hz, 2 arom. H), 7.54–7.63 (m, 3 arom. H). ^{13}C NMR: 19.4 (CH_3), 38.7 (CH), 61.6 ($C(CN)_2$), 109.3 (CN), 113.8 (CN), 128.6 (2CH), 130.1 (CH), 131.6 (2CH), 134.3 (C_{ar}), 167.4 (CO), 176.3 (CNSe). CI-MS: 321 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{13}H_9N_3OSe$ (302.19): C 51.67, H 3.00, N 13.91; found: C 51.50, H 4.10, N 14.15.

4.3.9. 2-[5-Methyl-3-(4-methylphenyl)-4-oxo-1,3-selenazolidin-2-ylidene)malononitrile (13i). Yield: 220–310 mg (63–89%). White crystals. Mp 223–225 °C. IR: 2933w, 2216m, 2208m, 1741s, 1521s, 1216s, 1160w, 1071w, 996w, 814w, 771w, 734w. ^{1}H NMR: 1.92 (d, J=7.3 Hz, CH_3), 2.44 (s, CH_3), 4.53 (q, J=7.2 Hz, CH), 7.10, 7.35 (AA′BB′, J_{AB}=8.1 Hz, 4 arom. H). ^{13}C NMR: 19.4 (CH_3), 21.4 (CH_3), 38.6 (CH), 61.6 ($C(CN)_2$), 109.3 (CN), 113.9 (CN), 128.2 (2CH), 130.7 (2CH), 131.6 (C_{ar}), 142.2 (C_{ar}), 167.5 (CO), 176.4 (CNSe). CI-MS: 335 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{14}H_{11}N_3OSe$ (316.22): C 53.18, H 3.51, N 13.29; found: C 53.31, H 43.59, N 13.30.

4.3.10. Ethyl 2-cyano-2-(4-oxo-3-phenyl-1,3-selenazolidin-2-ylidene)acetate (13k). Yield: 236 mg (64%). Brownish crystals. Mp 189–191 °C. IR: 2982w, 2936w, 2206s, 1739s, 1679s, 1595w, 1511s, 1496s, 1367w, 1355m, 1290s, 1210s, 1176s, 1167s, 1119s, 1016w, 846w, 768w, 696m. ^{1}H NMR: 1.31 (t, J=7.2 Hz, CH_3), 3.83 (s, CH_2), 4.29 (q, J=7.1 Hz, CH_2O), 7.26 (d, J=8.2 Hz, 2 arom. H), 7.52–7.62 (m, 3 arom. H). ^{13}C NMR: 14.1 (CH_3), 24.2 (CH_2), 62.2 (CH_2), 81.4 (C(CN)), 111.7 (CN), 128.7 (2CH), 129.8 (2CH), 131.0 (CH), 135.8 (C_{ar}), 166.4, 168.1 (CO, CO_2), 174.6 (CNSe). CI-MS: 354 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{14}H_{12}N_2O_3Se$ (335.22): C 50.16, H 3.61, N 8.36; found: C 50.01, H 3.93, N 8.04.

Suitable crystals for the X-ray crystal structure determination were grown from CH_2Cl_2 by slow evaporation of the solvent.

4.3.11. Ethyl 2-[3-(4-bromophenyl)-4-oxo-1,3-selenazolidin-2-ylidene]-2-cyanoacetate (13l). Yield: 392 mg (86%). Pale yellow crystals. Mp 191–193 °C. IR: 2984w, 2206s, 1743s, 1678s, 1509s, 1498s, 1486s, 1360m, 1292s, 1210m, 1176s, 1165s, 1129m, 1066w, 1013m, 845w, 834w, 821w, 770w, 714w. ^{1}H NMR: 1.31 (t, J=7.2 Hz, CH_3), 3.81 (s, CH_2), 4.29 (q, J=7.1 Hz, CH_2O), 7.12, 7.67 (AA′BB′, J_{AB}=8.3 Hz, 4 arom. H). ^{13}C NMR: 14.0 (CH_3), 24.1 (CH_2), 62.3 (CH_2), 81.6 (C(CN)), 111.9 (CN), 125.3 (C_{ar}), 130.3 (2CH), 133.1 (2CH), 134.7 (C_{ar}), 166.2, 167.4 (CO, CO_2), 174.3 (CNSe). CI-MS: 434 (80, [M(^{80}Se, ^{81}Br)+NH_4]$^+$), 432 (100, [M(^{80}Se, ^{79}Br)+NH_4]$^+$). Anal. Calcd for $C_{14}H_{11}N_2O_3SeBr$ (414.12): C 40.60, H 2.68, N 6.76; found: C 40.71, H 2.91, N 6.68.

4.3.12. Ethyl 2-cyano-2-[4-oxo-3-(4-methylphenyl)-1,3-selenazolidin-2-ylidene)acetate (13m). Yield: 300 mg (78%). Pale yellow crystals. Mp 187–189 °C. IR: 2982w, 2930w, 2204s, 1740s, 1679s, 1505s, 1359m, 1291m, 1211s, 1180s, 1169s, 1117m, 1016w, 846w, 770w, 716w. ^{1}H NMR: 1.30 (t, J=7.2 Hz, CH_3), 2.44 (s, CH_3), 3.81 (s, CH_2), 4.28 (q, J=7.1 Hz, CH_2O), 7.12, 7.33 (AA′BB′, J_{AB}=8.3 Hz, 4 arom. H). ^{13}C NMR: 14.0 (CH_3), 21.4 (CH_3), 24.2 (CH_2), 62.2 (CH_2), 81.3 (C(CN)), 111.8 (CN), 128.4 (2CH), 130.5 (2CH), 133.1 (C_{ar}), 141.3 (C_{ar}), 166.5, 168.4 (CO, CO_2), 174.7 (CNSe). CI-MS: 368 (100, [M(^{80}Se)+NH_4]$^+$). Anal. Calcd for $C_{15}H_{14}N_2O_3Se$ (349.25): C 51.59, H 4.04, N 8.02; found: C 52.06, H 4.38, N 7.94.

4.4. X-ray crystal-structure determination of 10a, 10c, 13a, and 13k

All measurements were performed on a Nonius KappaCCD area-diffractometer[46] using graphite-monochromated Mo K_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below[47] and views of the molecules are shown in Figures 1–3. Data reduction was performed with HKL Denzo and Scalepack.[48] The intensities were corrected for Lorentz and polarization effects, and absorption corrections based on the multi-scan method[49] were applied. Equivalent reflections, other than the Friedel pairs in **13a**, were merged. The structures were solved by direct methods using SIR92,[50] which revealed the positions of all non-H-atoms. In the case of **10a**, the two CH_2 groups in the five-membered ring are disordered over two conformations. Two sets of positions were defined for the atoms of these groups and the site occupation factor of the major conformation refined to 0.51(1). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms. In the case of **13k**, there are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON,[51] but none could be found. The terminal ethyl group in one molecule is disordered over two conformations. Two sets of overlapping positions were defined for the atoms of this group and the site occupation factor of the major conformation of this group refined to 0.58(2). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighboring atoms within and between each conformation of the disordered ethyl group were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinement of each structures was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2-F_c^2)^2$. Corrections for secondary extinction were applied in the cases of **10c**, **13a**, and **13k**. In **10a** and in **10c**, one reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement. Refinement of the absolute structure parameter[52] of **13a** yielded a value of −0.021(7), which confidently confirms that the refined coordinates represent the true absolute structure. Neutral atom scattering factors for non-H-atoms were taken from,[53] and the scattering factors for H-atoms were taken from Ref. 54. Anomalous dispersion effects were included in F_c;[55] the values for f' and f'' were those of Ref. 56. The values of the mass attenuation coefficients are those of Ref. 57. All calculations were performed using the SHELXL97[58] program.

Crystal data for **10a**. $C_{12}H_9N_3Se$, $M=274.12$, pale yellow, prism, crystal dimensions $0.07\times0.12\times0.20$ mm, monoclinic, space group $P2_1/c$, $Z=4$, reflections for cell determination 22243, 2θ range for cell determination 4–60°, $a=7.5986(1)$ Å, $b=16.6005(3)$ Å, $c=8.8620(1)$ Å, $\beta=94.199(1)°$, $V=1114.86(3)$ Å^3, $T=160$ K, $D_X=1.633$ g cm^{-3}, μ(Mo K_α)$=3.339$ mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}=60°$, transmission factors (min; max) 0.542; 0.792, total reflections measured 33680, symmetry independent reflections 3253, reflections with $I>2\sigma(I)$ 2814, reflections used in refinement 3252, parameters refined 164; restraints 3, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0267$, $wR(F^2)$ [all data]$=0.0647$ ($w=[\sigma^2(F_o^2)+(0.0275P)^2+0.5667P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.058, final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) $=0.41$; -0.73 e Å^{-3}.

Crystal data for **10c**. $C_{13}H_{11}N_3OSe$, $M=304.15$, pale yellow, prism, crystal dimensions $0.10\times0.23\times0.28$ mm, triclinic, space group $P\bar{1}$, $Z=2$, reflections for cell determination 13000, 2θ range for cell determination 4–60°, $a=8.4715(2)$ Å, $b=8.6795(2)$ Å, $c=8.8012(2)$ Å, $\alpha=98.756(2)$, $\beta=91.399(2)°$, $\gamma=100.280(1)$, $V=628.44(3)$ Å^3, $T=160$ K, $D_X=1.607$ g cm^{-3}, μ(Mo K_α)$=2.976$ mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}=60°$, transmission factors (min; max) 0.489; 0.751, total reflections measured 18210, symmetry independent reflections 3671, reflections with $I>2\sigma(I)$ 3252, reflections used in refinement 3670, parameters refined 165; $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0326$, $wR(F^2)$ [all data]$=0.0838$ ($w=[\sigma^2(F_o^2)+(0.0458P)^2+0.1693P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.058, secondary extinction coefficient 0.012(2), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)$=0.74$; -0.95 e Å^{-3}.

Crystal data for **13a**. $C_{12}H_7N_3OSe$, $M=288.11$, colorless, needle, crystal dimensions $0.10\times0.10\times0.28$ mm, monoclinic, space group Cc, $Z=4$, reflections for cell determination 9429, 2θ range for cell determination 4–60°, $a=17.0737(4)$ Å, $b=9.5587(2)$ Å, $c=7.0931(2)$ Å, $\beta=104.623(1)°$, $V=1120.11(5)$ Å^3, $T=160$ K, $D_X=1.708$ g cm^{-3}, μ(Mo K_α)$=3.335$ mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}=60°$, transmission factors (min; max) 0.508; 0.723, total reflections measured 14521, symmetry independent reflections 3197, reflections with $I>2\sigma(I)$ 3084, reflections used in refinement 3197, parameters refined 155; restraints 2, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0236$, $wR(F^2)$ [all data]$=0.0544$ ($w=[\sigma^2(F_o^2)+(0.0253P)^2+0.7032P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.046, secondary extinction coefficient 0.0064(5), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)$=0.30$; -0.46 e Å^{-3}.

Crystal data for **13k**. $C_{14}H_{12}N_2O_3Se$, $M=335.16$, yellow, prism, crystal dimensions $0.10\times0.22\times0.25$ mm, monoclinic, space group $P2_1/c$, $Z=8$, reflections for cell determination 89915, 2θ range for cell determination 4–55°, $a=9.6396(1)$ Å, $b=12.9321(2)$ Å, $c=21.8547(3)$ Å, $\beta=94.4025(8)°$, $V=2716.37(6)$ Å^3, $T=160$ K, $D_X=1.639$ g cm^{-3}, μ(Mo K_α)$=2.771$ mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}=55°$, transmission factors (min; max) 0.590; 0.761, total reflections measured 55029, symmetry independent reflections 6222, reflections with $I>2\sigma(I)$ 5276, reflections used in refinement 6222, parameters refined 384; restraints 39, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0305$, $wR(F^2)$ [all data]$=0.0712$ ($w=[\sigma^2(F_o^2)+(0.0288P)^2+2.26P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.046, secondary

extinction coefficient 0.0012(2), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)=0.60; −0.49 e Å^{-3}.

Acknowledgements

We thank the analytical units of our institute for spectra and analyses and Mr. B. Bürgi for his assistance with the determination of the crystal structures. Financial support of this work by the Dr. Helmut Legerlotz-Foundation and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

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Synthesis of conjugated 2,7-bis(trimethylsilylethynyl)-(phenylethynyl)$_n$fluoren-9-one and 9-(*p*-methoxyphenyl)-9-methyl derivatives: optical properties

J. Gonzalo Rodríguez,[a,*] J. Luis Tejedor,[a] Teresa La Parra[a] and Cristina Díaz[b]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain*
[b]*Departamento de Química Física, Facultad de Ciencias, Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain*

Received 4 November 2005; revised 12 January 2006; accepted 17 January 2006

Available online 13 February 2006

Abstract—2,7-Substituted 9-fluorenones and 9,9-disubstituted fluorene have been synthesized and their fluorescence properties analyzed. The synthesis of conjugated 2,7-bis(trimethylsilylethynyl)-(phenylethynyl)$_n$fluoren-9-one (or the 9-(*p*-methoxyphenyl)-9-methyl) structures was carried out by the heterocoupling reaction between the 2,7-di(halo)fluoren-9-one (or 2,7-dibromo-9-(*p*-methoxyphenyl)-9-methylfluorene) and *p*-trimethylsilylethynyl(phenylethynyl)$_n$ ($n=1,2$), catalyzed by the dichloro bis(triphenylphosphine)palladium and cuprous iodide system, in a divergent synthesis.The π-extended conjugated compounds exhibit fluorescence radiation emission (blue light-emitting), with important quantum yield for the 9-(*p*-methoxyphenyl)-9-methyl-2,7-bis(trimethylsilylethynyl)-(phenylethynyl)$_n$fluorenes which increases with the conjugation.
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1. Introduction

In the last decade the research on the synthesis of carbon-rich organic and organometallic compounds for the widespread applications in the field of materials science as remarkably increased.[1]

In this context, the use of π-conjugated rigid fluorenyl chromophores and their derivatives offers exciting perspectives for the design of new molecular oligomeric and polymeric materials for various optoelectronic applications.[2] The fluorene ring has been used to prepare conjugated 2,7- and 9-one or 9,9-disubstituted compounds because the conjugated ring exhibits fluorescence radiation emission (fluorene, Φ, 0.80 in cyclohexane).[3]

Synthesis of conjugated co-polymers including fluorenyl-acetylene–arylidene,[4] and a family of poly(2,7-diethynyl)-9,9-disubstituted fluorenes,[5] showing electroluminescent properties, have been reported.

Polyfluorenes (PFs) are a class of conjugated polymers, which are used as the blue light-emitting diodes (PLEDs).[6] The PFs exhibit high photoluminescence (PL) efficiency, good charge transport and thermal stability by chemical modification and copolymerization. Moreover, as a host material, the PFs can enable full color (blue, green, and red) via energy transfer, to longer wavelength emitters in blends with other conjugated polymers with phosphorescent dyes.[7]

However, the presence of the carbonyl group in fluoren-9-one considerably stabilizes the ring system but decreases the quantum yield of the fluorescent emission (Φ, 0.02 in dichloromethane). Thus, the PFs structure suffers photo-oxidation in the solid state in short times giving 9-fluorenone keto defects, which show guest emitters behaviour,[8] that produces an important decreasing in the fluorescence quantum yield.[9] Some key constitutional aspects have been considered.[10]

Moreover, the 2,7-disubstituted fluoren-9-one derivatives can present electrical and nonlinear optical properties.[11]

On the other hand, substituent derivatization at the C-9 position of the monomeric fluorenes offers the prospect of controlling polymer properties such as solubility, emission wavelengths, processability, and potential interchain interactions in films.[1]

Keywords: 2,7-Di(ethynylphenyl)$_x$fluoren-9-one; 9,9-Disubstituted fluorene; *p*-(Trimethylsilyl)phenylethynyl; π-Extended conjugation; Fluorescence; Sonogashira reaction.
* Corresponding author. Tel.: +34 914974715; fax: +34 914973966; e-mail: gonzalo.rodriguez@uam.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.058

We report the synthesis of the 2,7-bis(trimethylsilylethynyl)-fluoren-9-one and their 9,9-disubstituted conjugated compounds, to verify the effect of the chains on the fluorescence emission.

2. Results and discussion

A relevant starting unit with synthetic versatility to prepare oligomeric fluorenone structures including the fluoren-9-one ring was the 2,7-di(halo)fluoren-9-one (Br, **1** or I, **3**). Compound **1** was obtained by treatment of 2,7-dibromofluorene with chromium oxide in anhydrous acetic acid at room temperature, in practically quantitative yield, Scheme 1. The more active 2,7-diiodofluoren-9-one (**3**) has been obtained by direct fluorene iodination followed by chromic oxidation.[12] We have synthesized the diiodo **3** from 2,7-dinitrofluoren-9-one, by reduction with stannous chloride in ethyl acetate, to 2,7-diaminofluoren-9-one (**2**),[13] as a brown solid, in excellent yield (97%). Finally **2** was treated with sodium nitrite in concentrated sulfuric acid to prepare the double diazonium salt, which by reaction with potassium iodide gives 2,7-diiodofluoren-9-one (**3**), yellow solid, in good yield (62%), Scheme 1.

No fluorescence radiation emission was observed for the 2,7-di(halo)fluoren-9-one (**1** or **3**), due to the presence of heavy-atoms on the 2,7-positions and the 9-carbonyl group. In this way, were prepared the 2,7-dibromo derivatives without the 9-carbonyl group by treatment of **1** with methylmagnesium iodide to give the 9-hydroxy-9-methyl **4** or the elimination product 9-methylidene **5**, which do not emit fluorescence radiation. The 9-(*p*-methoxyphenyl)-9-methyl compound **6** was obtained by sulfuric acid catalyst treatment of the methylidene compound **5** with anisole, Scheme 1. Compound **6** shows very low fluorescence quantum yield, Table 1. All these data accord well with that reported in advance for aromatic rings containing heavy-atoms.[14]

On the other hand, to prove the effect of the conjugated carbonyl group on the fluorescence emission, the conjugated 2,7-bis(trimethylsilylethynyl)fluoren-9-one (**7**),[2,15] and their 9-(*p*-methoxyphenyl)-9-methyl derivative **9**, were obtained. The heterocoupling between trimethylsilylacetylene and 2,7-dibromofluoren-9-one (**1**) (or **6**) in triethylamine at 50 °C, catalyzed by the palladium–copper system, gives a pale-yellow solid in good yield (78%), (or **9**, a white solid, 94% yield). Scheme 2.

Catalytic deprotection of the trimethylsilylethynyl group in compound **7** (or **9**) was carried out with potassium carbonate in tetrahydrofuran–methanol (4/1), at room temperature, giving 2,7-diethynylfluoren-9-one (**8**),[2,16] pale-yellow solid in 98% yield, (or **10**, white solid in quantitative yield).

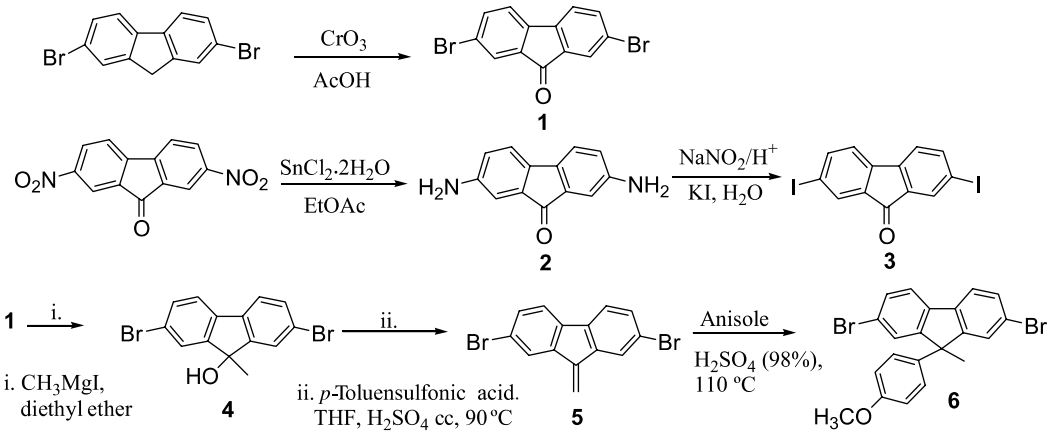
Compounds **7**–**10** exhibit fluorescence radiation emission in dichloromethane, the 9,9-disubstituted **9** and **10** show a very important quantum yield, Table 1.

Afterwards, the more extended conjugated 2,7-di[(*p*-trimethylsilylethynylphenyl)ethynyl]fluoren-9-one (**14**) was synthesized by double heterocoupling reaction between *p*-(trimethylsilylethynyl)phenylacetylene (**13**) and 2,7-diiodo derivative **3** (2,7-dibromofluoren-9-one, fails), in triethylamine at 50 °C, catalyzed by the palladium–copper system. Compound **14** was obtained as an orange solid, in good yield (73%), Scheme 3.

The monoacetylene **13** was obtained by specific deprotection[17] of the propargylic compound **12** with powdered sodium hydroxide in dry toluene at reflux temperature, as a white solid in quantitative yield.

The specific method for deprotection of 2-methyl-3-butyn-2-ol in dry toluene, in presence of the trimethylsilyl protector group, requires rigorous dry conditions. There are many references for trimethylsilyl deprotection with different bases such as aqueous sodium hydroxide.[18] Under dry conditions, sodium hydroxide dissociation is avoided and thus, the sodium hydroxide can only behave as a basic group abstracting the acid proton of the alcohol with elimination of acetone. In contrast, in presence of a little amount of water or MeOH, the sodium hydroxide is partially dissociated and a nucleophilic attack of the OR anion to the silicon atom takes place, with formation of Me_3Si-OR and the elimination of the trimethylsilyl group.[17]

The doubly protected 4-[*p*-(trimethylsilylethynyl)phenyl]-2-methyl-3-butyn-2-ol (**12**) was prepared by heterocoupling between the iodo derivative **11** and trimethylsilylacetylene



Scheme 1.

Table 1. UV–vis and fluorescence spectra of the fluorene compounds

Compound	UV–vis (CH_2Cl_2) λ_{max} (nm)[a]	ε (M^{-1} cm^{-1})	F (CH_2Cl_2) λ_{max} (nm)[b]	Φ_f
6	318	26,300	334	0.4×10^{-2}[c]
7	340	6620	527	0.04[d]
8	334	21,800	523	0.03[d]
9	344	93,000	351 and 363	0.79[c]
10	332	58,100	355	0.52[c]
14	358	15,800	531	0.03[d]
17	374	25,900	531	0.03[d]
18	337	6600	502	0.10[d]

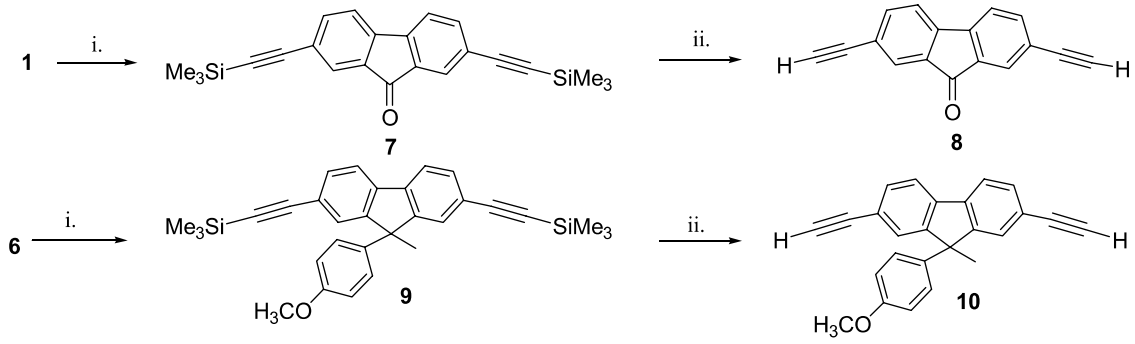
[a] At room temperature.
[b] At room temperature and [c] $\cong 10^{-8}$ M.
[c] Fluorescence quantum yield was in dichloromethane relative to 2-aminopyridine in 0.1 N H_2SO_4.
[d] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.

in triethylamine, catalyzed by the palladium–copper system, in practically quantitative yield, as a white solid.

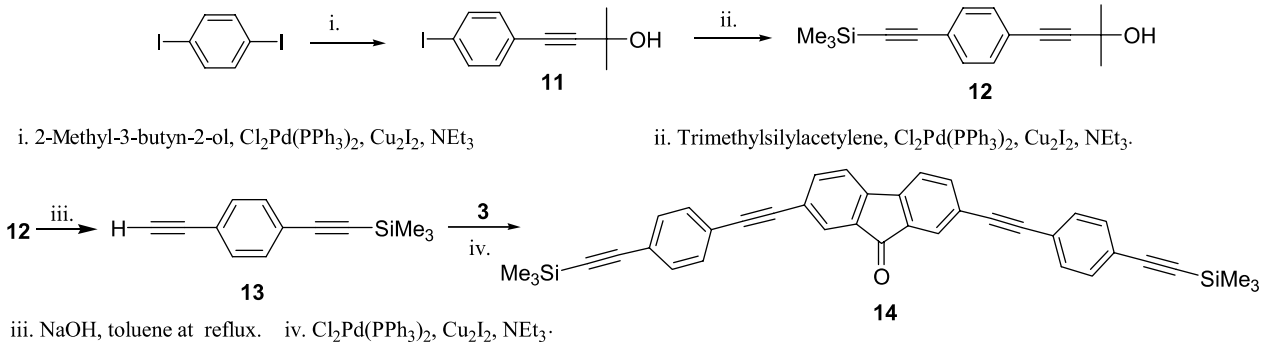
Compound **11** was prepared by the monoheterocoupling between 1,4-diiodobenzene and 2-methyl-3-butyn-2-ol, in triethylamine, catalyzed by the palladium–copper system, as a white solid in good yield (78%).[19]

Moreover, the conjugated 2,7-di[*p*-(*p*-{trimethylsilylethynyl}phenylethynyl)phenylethynyl]fluoren-9-one (**17**), was synthesized by heterocoupling between the terminal acetylene **16** and 2,7-diiodo derivative **3** in triethylamine at 60 °C, in presence of the palladium–copper system, as an orange solid in good yield (82%), Scheme 4.

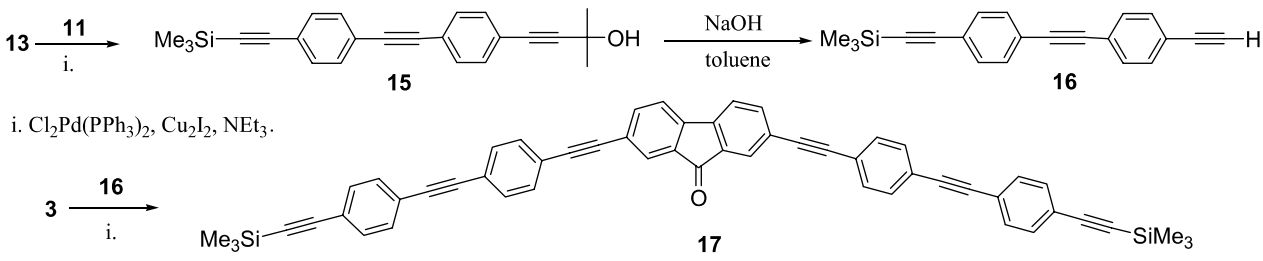
The terminal acetylene **16** was quantitatively obtained as a white solid, by treatment of **15** with catalytic powdered sodium hydroxide in dry toluene at the reflux temperature.



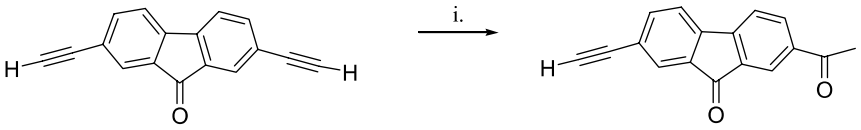
Scheme 2.



Scheme 3.



Scheme 4.



8 i. *p*-Toluensulfonic ac. / H_2O . **18**

Scheme 5.

The precursor 4-[*p*-(*p*-{trimethylsilylethynyl}phenylethynyl)phenyl]-2-methyl-3-butyn-2-ol (**15**) was prepared by heterocoupling between the terminal acetylene **13** and the iodoarene **11**, in triethylamine, catalyzed by the palladium–copper system, giving a white solid in practically quantitative yield.

All the 2,7-di(ethynylphenyl)$_n$fluoren-9-one compounds show fluorescence emission radiation with low quantum yields, by the presence of the 9-carbonyl group and also by the homo diethynyl 2,7-substitution. The last effect can be proved by the partial mild hydrolysis of the terminal acetylene **8**, with *p*-toluensulfonic acid with a little amount of water, to obtain 2-acetyl-7-ethynylfluoren-9-one (**18**), as a pale-yellow solid in 88% yield. Compound **18** shows fluorescence radiation emission with the quantum yield increasing significantly with respect to **8**, Scheme 5, Table 1.

Table 1, shows the UV–vis absorption of **17**, red-shifted by 18 nm compared to **14** and 34 nm respect **7**, due to the extended conjugation, while the fluorescent emission of the same compounds do not show or red-shifted by only 4 nm, respectively. Hence, the UV–vis absorption and the weak fluorescent emission are dominated from different transitions. The fluorescent emission of these fluorenones should be attributed to the n-π transition, which is not so substituent dependent. The 9-(*p*-methoxyphenyl)-9-methyl compounds **9** and **10** show fluorescence emission (blue light-emitting) with very important quantum yield.

Moreover, it was noticeable the large Stokes shift of the fluorescent wavelength emission for the fluoren-9-ones, in contrast with the moderate shift for the 9,9-disubstituted compounds **9** and **10**.

3. Conclusions

Conjugated 2,7-disubstituted 9-fluorenones and 9,9-disubstituted fluorene compounds have been efficiently synthesized and their fluorescence properties analyzed. The conjugated 2,7-bis(trimethylsilylethynyl)-(phenylethynyl)$_n$-fluoren-9-one structures have been satisfactory synthesized by means of the Sonogashira heterocoupling reaction between the 2,7-di(halo)fluoren-9-one (or 2,7-di(halo)-9-(*p*-methoxyphenyl)-9-methylfluorene) and *p*-trimethylsilylethynyl(phenylethynyl)$_n$ ($n=1,2$), catalyzed by the dichloro bis(triphenylphosphine)palladium, in a divergent synthesis. The starting 2,7-dibromo-9-(*p*-methoxyphenyl)-9-methylfluorene was obtained in good yield by reaction of the appropriate 9-one derivative with methylmagnesium iodide followed the acid catalysis reaction on *p*-methoxybenzene. The π-extended conjugated compounds exhibit fluorescence radiation emission with significant quantum yield for the 9-(*p*-methoxyphenyl)-9-methyl-2,7-bis(trimethylsilylethynyl)-(phenylethynyl)$_n$fluorenes.

4. Experimental

4.1. General

Melting points were determined in open capillaries using a Buchi or Reichert hot stage microscope and are uncorrected. IR spectra of solids were recorded as KBr pellets and IR spectra of oils were recorded as thin films on NaCl plates with a Bruker Vector 22 spectrophotometer, and the wave numbers are given in cm^{-1}. ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker Aspect spectrometer. Chemical shifts are given in δ with TMS as an internal reference and constants coupling J are given in Hz, the solvent is $CDCl_3$. Mass spectra were recorded on a VG AutoSpec spectrometer at 70 eV and the MALDI-TOF spectra were recorded on a Bruker Reflex III spectrometer. Elemental analyses were performed with a LECO CHN-900. The UV–vis spectra were recorded on a Hewlett Packard 8453 spectrometer, frequencies are given in nm and ε in L mol^{-1} cm^{-1}. All fluorescence spectra were recorded at room temperature at 10^{-8} M on a SLM Aminco Bowman series 2, the fluorescence quantum yield was determined in dichloromethane on freshly prepared samples (air-equilibrated) with absorbances at the excitation wavelength (365 nm for the standard quinine sulfate). The samples quinine sulfate in 1 N H_2SO_4 and 2-aminopyridine in 0.1 N H_2SO_4 were employed as a standard ($\Phi_f=0.55$ and 0.66, respectively) to measure the fluorescence quantum yields, which were corrected taking into account the refractive indices of the solvents used. Yields are given after chromatography column separation on silica gel 60 (200–400 mesh) using the indicated solvents or solvent crystallization.

4.1.1. 2,7-Dibromofluoren-9-one (1). To a suspension of 2,7-dibromofluorene (5 g, 15 mmol) in anhydrous acetic acid (50 mL), was added a solution of chromium oxide in anhydrous acetic acid (50 mL, 10%). The mixture was stirred at room temperature for 6 h and then, the pH of the mixture was neutralized by addition a solution of sodium bicarbonate. The yellow solid was filtered through a Büchner funnel and was washed with H_2O to give a residue, which was purified by recrystallization in ethanol/toluene, giving 2,7-dibromofluoren-9-one (**1**) as a yellow solid, mp 205–206 °C, 5.1 g (98%) yield, which agrees well with a commercial sample.

4.1.2. 2,7-Diaminofluoren-9-one (2). To a solution of 2,7-dinitrofluoren-9-one (2.7 g, 10 mmol) in ethyl acetate (freshly distilled) (200 mL), was added $SnCl_2$–$2H_2O$ (7.5 g, 33 mmol), under argon atmosphere. The mixture

was stirred for 24 h at the reflux temperature and then poured onto ice (100 g). The pH of the mixture was made basic (9–10) by addition of aqueous sodium hydroxide and finally was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and after filtration the solvent was removed. The residual brown solid was purified by silica gel column chromatography eluting with hexane–ethyl acetate (2/1), giving **2** as a brown solid, mp 276–278 °C (lit. 278–279 °C),[13] 2.0 g (97%) yield.

4.1.3. 2,7-Diiodofluoren-9-one (3). To a solution of sodium nitrite (304 mg, 4.4 mmol) in concentrated sulfuric acid (20 mL) at 0 °C, was added dropwise a solution of compound **2** (400 mg, 1.9 mmol) in glacial acetic acid (10 mL). The mixture was stirred for 15 min and after poured onto ice (8 g) and urea (47.3 mg, 0.78 mmol) and then, a solution of potassium iodide (43 g, 269 mmol) in water (40 mL) was added and stirred overnight under reduced pressure. The solid was filtered, dried, and extracted with dichloromethane. The combined extracts were refluxed with charcoal and finally purified by silica gel column chromatography (hexane/dichloromethane, 2:1) giving **3** as a yellow solid, mp 198–199 °C (lit. 201–202 °C),[12] 508 mg (62%) yield.

4.1.4. 2,7-Dibromo-9-hydroxy-9-methylfluorene (4). To a solution of compound **1** (100 mg, 0.3 mmol) in dry Et_2O (20 mL), under argon atmosphere at 0 °C, was added dropwise a solution of methylmagnesium iodide (100 mg, 0.6 mmol). The white solution was stirred for 3 h and then, was added a saturated aqueous ammonium chloride solution. The mixture was stirred for 15 min and extracted with Et_2O. The extracts were dried on anhydrous sodium sulfate and after filtration; the solvent was removed to give a white solid, which was purified by silica gel column chromatography (dichloromethane). Compound **4** was isolated as a white solid, mp 161–162 °C, 104 mg (98%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 289 (ε, 21,600), 305s (ε, 14,400). IR (KBr, cm^{-1}): 3314, 1100, 1061, 886, 865, 818. ^1H NMR ($CDCl_3$): δ 7.63 (d, 2H, $J=1.7$ Hz), 7.48 (dd, 2H, $J=8.0$, 1.7 Hz), 7.43 (d, 2H, $J=8.0$ Hz), 2.20 (s, 1H), 1.66 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.4, 136.1, 132.3, 126.7, 122.2, 121.5, 86.2, 26.1. $C_{14}H_{10}Br_2O$ (354.04). Anal. Calcd: C 47.50, H 2.85. Found: C 47.42, H 2.98.

4.1.5. 2,7-Dibromo-9-methylidenefluorene (5). To a solution of compound **4** (100 mg, 0.28 mmol) and *p*-toluensulfonic acid (96 mg, 0.56 mmol) in dry THF (20 mL), under argon atmosphere, was added concentrated sulfuric acid (1 mL). The mixture was stirred for 30 h at 90 °C and then, the solvent was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration; the solvent was removed to give a solid residue, which was purified by silica gel column chromatography (hexane/dichloromethane, 4:1). Compound **5** was isolated as a pale-yellow, mp 209–210 °C, 92 mg (98%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 256 (ε, 40,000), 264 (ε, 58,000), 280 (ε, 17,700), 299 (ε, 20,000), 312 (ε, 21,300). IR (KBr, cm^{-1}): 1850, 1055, 914, 878, 852, 806. ^1H NMR ($CDCl_3$): δ 7.81 (s, 2H), 7.48 (s, 4H), 6.08 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 141.5, 139.5, 138.0, 131.8, 124.4, 121.3, 121.1, 110.4. $C_{14}H_8Br_2$ (336.02). Anal. Calcd: C 50.04, H 2.40. Found: C 50.38, H 2.62.

4.1.6. 2,7-Dibromo-9-(*p*-methoxyphenyl)-9-methylfluorene (6). To a solution of compound **5** (100 mg, 0.3 mmol) in anisole (10 mL), under argon atmosphere, was added concentrated sulfuric acid (85%, 1 mL). The mixture was stirred for 24 h at 110 °C and then, the solvent was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration; the solvent was removed to give a solid, which was purified by silica gel column chromatography (hexane/dichloromethane, 1:1). Compound **6** was isolated as a white solid, mp 115–116 °C, 100 mg (75%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 289 (ε, 40,000), 306 (ε, 18,700), 318 (ε, 26,300). Fluorescence (CH_2Cl_2), λ_{max} (nm): 334 ($\phi=0.4\times10^{-2}$). IR (KBr, cm^{-1}): 2926, 1253, 1061, 881, 867, 809, 834. ^1H NMR ($CDCl_3$): δ 7.58 (d, 2H, $J=8.2$ Hz), 7.47 (dd, 2H, $J=8.2$, 1.8 Hz), 7.32 (d, 2H, $J=1.8$ Hz), 7.03 (d, 2H, $J=8.9$ Hz), 6.78 (d, 2H, $J=8.9$ Hz), 3.77 (s, 3H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.5, 155.8, 137.5, 135.1, 130.5, 127.47, 127.45, 121.8, 121.5, 113.9, 55.2, 54.4, 25.2. $C_{21}H_{16}Br_2O$ (446.16). Anal. Calcd: C 56.79, H 3.63. Found: C 56.61, H 3.45.

4.1.7. 2,7-Bis(trimethylsilylethynyl)fluoren-9-one (7). General procedure for the heterocoupling reaction. To a solution of 2,7-dibromofluoren-9-one (**1**) (750 mg, 2.2 mmol) and trimethylsilylacetylene (0.69 mL, 4.9 mmol) in freshly distilled triethylamine (50 mL), under argon atmosphere and 50 °C, was added dichloro bis(triphenylphosphine)palladium (78 mg, 0.11 mmol) and cuprous iodide (4.2 mg, 0.03 mmol). The mixture was stirred for 15 h and then, the amine was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution with a little amount of KCN, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration; the solvent was removed to give a brown solid, which was purified by silica gel column chromatography (hexane/dichloromethane, 2:1). Compound **7** was isolated as a pale-yellow solid, mp 165–168 °C (lit. 164–168 °C),[2] 645 mg (78%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 277 (ε, 17,400), 287 (ε, 26,100), 312 (ε, 3830), 326 (ε, 5950), 340 (ε, 6620). Fluorescence (CH_2Cl_2), λ_{max} (nm): 527 ($\phi=0.04$).

4.1.8. 2,7-Diethynylfluoren-9-one (8). General procedure. To a solution of 2,7-bis(trimethylsilylethynyl)fluoren-9-one (**7**) (480 mg, 1.28 mmol) in THF–MeOH (80 mL/40 mL), under argon atmosphere, was added potassium carbonate (709 mg, 5.13 mmol). The mixture was stirred at room temperature for 4 h and then, the solvent was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution and extracted with dichloromethane. The extracts were dried on anhydrous

sodium sulfate and after filtration; the solvent was removed to give a residue, which was purified by silica gel column chromatography (hexane/dichloromethane, 2:1). Compound **8** was isolated as a pale-yellow solid, mp 237–239 °C (lit. 239–241 °C),[2] 290 mg (98%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 269 (ε, 134,800), 279 (ε, 242,300), 308 (ε, 24,100), 321 (ε, 31,200), 334 (ε, 21,800). Fluorescence (CH_2Cl_2), λ_{max} (nm): 523 ($\phi=0.03$).

4.1.9. 9-(*p*-Methoxyphenyl)-9-methyl-2,7-bis(trimethylsilylethynyl)fluorene (9). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (16 mg, 0.02 mmol), Cu_2I_2 (0.4 mg, 0.002 mmol), compound **6** (50 mg, 0.11 mmol), trimethylsilylacetylene (24 mg, 0.24 mmol), and NEt_3 (30 mL) was stirred for 16 h at 50 °C. By silica gel flash column chromatography (hexane/dichloromethane, 2:1) was isolated **9** as a white solid, mp 195–196 °C, 50 mg (94%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 301 (ε, 35,400), 311 (ε, 56,800), 328 (ε, 50,800), 344 (ε, 83,000). Fluorescence (CH_2Cl_2), λ_{max} (nm): 351 and 363 ($\phi=0.79$). IR (KBr, cm^{-1}): 2959, 2154, 1253, 1250, 1061, 893, 859, 760. ^{1}H NMR ($CDCl_3$): δ 7.66 (d, 2H, $J=7.9$ Hz), 7.47 (dd, 2H, $J=7.9$, 1.4 Hz), 7.31 (d, 2H, $J=1.4$ Hz), 7.04 (d, 2H, $J=8.9$ Hz), 6.77 (d, 2H, $J=8.9$ Hz), 3.76 (s, 3H), 1.82 (s, 3H), 0.24 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 158.3, 154.4, 139.2, 135.7, 131.4, 127.7, 127.6, 122.4, 120.1, 113.8, 105.6, 94.6, 55.2, 54.0, 25.1, −0.1. $C_{31}H_{34}OSi_2$ (478.77). Anal. Calcd: C 77.77, H 7.16. Found: C 77.95, H 7.02.

4.1.10. 2,7-Diethynyl-9-(*p*-methoxyphenyl)-9-methylfluorene (10). Following the general method used for the synthesis of **8**, a mixture of potassium carbonate (304 mg, 2.2 mmol), compound **9** (50 mg, 0.11 mmol), and THF–MeOH (16 mL/4 mL) was stirred at room temperature for 3 h. By silica gel flash column chromatography (hexane/dichloromethane, 2:1) was isolated **10** as a white solid, mp 183–184 °C, 37 mg (99%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 293 (ε, 42,700), 304 (ε, 61,500), 321s (ε, 34,200), 332 (ε, 58,100). Fluorescence (CH_2Cl_2), λ_{max} (nm): 355 ($\phi=0.52$). IR (KBr, cm^{-1}): 2103, 2934, 2103, 1263, 894, 825. ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2H, $J=7.9$ Hz), 7.49 (d, 2H, $J=7.9$ Hz), 7.35 (s, 2H), 7.04 (d, 2H, $J=8.9$ Hz), 6.77 (d, 2H, $J=8.9$ Hz), 3.76 (s, 3H), 3.08 (s, 2H), 1.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.3, 154.4, 139.4, 135.5, 131.5, 127.9, 127.5, 121.5, 120.3, 113.8, 84.1, 77.6, 55.2, 54.0, 25.2. MS (70 eV): 334 (M^+, 75), 319 (100), 276 (20), 250 (6), 226 (9), 159 (15). $C_{25}H_{18}O$ (334.41). Anal. Calcd: C 89.79, H 5.43. Found: C 89.88, H 5.68.

4.1.11. 4-(*p*-Iodophenyl)-2-methyl-3-butyn-2-ol (11). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (21 mg, 0.03 mmol), Cu_2I_2 (0.6 mg, 0.003 mmol), 1,4-diiodobenzene (1 g, 3.03 mmol), 2-methyl-3-butyn-2-ol (255 mg, 3.03 mmol), and NEt_3 (100 mL) was stirred at room temperature for 12 h. By silica gel flash column chromatography (hexane/ethyl acetate, 4:1) was obtained **11** as a white solid, mp 89–90 °C, 676 mg (78%) yield.

^{1}H NMR ($CDCl_3$): δ 7.63 (d, 2H, $J=8.1$ Hz), 7.12 (d, 2H, $J=8.1$ Hz), 1.60 (s, 6H).

4.1.12. 4-[*p*-(Trimethylsilylethynyl)phenyl]-2-methyl-3-butyn-2-ol (12). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (400 mg, 0.73 mmol), Cu_2I_2 (14 mg, 0.073 mmol), compound **11** (2.1 g, 7.32 mmol), trimethylsilylacetylene (718 mg, 7.31 mmol), and NEt_3 (100 mL) was stirred at room temperature for 12 h. By silica gel column chromatography (hexane/dichloromethane, 2:1) was obtained **12** as a white solid, mp 108–109 °C, 1.8 g (98%) yield.

IR (KBr, cm^{-1}): 3286, 2157, 1497, 1250, 833, 759. ^{1}H NMR ($CDCl_3$): δ 7.40 (d, 2H, $J=8.6$ Hz), 7.33 (d, 2H, $J=8.6$ Hz), 1.6 (s, 6H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 131.7, 131.4, 122.8, 122.7, 104.5, 96.0, 95.6, 81.7, 65.5, 31.3, −0.1.

4.1.13. *p*-(Trimethylsilylethynyl)phenylacetylene (13). General procedure. To a solution of 4-[*p*-(trimethylsilylethynyl)phenyl]-2-methyl-3-butyn-2-ol (**12**) (204 mg, 0.8 mmol) in dry toluene (40 mL) was added finely powdered sodium hydroxide (3.2 mg, 0.08 mmol), under argon atmosphere, and the mixture was warmed at the reflux temperature for 2 h, and then filtered. The solvent was removed at reduced pressure and the solid residue was purified by silica gel column chromatography (hexane/dichloromethane, 1:1) giving **13** as a white solid, mp 52–53 °C, 158 mg (99%) yield.

IR (KBr, cm^{-1}): 3302, 2162, 1580, 1413, 1250, 760. ^{1}H NMR ($CDCl_3$): δ 7.45 (s, 4H), 3.20 (s, 1H), 0.30 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 131.8, 131.7, 123.5, 122.1, 104.3, 96.4, 83.1, 78.9, −0.1. $C_{13}H_{14}Si$ (189.34). Anal. Calcd: C 78.72, H 7.11. Found: C 78.86, H 7.04.

4.1.14. 2,7-Di[(*p*-trimethylsilylethynylphenyl)ethynyl]-fluoren-9-one (14). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol), Cu_2I_2 (1 mg, 0.005 mmol), compound **3** (100 mg, 0.25 mmol), compound **13** (99 mg, 0.5 mmol), and NEt_3 (30 mL) was stirred for 12 h at 50 °C. By silica gel flash column chromatography (hexane/dichloromethane, 5:1), was obtained **14** as an orange solid, mp > 300 °C, 104 mg (73%) yield.

IR (KBr, cm^{-1}): 3012, 2157, 1592, 1473, 1254, 759. UV–vis (CH_2Cl_2), λ_{max} (nm): 310 (ε, 11,200), 358 (ε, 15,800). Fluorescence (CH_2Cl_2), λ_{max} (nm): 531 ($\phi=0.03$). ^{1}H NMR ($CDCl_3$): δ 7.80 (dd, 2H, $J=6.2$, 1.6 Hz), 7.64 (dd, 2H, $J=6.2$, 1.6 Hz), 7.53 (m, 8H), 7.35 (d, 2H, $J=6.2$ Hz), 0.26 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 189.7, 141.2, 135.4, 132.5, 132.0, 131.1, 127.5, 123.5, 122.3, 121.8, 120.7, 103.8, 97.4, 85.1, 78.3, −0.1. $C_{39}H_{32}OSi_2$ (572.84). Anal. Calcd: C 81.77, H 5.63. Found: C 81.50, H 5.85.

4.1.15. 4-[*p*-(*p*-{Trimethylsilylethynyl}phenylethynyl)-phenyl]-2-methyl-3-butyn-2-ol (15). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol), Cu_2I_2 (1.2 mg, 0.005 mmol), compound **11** (143 mg, 0.5 mmol), compound **13** (100 mg, 0.5 mmol), and NEt_3 (100 mL) was stirred at

room temperature for 12 h. By silica gel flash column chromatography (hexane/ethyl acetate, 3:1) gives **15** as a white solid, mp > 300 °C, 176 mg (99%) yield.

IR (KBr, cm^{-1}): 3355, 2154, 1576, 1511, 1250, 1161, 840, 758. ^1H NMR ($CDCl_3$): δ 7.56–7.37 (m, 8H), 1.64 (s, 6H), 0.28 (s, 9H).

4.1.16. 4-[*p*-(Trimethylsilylethynyl)phenylethynyl]-phenylacetylene (16). Following the general method used for the synthesis of **13**, a mixture of compound **15** (100 mg, 0.28 mmol), dry toluene (25 mL), and finely powdered sodium hydroxide (1.1 mg, 0.03 mmol) was stirred for 5 h and then filtered. The residual solid was purified by silica gel column chromatography (hexane/dichloromethane, 1:1) giving **16** as a white solid, mp 72–75 °C, 82 mg (98%) yield.

IR (KBr, cm^{-1}): 2148, 1582, 1521, 1246, 836, 752. ^1H NMR ($CDCl_3$): δ 7.48 (s, 8H), 3.18 (s, 1H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 137.5, 133.4, 131.9, 131.6, 123.4, 122.9, 122.6, 104.8, 96.8, 94.2, 89.3, 88.9, 85.8, 79.0, −0.1. MS (70 eV): 298 (M^+, 100), 297 (20), 224 (15), 125 (8). $C_{21}H_{18}Si$ (298.12). Anal. Calcd: C 84.51, H 6.08. Found: C 84.79, H 6.21.

4.1.17. 2,7-Di[*p*-(*p*-{trimethylsilylethynyl}phenyl-ethynyl)phenylethynyl]fluoren-9-one (17). Following the general method used for the synthesis of **7**, a mixture of $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol), Cu_2I_2 (1 mg, 0.005 mmol), compound **3** (100 mg, 0.25 mmol), compound **16** (149 mg, 0.5 mmol), and NEt_3 (30 mL) was stirred for 48 h at 50 °C. By silica gel flash column chromatography (hexane) was obtained **14** as an orange solid, mp > 300 °C, 158 mg (82%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 260 (ε, 7600), 323 (ε, 16,800); 374 (ε, 25,900). Fluorescence (CH_2Cl_2), λ_{max} (nm): 531 (ϕ = 0.03). IR (KBr, cm^{-1}): 2178, 1597, 1531, 1256, 830, 748. ^1H NMR ($CDCl_3$): δ 7.67 (s, 6H), 7.44 (s, 8H), 7.23 (s, 8H), 0.27 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 143.9, 137.5, 136.9, 134.5, 133.0, 131.9, 131.3, 127.3, 124.7, 123.4, 122.8, 122.4, 122.2, 104.5, 96.4, 94.4, 90.3, 90.2, 86.5, 78.3, −0.2. MS (70 eV): 773 (M^+, 100). $C_{55}H_{40}OSi_2$ (773.08). Anal. Calcd: C 85.45, H 5.22. Found: C 85.27, H 5.45.

4.1.18. 2-Acetyl-7-ethynylfluoren-9-one (18). To a solution of the compound **8** (80 mg, 0.35 mmol) and *p*-toluensulfonic acid (181 mg, 1.01 mmol) in CCl_4 (20 mL), under argon atmosphere, was added H_2O (1 mL). The mixture was warmed at the reflux temperature for 24 h and then, the solvent was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration; the solvent was removed to give a solid residue, which was purified by silica gel column chromatography (hexane/dichloromethane, 1:3). Compound **18** was isolated as a pale-yellow solid, mp 228–230 °C, 77 mg (88%) yield.

UV–vis (CH_2Cl_2), λ_{max} (nm): 281 (ε, 62,100), 308 (ε, 8700), 324 (ε, 9700), 337 (ε, 6600). Fluorescence (CH_2Cl_2), λ_{max} (nm): 502 (ϕ = 0.096). IR (KBr, cm^{-1}): 3247, 2159, 1715, 1682, 1661, 882, 838, 804. ^1H NMR ($CDCl_3$): δ 8.21 (d, 2H, J = 1.7 Hz), 8.16 (d, 2H, J = 7.0 Hz), 7.81 (s, 1H), 7.68 (dd, 2H, J = 7.0, 1.7 Hz), 7.64 (d, 2H, J = 7.0 Hz), 7.58 (d, 2H, J = 7.0 Hz), 3.22 (s, 1H), 2.64 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 196.4, 191.7, 147.7, 143.0, 138.5, 138.1, 135.1, 134.9, 134.5, 128.1, 124.3, 124.2, 121.2, 120.8, 82.4, 79.6, 29.7. MS (70 eV): 246 (M^+, 75), 231 (100), 203 (31), 175 (52), 149 (12). $C_{17}H_{10}O_2$ (246.26). Anal. Calcd: C 82.91, H 4.09. Found: C 83.10, H 4.35.

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Regioselectivity in the formation of norbornene-fused pyrazoles: preparation of 1-substituted derivatives of 4,5,6,7-tetrahydro-1*H*-4,7-methanoindazole

Franco Fernández,[a] Olga Caamaño,[a,*] Marcos Daniel García,[a] Ibon Alkorta[b] and José Elguero[b]

[a]*Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*
[b]*Instituto de Química Médica, CSIC, Juan de la Cierva 3, E-28006 Madrid, Spain*

Received 17 October 2005; revised 13 January 2006; accepted 17 January 2006

Available online 14 February 2006

Abstract—The structural characteristics of (±)-(*exo*,*exo*)-3-(hydroxymethylene)-5,6-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one make the reactions between this β-diketone and hydrazines particularly interesting for elucidating the mechanism of pyrazole formation. The isolation and X-ray structure determination of two 5-hydroxy substituted Δ^2-pyrazolines [(±)-(3a*R**,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-hydroxy-5,6-(isopropylidenedioxy)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole] and [(±)-(3a*S**,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-hydroxy-5,6-(isopropylidene-dioxy)-1-phenyl-3a,4,5,6,7,7a-hexa-hydro-4,7-methano-1*H*-indazole] has been determinant for proposing a mechanism. Besides B3LYP/6-31G* calculations have been carried out on all intermediate dihydroxypyrazolidines and 5-hydroxypyrazolines. Finally, the annular tautomerism of the NH-methanotetrahydroindazoles has been studied both experimentally (^{13}C NMR) and theoretically: the Mills–Nixon effect favours the 2*H*-tautomer.
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1. Introduction

The reaction between a β-dicarbonyl compound and a hydrazine constitutes the main synthetic approach to the pyrazole ring.[1–5] The mechanism of this reaction has been studied several times,[6] we have represented in Scheme 1 a simplified plausible version. Recently, the **4**→**5** step has been studied in detail thanks to the isolation of several 5-hydroxypyrazolines **4**.[7] Note that when R^1=H, **5a** and **5b** become identical due to annular tautomerism, besides when R^1=H, **3a**=**3b**.

In this mechanism it is assumed that the dehydration steps, **3**→**4** and **4**→**5** are irreversible. An aspect that has not been clarified is the reversibility or not of the first step. It is possible that the reaction **1**+**2**→**3** is also irreversible and, consequently, the proportion of pyrazoles **5a** and **5b** will be determined by the structure of the dihydroxypyrazolidines **3a** and **3b**. But it is also possible that the dihydroxypyrazolidines **3a** and **3b** are in rapid equilibrium (through dissociation into **1**+**2**). If this is the case, then the rate-determining step will be the **3**→**4** transformation. Once pyrazolines **4** are formed, the final structure of pyrazoles **5** is decided.

Some of us have isolated and characterized a dihydroxypyrazolidine **3** [3,5-dihydroxy-3,5-bis(trifluoromethyl)-pyrazolidine],[8] as well as a series of 5-hydroxy-Δ^2-pyrazolines **3** stabilized by a CF_3 group at position 5 and/or by electron-withdrawing substituents at position N1 of the ring.[6] Other authors have characterized by ^{1}H NMR the intermediate dihydroxypyrazolidines **3** (with a spiro 4,4′-substituent).[9] It is therefore reasonable to assume the mechanism represented in Scheme 1.

In the general case of an asymmetrically substituted β-dicarbonyl compound ($R^2 \neq R^3$), the reaction can lead to a mixture of pyrazole isomers, **5a** and **5b** (Schemes 1 and 2). It is important to notice that the presence of two reactive centres in the hydrazine (**Z**, **Y**) and four more for the set of three tautomers of the dicarbonyl compound (**X**, **W**, **V**, **U**), results in eight different approximations for the reaction path (four for each final regioisomer).

In a preceding paper, we have described the synthesis and NMR structural determination of a series of pyrazoles fused to a bicyclo[2.2.1]heptane skeleton as synthetic

Keywords: Pyrazolines; Pyrazolidines; Stabilizing effect; Regioselectivity; Norbornene-fused pyrazoles.
* Corresponding author. Tel.: +34 981 563100x15047; fax: +34 981 594912; e-mail: qoolga@usc.es

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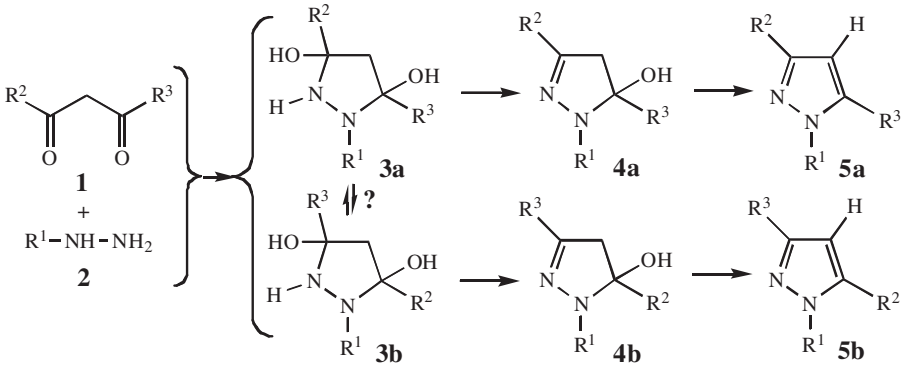
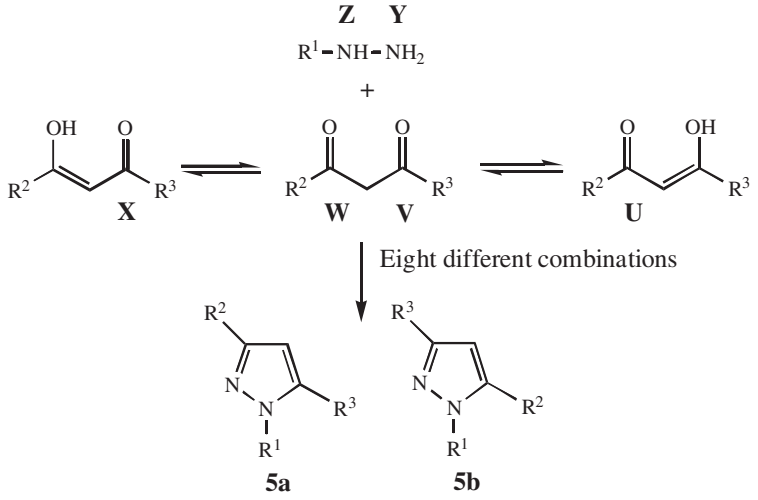
doi:10.1016/j.tet.2006.01.059



Scheme 1. The mechanism proposed for the synthesis of pyrazoles.



Scheme 2. The different ways to attain pyrazoles **5a** and **5b**.

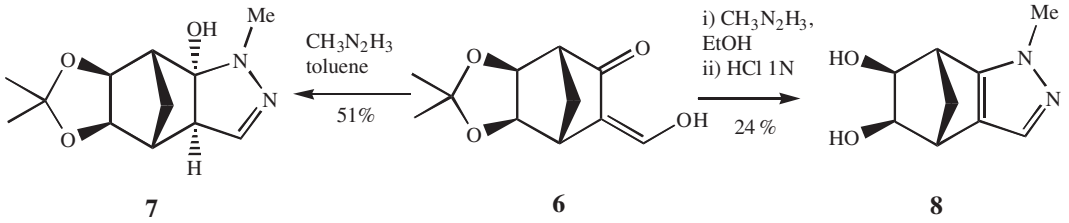
intermediates for the preparation of new azolo-condensed carbonucleosides.[10,11] The starting material was *exo*,*exo*-3-(hydroxymethylene)-5,6-(isopropylidenedioxy)bicyclo-[2.2.1]heptan-2-one (**6**), which reacted with several hydrazines to afford the corresponding pyrazoles. Amongst the interesting results is the fact that when **6** reacted with methylhydrazine during 3 h at room temperature in dry toluene, the only isolated compound (51% yield) was 5-hydroxy-Δ^2-pyrazoline **7** (Scheme 3). However, when, an acid catalysis was used (HCl aq in EtOH at reflux), in order to favor the formation of the pyrazole ring, the only isolated compound was **8** (24% yield). The easy isolation of **7** was a surprise since this structure lacks the two structural conditions we have previously reported (5-CF_3 and/or an EWG at position 1). We will discuss further on why the dehydration of **7** (Scheme 1, **4**→**5**) is difficult with the consequence that it can be isolated.

The total regioselectivity of this reaction (no N2-substituted derivatives were obtained) prompted us to study the reaction of **6** with other hydrazines and to gain a better understanding of the mechanism accounting for the results obtained.[12]

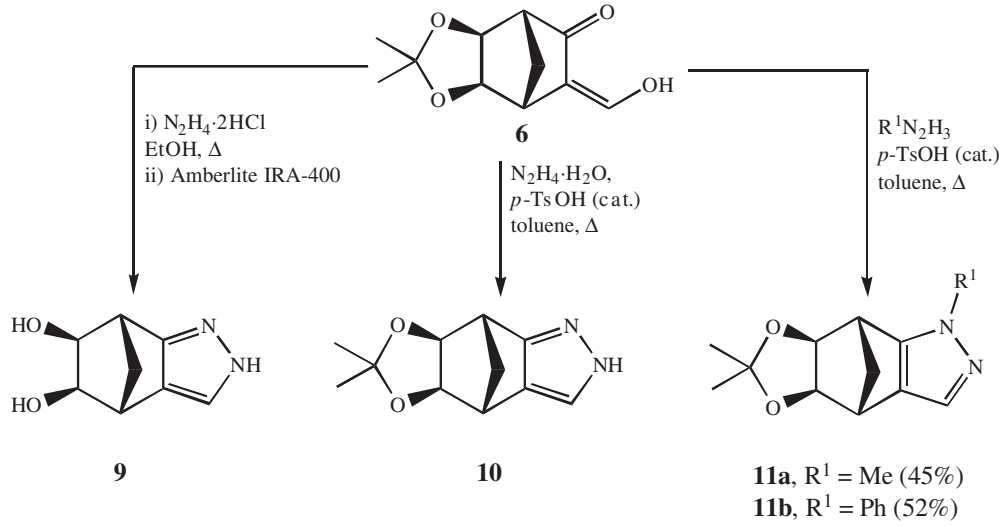
We will describe in the present work the study of the reactivity of hydroxymethyleneketone **6** with different hydrazines. We have isolated as many reaction intermediates as possible and studied their transformation into the corresponding pyrazole derivatives. Finally, a theoretical study will be reported describing our attempts to justify the observed regioselectivity.

2. Results and discussion

The first experiments were aimed to the direct preparation of pyrazoles from **6** and hydrazine dihydrochloride or



Scheme 3. Synthesis of pyrazoles **7** and **8** from the common precursor **6**.



Scheme 4. Preparation of pyrazoles **9**–**11**.

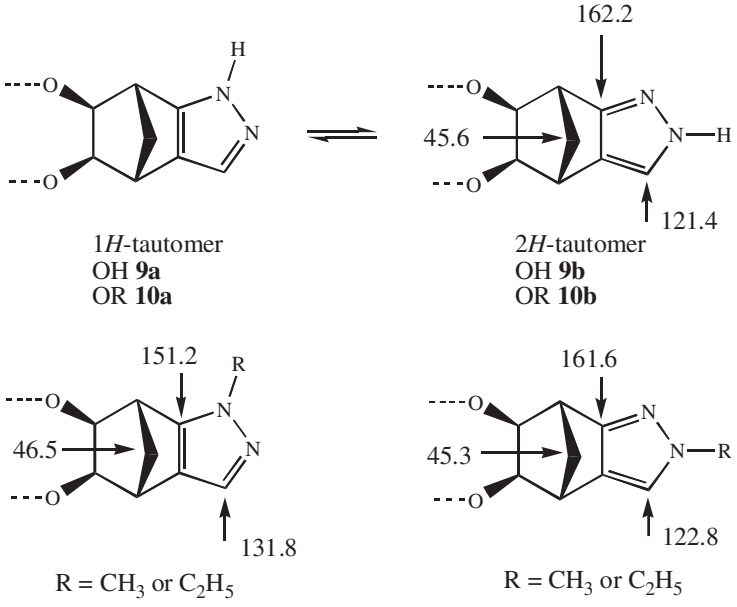
hydrazines in the presence of an acid catalyst to determine the synthetic accessibility of the resulting pyrazoles as well as the possible formation of isomer mixtures in the case of substituted hydrazines. Thus, NH-methanoindazoles **9** and **10** were obtained in acceptable yields (Scheme 4).[10,12]

The annular tautomerism of compounds **9** and **10** is interesting being related to the Mills–Nixon effect. We have been the first to extend the Mills–Nixon effect from its original definition concerning resonance forms[13] to the equilibrium present in tautomerism, first to pyrazoles[14–16] and then to enols of β-diketones.[17] These studies show that small rings favour the 2*H*-tautomers with an *endocyclic* single bond. A comparison of the ^{13}C chemical shifts of some selected C atoms (Scheme 5) leaves no doubt that these compounds are 2*H*-tautomers **b** as previously described.[10] Therefore, the bicyclo[2.2.1] ring system acts as a strained Mills–Nixon substituent.

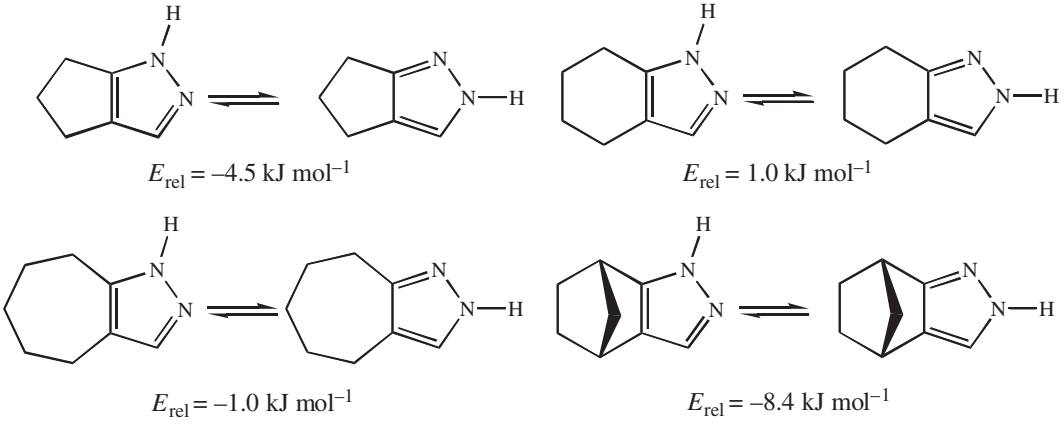
We have carried out computations (B3LYP/6-31G** together with frequency calculations) on four systems to assess the influence of the ring strain on the tautomerism of pyrazoles (Scheme 6).

It appears that the bicyclic system present in the compounds here described is much more efficient in directing the tautomerism towards 2*H*-pyrazoles than the five-membered ring. Compound **7** lacks both EWGs at positions 1 and 5, and so the reason of its stability must be different. We think it is related to the Mills–Nixon effect since pyrazole **11a** obtained from **7** has an endocyclic double bond, a situation clearly endergonic.

The reaction of the β-dicarbonyl compound **6** with methyl- and with phenylhydrazine in toluene at reflux and acid catalysis in a Dean–Stark apparatus afforded as sole reaction products the corresponding pyrazole derivatives substituted on N1, **11a** and **11b** (Scheme 4). A plausible explanation of



Scheme 5. The annular tautomerism of methanoindazoles **9** and **10**.



Scheme 6. Effect of ring strain on the annular tautomerism of polymethylenepyrazoles.

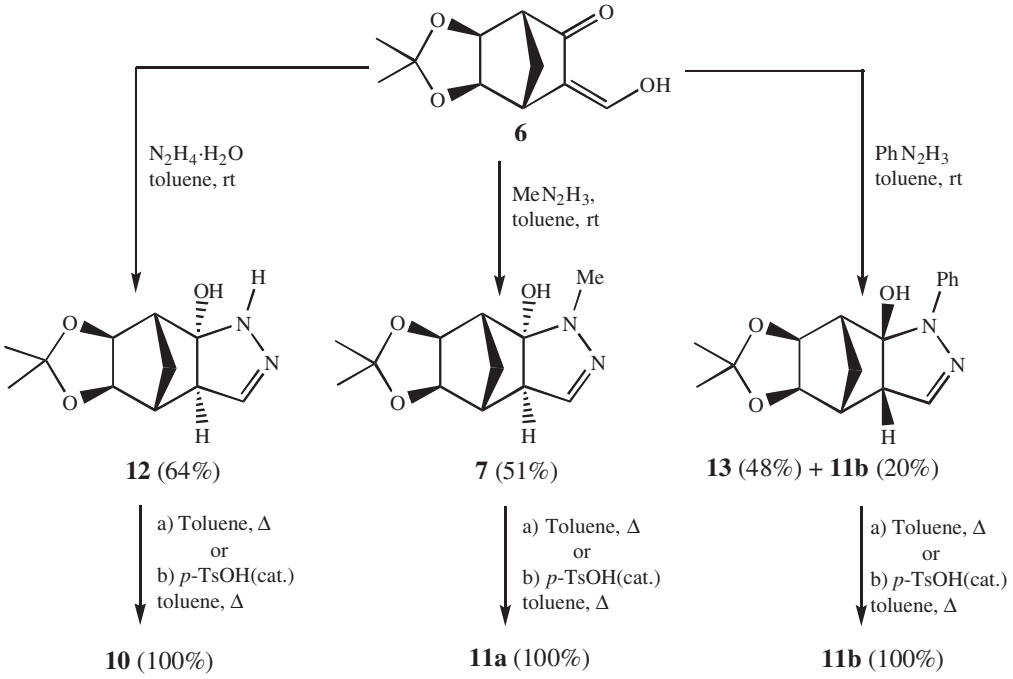
the observed regioselectivity is the existence of marked kinetic differences in the dehydration step of the proposed dihydroxypyrazolidines leading to the Δ^2-pyrazolines (Scheme 1, **2**→**3**).

To establish that the steps following the formation of the hydroxypyrazolines do not affect the final outcome and taking advantage of the stability of 1-methyl-5-hydroxypyrazoline **7** (Scheme 3),[10] we decided to isolate and characterize the remaining hydroxypyrazolines as well as to study their transformation into the corresponding pyrazoles (Scheme 7).

The experiments we decided to carry out were: (i) to use the experimental conditions that allow isolating the intermediate **7** from **6**,[10] (ii) to determine the structure of the isolated compounds (in particular the possible existence of regio- and/or stereoisomers) and (iii) the study of the conversion of the hydroxypyrazolines into pyrazoles with and without acid catalysis.

From the experiments we carried out, it is worth to note the formation of the hydroxypyrazolines **7**, **12** and **13** that were isolated in acceptable yields (Scheme 7). The hydroxypyrazolines **12**, **7** and **13** were quantitatively transformed into the corresponding pyrazoles **10**, **11a** and **11b**, independently of the use or not of acid catalysis, only changing the reaction times (Table 1).

In the reaction with phenylhydrazine although the conditions were those to obtain **13**, a significant amount (20%) of pyrazole **11b** was isolated. We will turn now to the reason why the *N*-phenylpyrazoline **13** dehydrates more easily than the *N*-H **12** and *N*-methyl **7** pyrazolines. As we discussed before, an EWG R^1 at position 1 (**4**) stabilizes the hydroxypyrazoline; it is true that the electronic properties of the phenyl group are not so marked as those of typical stabilizing groups such as $CONH_2$ (σ_p=0.38), SO_2R (σ_p=0.73) that allow to isolate **4**,[6] but nevertheless, the phenyl group (σ_p=0.01) is more EWG than the methyl (σ_p=−0.17).[18] The additional conjugation between the



Scheme 7. The 5-hydroxy-Δ^2-pyrazolines and their conversion into pyrazoles.

Table 1. Conditions to transform hydroxypyrazolines **12**, **7** and **13** into the corresponding pyrazoles **10**, **11a** and **11b**

Process	Catalysis	Time (h)	Conversion (%)
12→10	None	48	100
12→10	TsOH	0.25	100
7→11a	None	60	100
7→11a	TsOH	0.25	100
13→11b	None	48	100
13→11b	TsOH	0.25	100

phenyl group and the pyrazole ring in **5** (**11b** in Scheme 7) could be the driving force that facilitates the dehydration in the case of pyrazoline **13** compared with **7** and **12**.

The structural assignment and the stereochemistry of the hydroxypyrazolines **12** and **13** was determined by X-ray diffraction on single crystals of these two compounds (Figs. 1 and 2).

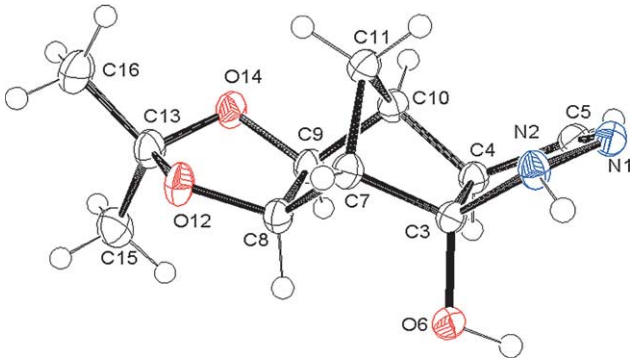


Figure 1. ORTEP projection of the molecular structures of compound **12**.

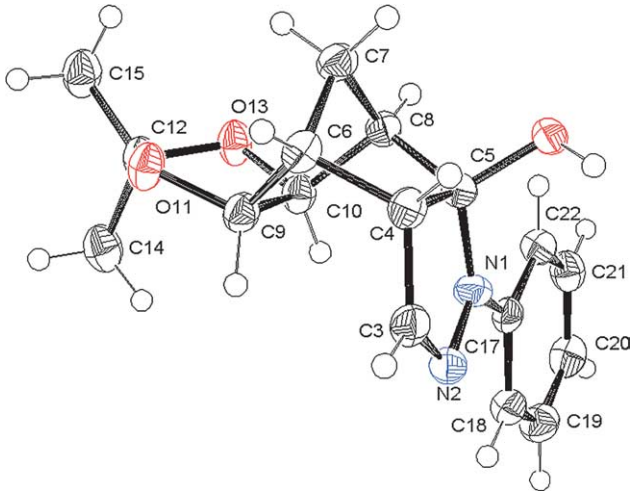


Figure 2. ORTEP projection of the molecular structures of compound **13**.

We have represented in Scheme 8 a more detailed mechanism than that depicted in Scheme 1 in what concerns the intermediate steps of the 3,5-dihydroxypyrazolidines and hydroxypyrazolines only for $R^1=H$ (**1** series) and $R^1=CH_3$ (**2** series) and $R^1=C_6H_5$ (**3** series). We have included tentatively equilibrium arrows between the pyrazolidines. When $R^1=H$, **A1**=**C1**, **B1**=**D1**, **E1**=**G1** and **F1**=**H1**. Remember that the two hydroxypyrazolines that have been isolated and their X-ray structure determined correspond to the following molecules in Scheme 8: **12** and **13** are, respectively, **K1** and **N3**.

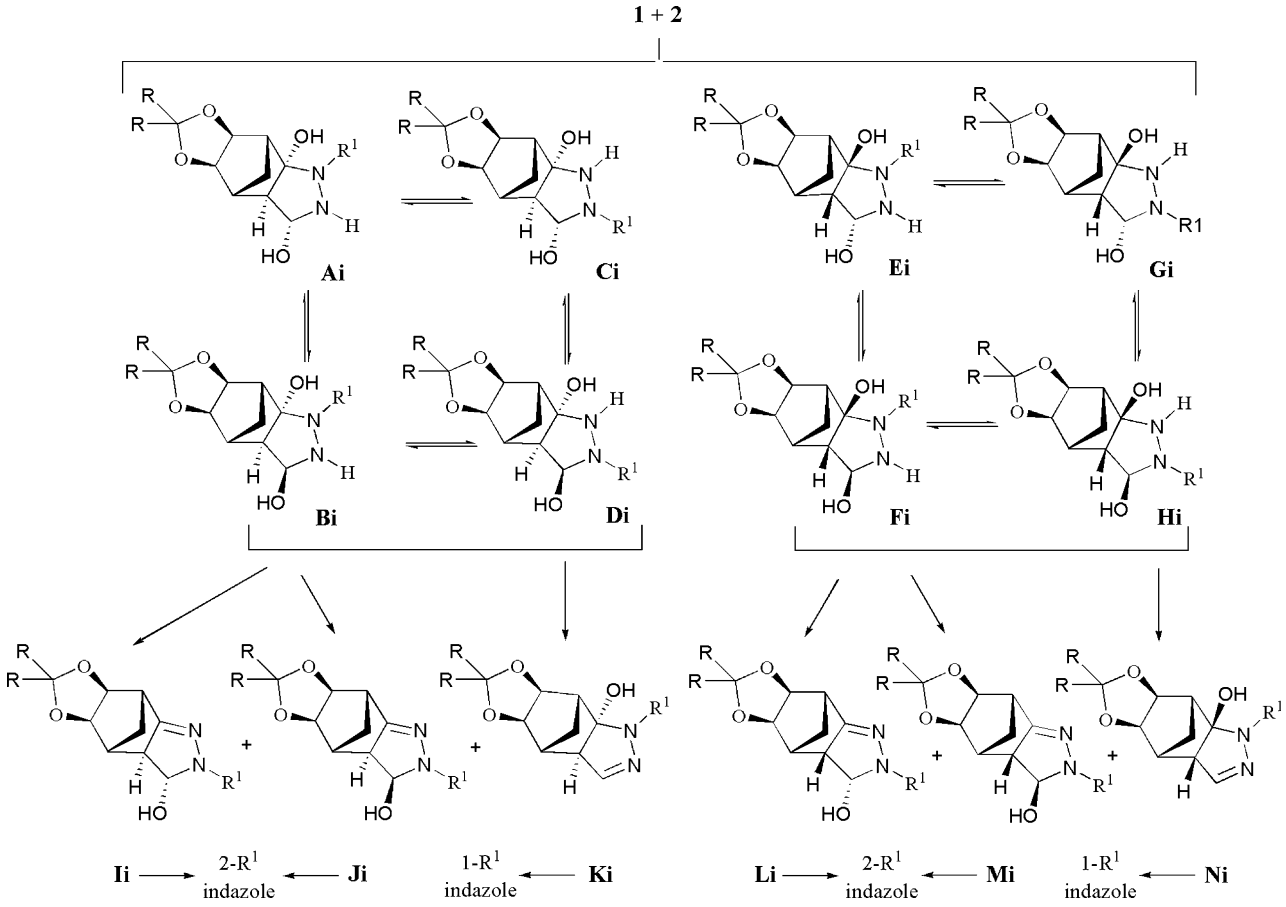
We carried out B3LYP/6-31G* calculations of the compounds of Scheme 8 belonging to the series **1** and **2**: four NH pyrazolidines, six NH pyrazolines, eight *N*-methyl pyrazolidines and six *N*-methylpyrazolines with the only simplification of replacing the methyl groups R of the 1,3-dioxolane ring by protons. The results are reported in Table 2. Although it is probable that the ordering of relative energies calculated for the *N*-methyl series **2** should be approximately valid for the *N*-phenyl series **3**, some discrepancies could be related to a specific effect of the phenyl ring.

Table 2 deserves some comments.

(1) The most stable hydroxypyrazolines have the structure **Ki**. Structure **K1** corresponds to compound **12** but the isolated *N*-phenyl derivative has the structure **N3**, which, in the *N*-methyl series is **N2** that lies only 10.6 kJ mol^{-1} above the minimum **K2**.
(2) The most stable dihydroxypyrazolidines have the structures **A1** (or **C1**) followed by **B1** (or **D1**) in the NH series **1** while in the *N*-methyl series the stability order is **D2**>**C2**>**A2**>**B2**.
(3) The final pyrazoles having the structures **11a** and **11b** must be formed by dehydration of **Ki** or **Ni**. The NH derivative **10** cannot be used for this discussion because all the ways led to tautomer 2*H*.
(4) The synthetic sequences could be: NH-series, **A1**→**K1**→**10**; *N*-methyl series, **D2**→**K2**→**11a**; *N*-phenyl series, **H3**→**N3**→**11b**. It is not necessary to assume an equilibration of the pyrazolidines.
(5) This analysis assumes that the process from the initial substrates (the hydroxymethyleneketone **6** and the corresponding hydrazine) to the different hydroxypyrazolines must be endergonic. Thus, even if this is a kinetic controlled process, the Hammond principle should apply, that is, the transition states should be product-like and their relative stabilities must be proportional to the relative stabilities of the products that will be formed.

3. Conclusions

Reactions of substituted hydrazines with appropriate derivatives of bicyclo[2.2.1]heptane preferably lead to the formation of 1-substituted derivatives of 4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole. This regioselectivity can be explained taking into account a plausible mechanism for the formation of pyrazoles from 1,3-dicarbonyl compounds, the structures of the isolated intermediate hydroxypyrazolines and the theoretical calculations of the stability of the intermediate dihydroxypyrazolidines and hydroxypyrazolines. Angular tension due to the carbocyclic system fused to the heterocyclic moiety seems to be a stabilizing factor of the hydroxypyrazolines structures as efficient as an EWG in the case of acyclic precursors.



R^1 = H, series **1**, R^1 = Me, series **2**, R^1 = Ph, series **3** ($\mathbf{A_1}$ to $\mathbf{N_3}$). Experimental R = CH_3, calculated R = H

Scheme 8. Dihydroxypyrazolidine and hydroxypyrazoline intermediates.

Table 2. Relative values of the energy (kJ mol^{-1}) of the molecules of Scheme 8

Compound	Series **1** (*N*-H)	E_{rel}	Series **2** (*N*-CH_3)	E_{rel}
Ai	**A1**	**0.00**	**A2**	7.72
Bi	**B1**	5.12	**B2**	10.08
Ci	**C1**	[0.00]	**C2**	3.26
Di	**D1**	[5.12]	**D2**	**0.00**
Ei	**E1**	23.18	**E2**	31.86
Fi	**F1**	13.04	**F2**	18.23
Gi	**G1**	[23.18]	**G2**	16.91
Hi	**H1**	[13.04]	**H2**	13.38
Ii	**I1**	44.96	**I2**	40.01
Ji	**J1**	40.20	**J2**	40.44
Ki	**K1**	**0.00**	**K2**	**0.00**
Li	**L1**	43.28	**L2**	43.08
Mi	**M1**	45.59	**M2**	40.21
Ni	**N1**	9.93	**N2**	10.61

4. Experimental

4.1. General

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. Hydroxymethyleneketone **6** was freshly prepared before its use.[19] Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded in a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in a Bruker AMX 300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin-Elmer 240B Elemental Analyser at the University of Santiago Microanalysis Service. Analyses indicated by the symbols of elements were within $\pm$0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm). X-ray diffraction data were collected in an Enraf-Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.[20]

4.1.1. ($\pm$)-(3a*R,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-Hydroxy-5,6-(isopropylidenedioxy)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole (12).** Hydrazine monohydrate (0.28 mL, 9.04 mmol) was added under argon to a well-stirred solution of freshly prepared **6** (0.95 g, 4.52 mmol) in dry toluene (25 mL), and the mixture was stirred for 3 h at room temperature. By simple filtration of the reaction mixture compound **12** was isolated (0.65 g; 64%). Compound **12** is a lightly coloured solid that was crystallized from EtOAc; mp 192–195 °C. IR (KBr) ν (cm^{-1}): 3314, 3098, 2994, 2973, 2950, 2910, 2860, 1594, 1460,

1406, 1380, 1304, 1272, 1206, 1180, 1165, 1122, 1068, 1047, 866, 846, 653. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.64 (s, 1H, 3-H); 5.80 (br s, 1H, D_2O exchange, NH); 4.68 (d, 1H, J=5.4 Hz, 6-H); 4.30 (d, 1H, J=5.1 Hz, 5-H); 2.47 (virtual s, 1H, D_2O exchange, OH); 2.42–2.39 (m, 3H); 1.70 (dd, 1H, J=11.3, 1.6 Hz, 8-H*H*); 1.45 (s, 3H, CH_3); 1.32 (s, 3H, CH_3); 1.25 (dd, 1H, J=11.3, 1.3 Hz, 8-*H*H). ^{13}C NMR and DEPT ($CDCl_3$) δ (ppm): 124.90 (C), 121.56 (CH), 114.89 (C), 83.24 (CH), 82.18 (CH), 45.93 (CH_2), 42.88 (CH), 41.72 (CH), 26.29 (CH_3), 24.67 (CH_3). EIMS *m*/*z* (%): 224 (M, 4), 209 (19), 149 (41), 119 (21), 97 (26), 85 (100), 84 (23), 83 (27), 82 (52), 81 (18), 77 (15), 66 (15), 65 (16), 59 (16), 55 (30), 53 (18). Single crystals suitable for X-ray diffractometry were obtained by dissolving crystals of **12** in the minimum quantity of cold ether in an open vial that was then placed in a larger container with a little pentane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals.

4.1.2. (±)-(3a*S,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-Hydroxy-5,6-(isopropylidenedioxy)-1-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole (13) and (±)-(*exo*,*exo*)-5,6-(isopropylidenedioxy)-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11b).** Phenylhydrazine (1.7 mL, 8.66 mmol) was added under argon to a well-stirred solution of freshly prepared **6** (0.91 g, 4.33 mmol) in dry toluene (25 mL) and the mixture was stirred for 5 h at room temperature, after which removal of the solvent under reduced pressure left a reddish solid residue (2.56 g) that was purified by column chromatography over silica gel using as eluent mixtures of hexane/EtOAc of different ratios 15/1, 10/1 and 5/1. From the fractions of the second eluent mixture (10/1) was obtained **11b** after removing the solvent under reduced pressure (0.25 g, 20%). Similarly, from the fractions corresponding to the third eluent (5/1) was obtained **13** (0.62 g, 48%) as a reddish residue that mixed with pentane and filtered afford a slightly coloured solid. Compound **11b**. White solid that was crystallized from pentane; mp=102–103 °C. IR (KBr) ν (cm^{-1}): 3006, 2982, 2952, 2920, 1600, 1511, 1486, 1454, 1427, 1378, 1205, 1165, 1024, 998, 982, 902, 867, 787, 759, 692, 639. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.62 (d, 2H, J=7.9 Hz, 2′H+6′H); 7.43 (t, 2H, J=7.7 Hz, 3′H+5′H); 7.38 (s, 1H, 3-H); 7.28–7.27 (m, 1H, 4′-H); 4.32 (dd, 2H, J=16.3, 4.7 Hz, 5-H+6-H); 3.61 (virtual s, 1H, 7-H); 3.28 (virtual s, 1H, 4-H); 2.56 (d, 1H, J=9.2 Hz, 8-*H*H); 2.35 (d, 1H, J=9.2 Hz, 8-H*H*); 1.53 (s, 3H, CH_3); 1.31 (s, 3H, CH_3). ^{13}C NMR and DEPT ($CDCl_3$) δ (ppm): 149.97 (C), 139.87 (C), 133.92 (CH), 133.89 (CH), 129.79 (C), 129.43 (CH), 126.45 (CH), 119.55 (CH), 114.45 (C), 82.88 (CH), 81.06 (CH), 46.57 (CH_2), 44.76 (CH), 41.82 (CH), 26.03 (CH_3), 24.39 (CH_3). EIMS *m*/*z* (%): 283 (M+1, 2), 282 (M, 5), 196 (16), 195 (100), 183 (10), 182 (61), 181 (16), 168 (14), 167 (21), 154 (12), 128 (7), 115 (6), 92 (10), 85 (18), 77 (88), 63 (13), 59 (22), 52 (16), 51 (70). Compound **13**. Yellowish solid that was crystallized from Et_2O/hexane; mp=180–185 °C. IR (KBr) ν (cm^{-1}): 3382, 2990, 2972, 2942, 1601, 1503, 1382, 1363, 1272, 1263, 1242, 1208, 1159, 1118, 1083, 1063, 1048, 1036, 971, 900, 870, 860, 792, 743. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32–7.28 (m, 4H); 6.94–6.89 (m, 1H, 4′-H); 6.69 (d, 1H, J=1.6 Hz, 3-H); 4.01 (d, 1H, J=4.7 Hz, 6-H); 3.89 (d, 1H, J=5.4 Hz, 5-H); 3.28 (d, 1H, J=4.8 Hz, 3a-H); 3.01 (virtual s, 1H, 7-H); 2.68 (d, 1H, J=5.1 Hz, 4-H); 2.52 (s, 1H, D_2O exchange, OH); 2.04 (d, 1H, J=10.8 Hz, 8-*H*H); 1.89 (dd, 1H, J=9.3, 1.4 Hz, 8-H*H*); 1.41 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). FABMS: *m*/*z* (%): 300.12 (M, 8), 283.12 (M−OH, 100). Single crystals suitable for X-ray diffractometry were obtained by dissolving crystals of **13** in the minimum quantity of cold ether in an open vial that was then placed in a larger container with a little hexane or cyclohexane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals.

4.2. Preparation of methanoindazoles by reaction de (±)-(*exo*,*exo*)-3-(hydroxymethylene)-5,6-(isopropylidendioxi)-bicyclo[2.2.1]heptan-2-one (6) with hydrazine and mono-substituted hydrazines. General method

To a rapidly-stirred solution of **6** (1 mmol) in freshly prepared dry toluene under Ar atmosphere and at room temperature was added in a single addition the corresponding hydrazine (1.2 mmol) and a catalytic amount of TsOH. The reaction mixture was refluxed in a Dean–Stark apparatus for 12 h. Once eliminated the solvents under reduced pressure, the remaining residue was purified by column chromatography over silica gel.

4.2.1. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (10). Eluent, hexane/EtOAc 1:1. Yield 67%. White solid with mp and spectroscopic features identical to those previously described.[10]

4.2.2. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-1-methyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11a). Eluent, hexane/EtOAc 1:1. Yield 45%. Dense colourless oil with spectroscopic features identical to those previously described.[10]

4.2.3. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11b). Eluent, hexane/EtOAc 15:1. Yield 52%. The spectroscopic data are identical to those above reported for the compound **11b**.

4.3. Transformation of pyrazolines into pyrazoles. General method

The corresponding pyrazoline (**12**, **7** or **13**; 0.21 mmol) dissolved in dry toluene (15 mL) was heated at reflux in a Dean–Stark apparatus during the time indicated in Table 1. When the reaction is completed (followed by TLC), the solvent was eliminated under reduced pressure and the resulting pyrazoles (**10**, **11a** and **11b**) were identified by their spectroscopic data. In the case of reactions carried out under acid catalysis, to the initial toluene solution was added a small amount of TsOH (3–5 mg) resulting in a much shorter reaction time (Table 1).

4.4. Computational details

B3LYP/6-31G* calculations with complete optimization of the geometry (maxima have been checked with frequency calculations) have been carried out.[21,22] In the case of the annular tautomerism (Scheme 6) the absolute values of

the energy of the most stable tautomer are: trimethylenepyrazole (2*H*: −342.94089 hartree); tetramethylenepyrazole (1*H*: −382.27423 hartree); pentamethylenepyrazole (2*H*: −421.59084 hartree); bicyclic derivative (2*H*: −420.34352 hartree). Particular care is necessary to obtain the minimum energy conformations of the seven membered rings, the pseudo-chair form.[23]

In the case of the pyrazolidines and pyrazolines of Scheme 8, we have calculated two conformations of the OH group (compounds **Li**, **Mi** and **Ni**) that with the OH pointing towards the interior of the ring being the most stable. The energies of the absolute minima are: **A1**=**C1** (R^1=H, −761.69862 hartree), **K1** (R^1=H, −685.27996 hartree), **D2** (R^1=CH_3, −761.69862 hartree), **K2** (R^1=CH_3, −724.59130 hartree).

Acknowledgements

We thank Xunta de Galicia for financial support (under project no. PGIDIT02BTF20305PR) as well as the Ministries of Education and Science and Health (projects no. BQU2003-01251 and SAF-2003-08003-C02-02).

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Tetrahedron 62 (2006) 3370–3379
Tetrahedron

Synthesis of optically active amphiphilic tetrathiafulvalene derivatives

Elba Gomar-Nadal, Concepció Rovira and David B. Amabilino*

Departament de Nanociència Molecular i Materials Orgànics, Institut de Ciència de Materials de Barcelona (ICMAB), Consejo Superior de Investigaciones Científicas (CSIC), Campus Universitari, 08193 Bellaterra, Catalonia, Spain

Received 10 October 2005; revised 10 January 2006; accepted 17 January 2006

Available online 17 February 2006

Abstract—The synthesis and characterization of novel chiral tetrathiafulvalenes bearing two long alkyl chains at one end of the π-electron rich unit and different functional groups—ester, acid or thiolate—at the other extreme is described. The synthetic method requires the preparation of 1,3-dithiol derivatives with two stereogenic centers. Different routes and reaction conditions were explored to form these compounds, whose optimized synthesis involved the nucleophilic substitution of a chiral bromo methylene derivative with tetrabutylammonium bis(2-thioxo-1,3-dithiole-4,5-dithiolate)zincate. The tetrathiafulvalenes were prepared by coupling the 1,3-dithiol derivative with 4,5-bis(methoxycarbonyl)-1,3-dithiol-2-one or 4,5-bis(2-cyanotehylthio)-1,3-dithiol-2-thione. The products were fully characterized, including by circular dichroism spectroscopy, which confirmed their optical activity. They are promising candidates to be used as building blocks in supramolecular materials for molecular electronics, to produce systems with unique electrical, magnetic or optical properties that stem from their chirality.
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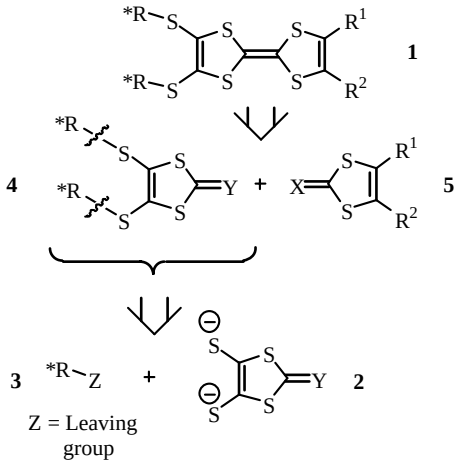
1. Introduction

The stereochemistry of molecular components has significant consequences for the properties of chemical systems of which they form a part, such us magnetic and conducting properties.[1] Tetrathiafulvalene (TTF) derivatives[2] are very versatile electro-active molecules widely used as building blocks to prepare organic metals, for supramolecular functions[3] and in molecular electronics.[4] The preparation of optically active compounds of this type offers, then, the creation of new substances with novel characteristics. Some chiral TTF derivatives have been previously reported.[5–8] These compounds have been used to form chiral conducting charge transfer complexes and salts mainly.[5,7] However, away from the constrictions of crystal space, they are also interesting for preparing multifunctional materials in the form of liquid crystals, thin films, self-assembled monolayers (SAMs), dendrimers and polymers for use in molecular (opto)electronic devices with new properties that arise from the chirality of the molecule, and in which (more often than not) an amphiphilic character is present.

In these systems it is often necessary to prepare components with long alkyl chains, which provide the amphiphilic nature, to ensure liquid crystallinity, solubility and processing characteristics in general. To the best of our knowledge, the synthetic routes to chiral TTFs reported to date have not incorporated long alkyl chains. The efficiency of the cyclic sulphate ester route to chiral TTFs suffers when the size of the substituent on the cyclic sulphate is increased.[5,8] To overcome these problems, we envisaged the preparation of TTFs of type **1** (see Scheme 1) introducing directly two chiral chains (**3**) by reaction of the readily available di-anion 2-thioxo-1,3-dithiole-4,5-



Scheme 1.

Keywords: Stereochemistry; Circular dichroism; Molecular electronics; π-Donor.
* Corresponding author. Tel.: +34 935801853; fax: +34 935805729; e-mail: amabilino@icmab.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.056

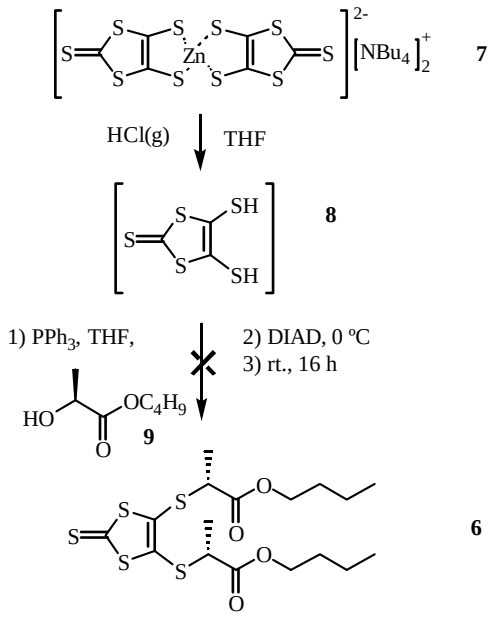
dithiolate (**2**), where a great body of literature exists for achiral components with long alkyl chains,[9] to give a 1,3-dithiole derivative with general structure **4**. Subsequently, coupling of 1,3-dithio-l,2-ones (or -thiones) **4** and **5** with trialkyl phosphites[10] would afford the desired compounds **1**.

Here, we describe the synthesis of new chiral TTFs of type **1** with two stereogenic centers in long alkyl chains at one extreme of the π-electron rich unit, and functional groups at the other that will help to incorporate the molecule into chemical systems.

2. Results and discussion

2.1. Synthesis of enantiomeric 1,3-dithiol-2-thiones

Different strategies were considered for the preparation of optically active 1,3-dithiol derivatives with two stereogenic centers and long alkyl chains (**4**). The synthesis of the chiral 1,3-dithiol-2-thione **6** (Scheme 2) was attempted, taking advantage of the stereoselectivity of the Mitsunobu[11,12] reaction for the introduction of stereogenic centers in the α-position to heteroatoms. A stable form of the synthon **2** is tetrabutylammonium bis(2-thioxo-1,3-dithiole-4,5-dithiolate)zincate[13] (**7**, Scheme 2). The complex was treated with dry hydrogen chloride in THF, and a change in color of the solution was observed—from purple to yellow, presumably resulting from decomplexation of the metal ion and the formation of the unstable[14] dithiol **8**. After bubbling nitrogen through the solution to eliminate the excess of hydrogen chloride, treatment of the intermediate with the lactate **9** under Mitsunobu reaction conditions[11,12] did not give the desired product (**6**) despite the fact that this type of coupling between alcohols and thiols has been reported in the past.[15]



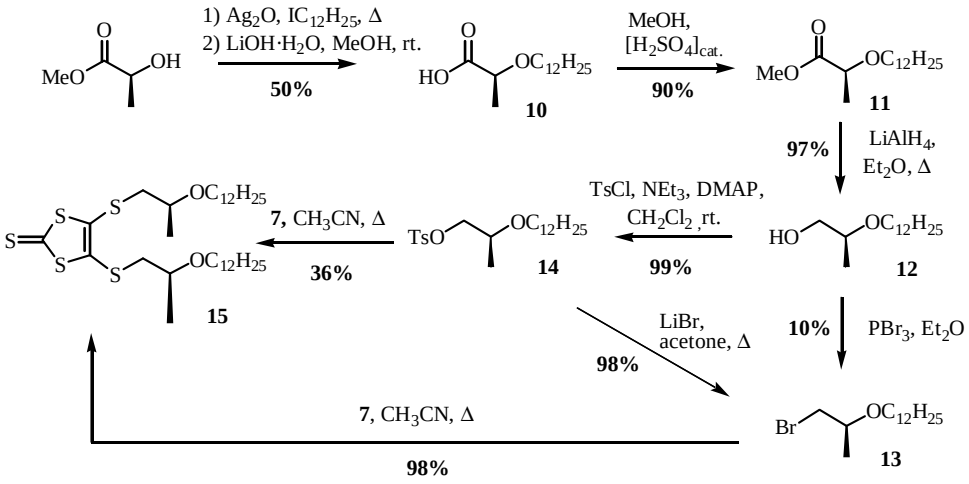
Scheme 2.

The direct reaction of alcohols and zinc complexes has also been reported using the Mitsunobu procedure.[16] However, treatment of the zinc complex with lactate **9** adding 4.1 equiv of acetic acid (or without adding any acid) under these conditions did not lead to the formation of **6** either, presumably because of the strength of the chelate. Another route explored to synthesize **6** was the mono-deprotection of 4,5-bis(2-cyanotehylthio)-1,3-dithiol-2-thione[17] with 1 equiv of CsOH and subsequent reaction of the resulting thiolate salt with lactate **9** under Mitsunobu conditions, but again no reaction was observed. The lack of success in all these reactions is most probably related to: (i) the role of the proton source[12] in the Mitsunobu reaction and (ii) the sterical impediment of the stereogenic center hindering the reactivity with the bulky (di)sulfide, a statement that was corroborated for the experimental data presented in this article (see below) and by Wallis and co-workers[8] research.

To avoid the possible reactivity problems caused by the proximity of the stereogenic carbon atom to the electrophilic group, a synthetic route where the introduction of the chiral 'tails' took place through a nucleophilic substitution one atom further from the chiral center was envisaged (Scheme 3). This synthetic pathway started with the preparation of the chiral acid **10** in two steps,[18] conversion to ester **11** whose treatment with $LiAlH_4$ led to alcohol **12**. Bromoderivative **13** was prepared by two methods (Scheme 3). The first one consisted of treating **12** with PBr_3,[19] which gave a mixture of the desired product (**13**) and the characteristic intermediates of the reaction,[20] which, even after passing HBr, were not completely transformed into the desired product, so very low yields were attained (~10%, Table 1). Alternatively, alcohol **12** was first tosylated and the functional group of the resulting product (**14**) was subsequently exchanged for bromide by reaction with LiBr in refluxing acetone, giving **13**. The yield of the reaction depends strongly on the refluxing time (Table 1). Long reaction times ensured a quantitative conversion of **14** to **13**. When NaBr was used, instead of LiBr, the reaction did not take place.

To optimize the reaction conditions to synthesize 4,5-bis((*S*)-2-dodecyloxy-propanyl)-1,3-dithiol-2-thione (**15**, Scheme 3), the synthesis of the analogous achiral thione 4,5-bis(decacyl)-1,3-dithiol-2-thione (**16**, Scheme 4) was used as a reference. The nucleophilic substitution reaction with the zinc complex **7** to form **16** gave higher yields using 1-bromodecane than tosylate **17** (Table 2). Addition of NaI to interchange the tosylate group for iodine in situ increased the yield of the reaction, which even so was lower than using 1-bromodecane as a starting material. Bromine and tosylate are both very good leaving groups for nucleophilic substitution reactions; so, the differences in yield observed are most likely due to steric impediment. [21]

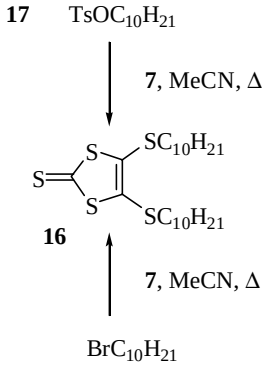
The same tendency was observed when the reactions were done with the analogous chiral reactants (Table 2). The efficiency of the reaction to form the chiral thione **15** (Scheme 3) was higher using the chiral bromide derivative (**13**) than the corresponding chiral tosylate (**14**). Comparing the reactions done under the same conditions for **15** and **16** the influence of the stereogenic carbon atom in the reaction (mentioned before) was evident. Longer refluxing times were necessary for the formation of the chiral 1,3-dithiol-2-



Scheme 3.

Table 1. Reaction conditions tested to produce **13**

Starting material	Reaction conditions	Yield **13** (%)
12	(1) PBr_3 in CCl_4; (2) 20 min; (3) HBr	11
	(1) PBr_3 in Et_2O; (2) 3 days; (3) HBr	9
14	(1) LiBr, acetone; (2) 2 h reflux	45
	(1) NaBr, acetone; (2) 3 h reflux	0
	(1) LiBr, acetone; (2) 20 h reflux	98



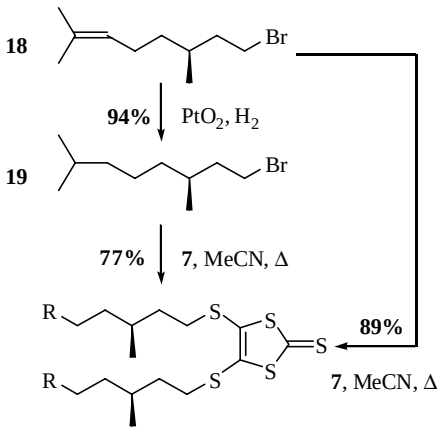
Scheme 4.

Table 2. Comparison of the reactions condition examined to form **15** and **16**

Starting material	Reaction conditions	Product	Isolated yield (%)
17	**7**, MeCN, reflux 3 h	**16**	3
	7, MeCN, NaI, reflux 3 h	**16**	60
$BrC_{10}H_{21}$	**7**, MeCN, reflux 3 h	**16**	87
14	(1) **7**, MeCN, reflux 2h; (2) NaI, reflux 1h	**15**	12
	7, MeCN, reflux 20 h	**15**	36
13	**7**, MeCN, reflux 20 h	**15**	98

thione (**15**) than for the comparable achiral thione (**16**) in order to have the same yield, because of the steric impediment created by the stereogenic center close to the electrophilic carbon atom. The thione **15** gave NMR and IR spectra in accord with the proposed structure. No evidence of the presence of diastereomers was observable. The laser desorption–ionization mass spectrum showed a characteristic peak corresponding to the addition of one of the alkyl substituent fragment at the thiol to the thione sulphur atom.

The preparation of 1,3-dithiol derivatives of type **4** (Scheme 1) which contain the stereogenic centers located further from the TTF moiety was achieved (Scheme 5) by reaction of the zinc complex **7** with (*S*)-(+)-citronellyl bromide (**18**) and **19**—that was obtained reducing **18** with Adam's catalyst. The chiral 1,3-dithiol-2-thiones **20** and **21** were formed in high yields (80–90%), which are comparable to the ones obtained with achiral bromides for the same refluxing times (see e.g., reaction of 1-bromodecane with **7**, in Table 2). The presence of a stereogenic atom two atoms away from the electrophilic carbon atom (one atom further away than in the synthesis of **15**) did not affect the yield of the reaction. Hence, the position of the stereogenic atom with respect to the atom on which the reaction takes place is important and can dramatically affect the yield of the reaction, to the point that we were unable to prepare the compound where the stereogenic center is adjacent to the electrophilic sulphur atoms.



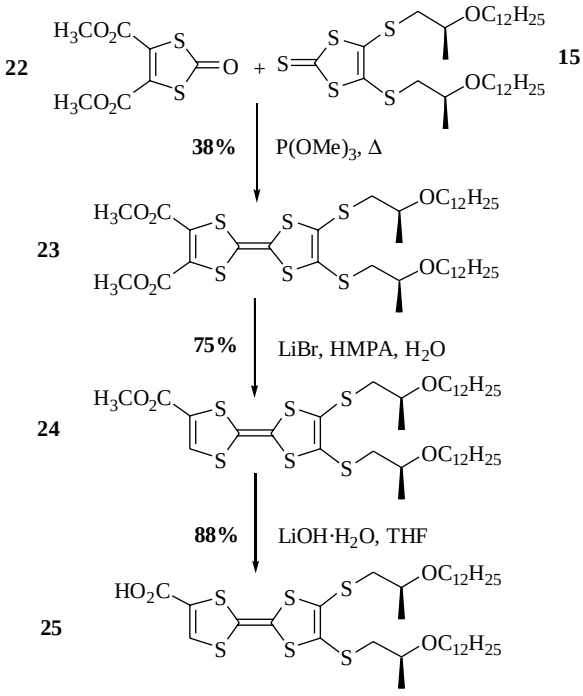
20 R = –CH=C(CH$_3$)$_2$

21 R = –CH$_2$CH(CH$_3$)$_2$

Scheme 5.

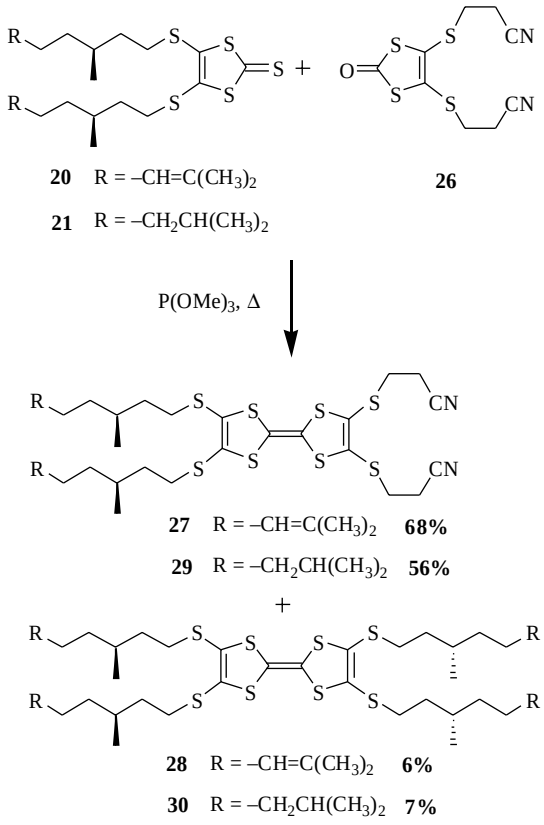
2.2. Synthesis and characterisation of chiral TTF derivatives

Coupling of the appropriate 1,3-dithio-2-thiones (or -ones) with trimethyl phosphite[10] allowed the preparation of chiral TTF derivatives of type **1** directly (Scheme 1). Thus, the cross-coupling reaction of **15** and 4,5-bis(methoxycarbonyl)-1,3-dithiol-2-one (**22**)[22] gave the chiral bisester TTF **23** in about 40% yield (Scheme 6), a good result considering that the symmetrical TTF derivatives are also formed during the reaction.[10] The redox properties of this TTF are those to be expected of a compound of this type with two strongly electron withdrawing ester groups at one extreme of the molecule. The first oxidation process—from neutral to cation radical—takes place at 683 mV, while further oxidation to the dication occurs at 1055 mV (in CH_2Cl_2, 0.1 M $[NBu_4][PF_6]$, Pt-electrodes and a Ag/AgCl electrode as reference). Treatment of the bisester **23** with an excess of LiBr in HMPA at 80 °C produced monodecarboxymethylation and basic hydrolysis of the resulting monoester **24** led to the chiral acid functionalized TTF **25** (Scheme 6). Monoester **24** exhibited oxidation waves at 635 and 1051 mV (conditions as for **23**).



Scheme 6.

In the same way as for the preparation of **23**, coupling of oxo compound **26** with either thione **20** or **21** leads to excellent yields of the corresponding TTFs **27** and **29**, respectively (Scheme 7), in which the stereogenic centers are one carbon further away from the π-electron rich core than in **23**, and here the propionitrile protecting groups are incorporated. This group can be sequentially removed using base,[17] and thus **27** and **29** are useful building blocks for a variety of structures, including chiral phthalocyanine TTF composite molecules.[22] The yield of **27** (68%) is notably high for this



Scheme 7.

type of coupling reaction. Cyclic voltammetry of **27** and **29** gave oxidation waves at identical positions, 650 and 1015 mV (in CH_2Cl_2, 0.1 M $[NBu_4][PF_6]$, Pt-electrodes and a Ag/AgCl electrode as reference).

All the TTF derivative compounds were identified clearly by laser desorption–ionization time-of-flight mass spectrometry, which shows the molecular ion peaks as the most abundant species in positive mode, with the exception of the carboxylic acid derivatives, which decarboxylate under the mass spectrometric conditions. The NMR spectra are also fully consistent with the structures of the compounds.

The optical activity of the TTF compounds was studied by circular dichroism (CD) spectroscopy, which provides direct information on the chromophores present in the molecule. It was not possible to use polarimetry to compare the optical activity because the ratio of absorption to rotation is too high. The CD spectra of representative examples of the two families of compounds, with the different stereogenic centers, are shown in Figure 1. Compound **23** shows a weak negative Cotton effect at 400 nm and a stronger positive one at 300 nm, below which the absorption becomes too strong to reliably measure the spectrum. The spectra of **24** and **25** are practically superimposable on this one. The TTF derivative **29** shows just one broad Cotton effect centerd on 350 nm. The slightly weaker Cotton effect in this compound compared with **23** is most likely due to the slightly larger distance between the stereogenic centre and the chromophore.

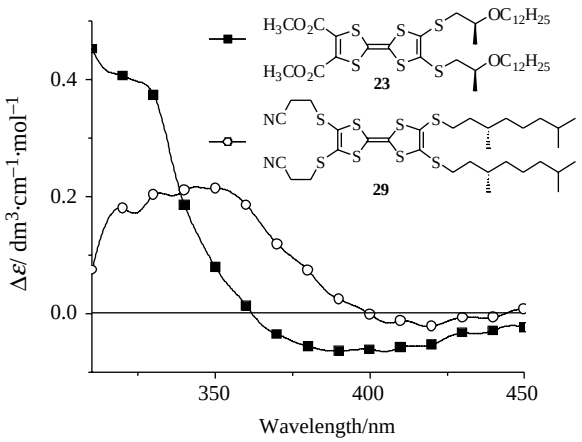


Figure 1. Circular dicroism spectra of **23** and **29** in THF.

3. Conclusion

In the synthesis of this series of chiral TTF derivatives using the routes described here the yield of the thione precursors depends critically on the position of the chiral center in the lateral chains. Steric interactions between the thiolate groups in 2-thioxo-1,3-dithiole-4,5-dithiolate and the incoming chiral electrophile mean that at least one methylene unit is necessary between the sulphur atom and the stereogenic center. Once formed, the TTFs show all the characteristics of this family of compounds, but also optical activity. This fact and their inherent chirality—which has important consequences during organization of π-functional molecules—makes them, and related compounds, very interesting for preparing multifunctional materials with new properties that arise from the chirality of the molecular building blocks.

4. Experimental

4.1. Materials and methods

Tetrabutylammonium bis(2-thioxo-1,3-dithiole-4,5-dithiolate)zincate (**7**),[13] 4,5-bis(methoxycarbonyl)-1,3-dithiol-2-one (**22**)[23] and 4,5-bis(2-cyanoethylthio)-1,3-dithiol-2-one (**26**)[24] were synthesized using procedures reported in the literature. All other chemicals were commercial products and were used as obtained. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium/benzophenone, acetone over K_2CO_3, and CH_2Cl_2 and MeCN over P_2O_5. Thin-layer chromatography (TLC) was performed on aluminium plates coated with Merck Silica gel 60 F254. Developed plates were air-dried and scrutinized under a UV lamp except for compounds **10** and **11** that were visualized by putting the plate in an iodine chamber. Silica gel 60 (35–70 mesh, SDS) was used for column chromatography.

Melting points were determined using a Melting Point SMP10, BIBBY Stuart Scientific instrument and are uncorrected. LDI-TOF-MS were obtained using a Kratos Kompact Maldi 2 K-probe (Kratos Analytical) operating with pulsed extraction of the ions in positive and linear high power mode. The samples were deposited directly onto a non-polished stainless steel sample plate from CH_2Cl_2 solution.

Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum One spectrometer. ^1H and ^{13}C NMR spectra were obtained using a Bruker Avance 250 spectrometer with deuterated solvent as lock and tetramethylsilane as internal reference. Polarimetry was performed using a Dr. Krenchen+Electronik Propol polarimeter in a 1 cm cell (20 mg/ml using as a solvent CH_2Cl_2). Cyclic voltammograms were recorded with the conventional three-electrode configuration in dry CH_2Cl_2 containing 0.1 M $[NBu_4][PF_6]$, as a supporting electrolyte, with Pt-electrodes and a Ag/AgCl electrode as a reference one.

4.1.1. (*S*)-2-Dodecyloxypropanoic acid (10). To a solution of (−)-methyl L-lactate (2.0 ml, 21 mmol) and 1-iodododecane (12.0 ml, 49 mmol) was added silver (I) oxide (6.53 g, 28 mmol). The mixture was sonicated for 10 min before refluxing for 24 h in the dark. The suspension was filtered through Celite, washed with diethyl ether, and the solvent was removed under vacuum. To the remaining oil (which contained the ester and by-products such as starting material, iodoalkane, alkanol, and alkyl ether) was added MeOH (70 ml), H_2O (30 ml) and $LiOH\cdot H_2O$ (2.80 g, 67 mmol), and the mixture was stirred overnight at room temperature. After this time, NaOH (aqueous, 75 ml, 3.5%) was added and the organic products were extracted with diethyl ether. The aqueous phase, which contains the salt of the chiral acid, was acidified with HCl (aqueous, 2 N). The product was extracted with CH_2Cl_2 (3×100 ml) and dried over $MgSO_4$, and the solvent evaporated. The colorless residue was purified by flash chromatography using hexane–EtOAc [9/1] mixture as eluent to obtain 2.60 g (50%) of a transparent oil. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): −4.05 deg cm^2 g^{-1}. FT-IR (NaCl discs): 3300–2500 (w, OH), 2925 (s), 2855 (s), 1723 (s, C=O), 1462 (w), 1421 (w), 1371 (w), 1287 (w), 1241 (w), 1130 (m, C–O–C), 1013 (w), 932 (w), 828 (w), 721 (w), 658 (w), 561 (w), 523 (w), 489 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 9.60 (br s, 1H, –O*H*), 3.99 (q, J=6.8 Hz, 1H, –C*H*(CH_3)), 3.60 (dt, J=8.8, 6.6 Hz, 1H, –OCH_2), 3.43 (dt, J=8.8, 6.6 Hz, 1H, –OCH_2), 1.61 (m, J=6.8 Hz, 2H, –OCH$_2$CH_2), 1.45 (d, J=6.8 Hz, 3H, –CH(CH_3)), 1.40–1.20 (m, 18H, –(CH_2)$_9$CH$_3$), 0.89 (t, J=6.6 Hz, 3H, –(CH$_2$)$_9$CH_3) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 178.4 (*C*=O), 74.5 (–*C*H(CH_3)), 70.6 (–OCH_2), 31.9 (–O(CH$_2$)$_9$*C*H$_2$), 29.6 (–OCH$_2$*C*H$_2$), 29.6, 29.5, 29.4 and 29.3 (–O(CH$_2$)$_3$(*C*H$_2$)$_6$), 26.0 (–O(CH$_2$)$_2$*C*H$_2$), 22.7 (–*C*H$_2$CH$_3$), 18.3 (–CH(*C*H$_3$)), 14.0 (–(CH$_2$)$_{11}$*C*H$_3$) ppm.

4.1.2. Methyl (*S*)-2-dodecyloxypropanoate (11). A solution of (*S*)-2-dodecyloxypropanoic acid (**10**, 722 mg, 2.952 mmol) and sulphuric acid (three drops, 95–98%) in MeOH (45 ml) was refluxed for 5 h. After this time, the mixture was cooled to room temperature and $NaHCO_3$ (5 ml, saturated aqueous solution) was added. The MeOH was evaporated and the aqueous phase was extracted with CH_2Cl_2 (3×20 ml). The organic phase was washed with (3×100 ml) and dried over $MgSO_4$, and the solvent evaporated. The remaining oil (763 mg) was purified by flash chromatography using hexane–EtOAc [19/1] mixture as eluent to obtain 687 mg (90%) of a slightly yellow transparent oil. Anal. Calcd for $C_{16}H_{32}O_3$: C 70.54, H 11.84;

Found: C 70.05, H 11.98. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): −45.43 deg cm^2 g^{-1}. FT-IR (NaCl discs): 2987 (w), 2925 (s), 2855 (s), 1758 (s, C=O), 1740 (m, C=O), 1460 (w), 1371 (w), 1330 (w), 1273 (w), 1202 (m, C–O), 1148 (m, C–O–C), 1075 (w), 982 (w), 843 (w), 754 (w), 722 (w), 656 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 4.00 (q, J=6.8 Hz, 1H, –C*H*(CH_3)), 3.74 (s, 3H, –CO_2C*H*$_3$), 3.54 (dt, J=8.9, 4.4 Hz, 1H, –OC*H*$_2$), 3.35 (dt, J=8.9, 4.4 Hz, 1H, –OC*H*$_2$), 1.59 (qi, J=7.0 Hz, 2H, –OCH_2C*H*$_2$), 1.39 (d, J=6.9 Hz, 3H, –CH(C*H*$_3$)), 1.40–1.20 (m, 18H, –(C*H*$_2$)$_9$$CH_3$), 0.88 (t, J=6.5 Hz, 3H, –$(CH_2)_{11}$C*H*$_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 173.9 (*C*=O), 74.9 (–*C*H(CH_3)), 70.5 (–O*C*H$_2$), 51.7 (–CO_2*C*H$_3$), 31.9(–*C*H$_2$$CH_2$$CH_3$), 29.7 (–$OCH_2$*C*H$_2$), 29.7, 29.6, 29.6, 29.6, 29.4 and 29.3 (–(*C*H$_2$)$_6$(CH_2)$_2$$CH_3$), 26.0 (–($CH_2$)$_2$*C*H$_2$), 22.7 (–*C*H$_2$$CH_3$), 18.6 (–CH(*C*H$_3$)), 14.1 (–O($CH_2$)$_9$*C*H$_3$) ppm.

4.1.3. (*S*)-2-Dodecyloxypropan-1-ol (12). To a suspension of $LiAlH_4$ (39 mg, 1.03 mmol) in dry diethyl ether (15 ml) was added drop-wise a solution of methyl (*S*)-2-dodecyloxy-propanoate (**11**, 288 mg, 1.11 mmol) in dry diethyl ether (15 ml) during 15 min. The mixture was refluxed for 1 h. After this, the solution was cooled to room temperature and then to 0 °C introducing it in an ice bath, and H_2O was added drop-wise to eliminate the remaining $LiAlH_4$. The reaction product was filtered from the white sludge, the filtrate was dried over $MgSO_4$ and the solvent evaporated leaving a slightly yellow transparent oil (270 mg). The sludge in the filter funnel was dissolved in sulphuric acid (aqueous, 20%) and the resulting solution was extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The residual oil obtained from the sludge treatment (85 mg) was combined with the first oil and they were purified by flash chromatography using hexane–EtOAc [3/1] mixture as eluent to obtain 240 mg (94%) of a slightly yellow transparent oil. Anal. Calcd for $C_{15}H_{32}O_2\cdot 1/4H_2O$: C 72.38, H 13.16; Found: C 72.43, H 13.29. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): +27.12 deg cm^2 g^{-1}. FT-IR (NaCl discs): 3700–3200 (w, wide, OH), 2925 (s), 2855 (s), 1465 (w), 1374 (w), 1343 (w), 1147 (w), 1096 (m, C–O–C), 1048 (m), 989 (w), 915 (w), 834 (w), 721 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 3.65–3.35 (m, 5H, –CH_2C*H*(CH_3)OCH_2), 2.38 (br s, 1H, –O*H*), 1.58 (m, J=6.9 Hz, 2H, –OCH_2C*H*$_2$), 1.45–1.20 (m, 18H, –(C*H*$_2$)$_9$$CH_3$), 1.40 (d, J=6.1 Hz, 3H, –CH(C*H*$_3$)O), 0.88 (t, J=6.6 Hz, 3H, –O(CH_2)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 75.8 (–*C*H(CH_3)), 68.9 (–*C*H_2OH), 66.3 (–O*C*H$_2$), 31.9 (–*C*$H_2$$CH_2$$CH_3$), 30.1 (–$OCH_2$*C*H$_2$), 29.7, 29.60, 29.5, 29.4 and 29.3 (–O(CH_2)$_3$(*C*H$_2$)$_6$), 26.2 (–O(CH_2)$_2$*C*H$_2$), 22.7 (–*C*$H_2$$CH_3$), 15.9 (–CH(*C*H$_3$)), 14.1 (–($CH_2$)$_{11}$*C*H$_3$) ppm.

4.1.4. 1-((*S*)-2-Bromo-1-methyl-etoxy)-dodecane (13). *Method A*. To a solution of (*S*)-2-dodecyloxy-propan-1-ol (**12**, 221 mg, 0.967 mmol) in diethyl ether (5 ml) at 0 °C under argon atmosphere was added drop-wise a solution of PBr_3 (0.100 ml, 1.064 mmol) in diethyl ether (5 ml) for 1 h. The reaction was then stirred for 2 days. The excess PBr_3 was destroyed with water, and the organic layer was separated, washed successively with equal volumes of H_2O, orthophosphoric acid (aqueous 85%), and $NaHCO_3$ (saturated aqueous solution) and twice with H_2O, and was dried over $MgSO_4$. The infrared spectrum of the residue obtained after evaporating the solvent showed the peaks at 1250, 950–1000, and 2400 cm^{-1} characteristic of partially converted phospite esters. Dry HBr gas was bubbled through the ether solution at a slow rate for about 15 min at room temperature. The diethyl ether solution was carefully washed with H_2O, $NaHCO_3$ (saturated aqueous solution), H_2O, dried over $MgSO_4$ and the solvent evaporated. The remaining oil (150 mg) was purified by flash chromatography using hexane–CH_2Cl_2 [1/1.5] mixture as eluent to obtain 28 mg (10%) of a slightly yellow transparent oil.

Method B. A solution of (*S*)-2-dodecyloxypropyl toluene-4-sulphonate (**14**, 358 mg, 1.098 mmol) and LiBr (2.3 g, 26 mmol) in acetone (10 ml) was refluxed overnight. The acetone was removed and diethyl ether (30 ml) was added. The diethyl ether solution was washed with H_2O, dried over $MgSO_4$ and the solvent evaporated. The remaining oil (358 mg) was purified as in Method A to give a yield of 94%. Anal. Calcd for $C_{15}H_{31}BrO$: C 58.62, H 10.17; Found: C 59.08, H, 10.36. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): +4.09 deg cm^2 g^{-1}. FT-IR (NaCl discs): 2925 (s), 2854 (s), 1466 (w), 1376 (w), 1326 (w), 1229 (w), 1196 (w), 1140 (w), 1099 (m, C–O–C), 920 (w), 722 (w), 671 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 3.64 (sxd, J=6.1, 1.2 Hz, 1H, –C*H*(CH_3)), 3.50 (t, J=6.5 Hz, 2H, –OC*H*$_2$), 3.41 (dd, J=23.3, 10.2 Hz, 1H, –C*H*$_2$Br), 3.39 (dd, J=23.3, 10.2 Hz, 1H, –C*H*$_2$Br), 1.70–1.20 (m, 23H, –CH(C*H*$_3$)OCH_2(C*H*$_2$)$_{10}$-CH_3), 0.91 (t, J=6.7 Hz, 3H, –O(CH_2)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 76.6 (–*C*H(CH_3)), 69.5 (–O*C*H_2(CH_2)$_{10}$), 36.5 (–*C*H_2Br), 32.0 (–*C*$H_2$$CH_2$-$CH_3$), 30.0 (–$OCH_2$*C*H$_2$), 29.7, 29.6, 29.5 and 29.4 (–(*C*H_2)$_6$(CH_2)$_2$$CH_3$), 26.2 (–O($CH_2$)$_2$*C*H$_2$), 22.7 (–*C*$H_2$$CH_3$), 19.0 (–CH(*C*H$_3$)), 14.1 (–O($CH_2$)$_{11}$*C*H$_3$) ppm.

4.1.5. (*S*)-2-Dodecyloxypropyl toluene-4-sulphonate (14). (*S*)-2-Dodecyloxypropan-1-ol (**12**, 195 mg, 0.853 mmol) is dissolved in CH_2Cl_2 (25 ml) and cooled in an ice bath (0 °C). NEt_3 (0.130 ml, 0.938 mmol) and dimethylamino-pyridine (DMAP, two small crystals) were then added, followed by the addition of toluene–*p*-sulphonyl chloride (TsCl, 179 mg, 0.938 mmol) in small portions with constant stirring. The resulting solution was stirred overnight. Ice (25 g), HCl (aqueous 10%, 5 ml) and H_2O (36 ml) are added and the mixture was stirred until the ice was melted. The organic layer was washed with H_2O (3×50 ml), dried over $MgSO_4$ and the solvent was evaporated. The remaining oil was purified by flash chromatography using hexane–CH_2Cl_2 [1/3] mixture as eluent to obtain 267 mg (84%) of a slightly yellow transparent oil. FT-IR (NaCl discs): 2925 (s), 2855 (s), 1919 (w), 1754 (w), 1599 (w), 1496 (w), 1457 (m), 1367 (s, –SO_2–), 1307 (w), 1292 (w), 1210 (w), 1188 (s, –SO_2–), 1178 (s, –SO_2–), 1098 (m, C–O–C), 1020 (w), 988 (m), 820 (m), 814 (m), 792 (w), 722 (w), 706 (w), 688 (w), 667 (m), 575 (w), 555 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 7.81 (d, J=8.4 Hz, 2H, $CH_3CCH_{ar}CH_{ar}$C–), 7.35 (d, J=8.4 Hz, 2H, $CH_3CCH_{ar}CH_{ar}$C–), 3.97 (dd, J=7.68, 3.28 Hz, 1H, –C*H*$_2$OTs), 3.93 (dd, J=7.68, 3.28 Hz, 1H, –C*H*$_2$OTs), 3.62 (sx, 1H, J=6.2 Hz, –C*H*(CH_3)), 3.43 (dt, J=8.8, 6.6 Hz, 1H, –OC*H*$_2$), 3.35 (dt, J=8.8, 6.6 Hz, 1H, –OC*H*$_2$), 2.46 (s, 3H, $CH_3CCH_{ar}CH_{ar}$C–), 1.50–1.20 (m, 18H, –(C*H*$_2$)$_9$$CH_3$), 1.12 (d, J=6.2 Hz, 3H, –CH(C*H*$_3$)), 0.89 (t, J=6.4 Hz, 3H, –O(CH_2)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 144.7 (CH_3*C*$CH_{ar}CH_{ar}$C–), 133.4 ($CH_3CCH_{ar}CH_{ar}$*C*–), 129.7 (CH_3C*C*$H_{ar}CH_{ar}$C–), 127.9 (CH_3CCH_{ar}*C*H_{ar}C–), 72.8

(–*C*H(CH$_3$)), 72.7 (–*C*H$_2$CH(CH$_3$)), 69.6 (–O*C*H$_2$CH$_2$), 31.9 (–*C*H$_2$CH$_2$CH$_3$), 29.9 (–OCH$_2$*C*H$_2$), 29.6, 29.6, 29.4 and 29.3 (–(*C*H$_2$)$_6$(CH$_2$)$_2$CH$_3$), 26.0 (–O(CH$_2$)$_2$*C*H$_2$), 22.6 (–*C*H$_2$CH$_3$), 21.6 (*C*H$_3$CCH$_{ar}$CH$_{ar}$C–), 16.8 (–CH(*C*H$_3$)), 14.1 (–(CH$_2$)$_{11}$*C*H$_3$) ppm.

4.1.6. 4,5-Bis((*S*)-2-dodecyloxypropanyl)-1,3-dithiol-2-thione (15). A solution of the alkyl derivative (**13** or **14** see Table 2 and text, 4.1 mmol) and [Zn(dmit)$_2$][NBu$_4$]$_2$ (**7**, 1 mmol) in MeCN (5 ml for 100 mg of alkyl derivative) was refluxed under nitrogen overnight. MeCN was added and the resulting solution was extracted with hexane. The hexane phases were combined and washed with MeCN, H_2O and dried over $MgSO_4$, and the solvent was evaporated. The remaining oil was purified by flash chromatography using hexane–CH_2Cl_2 [1/2] mixture as eluent to obtain the product as a yellow oil (yield of 36 and 88% starting from **13** and **14**, respectively). LDI-TOF *m/z* (%): 877.7 (Adduct [Cycle=S–CH$_2$CH(CH$_3$)OC$_{12}$H$_{25}$]$^+$, 100). Anal. Calcd for $C_{33}H_{62}O_2S_5$: C 60.87, H 9.60; Found: C 61.39, H 9.86. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): +36.6 deg cm^2 g^{-1}. FT-IR (NaCl discs): 2925 (s), 2854 (s), 1464 (w), 1373 (w), 1328 (w), 1136 (w), 1070 (s, C=S), 829 (w), 721 (w), 515 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 3.61 (sp, *J*=6.2 Hz, 2H, –C*H*(CH$_3$)), 3.46 (dt, *J*=8.8, 6.6 Hz, 2H, –OC*H*$_2$), 3.42 (dt, *J*=8.8, 6.6 Hz, 2H, –OC*H*$_2$), 3.05 (dd, *J*=15.6, 13.2 Hz, 2H, –SC*H*$_2$), 2.93 (dd, *J*=15.6, 13.2 Hz, 2H, –SC*H*$_2$), 1.57 (c, *J*=6.4 Hz, 4H, –C*H*$_2$(CH$_2$)$_7$CH$_3$), 1.40–1.20 (m, 42H, –CH(C*H*$_3$)O(CH$_2$)$_2$(C*H*$_2$)$_9$CH$_3$), 0.90 (t, *J*=6.4 Hz, 6H, –O(CH$_2$)$_{11}$C*H*$_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 211.1 (*C*=S), 136.5 (*C*=*C*), 74.4 (–*C*H(CH$_3$)-OC$_{12}$H$_{25}$), 69.4 (–O*C*H$_2$(CH$_2$)$_{10}$CH$_3$), 42.7 (–*C*H$_2$-CH(CH$_3$)OC$_{12}$H$_{25}$), 31.9 (–O(CH$_2$)$_9$*C*H$_2$CH$_2$CH$_3$), 30.0 (–OCH$_2$*C*H$_2$(CH$_2$)$_{10}$), 29.7, 29.7, 29.5 and 29.4 (–O(CH$_2$)$_3$(*C*H$_2$)$_6$(CH$_2$)$_2$CH$_3$), 26.2 (–O(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_8$-CH$_3$), 22.7 (–O(CH$_2$)$_{10}$*C*H$_2$CH$_3$), 19.3 (–CH(*C*H$_3$)OC$_{12}$-H$_{25}$), 14.1 (–O(CH$_2$)$_{11}$*C*H$_3$) ppm.

4.1.7. (*S*)-1-Bromo-3,7-dimethyloctane (19). To a solution of (*S*)-8-bromo-2,6-dimethyloct-2-ene ((*S*)-(+)-citronellyl bromide, **18**, 2 ml, 10 mmol) in EtOAc (15 ml) was added Adam's PtO_2 catalyst (40 mg, 0.176 mmol). H_2 gas was bubbled through the solution slowly for about 30 min and the reaction was left under H_2 atmosphere overnight. The suspension was filtered through Celite, washed with diethyl ether, and the solvent was removed under vacuum, leaving 2.1 g (94%) of a colourless transparent oil. FT-IR (NaCl discs): 2956 (s), 2928 (s), 2869 (m), 1465 (m), 1382 (w), 1366 (w), 1261 (w), 1217 (w), 1170 (w), 1011 (w), 933 (w), 649 (w), 568 (w), 488 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 3.47 (m, 2H, –C*H*$_2$Br), 1.87 (m, 1H, –C*H*(CH$_3$)), 1.75–1.42 (m, 3H, –C*H*(CH$_3$)C*H*$_2$CH$_2$Br), 1.35–1.15 (m, 6H, –(C*H*$_2$)$_3$CH(CH$_3$)$_2$), 0.88 (d, 3H, *J*=6.35 Hz, –CH(C*H*$_3$)), 0.86 (d, 6H, 6.52 Hz, –CH(C*H*$_3$)$_2$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 40.14 (–*C*H$_2$CH(CH$_3$)$_2$), 39.21 (–*C*H$_2$CH$_2$Br), 36.75 (–*C*H$_2$CH(CH$_3$)(CH$_2$)$_2$Br), 32.13 (–C*H*(CH$_3$)(CH$_2$)$_2$Br), 31.70 (–*C*H$_2$Br), 27.98 (–*C*H(CH$_3$)$_2$), 24.58 (–*C*H$_2$CH$_2$CH(CH$_3$)$_2$), 22.70 and 22.60 (–CH(*C*H$_3$)$_2$) 18.99 (–CH(*C*H$_3$)(CH$_2$)$_2$Br) ppm.

4.1.8. 4,5-Bis((*S*)-3,7-dimethyloct-6-enylthio)-1,3-dithiole-2-thione (20). A solution of the (*S*)-8-bromo-2,6-dimethyloct-2-ene ((*S*)-(+)-citronellyl bromide, **18**, 1.4 ml, 7.1 mmol) and [Zn(dmit)$_2$][NBu$_4$]$_2$ (**7**, 1.6 g, 1.7 mmol) in MeCN (30 ml) under nitrogen was refluxed for 4 h. After this time, MeCN was added and the resulting solution was extracted with hexane. The hexane phases were combined and washed with MeCN, H_2O and dried over $MgSO_4$. The remaining oil was purified by flash chromatography using hexane–CH_2Cl_2 [3/1] mixture as eluent to obtain 1.5 g (89%) of a yellow oil. LDI-TOF *m/z* (%): 614.3 (Adduct [CycleS–R*]$^+$, 100). Anal. Calcd for $C_{23}H_{38}S_5$ C 58.17, H 8.07; Found: C 58.41, H 7.98. $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): 49.1 deg cm^2 g^{-1}. FT-IR (NaCl discs): 2962 (s), 2921 (s), 2853 (m), 1455 (m), 1378 (w), 1277 (w), 1069 (s, C=S), 886 (w), 515 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 5.08 (tsp, *J*=7.03, 1.34 Hz, 2H, –C*H*=C(CH$_3$)$_2$), 2.88 (m, 4H, –SC*H*$_2$–), 1.96 (m, 4H, –C*H*$_2$CH=C(CH$_3$)$_2$), 1.88–1.10 (m, 10H, –SCH$_2$C*H*$_2$C*H*(CH$_3$)C*H*$_2$–), 1.66 (d, *J*=10.12 Hz, 12H, –CH=C(C*H*$_3$)$_2$), 0.91 (d, *J*=6.35 Hz, 6H, –CH$_2$-CH(C*H*$_3$)CH$_2$–) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 211.6 (*C*=S), 136.2 (*C*=*C*), 131.4 (–CH=*C*(CH$_3$)$_2$), 124.3 (–*C*H=C(CH$_3$)$_2$), 36.7 (–S(CH$_2$)$_2$CH(CH$_3$)*C*H$_2$–), 36.6 (–SCH$_2$*C*H$_2$), 34.7 (–S(CH$_2$)$_2$*C*H(CH$_3$)–), 31.7 (–S*C*H$_2$–), 25.7 (–CH=C(*C*H$_3$)$_{trans}$(CH$_3$)$_{cis}$), 19.1 (–S(CH$_2$)$_2$-CH(*C*H$_3$)–), 17.65 (–CH=C(CH$_3$)$_{trans}$(*C*H$_3$)$_{cis}$) ppm.

4.1.9. 4,5-Bis((*S*)-3,7-dimethyloctylthio)-1,3-dithiole-2-thione (21). A solution of the (*S*)-1-bromo-3,7-dimethyl-octane (**19**, 2.1 g, 9.4 mmol) and [Zn(dmit)$_2$][NBu$_4$]$_2$ (**7**, 2.20 g, 2.3 mmol) in MeCN (30 ml) under nitrogen was refluxed for 3 h. After this time, MeCN was added and the resulting solution was extracted with hexane. The hexane phases were combined and washed with MeCN, H_2O and dried over $MgSO_4$. The remaining oil was purified by flash chromatography using hexane–CH_2Cl_2 [4/1] mixture as eluent to obtain 1.7 g (77%) of a yellow oil. Anal. Calcd for $C_{23}H_{42}S_5$ C 57.68, H. 8.84; Found: C 57.75, H 8.63. LDI-TOF *m/z* (%): 620.4 (Adduct [CycleS–R*]$^+$, 100). $[\alpha]_{546}^{25}$ (CH_2Cl_2, 20 mg/ml): 40.5 deg cm^2 g^{-1}. FT-IR (NaCl discs): 2955 (s), 2926 (s), 2868 (m), 1463 (m), 1283 (w), 1070 (s, C=S), 919 (w), 881 (w), 815 (w), 715 (w), 623 (w), 575 (w), 516 (w), 470 (w) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 2.87 (m, 4H, –SC*H*$_2$–), 1.70–1.40 (m, 8H, –SCH$_2$C*H*$_2$C*H*(CH$_3$)(CH$_2$)$_3$C*H*(CH$_3$)$_2$), 1.30–1.00 (m, 12H, –C*H*$_2$CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 0.88 (d, 6H, *J*=6.52 Hz, –S(CH$_2$)$_2$CH(C*H*$_3$)–), 0.85 (d, 12H, *J*=6.68 Hz, –CH(C*H*$_3$)$_2$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 211.7 (*C*=S), 136.2 (*C*=*C*), 39.1 (–S*C*H$_2$–), 36.7 (–*C*H$_2$(CH$_2$)$_2$-CH(CH$_3$)$_2$), 34.7 (–SCH$_2$*C*H$_2$–), 32.1 (–S(CH$_2$)$_2$*C*H(CH$_3$)–), 27.9 (–*C*H(CH$_3$)$_2$), 24.6 (–*C*H$_2$CH$_2$CH(CH$_3$)$_2$), 22.7 and 22.6 (–CH(*C*H$_3$)$_2$), 19.20 (–S(CH$_2$)$_2$CH(*C*H$_3$)–) ppm.

4.1.10. 2,3-Bis((*S*)-2-dodecyloxy-propanylthio)-6,7-bis-(methoxycarbonyl)tetrathiafulvalene (23). A solution of 4,5-bis(methoxycarbonyl)-1,3-dithiol-2-one[22] (**22**, 163 mg, 0.295 mmol) and 4,5-bis((*S*)-2-dodecyloxy-propanyl)-1,3-dithiol-2-thione (**15**, 90 mg, 0.384 mmol) in freshly distilled trimethyl phosphite (4 ml) was brought to reflux for 3 h under an Ar atmosphere. The solvent is evaporated and the residual oil was purified by flash chromatography using hexane–CH_2Cl_2 [1/2] mixture as eluent to obtain 89 mg (38%) of **23** as a red oil. The symmetrical chiral TTF (18 mg, 8%) was also obtained as a side product of the reaction. Compound **23**: Anal. Calcd for $C_{40}H_{68}O_6S_6$ C 57.37, H. 8.19; Found: C 56.96, H 8.43. LDI-TOF *m/z* (%): 836.2 (M$^+$, 100) ppm.

FT-IR (NaCl disk): 2924 (w), 2853 (m), 1733 (m, C=O), 1579 (w), 1434 (w), 1375 (w), 1255 (m, C–O), 1135 (w), 1091 (w, C–O–C), 1027 (w), 765 (w), 470 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 3.86 (s, 6H, $-CO_2CH_3$), 3.57 (sx, $J=6.1$ Hz, 2H, $-CH(CH_3)$), 3.50 (dt, 2H, $-OCH_2$), 3.44 (dt, 2H, $-OCH_2$), 3.03 (dd, $J=13.2$, 6.0 Hz, 2H, $-SCH_2$), 2.83 (dd, $J=13.2$, 6.0 Hz, 2H, $-SCH_2$), 1.57 (qi, $J=6.5$ Hz, 4H, $-OCH_2CH_2$), 1.40–1.20 (m, 42H, $-CH(CH_3)O(CH_2)_2(CH_2)_9$), 0.90 (t, $J=6.6$ Hz, 6H, $-CH_2CH_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 159.9 ($-CO_2CH_3$), 132.0 and 128.10 (lateral C=C), 112.5 and 108.2 (central C=C), 74.6 ($-CH(CH_3)$), 69.3 ($-OCH_2$), 53.3 ($-CO_2CH_3$), 42.2 ($-SCH_2$), 31.9 ($-CH_2CH_2CH_3$), 30.1 ($-OCH_2CH_2$), 29.7, 29.7, 29.5 and 29.7 ($-O(CH_2)_3(CH_2)_6(CH_2)_2CH_3$), 26.2 ($-O(CH_2)_2CH_2$), 22.7 ($-CH_2CH_3$), 19.3 ($-CH(CH_3)$), 14.1 ($-CH_2CH_3$). $E_{1/2}(0/\cdot+)=683$ mV and $E_{1/2}(\cdot+/2+)=1055$ mV. Symmetrical chiral TTF: LDI-TOF *m/z* (%): 1236.7 (M^+, 100). FT-IR (NaCl discs): 2924 (s), 2854 (s), 1455 (w), 1373 (w), 1136 (w), 1099 (w), 805 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 3.58 (sx, $J=6.0$ Hz, 4H, $-CH(CH_3)$), 3.51 (dt, 4H, $-OCH_2$), 3.50 (dt, 4H, $-OCH_2$), 3.04 (dd, $J=13.1$, 7.0 Hz, 4H, $-SCH_2$), 2.84 (dd, $J=13.1$, 7.0 Hz, 4H, $-SCH_2$), 1.57 (qi, 8H, $-OCH_2CH_2$), 1.40–1.20 (m, 84H, $-CH(CH_3)O(CH_2)_2(CH_2)_9$), 0.90 (t, $J=6.7$ Hz, 12H, $-CH_2CH_3$) ppm.

4.1.11. 2,3-Bis((*S*)-2-dodecyloxy-propanylthio)-6-methoxycarbonyltetrathiafulvalene (24). A solution of 2,3-bis((*S*)-2-dodecyloxy-propanylthio)-6,7-bis(methoxycarbonyl)tetrathiafulvalene (**23**, 194 mg, 0.262 mmol) and LiBr (289 mg, 3.327 mmol) in HMPA (3 ml) with a drop of H_2O was heated to 80 °C, causing evolution of gas (CH_3Br). When no more gas was evolved, the mixture was cooled to room temperature, H_2O (10 ml) was added and the aqueous phase was extracted successively with hexane until the organic phase was colorless. The combined organic fractions were washed with H_2O and were dried over $MgSO_4$, filtered, and evaporated to dryness, leaving an orange oil, which was purified by column chromatography on alumina using as eluent hexane–CH_2Cl_2 [1/1] mixture obtaining 134 mg (75%) of an orange oil. Anal. Calcd for $C_{38}H_{66}O_4S_6$ C 58.56, H. 8.54; Found: C 58.17, H 8.73. LDI-TOF *m/z* (%): 778.4 (M^+, 100). FT-IR (NaCl disk): 2925 (s), 2854 (s), 1716 (m, C=O), 1566 (w), 1538 (w), 1456 (w), 1374 (w), 1327 (w), 1284 (m, C–O), 1251 (m, C–O), 1199 (w), 1095 (m, C–O–C), 1060 (w, C–O–O), 890 (w), 761 (w), 727 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 7.38 (s, 1H, C=C*H*), 3.84 (s, 3H, $-CO_2CH_3$), 3.58 (sx, $J=6.0$ Hz, 1H, $-CH(CH_3)$), 3.57 (sx, $J=6.0$ Hz, 1H, $-CH(CH_3)$), 3.51–3.44 (m, 4H, $-OCH_2$), 3.04 (dd, $J=13.2$, 6.0 Hz, 2H, $-SCH_2$), 2.85 (dd, $J=13.2$, 7.1 Hz, 1H, $-SCH_2$), 2.83 (dd, $J=13.2$, 7.1 Hz, 1H, $-SCH_2$), 1.58 (qi, $J=7.0$ Hz, 4H, $-OCH_2CH_2$) 1.40–1.20 (m, 42H, $-CH(CH_3)OCH_2CH_2(CH_2)_9$), 0.91 (t, $J=6.6$ Hz, 6H, $-CH_2CH_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 159.77 (C=O), 131.8, 128.4, 128.2 and 127.6 (lateral C=C), 112.6 and 109.7 (central C=C), 74.6 ($-CH(CH_3)$), 69.3 ($-OCH_2$), 52.7 ($-CO_2CH_3$), 42.1 ($-SCH_2$), 32.0, 30.4, 30.1, 30.1, 29.9, 29.7, 29.7, 29.6 and 29.4 ($-O(CH_2)_3(CH_2)_6(CH_2)_2CH_3$), 26.3 ($-O(CH_2)_2CH_2$), 22.7 ($-CH_2CH_3$), 19.4 ($-CH(CH_3)$), 14.1 ($-CH_2CH_3$) ppm. $E_{1/2}(0/\cdot+)=593$ mV and $E_{1/2}(\cdot+/2+)=998$ mV.

4.1.12. 2,3-Bis((*S*)-2-dodecyloxy-propanylthio)-6-(carboxy)tetrathiafulvalene (25). $LiOH\cdot H_2O$ (500 mg, 12 mmol) in 5 ml H_2O was added drop-wise to a stirred solution of 2,3-bis((*S*)-2-dodecyloxy-propanyl)-6-methoxycarbonyltetrathiafulvalene (**24**, 617 mg, 0.792 mmol) in THF (50 ml). After stirring for 12 h, the mixture was diluted with ether (25 ml) and hydrochloric acid (0.5 M, 10 ml) was added. The dark organic phase was dried ($MgSO_4$) and the evaporation of the solvent gave 543 mg (88%) of purple oily solid. Anal. Calcd for $C_{37}H_{64}O_4S_6$ C 58.07, H 8.43; Found: C 57.77, H 8.21. LDI-TOF *m/z* (%): 764.4 ($[M]^+$, 40) and 720.3 ($[M-CO_2H]^+$, 100). FT-IR (KBr): 2924 (s), 2854 (s), 1712 (m, C=O free), 1682 (m, C=O bound), 1564 (m), 1531 (m), 1455 (m), 1417 (m), 1373 (m), 1289 (m), 1199 (w), 1135 (m), 1094 (m), 891 (w), 775 (w), 729 (m), 662 (d), 496 (d) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 7.48 (br s, 1H, C=C*H*), 4.8 (br s, –O*H*), 3.60 (m, 2H, $-CH(CH_3)$), 3.49 (m, 4H, $-OCH_2$), 3.60 (dd, $J=12.9$, 7.0 Hz, 2H, $-SCH_2$), 2.85 (m, 2H, $-SCH_2$), 1.58 (m, 4H, $-OCH_2CH_2$) 1.40–1.20 (m, 19H, $-CH(CH_3)$-$OCH_2(CH_2)_{10}$), 0.91 (t, $J=6.5$ Hz, 3H, $-CH_2CH_3$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 163.2 (C=O), 134.4, 128.5, 130.0 and 127.5 (lateral C=C), 112.1 and 110.3 (central C=C), 74.7 ($-CH(CH_3)$), 69.4 ($-OCH_2$), 42.0 ($-SCH_2$), 32.0, 30.1, 29.7, 29.6 and 29.4 ($-O(CH_2)_3(CH_2)_6(CH_2)_2$-$CH_3$), 26.2 ($-O(CH_2)_2CH_2$), 22.7 ($-CH_2CH_3$), 19.4 ($-CH(CH_3)$), 14.1 ($-CH_2CH_3$) ppm. $E_{1/2}(0/\cdot+)=586$ mV and $E_{1/2}(\cdot+/2+)=1050$ mV.

4.1.13. 2,3-Bis(2-cyanoethylthio)-6,7-bis((*S*)-3,7-dimethyloct-6-enylthio)tetrathiafulvalene (27). A solution of 4,5-bis(2-cyanoethylthio)-1,3-dithiol-2-one[24] (**26**, 125 mg, 0.441 mmol) and 4,5-bis((*S*)-3,7-dimethyloct-6-enylthio)-1,3-dithiole-2-thione (**20**, 190 mg, 0.400 mmol) in freshly distilled trimethyl phosphite (4 ml) was brought to reflux for 7 h under an Ar atmosphere. Evaporation of solvent and purification of the residual oil by flash chromatography using hexane–CH_2Cl_2 [1/4] mixture as eluent gave 197 mg (68%) of **27** as an orange solid. The symmetrical chiral TTF **28** (18 mg, 6%) was also obtained as a side product of the reaction as an oily material. Compound **27**: mp: 64–65 °C. Anal. Calcd for $C_{32}H_{46}N_2S_8$ C 53.74, H. 6.48; Found: C 53.48, H 6.64. LDI-TOF *m/z* (%): 714.1 ($[M]^+$, 100). FT-IR (KBr): 2956 (s), 2923 (s), 2851 (s), 2249 (w, CN), 1473 (m), 1416 (m), 1379 (m), 1294 (w), 1264 (w), 1232 (w), 1127 (w), 891 (w), 800 (w), 771 (w), 728 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 5.08 (tt, 2H, $J=7.02$, 1.30 Hz, $-CH=C(CH_3)_2$), 3.08 (t, 4H, $J=7.35$ Hz, $-CH_2CH_2CN$), 2.82 (m, 4H, $-SCH_2CH_2CH(CH_3)-$), 2.73 (t, 4H, $J=7.35$ Hz, $-CH_2CH_2CN$), 1.96 (sx, 4H, $J=7.02$ Hz, $(-CH_2CH=CCH_3)_2$), 1.70–1.00 (m, 10H, $-SCH_2CH_2$-$CH(CH_3)CH_2-$), 1.65 (d, 12H, $J=11.25$ Hz, $-C(CH_3)_2$), 0.90 (d, 6H, $J=6.35$ Hz, $-S(CH_2)_2CH(CH_3)-$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 131.6 ($C=C(CH_3)_2$), 128.3, 128.1 (outer TTF C=C), 124.9 ($C=C(CH_3)_2$), 117.9 (CN), 114.6, 107.1 (central TTF C=C), 37.1, 37.0 ($-SCH_2-$), 34.5 ($-SCH_2CH_2-$), 32.0 ($-CH_2CH(CH_3)CH_2-$), 31.6 ($-CH_2$ $CH_2CHC(CH_3)_2$), 26.1 ($-CH(CH_3)$), 25.8 (CH_2CHC $(CH_3)_2$), 19.6 (CH_2CN), 19.3, 18.1 ($C(CH_3)_2$) ppm. $E_{1/2}(0/\cdot+)=650$ mV and $E_{1/2}(\cdot+/2+)=1015$ mV. Compound **28**: Anal. Calcd for $C_{46}H_{76}S_8$ C 62.38, H. 8.65; Found: C 62.43, H 8.50. LDI-TOF *m/z* (%): 884.4 ($[M]^+$, 100). FT-IR (KBr): 2956 (m), 2923 (s), 2853 (m), 1455 (w),

1377 (w), 1221 (w), 1073 (w), 825 (w), 772 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 5.08 (tt, 4H, $J=7.18$, 1.50 Hz, $-CH{=}C(CH_3)_2$), 2.82 (m, 8H, $-SCH_2CH_2CH(CH_3)-$), 1.97 (m, 8H, $(-CH_2CH{=}CCH_3)_2$), 1.80–1.00 (m, 20H, $-SCH_2CH_2CH(CH_3)CH_2-$), 1.64 (d, 24H, $J=$ 19.75 Hz, $-C(CH_3)_2$), 0.90 (d, 12H, $J=6.35$ Hz, $-S(CH_2)_2$-$CH(CH_3)-$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 131.6 ($C{=}C(CH_3)_2$), 128.3 (outer TTF C=C), 124.9 ($C{=}C(CH_3)_2$), 109.4 (central TTF C=C), 37.1 ($-SCH_2-$), 34.4 ($-SCH_2CH_2-$), 32.0 ($-CH_2CH(CH_3)CH_2-$), 31.7 ($-CH_2CH_2CHC(CH_3)_2$), 26.1 ($-CH(CH_3)$), 25.8 (CH_2-$CHC(CH_3)_2$), 19.4, 18.1 ($C(CH_3)_2$) ppm. $E_{1/2}(0/\cdot+)=$ 510 mV and $E_{1/2}(\cdot+/2+)=978$ mV.

4.1.14. 2,3-Bis(2-cyanoethylthio)-6,7-bis((*S*)-3,7-dimethyloctylthio)tetrathiafulvalene (29). A solution of 4,5-bis(2-cyanoethylthio)-1,3-dithiol-2-one[24] (**26**, 858 mg, 3.03 mmol) and 4,5-bis((*S*)-3,7-dimethyloctylthio)-1,3-dithiole-2-thione (**21**, 1.44 g, 3.03 mmol) in freshly distilled trimethyl phosphite (10 ml) was brought to reflux for 4 h under an atmosphere of argon. After this time, the solvent was evaporated and the residual oil was purified by flash chromatography using CH_2Cl_2 as eluent to obtain 1.20 g (56%) of **29** as an orange solid. The symmetrical chiral TTF **30** (151 mg, 7%) was also obtained as a side product of the reaction. Compound **29**: mp: 76–77 °C. Anal. Calcd for $C_{32}H_{50}N_2S_8$ C 53.43, H. 7.01; Found: C 53.35, H 6.99. LDI-TOF *m/z* (%): 718.2 ($[M]^+$, 100). FT-IR (KBr): 2956 (s), 2923 (s), 2851 (m), 2249 (w, CN), 1473 (m), 1416 (m), 1380 (m), 1293 (w), 1264 (w), 1232 (w), 1126 (w), 891 (w), 800 (w), 770 (w), 728 (w) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 3.06 (t, 4H, $J=7.06$ Hz, $-CH_2CH_2CN$), 2.82 (m, 4H, $-SCH_2CH_2CH(CH_3)-$), 2.72 (t, 4H, $J=7.06$ Hz, $-CH_2CN$), 1.70–1.35 (m, 8H, $-CH_2CH(CH_3)(CH_2)_3$-$CH(CH_3)_2$), 1.30–1.05 (m, 12H, $-(CH_2)_3CH(CH_3)_2$), 0.87 (d, 6H, $J=5.58$ Hz, $-CH_2CH(CH_3)CH_2-$), 0.84 (d, 12H, $J=6.70$ Hz, $-CH(CH_3)_2$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 128.5, 128.2 (outer $C{=}C$), 117.9 (CN), 114.9, 107.0 (central C=C), 39.1, 37.3 ($-SCH_2-$), 34.7 ($-SCH_2CH_2-$), 32.5 ($-CH_2CH(CH_3)CH_2-$), 31.7 ($-CH_2(CH_2)_2CH(CH_3)_2$), 28.4 ($-CH(CH_3)_2$), 25.1 ($-CH_2$-$CH_2CH(CH_3)_2$), 23.2 ($-CH_2CH(CH_3)_2$), 23.1 ($-CH(CH_3)$), 19.8 (CH_2CN) and 19.4 ($CH(CH_3)_2$) ppm. $E_{1/2}(0/\cdot+)=$ 650 mV and $E_{1/2}(\cdot+/2+)=1015$ mV. Compound **30**: Anal. Calcd for $C_{46}H_{84}S_8$ C 61.82, H. 9.47; Found: C 62.08, H 9.18. LDI-TOF *m/z* (%): 892.4 ($[M]^+$, 100). ^1H NMR (250 MHz, $CDCl_3$): 2.81 (m, 8H, $-SCH_2CH_2$-$CH(CH_3)-$), 1.70–1.35 (m, 16H, $-CH_2CH(CH_3)(CH_2)_3$-$CH(CH_3)_2$), 1.30–1.05 (m, 24H, $-(CH_2)_3CH(CH_3)_2$), 0.88 (d, 12H, $J=5.03$ Hz, $-CH_2CH(CH_3)CH_2-$), 0.86 (d, 24H, $J=6.68$ Hz, $-CH(CH_3)_2$) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): 128.3 (outer $C{=}C$), 109.4 (central C=C) 38.9, ($-SCH_2-$), 34.6 ($-SCH_2CH_2-$), 32.5 ($-CH_2CH(CH_3)CH_2-$), 31.8 ($-CH_2(CH_2)_2CH(CH_3)_2$), 28.3 ($-CH(CH_3)_2$), 25.1 ($-CH_2CH_2CH(CH_3)_2$), 23.2 ($-CH_2CH(CH_3)^2$), 23.1 ($-CH(CH_3)$) and 19.5 ($CH(CH_3)_2$) ppm. $E_{1/2}(0/\cdot+)=$ 506 mV and $E_{1/2}(\cdot+/2+)=980$ mV.

Acknowledgements

This work was supported by the Programa General de Conocimento of the Dirección General de Investigación, Ciencia y Tecnología (Spain), under the project BQU2003-00760, DGR, Catalonia (Project 2005SGR00591), and the European Integrated Project project NAIMO (NMP4-CT-2004-500355). E.G.-N. is grateful to the Generalitat de Catalunya for a predoctoral grant.

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Tetrahedron 62 (2006) 3380–3388
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Catalytic enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one by chiral copper catalyst

Yosuke Takenaka, Hisanaka Ito,* Mineki Hasegawa and Kazuo Iguchi*

School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 10 November 2005; accepted 16 January 2006

Available online 13 February 2006

Abstract—A new catalytic system for enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one with thioacetylene derivatives is described. The use of a catalytic amount (20–30 mol%) of copper(II) salt with chiral bis-pyridine ligand was found to be effective in promoting the [2+2]-cycloaddition reaction, furnishing the corresponding bicyclic compound in good yield and good enantioselectivity.
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1. Introduction

[2+2]-Cycloaddition reaction has been recognized as a powerful tool for the construction of a functionalized four-membered ring system.[1] The reaction usually proceeds under photo-irradiation or Lewis acid (also Brønsted acid)-catalyzed conditions.[1b] Among them, the Lewis acid-catalyzed condition is an attractive method, because the reaction proceeds under mild conditions with high siteselectivity.[2–4] Chiral Lewis acid-catalyzed enantioselective [2+2]-cycloaddition reaction is a useful tool for the synthesis of a poly-functionalized four-membered ring system as an optically active form. Narasaka et al. reported a Ti–TADDOL complex catalyzed enantioselective [2+2]-cycloaddition reaction of acryloyl oxazolidinone derivatives and the reaction provided excellent enantioselectivity (Eq. 1).[5,6] On the other hand, the enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (**1**), which can be useful for preparation of a chiral bicyclic system, has not yet been reported (Eq. 2). The preparation of a bicyclic system containing a four-membered ring as optically active form is important for the synthesis of natural and biologically active compounds. Although asymmetric 1,4-addition of a nucleophile such as ketene silyl acetal to 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) have been reported by several groups, the yield and enantio- or diastereoselectivity were moderate.[7–10] We tried to develop a chiral catalytic system (Scheme 1) for the addition of a nucleophile to 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) and report herein a catalytic enantioselective [2+2]-cycloaddition of 2-alkoxycarbonyl-2-cycloalken-1-one with thioacetylene derivatives for the construction of a chiral bicyclic system.[11]

2. Results and discussion

2.1. The [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one catalyzed by Lewis acid

The Lewis acid catalyst for the [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) was examined. The substrates **1** and **2** were prepared according to the literature procedure.[12,13] Substrate **1** was used for [2+2]-cycloaddition reaction without purification due to instability (>90% from ^{1}H NMR). The result of the [2+2]-cycloaddition reaction is shown in Table 1. In the presence of 30 mol% of titanium chloride or zirconium chloride, the reaction proceeded to give cycloaddition product **3** along with a significant amount of by-product **4** and other by-products (entries 1 and 2). Another halogenated metal-catalyzed reaction also gave by-product **4**. Only under zinc bromide-catalyzed conditions, the reaction smoothly proceeded to provide the desired product **3** in 59% yield without a halogenated by-product (entry 5). The best result was obtained by employing 10 mol% of zinc bromide as a catalyst to prevent the decomposition of the product **3** (entry 6).

A plausible mechanism for the formation of **4** is shown in Scheme 2. The 1,4-addition of phenylthioacetylene (**2**) to

Keywords: [2+2]-Cycloaddition reaction; Ligand; Copper salt.
* Corresponding authors. Tel.: +81 426 76 5473; fax: +81 426 76 7282 (H.I.); tel.: +81 426 76 7273; fax: +81 426 76 7282 (K.I.); e-mail addresses: itohisa@ls.toyaku.ac.jp; onocerin@ls.toyaku.ac.jp

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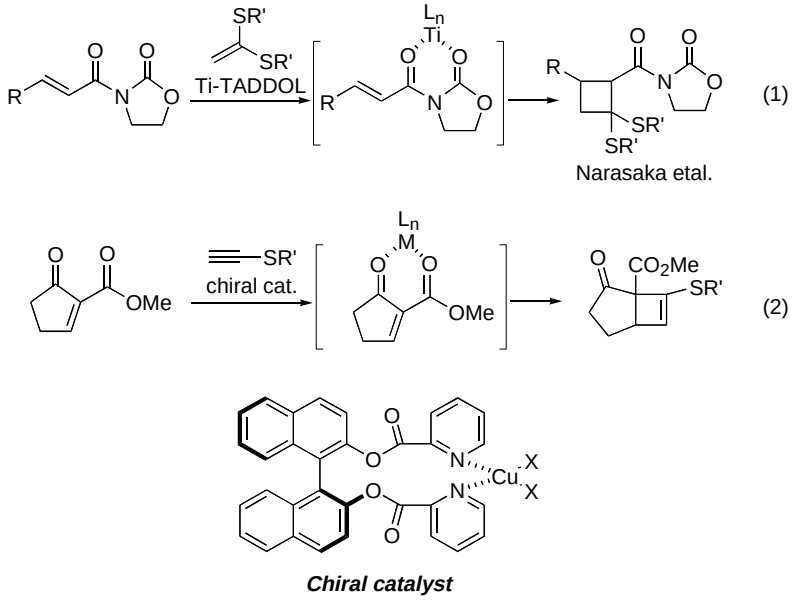
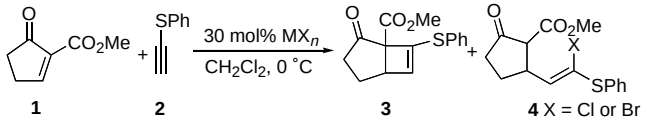
doi:10.1016/j.tet.2006.01.050



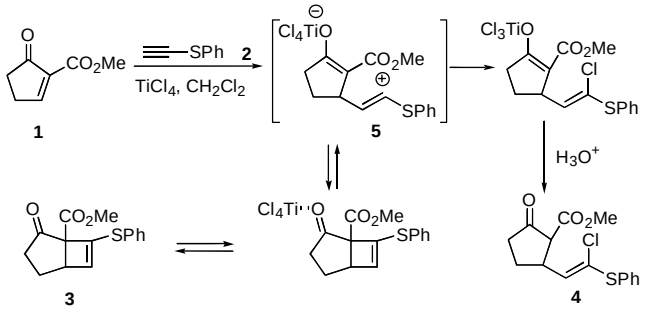
Scheme 1.

Table 1. Survey of metal salt catalysts for the [2+2]-cycloaddition reaction



Entry	MX_n	Time (h)	**3**:**4**[a]	Yield of **3** (%)[b]
1	$TiCl_4$	0.5	1:1.1	32
2	$ZrCl_4$	0.5	1:1.9	26
3	$MgBr_2 \cdot OEt_2$	1	1:0.9	16
4	$CuCl_2$	48	1:0.8	33
5	$ZnBr_2$	0.5	1:0	59
6[c]	$ZnBr_2$	2	1:0	84
7	$Sc(OTf)_3$	0.5	1:0	42
8[c]	$Sc(OTf)_3$	0.5	1:0	65
9	$Yb(OTf)_3$	0.5	1:0	57
10[c]	$Yb(OTf)_3$	1.3	1:0	75
11	$Cu(OTf)_2$	0.5	1:0	51
12[c]	$Cu(OTf)_2$	0.5	1:0	80

[a] Ratio was determined by ^{1}H NMR analysis.
[b] Isolated yield.
[c] Catalyst (10 mol%) was employed.



Scheme 2.

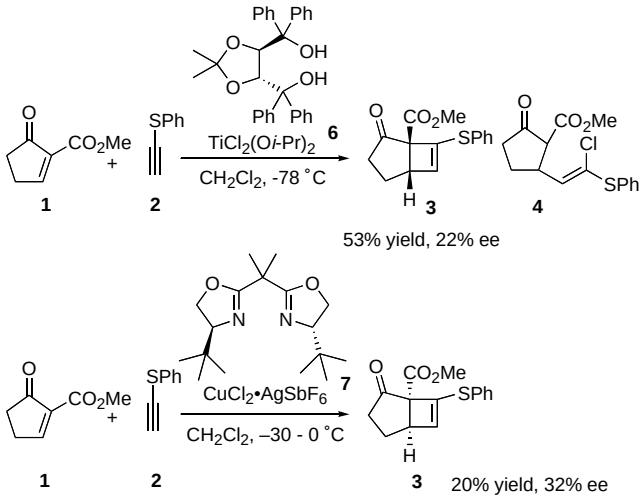
the substrate **1** gave intermediate **5**. The intramolecular reaction of the resulting titanium enolate to the carbocation on the carbon bearing the thiophenyl group gave the desired [2+2]-cycloadduct **3**. During this pathway, the reaction of the chloride anion to the carbocation in the intermediate **5** proceeded competitively to give by-product **4**. Another plausible route for the formation of **4** is as follows. After the formation of cycloadduct **3**, the decomposition of **3** proceeded based on the coordination of Lewis acid to the carbonyl group on the cyclopentane ring. Actually, compound **4** was obtained by the treatment of **3** with titanium chloride (vide infra).

To prevent the side-reaction, metal triflate catalyst was examined due to the low nucleophilicity of triflate anion and the results are shown in Table 1 (entries 7–12). Under the metal triflate-catalyzed conditions, the uncyclized compound such as **4** was not detected. Most of the examined triflates worked nicely, and the reaction in the presence of 10 mol% of copper triflate at 0 °C gave the best result (entry 12).

2.2. Enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one by reported chiral catalyst

Based on the result of the examination of Lewis acid catalysts, several reported chiral Lewis acid catalysts were examined for the asymmetric [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) with phenylthioacethylene (**2**) prior to the development of a novel catalyst. The result is shown in Scheme 3.

As mentioned above, the Ti–TADDOL catalyst was effective for the [2+2]-cycloaddition reaction of acryloyloxazolidinone derivatives with thioacetylenes or ketene dithioacetals.[5] Therefore, this catalytic system was examined at first. Although moderate yield (53% yield) along with by-product **4** was obtained under 30 mol% of Ti–TADDOL complex **6**-catalyzed conditions, the enantiomeric excess of the product was not satisfactory (22% ee). We also examined the reaction catalyzed by a chiral copper catalyst.[9d,14] Under the presence of 20 mol% of a copper-BOX complex **7**, the reaction proceeded to give cycloadduct



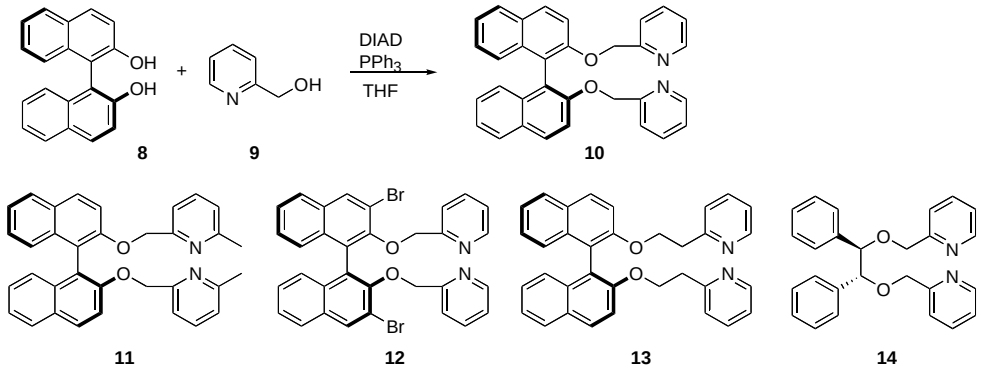
Scheme 3.

3 in moderate enantiomeric excess (32% ee), but the yield was very low (20% yield). The titanium–BINOL catalyst[15] was also examined. Although good enantioselectivity was observed (79% ee), the yield was quite low (8% yield).

2.3. Enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one by novel copper catalyst

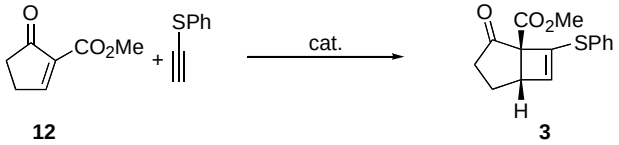
Based on the examination of the reported chiral catalyst as shown in Scheme 3, the development of a novel catalyst was examined. We employed copper(II) salt as Lewis acid and a novel and simple C_2-symmetric ligand having a binaphthyl moiety as a chiral source and two pyridine moieties as a coordination site to copper salt with appropriate binding affinity.

Novel chiral ligand **10** having two pyridine moieties was prepared from (*S*)-binaphthol (**8**) with 2-pyridinemethanol (**9**) by Mitsunobu reaction[16] (Scheme 4). Other modified chiral ligands **11**–**13** were also prepared in the same manner. The results of the enantioselective [2+2]-cycloaddition reaction of compound **1** with phenylthioacetylene (**2**) are shown in Table 2. In the case of a catalyst prepared from ligand **10** with copper triflate, the reaction proceeded at 0 °C and moderate ee was obtained but the yield was unsatisfactory (entry 1). The use of toluene or THF as a solvent instead of CH_2Cl_2 significantly decreased both the yield and ee (entries 2 and 3). In these cases, the low yield



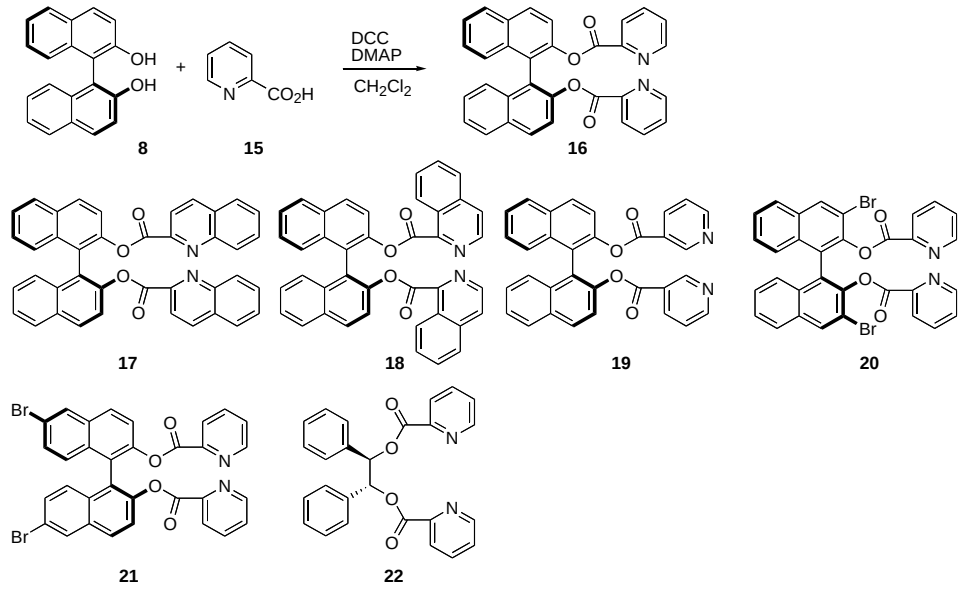
Scheme 4.

Table 2. Chiral copper-catalyzed [2+2]-cycloaddition reaction



Entry	Ligand	Copper salt	Mol%	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	**10**	$Cu(OTf)_2$	30	CH_2Cl_2	−78 to 0	13	13	44
2	**10**	$Cu(OTf)_2$	30	Toluene	−78 to 0	17	7	20
3	**10**	$Cu(OTf)_2$	30	THF	−78 to 0	17	NR	—
4	**10**	$Sc(OTf)_2$	30	CH_2Cl_2	0	17	13	11
5	**10**	$CuCl_2+AgSbF_6$	30	CH_2Cl_2	−78 to −30	14	56	41
6	**10**	$CuCl_2+AgSbF_6$	50	CH_2Cl_2	−78 to −30	14	69	40
7	**10**	$CuCl_2+AgSbF_6$	100	CH_2Cl_2	−30	19	65	39
8	**11**	$Cu(OTf)_2$	30	CH_2Cl_2	−30 to 0	13	6	16
9	**11**	$CuCl_2+AgSbF_6$	30	CH_2Cl_2	−30 to 0	19	<5	—
10	**12**	$CuCl_2+AgSbF_6$	30	CH_2Cl_2	0	12	24	30
11	**13**	$CuCl_2+AgSbF_6$	30	CH_2Cl_2	0	5	18	29
12	**14**	$CuCl_2+AgSbF_6$	30	CH_2Cl_2	−30	10	50	25

[a] Isolated yield.
[b] Ratio was determined by chiral HPLC analysis.



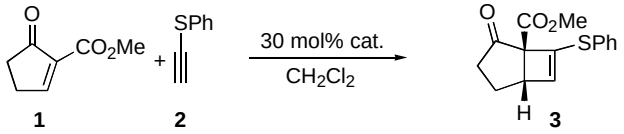
Scheme 5.

was observed due to the decomposition of substrate **1** during the long reaction time at 0 °C. To improve the ee and yield, other metal salts were examined and the best results were obtained with the use of hexafluoroantimonate as a counter anion of copper[9] (entries 5–7). With the increase of the Lewis acidity, the reaction proceeded even at −30 °C and the yield was significantly improved due to avoid the decomposition of substrate **1**. In the presence of 50 mol% of catalyst, best yield was obtained (69%, entry 6). The use of other modified ligands **11**–**14** decreased both the yield and ee (entries 8–12). These results indicated that the catalytic activity is not enough in the present catalysts due to the strong Lewis basicity of the nitrogen atom on the ligand. Therefore, novel ligands having a picolinate moiety to decrease the Lewis basicity of the coordination site to the metal center were designed.

The ligand **16** was prepared from (*S*)-binaphthol (**8**) with picolinic acid (**15**) by a condensation reaction using dicyclohexylcarbodiimide in 94% yield (Scheme 5). Other modified ligands **17**–**22** were prepared in the same manner.

The reaction of compound **1** with **2** catalyzed by the picolinate catalyst prepared from ligand **16** with copper triflate proceeded at 0 °C to give the [2+2]-adduct **3** in 31% yield with 24% ee (Table 3). This result showed significant improvement of the yield compared with the result of the 30 mol% of catalyst prepared from ligand **10** with copper triflate. The use of hexafluoroantimonate as a counter anion of copper instead of triflate increased the catalytic activity and the reaction proceeded at low temperature and the product **3** was obtained at −30 °C in 62% yield with 53% ee (entry 2). The reaction also proceeded at −78 °C and 64% ee was obtained (entry 3). The catalytic activities of the modified chiral ligands **17**–**22** were also examined. The ligand **17** and **18**, which is larger than pyridine ring, were prepared to increase the steric repulsion between catalyst and substrate and the reaction

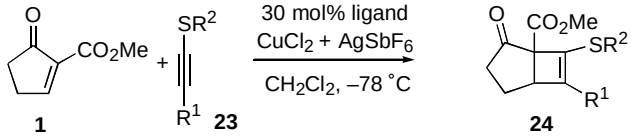
Table 3. Chiral copper catalyst catalyzed [2+2]-cycloaddition reaction



Entry	Ligand	Copper salt	Temperature (°C)	Time (h)	Yield (%)[a]	ee (%)[b,c]
1	**16**	$Cu(OTf)_2$	0	2.5	31	24
2	**16**	$CuCl_2+AgSbF_6$	−30	0.6	62	53
3	**16**	$CuCl_2+AgSbF_6$	−78	3	48	64
4	**17**	$Cu(OTf)_2$	−30	2	35	23
5	**17**	$CuCl_2+AgSbF_6$	−30	3	38	24
6	**18**	$Cu(OTf)_2$	−30 to 0	1.5	14	12
7	**18**	$CuCl_2+AgSbF_6$	−30	0.8	45	19
8	**19**	$CuCl_2+AgSbF_6$	−30	12	7	13
9	**20**	$CuCl_2+AgSbF_6$	−30	3	35	0
10	**21**	$CuCl_2+AgSbF_6$	−78	1.5	13	73
11	**22**	$CuCl_2+AgSbF_6$	−30	4	41	13

[a] Isolated yield.
[b] Ratio was determined by chiral HPLC analysis.
[c] The absolute configurations of the major enatiomer were (1*R*,5*S*) except for entry 11.

Table 4. Chiral copper-catalyzed [2+2]-cycloaddition reaction of substituted thioacetylene derivatives



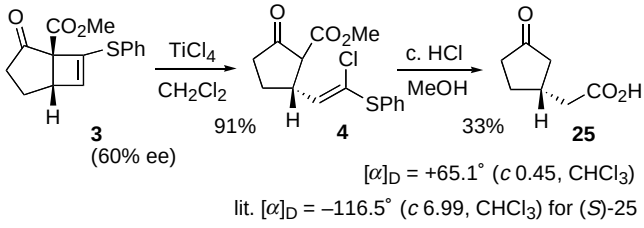
Entry	23	Ligand	Time (h)	Product	Yield (%)[a]	ee (%)[b]
1	R^1=*n*Bu, R^2=Ph (**23a**)	**10**	16	**24a**	9	45
2	R^1=*n*Bu, R^2=Ph (**23a**)	**16**	16	**24a**	75	32
3	R^1=TMS, R^2=Ph (**23b**)	**16**	16	—	NR	—
4	R^1=TMS, R^2=Me (**23c**)	**10**	16	**24c**	3	73
5	R^1=*n*Bu, R^2=Me (**23c**)	**16**	2	**24c**	51	15

[a] Isolated yield.
[b] Ratio was determined by chiral HPLC analysis.

gave product **3** but the ee was decreased in both cases (entries 4–7). The ligand **19** having a nicotinate moiety instead of picolinate was also examined and the product **3** was obtained with low yield and ee (entry 8). To increase the steric bulkiness of the naphthalene ring, modification of the BINOL moiety was also examined. The reaction of the ligand **20** prepared from 3,3′-dibromobinaphthol gave racemate **3**. In the case of ligand **21** derived from 6,6′-dibromobinaphthol, the reaction proceeded at −78 °C and the product **3** was obtained in 13% yield with 73% ee (entry 10).

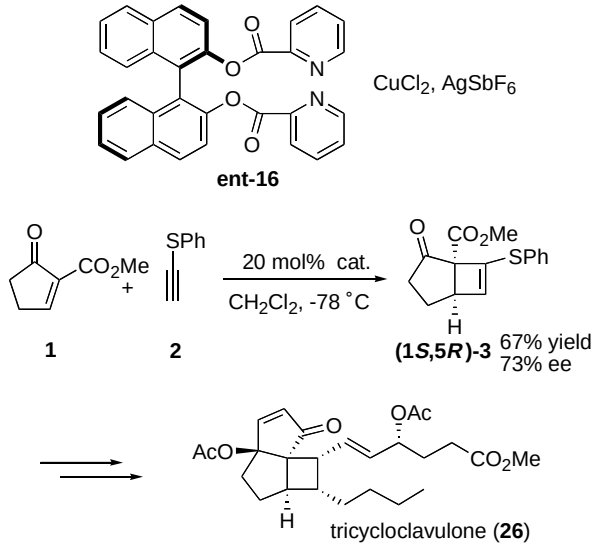
The [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) with thioacetylene derivatives **23**[17] was also examined and the results are shown in Table 4. In the case of compound **23a**, good enantiomeric excess was found by using both ligand **10** and **16** (entries 1 and 2). As mentioned above, the use of ligand **10** decreased the yield of the cycloaddition product (entries 1 and 4). Although the yield was low, high enantiomeric excess was achieved in the case of TMS-substituted substrate **23c** (entry 4).

The absolute stereochemistry of the product was determined by comparison of the $[\alpha]_D$ value after conversion of compound **3** to known compound **25**[18] as shown in Scheme 6. Compound **3** (60% ee) prepared by the use of ligand **16** derived from (*S*)-binaphthol was treated with titanium chloride to cleave the four-membered ring to give chlorinated compound **4** (vide supra). The acid hydrolysis and decarboxylation of compound **4** with concentrated HCl in MeOH gave known compound **25**. A comparison of the optical rotation value with that of (*S*)-**25** suggested that the absolute configuration of the chiral center of compound **25** was *R* configuration. According to the above-mentioned conversion, the absolute configuration of the major enantiomer of the [2+2]-adduct **3** could be determined as (1*R*,5*S*) configuration.



Scheme 6.

The present enantioselective [2+2]-cycloaddition reaction was applied to the first step of an enantioselective total synthesis of (+)-tricycloclavulone (**26**) as shown in Scheme 7.[11] For the synthesis of tricycloclavulone as a natural form, the ligand **ent-16** derived from (*R*)-binaphthol was employed. In a 20 mmol scale reaction under the presence of 20 mol% of the catalyst, the reaction proceeded and the best enantioselectivity was achieved (73% ee). One cause of the improvement of the enantioselectivity is that both substrates were prepared just before use.



Scheme 7.

3. Conclusion

We have shown our efforts for the development of a catalytic system for [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one with thioacetylene derivatives. Among the survey of Lewis acid catalysts to accelerate the cycloaddition reaction, zinc bromide and copper triflate worked efficiently to give a four-membered ring product. Based on this result, we prepared a simple chiral ligand from BINOL and picolinic acid having the coordination ability to copper salt. The presented chiral

catalyst worked to give [2+2]-cycloadduct in good yield and enantiomeric excess. This catalytic system was applied to the enantioselective total synthesis of marine prostanoid tricycloclavulone.

4. Experimental

4.1. General procedure for the preparation of ligand 10–13

4.1.1. 2,2′-Bis(2-pyridylmethoxy)-(1*S*)-1,1′-binaphthalene (10). To a solution of (*S*)-BINOL (1.0 g, 3.49 mmol) in THF (30 mL) was added triphenylphosphine (2.0 g, 7.68 mmol), 2-(hydroxymethyl)pyridine (0.70 mL, 7.68 mmol) and a solution of diisopropyl azodicarboxylate (1.5 mL, 7.68 mmol) in THF (2 mL) at room temperature. After being stirred for 15 h, the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/AcOEt, 1:1–1:3 and $CHCl_3$/AcOEt, 2:1) to afford compound **10** (1.31 g, 2.80 mmol, 80% yield). White amorphous solid. $[\alpha]_D^{28}$ −63.6 (*c* 0.53, $CHCl_3$). IR (KBr) ν cm^{-1}; 1685, 1654, 1636, 1618, 749. ^1H NMR (300 MHz, $CDCl_3$) δ; 5.22 (4H, s), 6.72 (2H, d, J=7.9 Hz), 7.04 (2H, dd, J=5.2, 7.2 Hz), 7.23–7.28 (6H, m), 7.35 (2H, m), 7.46 (2H, d, J=9.0 Hz), 7.90 (2H, d, J=8.2 Hz), 7.98 (2H, d, J=9.0 Hz), 8.45 (2H, d, J=4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 71.4, 115.0, 120.1, 120.7, 122.1, 123.8, 125.4, 126.5, 127.9, 129.5, 134.1, 136.4, 148.6, 153.6, 157.7, 162.3. HRESIMS calcd for $C_{32}H_{25}N_2O_2$: 469.1916 $(M+H)^+$, found: 469.1911. Anal. Calcd for $C_{32}H_{24}N_2O_2$: C, 82.03; H, 5.16; N, 5.98. Found: C, 81.85; H, 5.21; N, 5.97.

4.1.2. 2,2′-Bis[6-methyl(2-pyridylmethoxy)]-(1*S*)-1,1′-binaphthalene (11). Colorless crystals. Mp 130–132 °C (from hexane–AcOEt). $[\alpha]_D^{28}$ −56.0 (*c* 0.53, $CHCl_3$). IR (KBr) ν cm^{-1}; 1618, 1593, 806, 775. ^1H NMR (300 MHz, $CDCl_3$) δ; 2.47 (6H, s), 5.18 (4H, s), 6.53 (2H, d, J=7.7 Hz), 6.88 (2H, d, J=7.6 Hz), 7.15 (2H, t, J=7.7 Hz), 7.24–7.26 (4H, m), 7.30–7.37 (2H, m), 7.44 (2H, d, J=4.0 Hz), 7.88 (2H, d, J=8.1 Hz), 7.96 (2H, d, J=9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 24.2, 71.4, 114.9, 117.5, 120.0, 121.6, 123.7, 125.4, 126.4, 127.9, 129.3, 129.5, 134.1, 136.7, 153.7, 157.0, 157.2. HRESIMS calcd for $C_{34}H_{29}N_2O_2$: 497.2229 $(M+H)^+$, found: 497.2225.

4.1.3. 2,2′-Bis(2-pyridylmethoxy)-(1*S*)-[3,3′-dibromo-1,1′-binaphthalene] (12). Colorless crystals. Mp 138–140 °C (from ether). $[\alpha]_D^{27}$ +40.0 (*c* 0.87, $CHCl_3$). IR (KBr) ν cm^{-1}; 1595, 1572, 760. ^1H NMR (300 MHz, $CDCl_3$) δ; 4.71 (2H, d, J=13.1 Hz), 5.12 (2H, d, J=13.1 Hz), 6.89 (2H, d, J=7.9 Hz), 7.01 (2H, t, J=8.4 Hz), 7.42 (4H, q, J=8.1, 15.9 Hz), 7.75 (2H, d, J=8.1 Hz), 8.12 (2H, s), 8.31 (2H, br d, J=4.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 75.5, 117.3, 120.6, 122.0, 125.8, 126.1, 126.7, 127.0, 127.2, 131.5, 132.9, 133.0, 136.4, 148.3, 151.8, 157.0. HRESIMS calcd for $C_{32}H_{23}N_2O_2Br_2$: 625.0126 $(M+H)^+$, found: 625.0132.

4.1.4. 2,2′-Bis(2-pyridylethoxy)-(1*S*)-1,1′-binaphthalene (13). Colorless oil. $[\alpha]_D^{22}$ −43.2 (*c* 0.75, $CHCl_3$). IR (neat) ν cm^{-1}; 1591, 1508, 809, 748. ^1H NMR (300 MHz, $CDCl_3$) δ; 2.81 (4H, td, J=6.3, 1.7 Hz), 4.24 (4H, t, J=6.3 Hz), 6.26 (2H, d, J=7.8 Hz), 6.89 (2H, ddd, J=1.0, 4.9, 7.4 Hz), 6.99–7.21 (6H, m), 7.30 (2H, ddd, J=1.5, 6.5, 8.0 Hz), 7.38 (2H, d, J=9.0 Hz), 7.86 (2H, d, J=8.2 Hz), 7.93 (2H, d, J=9.0 Hz), 8.33 (2H, dt, J=0.9, 4.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 38.2, 68.3, 114.9, 120.1, 120.9, 123.4, 123.7, 125.3, 126.0, 127.6, 129.0, 129.1, 134.0, 135.6, 148.6, 153.9, 158.3. HRESIMS calcd for $C_{34}H_{29}N_2O_2$: 497.2229 $(M+H)^+$, found: 497.2201. Anal. Calcd for $C_{34}H_{28}N_2O_2$: C, 82.23; H, 5.68; N, 5.64. Found: C, 82.17; H, 5.74; N, 5.45.

4.1.5. (*R*,*R*)-1,2-Diphenyl-1,2-bis(2-pyridylethoxy)ethane (14). Colorless crystals. Mp 78–80 °C (from hexane–AcOEt). $[\alpha]_D^{28}$ −59.1 (*c* 0.65, $CHCl_3$). IR (KBr) ν cm^{-1}; 1597, 1589, 760, 698. ^1H NMR (300 MHz, $CDCl_3$) δ; 4.57 (2H, d, J=14.0 Hz), 4.70 (2H, s), 4.70 (2H, d, J=14.0 Hz), 7.08–7.26 (12H, m), 7.48 (2H, d, J=7.8 Hz), 7.61 (2H, dt, J=1.8, 7.7 Hz), 8.47 (2H, d, J=4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 72.1, 85.8, 121.2, 122.0, 127.7, 127.8, 127.9, 136.5, 138.1, 148.8, 159.0. HRESIMS calcd for $C_{26}H_{25}N_2O_2$: 397.1916 $(M+H)^+$, found: 397.1915. Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.66; H, 6.01; N, 6.94.

4.2. General procedure for the preparation of ligand 16–22

4.2.1. 2,2′-Bis(picolinyloxy)-(1*S*)-1,1′-binaphthalene (16). To a solution of (*S*)-BINOL (1.0 g, 3.49 mmol), picolinic acid (946 mg, 7.68 mmol) and 4-dimethylaminopyridine in CH_2Cl_2 (10 mL) was added a solution of dicyclohexylcarbodiimide (1.66 g, 8.03 mmol) in CH_2Cl_2 (5 mL) at room temperature. After being stirred for 15 h, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt, 1:5) to afford compound **16** (1.63 g, 3.28 mmol) in 94% yield. White amorphous solid. $[\alpha]_D^{28}$ −84.9 (*c* 0.59, $CHCl_3$). IR (KBr) ν cm^{-1}; 1752, 1685, 1654, 1582, 745. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.31–7.48 (14H, m), 7.56–7.61 (4H, m), 7.90 (2H, d, J=8.1 Hz), 8.00 (2H, d, J=8.9 Hz), 8.63 (2H, d, J=4.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 121.5, 123.5, 125.4, 125.9, 126.1, 126.9, 127.1, 127.9, 129.8, 131.6, 133.3, 136.9, 146.8, 147.0, 150.0, 162.8. HRESIMS calcd for $C_{32}H_{21}N_2O_4$: 497.1501 $(M+H)^+$, found: 497.1496. Anal. Calcd for $C_{32}H_{20}N_2O_4$: C, 77.41; H, 4.06; N, 5.64. Found: C, 77.20; H, 4.15; N, 5.58.

4.2.2. 2,2′-Bis(2-quinolinecarbonyloxy)-(1*S*)-1,1′-binaphthalene (17). Colorless crystals. Mp 193–195 °C (from hexane–AcOEt). $[\alpha]_D^{28}$ +53.7 (*c* 0.51, $CHCl_3$). IR (KBr) ν cm^{-1}; 1768, 1744, 1654, 839, 777. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.34–7.79 (16H, m), 7.91 (2H, d, J=8.0 Hz), 8.02 (2H, d, J=8.9 Hz), 8.06 (2H, d, J=8.6 Hz), 8.18 (2H, d, J=8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 121.5, 122.0, 123.9, 126.3, 126.6, 127.6, 127.8, 128.4, 129.0, 129.6, 130.2, 130.5, 131.0, 131.2, 133.7, 137.6, 147.4, 147.5, 148.1, 163.4. HRESIMS calcd for $C_{40}H_{25}N_2O_4$: 597.1814 $(M+H)^+$, found: 597.1768. Anal. Calcd for $C_{40}H_{24}N_2O_4$: C, 80.52; H, 4.05; N, 4.70. Found: C, 80.43; H, 4.04; N, 4.71.

4.2.3. 2,2′-Bis(2-isoquinolinecarbonyloxy)-(1*S*)-1,1′-binaphthalene (18). Colorless crystals. Mp 209–211 °C (from hexane–AcOEt). $[\alpha]_D^{28}$ +6.4 (*c* 0.5, $CHCl_3$). IR (KBr) ν cm^{-1}; 1735, 1701, 1654, 1560, 801. ^1H NMR δ; (300 MHz, $CDCl_3$) 712–7.22 (4H, m), 7.39–7.44 (2H, m), 7.49–7.59 (6H, m), 7.63 (2H, d, *J*=8.9 Hz), 7.65–7.75 (4H, m), 7.98 (2H, d, *J*=8.9 Hz), 8.04 (2H, d, *J*=8.9 Hz), 8.49 (2H, d, *J*=5.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 121.9, 123.7, 124.0, 125.7, 126.0, 126.1, 126.6, 126.7, 127.1, 128.0, 128.2, 130.1, 130.4, 132.0, 133.5, 136.4, 141.4, 147.4, 148.9, 164.6. HRESIMS calcd for $C_{40}H_{25}N_2O_4$: 597.1814 $(M+H)^+$, found: 597.1768. Anal. Calcd for $C_{40}H_{24}N_2O_4$: C, 80.52; H, 4.05; N, 4.70. Found: C, 80.31; H, 4.28; N, 4.67.

4.2.4. 2,2′-Bis(nicotinyloxy)-(1*S*)-1,1′-binaphthalene (19). White amorphous solid. $[\alpha]_D^{28}$ −74.1 (*c* 0.56, $CHCl_3$). IR (KBr) ν cm^{-1}; 1741, 1589, 1508, 1420, 730. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.20 (2H, ddd, *J*=0.8, 4.9, 8.0 Hz), 7.32–7.42 (4H, m), 7.49 (2H, ddd, *J*=2.3, 5.8, 8.3 Hz), 7.55 (2H, d, *J*=8.9 Hz), 7.86 (2H, td, *J*=2.0, 8.0 Hz), 7.93 (2H, d, *J*=8.2 Hz), 8.01 (2H, d, *J*=8.9 Hz), 8.65 (2H, dd, *J*=1.7, 4.9 Hz), 8.75 (2H, dd, *J*=0.8, 2.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 121.4, 123.2, 123.5, 125.1, 125.9, 126.1, 127.1, 128.2, 129.9, 131.6, 133.2, 146.5, 151.0, 153.6, 163.4. HRESIMS calcd for $C_{32}H_{21}N_2O_4$: 497.1510 $(M+H)^+$, found: 497.1496. Anal. Calcd for $C_{32}H_{21}N_2O_4$: C, 77.41; H, 4.06; N, 5.64. Found: C, 77.07; H, 4.21; N, 5.61.

4.2.5. 2,2′-Bis(picolinyloxy)-(1*S*)-[3,3′-dibromo-1,1′-binaphthalene] (20). Colorless crystals. Mp 156–158 °C (from acetone). $[\alpha]_D^{24}$ −2.7 (*c* 0.75, $CHCl_3$). IR (KBr) ν cm^{-1}; 1764, 1578, 745. ^1H NMR (300 MHz, acetone-d_6) δ; 7.23 (2H, d, *J*=8.3 Hz), 7.41 (2H, t, *J*=7.6 Hz), 7.47–7.61 (4H, m), 7.83–8.09 (6H, m), 8.43 (2H, s), 8.61 (2H, br d, *J*=4.5 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ; 115.6, 125.9, 126.3, 126.5, 127.5, 127.8, 127.9, 128.0, 132.4, 133.6, 137.5, 144.9, 146.9, 150.5, 162.1. HRESIMS calcd for $C_{32}H_{19}N_2O_4Br_2$: 652.9712 $(M+H)^+$, found: 652.9655.

4.2.6. 2,2′-Bis(picolinyloxy) -(1*S*)-[6,6′-dibromo-1,1′-binaphthalene] (21). Colorless crystals. Mp 78–80 °C (from ether–hexane). $[\alpha]_D^{24}$ −80.1 (*c* 0.71, $CHCl_3$). IR (KBr) ν cm^{-1}; 1756, 1584, 744. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.21 (2H, d, *J*=9.0 Hz), 7.36 (2H, d, *J*=6.1 Hz), 7.41 (2H, dd, *J*=1.3, 9.2 Hz), 7.54–7.69 (6H, m), 7.90 (2H, d, *J*=9.0 Hz), 8.06 (2H, s), 8.65 (2H, br d, *J*=4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 122.0, 122.7, 123.2, 125.4, 127.1, 127.6, 129.1, 130.0, 130.1, 131.6, 132.6, 137.0, 146.6, 147.1. HRESIMS calcd for $C_{32}H_{19}N_2O_4Br_2$: 652.9712 $(M+H)^+$, found: 652.9692. Anal. Calcd for $C_{32}H_{18}N_2O_4Br_2$: C, 58.74; H, 2.77; N, 4.28. Found: C, 58.53; H, 2.85; N, 4.05.

4.2.7. (*R*,*R*)-1,2-Diphenyl-1,2-bis(picolinyloxy)ethane (22). White amorphous solid. $[\alpha]_D^{28}$ +72.4 (*c* 0.51, $CHCl_3$). IR (KBr) ν cm^{-1}; 1733, 1582, 697. ^1H NMR (300 MHz, $CDCl_3$) δ; 6.58 (2H, s), 7.20–7.35 (10H, m), 7.41 (2H, ddd, *J*=0.9, 4.6, 7.6 Hz), 7.78 (2H, dt, *J*=1.7, 7.7 Hz), 8.11 (2H, d, *J*=7.8 Hz), 8.71 (2H, d, *J*=4.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 78.5, 125.2, 126.8, 127.9, 128.3, 128.7, 135.5, 137.0, 147.7, 150.1, 163.7. HRESIMS calcd for $C_{26}H_{21}N_2O_4$: 425.1501 $(M+H)^+$, found: 425.1536.

4.3. General procedure for the enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (1) with thioacetylene derivatives

4.3.1. (1*S*,5*R*)-1-Methoxycarbonyl-2-oxo-7-(phenylthio)-bicyclo[3.2.0]hept-6-ene (3). To a suspension of copper(II) chloride (1.3 g, 9.7 mmol) and ligand **ent-16** (5.76 g, 11.6 mmol) in CH_2Cl_2 (110 mL) was stirred at ambient temperature for 30 min and silver hexafluoroantimonate (7.0 g, 20.4 mmol) was added to the resulting mixture in the dark. After being stirred for 1 h at ambient temperature, a solution of 2-methoxycarbonyl-2-cyclohexen-1-one (**1**) (6.40 g, 45.7 mmol) and phenylthioacetylene (**2**) (7.24 g, 54.8 mmol) in CH_2Cl_2 (130 mL) was added to the mixture at −78 °C. After being stirred for 1.5 h at the same temperature, phosphate buffer (pH 6.86, 150 mL) was added to the mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 7:1) to afford compound **3** (8.44 g, 30.8 mmol) in 67% yield. 73% ee (Chiralcel OJ-H, hexane/IPA=95:5). Pale yellow oil. $[\alpha]_D^{22}$ +499 (*c* 1.33, $CHCl_3$). IR (neat) ν cm^{-1}; 1746, 1731, 1294, 747. ^1H NMR (300 MHz, $CDCl_3$) δ; 1.89 (1H, bdd, *J*=9.1, 13.5 Hz), 2.13 (1H, dddd, *J*=6.9, 8.7, 11.9, 13.5 Hz), 2.39 (1H, ddd, *J*=1.0, 8.7, 18.3 Hz), 3.02 (1H, ddd, *J*=9.1, 11.9, 18.3 Hz), 3.67 (1H, d, *J*=6.9 Hz), 3.75 (3H, s), 5.88 (1H, s), 7.26–7.38 (3H, m), 7.49–7.53 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 22.4 (CH_2), 34.9 (CH_2), 48.3 (CH), 52.3 (CH_3), 66.2 (C), 128.8 (CH), 129.4 (CH), 129.7 (C), 133.0 (CH), 133.8 (CH), 140.5 (C), 167.6 (C), 208.4 (C). EI-MS *m*/*z*: 274 (M^+). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.55; H, 5.11.

4.3.2. 1-Methoxycarbonyl-2-oxo-6-butyl-7-(phenylthio)-bicyclo[3.2.0]hept-6-ene (24a). Pale yellow oil. $[\alpha]_D^{26}$ −148 (32% ee, *c* 0.71, $CHCl_3$). IR (neat) ν cm^{-1}; 1743, 1734, 1730. ^1H NMR (300 MHz, $CDCl_3$) δ; 0.88 (3H, t, *J*=7.3 Hz), 1.19–1.50 (4H, m), 1.88–2.25 (4H, m), 2.34 (1H, ddd, *J*=1.3, 8.6, 18.3 Hz), 2.84 (1H, ddd, *J*=9.3, 11.9, 18.3 Hz), 3.53 (3H, s), 3.64 (1H, d, *J*=7.0 Hz), 7.20–7.33 (3H, m), 7.36–7.45 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 13.4, 20.3, 22.6, 27.5, 28.4, 35.0, 49.4, 51.9, 65.3, 127.5, 128.8, 129.5, 132.1, 132.4, 160.0, 168.1, 207.7. HRESIMS calcd for $C_{19}H_{23}O_3S$: 331.1368 $(M+H)^+$, found: 331.1384.

4.3.3. 1-Methoxycarbonyl-2-oxo-6-trimethylsilyl-7-(methylthio)bicyclo[3.2.0]hept-6-ene (24c). Pale yellow oil. $[\alpha]_D^{26}$ −383 (73% ee, *c* 0.35, $CHCl_3$). IR (neat) ν cm^{-1}; 1747, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ; 0.16 (9H, s), 1.89 (1H, dd, *J*=9.0, 13.5 Hz HH), 2.06–2.13 (1H, m), 2.33 (3H, s), 2.29–2.41 (1H, m), 2.96 (1H, ddd, *J*=9.0, 12.2, 18.2 Hz), 3.54 (1H, d, *J*=6.8 Hz), 3.74 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ; −1.7, 13.9, 22.9, 35.1, 49.9, 52.2, 68.5, 149.0, 151.4, 168.4, 210.0. HRESIMS

calcd for $C_{13}H_{20}O_3NaSiS$: 307.0800 $(M+Na)^+$, found: 307.0808.

4.3.4. 2-(Methoxycarbonyl)-3-(2-chloro-2-phenylthioethenyl)cyclopentan-1-one (4). To a solution of **3** (60% ee) (135 mg, 0.429 mmol) in CH_2Cl_2 (2 mL) was added titanium tetrachloride (53 μL, 0.428 mmol) at 0 °C. After being stirred for 30 min at same temperature, neutral phosphate buffer solution (pH 6.86, 1 mL) was added to the reaction mixture. The resulting mixture was extracted with AcOEt and the organic layer was dried over $MgSO_4$ and consentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford compound 4 (140 mg, 0.45 mmol) in 91% yield. $[\alpha]_D^{28}$ +267 (*c* 0.51, $CHCl_3$). IR (neat) $\nu\,cm^{-1}$; 1760, 1730, 1584. ^1H NMR (300 MHz, $CDCl_3$) δ; 1.68–1.79 (1H, m), 2.25–2.23 (3H, m), 3.08 (1H, d, $J=11.3$ Hz), 3.73 (3H, s), 3.88–3.98 (1H, m), 6.15 (1H, d, $J=9.5$ Hz), 7.30–7.39 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 27.5, 37.8, 42.8, 52.6, 60.6, 127.8, 129.2, 129.5, 130.5, 132.1, 139.1, 168.4, 209.3. HRESIMS calcd for $C_{15}H_{15}O_3NaSCl$: 333.0328 $(M+Na)^+$, found: 333.0302.

4.3.5. 3-(Hydroxycarbonylmethyl)cyclopentan-1-one (25). The mixture of compound **4** (60 mg, 0.193 mmol) and concentrated HCl (0.1 mL) in MeOH (1 mL) was heated at 60 °C. After being stirred for 12 h at same temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/isopropanol, 1:5) to afford compound **25**[18] (9 mg, 0.063 mmol) in 33% yield. $[\alpha]_D^{28}$ +65.1 (*c* 0.45, $CHCl_3$). IR (neat) $\nu\,cm^{-1}$; 1737. ^1H NMR (300 MHz, $CDCl_3$) δ; 1.20–1.25 (1H, m), 1.53–1.70 (1H, m), 1.86–1.96 (1H, m), 2.14–2.39 (3H, m), 2.48–2.68 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 29.1, 33.1, 38.3, 39.3, 44.5, 177.7, 218.3.

Acknowledgements

We thank the Uehara Memorial Foundation for financial support.

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New non-volatile and odorless organosulfur compounds anchored on ionic liquids. Recyclable reagents for Swern oxidation

Xun He and Tak Hang Chan*

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

Received 23 October 2005; revised 13 January 2006; accepted 13 January 2006

Available online 3 February 2006

Abstract—A new class of odorless and non-volatile organosulfur compounds grafted to imidazolium ionic liquid scaffold has been synthesized. The sulfoxides can be used effectively for the oxidation of primary allylic and benzylic alcohols into aldehydes and secondary alcohols to ketones under Swern oxidation conditions and the corresponding sulfides can be recovered and recycled.
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1. Introduction

Organosulfur compounds have played an important role in organic chemistry.[1] An array of organosulfur compounds have been introduced for use in pesticides, medicines,[2] and more recently material sciences.[3] Many organosulfur reagents have important use in synthetic organic chemistry.[4] Volatile organosulfur compounds, especially thiols, often have very unpleasant smells and some are toxic.[2] These properties have reduced their attractiveness for applications. We report here the synthesis of a new class of organosulfur compounds anchored on the imidizolium scaffold commonly used for ionic liquids. Ionic liquids have received much attention in recent years as environmentally benign reaction media for organic reactions.[5] This is due to some intriguing properties of ionic liquids: high thermal and chemical stability, non-flammability, lack of measurable vapor pressure and high loading capacity. By modifying the structure of the cation or the anion, the solubilities of the ionic liquids can be tuned readily so that they can phase separate from organic as well as aqueous media. By anchoring the sulfur function to the ionic liquid moiety, we expect to render the organosulfur compounds non-volatile, and easily recoverable and recyclable. We then demonstrate the application of these new organosulfur compounds as reagents for the Swern oxidation.

2. Results and discussion

The preparation of the ionic liquid-supported sulfur compounds started from 1,2-dimethylimidazole **1** and bromoalkyl alcohols **2** (Scheme 1). The reaction was conducted without solvent at 60–70 °C and the product **3** was obtained in nearly quantitative yield simply by washing the reaction mixture with diethyl ether to remove the trace amount of unreacted starting materials. This was followed by anion exchange to give the triflate salt **4** quantitatively. Mass spectroscopic analysis showed that the anion exchange was complete based on the spectra on anions, which showed the absence of bromide anion. Sodium triflate also worked for the anion exchange reaction, but the reaction went faster with silver triflate. The methanesulfonylation of alcohols **4** was conducted at room temperature under the basic condition provided by Cs_2CO_3 in acetonitrile. This gave excellent yields of product mesylates **5**. The inorganic salt was simply removed by filtration and the organic impurity was easily washed away with diethyl ether. The mesylates **5** were then transformed to the ionic liquid-supported sulfides **10** in one pot with a sequence of reactions but without need of purification of the intermediate products. First, treatment of **5** with thiourea in acetonitrile gave the thiouronium salt **6**.[6] Base hydrolysis of **6** gave the odorless ionic liquid-supported thiol **8** together with the disulfide **9** as a mixture. The sole formation of pure thiol **8** was difficult even though a number of reaction conditions were tested including using different bases such as LiOH, NaOH, KOH and CsOH, or solvents such as THF and acetonitrile, and temperature from room temperature to 60 °C. This is due to ease of thiol oxidative dimerization in air under basic conditions. However, we were able to trap the thiolate intermediate **7** readily as the methyl sulfide **10** by quenching the base hydrolytic reaction mixture with dimethyl sulfate.[7] The conversion of the ionic liquid **4** to the sulfur compound **10** could be achieved in >92% overall yield with no need of chromatographic

Keywords: Odorlessorganosulfur compounds; Ionic liquids; Swern oxidation; Supported reagents.
* Corresponding author. Tel.: +514 398 2094;
e-mail: tak-hang.chan@mcgill.ca

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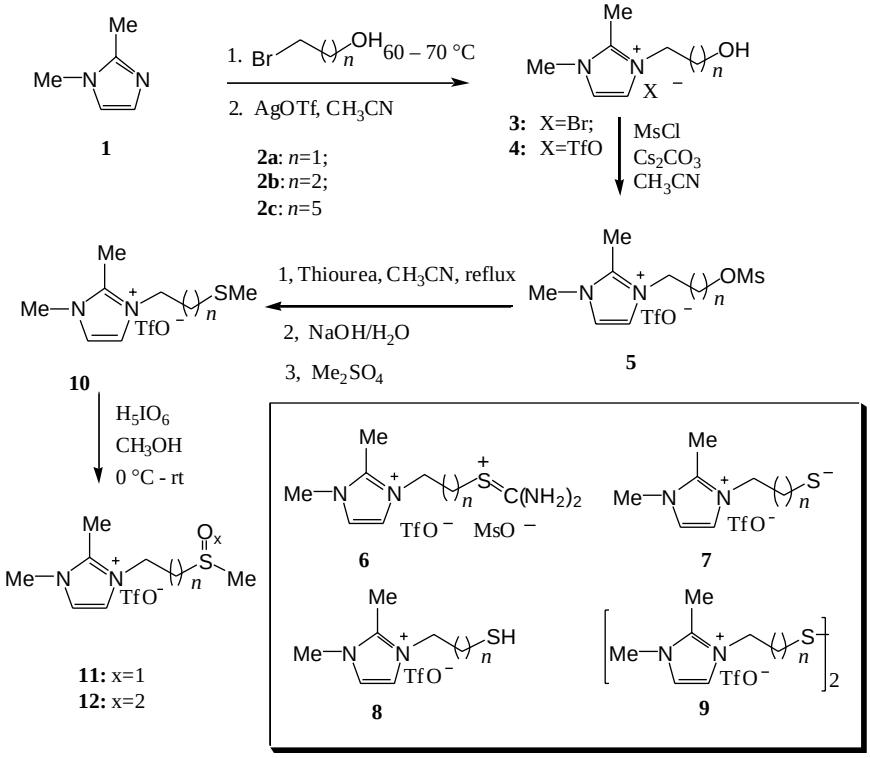
doi:10.1016/j.tet.2006.01.045



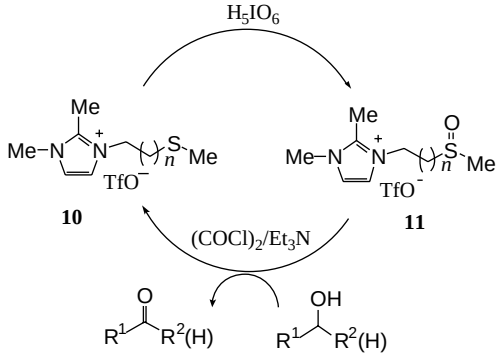
Scheme 1. Preparation of ionic liquid-grafted sulfides and sulfoxides.

purification of intermediates and there was no foul smell released in any of the operations. This is because in all the reaction steps, the products were separated from the excess organic or inorganic reagents by simply washing with organic or aqueous solvents, an advantage, which we have demonstrated previously in ionic liquid-supported synthesis of small molecules,[8] oligopeptides[9] and oligosaccharides.[10] The whole synthetic sequence was odor-free as no volatile organosulfur compounds were used or generated. Previously, sulfur containing imidazolium ionic liquid had been synthesized from *N*-methylimidazole and 2-(chlorethyl)ethyl sulfide.[11] However, this involved the use of odorous volatile sulfur compound for the synthesis, and ethyl sulfoxides in general are not used for Swern oxidation.

The oxidation of the sulfides **10** with periodic acid generated very cleanly the sulfoxides **11** without over-oxidation to the sulfone **12** under the experimental condition.[12] Potassium periodate did not oxidize **10** under neutral conditions, but under acidic conditions converted **10** to a mixture of sulfoxide **11** as well as sulfone **12** in a ratio of 3 to 1 according to ^{1}H NMR spectra. *m*-Chloroperoxybenzoic acid (*m*CPBA) also oxidized the sulfide **10** to give similar results as acidified potassium periodate. The oxidation of the sulfides with peracetic acid, on the other hand, proceeded slowly at room temperature. It only generated a very small amount of sulfoxide **11** after stirring for 24 h at room temperature.

The conversion of alcohols to aldehydes and ketones is one of the key functional transformations in organic chemistry. The Swern oxidation and its numerous variations[13,14] have been used extensively for that purpose. A major drawback of the Swern oxidation is that dimethyl sulfide, generated in stoichiometric amount, is volatile, malodorous, toxic and difficult to be recovered. This mitigates against its use on a large scale. A number of research groups have attempted to overcome the problem by using polymer-supported sulfoxide reagents,[15] fluorous sulfoxides[16] or dodecyl methyl sulfoxide.[17] Each of these has some inherent deficiencies. In the dodecyl methyl sulfoxide case, recovery of the product sulfide was difficult. The fluorous sulfoxides and sulfides are likely to be expensive and relatively volatile. Polymer-supported sulfoxide reagents,[15] whether using insoluble or soluble polymer support, usually have a low loading level of the effective functional group.

We examined therefore the ionic liquid-supported sulfoxides **11** as recoverable and recyclable reagents for the Swern oxidation reaction (Scheme 2).



Scheme 2. Recycle of ionic liquid-supported sulfides and sulfoxides in Swern oxidation.

The Swern oxidations were conducted under standard conditions, using oxalyl chloride as activator and triethylamine as base in acetonitrile/dichloromethane at low temperature. The ionic liquid-attached sulfoxides **11b** or **11c** were quite reactive. A number of alcohols were converted to the corresponding aldehydes or ketones in high yields (Table 1). The carbonyl product was easily separated from the ionic liquid anchored sulfide **10** (**b** or **c**) by simple phase separations with diethyl ether after Swern oxidation. However, it should be pointed out that the sulfoxide **11a**, which has two methylene spacers between the ionic liquid moiety and the sulfoxide part, did not work well as Swern oxidation reagent. It is possible that facile β elimination may have occurred leading to the fragmentation of the imidazolium moiety from the sulfoxide. The oxidation of secondary alcohols to the corresponding ketones worked very efficiently under the reaction conditions (Table 1). On the other hand, oxidation of primary alcohols to aldehydes appears to have worked well only for benzylic or allylic alcohols. Simple aliphatic primary alcohols tended to give low yield, possibly because the sulfoxide **11b** or **11c** reagent was not employed in large excess, in contrast to what was normally used for DMSO.[14] We have conducted one reaction on a larger (10–50 mmol) scale for the oxidation of benzhydrol to benzophenone. The isolated yield of the product was 91%.

The use of ionic liquid-supported reagents allows for the opportunity of recovery and recycle. The sulfide **10b** or **10c**, insoluble in ether, was recovered after aqueous treatment with K_2CO_3 and extraction with acetonitrile/dichloromethane.[18] The recovered sulfide **10b** or **10c** can be re-oxidized with periodic acid and used for the Swern oxidation again. Oxidation of benzhydrol to benzophenone was chosen as an example to test the recovery and recycling efficiency of the **11b**↔**10b** system. The results are summarized in Table 2, which show that the product yields and recovered sulfide yields were still quite acceptable after four recycles (Table 2).[18]

Table 1. Swern oxidation using ionic liquid-supported sulfoxides

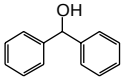
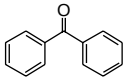
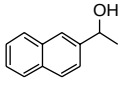
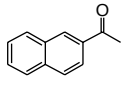
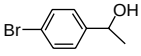
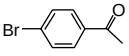
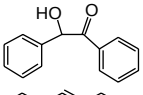
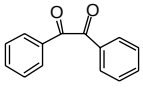
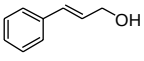
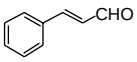
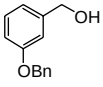
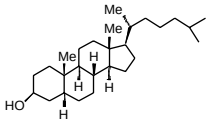
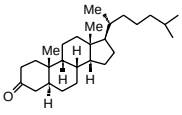
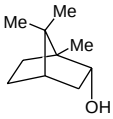
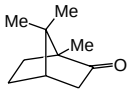
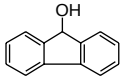
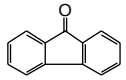
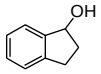
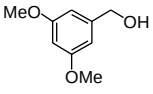
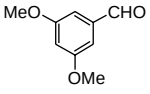
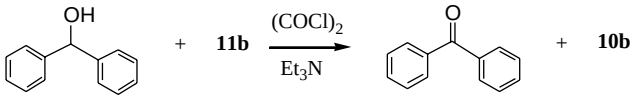
Entry	Sulfoxide	Substrate	Product	Yield (%)
1	**11b**			90
2	**11b**			95
3	**11b**			86
4	**11b**			85
5	**11b**			88
6	**11b**			95
7	**11b**			82
8	**11b**			85
9	**11b**			90
10	**11c**			95
11	**11c**			82
12	**11c**			97

Table 2. Recycle of ionic liquid-supported sulfide **10b** in Swern oxidation of benzhydrol to benzophenone



Recycle times	1	2	3	4
Product yield (%)	90	87	86	81
Recovered sulfide (%)	88	82	82	80

3. Conclusions

We have prepared a class of novel sulfur containing compounds anchored onto an imidazolium ionic liquid scaffold. Because of the lack of vapour pressure of these ionic liquids, the sulfur compounds do not possess odor. The sulfoxide compounds **11b** and **11c** can be used effectively for the oxidation of alcohols to carbonyl compounds under the Swern oxidation conditions. The product sulfide **10b** can be recovered easily from the reaction mixture and regenerated to **11b** and thus reused for at least 4 cycles.

4. Experimental

4.1. General

The procedures to make ionic liquid-attached compounds with two, three, six methylene spacers in the Scheme 1 were the same.

4.1.1. 1-(3′-Hydroxypropyl)-2,3-dimethylimidazolium triflate (4b). To a flask containing 1,2-dimethylimidazole (10.0 mL, 113 mmol) was added 3-bromopropanol (10.0 mL, 114 mmol). The mixture was heated to 70 °C and stirred for 2 h under nitrogen and then cooled to room temperature. The crude product solidified during the cooling process. The solid was washed with diethyl ether for four times and dried in vacuo for 3 h to afford

4.1.2. 1-(3′-Hydroxypropyl)-2,3-dimethylimidazolium bromide (3b). As white solid (26.2 g, 98% yield). Mp 58–60 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.24 (d, 1H, J= 2 Hz), 7.20 (d, 1H, J=2 Hz), 4.10 (t, 2H, J=7.2 Hz), 3.65 (s, 3H), 3.50 (t, 2H, J=6.4 Hz), 2.48 (s, 3H), 1.93 (m, 2H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.4, 120.9, 58.2, 45.3, 35.0, 31.6, 9.4; HRMS (ESI): calcd for $C_8H_{15}N_2O$ (M^+) 155.1179, found: 155.1178.

To a solution of 1-(3′-hydroxypropyl)-2,3-dimethylimidazolium bromide (**3b**) (4.97 g, 21.1 mmol) in dry acetonitrile (20 mL) was added silver triflate (5.43 g, 21.1 mmol). The mixture was stirred for 2 h in the dark under nitrogen. The mixture was filtered to remove the yellow salt and the filtrate was evaporated by rotary evaporation under vacuum and dried in vacuo to generate the product **4b** as a clear liquid with a very light brown color (6.42 g, 100% yield). ^{1}H NMR (300 MHz, D_2O): δ 7.27 (d, 1H, J= 1.8 Hz), 7.23 (d, 1H, J=1.8 Hz), 4.12 (t, 2H, J=7.2 Hz), 3.68 (s, 3H), 3.53 (t, 2H, J=6.3 Hz), 2.51 (s, 3H), 1.96 (m, 2H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.4, 120.9, 58.1, 45.2, 34.9, 31.6, 9.1; HRMS (ESI): calcd for $C_8H_{15}N_2O$ (M^+) 155.1179, found: 155.1180.

4.1.3. 1-(2′-Hydroxyethyl)-2,3-dimethylimidazolium triflate (4a). Yield: 100% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.28 (d, 1H, J=2.0 Hz), 7.24 (d, 1H, J=2.0 Hz), 4.15 (t, 2H, J=5.6 Hz), 3.82 (t, 2H, J=6 Hz), 3.69 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.5, 121.2, 60.2, 50.4, 35.0, 9.4; HRMS (ESI): calcd for $C_7H_{13}N_2O$ (M^+) 141.1018, found: 141.1022.

4.1.4. 1-(6′-Hydroxyhexyl)-2,3-dimethylimidazolium triflate (4c). Yield: 100% as clear liquid; ^{1}H NMR (300 MHz, D_2O): δ 7.21 (d, 1H, J=2.4 Hz), 7.17 (d, 1H, J=2.4 Hz), 3.98 (t, 2H, J=6.9 Hz), 3.64 (s, 3H), 3.46 (t, 2H, J= 6.6 Hz), 2.46 (s, 3H), 1.70 (m, 2H), 1.42 (m, 2H), 1.23 (m, 4H); ^{13}C NMR (300 MHz, D_2O): δ 144.2, 122.2, 120.8, 61.9, 48.3, 34.8, 31.4, 29.2, 25.5, 24.9, 9.1; HRMS (ESI): calcd for $C_{11}H_{21}N_2O$ (M^+) 197.1648, found: 197.1646.

4.1.5. Compound 5b. To a flask containing **4b** (6.00 g, 19.7 mmol) and cesium carbonate (8.05 g, 24.7 mmol) was added acetonitrile (30 mL). The mixture was cooled to 0 °C and methanesulfonyl chloride (2.30 mL, 29.6 mmol) was added dropwise. After 2 h of stirring at 0 °C, the mixture was warmed to room temperature and stirring continued for 20 h. The insoluble inorganic salt was filtered off and the filtrate was evaporated by rotary evaporation and dried in vacuo overnight. The crude product was washed with diethyl ether for four times to afford white solid product **5b** (7.31 g, 97% yield). Mp 47–49 °C; ^{1}H NMR (400 MHz, D_2O): δ 7.25 (d, 1H, J=2.0 Hz), 7.21 (d, 1H, J=2.0 Hz), 4.23 (t, 2H, J=5.6 Hz), 4.16 (t, 2H, J=7.2 Hz), 3.64 (s, 3H), 3.06 (s, 3H), 2.46 (s, 3H), 2.19 (m, 2H); ^{13}C NMR (400 MHz, D_2O): δ 144.7, 122.6, 120.9, 68.2, 44.8, 36.6, 34.9, 28.8, 9.2; HRMS (ESI): calcd for $C_9H_{17}N_2O_3S$ (M^+) 233.0954, found: 233.0953.

4.1.6. Compound 5a. Yield: 94% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.30 (d, 1H, J=1.6 Hz), 7.23 (d, 1H, J=1.6 Hz), 4.51 (t, 2H, J=4.8 Hz), 4.42 (t, 2H, J=5.6 Hz), 3.65 (s, 3H), 3.05 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (400 MHz, D_2O): δ 145.4, 122.8, 121.3, 68.6, 47.3, 36.9, 35.1, 9.5; HRMS (ESI): calcd for $C_8H_{15}N_2O_3S$ (M^+) 219.0795, found: 219.0798.

4.1.7. Compound 5c. Yield: 95% as clear liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.16 (d, 1H, J=2.4 Hz), 7.12 (d, 1H, J=2.4 Hz), 4.15 (t, 2H, J=6.0 Hz), 3.94 (t, 2H, J=7.2 Hz), 3.58 (s, 3H), 3.00 (s, 3H), 2.41 (s, 3H), 1.68 (m, 2H), 1.59 (m, 2H), 1.28 (m, 2H), 1.17 (m, 2H); ^{13}C NMR (400 MHz, CD_3CN): δ 144.6, 122.5, 121.0, 71.1, 48.4, 36.8, 35.1, 29.5, 28.9, 25.6, 25.0, 9.6; HRMS (ESI): calcd for $C_{12}H_{23}N_2O_3S$ (M^+) 275.1424, found: 275.1420.

4.1.8. Compound 10b. To a flask containing **5b** (1.00 g, 2.61 mmol) and thiourea (0.32 g, 4.20 mmol) was added dry acetonitrile (20 mL). The mixture was refluxed for 10 h under nitrogen. After removing the solvent, NaOH (0.42 g, 10.5 mmol) and degassed water (20 mL) were added and the mixture was stirred at 45 °C overnight under nitrogen. Dimethyl sulfate (0.30 mL, 3.15 mmol) was added and the mixture was stirred at room temperature for 20 h.

After the pH of the mixture was adjusted to 7 with the addition of aqueous HCl, the mixture was freeze dried to remove water. Acetonitrile was added to the residue to extract the product. The acetonitrile solution was filtered to remove the insoluble inorganic salt, and the filtrate was rotary evaporated under vacuum and then dried in vacuo to give product **10b** as clear oil (0.87 g, 99% yield). ^{1}H NMR (400 MHz, D_2O): δ 7.22 (d, 1H, J=2.4 Hz), 7.17 (d, 1H, J=2.4 Hz), 4.08 (t, 2H, J=6.8 Hz), 3.62 (s, 3H), 2.47 (s, 3H), 2.41 (t, 2H, J=6.8 Hz), 1.97 (m, 5H); ^{13}C NMR (300 MHz, D_2O): δ 144.5, 122.5, 120.8, 46.9, 34.9, 29.9, 28.3, 14.4, 9.2; HRMS (ESI): calcd for $C_9H_{17}N_2S$ (M^+) 185.1107, found: 185.1103.

4.1.9. Compound 10a. Yield: 99% as clear oily liquid; ^{1}H NMR (400 MHz, D_2O): δ 7.28 (d, 1H, J=2.0 Hz), 7.21 (d, 1H, J=2.0 Hz), 4.22 (t, 2H, J=6.4 Hz), 3.66 (s, 3H), 2.83 (t, 2H, J=6.4 Hz), 2.51 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (400 MHz, D_2O): δ 144.7, 122.4, 121.1, 47.2, 35.0, 33.4, 14.7, 9.4; HRMS (ESI): calcd for $C_8H_{15}N_2S$ (M^+) 171.0950, found: 171.0949.

4.1.10. Compound 10c. Yield: 98% as clear oily liquid; ^{1}H NMR (300 MHz, D_2O): δ 7.16 (d, 1H, J=1.8 Hz), 7.13 (d, 1H, J=1.8 Hz), 3.94 (t, 2H, J=7.2 Hz), 3.60 (s, 3H), 2.42 (s, 3H), 2.36 (t, 2H, J=7.2 Hz), 1.92 (s, 3H), 1.65 (m, 2H), 1.43 (m, 2H), 1.52 (m, 4H); ^{13}C NMR (300 MHz, D_2O): δ 144.2, 122.2, 120.8, 48.3, 34.7, 33.4, 29.1, 28.3, 27.6, 25.3, 14.4, 9.1; HRMS (ESI): calcd for $C_{12}H_{23}N_2S$ (M^+) 227.1576, found: 227.1575.

4.1.11. Compound 11b. To a solution of **10b** (5.05 g, 15.1 mmol) in methanol (50 mL), which was cooled with ice bath, was added dropwise a solution of periodic acid (3.45 g, 15.1 mmol) in methanol (15 mL). The mixture was stirred at 0 °C for 2 h. The ice bath was removed and stirring was continued for 20 h. To the orange mixture was added aqueous $Na_2S_2O_3$ solution until the orange color disappeared. The solvent methanol was removed by rotary evaporation in vacuo and water was removed by freeze drying. To the residue was then added the mixed solvent (100 mL) of acetonitrile and dichloromethane (v/v=1:1). After filtering off the inorganic salt, the filtrate was rotary evaporated under vacuum and dried in vacuo to afford the product as white sticky foam (5.18 g, 98% yield). ^{1}H NMR (400 MHz, D_2O): δ 7.24 (d, 1H, J=2 Hz), 7.17 (d, 1H, J=2 Hz), 4.14 (t, 2H, J=7.2 Hz), 3.61 (s, 3H), 2.84–2.72 (m, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.15 (m, 2H); ^{13}C NMR (400 MHz, D_2O): δ 144.6, 122.7, 120.8, 49.1, 46.9, 37.1, 35.1, 23.0, 9.4; HRMS (ESI): calcd for $C_9H_{17}N_2SO$ (M^+) 201.1056, found: 201.1056.

4.1.12. Compound 11a. Yield: 99% as thick oil; ^{1}H NMR (400 MHz, D_2O): δ 7.33 (d, 1H, J=2.4 Hz), 7.26 (d, 1H, J=2.4 Hz), 4.53 (t, 2H, J=6.0 Hz), 3.68 (s, 3H), 3.33 (m, 1H), 3.24 (m, 1H), 2.68 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (300 MHz, D_2O): δ 144.9, 123.0, 121.0, 52.1, 42.3, 37.5, 35.2, 9.5; HRMS (ESI): calcd for $C_8H_{15}N_2SO$ (M^+) 187.0900, found: 187.0898.

4.1.13. Compound 11c. Yield: 96% as thick oil; ^{1}H NMR (300 MHz, D_2O): δ 7.16 (d, 1H, J=2.1 Hz), 7.13 (d, 1H, J=2.1 Hz), 3.95 (t, 2H, J=6.9 Hz), 3.59 (s, 3H), 2.71 (m, 2H), 2.52 (s, 3H), 2.42 (s, 3H), 1.67 (m, 2H), 1.58 (m, 2H), 1.35 (m, 2H), 1.19 (m, 2H); ^{13}C NMR (400 MHz, D_2O): δ 144.2, 122.2, 120.8, 52.8, 48.3, 36.7, 34.9, 29.0, 27.5, 25.4, 22.0, 9.2; HRMS (ESI): calcd for $C_{12}H_{23}N_2SO$ (M^+) 243.1526, found: 243.1525.

4.2. General procedure for the Swern oxidation

A solution of ionic liquid-attached sulfoxide **11** (0.9 mmol, 3 equiv) in dichloromethane (2.5 mL) and acetonitrile (2.5 mL) was cooled to −78 °C and oxalyl chloride (0.9 mmol, 3 equiv) was added dropwise. The mixture was stirred at −78 °C for 40 min and then the alcohol (0.3 mmol, 1 equiv) solution in dichloromethane (2.5 mL) was added dropwise in 10 min. After stirring at low temperature for 1.5 h, triethylamine (0.25 mL, 6 equiv) was added and the mixture was slowly warmed to room temperature. The solvent was removed by rotary evaporation and the product in the residue was extracted with diethyl ether (6 mL) for five times. The ether extract was evaporated by rotary evaporation in vacuo. The product residue was subject to flash column chromatography (silica gel 60A, 230–400 mesh) using hexane and ethyl acetate as eluant to afford the pure product.

4.3. Swern oxidation in larger scale

A solution of ionic liquid-attached sulfoxide **11b** (16.73 g, 48 mmol) in dichloromethane (50 mL) and acetonitrile (75 mL) was cooled to −78 °C and oxalyl chloride (4.8 mL, 55 mmol) was added dropwise. The mixture was stirred at −78 °C for 40 min and then the alcohol benzhydrol (2.92 g, 16 mmol) solution in dichloromethane (25 mL) was added dropwise in 10 min. After stirring at low temperature for 1.5 h, triethylamine (14 mL, 100 mmol) was added and the mixture was slowly warmed to room temperature in 2 h. The solvent was removed by rotary evaporation and the product in the residue was extracted with diethyl ether (60 mL) for 10 times. The ether extract was evaporated by rotary evaporation in vacuo. The product residue was subject to flash column chromatography (silica gel 60A, 230–400 mesh) using hexane and ethyl acetate as eluant to afford the product benzophenone (2.62 g, 91% yield).

4.4. General procedure to recover ionic liquid-attached sulfide after Swern oxidation

After the extraction of the product with diethyl ether described above, water (10 mL) was added to the residue. The aqueous phase was collected and to which K_2CO_3 (0.16 g, 1.1 mmol) was added. The aqueous phase was stirred for 3 h at room temperature and water was removed by freeze–dry by lypholyser. To the solid residue was then added acetonitrile (10 mL), dichloromethane (5 mL) and anhydrous Na_2SO_4. The mixture was stirred for 20 min to extract the expected sulfide into the organic phase. After filtering off the insoluble inorganic salts, the organic filtrate was evaporated by rotary evaporation under vacuum and dried in vacuo to generate the recovered ionic liquid-attached sulfide **10** (Table 2). The NMR spectra of the recovered sulfide showed the same NMR as that of **10** before reaction. The recovered sulfide was used as is for the next cycle. The recovery yield was about 80%, due to

mechanical loss associated with the small scale experimental conditions.

Acknowledgements

We thank Merck Frosst Canada and Natural Science and Engineering Research Council (NSERC) of Canada for financial support. We also thank Dr. O. Mamer and Dr. A. Lesimple for high-resolution mass spectrometric analyses.

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18. The sulfide **10b** or **10c** were recovered in 75–88% yield of the sulfoxide used. The loss was attributed to mechanical loss because of the small amount of sulfoxide used (0.9 mmol) and the difficulty of complete recovery during transfer between flasks.

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Tetrahedron 62 (2006) 3395–3401

Oxazoline Chemistry. Part 11: Syntheses of natural and synthetic isoflavones, stilbenes and related species via C–C bond formation promoted by a Pd–oxazoline complex☆

Charles R. Eisnor, Robert A. Gossage* and Paras N. Yadav

The Chester Woodleigh Small Laboratory of Organic Chemistry, Department of Chemistry, Acadia University, 6 University Avenue, Elliott Hall, Wolfville, NS, Canada B4P 2R6

Received 17 September 2005; revised 6 January 2006; accepted 13 January 2006

Abstract—The complex *trans*-[$PdCl_2$(2-ethyl-2-oxazoline-κ^1N)$_2$] (**1**) is shown to be an active and oxidatively robust catalyst for C–C bond forming reactions (Heck, Sonogashira, Ullmann, Miyaura–Suzuki, etc.). These reactions can be carried out in air without rigorous solvent/substrate purification and in the absence of additional free ligand. The general methodology described above has been applied to the high yield and regio-selective formation, via Miyaura–Suzuki coupling, of natural and synthetic isoflavones (i.e., isoflavone, 2′-methylisoflavone [**7b**], 3′-methylisoflavone [**7c**] and 3′,4′-benzoisoflavone: [**7d**]). Compounds **7c** and **7d** are previously unknown. In addition, the synthesis of (*E*)-tris-*O*-methylresveratrol and (*E*)-3,5-dimethoxystilbene is also described; the former is a recognized anti-cancer agent while the latter is a biologically active extract from the bark of the conifer species *Pinus armandii*. Both of these latter products are produced as a result of a Heck coupling reaction promoted by **1**.
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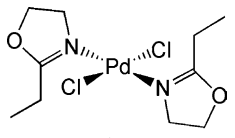
1. Introduction

The creation of a bond between two carbon atoms is a central theme in organic chemistry. In the last 40 years, commodity chemical syntheses have increasingly relied on transition metal complexes as mediators of C–C bond formation in, for example, the catalytic hydroformylation or polymerisation of olefins.[1] In fine chemical syntheses, palladium complexes are quickly taking on a central role in such chemistry and currently a wide variety of Pd compounds are known to be useful for regio- and enantio-selective (catalytic) C–C bond formation.[1,2] These reactions are typically facilitated by Pd (pseudo-) halide complexes, which incorporate other metal binding agents, of which phosphine (i.e., PR_3), carbene and *N*-donor ligands are the most common.[1,2] One of the few drawbacks to the industrial application of a majority of these Pd derivatives is the air-sensitive nature of the active species and/or catalytic reaction intermediates, which are likely Pd(0) complexes. A further recurring problem is the potential for oxidation of 'free' ligands (e.g., PR_3) that are formed following a dissociation step in the catalytic cycle. Hence, inert atmosphere conditions are often necessary for efficient catalysis. In some cases, it is also necessary to add quantities of free ligand to stabilize the Pd during the reaction; this situation can hamper later product purification.[1,2] Therefore, there is still a need for new and oxidatively robust Pd-based systems for applications in synthetic organic chemistry.[3] Recently, we briefly communicated[4] the synthesis and use of *trans*-[bis-(2-ethyl-2-oxazoline-κ^1N) palladium(II) dichloride] (Fig. 1: complex **1**) as a promoter of C–C bond formation (Heck, Ullmann, Miyaura–Suzuki reactions, etc.).



1

Figure 1.

Compound **1** can efficiently operate in open air and does not require addition ligand (i.e., 2-ethyl-2-oxazoline: Etox) to be added to the reaction mixtures to give adequate product yields. In this report, we expand our preliminary

☆ For Part X, see: Berg, D. J.; Zhou, C.; Barclay, T.; Fei, X.; Feng, S.; Ogilvie, K. A.; Gossage, R. A.; Twamley, B.; Wood, M. *Can. J. Chem.* **2005**, *83*, 449.

Keywords: C–C bond formation; Heck coupling; Ullman coupling; Miyaura–Suzuki coupling; Sonogashira coupling; Oxazoline; 4,5-Dihydro-2-oxazole; Stilbene; Isoflavone; Biphenyl; Palladium complex.
* Corresponding author. Tel.: +1 902 585 1109; fax: +1 902 585 1114; e-mail: rob-gossage@acadiau.ca

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doi:10.1016/j.tet.2006.01.046

Table 1. Catalysis results using complex **1** as mediator of C–C bond formation[a]

Entry	Aryl-X	Substrate	Product	Time (h)	Yield (%)	TON
1	PhI	Styrene	*t*-Stilbene	48	87	860
2	PhI	Styrene	*t*-Stilbene	24	84	1700
3	PhI	Styrene	*t*-Stilbene	18	77	2000
4[b]	PhI	Styrene	*t*-Stilbene	18	71	1900
5	*p*NO_2PhI	Styrene	*t*-NO_2-stilbene	24	>99	>2000
6	PhBr	Styrene	*t*-Stilbene	24	77	1500
7	*p*BrAn	Styrene	*t*-MeO-stilbene	24	65	1300
8	PhBr	PhBR_2	Biphenyl	3	>99	>1300
9	*p*BrAn	PhBR_2	*p*PhAn	3	>99	>1300
10	PhI	PhI	Biphenyl	3	45	11
11	PhI	PhC≡CH	PhC≡CPh	3	32	190
12[c,d]	**6a**	**6b**	**5b**	48	14	<1
13[c,d]	**6a**	Styrene	**5c**	48	22	<1
14[e]	**8a**	(2-Napthyl)BR_2	**7d**	24	60	0.83
15[e]	**8b**	(2-Napthyl)BR_2	**7d**	24	45	0.6
16[e]	**8b**	PhBR_2	**7a**	24	>99	>1.4
17[e]	**8b**	(*o*MePh)BR_2	**7b**	24	>99	>1.4
18[e]	**8b**	(*m*MePh)BR_2	**7c**	24	>99	>1.4

[a] Experimental details are given in the Section 3. TON, average turn over number per hour; Ph, phenyl; *t*-stilbene, (*E*)-stilbene; *p*NO_2PhI, 4-nitroiodobenzene; *p*BrAn, 4-bromoanisole; *p*PhAn, 4-methoxybiphenyl; *t*-NO_2-stilbene, (*E*)-4-nitrostilbene; *t*-MeO-stilbene, (*E*)-4-methoxystilbene; BR_2, B$(OH)_2$.
[b] Compound **1** (5.3 mmol) used.
[c] Ar-X (5 mmol); 6 mmol olefin; 10 mol% of **1** used.
[d] See Figure 2.
[e] See Eq. 1.

communication and detail the use of **1** for the selective formation of C–C bonds. In turn, this technology is applied to the synthesis of a number of biologically relevant isoflavone and stilbene derivatives.[5]

2. Results and discussion

The synthesis of air-stable [$PdCl_2$(Etox)$_2$] (**1**: Fig. 1) is a straightforward procedure[4] involving the treatment of methanolic solutions of Li_2PdCl_4 with Etox; this latter reagent is an inexpensive and commercially available polymer precursor.[12] Analyses of **1** via single crystal X-ray diffraction[4] has revealed that it exists as the trans-isomer in the solid-state and presumably only the trans form is present in any detectable amount (NMR) in solution.[†] As expected, the oxazoline ligands are found to coordinate through the *N*-donor atom.[13] There are only a few reported structural analogues of **1** in the literature.[14–16] The complex *trans*-[$PdCl_2$(2-phenyl-2-oxazoline-κ^1N)$_2$] (**2**) has been described by Dunina et al.;[14] a related naphthalene compound has also been reported[15] by van Koten's group (viz., *trans*-[$PdCl_2$(4,4-dimethyl-2-{2′-napthyl}-2-oxazoline-κ^1N)$_2$]: **3**). Complex **3** exists as a mixture of cis and trans isomers in solution,[15] although in the solid phase only the trans form is found. This is in contrast to our recent NMR observations of **1**[4] and earlier independent studies of **2**.[14] A structurally analogous oxazole complex, *trans*-[$PdCl_2$(2-oxazole-κ^1N)$_2$] (**4**), has also been reported.[16] No evidence for isomerisation of this material was noted. The catalytic potentials of **2**–**4** do not appear to have been investigated.[14–16]

Our interests are centred on the synthesis,[17] coordination[2a,4,18] and medicinal inorganic chemistry of 2-oxazolines (i.e., 4,5-dihydro-2-oxazoles) and the application of such complexes in catalysis.[2a,4] One of our objectives is to design robust materials for use in catalysis under non-inert atmosphere conditions. We therefore tested solutions of **1** for its catalytic potential under standard bench-top conditions in open air. No free ligand was added to the reaction mixtures. Palladium complexes[1–3] are typically tested on a single class of C–C bond forming reaction (e.g., for Heck coupling). We have found that **1** can be used for a variety of such processes (Table 1) including the Heck (entries 1–7, 12 and 13), Miyaura–Suzuki (entries 8–9 and 14–18), Ullmann (entry 10) and Sonogashira (entry 11) coupling reactions under typical conditions.[1–3]

Complex **1** is an effective catalyst for all of these classes of C–C bond forming reactions although turnover numbers are admittedly moderate. There are few fully characterised (pre-formed) Pd-based systems that have been shown to be effective for a plethora of different C–C bond forming processes and even fewer that can operate in air and without additional ligand.[1–3] This system effectively combines these two aspects with the further advantage of using a simple, very inexpensive (or readily synthesised) and air-stable ligand. Etox, like most oxazolines, is very stable to oxidative decomposition. This aspect gives a clear advantage over the use of air-sensitive phosphine and carbene ligands.

Unfortunately, the main disadvantage with this system is that aryl-chlorides are not activated to any significant extent by **1**. Our tests with this complex (in air) under the standard Heck conditions using a combination of PhCl and styrene as substrates gave no evidence for the formation of the desired stilbene product. In addition, **1** is ineffective as a catalyst for the Sonogashira reaction in the absence of CuI (yields <10%). The use of pyrrolidine as solvent is also crucial for Sonogashira coupling as reactions performed in refluxing toluene or NEt_3 gave no coupled product; likewise only a trace of product (~1%) was found using DMF as reaction

[†] We have previously disclosed[4] the full experimental details of the synthesis and characterisation (NMR, X-ray, etc.) of **1**.

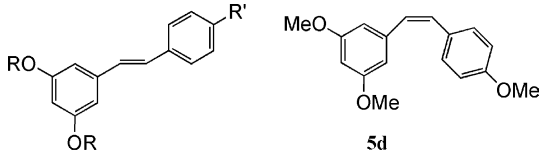
medium. Not surprisingly, 1,4-dihydroquinone was found to be essential for the Ullmann coupling.

A further observation is that **1** does not promote the Stille reaction.[1,2] Our examination of this process involved using **1** in the presence of PhI or *p*-bromoacetophenone in combination with either $R_3SnC_6H_5$ or $R_3SnCH_2CH{=}CH_2$ (R = *n*-Bu; conditions: toluene, 100 °C, 8 h). These experiments yielded no detectable (coupled) product[4] and hence further Stille-type reactions were not attempted.

The Heck reaction was used as a means to further explore the effects of temperature, the nature of base, solvent, substrate and added free ligand to the overall yield of stilbene product. The use of aryl-halides with electron-withdrawing groups appears to enhance the yields of coupled product (Table 1; entries 3 and 5), whereas electron-donating groups give the opposite effect (Table 1; entries 6 and 7). Adjusting the nature of added base from sodium acetate to potassium carbonate or to NEt_3 had no effect on the overall yield of product nor did changing the solvent from DMF to NEt_3. However, the addition of five-fold excess of free ligand (Etox) reduced the overall yield to only 25% under identical conditions. This strongly suggests that dissociation of one or more equivalents of Etox is a key component of the rate determining step(s) during catalysis.[‡] The importance of (formally) 14-(valence metal) electron intermediates, for example, $[PdCl_2(Etox)]$, have been proposed previously in related Heck systems[1,2] and may also be important here. There is a pronounced temperature effect on this reaction; adjusting the bath temperature from 140 to 120 °C leads to greatly reduced yields (25%). Running the reaction at even lower temperature (100 °C) gives only a trace (7%) of product stilbene.

Having established some of the limitations and potential of **1** in C–C coupling chemistry,[4] we felt that this technology would be more useful if it can be shown to produce more elaborate and/or desirable organic products.

Many (substituted) (*E*)-stilbenes (i.e., derivatives of stilbene itself) can be extracted from natural sources.[5b,19] In particular, resveratrol (**5a**) and its tris-*O*-Me analogue (**5b**: Fig. 2) have been of recent interest due to the health benefits that are attributed to consumption of such compounds by mammalian organisms. Resveratrol is a component of many red wines[20] and it has been linked as a possible causative agent of the so-called 'French paradox'. This involves the statistical fact that the intake of high fat foods, which is common in the diet of French citizens, does not result in a significant increase in heart disease or other aliments within the general population.[21] For this and other reasons, **5a** and its analogues are currently at the centre of considerable scrutiny within medicinal chemistry. A key component in a retro-synthetic pathway to **5a** is **5b**, which upon methyl–proton exchange obviously yields **5a**.[8] Compound **5b** is of interest in its own right due of its documented anti-cancer properties and because it is a key precursor to its (*Z*)-isomer **5d** (Fig. 2), which has been shown to be a more effective anti-cancer agent then resveratrol itself.[22] The related stilbene **5c** (Fig. 2), isolated from the bark of the conifer species *Pinus armandii*,[9] has also been investigated for its medicinal properties.[23] We therefore choose to target **5b** and **5c** for synthesis using **1**. Previously reported routes to these two compounds have included multi-step Wittig and/or McMurray reactions[23] and the Perkin reaction.[19] Palladium-catalysed Heck reactions[24a] have also been used; this can involve the use of acetate protected 5-vinylresorcinol (produced in five steps), vinylsilanes as the olefin source[24b] or other substrates.[3k,25] We decided to investigate the use of **1** as a mediator of C–C coupling to yield **5b** or **5c** using commercially available organic precursors: viz. 3,5-dimethoxy-1-bromobenzene (**6a**) combined with either 4-vinylanisole (**6b**: for the synthesis of **5b**) or styrene (for **5c**). Thus, treatment of solutions **6a** and **6b**, under conditions as described in Table 1 (Entry 12 and the Section 3), produced **5b** in a poor isolated yield of only 14%. In turn, the treatment of **6a** with styrene, under similar conditions, led to the isolation of **5c** (22% yield: Table 1; entry 13). These two syntheses, with reduced yields versus that of stilbene itself (vide supra), support the previous observations that electron-donating groups (Table 1) on the haloarene substrate lead to a reduction of the rate and/or efficiency of Heck coupling. This may be due to an unusually stable aryl-Pd complex formed during the catalytic cycle[1–3] and hence base promoted reductive elimination of the desired stilbene is sluggish.[3w,‡] Thus, yields are unimpressive of these two products. However, these reactions do represent a facile alternative strategy for the synthesis of **5b** and **5c** that employs simple (commercial) organic starting materials and an easily produced catalyst precursor.



5a: R = H, R' = OH;
5b: R = Me, R' = OMe;
5c: R = Me, R' = H

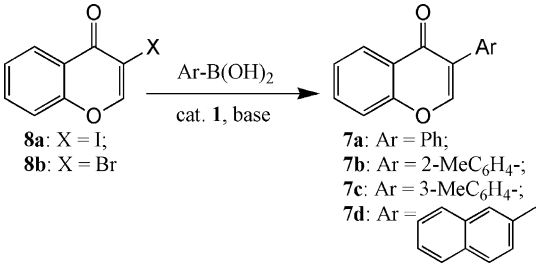
5d

Figure 2.

A survey of entries 1–13 in Table 1 reveals that of all the types of C–C coupling that we have attempted, the Miyaura–Suzuki reaction is the cleanest and generally gives the best yields of coupled product. Coincidently, as part of one of our structure–activity relationship studies, we required a quantity of substituted bicyclic compounds of the isoflavone class (Eq. 1; e.g., **7a**–**7d**). These derivatives therefore presented us with a good series of candidates for our investigations of coupling chemistry using **1**. Isoflavones represent a very important class of natural products[26] because they display a wide variety of biological properties that include anti-cancer, anti-oxidant, anti-inflammatory, anti-bacterial and anti-fertility activity. In addition, isoflavones have been shown to act as selective enzyme inhibitors[5b–f,26], to alleviate erectile dysfunction[27] and have been investigated as medicinal agents for the

[‡] The effect of added free ligand is not as pronounced when using **1** to perform Miyaura–Suzuki coupling reactions. Full experimental and theoretical mechanistic investigations of these reactions will be the subject of a later publication.

treatment of alcohol addiction.[28] Our synthetic methodology revolves around the use of the readily available[6] 3-halochromones **8a** and **8b** (Eq. 1; also see Section 3) in a Miyaura–Suzuki reaction in combination with arylboronic acid derivatives.[11,29]



8a: X = I;
8b: X = Br

7a: Ar = Ph;
7b: Ar = 2-MeC_6H_4-;
7c: Ar = 3-MeC_6H_4-;
7d: Ar =

(1)

Thus, the treatment of **8a** (Table 1; entries 18) or **8b** (entries 14–17) with a variety of arylboronic acids (Eq. 1) gives excellent yields of the known isoflavones **7a** (i.e., isoflavone) and **7b** (2′-methylisoflavone) in addition to the novel compound **7c** (3′-methylisoflavone). Only in the case of previously unknown **7d** (i.e., 3′,4′-benzoisoflavone) is the yield moderate. We attribute this to steric effects of the large naphthalene group. A marginal improvement in yield could be obtained by the use of **8a** instead of the bromo analogue **8b**.

The chemistry described above has indicated that a simple and air-stable oxazoline complex can be used in several 'benchmark' C–C bond forming reactions and that such methodology can be applied to produce desirable organic products.

3. Experimental

3.1. General procedures

All reactions were carried out using standard bench-top laboratory techniques using commercially available, reagent-grade solvents. Unless otherwise stated, literature mp, IR and ^{1}H NMR data were obtained from the Aldrich Chemical Co. Catalogue (2005–2006 Ed.) and/or the Aldrich Libraries of FT-IR or FT NMR Spectra. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded from chloroform-*d* solutions at 300 MHz using a Bruker Advance™ 300 MHz NMR spectrometer operating at room temperature (rt). Chemical shift values are reported in parts per million relative to TMS ($\delta = 0.00$ ppm) as external standard; coupling constants (*J*) are reported in Hertz. Mass spectra (MS) were obtained from the Dalhousie University Mass Spectral Facility and were performed in electron impact (EI) mode. Microanalyses were recorded at the analytical services department (ANALEST) of the University of Toronto. IR spectra were obtained as Nujol muls or as KBr disks using a Perkin Elmer 683 IR spectrometer or a Nicolet Magna 560 FT-IR spectrometer. Melting point data was obtained using a Mel-Temp II apparatus and reported values are uncorrected. The synthesis of compound **1** was carried out as described in the literature.[4] 3-(Dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one and 3-bromochromone (**8a**) were produced as described by Gammill.[6] All yields in Table 1 refer to the pure (^{1}H NMR, mp, IR) products isolated by extraction and flash column chromatography and/or recrystallisation as detailed for the individual components below, unless otherwise stated.

3.2. Syntheses of *trans*-stilbene, (*E*)-4-nitrostilbene, 5b and 5c

The synthesis of these four compounds was carried out as described below for *trans*-stilbene except where noted.

3.2.1. Synthesis of *trans*-stilbene. A 25 mL quantity of DMF was added to a 50 mL round-bottomed flask. This flask was then charged with 0.00053 mmol (0.15 mg) of **1**, 25 mmol (5.1 g) of iodobenzene (or 3.9 g of bromobenzene), 30 mmol (3.1 g) of styrene and 30 mmol (2.5 g) of sodium acetate. The mixture was then heated to between 140 and 150 °C for the amount of time specified in Table 1 (entries 1–4, 6 and 8). The reaction mixture was cooled to rt and then all volatile components were evaporated in vacuo. The residue was purified by flash chromatography on silica gel (230–400 mesh) using hexanes–EtOAc (9/1) as eluent. The product *trans*-stilbene thus isolated gave a correct ^{1}H NMR spectrum and mp (and a non-depressed mixed mp) when compared to an authentic (commercial) sample.

3.2.2. Synthesis of (*E*)-4-nitrostilbene. Yield: >98% (purity: >97% [NMR]); mp 140 °C (lit.:[7a] 157 °C); correct ^{1}H NMR spectrum.[7b]

3.2.3. Synthesis of (*E*)-3,5,4′-trimethoxyresveratrol (5b). Yield: 14%; mp 52–53 °C (lit.:[8] 56–57 °C); correct IR and ^{1}H NMR spectrum.[9] A 10 mol% quantity of catalyst was used.

3.2.4. Synthesis of (*E*)-3,5-dimethoxystilbene (5c). Yield: 22%; mp 54–55 °C (lit.:[10] 54–55 °C); correct ^{1}H NMR spectrum. A 10 mol% quantity of catalyst was used.

3.3. Synthesis of biphenyl and *p*-phenylanisole via Suzuki coupling

The synthesis of these two compounds was carried out as described for biphenyl below.

3.3.1. Synthesis of biphenyl. A 2 mmol (0.31 g) quantity of bromobenzene was mixed with 4 mmol (0.56 g) of K_2CO_3, 3 mmol (0.37 g) of phenylboronic acid, 0.00053 mmol (0.15 mg) of **1** and a 10 mL quantity of toluene. The mixture was heated at 110 °C for 3 h. After the reaction mixture was cooled to rt, the volatile components were then removed (vacuo) and the crude mixture was extracted with water and EtOAc (20 mL each). The organic layer was washed with further EtOAc (2×20 mL) and the organic fractions combined, dried (Na_2SO_4), and evaporated to give the crude product. The desired compound, biphenyl (correct mp, IR and ^{1}H NMR spectrum; yield >99%), was isolated by recrystallisation from a mixture of EtOAc and hexanes.

3.3.2. Synthesis of 4-phenylanisole. Yield >99%; mp 87–88 °C (lit.: 86–90 °C).

3.4. Synthesis of biphenyl via Ullman coupling

A DMF (5 mL) solution was prepared that consisted of 2 mmol (0.41 g) of iodobenzene, 2 mmol (0.28 g) of K_2CO_3, 1 mmol (0.11 g) of 1,4-dihydroquinone, and 0.014 mmol (4 mg) of **1**. The mixture was heated at 110 °C for 3 h. Volatile components of the mixture were removed (vacuo) and the residue purified by flash column chromatography (hexanes) to yield biphenyl (45%).

3.5. Synthesis of diphenylacetylene

A 0.0011 mmol (0.4 mg) sample of **1** was added to a mixture of 2 mL pyrollidine, 2 mmol (0.41 g) iodobenzene, 1 mmol (0.19 g) of CuI and 2.4 mmol (0.25 g) of phenylacetylene in a 25 mL round-bottomed flask. The contents of the reaction vessel were then heated to 90 °C for 3 h. The volatile components were then removed (vacuo) and the crude mixture was extracted with water and EtOAc (20 mL). The aqueous layer was washed with further EtOAc (2×20 mL) and the organic fractions combined, dried ($MgSO_4$) and evaporated to give the crude product(s). The desired compound, diphenylacetylene (correct IR and ^{1}H NMR spectrum), was isolated (32%) by flash column chromatography using 9:1 hexanes/EtOAc as eluent.

3.6. Synthesis of 3-iodochromone (i.e., 3-iodo-4*H*-benzopyran-4-one: 8a)

In a modification of the synthesis of **8b**,[6] a sample (2.0 g: 11 mmol) of 3-(dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one was dissolved in chloroform (20 mL) and the mixture cooled to 0 °C. A solution of I_2 (2.7 g: 22 mol) was added dropwise over a period of several minutes. The mixture is then diluted with water (20 mL) and stirred vigorously for 15 min. Excess iodine was then neutralized with aqueous $Na_2S_2O_3$. The organic layer was then separated, dried ($MgSO_4$) and then the volatile components were removed (vacuo). The crude yellow compound was purified by flash column chromatography (hexanes/EtOAc: 3:1) to give the yellow-coloured product 3-iodochromone (1.0 g: 35%); mp 87–88 °C (lit.:[9] 93–94 °C); IR, MS and ^{1}H NMR spectrum are consistent within experimental error to the known properties of **8a**.[9]

3.7. Syntheses of isoflavones 7a–7d

The synthesis of isoflavone (**7a**) is a representative example.

3.7.1. Synthesis of isoflavone (7a). A 0.112 g sample of **8b** (0.50 mmol) was dissolved in 10 mL of toluene in the presence of 0.75 mmol of phenylboronic acid (0.091 g), 1 mmol of K_2CO_3 (0.14 g) and 0.015 mmol (3 mol%: 0.0041 g) of **1**. The reaction mixture was then heated to reflux temperature for a period of 24 h; the flask was then allowed to cool to rt. Volatile components of the reaction vessel were then removed (vacuo) and the crude mixture was then partitioned between EtOAc (20 mL) and water. The aqueous layer was separated and extracted twice with EtOAc (40 mL total) and then the organic fractions were combined together, dried (Na_2SO_4), filtered and then the solvent was removed (vacuo). The residue was then subjected to separation via column chromatography (flash: SiO_2) with hexanes–EtOAc (9/1) as eluent to give the product isoflavone (**7a**: 0.11 g: >99% yield; R_f=0.52). The physical properties (mp, IR, ^{1}H NMR) of **7a** isolated in this way were fully consistent with the previously reported data.[11]

3.7.2. Synthesis of 2′-methylisoflavone (7b). Yield 0.11 g: >99% using 2-tolylboronic acid. ^{1}H and ^{13}C{^{1}H} NMR spectra were consistent with **7b**;[11] mp=112–113 °C (lit.:[11] 113.5–114 °C).

3.7.3. 3′-Methylisoflavone (7c). Yield 0.11 g: >99% using 3-tolylboronic acid. R_f=0.54 (hexanes/EtOAc: 9:1); mp=87–89 °C; IR (KBr): 1646 cm^{-1} (C=O); ^{1}H NMR: δ=2.43 (s, 3H, C*H*$_3$), 7.22 (d, 1H, J=6.6 Hz, Ar*H*), 7.34–7.50 (m, 5H, Ar*H*), 7.69 (t, 1H, J=7.2 Hz, Ar*H*), 8.02 (s, 1H, =C*H*), 8.35 (d, 1H, J=6.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR: 176.4, 156.7, 153.8, 134.1, 133.8, 133.5, 129.9, 128.6, 128.4, 128.3, 128.1, 127.4, 126.9, 126.7, 125.8, 125.7, 125.1, 118.5. MS (EI, 70 eV): 236 (100%; M+: calcd: 236). Anal. Calcd for $C_{16}H_{12}O_2$ (%): C 81.34, H 5.12; found: C 80.83, H 5.12.

3.7.4. Synthesis of 3′,4′-benzoisoflavone (7d). Synthesised from 2-napthylboronic acid and **8b** (yield 45%; 0.061 g) or **8a** (yield 60%). R_f=0.47 (hexanes/EtOAc: 9:1); mp=184–186 °C; IR (KBr): 1645 cm^{-1} (C=O); ^{1}H NMR: δ=7.45–7.56 (m, 4H, Ar*H*), 7.71–7.76 (m, 2H, Ar*H*), 7.87–7.95 (m, 3H, Ar*H*), 8.08 (s, 1H, =C*H*), 8.35 (d, 1H, J=6.9 Hz, Ar*H*); ^{13}C{^{1}H} NMR: 176.9, 156.7, 153.8, 134.1, 133.8, 133.5, 129.9, 128.6, 128.4, 128.3, 128.1, 127.4, 126.9, 126.7, 125.8, 125.7, 125.1, 118.5. MS (EI, 70 eV): 272 (60%; M+: calcd: 272). Anal. Calcd for $C_{19}H_{12}O_2\cdot H_2O$ (%): C 81.12, H 4.66; found: C 81.13, H 4.61.

4. Conclusions

In conclusion, Pd complex **1** has been found to be an effective catalyst, in open air, for a number of C–C bond forming reactions; this compound can be used for the synthesis of pharmaceutically relevant isoflavones and stilbenes. These results suggest that simple oxazoline–Pd complexes should be further investigated for their potential applications in catalysis. Complex **1** is best suited for Miyaura–Suzuki coupling reactions and is somewhat sluggish for the Heck, Ullmann and Sonogashira processes. Stille-type coupling reactions are not catalysed by **1** (in open air). We are currently expanding this chemistry to include enantio-selective substrate activation using chiral oxazoline ligands; the investigation of the mechanism of reactions mediated by **1** and its (chiral) analogues will be disclosed in a future publication.

Acknowledgements

Support for this work was provided by the Natural Sciences and Engineering Research Council of Canada (NSERC). Johnson-Matthey Ltd is thanked for a generous loan of Pd salts. C.R.E. thanks WAAG for support. Professor Hilary A. Jenkins (St. Mary's University) and Dr. Gordon G. Cross are thanked for fruitful discussions. Professor A. Jha and Dr. N. Paul are thanked for recording the ^{13}C{^{1}H} NMR spectra.

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Tetrahedron 62 (2006) 3402–3411
Tetrahedron

Triadic analysis of substituent effects—gas-phase acidity of *para*-substituted phenols

Robert Vianello and Zvonimir B. Maksić*

Quantum Organic Chemistry Group, Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, POB 180, 10 002 Zagreb, Croatia

Received 28 October 2005; revised 20 December 2005; accepted 12 January 2006

Available online 8 February 2006

Abstract—A large variety of *para*-substituted phenols was examined and their acidities in the gas-phase were rationalized by a triadic formula, which is capable of delineating the initial, intermediate and final state effects in the deprotonation process. It is shown that triadic analysis is equivalent to the homodesmotic reactions approach, while being much more informative at the same time. The applied MP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) theoretical method gives acidities in very good agreement with available measured values, meaning that calculations can safely replace the missing experimental data for compounds not easily amenable to laboratory examinations. It is found that the underlying principle leading to enhanced acidity of *para*-substituted phenols containing strong π-electron acceptor groups is the final state effect. It reflects a more pronounced ability to accommodate the excess negative charge. Particular attention has been focused on superacidifying NO_2, SO_2CF_3 and $S(O)(=NSO_2CF_3)CF_3$ and $C(CN)=C(CN)_2$ moieties. It is shown that their influence on acidity is strong and that the deprotonation ability increases along the sequence of substituents $NO_2 < SO_2CF_3 < S(O)(=NSO_2CF_3)CF_3 < C(CN)=C(CN)_2$. On the contrary, the electron releasing substituents NH_2, OCH_3, OH and CH_3 decrease acidity of phenol albeit to a small extent. Finally, it is demonstrated that pentacyano derivative of phenol is a powerful OH superacid as evidenced by ΔH_{acid} value of 287.5 kcal mol^{-1}.
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1. Introduction

Substituent effects belong to the most important concepts in chemistry developed by empirical observations. They describe the influence of the spatial and electronic structural features on the chemical, physicochemical and biochemical properties of compounds. By definition, a substituent is understood as a smaller structural subunit, which affects the properties of a molecular system in a quantitative sense by preserving its general character. The latter is determined by a dominating functional group and/or by the molecular backbone itself.[1] In other words, the substituent perturbs the parent molecule in a measurable, but not dramatic way by somewhat modifying its spatial and electronic structure and consequently its behaviour. The importance of the concept can be documented by its occurrence in the literature. According to Krygowski and Stepień[2] about 20 papers daily have appeared in the period 1996–2004 involving the term substituent in the title, keywords or abstract.

Historically, the concept of substituents received a strong impetus by Hammett, who studied deprotonation of benzoic acid and its *para*-substituents in water.[3] The corresponding Hammett equation was a milestone in development of the structure–property relations, which in turn have played a crucial role in physical organic chemistry. This development triggered an explosion of papers dealing with the substituent effects in chemistry lasting for many decades, but also resulting in some reports on its applications in biology.[4] It is both surprising and gratifying that Hammett's σ-constants, deduced from the ionization of organic acids in solutions, can successfully predict equilibrium and rate constants for a wide variety of chemical reactions. It should be noted that the Hammett equation is an example par excellence of the more general linear free energy relationships. It is fair to mention that many researchers have contributed to the applications and extensions of the Hammett equation.[5–11] One of the most recent compilations of various σ-constants was published by Hansch, Leo and Taft.[12] An early attempt to rationalize the σ-constants and substituent effects in general by ab initio methods was made by Topsom[13] and Pross with coworkers.[14] An important theoretical contribution to the field was introduction of the homodesmotic reactions[15] in studying the substituent effects.[16] This topic was extensively discussed in a recent review.[2]

The original σ-constants for describing the effects of substituents placed at the *para*-position relative to the reactive site have been based upon aqueous acidities of

Keywords: Acidity; Phenol; Substituent effect; Superacidifiers; Triadic analysis.
* Corresponding author. Tel.: +385 1 4561117; fax: +385 1 4561118; e-mail: zmaksic@spider.irb.hr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.049

substituted benzoic acids.[3] The *para*-substituted phenols and the corresponding phenoxide ions provided another important test case for the concept of substituents and their effect on acidity. Concomitantly, they were the subject matter of numerous investigations.[14,17–25] Perhaps this is not surprising because of two reasons: (1) phenol is one of the simplest substituted aromatic systems capable of electron lone pair donation to the aromatic nucleus and to the possible *ortho*- and *para*-electron accepting substituents and (2) it is one of the most important organic species with appreciable biological activity.[21]

Recently, we introduced a triadic formula for interpreting the proton affinities of bases[26] and deprotonation energies of acids,[27] which was subsequently used in rationalizing substituent effects in *para*-substituted benzoic acids.[28] This approach seems to possess some advantages compared to other conventional models.[29] Hence, we felt it worthwhile to extend triadic analysis to *para*-substituted phenols and their intrinsic (gas-phase) acidities, which might throw new light onto this old problem. A wide range of different substituents is examined including some exhibiting extremely strong electron withdrawing power like NO_2, SO_2CF_3, $S(O)(=NSO_2CF_3)CF_3$ and $C(CN)=C(CN)_2$.

2. Theoretical approach

Acidity is defined as the change in enthalpy (ΔH_{acid}) for the reaction:

$$AH(g) \rightarrow A^-(g) + H^+(g) \quad (1)$$

leading to:

$$\Delta H_{acid} = \Delta E_{acid} + \Delta(pV) \quad (2)$$

where g denotes the gas-phase, ΔE_{acid} is the change in the total molecular energy of the species entering Eq. 1, including the zero-point vibrational energy (ZPVE) and the finite temperature thermal correction from 0 to 298.15 K. The pressure–volume work term is denoted by $\Delta(pV)$. It is useful to keep in mind that stronger acids have smaller numerical ΔH_{acid} values, which implies easier release of the acidic proton. Theoretical MP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) model (hereafter denoted as MP2) represents a good compromise between accuracy and feasibility combined with practicality. The resulting acidities compare well with experiment and considerably more demanding G2 method.[30,31] Additionally, the MP2 model offers a useful interpretation of acidities via triadic (trichotomy) formula:[27,32]

$$PA(A^-)_\alpha = -IE(A^-)_n^{Koop} + E(ei)_{rex}^{(n)} + (BAE)_\alpha^{\cdot} + 313.6 \text{ kcal/mol} \quad (3)$$

(1 kcal/mol=4.184 kJ/mol). This formula describes protonation of the conjugate base (anion A^-), or in other words a reversed deprotonation of a neutral acid. Here, the site of protonation is denoted by α and $IE(A^-)_n^{Koop}$ is the *n*th Koopmans' ionization energy of the anion A^- calculated in the fixed nuclei and frozen electron density approximation. The electron affinity of the proton is 313.6 kcal/mol. The reorganization of both the nuclei and electrons occurring due to the fact that ionization is not a sudden event is denoted by $E(ei)_{rex}^{(n)}$. It is taken for granted that the relaxation in the $A^- + H^+$ protonation process is completed before the $H^{\cdot}$ and $A^{\cdot}$ radicals start to interact and form a new A–H bond. Hence, the relaxation energy is defined as:

$$E(ei)_{rex}^{(n)} = IE(A^-)_n^{Koop} - IE(A^-)_1^{ad} \quad (4)$$

where $IE(A^-)_1^{ad}$ is the first adiabatic ionization energy. Several comments are necessary here. Firstly, Koopmans' ionization energy is calculated within the one-electron Hartree–Fock (HF) picture employing the 6-311+G(d,p) basis set, which enables simple interpretation of the genuine properties of the final state (A^-). Since $IE(A^-)_n^{Koop}$ describes ionization from the *n*th molecular orbital, it can be selected in such a way that it corresponds to MO, which is pivotal in the protonation process. For example, the *n*th MO in most cases belongs to the lone pair, which is attacked by the proton thus mirroring the properties of the reaction site as closely as possible. This is not possible, if the first adiabatic ionization energy $IE(A^-)_1^{ad}$ is considered. It follows as a corollary that the relaxation energy $E(ei)_{rex}^{(n)}$ has two components. The first is provided by $IE(A^-)_n^{Koop} - IE(A^-)_h^{Koop}$, where the index *h* stands for the highest occupied MO(HOMO). It describes stabilization by a transfer of an electron from the HOMO to a hole in the *n*th MO created by ionization given in the approximation of the frozen nuclear and electronic charge distributions. The second term in $E(ei)_{rex}^{(n)}$ is the relaxation effect accompanying ionization from the HOMO yielding $E(ei)_{rex}^{(n)} = IE(A^-)_h^{Koop} - IE(A^-)_1^{ad}$. We shall consider only a lump sum of these two relaxation effects in this paper defined by Eq. 4. Secondly, the formation of the new bond causes an additional relaxation effect, which is not separately considered, but it is included in the bond association energy $(BAE)_\alpha^{\cdot}$ instead.

The triadic analysis carried out here is based on the MP2 method. Koopmans' ionization energies are calculated by the restricted HF/6-311+G(d,p)//B3LYP/6-31G(d) model. Bond dissociation energies are obtained by the use of the restricted open-shell MP2 approach. All calculations were performed by using the GAUSSIAN 98 program.[33]

3. Results and discussion

3.1. Substituents effect on acidity of phenols

A large variety of substituents exhibiting widely different electron donor and acceptor abilities is examined (Fig. 1). They encompass F, Cl, Br, CH_3, $C(CH_3)_3$, $CH=CH_2$, $C\equiv CH$, CHO, COOH, CF_3, BH_2, $B(CH_3)_2$, NH_2, $N(CH_3)_2$, OH, OCH_3, SH, SCH_3, CN, NO_2, SO_2CF_3, $S(O)(=NSO_2CF_3)CF_3$, $C(CN)=C(CN)_2$ and $(CN)_5$. The latter system is the only multiply substituted phenol studied here in order to find out whether the pentacyano derivative acts as a superacid as was the case with polycyano substituted benzoic acid[28] and by a number of other aromatic compounds.[34–36] Perusal of the data presented in Table 1

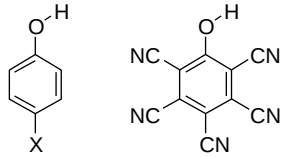


Figure 1. Schematic representation of the studied phenols.

reveals a very good agreement between the calculated and measured proton affinities, which lends credence to the method applied. Particularly interesting is the result obtained for the parent phenol, which in turn has been explored by a number of experimental researchers and theoreticians over a large span of years.[17–24] The most recent experimental value for its acidity of Angel and Erwin[23] is 347.5 ± 1.9 kcal mol^{-1}, which is in a nice accordance with our computational result (348.3 kcal mol^{-1}). It is worth mentioning that our adopted computational procedure is useful in discriminating the experimental data. The value cited by NIST Database of 350.0 ± 2.0 kcal mol^{-1} is the average value of five measurements carried out in the time span of 26 years. Although their average is in agreement with our result, if the lower error bar is taken into account, we feel that the measured value obtained by Angel and Erwin[23] is more accurate. It appears that phenol is less acidic than the benzoic acid, where ΔH_{acid} assumes 339.5 kcal mol^{-1} ($\Delta H_{\text{acid}}(\text{exp}) = 340.2 \pm 2.2$ kcal mol^{-1}).[28] Triadic analysis 3 is well suited to interpret this difference. For this purpose a compact formula can be written such as:

$$\Delta\text{PA}(\text{A}^-) = \left[\Delta(-\text{IE}_n^{\text{Koop}}); \Delta E(\text{ei})_{\text{rex}}^{(n)}; \Delta(\text{BAE})_{\alpha}^{\cdot}\right] \quad (5)$$

where Δ is the difference between the corresponding entities of the examined and reference molecule or anion, while squared parentheses imply summation of the embraced three terms. We shall select phenol as a standard system for measuring variations in acidity, if not stated otherwise. It turns out that the increase in acidity of benzoic acid (PA = $[-15.5; -6.7; 13.4] = -8.8$ kcal mol^{-1} is a consequence of two contributions, the first being a more stabilized MO describing the in-phase combination of the lone pairs AOs of oxygen to be protonated in the σ-plane of the benzoic acid anion. The reason behind is that the corresponding MO is quite stable being HOMO-3 orbital,[28] possessing orbital energy as low as -0.22200 a.u. In the phenoxide anion, on the other hand, the molecular orbital describing the σ-distribution of the oxygen lone pairs is given by the out-of-phase combination of the oxygen AOs yielding HOMO-2 (Fig. 2). The latter is energetically higher (-0.19741 a.u.) by 15.5 kcal mol^{-1}. This means that formation of the new O–H bond upon protonation of the benzoic acid anion is more costly by that amount, since an electron has to be activated from the energetically lower MO. Consequently, benzoic acid should be more acidic. To put it in another way, one can say that deprotonation of the benzoic acid leaves the electron in a more stable HOMO-3 orbital. Hence, the excess negative charge is better

Table 1. Triadic analysis of proton affinities (PAs) of conjugate bases of *para*-substituted phenols obtained by applying ROMP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) method and formula 3[a,b]

Substituent	$(\text{IE})_n^{\text{Koop}}$	$(\text{IE})_1^{\text{ad}}$	$E(\text{ei})_{\text{rex}}^{(n)}$	$(\text{BAE})^{\cdot}$	PA(thr)	PA(exp)[c]
NH_2	$(123.5)_3$	36.5	87.0	74.5	351.6	352.5 ± 2.1
OCH_3	$(122.9)_3$	39.7	83.2	76.4	350.3	350.4 ± 2.1
OH	$(122.8)_3$	40.6	82.2	76.8	349.8	350.4 ± 2.1
CH_3	$(122.9)_3$	43.6	79.3	79.5	349.5	350.3 ± 2.1
H	$(123.9)_3$	51.9	72.0	86.6	348.3	347.5 ± 1.9[d]
$C(CH_3)_3$	$(125.1)_3$	45.5	79.6	79.7	347.8	348.5 ± 2.1
$N(CH_3)_2$	$(125.4)_3$	40.0	85.4	73.6	347.2	351.3 ± 2.1
F	$(128.0)_3$	52.5	75.5	84.4	345.5	346.8 ± 2.1
Cl	$(133.7)_3$	50.4	83.3	79.6	342.8	343.1 ± 2.1
$CH{=}CH_2$	$(136.3)_3$	51.0	85.3	79.9	342.5	
SMe	$(133.9)_3$	50.1	83.8	78.6	342.1	
SH	$(77.2)_2$	65.9	11.3	94.0	341.7	
Br	$(135.6)_3$	52.0	83.6	79.9	341.5	
C≡CH	$(141.1)_3$	54.3	86.8	81.0	340.3	
$B(CH_3)_2$	$(140.3)_3$	59.5	80.0	83.3	337.4	
CF_3	$(142.3)_3$	69.9	72.4	91.7	335.4	337.0 ± 2.1
COOH	$(146.4)_3$	61.2	85.2	82.7	335.1	335.9 ± 2.1
BH_2	$(143.7)_3$	65.6	78.1	85.3	333.3	
CHO	$(148.3)_3$	64.1	84.2	83.2	332.7	333.0 ± 2.1
CN	$(149.0)_3$	64.9	84.1	83.0	331.7	332.2 ± 2.1
NO_2	$(159.7)_3$	69.0	90.7	83.1	327.7	327.8 ± 2.1
SO_2CF_3	$(162.5)_3$	86.7	75.8	95.6	322.5	322.6 ± 2.1
$S(O)(=NSO_2CF_3)CF_3$	$(176.2)_3$	118.7	57.5	118.9	313.8	
$C(CN){=}C(CN)_2$	$(185.7)_4$	86.8	98.9	85.2	312.0	
$(CN)_5$	$(211.6)_3$	114.8	96.8	88.7	287.5	

All terms are given in kcal mol^{-1}.

[a] Koopmans' ionization energies $(\text{IE})_n^{\text{Koop}}$ are obtained by the HF/6-311+G(d,p)//B3LYP/6-31G(d) calculations. It should be noted that index n corresponds to HOMO-n+1 molecular orbital.

[b] $(\text{IE})_n^{\text{Koop}}$ and $(\text{IE})_1^{\text{ad}}$ are Koopmans' nth and the first adiabatic ionization energies, respectively.

[c] Experimental data are taken from Lias, S. G.; Liebman, J. F., *Ion Energetics Data*, in *NIST Chemistry WebBook*, NIST Standard Reference Database Number 69, Linstrom, P. J.; Mallard, W. G. (Eds.), March 2003, National Institute of Standards and Technology, Gaithersburg MD, 20899 (http://webbook.nist.gov) if not stated otherwise.

[d] Ref. 23.

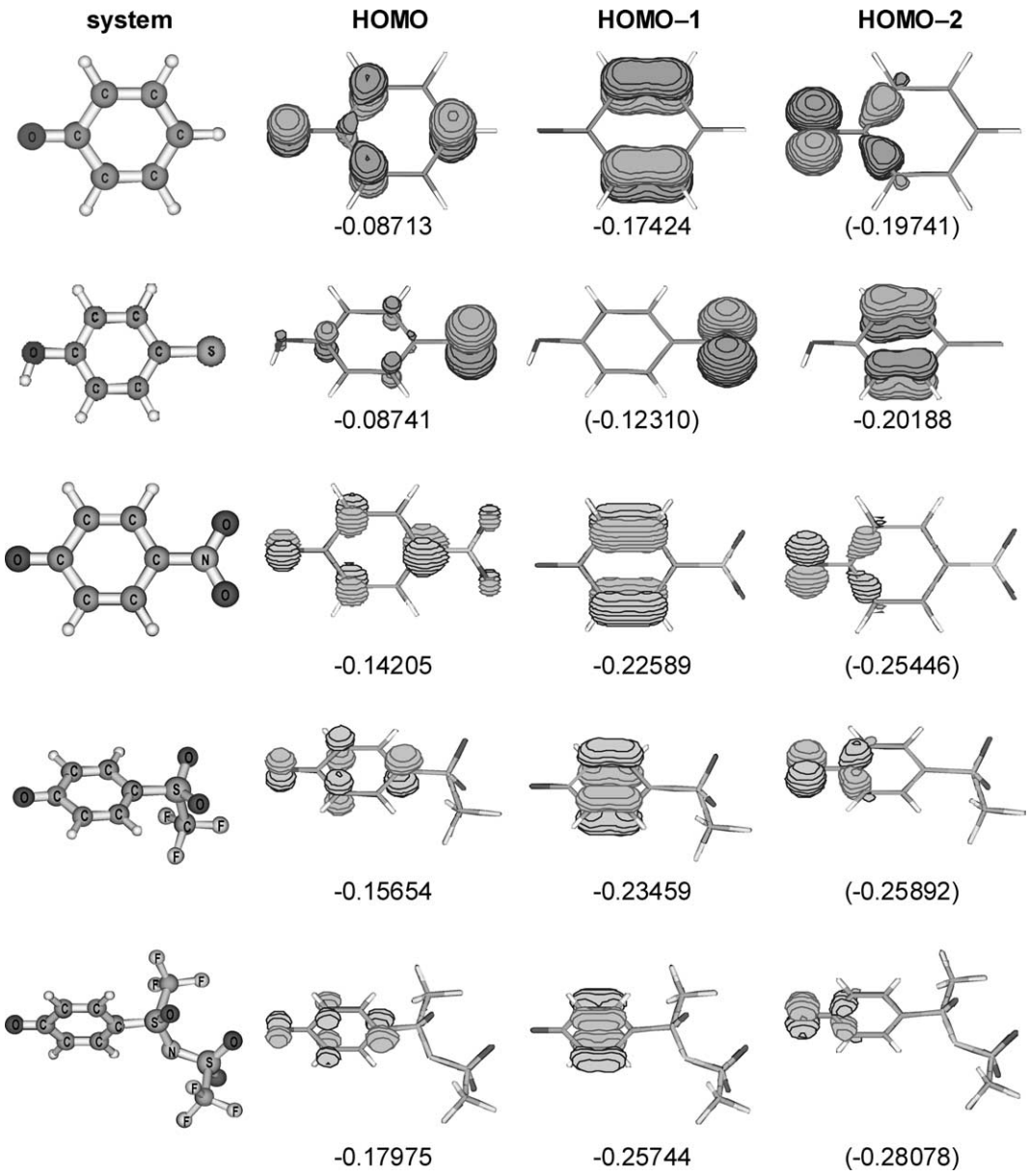


Figure 2. Schematic representation of the three highest occupied molecular orbitals for some characteristic conjugated bases under consideration together with their orbital energies (in a.u.) obtained by HF/6-311+G(d,p)//B3LYP/6-31G(d) level of theory in Koopmans' approximation. The orbital energies of MOs participating in protonation of anions most frequently are given within parentheses.

accommodated in benzoic acid anion than in phenoxide thus contributing to greater acidity of the former compound. This is a typical final state effect, which will play an increasingly important role in systems possessing the *para*-substituted electron accepting group (vide infra). Secondly, the relaxation energy is 6.7 kcal mol^{-1} higher in phenoxide, which decreases acidity of phenol. On the other hand, the homolytic O–H bond dissociation energy in phenol is 13.4 kcal mol^{-1} lower than that in benzoic acid, which diminishes the difference in acidity between these two species. We note in passing that the calculated O–H bond energy of phenol is 86.6, being in a very good agreement with the recent experimental estimate of 85.8 ± 1.9 (in mol^{-1}).[23] It follows that benzoic acid is more acidic in spite of the fact that its O–H bond is considerably stronger than that in phenol. This is in harmony with a common knowledge that acidity cannot be reduced to the strength of the X–H bond energy only, as conclusively illustrated by the triadic analysis here and elsewhere.[26–28] We shall comment on the difference in acidities between some substituted benzoic acids and phenols later on.

Let us focus now on the variation in acidity of phenols upon *para*-substitution taking the parent phenol as a reference system. The relevant data are presented in Table 2. It appears that the strongest acidifying moiety is tricyanovinyl $C(CN)=C(CN)_2$ as evidenced by the most negative ΔPA value of -36.3 kcal mol^{-1}, which is followed by so called superacidifiers $S(O)(=NSO_2CF_3)CF_3$ (ΔPA $= -34.5$ kcal mol^{-1}) and SO_2CF_3 (ΔPA $= -25.8$ kcal mol^{-1}). On the other hand, NO_2 increases the acidity of phenol by 'only' 20.6 kcal mol^{-1}. This is interesting in view of a long-standing discussion in the literature whether SO_2CF_3 is a stronger electron withdrawing group than NO_2 or not.

Table 2. Relative contributions to proton affinities (PA) of the investigated molecules obtained by triadic formula 3 taking phenol as a gauge molecule[a]

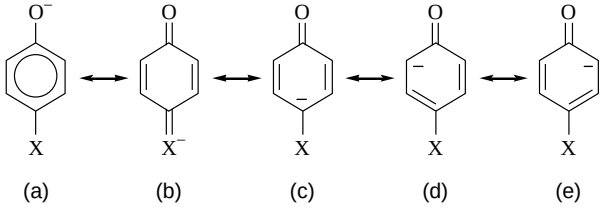
Substituent	$\Delta(IE)_n^{Koop}$	$\Delta E(ei)_{rex}^{(n)}$	$\Delta(BAE)^{\cdot}$	ΔPA (thr)	σ_p	σ_p^-
NH_2	0.4	15.0	−12.1	3.3	−0.66	−0.15
OCH_3	1.0	11.2	−10.2	2.0	−0.27	−0.26
OH	1.1	10.2	−9.8	1.5	−0.37	−0.37
CH_3	1.0	7.3	−7.1	1.2	−0.17	−0.17
H	0.0	0.0	0.0	0.0	0.00	0.00
$C(CH_3)_3$	−1.2	7.6	−6.9	−0.5	−0.20	−0.13
$N(CH_3)_2$	−1.5	13.4	−13.0	−1.1	−0.83	−0.12
F	−4.1	3.5	−2.2	−2.8	0.06	−0.03
Cl	−9.8	11.3	−7.0	−5.5	0.23	0.19
$CH{=}CH_2$	−12.4	13.3	−6.7	−5.8	−0.04	
SMe	−10.0	11.8	−8.0	−6.2	0.00	0.06
SH	46.7	−60.7	7.4	−6.6	0.15	
Br	−11.7	11.6	−6.7	−6.8	0.23	0.25
C≡CH	−17.2	14.8	−5.6	−8.0	0.23	0.53
$B(CH_3)_2$	−16.4	8.8	−3.3	−10.9		
CF_3	−18.4	0.4	5.1	−12.9	0.54	0.65
COOH	−22.5	13.2	−3.9	−13.2	0.45	0.77
BH_2	−19.8	6.1	−1.3	−15.0		
CHO	−24.4	12.2	−3.4	−15.6	0.42	1.03
CN	−25.1	12.1	−3.6	−16.6	0.66	1.00
NO_2	−35.8	18.7	−3.5	−20.6	0.78	1.27
SO_2CF_3	−38.6	3.8	9.0	−25.8	0.96	1.63
$S(O)(=NSO_2CF_3)CF_3$	−52.3	−14.5	32.3	−34.5	1.35	2.30
$C(CN){=}C(CN)_2$	−61.8	26.9	−1.4	−36.3	0.98	1.70
$(CN)_5$	−87.7	24.8	2.1	−60.8		

All values are in kcal mol^{-1}.

[a] Hammett's σ-constants are taken from Ref. 12 except for $S(O)(=NSO_2CF_3)CF_3$, which originate from Ref. 46. It should be noted that index n corresponds to HOMO-n+1 molecular orbital.

Briefly, the SO_2CF_3 group was introduced as a strong acidifying factor by Yagupolskii[37,38] and Sheppard.[39,40] More recently, new superacceptor electron groups were discussed by replacing one or two oxygen atom(s) in SO_2CF_3 by intrinsically even stronger electron withdrawing moieties like, for example, $=NSO_2CF_3$.[41–44] Goumont et al.[45] provided convincing experimental evidence of the unusually strong electron transmission ability of the highly acidifying SO_2CF_3 group, which was considered to be a consequence of its high polarizability. Finally, an extremely strong electron withdrawing power of the $S(O)(=NSO_2CF_3)CF_3$ moiety has been established experimentally by Terrier et al.[46] Triadic analysis provides a penetrating insight into the *para*-NO_2 acidifying effect in phenol compared to that exerted by SO_2CF_3, $S(O)(=NSO_2CF_3)CF_3$ and $C(CN){=}C(CN)_2$ groups. Let us start with the former group. The triadic formula yields a change caused by *para*-NO_2 relative to the parent phenol: $\Delta PA(NO_2) = [-35.8;\ 18.7;\ -3.5] = -20.6$ kcal mol^{-1} implying that the better distribution of the negative charge in the anion (final state effect) is of paramount importance in increasing the acidity by 20.6 kcal mol^{-1}. Analogously, $\Delta PA(SO_2CF_3) = [-38.6;\ 3.8;\ 9.0] = -25.8$ kcal mol^{-1} indicating that the final state effect is decisive again, but the influence of the relaxation and bond association energy (BAE) is different to that in *para*-NO_2 phenol. This is evident by calculating $PA(SO_2CF_3)$ relative to $PA(NO_2)$: $PA(SO_2CF_3) - PA(NO_2) = [-2.8;\ -14.9;\ 12.5] = -5.2$ kcal mol^{-1}. Thus, it appears that the relaxation energy is by 14.9 kcal mol^{-1} smaller in SO_2CF_3 *para*-derivative of phenol. This finding is in accordance with a generally accepted idea that the NO_2 group is stabilized by substantial resonance $^{-}O{-}N^{+}{=}O \leftrightarrow O{=}N^{+}{-}O^{-}$, which is particularly pronounced in the anionic state. In contrast, the SO_2CF_3 seems to stabilize the excess negative charge via polarizability effect,[45,46] while the resonance effect is very modest. Finally, the bond association energy is by 12.5 kcal mol^{-1} larger in *para*-SO_2CF_3 phenol. The combined effect of the bond association O–H energy and the relaxation energy contributes 2.4 kcal mol^{-1} to the increased acidifying effect of the SO_2CF_3 group. The rest (2.8 kcal mol^{-1}) is due to a better accommodation of the negative charge in the *para*-SO_2CF_3 phenol anion as reflected by a more stable HOMO-2 orbital. Hence, the physical origin of the stronger acidifying ability of SO_2CF_3 group is perfectly clear. Similar analysis related to *para*-$S(O)(=NSO_2CF_3)CF_3$ phenol gives $\Delta PA[S(O)(=NSO_2CF_3)CF_3] = [-52.3;\ -14.5;\ 32.3] = -34.5$ kcal mol^{-1} relative to the parent phenol. The dramatic increase in acidity is primarily due to a strong stabilization of the HOMO-2 orbital, which hosts the two electrons of the lone pair created upon deprotonation of the OH group. Additional contribution to acidity originates from a decreased relaxation energy in *para*-$S(O)(=NSO_2CF_3)CF_3$ substituted phenol. These two synergistic effects are somewhat diminished by the strongly increased O–H bond energy by 32.3 kcal mol^{-1}. As a final comment let us compare the acidity of the $C(CN){=}C(CN)_2$ *para*-substituted phenol against acidity of the parent molecule: $\Delta PA[C(CN){=}C(CN)_2] = [-61.8;\ 26.9;\ -1.4] = -36.3$ kcal mol^{-1}. The influence of the final state is dramatic indeed due to the fact that deprotonation leaves the lone pair placed in a low energy HOMO-3 orbital. The present analysis provides conclusive evidence that the intrinsic acidifying power in the gas-phase decreases along the series $C(CN){=}C(CN)_2 > S(O)(=NSO_2CF_3)CF_3 > SO_2CF_3 > NO_2$ in *para*-substituted phenols, which resolves a longstanding dilemma. It is somewhat surprising that tricyanovinyl is a stronger acidifier than superacidifiers[45,46] SO_2CF_3 and $S(O)(=NSO_2CF_3)CF_3$.

In order to get a big picture on the acidity of substituted phenols let us consider the data presented in Table 2. Their perusal leads to a conclusion that there are two widely different types of *para*-substituents, namely, very strong π-electron acceptors and π-electron donors. The first group is rather large yielding considerable enhancement in acidity. It is comprised of CHO, COOH, CF_3, BH_2 and CN groups apart from the already discussed NO_2, SO_2CF_3, $S(O)(=NSO_2CF_3)CF_3$ and $C(CN)=C(CN)_2$ strongly acidifying moieties. It is easy to see that these groups stabilize the resulting conjugate bases as illustrated by Scheme 1, where Pauling's resonance structures are sequenced according to decreasing importance. The first resonance structure (a) describes the most stable pattern of the π-electron spin coupling. The second structure (b) corresponds to the long range π-electron density transfer to a strongly electron withdrawing group X. The third resonance structure (c) should considerably contribute to the stability of the anion too as a rule, since the negative charge is placed at the nearest neighbour of the group X. The latter is attached to the *para*-carbon by an atom, which carries appreciable positive charge. Terrier et al.[46] provided some evidence that the resonance structure (b) is only moderately important for SO_2CF_3 and $S(O)(=NSO_2CF_3)CF_3$ moieties. It should be noticed that similar resonance structures can be written for the initial neutral acids too, but they contain a bipolar (zwitterionic) distribution of the charge. These structures are less stabilizing than the corresponding ones in the conjugate bases (Scheme 1) implying that the anions are better stabilized. Consequently, it is intuitively clear that deprotonation should be more favourable for the electron captive substituents. This qualitative conjecture is in accordance with the increased acidity in phenols substituted by the group 1 substituents (Table 2). Triadic analysis offers a more detailed description of this phenomenon. It turns out that the excess negative charge produced by deprotonation is placed in very stable HOMO-2 orbitals in CHO, COOH, CF_3, BH_2, CN, NO_2, SO_2CF_3 and $S(O)(=NSO_2CF_3)CF_3$ (Table 2) thus contributing considerably to the stability of anions. A subset of this group of compounds is given by substituents with less pronounced π-electron withdrawing power. Typical representatives are halogens F, Cl and Br. The stabilization contributions of their HOMO-2 orbitals in anions are small to modest being −4.1, −9.8 and −11.7 (in kcal mol^{-1}), respectively. The second distinctly different group of substituents is provided by the π-electron releasing atoms like nitrogen and oxygen in NH_2, OH and OCH_3. It is obvious that two π-electron donors placed at *para*-positions will interfere in a way to destabilize the initial acid and somewhat more so



Scheme 1.

the corresponding anion. Hence, the substituted phenols should be less acidic. The actual numbers given in Table 2 show that this effect takes place indeed, but that it is rather small at the same time. Survey of the data in Table 2 indicates that there are two opposing effects in these systems: the relaxation energy and the bond association energy. The former diminishes the acidity of phenols and prevails over a decrease in the $(BAE)^{\cdot}$ term, which contributes towards an increase in acidity.

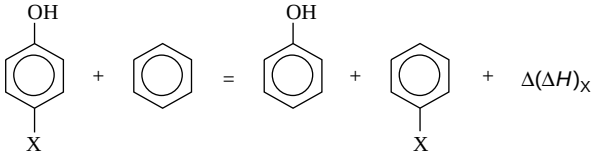
The substituent, which represents a notable exception is the SH group, since the site of deprotonation in *para*-substituted phenol is not the OH but the SH group instead just like in the benzoic acid.[28] This has a profound influence on the values of contributions entering triadic formula. Firstly, the lone pair molecular orbital created by deprotonation belongs to the sulfur atom. It is the HOMO-1 orbital of σ-symmetry (Fig. 2) and not the HOMO-2 orbital like in all other compounds. The corresponding ionization energy within Koopmans' approximation assumes 77.2 kcal mol^{-1}, which is dramatically lower than in the parent phenol. Taking into account other terms entering Eq. 3 one obtains $\Delta PA(SH)=[46.7;\ -60.7;\ 7.4]=-6.6$ kcal mol^{-1} relative to free phenol indicating that the dominating effect leading to the higher acidity of *para*-SH derivative is given by the very small relaxation energy (11.3 kcal mol^{-1}). The contribution of relaxation energy to proton affinity of anion is negative being as low as −60.7 kcal mol^{-1}, thus exerting a predominating effect leading to increased acidity. This overwhelms the combined positive contributions of the Koopmans' term and the higher bond association energy. Methylation at the SH group completely changes this picture, since in this case we are left without the acidic proton at the sulfur atom. Concomitantly, *para*-SCH_3 phenol is deprotonated at the hydroxyl group. Hence, the triadic terms related to SCH_3 substituent are more compatible with those of other substituents. Specifically: $\Delta PA(SMe)=[-10.0;\ 11.8;\ -8.0]=-6.2$ kcal mol^{-1}. It appears that a synergistic effect of Koopmans' ionization potential and bond association energy leads to an enhancement of acidity by 6.2 kcal mol^{-1}. This is practically the same as that of the SH group. It is important to realize, however, that both the site of deprotonation and the underlying physical picture are completely different in these two cases.

A point of considerable importance is the pentacyano derivative of phenol, which is highly acidic as evidenced by PA of 287.5 kcal mol^{-1}. This is comparable in its strength to some strong mineral acids like HNO_3, H_2SO_4 and $HClO_4$. Their experimental gas-phase ΔH_{acid} values are 324.5, 306.3 and 288.0 kcal mol^{-1}, respectively. The reason behind such a high acidity of pentacyanophenol is the large stabilization of the HOMO-2 orbital in the conjugate base, which contributes −87.7 kcal mol^{-1} to acidity of this simple superacid. It is also noteworthy that pentacyano derivative of phenol, where the cyano groups are attached to the aromatic nucleus is considerably stronger acid than the corresponding pentacyano benzoic acid (PA=303.0 kcal mol^{-1}) although the effect of the single cyanation at the *para*-position is very close in both systems. One of the main reasons is that the O–H bond association energy in benzoic acid is 17 kcal mol^{-1} larger than that in phenol.[28]

It is of some interest to compare and comment on the effects of single *para*-substitutions in phenol and benzoic acid. One can distinguish two distinctly different sets. The first set of substituents is embodied by Cl, CH_3, NH_2, OH, OCH_3 and SH. They do not change the difference in acidity of the parent systems to a large extent. In other words, the derivatives of benzoic acid are more acidic by approximately 9 kcal mol^{-1}, which corresponds to a difference in acidity between unsubstituted benzoic acid and phenol. The second group of substituents is given by CHO, COOH, BH_2, $B(CH_3)_2$, NO_2 and CN, which increase the acidity of the substituted phenols in such a way that they become practically the same as the corresponding substituted benzoic acids. Since these substituents exhibit appreciable electron withdrawing power, which strongly stabilizes the corresponding anions, it follows that their π-electrons resonance effect with O^- in phenoxide is more pronounced than with carboxyl COO^- group in benzoic acid anions. This has some important consequences. It means that Hammett's σ-constants do not depend only on the nature of the substituent and its position on the (aromatic) perimeter, but also on the intrinsic properties of the reaction center. It should be noted that the differences in acidities between derivatives of benzoic acid and phenol (not given here) can be easily analyzed by using the earlier data[28] and present results employing triadic formula.

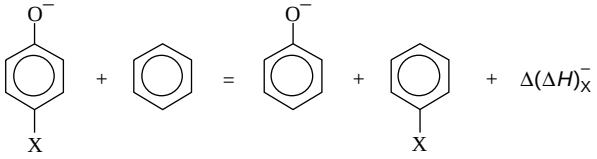
3.2. Homodesmotic reactions and triadic analysis

Let us describe the influence of *para*-substituents on the acidity of phenol by homodesmotic reactions. Consider for this purpose the enthalpies of the following reactions:



(6)

and



(7)

The difference of relations 7 and 6 gives:

$$\Delta H_{\mathrm{acid}}(\mathrm{ph})_{\mathrm{X}} = \Delta H_{\mathrm{acid}}(\mathrm{ph}) + \left[\Delta(\Delta H)_{\mathrm{X}}^{-} - \Delta(\Delta H)_{\mathrm{X}}\right] \quad (8)$$

where $\Delta(\Delta H)_{\mathrm{X}}$ and $\Delta(\Delta H)_{\mathrm{X}}^{-}$ yield the enthalpies of interactions between the *para* situated groups in phenol and phenoxide, respectively. It appears that the change in deprotonation energy of phenol upon *para*-substitution by X—the increment $I(\mathrm{X})_p$—is determined by $\Delta(\Delta H)_{\mathrm{X}}^{-} - \Delta(\Delta H)_{\mathrm{X}}$. However, the same magnitude is obtained by Eq. 5. Hence, it follows:

$$I(\mathrm{X})_p = \Delta(\Delta H)_{\mathrm{X}}^{-} - \Delta(\Delta H)_{\mathrm{X}}$$

$$= \left[\Delta(-\mathrm{IE}_n^{\mathrm{Koop}}); \Delta E(\mathrm{ei})_{\mathrm{rex}}^{(n)}; \Delta(\mathrm{BAE})_{\alpha}^{\cdot}\right] \quad (9)$$

where Δ in the triadic formula denotes a change occurring in phenol derivative imposed by substituent X relative to the parent phenol. It follows that triadic analysis is equivalent to the homodesmotic reactions approach, but provides more information on the effect of substituents on the acidity of the initial acid. It enables dissection of the deprotonation process into the initial, intermediate and final state effects at the global level, which is conceptually advantageous. Notice that the homodesmotic reactions approach describes the influence of the initial and final states (relative to the parent phenol) by $\Delta(\Delta H)_{\mathrm{X}}$ and $\Delta(\Delta H)_{\mathrm{X}}^{-}$, respectively. It does not provide, for example, information on the site of deprotonation reflected in the $(\mathrm{IE})_n^{\mathrm{Koop}}$ term included in the trichotomy analysis.

3.3. Acidity and Hammett's σ_p^- constants

A relation between the proton affinities of the conjugate bases and Hammett's σ-constants is of general importance. A correlation between $\Delta\mathrm{PAs}(\mathrm{A}^-)$ relative to phenoxide anions and σ_p constants for 'neutral' substituents is plotted in Figure 3a. It is poor as reflected in R^2 coefficient 0.839. The average absolute deviations AAD for $\Delta\mathrm{PA}(\mathrm{A}^-)$ is rather high (2.5 kcal mol^{-1}). This is not surprising because the acidity of substituted phenols is predominantly determined by the final conjugate base anionic states. Consequently, a correlation against the σ_p^- constants should be more adequate. Indeed, much better correlativity is obtained by σ_p^- constants ($R^2=0.971$) as illustrated by Figure 3b. The AAD dropped to 1.0 kcal mol^{-1}. It should be mentioned that the SH group is not considered in these calculations, because it deprotonates at sulfur atom. A decisive influence of the final state in determining acidity is mirrored by Koopmans' ionization energies $\Delta(\mathrm{IE})_n^{\mathrm{Koop}}$ and ΔPAs, which is pictorially represented by Figure 4a. The corresponding correlation coefficient is $R^2=0.973$ with AAD of 1.0 kcal mol^{-1}. Finally, a high correlativity between $\Delta(\mathrm{IE})_n^{\mathrm{Koop}}$ and σ_p^- constants ($R^2=0.979$) is evident from Figure 4b, which is of considerable interest, because $\Delta(\mathrm{IE})_n^{\mathrm{Koop}}$ is a gas-phase parameter, whereas σ_p^- constants are developed by studying reactivity in (aqueous) solutions. A high degree of their compatibility indicates that intrinsic properties of substituted phenols are greatly preserved in solutions.

It is of interest to use these correlations in order to estimate σ_p^- constants for superacidifiers $C(CN)=C(CN)_2$ and $S(O)(=NSO_2CF_3)CF_3$. The former moiety should have σ_p^- constants of 2.39 and 2.65 using correlations given Figures 3b and 4b, respectively. It appears that these values are appreciably higher than $\sigma_p^- = 1.70$ deduced from experiments in solution.[12] Similarly, the σ_p^- constant for $S(O)(=NSO_2CF_3)CF_3$ deduced from Figures 3b and 4b should be 2.27 and 2.20, respectively. The former value is close to $\sigma_p^- \cong 2.30$ estimated by Terrier et al.[46] by experiments in aqueous solution. Hence, it is possible that $S(O)(=NSO_2CF_3)CF_3$ is a stronger acidifier than

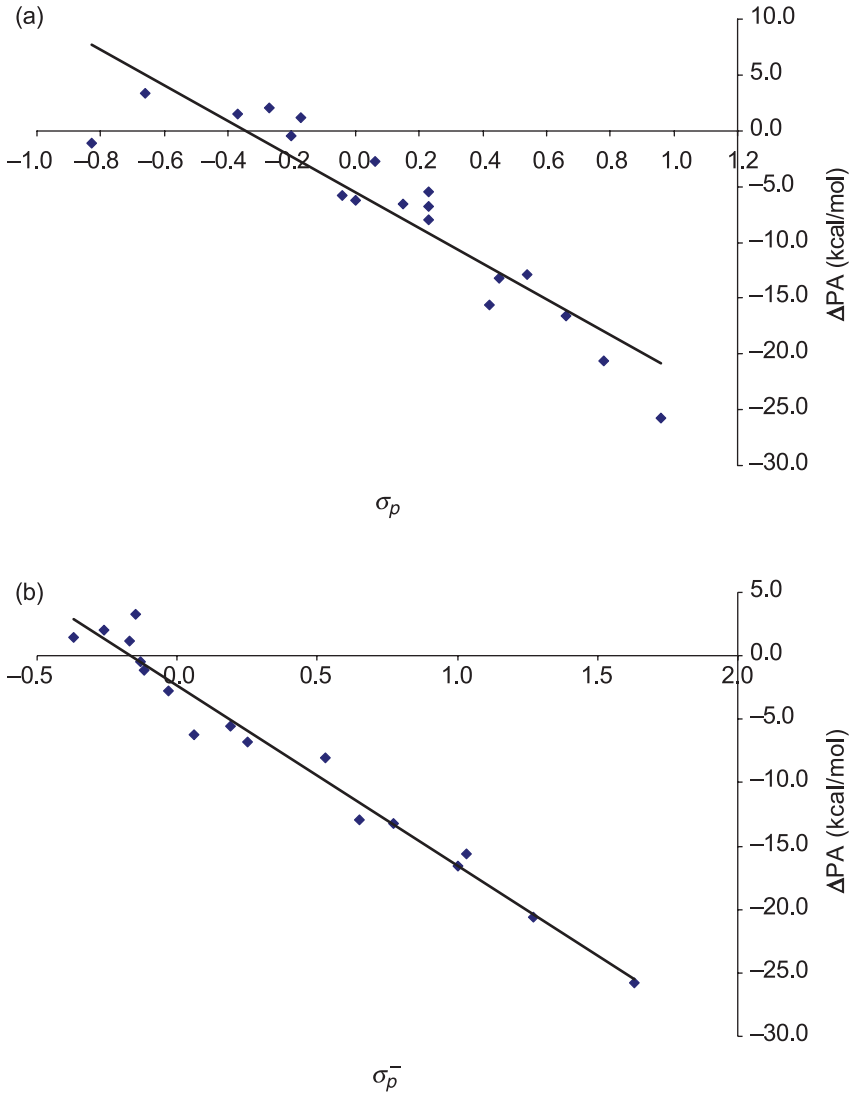


Figure 3. (a) A plot of proton affinities of anions relative to phenoxide ΔPA against Hammett's σ_p constants ($\Delta PA(A^-) = -15.92\sigma_p - 5.55$). (b) Approximate linear relationship between ΔPA(A^-) and Hammett's σ_p^- constants ($\Delta PA(A^-) = -14.18\sigma_p^- - 2.38$).

C(CN)═C(CN)$_2$ in H_2O implying that the hydrogen bonding of S(O)(═NSO$_2$CF$_3$)CF$_3$ with water molecules is much more effective than is the case with the cyano groups in the *para*-tricyanovinyl phenol. As a final remark it should be noted that σ_p^- values for the NO_2 group developed from correlations depicted in Figures 3b and 4b are 1.29 and 1.43 thus being in good accordance with the experimental $\sigma_p^-(\text{exp}) = 1.27$.[12] It is fair to conclude that theoretical (gas-phase) results correlate well with experiment even in the case of extremely strong acidifiers, C(CN)═C(CN)$_2$ being a notable exception.

In order to put the present results into a proper perspective, we shall briefly comment on some local descriptors used in interpreting acidities of phenols. The simplest descriptor is the formal atomic charge of the oxygen and hydrogen atoms pertaining the reaction OH center. Gross and Seybold[21] examined Mulliken charges,[47] the electrostatic atomic charges of Merz, Singh and Kollman[48] and the natural population charges of Weinhold et al.[49] of H atom in neutral phenols and O^- atom in the corresponding phenoxide anions. Both descriptors correlated very poorly with the experimental pK_a values. Romero and Méndez[22] used the hydrogen atomic charge in *para*-substituted phenols in combination with the electronegativity of the X–C6H4O$^\cdot$ fragment and concluded that Mulliken q(H) was pivotal in rationalizing acidities of phenols. This finding should be taken with caution, because q(H) reflects properties of the initial state, thus being in contradiction with evidence that acidities of *para*-substituted phenols containing electron accepting groups are determined by the final state. More sophisticated local descriptors are provided by the minima of the electrostatic potential in the vicinity of the reactive center V_{min}[50] and the average local ionization energy $I(r)$.[51] The latter is calculated on molecular surface of constant density, where $I(r)$ has its lowest value $I_{s,min}$, which in turn corresponds to a site expected to be the most reactive towards electrophiles. Haeberlein and Brinck[19] found an excellent correlation between $I_{s,min}$ and selection of σ_p^- constants for 11 *para*-substituted phenols ($R^2 = 0.994$) by using HF/6-31+G(d) model. Furthermore, they found very good correlations between the B3LYP/6-31+G(d) acidities and V_{min} calculated near the hydroxyl oxygen in both phenoxide anions and phenols. Based on these results, they reached a somewhat conflicting conclusion that it is sufficient

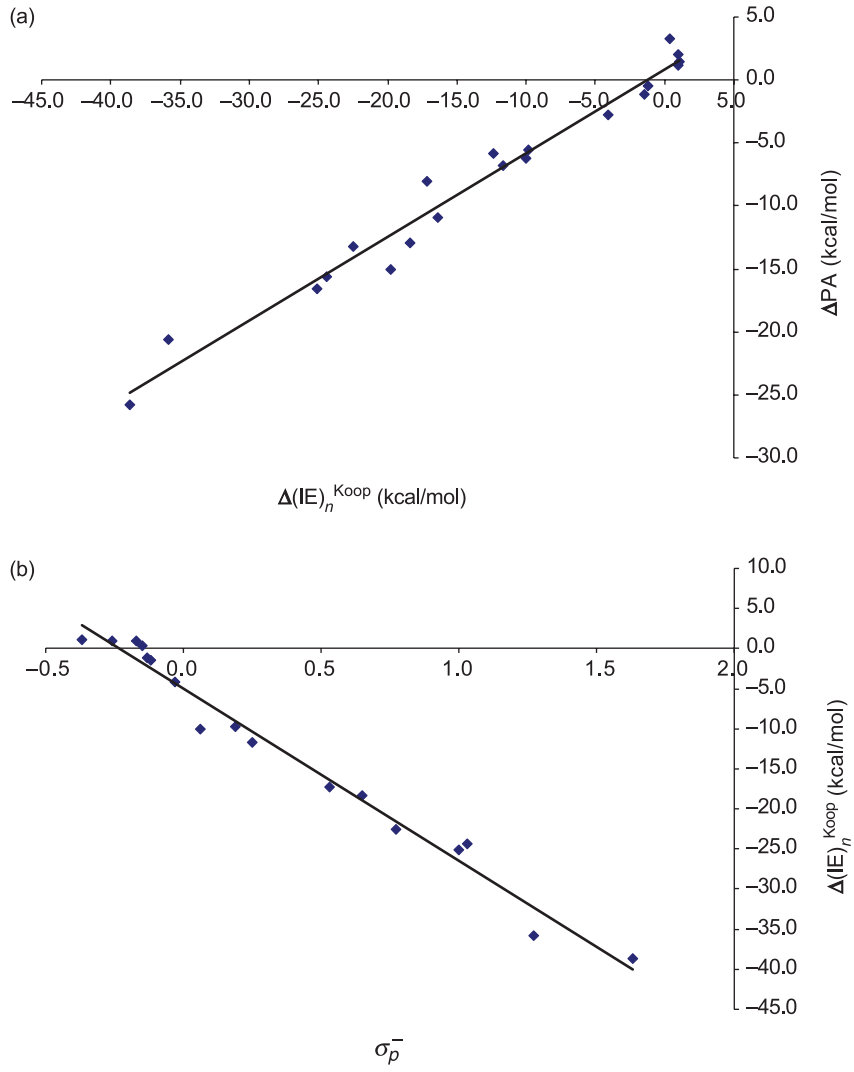


Figure 4. (a) Correlation between $\Delta PA(A^-)$ and relative Koppmans' ionization energies $\Delta(IE)_n^{Koop}$ reflecting the final state effect ($\Delta PA(A^-) = 0.66\Delta(IE)_n^{Koop} + 0.85$). (b) Linear relation between $\Delta(IE)_n^{Koop}$ and Hammett's σ_p^- constants ($\Delta(IE)_n^{Koop} = -21.48\sigma_p^- - 4.98$).

to do calculations on either substituted phenols or the corresponding phenoxide ions. The point is that it cannot be true both ways since properties of phenols correspond to the initial state, whereas features of phenoxides reflect the final state effects. We have shown that in phenols substituted by electron releasing groups the intermediate relaxation energy plays a decisive role in decreasing acidity (vide supra), while in phenols possessing very strong electron accepting substituents the final state is a governing factor. It follows that local descriptors of acidity should be taken with due caution.

4. Conclusion

Triadic analysis provides a global description of the deprotonation process, which can be dissected in three stages: the initial, intermediate and final step. The corresponding energy contributions provide useful insight into the phenomenon, which includes properties of the initial acid reflected in the homolytic dissociation energy, ability of the final anion to accommodate excess negative charge in the molecular orbital undergoing a drastic change in deprotonation and the intermediate relaxation of the electron charge density and the nuclei in the anion. An important result of the present analysis is that substituents can be clearly distinguished by their electron donor and electron acceptor capability. The former decrease the acidity of phenol, whereas the latter increase its acidity albeit to a small extent. The electron accepting substituents influence acidity via the final state mirrored by Koopmans' ionization energy of the MO hosting the excess electron. The strongest acidifying effect is exerted by SO_2CF_3, $S(O)(=NSO_2CF_3)CF_3$ and $C(CN)=C(CN)_2$ groups, which surpass that of the NO_2 group. Finally, it is demonstrated that pentacyano derivative of phenol offers itself as a powerful OH superacid as evidenced by ΔH_{acid} value of 287.5 kcal mol^{-1}.

As to Hammett's 'experimental' σ_p^- constants, they correlated well with $\Delta PA(A^-)$ and Koopmans' ionization $\Delta(IE)_n^{Koop}$ energies of the conjugate bases, where Δ denotes values relative to the parent phenol. This is remarkable, since σ_p^- constants are derived from the experimental values in solutions, whereas calculations refer to the gas-phase. It is our strong belief that σ-constants should be developed by careful ab initio calculations on single molecules in

the future, to be subsequently supplemented by experiments and computations including solvent effects.

Acknowledgements

We would like to thank the Computing Center of the University of Zagreb SRCE for allocation of some computer time on the Isabella cluster.

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The enolate anions of chlorophylls *a* and *b* as ambident nucleophiles in oxidations with (−)- or (+)-(10-camphorsulfonyl)oxaziridine. Synthesis of 13^2(*S*/*R*)-hydroxychlorophylls *a* and *b*

Paavo H. Hynninen,[a,*] Tuomo S. Leppäkases[a] and Markku Mesilaakso[b]

[a]*Laboratory of Organic Chemistry, Department of Chemistry, PO Box 55 (A.I. Virtasen Aukio 1), FI-00014 University of Helsinki, Finland*
[b]*Finnish Institute for Verification of the Chemical Weapons Convention, PO Box 55 (A.I. Virtasen Aukio 1), FI-00014 University of Helsinki, Finland*

Received 24 October 2005; revised 16 December 2005; accepted 12 January 2006

Available online 17 February 2006

Abstract—The enolate anions of chlorophylls (Chl) are ambident nucleophiles that are of considerable organic chemical interest in relation to the theory of electron delocalization (aromaticity) and charge-transfer in large conjugated π-systems, as well as for their chemical reactivity. Under deaerated conditions, the (−)- and (+)-enantiomers of (10-camphorsulfonyl)oxaziridine (CSOAI) are effective oxidants for the enolate anions of Chl *a* and Chl *b*, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) serves as a base. In this study, the use of these sterically hindered reagents to hydroxylate Chl *a* and Chl *b* is described for the first time. The total yield of 13^2(*S*/*R*)-HO-Chl *a* was 71 and 90% for the oxidations of Chl *a* with (−)-CSOAI and (+)-CSOAI, respectively. Chl *b*, however, behaved clearly differently from Chl *a*. The total yield of 13^2(*S*/*R*)-HO-Chl *b* was 40% in the oxidation with (−)-CSOAI and 60% in the reaction with (+)-CSOAI. A competing side-reaction, which resulted in the 15^2-methyl, 17^3-phytyl ester of Mg-15^1(*S*/*R*)-unstable rhodin, was found to lower the yields of the desired main products. The formation of the side-products was largely avoided and the yield of 13^2(*S*/*R*)-HO-Chl *b* was improved by increasing the volume of hexane and using phosphate buffer in the first step of the work-up. With (−)-CSOAI, a 94% diastereomeric excess (de) was achieved for 13^2(*R*)-HO-Chl *a*, whereas the de for 13^2(*R*)-HO-Chl *b* was 66%. With (+)-CSOAI, the de was 10% for 13^2(*R*)-HO-Chl *a* and 8% for 13^2(*R*)-HO-Chl *b*. The results were interpreted in terms of a nucleophilic reaction mechanism, kinetically controlled by steric hindrance, originating on the one hand in the 17-propionate phytyl ester side-chain, protruding over the isocyclic ring E of the Chl enolate ion, and on the other hand in the bulky camphorsulfonyl unit of CSOAI. Possible reasons for the different results from the Chl *b* oxidations as compared with those of the Chl *a* oxidations are discussed. Comparison of the differences in the NMR δ_C-values between 13^2(*S*)- and 13^2(*R*)-HO-Chl *a* as well as those between 13^2(*S*)- and 13^2(*R*)-HO-Chl *b*, indicated that the change of stereochemical configuration at C-13^2 induces only slight differences in the δ_C-values. Of special interest are the δ_C-values of C-13^2, which are at ca. 91 ppm for the *a*- and *b*-series diastereomers. This carbon is deshielded by ca. 25 ppm relative to the C-13^2 of 13^2(*R*)-Chl *a* (δ_C=65.5). Owing to this, ^{13}C NMR spectroscopy is a good method to distinguish the 13^2-hydroxylated chlorophylls from the intact, naturally occurring chlorophylls.
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1. Introduction

Chlorophyll (Chl) *a* (**1**) and Chl *b* (**5**) occur as pivotal photosynthetic pigments in all green plants. Both chlorophylls, together with carotenoids, are needed to form with protein subunits the light-harvesting Chl *a*/*b* complexes (LHC) of the antenna system (AS), which is responsible for capturing light quanta and conveying the excitation energy to the photosynthetic reaction centre (RC).[1,2] Nevertheless, recent X-ray crystallographic studies[3–5] suggest that only Chl *a* [**1**, 13^2(*R*)-Chl *a*] and/or its close derivatives, such as Chl *a*′ [**2**, 13^2(*S*)-Chl *a*] and pheophytin *a* [**9**, 13^2(*R*)-Pheo *a*], also have the redox-function in the RC, where the excitation energy from AS is converted into chemical energy by a charge separation process. Hence, Chl *b*, in contrast, does not appear to participate in the electron-transfer events of the RC. The chemical basis of this prominent functional difference between Chl *a* and Chl *b* in the photosynthetic process has seldom attracted attention and the comparative investigations in vitro on the chemical reactivities of Chl *a* and Chl *b* have also remained extremely rare. There is another peculiarity, which concerns the difference in behaviour of the two Chls in biological degradation. It has been reported[6] that, in the early stages of plant senescence, endogenous Chl *a* is oxidized to 13^2(*S*/*R*)-HO-Chl *a* (**3**/**4**), but there is no report of the formation of

Keywords: Tetrapyrrole; Porphyrin; Chlorophyll; Oxidation; Enolate; Reaction mechanism; NMR.
* Corresponding author. Fax: +358 9 19150466; e-mail: paavo.hynninen@helsinki.fi

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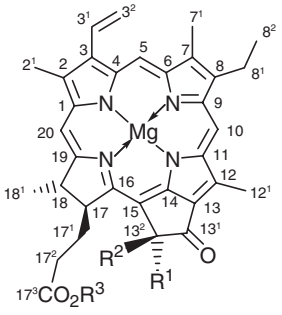
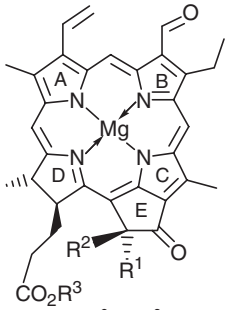
doi:10.1016/j.tet.2006.01.043

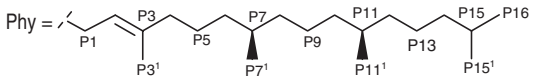
13^2(*S*/*R*)-HO-Chl *b* (**7**/**8**) under comparable conditions. To achieve a deeper insight into the reactivity differences between Chl *a* and Chl *b*, we have recently compared the reactivities of the Chls in the Willstätter allomerization reaction (for reviews, see Refs. 7–12), that is, oxidation by ground state (triplet) oxygen, $^3O_2$. Unexpectedly, we found that the two Chls behave differently under comparable reaction conditions. While Chl *a* yielded 13^2(*S*/*R*)-HO-Chl *a* as major oxidation products, Chl *b* in contrast produced only traces of 13^2(*S*/*R*)-HO-Chl *b*. Instead, we found an appreciable amount of an entirely new chlorophyll derivative, the 10-CH_3O-13^2(*S*)-HO-Chl *b* (**13**).[11–16] As the Chl enolate anion is the first intermediate that is highly reactive with $^3O_2$ in the allomerization mechanism, these results can be interpreted as reflecting the electronic differences between the enolate anions[17] of the two chlorophylls, formed through 13^2-deprotonation in the isocyclic ring E, carrying the same enolizable β-keto ester system in both cases.

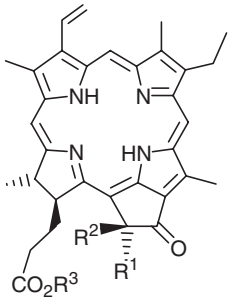


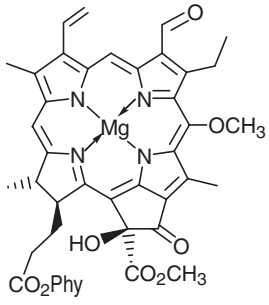


1 R^1=CO_2CH_3; R^2=H; R^3=Phy;
2 R^1=H; R^2=CO_2CH_3; R^3=Phy;
3 R^1=CO_2CH_3; R^2=OH; R^3=Phy;
4 R^1=OH; R^2=CO_2CH_3; R^3=Phy;

5 R^1=CO_2CH_3; R^2=H; R^3=Phy;
6 R^1=H; R^2=CO_2CH_3; R^3=Phy;
7 R^1=CO_2CH_3; R^2=OH; R^3=Phy;
8 R^1=OH; R^2=CO_2CH_3; R^3=Phy;

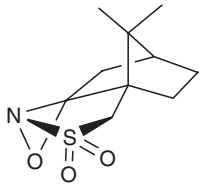




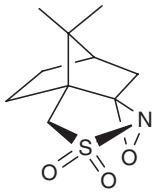


9 R^1=CO_2CH_3; R^2=H; R^3=Phy;
10 R^1=CO_2CH_3; R^2=H; R^3=CH_3;
11 R^1=CO_2CH_3; R^2=OH; R^3=H;
12 R^1=OH; R^2=CO_2CH_3; R^3=H;

13



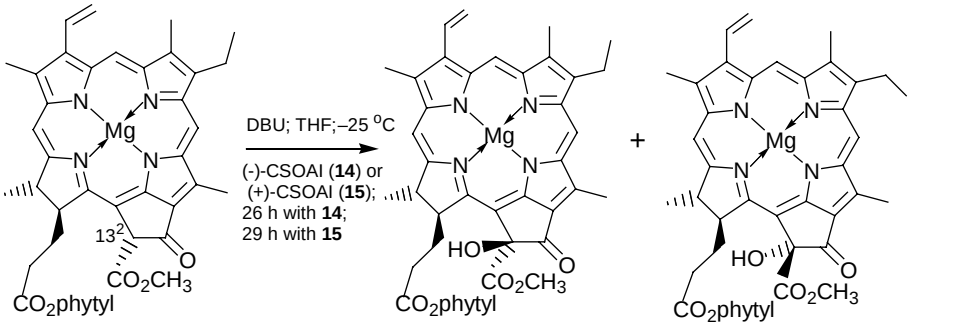
14 (-)-CSOAI



15 (+)-CSOAI

In this investigation, we compare the results from the hydroxylations of the enolate anions of Chl *a* (**1**) and Chl *b* (**5**) using a sterically hindered oxidant, such as the (1*R*)-(−)-enantiomer (**14**) or (1*S*)-(+)-enantiomer (**15**) of (10-camphorsulfonyl)oxaziridine (CSOAI).[18–21] The enolate anion of each Chl is generated with a sterically hindered base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These reagents were introduced to synthetic organic chemistry by Davies and co-workers[18,19] and were applied by Ma and Dolphin[20,21] to hydroxylate demetallated Chl *a* derivatives, such as pheophytin *a* (**9**) and methyl pheophorbide *a* (**10**). To our knowledge, these reagents have never been applied to hydroxylate Chl *a* and Chl *b* or any of the demetallated Chl *b* derivatives. It is noteworthy that the presence of the central Mg-atom, whose coordination number is 5 or 6, depending on the nature of the nucleophilic solvent, influences the conformation and electronic structure of the whole macrocycle and its peripheral substituents. Therefore, especially with sterically hindered reagents, the outcome of the reaction with an Mg-complexed chlorin would be expected to differ noticeably from that typical of the corresponding metal-free chlorin. This conclusion is supported by the observation that the central Mg-atom makes the Chls more susceptible to allomerization as compared with the corresponding metal-free derivatives.[7,22] In addition, the strongly electron-withdrawing formyl group at C-7 of Chl *b* is expected to have a certain effect on the amounts and species of oxidation products yielded by Chl *b* with CSOAI (**14**/**15**) as compared with those produced by Chl *a*.

Consequently, in our study, we seek to clarify the reactivity differences of Chl *a* and Chl *b* under comparable reaction conditions, both regarding the yields of the major/minor oxidation products as well as regarding the diastereoselectivity of each hydroxylation reaction, expressed in terms of diastereomeric excess (de). We will also examine, with unprecedented thoroughness, a likely mechanism for the reactions. This is done because the enolate anions of Chls are ambident nucleophiles that are of considerable organic chemical interest in relation to the theory of electron delocalization (aromaticity) and charge-transfer in large conjugated π-systems, as well as the chemical reactivity of such systems.[17] The examination of a detailed reaction mechanism was also found necessary in seeking a reasonable interpretation for the differences observed in the oxidation results. Further, we will describe in detail the separation and purification of the oxidation products by medium-pressure liquid chromatography (MPLC) on a semi-preparative sucrose column and by normal phase high-pressure liquid chromatography (NP-HPLC) on a silica column.[23,24] The products are thoroughly characterized using ^{1}H and ^{13}C NMR spectroscopy, electronic absorption spectroscopy (UV–vis) as well as electrospray ionization mass spectrometry (ESI-MS). To our knowledge, completely assigned ^{1}H and ^{13}C NMR spectra for 13^2(*S*)- and 13^2(*R*)-HO-Chl *b* have not been published before.[15,25–27]

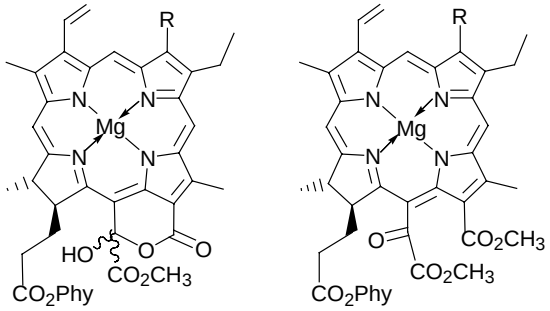


Scheme 1.

2. Results and discussion

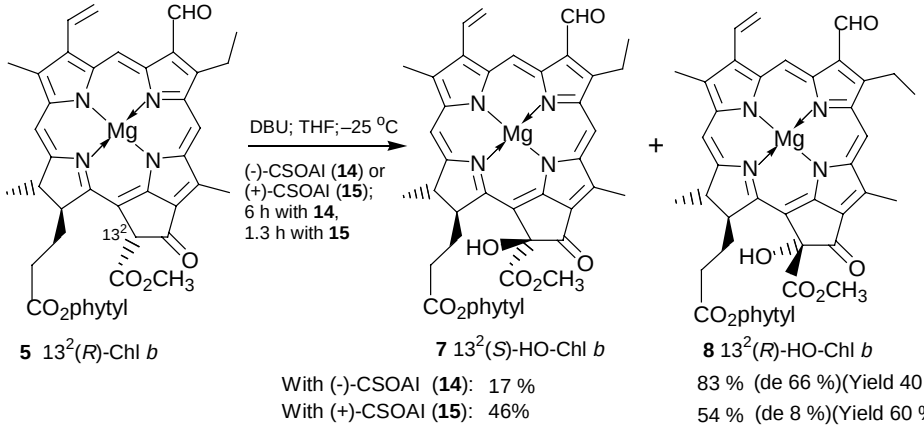
2.1. Total yield and diastereoselectivity in the 13^2-hydroxylations of the chlorophylls with the (−)- and (+)-enantiomers of (10-camphorsulfonyl)oxaziridine

Under deaerated conditions, the (−)- and (+)-enantiomers of CSOAI are effective oxidants for the enolate anions of Chl *a* (**1**) and Chl *b* (**5**). The total yield of 13^2(*S*/*R*)-HO-Chl *a* (**3**/**4**) was 71 and 90% for the oxidations of Chl *a* with (−)-CSOAI (**14**) and (+)-CSOAI (**15**), respectively, (Scheme 1). These yields are of approximately the same magnitude but in reversed order as compared with those reported by Ma and Dolphin for the oxidations of pheophytin *a* (**9**) or methyl pheophorbide *a* (**10**).[20] We ascribe this noticeable difference in the yields to originate from the effect of the 6-coordinated central magnesium on the conformation and reactivity of Chl *a*. The macrocycle of pheophytin *a*–Mg(II)·2THF is likely to have a more planar and more rigid conformation as compared with the metal-free pheophytin *a*. Only negligible amounts of side-products, such as the 15^2-methyl, 17^3-phytyl ester of Mg-15^1(*S*/*R*)-unstable chlorin-7 (**16**) [Mg-3^1,3^2-didehydro-15^1,15^1-dihydroxy-rhodochlorin-15-acetic acid-15^1(*S*/*R*)-δ-lactone][9,23,28–33] was occasionally detected by UV–vis spectroscopy and by converting the lactone diastereomers with diazomethane[34] to the 13^1,15^2-dimethyl, 17^3-phytyl ester of Mg-purpurin-7 (**18**) [Mg-3^1,3^2-didehydro-rhodochlorin-15-glyoxylic acid].[9,23,28–30,33]



Under comparable reaction conditions, Chl *b*, however, clearly behaved differently from Chl *a*. The total yield of 13^2(*S*/*R*)-HO-Chl *b* (**7**/**8**) was 40% in the oxidation with (−)-CSOAI (**14**) and 60% in the reaction with (+)-CSOAI (**15**) (Scheme 2).

A competing side-reaction, which resulted in a very polar Chl *b* derivative, accounts largely for the lower yields of **7**/**8**. This polar Chl *b* derivative was identified as the 15^2-methyl, 17^3-phytyl ester of Mg-15^1(*S*/*R*)-unstable rhodin (**17**)



Scheme 2.

[Mg-3^1,3^2-didehydro-15^1,15^1-dihydroxy-7^1-oxo-rhodochlorin-15-acetic acid-15^1(*S*/*R*)-δ-lactone][15,28,29,31] on the basis of the UV–vis spectrum, ESI-MS and by converting the lactone diastereomers with diazomethane to the 13^1,15^2-dimethyl, 17^3-phytyl ester of Mg-7^1-oxo-purpurin-7 (**19**) [Mg-3^1,3^2-didehydro-7^1-oxo-rhodochlorin-15-glyoxylic acid].[15,28,29] The formation of the Mg-unstable rhodin side-products was largely avoided and the yield of 13^2(*S*/*R*)-HO-Chl *b* was improved by increasing the volume of hexane and using 0.1 M phosphate buffer, pH 5.5, instead of pure water in the first step of the work-up, that is, when washing the hexane solution of the reaction mixture for the first time.

The diastereoselectivity of each hydroxylation reaction was determined by NP-HPLC.[23,24] A complete resolution between the 13^2(*S*)- and 13^2(*R*)-diastereomers was achieved in each separation. The de was 94% for 13^2(*R*)-HO-Chl *a* (**4**) in the oxidation of Chl *a* (**1**) with (−)-CSOAI (**14**), but only 10% when (+)-CSOAI (**15**) was used as oxidant (Scheme 1, Fig. 1).

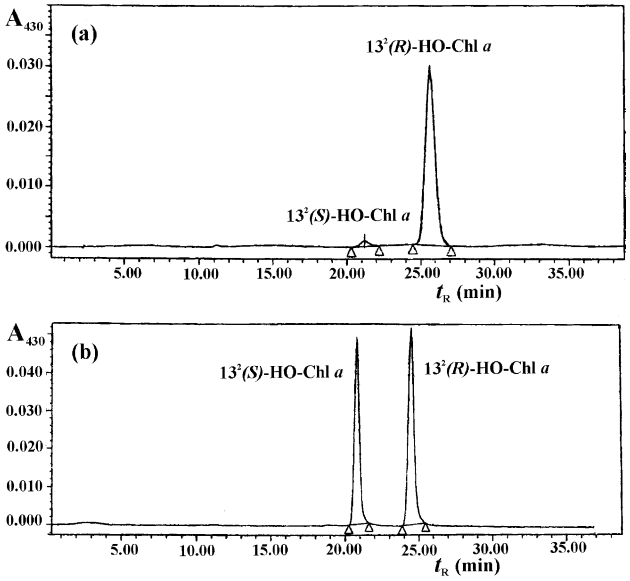


Figure 1. Normal-phase HPLC separation of 13^2(*S*)-HO-Chl *a* (**3**) and 13^2(*R*)-HO-Chl *a* (**4**) on the LiChrospher Si 60 column (250×4.0 mm i.d., 5 μm, Merck). Mobile phase: 1.0% (v/v) 2-PrOH in hexane. (a) Products obtained with (−)-CSOAI, (b) products obtained with (+)-CSOAI.

The oxidation of Chl *b* (**5**) with (−)-CSOAI and (+)-CSOAI resulted in a 66 and 8% de, respectively, in favour of 13^2(*R*)-HO-Chl *b* (**8**) (Scheme 2, Fig. 2). We seek to interpret the foregoing results regarding the total yield and diastereoselectivity by examining the detailed mechanism of the reactions.

2.2. Mechanism of the 13^2-hydroxylations of the chlorophylls with the (−)- and (+)-enantiomers of (10-camphorsulfonyl)oxaziridine

The (−)- and (+)-CSOAI (**14**,**15**) are effective oxidants of the Chl enolate anion (**20**, Scheme 3), produced from Chl as a result of C-13^2 deprotonation by DBU [pK_a (THF)=16.8; pK_{ip} (THF)=18.0 (subscript ip refers to a correction for ion-pairing using the Fuoss equation);[35,36] pK_a (acetonitrile)=24.0[37,38]]. The Chl enolate anion can be envisaged as

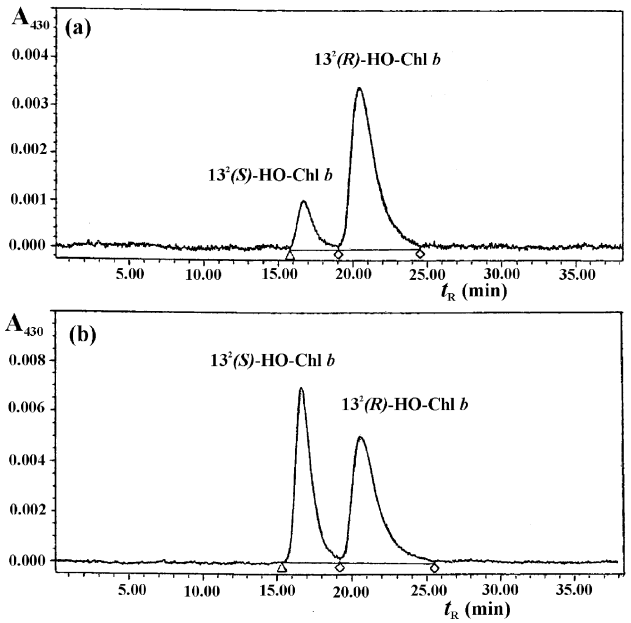
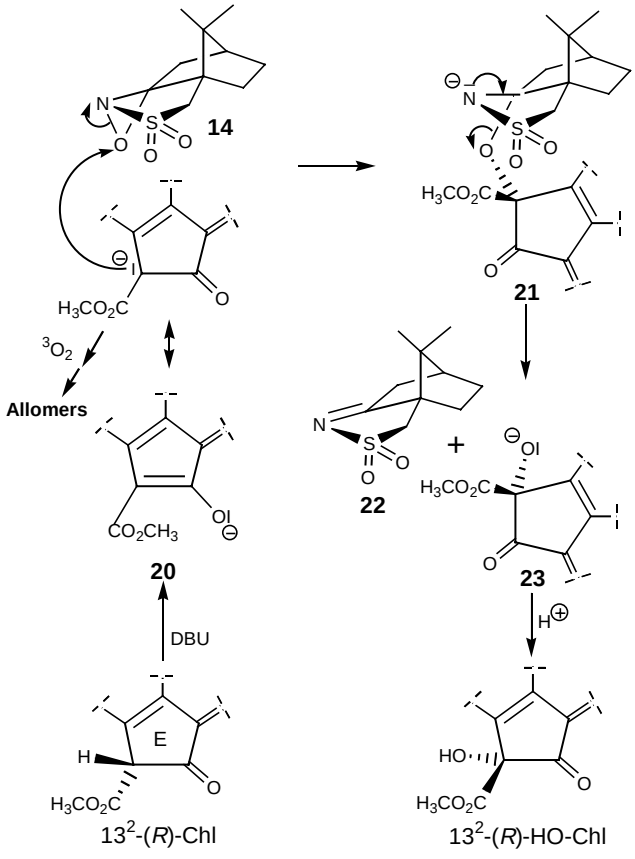


Figure 2. Normal-phase HPLC separation of 13^2(*S*)-HO-Chl *b* (**7**) and 13^2(*R*)-HO-Chl *b* (**8**) on the LiChrospher Si 60 column (250×4.0 mm i.d., 5 μm, Merck). Mobile phase: 2.0% (v/v) 2-PrOH in hexane. (a) Products obtained with (−)-CSOAI, (b) products obtained with (+)-CSOAI.

an ambident nucleophile (reviewed in Ref. 39, pp 322–325), which in the transition state of the reaction behaves as the C-13^2 carbanion, attacking the oxygen atom of the three-membered oxaziridine ring (Scheme 3).[18,39] The ring is opened while the bonding electron pair between O and N



Scheme 3.

is transferred to the nitrogen atom. The resulting indermediate (**21**) disintegrates into the camphoryl-*N*-sulfate imine (**22**) and the 13^2-oxide anion of Chl (**23**). Protonation of the latter affords the final product, which is almost exclusively the $13^2(R)$-hydroxy-Chl, when (−)-CSOAI (**14**) is used as oxidant.

The diastereoselectivity, favouring the formation of $13^2(R)$-HO-Chl, especially with (−)-CSOAI (**14**), can be explained in terms of kinetic control, arising from steric hindrance, exerted by the 17-propionate phytyl ester group of the Chl enolate ion on the one hand and by the bulky camphorsulfonyl unit of the oxaziridines on the other hand. The highly space-demanding 17-propionate phytyl ester group, protruding over the front side of the isocyclic ring E, prevents the (−)-CSOAI oxidant from approaching the C-13^2 of the Chl enolate ion from the front side, but allows it to approach from the more open back side (*re*-face). This results in a moderate total yield of $13^2(S/R)$-HO-Chl, but high diastereomeric excess, favouring $13^2(R)$-HO-Chl as the prevailing diastereomer. The camphorsulfonyl unit of the (+)-enantiomer of CSOAI (**15**) causes less steric hindrance than the unit of the (−)-enantiomer (**14**). Consequently, (+)-CSOAI can approach the C-13^2 of the Chl enolate ion almost equally from either side. This results in a high total yield of $13^2(S/R)$-HO-Chl, but low diastereomeric excess, favouring only slightly $13^2(R)$-HO-Chl. In addition, it is noteworthy that the $13^2(R)$- and $13^2(S)$-diastereomers of 13^2-HO-Chl are not interconvertible (cf. thermodynamic control), because enolization in ring E is not possible in these Chl derivatives. Possible reasons for the different results of the Chl *a* and Chl *b* oxidations are discussed below.

2.3. Comparison of the ^{1}H and ^{13}C chemical shifts of the $13^2(S)$- and $13^2(R)$-diastereomers of 13^2-HO-Chl *a* (3/4) and 13^2-HO-Chl *b* (7/8)

Tables 1 and 2 present the ^{1}H and ^{13}C NMR δ-values for the $13^2(S)$- and $13^2(R)$-diastereomers of 13^2-HO-Chl *a* and 13^2-HO-Chl *b*. Comparison of the δ_H-values of $13^2(S)$-HO-Chl *a* and $13^2(R)$-HO-Chl *a* shows that the greatest differences occur for the 17-CH, 17^1-CH_2 (H_a, $H_{a'}$) and 17^2-CH_2 (H_b, $H_{b'}$) protons. These differences can be interpreted as arising from the conformational alterations occurring in the propionate phytyl ester side-chain and ring D as a result of the change of stereochemical configuration at C-13^2. However, the stereochemical alterations also induce small differences in the case of the methine-bridge 5-CH and 10-CH protons, as well as the 13^2-COH proton. The δ_H-values, 6.01 and 6.04, of the 13^2-COH proton, deserve special attention, because these values are very close to the corresponding values, 6.15 and 6.06, of $13^2(R)$-Chl *a* and $13^2(S)$-Chl *a*.[40] Hence, it would be very difficult to distinguish the 13^2-hydroxylated chlorophylls from the intact, naturally occurring chlorophylls solely on the basis of the ^{1}H NMR and UV–vis spectra; [the UV–vis spectra are identical for $13^2(S/R)$-HO-Chl *a* and $13^2(S/R)$-Chl *a* as well as for $13^2(S/R)$-HO-Chl *b* and $13^2(S/R)$-Chl *b*].

Inspecting next the differences in the δ_H-values between $13^2(S)$-HO-Chl *b* and $13^2(R)$-HO-Chl *b*, we observe that the differences are comparable to those in the *a*-series compounds. In the case of the *b*-series compounds, attention should be focused on the effect of the electron-withdrawing C-7 formyl group on the δ_H-values. As expected, there is a clear deshielding effect in the case of the 5-CH proton.

Table 1. ^{1}H NMR chemical shifts (δ_H, ppm, relative to Me_4Si in acetone-d_6) for $13^2(R)$-HO-Chl *a* (**4**), $13^2(S)$-HO-Chl *a* (**3**), $13^2(R)$-HO-Chl *b* (**8**) and $13^2(S)$-HO-Chl *b* (**7**)

Proton	Multiplicity, $^nJ_{H-H}$ (Hz)	**4**[a]	**3**[a]	**8**[b]	**7**[b]
2^1-CH_3	s	3.36	3.36	3.30	3.30
3^1-CH (H_X)	dd, $^3J_{cis}=11.6$, $^3J_{trans}=17.8$	8.14	8.14	8.30	8.30
3^2-CH_2 (H_{cis})	dd, $^2J_{gem}=1.5$, $^3J_{cis}=11.6$	6.02	6.02	6.04	6.04
3^2-CH_2 (H_{trans})	dd, $^2J_{gem}=1.5$, $^3J_{trans}=17.8$	6.23	6.23	6.28	6.28
5-CH	s	9.45	9.48	10.17	10.17
7^1-CH_3	s	3.31	3.31	—	—
7^1-CHO	s	—	—	11.20	11.20
8^1-CH_2	q, $^3J_{8^1-8^2}=7.6$	3.83	3.83	4.19	4.19
8^2-CH_3	t, $^3J_{8^1-8^2}=7.6$	1.72	1.71	1.79	1.79
10-CH	s	9.78	9.80	9.92	9.92
12^1-CH_3	s	3.64	3.64	3.62	3.62
13^2-COH	s	6.01	6.04	6.12	6.16
13^4-CH_3	s	3.61	3.59	3.60	3.60
17-CH	m	4.66	4.16	4.63	4.08
17^1-CH_2 ($H_{a'}$)	m	2.20[c]	2.85[c]	2.20[c]	2.30[c]
17^1-CH_2 (H_a)	m	2.20[c]	2.57[c]	2.20[c]	2.10[c]
17^2-CH_2 ($H_{b'}$)	m	2.37[c]	2.43[c]	2.37[c]	2.50[c]
17^2-CH_2 (H_b)	m	1.90[c]	2.06[c]	1.90[c]	2.20[c]
18-CH	dq, $^3J_{18-18^1}=7.3$	4.55	4.55	4.50	4.49
18^1-CH_3	d, $^3J_{18-18^1}=7.3$	1.65	1.57	1.64	1.64
20-CH	s	8.62	8.62	8.52	8.49
P1–CH_2 (H_a)	d/m, $^3J_{P2-P1}=7.1$	4.44	4.45	4.42	4.42
P1–CH_2 (H_b)	d/m, $^3J_{P2-P1}=7.1$	4.44	4.49	4.42	4.42
P2–CH	tq, $^3J_{P2-P1}=7.1$	5.16	5.17	5.13	5.24
$P3^1$–CH_3	s	1.57	1.60	1.55	1.55
P4–CH_2[d]	m	1.90	1.90	1.87	1.87

[a] Values consistent with those published earlier in Ref. 24.
[b] Values measured on a Bruker Avance spectrometer, ν (^{1}H)=500 MHz.
[c] Requires spin simulation for the fragment 17-CH–17^1-CH_2–17^2-CH_2.
[d] The P5–P16 part of the phytyl group spectrum was as reported in Ref. 46.

Table 2. Broad-band proton decoupled ^{13}C NMR chemical shifts (δ_C, ppm, relative to Me_4Si in acetone-d_6) for $13^2(R)$-HO-Chl *a* (**4**), $13^2(S)$-HO-Chl *a* (**3**), $13^2(R)$-HO-Chl *b* (**8**) and $13^2(S)$-HO-Chl *b* (**7**).

Carbon	**4**[a]	**3**[a]	**8**[b]	**7**[b]
1	155.51	155.54	157.43	157.52
2	136.07	136.11	136.94	136.84
2^1	12.54	12.55	12.39	12.39
3	139.93	139.97	141.08	141.08
3^1	131.37	131.37	130.87	130.85
3^2	120.19	120.29	120.85	120.81
4	148.75	148.70	149.74	149.80
5	100.94	101.05	104.15	104.22
6	152.53	152.44	149.20[c]	149.37[c]
7	134.71	134.84	131.59	131.62
7^1	11.14	11.14	188.47	188.48
8	144.87	144.97	155.77	155.64
8^1	19.98	19.96	19.75	19.57
8^2	18.01	18.02	19.56	19.39
9	146.87	146.87	143.49	143.59
10	108.09	108.21	111.03	111.11
11	148.33	148.42	149.16[c]	149.25[c]
12	134.98	134.75	139.26	138.85
12^1	12.74	12.71	12.82	12.79
13	129.29	129.74	130.54	130.53
13^1	192.80	193.04	193.38	193.48
13^2	90.77	90.75	90.68	90.50
13^3	174.66	174.09	174.44	173.78
13^4	53.29	53.04	53.42	53.17
14	162.42	162.27	163.83	163.85
15	109.28	109.12	109.15	108.86
16	157.61	158.23	160.42	161.37
17	50.30	51.91	50.36	52.19
17^1	31.30	32.17	31.02[d]	32.20[d]
17^2	31.10	31.27	30.97[d]	31.62[d]
17^3	173.40	173.69	173.32	173.75
18	50.40	49.81	50.31	49.73
18^1	23.39	23.36	23.32	23.32
19	169.95	169.85	171.70	171.63
20	94.04	94.23	94.22	94.39
P1	61.41	61.42	61.43	61.55
P2	119.32	119.48	119.30	119.57
P3	142.67	142.52	142.79	141.08
$P3^1$	16.22	16.24	16.21	16.31
P4[e]	40.30	40.34	40.30	40.40

[a] Values consistent with those published earlier in Ref. 24.
[b] Values measured on a Bruker Avance spectrometer, ν (^{13}C)=125 MHz.
[c] The assignments of carbons 6 and 11 are interchangeable.
[d] The assignments of carbons 17^1 and 17^2 are interchangeable.
[e] The P5–P16 part of the phytyl group spectrum was as reported in Ref. 46.

The 8^1-CH_2, 10-CH, and 13^2-COH protons also exhibit deshielding, but the effect is attenuated the farther the proton is located from the formyl group.

Comparison of the differences in the δ_C-values (Table 2) between $13^2(S)$-HO-Chl *a* and $13^2(R)$-HO-Chl *a* as well as those between $13^2(S)$-HO-Chl *b* and $13^2(R)$-HO-Chl *b*, indicates that the change of stereochemical configuration at C-13^2 induces only slight differences in the values both in the *a*-series and the *b*-series compounds. Of special interest are the δ_C-values of C-13^2, which are at ca. 91 ppm for the diastereomers of both series. This carbon is deshielded by approximately 25 ppm relative to the C-13^2 of $13^2(R)$-Chl *a* (δ_C=65.5).[24] Owing to this, ^{13}C NMR spectroscopy is a good method to distinguish the 13^2-hydroxylated chlorophylls from the intact, naturally occurring chlorophylls.

In addition, ^{13}C NMR spectroscopy is expected to give valuable information regarding the effect of the electron-withdrawing C-7 formyl group on the electron densities of the macrocyclic carbons. Inspection of the δ_C-values in Table 2 shows that most macrocyclic carbons of $13^2(S/R)$-HO-Chl *b* experience deshielding relative to the corresponding carbons of $13^2(S/R)$-HO-Chl *a*. The deshielding effect is attenuated the farther the carbon is located from the formyl group. However, carbons 6 and 9 represent a clear exception to this rule. Contrary to expectations, these carbons are shielded by ca. 3 ppm relative to the *a*-series compounds.

2.4. Possible reasons for the different results of the Chl *a* and Chl *b* oxidations

A conspicuous feature in the foregoing synthesis results is the outcome of the Chl *b* oxidations, which is clearly different from that of the Chl *a* oxidations, despite the use of comparable reaction conditions in both oxidations. In particular, when Chl *b* was oxidized with (−)-CSOAI, the total yield of $13^2(S/R)$-HO-Chl *b* (**7/8**) remained quite modest (40%) and also the diastereoselectivity (de 66%) was clearly lower than that (de 94%) achieved in the corresponding Chl *a* oxidation. In seeking a reasonable interpretation for the different outcome of the Chl *b* oxidations, we will first consider the possibility of the formation of the Mg-$15^1(S/R)$-unstable rhodin side-products (**17**) in the reaction mixture during the reaction period.

The side-products **17** and $13^2(S/R)$-HO-Chl *b* might both be formed in the reaction mixture via the allomerization reaction, if some adventitious ground-state (triplet) oxygen and water remained in the mixture in spite of the careful deaeration and drying procedures of the reagent solutions (cf. Section 4). Being very reactive with the enolate anion of Chl *b* (**20**, Scheme 3), the triplet oxygen would be kinetically capable of competing with CSOAI and initiating the free-radical allomerization (FRA),[16] which, in the presence of water/hydroxide ion, would be expected to yield $13^2(S/R)$-HO-Chl *b* and the Mg-$15^1(S/R)$-unstable rhodin products **17** from Chl *b*. As Chl *b* is more difficult to dehydrate than Chl *a*, it is possible that an equimolar amount of water was introduced with Chl *b* into the reaction mixture, where the H_2O was deprotonated by DBU (a strong base, but a weak nucleophile) to give the HO^- ion. Being a strong base and a strong nucleophile, the latter is probably capable of reacting with the oxaziridine ring of the (−)- or (+)-enantiomer of CSOAI, thus reducing the concentration of the reactive oxidant in the desired reaction. However, it is also possible that the strongly electron-withdrawing effect of the C-7 formyl group of the Chl *b* enolate anion was mediated down to the isocyclic ring E,[17] thereby reducing the nucleophilicity of the Chl *b* enolate anion and the probability of its desired oxidation by CSOAI. Furthermore, the conformational alterations, induced by the electron-withdrawing C-7 formyl group in the reduced sub-ring D and the C-17 propionate phytyl ester group,[17] are likely to influence the oxidation results of Chl *b*.

In trying to estimate the possibility of the second alternative, that is, that the side-products **17** were formed, when the reaction mixture was poured into the hexane/water partition system, it is noteworthy that a minor part of $13^2(S/R)$-HO-Chl *b* and presumably all of the side-products **17** went into the aqueous phase and were lost, because this phase was discarded (cf. Section 4). It is possible that these

allomerization products were formed from some unreacted Chl *b* enolate anion in the first partition step of the work-up, where plenty of triplet oxygen, water and presumably also hydroxide ion were present. Further, it seems also possible that the strongly basic conditions hindered protonation of the Chl *b* 13^2-oxide anion (**23**, Scheme 3), which, due to its negative charge, would be distributed largely into the aqueous phase of the first hexane/water partition system. Such a hindrance would explain why a noticeable part of 13^2-HO-Chl *b* was found in the water phase, because the negative charge of its anion would make it highly soluble in water. This interpretation is supported by the observation that the formation of the side-products **17** was largely avoided and the yield of 13^2(*S*/*R*)-HO-Chl *b* was improved by increasing the volume of hexane and using 0.1 M phosphate buffer, pH 5.5, instead of water in the first washing of the hexane solution of the reaction mixture [cf. the synthesis of 13^2(*S*/*R*)-HO-Chl *b* with (+)-CSOAI]. These changes in the work-up also seemed to lessen the difficulty encountered in the handling of the polar Chl *b* derivatives, which had a high tendency to form aggregates and emulsions on equilibrating the hexane phase with water in the work-up.

3. Conclusions

The results obtained verify that the use of the sterically hindered reagents, (−)- or (+)-CSOAI (oxidant) and DBU (base), results in a high total yield of 13^2(*S*/*R*)-HO-Chl *a* or 13^2(*S*/*R*)-HO-Chl *b*, starting from 13^2(*R*)-Chl *a* or -Chl *b*, respectively. Owing to steric factors, a high diastereoselectivity is also achieved using (−)-CSOAI, which affords 13^2(*R*)-HO-Chl as the prevailing diastereomer. The mechanism of the reactions involves the formation of the Chl enolate anion, which can be envisaged as an ambident nucleophile, attacking, in the transition state of the reaction, as the 13^2-carbanion the oxygen atom of the oxaziridine ring of CSOAI. Several factors were found possible to explain the differences observed in the oxidation results of Chl *a* and Chl *b*. The synthesis procedures described in this article represent the best methods so far developed for the preparation 13^2(*S*/*R*)-hydroxychlorophylls *a* and *b*, both regarding the regioselectivity and the stereoselectivity of the reactions.

4. Experimental

4.1. Reagents, solvents and preparation of Chl *a* (1) and Chl *b* (5)

(1*R*)-(−)-(10-Camphorsulfonyl)oxaziridine (98%), (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (98%), and 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU (98%) were purchased from Aldrich and used without further purification. Et_2O (dried, stabilized with butylated hydroxytoluene, BHT), 1-PrOH, and 2-PrOH were of Merck's analytical grade purity and were used as provided, unless otherwise stated. THF (Merck, analytical grade, stabilized with BHT) was dried with Na wire and distilled just before use. Hexane (LabScan, HPLC grade) was distilled through a Vigreux column. Chloroform (Merck, LiChrosolv, stabilized with amylene) was dried with silica gel.

Chl *a* and Chl *b* were isolated from clover leaves by the method described earlier,[41] but since then modified for large-scale preparation.[42] The purity of each chlorophyll preparation was ascertained by electronic absorption spectra,[43] ^{1}H NMR spectra,[43] TLC on sucrose,[44] and NP-HPLC.[23] The spectroscopic properties of the preparations were identical with those described previously.[43] The ^{1}H NMR spectra showed water as the only impurity (present in a ratio smaller than 1:1). The sucrose TLC with fluorescence detection under UV light (λ=366 nm) and NP-HPLC revealed trace amounts of Chl *a*′ (13^2(*S*)-Chl *a*] and pheophytin *a* in the Chl *a* preparation, and a small amount (<1%) of Chl *b*′ in the Chl *b* preparation.

4.2. Synthesis of 13^2(*S*/*R*)-hydroxychlorophylls *a* and *b*

4.2.1. Diastereoselective synthesis of 13^2(*R*)-hydroxychlorophyll *a* (4) with (−)-CSOAI (14). Solid 13^2(*R*)-Chl *a* (**1**) (20 mg, 0.22×10^{-4} mol) was weighed into a dry two-necked reaction flask (25 mL; the middle-neck was provided with a two-way stopcock, one way of which was connected to a vacuum pump and the other way to an argon balloon; the side-neck was provided with a septum) and dissolved in dry THF (10 mL). The solution was deaerated applying the freeze-pump-thaw technique with three cycles, after which an argon atmosphere was let to flow into the reaction flask. In another two-necked flask, (−)-CSOAI (**14**) (6.2 mg, 0.27×10^{-4} mol) was dissolved in THF (5.0 mL). DBU (3.5 mL, 0.022 mol) was measured into a third two-necked flask. Applying the freeze-pump-thaw technique, air was removed from both flasks and replaced with argon. Then the Chl *a* solution in the reaction vessel was cooled to a temperature of −25 °C on a bath consisting of a mixture of solid CO_2 and CCl_4, and vigorous magnetic stirring of the solution was started. The DBU solution at room temperature was withdrawn with a syringe through the septum from its flask and injected slowly into the reaction vessel. No clear change in the colour of the mixture (dark green) was observed on the addition of the base. After 15 min, the THF solution of (−)-CSOAI (**14**) was withdrawn with a syringe through the septum from its flask and injected into the reaction mixture. The progress of the reaction was followed by taking 0.1 mL aliquots of the reaction mixture, which were analyzed by TLC on sucrose (eluent: 1-PrOH/hexane, 1:99, w/w).[44] For TLC, hexane (3 mL) was added to each aliquot in a small separatory funnel and the solution was washed with distilled water (3×15 mL). The hexane solution was evaporated to dryness in a small tube with the aid of an argon stream, the residue dissolved in a suitable volume of Et_2O, and the solution applied with a capillary onto a sucrose TLC plate. After development, the components on the chromatogram were identified by comparing the R_f-values with those reported by Sahlberg and Hynninen.[44] As the reaction was not complete after 4 h, the reaction vessel was placed into a freezer (−20 °C) and kept overnight, without stirring. After 26 h, only a few percent of Chl *a* was left and, therefore the reaction was terminated by pouring the mixture into 80 mL of hexane in a separatory funnel. The hexane solution was washed with distilled water (3×150 mL) to remove all

water-soluble components. Judging from the pale wash water, only small amounts of dephytylated, water-soluble Chl derivatives, such as chlorophyllide, pheophorbide, and their hydroxylated derivatives, were formed in the reaction. The washed hexane solution of the products was evaporated to dryness at reduced pressure by a rotary evaporator.

The oxidation products were purified by MPLC on a semi-preparative sucrose column. The sample for chromatography was prepared by dissolving the residue in the rotary evaporator flask in 2 mL of Et_2O and adding 8 mL of the eluent (THF/2-PrOH/hexane, 0.5:1.0:98.5, w/w/w) to the solution. Isocratic elution resolved the main products as a separate zone from the two faster migrating zones, containing non-reacted Chl *a* and its $13^2(S)$-epimer, Chl *a*′. The combined fractions of each zone were evaporated to dryness by a rotary evaporator and the possible small amount of water removed from the samples by chloroform co-distillation (three times).[23] The residual solvents were removed from the samples on a vacuum line (0.01 mbar). The yield of the main product, 13^2-HO-Chl *a*, was 14.5 mg (71%) and that of Chl *a* and Chl *a*′ 3.6 mg (18%). The spectrometric data of the main product (^{1}H and ^{13}C NMR spectra, UV–vis spectrum, and ESI-MS) were consistent with the structural data published earlier for $13^2(R)$-HO-Chl *a*.[24] The $13^2(S)$- and $13^2(R)$-diastereomers of HO-Chl *a* were only partially resolved from one another by MPLC on the sucrose column, but were completely resolved by NP-HPLC. A 94% diastereomeric excess for $13^2(R)$-HO-Chl *a* was obtained by NP-HPLC (Fig. 1a).

4.2.2. Synthesis of $13^2(S/R)$-hydroxychlorophyll *a* (3/4) with (+)-CSOAI (15). The synthesis procedure was nearly equivalent to that used in the diastereoselective synthesis of $13^2(R)$-HO-Chl *a*. Some differences were, however, introduced. The amounts of reagents and THF were doubled and (−)-CSOAI (**14**) was replaced with (+)-CSOAI (**15**). The addition of DBU into the reaction flask (50 mL) turned instantly the dark green colour of the reaction mixture reddish, indicating the formation of the Chl enolate anion. The (+)-CSOAI, dissolved in THF (10 mL), was injected into the reaction mixture after 5 min from the addition of DBU while the temperature stayed at −25 °C. The reaction was monitored by sucrose–TLC with THF/2-PrOH/hexane (0.5:2.0:97.5, w/w/w) as eluent. This more polar eluent resolved the $13^2(S)$- and $13^2(R)$-diastereomers of HO-Chl *a* into two separate spots. As the reaction was not complete after 8 h, the reaction flask was placed into a freezer (−20 °C) for 15 h. After a total reaction time of 29 h, only a trace of Chl *a* was observed on the sucrose TLC plate under UV-light by fluorescence emission. Hence, the reaction mixture was poured into 200 mL of hexane in a separatory funnel and the hexane phase was washed with distilled water (6×330 mL).

The oxidation products were purified by MPLC on a semi-preparative sucrose column. The sample for chromatography was prepared by evaporating the hexane solution of the products to near dryness, dissolving the residue in the rotary evaporator flask in 4.0 mL of Et_2O and adding 16 mL of the eluent (THF/2-PrOH/hexane, 0.5:1.0:98.5, w/w/w) to the solution. Isocratic elution resolved the main products as a separate zone from the faster migrating two zones, containing the non-reacted Chl *a* and its $13^2(S)$-epimer, Chl *a*′. The $13^2(S/R)$-HO-Chl *a* zone was followed by a small amount (ca. 1 mg) of a bluish component, identified as the 15^2-methyl, 17^3-phytyl ester of Mg-unstable chlorin-7 (**16**) [Mg-3^1,3^2-didehydro-15^1,15^1-dihydroxy-rhodochlorin-15-acetic acid-15^1(*S*/*R*)-δ-lactone],[9,23,28–33] on the basis of the UV–vis spectrum, λ_{max} in Et_2O at 651.5 (0.474), 605 (0.074), 562 (0.036), 519 (0.032), 483 (0.018), 417.0 (1.000) nm, and by converting the lactone diastereomers with diazomethane to the 13^1,15^2-dimethyl, 17^3-phytyl ester of Mg-purpurin-7 (**18**) [Mg-3^1,3^2-didehydro-rhodochlorin-15-glyoxylic acid];[9,23,28–30,33] UV–vis spectrum: λ_{max} in Et_2O at 669.0 (0.394), 572 (0.088), 525 (0.038), 495 (0.025), 422.0 (1.000) nm.

Only traces of immobile pigments were retained in the pre-column. The combined effluent fractions of each zone were evaporated to dryness at reduced pressure and the possible small amount of water removed from the samples by chloroform co-distillation (three times). The residual solvents were removed from the samples on a vacuum line (0.01 mbar). The yield of the main products, $13^2(S/R)$-HO-Chl *a*, was 38.4 mg (90%) and that of Chl *a* and Chl *a*′ 2 mg (5%). A 10% diastereomeric excess for $13^2(R)$-HO-Chl *a* was obtained by NP-HPLC (Fig. 1b). The spectrometric data of the main products (^{1}H and ^{13}C NMR spectra, UV–vis spectrum, and ESI-MS) were consistent with the structural data published earlier for $13^2(S)$- and $13^2(R)$-HO-Chl *a*.[24] The ^{1}H and ^{13}C NMR assignments for **3** and **4** appear from Tables 1 and 2. ESI-MS: *m*/*z* 909.4 $(M+1)^+$; $C_{55}H_{72}N_4O_5Mg$ requires 908.5. UV–vis spectrum in Et_2O: λ_{max} at 661.6 (0.847), 614.5 (0.139), 573.5 (0.076), 530.3 (0.043), 429.3 (1.000) and 410.9 (sh, 0.761) nm.

4.2.3. Diastereoselective synthesis of $13^2(R)$-hydroxychlorophyll *b* (8) with (−)-CSOAI (14). The synthesis procedure corresponded to that used in the diastereoselective synthesis of $13^2(R)$-HO-Chl *a*, but double amounts of reagents were now used. $13^2(R)$-Chl *b* (**5**) (40.5 mg, 0.45×10^{-4} mol) was weighed into the reaction flask (50 mL) and dissolved in THF (20 mL). The addition of DBU (6.8 mL, 0.045 mol) to the solution immediately turned the dark green Chl *b* solution dark brown, indicating the formation of the Chl *b* enolate anion. Enolization seemed to occur more rapidly for Chl *b* than for Chl *a*. After 10 min, (−)-CSOAI (**14**) (12.2 mg, 0.53×10^{-4} mol) in THF (10 mL) was added to the solution at −25 °C. Monitoring of the reaction by sucrose TLC (eluent: 1-PrOH/hexane, 1.0:99.0, w/w) indicated that, after ca. 5 h from the addition of the oxidant, all of the original Chl *b* had reacted. Hence, after 6 h, the reaction mixture was poured into 350 mL of hexane and 1000 mL of water in a separatory funnel. On equilibrating the phases, a major part of the green pigments was distributed into the hexane phase, while a minor part went into the water phase. The partition work-up was hampered by the strong aptitude of the polar Chl *b* derivatives to form aggregates and emulsions. The hexane phase (ca. 350 mL) was washed with distilled water (2×1000 mL) and evaporated to dryness at reduced pressure. The products in the residue were purified by MPLC on a semi-preparative sucrose column (eluent: THF/2-PrOH/hexane, 0.5:1.0:98.5, w/w/w). The sample was prepared by dissolving the residue in the evaporator flask in 4 mL of Et_2O, to which 16 mL of the eluent was

added. In the MPLC, the aggregated and very polar pigments behaved as an immobile green material, firmly adsorbed on the sucrose of the pre-column. The 13^2(*S*)- and 13^2(*R*)-diastereomers of HO-Chl *b* were only partially resolved from one another by MPLC on the sucrose column. After high-vacuum treatment, their total yield was 16.6 mg (40%). The diastereomers (**7/8**) were completely resolved by NP-HPLC (Fig. 2a). A 66% diastereomeric excess for 13^2(*R*)-HO-Chl *b* was obtained by NP-HPLC (Fig. 2a).

The green pigments, distributed into the water phase, were discarded after they were analyzed by TLC on sucrose (eluent: 1-PrOH/hexane, 1.0:99.0, w/w). For TLC, the pigments were salted out with NaCl into Et_2O (LabScan) from the water phase. The TLC results showed that the water phase contained 13^2-HO-Chl *b* (ca. 80% of the water-phase pigments) and a very polar Chl *b* derivative (ca. 20%). The latter was identified as the Mg-15^1(*S/R*)-HO-lactone **17** from Chl *b*, that is, the 15^2-methyl, 17^3-phytyl ester of Mg-unstable rhodin [Mg-3^1,3^2-didehydro-15^1,15^1-dihydroxy-7^1-oxo-rhodochlorin-15-acetic acid-15^1(*S/R*)-δ-lactone] [15,28,29,31] on the basis of the UV–vis spectrum, [λ_{max} in Et_2O at 630.0 (0.218), 584 (0.055), 535 (0.037), 443.0 (1.000) nm] and ESI-MS [$(M+1)^+$ at *m/z* 939.6; $C_{55}H_{70}N_4O_8Mg$ requires 938.5], and by converting the lactone diastereomers with diazomethane to the 13^1,15^2-dimethyl, 17^3-phytyl ester of Mg-*b*-purpurin-7 (**19**) [Mg-3^1,3^2-didehydro-7^1-oxo-rhodochlorin-15-glyoxylic acid];[15,28,29] UV–vis spectrum: λ_{max} in Et_2O at 639.0 (0.154), 535 (0.037), 447.0 (1.000) nm. The identification of the latter compound was confirmed by co-elution with an authentic compound[15] on a sucrose TLC plate. As shown below, the yield of 13^2(*S/R*)-HO-Chl *b* can be improved by increasing the volume of hexane in the work-up and by using 0.1 M phosphate buffer, pH 5.5, instead of pure water when washing the hexane solution of the reaction mixture for the first time.

4.2.4. Synthesis of 13^2(*S/R*)-hydroxychlorophyll *b* (7/8) with (+)-CSOAI (15). As in the preceding cases, the synthesis was carried out at −25 °C under an argon atmosphere. 13^2(*R*)-Chl *b* (**5**) (32.9 mg, 0.36×10^{-4} mol) was weighed into the reaction flask (50 mL) and dissolved in THF (17 mL). The addition of DBU (4.3 mL, 0.029 mol) to the solution immediately turned the dark green Chl *b* solution dark brown, indicating the formation of the Chl *b* enolate ion. After 3 min, (+)-CSOAI (**15**) (10 mg, 0.44×10^{-4} mol) in THF (10 mL) was added to the solution. With 0.029 mol of DBU, the oxidation seemed to take place fast. Therefore, the reaction mixture was poured after 1 h 18 min into a separatory funnel, containing 500 mL of hexane and 500 mL of 0.1 M phosphate buffer, pH 5.5. The partial distribution of 13^2(*S/R*)-HO-Chl *b* into the water phase and the formation of the Mg-unstable rhodin side-products **17** was largely avoided by increasing the volume of hexane and using the phosphate buffer when washing the hexane solution of the products for the first time. In the second and third washings, distilled water was used. After the washings, the hexane solution was evaporated to dryness at reduced pressure. The products in the residue were purified by MPLC on a semi-preparative sucrose column (eluent: THF/2-PrOH/hexane, 0.5:1.0:98.5, w/w/w). The sample was prepared by dissolving the residue in the evaporator flask in 4 mL of Et_2O+3 mL of THF +25 mL of the eluent. The 13^2(*S*)- and 13^2(*R*)-diastereomers of HO-Chl *b* were only partially resolved from one another by MPLC on the sucrose column. After high-vacuum treatment, their total yield was 20.1 mg (60%). The diastereomers (**7/8**) were completely resolved by NP-HPLC (Fig. 2b). An 8% diastereomeric excess for 13^2(*R*)-HO-Chl *b* was obtained by NP-HPLC (Fig. 2b). The ^{1}H and ^{13}C NMR assignments for **7** and **8** appear from Tables 1 and 2. ESI-MS: *m/z* 923.6 $(M+1)^+$; $C_{55}H_{70}N_4O_7Mg$ requires 922.5. UV–vis spectrum in Et_2O: λ_{max} at 642.5 (0.360), 593.6 (0.067), 566.0 (0.047), 452.1 (1.000) and 429.1 (sh, 0.335) nm.

4.3. Semi-preparative MPLC separations on a sucrose column

The semi-preparative MPLC separations of the Chl derivatives on a sucrose column were carried out using an equipment composed of a pump (Büchi 688), a separation column (Büchi 685, height 500 mm, i.d. 35 mm), a pre-column (Büchi, height 150 mm, i.d. 10 mm), and an argon-pressured feeding column for samples (Büchi). The separation column was packed with powdered sugar (Finnsugar Ltd, Suomen Sokeri Oy, FI-02460 Kantvik, Finland), having the following properties: mean particle size 0.035 mm, sucrose 98.4%, water 0.10%, tricalcium phosphate 1.5% and sulfur dioxide max. 10 mg/kg. The sugar was passed through a 180 μm sieve and mixed with hexane to form a suitable suspension, which was poured into the column. The sugar was allowed to settle while occasionally rotating the column in an upright position clockwise and counterclockwise about its long axis. The layer was made compact by pumping eluent through it until no settling movement was observed (pump pressure was then 20 bar). The separation column was packed up to the top of the column so that there was no void volume above the sugar layer. The use of the pre-column, which was packed in a similar fashion, proved important, because it retained the aggregated and very polar impurities of the Chl samples, preventing the impurities from spreading into the main sugar column. Thus, there was no need to repack the main column for every new separation; one only had to repack the pre-column. This enabled us to perform even 15 separations with the same sugar packing in the main column. The flowing rate of liquid in the separations was 2–10 mL/min, corresponding to the pump pressure of 2–15 bar. A rise in the pump pressure indicated obstruction of the sugar layer. THF–2-PrOH–hexane was used as eluent, varying the ratio of the solvent components in different separations. To avoid aggregation of Chl derivatives in the feeding procedure, the solvent for the sample to be fed had to be more polar than the eluent.

4.4. High-performance liquid chromatography

The use of semi-preparative and analytical NP-HPLC silica columns has been previously described by our group to separate various oxidation products of chlorophylls *a* and *b*.[15,23,24] The silica column, LiChrospher Si 60 (250×4.0 mm, 5 μm, Merck), was employed in this work to determine the de for the synthesis products. A complete resolution between the 13^2(*S*)- and 13^2(*R*)-diastereomers of HO-Chl *a* was achieved using 2-PrOH/hexane, 1.0:99.0,

v/v, as eluent (Fig. 1). The same solvent system with a higher proportion of the polar solvent, that is, 2-PrOH/hexane, 2.0:98, v/v, resolved completely the $13^2(S)$- and $13^2(R)$-diastereomers of HO-Chl *b* (Fig. 2). The solvent system for each 13^2-HO-Chl sample (THF/hexane, 10:90, v/v) had to be more polar than the eluent to avoid aggregation of the sample in the beginning of the separation. A 20 μL volume of a dilute solution of each 13^2-HO-Chl sample was injected into the apparatus. The flowing rate of the eluent was 1.0 mL min^{-1}. Absorbance of the effluent was monitored at 430 nm and the relative amounts of the diastereomers were obtained by integrating the concentration zones. The $13^2(R)$-diastereomer of HO-Chl *a* or HO-Chl *b*, completely characterized by NMR, served as an internal standard to determine the mutual order of the $13^2(S)$-and $13^2(R)$-diastereomers.

4.5. Spectrometric characterization of the products

We aimed at obtaining completely assigned ^1H and ^{13}C NMR spectra (Tables 1 and 2) for the $13^2(S)$- and $13^2(R)$-diastereomers of 13^2-HO-Chl *a* and 13^2-HO-Chl *b*, utilizing the two-dimensional (2D) techniques, ^1H,^{13}C HSQC and ^1H,^{13}C HMBC.[24,45,46] The 200 MHz ^1H NMR spectra were recorded on a Varian Gemini FT spectrometer. The 500 MHz ^1H, 125 MHz $^{13}C\{^1H\}$, 1D NOE, and 2D heteronuclear correlation NMR spectra were measured at room temperature on a Bruker Avance FT spectrometer. The NMR sample was prepared by dissolving in a 0.5 mm NMR tube 7–16 mg of purified Chl derivative in 0.7 mL of acetone-d_6 (ampoules from Fluka, 0.7 mL, *d*% 99.95, or from Euriso-Top, 0.75 mL, *d*% 99.8). The 1D NOE method[47,48] was used to determine the stereochemical configuration at C-13^2. For the $13^2(R)$-diastereomer, the NOE experiment showed correlations between the 13^4-CH_3 protons and the 17^1-CH_2/17^2-CH_2 protons, as well as between the 13^2-COH proton and the 17-CH proton, implying that these proton groups were spatially close to one another. In the case of the $13^2(S)$-diastereomer, such correlations could not be observed. The mass spectra were measured on a Mariner time-of-flight (TOF) mass spectrometer (PerSeptive Biosystems, Framingham, MA), using the positive-mode electrospray ionization (ESI), as described previously.[16] The electronic absorption spectra (UV–vis) were recorded on a Varian Cary 5E UV–vis–NIR spectrophotometer. The samples were dissolved in Et_2O (Merck, analytical grade, SeccoSolv).

Acknowledgements

We thank Dr. Kristiina Hyvärinen for helping us to carry out the normal-phase HPLC separations.

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Tetrahedron
Tetrahedron 62 (2006) 3423–3434

Palladium-mediated fragmentation of *meta* photocycloadducts using carbon based electrophiles. Part 1

Clive S. Penkett,[a,*] Rupert O. Sims,[a] Paul W. Byrne,[b] Lee Kingston,[c] Richard French,[a] Lauriane Dray,[a] Simon Berritt,[a] Jason Lai,[a] Anthony G. Avent[a] and Peter B. Hitchcock[a]

[a]*Department of Chemistry, University of Sussex, Brighton BN1 9QJ, UK*
[b]*Tocris-Cookson Ltd, Avonmouth, Bristol BS11 8TA, UK*
[c]*AstraZeneca R&D Charnwood, Loughborough LE11 5RH, UK*

Received 29 September 2005; revised 19 December 2005; accepted 12 January 2006

Available online 8 February 2006

Abstract—Substituted benzene derived *meta* photocycloadducts have been shown to undergo a fragmentation/arylation reaction under Heck reaction conditions to give bridged bicyclo[3.2.1] compounds in a highly atom-efficient manner. When an anisole derived *meta* photocycloadduct is used, a bridgehead ketone is generated. However, if an alkylbenzene derived *meta* photocycloadduct is used, a bridgehead alkene is formed. This strategy has been used to create novel enol ether and transient allyl silane compounds.
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1. Introduction

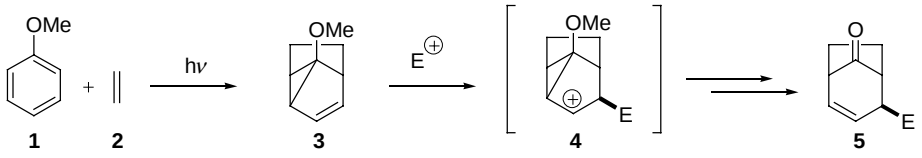
The remarkable *meta* photocycloaddition reaction[1] between an alkene and an arene has inspired considerable interest for the formation of complex polycyclic molecules.[2] Although generally stable under ambient conditions, *meta* photocycloadducts are highly strained chemical entities and hence are inclined to undergo relief of ring strain in the presence of certain reagents. Wender and co-workers[1d–f] have been the greatest exponent of this reaction's synthetic potential and they have used a variety of strategies to cleave the strained three-membered ring. Radical based methods involving dissolving metal conditions[3] and thiophenol[4] have been used to prepare the angular and linear fused triquinanes silphinene and coriolin, respectively. More commonly electrophiles have been employed in conjunction with anisole derived *meta* photocycloadducts, which add to the electron rich olefin portion of the oxygen-substituted photocycloadduct and the resulting cationic intermediate fragments to give a [3.2.1] bridged bicyclic ketone (Scheme 1).

In this context an acid[5] has acted as a source of H^+, bromine[6] or *N*-bromosuccinimide[7] as a source of Br^+ and *m*CPBA[7] as a source of OH^+ (via an epoxide), however, the synthetic potential of this reaction would be significantly enhanced if a carbocation-mediated equivalent could be developed. We reasoned that an aryl halide would behave as a carbon based electrophile in the presence of a palladium catalyst to cause an analogous fragmentation[8] and we now describe the Heck reaction of *meta* photocycloadducts.

2. Results and discussion

2.1. Arylation of anisole derived photoadducts

The palladium-mediated Heck reaction[9] has become one of the most versatile carbon–carbon bond forming methods



Scheme 1.

Keywords: Photoaddition; Palladium; Heck reaction; Tandem reaction; Atom efficiency; Allylsilane formation.
* Corresponding author. Tel.: +44 1273 877374; e-mail: c.s.penkett@sussex.ac.uk

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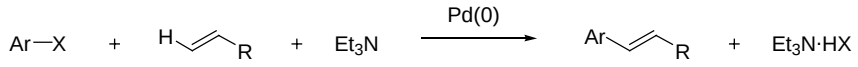
doi:10.1016/j.tet.2006.01.042



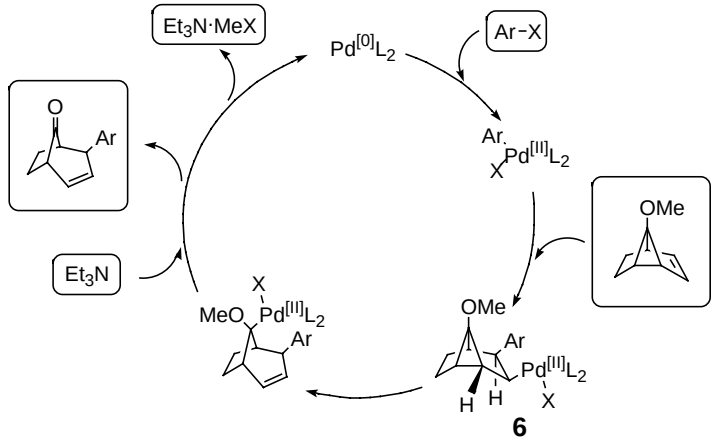
Scheme 2.

known to synthetic chemists. During this process an aryl halide is commonly coupled to an alkene in the presence of a palladium catalyst and a base to yield an arylated olefin along with a salt bi-product (Scheme 2).

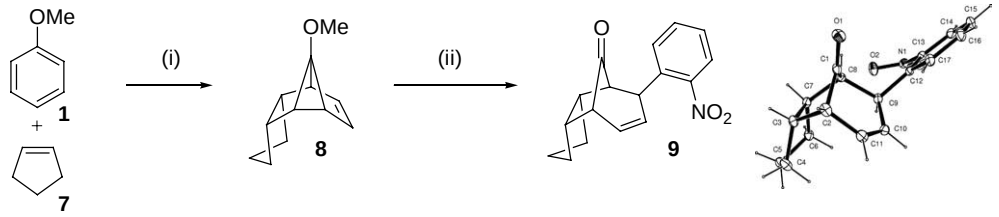
A modified version of the generally accepted catalytic cycle can be proposed for the reaction of an anisole derived *meta* photoadduct with an aryl halide in the presence of a palladium(0) catalyst (Scheme 3). The initial steps involving oxidative addition of the aryl halide with the palladium(0) catalyst and *syn* carbopalladation of the alkene portion are common to the classic mechanism, however, the rigid structure of **6** does not allow the carbon–palladium σ-bond to align *syn* with a β hydrogen atom. This prevents β-hydride elimination from taking place and cyclopropane ring fragmentation occurs as a consequence. The final stages of the catalytic cycle involve the formation of an arylated bicyclic ketone product and the regeneration of the palladium(0) catalyst with the assistance of the base.

To verify this proposed mechanism we carried out some preliminary studies using the simple anisole/cyclopentene sourced *meta* photocycloadduct **8**.[5] This was prepared predominantly as the *endo* isomer by irradiating a solution of anisole and cyclopentene in cyclohexane using 254 nm UV light, with the powerful electron donating properties of anisole's methoxy group directing the addition of the olefin between the 2- and 6- positions of the aromatic ring. This photoadduct **8** was separated from the crude photolysis mixture by distillation under reduced pressure and used without any further purification during the modified Heck reaction. Our initial attempt at a palladium-mediated arylation reaction involved heating a solution of the photoadduct **8** and 1-iodo-2-nitrobenzene in DMF with palladium(II) acetate and dppe ligand as the catalyst and triethylamine as the base.[10] The reaction mixture was heated at 80 °C until the starting material was no longer observed by TLC analysis and we were delighted to find that our predictions about the reactivity of the *meta* photocycloadduct proved correct for the formation of the desired fragmentation/arylation product **9** (Scheme 6). This compound was obtained in 20% yield as a yellow crystalline solid[8] and as expected the aryl group had been introduced onto the *exo*-face of the bridged bicyclic ketone **9** (Scheme 4).

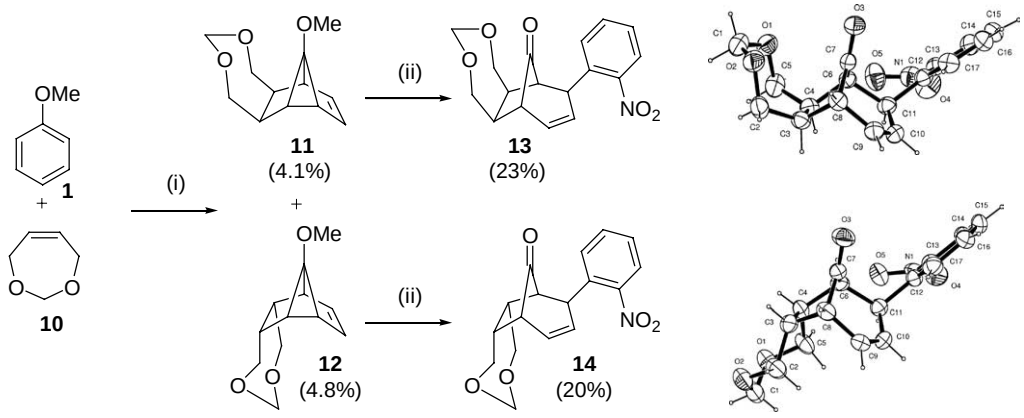
A second series of compounds was prepared from the photoadducts derived from anisole and *cis*-4,7-dihydro-1,3-dioxepin **10**. A solution of anisole and the alkene in cyclohexane was irradiated using 254 nm UV light and both *exo* and *endo* photoadducts (**11** and **12**) were isolated separately. These were then subjected to the same Heck reaction conditions using 1-iodo-2-nitrobenzene to afford the arylation/fragmentation products **13** and **14**, whose structures were again confirmed by X-ray crystallography[11a,b] (Scheme 5).



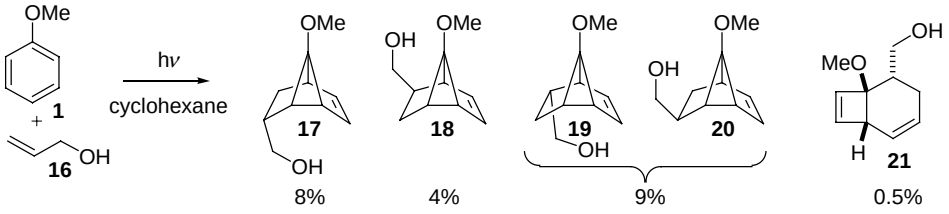
Scheme 3.



Scheme 4. Reagents and conditions: (i) hν, cyclohexane, 19%; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol%), dppe (5 mol%), NEt_3, DMF, 80 °C, 32 h, 20%.



Scheme 5. Reagents and conditions: (i) hν, cyclohexane; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol%), dppe (5 mol%), NEt_3, DMF, 80 °C, 32 h.



Scheme 6.

2.2. A gelsemine model

One of the initial aims of this research was to establish a rapid method of assembling the core structure of the alkaloid gelsemine **15**.[7,12] Gelsemine provides a unique challenge to the synthetic organic chemist, as six rings (one spirofused with another) and seven chiral centres (two of which are quaternary) are contained within its compact structure. The level of interest shown towards this alkaloid is probably more a reflection of its complex molecular architecture than any intrinsic biological activity and the varied strategies used for its assembly have been the focus of a recent review by Danishefsky and Lin.[13]

The basic carbon framework of gelsemine lends itself to being assembled by the fragmentation of an appropriate *meta* photocycloadduct. Preliminary studies were aimed at the formation of its core structure and were focused on the use of *meta* photocycloadducts derived from anisole and allyl alcohol. These were prepared by the irradiation of a solution of anisole and allyl alcohol in cyclohexane using 254 nm UV light. The electron donating properties of anisole's methoxy group directed the addition of the olefin between the 2- and 6- positions of the aromatic ring during the photochemical reaction and four *meta* photocycloadduct isomers were formed (Scheme 6). The 7-*endo* and the 6-*exo* isomers **17** and **18** could be obtained as single compounds, but the 6-*endo* and the 7-*exo* isomers **19** and **20** co-eluted as a mixture. In addition to these compounds a small amount of the *ortho* photoadduct **21** was also obtained. Although the percentage yields of products for this process tended to be low, multigram quantities of the desired photoadducts could be easily separated from the simple starting materials and it is difficult to conceive of a more straight-forward synthetic route to these complex products.

In our approach to gelsemine a nitrogen-substituted aryl group needed to be introduced onto the alkene of an appropriate *meta* photoadduct at what would become the C7 position of gelsemine (see Fig. 1). Fortunately the more plentiful 7-*endo* photocycloadduct **17** was also the isomer most closely related to the structure of gelsemine. When the same arylation conditions as before were used (heating a solution of the photoadduct **17**, 1-iodo-2-nitrobenzene, palladium(II) acetate, dppe and triethylamine in DMF at 80 °C), the familiar arylation/fragmentation reaction occured to provide compound **22**[8] in 21% yield (Scheme 7). It was interesting to note that an unprotected hydroxyl group in the substrate did not appear to significantly hinder the palladium(0) catalysed process.

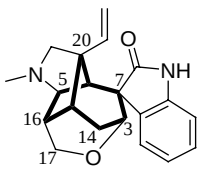
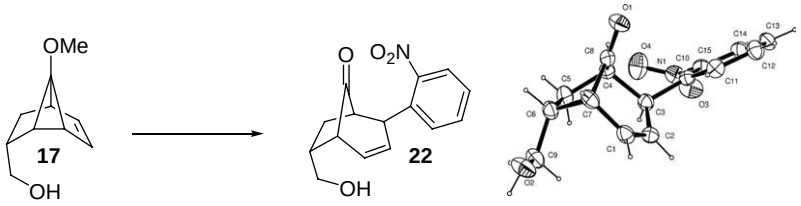


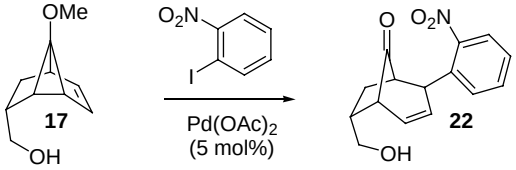
Figure 1. The alkaloid gelsemine **15** with its numbering system shown.

Various experiments were then undertaken with a view to improving the yield of **22** from **17** by altering the ligand, base, solvent, temperature and time of the reaction with the results being summarised in Table 1. Initially reactions were carried out at 80 °C and doubling the reaction time from 32 to 64 h had a detrimental effect on the yield of **22**. Silver salts are known to improve the reactivity of electron rich



Scheme 7. Reagents and conditions: 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol%), dppe (5 mol%), NEt_3, DMF, 80 °C, 32 h, 21%.

Table 1. Optimisation studies for the conversion of **17** to **22**



Variables: ligand, base, solvent, temperature, time, solvent.

Entry	Ligand	Base	Solvent	Temperature (°C)	Time (h)	Yield of **22** (%)
1	Dppe	NEt_3	DMF	80	32	21
2	Dppe	NEt_3	DMF	80	68	8
3	Dppe	$AgCO_3$	DMF	80	32	11
4	PPh_3	NEt_3	DMF	80	32	28
5	P(*o*-Tol)$_3$	NEt_3	DMF	80	32	36
6	P(*o*-Tol)$_3$	NEt_3	DMF	120	32	17
7	P(*o*-Tol)$_3$	NEt_3	DMF	120	24	24
8	P(*o*-Tol)$_3$	NEt_3	DMF	120	12	42
9	P(*o*-Tol)$_3$	NEt_3	DMF	120	8	37
10	P(*o*-Tol)$_3$	NEt_3	DMF	120	4	37
11	P(*o*-Tol)$_3$	NEt_3	DMF	120	2	35
12	P(*o*-Tol)$_3$	NEt_3	DMF	120	0.5	28
13	P(*o*-Tol)$_3$	NEt_3	DMSO	120	12	35
14	P(*o*-Tol)$_3$	NEt_3	Dioxane	120	12	0
15	P(*o*-Tol)$_3$	NEt_3	Acetonitrile	120	12	<5%

alkenes during Heck reactions,[14] but the use of silver carbonate as a base led to less **22** being obtained. Using the monodentate ligand triphenylphosphine instead of the bidentate dppe ligand brought about an improvement in yield indicating that cyclopropane fragmentation required a vacant coordination site, as the bidentate ligand appeared to slow down the rate of catalysis. The yield of **22** was further improved by the use of tri-*ortho*-tolylphosphine, which was advantageous as this ligand was known to exhibit good thermal stability at elevated temperatures.[9c] After raising the reaction temperature to 120 °C it was found that the highest yield of **22** was obtained after 12 h. Other solvents were used, but DMF remained the solvent of choice.

It was interesting to note that at the higher temperature of 120 °C another isomeric compound **23** (Fig. 2) was obtained and in the case of entry 8 (Table 1) **23** was obtained in 9% yield.

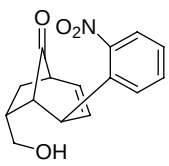


Figure 2. The minor isomeric compound **23**.

The presence of **23** in the product mixture indicates that the proposed mechanism in Scheme 4 is either flawed or another mechanism is operating, which may involve the formation of a π-allyl palladium species **24**[15] (Fig. 3). It may also be that this alternative reaction pathway only becomes significant at higher reaction temperatures.

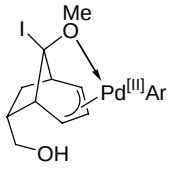
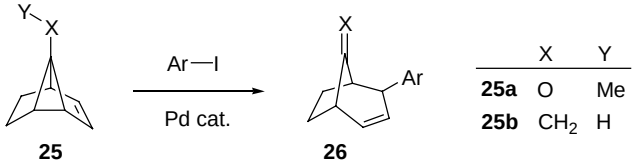


Figure 3. The proposed π-allyl palladium species **24**.

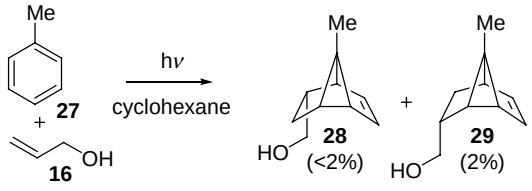
2.3. Formation of a bridgehead alkene using an alkylbenzene derived photoadduct

So far we had shown that *meta* photocycloadducts obtained from oxygen-substituted benzene derivatives would undergo a palladium-catalysed arylation/fragmentation process in the presence of an aryl halide. This transformation can be summarised as the conversion of **25a** to **26a** (Scheme 8) with X_a as oxygen and Y_a as methyl.



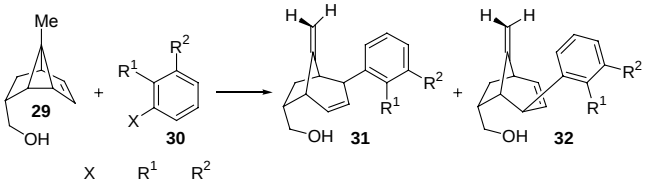
Scheme 8.

We wondered if X_b could be CH_2 and Y_b could be H and then employ palladium's versatile reactivity to initiate a similar arylation/fragmentation process of an alkyl substituted *meta* photoadduct **25b** to generate an alkenyl bridgehead compound **26b** (Scheme 9). To test this hypothesis a simple alkyl substituted *meta* photoadduct system was prepared by irradiating a solution of toluene and allyl alcohol in cyclohexane using 254 nm UV light. The electron donating methyl group directed *meta* addition of the alkene across the 2,6 positions of toluene during the photoreaction, however, only the 6 and 7-*endo* photoadducts **28** and **29** were obtained on this occasion (Scheme 9) and the 6-*endo* isomer **28** proved inseparable from a co-eluting impurity.



Scheme 9.

The 7-*endo* photoadduct **29** was reacted with a variety of aryl halides **30** using the best yielding conditions from the anisole variant **17** (Table 1, entry 8) and as predicted a range of [3.2.1] bicyclic dienes were formed that exhibited a methylene group at the bridgehead position instead of a ketone (Scheme 10). Again a major isomer **31** and a minor isomer **32** were formed in a similar fashion to the anisole variants **22** and **23** and we found the reaction to be equally tolerant of electron rich bromides as to electron-poor iodides, but the less reactive chlorobenzene failed to afford any arylation products. The spectroscopic details of the minor 1-bromo-3-methylbenzene derivative **32b** are not quoted in the Section 4 as it could not be obtained free of co-eluting impurities.



	X	R^1	R^2				
30a	I	NO_2	H	**31a**	29%	**32a**	13%
30b	Br	H	Me	**31b**	30%	**32b**	<10%
30c	Cl	H	H	**31c**	0%	**32c**	0%

Scheme 10. Reagents and conditions: $Pd(OAc)_2$ (5 mol%), P(*o*-Tol)$_3$, (10 mol%), NEt_3, DMF, 120 °C, 12 h.

2.4. Tandem formation of an allylsilane and an enol ether

Inspired by Fleming's allylsilane approach[16] to create the key quaternary centre at the C20 position of gelsemine (Fig. 1), we contemplated a novel strategy for preparing a similar bridgehead allylsilane using a version of the chemistry described above. We have shown that the arylation/fragmentation of a simple methylbenzene-derived photoadduct would give rise to a [3.2.1] bicycle with an alkene at the bridgehead position and conceived that a similar alkene could also form part of an allylsilane unit (see compound **33**, Fig. 4).

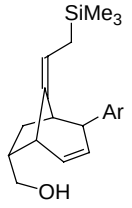
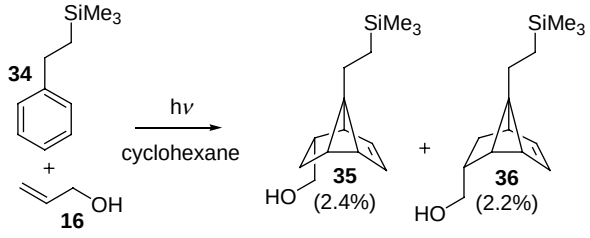


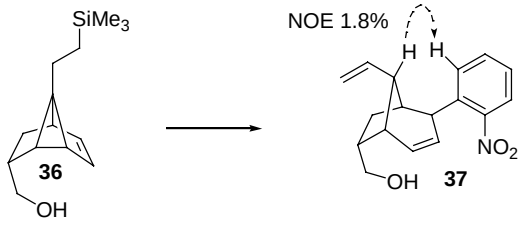
Figure 4. Compound **33** with a bridgehead allylsilane unit.

An appropriate photoadduct to attempt this arylation/fragmentation reaction was prepared by the irradiation of a solution of trimethyl phenethyl silane **34**[17] and allyl-alcohol in cyclohexane using 254 nm UV light. Two *meta* photoadducts were isolated from the crude reaction mixture after chromatographic separation and their structures were identified as the 6 and 7-*endo* isomers **35** and **36** using NMR techniques (Scheme 11).



Scheme 11.

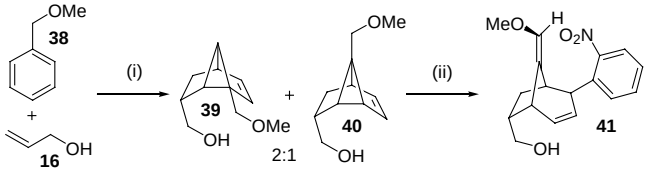
After subjecting the 7-*endo* isomer (**36**) to the arylation/fragmentation process, compound **37** was obtained after chromatographic separation from the crude reaction mixture (Scheme 12). It would appear that a bridgehead allylsilane similar to compound (Fig. 4) had formed, but underwent



Scheme 12. Reagents and conditions: 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol%), P(*o*-Tol)$_3$, (10 mol%), NEt_3, DMF, 120 °C, 12 h, 15%.

proto-desilylation to give the vinyl group under the reaction conditions. It is interesting to note that the hydrogen atom at the bridgehead position had been introduced on to what was the more sterically encumbered face of the allylsilane next to the aryl group during the proto-desilylation stage. This reaction was repeated in the presence of Eschenmoser's salt in the hope of trapping the in situ formed allylsilane **33** with an iminium ion, but the same proto-desilylated compound **37** was obtained again. In an attempt to form a more stable allylsilane variant during the arylation/fragmentation stage, triisopropyl phenethyl silane was prepared using the same procedure as for compound **34** and irradiated in the presence of allylalcohol, however, no evidence could be found of *meta* photocycloaddition between the two.

During the course of studying enantioselective intramolecular versions of the Heck reaction, Overman and Shibasaki showed how silyl enol ethers could be prepared in high yield from silyl protected allylic alcohols.[18] The apparent stability of these functional groups under Heck reaction conditions led us to contemplate the formation of an enol ether at the bridgehead position after initiating an arylation/fragmentation procedure on an appropriate *meta* photocycloadduct. Various benzyl silyl ethers were prepared and irradiated in the presence of allyl alcohol, but no evidence of *meta* photocycloaddition could be detected. However, benzyl methyl ether did undergo *meta* photocycloaddition with allyl alcohol, although the 2,6 *meta* photoadduct isomer of interest (**40**) co-eluted with what was tentatively assigned as the 2,4 *meta* photoadduct isomer **39**. This mixture was subjected to the arylation/fragmentation process and afforded the bridgehead methyl enol ether compound **41** (Scheme 13).



Scheme 13. Reagents and conditions: (i) hν, cyclohexane, 6.8%; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%), NEt_3, DMF, 120 °C, 12 h, 15%.

3. Conclusion

A unique fragmentation/carbon–carbon bond forming process has been shown to occur when a Heck reaction is performed with various *meta* photocycloadducts for the formation of complex polycyclic compounds. The degree of added molecular complexity after only two synthetic operations is remarkable and, depending on the nature of the substituted benzene used during the photoaddition stage, [3.2.1] bicycles can be prepared with either a ketone or an alkene at the bridgehead position. This methodology has been shown to be tolerant of unprotected hydroxyl groups and its versatility has been demonstrated for the formation of bridgehead ketones, alkenes, enol ethers and in situ generated allylsilanes.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Bruker DPX300, Varian unityINOVA-400 or Bruker AMX500 Fourier transform spectrometers at 300, 400 or 500 MHz, respectively. Chemical shifts (δ) are quoted in ppm using tetramethylsilane or residual chloroform as internal reference (δ= 0.00 ppm), and coupling constants (J) are quoted in Hz. ^{13}C NMR spectra were recorded using the same instruments, and chemical shifts (δ) are quoted in ppm using $CDCl_3$ as internal reference (δ=77.0 ppm).

IR spectra were recorded on Perkin-Elmer Spectrum One Fourier transform instruments and frequencies (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Low- and high-resolution electron impact (EI) and chemical impact (CI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionisation (ESI) mass spectra were recorded using a Bruker Daltonics APEXIII instrument.

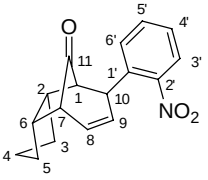
The starting materials for the synthesis of the compounds were obtained from the usual suppliers (Sigma–Aldrich–Fluka, Lancaster, Fisher etc.) unless otherwise stated. The anhydrous solvents were obtained from Aldrich Chemicals in Sure/Seal™ bottles and were used without further purification. Petrol refers to petroleum ether with a boiling range of 40–60 °C. Flash column chromatography was performed using Fisher Matrex 60 (35–70 μm) silica. Analytical thin-layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity) developed with UV light or an alkaline solution of potassium permanganate followed by heating to give yellow spots.

Irradiations were carried out in quartz immersion-well reactors fitted with 6 or 16 W low-pressure mercury vapour lamps or 125 or 400 W medium-pressure mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent for 15 min at rt. Experiments were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

4.1.1. *rac*-(1*R*,2*S*,6*R*,7*R*,10*S*)-10-(2′-Nitrophenyl)tricyclo[5.3.1.0^{2,6}]undec-8-en-11-one 9. A solution of anisole (34.5 g, 320 mmol) and cyclopentene (21.8 g, 320 mmol) in cyclohexane (270 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 10 min. This solution was then irradiated with short wavelength UV light for 35 h using a 400 W medium-pressure mercury vapour lamp. The solvent and unreacted starting materials were removed in vacuo and the residue was distilled under reduced pressure using an oil rotary pump to yield the photoadduct as a colourless oil (10.7 g, 19%). This photoadduct was primarily the 2,6 *endo* adduct

and was used without further purification during the arylation reaction.

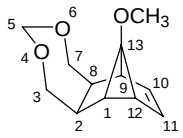
A mixture of the *endo meta* photoadduct (4.00 g, 23.4 mmol), 2-iodo-1-nitrobenzene (5.80 g, 23.4 mmol), triethylamine (89 mg, 0.88 mmol), palladium (II) acetate (260 mg, 1.16 mmol) and 1,2-bis(diphenylphosphine) ethane (466 mg, 1.17 mmol) and dry DMF (70 ml) was heated at 80 °C for 32 h. The reaction was poured into 2 M hydrochloric acid (150 ml) and the aqueous portion was washed with ethyl acetate (3×150 ml). The combined organics were washed with brine (150 ml), water (150 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography to afford the product **9** (1.32 g, 20%) as a yellow crystalline solid (for crystallographic details see Ref. 8) mp 147–149 °C.



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.9 (6H, m, H-3, H-4, H-5), 2.4–2.6 (4H, m, H-1, H-2, H-6, H-7), 4.60 (1H, m, H-10), 5.51 (1H, ddd, J=1.2, 3.4, 9.2 Hz, H-9), 5.94 (1H, dd, J=6.2, 9.2 Hz, H-8), 7.23–7.32 (2H, m, H-4′, H-6′), 7.44 (1H, t, J=7.6 Hz, H-5′), 7.83 (1H, d, J=8.1 Hz, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.7, 28.0, 40.3, 43.7, 47.2, 48.2, 52.0, 124.9, 127.9, 129.1, 130.6, 133.2, 133.5, 136.1, 148.2, 214.8; IR 1605, 1740, 2923 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{17}H_{17}NNaO_3$ $[M+Na]^+$ 306.1101, found 306.1083.

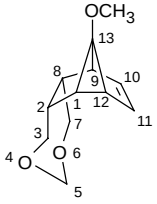
4.1.2. *rac*-(1*S*,2*S*,8*R*,9*S*,13*R*)-13-Methoxy-4,6-dioxatetracyclo[7.3.1.0.^{2,8}0^{12,13}]tridec-10-ene (*exo* isomer) 11 and *rac*-(1*S*,2*R*,8*S*,9*S*,13*R*)-13-methoxy-4,6-dioxatetracyclo-[73.1.0.^{2,8}0^{12,13}]tridec-10-ene (*endo* isomer) 12. A solution of anisole (1.35 g, 12 mmol) and *cis*-4,7-dihydro-1,3-dioxepin (1.29 g, 12 mmol) in cyclohexane (175 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 10 min. This solution was then irradiated with 254 nm UV light for 16½ h using a 6 W low-pressure mercury vapour lamp. The solvent was removed in vacuo and the residue subjected to column chromatography (silica, petrol/ether 3:1) to obtain the *exo* isomer **11** (0.105 g, 4.1%) and *endo* isomer **12** (0.113 g, 4.5%) as light green oils.

Compound **11**



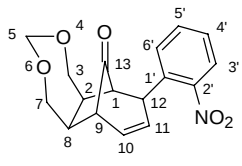
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (1H, m, H-2a), 2.09 (1H, dd, J=1.6, 8.4 Hz, H-1), 2.21 (1H, m, H-8a), 2.22 (1H, ddd, J=1.4, 2.4, 8.4 Hz, H-12), 2.79 (1H, d, J=2.7 Hz, H-9), 3.30 (3H, s, OCH_3), 3.72 (1H, ddd, J=0.9, 4.5, 12.0 Hz, H-7a), 3.90 (1H, dd, J=3.4, 12.4 Hz, H-3b), 3.97 (1H, dd, J=2.7, 12.4 Hz, H-3a), 4.04 (1H, t, J=11.7 Hz, H-7b), 4.77 (1H, d, J=4.5 Hz, H-5b), 4.78 (1H, d, J=4.6 Hz, H-5a), 5.58 (1H, ddd, J=1.4, 2.7, 5.7 Hz, H-10), 5.64 (1H, dd, J=2.4, 5.7 Hz, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.5, 37.4, 40.7, 52.7, 56.0, 56.4, 66.6, 67.6, 89.9, 95.5, 127.5, 131.9; IR 1645, 2935, 3053 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.0992, found 231.0989.

Compound **12**



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (1H, ddd, J=1.2, 2.4, 8.4 Hz, H-12), 1.77 (1H, dd, J=6.3, 8.4 Hz, H-1), 2.07 (1H, ddd, J=1.6, 2.6, 5.7 Hz, H-9), 2.89 (1H, m, H-8b), 2.94 (1H, m, H-2b), 3.07 (3H, s, OCH_3), 3.20 (1H, dd, J=9.1, 12.5 Hz, H-7a), 3.51 (1H, ddd, J=0.4, 3.8, 12.0 Hz, H-3b), 3.58 (1H, dd, J=10.6, 12.0 Hz, H-3a), 3.65 (1H, dd, J=5.5, 12.5 Hz, H-7b), 4.22 (1H, d, J=6.3 Hz, H-5a), 4.93 (1H, d, J=6.3 Hz, H-5b), 5.42 (1H, ddd, J=0.4, 2.4, 5.8 Hz, H-11), 5.48 (1H, ddd, J=1.2, 2.6, 5.8 Hz, H-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 37.7, 47.6, 53.1, 54.1, 56.5, 70.3, 71.4, 92.0, 99.8, 131.0, 134.3; IR 1644, 2930, 3051 cm^{-1}; HRMS (EI) *m/z* calcd $C_{12}H_{17}O_3$ $[M+H]^+$ 209.1178, found 209.1170.

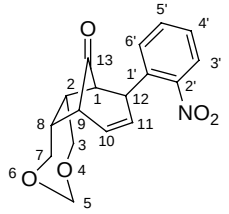
4.1.3. *rac*-(1*S*,2*R*,8*S*,9*R*,12*S*)-12-(2′-Nitrophenyl)-4,6-dioxatricyclo[7.3.1.0^{2,8}]tridec-10-en-13-one 13. A mixture of the *exo meta* photoadduct **11** (171 mg, 0.822 mmol), 2-iodo-1-nitrobenzene (222 mg, 0.891 mmol), triethylamine (89 mg, 0.88 mmol), palladium (II) acetate (7 mg, 0.03 mmol) and 1,2-bis(diphenylphosphine) ethane (57 mg, 0.14 mmol) and dry DMF (3.5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 80 °C for 32 h. The reaction was poured into water (50 ml) and acidified with 2 M HCl. The aqueous portion was washed with ethyl acetate (5×10 ml) and the combined organics washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/ethyl acetate 3:1) to afford the product **13** (60 mg, 23%) as an off-white crystalline solid (for crystallographic details see Ref. 11a) mp 190.6–191.3 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (1H, m, H-1), 2.45 (1H, dd, J=2.0, 7.2 Hz, H-9), 2.87 (2H, m, H-2a, H-8a), 3.81 (1H, ddm, J=6.6, 13.0 Hz, H-3), 3.86 (1H, ddm, J=3.8, 13.0 Hz, H-3), 4.01 (1H, ddm, J=5.7, 12.9 Hz, H-7), 4.06 (1H, ddm, J=3.1, 12.8 Hz, H-7), 4.64 (1H, d, J=6.7 Hz,

H-5b), 4.70 (1H, m, H-12a), 4.74 (1H, d, J=6.7 Hz, H-5a), 5.60 (1H, ddd, J=1.3, 3.5, 9.1 Hz, H-11), 6.27 (1H, ddd, J=1.3, 7.2, 8.9 Hz, H-10), 7.33 (1H, dd, J=1.4, 7.8 Hz, H-6′), 7.41 (1H, ddd, J=1.4, 7.4, 8.1 Hz, H-4′), 7.54 (1H, ddt, J=0.4, 1.4, 7.4 Hz, H-5′) 7.94 (1H, dd, J=1.4, 8.1 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.6, 48.2, 51.4, 53.3, 55.0, 72.0, 73.4, 99.2, 125.0, 127.2, 128.3, 130.1, 133.3, 134.5, 135.0, 148.3, 213.5; IR 1599, 1630, 1744, 2855, 2922 cm^{-1}; HRMS (ESI) m/z calcd $C_{17}H_{18}NO_5$ $[M+H]^+$ 316.1185, found 316.1196.

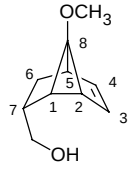
4.1.4. *rac*-(1*S*,2*S*,8*R*,9*R*,12*S*)-12-(2′-Nitrophenyl)-4,6-dioxatricyclo[7.3.1.0^{2,8}]tridec-10-en-13-one 14. A mixture of the *endo meta* photoadduct **12** (474 mg, 2.28 mmol), 2-iodo-1-nitrobenzene (615 mg, 2.46 mmol), triethylamine (474 mg, 2.43 mmol), palladium (II) acetate (19 mg, 0.084 mmol) and 1,2-bis(diphenylphosphine) ethane (157 mg, 0.394 mmol) and dry DMF (9 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 80 °C for 32 h. The reaction was poured into water (100 ml) and acidified with 2 M HCl. The aqueous portion was washed with ethyl acetate (5×25 ml) and the combined organics washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/ether 1:1) to afford the product **14** (143 mg, 20%) as a white crystalline solid (for crystallographic details see Ref. 11b) mp 198.0–198.4 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (1H, dd, J=5.6, 6.4 Hz, H-9), 2.75 (1H, d, J=7.6 Hz, H-1), 2.87 (1H, m, H-8a), 3.00 (1H, m, H-2a), 4.05 (2H, t, J=12.0 Hz, H-7b, H-3b), 4.27 (1H, dd, J=4.8, 12.8 Hz, H-7a), 4.53 (1H, d, J=7.2 Hz, H-5b), 4.59 (1H, dd, J=3.6, 12.0 Hz, H-3a), 4.75 (1H, m, H-12a), 5.18 (1H, d, J=7.2 Hz, H-5a), 5.69 (1H, dd, J=2.4, 8.8 Hz, H-11), 6.12 (1H, dd, J=7.2, 8.8 Hz, H-10), 7.27 (1H, d, J=8.2 Hz, H-6′), 7.43 (1H, dt, J=1.2, 7.8 Hz, H-4′), 7.56 (1H, dt, J=1.2, 7.6 Hz, H-5′) 7.99 (1H, d, J=8.4 Hz, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 43.6, 46.6, 47.9, 52.5, 71.1, 72.0, 100.0, 125.3, 128.4, 129.2, 130.4, 132.5, 133.3, 134.9, 148.1, 211.1; IR 1602, 1641, 1753, 2876, 2956 cm^{-1}; HRMS (ESI) m/z calcd $C_{17}H_{17}NNaO_5$ $[M+Na]^+$ 338.1004, found 338.1000.

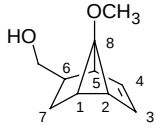
4.1.5. *rac*-(1*S*,2*R*,5*R*,7*R*,8*S*)-7-Hydroxymethyl-8-methoxytricyclo[3.2.1.0^{2,8}]oct-3-ene 17 and *rac*-(1*S*,2*R*,5*S*,6*R*,8*R*)-6-hydroxymethyl-8-methoxytricyclo[32.1.0^{2,8}]oct-3-ene 18 and *rac*-(1*S*,2*R*,6*R*)-1-methoxy-2-hydroxymethylbicyclo[42.0]octa-4,7-diene 21. A solution of anisole (43.2 g, 400 mmol) and allyl alcohol (46.4 g, 800 mmol) in cyclohexane (302 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with 254 nm UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed in vacuo and the residue subjected to column chromatography to obtain the *ortho* photoadduct **21** (350 mg, 0.5%), the 6-*exo* isomer **18** (2.65 g, 4%), a mixture of the 6-*endo* and 7-*exo* isomers **19** and **20** (6.0 g, 9%) and the 7-*endo* isomer **17** (5.3 g, 8%).

Compound **17**



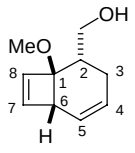
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (1H, dd, J=1.3, 12.9 Hz, H-6a), 2.05 (1H, br s, –OH), 2.09 (1H, ddd, J=0.6, 2.2, 8.5 Hz, H-2), 2.15 (1H, dd, J=6.2, 8.5 Hz, H-1), 2.43 (1H, ddd, J=6.6, 11.4, 12.9 Hz, H-6b), 2.75 (1H, m, H-7b), 3.18 (1H, ddd, J=1.3, 2.7, 6.8 Hz, H-5), 3.37 (3H, s, OCH_3), 3.51 (1H, dd, J=7.2, 10.3 Hz, –C*H*HO–), 3.59 (1H, dd, J=8.4, 10.3 Hz, –CH*H*O–), 5.57 (1H, dddd, J=0.6, 1.3, 2.7, 5.6 Hz, H-4), 5.65 (1H, dd, J=2.2, 5.6 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 38.9, 40.0, 44.9, 51.2, 56.2, 65.7, 91.4, 129.1, 136.5; IR 1645, 2933, 3403 cm^{-1}; HRMS (EI) m/z calcd $C_{10}H_{14}O_2$ $[M]^+$ 166.0994, found 166.0996.

Compound **18**



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (1H, ddd, J=1.4, 6.3, 13.9 Hz, H-7a), 1.68 (1H, dddd, J=0.5, 1.7, 6.7, 13.9 Hz, H-7b), 2.05 (1H, ddd, J=1.4, 6.3, 8.4 Hz, H-1), 2.06 (1H, dddd, J=0.5, 6.3, 7.0, 7.9 Hz, H-5), 2.10 (1H, br s, –OH), 2.18 (1H, dddd, J=0.6, 1.4, 2.4, 8.4 Hz, H-2), 3.12 (1H, dd, J=1.7, 2.7 Hz, H-5), 3.32 (3H, s, OCH_3), 3.58 (1H, dd, J=7.0, 10.6 Hz, –C*H*HO–), 3.69 (1H, dd, J=7.9, 10.6 Hz, –CH*H*O–), 5.55 (1H, ddd, J=1.4, 2.7, 5.7 Hz, H-4), 5.60 (1H, dd, J=2.4, 5.7 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 34.5, 36.6, 52.3, 53.1, 56.4, 63.6, 89.8, 126.8, 132.2; IR 1645, 2931, 3409 cm^{-1}; HRMS (ESI) m/z calcd $C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.0891, found 189.0885.

Compound **21**

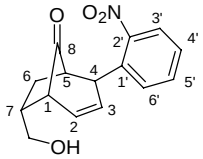


^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (1H, br s, –OH), 1.60–1.69 (1H, m, H-3), 1.94–2.06 (1H, m, H-2b, H-3), 3.35 (3H, s, –OCH_3), 3.36 (1H, dd, J=0.9, 5.7 Hz, H-6b), 3.54 (1H, dd, J=4.5, 10.6 Hz, –C*H*HO–), 3.71 (1H, dd, J=8.5, 10.6 Hz, –CH*H*O–), 5.70 (1H, dddd, J=0.5, 3.3, 5.9,

9.7 Hz, H-5), 5.87 (1H, ddd, J=2.1, 6.8, 9.6 Hz, H-4), 6.11 (1H, dd, J=0.9, 2.9 Hz, H-7), 6.15 (1H, d, J=2.9 Hz, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 42.3, 46.4, 50.9, 64.8, 88.1, 126.1, 129.4, 134.2, 139.6; IR 1644, 3419 cm^{-1}; HRMS (ESI) m/z calcd $C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.0891, found 189.0889.

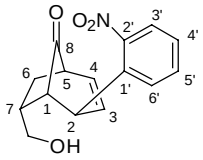
4.1.6. *rac*-(1*R*,4*S*,5*R*,7*R*)-4-(2′-Nitrophenyl)-7-hydroxymethylbicyclo[3.2.1]oct-2-en-8-one 22 and *rac*-(1*R*,2*R*,5*R*,7*R*)-2-(2′-nitrophenyl)-7-hydroxymethylbicyclo[3.2.1]oct-3-en-8-one 23. A mixture of the 7-*endo* allyl alcohol/anisole derived *meta* photoadduct **17** (330 mg, 1.21 mmol), 2-iodo-1-nitrobenzene (303 mg, 1.22 mmol), triethylamine (123 mg, 1.22 mmol), palladium (II) acetate (13 mg, 0.060 mmol) and tri-*ortho*-tolylphosphine (37 mg, 0.12 mmol) and dry DMF (4 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 120 °C for 12 h. The reaction was poured into 2 M hydrochloric acid (50 ml) and the aqueous portion was washed with ethyl acetate (5× 40 ml) and the combined organic portions were washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 1:1) to afford **22** (139 mg, 42%) as a yellow oil that became crystalline upon standing (for crystallographic details see Ref. 8) (mp 118.5–119.4 °C) and **23** (33 mg, 10%) as a pale yellow oil.

Compound **22**



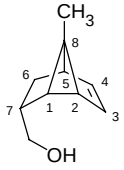
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (1H, ddd, J=1.5, 7.7, 13.5 Hz, H-6a), 1.67 (1H, br s, –OH), 2.44 (1H, ddd, J=8.4, 9.8, 13.5 Hz, H-6b), 2.54 (1H, dm, J=8.4 Hz, H-5), 2.59 (1H, m, H-7b), 2.83 (1H, ddd, J=1.5, 5.3, 6.8 Hz, H-1), 3.79–3.83 (2H, m, –CH_2O–), 4.56 (1H, ddm, J=1.1, 3.6 Hz, H-4a), 5.72 (1H, ddd, J=1.3, 3.6, 9.2 Hz, H-3), 6.14 (1H, ddd, J=1.1, 6.8, 9.1 Hz, H-2), 7.32 (1H, dd, J=1.4, 7.8 Hz, H-6′), 7.42 (1H, dt, J=1.4, 8.2 Hz, H-4′), 7.55 (1H, dt, J=1.3, 7.6 Hz, H-5′), 7.94 (1H, dd, J=1.4, 8.1 Hz, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 43.1, 47.4, 48.7, 55.0, 63.3, 124.8, 128.2, 129.1, 130.0, 131.0, 133.0, 134.9, 148.4, 214.5; IR 1606, 1632, 1751, 2871, 2931, 3415 cm^{-1}; HRMS (ESI) m/z calcd $C_{15}H_{15}NNaO_4$ $[M+Na]^+$ 296.0899, found 296.0901.

Compound **23**



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (1H, dd, J=4.7, 12.8 Hz, H-6a), 2.19 (1H, ddd, J=6.4, 10.6, 12.7 Hz, H-6b), 2.43 (1H, s, –OH), 2.6–2.7 (3H, m, H-1, H-5, H-7b), 3.81 (1H, dd, J=6.4, 10.9 Hz, –C*H*HO–), 4.09 (1H, dd, J=8.2, 10.9 Hz, –C*H*HO–), 4.79 (1H, dm, J=3.5 Hz, H-2a), 5.55 (1H, ddd, J=1.2, 3.6, 9.1 Hz, H-3), 6.27 (1H, ddd, J=1.1, 7.0, 9.1 Hz, H-4), 7.33 (1H, dd, J=1.4, 7.9 Hz, H-6′), 7.40 (1H, dt, J=1.4, 7.8 Hz, H-4′), 7.54 (1H, dt, J=1.4, 7.7 Hz, H-5′), 7.90 (1H, dd, J=1.4, 8.1 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.5, 36.7, 44.8, 46.1, 50.9, 64.1, 124.9, 127.6, 128.2, 130.6, 133.1, 135.1, 136.4, 148.3, 214.2; IR 1606, 1635, 1748, 2874, 2936, 3406 cm^{-1}; HRMS (ESI) m/z calcd $C_{15}H_{15}NNaO_4$ $[M+Na]^+$ 296.0899, found 296.0885.

4.1.7. *rac*-(1*R*,2*R*,5*R*,7*R*,8*R*)-7-Hydroxymethyl-8-methyltricyclo[3.2.1.0^{2,8}]oct-3-ene 29. A solution of total volume (400 ml) containing toluene (36.8 g, 400 mmol), allyl alcohol (46.4 g, 800 mmol) and cyclohexane was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with 254 nm UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed in vacuo and the residue subjected to column chromatography to obtain the 7-*endo* isomer **29** as a pale yellow oil (1.23 g, 2%).

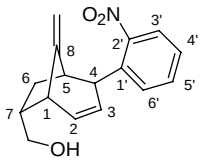


^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (3H, s, –CH_3), 1.48 (1H, br s, –OH), 1.48 (1H, d, J=12.8 Hz, H-6a), 1.53 (1H, dd, J=6.3, 7.1 Hz, H-1), 1.56 (1H, dm, J=7.2 Hz, H-2), 2.36 (1H, ddd, J=6.2, 11.3, 12.8 Hz, H-6b), 2.72–2.78 (1H, m, H-7b), 2.78 (1H, dm, J=6.0 Hz, H-5), 3.64 (1H, dd, J=7.3, 10.3 Hz, –C*H*HO–), 3.74 (1H, dd, J=8.4, 10.2 Hz, –CH*H*O–), 5.45 (1H, dddd, J=0.8, 0.8, 2.4, 5.3 Hz, H-4), 5.66 (1H, dd, J=2.0, 5.3 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 37.6, 37.9, 41.3, 45.6, 46.4, 54.6, 66.4, 129.8, 136.7; IR 1596, 2923, 3308 cm^{-1}; HRMS (EI) m/z calcd $C_{10}H_{14}O$ $[M]^+$ 150.1045, found 150.1045.

4.1.8. *rac*-(1*R*,4*S*,5*R*,7*R*)-4-(2′-Nitrophenyl)-7-hydroxymethyl-8-methylenebicyclo[3.2.1]oct-2-ene 31a and *rac*-(1*R*,2*R*,5*R*,7*R*)-2-(2′-nitrophenyl)-7-hydroxymethyl-8-methylenebicyclo[3.2.1]oct-3-ene 32a. A mixture of the 7-*endo* allyl alcohol/toluene-derived *meta* photoadduct **29** (150 mg, 1.00 mmol), 2-iodo-1-nitrobenzene (299 mg, 1.20 mmol), triethylamine (121 mg, 1.20 mmol), palladium (II) acetate (11 mg, 0.050 mmol) and tri-*ortho*-tolylphosphine (30 mg, 0.10 mmol) and dry DMF (3 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 120 °C for 12 h. The reaction was poured into 2 M hydrochloric acid (50 ml) and the aqueous portion was washed with ethyl acetate (5×40 ml) and the combined organic portions were washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O

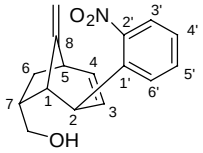
3:2) to afford **31a** (78 mg, 29%) as a yellow oil and **32a** (35 mg, 13%) as a yellow oil.

Compound **31a**



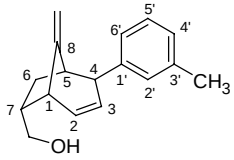
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (1H, ddd, J=1.2, 7.2, 13.4 Hz, H-6a), 1.65 (1H, br s, –OH), 2.29 (1H, ddd, J=7.8, 10.0, 13.3 Hz, H-6b), 2.42–2.49 (1H, m, H-7b), 2.66 (1H, dm, J=7.9 Hz, H-5), 2.96 (1H, ddd, J=1.1, 5.2, 6.4 Hz, H-1), 3.69 (1H, dd, J=9.2, 10.4 Hz, –C*H*HO–), 3.74 (1H, dd, J=6.1, 10.4 Hz, –CH*H*O–), 3.98 (1H, m, H-4a), 4.17 (1H, d, J=1.1 Hz, =C*H*H), 4.74 (1H, d, J=0.7 Hz, =CH*H*), 5.49 (1H, ddd, J=1.6, 3.6, 9.4 Hz, H-3), 6.13 (1H, ddd, J=1.7, 6.4, 9.3 Hz, H-2), 7.34–7.37 (2H, m, H-4′, H-6′), 7.50 (1H, ddd, J=1.4, 7.1, 8.4 Hz, H-5′), 7.87 (1H, ddd, J=0.7, 1.4, 7.8 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.1, 44.0, 46.4, 49.1, 50.3, 64.4, 102.9, 124.1, 127.2, 127.7, 131.7, 132.0, 132.5, 136.3, 148.8, 150.3; IR 1606, 1634, 2866, 2926, 3469 cm^{-1}; HRMS (ESI) *m*/*z* calcd $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1106, found 294.1101.

Compound **32a**



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dd, J=4.7, 12.2 Hz, H-6a), 1.60 (1H, br s, –OH), 2.06 (1H, dddd, J=0.8, 6.4, 11.3, 12.2 Hz, H-6b), 2.57–2.64 (1H, m, H-7b), 2.76 (1H, ddm, J=1.4, 6.9 Hz, H-1), 2.81 (1H, ddd, J=1.2, 5.8, 6.6 Hz, H-5), 3.75 (1H, dd, J=6.3, 11.1 Hz, –C*H*HO–), 3.97 (1H, dd, J=9.0, 11.1 Hz, –CH*H*O–), 4.22 (1H, m, H-2a), 4.23 (1H, d, J=1.1 Hz, =C*H*H), 4.74 (1H, m, =CH*H*), 5.34 (1H, ddd, J=1.5, 3.7, 9.2 Hz, H-3), 6.27 (1H, ddd, J=1.4, 6.6, 9.2 Hz, H-4), 7.37 (1H, ddd, J=1.5, 7.3, 8.1 Hz, H-4′), 7.41 (1H, dd, J=1.5, 7.9 Hz, H-6′), 7.52 (1H, ddd, J=1.4, 7.5, 7.5 Hz, H-5′), 7.88 (1H, ddd, J=0.3, 1.4, 8.1 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 41.5, 41.7, 42.7, 48.5, 64.8, 103.2, 124.3, 125.6, 127.3, 132.1, 132.5, 136.5, 137.8, 148.5, 150.6; IR 1640, 2955, 3422 cm^{-1}; HRMS (ESI) *m*/*z* calcd $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1106, found 294.1102.

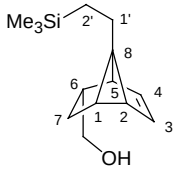
4.1.9. *rac*-(1*R*,4*S*,5*R*,7*R*)-4-(3′-Methylphenyl)-7-hydroxymethyl-8-methylenebicyclo[3.2.1]oct-2-ene 31b. A mixture of the 7-*endo* allyl alcohol/toluene-derived *meta* photoadduct **29** (150 mg, 1.00 mmol), 3-bromotoluene (205 mg, 1.20 mmol), triethylamine (121 mg, 1.20 mmol), palladium (II) acetate (11 mg, 0.050 mmol) and tri-*ortho*-tolylphosphine (30 mg, 0.10 mmol) and dry DMF (3 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 120 °C for 12 h. The reaction was poured into 2 M hydrochloric acid (50 ml) and the aqueous portion was washed with ethyl acetate (5×40 ml) and the combined organic portions were washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O 2:1) to afford **31b** (71 mg, 30%) as a yellow oil. The minor isomer **32b** (24 mg, <10%) was also obtained but could not be separated from some co-eluting impurites.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (1H, ddd, J=1.0, 7.1, 13.0 Hz, H-6a), 1.60 (1H, br s, –OH), 2.23 (1H, ddd, J=7.8, 10.1, 13.0 Hz, H-6b), 2.33 (3H, s, –CH_3), 2.39–2.46 (1H, m, H-7b), 2.51 (1H, dm, J=8.0 Hz, H-5), 2.89 (1H, ddd, J=1.0, 5.1, 6.4 Hz, H-1), 3.43 (1H, m, H-4a), 3.73–3.75 (2H, m, –CH_2O–), 4.20 (1H, d, J=1.4 Hz, =C*H*H), 4.71 (1H, d, J=0.8 Hz, =CH*H*), 5.59 (1H, ddd, J=1.5, 3.6, 9.4 Hz, H-3), 6.02 (1H, ddd, J=1.6, 6.4, 9.6 Hz, H-2), 6.98 (3H, m, H-2′, H-4′, H-6′), 7.17 (1H, t, J=7.5 Hz, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 33.4, 43.9, 47.5, 49.3, 56.3, 64.7, 102.0, 125.4, 127.0, 127.7, 129.0, 129.1, 130.8, 137.3, 142.7, 150.8; IR 1637, 2924, 3433 cm^{-1}; HRMS (ESI) *m*/*z* calcd $C_{17}H_{20}NaO$ $[M+Na]^+$ 263.1412, found 263.1414.

4.1.10. *rac*-(1*S*,2*R*,5*S*,6*S*,8*S*)-6-Hydroxymethyl-8-(2′-trimethylsilanylethyl)tricyclo[3.2.1.0^{2,8}]oct-3-ene 35 and *rac*-(1*R*,2*R*,5*R*,7*R*,8*R*)-7-hydroxymethyl-8-(2′-trimethylsilanylethyl)tricyclo[32.1.0^{2,8}]oct-3-ene 36. A solution of total volume (400 ml) containing phenethyltrimethyl silane[16] (14.2 g, 80 mmol), allyl alcohol (14 g, 240 mmol) and cyclohexane was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with UV light for 13 h using a 400 W medium-pressure mercury vapour lamp. The solvent and unreacted allyl alcohol were removed in vacuo and the residue subjected to column chromatography to obtain the 6-*endo* isomer **35** (453 mg, 2.4%) and the 7-*endo* isomer **36** (415 mg, 2.2%).

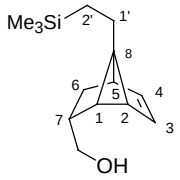
Compound **35**



^{1}H NMR (500 MHz, $CDCl_3$) δ −0.03 (9H, s, –Si(CH_3)$_3$), 0.47 (1H, ddd, J=5.0, 12.5, 14.2 Hz, Si–C*H*H–), 0.53 (1H, ddd, J=5.0, 12.5, 14.2 Hz, Si–CH*H*–), 1.22 (1H, ddd, J=1.5, 10.7, 13.0 Hz, H-7a), 1.44 (1H, ddd, J=1.5, 7.0, 7.0 Hz, H-1), 1.55 (1H, ddd, J=5.0, 12.6, 14.1 Hz, C(8)–CH*H*–), 1.61 (1H, m, H-2), 1.63 (1H, ddd, J=5.0, 12.6, 14.1 Hz, C(8)–C*H*H–), 1.78 (1H, br s, –OH), 1.89 (1H, dddd, J=1.4, 6.6, 7.9, 12.9 Hz, H-7b), 2.53–2.68 (1H, m,

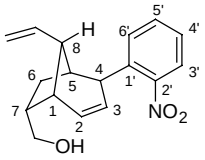
H-6b), 2.87 (1H, ddd, J=1.3, 2.4, 5.1 Hz, H-5), 3.42 (2H, d, J=7.5 Hz, –CH_2O–), 5.47 (1H, dd, J=2.4, 5.5 Hz, H-4), 5.69 (1H, dd, J=2.3, 5.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, 13.5, 26.2, 26.8, 30.2, 35.7, 53.1, 53.2, 57.1, 63.2, 129.8, 130.1; IR 2952, 3429 cm^{-1}; HRMS (EI) m/z calcd $C_{14}H_{24}OSi$ $[M]^+$ 236.1608, found 236.1596.

Compound **36**



^{1}H NMR (500 MHz, $CDCl_3$) δ −0.02 (9H, s, –Si(CH_3)$_3$), 0.52 (1H, ddd, J=5.0, 12.6, 14.2 Hz, Si–CHH–), 0.57 (1H, ddd, J=4.9, 12.6, 14.2 Hz, Si–CHH–), 1.48 (1H, dd, J=1.2, 12.8 Hz, H-6a), 1.58 (2H, m, H-1, C(8)–CHH–), 1.63 (1H, ddd, J=5.1, 12.6, 14.1 Hz, C(8)–CHH–), 1.69 (1H, br s, –OH), 1.72 (1H, ddd, J=5.2, 12.6, 14.2 Hz, C(8)–CHH–), 2.31 (1H, ddd, J=6.2, 11.3, 12.8 Hz, H-6b), 2.69–2.76 (1H, m, H-7b), 2.85 (1H, ddd, J=1.3, 2.5, 6.0 Hz, H-5), 3.64 (1H, dd, J=7.3, 10.3 Hz, –CHHO–), 3.74 (1H, dd, J=8.4, 10.2 Hz, –CHHO–), 5.47 (1H, dddd, J=0.8, 0.8, 2.4, 5.3 Hz, H-4), 5.66 (1H, dd, J=1.9, 5.3 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, 13.4, 26.7, 36.0, 36.2, 41.6, 45.6, 52.7, 53.7, 66.4, 130.0, 136.9; IR 1597, 1637, 2922, 3350 cm^{-1}; HRMS (ESI) m/z calcd $C_{14}H_{24}NaOSi$ $[M+Na]^+$ 259.1494, found 259.1489.

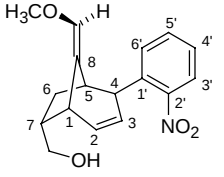
4.1.11. *rac*-(1*R*,4*R*,5*S*,7*R*,8*R*)-4-(2′-Nitrophenyl)-7-hydroxymethyl-8-vinylbicyclo[3.2.1]oct-2-ene 37. A mixture of the 7 *endo* phenethyltrimethyl silane derived *meta* photoadduct **36** (300 mg, 1.27 mmol), 2-iodo-1-nitrobenzene (380 mg, 1.53 mmol), triethylamine (154 mg, 1.53 mmol), palladium (II) acetate (14 mg, 0.060 mmol) and tri-*ortho*-tolylphosphine (39 mg, 0.13 mmol) and dry DMF (8 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 80 °C for 12 h. The reaction was poured into 2 M hydrochloric acid (75 ml) and the aqueous portion was washed with ethyl acetate (5×50 ml) and the combined organic portions were washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 5:1) to afford **37** (54 mg, 15%) as a yellow oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (1H, dd, J=6.3, 13.8 Hz, H-6a), 1.58 (1H, br s, –OH), 2.27 (1H, ddd, J=7.7, 10.0, 13.9 Hz, H-6b), 2.37 (1H, dm, J=7.7 Hz, H-5), 2.51 (1H, dm, J=5.8 Hz, H-8), 2.53–2.59 (2H, m, H-1, H-7b), 3.69 (1H, dd, J=8.5, 10.3 Hz, –CHHO–), 3.74 (1H, dd, J=6.1, 10.3 Hz, –CHHO–), 3.91 (1H, ddd, J=1.8, 1.8, 3.6 Hz, H-4a), 4.94 (1H, dd, J=1.7, 17.2 Hz, =CHH), 4.96 (1H, dd, J=1.6, 10.7 Hz, =CHH), 5.56 (1H, ddd, J=1.7, 3.6, 9.5 Hz, H-3), 5.73 (1H, ddd, J=5.8, 10.7, 17.2 Hz, C(8)–CH=), 6.26 (1H, ddd, J=2.0, 6.8, 9.5 Hz, H-2), 7.39 (1H, ddd, J=1.5, 7.3, 8.1 Hz, H-4′), 7.45 (1H, dd, J=1.5, 7.8 Hz, H-6′), 7.56 (1H, ddd, J=1.4, 7.7, 7.7 Hz, H-5′), 7.92 (1H, dd, J=1.3, 8.1 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.9, 42.1, 43.9, 44.3, 47.6, 48.1, 64.8, 114.4, 124.9, 126.9, 127.3, 131.2, 132.6, 134.6, 138.3, 139.7, 149.0; IR 1606, 1637, 2929, 3365 cm^{-1}; HRMS (ESI) m/z calcd $C_{17}H_{19}NNaO_3$ $[M+Na]^+$ 308.1263, found 308.1260.

4.1.12. *rac*-(1*R*,4*S*,5*R*,7*R*)-4-(2′-Nitrophenyl)-7-hydroxymethyl-8(*Z*)-methoxymethylenebicyclo[3.2.1]oct-2-ene 41. A solution of total volume (400 ml) containing benzylmethylether (4.89 g, 40 mmol), allyl alcohol (6.96 g, 120 mmol) and cyclohexane was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with 254 nm UV light for 87 h using a 16 W medium-pressure mercury vapour lamp. The solvent and unreacted starting materials were removed in vacuo and the residue subjected to column chromatography to obtain a 2:1 mixture of the 2,4 *meta* photoadduct **39** and the 2,6 *meta* photoadduct **40** (487 mg, 6.8%) as a pale green oil.

This inseparable mixture of photoadducts **39** and **40** (487 mg, 2.70 mmol) was added to a re-sealable reaction tube along with 2-iodo-1-nitrobenzene (674 mg, 2.70 mmol), triethylamine (328 mg, 3.25 mmol), palladium (II) acetate (30 mg, 0.135 mmol) and tri-*ortho*-tolylphosphine (82 mg, 0.27 mmol) and dry DMF (10 ml). The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 120 °C for 2 h. The reaction was poured into 2 M hydrochloric acid (75 ml) and the aqueous portion was washed with ethyl acetate (5×50 ml) and the combined organic portions were washed with brine (100 ml), water (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 2:1) to afford **41** (54 mg, 15% with respect to the mixture of photoadducts **39** and **40**) as an orange oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (1H, ddm, J=6.7, 13.2 Hz, H-6a), 1.65 (1H, br s, –OH), 2.26 (1H, ddd, J=7.8, 10.1, 13.2 Hz, H-6b), 2.38–2.46 (1H, m, H-7b), 2.59 (1H, tm, J=7.9 Hz, H-5), 3.44 (1H, tm, J=5.7 Hz, H-1), 3.47 (3H, s, –OCH_3), 3.68 (1H, dd, J=9.2, 10.5 Hz, –CHHO–), 3.74 (1H, dd, J=6.2, 10.5 Hz, –CHHO–), 3.88 (1H, m, H-4a), 5.19 (1H, s, =CHO–), 5.47 (1H, ddd, J=1.6, 3.7, 9.4 Hz, H-3), 6.15 (1H, ddd, J=1.7, 6.4, 9.3 Hz, H-2), 7.34–7.37 (2H, m, H-4′, H-6′), 7.52 (1H, ddd, J=1.4, 7.6, 7.6 Hz, H-5′), 7.86 (1H, dd, J=1.3, 8.0 Hz, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.7, 36.7, 43.2, 49.6, 49.9, 59.6, 64.5, 119.4, 124.1, 127.1, 127.9, 131.9, 132.1, 132.3, 135.1,

136.5, 148.8; IR 1636, 2930, 3417 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{17}H_{19}NNaO_4$ $[M+Na]^+$ 324.1212, found 324.1204.

Acknowledgements

We gratefully acknowledge the funding for this research from Tocris-Cookson Ltd and the EPSRC (GR/T08807/01). We have appreciated the opportunity to discuss this chemistry with Professor P. J. Parsons and Professor P. A. Wender. L.K. would like to thank AstraZeneca for the opportunity to undertake a part-time MSc course at the University of Sussex. We would also like to thank Dr. A. Abdul Sada for mass spectroscopy studies.

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10. We thank Mark Charles, DPhil thesis, University of Sussex, 2003 for suggesting these initial reaction conditions.
11. (a) The crystallographic data for compound **13** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 283162. Formula: $C_{17}H_{17}N_1O_5$ Unit cell parameters: *a* 7.1064(12) *b* 9.7290(16) *c* 11.6227(16) Å alpha 110.028(8) beta 106.858(8) gamma 91.824(6)° space group $P\bar{1}$. (b) The crystallographic data for compound **14** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 283163. Formula: $C_{17}H_{17}N_1O_5$ Unit cell parameters: *a* 9.1079(17) *b* 12.352(2) *c* 13.656(2) Å beta 107.32° space group *P*21/*n*.
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Efficient highly diastereoselective synthesis of 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines

Mehdi Adib,[a,*] Esmaeil Sheibani,[b] Manizheh Mostofi,[a] Khadijeh Ghanbary[a] and Hamid Reza Bijanzadeh[b]

[a]*Department of Chemistry, Faculty of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran*
[b]*Department of Chemistry, Tarbiat Modarres University, Tehran, Iran*

Received 26 May 2005; revised 25 July 2005; accepted 12 January 2006

Available online 20 February 2006

Abstract—1-Alkyl imidazoles react smoothly with dialkyl acetylenedicarboxylates in the presence of pyridine carboxaldehydes to diastereoselectively produce 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine derivatives in excellent yields.
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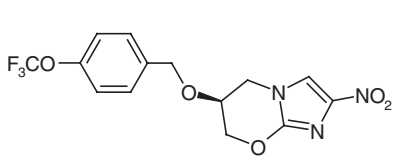
1. Introduction

The development of simple synthetic routes to widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[2] The interest in fused bicyclic 5–6 systems with one ring junction nitrogen atom and two extra heteroatoms, one nitrogen in the five-membered ring and one oxygen in the six-membered ring, stems from the appearance of saturated and partially saturated imidazo[2,1-*b*][1,3]oxazine ring systems in biologically active compounds. Derivatives containing the imidazo[2,1-*b*][1,3]oxazine ring system have been shown to possess antimicrobial activity. For example, PA-824, PA-822, PA-653, PA-647, PA-601, and PA-602, are all members of bicyclic nitroimidazopyran family, drugs related to nitroimidazoles that have been studied as potent antituberculous compounds against a disease that kills one person every 15 s across the globe. The most promising compound in this series, PA-824, {4-[((3*S*)-6-nitro(2*H*,3*H*,4*H*-imidazolo[2,1-*b*]1,3-oxazaperhydroin-3-yloxy))methyl]phenoxy}trifluoromethane (**1**) which has a novel mechanism of action against mycobacterium tuberculosis and *Helobacter pylori* comparable with that of isoniazid.[3–7] However, only a few synthetic methods have been reported for the preparation of imidazo[2,1-*b*][1,3]oxazine ring systems.[8–11] As part of our current studies on the development of new routes in heterocyclic synthesis,[12–16] we have recently described a simple one-pot synthesis of 5*H*-imidazo[2,1-*b*][1,3]oxazines **2** from the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one.[17] In this paper, we wish to report an efficient diastereoselective synthesis of highly functionalized imidazo[2,1-*b*][1,3]oxazines.



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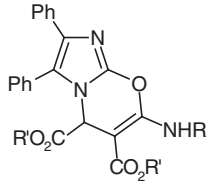

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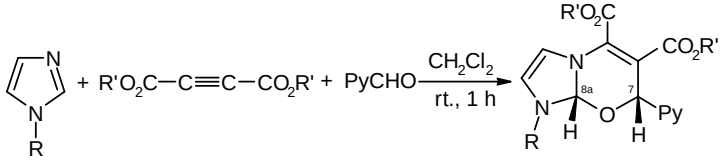
2. Results and discussion

The reaction of 1-alkyl imidazoles **3** with dialkyl acetylenedicarboxylates **4** in the presence of pyridine carboxaldehydes **5** in dichloromethane at ambient temperature leads to 1-alkyl-7-pyridin-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylates **6** in 93–97% yields (Scheme 1).

Keywords: Diastereoselective synthesis; Pyridine carboxaldehydes; Acetylenic esters; 1-Alkyl imidazoles; 1,8a-Dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines.
* Corresponding author. Tel./fax: +98 21 66495291; e-mail: madib@khayam.ut.ac.ir

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.048



3 **4** **5** **6**

3	R
a	Me
b	^{n}Bu

4	R'
a	Me
b	Et

5	Py
a	2-C_5H_4N
b	4-C_5H_4N

6	R	R'	Py	Yield %
a	Me	Me	2-C_5H_4N	97
b	Me	Et	2-C_5H_4N	96
c	Me	Me	4-C_5H_4N	97
d	^{n}Bu	Me	2-C_5H_4N	94
e	^{n}Bu	Et	2-C_5H_4N	93
f	^{n}Bu	Me	4-C_5H_4N	95

Scheme 1.

The reactions were carried out by first mixing the 1-alkyl imidazole **3** and the pyridine carboxaldehyde **5** and then the acetylenic ester **4** was added slowly. The reactions proceeded spontaneously in CH_2Cl_2, and were complete within an hour. The ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine derivatives **6**. Any product other than **6** could not be detected by NMR spectroscopy. The reaction is stereoselective and leads to one diastereoisomer. Our attempts to detect the second diastereoisomer in the reaction mixture were not successful.

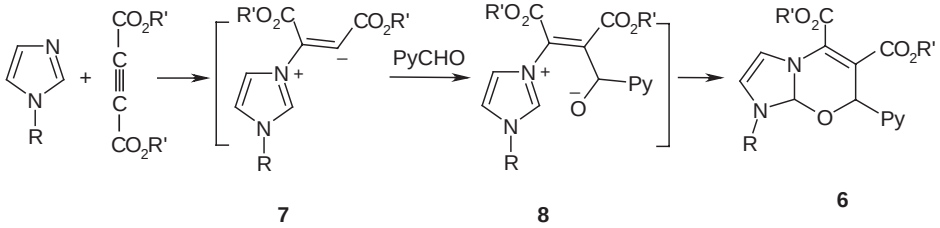
The structures of compounds **6a–f** were deduced from their elemental analyses, their IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of compound **6a** displayed molecular ion (M^+) peak at $m/z=331$, which is consistent with the 1:1:1 adduct of 1-methyl imidazole, dimethyl acetylenedicarboxylate, and pyridine-2-carboxaldehyde. The ^{1}H NMR spectrum of **6a** exhibited five sharp lines readily recognized as arising from N–CH_3 ($\delta=3.64$ ppm), methoxy ($\delta=3.67$ and 3.89 ppm), and methine ($\delta=5.46$ and 6.37 ppm) protons and two fairly broad singlets ($\delta=6.90$ and 7.00 ppm) for NCH=CHN moiety, along with characteristic multiplets for the aromatic protons. The proton decoupled ^{13}C NMR spectrum of **6a** showed 16 distinct resonances in agreement with the proposed structure.

The ^{1}H and ^{13}C NMR spectra of compounds **6b–f** are similar to those of **6a** except for the alkyl groups, the ester moieties, and the pyridine rings, which exhibit characteristic signals with appropriate chemical shifts and coupling constants. The signals of the two protons of the NCH=CHN moiety appeared as two doublets ($J=1.1$ Hz) only for **6d**.

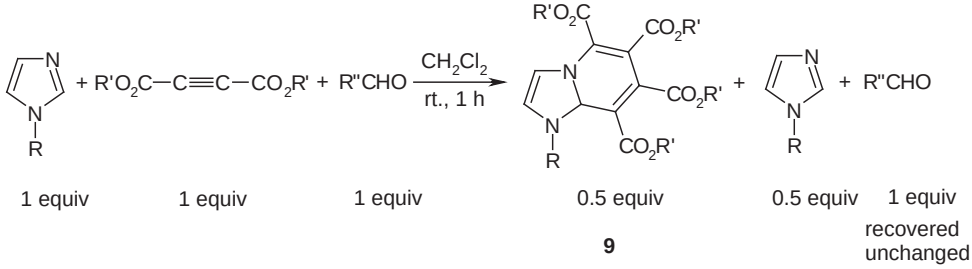
The stereochemistry of the products was established by nuclear Overhauser effect measurement.[18] Thus, when the resonance of C_7H proton of compound **6a** at $\delta=6.37$ ppm was saturated, the intensity of the signal of C_{8a}H proton at $\delta=5.46$ ppm increased by at least 10%. Thus the two protons are in a close *syn* relationship together.

Although we have not established the mechanism of the reaction between 1-alkyl imidazoles and acetylenic esters in the presence of pyridine carboxaldehydes in an experimental manner, a possible explanation is proposed in Scheme 2. The first step may involve addition of the 1-alkyl imidazole to the acetylenic ester and formation of the 1:1 adduct **7**. Subsequent nucleophilic attack of the adduct to the aldehyde would yield the 1:1:1 adduct **8**. The observed product is formed from the intramolecular addition of the oxygen anion to the imidazolium moiety.

Our attempts to carry out this reaction under the same reaction conditions with a wide range of aliphatic, aromatic, and heteroaromatic aldehydes, from highly electron-rich such as 4-(dimethylamino)benzaldehyde to highly electron-poor such as 4-nitrobenzaldehyde were not successful. For all of the aldehydes apart from 4-nitrobenzaldehyde the TLC and ^{1}H NMR spectrum of the reaction mixture clearly indicated the formation of 1,8a-dihydroimidazo[1,2-*a*]pyridine-5,6,7,8-tetracarboxylates **9** (Scheme 3), and the aldehyde recovered unchanged. Only with 4-nitrobenzaldehyde the TLC and ^{1}H NMR spectrum of the reaction mixture clearly indicated a complex mixture of at least five products together with some of the unreacted 1-alkyl imidazole and the aldehyde.



Scheme 2.



Scheme 3.

3. Conclusion

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides a simple one-pot method for the stereoselective preparation of polyfunctional 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines.

4. Experimental

Dimethyl- and diethyl acetylenedicarboxylates, 1-methyl- and 1-butyl imidazoles, and pyridine carbaldehydes were obtained from Merck (Germany) and were used without further purification. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.1. General procedure

To a magnetically stirred solution of the appropriate pyridine carbaldehyde (0.107 g, 1 mmol) and the appropriate 1-alkyl imidazole (1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a solution of the appropriate dialkyl acetylenedicarboxylate (1 mmol) in CH_2Cl_2 (2 mL) at −5 °C for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h. The solvent was removed and the residue was purified by column chromatography using ethyl acetate as eluent. The solvent was removed under reduced pressure and the product was obtained.

4.1.1. Dimethyl 1-methyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6a). Viscous brown oil, yield: 0.32 g, 97%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1720 (C=O), 1631, 1439, 1215, 1148, 761. MS, *m*/*z* (%): 331 (M^+, 2), 272 (28), 240 (51), 212 (25), 190 (12), 184 (27), 172 (100), 158 (23), 131 (17), 117 (21), 101 (31), 78 (66), 59 (69). Anal. Calcd for $C_{16}H_{17}N_3O_5$ (331.33): C, 58.00; H, 5.17; N, 12.68. Found: C, 58.2; H, 5.6; N, 11.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.64 (3H, s, NCH_3), 3.67 and 3.89 (6H, 2s, $2OCH_3$), 5.46 (1H, s, N_2CHO), 6.37 (1H, s, Ar-CH), 6.90 and 7.00 (2H, 2s, NCH=CHN), 7.28 (1H, dd, J=6.9, 4.9 Hz, CH), 7.63 (1H, d, J=7.8 Hz, CH), 7.80 (1H, t, J=7.8 Hz, CH), 8.57 (1H, d, J=4.9 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 33.28 (NCH_3), 51.60 and 52.99 ($2OCH_3$), 77.88 (Ar-CH), 96.82 (N_2CHO), 121.96, 123.05, 123.66, 128.22, and 137.30 (5CH), 142.66 (C), 149.34 (CH), 154.96 and 159.49 (2C), 163.54 and 165.90 (2C=O).

4.1.2. Diethyl 1-methyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6b). Viscous brown oil, yield: 0.35 g, 96%. IR (KBr) (υ_{max}/cm^{-1}): 1740 and 1718 (C=O), 1630, 1375, 1196, 1144, 1043, 910, 733. MS, *m*/*z* (%): 360 (M^++1, 6), 286 (29), 258 (20), 240 (55), 212 (40), 186 (44), 172 (100), 158 (34), 104 (24), 93 (39), 78 (70). Anal. Calcd for $C_{18}H_{21}N_3O_5$ (359.38): C, 60.16; H, 5.89; N, 11.69. Found: C, 59.9; H, 5.8; N, 11.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.13 and 1.26 (6H, 2t, J=7.1 Hz, $2OCH_2CH_3$), 3.60 (3H, s, NCH_3), 4.01 and 4.26 (4H, 2q, J=7.1 Hz, $2OCH_2CH_3$), 5.39 (1H, s, N_2CHO), 6.36 (1H, s, Ar-CH), 6.85 and 6.91 (2H, 2s, NCH=CHN), 7.21 (1H, dd, J=6.9, 5.3 Hz, CH), 7.56 (1H, d, J=7.9 Hz, CH), 7.72 (1H, t, J=7.6 Hz, CH), 8.48 (1H, d, J=4.5 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.68 and 13.96 ($2OCH_2CH_3$), 33.30 (NCH_3), 60.39 and 62.19 ($2OCH_2CH_3$), 77.45 (Ar-CH), 97.03 (N_2CHO), 121.92, 123.08, 123.62, 127.71, and 137.30 (5CH), 142.65 (C), 149.21 (CH), 154.90 and 159.36 (2C), 163.03 and 165.29 (2C=O).

4.1.3. Dimethyl 1-methyl-7-pyridin-4-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6c). Viscous brown oil, yield: 0.32 g, 97%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1724 (C=O), 1634, 1560, 1443, 1373, 1148, 910, 735. MS, *m*/*z* (%): 331 (M^+, 3), 272 (34), 244 (22), 212 (19), 186 (26), 172 (100), 157 (29), 131 (14), 106 (26), 86 (58), 84 (98), 59 (47). Anal. Calcd for $C_{16}H_{17}N_3O_5$ (331.33): C, 58.00; H, 5.17; N, 12.68. Found: C, 58.0; H, 5.2; N, 12.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.31 (3H, s, NCH_3), 3.49 and 3.76 (6H, 2s, $2OCH_3$), 5.43 (1H, s, N_2CHO), 6.29 (1H, s, Ar-CH), 6.73 and 6.87 (2H, 2s, NCH=CHN), 7.10 (2H, d, J=5.9 Hz, 2CH), 8.47 (2H, d, J=5.9 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 32.15 (NCH_3), 51.32 and 52.75 ($2OCH_3$), 77.05 (Ar-CH), 95.69 (N_2CHO), 120.44, 121.34, and 128.31 (3CH), 141.59 and 144.78 (2C), 150.05 (CH), 158.75 (C), 163.19 and 165.58 (2C=O).

4.1.4. Dimethyl 1-butyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6d). Viscous brown oil, yield: 0.35 g, 94%. IR (KBr) (υ_{max}/cm^{-1}):

1747 and 1722 (C═O), 1630, 1437, 1373, 1209, 1146, 910, 732. MS, *m/z* (%): 373 (M^+, 5), 314 (18), 282 (39), 258 (17), 240 (20), 214 (55), 186 (58), 172 (46), 158 (48), 123 (47), 101 (59), 78 (99), 69 (62), 59 (100). Anal. Calcd for $C_{19}H_{23}N_3O_5$ (373.41): C, 61.12; H, 6.21; N, 11.25. Found: C, 61.2; H, 6.2; N, 11.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.0 Hz, CH_2CH_3), 1.24–1.89 (4H, m, $CH_2CH_2CH_3$), 3.58 (3H, s, OCH_3), 3.80 (2H, dt, ^2J=10.1 Hz, ^3J=7.1 Hz, NCH_2), 3.83 (3H, s, OCH_3), 5.41 (1H, s, N_2CHO), 6.32 (1H, s, Ar-CH), 6.91 and 6.98 (2H, 2d, J=1.1 Hz, NCH═CHN), 7.23 (1H, dd, J=6.8, 5.2 Hz, CH), 7.58 (1H, d, J=7.8 Hz, CH), 7.75 (1H, t, J=7.5 Hz, CH), 8.52 (1H, dd, J=4.9, 1.1 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.86 (CH_2CH_3), 19.15 and 32.19 ($CH_2CH_2CH_3$), 45.72 (NCH_2), 51.08 and 52.46 ($2OCH_3$), 77.14 (Ar-CH), 96.37 (N_2CHO), 121.16, 121.71, 123.48, 128.33, and 137.30 (5CH), 142.29 (C), 149.23 (CH), 155.22 and 159.67 (2C), 163.47 and 165.96 (2C═O).

4.1.5. Diethyl 1-butyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6e). Viscous brown oil, yield: 0.37 g, 93%. IR (KBr) (υ_{max}/cm^{-1}): 1742 and 1721 (C═O), 1633, 1370, 1189, 1144, 915, 729. MS, *m/z* (%): 401 (M^+, 3), 330 (61), 303 (32), 284 (89), 256 (30), 231 (45), 217 (100), 201 (43), 188 (82), 174 (61), 160 (66), 135 (50), 124 (44), 119 (68), 106 (36), 96 (54), 80 (98), 58 (93). Anal. Calcd for $C_{21}H_{27}N_3O_5$ (401.46): C, 62.83; H, 6.78; N, 10.47. Found: C, 62.9; H, 6.9; N, 10.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.79 (3H, t, J=7.1 Hz, $CH_2CH_2CH_3$), 1.20 and 1.25 (6H, 2t, J=7.3 Hz, $2OCH_2CH_3$), 1.26–1.91 (4H, m, $CH_2CH_2CH_3$), 3.76 (2H, dt, ^2J=10.5 Hz, ^3J=7.4 Hz, NCH_2), 4.05 and 4.29 (4H, 2q, J=7.3 Hz, $2OCH_2CH_3$), 5.34 (1H, s, N_2CHO), 6.26 (1H, s, Ar-CH), 6.86 and 6.97 (2H, 2s, NCH═CHN), 7.25 (1H, dd, J=6.8, 5.0 Hz, CH), 7.69 (1H, d, J=7.5 Hz, CH), 7.83 (1H, t, J=7.8 Hz, CH), 8.44 (1H, d, J=4.6 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.77, 13.01, and 13.30 ($3CH_2CH_3$), 19.12 and 32.08 ($CH_2CH_2CH_2CH_3$), 45.61 (NCH_2), 59.93 and 61.70 ($2OCH_2CH_3$), 78.91 (Ar-CH), 96.54 (N_2CHO), 121.06, 121.56, 123.37, 128.31, and 137.16 (5CH), 142.38 (C), 149.11 (CH), 155.32 and 159.71 (2C), 163.04 and 165.38 (2C═O).

4.1.6. Dimethyl 1-butyl-7-pyridin-4-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6f). Viscous brown oil, yield: 0.35 g, 95%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1724 (C═O), 1633, 1599, 1442, 1373, 1209, 1147, 910, 735. MS, *m/z* (%): 373 (M^+, 2), 288 (18), 228 (46), 214 (21), 200 (24), 172 (33), 158 (29), 125 (100), 106 (25), 97 (77), 82 (73), 69 (30), 59 (47). Anal. Calcd for $C_{19}H_{23}N_3O_5$ (373.41): C, 61.12; H, 6.21; N, 11.25. Found: C, 61.1; H, 6.2; N, 11.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.80 (3H, t, J=7.3 Hz, CH_2CH_3), 1.22–1.86 (4H, m, $CH_2CH_2CH_3$), 3.51 and 3.78 (6H, 2s, $2OCH_3$), 3.81 (2H, dt, ^2J=10.1 Hz, ^3J=7.2 Hz, NCH_2), 5.52 (1H, s, N_2CHO), 6.38 (1H, s, Ar-CH), 6.81 and 6.92 (2H, 2s, NCH═CHN), 7.16 (2H, d, J=5.8 Hz, 2CH), 8.49 (2H, d, J=5.8 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.28 (CH_2CH_3), 19.49 and 32.82 ($CH_2CH_2CH_2CH_3$), 46.63 (NCH_2), 51.56 and 52.50 ($2OCH_3$), 75.60 (Ar-CH), 97.39 (N_2CHO), 120.36, 121.72, and 128.48 (3CH), 141.82 and 144.98 (2C), 150.20 (CH), 158.98 (C), 163.31 and 165.66 (2C═O).

Acknowledgements

This research was supported by the Research Council of University of Tehran as a research project (6102036/1/02).

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Tetrahedron 62 (2006) 3439–3445

Parallel synthesis of an indole-based library via an iterative Mannich reaction sequence

Charlotta Lindquist,[a,b] Oguz Ersoy[b,*] and Peter Somfai[a,*]

[a]*Organic Chemistry, Department of Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden*
[b]*Amersham Biosciences, S-751 84 Uppsala, Sweden*

Received 12 January 2005; revised 12 December 2005; accepted 12 January 2006

Available online 8 February 2006

Abstract—A library of 1,3-disubstituted indoles has been prepared via an iterative Mannich reaction sequence. The first Mannich reaction with secondary amines and formaldehyde preferentially yields 3-aminomethyl indoles, while the second Mannich reaction introduces an additional aminomethyl group at the N1-position of the indole ring. A library of 25 substituted indoles has thus been prepared in moderate to good yields with purity.
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1. Introduction

Affinity chromatography is a powerful technique where a ligand with specific affinity for a biological substance, usually a protein, is used for the purification of this substance.[1] Combinatorial synthesis[2] presents itself as a useful tool for the development of new affinity ligands. One such recent campaign has focused on the use of 1,3-substituted indoles as affinity chromatography ligands.

Indoles and related heterocyclic structures are found in numerous natural products with interesting biological activities, and several combinatorial synthesis studies have used the indole heterocycle as a core-function.[3] The N1- and C3-positions of the indole nucleus are relatively electron-rich and react with various types of electrophiles.[4] In the present study, the aim was to introduce functionality in the N1- and C3-positions while leaving the C2-position unsubstituted. For the N1-position, alkylation with an alkyl halide is a plausible option, but controlling the regioselectivity in such reaction can be difficult.[5] For derivatization at the C3-position, a Mannich-type addition was chosen as the lone pair of the resultant amine moiety was expected to participate in the binding interactions of the projected affinity ligands. Due to the known difficulty of selective alkylation at the N1-position, the Mannich reaction at the C3-position with a secondary amine and formaldehyde was chosen as the first step. Although this reaction proceeded efficiently, we were surprised to observe a bis-Mannich product when extended reaction times and excess reagents were applied. More surprisingly, this bis-Mannich product was quite stable under conditions typical to affinity chromatography. A review of the literature revealed only two accounts where similar bis-Mannich products had been observed, in both occasions as byproducts.[6] However, there were no accounts of the use on this dual reactivity to build compounds employing two different Mannich reactions.

Intrigued by this finding, we undertook the synthesis of an 1,3-aminomethyl indole library where two different Mannich reactions with secondary amines and formaldehyde were used in sequence to produce differentially substituted indole scaffolds. Methyl indole-5-carboxylate (**1**) was selected as the starting material, with the aim of using the carboxylic acid functionality as an attachment point to the chromatography matrix. Herein we describe the synthesis of 25 1,3-aminomethyl indole compounds.

2. Results and discussion

Mannich reactions between indole and secondary imines in water at low temperature are known to substitute the N1 position of indoles.[7] The products, *N*-aminal indoles, are relatively stable but convert to the thermodynamically more stable C3-substituted aminomethyl indoles upon heating at neutral pH or acid treatment at room temperature.[4] Accordingly, we devised a synthetic strategy where the C3-position of **1** was first substituted under standard

Keywords: Library synthesis; Mannich reaction; Affinity ligands.
* Corresponding authors. Tel.: +46 18 6121162; fax: +46 18 6121837 (O.E.); tel.: 46 8 7906960; fax: 46 8 7912333 (P.S.); e-mail addresses: ersoy@amersham.com; somfai@kth.se

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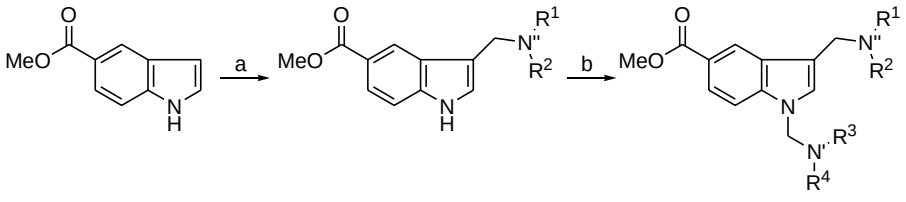
doi:10.1016/j.tet.2006.01.047



2 $R^1R^2N''H$=pyrrolidine, 77%
3 $R^1R^2N''H$=4-methylpiperidine, 93%
4 $R^1R^2N''H$=diethylamine, 78%
5 $R^1R^2N''H$=4-methylpiperazine, 45%
6 $R^1R^2N''H$=morpholine, 57%
7 $R^1R^2N''H$=benzylmethylamine, 66%

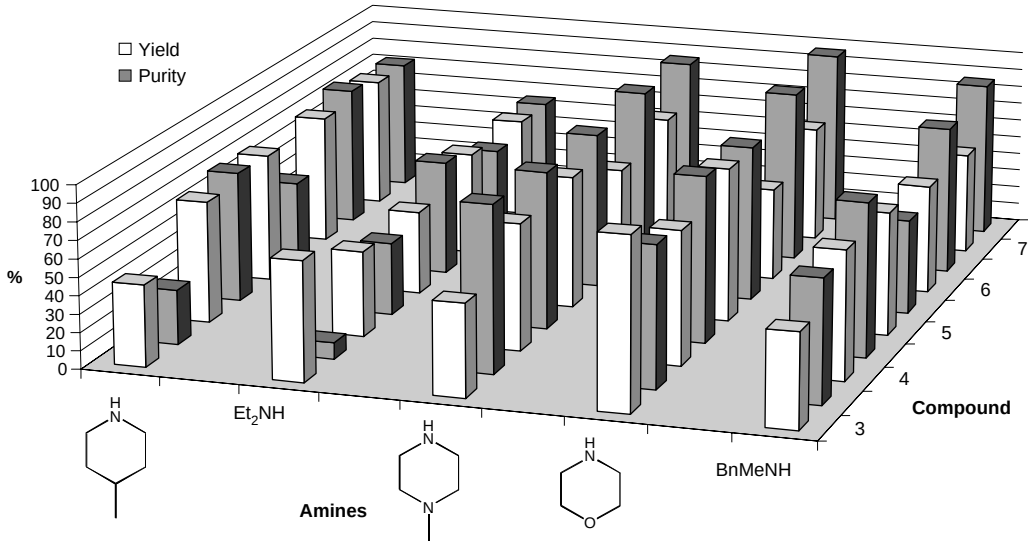
Scheme 1. (a) $R^1R^2N''H$ (1.2 equiv), HCHO (1.2 equiv), room temperature, 18 h; (b) $R^3R^4N'H$ (1.5 equiv), HCHO (1.5 equiv), room temperature, 48 h.

Mannich conditions to yield the corresponding thermodynamically stable products, 3-aminomethyl indoles **2–7** (Scheme 1).

Compounds **3–7** were then selected for further library synthesis. The combination of these compounds with five different secondary amines then gave a library of 25 novel compounds, **8–32** (Tables 1 and 2). The second Mannich reaction required prolonged reaction times to reach completion and all attempts with elevated reaction temperatures resulted in complicated reaction mixtures, perhaps due to scrambling of the secondary amine moieties on the indole scaffold. To simplify the purification of the library members excess amine was removed using a polymer bound electrophilic scavanger, methylisocyanate polystyrene.[11] As can be seen from the data in Table 1, the yields vary from good to moderate, the reason probably being that some product was lost during purification, and that the purities of the library compounds were generally high. However, when Et_2NH was used in the second Mannich reaction, that is, formation of compounds **9**, **14**, **19**, **24** and **29**, products with lower purities were obtained, which might be due to the more sterically hindered amine moiety.

In order to exclude the possibility of scrambling of the N1- and C3-substituents during the second Mannich reaction,

Table 1. Yields and purity of library compounds[a]

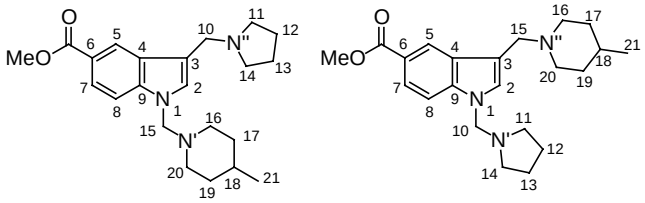


[a] Purity was determined from relative peaks areas of HPLC chromatogram (runs with gradient of 0–100% acetonitrile in water (0.05% TFA) for 10 min at λ= 214 nm). Yield was calculated from weight after removal of excess amine by scavanger resin. Reaction conditions: substrate (1 equiv), R^3R^4NH (1.5 equiv), HCHO (1.5 equiv), dioxane:HOAc, room temperature, 48 h.

Table 2. Compound numbering

Compound	4-Methylpiperidine	Diethylamine	1-Methylpiperazine	Morpholine	Benzylmethylamine
3	**8**	**9**	**10**	**11**	**12**
4	**13**	**14**	**15**	**16**	**17**
5	**18**	**19**	**20**	**21**	**22**
6	**23**	**24**	**25**	**26**	**27**
7	**28**	**29**	**30**	**31**	**32**

compounds **33** and **34** were prepared from **2** (64%) and **3** (62%), respectively, by using the same reaction conditions as those employed for the library synthesis. Each reaction yielded a single detectable Mannich product. To confirm the structures of **33** and **34**, 1D ^{1}H and ^{13}C NMR spectra together with 2D $^{1}H,^{1}H$-COSY, $^{1}H,^{13}C$-HMQC[8] and $^{1}H,^{13}C$-HMBC[9,10] spectra were recorded and interpreted. First, assignments of all proton and carbon signals in **33** and **34** were made with assistance of the 2D COSY and HMQC spectra. Secondly, information about long-range ^{1}H, ^{13}C couplings extracted from the HMBC spectra was used to determine the linkage position of the piperidine and pyrrolidine groups on the indole ring. For both compounds the identity of the methylene group C15 was determined by the $^{3}J_{HC}$ coupling between H15 and C16/C20. In a similar way, the identity of the C10 methylene moiety was determined by the $^{3}J_{HC}$ coupling between H10 and C11/C14. In compound **33**, the position of the piperidine group was deduced by the $^{3}J_{HC}$ couplings between H15 and C2/C9 and the position of the pyrrolidine group was deduced by the $^{2}J_{HC}$ coupling between H10 and C3 together with the $^{3}J_{HC}$ couplings between H10 and C2/C4. In compound **34** the situation was reversed, H15 now showed a $^{2}J_{HC}$ coupling to C3 and a $^{3}J_{HC}$ couplings to C2 and C4 while H10 showed $^{3}J_{HC}$ couplings to C2 and C9, thus confirming the postulated structures and verifying that no scrambling of the N1- and C3-substituents occur during the second Mannich reaction (Fig. 1).



33 **34**

Figure 1. Structure and numbering of compounds **33** and **34**.

3. Conclusions

A library of 25 novel bis-1,3-aminomethyl indole compounds has been prepared in moderate to good yields by sequential use of two Mannich reactions. The average purity of the library is greater than 70%. It have also been shown that no scrambling of the amino substituents between the N1- and C3-positions occurs during the second Mannich reaction. Despite the modest library size, these results show that iterative Mannich reactions with different secondary amines and formaldehyde, is a useful method to build libraries of 1,3-aminomethyl indoles. The mild reaction conditions that are employed make this a particularly attractive reaction sequence.

4. Experimental

4.1. Material and methods

Reactions were performed in individual glass tubes placed in IKA-VIBRAX-VXR parallel agitation equipment. Evaporation of solvents was done parallel in a centrifugal evaporator (Speed Vac SC201A, Savant). Scavanger reactions were performed in individual polypropylene tubes (PD-10 columns, Amersham Biosciences). All chemicals and solvents were obtained from commercial sources and were used as received. NMR spectra were obtained on a Bruker Avance 300 in using $CDCl_3$ as solvent and shifts are reported downfield from $(CH_3)_4Si$ (δ 0). LS-MS were obtained on a Hewlett Packard HP1100 MSD (ESI, positive mode) using an YMC C_{18}-hydrosphere column (flow rate: 0.5 mL/min, gradient: 0–100% acetonitrile in water (0.05% TFA) for 10 min, $\lambda=214$ nm). The purity of all compounds were analyzed by analytic RP-HPLC on a Shimadzu 10A system using an ACE C_{18}-column (flow rate: 2 mL/min, gradient: 0–100% acetonitrile in water (0.05% TFA) for 10 min, $\lambda=214$ nm).

4.2. General procedures and spectral data

4.2.1. Typical procedure for the first Mannich reaction. Methyl 3-((pyrrolidin-1-yl)methyl)-1*H*-indole-5-carboxylate (2). To a solution of **1** (300 mg, 1.71 mmol) in dioxane–HOAc (4/1, 2.0 mL) was added a mixture of pyrrolidine (170 μL, 2.06 mmol) and formaldehyde (154 μL, 2.06 mmol, 37 wt% solution in water) in dioxane–HOAc (4/1, 2.0 mL). The resultant mixture was agitated at room temperature overnight. Evaporation of the solvents and flash chromatography (CH_2Cl_2/MeOH/Et_3N, v/v/v 90:10:1) gave **2**·HOAc (419 mg, 77%). HPLC-MS (ESI^+): $t_R=4.34$ min, *m/z* 259 ($M+H^+$, 50%), 188 (100); δ_H (300 MHz, $CDCl_3$) 2.03 (m, 4H, C*H*HCH$_2$N′CH$_2$C*H*H), 2.30 (m, 4H, CH$_2$N′CH$_2$), 3.92 (s, 3H, OMe), 4.52 (s, 2H, CH$_2$N′), 7.49 (d, 1H, $J=8.7$ Hz, H8), 7.61 (s, 1H, H2), 7.88 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.52 (d, 1H, $J=1.5$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 23.0, 47.9, 51.9, 52.0, 105.7, 111.8, 120.5, 122.2, 123.4, 126.9, 129.4, 138.8, 168.0; IR (film) 2953, 1709, 1621 cm^{-1}.

4.2.2. Methyl 3-((4-methylpiperidin-1-yl)methyl)-1*H*-indole-5-carboxylate (3). Prepared from **1** (200 mg, 1.14 mmol), 4-methylpiperidine (162 μL, 1.37 mmol) and formaldehyde (103 μL, 1.37 mmol, 37 wt% solution in water) as described for compound **2** to give **3** (304 mg, 93%). HPLC-MS (ESI^+): $t_R=4.81$ min, *m/z* 287 ($M+H^+$, 100%), 188 (58); δ_H (300 MHz, $CDCl_3$) 0.96 (d, 3H, $J=5.7$ Hz, CHC*H*$_3$), 1.51 (m, 3H, C*H*HCH$_2$N′CH$_2$C*H*H), 1.71 (m, 2H, C*H*HCH$_2$N′CH$_2$C*H*H), 2.42 (m, 2H, C*H*HN′C*H*H), 3.27 (m, 2H, CH*H*N′CH*H*), 3.94 (s, 3H, OMe), 4.09 (s, 2H, CH$_2$N′), 7.43 (d, 1H, $J=8.7$ Hz, H8), 7.57 (s, 1H, H2), 7.91 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.35 (d, 1H, $J=1.5$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 20.8, 30.8, 33.8, 51.0, 51.9, 52.0, 104.6, 111.8, 120.6, 122.2, 123.4, 127.4, 130.0, 138.8, 168.1; IR (film) 2956, 1697, 1621 cm^{-1}.

4.2.3. Methyl 3-((diethylamino)methyl)-1*H*-indole-5-carboxylate (4). Prepared from **1** (300 mg, 1.71 mmol), diethylamine (212 μL, 2.06 mmol) and formaldehyde (154 μL, 2.06 mmol, 37 wt% solution in water) as described for compound **2** to give **4** (349 mg, 78%). HPLC-MS (ESI^+): $t_R=4.30$ min, *m/z* 261 ($M+H^+$, 23%), 188 (100); δ_H (300 MHz, $CDCl_3$) 1.25 (m, 6H, $J=7.5$ Hz, N′CH$_2$C*H*$_3$), 2.94 (m, 4H, $J=7.5$ Hz, N′C*H*$_2$-CH$_3$), 3.92 (s, 3H, OMe), 4.20 (s, 2H, CC*H*$_2$N′), 7.42 (d,

1H, J=8.7 Hz, H8), 7.58 (s, 1H, H2), 7.88 (dd, 1H, J= 8.7, 1.5 Hz, H7), 8.34 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 8.6, 44.9, 46.4, 52.0, 104, 6, 111.8, 120.3, 122.2, 123.4, 127.2, 129.9, 138.8, 168.0; IR (film) 2952, 1704, 1622 cm^{-1}.

4.2.4. Methyl 3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole-5-carboxylate (5). Prepared from **1** (300 mg, 1.71 mmol), 1-methylpiperazine (228 μL, 2.06 mmol) and formaldehyde (154 μL, 2.06 mmol, 37 wt% solution in water) as described for compound **2** to give **5** (231 mg, 45%). HPLC-MS (ESI^+): t_R=3.74 min, m/z 288 ($M+H^+$, 100%), 188 (87), 130 (8); δ_H (300 MHz, $CDCl_3$) 2.52 (s, 3H, NCH_3), 2.75–3.00 (m, 8H, $CH_2CH_2N'CH_2CH_2$), 3.94 (s, 3H, OMe), 3.98 (s, 2H, CCH_2N'), 7.46 (s, 1H, H2), 7.47 (d, 1H, J=8.7 Hz, H8), 7.91 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.40 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 43.8, 50.0, 51.9, 52.0, 52.7, 109.9, 111.2, 121.8, 121.9, 123.5, 127.0, 127.2, 139.0, 168.2; IR (film) 2954, 1706, 1619 cm^{-1}.

4.2.5. Methyl 3-(morpholinomethyl)-1*H*-indole-5-carboxylate (6). Prepared from **1** (300 mg, 1.71 mmol), morpholine (179 μL, 2.06 mmol) and formaldehyde (154 μL, 2.06 mmol, 37 wt% solution in water) as described for compound **2** to give **6** (324 mg, 57%). HPLC-MS (ESI^+): t_R=4.20 min, m/z 275 ($M+H^+$, 10%), 188 (100); δ_H (300 MHz, $CDCl_3$) 2.73 (m, 4H, $CH_2N'CH_2$), 3.73 (m, 4H, CH_2OCH_2), 3.92 (s, 3H, OMe), 3.96 (s, 2H, CH_2N'), 7.41 (d, 1H, J=8.7 Hz, H8), 7.45 (s, 1H, H2), 7.84 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.47 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 43.3, 51.9, 52.0, 64.4, 108.8, 111.3, 121.5, 122.0, 123.5, 127.5, 127.6, 138.8, 168.1; IR (film) 2948, 1696, 1566, 1112 cm^{-1}.

4.2.6. Methyl 3-((*N*-benzyl-*N*-methylamino)methyl)-1*H*-indole-5-carboxylate (7). Prepared from **1** (50 mg, 285 μmol), *N*-benzylmethylamine (44 μL, 343 μmol) and formaldehyde (26 μL, 343 μmol, 37 wt% solution in water) as described for compound **2** to give **7** (58 mg, 66%). HPLC-MS (ESI^+): t_R=5.47 min, m/z 309 ($M+H^+$, 10%), 188 (27), 122 (100); δ_H (300 MHz, $CDCl_3$) 2.22 (s, 3H, $N'CH_3$), 3.57 (s, 2H, $N'CH_2Ph$), 3.74 (s, 2H, CH_2N'), 3.94 (s, 3H, OMe), 7.12–7.43 (m, 7H, H2, H8, Ar), 7.88 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.50 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 38.5, 50.2, 52.0, 59.1, 106.4, 111.6, 121.0, 122.2, 123.5, 127.3, 129.0, 129.1, 129.2, 130.7, 131.4, 138.9, 168.1; IR (film) 2950, 1698, 1622 cm^{-1}.

4.2.7. Typical procedure for the second Mannich reaction. Compound 23. To a solution of compound **6** (40.0 mg, 145.8 μmol) in dioxane–HOAc (4/1 v/v, 0.5 mL) was added a mixture of 4-methylpiperidine (25.9 μL, 218.7 μmol) and formaldehyde (24.3 μL, 218.7 μmol, 37 wt% solution in water) in dioxane–HOAc (4/1, 0.5 mL). The resultant mixture was agitated for 48 h. The solvents were removed and the residue dissolved in CH_2Cl_2 (1 mL) and added to a slurry of methyl isocyanate polystyrene HL (99 mg, 219 μmol, prewashed and pre-swollen) in CH_2Cl_2 (1 mL). The resultant slurry was agitated for 2 h. Filtration, washing of the resin and removal of the solvents gave compound **23** that was characterized by ^1H NMR and LC-MS. HPLC-MS (ESI^+): t_R=3.91 min, m/z 408 ($M+Na^+$, 61%), 444 (12), 424 (7), 297 (8), 287 (13), 202 (7), 194 (34), 188 (100), 150 (11), 130 (6); δ_H (300 MHz, $CDCl_3$) 0.88 (d, 3H, J=5.7 Hz, $CHCH_3$), 1.22 (m, 3H, $CHHCH(CH_3)CHH$), 1.60 (m, 2H, $CHHCH(CH_3)CHH$), 2.12 (m, 2H, $CHHN''CHH$), 2.55 (m, 4H, $CH_2N'CH_2$), 2.88 (m, 2H, $CHHN''CHH$), 3.75 (m, 4H, CH_2OCH_2), 3.79 (s, 2H, CH_2N'), 3.95 (s, 3H, OMe), 4.82 (s, 2H, CH_2N'), 7.22 (s, 1H, H2), 7.44 (d, 1H, J=8.7 Hz, H8), 7.92 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.46 (d, 1H, J= 1.5 Hz, H5); δ_H (75 MHz, $CDCl_3$) 22.2, 30.7, 34.5, 51.6, 52.3, 53.7, 53.8, 67.0, 68.9, 110.3, 121.9, 122.7, 123.6, 128.4, 130.5, 140.3, 168.5; HRMS (FAB+) calculated for $C_{22}H_{32}N_3O_3$ ($M+H$): 386.2444, found: 386.2428.

4.2.8. Compound 8. Prepared as outlined for compound **23** in 45% yield. HPLC-MS (ESI^+): t_R=4.76 min, m/z 398 ($M+H^+$, 38%), 456 (10), 359 (7), 299 (16), 287 (39), 199 (48), 188 (23), 150 (11), 142 (100), 128 (84); δ_H (300 MHz, $CDCl_3$) 0.87 (d, 3H, J=5.7 Hz, $CHCH_3$), 0.98 (d, 3H, J= 6.3 Hz, $CHCH_3$), 1.60 (m, 6H, $CHHCH(CH_3)CHH$), 1.75 (m, 4H, $HHCCH(CH_3)CHH$), 2.12 (m, 2H, $H_2CCH_2N'CH_2CH_2$), 2.58 (m, 2H, $CHHN'CHH$), 2.87 (m, 2H, $CHHN''CHH$), 3.38 (m, 2H, $CHHN''CHH$), 3.95 (s, 3H, OMe), 4.21 (s, 2H, CH_2N'), 4.86 (s, 2H, CH_2N''), 7.51 (d, 1H, J=8.7 Hz, H8), 7.64 (s, 1H, H2), 7.85 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.32 (d, J=1.5 Hz, 1H, H5); δ_C (75 MHz, DMSO) 21.0, 21.7, 29.8, 30.3, 33.5, 33.7, 45.9, 50.3, 51.7, 67.4, 111.6, 120.6, 121.4, 121.5, 122.3, 127.1, 138.7, 167.3; IR (film) 2974, 1711, 1614 cm^{-1}; HRMS (FAB+) calculated for $C_{24}H_{36}N_3O_2$ ($M+H$): 398.2808, found: 398.2808.

4.2.9. Compound 9. Prepared as outlined for compound **23** in 66% yield. HPLC-MS (ESI^+): t_R=3.99 min, m/z 372 ($M+H^+$, 19%), 430 (15), 404 (38), 348 (24), 299 (23), 287 (100), 202 (16), 188 (46), 150 (32), 122 (10); δ_H (300 MHz, $CDCl_3$) 0.97 (d, 3H, J=5.7 Hz, $CHCH_3$), 1.30 (t, 6H, J= 7.5 Hz, $N''CH_2CH_3$), 1.40–1.83 (m, 5H, $H_2CCH(CH_3)CH_2$), 2.60 (m, 2H, $H_2CCHN'CH_2CH_2$), 3.05 (q, 4H, J=7.5 Hz, NCH_2CH_3), 3.39 (m, 2H, $CHHN''CHH$), 3.93 (s, 3H, OMe), 4.24 (s, 2H, CH_2N'), 4.82 (s, 2H, CH_2N''), 7.47 (d, 1H, J= 8.7 Hz, H8), 7.63 (s, 1H, H2), 7.85 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.28 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 21.3, 23.7, 29.5, 31.5, 51.3, 52.1, 52.4, 107.0, 112.3, 121.0, 122.6, 123.7, 127.9, 130.2, 139.2, 168.5; IR (film) 2956, 1702, 1660 cm^{-1}.

4.2.10. Compound 10. Prepared as outlined for compound **23** in 51% yield. HPLC-MS (ESI^+): t_R=4.27 min, m/z 399 ($M+H^+$, 100%), 457 (14), 287 (17), 212 (13), 200 (37), 188 (83), 142 (8); δ_H (300 MHz, $CDCl_3$) 0.96 (d, 3H, J= 5.7 Hz, $CHCH_3$), 1.52 (m, 3H, $CHHCH(CH_3)CHH$), 1.71 (m, 2H, $CHHCH(CH_3)CHH$), 2.25 (s, 3H, NCH_3), 2.40 (m, 2H, $CH_2N(CH_2C)CH_2$), 2.45 (m, 4H, $CH_2N(CH_3)CH_2$), 2.58 (m, 4H, $CH_2N''CH_2$), 3.28 (m, 2H, $CHHN'CH_3H$), 3.95 (s, 3H, OMe), 4.09 (s, 2H, CH_2N'), 4.85 (s, 2H, CH_2N''), 7.48 (d, 1H, J=8.7 Hz, H8), 7.54 (s, 1H, H2), 7.93 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.32 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 21.6, 30.2, 32.6, 46.1, 50.5, 51.9, 52.4, 52.8, 54.9, 68.5, 110.7, 121.7, 122.6, 123.8, 128.7, 132.6, 139.8, 168.3; IR (film) 2949, 1708, 1620 cm^{-1}; HRMS (FAB+) calculated for $C_{23}H_{35}N_4O_2$ ($M+H$): 399.2760, found: 399.2757.

4.2.11. Compound 11. Prepared as outlined for compound **23** in 95% yield. HPLC-MS (ESI): t_R=4.61 min, *m*/*z* 386 (M+H$^+$, 100%); δ_H (300 MHz, $CDCl_3$) 0.98 (d, 3H, *J*=5.7 Hz, CHC*H*$_3$), 1.25 (m, 2H, C*H*$_2$N CH$_3$), 1.48–1.82 (m, 5H, *H*$_2$CC*H*(CH$_3$)C*H*$_2$), 2.36 (m, 2H, C*H*$_2$N″C*H*$_2$), 2.40 (m, 2H, C*H*$_2$N(CH$_2$C)C*H*$_2$), 2.45 (m, 4H, C*H*$_2$N(CH$_3$)C*H*$_2$), 2.54 (m, 4H, C*H*$_2$N′C*H*$_2$), 2.58 (m, 4H, C*H*$_2$N″C*H*$_2$), 2.69 (m, 4H, C*H*$_2$OC*H*$_2$), 3.95 (s, 3H, OMe), 4.20 (s, 2H, CH$_2$N′), 4.83 (s, 2H, CH$_2$N″), 7.50 (d, 1H, *J*=8.7 Hz, H8), 7.70 (s, 1H, H2), 7.94 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.32 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 21.4, 30.1, 31.8, 51.1, 51.3, 52.5, 67.0, 69.0, 106.2, 110.9, 121.3, 123.0, 124.0, 128.7, 133.8, 139.7, 168.2; IR (film) 2953, 1711, 1615, 1115 cm^{-1}; HRMS (FAB+) calculated for $C_{22}H_{32}N_3O_3$ (M+H): 386.2444, found: 386.2448.

4.2.12. Compound 12. Prepared as outlined for compound **23** in 52% yield. HPLC-MS (ESI$^+$): t_R=4.94 min, *m*/*z* 420 (M+H$^+$, 19%), 287 (13), 233 (7), 188 (42), 134 (100); δ_H (300 MHz, $CDCl_3$) 0.93 (d, 3H, *J*=5.7 Hz, CHC*H*$_3$), 1.58 (m, 2H, C*H*HCH(CH$_3$)C*H*H), 1.68 (m, 3H, C*H*HC*H*(CH$_3$)-C*H*H), 2.25 (s, 3H, N″CH$_3$), 2.50 (m, 2H, C*H*HN′C*H*H), 3.33 (m, 2H, C*H*HN′C*H*H), 3.62 (s, 2H, N″C*H*$_2$Ph), 3.95 (s, 3H, OMe), 4.18 (s, 2H, CH$_2$N′), 4.90 (s, 2H, CH$_2$N″), 7.25–7.35 (m, 5H, Ar), 7.40 (d, 1H, *J*=8.7 Hz, H8), 7.64 (s, 1H, H2), 7.93 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.33 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 20.9, 29.7, 31.1, 40.2, 51.1, 51.8, 52.0, 59.0, 67.6, 104.9, 110.7, 120.4, 122.4, 123.5, 127.4, 128.4, 128.5, 133.2, 137.9, 139.3, 168.0; IR (film) 2951, 1716, 1617, 1251 cm^{-1}; HRMS (FAB+) calculated for $C_{26}H_{34}N_3O_2$ (M+H): 420.2651, found: 420.2652.

4.2.13. Compound 13. Prepared as outlined for compound **23** in 67% yield. δ_H (300 MHz, $CDCl_3$) 0.87 (d, 3H, *J*=5.7 Hz, CHC*H*$_3$), 1.25 (m, 3H, C*H*HC*H*(CH$_3$)C*H*H), 1.30 (tr, 6H, *J*=7.5 Hz, N′CH$_2$*CH*$_3$), 2.12 (m, 2H, C*H*HCH(CH$_3$)C*H*H), 2.85 (m, 2H, C*H*HN′C*H*H), 3.05 (q, 4H, *J*=7.5 Hz, N′C*H*$_2$CH$_3$), 3.95 (s, 3H, OMe), 4.29 (s, 2H, CH$_2$N′), 4.88 (s, 2H, CH$_2$N″), 7.52 (d, 1H, *J*=8.7 Hz, H8), 7.62 (s, 1H, H2), 7.93 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.33 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 10.7, 22.2, 30.7, 34.4, 46.1, 47.1, 51.6, 52.3, 69.0, 109.6, 110.6, 121.8, 122.2, 123.6, 128.4, 131.9, 140.0, 168.4; IR (film) 2949, 1716, 1614 cm^{-1}; HRMS (FAB+) calculated for $C_{22}H_{34}N_3O_2$ (M+H): 372.2651, found: 372.2662.

4.2.14. Compound 14. Prepared as outlined for compound **23** in 47% yield. δ_H (300 MHz, $CDCl_3$) 1.06 (t, 6H, *J*=7.2 Hz, NCH$_2$NCH$_2$*CH*$_3$), 1.30 (tr, 6H, *J*=7.5 Hz, N′CH$_2$-*CH*$_3$), 2.62 (q, 4H, *J*=7.2 Hz, N″C*H*$_2$CH$_3$), 3.00 (q, 4H, *J*=7.5 Hz, N′C*H*$_2$CH$_3$), 3.93 (s, 3H, OMe), 3.94 (s, 2H, CH$_2$N′), 4.30 (s, 2H, CH$_2$N″), 7.39 (d, 1H, *J*=8.7 Hz, H8), 7.65 (s, 1H, H2), 7.89 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.45 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 9.1, 12.4, 45.2, 45.3, 46.6, 46.8, 52.2, 70.2, 105.7, 112.1, 120.6, 122.4, 123.6, 127.5, 132.6, 139.0, 168.2; IR (film) 2950, 1709, 1263 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{32}N_3O_2$ (M+H): 346.2495, found: 346.2483.

4.2.15. Compound 15. Prepared as outlined for compound **23** in 70% yield. δ_H (300 MHz, $CDCl_3$) 1.30 (tr, 6H, *J*=7.5 Hz, N′CH$_2$*CH*$_3$), 2.36 (s, 3H, NC*H*$_3$), 2.61 (m, 8H, C*H*$_2$C*H*$_2$N″C*H*$_2$C*H*$_2$), 3.02 (q, 4H, *J*=7.5 Hz, N′C*H*$_2$CH$_3$), 3.94 (s, 3H, OMe), 4.29 (s, 2H, CH$_2$N′), 4.82 (s, 2H, CH$_2$N″), 7.48 (d, 1H, *J*=8.7 Hz, H8), 7.65 (s, 1H, H2), 7.94 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.33 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 10.0, 45.6, 45.8, 46.7, 50.2, 52.4, 54.7, 68.4, 108.2, 110.7, 121.6, 122.6, 128.5, 123.9, 132.5, 139.7, 168.3; IR (film) 2951, 1704, 1616 cm^{-1}; HRMS (FAB+) calculated for $C_{21}H_{33}N_4O_2$ (M+H): 373.2604, found: 373.2610.

4.2.16. Compound 16. Prepared as outlined for compound **23** in 74% yield. δ_H (300 MHz, $CDCl_3$) 1.28 (t, 6H, *J*=7.2 Hz, N′CH$_2$*CH*$_3$), 2.55 (t, 4H, *J*=4.5 Hz, C*H*$_2$N″C*H*$_2$), 2.95 (q, 4H, *J*=7.2 Hz, N′C*H*$_2$CH$_3$), 3.69 (t, 4H, *J*=4.5 Hz, C*H*$_2$OC*H*$_2$), 3.94 (s, 3H, OMe), 4.22 (s, 2H, CH$_2$N′), 4.82 (s, 2H, CH$_2$N″), 7.48 (d, 1H, *J*=8.7 Hz, H8), 7.59 (s, 1H, H2), 7.94 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.36 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 10.5, 46.0, 47.1, 51.1, 52.4, 67.0, 68.8, 109.9, 110.5, 121.9, 122.5, 123.8, 128.6, 131.7, 139.8, 168.3; IR (film) 2967, 1709, 1614, 1116 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{30}N_3O_3$ (M+H): 360.2287, found: 360.2289.

4.2.17. Compound 17. Prepared as outlined for compound **23** in 71% yield. δ_H (300 MHz, $CDCl_3$) 1.29 (t, 6H, *J*=7.5 Hz, N′CH$_2$*CH*$_3$), 2.27 (s, 3H, N″C*H*$_3$), 2.95 (q, 4H, *J*=7.5 Hz, N′C*H*$_2$CH$_3$), 3.62 (s, 2H, N″C*H*$_2$Ph), 3.92 (s, 3H, OMe), 4.24 (s, 2H, CH$_2$N′), 4.90 (s, 2H, CH$_2$N″), 7.22–7.38 (m, 5H, Ar), 7.40 (d, 1H, *J*=8.7 Hz, H8), 7.62 (s, 1H, H2), 7.92 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.35 (d, 1H, *J*=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 10.7, 40.6, 46.1, 47.2, 52.4, 59.4, 67.8, 109.8, 110.7, 121.9, 122.3, 123.7, 127.8, 128.6, 128.7, 128.9, 129.1, 131.7, 138.4, 139.9, 168.4; IR (film) 2950, 1709, 1614, 1247 cm^{-1}; HRMS (FAB+) calculated for $C_{24}H_{32}N_3O_2$ (M+H): 394.2495, found: 394.2494.

4.2.18. Compound 18. Prepared as outlined for compound **23** in 71% yield. HPLC-MS (ESI): t_R=3.62 min, *m*/*z* 421 (M+Na$^+$, 13%), 202 (34), 150 (100), 128 (6); δ_H (300 MHz, $CDCl_3$) 0.89 (d, 3H, *J*=5.7 Hz, CHC*H*$_3$), 1.62 (m, 3H, *H*$_2$CC*H*(CH$_3$)C*H*$_2$), 2.19 (m, 2H, *H*$_2$CCH(CH$_3$)-C*H*$_2$), 2.62 (s, 3H, NC*H*$_3$), 2.88–3.18 (m, 10H, C*H*HN″C*H*H, C*H*$_2$C*H*$_2$N′C*H*$_2$C*H*$_2$), 3.94 (s, 2H, CH$_2$N′), 3.95 (s, 3H, OMe), 4.89 (s, 2H, CH$_2$N″), 7.39 (d, 1H, *J*=8.7 Hz, H8), 7.61 (s, 1H, H2), 7.92 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.37 (d, 1H, *J*=1.5 Hz, H5); IR (film) 2951, 1708, 1617 cm^{-1}; HRMS (FAB+) calculated for $C_{23}H_{35}N_4O_2$ (M+H): 399.2760, found: 399.2762.

4.2.19. Compound 19. Prepared as outlined for compound **23** in 46% yield. HPLC-MS (ESI): t_R=3.43 min, *m*/*z* 395 (M+Na$^+$, 31%), 431 (21), 348 (13), 288 (20), 217 (6), 202 (78), 150 (100), 130 (15), 120 (5); δ_H (300 MHz, $CDCl_3$) 1.40 (tr, 6H, *J*=7.2 Hz, N′CH$_2$C*H*$_3$), 2.56 (s, 3H, NCH$_3$), 3.10 (q, 4H, *J*=7.2 Hz, NC*H*$_2$CH$_3$), 2.80–3.20 (m, 8H, C*H*$_2$C*H*$_2$N″C*H*$_2$C*H*$_2$), 3.92 (s, 2H, CH$_2$N′), 3.93 (s, 3H, OMe), 4.06 (s, 2H, CH$_2$N″), 7.28 (s, 1H, H2), 7.52 (d, 1H, *J*=8.7 Hz, H8), 7.88 (dd, 1H, *J*=8.7, 1.5 Hz, H7), 8.35 (d, 1H, *J*=1.5 Hz, H5); IR (film) 2717, 1697, 1621 cm^{-1}.

4.2.20. Compound 20. Prepared as outlined for compound **23** in 73% yield. HPLC-MS (ESI): t_R=3.52 min, *m*/*z* 422 (M+Na$^+$, 31%), 458 (15), 438 (8), 400 (8), 348 (6), 288

(30), 200 (8), 188 (100), 130 (12); δ_H (300 MHz, $CDCl_3$) 1.42 (s, 3H, N″$CH_2CH_2NCH_3$), 2.59 (s, 3H, N′CH_2CH_2-NCH_3), 2.70 (m, 8H, CH_2CH_2N″CH_2CH_2), 2.82–3.02 (m, 8H, CH_2CH_2N′CH_2CH_2), 3.91 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.82 (s, 2H, CH_2N″), 7.32 (s, 1H, H2), 7.43 (d, 1H, J=8.7 Hz, H8), 7.92 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.49 (d, 1H, J=1.5 Hz, H5); IR (film) 2953, 1701, 1615 cm^{-1}; HRMS (FAB+) calculated for $C_{22}H_{34}N_5O_2$ (M+H): 400.2713, found: 400.2712.

4.2.21. Compound 21. Prepared as outlined for compound **23** in 85% yield. HPLC-MS (ESI^+): t_R=3.71 min, *m/z* 387 ($M+H^+$, 55%), 445 (12), 425 (8), 409 (29), 300 (6), 288 (24), 202 (78), 188 (18), 150 (100), 130 (7); δ_H (300 MHz, $CDCl_3$) 2.55 (t, 4H, J=4.2 Hz, CH_2N″CH_2), 2.66 (s, 3H, NCH_3), 2.85–3.25 (m, 8H, CH_2CH_2N′CH_2CH_2), 3.69 (t, 4H, J=4.2 Hz, CH_2OCH_2), 3.92 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.81 (s, 2H, CH_2N″), 7.29 (s, 1H, H2), 7.47 (d, 1H, J=8.7 Hz, H8), 7.93 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.40 (d, 1H, J=1.5 Hz, H5); IR (film) 2951, 1707, 1614, 1115 cm^{-1}; HRMS (FAB+) calculated for $C_{21}H_{31}N_4O_3$ (M+H): 387.2396, found: 387.2392.

4.2.22. Compound 22. Prepared as outlined for compound **23** in 68% yield. HPLC-MS (ESI^+): t_R=4.32 min, *m/z* 443 ($M+Na^+$, 39%), 479 (7), 231 (6), 202 (77), 188 (100), 150 (52), 134 (100), 122 (36); δ_H (300 MHz, $CDCl_3$) 2.28 (s, 3H, N″CH_3), 2.65 (s, 3H, NCH_3), 2.85–3.25 (m, 8H, CH_2CH_2-N′CH_2CH_2), 3.62 (s, 2H, N″CH_2Ph), 3.92 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.88 (s, 2H, CH_2N″), 7.22–7.36 (m, 6H, H2, Ar), 7.39 (d, 1H, J=8.7 Hz, H8), 7.92 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.37 (d, 1H, J=1.5 Hz, H5); IR (film) 2950, 1709, 1616, 1248 cm^{-1}; HRMS (FAB+) calculated for $C_{25}H_{33}N_4O_2$ (M+H): 421.2604, found: 421.2613.

4.2.23. Compound 24. Prepared as outlined for compound **23** in 57% yield. HPLC-MS (ESI^+): t_R=3.56 min, *m/z* 382 ($M+Na^+$, 100%), 418 (14), 404 (11), 297 (16), 287 (29), 202 (18), 188 (27), 158 (6), 144 (10), 137 (9), 120 (10); δ_H (300 MHz, $CDCl_3$) 1.08 (t, 6H, J=7.2 Hz, N″CH_2CH_3), 2.58 (m, 4H, CH_2N′CH_2), 2.61 (q, 4H, J=7.2 Hz, N″CH_2-CH_3), 3.75 (m, 4H, CH_2OCH_2), 3.80 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.87 (s, 2H, CH_2N″), 7.27 (s, 1H, H2), 7.48 (d, 1H, J=8.7 Hz, H8), 7.89 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.48 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 12.6, 45.4, 51.2, 52.3, 53.6, 53.8, 67.0, 68.7, 110.0, 111.4, 122.1, 122.6, 122.9, 123.9, 127.9, 128.6, 139.3, 168.7; IR (film) 2951, 1709, 1619, 1115 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{30}N_3O_3$ (M+H): 360.2287, found: 360.2282.

4.2.24. Compound 25. Prepared as outlined for compound **23** in 55% yield. HPLC-MS (ESI^+): t_R=3.79 min, *m/z* 409 ($M+Na^+$, 100%), 445 (20), 425 (6), 348 (7), 288 (8), 188 (100), 122 (7); δ_H (300 MHz, $CDCl_3$) 2.30 (s, 3H, NCH_3), 2.40–2.68 (m, 12H, CH_2N′CH_2, CH_2CH_2N″CH_2CH_2), 3.73 (m, 4H, CH_2OCH_2), 3.75 (s, 2H, CH_2N′), 3.94 (s, 3H, OMe), 4.80 (s, 2H, CH_2N″) 7.17 (s, 1H, H2), 7.43 (d, 1H, J=8.7 Hz, H8), 7.91 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.46 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 46.0, 50.4, 52.3, 53.8, 53.9, 55.0, 67.3, 68.4, 110.2, 122.0, 122.9, 123.7, 128.6, 129.9, 140.1, 168.5; IR (film) 2952, 1698, 1615, 1113 cm^{-1}; HRMS (FAB+) calculated for $C_{21}H_{31}N_4O_3$ (M+H): 387.2396, found: 387.2281.

4.2.25. Compound 26. Prepared as outlined for compound **23** in 51% yield. HPLC-MS (ESI): t_R=3.90 min, *m/z* 396 ($M+Na^+$, 100%), 432 (17), 412 (8), 287 (14), 188 (11), 144 (18); δ_H (300 MHz, $CDCl_3$) 2.53 (m, 4H, CH_2N″CH_2), 2.60 (m, 4H, CH_2N′CH_2), 3.68 (m, 4H, CH_2CH_2N″CH_2-CH_2), 3.76 (m, 4H, CH_2CH_2N′CH_2CH_2), 3.80 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.79 (s, 2H, CH_2N″), 7.27 (s, 1H, H2), 7.45 (d, 1H, J=8.7 Hz, H8), 7.93 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.45 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 50.8, 52.0, 53.2, 66.7, 68.4, 109.9, 122.0, 122.3, 123.5, 128.2, 130.5, 139.6, 168.0; IR (film) 2923, 1710, 1614, 1115 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{28}N_3O_4$ (M+H): 374.2080, found: 374.2081.

4.2.26. Compound 27. Prepared as outlined for compound **23** in 60% yield. HPLC-MS (ESI^+): t_R=4.52 min, *m/z* 430 ($M+Na^+$, 100%), 466 (13), 446 (9), 188 (94), 134 (74), 122 (8); δ_H (300 MHz, $CDCl_3$) 2.27 (s, 3H, N″CH_3), 2.61 (m, 4H, CH_2N′CH_2), 3.61 (s, 2H, N′CH_2Ph), 3.77 (m, 4H, CH_2OCH_2), 3.83 (s, 2H, CH_2N′), 3.94 (s, 3H, OMe), 4.86 (s, 2H, CH_2N″), 7.24–7.35 (m, 6H, H2, Ar), 7.38 (d, 1H, J= 8.7 Hz, H8), 7.91 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.45 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 40.6, 52.3, 53.5, 53.7, 59.4, 66.9, 67.7, 110.5, 122.2, 122.6, 123.7, 127.8, 128.5, 128.9, 129.1, 138.4, 140.1, 168.5; IR (film) 2923, 1709, 1614, 1254, 1116 cm^{-1}; HRMS (FAB+) calculated for $C_{24}H_{30}N_3O_3$ (M+H): 408.2287, found: 408.2300.

4.2.27. Compound 28. Prepared as outlined for compound **23** in 72% yield. HPLC-MS (ESI^+): t_R=4.65 min, *m/z* 442 ($M+Na^+$, 44%), 231 (100), 188 (7), 142 (20), 122 (13); δ_H (300 MHz, $CDCl_3$) 0.88 (d, 3H, J=5.7 Hz, $CHCH_3$), 1.23 (m, 3H, CHHCH(CH_3)CHH), 1.59 (m, 2H, CHHCH(CH_3)-CHH), 2.13 (m, 2H, CHHN″CHH), 2.24 (s, 3H, N′CH_3), 2.88 (m, 2H, CHHN″CHH), 3.60 (s, 2H, N′CH_2Ph), 3.77 (s, 2H, CH_2N′), 3.95 (s, 3H, OMe), 4.83 (s, 2H, CH_2N″), 7.15–7.47 (m, 7H, H2, H8, Ar), 7.90 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.46 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 22.2, 30.7, 34.5, 51.6, 52.2, 52.7, 62.2, 68.8, 110.2, 121.7, 123.0, 123.6, 127.6, 128.3, 128.7, 129.6, 140.4, 168.6; IR (film) 2924, 1716, 1614, 1245 cm^{-1}; HRMS (FAB+) calculated for $C_{26}H_{34}N_3O_2$ (M+H): 420.2651, found: 420.2640.

4.2.28. Compound 29. Prepared as outlined for compound **23** in 55% yield. HPLC-MS (ESI^+): t_R=4.42 min, *m/z* 416 ($M+Na^+$, 14%), 309 (8), 231 (28), 188 (40), 122 (100); δ_H (300 MHz, $CDCl_3$) 1.06 (t, 6H, J=7.2 Hz, N″CH_2CH_3), 2.24 (s, 3H, N′CH_3), 2.61 (q, 4H, J=7.2 Hz, N″CH_2CH_3), 3.61 (s, 2H, N′CH_2Ph), 3.79 (d, 2H, J=4.2 Hz, CH_2N′), 3.95 (s, 3H, OMe), 4.86 (s, 2H, CH_2N′), 7.18–7.44 (m, 7H, H2, H8, Ar), 7.90 (dd, 1H, J=8.7, 1.5 Hz, H7), 8.46 (d, 1H, J=1.5 Hz, H5); δ_C (75 MHz, DMSO) 21.0, 41.7, 51.6, 51.7, 58.3, 61.0, 66.8, 111.3, 122.4, 127.0, 127.4, 128.2, 128.5, 128.7, 136.1, 138.5, 139.7, 149.6, 167.3; IR (film) 2947, 1709, 1614, 1251 cm^{-1}; HRMS (FAB+) calculated for $C_{24}H_{32}N_3O_2$ (M+H): 394.2495, found: 394.2487.

4.2.29. Compound 30. Prepared as outlined for compound **23** in 63% yield. HPLC-MS (ESI^+): t_R=4.46 min, *m/z* 443 ($M+Na^+$, 67%), 459 (8), 277 (7), 188 (71), 180 (28), 134 (13), 122 (100); δ_H (300 MHz, $CDCl_3$) 2.24 (s, 3H, N′CH_3), 2.28 (s, 3H, NCH_3), 2.35–2.72 (m, 8H, CH_2CH_2N″CH_2-CH_2), 3.60 (s, 2H, N′CH_2Ph), 3.76 (s, 2H, CH_2N′), 3.95

(s, 3H, OMe), 4.79 (s, 2H, CH_2N''), 7.14–7.45 (m, 7H, H2, H8, Ar), 7.91 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.46 (d, 1H, $J=$ 1.5 Hz, H5); δ_C (75 MHz, $CDCl_3$) 46.1, 50.5, 52.3, 52.6, 55.0, 62.1, 68.4, 110.2, 121.9, 123.0, 123.7, 127.5, 128.5, 128.7, 129.6, 140.2, 168.6; IR (film) 2947, 1709, 1614, 1251 cm^{-1}; HRMS (FAB+) calculated for $C_{25}H_{33}N_4O_2$ (M+H): 421.2604, found: 421.2609.

4.2.30. Compound 31. Prepared as outlined for compound **23** in 64% yield. HPLC-MS (ESI^+): $t_R=4.60$ min, *m/z* 430 ($M+Na^+$, 74%), 446 (10), 362 (20), 231 (100), 180 (8), 134 (6), 122 (14); δ_H (300 MHz, $CDCl_3$) 2.25 (s, 3H, $N'CH_3$), 2.52 (t, 4H, $J=4.5$ Hz, $CH_2N''CH_2$), 3.62 (s, 2H, $N'CH_2Ph$), 3.69 (t, 4H, $J=4.5$ Hz, CH_2OCH_2), 3.78 (s, 2H, CH_2N'), 3.95 (s, 3H, OMe), 4.78 (s, 2H, CH_2N''), 7.18–7.45 (m, 7H, H2, H8, Ar), 7.91 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.46 (d, 1H, $J=1.5$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 40.6, 52.3, 52.5, 59.4, 62.3, 67.6, 110.3, 121.8, 123.1, 123.7, 127.8, 128.5, 128.8, 128.9, 129.2, 138.4, 140.2, 168.6; IR (film) 2947, 1716, 1614, 1247 cm^{-1}.

4.2.31. Compound 32. Prepared as outlined for compound **23** in 56% yield. HPLC-MS (ESI^+): $t_R=5.10$ min, *m/z* 464 ($M+Na^+$, 56%), 480 (7), 231 (8), 188 (100), 134 (65), 122 (52); δ_H (300 MHz, $CDCl_3$) 2.26 (s, 6H, NCH_3), 3.61 (m, 4H, NCH_2Ph), 3.79 (s, 2H, CH_2N'), 3.95 (s, 3H, OMe), 4.86 (s, 2H, CH_2N''), 7.15–7.43 (m, 7H, H2, H8, Ar), 7.90 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.47 (d, 1H, $J=1.5$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 51.2, 52.3, 52.5, 67.1, 68.7, 110.2, 121.8, 123.0, 123.8, 128.5, 128.8, 129.7, 140.1, 168.5; IR (film) 2920, 1710, 1614, 1247, 1115 cm^{-1}; HRMS (FAB+) calculated for $C_{28}H_{32}N_3O_2$ (M+H): 444.2495, found: 444.2495.

4.2.32. Compound 33. To compound **2** (50.0 mg, 193.5 μmol) in dioxane–HOAc (4/1, 1.0 mL) was added a mixture of 4-methylpiperidine (34.3 μL, 290.2 μmol) and formaldehyde (21.7 μL, 290.2 μmol, 37 wt% solution in water) in dioxane–HOAc (4/1, 1.0 mL). The resultant mixture was agitated at room temperature for 66 h. Evaporation of the solvents and flash chromatography (CH_2Cl_2/MeOH/Et_3N, v/v/v 90:10:1) yielded **33** (46 mg, 64%). HPLC-MS (ESI^+): $t_R=4.12$ min, *m/z* 370 ($M+H^+$); δ_H (300 MHz, $CDCl_3$) 0.87 (d, 3H, $J=5.4$ Hz, H-21), 1.21 (m, 3H, H-19, H18, H17), 1.60 (m, 2H, H19, H17), 1.88 (m, 4H, H13, H12), 2.13 (m, 2H, H20, H16), 2.81 (m, 4H, H14, H11), 2.88 (m, 2H, H-20, H-16), 3.94 (s, 3H, OMe), 4.01 (s, 2H, H10), 4.84 (s, 2H, H15), 7.38 (s, 1H, H2), 7.49 (d, 1H, $J=8.7$ Hz, H8), 7.91 (dd, 1H, $J=8.7$, 1.6 Hz, H7), 8.39 (d, 1H, $J=1.6$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 22.2 (C21), 23.8 (C13, C12), 30.7 (C18), 34.4 (C19, C17), 50.0 (C20), 51.6 (C16), 52.3 (C10), 54.1 (C11, C14), 68.9 (C15), 110.5 (C8), 111.8 (C3), 121.8 (C6), 122.1 (C5), 123.6 (C7), 128.1 (C4), 130.9 (C2), 140.0 (C9), 168.5 (CO).

4.2.33. Compound 34. To compound **3** (104 mg, 362 μmol) in dioxane–HOAc (4/1, 1.0 mL) was added a mixture of pyrrolidine (45 μL, 543 μmol) and formaldehyde (41 μL, 543 μmmol, 37 wt% solution in water) in dioxane–HOAc (4/1, 1.0 mL). After agitation of the resultant mixture for 48 h at room temperature, an additional portion of pyrrolidine (90 μL, 1.09 mmol) and formaldehyde (82 μL, 1.09 mmol, 37 wt% solution in water). After agitation for an additional 18 h at the solvents were removed and the residue was flash chromatographed (CH_2Cl_2/MeOH/Et_3N, v/v/v 90:10:1) to give **34** (83 mg, 62%). δ_H (300 MHz, $CDCl_3$) 0.91 (d, 3H, $J=5.7$ Hz, H21), 1.30 (m, 3H, H19, H18, H17), 1.60 (m, 2H, H19, H17), 1.75 (m, 4H, H13, H12), 2.03 (m, 2H, H20, H16), 2.64 (m, 4H, H14, H11), 2.96 (m, 2H, H20, H16), 3.75 (s, 2H, H15), 3.93 (s, 3H, OMe), 4.96 (s, 2H, H10), 7.23 (s, 1H, H2), 7.44 (d, 1H, $J=8.7$ Hz, H8), 7.91 (dd, 1H, $J=8.7$, 1.5 Hz, H7), 8.43 (d, 1H, $J=1.5$ Hz, H5); δ_C (75 MHz, $CDCl_3$) 22.2 (C21), 24.0 (C12, C13), 31.0 (C18), 34.4 (C17, C19), 51.4 (C14, C11), 52.2 (MeO), 53.4 (C15), 54.0 (C20, C16), 64.9 (C10), 110.0 (C8), 112.7 (C3), 121.8 (C6), 122.6 (C5), 123.4 (C7), 128.7 (C4), 130.3 (C2), 139.9 (C9), 168.6 (CO).

Acknowledgements

This work was supported financially by Amersham Biosciences and the Royal Institute of Technology. We also wish to thank Dr. Herbert Baumann, Amersham Biosciences, for assistance with the NMR experiments.

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Tetrahedron 62 (2006) 3446–3454
Tetrahedron

Self-assembly of aromatic sulfonamide–amide hybridized molecules: formation of 2D layers and 3D microporous networks in the solid state

Zhi-Qiang Hu and Chuan-Feng Chen*

Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Center for Molecular Science, Beijing 100080, China

Received 27 July 2005; revised 9 December 2005; accepted 9 December 2005

Abstract—Three sulfonamide–amide hybridized molecules and one cyclic analogue were synthesized and their assembling behaviors in the solid state were investigated by X-ray crystallography. The results showed that the hybridized molecules could be not only induced to take up helical secondary structures by a network of intramolecular hydrogen bonds, but also utilized as useful building blocks for assembling into 1D zigzag chains and superhelices, 2D layers and further 3D networks. Moreover, it was found that the multiple C–H···O═S hydrogen bonds played an important role in the assembling processes.
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1. Introduction

There has been intense interest in designing molecules that can assemble into molecular crystals.[1,2] Some recent efforts in this field have focused on the assembly of organic molecule[3] through the non-covalent interactions and these organic crystals with predefined solid state structures can find many important applications for developing new materials with nonlinear optical properties or other functions.[4] Because of high selectivity and directionality, hydrogen bonds are the most widely used interactions.[5] Recently, weaker interactions have received increasing interest in self-assembly of organic molecules.[6] The properties of the materials are determined by three-dimensional array of individual molecules, so it is important to construct higher order superstructures, such as microporous networks[7] with potential applications as materials in selective separation, gas absorption, and heterogeneous catalysis. However, current works in assembling molecular solids focus mainly on one-dimensional aggregates such as chains[8] because controlling the crystal architecture in all three dimensions is difficult.

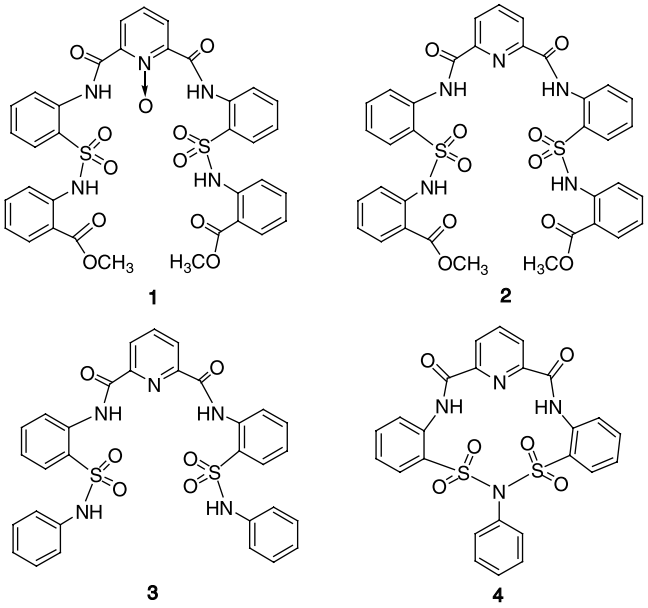
Discovery of molecular building block bearing different functional groups that can assemble to form higher order superstructures is of paramount importance in the controlled assembly of solid-state structures for developing new materials. Being easy to form hydrogen bonds, the assemblies of organic molecules containing amide group have been widely investigated to form superstructure such as superhelice[9] and layers.[10] Compared with the wide application of organic amides in different assembling systems, little is known[11] about the assembly of organic molecules bearing sulfonamide groups although organic molecules bearing $RNHSO_2NHR$ groups can self-assemble into robust two-dimensional molecular layers through H···O═S hydrogen bonds network.[12]

Different from the planar amide group, the sulfonamide group adopts tetrahedral geometry and O atoms in sulfonamide group are easier to form hydrogen bonds in higher dimensions. This makes organic molecules containing sulfonamide group to be potential building blocks for controlled assembly into higher order superstructure. Moreover, the sulfonamide is a stronger hydrogen-bond donor than the amide. Sulfonamide group also shows a small rotational barrier of the S–N bond and one of the H–N–S═O torsion angles is near 0°.[13] With these different structural features from those of the amide, we envisioned that a rational designed aromatic sulfonamides could be a useful building block for self-assembly along different directions into unique highly ordered supramolecular architectures through hydrogen bonds and π–π stacking interactions. Herein, we described that aromatic sulfonamide–amide hybridized molecules **1**–**3** with helical secondary structures and the cyclic analogue **4** could serve as units to assemble into 2D layers and 3D microporous

Keywords: Sulfonamide; Self-assembly; Superhelice; 2D Layer; 3D Microporous network; Hydrogen bond.
* Corresponding author. Tel.: +86 10 62588936; fax: +86 10 62554449; e-mail: cchen@iccas.ac.cn

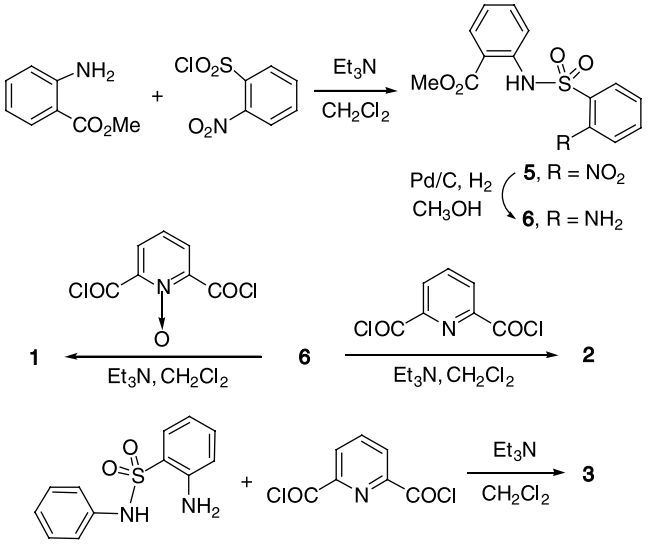
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.12.058

networks in the solid state. Moreover, the hydrogen bonds involving sulfonamide groups played an important role in the assembling processes.



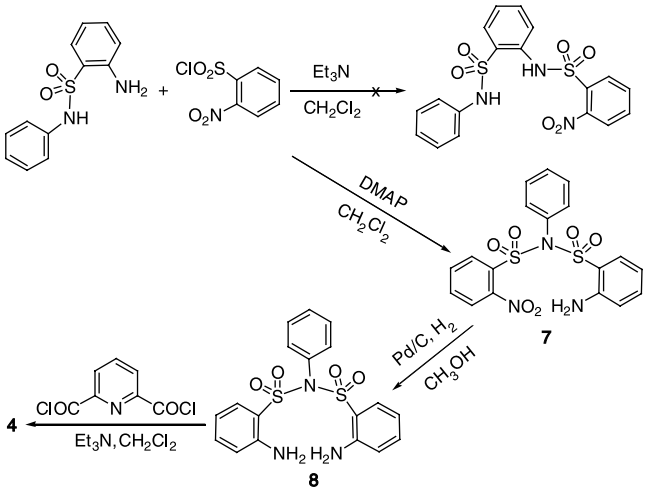
2. Results and discussion

Synthesis of **1**–**3** was depicted in Scheme 1. Compound **1** was readily synthesized by the reaction of 2,6-bis(chloroformyl)pyridine *N*-oxide with intermediate **6**, *N*-(2-methoxycarbonylphenyl)-2-amino-benzenesulfonamide, in the presence of Et_3N. **6** was prepared by treatment of 2-nitrobenzenesulfonyl chloride with methyl anthranilate in the presence of Et_3N, followed by catalytic hydrogenation. Under the similar reaction conditions, compounds **2** and **3**[14] were synthesized by the reactions of 2,6-bis(chloroformyl)-pyridine with **6** and *N*-phenyl-2-amino-benzenesulfonamide, respectively.



Scheme 1. Synthesis of compounds **1**–**3**.

When we intended to synthesize the oligosulfonamide through coupling *N*-phenyl-2-aminobenzenesulfonamide with 2-nitrobenzenesulfonyl chloride in the presence of Et_3N, it was found that no reaction occured. The same result was obtained by replacing Et_3N with Na_2CO_3. This might be due to the electron withdrawing effect of sulfonamide group and intramolecule hydrogen bond between NH_2 and SO_2 groups. When the stronger base, 4-dimethylamino-pyridine (DMAP), was used, we found that 2-nitrobenzenesulfonyl chloride reacted with NH in sulfonamide group rather than NH_2 group, which resulted in **7**. Compound **7** was reduced by catalytic hydrogenation in methanol to yield **8** in quantitative yield, which was further reacted with 2,6-bis(chloroformyl) pyridine to give a cyclic compound **4** (Scheme 2).



Scheme 2. Synthesis of compound **4**.

The assemblies of **1**–**4** in the solid states were investigated through X-ray diffraction analysis.

We first obtained crystals of **1** suitable for X-ray analysis from a mixture of CH_2Cl_2/CH_3OH. The crystal named as crystal **I** belonged to *P*2/*n* space group. As expected, bifurcated intramolecular hydrogen bonds involving both pyridine *N*-oxide O6 and sulfonyl inward O4 atoms as acceptors (N2···O6, 2.58 Å and N2···O4, 2.88 Å) were existed in the crystal **I** (Fig. 1a). Pyridine ring and two adjacent benzene rings were not planar, and the two benzene rings were above and below the plane of pyridine ring about 30°. With the torsion angle of H–N1–S–O4 of 9.51° and O3 atoms outward, the terminal rings were far apart and positioned above and below the respective adjacent ring of all 67°. The results led to molecule **1** to take up a 'Gelander' helical conformation,[15] which was different from that of oligoanthranilamides.[16]

As shown in Figure 1b, **1** in the crystal **I** could assemble along the [1 0 1] direction into a twisted zigzag structure. The main driving forces were the C11–H···O4 hydrogen bonds (H···O, 2.63 Å) and the π–π stacking interactions between the benzenesulfonamide rings of adjacent molecules with centroid distance of 3.94 Å.

Interestingly, we found that the assembled zigzag chains could further associate into higher order supramolecular structures

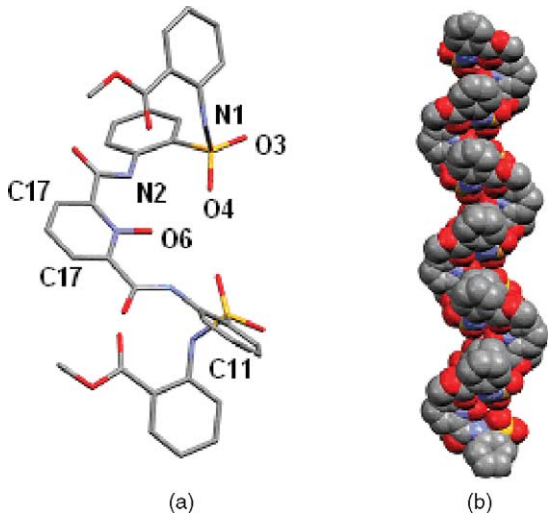


Figure 1. (a) X-ray crystal structure of **1** in the crystal **I**. Hydrogen atoms were omitted for clarity. (b) Side view of the assembled zigzag chain.

through π–π stacking interactions and C–H···O═S hydrogen bonds. Firstly, the zigzag structures assembled along the *b*-axis into a 2D layer through (C17) H···O3 (H···O, 2.57 Å) hydrogen bonds between 3 and 5-protons of pyridine rings in a zigzag chain and sulfonyl outward O atoms of the adjacent zigzag chain (Fig. 2a and b). Then, the 2D layers stack along [$\bar{1}$01] direction into 3D microporous networks through π–π stacking interactions between the terminal rings of **1** with the centroid distance of 3.67 Å. When it was viewed along the [101] direction (Fig. 3a), there were channels formed by the interlocked zigzag chains with the size of ca. 7.5×16.6 Å and carbonate groups occupied inside. When it was viewed along the [$\bar{1}$01] direction (Fig. 3b), there was another kind of channels with size of ca. 6.5×7.4 Å, in which CH_2Cl_2 molecules were positioned.

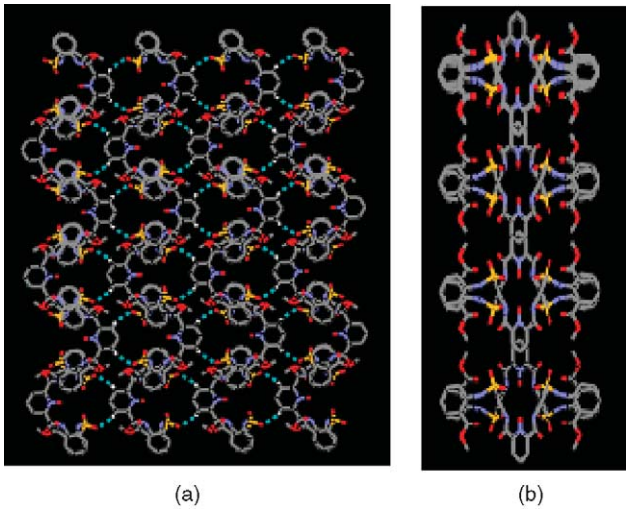


Figure 2. (a) Side view of a 2D layer along *a*-axis. Dashed lines represent the C–H···O═S hydrogen bonds. (b) Top view of a 2D layer.

To investigate the effect of environment on the assembly of **1**, another kind of crystal of **1** was obtained from a mixture of CH_2Cl_2/*n*-C_6H_{14} and named as crystal **II**. Interestingly, we found that the crystal **II** belonged to the non-centrosymmetric space group of $P2_12_12_1$.[17] As shown in Figure 4a, **1** also takes up a 'Gelander'helical secondary structure in the crystal **II**, which is stabilized by a network of intramolecular hydrogen bonds (N1···O2, 2.60 Å; N2···O4, 2.90 Å; N2H···O6, 2.61 Å; N3···O6, 2.61 Å; N3···O8, 2.90 Å; N4···O10, 2.61 Å).

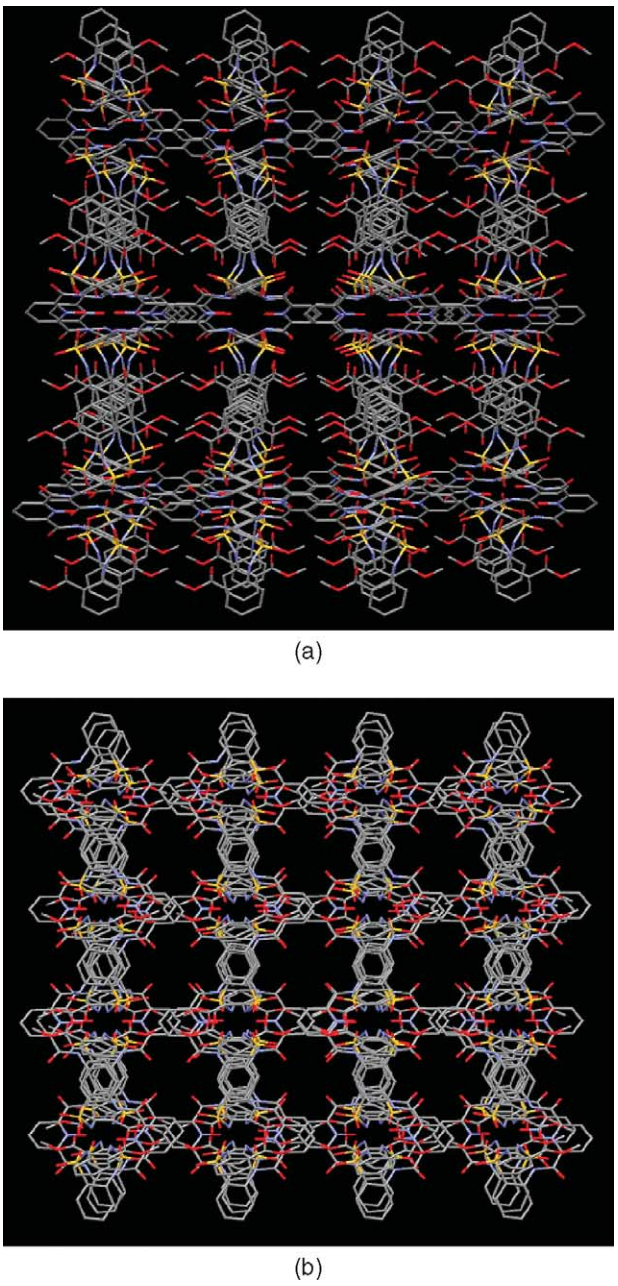


Figure 3. View of microporous networks presented in the crystal **I** (a) along [101] direction; (b) along [$\bar{1}$01] direction. Hydrogen atoms and solvent molecules were omitted for clarity.

Different from the assembling way in crystal **I**, **1** in the crystal **II** could assemble along the *b*-axis to form a helical superstructure (Fig. 4b). In view of the occurrence of helical structures and superstructures[18] in many biological systems and their importance in biomimetic and material sciences, this may be important. In the superhelice, two kinds of C–H···O═S (H···O, 2.50 and 2.72 Å) hydrogen bonds were existed

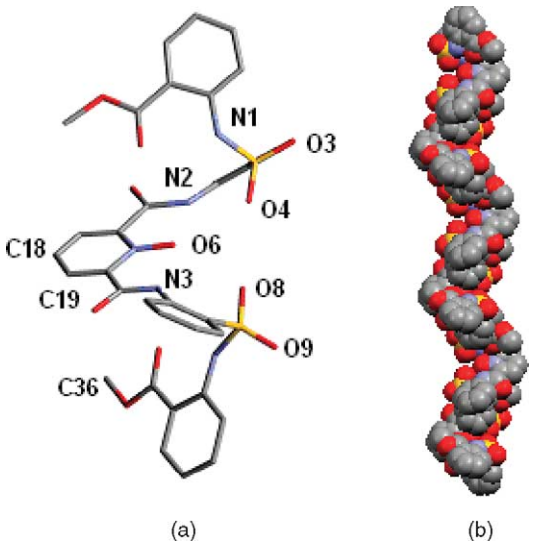


Figure 4. (a) X-ray crystal structure of **1** in the crystal **II**. Hydrogen atoms are omitted for clarity. (b) Side view of the assembled superhelice.

between the sulfonyl inward O atoms of one molecule and the 5-protons of the terminal benzene ring of its adjacent two molecules. Also, two kinds of π–π stacking interactions were present between the benzenesulfonamide rings of one molecule and the terminal rings of its adjacent two molecules with the centroid distances of 3.71 and 3.85 Å, respectively. In addition, C–H···O═C (H···O, 2.59 Å) hydrogen bond was existed between a carbonate O atom of a molecule and 4-proton of a terminal ring of the adjacent molecule. The pitch of superhelice was 20.79 Å.

Further assembly of the helical structure is very important. Although more and more efforts to self-assembled superhelices[9,19] have been made, most of them were still limited to one dimension along the helical axis.[20] We found that the superhelices in crystal **II** can further assemble to form highly ordered architectures. Firstly, they associate along the *c*-axis resulting in formation of 2D layers, in which a network of intermolecular C–H···O═S hydrogen bonds (C18H···O8, 2.45 Å; C18H···O4, 2.48 Å; C19H···O3, 2.67 Å; C36H···O3, 2.69 Å) were utilized as main driving forces (Fig. 5a and b). Secondly, through the π–π stacking

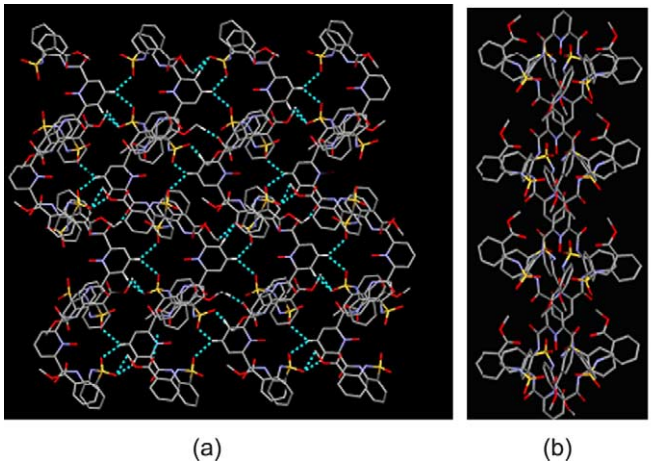


Figure 5. (a) Side view of a 2D layer. Dashed lines represent the C–H···O═S hydrogen bonds. (b) Top view of a 2D layer.

interactions between the benzene rings not involved in formation of the superhelice with the centroid distances of 3.71 and 3.85 Å, the 2D layers were then stacked along [$\bar{1}$01] direction into a 3D microporous network with channels of ca. 5.3×8.0 Å (Fig. 6), in which water molecules[21] were located.

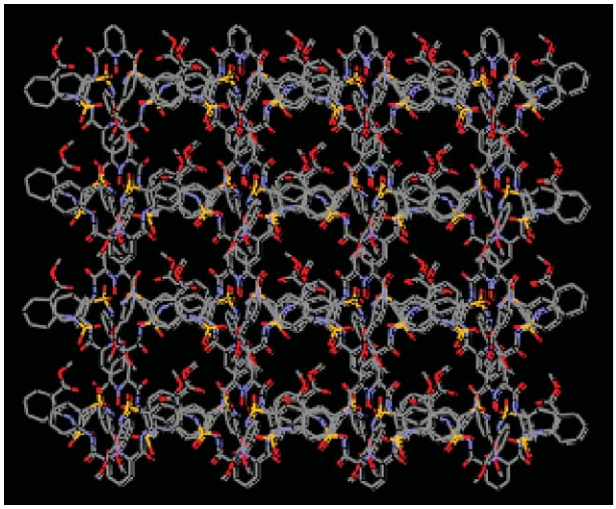


Figure 6. View of a microporous network along [110] direction.

The X-ray crystal structure of **2** confirmed that it took up a similar conformation with **1** in the solid state (Fig. 7a), and the helical arrangement of the rings was also stabilized by a network of intramolecular hydrogen. Similar to the case of **1** in the crystal **I**, molecule **2** could assemble into zigzag structure (Fig. 7b). It could also further assemble into 2D layers along the *a*-axis (Fig. 8a and b) and then 3D networks along the *c*-axis (Fig. 9), in which the C–H···O═S hydrogen bonds also played an important role. In the 3D microporous network, there existed the channels of ca. 7.5×16.6 Å, in which $CHCl_3$ molecules were included.

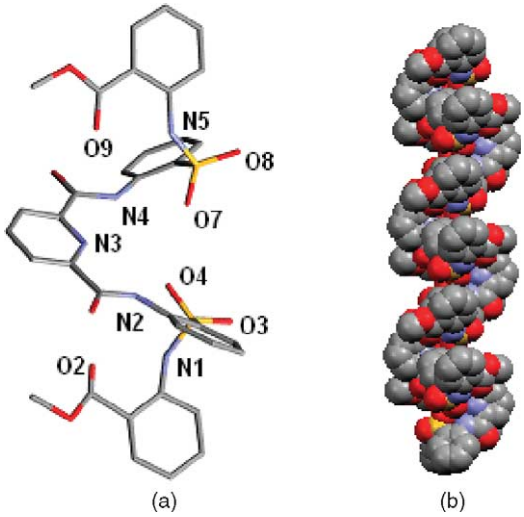


Figure 7. (a) X-ray crystal structure of **2** in the crystal. (b) Side view of the assembled zigzag chain. Hydrogen atoms were omitted for clarity.

The single crystal of **3** obtained from a mixture of CH_2Cl_2/CH_3OH had similar helical secondary structure with **2**. The

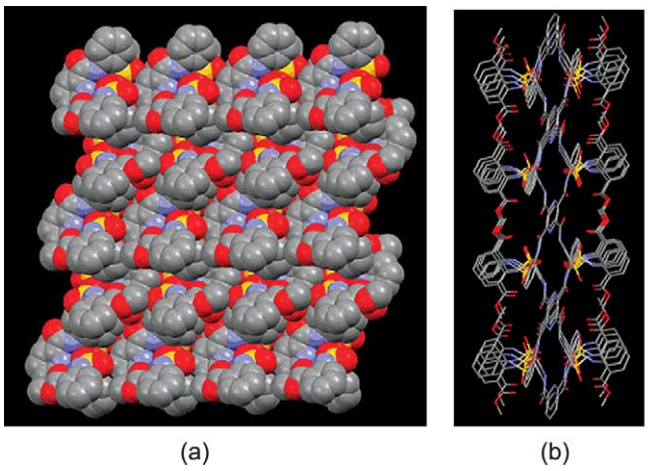


Figure 8. (a) Side view and (b) top view of a 2D layer. Hydrogen atoms were omitted for clarity.

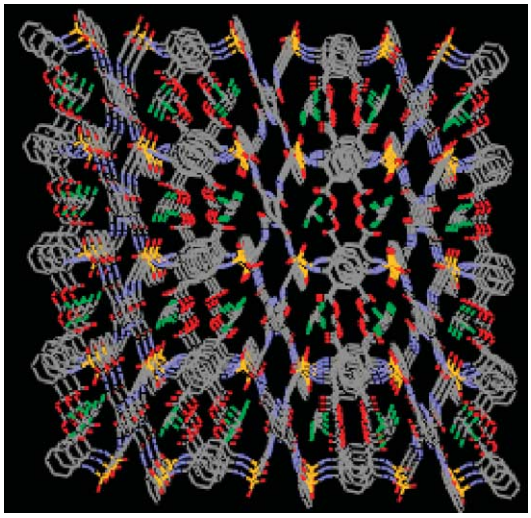


Figure 9. View of a microporous network along the *c*-axis with $CHCl_3$ molecules included in the channels. Hydrogen atoms were omitted for clarity.

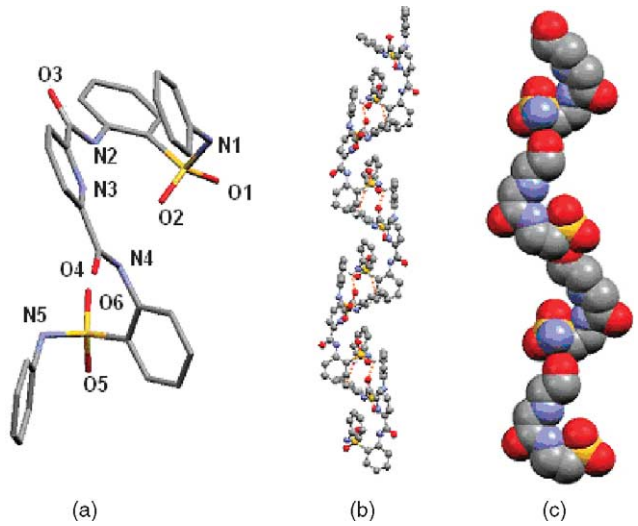


Figure 10. (a) X-ray crystal structure of **3**. Hydrogen atoms were omitted for clarity. (b) View of assembled superhelices. along *b*-axis. (c) View of assembled superhelice along *b*-axis; only the atoms in track of helice were shown.

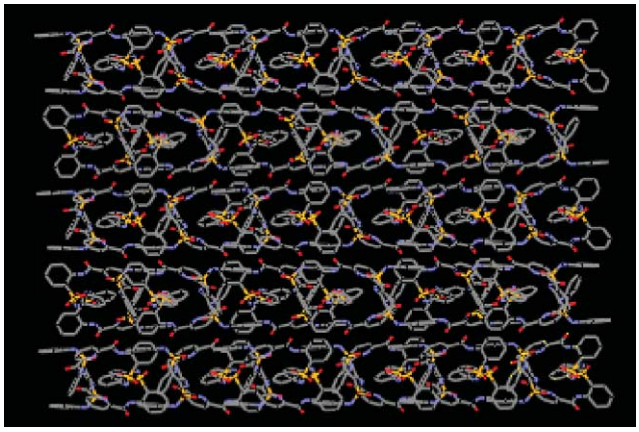


Figure 11. View of 3D array along *c*-axis. Hydrogen atoms were omitted for clarity.

only difference was almost parallel to pyridine ring because of π–π stacking interactions with centroid distance of 3.88 Å and dihedral angle between them was 4.4° (Fig. 10a). This difference led to the assembly of **3** in the solid state in the different way from that of **2**.

Firstly, **3** assembled along *a*-axis to form superhelices (Fig. 10b and c) mainly through complementary hydrogen bonds between one of O atoms in carboxamide groups and one of H atoms in sulfonamide groups (N1···O4, 2.80 Å). In addition, there existed C–H···π interactions ($d_{H\cdots\pi}$ is 2.88 Å) to stabilize this structure. The superhelices could further associate to form 2D layers through C–H···O═S hydrogen bonds (C29H···O6, 2.63 Å). All of other O atoms (O3) in carboxamide groups pointed outward the layer. The layers stacked with two adjacent layers in opposite direction along *c*-axis to form 3D array (Fig. 11) through the complementary hydrogen bonds between the O3 and another H atoms in sulfonamide groups (N5···O3, 2.81 Å), C–H···O═S hydrogen bonds (C15H···O6, 2.60 Å) and C–H···π interactions ($d_{H\cdots\pi}$ is 2.89 Å). As above mentioned, sulfonamide group is a strong hydrogen-bond donor and carboxamide group is a strong hydrogen bond acceptor, and this kind of complementary hydrogen bonds between sulfonamides and carboxamides may be important in future design of molecular crystal.[13b,22]

Furthermore, we found the cyclic compound **4** could also assemble into highly ordered architectures in the solid state and C–H···O═S hydrogen bonds played an important role in the assembling process. The crystals of **4** were obtained from a mixture of CH_2Cl_2/CH_3OH. There were two crystallographically independent molecules of **4** in the crystal named as A and B. They adopted similar helical conformations but their chiralities were opposite. A was right-handed with dihedral angles between pyridine ring and two adjacent benzene rings about 15.3 and 19.4°, but B was left-handed with two dihedral angles about 13.7 and 21.2° (Fig. 12).

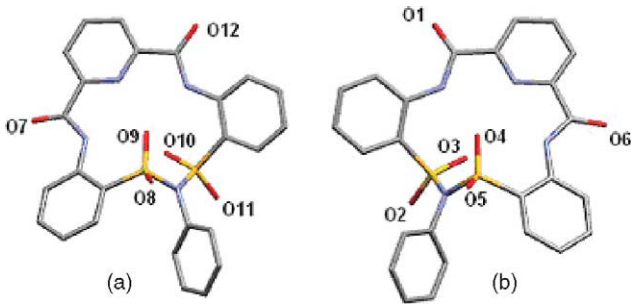


Figure 12. Two crystallographically independent molecules with opposite chirality of **4** in the crystal: A was right-handed, and B was left-handed. Hydrogen atoms were omitted for clarity.

A and B were alternated to connect each other along *b*-axis to form chain structures. The connection was driven by π–π stacking interactions between the pyridine ring of A or B and one of benzene rings adjacent to pyridine ring of B or A with centroid distances of 3.67 and 3.62 Å, and C–H···O═S hydrogen bonds (H···O, 2.59 Å and H···O, 2.67 Å) between O atoms in sulfonamide groups of A or B and H atoms in 3 and 4 position of pyridine rings of B and A. The cavities of A and B were located in two sides of the chain, respectively (Fig. 13a).

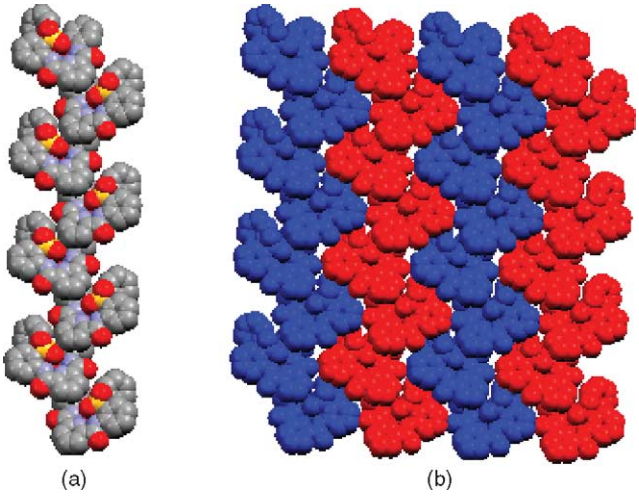


Figure 13. (a) View of assembled chain structure along *c*-axis. (b) View of a 2D layer along *c*-axis. Hydrogen atoms were omitted for clarity.

The chains were interlocked each other like zippers through π–π stacking interactions and C–H···O hydrogen bonds along *a*-axis to form 2D layers (Fig. 13b). The π–π stacking interactions were present between the benzene rings connecting with *N* atoms in sulfonamide group of one chain and benzene ring adjacent to the pyridine ring of another chain with centroid distance about 4.48 and 4.56 Å. The layers were consisted of two planes with S–N bonds as 'pillar'. The first plane named as plane **I** was made up with all pyridine rings and one of benzene rings adjacent to them and O6 and O7 atoms in carboxamide groups pointing outward this plane. The second plane named as plane **II** was made up of the rest two benzene rings in all constituent molecules and O2 and O10 atoms in sulfonamide groups pointing out this plane (Fig. 14a).

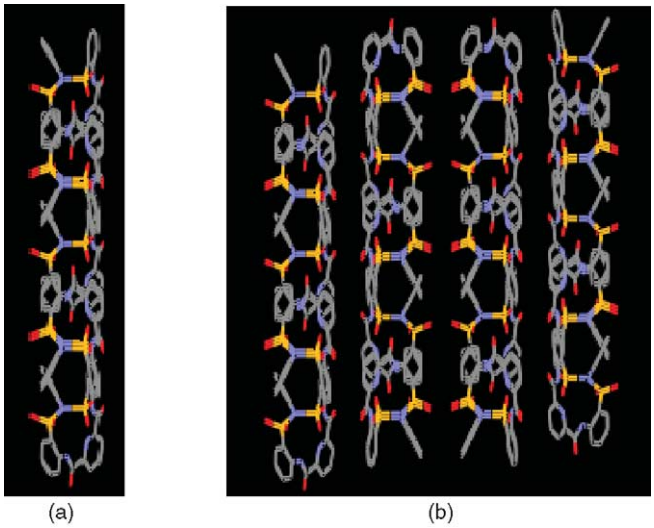


Figure 14. View of 2D layers (a) and the crystal lattic along the *a*-axis of the cell (b) of **4**, hydrogen atoms were omitted for clarity.

The layers were further associated along *c*-axis to form 3D array in two fashions (Fig. 14b). The first was through the interactions between plane **I** of two layers. The interactions included π–π stacking interactions between the pyridine rings in one layer and benzene rings adjacent to pyridine rings in another layer with centroid distance about 3.74 and 3.97 Å, and the C–H···O hydrogen bonds (H···O, 2.48 Å) between the O6 and O7 atoms of carboxamide groups in one layers and aromatic H atoms in other layers. The second was through the interactions between plane **II** of two layers, which was mainly through C–H···O hydrogen bonds (H···O, 2.62 Å) between the O2 and O10 atoms of sulfonamide groups in one layer and aromatic H in another layer.

3. Conclusions

In conclusion, we have synthesized three sulfonamide–amide hybridized molecules and one cyclic analogue, and demonstrated that aromatic sulfonamide-based subunits could be induced to take up helical secondary structures by a network of intramolecular hydrogen bonds. In particular, the helical molecules could be utilized as useful building blocks for assembly into not only 1D zigzag chains and superhelices, but also 2D layers and 3D microporous networks in the solid state. Moreover, we found that the multiple C–H···O═S hydrogen bonds and other hydrogen bonds involving sulfonamide groups played an important role in the assembling processes, which would be helpful for design and construction of other unique supramolecular architectures. The further studies on sulfonamide-based building blocks for the assembly into new highly order structures are under the way.

4. Experimental

4.1. General

Melting points were measured on a micro melting-point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM300 (300 MHz, chemical shifts in

ppm relative to internal TMS, *J* in Hertz). Mass spectra were obtained by EI and MALDI-TOF techniques. Elemental analyses were performed on a Vario ELIII and Carlo Erba 1106 analytical instrument. Solvents were dried and distilled before use according to standard procedures. *N*-Phenyl-2-aminobenzenesulfonamide[23] was prepared according to the published procedure.

4.1.1. Compound 5. To a solution of methyl anthranilate (1 mmol) and Et_3N (1.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C, 2-nitrobenzenesulfonyl chloride (1.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 10 h and then washed with 2 N HCl and water. The organic phase was dried over anhydrous $MgSO_4$ and then concentrated. The crude product was purified by flash chromatography (1:1 DCM/petroleum ether) to give the product **5** as a white solid (218 mg, 65%). Mp 143–144 °C. ^{1}H NMR ($CDCl_3$): δ 11.18 (s, 1H), 8.16 (m, 1H), 7.98 (d, J=8.0 Hz, 1H), 7.83–7.78 (m, 2H), 7.74–7.69 (m, 2H), 7.49 (t, J=8.0 Hz, 1H), 7.08 (t, J=7.8 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 167.9, 148.2, 139.3, 134.5, 134.2, 132.9, 132.4, 131.6, 131.3, 125.4, 123.2, 117.9, 116.3, 52.8; EI-MS: *m*/*z* 336 $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{12}N_2O_6S$: C 50.00, H 3.60, N 8.33; found: C 50.03, H 3.60, N 8.24.

4.1.2. Compound 6. A mixture of compound **5** (1 mmol) dissolved in CH_3OH (15 mL) and 10% Pd/C (10 mg) was stirred at ambient temperature under an atmosphere of hydrogen for 10 h. The reaction mixture was filtered through Celite and CH_3OH was evaporated to afford **6** as a white solid in quantitative yield. The product was pure and used without further purification. Mp 164–165 °C. ^{1}H NMR ($CDCl_3$): δ 10.85 (s, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.23 (t, J=8.5 Hz, 1H), 7.00 (t, J=7.7 Hz, 1H), 6.71–6.65 (m, 2H), 4.88 (broad, 2H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3, 145.5, 148.5, 140.4, 134.5, 134.4, 131.1, 130.1, 122.6, 120.3, 118.4, 117.6, 117.2, 115.7, 52.5; EI-MS: *m*/*z* 306 $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_4S$: C 54.89, H 4.61, N 9.14; found: C 54.72, H 4.65, N 9.13.

4.1.3. Compound 1. A solution of 2,6-pyridinedicarboxylic acid *N*-oxide (1 mmol) in excess $SOCl_2$ was refluxed for 2 h, $SOCl_2$ was then removed by reduced pressure. The acid chloride obtained was dissolved in anhydrous CH_2Cl_2 (10 mL), and added dropwisely over a period of 10 min to a solution of **6** (1 mmol) and Et_3N (3 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 4 h. The organic phase was washed with 2 N HCl twice, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography (20:1 DCM/EA) to give desired product **1** as a white solid (342 mg, 45%). Mp 268–270 °C. ^{1}H NMR (DMSO-d_6): δ 13.11 (s, 2H), 10.78 (s, 2H), 8.61 (d, J=8.0 Hz, 2H), 8.14 (d, J=8.0 Hz, 2H), 8.03 (d, J=7.8 Hz, 2H), 7.96 (t, J=7.9 Hz, 1H), 7.79–7.72 (m, 4H), 7.56–7.41 (m, 6H), 7.07 (t, J=7.4 Hz, 2H), 3.48 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 167.3, 167.2, 157.9, 157.8, 140.8, 138.6, 138.4, 134.5, 134.4, 134.3, 134.1, 131.6, 131.0, 129.9, 129.7, 129.6, 128.9, 126.5, 126.4, 125.6, 123.8, 119.2, 116.7, 52.1; MALDA-TOF MS: *m*/*z* 758.3 $[M-H]^+$; elemental analysis calcd (%) for $C_{35}H_{29}N_5O_{11}S_2$: C 55.33, H 3.85, N 9.22; found: C 55.33, H 3.97, N 8.92.

4.1.4. Compound 2. Following the method described above for **1**, **2** was obtained in 54% yield by the reaction of 2,6-pyridinedicarboxylic acid with **6**. Mp 256–258 °C. ^{1}H NMR ($CDCl_3$): δ 11.37 (s, 2H), 10.65 (s, 2H), 8.49 (d, J=7.8 Hz, 2H), 8.27 (d, J=7.3 Hz, 2H), 8.18 (t, J=7.8 Hz, 1H), 7.83 (d, J=8.0 Hz, 2H), 7.76 (d, J=8.0 Hz, 2H), 7.64–7.55 (m, 4H), 7.33 (t, J=7.5 Hz, 2H), 7.18 (t, J=7.6 Hz, 2H), 6.96 (t, J=7.1 Hz, 2H), 3.66 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 166.9, 161.2, 161.1, 147.9, 140.4, 137.7, 137.6, 135.0, 134.8, 134.6, 134.0, 130.7, 129.8, 129.3, 129.1, 129.0, 125.4, 125.2, 125.1, 125.0, 124.95, 124.89, 124.4, 121.1, 118.4, 52.2; MALDA-TOF MS: *m*/*z* 766.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{35}H_{29}N_5O_{10}S_2$: C 56.52, H 3.93, N 9.42; found: C 56.54, H 3.92, N 9.33.

4.1.5. Compound 7. To a solution of *N*-phenyl-2-aminobenzenesulfonamide (1 mmol) and DMAP (1.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 2-nitrobenzenesulfonyl chloride (1.2 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was refluxed for 10 h and then washed with 2 N HCl and water. The organic phase was dried over anhydrous $MgSO_4$ and then concentrated. The crude product was purified by flash chromatography (1:1 DCM/petroleum ether) to give desired product **7** as a white solid (294 mg, 68%). Mp 138–140 °C. ^{1}H NMR ($CDCl_3$): δ 8.44–8.41 (m, 1H), 7.78–7.75 (m, 2H), 7.67–7.65 (m, 1H), 7.49 (d, J=8.3 Hz, 1H), 7.41–7.38 (m, 1H), 7.34–7.26 (m, 5H), 6.64–6.57 (m, 2H), 4.88 (broad, 2H). ^{13}C NMR ($CDCl_3$): δ 148.2, 147.1, 136.1, 135.1, 132.8, 132.7, 132.66, 132.1, 132.0, 131.3, 130.6, 129.1, 124.3, 117.4, 117.0, 116.7; MALDA-TOF MS: *m*/*z* 432.4 $[M-H]^-$; elemental analysis calcd (%) for $C_{18}H_{15}N_3O_6S_2$: C 49.88, H 3.49, N 9.69; found: C 49.75, H 3.49, N 9.75.

4.1.6. Compound 8. A mixture of compound **7** (1 mmol) dissolved in CH_3OH (25 mL) and 10% Pd/C (15 mg) was stirred at ambient temperature under an atmosphere of hydrogen for 10 h. The reaction mixture was filtered through Celite and CH_3OH was evaporated to afford **8** as a white solid in quantitative yield. The product was pure and used without further purification. Mp 162–164 °C. ^{1}H NMR ($CDCl_3$): δ 7.49 (d, J=8.2 Hz, 2H), 7.38–7.15 (m, 7H), 6.70–6.61 (m, 4H), 4.86 (broad, 4H). ^{13}C NMR ($CDCl_3$): δ 146.4, 135.6, 133.8, 132.0, 131.3, 130.2, 128.9, 119.0, 117.4, 116.7; MALDA-TOF MS: *m*/*z* 404.3 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{17}N_3O_4S_2$: C 53.58, H 4.25, N 10.41; found: C 53.38, H 4.31, N 10.21.

4.1.7. Compound 4. Following the method described for **1**, compound **4** was obtained as a white solid in 71% yield by the reaction of 2,6-pyridinedicarboxylic acid with **8**. Mp > 300 °C. ^{1}H NMR ($CDCl_3$): δ 12.70 (s, 2H), 8.98 (d, J=8.2 Hz, 2H), 8.42 (d, J=7.7 Hz, 2H), 8.22 (t, J=7.7 Hz, 1H), 7.71 (t, J=7.9 Hz, 2H), 7.61–7.50 (m, 3H), 7.40–7.35 (m, 4H), 7.17 (t, J=7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 160.8, 147.8, 140.5, 136.9, 136.0, 134.3, 132.3, 131.2, 129.6, 126.9, 124.8, 123.5, 121.3; EI-MS: *m*/*z* 534 $[M]^+$; elemental analysis calcd (%) for $C_{25}H_{18}N_4O_6S_2$: C 56.17, H 3.39, N 10.48; found: C 55.96, H 3.36, N 10.39.

4.2. X-ray crystallographic study

Data were collected using a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα

(λ=0.71073 Å) radiation, and were corrected for Lorentzian, polarization, and absorption. Structures were solved by direct methods, and refined by full matrix least-squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were placed in calculated position. CCDC-259979 (**1**–**I**), CCDC-259977 (**1**–**II**), CCDC-259978 (**2**), CCDC-264356 (**3**) and CCDC-264357 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

Compound **1** *(crystal I)*. $C_{37}H_{29}Cl_4N_5O_{13}S_2$, *M* 957.57, crystal dimensions 0.80×0.50×0.10 mm^3, monoclinic, space group *P*2/*n*, *a*=15.053(3) Å, *b*=9.810(2) Å, *c*=16.063(3) Å, *V*=2190.1(8) Å^3, D_c=1.452 Mg m^{-3}, *Z*=2, 19578 reflections collected, 4853 independent [*R*(int)=0.0426], giving R_1=0.1003 for observed unique reflection [$F^2>2s(F^2)$] and wR_2=0.3697 for all data.

Compound **1** *(crystal II)*. $C_{35}H_{31}N_5O_{12}S_2$, *M* 777.77, crystal dimensions 0.51×0.49×0.09 mm^3, orthorhombic, space group *P*2(1)2(1)2(1)*c*, *a*=14.4682(7) Å, *b*=14.9321(9) Å, *c*=18.4391(10) Å, *V*=7970(3) Å^3, D_c=1.297 Mg m^{-3}, *Z*=4, 25091 reflections collected, 5026 independent [*R*(int)=0.0973], giving R_1=0.0793 for observed unique reflection [$F^2>2s(F^2)$] and wR_2=0.2259 for all data.

Compound **2**. $C_{36}H_{30}Cl_3N_5O_{10}S_2$, *M* 863.12, crystal dimensions 0.34×0.16×0.09 mm^3, triclinic, space group *P*-1, *a*=9.5294(19) Å, *b*=13.151(3) Å, *c*=16.255(3) Å, α=87.84(3)°, β=80.53(3)°, γ=85.97(7)°, *V*=2003.6(7) Å^3, D_c=1.431 Mg m^{-3}, *Z*=2, 17719 reflections collected, 6715 independent [*R*(int)=0.0972], giving R_1=0.089 for observed unique reflection [$F^2>2s(F^2)$] and wR_2=0.2018 for all data.

Compound **3**. $C_{32}H_{27}Cl_2N_5O_6S_2$, *M* 712.61, crystal dimensions 0.672×0.393×0.288 mm^3, orthorhombic, space group *Pbca*, *a*=18.967(4) Å, *b*=17.030(3) Å, *c*=20.597(4) Å, *V*=6653(2) Å^3, D_c=1.423 Mg m^{-3}, *Z*=8, 52803 reflections collected, 7568 independent [*R*(int)=0.0512], giving R_1=0.0680 for observed unique reflection [$F^2>2s(F^2)$] and wR_2=0.2164 for all data.

Compound **4**. $C_{25.5}H_{26}N_4O_{7.5}S_2$, *M* 572.62, crystal dimensions 0.55×0.52×0.24 mm^3, triclinic, space group *P*-1, *a*=12.3181(7) Å, *b*=14.1384(7) Å, *c*=16.2761(8) Å, α=110.964(2)°, β=107.2170(18)°, γ=90.150(2)°, *V*=2509.6(2) Å^3, D_c=1.516 Mg m^{-3}, *Z*=4, 11070 reflections collected, 7138 independent [*R*(int)=0.0532], giving R_1=0.0698 for observed unique reflection [$F^2>2s(F^2)$] and wR_2=0.1959 for all data.

Acknowledgements

We thank the National Natural Science Foundation of China and the Chinese Academy of Sciences for financial support.

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Corrigendum

Corrigendum to: 'Photoinduced cycloadditions of *N*-methyl-1,8-naphthalenedicarboximides with alkynes' [Tetrahedron 62 (2006) 1131]

Qing-Jian Liu,[a] Yong-Miao Shen,[a] Hui-Ying An,[a] Günter Grampp,[b] Stephan Landgraf[b] and Jian-Hua Xu[a,*]

[a]*Department of Chemistry, Nanjing University, Nanjing 210093, People's Republic of China*
[b]*Institute of Physical and Theoretical Chemistry, Graz University of Technology, Technikerstrasse 4/I, A-8010 Graz, Austria*

Available online 14 February 2006

In the experimental section, the X-ray structure analysis of compound **3b** should be as follows:

X-ray structure analysis: $C_{21}H_{14}BrNO_2$, $M=392.24$. triclinic, space group P-1, $a=9.849(1)$ Å, $b=12.677(2)$ Å, $c=14.493(2)$ Å, $\alpha=90.55(1)$, $\beta=102.96(1)$, $\gamma=107.09(1)^\circ$, $V=1680.0(4)$ Å^3, $Z=4$, $D_c=1.551$ g cm^{-3}, $F(000)=792$, absorption coefficient 2.461 mm^{-1}, scan range for data collection $1.45\leq\theta\leq25.00^\circ$, 6514 measured reflections, 5848 independent reflections, 3555 reflections with $I>2\sigma(I)$, $R_{int}=0.0098$, 454 refinable parameters, $R[F^2>2\sigma(F^2)]=0.0330$, $wR_2(F^2)=0.0726$.

In the X-ray structure analysis of compound **7e**, the cell parameter b should be replaced by $b=10.465(2)$.

DOI of original article: 10.1016/j.tet.2005.10.076
* Corresponding author. Tel.: +86 25 3592709; fax: +86 25 3317761; e-mail: xujh@nju.edu.cn

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doi:10.1016/j.tet.2006.01.074