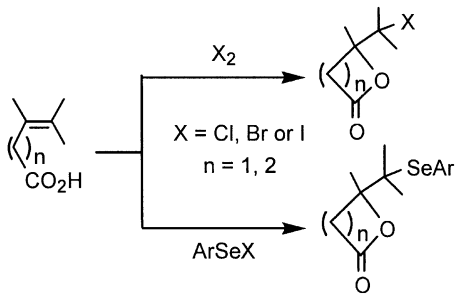
ELSEVIER

Tetrahedron

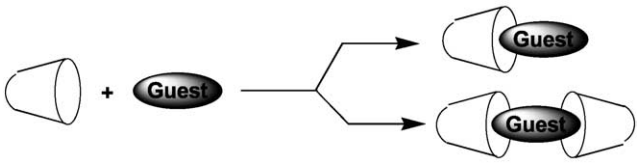
Tetrahedron Vol. 60, No. 25, 2004

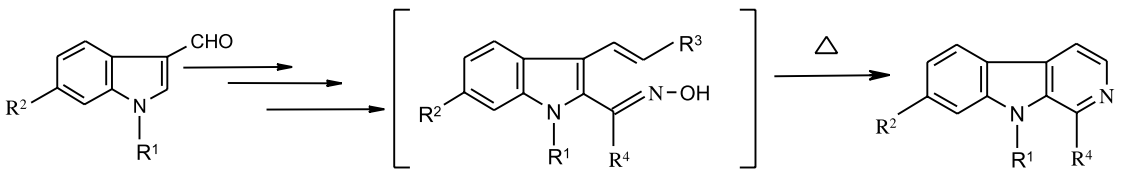
Contents

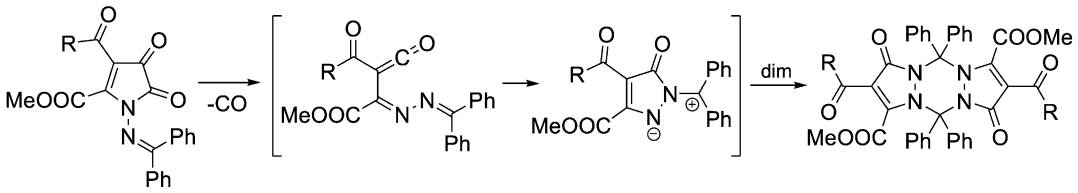
REPORT

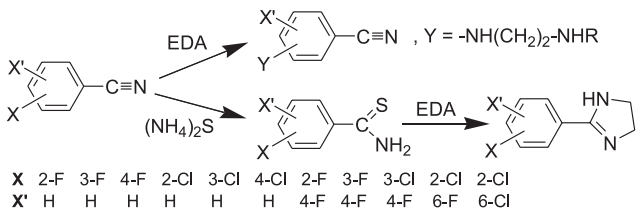


ARTICLES

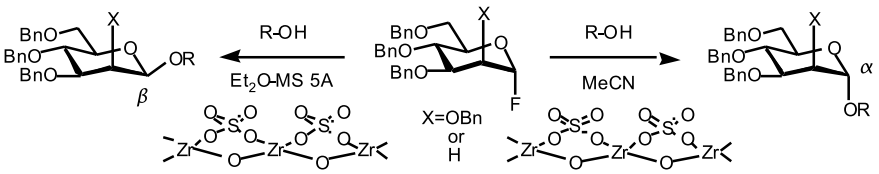


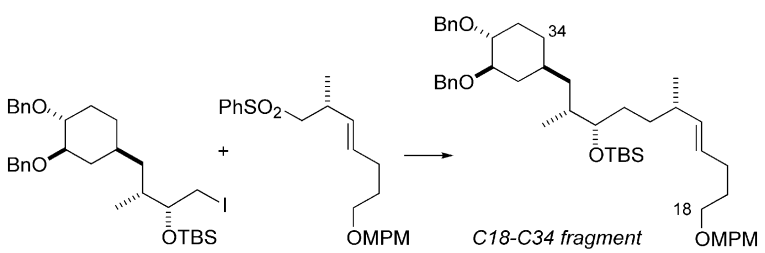


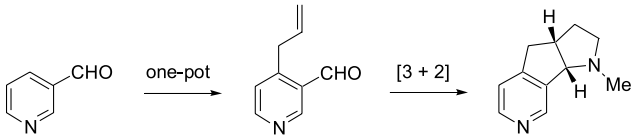


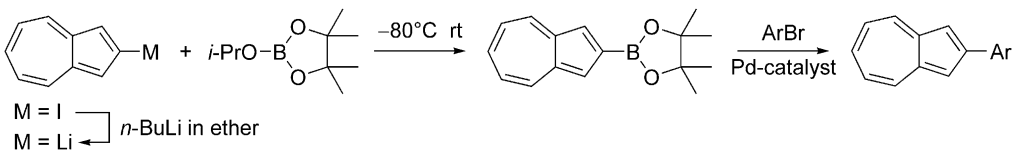


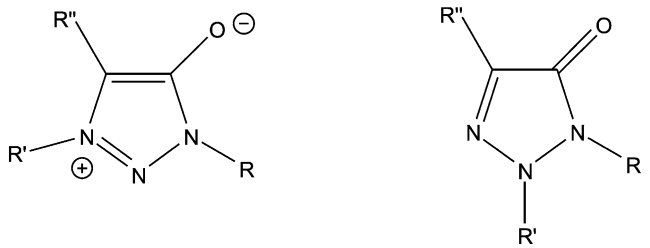
X	2-F	3-F	4-F	2-Cl	3-Cl	4-Cl	2-F	3-F	3-Cl	2-Cl	2-Cl
X'	H	H	H	H	H	H	4-F	4-F	4-F	6-F	6-Cl

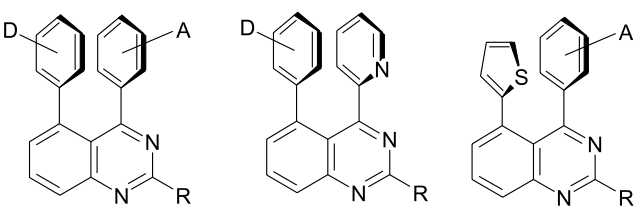


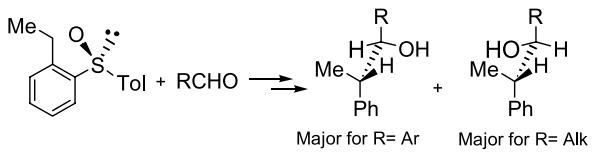


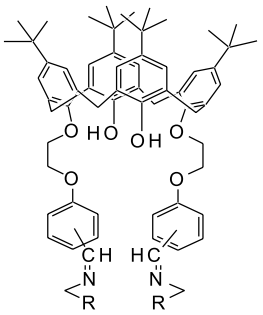


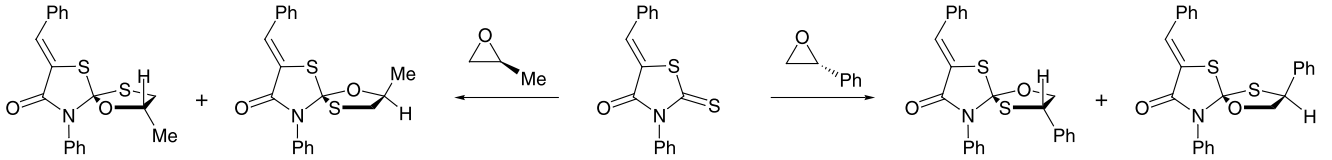


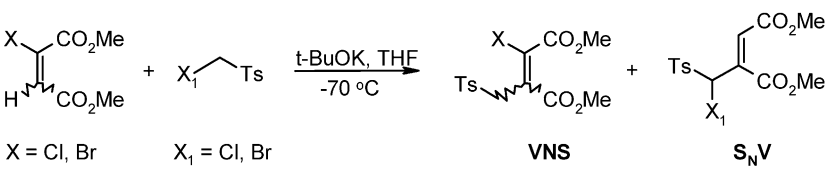


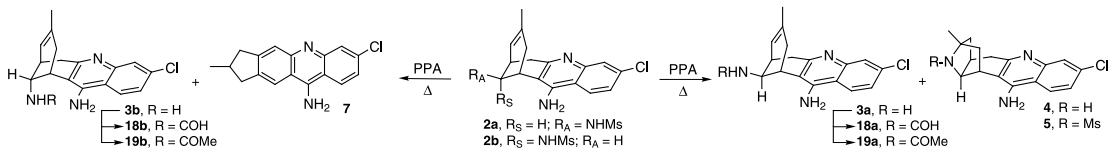


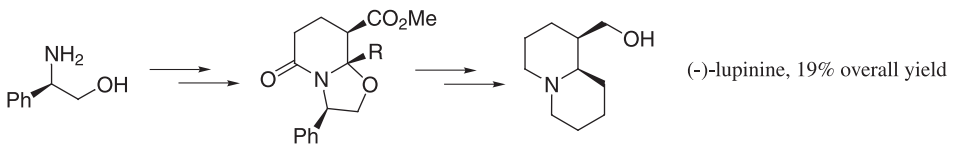


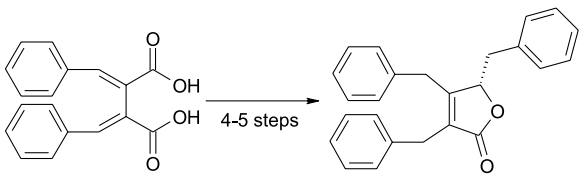




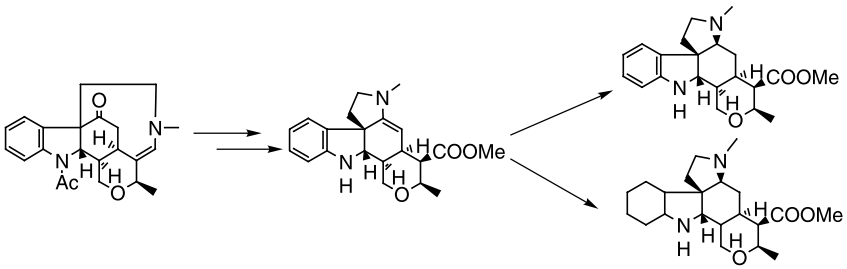


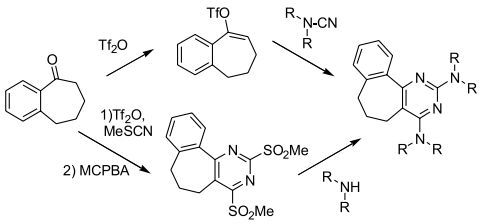


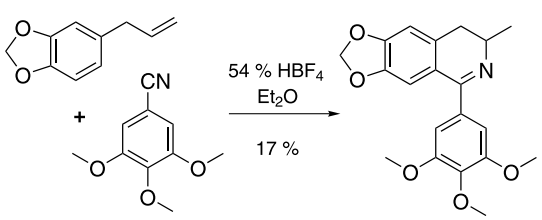


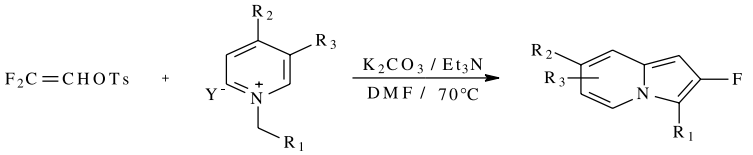


The covalent union of both hydrophobic and cationic peptides stabilizes short chain (6/7-mer) DNA duplexes, but its influence on the stability of >15-mer duplexes is virtually nil.









2a **3** **4**

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5273–5308
Tetrahedron

Tetrahedron report number 679

Halo- and selenolactonisation: the two major strategies for cyclofunctionalisation☆

Subramania Ranganathan,[a,b,*] K. M. Muraleedharan,[a] Narendra K. Vaish[a] and Narayanaswamy Jayaraman[c,*]

[a]*Discovery Laboratory, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore 560 012, India*
[c]*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

Received 12 March 2004

Contents

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.04.014

Keywords: Carboxylic acid; Lactonisation; Stereoselectivity.

Abbreviations: Ac, Acetyl; Bn, Benzyl; Boc, ^{t}Butoxycarbonyl; Cbz, Benzyloxycarbonyl; Cp, Cyclopentadienyl; mCPBA, *m*-Chloroperbenzoic acid; CSA, Camphorsulphonic acid; DCN, Dicyanonaphthalene; DME, Dimethoxyethane; DMF, Dimethylformamide; DMSO, Dimethylsulphoxide; MOM, Methoxymethyl; NBS, *N*-Bromosuccinimide; *m*-NBSP, *m*-Nitrobenzenesulphonyl peroxide; NIS, *N*-Iodosuccinimide; NPSP, *N*-(Phenylselenyl)phthalimide; PDC, Pyridinium dichromate; Pht, Phthaloyl; PMB, *para*-Methoxy benzyl; PPTS, Pyridinium (*para*-toluenesulphonate); Phth-N-Br, *N*-Bromophthalimide; TBAF, Tetrabutylammonium fluoride; TBAX, Tetrabutylammonium salt (X=ClO_4, Cl, Br); TBDMS, (or) TBS, ^{t}Butyldimethylsilyl; Tf, Trifluoromethanesulphonyl; TFA, Trifluoroacetic acid; TIPS, Triisopropylsilyl; TMS, Trimethylsilyl; TMSE, 2-(Trimethylsilyl)ethyl; Ts, *p*-Toluenesulphonyl.

* Corresponding authors. Tel.: +91-80-2293-2406/2578; fax: +91-80-2360-0529/0683; e-mail address: jayaraman@orgchem.iisc.ernet.in

doi:10.1016/j.tet.2004.04.014

1. Introduction

At the turn of the 20th century, Bougoult made a detailed and systematic study of the conversion of β,γ- and γ,δ-unsaturated carboxylic acids to iodolactones with iodine in aqueous $NaHCO_3$. He showed that, when the double bond was further removed from the carboxylic acid functionality, no reaction took place. He considered that these reactions involved the addition of nascent hypoiodous acid, followed by lactonisation of the resulting hydroxy acid.[1] Intervening developments in this area as well as in mechanistic studies enabled van Tamelen and Shamma to propose, in 1954, the currently accepted view of this process, namely that halolactonisation arise by the intramolecular carboxylic acid-mediated opening of the initially-formed halonium ion intermediate (Fig. 1).[2]

Since these initial studies were carried out, halolactonisation has received sustained attention and has become a very reliable strategy in synthetic design. In early developments, a major attraction of this reaction was that it belonged to a small number of pathways for the introduction of stereoselectivity in open-chain compounds. A detailed analysis of this property led to the important discovery that the conditions are amenable to either kinetic or thermodynamic control and, in favourable cases, can lead to products having opposite stereoselectivity. The scope of the reaction was augmented further by the extension of the process to esters, phosphates and amides, the latter compounds providing an excellent opportunity for the attachment of chiral auxiliaries, leading to products of high enantiomeric purities.

A development worthy of special note is the related cyclisation of unsaturated acids by arylselenium halides, first reported by Campos and Petragnani in 1960.[3] The same authors also studied lactonisation brought about by tellurium compounds,[4] but this work has not received wide attention. Selenolactonisation results from the intramolecular opening of an *epi*-selenide by an appropriately placed carboxylic acid (Fig. 2). With the emergence of the carbon–selenium bond as an extraordinarily versatile unit for further elaboration,[5] selenolactonisation was rapidly accepted as a very useful synthetic strategy.

Halo- and selenolactonisation reactions are an important synthetic subset in the broader reaction domain involving

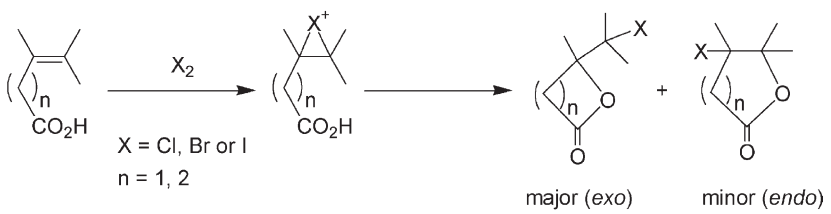


Figure 1.

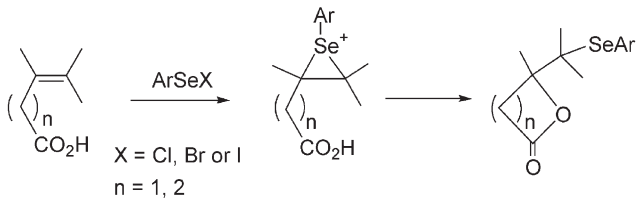


Figure 2.

heteroatom cyclisations mediated by electrophilic attack on a proximal π-bond, collectively called 'cyclofunctionalisation reactions'. Other important reactions in this category include cyclofunctionalisation of unsaturated hydroxy compounds, unsaturated amino compounds, unsaturated sulphur and phosphorus compounds, and electrophilic heteroatom-containing unconjugated dienes.

Since the excellent review by Dowle and Davies in 1979,[6] no other account has been forthcoming in the literature, although a number of reports on halo- and selenolactonisation have appeared.[7–10]

Halo- and selenolactonisation reactions, now forming a general class of reactions adaptable to a variety of situations in organic synthesis, have been explored in detail and a wealth of knowledge is available on a number of aspects associated with these reactions. We have formalised this report by discussing the most prominent and versatile features of these reactions, with the following major topics: (i) mechanism and stereochemistry; (ii) methods of halo- and selenolactonisation; (iii) asymmetric halo- and selenolactonisation; (iv) scope and limitations; (v) synthetic utility in representative reaction types; (vi) general comparison of these reactions; and (vii) varieties of reagents used to mediate the reactions. An exhaustive compilation of halo- and selenolactonisation reactions, often forming the intermediate steps of multistep organic synthesis, is presented as a Supplementary Section of this Report. This compilation of reactions, presented as Tables, was constituted from nearly 450 references, in which the use of these reactions has been described. While we have undertaken to discuss the salient features of the reactions in the following text, the Supplementary Section should serve to explore more features associated with this general class of reactions.

2. Mechanism and stereochemistry

Halo- and selenolactonisation reactions proceed by a common mechanistic pathway in which the transition state generally reflects an intramolecular opening of the 3-membered ring intermediate, which arises from acceptance of either the halogen- or selenium-derived electrophiles, by a heteroatom oxygen. The heteroatom oxygen could be part of a carboxylic acid, an ester or an amide. Factors that influence the electrophile acceptance by a proximal double bond and the requirement for a proper orientation of the 3-membered ring intermediate for the subsequent nucleophilic attack dictate the course of the reaction.

2.1. Control of stereo- and regioselectivities in halo- and selenolactonisation

2.1.1. Stereoselectivity. The factors that govern stereoselectivity pertaining to the iodolactonisation of γ,δ-unsaturated acids under kinetic conditions can be assessed on the basis of the following simplified profile (Fig. 3).[11–13]

Halo- and selenolactonisations that transform acyclic to cyclic precursors can lead to stereoisomers. The practical utility of these reactions arises mainly from the fact that the course and selectivity of the process are predictable. As shown in Figure 3, the diastereotopic π-faces bifurcate the ligands at the allylic and homoallylic positions. The kinetic preference would be for the approach of the electrophile in a conformation where the steric interactions from the ligands are minimised. Assuming 'e' as the smaller ligand, the primary control would be to place 'e' in the path of the electrophile, in order to lead to a *cis* orientation of the ligand 'd' and the iodine-carrying terminus in the product. In this process, 'd' and 'a' would come closer. When the steric repulsion between 'd' and 'a' does not permit such a process, however, the electrophile approach can reverse, leading to a *trans* orientation of the ligand 'd' and the iodine-carrying terminus. Such considerations additionally apply to the ligands 'f' and 'g'. The stereoselectivities are discussed in detail in Section 2.3.

2.1.2. Regioselectivity. The nature of the electrophile and the substrate structure dictates the course of regioselectivity in halolactonisation and these factors are exemplified by the systematic investigation of Snider and Johnston.[14] The halolactonisations of γ,δ-unsaturated acids (**1**–**7**), under kinetic conditions, are such that the γ-lactones predominate over δ-lactone formation during iodolactonisation, compared with that observed during bromolactonisation (Table 1). The regioselectivity differences are profound, depending on the nature of the electrophile. The preference for a γ-lactone in the case of iodolactonisation and a δ-lactone in the case of bromolactonisation is rationalised on the basis

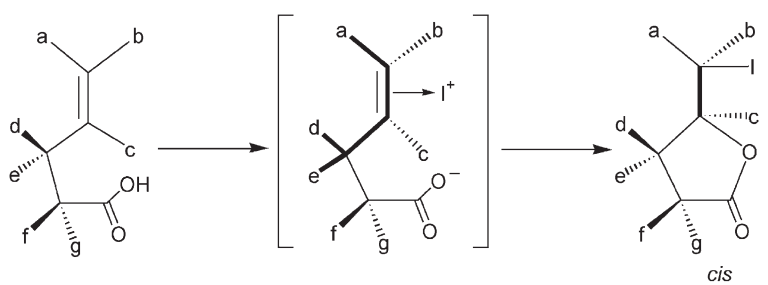
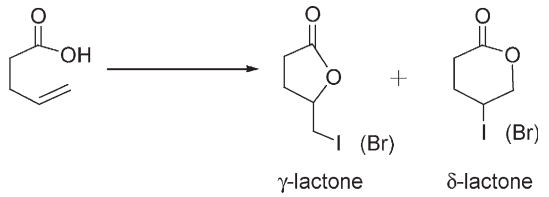
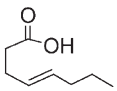
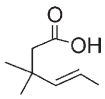
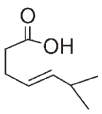
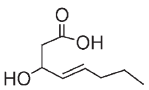
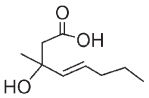


Figure 3.

Table 1. Regioselectivities in iodo- and bromolactonisations of γ,δ-unsaturated acids



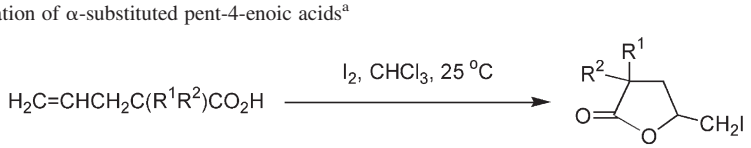
Acid		Ratio of γ to δ lactones (% yield of γ-isomer)			
		I_2/KI, $NaHCO_3$	I_2, Et_2O/THF, $NaHCO_3$	NBS/THF, AcOH	Br_2/MeOH, $NaHCO_3$, −78 °C
	**1**	>20:1 (85)	24:1 (71)	2.7:1 (91)	1:1 (46)
	**2**	>15:1 (91)	—	2.7:1 (85)	2.7:1 (50)
	**3**	6.5:1 (88)	1.5:1 (83)	1:1.2 (78)	1:1.2 (66)
	**4**	1.1:1 1.2 (86)	1:1 (81)	1:2.4 (86)	1:2.5 (93)
	**5**	>9:1 (70)	—	>9:1 (76)	>9:1 (38)
	**6**	5:1 (70)	5:1 (76)	2.3:1 (9.2)	2:1 (45)
	**7**	1:3.4 (74)	1:3.5 (85)	<1:9 (93)	<1:9 (89)

that the rate-determining step of the former product is the attack of the carboxylate on the iodine-double bond complex, while that in the latter compound is the attack of bromine on the double bond to give the bromonium ion.

The halolactonisation reaction with a prototypical substrate, namely pent-4-enoic acid and its α-substituted derivatives **8**–**10**, illustrates the effect of α-substitution on nucleophilic attack of the proximal carboxylic acid at the halonium ion intermediate (Table 2).[15]

The fact that α,α′-disubstitution reduces the entropic barrier, thereby enhancing the rate of iodolactonisation, suggests that such disubstitution allows an enhanced population of the conformation needed for cyclisation. At the same time, such groups, by way of eclipsing the interactions with the neighbouring hydrogen, enhance the enthalpy of activation. The consequence of the so-called 'buttressing effect,' in which proximal substitution enhances the rate of the addition, is clearly seen where R_1=R_2=Ph.

Table 2. Kinetics of iodolactonisation of α-substituted pent-4-enoic acids[a]



Acid	R^1	R^2	k	$\Delta H^{\#}$	$\Delta S^{\#}$
8	H	H	0.51	3.3	−59
9	H	Ph	0.6	5.8	−51
10	Ph	Ph	200	9.0	−28

[a] Values of k and $\Delta H^{\#}$, $\Delta S^{\#}$ are expressed in M^{-1} min^{-1} and kcal mol^{-1}, respectively.

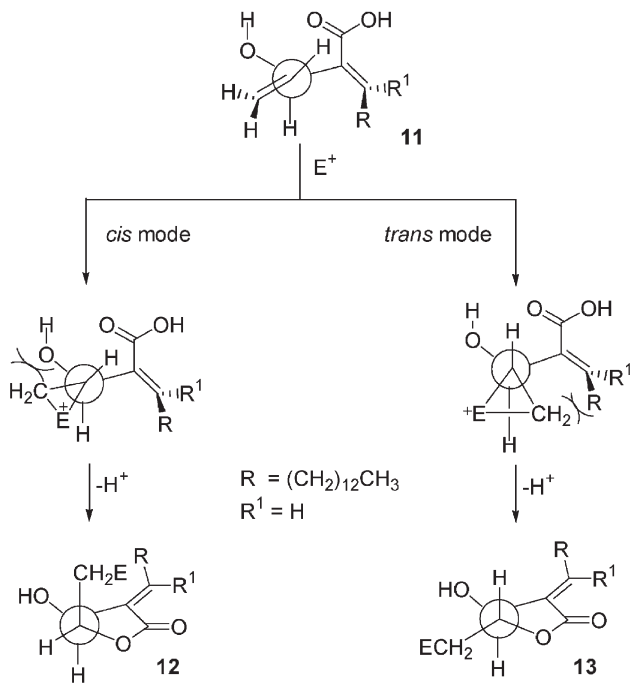


Figure 4.

2.2. Kinetic and thermodynamic control in halo- and selenolactonisation

A particularly useful aspect of iodolactonisation is that it permits reaction conditions which are either kinetically (aq. $NaHCO_3$, I_2, KI) or thermodynamically (I_2, MeCN) controlled.[10,16,17] Iodolactonisation under thermodynamically favoured conditions produces the *trans* product for both the γ and δ-lactones with a high selectivity. Similar controls are also possible in selenolactonisation reactions involving phenylselenyl triflate and *N*-(phenylselenyl)phthalimide (NPSP).

Interestingly, whilst stereochemical control is modest in selenolactonisation leading to γ-lactones, those reactions leading to δ-lactones show better selectivity. Further, amongst several selenium reagents, PhSeCl brings about a better selectivity than NPSP.[18]

While it is generally true that *cis* products arise under kinetic control and *trans* isomers predominate under equilibrating conditions, an exception is the hydroxy acid **11**, from which the *cis* product (**12**) predominate under all conditions. This unusual outcome is rationalised on the basis of steric constraints in the transition state that restrict the formation of the *trans* product **13** (Fig. 4).[19]

A precise mechanism of iodolactonisation under kinetic and thermodynamic conditions was studied by Willis and co-workers on the γ,δ-unsaturated α-hydroxy acid **14** (Fig. 5).[20]

The following iodolactonisation mechanism was proposed to account the formation of the above products. A nucleophilic attack at the carbocation, formed initially, can occur by four possible pathways (Fig. 6) and the

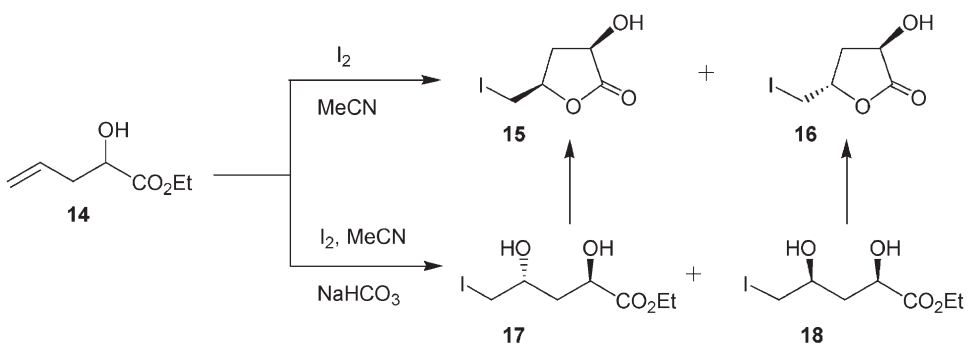


Figure 5.

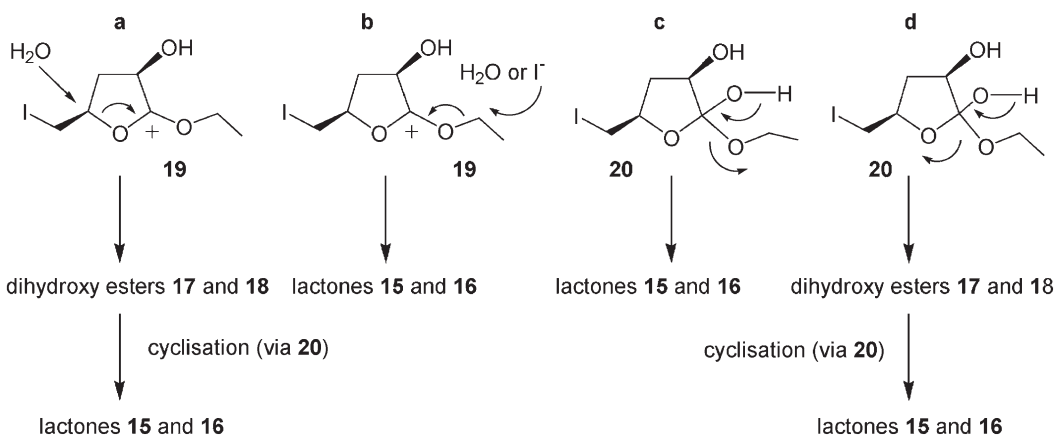


Figure 6.

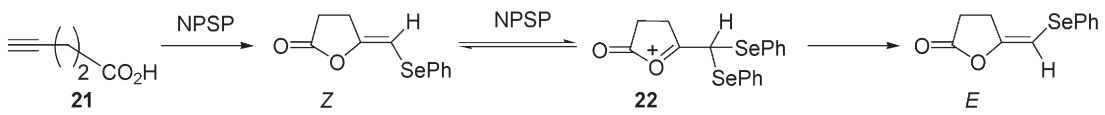


Figure 7.

mechanism was investigated using ^{18}O labelling. Under thermodynamic conditions, which do not involve **17** and **18** as intermediates, more than 75% ^{18}O incorporation at the carbonyl oxygen was observed for both *syn* and *anti* isomers and pathway **c**, involving orthoester intermediate **20**, was established. Instead of simultaneous addition of $H_2^{18}O$ along with I_2/MeCN, however, when $H_2^{18}O$ was used to quench the reaction of **14** with I_2/MeCN, no incorporation of ^{18}O was noticed and pathway **b**, involving carbocation intermediate **19**, was therefore identified as the mechanistic route. Under kinetic conditions (I_2, MeCN, $NaHCO_3$), formation of the initial iodo-dihydroxy esters **17** and **18** occurred, via pathways **a** and **d**, and these dihydroxy esters cyclised slowly to the iodolactones **15** and **16**. Here too, workup of the reaction mixture with $H_2^{18}O$ afforded good incorporation of ^{18}O at the carbonyl oxygen, indicating that the pathway **a**, via intermediate **20**, predominated in course of the reaction.

It should be further noted that these cyclisations involving the ester lead to better *syn*/*anti* selectivity under thermodynamic conditions in which the intermediate cyclic cation is in equilibrium with the starting material.[21–23]

Equilibration is also equally observed in selenolactonisations. For example, in the selenolactonisation of acetylinic acid **21**, *E*-phenylseleno-γ-lactones are exclusively formed with NPSP. Interestingly, when the minor *Z*-isomer is treated with NPSP, isomerisation to the *E*-form takes place. Equilibration through an oxycarbonium ion (**22**) intermediate would account for such a process (Fig. 7).[24]

A rather puzzling reaction is the isomerisation of the iodolactone **24**, derived from the hydroxy acid **23**, to the regioisomeric iodolactone **25** at pH 8. This has been explained on the basis of the common intermediate **26**. The ability of I_2 to assume a quasi-equatorial disposition may play a key role in the isomerisation (Fig. 8).[25]

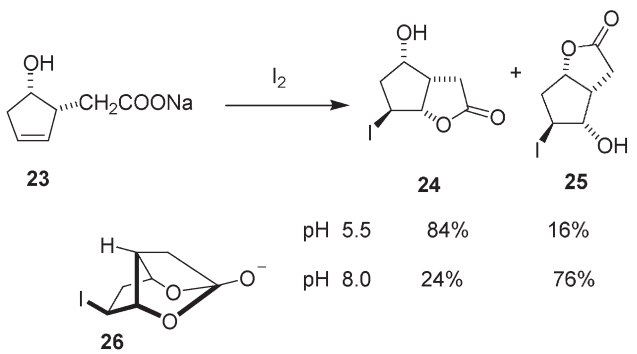


Figure 8.

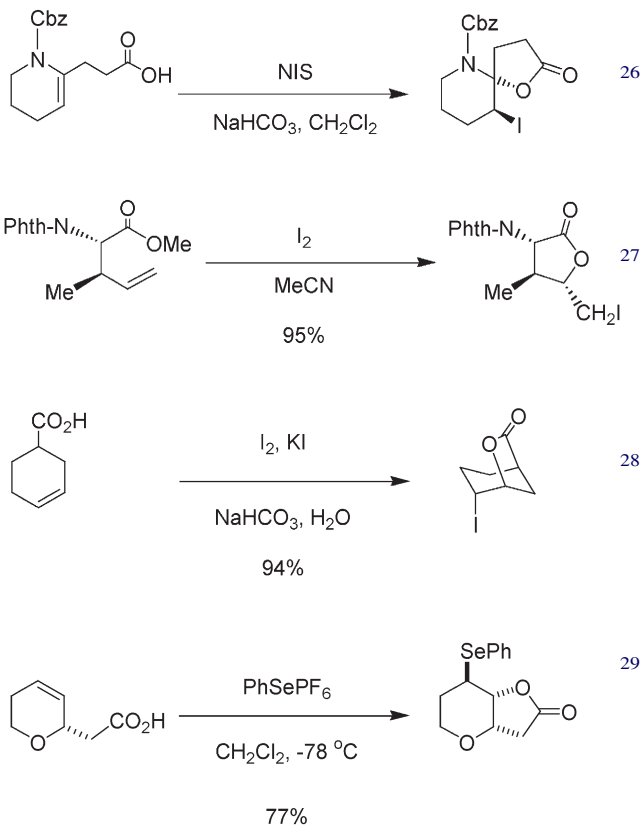
2.3. Stereochemical aspects of halo- and selenolactonisation

Substituents on the unsaturated carboxylic acids have considerable influence on the stereoselectivity of halo- and selenolactonisations. Systematic studies on both acyclic and cyclic unsaturated carboxylic acids allow the following generalisations of the stereochemical outcome in these heteroatom cyclisations to be inferred.

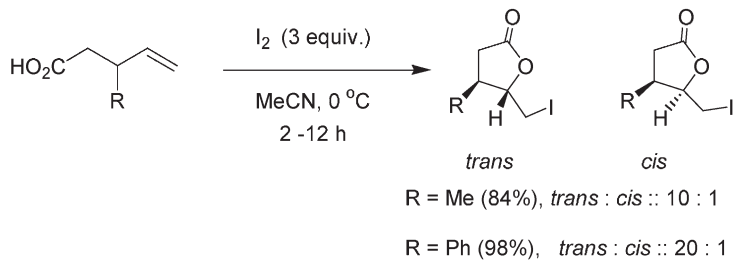
(i) In the absence of a substituent in the γ,δ-unsaturated acids, an *exo*-mode of cyclisation, leading to γ-lactones, is favoured under kinetic conditions, particularly in iodolactonisations.

(ii) Halo- and selenolactonisations are completely stereospecific in that the discrete halonium or selenonium ion intermediate undergoes attack by the internal nucleophile exclusively with inversion, in the absence of other directing influences. A few examples are given below.

(iii) The presence of chiral carbons in unsaturated acids leads to products with high asymmetric induction. Under thermodynamic control, this relates to the predominant formation of either the 1,2-*trans* or the 1,3-*cis* or the 1,4-*trans* product. Kinetic control does not offer such a high asymmetric induction.[18] The following examples illustrate the asymmetric induction in halolactonisation.



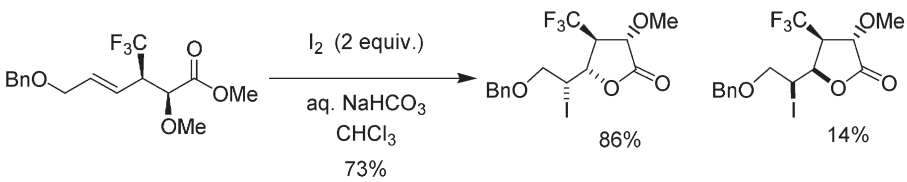
1,2-Asymmetric induction.



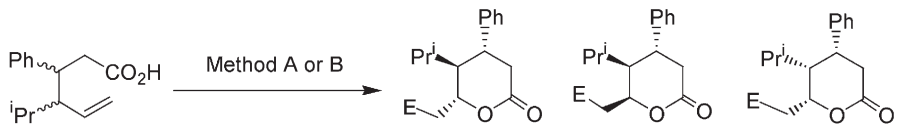
16

R = Me (84%), *trans* : *cis* :: 10 : 1

R = Ph (98%), *trans* : *cis* :: 20 : 1



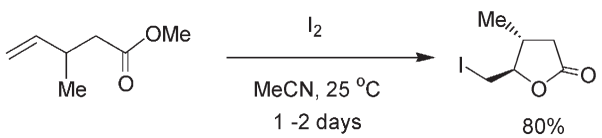
30



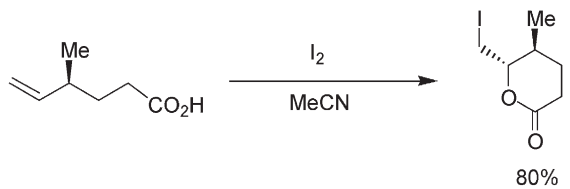
31

Method A: I_2 (3 equiv.), $NaHCO_3$ (3 equiv.) MeCN, 0 °C to rt, 48 h 65% — 100% (E = I) — - — -

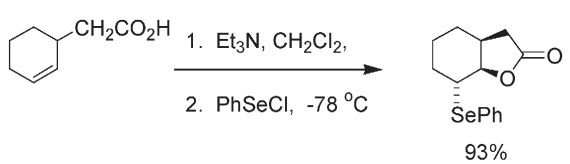
Method B: PhSeCl (1.1 equiv.), pyridine, (1.1 equiv.), CH_2Cl_2, -78 °C to rt, 24 h 71% — 96% (E = SePh) — - — 4%



32

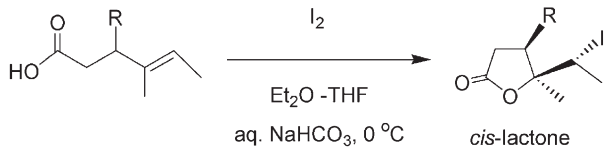


33

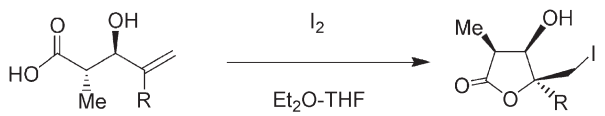


34

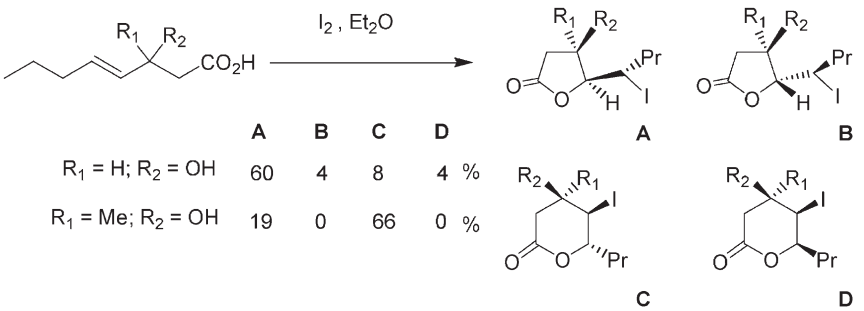
While 1,2-asymmetric induction, resulting from an allylic substituent of an unsaturated acid, usually leads to a 1,2-*trans*-configured product, the presence of hydroxy and alkoxy substituents at the allylic position reverses the configuration to 1,2-*cis*. Such a reversal of configuration necessarily requires the participation of the internal nucleophile in stabilising the halonium ion intermediate (Fig. 4). The *cis*-selective halolactonisation generally holds good for other polar substitutents at the C-2, as well as the C-3 positions.



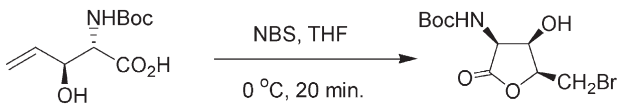
R = OH: 96%; R = $OSiR_3$: 96%; R = OAc: 94% 11



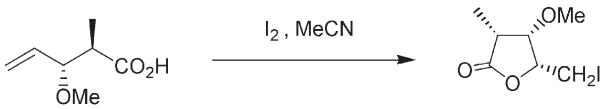
R = H: 87%; R = Me: 96% 11



14

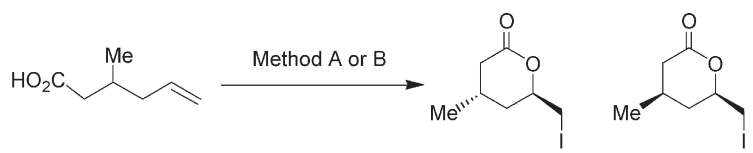


35



36

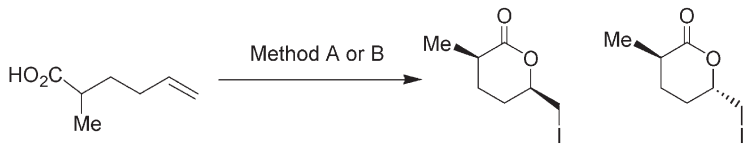
1,3- and 1,4-Asymmetric inductions.While 1,2-asymmetric induction is the most profound in halolactonisation with substrates having allylic substituents, the presence of such substituents at other locations within the unsaturated acids can also induce asymmetric inductions, namely, 1,3- and 1,4-asymmetric inductions. From the limited number of examples known for these acids, it becomes clear that a predictable streocontrol is possible during the cyclisation process. Early examples of such asymmetric inductions are revealed from the pioneering reports of Bartlett and co-workers.[18] When pertaining to δ-lactones, 1,3-asymmetric induction produces the 1,3-disubstituted *cis*-isomer as the major product. The observed 1,4-asymmetric inductions are, however, not profound, reflecting the near absence of any control by substituents beyond the allylic and homo-allylic positions.



Method A: I_2 (3 equiv.), MeCN, $NaHCO_3$, 0 °C 1 3
97%

Method B: I_2 (3 equiv.), MeCN, 0 °C 1 6
97%

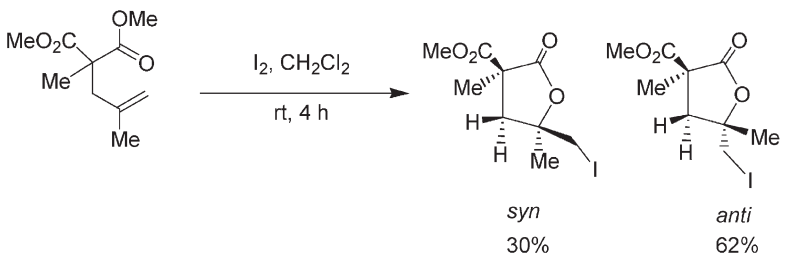
18



Method A: I_2 (3 equiv.), MeCN, $NaHCO_3$, 0 °C 1 1.8
78%

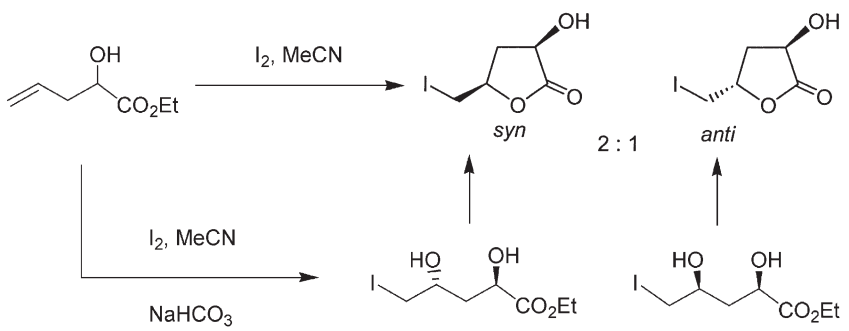
Method B: I_2 (3 equiv.), MeCN, 0 °C 1 1.1
68%

18

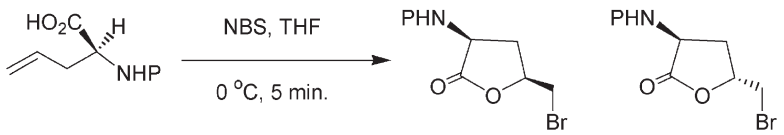


syn 30% *anti* 62%

37

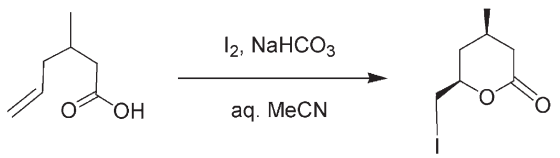


20

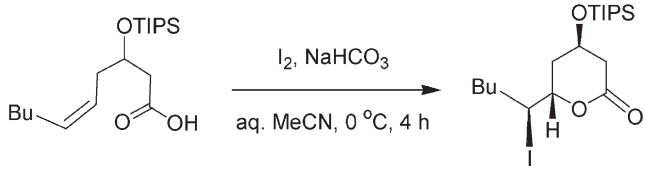


38

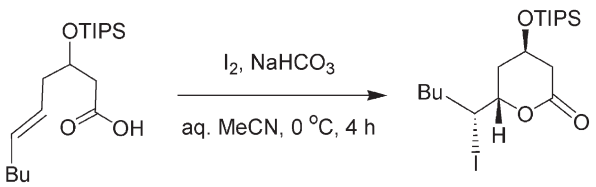
P = Cbz, Boc, Pht, Ts	8	1	(80-100%)
P = CHO	8	1	(40%)



39

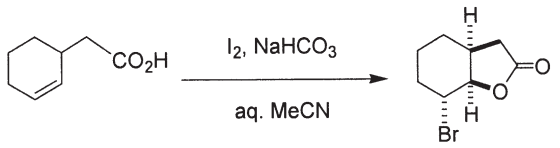


39

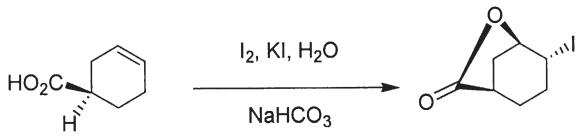


39

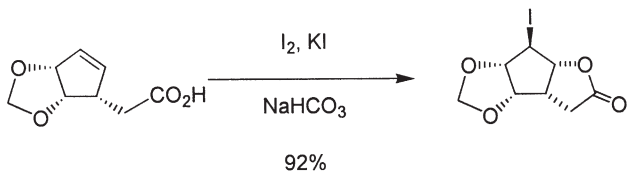
(iv) Among the substrates for cyclisation allowing complete stereocontrol are those that contain the double bond within a ring. The resulting fused or bridged lactones highly preserve a *cis* stereochemistry at the ring junction, as shown in the following examples.



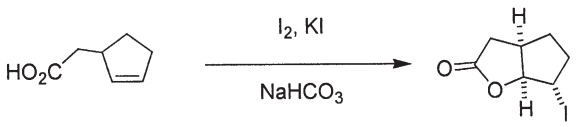
40



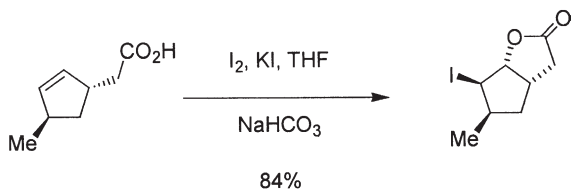
41



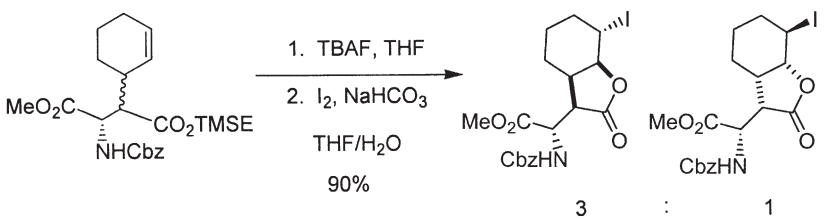
42



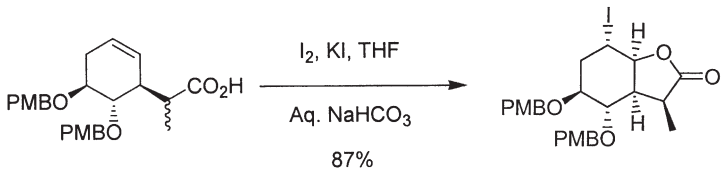
43



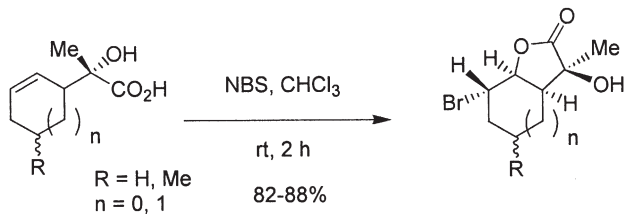
44



45

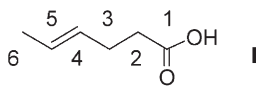


46



47

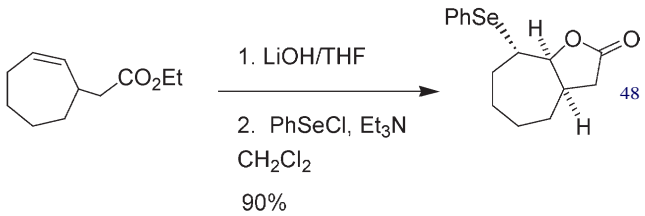
(v) Useful generalisations relating to the halolactonisation of γ,δ-unsaturated acids have been made using (*E*)-4-hexenoic acid (**I**) as the probe.



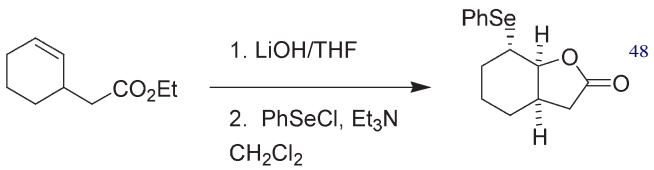
I

With most substrates related to **I**, iodolactonisation affords the γ-lactones preponderantly over the δ-isomers. In bromolactonisation, however, the preference is narrower and, in some cases, the δ-lactones actually predominate. This preference can be overcome by increasing the steric requirement of the π-terminal ligand and 6-methyl substitution of **I** (**27**) leads preponderantly to the γ-lactones in both iodo- and bromolactonisation. On the other hand, substitution at the 3-position (**28** and **29**), which makes nucleophilic attack at the 4-position more difficult, narrows the preference in iodolactonisation and affords more δ-lactone in bromolactonisation (Table 3). As stated previously, a 3-hydroxy substituent (**30**) gives mostly a *cis*-oriented product.[14]

(vi) Selenolactonisation of unsaturated cyclic olefins also lead to *cis*-fused bicyclic lactones stereoselectively. The following examples illustrate the selenolactonisation of unsaturated cycloalkenes.

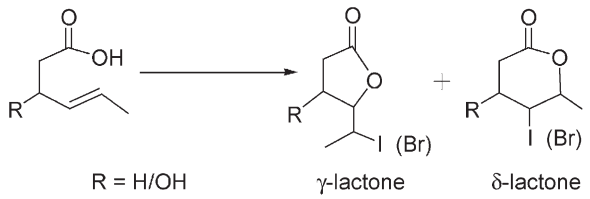


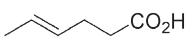
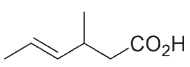
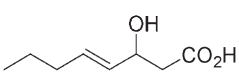
48



48

Table 3. Halolactonization of γ,δ-unsaturated acids



		Ratio of γ to δ lactones (% yield of γ-isomer)		
		I_2/KI, $NaHCO_3$	I_2, ether/THF, $NaHCO_3$	NBS, THF–AcOH
	**27**	>20:1 (85)	24:1 (71)	2.7:1 (91)
	**28**	6.5:1 (88)	1.5:1 (83)	1:1.2 (78)
	**29**	1.1:1 (86)	1:1 (81)	1:2.4 (86)
	**30**	5:1 (70)	5:1 (76)	2.3:1 (92)

2.4. β-→γ-Lactone equilibration

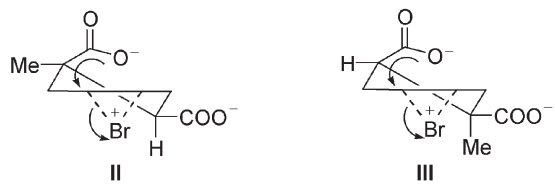
β,γ-Unsaturated carboxylic acids are exceptions to the notion that halolactonisation in bicarbonate solution is kinetically controlled. The initially-formed β-lactones, on standing, rearrange to the thermodynamically more stable γ-lactones. Thus, 1-cyclohexenylacetic acid (**31**), in a short period of time, affords the spiro β-lactone **32**, which rearranges to the γ-lactone **34** (Fig. 9). The equilibrium is likely to involve an iodonium intermediate **33**, the formation of which is facilitated by the strained β-lactone system **32**.[49,50]

2.5. *cis*-Halolactonisation by a double inversion mode

In halo- and selenolactonisations, the heteroatom nucleophile opens the electrophilic 3-membered intermediate from the opposite side, thus placing the halo- or seleno-substituent and the heteroatom in a *trans* orientation. It has been reported[51] that bromolactonisations using DMSO–TMSBr–Et_3N lead, in a few cases, to products having a *cis* orientation (Fig. 10). Analysis of these anomalous reactions indicates that a conformational change is required in order to place the carboxy residue in the correct orientation for opening the bromonium ion intermediate. This enables incursion by attack of external nucleophiles. The actual reagent in the TMSBr–DMSO reaction is the in situ formed Me_2SBr, bromonium ion intermediate formation generating Me_2S, which, in these cases, effects the opening of the former species. Subsequent elimination of Me_2S by an intramolecular attack by the carboxylate would lead to the observed *cis* orientation. The *cis* mode of halolactonisation is therefore actually an example of double inversion.[40,51]

2.6. Conformational control in halolactonisation

A noteworthy example of conformational control in bromolactonisation is that pertaining to the dicarboxylic acid arising from the cycloaddition of methyl maleic anhydride and 1,3-butadiene. Here, the carboxylic acid function at the quaternary carbon site is exclusively involved in the bromolactonisation and this has been explained on the basis of the preference of conformation **II** over **III**.[52]



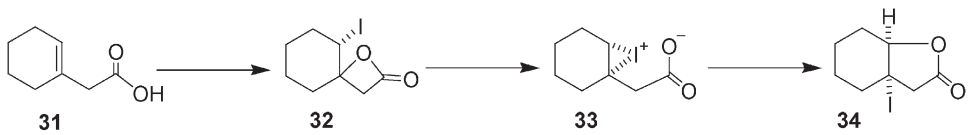


Figure 9.

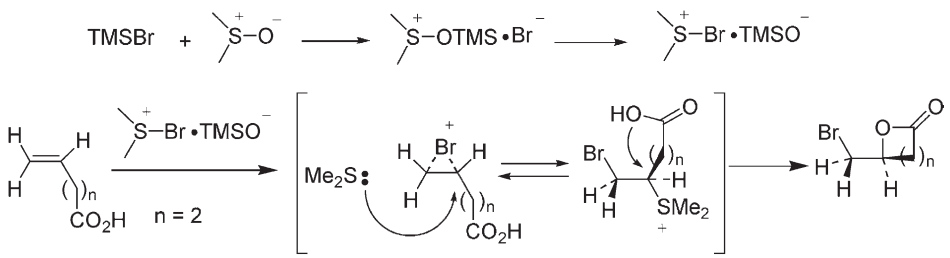


Figure 10.

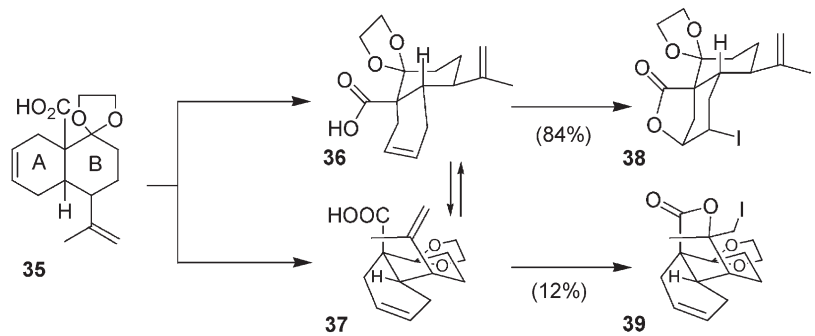


Figure 11.

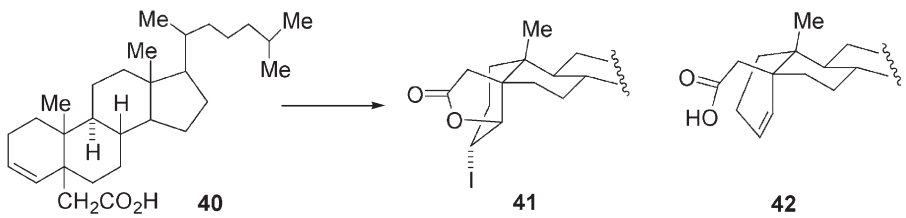


Figure 12.

The normal principles of conformational analysis may be used advantageously to predict the outcome of iodolactonisation and this is illustrated with two elegant examples (Fig. 11). In these instances, molecular (Dreiding) models of **35** show the preference for conformation **36** over **37**. Iodolactonisation under kinetic conditions therefore selectively affords 5-membered iodolactone **38** over 6-membered iodolactone **39**.[53]

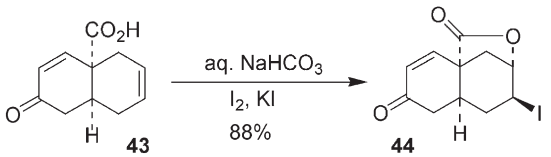


Figure 13.

The exclusive formation of **41** on iodolactonisation of **40** is rationalised on the basis of the preferred conformation relating to the acceptance of the I^+ species. Molecular models support a preference for the quasiboat arrangement (**42**) (Fig. 12).[54]

2.7. π-Selectivity in halolactonisation

In polyolefinic systems, in which the carboxylic acid location is amenable to multiple modes of iodolactonisation, the course of the reaction can be predicted on the basis of the propensity of the π-system to accept the electrophilic species. The high selectivity that can be seen in this instance is illustrated in Figure 13 in the conversion of carboxylic acid **43** to iodolactone **44**.[55]

The following example illustrates the operation of kinetic and thermodynamic controls in π-selectivity during iodolactonisation of the acid **45** (Fig. 14).[56] Under kinetically-controlled conditions, the two regioisomers **46** and **47** are obtained in the ratio 2.5:1 in favour of **46**. Under equilibrating conditions, however, the thermodynamically more stable product **47** is formed exclusively in 75% yield.

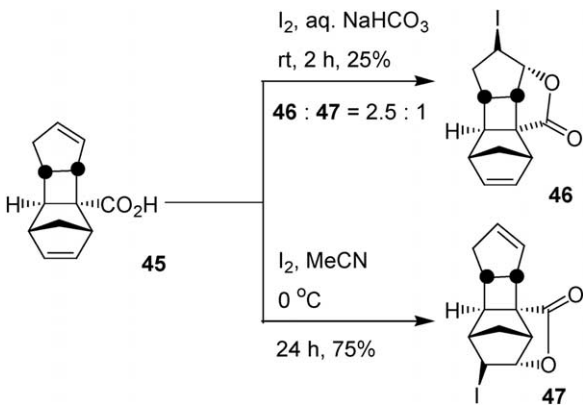


Figure 14.

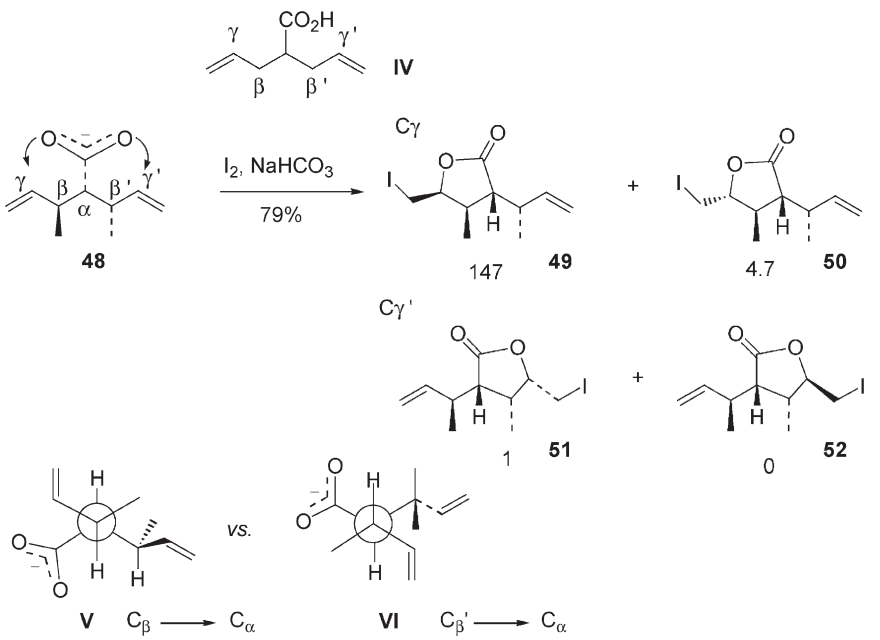


Figure 15.

The iodolactonisation of the heptadienoic acid **IV** under kinetic conditions has been studied in detail.[57,58]

The system represented by **IV** is an ideal framework for the assessment of conformational, steric and electronic factors that lead to olefin selectivity (γ/γ'). Indeed, a high selectivity is observed with several derivatives of **IV**, prominent amongst which is the heptadienoate **48**. Iodolactonisation of **48** under kinetic conditions afforded excellent olefin (**49**–**51**=147:1) and facial selectivity (**49**–**50**=30:1) (Fig. 15). Conformational control, affording **49**–**51** and none of **52**, is at the root of this preference. Of the two possible transition states, conformation **V**, leading to β-selectivity, is favoured over **VI**.

The high γ-selectivity observed with the methallyl derivative **53**, leading to **54** and **55** as opposed to γ' selectivity which affords **56** and **57**, is predictable on the basis of electronic control (Fig. 16) under these kinetic iodolactonisation conditions.

These two examples illustrate that, in the absence of a directing group in the substrate, the lactonisation becomes subjected to conformational control, while, in the presence of a directing group, the lactonisation is dominated by electronic control. In either case, it should be noted that the diastereoselectivity is more pronounced than the enantioselectivity during the cyclisation.

2.8. Control of regioselectivity in halolactonisation of proximately aligned and rigidly held 1,2-dicarboxylates

A detailed study of the effect of substitution on the bromolactonisation of dicarboxylic acids arising from the addition of methylmaleic anhydride and acetoxymaleic anhydride to cyclopentadiene has emphasised the interplay of steric and electronic effects on the course of the bromolactonisation (Fig. 17).[59] While the compound **58** undergoes exclusive bromolactonisation involving the carboxy group at the tertiary carbon site with bromine-bicarbonate (pH 8.3) to afford bromolactone **59**, the carboxy group at the quaternary carbon site is selectively bromolactonised to **60** with bromine-water (pH 3–4). Interestingly, bromolactonisation of **61** under both conditions gives products from the exclusive bromolactonisation of the quaternary carboxyl group to afford bromolactone **62**. Had steric considerations prevailed, the buttressing effects would have promoted bromolactonisation involving the carboxy group at the quaternary carbon under all conditions. Electronic factors, however, make the carboxylate group at the quaternary site more basic than the tertiary carboxylate in **58**. The situation is, however, reversed in **61**. These observations show that the bromolactonisation of proximately aligned and rigidly held 1,2-dicarboxylates takes place via the intermediate **63**, arising from the addition of the more basic carboxylate unit to its neighbour. Significant unfavourable electrostatic interactions could be avoided by the formation of the intermediate **63**, in which the carboxylic acid unit attached to the carbon bearing Y is more basic.

2.9. Synthesis of β-lactones from halolactonisation of β,γ-olefinic acids

β-Lactones are formed from β,γ-olefinic acids by iodolactonisation under kinetic conditions. A study of the effect of

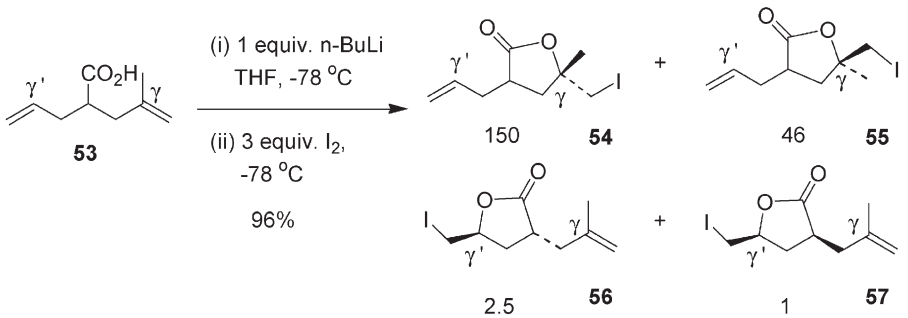


Figure 16.

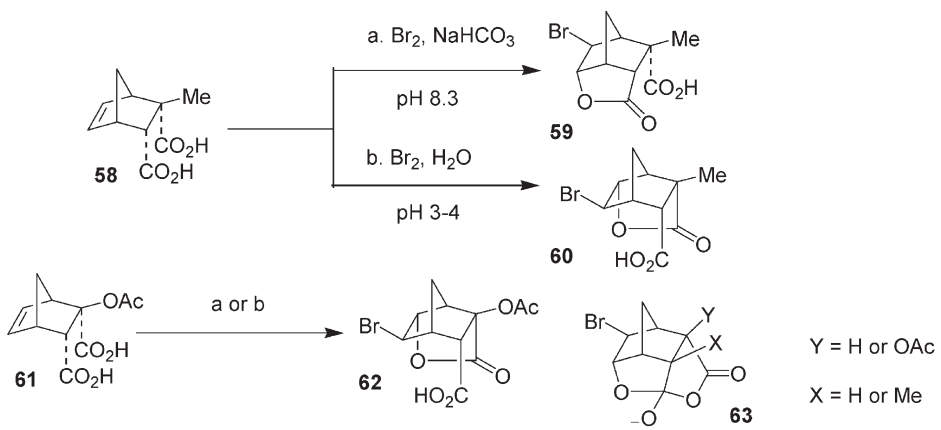


Figure 17.

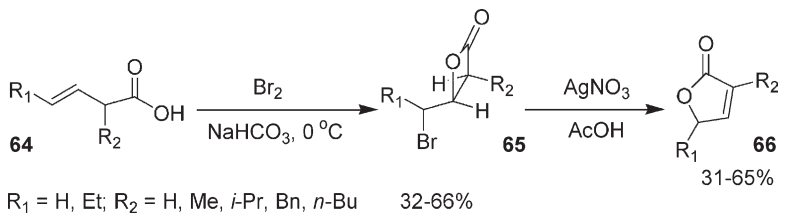


Figure 18.

the α-substituent in **64** (H, Me, *i*-Pr, Bn, *n*-Bu) on the yields of the β-lactones **65** was inconclusive. Regardless of the nature of the substituent at the α-position, however, the lactones obtained have been converted to the corresponding butenolides **66** via a cation-initiated ring expansion/elimination strategy (Fig. 18).[60]

Bromolactonisation of the Birch reduction products of various methyl-substituted benzoic acids provides interesting results. The reduction product of *o*-toluic acid affords exclusively a β-lactone at the carbon carrying the methyl substituent, which is expected on the basis of stabilisation of the carbocation centre. This aspect is highlighted with the bromolactonisation of the reduction product of *m*-toluic acid **67**, where bicyclic lactones **68** and **69** involving highly substituted carbon centre, are formed exclusively (Fig. 19).[61]

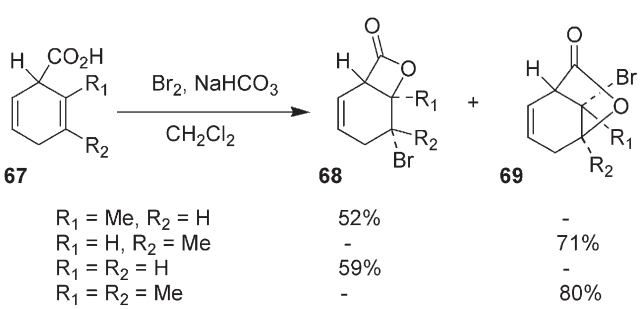


Figure 19.

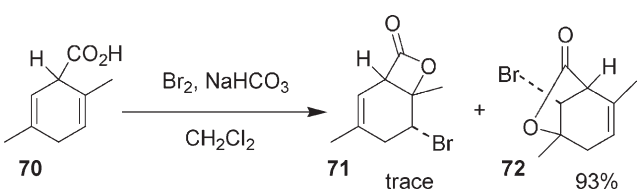


Figure 20.

In a competitive experiment on the reduction product of 2,3-dimethylbenzoic acid, the product was the bicyclic lactone, which is favoured by stabilisation of the electrophilic centre as well as by strain factors. Similar results leading to γ-lactones **71** and **72** are obtained from the Birch reduction product of 2,5-dimethylbenzoic acid **70** (Fig. 20).[61]

2.10. Formation of γ- and δ-lactones from β-hydroxy-γ,δ-unsaturated acids

A detailed study on the selenolactonisation of the β-hydroxy acid **73** has led to the stereocontrolled synthesis of δ- and γ-lactones.[62a] The selenolactonisation of **73** (PhSeCl (1 mol. equiv.)/K_2CO_3/CH_2Cl_2) initially gave the lactones **74** and **75** with low selectivity. The major diastereomer comes via the transition state **VII** that displays the intramolecular hydrogen bonding, in addition to the stabilising Se···O interaction, which is absent in the transition state **VIII** leading to the minor diastereomer (Fig. 21).

An increase in diastereoselectivity was observed on using 2 and 3 M equiv. of PhSeX (X=I, Br, Cl) [ratio of **74**–**75**, 57:43; 76:24 and 89:11 for 1, 2 and 3 M equiv. of PhSeCl, respectively]. Similar diastereomeric preferences were obtained on using PhSeX in combination with TBAX (X=ClO_4^-, Cl, Br). The influence of X^- in bringing about the selectivities can be explained in terms of the probable transition states **IX** and **X** that can arise during selenolactonisation (Fig. 22). The seleniranium transition state **X** is more stable and the activation energy for cyclisation is higher, whereas **IX** is less stable, with a lower activation energy for cyclisation. Further, **X** is sufficiently long lived to undergo intermolecular attack by Cl^-, Br^- or ClO_4^- at the positively charged selenium centre, which destroys the intermediate to give the starting material and PhSeX, thus driving the reaction in favour of **74**. It is also evident that it is possible to maintain the Se–O interaction, which is primarily an n–σ* type interaction,[62b,c] during the

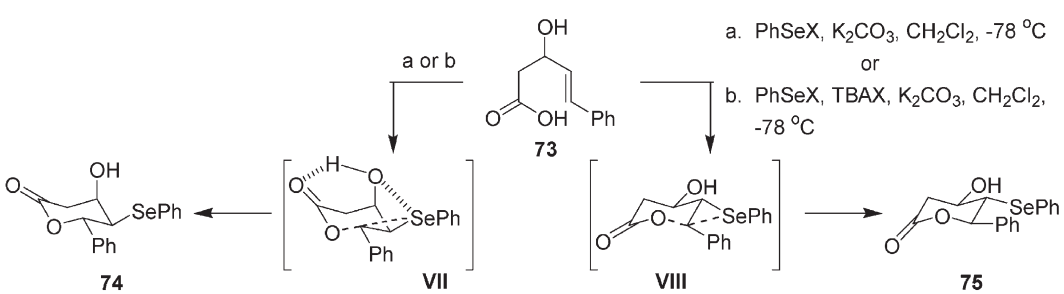


Figure 21.

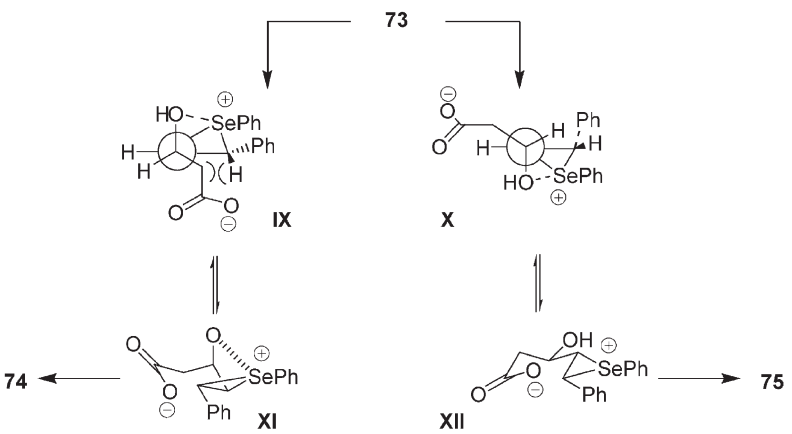


Figure 22.

cyclisation from **IX** whereas, in **X**, this interaction is lost (**XI** and **XII**, respectively).

A selenolactonisation strategy has also been used in the synthesis of the 4,6-diequatorial δ-lactone **79** from the β-hydroxy ester **76** through the intermediacy of the 1,3-antidiol **78**, arising by the attack of water on the seleniranium on **77** (Fig. 23).

Interestingly, a mixture of **74** and **75** in CH_2Cl_2 when stirred with silica gel afforded the γ-lactone **80** in excellent yield and diasteroselectivity (**80**–**81**=95:5) (Fig. 24). Here, the acidic conditions from the silica gel caused the protonation of the δ-lactones and the intramolecular Se attack at C6, causing the ring opening. The intermediate seleniranium ions **XIII** and **XIV** then cyclised to give the thermodynamically more stable γ-lactone **81** with excellent stereoselectivity.

2.11. Controls that promote halolactonisation to medium rings

The formation of medium-ring lactones and ether lactones by iodolactonisation has been examined.[63–65] The common reagents used for iodolactonisation do not work well in these cases. Satisfactory results can be obtained by using iodonium di(*sym*-collidine) hexafluorophosphate.

Iodolactonisation as a function of geminal dimethyl substitution afforded no great advantage in terms of the yields of products using the above reagent up to ε-caprolactones. Beyond this ring size, however, the effects were rather dramatic. Whereas iodolactonisation of 7-octenoic acid with the halonium di(*sym*-collidine) reagent afforded only 5% yield of the 8-membered lactone, the incorporation of geminal dimethyl groups at the 4-location (**82**) afforded not only 26% yield of the 8-membered lactone **83** (*m*=1,

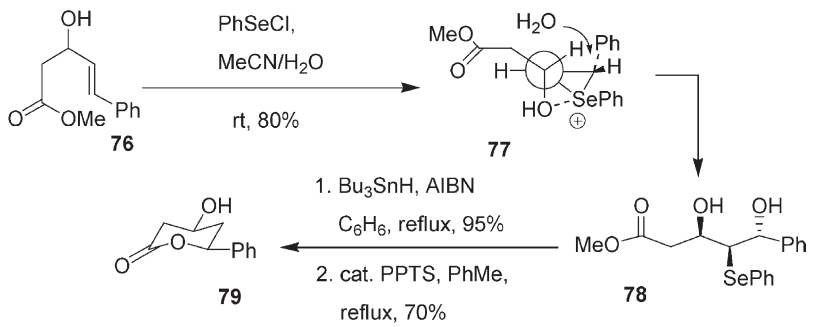


Figure 23.

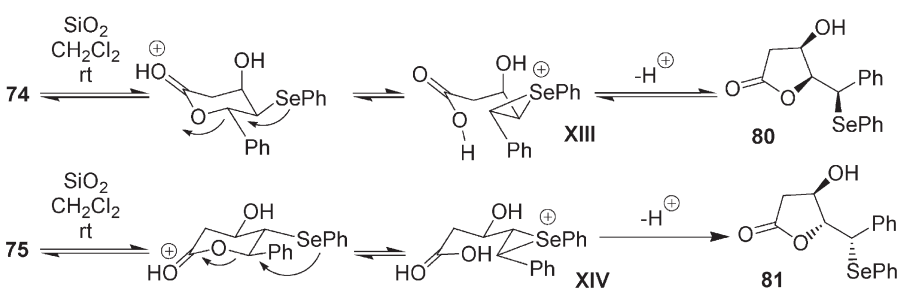


Figure 24.

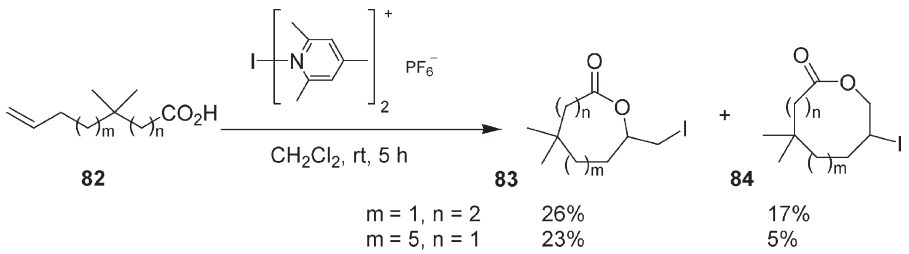


Figure 25.

n=2) by exocyclisation, but also 17% yield of the 9-membered lactone **84** (*m*=1, *n*=2) from endocyclisation (Fig. 25). This strategy has been used in the preparation of 11- and 12-membered lactones in reasonable yields. Apart from the fact that the incorporation of the geminal dimethyl group at the 2-position is not recommended, no generalisations could be made relating to the placement of these groups at various locations so that a maximum yield could be obtained. The strategy here, however, provides a practical approach towards the synthesis of medium-ring cyclic lactones. It would be interesting to replace the geminal methylation groups with other units, such as ketals and dithioketals, so that the products could be elaborated to useful synthetic objectives.

Interestingly, the replacement of carbons by ether linkages proximal to the acid function, as in **85**, also leads to the formation of medium-ring cyclic lactones **86** and **87**, in satisfactory yields, using the iodonium di(*sym*-collidine) reagent (Fig. 26). The oxygen effect here has been rationalised on the basis of the opening of the initially formed iodonium ion with the ether linkage, followed by lactonisation.

The *endo*/*exo* preferences in the formation of 7- to 20-membered ring sizes from 2-alkenyl benzoic acids using iodonium or bromonium di(*sym*-collidine) hexafluorophosphate has been studied.[66] Steric and electronic factors are the major control elements that dictate the observed preference (Table 4). The unique formation of *exo* lactones **89a**,**b** and **90a**,**b** from **88a**, **b** is mainly controlled by electronic factors. The gradual increase in the *endo* lactone

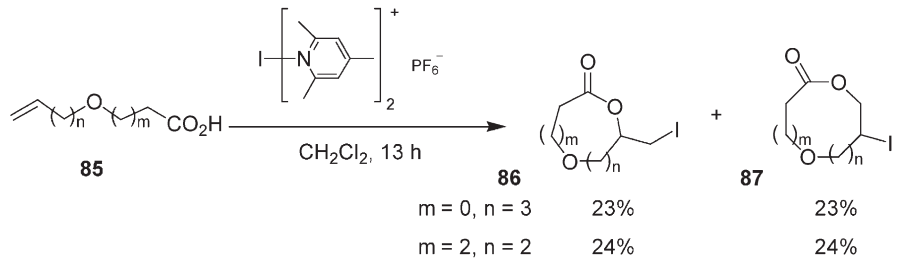
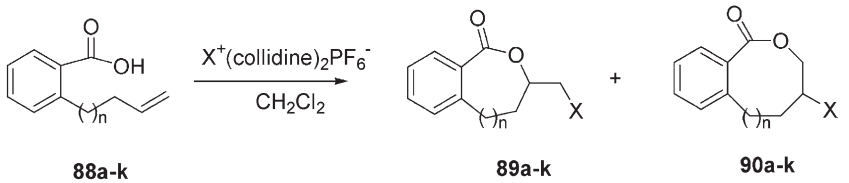


Figure 26.

Table 4. Halolactonisation of acids **88a–k**



Acid	Ring size of *exo-endo* lactones	Iodolactones; X=I		Bromolactones; X=Br	
		Overall yield (%)	*exo*/*endo*	Overall yield (%)	*exo*/*endo*
88a	7:8	**89a**:**90a** (93)	100:0	**89a**:**90a** (95)	100:0
88b	8:9	**89b**:**90b** (80)	98:2	**89b**:**90b** (78)	80:20
88c	9:10	**89c**:**90c** (84)	69:31	**89c**:**90c** (50)	66:34
88d	10:11	**89d**:**90d** (52)	60:40	**89d**:**90d** (40)	52:48
88e	11:12	**89e**:**90e** (46)	53:47	**89e**:**90e** (35)	47:53
88f	12:13	**89f**:**90f** (48)	82:18	**89f**:**90f** (35)	64:36
88g	13:14	**89g**:**90g** (55)	84:16	**89g**:**90g** (40)	72:28
88h	14:15	**89h**:**90h** (62)	85:15	**89h**:**90h** (40)	75:25
88i	15:16	**89i**:**90i** (55)	81:19	**89i**:**90i** (45)	70:30
88j	16:17	**89j**:**90j** (46)	76:24	**89j**:**90j** (30)	66:34
88k	19:20	**89k**:**90k** (53)	67:33	**89k**:**90k** (35)	50:50

ratio (**89c–k** and **90c–k**) with chain ring sizes from 8–11 (**88c–k**) implies that the steric hindrance induced by an *endo* approach is lower than that of an *exo* approach.

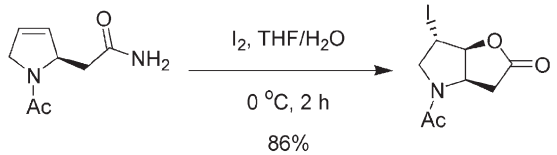
For larger ring sizes (from 12–14), however, the trans-annular interactions become too small and insignificant compared to other effects,[67] which accounts for the observed preference in favour of the *exo* isomer. *exo*-Lactone formation appears again to be disfavoured for larger ring sizes (≥14), presumably due to the conformational preferences.

2.12. Diastereomeric preferences in the halolactonisation of amides

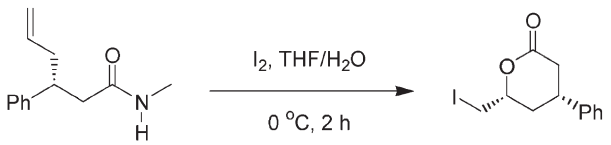
Examples of primary and secondary amide substrates undergoing halolactonisations are comparatively less than those of the tertiary amides substrates. The following examples illustrate iodolactonisation of primary and secondary amides. It is important to note that, apart from the oxygen mode of cyclisation, a nitrogen mode of cyclisation, affording lactams, is also possible with these amide substrates.

The best-known examples of the lactonisation of amide substrates originate from the tertiary amides. As discussed earlier, the tertiary amide as an internal nucleophile to react at the halonium intermediate usually leads with high stereoselectivity to predominantly 1,2-*trans* orientation of the oxygen nucleophile and the halogen substituent. On the other hand, an allylic substituent such as a hydroxyl group affords the 1,2-*cis* isomer as the predominant lactone.

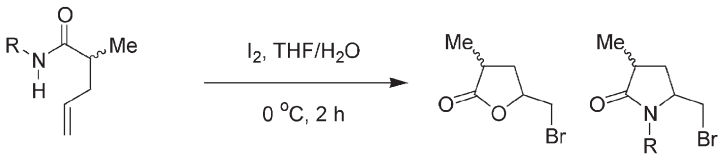
As illustrated previously, an oxygen centre, proximally aligned to the π-bond, undergoing *exo* iodolactonisation, provides a very powerful *cis*-directing influence. That this property can be used efficiently in the cyclofunctionalisation involving tertiary amides has been shown by a detailed study of the iodolactonisation of the *threo* and *erythro* isomers of α-alkyl-β-oxy-4-pentenamide substrates. On the



68



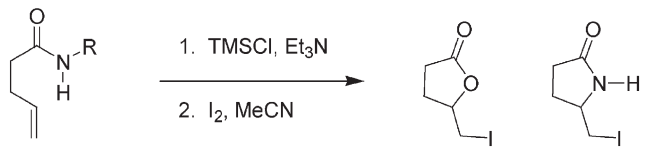
69



R = 75% -

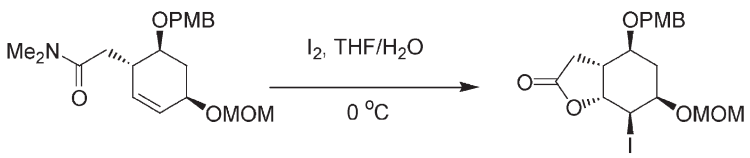
R = 75% -

70

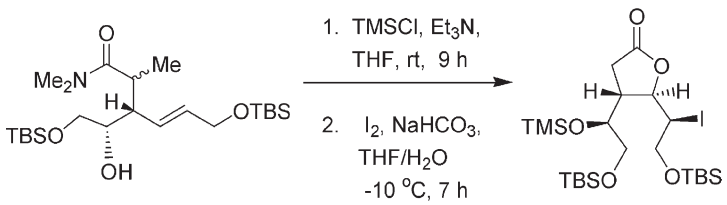


R =	1	2
R =	1	3
R = ^{n}Bu	1	1.2

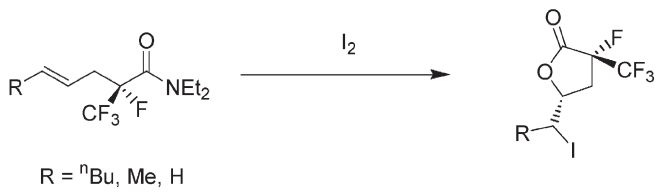
71,72



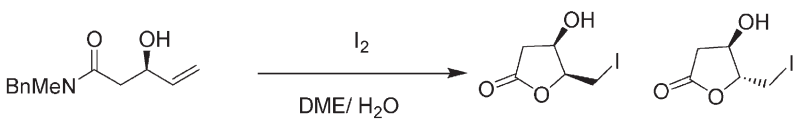
73



74



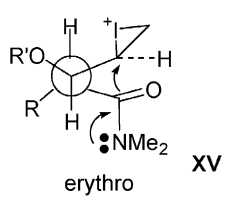
75



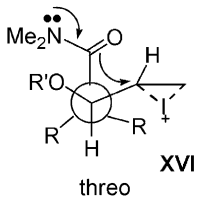
76

basis of oxygen control, the iodolactonisation (I_2, THF/H_2O) of the *erythro* and *threo* isomers proceeds through, respectively, the intermediates **XV** and **XVI**, with exceptionally high selectivity, while generating three contiguous chiral centres in a predictable manner. This reaction, when performed in conjunction with a chiral auxiliary, may provide a practical route to optically active γ-lactones.[77a]

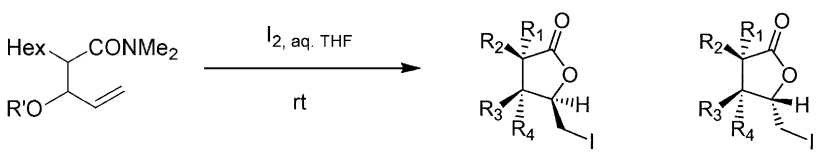
Iodocyclisation of an *N*-methoxy tertiary amide, using a haloazide as the reagent, leads to α-deprotonation of the ammonium intermediate, which accepts another halonium



XV

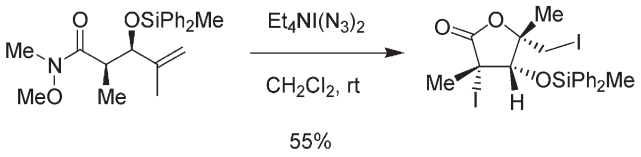


XVI



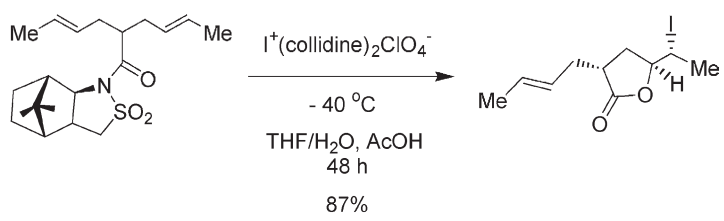
erythro- (R' = OH)	R_1 = alkyl; R_2 = H R_3 = OH; R_4 = H	7	(60%)	1
threo- (R' = OH)	R_1 = alkyl; R_2 = H R_3 = OH; R_4 = H	1	(74%)	6
erythro- (R' = PentCO)	R_1 = alkyl; R_2 = H R_3 = ester; R_4 = H	>95	(86%)	5
threo- (R' = PentCO)	R_1 = alkyl; R_2 = H R_3 = H; R_4 = ester	2	(89%)	1

species to afford the dihalolactone as shown below.[77b]

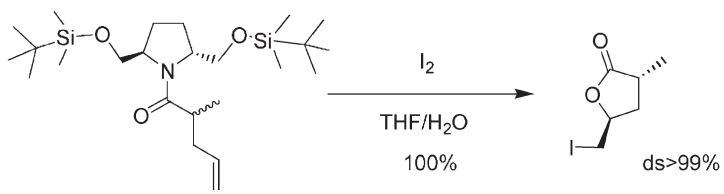


2.13. Chiral auxiliary approaches in halo- and selenolactonisation

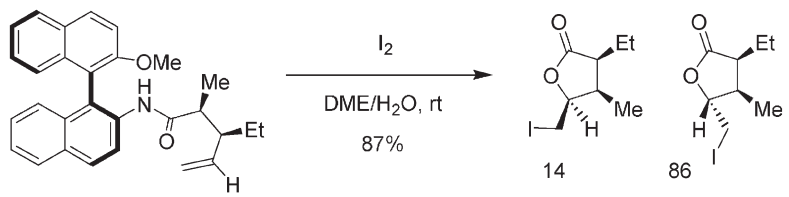
Enantioselective and diastereoslective halo- and selenolactonisations have been explored in detail, primarily using C_2-symmetric chiral auxiliaries. Stereoselective halolactonisations have largely been reported with unsaturated



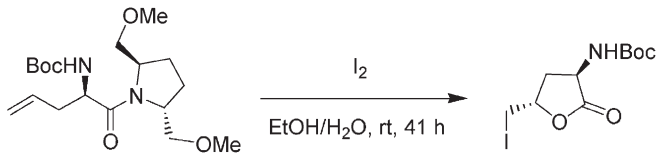
78



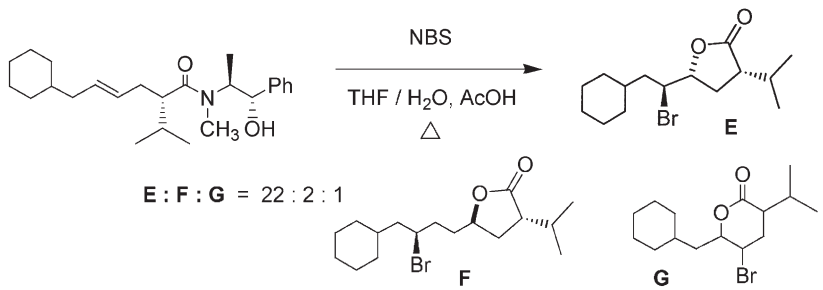
79



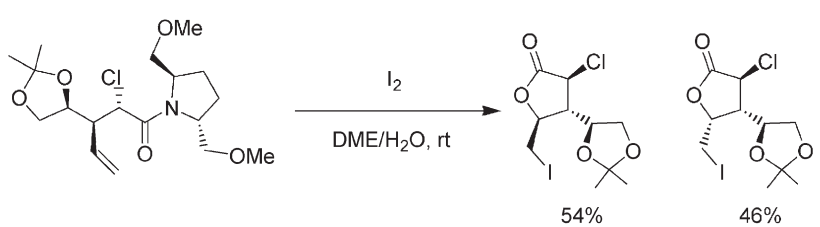
80



81



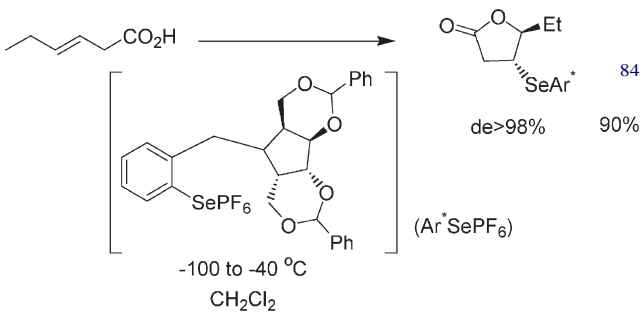
82

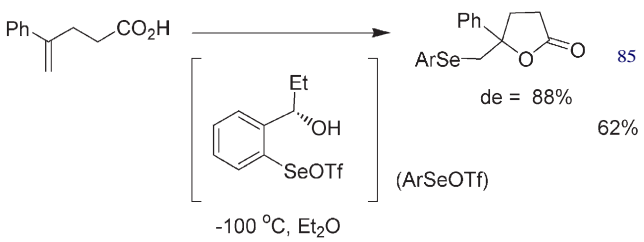


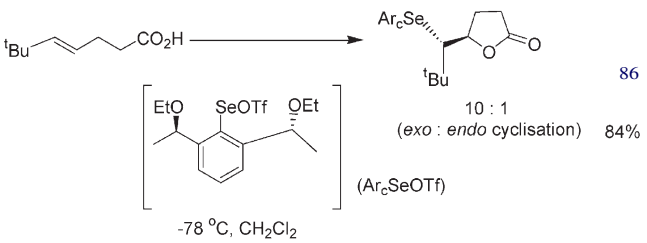
83

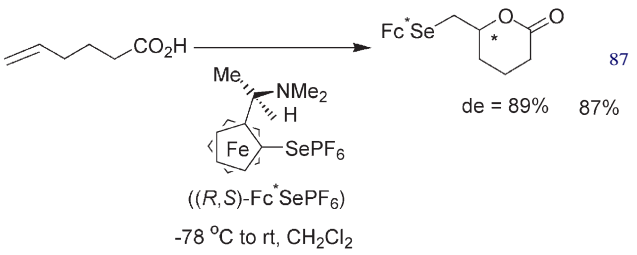
tertiary amides. With other substrates, strategies were evolved to achieve high stereoselectivities by controlling the restricted rotation about the tertiary amide bonds, by way of incorporating electron-deficient carbonyl or sulphone functions[78] and increasing the interference by bulky substituents on the *tert*-amide chiral auxiliary.[79] Chiral secondary amides are also used for diastereoselective iodolactonisation.[80] These asymmetric halolactonisations are observed to afford halolactones with high asymmetric inductions, in favour of a 1,2- and 1,3-*trans* arrangement of the existing and newly-created chiral centres. This *trans*-relationship is even more pronounced when there is a polar group α- to the carbonyl function. The following examples illustrate the developments in stereoselective halolactonisations.

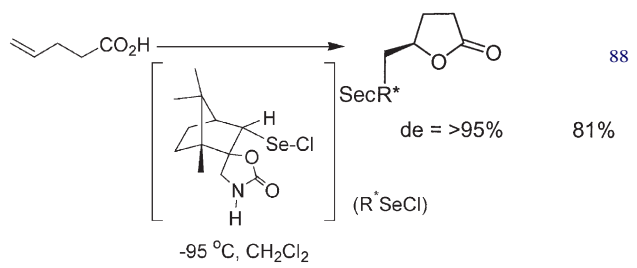
Electrophilic selenium reagents were also prepared for asymmetric selenolactonisations. These reagents include chiral aryl, organometallic and camphor-derived selenides.[84–88] A chiral arylselenium electrophile, bearing a heteroatom at the chiral centre, generally assists in stabilising the selenonium cation intermediate in a preferred conformation. Upon addition of the alkene, the chirality is transferred to the newly-formed asymmetric centres. The high 1,2-asymmetric induction results are as anticipated, due to the approach of the chiral selenium reagent from the less-sterically hindered direction to afford a chiral selenonium cation, followed by an intramolecular *anti*-attack of the nucleophile. For the γ,δ- and δ,ε-unsaturated acids, the *exo*-mode of cyclisation predominates, so as to afford the 5- and 6-membered lactones, respectively, with high facial selectivity. Some developments in asymmetric selenolactonisations are illustrated in the following examples.











3. Scope and limitations

As stated in Section 1, halo- and selenolactonisation belong to the class of cyclofunctionalisation reactions, in which heteroatoms play a key role. Halo- and selenolactonisation reactions have a special appeal, not only with respect to the controls, but also to the carbon–heteroatom bonds present in the products, which allow further elaborations to be possible. Additionally, the protocols developed for these reactions can be transposed in most cases, thereby widening their scope and application. In terms of their range and applicability, only a few reactions are therefore as versatile as the halo- and selenolactonisations.

Limitations arise, however, as a result of competing reactions with other nucleophiles present within the substrate. Preferences, with respect to the location, the nature of the nucleophile and the transition state geometry, are quite profound in cyclisation reactions involving substrates having more than one nucleophile. Prominent

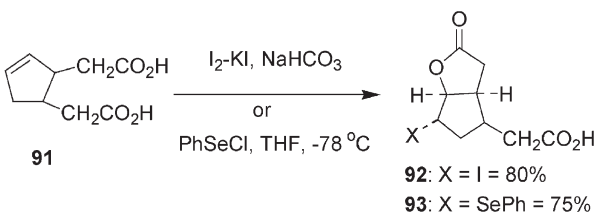


Figure 27.

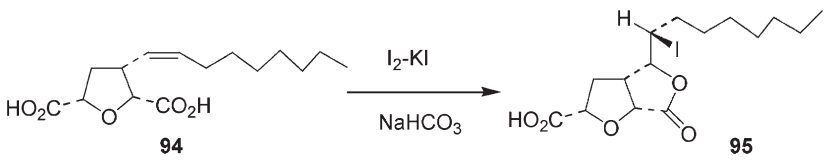


Figure 28.

selectivities among various nucleophiles are summarised below.

3.1. Carboxyl group selectivity in halo and selenolactonisations

Carboxyl group selectivity depending on the location of the carboxylic acid is illustrated by *cis*-3-cyclopentene-1,2-diacetic acid **91**, having two CH_2CO_2H functionalities. This substrate provides options for either a δ-lactone that would proceed through a chair-like transition state, leading to a bicyclic system, or a γ-lactone arising from halolactonisation of the proximal acetic acid unit (Fig. 27). In the event, iodolactonisation under kinetically controlled conditions leads exclusively to the formation of the γ-lactone **92**. This profile, by and large, is general in the sense that the formation of the γ-lactone is much more facile than that of the δ-lactone.[89]

The selenolactonisation of **91** also proceeds in the same manner, leading to the exclusive formation of the γ-lactone **93**. Such chemoselectivity of equivalent carboxyl group side chains provides a reliable synthetic strategy, since products from either halo or selenolactonisation can be transformed to a variety of further products.[90]

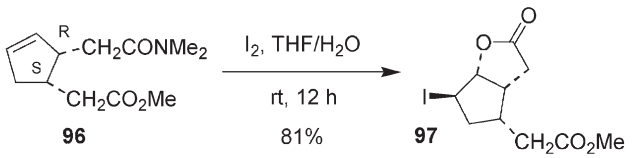


Figure 29.

Carboxyl group selectivity can be predicted on the basis of the nature of the transition state. An interesting example is that of the acid **94**, where the iodolactonisation leads exclusively to the γ-lactone **95** by an *exo-trig*-cyclisation (Fig. 28).[91]

3.2. *tert*-Amide vs ester preference—cyclopentadiene to prostanoids

In the iodolactonisation of amides and esters, the required nucleophilic centre is promoted by either a nitrogen or an oxygen lone pair. The former is more effective, leading to a preferential mode to the prostanoid **97**, as illustrated below with amide **96** (Fig. 29).[92]

3.3. Carboxylic acid vs phosphonate preference—acetate to 3-methylene γ-lactones

Under kinetically-controlled conditions, selective iodo- and selenolactonisations of a carboxylic acid group can be achieved in the presence of a phosphoryl residue attached to the same carbon, as in acid **98**. This preference has been used in an efficient preparation of lactone **99** as a precursor of 3-methylene-γ-lactone **100** (Fig. 30).[93]

3.4. Carboxylic acid vs sulphinate preference

The attack of a sulphinate ester instead of carboxylate at a distal alkene leads to iodosultinisation (Fig. 31).[94] This reaction, conducted with TFA and I_2, in the presence of Ag^+, involves the attack of sulphinyl oxygen at the activated carbon on the opposite side of the molecule and, after loosing the ethyl group, leads to the sultine (**103**) possessing the sulphinyl group with an opposite

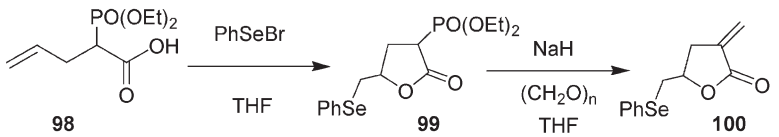


Figure 30.

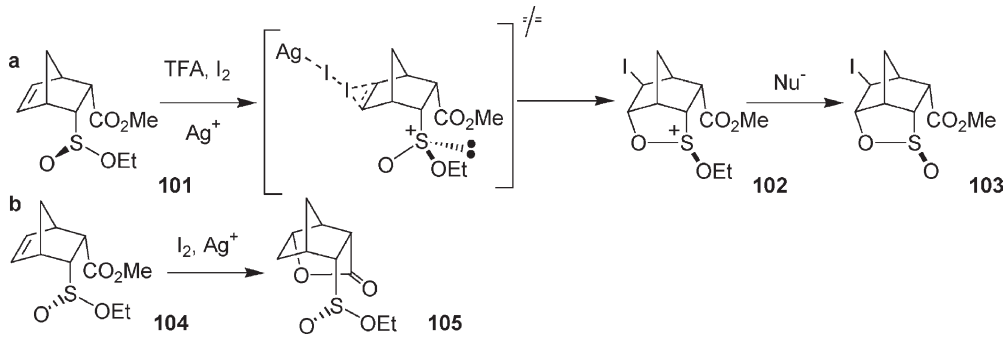
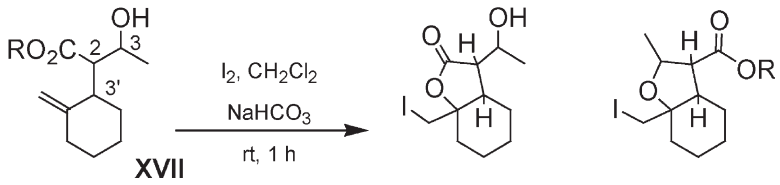


Figure 31.

Table 5. Results for the iodolactonisation of XVII



Isomer	Lactone (%)	Ether (%)
3′*S*,2*S*,3*S*		
R=H	87	—
R=Me	79	—
3′*R*,2*S*,3*S*		
R=Me	9	87
3′*R*,2*R*,3*S*		
R=H	76	5
R=Me	52	48
3′*S*,2*R*,3*S*		
R=Me		66
R=H		66

configuration of the starting sulphinate. The steric barrier of the sulphoxide with respect to the carboxylic acid indeed dictates that the *endo* sulphinate participates in the iodocyclisation, rather than the potentially competing *endo* carboxylic ester. In the iodosulitinisation of **101**, the intermediate species **102** positions the ethoxy group *anti* to the existing bicyclic system, thereby minimising the steric barrier for the cyclisation. Such an intermediate for **104** would, however, have a severe steric interaction between the ethoxy group and the *endo* carboxylic ester moiety, making the iodosultinisation unfavourable. On the other hand, when one of the two groups, that is, sulphinate or carboxylic ester, is situated at the *exo* position of the bicyclic system, the preferential attack by the functionality at the *endo* face then predominates, affording either the iodosultinisation or iodolactonisation product **105**.

3.5. Carboxylic acid vs hydroxyl group selectivity in cyclofunctionalisation

3-Hydroxy-2-(2-methylenecyclohexan-1-yl)butyric acid **XVII** is a typical example of systems in which two different nucleophiles (OH and CO_2H) compete for a single electrophilic centre such as that involved in iodolactonisation reactions. Cyclofunctionalisation here could therefore result in either an ether or a lactone. The minimum energy conformations can be correlated to the three contiguous chiral centres present in the molecule. The results for iodolactonisation (I_2, CH_2Cl_2, $NaHCO_3$, rt, 1 h) of the various isomers are presented in Table 5.[95]

These results have been correlated with calculations of the ground state minimum energy conformational orientations, which indicate that the selectivity is determined by the proximity of either the carboxy or the hydroxy group to the π-bond. This conclusion is reasonable, since the conditions for iodolactonisation are under kinetic control.

3.6. O- vs N-Cyclofunctionalisation of unsaturated amides

As stated previously, cyclofunctionalisation reactions involving a terminal amide group play an important role in halolactonisation processes, particularly since the nitrogen function can be effectively used as a chiral auxiliary, which is subsequently eliminated. The amide function also gives the opportunity for cyclofunctionalisation via the nitrogen, in which case a lactam results.

In these reactions, alkyl and aryl substitution on the amide nitrogen, as in amide **106**, generally leads to lactonisation. Interestingly, substitution on the benzene unit with either a

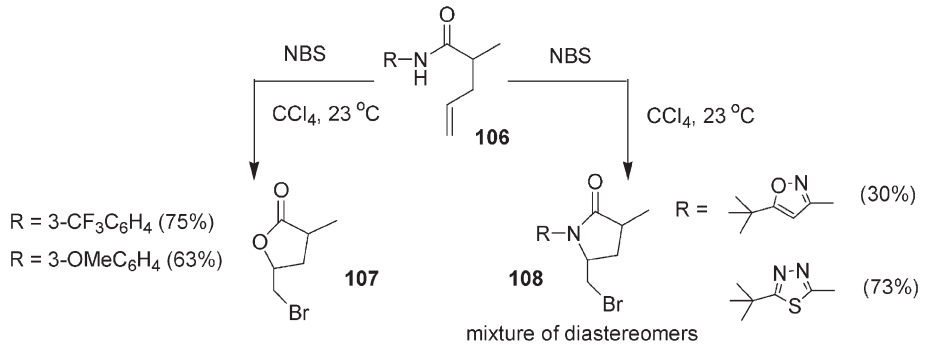


Figure 32.

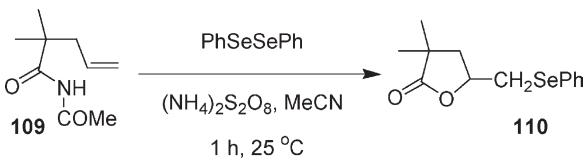


Figure 33.

3-trifluoromethyl or a 3-methoxy group leads to lactone **107**. When the nitrogen is linked to a heterocyclic aromatic system, lactams usually result from nitrogen-mediated cyclofunctionalisation. Indeed, the cyclofunctionalisation of heterocyclic derivatives of 3-butenoic acid amides **106** with *N*-bromosuccinimide to functionalised β-lactams **108** is a useful strategy. The cyclofunctionalisation with *N*-terminal amides can therefore be controlled by the nature of the substituent on the amide nitrogen (Fig. 32).[70]

An interesting example of the reversal of this preference of an amide substrate carrying an electron-withdrawing group is the selenolactonisation of the amide **109** containing a terminal double bond, which forms exclusively the lactone **110**. It is likely that the reversal of preference arises from the enol form of **109** (Fig. 33).[96]

The reaction pathways that govern O- vs N-cyclofunctionalisation of terminal amides in selenolactonisation are similar to those in halolactonisation, although the number of studies is rather limited. In general, *N*-alkyl amides afford lactones and *N*-acyl systems lead to lactams.[97]

3.7. Bromolactonisation of aromatic systems

Carboxylic acids are known to preponderantly involve the aromatic ring during halolactonisation.[98] The following examples illustrate this unusual halolactonisation (Fig. 34). It is rationalised on the basis that the halolactonisation of *endo*-bicyclic acid **111** occurs through a carbocation formation on the aromatic ring during bromination of bromonapthalene derivative **112**, followed by an internal attack of the carboxylate at the carbocation to afford δ-lactone **113**.

A noteworthy application of bromolactonisation is the transformation of histidine dihydrochloride (**114**) to a spiro compound **115** with bromine water, which occurs within 7 min (Fig. 35).[99]

Other readily available aromatic compounds can also be transformed to polycyclic systems by halo- and seleno-lactonisation strategies.[61,100,101]

4. Synthetic utility of halo- and selenolactonisations

Halo- and selenolactonisation reactions are finding increasing application in organic synthesis, as may be seen from the frequency of publications from the current literature. A major factor contributing to this trend is that these reactions are highly adaptable to the developing methods in organic synthesis, such as chiral induction, regio- and stereoselectivity and avenues for further elaborations. A few representative applications of these cyclisation reactions in organic synthesis and separations are presented below.

4.1. Iodolactonisation as a practical strategy for the separation of plant and animal-derived fatty acids

The separation of enriched fatty acids from plant and animal sources is generally a difficult process and, because of their biological significance in key metabolic processes, such separations are, however, necessary. Halolactonisation provides a useful method for the separation of closely-related polyenoic acids, taking advantage of two key

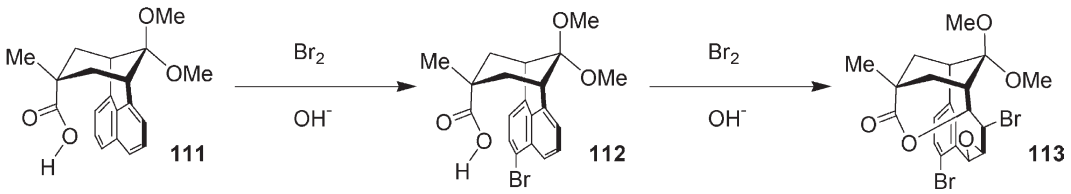


Figure 34.

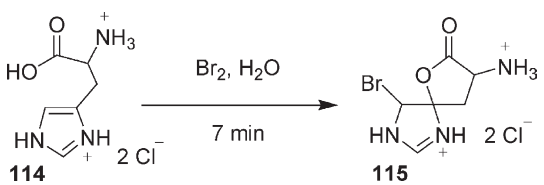


Figure 35.

features: first, halolactonisation leading to γ-lactones can be carried out selectively in the presence of competing substrates that can lead only to δ-lactones; secondly, δ-lactones arising from iodolactonisation can be selectively reverted to the parent unsaturated acids in the presence of competing γ-lactone-forming substrates.

An illustration of the method is the enrichment of

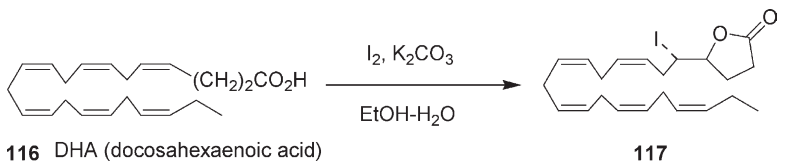


Figure 36.

arachidonic acid—a precursor to prostaglandins and several related systems—from liver fatty acids, from 22.2 to 97.8%. The success here is centred on the fact that, whilst arachidonic acid on iodolactonisation can lead to only δ-lactones, the other related fatty acids can give rise to γ-lactones. Since k_{γ}-lactone$\gg k_{\delta}$-lactone, the enrichment involves iodolactonisation under standard conditions to remove non-arachidonic acid substrates.[102]

Iodolactonisation also provides an easy and practical approach for the isolation of polyenoic acids from natural sources. An illustration is the enrichment of DHA **116** in fatty acids of fish oil, containing 35% of DHA to 62% of DHA in its iodolactone for **117** (Fig. 36).[103]

4.2. Tandem Birch reduction–halolactonisation to form strained bicyclic systems

Aromatic carboxylic acid **118** can be transformed regioselectively to functionalised cyclohexene **120** by a combination of Birch reduction, leading to **119**, and halolactonisation (Fig. 37).[61]

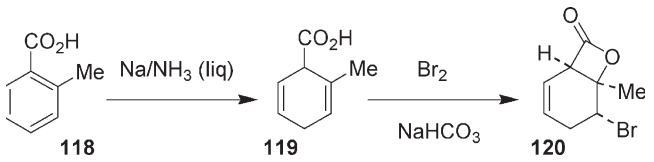


Figure 37.

4.3. A practical 7-*syn* Me_3Si→7-*anti* OH change in norbornene, using the halolactonisation strategy

An elegant demonstration of halolactonisation in synthetic strategy is the highly efficient transformation of the *syn*-7-trimethylsilyl norbornene **121** to the corresponding *anti* alcohol **122** (Fig. 38).[104]

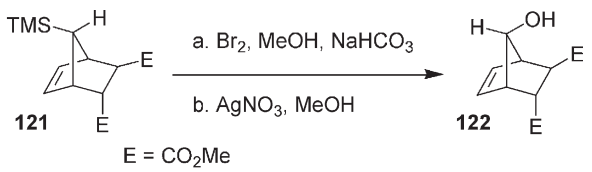


Figure 38.

4.4. Norbornene to prostanoids via Baeyer–Villiger oxidation and iodolactonisation

In the early work on the synthesis of prostaglandins, a major challenge was the creation of four contiguous asymmetric centres in a 5-membered framework. This was most effectively carried out by involving a key iodolactonisation step. Using this strategy, 7-*syn* substituted norbornene-2-ones **123**—readily available from the addition of 5-substituted cyclopentadienes to ketene equivalents—afforded the desired framework **124**, in a single operation, involving Baeyer–Villiger oxidation and iodolactonisation (Fig. 39).[105]

4.5. Synthetic transformations based on iodolactonisation

A noteworthy reaction of iodolactones (e.g., **125**) is their regioselective transformation to rearranged hydroxylactones **126** on treatment with $(Bu_3Sn)_2O$. The overall process is a carboxylic acid-directed regioselective *cis* hydroxylation (Fig. 40).[106]

Camphanic acid has found use as a chiral auxiliary in asymmetric synthesis. A closely related framework **128** has been constructed in a single step by the iodolactonisation of *cis*-2-methylcyclopent-3-ene carboxylic acid **127** (Fig. 41).[107]

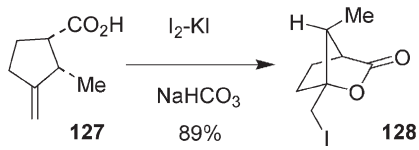


Figure 41.

The 2-*endo* carboxyl unit in the norbornene system **129** can be used effectively to bring about exclusive *endo*-epoxidation product **131** via the iodolactonisation intermediate **130**. This strategy is significant in the light of the exclusive preference for *exo* acceptance of electrophiles (Fig. 42).[108]

4.6. Bislactones from primary halolactonisation

Silver salts of appropriately-constructed unsaturated dicarboxylic acids (e.g., **132** and **134**) afford bislactones **133** and

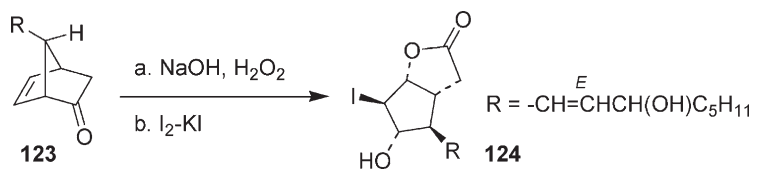


Figure 39.

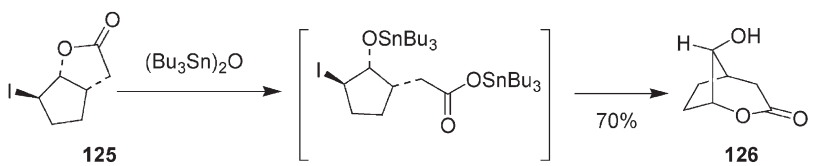


Figure 40.

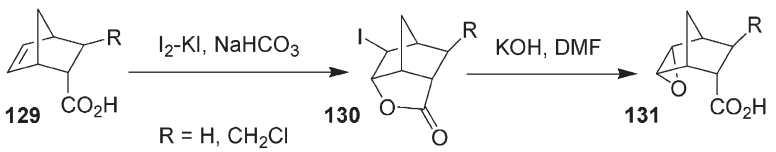


Figure 42.

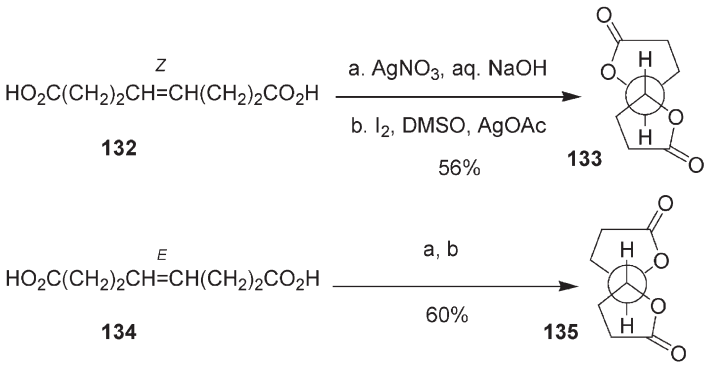


Figure 43.

135, respectively, in good yields, in one step. These examples (Fig. 43) will show that this method has potential in organic synthesis.[109,110]

4.7. Cyclofunctionalisation of ureas and urethanes

An obvious extension of iodolactonisation is to interpose a heteroatom between a carboxamide unit and the proximate carbon centre. In the event of the heteroatom being nitrogen, the substrates are urea derivatives, and, if it is oxygen, urethanes result. Homoallylic alcohols can be readily transformed to urethanes via the addition of isocyanates. Cyclisation of such urethanes carrying an electrophilic substituent such as the tosyl group have been studied, leading to noteworthy observations as illustrated below.[111]

In a two-phase system consisting of Et_2O and aqueous $NaHCO_3$, treatment of the tosylamide **136** with I_2 for 20 min gives largely the cyclic urethane **137** arising from the reaction at nitrogen. When the reaction time is longer, however, the amount of cyclic carbonate arising from nucleophilic attack by oxygen increases steadily, and, after 3 h, only the carbonate **138** is formed (Fig. 44). This simple method provides an elegant route to distal asymmetric induction. Interestingly, when the reaction is carried out in CCl_4 in the presence of aqueous K_2CO_3, the product is the cyclic urethane (**137**).

4.8. Halolactonisation-mediated *syn* dihydroxylation

A halolactonisation strategy has been employed in the *syn* dihydroxylation of a double bond *cis* to a hydroxymethyl substituent. Since the halolactonisation involves the addition of an oxygen nucleophile from the *syn* face and the introduction of a leaving group (halogen atom) in the *anti* face across the double bond, a second nucleophilic displacement of the halogen by an oxygen nucleophile essentially leads to *syn* hydroxylation (Fig. 45).[112] This

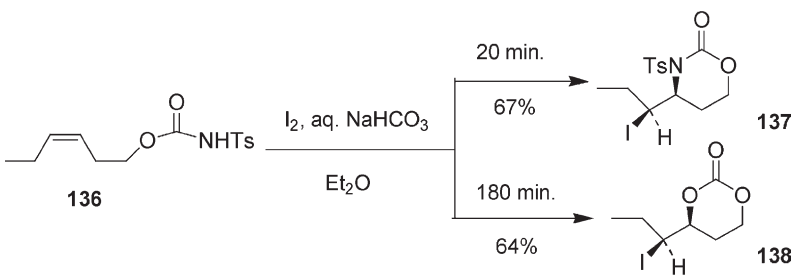


Figure 44.

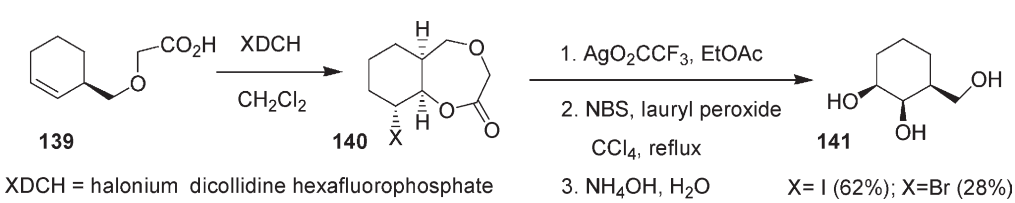


Figure 45.

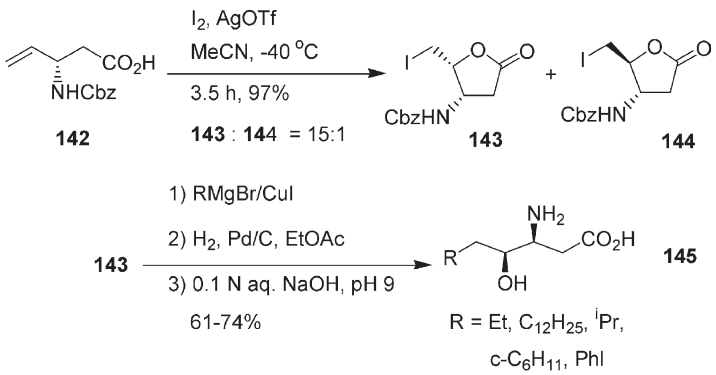


Figure 46.

strategy is exemplified with the following example in the conversion of acid **139** to the *syn*-dihydroxylated product **141** via the lactone **140**.

4.9. Formation of γ-hydroxy-β-amino acids from iodolactones

Iodolactonisation offers an excellent route towards the synthesis of *syn*-β-amino-γ-hydroxy amino acids (Fig. 46).[113] The stereoselective iodolactonisation of (*S*)-3-*N*-benzyloxycarbonyl-4-pentenoic acid **142** to lactones **143** and **144**, followed by CuI-mediated cross-coupling of the appropriate Grignard reagents and hydrolysis affords the substituted β-amino acids **145** in excellent yields.

4.10. Rearrangement of iodolactones to α-methylene δ-iodomethyl tetrahydrofurans

The products of iodolactonisation (e.g., **146**) can be transformed to functionalised tetrahydrofurans **148** in a single step, with lithium reagents, in a highly stereoselective manner (Fig. 47), via the proposed intermediate **147**.[114]

4.11. π-Bond surrogates in halolactonisation—a facile route to enol lactones

An interesting application of halo- and selenolactonisation processes is the ready formation of haloenol lactones **150** and **151** by treatment of phosphoranes derived from adipic acid β-keto ester **149**. This reaction largely yields the expected *E*-γ-lactones (Fig. 48).[115]

4.12. Halolactonisation of 1,3-dienoic acids

cis-Constrained 1,3-dienes containing electrophilic units are excellent components for cycloadditions. The preparation of these compounds is not, however, easy. On the other hand, the open-chain systems are more readily accessible. In this context, the ready formation of the lactones, such as **153**, precursors for such 1,3-dienes, from 5-substituted pentane-1(*E*),3(*E*)-dienoic acids **152** is noteworthy (Fig. 49).[116]

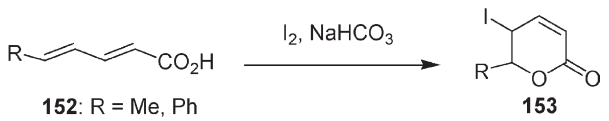


Figure 49.

4.13. Nitriles to selenolactones by a reverse mechanistic path

A variant of the selenolactonisation reaction involves the use of a nitrile group in place of the carboxyl group. A variety of 4-pentenonitriles (**154**) carrying substituents at the 2-position, on treatment with diphenyl diselenide, ammonium persulphate and trifluoromethanesulphonic acid in aqueous dioxane at 70 °C afford the selenolactones **155** in good yields, arising from the corresponding

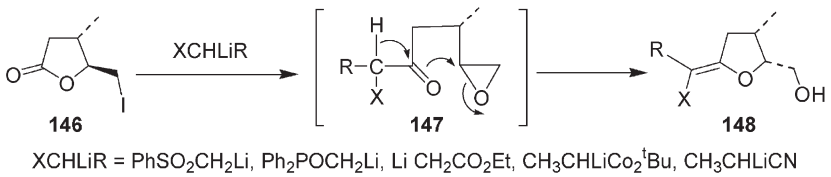


Figure 47.

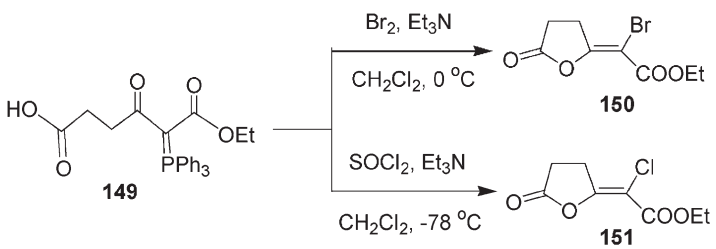


Figure 48.

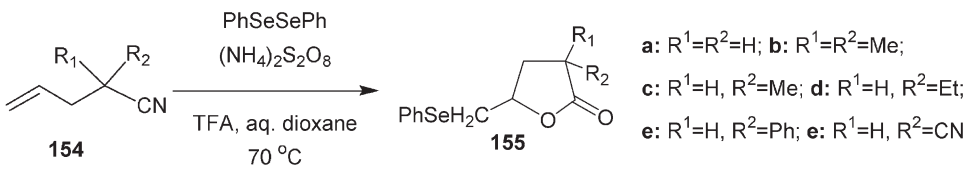


Figure 50.

carboxylic acids. The reaction proceeds in a reverse manner from that of selenolactonisation, where the initially-formed PhSeOH adducts react intramolecularly with the nitrile function (Fig. 50).[117]

Whilst a broader picture of the scope of halo- and selenolactonisation can be assessed, a few aspects that highlight the use of these reactions in organic synthesis are presented below.

4.14. Precursors for halo- and selenolactonisation from 1,3-diene metal complexes

The readily accessible metal carbonyl complexes of 1,3-cyclohexadiene **156** can be transformed to bicyclic furanones **157** in one operation (Fig. 51).[118] Similarly, the 1,3-butadiene fumarate adduct can be transformed to the functionalised tricyclic lactone in a single step.[119]

4.15. Cyclononatriene to prostanoids by anionic Cope rearrangement and halolactonisation strategies

A combination of kinetically-driven anionic Cope rearrangement, oxidation, leading to acid **159**, and iodolactonisation comprise key steps in the transformation of cyclononatriene **158** to prostaglandin intermediates **160** (Fig. 52).[120]

4.16. Allylic alcohols to iodolactones by tandem *ortho*-Claisen rearrangement and halolactonisation

A useful development is the generation of the terminal unsaturated systems, necessary for halo- and selenolactonisation, from allyl alcohol precursors, involving a clean transposition of the π-bond by an *ortho*-Claisen rearrangement (Fig. 53). Thus, tandem *ortho*-Claisen rearrangement–halolactonisation has found excellent application in organic

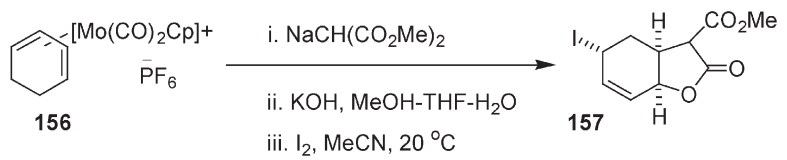


Figure 51.

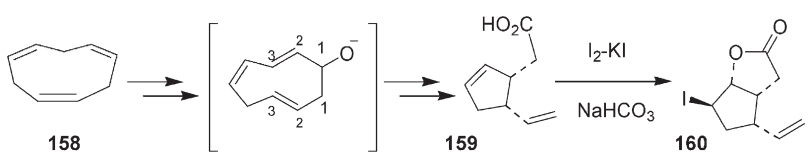


Figure 52.

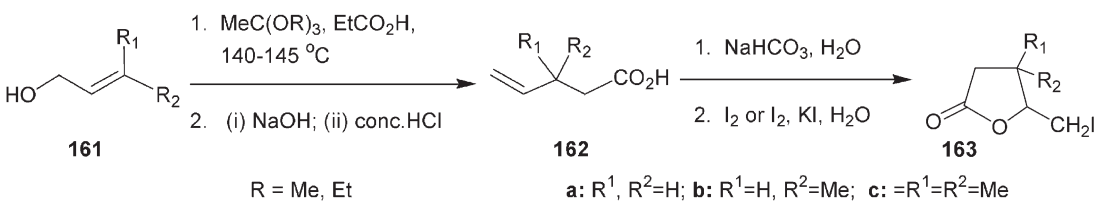


Figure 53.

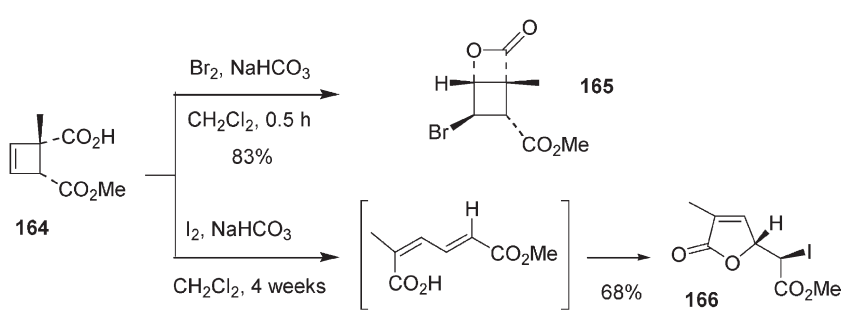


Figure 54.

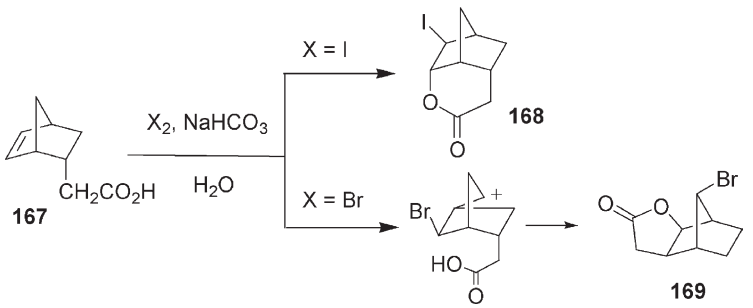


Figure 55.

synthesis.[17] This strategy is illustrated by the conversion of allylic alcohol **161** to acid **162**, then to iodolactone **163**.

5. Comparison of halo- and selenolactonisation

As stated previously, experimental protocols developed in either of the two areas of halolactonisation and selenolactonisation can, in most cases, be transposed, which significantly widens the scope of the reaction. Whilst the application of iodolactonisation is extensive, that of bromolactonisation is limited and chlorolactonisation is rather rare. The major factor here is the ease with which the iodine-containing products could be further elaborated. This, in turn, is in accord with the fact that, whilst a range of reaction conditions is available for iodolactonisation, those related to the other halogens are rather limited.

Iodolactonisation is a slower process compared to bromolactonisation and, with unstable starting materials, the latter process would therefore be advantageous. This aspect is illustrated below (Fig. 54) with the conversion of acid **164** to lactone **165** and **166**.[121]

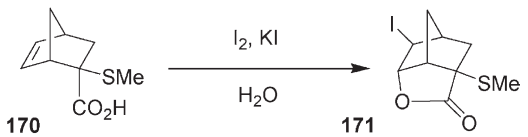


Figure 56.

Bromonium ion intermediates in a norbornane framework **167** show a propensity for rearrangement, this occurring through a hydride shift of the intermediate, which facilitates the ring closure to afford the lactone **169**. The iodine-containing intermediates undergo smooth lactonisation to afford lactone **168** (Fig. 55).[122]

Sulphur-containing products generally afford bromolactone S-oxides under bromolactonisation conditions.[123] On the contrary, the sulphur unit does not undergo any oxidation during iodolactonisation as illustrated in the conversion of methylthio derivative **170** to **171** (Fig. 56).[124]

In planning synthetic strategies, there can arise situations where a choice has to be made between halo- and selenolactonisation. The following summaries outline the merits and drawbacks of these two processes.

5.1. Tellurium extension of selenolactonisation

Surprisingly, there appears to be only one study relating to the lactonisation of unsaturated carboxylic acids with tellurium compounds. Unusual products are formed on using either $TeCl_4$ or $ArTeCl_3$. With the former compound, bislactonisation products are isolated in quantitative yields, in which the tellurium is still bonded to two halogen atoms.

Halolactonisation	
Merits	
1.	Process inexpensive
2.	No toxic contamination in products
3.	Produces β-lactones to medium-size lactones
4.	Kinetic and thermodynamic control can be brought about with confidence, making the stereochemical outcome reliable
5.	The reaction conditions are mild and amenable to wide variations; the process does not require any catalysis
6.	In the domain of asymmetric synthesis, this reaction exhibits maximum applications
Drawbacks	
1.	In substrates having centres susceptible to oxidation (sulphur compounds), this can be a competitive reaction in bromolactonisation
2.	Some protecting groups (*e.g.* TBDMS) are not very stable to halolactonisation conditions.

Selenolactonisation	
Merits	Drawbacks
1. The conditions for seleno-lactonisation are milder (−78 °C to rt)	1. Selenium reagents are expensive
2. The conditions are not oxidative and therefore applicable to a wider range of substrates	2. Selenium toxicity can be a problem if the product is assessed for therapeutic use, since even ppm levels of selenium would not be acceptable
3. Nearly all protecting groups are stable to the reaction	3. The control of stereoselectivity in selenolactonisation is less certain. This is in part because the reactions are generally carried out in nonpolar media using acid or base catalysis
4. The selenium centre of the product is amenable for further elaboration (reduction, elimination, radical addition to π-bonds)	
5. The availability of crystalline reagents (NPSP) makes the operation easy	
6. Selenolactonisation offers an excellent strategy for chiral induction	

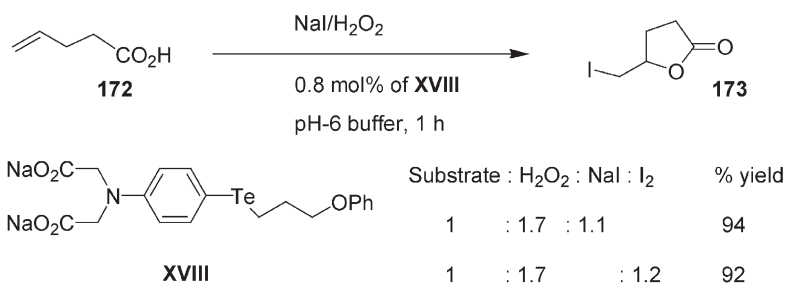


Figure 57.

In the case of $ArTeCl_3$, monomeric γ-lactones are produced in excellent yields with CCl_3 incorporation. The presence of this group strongly suggests that the mechanism follows a radical pathway and the presence of CCl_3 can be explained as arising from the chloroform solvent used.[4]

Recently, organotellurides have been shown to activate H_2O_2 in the oxidation of halide salts to positive halogen species required for halolactonisation.[125] The following example of conversion of acid **172** to lactone **173** demonstrates the efficiency of the telluride **XVIII** in halolactonisation (Fig. 57).

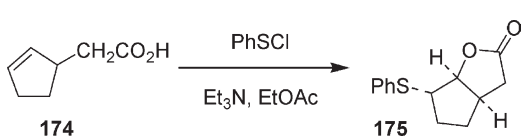


Figure 58.

5.2. PhSCl variation

PhSCl has found application in few cases to bring about lactonisation of proximate π-bonds (Fig. 58).[126] This possibility is illustrated in the conversion of acid **174** to lactone **175** with the aid of PhSCl.

5.3. Palladium(II)-catalysed halolactonisations

Pd(II)-catalysed lactonisation of allenes **176** has been recently developed,[127] which proceeds via a π-allyl intermediate formed from attack by the first halide nucleophile, followed by an attack of the carboxylic acid group on the π-allyl moiety to afford bromolactone **177**. This reaction utilises mild oxidants such as *p*-benzoquinone or Cu(II) salts. The yields and selectivity are comparable to those obtained using the NBS reagent conditions. With higher homologues ($n>2$), however, better yields and selectivity are obtained under Pd-catalysed conditions (Fig. 59).

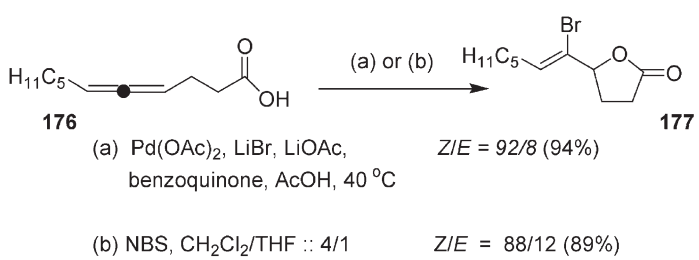
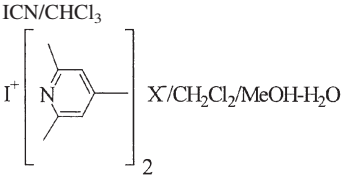
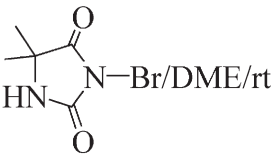


Figure 59.

Table 6. Reagents used for halo- and selenolactonisation

Reagents	Representative citation(s)
$AgOAc/I_2/AcOH$	128,129
$NH_4OAc/I_2/CHCl_3$	49
Benzeneselenyl-*p*-toluenesulphonate	130
$Ca(OCl)_2$	131
Cl_2/CH_2Cl_2	132
$I_2/AcOH-THF-H_2O$	133
$I_2/CH_2Cl_2/CCl_4/MeCN/THF$	19,38,134,135
$ICN/CHCl_3$	136
 $X^-/CH_2Cl_2/MeOH\text{-}H_2O$ $X = ClO_4$ $X = PF_6$	78,137,138
	63–65
$I_2/MeCN$	16
$I_2/PDC/CH_2Cl_2$	139
$I_2/{}^iPr_2NH/CH_2Cl_2$	140,141
$I_2/Py/CH_2Cl_2$	142
$I_2/Triton\ B/MeOH-H_2O-CH_2Cl_2$	136
$K_2CO_3/I_2/THF$	143,144
$KHCO_3/I_2/KI$	17
$KHCO_3/NIS/CH_2Cl_2$	145
$KI_3/NaHCO_3/MeCN$	146
$K_2CO_3/I_2/CHCl_3$	147
n-$BuLi/I_2/THF$	58
$Pb(OAc)_4/NaI/DME$	148
$Pb(OAc)_4/ZnBr_2/DME$	148
$Na_2CO_3/I_2/CHCl_3$	149
$NaHCO_3/Br_2$	51
$NaHCO_3/Br_2/CCl_4/CH_2Cl_2$	150,151
$NaHCO_3/I_2-KI$	1,49,135,150,152,136
$NaHCO_3/I_2/CH_2Cl_2$	57
$NaHCO_3/KI-I_2/CHCl_3$	153
$NaHCO_3/I_2/THF-Et_2O$	12
$NaHCO_3/I_2-KI/H_2O-THF$	29
$NaHCO_3/I_2/MeCN$	154
$NaHCO_3/I_2/MeOH$	155
$NaHCO_3/KI-I_2/{}^n PrOH-H_2O$	135
NaI/18-crown-6/*m*CPBA/CH_2Cl_2/0 °C	156,157
NBS/acetone/THF	35,38
$NBS/AcOH-THF-H_2O$	134,158
$NBS/DME-H_2O$	159
$NBS/KHCO_3/Bn_4NOH/CH_2Cl_2-H_2O$	146
$NBS/NH_4PF_6/MeOH$	160
	161
$NIS/THF/NaHCO_3$	162a
$NPSP/CSA\ (cat)/CH_2Cl_2$	97,163
$NPSP/SnCl_4/CH_2Cl_2$	97,162b
o-Nitrophenylselenium bromide/AcOH/reflux	3
$Pb(OAc)_4/ZnBr_2$	51
$PDC/CH_2Cl_2/I_2$/molecular sieves (4 Å)	140
$PhSeCl/CH_2Cl_2/-78$ °C/2 h	163–165
$PhSeOTf/CH_2Cl_2/PhMe$	166
$PhSePF_6/CH_2Cl_2$	29,167
$PhSeCl/Et_3N/CH_2Cl_2$	136,152
$PhSeSePh/CuOTf/CaCO_3/BaCO_3/CH_2Cl_2/DME$	168
PhSeSePh/DCN/hν	169
$PhSeSePh/MeOH/NH_4Br$ (electrolytic)	170,171
PhSeSePh/*m*-NBSP/MeCN	172
$PhSeSePh/(NH_4)_2S_2O_8$/70 °C/MeOH/MeCN	117
Phth-N-Br	173
$AgClO_4/I_2/MeCN$	49
$NaOAc/I_2/CH_2Cl_2$	49
$TeCl_4$/dioxane/reflux	4

(*continued on next page*)

Table 6 (*continued*)

Reagents	Representative citation(s)
$TeCl_3Ar/CHCl_3$	4
$Ti(O^iPr)_4/NIS/CH_2Cl_2$	174
$Tl_2CO_3/Br_2/CH_2Cl_2$	155,175
$TlOAc/I_2/Et_2O/CH_2Cl_2$	49,176
$TMSBr/DMSO/^iPr_2NH/CH_2Cl_2$	39,51
$TMSCl/I_2/Et_3N/MeCN$	71

6. Reagents used for halo- and selenolactonisation

It was considered useful to make a compilation of the reagents used for halo- and selenolactonisations. This is presented in Table 6, where the reagents are alphabetically arranged. Representative citations, where the use of a particular reagent combination can be found, are also included.

7. Conclusions and future prospects

The use of the halo- and selenolactonisation strategy in the stereocontrolled synthesis of complex organic molecules has significantly increased recently, as shown by the frequent publications relating to this topic.[177] Primarily among several features of these reactions is that it provides an easy access to compounds or their precursors, which are not readily accessible by other means. Since this reaction introduces oxygen and halogen (or selenium species) across the double bond in a largely *anti* orientation, various opportunities exist to further explore the resulting skeleton. These includes the generation of carbon–carbon bonds from the carbon–halogen (or –selenium) bonds via radical chemistry, substitution of the halogen atom with a second oxygen nucleophile to effect a net *syn*-hydroxylation across a double bond, and methanolysis of the iodolactone to form epoxy esters by lactone opening and halide displacement, which form an important fragment in the synthesis of various natural products. The adaptability of halo- and selenolactonisation to kinetic and thermodynamic conditions further enhances the scope of this strategy, as it affords products of different stereo- or regiochemistry.

Finally, halo- and selenolactonisation, elaborated in the previous pages, do show that the reaction has been found adaptable to many emerging strategies in organic synthesis, including the construction of highly functionalised compounds with several asymmetric centres. Cyclofunctionalisations on solid or soluble polymeric supports could provide not only practical methodologies, but also strategies for combinatorial chemistry. The methodologies developed in these cyclofunctionalisations await utilisation in other diverse areas of organic chemistry. Cyclofunctionalisation generates compact constructs carrying a halogen or selenium moiety. Such units should find application in a broad area of technology and in the design of materials with specified properties. It is reasonable to conclude that the future of these reactions, discovered a century ago, still appears to be very bright.

References and notes

1. Bougault, M. J. *C. R. Hebd. Seances. Acad. Sci.* **1904**, *139*, 864.
2. van Tamelen, E. E.; Shamma, M. *J. Am. Chem. Soc.* **1954**, *76*, 2315.
3. Campos, M. M.; Petragnani, N. *Chem. Ber.* **1960**, *93*, 317.
4. Campos, M. M.; Petragnani, N. *Tetrahedron* **1962**, *18*, 521.
5. (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (b) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1981.
6. Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.
7. (a) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272. (b) Knight, D. W. *Gen. Synth. Methods* **1982**, *5*, 100.
8. Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 411.
9. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
10. Harding, K. E.; Tiner, T. H. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, p 363.
11. Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
12. Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedon Lett.* **1981**, *22*, 4611.
13. Chamberlin, A. R.; Mulholland, Jr., R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.
14. Snider, B. B.; Johnston, M. I. *Tetrahedron Lett.* **1985**, *26*, 5497.
15. Amaral, L. D.; Melo, S. C. *J. Org. Chem.* **1973**, *38*, 800.
16. Bartlett, P. A.; Myerson, J. J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
17. Jäger, V.; Günther, H. J. *Tetrahedron Lett.* **1977**, *18*, 2543.
18. Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.
19. Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114.
20. Macritchie, J. A.; Peakman, T. M.; Silcock, A.; Willis, C. L. *Tetrahedron Lett.* **1998**, *39*, 7415.
21. Bartlett, P. A.; Myerson, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2118.
22. Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013.
23. Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, *20*, 1607.
24. Toru, T.; Fugita, S.; Maekawa, E. *J. Chem. Soc. Chem. Commun.* **1985**, 1092.
25. Tomoskozi, I.; Gruber, L.; Gulacsi, E. *Tetrahedron Lett.* **1985**, *26*, 3141.

26. Martin Lopez, M. J.; Bermejo, F. *Tetrahedron* **1998**, *54*, 12379.
27. Dong, Y.; Pai, N. N.; Ablaza, S. L.; Yu, S.-X.; Bolvig, S.; Forsyth, D. A.; Le Quesne, P. W. *J. Org. Chem.* **1999**, *64*, 2659.
28. Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854.
29. Jackson, R. F. W.; Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. C. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2159.
30. Konno, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, *8*, 223.
31. Greeves, N.; Lee, W.-M.; Barkley, J. V. *Tetrahedron Lett.* **1997**, *38*, 6453.
32. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
33. Williams, D. R.; Barner, B. A.; Nishitani, K.; Philips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.
34. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.
35. Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307.
36. Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.
37. Kim, K. M.; Ryu, E. K. *Tetrahedron Lett.* **1996**, *37*, 1441.
38. Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.
39. Hoshino, O.; Ishizaki, M.; Kamei, K.; Taguchi, M.; Nagao, T.; Iwaoka, K.; Sawaki, S.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 571.
40. Miyashita, K.; Tanaka, A.; Mizuno, H.; Tanaka, M.; Iwata, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 847.
41. Martin, S. F.; Colapret, J. A.; Dappen, M. S.; Dupre, B.; Murphy, C. J. *J. Org. Chem.* **1989**, *54*, 2209.
42. Pattenden, G.; Smith, G. F. *Tetrahedron Lett.* **1990**, *31*, 6557.
43. Ziegler, F. E.; Wang, Y. *Tetrahedron Lett.* **1996**, *37*, 6299.
44. Curran, D. P.; Chen, M. H.; Leszczweski, D.; Elliott, R. L.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612.
45. Hanessian, S.; Margarita, R.; Hall, A.; Luo, X. *Tetrahedron Lett.* **1998**, *39*, 5883.
46. Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205.
47. Muderawan, I. W.; Bott, R. C.; Young, D. J. *Synthesis* **1998**, 1640.
48. Jones, G. B.; Huber, R. S.; Chau, S. *Tetrahedron* **1993**, *49*, 369.
49. Cambie, R. C.; Kai, S. Ng.; Ruttedge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1979**, *32*, 2793.
50. Barnett, W. E.; Sohn, W. H. *Tetrahedron Lett.* **1972**, *13*, 1777.
51. Iwata, C.; Tanaka, A.; Mizuno, H.; Tanaka, M.; Miyashita, K. *Heterocycles* **1990**, *31*, 987.
52. Corey, E. J.; Sachdev, S. *J. Org. Chem.* **1975**, *40*, 579.
53. Boger, D. L.; Mullican, M. D.; Hellberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904.
54. Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198.
55. Danishefski, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.
56. Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*(16), 2533.
57. Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.
58. Kurth, M. J.; Brown, E. G.; Lewis, E. J.; McKew, J. C. *Tetrahedron Lett.* **1988**, *29*, 1517.
59. Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Tetrahedron* **1977**, *33*, 807.
60. Black, T. H.; Huang, J. *Tetrahedron Lett.* **1993**, *34*, 1411.
61. Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *40*, 2843.
62. (a) Gruttadauria, M.; Aprile, C.; Noto, R. *Tetrahedron Lett.* **2002**, *43*, 1669. (b) Wirth, T. *Liebigs. Ann. Recueil* **1997**, 2189. (c) Tiecco, T. L.; Bagnoli, L.; Marini, F.; Temperini, A.; Tomasini, C.; Santi, C. *Tetrahedron Lett.* **2000**, *41*, 3241.
63. Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4.
64. Simonot, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 4527.
65. Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *58*, 5912.
66. Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, *66*, 4304.
67. (a) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
68. Cinquin, C.; Bortolussi, M.; Bloch, R. *Tetrahedron: Asymmetry* **1996**, *7*, 3327.
69. Cutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542.
70. Balko, T. W.; Brinkmeyer, R. S.; Terando, N. H. *Tetrahedron Lett.* **1989**, *30*, 2045.
71. Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397.
72. Welch, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716.
73. Amano, S.; Tkemura, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Tetrahedron* **1999**, *55*, 3855.
74. Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829.
75. Ogu, K.-I.; Akazome, M.; Ogura, K. *Tetrahedron Lett.* **1998**, *39*, 305.
76. Takahata, H.; Chida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201.
77. (a) Rotella, D. P.; Li, X. *Heterocycles* **1990**, *31*, 1205. (b) Kirschning, A.; Hashem, Md. A.; Monenschein, H.; Rose, L.; Schöing, K.-U. *J. Org. Chem.* **1999**, *64*, 6522.
78. Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc. Chem. Commun.* **1992**, 728.
79. Moon, H.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504.
80. Metz, P.; Hungerhoff, B. *J. Org. Chem.* **1997**, *62*, 4442.
81. Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165.
82. Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1997**, *62*, 7872.
83. Nubbemeyer, U. *Angew. Chem. Int. Ed. Engl.* **1996**, *61*, 3677.
84. Fujita, K.-i.; Murata, K.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc. Chem. Commun.* **1995**, 1641.
85. Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1726.
86. Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660.
87. Takada, H.; Nishibayashi, Y.; Vemura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1511.
88. Back, T. G.; Dyk, B. P. *Chem. Commun.* **1996**, 2567.
89. Crombie, L.; Mistry, K. M. *J. Chem. Soc. Chem. Commun.* **1988**, 539.
90. Crombie, L.; Mistry, K. M. *J. Chem. Soc. Chem. Commun.* **1988**, 537.
91. Kotsuki, H.; Ohnishi, H.; Akitomo, Y.; Ochi, M. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3881.
92. Montforts, F. P.; Gesing-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, *72*, 1852.
93. Minami, T.; Hirakawa, K.; Koyanagi, S.; Nakamura, S.; Yasmaguchi, M. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2385.
94. Lear, Y.; Schwan, A. L. *J. Org. Chem.* **1999**, *64*, 8138.

95. Kurth, M. J.; Beard, R. L.; Olmstead, M.; Macmillan, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3712.
96. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429.
97. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.
98. Chen, Y.-S.; Kampf, J. W.; Lawton, R. G. *Tetrahedron Lett.* **1997**, *38*, 6831.
99. Ito, S. *J. Org. Chem.* **1985**, *50*, 3636.
100. Wenkert, F.; Liu, L. H.; Johnston, D. B. R. *J. Org. Chem.* **1965**, *30*, 722.
101. Suzuki, T.; Kagaya, S.; Tomino, A.; Unno, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2801.
102. Gaidai, N. V.; Imbs, A. B.; Kuklev, D. V.; Latyshev, N. A. *J. Am. Oil. Chem. Soc.* **1991**, *68*, 230.
103. Kuklev, D. V.; Aizdaicher, N. A.; Imbs, A. B.; Bezuglov, V. V.; Latyshev, N. A. *Phytochemistry* **1992**, *31*, 2401.
104. Fleming, I.; Michael, J. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1549.
105. Brown, E. D.; Lilley, T. J. *J. Chem. Soc. Chem. Commun.* **1975**, 39.
106. Shibata, I.; Matsuo, F.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1991**, *56*, 475.
107. Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467.
108. Christol, H.; Coste, J.; Plenat, F. *Tetrahedron Lett.* **1972**, *13*, 1143.
109. Kato, M.; Kageyama, M.; Tanaka, R.; Kawahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.
110. Kato, M.; Kageyama, M.; Yoshikoshi, A. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1305.
111. Hirama, M.; Iwashita, M.; Yamasaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 4963.
112. Clausen, R. P.; Bols, M. *J. Org. Chem.* **2000**, *65*, 2797.
113. Monache, G. D.; Misiti, D.; Salvatore, P.; Zappia, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1137.
114. Batmangherlich, S.; Davidson, A. H.; Proctor, G. *Tetrahedron Lett.* **1983**, *24*, 2889.
115. Abell, A. D.; Hoult, D. A.; Morris, K. B.; Taylor, J. M.; Trent, J. O. *J. Org. Chem.* **1993**, *58*, 1531.
116. Staninets, V. I.; Shilov, E. A.; Koryak, E. B. *Zh. Org. Khim.* **1968**, *4*, 268.
117. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *Tetrahedron* **1989**, *45*, 6819.
118. Pearson, A. J.; Khan, Md. N. I. *J. Am. Chem. Soc.* **1984**, *106*, 1872.
119. Bilyard, K. G.; Garratt, P. J. *Tetrahedron Lett.* **1981**, *22*, 1755.
120. Paquette, L. A.; Crouse, G. D. *Tetrahedron* **1981**, *37*, 281.
121. Askani, R.; Keller, U. *Justus Liebigs Ann. Chem.* **1988**, 61.
122. Davies, D. I.; Dowle, M. D.; Keynon, R. F. *Synthesis* **1979**, 990.
123. Bladon, C. M.; Ferguson, I. E. G.; Kirby, G. W.; Lochead, A. W.; McDougall, D. C. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1541.
124. Boucher, J. L.; Stella, L. *Tetrahedron* **1988**, *44*, 3595.
125. Higgs, D. E.; Nelen, M. I.; Detty, M. R. *Org. Lett.* **2001**, *3*(3), 349.
126. Clive, D. L. J.; Kale, V. N. *J. Org. Chem.* **1981**, *46*, 231.
127. Jonasson, C.; Horvath, A.; Backvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600.
128. Campbell, M.; Sainsbury, M.; West, R. *Tetrahedron Lett.* **1987**, *28*, 3865.
129. Campbell, M.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 5063.
130. Back, T. G.; Muralidharan, K. R. *J. Org. Chem.* **1991**, *56*, 2781.
131. Solas, D.; Wolinsky, J. *Synth. Commun.* **1981**, 609.
132. Wen, R.; Laronze, J. Y.; Levy, J. *Heterocycles* **1984**, *22*, 1061.
133. Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178.
134. Guenther, H. J.; Guntrum, E.; Jaeger, V. *Justus Liebigs Ann. Chem.* **1984**, 15.
135. Lawson, K. R.; McDonald, B. P.; Mills, O. S.; Steele, R. W.; Sutherland, J. K.; Wear, T. J.; Brewster, A.; Marsham, P. R. *J. Chem. Soc. Perkin Trans. 1* **1988**, 663.
136. Arnold, R. T.; Lindsay, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 1048.
137. Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.
138. Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 6999.
139. Labidalle, S.; Min, Z. Y.; Reynet, A.; Moskowitz, H.; Vierfond, J. M.; Miocque, M.; Bucourt, R.; Thal, C. *Tetrahedron* **1988**, *44*, 1159.
140. Martin, J. D.; Perez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 516.
141. Martin, J. D.; Perez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801.
142. Ishizuka, S.; Oshida, J.; Tsuruta, H.; Norman, A. W. *Arch. Biochem. Biophys.* **1985**, *242*, 82.
143. Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475.
144. Knochel, P.; Normant, J. F. *J. Organomet. Chem.* **1986**, *309*, 1.
145. Kraft, A. G.; Katznellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.
146. Tsuboi, S.; Wada, H.; Mimura, S.; Takada, A. *Chem. Lett.* **1987**, 937.
147. Brown, R. T.; Duckworth, D. M.; Santos, C. A. *Tetrahedron Lett.* **1991**, *32*, 1987.
148. Motohashi, S.; Satomi, M.; Fujimoto, Y.; Tatsuno, T. *Heterocycles* **1985**, *23*, 2035.
149. Antoniolette, E.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1988**, *29*, 4987.
150. Barnett, W. E.; McKenna, J. C. *J. Chem. Soc. Chem. Commun.* **1971**, 551.
151. Barnett, W. E.; Mckenna, J. C. *Tetrahedron Lett.* **1971**, *12*, 2595.
152. Hanson, G. L.; Russel, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751.
153. Campos, M. M.; Amaral, L. *Arch. Pharm.* **1965**, *92*, 1965.
154. Neykom, C.; Richardson, D. P.; Meyerson, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 5559.
155. Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, *20*, 335.
156. Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; Da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 3018.
157. Srebnik, M.; Mechoulam, R. *J. Chem. Soc. Chem. Commun.* **1984**, 1070.
158. Jung, M. E.; Vaccaro, W. D.; Buszek, K. R. *Tetrahedron Lett.* **1989**, *30*, 1893.
159. Kato, T.; Hirukawa, T.; Namiki, K. *Tetrahedron Lett.* **1992**, *33*, 1475.
160. Michael, J. P.; Blom, N. F.; Boeyens, J. C. A. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1739.

161. Cook, C. H.; Chung, Y. S. *Arch. Pharmacol. Res.* **1981**, *4*, 133.
162. (a) Barrett, A. G. M.; Barta, T. E.; Flygare, J. A.; Sabat, M.; Spilling, C. D. *J. Org. Chem.* **1990**, *55*, 2409. (b) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Braska, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B. *Tetrahedron* **1989**, *45*, 7161.
163. Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097.
164. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.
165. Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.
166. Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849.
167. Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. *Tetrahedron Lett.* **1982**, *23*, 2407.
168. Miyachi, N.; Sato, H.; Shibasaki, M. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2049.
169. Pandey, G.; Sekhar, B. B. V. S. *J. Org. Chem.* **1992**, *57*, 4019.
170. Vukicevic, R.; Konstantinivic, S.; Mihailovic, M. L. *Tetrahedron* **1991**, *47*, 859.
171. Konstantinivic, S.; Vukicevic, R.; Mihailovic, M. L. *Tetrahedron Lett.* **1987**, *28*, 6511.
172. Yoshida, M.; Sasage, S.; Kawamura, K.; Suzuki, T.; Kamigata, N. *Bull. Chem. Soc. Jpn* **1991**, *64*, 416.
173. Cook, C. H.; Kang, E. K. *Arch. Pharmacol. Res.* **1981**, *4*, 137.
174. Kitagawa, O.; Sato, T.; Taguchi, T. *Chem. Lett.* **1991**, 177.
175. Cambie, R. C.; Rutledge, P. S.; Somerville, R. F.; Woodgate, P. D. *Synthesis* **1988**, 1009.
176. Cambie, C. R.; Heyward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1864.
177. For recent reports on closely related selenocyclofunctionalisations and electrophilic cyclisation of unsaturated amides, see, respectively, (a) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411. (b) Robin, S.; Rousseau, G. *Tetrahedon* **1998**, *54*, 13681.

Biographical sketch

Professor S. Ranganathan began his research career at the University of Madras (MSc by research in Organic Chemistry, 1957) and obtained his PhD degree at the Ohio State University, Columbus, USA, in 1962. During postdoctoral period between 1962 and 1964 in the research group of Professor R. B. Woodward at Harvard University, Massachusetts, USA, he was engaged in the synthesis of vitamin B12 and later joined the Woodward Research Institute, Basel, Switzerland (1964–1966) to become part of the team on the synthesis of cephalasporin C. After three decades of research and teaching at the Indian Institute of Technology, Kanpur, India, 5 years of research at the Regional Research Laboratory, Trivandrum, India, as a Senior Scientist of the Indian National Science Academy, Professor S. Ranganthan is currently a distinguished scientist at the Indian Institute of Chemical Technology, Hyderabad, India. Professor Ranganathan is a recipient of many awards and recognitions and was conferred with Shanti Swarup Bhatnagar award in 1977. He is an elected Fellow of Indian Academy of Sciences, Bangalore (1975), Indian National Science Academy, New Delhi (1981) and National Academy of Sciences, Allahabad (1991). He has supervised 38 research students towards their PhD degree and has published nearly 150 research papers. He is author/co-author of a number of books on Art in Organic Synthesis, Art in Biosynthesis and Fascinating and Challenging Problems in Organic Reaction Mechanisms. His chief research activities included synthesis and biosynthesis of prostaglandins, molecular rearrangements, protein evolution, protein engineering and protein–DNA interactions. Currently his research interests are focused in understanding the assembly of surfaces and biosilicification.

Kannoth M. Muraleedharan received his MSc degree from the Mahatma Gandhi University, Kerala, India. He completed his PhD degree in 1999 under the joint supervision of Dr. D. Ranganathan and Professor S. Ranganathan at Regional Research Laboratory, Trivandrum, where he worked on synthesis of model chemical systems to understand molecular-assembly and -disassembly, the key phenomena involved in every biological function. In 2001, he joined the research group of Professor Mitchell A. Avery, at the University of Mississippi, Oxford, USA, where his postdoctoral research mainly focuses on the design and synthesis of broad-spectrum anti-infective agents.

Dr. Narendra Vaish earned his PhD degree in 1994 from Indian Institute of Technology, Kanpur, India, under the guidance of Professor S. Ranganathan. Between 1994 and 1995, he was a research associate in Regional Research Laboratory, Thiruvananthapuram, India. From 1995 to 1997, he was an Alexander von Humboldt fellow in Max-Planck Institute for Experimental Medicine, Goettingen, Germany, in the laboratory of Professor Fritz Eckstein, and later continued in the same laboratory till 1998 as a Max-Planck fellow. From 1998 to 2001 he was a research associate in Boston College, Boston in the laboratory of Professor Larry W. McLaughlin. From 1999 to 2001 he was also a visiting scientist at Harvard University in the laboratory of Professor Jack W. Szostak. In Goettingen and Boston, Dr. Vaish focused his research on molecular evolution of nucleic acids and peptides. Currently, he is working as a scientist at Sirna Therapeutics (formerly Ribozyme Pharmaceuticals, Inc.) at Boulder, Colorado in the field of RNAi.

Narayanaswamy Jayaraman, born in 1964, received his BSc degree (1984) from University of Madras, Chennai and MSc degree (1988) from Annamalai University, Chidambaram, India. He completed his PhD degree (1994) under the supervision of Professor S. Ranganathan at Indian Institute of Technology, Kanpur, India, where he worked on side chain modification of peptides, proteins and their DNA interactions. Between 1994 and 1999, he was a postdoctoral fellow in the research group of Professor J. F. Stoddart at the University of Birmingham, UK, then continued with Professor Stoddart at the University of California, Los Angeles, USA, and undertook synthesis and studies of a range of carbohydrate containing dendrimers, sugar coated fullerenes and carbohydrate based liquid crystals. Research in these areas had facilitated him visiting the research groups of Professor F. Diederich (ETH, Zurich, Switzerland) and Professor J. L. Serrano (University of Zaragoza, Zaragoza, Spain) in 1997. On return to India, Dr. Jayaraman joined the Indian Institute of Science, Bangalore, India, as an assistant professor in December 1999. His primary research activities are currently focused in the area of synthetic carbohydrate chemistry and dendrimer chemistry.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5309–5314
Tetrahedron

Stability and stoichiometry of some binary fluorophore–cyclodextrin complexes

Francesca D'Anna,* Serena Riela, Paolo Lo Meo and Renato Noto*

Dipartimento di Chimica Organica 'E. Paternò', Università di Palermo, Viale delle Scienze, Parco d'Orleans II, 90128 Palermo, Italy

Received 5 March 2004; revised 8 April 2004; accepted 29 April 2004

Abstract—The stability and stoichiometric ratio of binary complexes among five fluorophores and β-cyclodextrin (β-CD) or heptakis-(6-amino-6-deoxy)-β-cyclodextrin (am-β-CD) were determined by means of fluorescence measurements in borate buffer at pH=8.0 and 9.0. Structure of both host and guest affected the characteristics of the binary complexes. Pyrene and anthraquinone formed a 1:2 (fluorophore: cyclodextrin) complex with both cyclodextrins. Xanthone formed 1:1 complex with β-CD and 1:2 complex with am-β-CD. A more defined behaviour was observed for crysene. In fact, both stoichiometric different complexes were detected with both hosts. Only 1:1 complexes were observed for antracene. The complex stability was affected by the pH of the solution. MM2 calculations were performed in order to gain information about the forces working on the formation of complexes.

1. Introduction

Complexation reactions involving cyclodextrins are highly important in several fields.[1] These reactions also serve as excellent models for understanding general inclusion phenomena as well as enzyme-substrate interactions.[2] Recently, we have addressed our interest to the use of cyclodextrin complexes for chiral recognition.[3] This is one of the main topics that has attracted researchers' attention not only for its important applications in separation science and in medicinal chemistry, but also for its implications in supramolecular catalysis. Chiral recognition by native and modified cyclodextris (CDs) has had and still has a great of importance.

Data collected so far have usually been explained by two different theories: the 'lock-and-key mechanism',[4] that considers chiral recognition ability as a result of host and guest complementarity in size and in shape; the 'three-point-rule'[5] that, considers chiral recognition ability in terms of non covalent interactions such as electrostatic interactions, hydrogen bonds, and coordinate bonds.

However, results reported so far suggest that the ability of native and modified cyclodextrins to discriminate between enantiomers of a chiral guest is not very high. On this subject Tabushi et al.,[6] in their pioneering work on chiral recognition, reported that 6^A-amino-6^B-carboxy-6^A,6^B-deoxy-β-cyclodextrin has a poor enantioselectivity for enantiomers of tryptophan.

Similarly Kitae and Kano,[7] studying the binding properties of 6-amino-6-deoxy-β-cyclodextrin and heptakis-(6-amino-6-deoxy)-β-cyclodextrin versus *N*-acetylated-Trp, -Leu and -Phe, reported that protonated amino-β-cyclodextrins bind preferably with L-enantiomers and attributed low enantioselectivity values (1.04–1.54) to small structural differences between the complexes formed by enantiomers.

Good results have been obtained by Marchelli, Rizzarelli et al.,[8] who pointed out the particular affinity of Cu(II)-6-deoxy-6-histamine-β-cyclodextrin for D-enantiomer of some native α-aminoacids. Only recently, Liu et al.,[9] studying the binding properties of some organoseleno-modified-β-cyclodextrins, reported that mono-2-phenyl-seleno-2-deoxy-β-cyclodextrin gives a high L-enantioselectivity for the inclusion complexation of leucine (up to 8.4).

Recently, we reported data about the effect of some α-amino acids and their corresponding methyl esters on the stability of the binary complex formed by pyrene (Py) in the presence of heptakis-(6-amino-6-deoxy)-β-cyclodextrin (am-β-CD).[3] On that occasion it was pointed out that the binary complex Py/am-β-CD, having a 1:2 stoichiometric ratio, is a good chiral selector. In fact L-enantioselectivity determinated at pH=8.0, in borate buffer, ranges from 1.2 up to 7.4.

Owing to the nature of the complex formed, this significant chiral recognition ability was thought to be due to the

Keywords: Cyclodextrins; Binary complexes; Fluorescence.
* Corresponding authors. Tel.: +39091596919; fax: +39091596825; e-mail address: rnoto@unipa.it

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.078

extension of the empty volume of the CD cavity that could be differently occupied by enantiomers of the same amino acid.

Our opinion seems to agree with Buvári-Barcza et al.,[10] who observed that the chiral selectivity of different derivatives of β-CD changes with the degree of substitution, that in turn can influence the cavity size. It is possible, furthermore, that the stoichiometric ratio (1:1 and/or 1:2, fluorophore:CD) of the binary complex and that (1:1:1, 1:2:1 or 1:2:2, fluorophore:CD:ternary agent) of the ternary one may be relevant in determining the extent of the chiral recognition.

However, we believe that direct substrate-CD interaction is not comparable with substrate-binary complex interaction. Indeed, the former leads to the best host–guest fit, whereas the latter should consist of an acceptable arrangement of complex.

Therefore, in order to study the importance of size cavity in the chiral discrimination ability of binary complexes, we carried out this preliminary study on the structural characteristics of complexes formed by β-cyclodextrin and heptakis-(6-amino-6-deoxy)-β-cyclodextrin in the presence of some suitable different guests (Fig. 1).

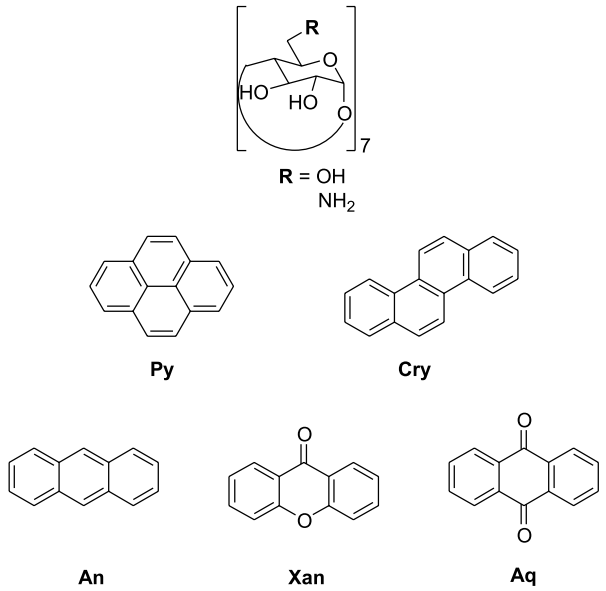


Figure 1. Hosts and guests structures.

This investigation was carried out by spectrofluorimetric titration, in borate buffer, at two pH values (8.0 and 9.0).

Hosts were chosen in order to evaluate the effect that substitution, on going from β-CD to am-β-CD, may exert on complex stability and stoichiometric ratio. These factors could also be influenced by the pH value, considering that am-β-CD, going from pH=8.0 to pH=9.0, passes from its charged form to its neutral form.[11]

Similarly, fluorophore guests were chosen for their different shapes and sizes, that can influence the size of the empty cavity, but also for their different polarities.

In order to have a better knowledge of the forces working on the formation of complexes, their models were elaborated in the gas phase by computational tools.

2. Results and discussion

In Table 1 the values of stability constant, as a function of pH value, and stoichiometric ratios are reported. In any case the stoichiometric ratio was determined by Job's plot[12] and this result was always confirmed by the Benesi-Hildebrand double-reciprocal plot.[13]

Table 1. Measured binding constants

Guest	Host	pH	Stoich. ratio	$\beta_2/10^6$ (M^{-2})	K_1 (M^{-1})	K_2 (M^{-1})
An	β-CD	8.0	1:1		190	
	β-CD	9.0	1:1		780	
	am-β-CD	8.0	1:1		680	
	am-β-CD	9.0	1:1		2500	
Cry	β-CD	8.0	1:1+1:2		2800	3800
	β-CD	9.0	1:1+1:2		2300	1560
	am-β-CD	8.0	1:1+1:2		2000	2700
	am-β-CD	9.0	1:2	3.4		
Py	β-CD	8.0	1:2	7.5		
	β-CD	9.0	1:2	12.0		
	am-β-CD	8.0	1:2	1.7		
	am-β-CD	9.0	1:2	4.8		
Aq	β-CD	8.0	1:2	2.4		
	β-CD	9.0	1:2	10.8		
	am-β-CD	8.0	1:2	1.4		
	Am-β-CD	9.0	1:2	2.3		
Xan	β-CD	8.0	1:1		420	
	β-CD	9.0	1:1		1100	
	Am-β-CD	8.0	1:2	3.7		
	Am-β-CD	9.0	1:2	4.5		

All stability constants were reproducible within 10%.

As can be seen from the data reported in Table 1, in many cases the complexation of fluorophore to β-CD or to am-β-CD can be described by sequential complexation of cyclodextrin molecules (Eqs. 1 and 2):[14]

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

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

The overall stability constant will be given by Eq. 3:

$$\beta_2 = K_1 K_2 = [S(CD)_2]/[S][CD]^2 \tag{3}$$

If $[CD] \gg [S]$ and if the complex having stoichiometric ratio 1:2 is predominant, the change of fluorescence intensity as function of CD concentration will be given by Eq. 4:

$$\Delta I = \Delta\alpha\beta_2 S_t [CD]_0^2/(1 + \beta_2 [CD]_0^2) \tag{4}$$

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

In the presence of β-CD at pH=8.0 and pH=9.0 or am-β-CD at pH=8.0, fluorescence spectra of **Cry** showed a particular trend. In fact, at a given wavelength, fluorescent intensity firstly increases with CD concentration, then decreases. In these cases, we have supposed that the two

different complexes (1:1 and 1:2) were present at comparable concentrations and we analysed experimental data using Eq. 5:

$$\Delta I = (S_t K_1 \Delta(1)[CD]_0 + S_t K_1 K_2 \Delta\alpha(2)[CD]_0^2)/ \\ (1 + K_1[CD]_0 + K_1 K_2[CD]_0^2) \quad (5)$$

where $\Delta\alpha(1)$ and $\Delta\alpha(2)$ are, respectively, the difference of emission quantum yields of free and complexed substrate from 1:1 and 1:2 complexes. Previously, studying the complex formation between α-CD and *para*-nitrosubstituted anilines via uv–vis spectroscopy, we observed that the absorbance maximum firstly increases then passes through a maximum and finally decreases on increasing the host concentration. This trend was explained by admitting that two different complexes, having 1:1 and 1:2 stoichiometric ratios, were formed.[15]

All substrates used in this work have shown a good sensitivity to microenvironmental changes. In fact, in all cases considered, we have detected significant changes of fluorescent intensity when the CD concentration increased. In particular all fluorescent probes, except for the **Xan**, showed a higher fluorescent intensity when they were included in CD cavity.

In the presence of **Xan**, in both cases, that is, in the presence of β-CD and am-β-CD, fluorescent intensity decreases when the cyclodextrin concentration increases. This result agrees with changes observed in fluorescent intensity by addition of a solvent less polar than water, such as 1,4-dioxane, to an aqueous solution of the ketone.[16]

The characteristics of the binary complex fluorophore:CD are obviously affected by different factors. Thus it is really important to consider the different structures of the hosts used.

Indeed, it is common knowledge that substitution of hydroxy groups on the primary rim of the β-CD can significantly modify its binding properties,[17] expecially in the presence of substituents, such as amino groups that, as in this case, change their charge when the pH value increases. Furthermore, it is important to realize that, the change of electrostatic charge on the am-β-CD could have significant consequences on the geometric arrangement of the host. Then pH variation can be important in determining both stability and stoichiometric ratio of complex.

On the other hand, the guest structure, with its different polarity or hydrophobicity could also affect the characteristics of the system.

2.1. Host structure

Data reported in Table 1 show that, when it is possible to compare complexes formed by the two different hosts, by virtue of the same stoichiometric ratio, the native β-CD seems to be a better (2–3 times) ligand than am-β-CD.

This result agrees with Kano's hypothesis[18] that attributes the lower binding ability of the am-β-CD, in its partially charged form, to the occurrence of a distorted structure, owing to electrostatic repulsion among charged groups. Furthermore, it should be considered that when amino groups are protonated, they are able to hamper the cavity desolvation process that has always been considered to be one of the essential steps to promote inclusion complex formation.[19]

The binding ability of both hosts is influenced by pH changes and, independent of the guest considered, they form less stable complexes at pH=8.0 than at pH=9.0.

Presumably the increasing base concentration could break the network of hydrogen bonds on the secondary rim allowing a best fit substrate–cyclodextrin complex.

Furthermore, in general, the increase of complex stability, with increasing pH value, is higher for β-CD than for am-β-CD. This result, appears anomalous, considering the extent of charge variation on the am-β-CD at increasing pH values, can be explained by considering characteristics of buffer used to carry out measurements.

On this topic, it has recently been reported that the stability of host–guest complexes, formed by charged cyclodextrin, can be influenced by the charge of the buffer used.[20] Under this light, in our opinion, we may presume that the borate anion, is able to partially compensate the positive charge on the am-β-CD, with an overall decrease of its unfavourable effect, at pH=8.0.

Also the stoichiometric ratio seems to be influenced by the binding ability of the am-β-CD. Probably the am-β-CD, owing to geometric modifications of the cavity and to strong solvation, includes the guest less deeply in its cavity. This could explain why in the presence of both **Cry** and **Xan**, on going from the β-CD to the am-β-CD, formation of 1:2 complexes, becomes favoured.

2.2. Guest structure

The guests studied have different polarity and hydrophobicity. In particular hydrophobicity increases going from **An** to **Py** or **Cry**, on increasing the number of fused aromatic rings.

Guests having three fused rings (**An**, **Xan** and **Aq**) differ for characteristics of their central ring. This is hydrophobic for **An**, moderately hydrophilic and symmetric for **Aq**, more hydrophilic and unsymmetric for **Xan**.

Data reported in Table 1 show that these structural characteristics are able to influence both the stability and stoichiometric ratio of complexes. On this subject, whereas **An** forms, both in the presence of β-CD and am-β-CD, complexes having a 1:1 stoichiometric ratio, more hydrophobic guests (**Py** and **Cry**) show a marked trend to form complexes having a 1:2 stoichiometric ratio.

However, comparison among these guests also shows that molecular shape is important. Indeed, the non linear structure of **Cry** seems to hamper the formation of species having a 1:2 stoichiometric ratio. This result could explain

why in the presence of this guest, having four aromatic rings as **Py**, both complexes (1:1 and 1:2) are present in comparable amounts.

Complex stability for guests of similar hydrophobicity changes with their shape. Indeed, considering 1:2 complexes (**Cry**/am-β-CD and **Py**/am-β-CD at pH=9.0) the more symmetric molecule forms a more stable complex.

Among guests having three fused rings, complexes having a 1:2 stoichiometric ratio begin to predominate going from **An** to **Aq**.

In the presence of β-CD, **Xan** forms a 1:1 complex. The same result was previously found by Bohne et al.[21] Probably, in this case, a favourable dipole–dipole interaction is operative. Indeed, the **Xan** molecule should be included in a such manner that its C_2 symmetry axis is not parallel to the secondary rim of β-CD. The endocyclic oxygen atom of the **Xan** molecule should be located near to the rim whereas the carbonyl group is directed towards the bulk of solution. This could justify the preference for the 1:1 complex with β-CD. This arrangement allows hydrogen bond formation between the secondary hydroxy groups of β-CD and oxygen atom of the guest. In our opinion, this additional interaction can explain why the complex formed by **Xan** is more stable than that formed by more hydrophobic **An**.

Aq forms complexes having a 1:2 stoichiometric ratio, both in the presence of β-CD and am-β-CD. Recently Dong et al.,[22] studying inclusion of some pharmaceutically related molecules, reported that **Aq**, in the presence of β-CD forms a 1:1 complex, where only the hydrophobic part of the guest penetrates in host cavity. This different result could be a consequence of the different host/guest ratios used in the two cases.

However, **Aq**/am-β-CD complexes are less stable than the **Xan**/am-β-CD ones. Probably, in this case, notwithstanding the same stoichiometric ratio, higher stability could be due to hydrogen bonds that **Xan** can form with secondary rim of am-β-CD.

2.3. Computational models

Further insights were achieved by means of suitable computational tools. Models of the complexes in the gas phase were elaborated and subjected to full geometry optimisation, by means of a MM2/QD[23] molecular mechanics method (see Section 4). Computational data, reported in Table 2, allowed us to calculate the energy variations $\Delta E_{r(1:1)}$ and $\Delta E_{r(1:2)}$ associated to the formation of the 1:1 and 1:2 complexes respectively. Noticeably, the am-β-CD was considered only in its neutral form (calculations in the gas phase on charged species do not allow reliable enough predictions).[23]

Data reported in Table 2 show that complexes having a 1:2 stoichiometric ratio are always favoured. This could be the result of increasing of hydrophobic interactions.

In the gas phase and in the presence of am-β-CD, **Xan**, **Py** and **Aq** show a higher tendency to form 1:2 complexes. This result perfectly agrees with that obtained in buffer solution at pH=9.0.

However, in order to perform a comparison with our experimental data in solution, $\Delta E_{r(1:2)}$ data are clearly overestimated. This could be due, in our opinion, to the mutual interaction between the two host hydroxylated rims.

The latter energy contribution, ΔE_{2h}, formally related to the ideal process (Eq. 6):

$$2CD \rightleftarrows (CD)_2 \quad (6)$$

can be easily calculated.

Nevertheless, we may reasonably presume that in solution, owing to the solvation of the rims, this contribution, should be less relevant.

As can be seen by comparing columns 5 and 8 of Table 2, MM2 calculations foresee only for the **Py** and **Cry** with β-CD a higher stability of 1:2 complexes with respect to 1:1 ones. For all other fluorophores the 1:1 complexes are calculated to be as stable as, or even, more stable than the

Table 2. Calculated (MM2) binding energies (kcal/mol)

Guest	Host	$E_{st/guest}$ [a]	$E_{st/cplx(1:1)}$ [b]	$E_{st/cplx(1:2)}$ [c]	$E_{st/2CD}$ [d]	$\Delta E_{r(1:1)}$ [e]	$\Delta E_{r(1:.2)}$ [f]	ΔE_{r2h} [g]	ΔE_r [h]
An	β-CD	−17.04	38.70	70.96	158.29	−35.35	−58.80	−23.83	−34.97
	Am-β-CD		34.03	64.00	144.40	−41.49	−62.59	−40.72	−21.87
Cry	β-CD	−17.40	30.35	54.49	160.30	−43.31	−66.92	−21.82	−45.1
	am-β-CD		25.72	54.00	142.54	−49.44	−64.28	−42.58	−21.7
Py	β-CD	−21.37	35.44	61.57	160.89	−34.25	−64.23	−21.23	−42.98
	am-β-CD		39.92	54.47	159.76	−31.27	−76.51	−25.36	−51.15
Aq	β-CD	8.05	56.34	95.35	163.12	−42.77	−52.05	−19.00	−33.05
	am-β-CD		62.75	86.22	153.23	−37.86	−69.09	−31.89	−37.2
Xan	β-CD	3.89	55.14	89.60	147.78	−39.81	−56.6	−34.34	−22.26
	am-β-CD		56.09	85.69	148.75	−37.00	65.96	−36.67	−29.29

[a] Steric energy of guest.
[b] Steric energy of 1:1 complex.
[c] Steric energy of 1:2 complex.
[d] Steric energy of two CD molecule in the (1:2) complex deprived of guest.
[e] Entalphy of reaction: CD+guest>Cplx (1:1).
[f] Entalphy of reaction: Cplx (1:1)+CD>Cplx (1:2).
[g] Entalphy of reaction: 2CD>$(CD)_2$.
[h] $\Delta E_{r(1:.2)} - \Delta E_{r2h} E_{ster/\beta\text{-CD}} = 91.06$ kcal/mol. $E_{ster/am\text{-}\beta\text{-CD}} = 92.56$ kcal/mol.

1:2 complexes. The latter results appear in fairly good agreement with experimental data. However, some discrepancies are still present. This could be due, in our opinion, partly to the neglect of any entropic contribution, partly to the fact that, in the absence of any explicit solvent environment in the calculation, only the 'naked' host–guest interaction is actually taken into account.

3. Conclusions

Data collected in the present work have allowed us to characterize some binary complexes fluorophore: cyclodextrins. We hope that these complexes, having significantly different properties, can show different chiral recognition abilities. Moreover, we have confidence that they will allow us to realize which factors determine the high or low ability of a receptor to act as chiral selector.

4. Experimental

4.1. Materials

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

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

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

4.2. Spectrometric measurements

The solutions of β-CD and am-β-CD (1.4×10^{-3} M) were filtered before use by a Millipore 0.45 mm filter. Guest aqueous solutions were prepared by injecting a guest solution (MeOH or 1,4-dioxane) ($\approx10^{-3}$ M) into a buffer solution. Measurement solutions were prepared by adding increasing volumes of CD to 1 ml of guest solution into a volumetric flask. In these solutions, the concentration of guest, reported in Table 3, was constant, while the concentrations of CD increased from 1.4×10^{-4} M to 1.3×10^{-3} M. All measurement solutions were de-aerated, before use, by Ar for 12 min.

Table 3. Experimental conditions

Guest	C_{guest} (M)	λ_{ex} (nm)	$\Delta\lambda_{em}$ (nm)	Solvent	Ex. slit (nm)	Em. slit (nm)
An	5×10^{-7}	261	360–450	MeOH	3	3
Cry	2×10^{-7}	276	350–450	MeOH	3	3
Py	2×10^{-7}	337	360–450	MeOH	1.5	1.5
Aq/β-CD	2×10^{-6}	310	320–600	Diox	5	5
Aq/am-β-CD	2×10^{-6}	310	320–600	Diox	3	5
Xan	4×10^{-6}	348	360–450	MeOH	1.5	3

Steady-state fluorescence spectra were acquired with a JASCO FP-777W spectrofluorimeter. Excitation, emission slits, excitation wavelength and emission interval are reported in Table 3.

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

4.3. Calculations

MM2 calculations were performed by means of the CS Chem 3D Pro™ 5.0 software package from the Cambridge Soft Corporation. Models of the host and their complexes were elaborated with the aid of the 'Quenched Dynamics' (QD) method outlined by Lipkowitz.[25] The behaviour of a suitable starting model of the complex at 300 K is simulated by molecular dynamics for a period of 1000 ps, in order to get a significant picture of the conformational space. Structures are sampled from the obtained 'simulation pool' and allowed to undergo full geometry optimisation by means of a simulated annealing procedure. In this way, only a limited number of energy minima are found. Data reported in Table 2 refer to the absolute minimum found for each complex.

Acknowledgements

Financial support from the University of Palermo (funds for selected research topics) and Italian MIUR within the National Research Project 'Non aromatic heterocycles in stereocontrolled process' is gratefully acknowledged.

References and notes

1. Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1917.
2. Bender, M. L.; Korniyama, M. *Cyclodextrin Chemistry*. Springer: Berlin, 1978.
3. D'Anna, F.; Riela, S.; Lo Meo, P.; Gruttadauria, M.; Noto, R. *Tetrahedron: Asymmetry* **2002**, 1755–1760.
4. Cramer, F. In *The Lock and Key Principle*. Behr, J.-P., Ed.; Wiley: Chichester, 1994; pp 1–23.
5. Ogston, A. G. *Nature* **1948**, *162*, 963.
6. Tabushy, I.; Kuroda, Y.; Mizutani, T. *J. Am. Chem. Soc.* **1986**, *108*, 4514–4518.
7. Kitae, T.; Kano, K. Abstracts of 11th Symphosium on Biofuctional Chemistry, Fukuoka, Japan, October 1996.
8. Corradini, R.; Dossena, A.; Impellizzeri, G.; Maccarrone, G.; Marchelli, R.; Rizzarelli, E.; Sartor, G.; Vecchio, G. *J. Am. Chem. Soc.* **1994**, *116*, 10267–10274.
9. Liu, Y.; You, C. C.; Zhang, H. Y.; Zhao, Y. L. *Eur. J. Org Chem.* **2003**, 1415–1422.
10. Buvári - Bacza, Á.; Bacza, L. *Talanta* **1999**, *49*, 577–585.
11. Hamelin, B.; Jullien, L.; Guillo, F.; Lehn, J. M.; Jardy, A.; De Robertis, L.; Driguez, H. *J. Phys. Chem.* **1995**, *99*, 17877–17885.
12. Job, P. *Ann. Chim.* **1928**, *9*, 113–203.

13. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
14. Xu, W.; Demas, J. N.; DeGraff, B. A.; Whaley, M. *J. Phys. Chem.* **1993**, *97*, 6546–6554.
15. Lo Meo, P.; D'Anna, F.; Riela, S.; Gruttadauria, M.; Noto, R. *Org. Biomol. Chem.* **2003**, *1*, 1584–1590.
16. Barra, M.; Bohne, C.; Scaiano, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 8075–8079.
17. (a) Eliseev, A. V.; Schneider, H. J. *J. Am. Chem. Soc.* **1994**, *116*, 6081–6088. (b) Kean, D. S.; May, B. L.; Clements, P.; Easton, C. J.; Lincoln, S. F. *Aust. J. Chem.* **1999**, *52*, 1157–1163. (c) Sandow, M.; Easton, C. J.; Lincoln, S. F. *Aust. J. Chem.* **1999**, *52*, 1151–1155.
18. Kitae, T.; Nakayama, T.; Kano, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 207–212.
19. Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916–919.
20. Gosh, M.; Zhang, R.; Lower, R. G.; Seto, C. T. *J. Org. Chem.* **2000**, *65*, 735–741.
21. Murphy, R. S.; Barros, T. C.; Barnes, J.; Mayer, B.; Marconi, G.; Bohne, C. *J. Phys. Chem. A* **1999**, *103*, 137–146.
22. Dong, X.-J.; Nie, M.-Y.; Tong, J.; Li, H.-L. *J. Electroanal. Chem.* **1998**, *448*, 61–67.
23. (a) D'Anna, F.; Lo Meo, P.; Riela, S.; Gruttadauria, M.; Noto, R. *Tetrahedron* **2001**, *57*, 6823–6827. (b) Lo Meo, P.; D'Anna, F.; Riela, S.; Gruttadauria, M.; Noto, R. *Tetrahedron* **2002**, *58*, 6039–6045.
24. Ashton, P. R.; Koniger, R.; Stoddart, J. F. *J. Org. Chem.* **1996**, *61*, 903–908.
25. (a) Lipkowitz, K. B. *Chem. Rev.* **1998**, *98*, 1829–1873. (b) Kozár, T.; Venanzi, C. A. *J. Mol. Struct.* **1997**, 395–396. (c) Kozár, T.; Venanzi, C. A. *J. Mol. Struct.* **1997**, *451*, 468.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5315–5318

Efficient one-pot synthesis of anti-HIV and anti-tumour β-carbolines

Radhika S. Kusurkar* and Shailesh K. Goswami

Department of Chemistry, University of Pune, Pune 411007, India

Received 17 February 2004; revised 5 April 2004; accepted 29 April 2004

Abstract—Thermal electrocyclisation of the azahexatriene system has been used as a key step for the synthesis of anti-HIV and anti-tumour compounds, harman, derivatives of harman and 1-aryl-β-carbolines. A one-pot reaction sequence was used to furnish these compounds in good yield.

1. Introduction

The β-carboline ring system is present in many naturally occurring alkaloids which exhibit[1] interesting biological activities. Harman **11** has been reported[2] to show mutagenic and co-mutagenic properties and to inhibit topoisomerase I. Harmine **14** showed[2] significant anti- tumour activity. Recently harman, harmine and their derivatives were shown[3] to possess potent anti-HIV activity. Numerous alkaloids of β-carboline series, with various substituents at α-position, display important biological properties.[4]

Amongst the variety of methods available for the synthesis of β-carboline alkaloids, the most extensively used[1] are the Pictet Spengler and Bischler-Napieralski condensations. However, there are a few routes in which electrocyclisation reactions have been used[5] for the synthesis. Recently, we reported[6] a preliminary communication, presenting the use of electrocyclisation reaction, of monoazahexatriene system as a key step, for the synthesis of harman and substituted harmans. We describe here, in full, details of the synthesis of harman, derivatives of harman and 1-aryl-β-carbolines.

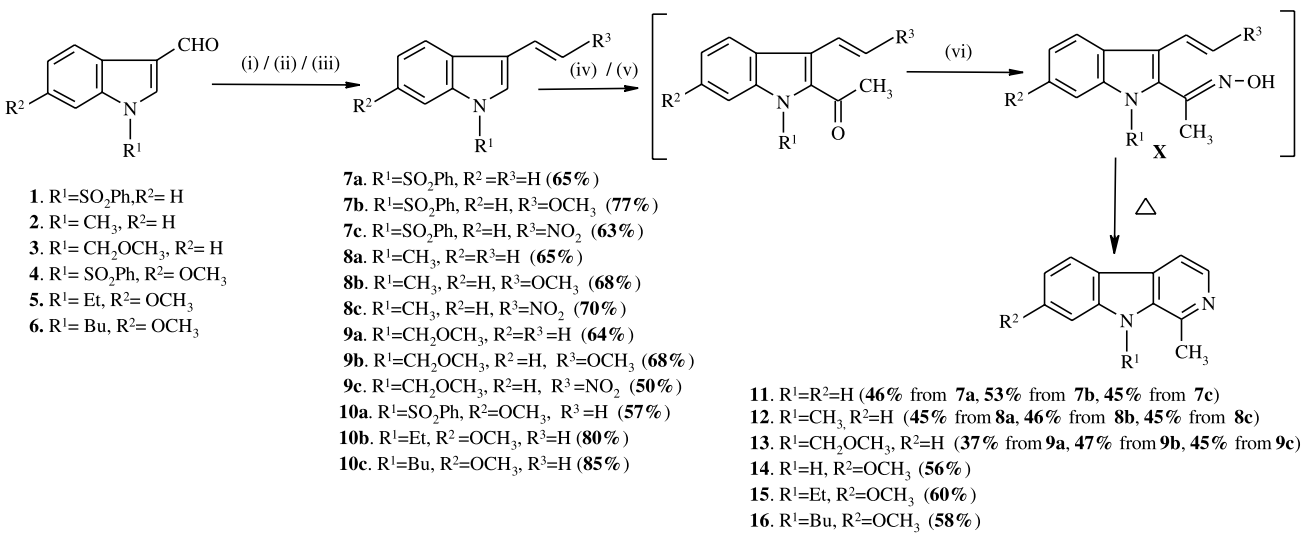
2. Results and discussion

The key intermediate for the electrocyclization step was the azatriene **X**. The synthesis of **X** was envisioned as involving functionalising the indole ring at the 3-position initially and subsequently at the 2-position as shown in Scheme 1.

Thus, indole was formylated[7] using the Vilsmeier Haack reaction to give 3-formyl indole. *N*-Protection was carried out with benzenesulphonyl chloride using the reported[5a] procedure. The protected aldehyde **1** was converted[8] into 3-vinyl indole **7a** using methylenetriphenylphosphorane. To functionalise the indole ring at 2-position, compound **7a** was lithiated using LDA/THF at −78 °C and then treated with *N*,*N*-dimethylacetamide. After work-up and washing with hexane to remove the unreacted starting materials, the reaction mixture, without further purification was treated with hydroxylamine hydrochloride and sodium acetate and refluxed in *o*-dichlorobenzene for 8 h to furnish β-carboline alkaloid harman **11**, in 46% yield starting from **7a**. It was characterized using ^{1}H, ^{13}C NMR spectroscopy and GC-MS spectral data, which were consistent with the reported[9] data. Thus, in this sequence, four steps, oxime formation, electrocyclisation and aromatization with deprotection occurred in a one-pot reaction sequence. Efforts to isolate the intermediate 2-keto compounds were unsuccessful due to its rapid decomposition. The protected indole-3-aldehyde **1** was converted[10] to 3-vinylindole **7b** and to 3-(β-nitrovinyl)indole **7c** using nitromethane and ammonium acetate. Treatment of **7b** and **7c** with LDA/THF at −78 °C, followed by *N*,*N*-dimethylacetamide, furnished two oily liquids. After washing with hexane to remove unreacted starting materials, the two oily compounds were treated with hydroxylamine hydrochloride and sodium acetate and refluxed in *o*-dichlorobenzene. Both of these reactions furnished harman **11** in 53 and 45% yields from **7b** and **7c**, respectively (Scheme 1). It was observed that the methoxy and nitro groups were eliminated during the reaction sequence probably during the aromatization step. A similar observation has been reported earlier.[11] Furthermore, by using *N*-methyl and *N*-methoxymethylindole-3-aldehydes **2** and **3**, the same sequence of reactions was followed.

Keywords: Harman; Harmine; β-Carboline; Electrocyclisation; 1-Aryl-β-carboline.
* Corresponding author. Tel.: +91-20-25601202; fax: +91-20-25691728; e-mail address: rsk@chem.unipune.ernet.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.079



1. R^1=SO_2Ph,R^2= H
2. R^1= CH_3, R^2= H
3. R^1= CH_2OCH_3, R^2= H
4. R^1= SO_2Ph, R^2= OCH_3
5. R^1= Et, R^2= OCH_3
6. R^1= Bu, R^2= OCH_3

7a. R^1=SO_2Ph, R^2 =R^3=H (**65%**)
7b. R^1=SO_2Ph, R^2=H, R^3=OCH_3 (**77%**)
7c. R^1=SO_2Ph, R^2=H, R^3=NO_2 (**63%**)
8a. R^1=CH_3, R^2=R^3=H (**65%**)
8b. R^1=CH_3, R^2=H, R^3=OCH_3 (**68%**)
8c. R^1=CH_3, R^2=H, R^3=NO_2 (**70%**)
9a. R^1=CH_2OCH_3, R^2=R^3 =H (**64%**)
9b. R^1=CH_2OCH_3, R^2 =H, R^3=OCH_3 (**68%**)
9c. R^1=CH_2OCH_3, R^2=H, R^3 =NO_2 (**50%**)
10a. R^1=SO_2Ph, R^2=OCH_3, R^3 =H (**57%**)
10b. R^1=Et, R^2 =OCH_3, R^3=H (**80%**)
10c. R^1=Bu, R^2=OCH_3, R^3=H (**85%**)

11. R^1=R^2=H (**46%** from **7a**, **53%** from **7b**, **45%** from **7c**)
12. R^1=CH_3, R^2=H (**45%** from **8a**, **46%** from **8b**, **45%** from **8c**)
13. R^1=CH_2OCH_3, R^2=H (**37%** from **9a**, **47%** from **9b**, **45%** from **9c**)
14. R^1=H, R^2=OCH_3 (**56%**)
15. R^1=Et, R^2=OCH_3 (**60%**)
16. R^1=Bu, R^2=OCH_3 (**58%**)

Scheme 1. Reagents: (i) $(Ph)_3PCH_3I$, *t*-BuOK, THF; (ii) $(Ph)_3PCH_2OCH_3Cl$, *t*-BuOK, THF (iii) CH_3NO_2, AcOH, AcONa; (iv) LDA, THF, *N*,*N*-dimethyl acetamide (for **7a**, **7b**, **7c**, **9a**, **9b**, **9c**, **10a**, **10b** and **10c**); (v) *n*-BuLi, THF, *N*,*N*-dimethylacetamide (for **8a**, **8b** and **8c**); (vi) $NH_2OH{\cdot}HCl$, AcONa, *o*-dichlorobenzene.

Reactions using 3-vinylindoles **8a**, **8b** and **8c** afforded *N*-methylharman **12** in 45–46% overall yields and using **9a**, **9b** and **9c** afforded *N*-methoxymethyl harman **13** in 37–47% overall yields (Scheme 1). In all these reactions, the methoxy and the nitro groups were eliminated during the one-pot reaction sequence. The vinyl compounds and the β-carbolines were characterized using spectral data. The NMR data of *N*-methylharman was consistent with that reported.[9]

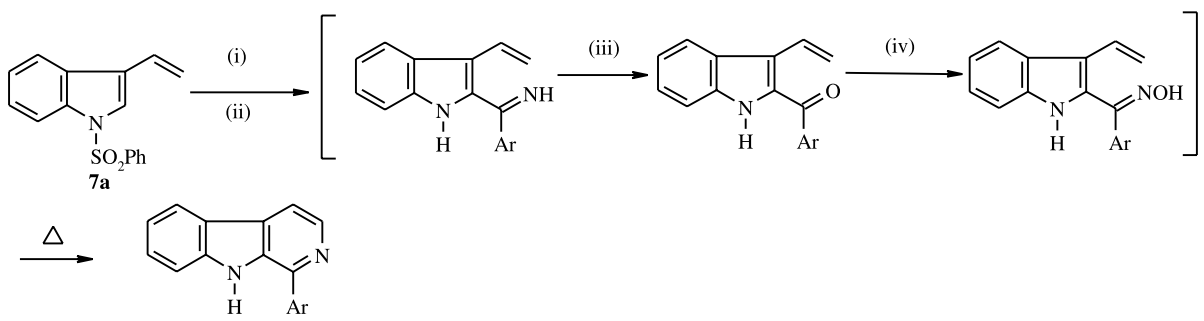
Recently in an activity evaluation report[3] of harmine and its derivatives, it was found that *N*-butylharmine was the most potent compound and possessed a good therapeutic index. *N*-ethylharmine was also potent and showed moderate therapeutic index. Introduction of methoxy group at the seven position methyl group at one position and alkylation of indole nitrogen of norharman led to the enhanced anti-HIV activity. *N*-Butylharmine was shown to be more active than *N*-ethylharmine, indicating that the length of the alkyl chain at this position is important to activity.

In view of the above report, the synthesis of other anti-tumour and anti-HIV active β-carbolines; harmine **14**, *N*-ethyl harmine **15** and *N*-butylharmine **16** was carried out using the same one-pot strategy involving electrocyclisation reaction. Thus starting from 6-methoxy-3-vinylindoles **10a**, **10b** and **10c** (Scheme 1) harmine, *N*-ethylharmine and *N*-butylharmine were synthesized in good yield.

In all these reactions, efforts were made to isolate the intermediate 2-keto compounds, however, all of them were shown to be unstable and light sensitive.

The presence of intermediate compounds was confirmed by analogy with the reaction sequence used in the synthesis of *N*-methylnorharman reported in our earlier communication.[6]

As 1-substituted-β-carbolines posses various biological activities, it was envisaged to use our one-pot strategy for the synthesis of 1-aryl-β-carbolines by changing the electrophile, used in the lithiation reaction. Initially, the use of *N*,*N*-dimethylbenzamide or *N*,*N*-dimethyl-2-furamide as an electrophile gave a complex mixture. Then nitrile was used as an electrophile in the lithiation reaction. There are a few reports[12] of the use of nitrile as an electrophile in lithiation reaction. Benzonitrile was then used as an electrophile expecting a formation of 2-imino or 2-keto-3-vinyl



7a

17. Ar= phenyl (76%)
18. Ar= 2-furyl (76%)
19. Ar= ***p***-methoxyphenyl (78%)

Scheme 2. Reagents and conditions: (i) LDA/THF; (ii) ArCN; (iii) H_2O; (iv) $NH_2OH{\cdot}HCl$, CH_3COONa, *o*-dichlorobenzene.

indoles as shown in Scheme 2. Attempts[13] to isolate these intermediates gave rapid decomposition. Thus the reaction mixture was stirred at −10 °C and after work-up, without purification, was treated with hydroxylamine hydrochloride and sodium acetate and refluxed in *o*-dichlorobenzene to furnish 1-phenyl-β-carboline **17**. Similar reaction sequence was used for the synthesis of 1-(2-furyl)-β-carboline **18** and 1-(*p*-methoxyphenyl)-β-carboline **19** in which furan-2-carbonitrile and *p*-methoxybenzonitrile were used as electrophiles respectively. The formation of the β-carbolines was explained as shown in Scheme 2. The imine produced in the lithiation reaction might be hydrolysed to keto compound. Treatment of this compound with hydroxylamine hydrochloride and sodium acetate gave an azatriene system. Further electrocyclisation, aromatization and deprotection furnished 1-substituted-β-carbolines.

By the analogy[3] to the anti HIV activity of *N*-substituted and 1-substituted-β-carbolines, the newly synthesized *N*-methoxymethylharman, and 1-phenyl, 1-(2-furyl) and 1-(*p*-methoxyphenyl)-β-carbolines, are expected to show anti-HIV activity.

In summary, some biologically important anti-tumour and anti-HIV active β-carboline alkaloids, harman **11**, *N*-methylharman **12**, *N*-methoxymethylharman **13**, harmine **14**, *N*-ethylharmine **15** and *N*-butylharmine **16**, were synthesized in a one-pot reaction sequence using electrocyclisation reactions in good yields. In addition, use of aryl nitrile as an electrophile in the lithiation reaction and a further one-pot sequence of the reactions furnished 1-phenyl-β-carboline **17**, 1-(2-furyl)-β-carboline **18** and 1-(*p*-methoxyphenyl)-β-carboline **19**.

3. Experimental

3.1. General

All recorded melting points are uncorrected. IR spectra (ν, cm^{-1}) were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer as a thin film or in nujol mull. NMR spectra were recorded on a Varian Mercury instrument (300 MHz for ^1H and 75 MHz for ^{13}C) with reference to TMS as an internal standard. Elemental analyses were carried out in a Hosli C, H-analyzer. As and when required the reactions were carried out in oven-dried glassware under dry N_2. *N*-Protected indole aldehydes were prepared[5a] from indole-3-aldehyde.Vinyl indoles **7a**, **7b**, **8a**, **8b**, **9a**, **9b**, **10a**, **10b** and **10c** were prepared[8,10] using Wittig reactions and β-nitrovinyl indoles **7c**, **8c** and **9c** were prepared using nitromethane and ammonium acetate.

3.2. General procedure for one-pot synthesis of β-carbolines

A solution of *N*-protected-3-vinyl indoles **7a**, **7b**, **7c**, **9a**, **9b**, **9c**, **10a**, **10b** and **10c** (0.002 mol) in freshly distilled anhydrous THF (5 mL) was added to freshly prepared LDA (0.004 mol) solution in THF at −78 °C and *n*-BuLi (2.3 M, 0.004 mol) in hexane was added to the solution of vinylindoles **8a**, **8b** and **8c** in THF at −78 °C. The resulting orange colored solution was stirred for 1 h and freshly distilled *N*,*N*-dimethylacetamide/aryl nitrile (0.002 mol) in anhydrous THF (10 mL) was added to this solution at −78 °C. The mixture was further stirred for 1 h. The temperature was allowed to rise up to −10 °C and it was stirred for another 3 h. After work up with brine, the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was washed with hexane and without further purification treated with hydroxylamine hydrochloride (0.04 mol) and NaOAc (0.04 mol) and refluxed for 8 h in *o*-dichlorobenzene. After removal of solvent the residue was chromatographed on neutral alumina using hexane and ethyl acetate (90/10 to 80/20) to give corresponding β-carbolines.

3.2.1. Harman (11). Mp 235–236 °C (Lit.[9] Mp 235–238 °C); (Found: C, 79.24; H, 5.45. $C_{12}H_{10}N_2$ requires C, 79.10; H, 5.53); ν_{max} (nujol) 1663 cm^{-1}; δ_H (DMSO-d_6) 2.85 (3H, s, ArCH_3), 7.21 (1H, td, *J*=7.5, 1.1 Hz, C_6–*H*), 7.51 (1H, td, *J*=7.1, 1.1 Hz, C_7–*H*), 7.58 (1H, d, *J*=7.9 Hz, C_8–*H*), 7.81 (1H, d, *J*=5.2 Hz, C_4–*H*), 8.07 (1H, d, *J*=8.0 Hz, C_5–*H*), 8.21 (1H, d, *J*=5.2 Hz, C_3–*H*), 11.31 (1H, bs, exchange with D_2O, N*H*); δ_C (DMSO-d_6) 18.71, 110.09, 110.68, 117.28, 119.27, 119.62, 125.24, 125.81, 132.78, 135.44, 138.65, 140.20.

3.2.2. *N*-Methylharman (12). Mp 104–105 °C (Lit.[9] Mp 102–104 °C); (Found: C, 79.67, H, 6.25. $C_{13}H_{12}N_2$ requires C, 79.56; H, 6.16); ν_{max} (nujol) 1668 cm^{-1}; δ_H (DMSO-d_6) 3.11 (3H, s, ArCH_3), 4.14 (3H, s, NCH_3), 7.1 (1H, t, *J*=7.5 Hz, C_6–*H*), 7.47 (1H, d, *J*=8.2 Hz, C_8–*H*), 7.63 (1H, t, *J*=7.1 Hz, C_7–*H*), 7.86 (1H, d, *J*=4.4 Hz, C_4–*H*), 8.15 (1H, d, *J*=7.7 Hz, C_5–*H*), 8.31 (1H, d, *J*=4.4 Hz, C_3–*H*); δ_C (DMSO-d_6) 22.93, 32.0, 110.03, 112.89, 119.29, 120.01, 121.35, 127.70, 128.1, 134.94, 136.64, 141.56.

3.2.3. *N*-Methoxymethyl harman (13). Mp 152–154 °C; (Found: C, 74.47; H, 6.45. $C_{14}H_{14}N_2O$ requires C, 74.31; H, 6.24); ν_{max} (nujol) 1660 cm^{-1}; δ_H (DMSO-d_6) 3.06 (3H, s, ArCH_3), 3.32 (3H, s, OCH_3), 5.79 (2H, s, NCH_2O), 7.26 (1H, t, *J*=7.4 Hz, C_6–*H*), 7.9 (1H, d, *J*=8.7 Hz, C_8–*H*), 7.60 (1H, m, C_7–*H*), 8.27 (2H, bd, *J*=5.2 Hz, C_4–*H* and C_5–*H*), 8.42 (1H, d, *J*=5.8 Hz, C_3–*H*); δ_C (DMSO-d_6) 20.30, 55.20, 82.80, 94.56, 109.10, 111.97, 114.82, 122.62, 127.25, 134.55, 137.73, 141.28, 141.97,160.10.

3.2.4. Harmine (14). Mp 262–263 °C (Lit.[14] Mp 262 °C); (Found: C, 73.40; H, 5.84. $C_{13}H_{12}N_2O$ requires C, 73.57; H, 5.70); ν_{max} (nujol) 1665 cm^{-1}; δ_H (DMSO-d_6) 2.59 (3H, s, ArCH_3), 3.73 (3H, s, *OCH*$_3$), 6.67 (1H, dd, *J*=2.2, 8.5 Hz, C_6–*H*), 6.88 (1H, d, *J*=2.2 Hz, C_8–*H*), 7.66 (1H, d, *J*=5.2 Hz, C_4–*H*), 7.90 (1H, d, *J*=8.8 Hz, C_5–*H*), 8.01 (1H, d, *J*=5.2 Hz, C_3–*H*), 11.32 (1H, bs, exchange with D_2O, N*H*); δ_C (DMSO-d_6) 20.32, 55.26, 94.56, 109.10, 111.97, 114.82, 122.62, 127.25, 134.55, 137.73, 141.28, 141.97, 160.09.

3.2.5. *N*-Ethyl harmine (15). Mp 251–252 °C; (Found: C, 74.87; H, 6.71. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71); ν_{max} (nujol) 1640 cm^{-1}; δ_H ($CDCl_3$) 1.43 (3H, t, *J*=7.2 Hz, N-CH_2CH_3), 3.01 (3H, s, ArCH_3), 3.97 (3H, s, OCH_3), 4.51 (2H,q, *J*=6.9 Hz, N-CH_2CH_3), 6.85 (2H, bd, *J*=9.2 Hz, C_6–*H* and C_8–*H*), 7.70 (1H, d, *J*=4.7 Hz, C_4–*H*), 7.94 (1H,

d, J=8.2 Hz, C_5–H), 8.25 (1H, d, J=5.2 Hz, C_3–H); δ_C ($CDCl_3$) 15.36, 23.01, 39.18, 55.44, 92.44, 108.48, 111.82, 114.87, 122.0, 128.97, 134.63, 137.73, 140.11, 142.22, 160.48.

3.2.6. *N*-Butyl harmine (16). Mp 221–222 °C; (Found: C, 76.20; H, 7.71. $C_{17}H_{20}N_2O$ requires C, 76.09; H, 7.51); ν_{max} (nujol) 1663 cm^{-1}; δ_H ($CDCl_3$) 0.95 (3H, t, J=7.4 Hz, N-$CH_2CH_2CH_2CH_3$), 1.45 (2H, m, N-$CH_2CH_2CH_2CH_3$), 1.80 (2H, m, N-$CH_2CH_2CH_2CH_3$), 3.01 (3H, s, ArCH_3), 3.94 (3H, s, OCH_3), 4.45 (2H,t, J=7.9 Hz, N-$CH_2CH_2CH_2$-CH_3), 6.86 (2H, bd, J=9.9 Hz, C_6–H and C_8–H), 7.71 (1H, d, J=4.4 Hz, C_4–H), 7.95 (1H, d, J=9.9 Hz, C_5-H), 8.25 (1H, d, J=4.4 Hz, C_3–H); δ_C ($CDCl_3$) 13.98, 20.27, 23.51, 32.78, 44.70, 55.68, 93.39, 108.39, 112.13, 115.13, 122.22, 129.17, 135.19, 138.10, 140.45, 142.91, 160.59.

3.2.7. 1-Phenyl-β-carboline (17). Mp 245–246 °C (Lit.[15] Mp 246–247 °C); (Found: C, 83.40; H, 4.82. $C_{17}H_{12}N_2$ requires C, 83.58; H, 4.95); ν_{max} (nujol) 1660 cm^{-1}; δ_H (DMSO-d_6) 7.14 (1H, m, C_6-H), 7.36–7.51 (5H, m, ArH), 7.88 (2H, d, J=7.3 Hz, C_7-H and C_8–H), 7.97 (1H, d, J=5.3 Hz, C_4-H), 8.10 (1H, d, J=8.0 Hz, C_5–H), 8.30 (1H, d, J=5.3 Hz, C_3–H), 11.43 (1H, bs, exchange with D_2O, NH).

3.2.8. 1-(2-Furyl)-β-carboline (18). Mp 167–168 °C (Lit.[16] Mp 167–168 °C); (Found: C, 76.80; H, 4.34. $C_{15}H_{10}N_2O$ requires C, 76.91; H, 4.30); ν_{max} (nujol) 1665 cm^{-1}; δ_H (DMSO-d_6) 6.70 (1H, d, J=1.8 Hz, C_4–H of furan), 7.18 (2H, bs, C_3–H of furan and C_6–H) 7.49 (1H, t, J=7.1 Hz, C_7-H), 7.67 (1H, d, J=7.9 Hz, C_8–H) 7.90 (1H, bs, C_5–H of furan), 8.0 (1H, bd, J=5.1 Hz, C_4–H), 8.27 (1H, d, J=7.9 Hz, C_5–H), 8.29 (1H, bd, J=5.1 Hz, C_3–H), 11.43 (1H, bs, exchange with D_2O, NH).

3.2.9. 1-(*p*-Methoxyphenyl)-β-carboline (19). Mp 159–160 °C (Lit.[15] Mp 159–160 °C); (Found: C, 78.76; H, 5.24. $C_{18}H_{14}N_2O$ requires C, 78.81; H, 5.14); ν_{max} (nujol) 1668 cm^{-1}; δ_H (DMSO-d_6) 3.0–3.8 (3H+, bs, OCH_3+ DMSO-d_6), 6.70 (2H, d, J=8.5 Hz, ArH), 6.87 (1H, m, C_6–H), 7.19 (2H, m, C_7–H and C_8–H), 7.37 (2H, d, J=8.5 Hz, ArH), 7.87 (2H, d, J=7.6 Hz, C_4–H and C_5–H), 7.99 (1H, d, J=6.1 Hz, C_3–H), 12.19 (1H, bs, exchange with D_2O, NH).

Acknowledgements

We are grateful to Mr. A. P. Gadgil for IR spectra, Mrs. J. P. Chaudhari for NMR spectra and Mr. Vishal Koske for GC-MS.

References and notes

1. Love, B. *Org. Prep. Proc. Int.* **1996**, *28*, 1–64.
2. Ishida, J.; Wang, H. K.; Bastow, K. F.; Chang-Q, H.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3319.
3. Ishida, J.; Wang, H. K.; Oyama, M.; Cosentino, M. L.; Chang, -Q. H.; Lee, K. H. *J. Nat. Prod.* **2001**, *64*, 958.
4. (a) Hirai, K.; Ishiba, T. *Heterocycles* **1975**, *3*, 217. (b) Allen, M. S.; Tan, Y. C.; Trundell, M. L.; Naeayan, K.; Schindler, L. R.; Matrin, M. J.; Schultz, C.; Hagen, T. J.; Koehler, K. F.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 2343.
5. (a) Hibino, S.; Sugini, S.; Yamochi, T.; Kuwata, M.; Hashimoto, H.; Sato, K.; Amanuma, F.; Karasawa, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2261. (b) Choshi, T.; Matsuya, Y.; Inada, K.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1998**, *39*, 2341. (c) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108. (d) Kannadasan, S.; Srinivasan, P. C. *Tetrahedron Lett.* **2002**, *43*, 3149. (e) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793.
6. Kusurkar, R. S.; Goswami, S. K.; Vyas, S. M. *Tetrahedron Lett.* **2003**, *44*, 4761.
7. Smith, G. *J. Chem. Soc.* **1954**, 3842.
8. Pindur, U.; Pfeuffer, L. *Monatsh. Chem.* **1989**, *120*, 157.
9. Seki, H.; Hashimoto, A.; Hino, T. *Chem. Pharm. Bull.* **1993**, *41*, 1169.
10. Pfeuffer, L.; Pindur, U. *Helv. Chim. Acta* **1987**, *70*, 1419.
11. Kusurkar, R. S.; Bhosale, D. K. *Synth. Commun.* **1990**, *20*, 101.
12. (a) Cherest, M.; Lusinchi, X. *Tetrahedron* **1986**, *42*, 3825. (b) Chikashita, H.; Ishibaba, M.; Ori, K.; Ito, K. *Chem. Pharm. Bull.* **1988**, *61*, 3637.
(c) Shafer, C. M.; Molinski, T. E. *J. Org. Chem.* **1998**, *63*, 551. (d) Pawlas, J.; Vedso, P.; Jakobsen, P.; Huusfeldt, P. O.; Begtrup, M. *Org. Chem.* **2001**, *66*, 4214. (e) Coleman, C. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054.
13. In order to check the possibility of an attack of an initially formed $>C{=}N^-$, on the vinyl group at 3-position the temperature of reaction mixture was raised to 28 °C and stirring continued overnight. However a complex mixture was obtained.
14. Faizi, S.; Naz, A. *Tetrahedron* **2002**, *58*, 6185.
15. Love, B. E.; Raje, P. S. *J. Org. Chem.* **1994**, *59*, 3291.
16. Kanamori, H.; Morimoto, K.; Kinae, N.; Tomita, I. *Chem. Pharm. Bull.* **1980**, *28*, 3143.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5319–5323

Stabilization of (*N*-methyleneamino)imidoylketenes: synthesis of dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazines

Natalia A. Lisowskaya,[a,*] Andrei N. Maslivets[a] and Zainutdin G. Aliev[b]

[a]*Department of Organic Chemistry, Perm State University, 15 Bukireva Str., 614990 Perm, Russian Federation*
[b]*Institute of Problems of Chemical Physics, Russian Academy of Science, 14 Institutskii Prosp, 142432 Chernogolovka, Moscow Region, Russian Federation*

Received 2 February 2004; revised 13 April 2004; accepted 29 April 2004

Abstract—Thermolysis of substituted methyl 1-methyleneamino-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **2a**,**b** led to substituted dimethyl 3,9-dioxo-1,5,7,11-tetrahydro-1*H*,7*H*-dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazine-1,7-dicarboxylates **4a**,**b** and methyl 2,5-dihydro-5-oxo-1*H*-pyrazole-3-carboxylates **5a**,**b** as minor products. The structure of compound **4a** was determined by X-ray crystallography. The proposed mechanism of this conversion includes generation of (*N*-methyleneamino)imidoylketenes **6a**,**b** and its intramolecular transformation to azomethine imines—5-oxo-2,5-dihydropyrazole-1-methylium-2-ides **7a**,**b**, which undergo dimerization in head-to-tail manner yielding products **4a**,**b** and partially hydrolyse to compounds **5a**,**b**.

1. Introduction

The chemistry of imidoylketenes was being extensively investigated during the last few decades from preparative, mechanistic and theoretical points of view.[1] Furthermore, these highly reactive molecules are of considerable current interest because of their wide use as building blocks in organic chemistry. The thermal cheletropic extrusion of CO from pyrrol-2,3(1*H*)-diones is the convenient method for the generation of these ketenes. The variation of substituents in the pyrrole ring leads to the generation of new imidoylketenes and widens their potential for the new types of transformation. As we and other authors have shown in the previous works, imidoylketenes can be involved into various types of intramolecular cyclization,[1,2] dimerization[3] and interaction with nucleophiles[4] and dienophiles.[5]

We report herein the synthesis and thermolysis of new pyrrole-2,3(1*H*)-diones—methyl 3-acyl-1-diphenylmethyleneamino-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates (**2a**,**b**) (Scheme 1). We also describe a new and unusual type of stabilisation of (*N*-methyleneamino)imidoylketenes[6] to produce the novel tetrazine derivatives, namely dimethyl 2,8-diacyl-3,9-dioxo-5,5,11,11-tetraphenyl-1,5,7,11-tetrahydro-1*H*,7*H*-dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazine-1,7-dicarboxylates (**4a**,**b**), whose structure was defined by X-ray crystallography (Fig. 1).

2. Results and discussion

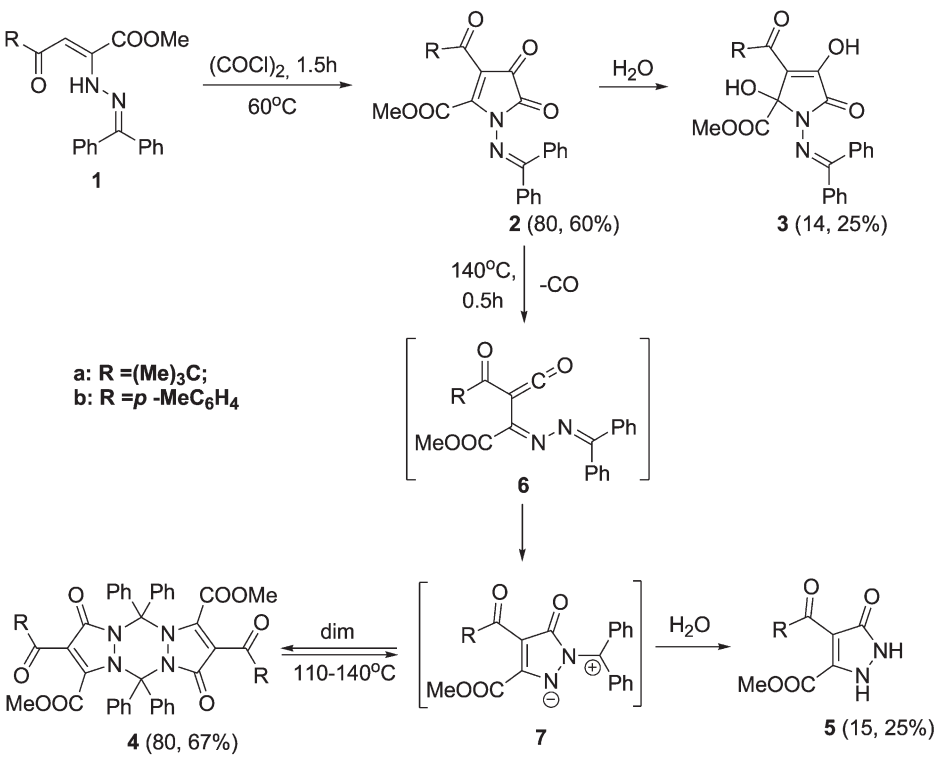
Reaction of primary β-enaminoketones with oxalyl chloride is the most common method of the pyrrole-2,3(1*H*)-diones[7] synthesis. The corresponding methyl 3-acyl-1-diphenylmethyleneamino-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates (**2a**,**b**) were obtained from methyl ethers of 4-acyl-2-diphenylmethylenehydrazino-4-oxo-2-butenoic acids[8] (**1a**,**b**) and oxalyl chloride in 80, 60% yield (Scheme 1). The spectroscopic data of pyrrole-2,3(1*H*)-diones **2a**,**b** are in good agreement with the other similar systems.[6,7,9]

Unfortunately, the quantitative isolation and further application of the deep red coloured pyrrole-2,3(1*H*)-diones **2a**,**b** appeared to be difficult since they are highly sensitive to moisture and easily hydrolyse to afford light yellow methyl 3-acyl-1-diphenylmethyleneamino-2,4-dihydroxy-2,5-dihydro-5-oxo-1*H*-pyrrole-2-carboxylates (**3a**,**b**), whose structure was confirmed by X-ray crystallography.[10]

We have noticed that the deep red solution of pyrrole-2,3(1*H*)-diones **2a**,**b** became deep blue at heating, this colour gradually disappeared after cooling and some colourless products were formed. The preparative thermolysis of **2a**,**b** (130–140 °C, *p*-xylene) resulted in substituted dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazines **4a**,**b** as the main products (80, 67%, respectively) and pyrazoles **5a**,**b** (15, 25%, respectively) as the by-products (Scheme 1). The structure of **4a** was defined by X-ray analysis. The structure of **5a**,**b** was established by elemental analysis, IR and ^{1}H NMR spectroscopic data.

Keywords: Pyrrole-2,3(1*H*)-diones; (*N*-Methyleneamino)imidoylketenes; Azomethine imines; Dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazines.
* Corresponding author. Tel./fax: +7-3422-396367;
e-mail address: lisowskaya@mail.ru

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.080



Scheme 1. Synthesis and thermolysis of 1-diphenylmethilenamino-2,3-dihydropyrrole-2,3-dione **2a**,**b**.

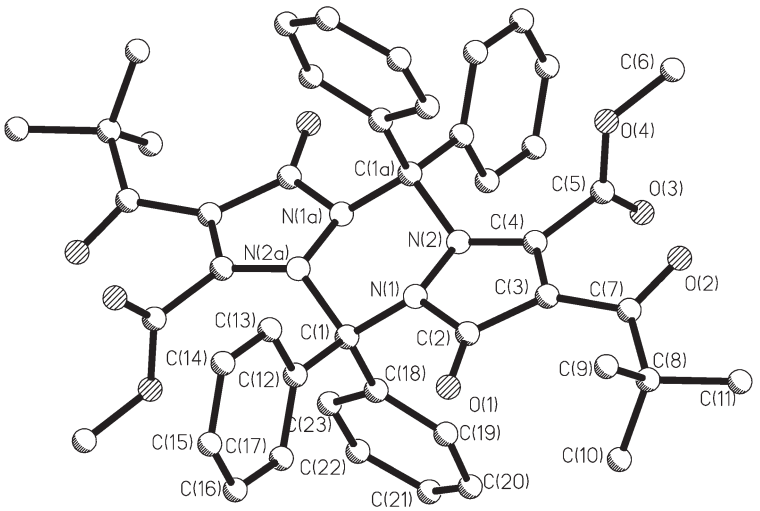


Figure 1. Perspective view of the structure of **4a**, showing the crystallographic labeling.

Crystals of **4a** suitable for X-ray analysis were obtained from a toluene solution. Figure 1 shows a perspective view of the structure, which crystallizes in the monoclinic space group $P2_1/c$. The molecule in the crystal lies in the centre of the symmetry. The tetrazine has a chair-conformation. The inflexion along N1···N2a line is 48.5° and the deviation of the C1 from the plane of four nitrogen atoms is 0.7 Å. The nitrogen atoms have a pyramidal structure. The sums of the valence angles around N1 and N2 are 347.5 and 348.6°, respectively. The pyrazole cycle with local double bond is planar. The C3–C4 distance in the five-membered ring is 1.368(4) Å, that corresponds to the C=C double bond length in the pyrazoles.[11] The plane of the methoxycarbonyl group at the C4 has an orthogonal position with respect to the pyrazole ring, and the plane of the pivaloyl fragment at the C3 an angle 14.7°. The torsion angle O2–C7–C3–C4 is 12.2°. Hydrogen bonds and other shortened intermolecular contacts were not found. The values of all bonds lengths in this molecule are in nice agreement with the other known data.[11]

We propose the following mechanism of pyrrole-2,3(1*H*)-diones **2a**,**b** conversion into dipyrazolo[1,2-*a*;1′,2′-*d*]-[1,2,4,5]tetrazines **4a**,**b** and pyrazoles **5a**,**b**. The thermal cheletropic extrusion of CO from **2a**,**b** affords the new (*N*-methyleneamino)imidoylketenes **6a**,**b**, which unexpectedly intermolecular cyclized into azomethine imines—4-acyl-3-methoxycarbonyl-5-oxo-2,5-dihydropyrazole-1-(diphenylmethylium)-2-ides **7a**,**b**. These intermediates undergo dimerization in head-to-tail manner yielding

products **4a**,**b**, while azomethine imines **7a**,**b** are partially hydrolysed under action of water traces in a solvent with ejection of benzophenone molecule to produce the compounds **5a**,**b**.

On the other hand, the dimerization of azomethine imines **7a**,**b** is a reversible process, in our opinion. The colourless solutions of dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazines **4a**,**b** in completely anhydrous inert solvents (such as *p*-xylene, toluene) become deep blue at heating (110–140 °C) and again colourless after cooling. Moreover, the analogous process is observed in mass spectrum of **4a**, where intense peak of the azomethine imine **7a** (*m*/*z* 390) is present.

An additional proof for the suggested mechanism is the dimerization of stable pyrazolidin-3-ones—azomethine imines, giving the centrally symmetric dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazine-1,7-diones and mirror-symmetric dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazine-1,9-diones early reported by Dorn and co-workers.[12]

3. Conclusion

In summary, the results showed that the thermolysis of methyl 3-acyl-1-diphenylmethyleneamino-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **2a**,**b** led to unexpected products **4a**,**b** and **5a**,**b**. We propose the mechanism of this conversion, including (*N*-methyleneamino)imidoylketenes **6a**,**b** generation, its further cyclization to azomethine imines **7a**,**b**, which dimerize into final compounds **4a**,**b**. A novel pathway of imidoylketenes stabilization via their preliminary cyclization to azomethine imines is an unusual process and it has never been observed before. Furthermore, the pyrazoles **5a**,**b** formation by hydrolysis of **7a**,**b** indirectly confirms the suggested mechanism.

The insertion of methyleneamino moiety to the nitrogen atom of pyrrole-2,3-diones has allowed us not only to obtain an attractive heterocyclic system and to expand the synthetic opportunities of five-membered 2,3-dioxoheterocycles, but also to offer a new synthetic way to arduous unsaturated azomethine imines formation through the intramolecular cyclization of (*N*-methyleneamino)imidoylketenes. Saturated azomethine imines have been prepared by catalytic nucleophilic addition of substituted pyrazolidin-3-ones to various aldehydes and ketones, as reported by Dorn,[12] Stanovnik,[13] Sharpless[14] and co-workers.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ solutions with HMDS as the internal standard on a Bruker AM-300 (300 MHz) and a Bruker DPX 400 (400 MHz) spectrometers. The IR spectra were recorded in Nujol mulls on a UR-20 spectrometer. The mass spectrum was recorded on a MX-1310 spectrometer (70 eV). The melting points are uncorrected. Reactions were monitored by TLC on Silufol UV-254 plates. Solvents were dried according to standard protocols.

X-ray crystallography. The unit cell parameters were measured on a four-circle automatic detector KM-4 (KUMA DIFRACTION) with χ-geometry (graphite monochromatised Cu K_α radiation, $\omega-2\theta$ scan mode, $2\theta \leq 80.5°$). The total number of data collected was 4249 [4119 of it were independent with *R*(int.) 0.081]. No correction for absorption was applied ($\mu=0.724\ mm^{-1}$). The structure was determined by a direct method by program SIR92[15] with the subsequent series of calculations of electronic density maps. The hydrogen atoms positions were calculated from geometrical terms. The final anisotropic specification LSM was completed by program SHELXL-97[16] at $R_1=0.0519$, $wR_2=0.1346$ on 1629 reflections with $I \geq 2\sigma(I)$ and $R_1=0.1721$; $wR_2=0.1911$ on all 4119 reflections, GOF=1.002.

Crystallographic data (excluding structural factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC No 229731. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. Methyl 1-diphenylmethyleneamino-3-pivaloyl-4,5-dihydro-4,5-dioxo-1*H*-pyrrole-2-carboxylate (2a). A solution of oxalyl chloride (0.25 mL, 28 mmol) in dry chloroform (1 mL) was added to a solution of **1a**[8] (1.00 g, 27 mmol) in dry chloroform (3 mL). The reaction mixture was heated for 1.5 h, solvent (2 mL) was evaporated and resulting solution was cooled. The solid was filtered off gave the title compound **2a** (0.92 g, 80%) as a deep red crystals, mp 138–140 °C; [Found: C, 68.97; H, 5.21; N, 6.72. $C_{24}H_{22}N_2O_5$ requires C, 68.89; H, 5.30; N, 6.69%]; ν_{max} 1760 (O–C=O, C^2=O); 1740 (C^3=O); 1680 (C^4–C=O); δ_H (400 MHz, $CDCl_3$) 7.10–7.62 (10H, m, 2Ph); 3.86 (3H, s, OMe); 1.05 (9H, s, Me_3C).

4.1.2. Methyl 1-diphenylmethyleneamino-2,4-dihydroxy-3-pivaloyl-2,5-dihydro-5-oxo-1*H*-pyrrole-2-carboxylate (3a). The residue solution after synthesis compound **2a** was allowed to contact with air moisture for 24 h. The solid was filtered off and recrystallized from chloroform–hexane (1:1) to give the title compound **3a** (0.17 g, 14%) as a light yellow crystals, mp 149–150 °C; [Found: C, 66.15; H, 5.12; N, 6.47. $C_{24}H_{24}N_2O_6$ requires C, 66.05; H, 5.22; N, 6.42%]; ν_{max} 3480, 3210 (OH); 1740 (O–C=O, C^2=O); 1680 (C^4–C=O); δ_H (300 MHz, DMSO-d_6) 7.12–7.84 (11H, m, 2Ph+C^5–O*H*); 3.84 (3H, s, OMe); 1.20 (9H, s, Me_3C).

4.1.3. Methyl 1-diphenylmethyleneamino-3-*p*-toluoyl-4,5-dihydro-4,5-dioxo-1*H*-pyrrole-2-carboxylate (2b). This compound was prepared from **1b**[8] (1.00 g, 25 mmol) and oxalyl chloride (0.22 mL, 26 mmol), according to above described method for **2a**. Yield compound **2b** (0.71 g, 60%) as a deep red crystals, mp 144–146 °C; [Found: C, 71.83; H, 4.35; N, 6.24. $C_{27}H_{20}N_2O_5$ requires C, 71.67; H, 4.46; N, 6.19%]; ν_{max} 1740 (O–C=O, C^2=O); 1725 (C^3=O); 1630 (C^4–C=O); δ_H (400 MHz, $CDCl_3$)

7.00–7.79 (14H, m, 2Ph+C_6H_4); 3.80 (3H, s, OMe); 2.29 (3H, s, Me).

4.1.4. Methyl 1-diphenylmethyleneamino-2,4-dihydroxy-3-*p*-toluoyl-2,5-dihydro-5-oxo-1*H*-pyrrole-2-carboxylate (3b). This compound was prepared according to above described method for **3a**. Purification crude precipitate from chloroform–hexane (1:1) to give compound **3b** (0.31 g, 25%) as a light yellow crystals, mp 164–166 °C; [Found: C, 68.98; H, 4.65; N, 6.00. $C_{27}H_{22}N_2O_6$ requires C, 68.93; H, 4.71; N, 5.95%]; ν_{max} 3395, 3150 (OH); 1760 (O–C=O, C^2=O); 1620 (C^4–C=O); δ_H (300 MHz, DMSO-d_6) 7.22–7.81 (15H, m, 2Ph+C_6H_4+C^5–O*H*); 3.87 (3H, s, OMe); 2.42 (3H, s, Me).

4.1.5. Dimethyl 2,8-dipivaloyl-5,5,11,11-tetraphenyl-1,5,7,11-tetrahydro-3,9-dioxo-1*H*,7*H*-dipyrazolo[1,2-*a*;1′,2′-*d*][1,2,4,5]tetrazine-1,7-dicarboxylate (4a). A solution of **2a** (1.00 g, 24 mmol) in dry *p*-xylene (6 mL) was held at 138–140 °C for 0.5 h and then cooled. The solid was isolated by filtration and then recrystallized from acetone to give title compound **4a** (0.75 g, 80%) as a colourless crystals, mp 223–224 °C; [Found: C, 70.93; H, 5.51; N, 7.22. $C_{46}H_{44}N_4O_8$ requires C, 70.75; H, 5.68; N, 7.17%]; ν_{max} 1760 (O–C=O); 1730, 1700 (N–$C^{1(7)}$=O); 1670 ($C^{2(8)}$–C=O); δ_H (400 MHz, DMSO-d_6) 7.10–7.54 (20H, m, 4Ph); 3.13 (6H, s, 2OMe); 1.07 (18H, s, 2Me_3C); δ_C (100.6 MHz, DMSO-d_6) 203.7, 163.2, 160.5, 155.3, 130.6, 129.7, 126.6, 120.6, 114.7, 88.1, 56.8, 44.5, 26.7; MS (*m*/*z*, %): 390 ($M/2^+$, 20), 333 ($M/2^+-Me_3C$, 100).

4.1.6. Methyl 4-pivaloyl-2,5-dihydro-1*H*-pyrazole-3-carboxylate (5a). The residue solution after synthesis compound **4a** was allowed to contact with air moisture for 0.5 h. The precipitate was filtered off and recrystallized from toluene to give the title compound **5a** (0.08 g, 15%) as a colourless solid, mp 201–203 °C; [Found: C, 53.14; H, 6.18; N, 12.40. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38%]; ν_{max} 3250 (NH); 1760 (O–C=O); 1720 (N–C=O); 1670 (C^4–C=O); δ_H (400 MHz, DMSO-d_6) 13.52 (1H, br s, N*H*); 10.15 (1H, br s, N*H*); 3.81 (3H, s, OMe); 1.20 (9H, s, Me_3C); δ_C (100.6 MHz, DMSO-d_6) 203.9, 163.5, 158.8, 157.2, 113.9, 51.6, 44.9, 26.6.

4.1.7. Dimethyl 5,5,11,11-tetraphenyl-2,8-ditoluoyl-1,5,7,11-tetrahydro-3,9-dioxo-1*H*,7*H*-dipyrazolo[1,2-*a*;1′,2′-*d*]-[1,2,4,5]tetrazin-1,7-dicarboxylate (4b). This compound was prepared from **2b** (1.00 g, 22 mmol) according to above described method for **4a**. Purification crude precipitate from ether to give compound **4b** (0.57 g, 67%) as colourless crystals, mp 207–209 °C. [Found: C, 72.93; H, 4.73; N, 6.84. $C_{50}H_{40}N_4O_8$ requires C, 72.80; H, 4.89; N, 6.79%]; ν_{max} 1760 (O–C=O); 1690 (N–$C^{1(7)}$=O); 1650 ($C^{2(8)}$–C=O); 1600 (C=C); δ_H (400 MHz, DMSO-d_6) 7.03–7.74 (28H, m, 4Ph+2C_6H_4); 3.45 (6H, s, 2 OMe); 2.35 (6H, s, 2Me); δ_C (100.6 MHz, DMSO-d_6) 187.8, 160.8, 158.7, 152.3, 141.9, 137.0, 132.1, 129.7, 129.5, 128.4, 127.4, 118.6, 113.3, 86.1, 54.1, 21.1.

4.1.8. Methyl 4-*p*-toluoyl-2,5-dihydro-1*H*-pyrazole-3-carboxylate (5b). This compound was prepared according to above described method for **5a**. Purification crude precipitate from toluene to give compound **5b** (0.14 g, 25%) as a colourless solid, mp 210–212 °C; [Found: C, 59.89; H, 4.63; N, 10.80. $C_{13}H_{12}N_2O_4$ requires C, 60.00; H, 4.65; N, 10.76%]; ν_{max} 3250 (NH); 1770 (O–C=O); 1670 (N–C=O); 1620 (C^4–C=O); δ_H (300 MHz, DMSO-d_6) 13.20 (1H, br s, N*H*); 10.35 (1H, br s, N*H*); 7.60 (2H, d, *J*=8.0 Hz, C_6H_4); 7.26 (2H, d, *J*=8.0 Hz, C_6H_4); 3.60 (3H, s, OMe); 2.40 (3H, s, Me).

Acknowledgements

This work was carried out with the financial support of the Russian Basic Research Fund (project No 04-03-33024). We thank Dr. Elena V. Shklyaeva for helpful discussions and Olga G. Stryapunina for experimental contributions.

References and notes

1. (a) Yrango, G. I.; Elguero, J.; Flammang, R.; Wentrup, C. *Eur. J. Org. Chem.* **2001**, 2209–2220. (b) Tidwell, T. T. *Ketene*; Wiley: New York, 1995; pp 254–259. (c) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219–1248.
2. (a) Briehl, H.; Lucosch, A.; Wentrup, C. *J. Org. Chem.* **1984**, *49*, 2772–2779. (b) Aliev, Z. G.; Maslivets, A. N.; Golovnina, O. V.; Krasnykh, O. P.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **2001**, *7*, 1255–1257, *Russ. Chem. Bull., Int. Ed.* **2000**, *7*, 1317–1319. (c) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Andreichikov, Yu. S.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **1997**, *3*, 563–565, *Russ. Chem. Bull., Int. Ed.* **1997**, *3*, 543–545. (d) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Andreichikov, Yu. S.; Stepanov, O. S.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **1999**, *11*, 2150–2153, *Russ. Chem. Bull., Int. Ed.* **1999**, *11*, 2127–2130. (e) Maslivets, A. N.; Krasnykh, O. P.; Smirnova, L. I.; Andreichikov, Yu. S. *Zh. Org. Khim.* **1989**, *5*, 1045–1053. (f) Beccalli, E. M.; Marchesini, A. *Tetrahedron* **1989**, *23*, 7485–7500. (g) Arya, F.; Bouquant, J.; Chuche, J. *Tetrahedron Lett.* **1986**, *17*, 1913–1914. (h) Alajarin, M.; Sanchez-Andrada, P.; Cossio, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 8470–8477.
3. (a) Maslivets, A. N.; Bozdyreva, K. S.; Smirnova, L. I.; Tolmacheva, I. A.; Mashevskaya, I. V. *Khim. Geterotsikl. Soedn.* **2002**, *4*, 563–565, *Chem. Heterocycl. Compd.* (Engl.Transl.) **2002**, *4*, 498–499. (b) Kuhn, A.; Plüg, C.; Wentrup, C. *J. Am. Chem. Soc.* **2000**, *122*, 1945–1948. (c) Maslivets, A. N.; Golovnina, O. V.; Krasnykh, O. P.; Aliev, Z. G. *Khim. Geterotsikl. Soedn.* **2000**, *5*, 699–700. (d) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Andreichikov, Yu. S.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **1999**, *11*, 2154–2158, *Russ. Chem. Bull., Int. Ed.* **1999**, *11*, 2131–2135.
4. (a) Reinecke, M. G.; Brown, E. S. *J. Org. Chem.* **1988**, *53*, 208–210. (b) Paterson, T.; Smalley, R.; Suschitzky, H. *Synthesis* **1975**, *3*, 187–189.
5. (a) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Andreichikov, Yu. S.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **1999**, *3*, 614–617, *Russ. Chem. Bull., Int. Ed.* **1999**, *3*, 608–611. (b) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Andreichikov, Yu. S.; Atovmyan, L. O. *Izv. Akad. Nauk. Ser. Khim.* **1993**, *9*, 1633–1636, *Russ. Chem. Bull., Int. Ed.* **1993**, *9*, 1569–1572.
6. Konyukhova, N. A.; Krasnykh, O. P.; Maslivets, A. N. *Khim.*

Geterotsikl. Soedn. **2001**, *5*, 700–702, *Chem. Heterocycl. Compd.* (Engl.Transl.) *2001*, *5*, 647–648.
7. (a) Kollenz, G.; Theuer, R.; Ott, W. *Heterocycles* **1988**, *27*, 479–494. (b) Kollenz, G. *Monatsh. Chem.* **1978**, *109*, 249–257. (c) Kollenz, G. *Monatsh. Chem.* **1972**, *103*, 947–950.
8. Solodnikov, S. Yu.; Miles, G. D.; Krasnykh, O. P.; Gun, E. A.; Naser, S. A.; Konyukhova, N. A.; Denisov, V. E.; Shilov, Yu. I. *Khim-Farm. Zh.* **2002**, *5*, 10–11, *Pharm. Chem. J.* (Engl. Transl.) **2002**, *36*, 229†231.
9. Konyukhova, N. A.; Krasnykh, O. P.; Maslivets, A. N. *Khim. Geterotsikl. Soedn.* **2001**, *6*, 842–843, *Chem. Heterocycl. Compd.* (Engl.Transl.) **2001**, *6*, 777–778.
10. Aliev, Z. G.; Krasnykh, O. P.; Konyukhova, N. A.; Maslivets, A. N.; Atovmyan, L. O. *Zh. Structurnoi Khim.* **2001**, *5*, 1008–1015, *J. Struct. Chem.* (Engl. Transl.) **2001**, *5*, 848–853.
11. Allen, F. H.; Kennard, O.; Watson, D.; Brammer, L.; Orpen, G.; Taylor, R. *J. Chem. Soc. Perkin Trans. II* **1987**, *12*, 1–19.
12. (a) Seidel, I.; Leibnitz, P.; Kutschabcky, L.; Dorn, H.; Kreher, T. Z. *Z. Chem.* **1990**, *30*, 407–408. (b) Seidel, I.; Leibnitz, P.; Kutschabcky, L.; Dorn, H.; Kreher, T. *Z. Chem.* **1990**, *30*, 408–409. (c) Dorn, H.; Kreher, T. *Tetrahedron Lett.* **1988**, *29*, 2939–2942. (d) Dorn, H.; Ozegowski, R. *J. Prakt. Chem.* **1977**, *319*, 177–187.
13. (a) Turk, C.; Svete, J.; Stanovnik, B.; Golic, L.; Golobic, A.; Selic, L. *Org. Lett.* **2000**, *2*, 423–424. (b) Turk, C.; Svete, J.; Stanovnik, B.; Golic, L.; Golobic-Grdadolnik, A. *Helv. Chim. Acta* **2001**, *84*, 146–156.
14. Chuang, T-H.; Sharpless, K. B. *Helv. Chim. Acta* **2001**, *83*, 146–156.
15. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Gualardi, A. *J. Appl. Cryst.* **1993**, *26*, 343–350.
16. Sheldrick, G. M. SHELXL-97; University of Göttingen, Germany, 1998.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5325–5330
Tetrahedron

Reactions of some *ortho* and *para* halogenated aromatic nitriles with ethylenediamine: selective synthesis of imidazolines☆

Louis J. Crane, Maria Anastassiadou, Jean-Luc Stigliani, Geneviève Baziard-Mouysset* and Marc Payard

Laboratoire de Chimie Pharmaceutique, Université Paul Sabatier, Faculté des Sciences Pharmaceutiques, 35, chemin des Maraîchers, 31062 Toulouse cedex 04, France

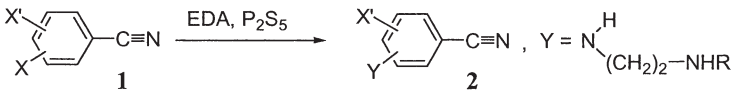
Received 18 December 2003; revised 21 April 2004; accepted 29 April 2004

Abstract—The reaction of ethylenediamine (EDA) with *ortho* and/or *para* halogenated benzonitriles did not lead to the imidazolines expected: a competitive aromatic nucleophilic substitution (S_NAr) was observed instead. The selective synthesis of these imidazolines was performed by nucleophilic addition of EDA to thiobenzamide derivatives. The difference in reactivity between the nitrile and thioamide derivatives was estimated by a frontier orbital approach at the RHF/6-31G** level which predicted a greater reactivity of substituted thiobenzamides towards the nucleophilic addition of EDA.

1. Introduction

Imidazoline derivatives exhibit significant biological and pharmacological activities, including antihypertensive,[1,2] antihyperglycemic,[3–8] antidepressive,[9] antihypercholesterolemic[10] and anti-inflammatory[11] activities. Due to these practical applications, we have expended considerable effort in the preparation of new imidazoline derivatives.

In a previous paper,[12] we synthesized imidazolines by the nucleophilic addition of ethylenediamine (EDA) to the corresponding nitriles in the presence of catalytic amounts of a sulfur reagent: P_2S_5,[13] CS_2[14] or S.[15] The preparation of 3-aromatic halogenated imidazolines was easily accomplished by this method[16] with yields of up to 80%. However, the formation of the imidazoline moiety does not take place with the 2- and/or 4-aromatic halogenated nitriles. The



1 **2**

	X	X'		Y	X'	R
1a	2-F	H	**2a**	2-	H	H
1c	4-F	H	**2c**	4-	H	H
1h	3-F	4-F	**2h**	4-	3-F	H
			2h'[a]	4-	3-F	CH_3CO
1i	3-Cl	4-F	**2i**	4-	3-Cl	H
1j	2-Cl	6-F	**2j**	6-	2-Cl	H
1k	2-Cl	6-Cl	**2k**	6-	2-Cl	H

[a] **2h** was converted to **2h'** by the action of Ac_2O

Scheme 1. Synthesis of 2-aminoethylamino-benzonitriles **2**.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.04.075

Keywords: Aromatic nucleophilic substitution; Nucleophilic addition; Phenylimidazolines; Benzonitriles; Thiobenzamides.
* Corresponding author. Tel.: +33-5-62-25-68-54; fax: +33-5-62-25-68-81; e-mail address: chimphar@cict.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.075

reaction observed is an aromatic nucleophilic substitution (S_NAr): the nitrile is electron-withdrawing thus favoring the displacement of the halogen[17] by EDA and resulting in a S_NAr.[18,19]

The aim of the present study was to selectively synthesize *ortho* and *para* halogenated aromatic imidazolines from the corresponding nitriles by avoiding a S_NAr and favoring nucleophilic addition of EDA.

2. Results and discussion

The addition of EDA in stoichiometric or excess amounts, to different benzonitriles, mono or disubstituted by fluorine and/or chlorine atoms (**1a**, **1c**, **1h**–**1k**), with or without catalytic amounts of P_2S_5 (Scheme 1), at 50 °C or under reflux, gave the 2-aminoethylamino-benzonitriles **2** (Table 1) resulting from the S_NAr of the EDA and not the expected imidazolines. Compound **2h** was not amenable to direct purification and identification because it was hygroscopic and sensitive to carbonation. In order to establish its structure, the free-amino group was acylated using acetic anhydride to give compound **2h′**.

Table 1. Physical data of compounds **2**

	Yield[a] (%)	Mp[b] (°C)	Molecular formula[c] (MW)
2a	90	97	$C_9H_{11}N_3$ (161)
2c	99	80	$C_9H_{11}N_3$ (161)
2h	99	112	$C_9H_{10}FN_3$ (179)
2h′	82	144	$C_{11}H_{12}FN_3O$ (221)
2i	41	109	$C_9H_{10}ClN_3$ (195,5)
2j	40	70	$C_9H_{10}ClN_3$ (195,5)
2k	38	70	$C_9H_{10}ClN_3$ (195,5)

[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

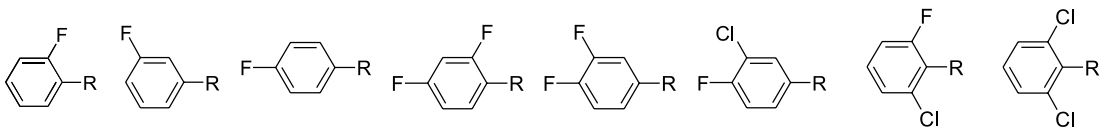
Only the displacement of the fluorine by EDA occurs in the disubstituted compounds **1i** and **1j**. Therefore, fluorine is the best leaving group among the halogens in S_NAr.

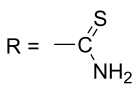
Aromatic nitriles are not a very reactive group because of resonance that stabilizes the reactant molecule. This explains why the number of aromatic halogenated imidazolines obtained by the addition of EDA to benzonitrile derivatives still remains limited. However, these compounds may be obtained by addition of EDA to the corresponding esters in the presence of trimethylaluminium[12] with moderate yields.

To avoid S_NAr of EDA on the aromatic ring, we decided to activate the cyano group by transforming it into a thioamide group. It is noteworthy that regardless of the choice of sulfur reagent used, the reaction occurring was always the same. All the current catalysts (P_2S_5, CS_2, S) generated H_2S in situ and led, in the presence of a nitrile, to the formation of a thioamide intermediate, a principal functional group in imidazoline preparation.[20,21]

The variability of reactivity between the nitrile and the

Table 2. Calculated properties of selected structures **1** and **3** optimized at the RHF/6-31G** theory level



R=–C≡N	**1a**	**1b**	**1c**	**1g**	**1h**	**1i**	**1j**	**1k**
LUMO (eV)	2.19	2.11	2.46	2.21	2.11	2.11	1.83	1.75
Atomic charges								
C_{ar}[a]	0.49	0.45	0.47	0.49 (*p*) 0.51 (*o*)	0.41 (*p*) 0.39 (*m*)	0.52 (*p*) −0.26 (*m*)	0.51 (F) −0.13 (Cl)	−0.14 −0.14
C_{CN}[b]	0.3	0.272	0.269	0.3	0.272	0.27	0.31	0.29
LUMO coefficients								
C_{ar}[a]	0.17	0.10	0.38	0.37 (*p*) 0.14 (*o*)	0.36 (*p*) 0.06 (*m*)	0.38 (*p*) 0.11 (*m*)	0.16 (F) 0.32 (Cl)	0.25 0.25
C_{CN}[b]	0.13	0.15	0.15	0.13	0.14	0.14	0.12	0.12
R = 	**3a**	**3b**	**3c**	**3g**	**3h**	**3i**	**3j**	**3k**
LUMO (eV)	1.71	1.92	2.05	1.79	1.80	1.81	2.71	2.76
Atomic charges								
C_{ar}[a]	0.47	0.45	0.46	0.49 (*p*) 0.49 (*o*)	0.40 (*p*) 0.39 (*m*)	0.51 (*p*) −0.26 (*m*)	0.50 (F) −0.15 (Cl)	−0.15 −0.15
C_{thio}[b]	0.259	0.213	0.22	0.25	0.218	0.216	0.213	0.19
LUMO coefficients								
C_{ar}[a]	0.21	0.09	0.27	0.3 (*p*) 0.21 (*o*)	0.27 (*p*) 0.02 (*m*)	0.28 (*p*) 0.1 (*m*)	0.08 (F) 0.29 (Cl)	0.23 0.22
C_{thio}[b]	0.34	0.33	0.37	0.35	0.34	0.34	0.27[c]	0.04
Torsion[d] (°)	2	38	34	19	35	36	83	89.5

[a] Mulliken atomic charges or LUMO coefficients of the halogen-bonded carbons.
[b] Mulliken atomic charges or LUMO coefficients of the nitrile or thioamide carbon atoms.
[c] Pointed perpendicular to the aromatic plane.
[d] Torsion angle defined by the aromatic and thioamide planes.

thioamide functions could actually be estimated from the empirical Hammet σ constants[22] which reflect the total electronic effects of compounds containing substituted phenyl groups. The average substituent constant σ_p is 0.62 for the nitrile group and 0.30 for the thioamide one. The nitrile function exhibits a stronger electron-withdrawing effect than the thioamide one. Thus S_NAr is facilitated by the nitrile function as it decreases the electronic density on the aromatic ring.

However, the Hammet equation is not applicable to *ortho* substituents and also some of the compounds studied were disubstituted. Because our aim was to include the effect of all substituents on the aromatic ring, we considered the reactivity of nitriles and thioamides using molecular-orbital theory. In the present case (nucleophilic attack of EDA) the frontier orbital treatment was based upon the interaction of the HOMO of EDA with LUMO of nitriles or thioamides. As the nucleophile was always the same (EDA), the lower the energy of the LUMO of aromatic derivatives, the greater the propensity to give a specific reaction.

2.1. Computational methods

Ab initio calculations were achieved using PC GAMESS version 6.2[23] of the GAMESS (US) quantum chemistry package.[24] The geometries of selected compounds were fully optimized at the RHF/6-31G** level[25] utilizing gradient techniques and default thresholds for convergence.

The energies of the LUMO of compounds **1** (nitriles) and **3** (thioamides) are shown in Table 2. This table also gives the molecular orbital coefficients (LU_{π^*}) and the charges of the carbons bonded to halogens, as well as those of the carbon of the function nitrile or thioamide.

For thioamides **3**, the torsion angles defined by the phenyl and thioamide planes are also included.

The ab initio calculations show that:

1. The thioamide group adopts an angle of approximately 35° with the aromatic ring or is nearly coplanar in the case of **3a** and **3g**; this can be explained by a favorable interaction between the *ortho* fluorine and the NH_2 group. On the other hand, the thioamide and the aromatic moieties are perpendiculars in **3j** and **3k**; this torsion may be explained by a strong steric hindrance between the bulky thioamide sulfur atom and the *ortho* halogens, which makes it impossible for the molecule to remain coplanar. It can be noticed that we observed the same phenomenon with **3a** and **3g** compounds: when calculations were performed with sulfur and *o*-fluorine atoms pointed on the same side, in both cases the resulting conformation exhibited a dihedral angle value of 62° and was energetically unfavorable compared with the latter described in Table 2.
2. The LUMO energy of thioamides **3a**–**3i** is lower than that of the nitriles **1**. The energy difference between the two series varies between 0.41 and 0.48 eV when the ring is *ortho* or *para* substituted (**a**, **c**, **g**) and between 0.19 and 0.31 eV when *meta* substituted (**b**, **h**, **i**). The **3j** and **3k** derivatives remain exceptions, as their orbital energy is respectively 0.88 and 1 eV greater than that of nitriles **1j** and **1k**. This fact reflects a loss of resonance between the aromatic and thioamide planes. These results suggest that thioamides **3a**–**3i** have a high potential to be attacked by EDA even when **3j** and **3k**, on the contrary, should not exhibit much reactivity towards nucleophilic addition.
3. For the benzonitrile derivatives, with the exception of the *meta* positions, the LUMO orbital coefficients of the halogen-bonded carbons are greater than the coefficient of the nitrile carbon. This is in agreement with the experimental data: with the exception of the *meta* derivative **1b** which gave the expected imidazoline, all the other nitriles reacted with EDA via a S_NAr mechanism. However, one can observe that for the disubstituted compound **1j**, the highest orbital coefficient is on the C_2–Cl carbon (0.32), and not on the C_6–F one (0.16). This would suggest a stronger reactivity at the C_2-position, which is not actually observed; the S_NAr occurs at the C_6-position. Both the small size of the fluorine atom compared with chlorine, and the strong positive charge of the C_6 carbon direct the reaction.
4. On the contrary, for the thioamide series, the orbital coefficient of the carbon on the thioamide function is highest than those found on the aromatic carbons. The compound **3j** is still an exception insofar as the C_2 and the thioamide carbon coefficients are equivalent (0.29 vs. 0.27). As for **3k**, the thioamide coefficient is insignificant. One might expect that the condensation of EDA on thiobenzamides would yield more easily to the related imidazolines.

However, an examination of the atomic charges does not enable us to differentiate a priori the reactivity of compounds **1** and **3**.

2.2. Imidazoline synthesis from thioamides

In an attempt to validate the theoretical results, we synthesized a series of thiobenzamides which were mono (**3a**–**3f**) or disubstituted (**3g**–**3k**) by fluorine and/or chlorine atoms (Table 3) by reaction of the related nitriles **1** with triethylamine (TEA) and an aqueous solution of ammonium sulfide[26,27] in pyridine. The choice of ammonium sulfide as an in situ H_2S generator was determined by the fact that

Table 3. Preparation of thioamides **3** from nitriles

	X	X′	Yield[a] (%)	Mp[b] (Mp lit.) (°C)	Molecular formula[c] (MW)
3a	2-F	H	65	83 (83)[33]	C_7H_6FNS (155)
3b	3-F	H	95	110 (110–111)[34]	C_7H_6FNS (155)
3c	4-F	H	85	148 (145–147)[35]	C_7H_6FNS (155)
3d	2-Cl	H	73	68 (65)[28]	C_7H_6ClNS (171,5)
3e	3-Cl	H	83	115 (121–122)[34]	C_7H_6ClNS (171,5)
3f	4-Cl	H	83	130 (130)[36]	C_7H_6ClNS (171,5)
3g	2-F	4-F	85	133	$C_7H_5F_2NS$ (173)
3h	3-F	4-F	55	105	$C_7H_5F_2NS$ (173)
3i	3-Cl	4-F	76	130	C_7H_5ClFNS (189,5)
3j	2-Cl	6-F	75	164 (161–162)[30]	C_7H_5ClFNS (189,5)
3k	2-Cl	6-Cl	73	152 (152)[37]	$C_7H_5Cl_2NS$ (206)

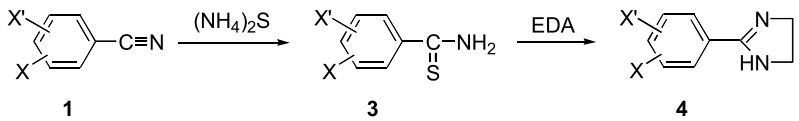
[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

Table 4. Preparation of imidazolines **4** from thioamides

	X	X′	Yield[a] (%)	Mp[b] (Mp lit.) (°C)	Molecular formula[c] (MW)
4a	2-F	H	65	83 (83)[12]	$C_9H_9FN_2$ (164)
4b	3-F	H	99	92 (92)[38]	$C_9H_9FN_2$ (164)
4c	4-F	H	72	153 (152–153)[39]	$C_9H_9FN_2$ (164)
4d	2-Cl	H	76	69 (69–70)[40]	$C_9H_9ClN_2$ (180,5)
4e	3-Cl	H	99	138 (136–137)[40]	$C_9H_9ClN_2$ (180,5)
4f	4-Cl	H	85	188 (186–187)[41]	$C_9H_9ClN_2$ (180,5)
4g	2-F	4-F	40	96	$C_9H_8F_2N_2$ (182)
4h	3-F	4-F	45	155	$C_9H_8F_2N_2$ (182)
4i	3-Cl	4-F	60	160 (160)[12]	$C_9H_8ClFN_2$ (198,5)
4j	2-Cl	6-F	–	–	$C_9H_8ClFN_2$ (198,5)
4k	2-Cl	6-Cl	–	–	$C_9H_8Cl_2N_2$ (215)

[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

hydrogen sulfide H_2S[28–31] is a particularly toxic agent.[32] The thiobenzamides were obtained with high yields, whether the aromatic nitrile was mono or disubstituted. The imidazolines **4** (Table 4) were synthesized by treating the thiobenzamides with a slight excess of EDA. The mixture was stirred under reflux for 3 days (Scheme 2).



1 **3** **4**

Scheme 2. Synthesis of imidazolines **4**.

All the thioamides, with the exception of the 2,6-disubstituted compounds (**3j** and **3k**), produced the corresponding imidazolines. The lack of nucleophilic addition with compounds **3j** and **3k** could be explained by the results of the theoretical study; particularly the high energy level of LUMO's and the perpendicular torsion of the thioamide group with regard to the aromatic moiety, associated with the strong steric hindrance of the chlorine atoms would prevent the addition to proceed.

3. Concluding remarks

The experimental results confirmed our analysis. The expected imidazolines were obtained with yields higher than 90%. The two-step protocol used thus favored the nucleophilic addition compared with nucleophilic substitution and produced high yields of the expected imidazolines.

4. Experimental

4.1. General

Melting points were determined by differential scanning calorimetry using a Shimadzu DSC-50 calorimeter. Infrared spectra were recorded on a Perkin–Elmer 983G spectrophotometer. All the imidazoline compounds gave the same IR absorption bands at approximately 3000 cm^{-1} (ν CH, CH_2, CH_3) and 3150 cm^{-1} (ν NH). ^1H NMR spectra were determined in the indicated solvent with a 250 MHz spectrometer, and peak positions given as s (singlet), d (doublet), t (triplet), q (quadruplet) or m (multiplet). The microanalyses were performed in the Microanalytical Laboratory of the Ecole Nationale Superieure de Chimie de Toulouse in Toulouse and the results obtained are within ±0.4% of the theoretical values. Reactions were monitored by thin-layer chromatography (TLC) and product mixtures were purified by column chromatography using silica gel 60 F-254, 70–200 mesh.

4.1.1. 2-(2-Aminoethylamino)-benzonitrile (2a).[20] A stirred mixture of 2-fluorobenzonitrile (2.64 g, 0.02 mol), EDA, in excess or in stoichiometric quantity, freshly distilled on KOH, and 0.15 g of P_2S_5 was heated at 120 °C in an oil bath for 4 h. The reaction mixture was then cooled, poured into cold water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude solid was collected and purified by recrystallization from cyclohexane. ^1H NMR ($CDCl_3$) δ: 1.76 (s, 2H, NH_2), 2.85 (m, 2H, CH_2NH_2), 3.14 (m, 2H, $CH_2CH_2NH_2$), 5.02 (s, 1H, NH), 6.60–7.26 (m, 4H, ArH). IR (KBr, cm^{-1}) 2250 (νCN), 2958 (νCH_2), 3076 (νCH), 3203 and 3400 (νNH). Elemental analysis calculated for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07; found: C, 67.22; H, 6.69; N, 26.17.

Compounds **2c**, **2h**, **2i**, **2j** and **2k** were prepared from the appropriate nitriles in the same way.

4.1.2. 4-(2-Aminoethylamino)-benzonitrile (2c). ^1H NMR ($CDCl_3$) δ: 1.31 (s, 2H, NH_2), 2.93 (m, 2H, CH_2NH_2), 3.14 (m, 2H, $CH_2CH_2NH_2$), 4.76 (s, 1H, NH), 6.53–7.36 (m, 4H, ArH) IR (KBr, cm^{-1}) 2252 (νCN), 2943 (νCH_2), 3084 (νCH), 3205 and 3407 (νNH). Elemental analysis calculated for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07; found: C, 67.15; H, 6.76; N, 25.89.

4.1.3. 3-Fluoro-4-(2-aminoethylamino)-benzonitrile (2h). The crude product obtained was acylated to produce compound **2h′** as described below.

4.1.4. 3-Chloro-4-(2-aminoethylamino)-benzonitrile (2i). ^1H NMR ($CDCl_3$) δ: 1.38 (s, 2H, NH_2), 3.28 (t, 2H, CH_2NH_2), 3.01 (t, 2H, $CH_2CH_2NH_2$), 4.95 (s, 1H, NH), 6.75–7.72 (m, 3H, ArH) IR (KBr, cm^{-1}) 2250 (νCN), 2901 (νCH_2), 3079 (νCH), 3205 and 3401 (νNH). Elemental analysis calculated for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; found: C, 55.19; H, 5.21; N, 21.32.

4.1.5. 3-Chloro-6-(2-aminoethylamino)-benzonitrile (2j). ^1H NMR ($CDCl_3$) δ: 2.81 (t, 2H, CH_2NH_2), 3.10 (s, 2H, NH_2), 3.24 (m, 2H, $CH_2CH_2NH_2$), 6.45 (t, 1H, NH), 6.85–7.46 (m, 3H, ArH) IR (KBr, cm^{-1}) 2253 (νCN), 2933 (νCH_2), 3074 (νCH), 3203 and 3405 (νNH).). Elemental analysis calculated for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; found: C, 55.32; H, 5.24; N, 21.40 for **2j**; C, 55.12; H, 5.17; N, 21.52 for **2k**.

4.1.6. 3-Fluoro-4-(2-acetamidoethylamino)-benzonitrile (2h′). 3-Fluoro-4-(2-aminoethylamino)-benzonitrile **2h** (3.22 g, 0.02 mol) in acetic anhydride (25 mL) was heated under reflux with stirring in an oil bath for 5 h. The reaction mixture was then cooled, and the anhydride was removed under reduced pressure. The crude product was washed with water, collected by filtration and purified on silica gel column using as eluent AcOEt/CH_2Cl_2 (1:1). ^{1}H NMR (DMSO-d_6) δ: 1.90 (s, 3H, CH_3), 3.31–3.48 (m, 4H, $2CH_2$), 6.73 (s, 1H, PhNH), 6.92–7.67 (m, 3H, ArH), 8.15 (s, 1H, CONH). IR (KBr, cm^{-1}) 1635 (νCO), 2247 (νCN), 2975 (νCH_2CH_3), 3081 (νCH), 3251 and 3395 (νNH). Elemental analysis calculated for $C_{11}H_{12}FN_3O$: C, 59.72; H, 5.47; N, 18.99; found: C, 59.53; H, 5.54; N, 19.06.

4.2. General procedure for thioamides 3

An appropriate aromatic halogenated nitrile **1** (about 0.03 mol) was dissolved in pyridine (20 mL), then triethylamine (0.033 mol, 5 mL) and ammonium sulfide 20 % wt solution in water (0.033 mol, 10 mL) were added into the mixture at 50 °C for 3–6 h. After cooling, the mixture was diluted with cold water (50 mL). The precipitated solid was filtered off, washed with cold water and crystallized from cyclohexane or purified by column chromatography with dichloromethane as eluent.

NMR data of compounds **3a**,[33] **3b**,[34] **3c**,[35] **3d**,[28] **3e**,[34] **3f**,[36] **3j**[30] and **3k**[37] are in agreement with literature data.

4.2.1. 2,4-Difluorothiobenzamide (3g). ^{1}H NMR ($CDCl_3$) δ: 6.86 (m, 1H, H_5), 6.99 (m, 1H, H_3), 7.76 and 8.04 (2s broad, 2H, NH_2), 8.46 (m, 1H, H_6) IR (KBr, cm^{-1}): 3366, 3292 (νNH_2), 3167 (νCH), 1630, 1602 (νC=C), 1283 (νC=S). Elemental analysis calculated for $C_7H_5F_2NS$: C, 48.55; H, 2.91; N, 8.09; S, 18.51; found: C, 48.52; H, 3.09; N, 7.92; S, 18.23

4.2.2. 3,4-Difluorothiobenzamide (3h). ^{1}H NMR ($CDCl_3$) δ: 7.11 (s broad, 2H, NH_2), 7.19 (m, 1H, H_5), 7.62 (m, 1H, H_6), 7.81 (m, 1H, H_2) IR (KBr, cm^{-1}): 3402, 3270 (νNH_2), 3155 (νCH), 1627, 1600 (νC=C), 1261 (νC=S). Elemental analysis calculated for $C_7H_5F_2NS$: C, 48.55; H, 2.91; N, 8.09; S, 18.51; found: C, 48.36; H, 2.85; N, 8.17; S, 18.62.

4.2.3. 3-Chloro-4-fluoro-thiobenzamide (3i). ^{1}H NMR ($CDCl_3$) δ: 7.19 (m, 1H, H_2), 7.64 (s, 2H, NH_2), 7.78 (m, 1H, H_5), 7.99 (dd, 1H, H_6) IR (KBr, cm^{-1}): 3442, 3206 (νNH_2), 3101, 3129 (νCH), 1618 (νC=C), 1262 (νC=S). Elemental analysis calculated for C_7H_5ClFNS: C, 44.34; H, 2.66; N, 7.39; S, 16.91; found: C, 44.41; H, 2.53; N, 7.21; S, 16.88.

4.3. General procedure for imidazolines 4

A stirred mixture of aromatic halogenated thiobenzamides **3** (0.02 mol) and EDA in stoichiometric quantity, freshly distilled on KOH was heated at 120 °C in an oil bath for several days. The reaction mixture was then cooled, poured into cold water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude free base was collected and purified by recrystallization from cyclohexane or by column chromatography with ethyl acetate/ethanol (1:1) as eluent. All imidazoline compounds present the same IR absorption bands towards 3000 cm^{-1} (νCH, CH_2) and 3150 cm^{-1} (νNH).

NMR data of compounds **4a**[12], **4b**[38], **4c**[39], **4d**[40], **4e**[40], **4f**[41] and **4i**[12] are in agreement with literature data.

4.3.1. 2-(2′,4′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (4g). ^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 4H, CH_2CH_2), 5.03 (s, 1H, NH), 6.89 (m, 2H, H_5, H_6), 8.08 (m, 1H, H_3). Elemental analysis calculated for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38; found: C, 59.28; H, 4.55; N, 15.23.

4.3.2. 2-(3′,4′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (4h). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 5H, CH_2CH_2 and NH), 7.17 (m, 1H, H_5), 7.49 (m, 1H, H_6), 7.61 (m, 1H, H_2). Elemental analysis calculated for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38; found: C, 59.31; H, 4.38; N, 15.52.

Acknowledgements

This work was carried out with the technical support of Mr L. Amielet. The authors thank the Laboratoires Servier for their support and particularly Mr D. H. Caignard and Mr P. Renard.

References and notes

1. Schorderet, M. *In Pharmacologie: Des Concepts Fondamentaux aux Applications Thérapeutiques*; Frison-Roche: Paris, 1992; pp 130–153.
2. (a) Blancafort, P. *Drugs of the Future* **1978**, *3*, p 592. (b) Serradell, M. N.; Castañer, J. *Drugs of the Future* **1986**, *6*, p 470.
3. Wang, X.; Rondu, F.; Lamouri, A.; Dokhan, R.; Marc, S.; Touboul, E.; Pfeiffer, B.; Manechez, D.; Renard, P.; Guardiola-Lemaitre, B.; Godfroid, J.-J.; Ktorza, A.; Penicaud, L. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 82–89.
4. Rondu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. *J. Med. Chem.* **1997**, *40*, 3793–3803.
5. Pele-Tounian, A.; Wang, X.; Rondu, F.; Lamouri, A.; Touboul, E.; Marc, S.; Dokhan, R.; Pfeiffer, B.; Manechez, D.; Renard, P.; Guardiola-Lemaitre, B.; Godfroid, J.-J.; Penicaud, L.; Ktorza, A. *Br. J. Pharmacol.* **1998**, *124*, 1591–1597.
6. Le Bihan, G.; Rondu, F.; Pele-Tounian, A.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1999**, *42*(9), 1587–1603.
7. Crane, L.; Anastassiadou, M.; El Hage, S.; Stigliani, J. L.; Baziard-Mouysset, G.; Payard, M.; Bizot-Espiard, J. G.; Caignard, D. H.; Renard, P., in preparation.
8. Chan, S. *Clin. Sci.* **1993**, *85*, 671–677.
9. Vizi, E. S. *Med. Res. Rev.* **1986**, *6*, 431.
10. Li, H. Y.; Drummond, S.; De Lucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153–11162.

11. Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharmacol.* **1995**, *17*, 597–603.
12. Anastassiadou, M.; Danoun, S.; Crane, L.; Baziard-Mouysset, G.; Payard, M.; Caignard, D.-H.; Rettori, M. C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585–592.
13. Korshin, E. E.; Sabirova, L. I.; Akhadullin, A. G.; Levin, Y. A. *Russian Chem. Bull.* **1994**, *43*, 431–438.
14. Corbel, J. C.; Uriac, P.; Huet, J.; Martin, C. A. E.; Advenier, C. *Eur. J. Med. Chem.* **1995**, *30*, 3–13.
15. Doyle, T. J.; Haseltine, J. *J. Heterocycl. Chem.* **1994**, *31*(6), 1417–1420.
16. Anastassiadou, M. PhD Thesis, University of Toulouse III, France, 1999.
17. (a) March, J. In *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*; 3rd ed.: (i) Aromatic nucleophilic substitution, p 576. (ii) Addition to carbon-hetero multiple bonds, p 780. Wiley: New York, **1985**. (b) Mathieu, J.; Panico, R. In *Mécanismes Réactionnels en Chimie Organique*: (i) Substitution de dérivés aromatiques, p 351. (ii) Additions nucléophiles, p 401. Herman: Paris, **1972**.
18. Camps, P.; Morral, J.; Munoz-Torrero, D. *J. Chem. Res. (s)* **1998**, 144–145.
19. Tidwell, R.; Kilgore Jones, S.; Dieter Geratz, J.; Og, K.; Cory, M.; Hall, J. *J. Med. Chem.* **1990**, *33*(4), 1252–1257.
20. Levesque, G.; Gressier, J. C.; Proust, M. *Synthesis* **1981**, 963–965.
21. Pascal, P. In *Nouveau Traité de Chimie Minérale*: (i) Pentasulfure de Phosphore, Vol. X; p 862; (ii) Soufre. Vol. XIII; p 911. Masson and Cie: Paris, **1960**.
22. (a) Hammet, L. P. *Physical Organic Chemistry*; Mc Graw-Hill: New York, 1940. (b) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191–261.
23. Granovsky, A. A. http://www.classic.chem.msu.su/gran/gamess/index.html.
24. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
25. Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; De Frees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
26. Milczarska, B.; Foks, H.; Janowiec, M.; Zwolska-Kwiek, Z. *Acta Pol. Pharm.* **1992**, *49*(5–6), 41–45.
27. Shiau, C. Y.; Chern, J. W.; Tien, J. H.; Liu, K. C. *J. Heterocycl. Chem.* **1989**, *26*(3), 595–596.
28. Cashman, J. R.; Hanzlik, R. P. *J. Org. Chem.* **1982**, *47*(24), 4645–4650.
29. Cassar, J.; Panossian, S.; Giordano, C. *Synthesis* **1978**, 917–919.
30. Inaci, Y.; Parlar, H. *Chemiker Zeitung* **1980**, *104*(12), 365–367.
31. Yates, J. (Shell Research Ltd) Patent GB 987253 19650324.
32. Beauchamp, Jr., R. O.; Bus, J. S.; Popp, J. A.; Boreiko, C. J.; Andjelkovich, D. A. *Crit. Rev. Tox.* **1984**, *13*(1), 25–97.
33. Bjorklund, M. D.; Coburn, M. D. *J. Heterocycl. Chem.* **1980**, *17*, 819–821.
34. Walczynski, K.; Timmerman, H.; Zuiderveld, O. P.; Zhang, M. Q.; Glinka, R. *Farmaco.* **1999**, *54*, 533–541.
35. Matsumoto, K.; Koh Ho P.; US Patent 4,322,428; **1982**.
36. Pappalardo, G. C.; Gruttadauria, S. *J. Chem. Soc. Perkin Trans. 2* **1974**(12), 1441–1443.
37. Buckingham, J. *Dictionary of Organic Compounds*, 5th ed; Chapman and Hall: London, **1982**, p 1782.
38. Klem, R. E.; Skinner, H. F.; Walba, H.; Isensee, R. W. *J. Heterocycl. Chem.* **1970**, *7*, 403–404.
39. Salgado-Zamora, H.; Campos, E.; Jimenez, R.; Cervantes, H. *Heterocycles* **1998**, *47*, 1043–1049.
40. Piskov, V. B.; et al. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1976**, *12*, 917. *Khim. Geterotsikl. Soedin.* **1976**, *12*, 1112.
41. Houlihan, W. J.; Boja, J. W.; Parrino, V. A.; Kopajtic, T. A.; Kuhar, *J. Med. Chem.* **1996**, *39*, 4935–4941.

Appendix A

Supporting information

Computed total energies and Cartesian coordinates of optimized structures of series **1** and **3**.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5331–5339
Tetrahedron

Stereocontrolled glycosidations using a heterogeneous solid acid, sulfated zirconia, for the direct syntheses of α- and β-manno- and 2-deoxyglucopyranosides

Kazunobu Toshima,* Hideyuki Nagai,† Ken-ichi Kasumi, Kanako Kawahara and Shuichi Matsumura

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 12 April 2004; revised 27 April 2004; accepted 28 April 2004

Abstract—Novel α- and β-stereocontrolled glycosidations using a heterogeneous solid acid, sulfated zirconia (SO_4/ZrO_2), as an activator have been developed. The glycosidations of manno- and 2-deoxyglucopyranosyl α-fluorides with several alcohols using SO_4/ZrO_2 in MeCN proceeded α-stereoselectively, while those with the same activator in the presence of MS 5A in Et_2O occurred with β-stereoselectivity. Thus, both the α- and β-manno- and 2-deoxyglucopyranosides were effectively obtained by the present glycosidations.

1. Introduction

Glycosubstances including glycoconjugates and oligosaccharides continue to be the central focus of research both in chemistry and biology.[1] Therefore, the development of efficient and stereoselective glycosidation methods has been one of the major concerns in synthetic organic chemistry due to the structural complexity and the biological significance of glycosubstances.[2] Since α- and β-mannopyranosides appear in many naturally occurring bioactive substances such as asparagine-linked glycoproteins and certain antibiotics, the stereocontrolled formation of α- and β-mannopyranosides is of considerable importance.[3] The stereoselective and direct construction of β-mannopyranoside, however, has proved particularly difficult to achieve, because the axial β-hydroxy group at the C2 position and the anomeric effect blocks access to the β-face. On the other hand, deoxy sugars are also present in the glycosidic components of the bioactive substances. Among them, 2-deoxyglycoside is one of the most common and important, and found in many biologically attractive natural products, especially in antitumor antibiotics. However, the direct and stereocontrolled glycosidation of a 2-deoxy sugar, particularly β-stereoselective glycosidation, is also difficult due to the lack of stereodirecting anchimeric assistance from the C2 position and the low stability of the glycosidic bond of a 2-deoxyglycoside linkage under acidic conditions.[4] To overcome these problems, a number of indirect methods have been developed and their high potential demonstrated.[5,6] However, it is clear that a direct method is an ideal procedure in terms of efficiency and practicality.[7,8] In this context, stereocontrolled (not stereoselective) glycosidations using a solid acid as an activator have never been reported.[2] We expected that the use of a solid acid would open a new way in the field of stereocontrolled glycosidation. In this paper, we report the novel stereocontrolled glycosidations of manno- and 2-deoxyglucopyranosyl α-fluorides with several alcohols using a heterogeneous solid acid, sulfated zirconia (SO_4/ZrO_2), for the direct and effective syntheses of both the α- and β-manno- and 2-deoxyglucopyranosides (Fig. 1).[9]

2. Results and discussion

2.1. Stereocontrolled α- and β-mannosidations

In 1981, Paulsen reported the pioneering work on the direct construction of the β-mannopyranoside linkage using α-mannopyranosyl halide and silver silicate.[10] In his study, the heterogeneous silver silicate was found to activate the α-mannopyranosyl halide and prompt a β-face attack of the alcohol via an S_N2 type pathway to exclusively produce β-mannopyranoside. With this result in mind, we chose several heterogeneous solid acids, montmorillonite K-10,[11] Nafion-H[12] and SO_4/ZrO_2,[13] all of which show Brønsted

Keywords: Glycosidation; Sulfated zirconia; Heterogeneous solid acid; Mannopyranoside; 2-Deoxypyranoside.
* Corresponding author. Tel.: +81-45-566-1576; fax: +81-45-566-1576; e-mail address: toshima@applc.keio.ac.jp
† Taken in part from the PhD Thesis of Hideyuki Nagai, Keio University, 2004.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.071

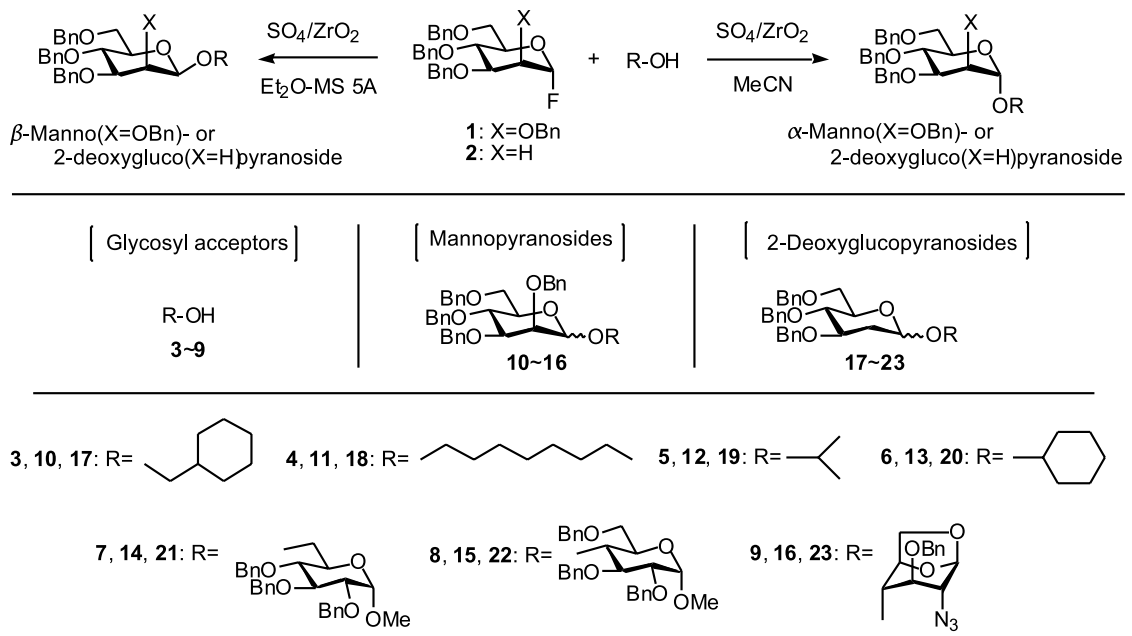
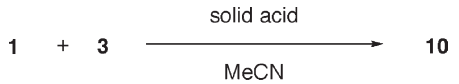


Figure 1. Stereocontrolled manno- and 2-deoxyglucosidations using a heterogeneous solid acid, SO_4/ZrO_2.

acidity and work as protic acids. These solid acids are well known as environmentally benign catalysts in organic synthesis because they could be easily recovered from the reaction mixture by filtration and reused. Neutralization of the reaction mixture is not required after the reaction was completed. Consequently, extraction of the product from the reaction mixture using an organic solvent is not needed in the work-up process. As a glycosyl donor, we selected a glycosyl fluoride. Since the proton is a hard acid and fluoride is a hard base by the HASAB rule, we expected that these solid acids would be effective activators of glycosyl fluoride.[14] Therefore, we first examined the glycosidations of the totally benzylated α-mannopyranosyl fluoride **1**[15] and cyclohexylmethanol (**3**) using these solid acids. These results are summarized in Table 1. It was found that these glycosidations in MeCN at 25 °C for 15 h smoothly proceeded to afford the mannopyranoside **10** in high yields. These results clearly indicated, for the first time, that a glycosyl fluoride was effectively activated by a solid acid. Furthermore, SO_4/ZrO_2 was shown to be superior to the others with respect to both chemical yield and α-stereoselectivity. These results showed that the heterogeneous solid acid, SO_4/ZrO_2, was very effective for the glycosidation of the mannopyranosyl fluoride **1**. Interestingly, the observed α-stereoselectivity was in sharp contrast to the β-stereoselectivity based on Paulsen's observation.[10] Our attention next turned to the solvent effect on this novel glycosidation. Thus, we tested the glycosidations of **1** and **3** using SO_4/ZrO_2 in various solvents such as MeCN, CH_2Cl_2, PhMe, THF and Et_2O. From the results shown in Table 2, MeCN was found to be the best solvent to selectively obtain the α-mannopyranoside **10**α (entries 1–5 in Table 2), and the use of 5 wt% the present activator was sufficient to perform this reaction at 40 °C with quite satisfactory chemical yield and α-stereoselectivity (entry 6 in Table 2). Moreover, interestingly, the stereoselectivity of the glycosidation was dramatically changed by the solvent, and a predominant β-stereoselectivity was observed when Et_2O was used as the solvent (entry 5 in Table 2). Furthermore, it was found that the chemical yield and the β-stereoselectivity were slightly improved as the quantity of SO_4/ZrO_2 increased (entry 7 in Table 2). Finally, we found that the use of molecular sieves 5A (MS 5A) as an additive in the

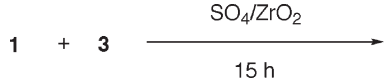
Table 1. Glycosidations of **1** and **3** by several solid acids in MeCN[a]



Entry	Solid acid	Wt% of solid acid	Yield (%)[b]	α/β Ratio[c]
1	Montmorillonite K-10	20	89	76/24
2	Nafion-H	20	92	89/11
3	SO_4/ZrO_2	20	93	91/9

[a] All reactions were carried out by use of 2.0 equiv. of **3** to **1**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

Table 2. Glycosidations of **1** and **3** by SO_4/ZrO_2 under several conditions[a]

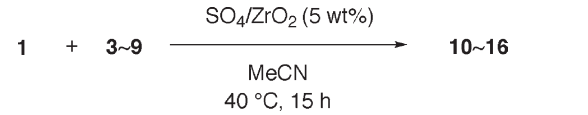


Entry	Solvent	Additive	Wt% of solid acid	Temp. (°C)	Yield (%)[b]	α/β Ratio[c]
1	MeCN	None	20	25	93	91/9
2	CH_2Cl_2	None	20	25	74	69/31
3	PhH	None	20	25	7	51/49
4	THF	None	20	25	2	52/48
5	Et_2O	None	20	25	24	34/66
6	MeCN	None	5	40	99	97/3
7	Et_2O	None	100	25	32	24/76
8	Et_2O	MS 5A	100	25	99	17/83

[a] All reactions were carried out using 2.0 equiv. of **3** to **1**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

glycosidation using Et_2O led to not only a high chemical yield but also to a good stereoselectivity for the β-mannopyranoside **10**β (entry 8 in Table 2). In addition, it was confirmed that MS 5A was shown to be superior to the other MSs such as MS 3A and MS 4A probably due to the acidic property of MS 5A and the basic nature of MS 3A and MS 4A.[14] Thus, the glycosidation of **1** and **3** using 5 wt% SO_4/ZrO_2 in MeCN at 40 °C for 15 h exclusively gave the α-mannopyranoside **10**α, while the glycosidation employing 100 wt% the same activator in the presence of equal amounts of MS 5A in Et_2O at 25 °C for 15 h afforded the β-mannopyranoside **10**β in high yield with good stereoselectivity. To enhance the synthetic utility of this novel and unusual reaction, the glycosidations using other primary and secondary alcohols **4**–**9** including sugar derivatives were next examined. Based on the results summarized in Table 3, all glycosidations of **1** and **4**–**9** using 5 wt% SO_4/ZrO_2 in MeCN at 40 °C for 15 h, as well as that of **3**, effectively proceeded to give the corresponding α-mannopyranosides **11**α–**16**α, respectively, in high yields with high stereoselectivities. On the other hand, the stereoselective syntheses of the corresponding β-mannopyranosides by the present glycosidation are outlined in Table 4. It was found that 200 wt% SO_4/ZrO_2 and 200 wt% MS 5A were required for the glycosidations of the sugar derivative alcohols **7**–**9** (entries 5–7 in Table 4). Although only β-mannopyranoside **15**β was produced in moderate yield with low stereoselectivity due to the low reactivity of **8** (entry 6 in Table 4), other β-mannopyranosides **11**β–**14**β and **16**β were obtained in good to high yields with good stereoselectivities by the glycosidations of **1** with **4**–**7** and **9** under conditions similar to that for **10**β. The anomeric configurations of the obtained mannopyranosides were determined by comparison with authentic samples, which were obtained by the previous procedures,[5,7] with the aid of ^1H NMR analysis.

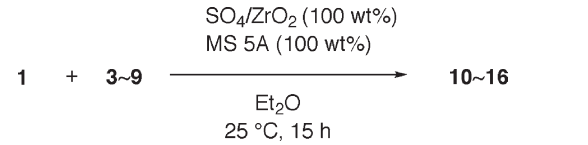
Table 3. α-Stereoselective glycosidations of **1** and several alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**3**	**10**	99	97/3
2	**4**	**11**	97	98/2
3	**5**	**12**	96	98/2
4	**6**	**13**	96	97/3
5	**7**	**14**	88	97/3
6	**8**	**15**	75	98/2
7	**9**	**16**	84	97/3

[a] All reactions were carried out using 2.0 equiv. of the alcohol to **1**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

Table 4. β-Stereoselective glycosidations of **1** and several alcohols[a]



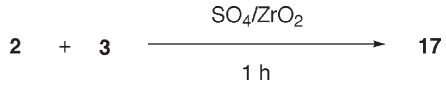
Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**3**	**10**	99	17/83
2	**4**	**11**	96	20/80
3	**5**	**12**	97	19/81
4	**6**	**13**	95	16/84
5[d]	**7**	**14**	84	27/73
6[d]	**8**	**15**	55	56/44
7[d]	**9**	**16**	80	21/79

[a] All reactions were carried out using 2.0 equiv. of the alcohol to **1**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.
[d] This reaction was carried out by use of SO_4/ZrO_2 (200 wt%) and MS 5A (200 wt%) to **1**.

2.2. Stereocontrolled α- and β-2-deoxyglucosidations

Based on the results for the stereocontrolled α- and β-mannosidations, we tried to apply the present glycosidation method to the stereocontrolled synthesis of 2-deoxyglycosides. Thus, the glycosidations of the benzylated 2-deoxy-α-glucopyranosyl fluoride **2**[16] and **3** using SO_4/ZrO_2 with or without MS 5A were examined under several conditions. These results are summarized in Table 5. It was found that the glycosidation of **2** and **3** using 5 wt% of SO_4/ZrO_2 in MeCN at 25 °C for 1 h smoothly proceeded to afford the corresponding 2-deoxyglucopyranoside **17** in high yield with high α-stereoselectivity (entry 2 in Table 5). Both the chemical yield and α-stereoselectivity decreased as the reaction temperature increased (entry 1 in Table 5). Moreover, the stereoselectivity of the glycosidation was dramatically changed by the solvent as observed in the glycosidation of **1**, and the corresponding 2-deoxy-β-glucopyranoside **17**β was predominantly produced when Et_2O was used as the solvent. Furthermore, it was found that the β-stereoselectivity was highly dependent on the reaction temperature and the amount of MS 5A (entries 3–8 in Table 5); the use of 500 wt% MS 5A as an additive along with 100 wt% SO_4/ZrO_2 in Et_2O at 0 °C led to the highest chemical yield and stereoselectivity for the 2-deoxy-β-glucopyranoside **17**β (entry 7 in Table 5). Thus, the glycosidation of **2** and **3** using 5 wt% SO_4/ZrO_2 in MeCN at 25 °C for 1 h predominantly gave the corresponding 2-deoxy-α-glucopyranoside **17**α, while the glycosidation employing 100 wt% of the same activator in the presence of five times the amount of MS 5A in Et_2O at 0 °C for 1 h afforded the corresponding 2-deoxy-β-glucopyranoside **17**β in high yield with good stereoselectivity. It is noteworthy that these optimized conditions for selectively obtaining both the 2-deoxy-α- and β-glycosides including the reaction temperature and time, and the ratio of SO_4/ZrO_2 and MS 5A significantly differed from those for the previously mentioned stereocontrolled mannosidations due to the higher reactivity of the 2-deoxyglycosyl donor **2** compared to that of the mannosyl donor **1**. With these optimized conditions in hand, the glycosidations using other primary and secondary alcohols **4**–**9** were next carried out to examine the scope and limitation of this glycosidation. Based on the results summarized in Table 6, the glycosidations of **2** with **4**–**7** and **9** using 5 wt% SO_4/ZrO_2 in MeCN at 25 °C for 1 h, as well as that of **3**, effectively proceeded to afford the corresponding 2-deoxy-α-glucopyranosides **18**α–**21**α and **23**α, respectively, in high yields with good stereoselectivities. Unfortunately, when the less reactive alcohol **8** was employed as the acceptor, a moderate yield of **22**α, which was contaminated with a considerable amount of the

Table 5. Glycosidations of **2** and **3** by SO_4/ZrO_2 under several conditions[a]

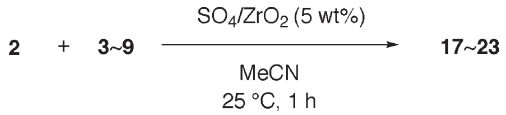


Entry	Solvent	Wt% of SO_4/ZO_2	Wt% of MS 5A	Temp. (°C)	Yield (%)[b]	α/β Ratio[c]
1	MeCN	5	0	45	74	85/15
2	MeCN	5	0	25	98	88/12
3	Et_2O	100	100	25	90	50/50
4	Et_2O	100	100	0	98	24/76
5	Et_2O	100	200	0	97	25/75
6	Et_2O	100	300	0	98	21/79
7	Et_2O	100	500	0	98	19/81
8	Et_2O	100	1000	0	96	18/82

[a] All reactions were carried out using 2.0 equiv. of **3** to **2**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

corresponding 2,3-unsaturated glycoside, was obtained (entry 6 in Table 6). The 2,3-unsaturated glycoside was probably produced by the Ferrier reaction[17] of the glycal **24**, which came from **2** by treatment with SO_4/ZrO_2, and the alcohol as shown in Figure 2. On the other hand, the stereoselective syntheses of the corresponding 2-deoxy-β-glucopyranosides **18**β–**23**β by the present glycosidation are outlined in Table 7. As observed for the α-stereoselective glycosidation, in the case of **8** and **9**, moderate yields and stereoselectivities were observed, and considerable amounts of the corresponding 2,3-unsaturated glycosides were produced (entries 6 and 7 in Table 7). However, the other 2-deoxy-β-glucopyranosides **18**β–**21**β were obtained in good to high yield with good stereoselectivities by the

Table 6. α-Stereoselective glycosidations of **2** and several alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**3**	**17**	98	88/12
2	**4**	**18**	92	84/16
3	**5**	**19**	97	82/18
4	**6**	**20**	92	83/17
5	**7**	**21**	82	86/14
6	**8**	**22**	53	88/12
7	**9**	**23**	80	80/20

[a] All reactions were carried out using 2.0 equiv. of the alcohol to **2**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

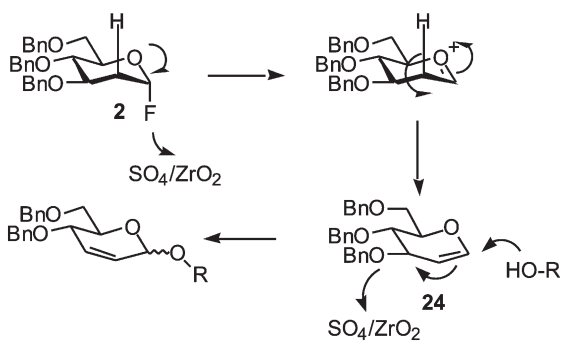
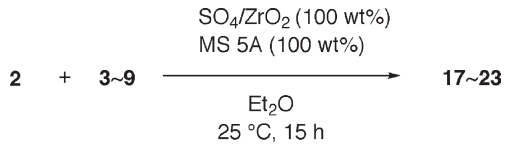


Figure 2. 2,3-Unsaturated glycoside formation in the glycosidation of **2**.

glycosidations of **2** and **4**–**7** as well as that of **3**. It was also confirmed that no epimerization of the formed β-glycoside bond was observed during the reaction. Comparing the two types of glycosidations, the mannosidation was more effectively performed rather than the 2-deoxyglucosidation by the present method because the formation of 2,3-unsaturated glycosides did not occur as a side reaction during the glycosidation of mannosyl fluoride **1** even when a low reactive alcohol was used as an acceptor.

Table 7. β-Stereoselective glycosidations of **2** and several alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**3**	**17**	98	19/81
2	**4**	**18**	96	15/85
3	**5**	**19**	99	19/81
4	**6**	**20**	97	20/80
5	**7**	**21**	81	28/72
6	**8**	**22**	50	30/70
7	**9**	**23**	56	33/67

[a] All reactions were carried out using 2.0 equiv. of the alcohol to **2**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

2.3. Mechanistic considerations

To investigate the mechanism of the present unusual stereocontrolled glycosidations, we examined the effect of the leaving group of the glycosyl donor and its stereochemistry. For this purpose, we prepared another glycosyl donor, mannopyranosyl sulfoxide **25**,[9c] possessing a β-configuration at the C1 position, and then examined the glycosidation with **3** under similar conditions employed for the glycosyl donor **1**. As shown in Figure 3, it was found that when the glycosidation was performed using SO_4/ZrO_2 in MeCN, the α-mannopyranoside **17**α (94%, α/β=90/10) was selectively obtained, while that with the same activator in the presence of MS 5A in Et_2O predominantly afforded the β-mannopyranoside **17**β (99%, α/β=19/81). These results showed exactly the same tendency as observed in the glycosidations using α-mannopyranosyl fluoride **1**. From

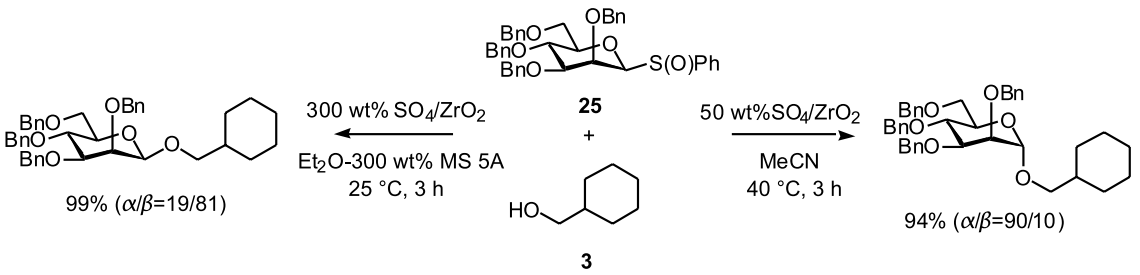


Figure 3. Mannosidations of mannosyl sulfoxide using a heterogeneous solid acid, SO_4/ZrO_2.

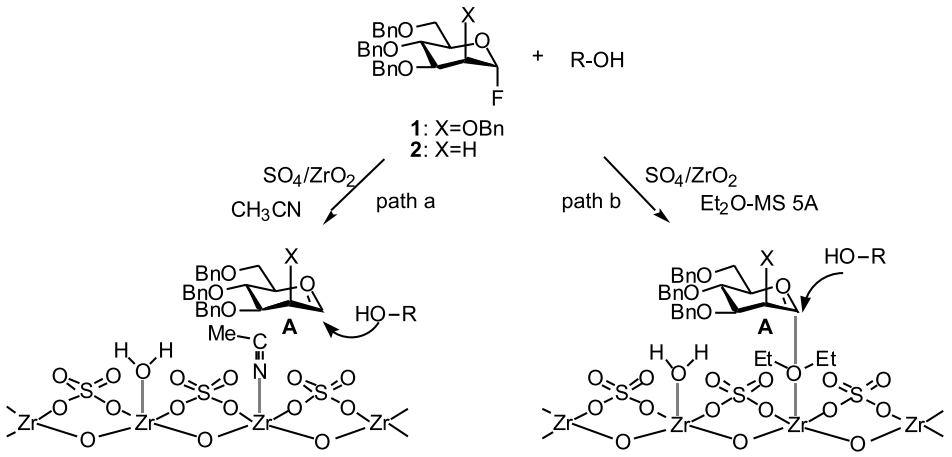


Figure 4. Presumed mechanism of the stereocontrolled glycosidation using SO_4/ZrO_2.

these results, it was clarified that the α- and β-stereoselectivities of the present glycosidations are completely independent of both the kind of leaving group at the anomeric position of the glycosyl donor and its configuration. Therefore, these glycosidations proceeds via an S_N1 type reaction and involves the oxonium intermediate **A** as indicated in Figure 4. When MeCN is used as a solvent, the alcohol attacks the α-face of the anomeric center of the oxonium intermediate **A** due to the steric interaction of the axial β-hydroxy group at the C2 position and the anomeric effect to generate the α-glycosidic bond (path a in Fig. 4). It is known, in some cases, that MeCN is coordinated with the α-face of the anomeric center of the oxonium intermediate, and then the alcohol attacks the β-face of the oxonium intermediate.[18] However, in the present case, MeCN is probably coordinated to Zr on SO_4/ZrO_2 rather than the oxonium intermediate **A** on the surface of SO_4/ZrO_2. Therefore, the solvent effect of MeCN producing the β-stereoselectivity was not observed. On the other hand, when Et_2O was used as the solvent, Et_2O could coordinate with both Zr on SO_4/ZrO_2 and the α-face of the oxonium intermediate **A** due to the bidentate coordinating nature of Et_2O. Therefore, SO_4/ZrO_2 coordinates with the α-face of the oxonium intermediate **A** through Et_2O. Consequently, an alcohol attacks the less hindered β-face of the oxonium intermediate **A** to form the β-glycosidic bond. In this case, MS 5A would play an important role to replace H_2O, originally coordinated with Zr on SO_4/ZrO_2, with Et_2O, and increase the Et_2O coordinated points on the surface of SO_4/ZrO_2.

3. Conclusion

We have presented a novel and stereocontrolled strategy for the direct syntheses of both the α- and β-manno- and 2-deoxyglucopyranosides from manno- and 2-doxyglucopyranosyl fluorides and alcohols using a heterogeneous solid acid. Furthermore, the results including the simple protocol and stereoselectivity should be instructive for further research that employs heterogeneous solid acids in glycosidation reactions. Moreover, the protocols should find wide application for the synthesis of biologically important natural products and functional materials.

4. Experimental

4.1. General methods

Melting points were determined on a micro hot-stage Yanako MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform unless otherwise noted. ^1H NMR spectra were recorded on a JEOL GSX 270 (270 MHz) or a Lambda 300 (300 MHz) in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 (0.25 mm) and Kanto Chemical Co., Inc Silica Gel 60 N (spherical, neutral), respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

4.2. Glycosidation protocols for the preparations of the α- and β-mannopyranosides

α-Mannopyranosides: to a stirred solution of the glycosyl fluoride **1** (0.5 mmol) and a glycosyl acceptor (1.0 mmol) in dry MeCN (5.0 ml) was added SO_4/ZrO_2 (5 wt% to the glycosyl donor **1**). After stirring for 15 h at 40 °C, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave mannopyranosides which predominately contained its α-anomer. β-Mannopyranosides: to a stirred solution of **1** (0.5 mmol) and a glycosyl acceptor (1.0 mmol) in dry Et_2O (5.0 ml) were added powdered MS 5A (100 wt% to **1**) and SO_4/ZrO_2 (100 wt% to **1**). After stirring for 15 h at 25 °C, the similar workup and purification mentioned above gave mannopyranosides, which included its β-anomer as a major product.

4.3. Glycosidation protocols for the preparations of the 2-deoxy-α- and β-glucopyranosides

2-Deoxy-α-glucopyranosides: to a stirred solution of the glycosyl fluoride **2** (0.5 mmol) and an alcohol (1.0 mmol) in dry MeCN (5.0 ml) was added SO_4/ZrO_2 (5 wt% to the glycosyl donor **2**). After stirring for 1 h at 25 °C, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave the 2-deoxyglucopyranosides which predominantly contained the α-anomer. 2-Deoxy-β-glucopyranosides: To a stirred solution of **2** (0.5 mmol) and an alcohol (1.0 mmol) in dry Et_2O (5.0 ml) were added powdered MS 5A (500 wt% to **2**) and SO_4/ZrO_2 (100 wt% to **2**). After stirring for 1 h at 0 °C, a similar workup and purification as that mentioned above gave the 2-deoxyglucopyranosides which selectively included the β-anomer.

4.3.1. Cyclohexylmethyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (10α). Colorless syrup. R_f 0.60 (4/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ +37.8° (*c* 0.94, $CHCl_3$); ^{1}H NMR δ 0.80–1.74 (11H, m), 3.15 (1H, dd, *J*=9.6, 6.0 Hz), 3.45 (1H, dd, *J*=9.6, 7.2 Hz), 3.68–3.81 (4H, m), 3.86–4.01 (2H, m), 4.48–4.79 (7H, m), 4.82 (1H, d, *J*=2.0 Hz), 4.87 (1H, d, *J*=10.4 Hz), 7.14–7.39 (20H, m). Anal. Calcd for $C_{41}H_{48}O_6$: C, 77.33; H, 7.60. Found: C, 77.27; H, 7.62.

4.3.2. Cyclohexylmethyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside (10β). White solid. R_f 0.60 (4/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ −52.9° (*c* 0.69, $CHCl_3$); mp 64.5–66.0 °C; ^{1}H NMR δ 0.83–1.87 (11H, m), 3.20 (1H, dd, *J*=8.8, 6.4 Hz), 3.44 (1H, ddd, *J*=7.6, 6.0, 2.0 Hz), 3.51 (1H, dd, *J*=8.8, 2.8 Hz), 3.71–3.92 (5H, m), 4.35 (1H, br s), 4.42 (1H, d, *J*=12.0 Hz), 4.50 (1H, d, *J*=12.0 Hz), 4.53 (1H, d, *J*=10.8 Hz), 4.59 (1H, d, *J*=12.4 Hz), 4.64 (1H, d, *J*=12.4 Hz), 4.87 (1H, d, *J*=13.2 Hz), 4.91 (1H, d, *J*=10.8 Hz), 5.00 (1H, d, *J*=13.2 Hz), 7.16–7.49 (20H, m). Anal. Calcd for $C_{41}H_{48}O_6$: C, 77.33; H, 7.60. Found: C, 77.31; H, 7.48.

4.3.3. *n*-Octyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (11α). Colorless syrup. R_f 0.55 (4/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ +31.9° (*c* 0.82, $CHCl_3$); ^{1}H NMR δ 0.90 (1H, t, *J*=6.4 Hz), 1.21–1.34 (10H, m), 1.48–1.57 (2H, m), 3.34 (1H, dt, *J*=9.6, 6.4 Hz), 3.60–3.79 (5H, m), 3.87–4.02 (2H, m), 4.50 (1H, d, *J*=10.8 Hz), 4.54 (1H, d, *J*=12.0 Hz), 4.63 (2H, s), 4.66 (1H, d, *J*=12.0 Hz), 4.70 (1H, d, *J*=12.4 Hz), 4.76 (1H, d, *J*=12.4 Hz), 4.84–4.89 (2H, m), 7.14–7.40 (20H, m). Anal. Calcd for $C_{42}H_{52}O_6$: C, 77.27; H, 8.03. Found: C, 77.22; H, 7.82

4.3.4. *n*-Octyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside (11β). White solid. R_f 0.55 (4/1 *n*-hexane/EtOAc); $[\alpha]_D^{27}$ −54.8° (*c* 0.44, $CHCl_3$); mp 35.5–37.0 °C; ^{1}H NMR δ 0.88 (1H, t, *J*=6.4 Hz), 1.21–1.43 (10H, m), 1.56–1.70 (2H, m), 3.36–3.52 (3H, m), 3.70–3.90 (4H, m), 3.98 (1H, dt, *J*=9.2, 6.4 Hz), 4.36 (1H, br s), 4.42 (1H, d, *J*=11.2 Hz), 4.50 (1H, d, *J*=11.2 Hz), 4.53 (1H, d, *J*=10.4 Hz), 4.58 (1H, d, *J*=12.4 Hz), 4.68 (1H, d, *J*=12.4 Hz), 4.87 (1H, d, *J*=12.4 Hz), 4.90 (1H, d, *J*=10.4 Hz), 4.99 (1H, d, *J*=12.4 Hz), 7.15–7.50 (20H, m). Anal. Calcd for $C_{42}H_{52}O_6$: C, 77.27; H, 8.03. Found: C, 77.20; H, 7.95.

4.3.5. Isopropyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (12α). White solid. R_f 0.49 (100/1 chloroform/EtOAc); $[\alpha]_D^{29}$ +39.5° (*c* 0.50, $CHCl_3$); mp 65.0–66.0 °C; ^{1}H NMR δ 1.06 (3H, d, *J*=6.0 Hz), 1.16 (3H, d, *J*=6.0 Hz), 3.67–4.04 (7H, m), 4.50 (1H, d, *J*=10.8 Hz), 4.57 (1H, d, *J*=12.0 Hz), 4.64 (2H, s), 4.67 (1H, d, *J*=12.0 Hz), 4.70 (1H, d, *J*=12.0 Hz), 4.78 (1H, d, *J*=10.8 Hz), 4.95 (1H, d, *J*=1.6 Hz), 7.13–7.40 (20H, m). Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26; H, 7.26. Found: C, 76.14; H, 7.05.

4.3.6. Isopropyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside (12β). White solid. R_f 0.25 (100/1 chloroform/EtOAc); $[\alpha]_D^{28}$ −70.4° (*c* 0.49, $CHCl_3$); mp 82.5–84.0 °C; ^{1}H NMR δ 1.16 (3H, d, *J*=6.0 Hz), 1.30 (3H, d, *J*=6.0 Hz), 3.43 (1H, ddd, *J*=8.4, 6.0, 2.4 Hz), 3.50 (1H, dd, *J*=9.6, 3.6 Hz), 3.69–3.88 (4H, m), 4.02 (1H, septet, *J*=6.0 Hz), 4.43 (1H, d, *J*=12.4 Hz), 4.46 (1H, br s), 4.50 (1H, d, *J*=12.4 Hz), 4.53 (1H, d, *J*=10.8 Hz), 4.57 (1H, d, *J*=11.6 Hz), 4.63 (1H, d, *J*=11.6 Hz), 4.90 (1H, d, *J*=10.8 Hz), 4.98 (1H, d, *J*=12.0 Hz), 5.00 (1H, d, *J*=12.0 Hz), 7.16–7.50 (20H, m). Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26; H, 7.26. Found: C, 76.21; H, 7.07.

4.3.7. Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (13α). Colorless syrup. R_f 0.40 (100/1 chloroform/EtOAc); $[\alpha]_D^{28}$ +44.7° (*c* 0.78, $CHCl_3$); ^{1}H NMR δ 1.09–1.88 (10H, m), 3.51–3.62 (1H, m), 3.65–4.02 (6H, m), 4.50 (1H, d, *J*=10.8 Hz), 4.53 (1H, d, *J*=12.4 Hz), 4.63 (2H, s), 4.66 (1H, d, *J*=12.4 Hz), 4.69 (1H, d, *J*=12.4 Hz), 4.76 (1H, d, *J*=12.4 Hz), 4.87 (1H, d, *J*=10.8 Hz), 4.98 (1H, d, *J*=1.6 Hz), 7.13–7.39 (20H, m). Anal. Calcd for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44. Found: C, 77.06; H, 7.31.

4.3.8. Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside (13β). White solid. R_f 0.30 (100/1 chloroform/EtOAc); $[\alpha]_D^{28}$ −60.9° (*c* 0.38, $CHCl_3$); mp 87.5–89.0 °C; ^{1}H NMR δ 1.73–2.03 (10H, m), 3.40–3.52 (2H, m), 3.67–3.88 (5H, m), 4.42 (1H, d, *J*=12.0 Hz), 4.50 (1H, br s), 4.50 (1H, *J*=12.0 Hz), 4.55 (1H, d, *J*=10.4 Hz), 4.58 (1H, d, *J*=12.0 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.90 (1H, d, *J*=12.4 Hz), 4.90 (1H, d, *J*=10.4 Hz), 5.01 (1H, d, *J*=12.4 Hz), 7.17–7.50 (20H, m). Anal. Calcd for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44. Found: C, 77.07; H, 7.29.

4.3.9. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside

(14α). Colorless syrup. R_f 0.30 (6/1 toluene/EtOAc); $[\alpha]_D^{28}$ +44.5° (*c* 0.54, $CHCl_3$); ^1H NMR δ 3.33 (3H, s), 3.44 (1H, dd, *J*=9.0, 3.0 Hz), 3.54–3.73 (5H, m), 3.78 (1H, dd, *J*=3.0, 1.0 Hz), 3.79–3.87 (2H, m), 3.91 (1H, dd, *J*=9.0, 8.8 Hz), 3.99 (1H, dd, *J*=9.0, 8.8 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.48 (1H, d, *J*=10.8 Hz), 4.55 (1H, d, *J*=3.2 Hz), 4.60 (1H, d, *J*=12.0 Hz), 4.61 (2H, s), 4.67 (1H, d, *J*=12.0 Hz), 4.68 (1H, d, *J*=12.2 Hz), 4.73 (1H, d, *J*=12.2 Hz), 4.78 (1H, d, *J*=12.0 Hz), 4.79 (1H, d, *J*=10.2 Hz), 4.85 (1H, d, *J*=10.8 Hz), 4.87 (1H, d, *J*=10.8 Hz), 4.96 (1H, d, *J*=1.0 Hz) 4.97 (1H, d, *J*=10.2 Hz), 7.10–7.39 (35H, m). Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.28; H, 6.43.

4.3.10. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (14β). White solid. R_f 0.28 (6/1 toluene/EtOAc); $[\alpha]_D^{28}$ −15.8° (*c* 1.04, $CHCl_3$); mp 122–123 °C; ^1H NMR δ 3.32 (3H, s), 3.34–3.50 (4H, m), 3.50 (1H, dd, *J*=9.2, 3.0 Hz), 3.66–3.88 (5H, m), 4.01 (1H, dd, *J*=9.0, 9.0 Hz), 4.11 (1H, br s), 4.16 (1H, dd, *J*=10.0, 1.2 Hz), 4.47 (1H, d, *J*=11.8 Hz), 4.51 (1H, d, *J*=11.0 Hz), 4.52 (1H, d, *J*=11.8 Hz), 4.49–4.55 (1H, m), 4.57 (1H, br s), 4.57 (2H, s), 4.66 (1H, d, *J*=11.6 Hz), 4.78 (1H, d, *J*=11.6 Hz), 4.81 (1H, d, *J*=11.0 Hz), 4.82 (1H, d, *J*=12.0 Hz), 4.83 (1H, d, *J*=3.2 Hz), 4.88 (1H, d, *J*=10.8 Hz), 4.93 (1H, d, *J*=12.0 Hz), 5.01 (1H, d, *J*=10.8 Hz), 7.14–7.44 (35H, m). Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.09; H, 6.55.

4.3.11. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (15α). Colorless syrup. R_f 0.41 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ +17.7° (*c* 1.31, $CHCl_3$); ^1H NMR δ 3.39 (3H, s), 3.50–3.60 (2H, m), 3.61–3.89 (9H, m), 3.97 (1H, dd, *J*=9.0, 9.0 Hz), 4.10 (1H, d, *J*=11.8 Hz), 4.21 (1H, d, *J*=11.8 Hz), 4.42 (1H, d, *J*=12.0 Hz), 4.42 (1H, d, *J*=11.4 Hz), 4.48 (1H, d, *J*=10.6 Hz), 4.52–4.64 (7H, m), 4.67 (1H, d, *J*=12.0 Hz), 4.83 (1H, d, *J*=10.8 Hz), 5.08 (1H, d, *J*=11.2 Hz), 5.29 (1H, d, *J*=1.2 Hz), 7.11–7.32 (35H, m). Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.16; H, 6.78.

4.3.12. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (15β). Colorless syrup. R_f 0.32 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ −20.7° (*c* 1.19, $CHCl_3$); ^1H NMR δ 3.24–3.32 (1H, m), 3.28 (1H, dd, *J*=9.0, 2.6 Hz), 3.37 (3H, s), 3.43–3.59 (4H, m), 3.64–3.77 (3H, m), 3.87 (1H, dd, *J*=9.0, 9.0 Hz), 3.91 (1H, dd, *J*=6.6, 2.0 Hz), 3.88–3.95 (1H, m), 4.36 (1H, d, *J*=11.8 Hz), 4.37 (1H, d, *J*=11.8 Hz), 4.40 (1H, d, *J*=12.0 Hz), 4.42 (1H, br s), 4.45–4.53 (3H, m), 4.57 (1H, d, *J*=3.0 Hz), 4.57 (1H, d, *J*=12.0 Hz), 4.59 (1H, d, *J*=11.8 Hz), 4.75 (1H, d, *J*=11.0 Hz), 4.77 (1H, d, *J*=11.8 Hz), 4.81–4.88 (1H, m), 4.83 (2H, s), 5.15 (1H, d, *J*=11.0 Hz), 7.16–7.42 (35H, m). Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.23; H, 6.47.

4.3.13. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-β-D-glucopyranose (16α). Colorless syrup. R_f 0.65 (4/1 toluene/EtOAc); $[\alpha]_D^{27}$ +63.2° (*c* 0.68, $CHCl_3$); ^1H NMR δ 3.08 (1H, br s), 3.41 (1H, dd, *J*=1.2, 1.2 Hz), 3.56–3.63 (2H, m), 3.68–4.01 (7H, m), 4.47–4.74 (10H, m), 4.81 (1H, d, *J*=1.6 Hz), 4.87 (1H, d, *J*=10.8 Hz), 5.48 (1H, s), 7.23–7.40 (25H, m). Anal. Calcd for $C_{47}H_{49}N_3O_9$: C, 70.57; H, 6.17; N, 5.25. Found: C, 70.55; H, 6.23; N, 5.13.

4.3.14. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-β-D-glucopyranose (16β). Colorless syrup. R_f 0.40 (4/1 toluene/EtOAc); $[\alpha]_D^{27}$ −36.5° (*c* 1.21, $CHCl_3$); ^1H NMR δ 3.25 (1H, br s), 3.47 (1H, ddd, *J*=9.6, 6.0, 2.4 Hz), 3.54 (1H, dd, *J*=9.6, 2.8 Hz), 3.69–3.78 (3H, m), 3.80 (1H, dd, *J*=0.8, 0.8 Hz), 3.88 (1H, dd, *J*=9.6, 9.6 Hz), 3.96 (1H, br s, H-4), 4.03 (1H, d, *J*=2.8 Hz), 4.08–4.18 (1H, m), 4.43–4.69 (9H, m), 4.86–5.04 (3H, m), 5.52 (1H, br s), 7.18–7.44 (25H, m). Anal. Calcd for $C_{47}H_{49}N_3O_9$: C, 70.57; H, 6.17; N, 5.25. Found: C, 70.48; H, 6.23; N, 5.16.

4.3.15. Cyclohexylmethyl 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranoside (17α). Colorless syrup. R_f 0.36 (5/2 *n*-hexane/ether); $[\alpha]_D^{29}$ +67.0° (*c* 0.88, $CHCl_3$); ^1H NMR δ 0.81–1.02 (2H, m), 1.05–1.35 (3H, m), 1.46–1.81 (7H, m), 2.27 (1H, br dd, *J*=12.4, 4.8 Hz), 3.15 (1H, dd, *J*=9.2, 6.0 Hz), 3.41 (1H, dd, *J*=9.2, 6.8 Hz), 3.56– 3.83 (4H, m), 3.98 (1H, ddd, *J*=11.2, 8.4, 4.8 Hz), 4.51 (2H, d, *J*=11.0 Hz), 4.64 (1H, d, *J*=11.0 Hz), 4.65 (1H, d, *J*=11.0 Hz), 4.68 (1H, d, *J*=11.0 Hz), 4.89 (1H, d, *J*=11.0 Hz), 4.91 (1H, br d, *J*=3.2 Hz), 7.14–7.20 (2H, m), 7.22–7.39 (13H, m). Anal. Calcd for $C_{34}H_{42}O_5$: C, 76.95; H, 7.98. Found: C, 76.93; H, 7.97.

4.3.16. Cyclohexylmethyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranoside (17β). White solid. R_f 0.45 (5/2 *n*-hexane/ether); $[\alpha]_D^{28}$ −18.5° (*c* 1.32, $CHCl_3$); mp 72.0–73.0 °C; ^1H NMR δ 0.82–1.02 (2H, m), 1.07–1.34 (3H, m), 1.50–1.84 (7H, m), 2.35 (1H, ddd, *J*=12.4, 4.8, 1.6 Hz), 3.22 (1H, dd, *J*=9.0, 6.4 Hz), 3.40 (1H, ddd, *J*=9.2, 4.4, 1.6 Hz), 3.49 (1H, dd, *J*=9.2, 8.0 Hz), 3.65 (1H, dd, *J*=11.0, 4.4 Hz), 3.69 (1H, ddd, *J*=12.0, 8.0, 4.8 Hz), 3.73 (1H, dd, *J*=9.0, 6.0 Hz), 3.77 (1H, dd, *J*=11.0, 1.6 Hz), 4.40 (1H, dd, *J*=9.6, 1.6 Hz), 4.55 (1H, d, *J*=10.8 Hz), 4.57 (1H, d, *J*=11.6 Hz), 4.59 (1H, d, *J*=12.4 Hz), 4.63 (1H, d, *J*=12.4 Hz), 4.69 (1H, d, *J*=11.6 Hz), 4.90 (1H, d, *J*=10.8 Hz), 7.17–7.23 (2H, m), 7.23–7.38 (13H, m). Anal. Calcd for $C_{34}H_{42}O_5$: C, 76.95; H, 7.98. Found: C, 76.97; H, 7.62.

4.3.17. *n*-Octyl 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranoside (18α). Colorless syrup. R_f 0.36 (5/2 *n*-hexane/ether); $[\alpha]_D^{29}$ +64.6° (*c* 1.40, $CHCl_3$); ^1H NMR δ 0.84–0.93 (3H, m), 1.20–1.37 (10H, m), 1.44–1.62 (2H, m), 1.72 (1H, ddd, *J*=12.8, 11.6, 3.6 Hz), 2.28 (1H, br dd, *J*=12.8, 6.4 Hz), 3.34 (1H, dt, *J*=9.6, 6.8 Hz), 3.55–3.82 (5H, m), 4.00 (1H, ddd, *J*=11.6, 8.8, 6.4 Hz), 4.43–4.60 (2H, m), 4.63 (1H, d, *J*=11.6 Hz), 4.65 (1H, d, *J*=12.0 Hz), 4.69 (1H, d, *J*=11.6 Hz), 4.89 (1H, d, *J*=10.4 Hz), 4.94 (1H, br d, *J*=3.6 Hz), 7.14–7.38 (15H, m). Anal. Calcd for $C_{35}H_{46}O_5$: C, 76.89; H, 8.48. Found: C, 76.90; H, 8.16.

4.3.18. *n*-Octyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranoside (18β). Colorless syrup. R_f 0.47 (5/2 *n*-hexane/ether); $[\alpha]_D^{28}$ −16.7° (*c* 0.98, $CHCl_3$); ^1H NMR δ 0.84–0.92 (3H, m), 1.19–1.40 (10H, m), 1.53–1.71 (3H, m), 2.34 (1H, ddd, *J*=12.8, 4.8, 1.6 Hz), 3.36–3.53 (3H, m), 3.61–3.79 (3H, m), 3.89 (1H, dt, *J*=9.2, 7.2 Hz), 4.42 (1H, dd, *J*=10.0, 1.6 Hz), 4.53–4.65 (4H, m) 4.68 (1H, d, *J*=11.6 Hz), 4.90 (1H, d, *J*=10.0 Hz), 7.16–7.37 (15H, m).

Anal. Calcd for $C_{35}H_{46}O_5$: C, 76.89; H, 8.48. Found: C, 76.92; H, 8.10.

4.3.19. Isopropyl 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranoside (19α). Colorless syrup. R_f 0.38 (30/1 chloroform/EtOAc); $[\alpha]_D^{28}$ +76.6° (*c* 1.88, $CHCl_3$); ^1H NMR δ 1.12 (3H, d, *J*=6.0 Hz), 1.16 (3H, d, *J*=6.0 Hz), 1.74 (1H, ddd, *J*=12.8, 11.6, 3.6 Hz), 2.24 (1H, br dd, *J*=12.8, 5.2 Hz), 3.58–3.69 (2H, m), 3.77–3.86 (2H, m), 3.88 (1H, septet, *J*=6.0 Hz), 4.01 (1H, ddd, *J*=11.6, 8.8, 5.2 Hz), 4.48–4.53 (2H, m), 4.63 (1H, d, *J*=11.6 Hz), 4.66 (1H, d, *J*=12.4 Hz), 4.68 (1H, d, *J*=11.6 Hz), 4.89 (1H, d, *J*=10.8 Hz), 5.08 (1H, br d, *J*=3.6 Hz), 7.14–7.38 (15H, m). Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.63; H, 7.41.

4.3.20. Isopropyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranoside (19β). Colorless syrup. R_f 0.27 (30/1 chloroform/EtOAc); $[\alpha]_D^{29}$ −25.9° (*c* 1.58, $CHCl_3$); ^1H NMR δ 1.15 (3H, d, *J*=6.0 Hz), 1.26 (3H, d, *J*=6.0 Hz), 1.65 (1H, ddd, *J*=12.8, 12.2, 10.0 Hz), 2.30 (1H, ddd, *J*=12.8, 5.6, 1.6 Hz), 3.36–3.51 (2H, m), 3.61–3.71 (3H, m), 4.01 (1H, septet, *J*=6.0 Hz), 4.49–4.65 (5H, m), 4.68 (1H, d, *J*=12.0 Hz), 4.89 (1H, d, *J*=10.8 Hz), 7.14–7.38 (15H, m). Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.65; H, 7.42.

4.3.21. Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranoside (20α). Colorless syrup. R_f 0.46 (30/1 chloroform/EtOAc); $[\alpha]_D^{28}$ +80.6° (*c* 0.82, $CHCl_3$); ^1H NMR δ 1.11–1.91 (11H, m), 2.24 (1H, br dd, *J*=12.8, 5.2 Hz), 3.49–3.69 (3H, m), 3.72–3.89 (2H, m), 4.02 (1H, ddd, *J*=11.6, 8.8, 5.2 Hz), 4.47–4.54 (2H, m), 4.64 (1H, d, *J*=10.8 Hz), 4.65 (1H, d, *J*=12.0 Hz), 4.68 (1H, d, *J*=10.8 Hz), 4.89 (1H, d, *J*=10.8 Hz), 5.12 (1H, br d, *J*=4.8 Hz), 7.14–7.39 (15H, m). Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.75; H, 7.49.

4.3.22. Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranoside (20β). White solid. R_f 0.35 (30/1 chloroform/EtOAc); $[\alpha]_D^{28}$ −26.6° (*c* 1.00, $CHCl_3$); mp 48.0–50.0 °C; ^1H NMR δ 1.13–2.05 (11H, m), 2.31 (1H, ddd, *J*=12.4, 5.2, 1.6 Hz), 3.47–3.51 (2H, m), 3.61–3.80 (4H, m), 4.53–4.65 (5H, m), 4.69 (1H, d, *J*=12.0 Hz), 4.90 (1H, d, *J*=10.8 Hz), 7.19–7.47 (15H, m). Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.74; H, 7.64.

4.3.23. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-α-D-glucopyranoside (21α). White solid. R_f 0.24 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{28}$ +65.4° (*c* 0.60, $CHCl_3$); ^1H NMR δ 1.69 (1H, ddd, *J*=12.4, 12.4, 4.0 Hz), 2.30 (1H, br dd, *J*=12.4, 5.2 Hz), 3.34 (3H, s), 3.44–3.69 (7H, m), 3.70–3.75 (1H, m), 3.78–3.84 (1H, m), 3.89–4.02 (2H, m), 4.36–4.70 (8H, m), 4.77–5.01 (6H, m), 7.12–7.38 (30H, m). Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 74.92; H, 6.66.

4.3.24. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)-α-D-glucopyranoside (21β). White solid. R_f 0.36 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{27}$ +23.5° (*c* 1.33, $CHCl_3$); mp 130.5–132 °C; ^1H NMR δ 1.53–1.68 (1H, m), 2.15 (1H, ddd, *J*=12.4, 4.8, 1.6 Hz), 3.36 (3H, s), 3.30–3.78 (9H, m), 3.56–3.75 (4H, m), 3.99 (1H, dd, *J*=9.6, 9.6 Hz), 4.07 (1H, dd, *J*=10.8, 2.0 Hz), 4.16 (1H, dd, *J*=10.0, 1.6 Hz), 4.49–4.68 (8H, m), 4.77–4.89 (4H, m), 5.00 (1H, d, *J*=10.8 Hz), 7.18–7.38 (30H, m). Anal. Calcd for $C_{55}H_{60}O_{10}$: C, 74.98; H, 6.86. Found: C, 74.97; H, 6.68.

4.3.25. 1,6-Anhydro-2-azido-3-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-2-deoxy-β-D-glucopyranose (23α). Colorless syrup. R_f 0.43 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{27}$ +87.1° (*c* 1.01, $CHCl_3$); ^1H NMR δ 1.73 (1H, ddd, *J*=12.8, 11.6, 4.0 Hz), 2.32 (1H, br dd, *J*=12.8, 4.8 Hz), 3.12 (1H, br s), 3.49–3.64 (4H, m), 3.70 (2H, d, *J*=3.6 Hz), 3.94 (1H, ddd, *J*=10.0, 4.0, 4.0 Hz), 4.00–4.13 (2H, m), 4.44–4.70 (8H, m), 4.90 (1H, d, *J*=10.8 Hz), 5.00 (1H, d, *J*=4.0 Hz), 5.49 (1H, br s), 7.16–7.40 (20H, m). Anal. Calcd for $C_{40}H_{43}N_3O_8$: C, 69.25; H, 6.25; N, 6.06. Found: C, 69.14; H, 5.96; N, 6.10.

4.3.26. 1,6-Anhydro-2-azido-3-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)-2-deoxy-β-D-glucopyranose (23β). Colorless syrup. R_f 0.30 (2/1 *n*-hexane/EtOAc); $[\alpha]_D^{27}$ +9.2° (*c* 0.85, $CHCl_3$); ^1H NMR δ 1.75 (1H, ddd, *J*=12.0, 12.0, 9.6 Hz), 2.44 (1H, ddd, *J*=12.4, 4.8, 1.6 Hz), 3.18 (1H, br s), 3.39–3.55 (2H, m), 3.62–3.77 (4H, m), 3.85 (1H, br s), 3.92 (1H, dd, *J*=1.2, 1.2 Hz), 4.08–4.16 (1H, m), 4.46–4.72 (9H, m), 4.92 (1H, d, *J*=11.2 Hz), 5.48 (1H, br s), 7.19–7.36 (20H, m). Anal. Calcd for $C_{40}H_{43}N_3O_8$: C, 69.25; H, 6.25; N, 6.06. Found: C, 69.20; H, 5.93; N, 6.01.

Acknowledgements

This research was partially supported by Grant-in-Aid for the 21st Century COE program 'KEIO Life Conjugate Chemistry' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. (a) *Carbohydrates in Chemistry and Biology*, Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vols. 1–4. (b) *Glycoscience Chemistry and Chemical Biology*, Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; Vols. 1–3.
2. For selective reviews, see: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235. (b) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519–528. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531. (d) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121. (e) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160.
3. For a recent review on mannosidation, see: Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471–1491.
4. For recent reviews on 2-deoxyglycosidation, see: (a) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285–332. (b) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385–8417.
5. For recent works on indirect mannosidations, see: (a) Shaban, M. A. E.; Jeanloz, R. W. *Carbohydr. Res.* **1976**, *52*, 115–127. (b) Kunz, H.; Günther, W. *Angew. Chem., Int. Ed. Engl.* **1988**,

27, 1086–1087. (c) Lichtenthaler, F. W.; Cuny, E.; Weprek, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 891–892. (d) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377. (e) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765–1767. (f) Ennis, S. C.; Fairbanks, A. J.; Tennant-Eyles, R. J.; Yeates, H. S. *Synlett* **1999**, 1387–1390. (g) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088. (h) Iimori, T.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 3415–3418. (i) Ziegler, T.; Lemanski, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3129–3132. (j) Abdel-Rahman, A. A.-H.; El Ashry, E. S. H.; Schmidt, R. R. *Carbohydr. Res.* **2002**, *337*, 195–206.

6. For recent works on indirect 2-deoxyglycosidations, see: (a) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377–379. (b) Roush, W. R.; Bennett, C. E.; Roberts, S. E. *J. Org. Chem.* **2001**, *66*, 6389–6393. (c) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, *5*, 81–84. (d) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523–4526. (e) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron Lett.* **2002**, *43*, 9047–9050. (f) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871–1874.
7. For recent works on direct mannosidations, see: (a) Tatsuta, K.; Yasuda, S. *Tetrahedron Lett.* **1996**, *37*, 2453–2456. (b) Kim, W.-S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 7797–7800. (c) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506–4507. (d) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335–2336. (e) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198–1199. (f) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435–436. (g) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348. (h) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069. (i) Nagai, H.; Kawahara, K.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2001**, *42*, 4159–4162. (j) Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972–2974. (k) Hashihayata, T.; Mandai, H.; Mukaiyama, T. *Chem. Lett.* **2003**, 442–443. (l) Nagai, H.; Matsumura, S.; Toshima, K. *Carbohydr. Res.* **2003**, *338*, 1531–1534. (m) Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Heterocycles* **2003**, *59*, 509–515.
8. For recent works on direct 2-deoxyglycosidations, see: (a) Hashimoto, S.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271–1273. (b) Meijin, H. L.; Zhao, K. *Tetrahedron Lett.* **1997**, *38*, 6143–6144. (c) Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946–949. (d) Nagai, H.; Matsumura, S.; Toshima, K. *Chem. Lett.* **2002**, 1100–1101. (e) Kim, K. S.; Park, J.; Joo, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 459–462.
9. For our preliminary communications of this work, see: (a) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1998**, 643–645. (b) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 813–815.
10. Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102–3114.
11. Montmorillonite K-10 was purchased from Aldrich Chemical Company, Inc. and dried at 200 (C/1 mm Hg for 12 h before using.
12. Nafion-H was purchased from Wako Pure Chemical Industries, Ltd as Nafion® NR-50 and dried at 25 (C/1 mm Hg for 2 h before using.
13. SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd and dried at 200 (C/1 mm Hg for 12 h before using..
14. (a) Mukaiyama, T.; Jona, H.; Takeuchi, K. *Chem. Lett.* **2000**, 696–697. (b) Jona, H.; Takeuchi, K.; Mukaiyama, T. *Chem. Lett.* **2000**, 1278–1279. (c) Jona, H.; Mandai, H.; Mukaiyama, T. *Chem. Lett.* **2001**, 426–427.
15. The fluoride **1** was prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose and DAST as previously described in the literature, see; Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5–8.
16. It was found that the fluoride **2** was effectively prepared in 92% yield by the treatment of 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose with HF/Py in dry CH_2Cl_2 at −30 to −20 °C for 30 min, see: Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747–1748.
17. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570–575.
18. Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5341–5352
Tetrahedron

Synthetic studies on antascomicin A: construction of the C18–C34 fragment

Haruhiko Fuwa,* Yumiko Okamura and Hideaki Natsugari*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

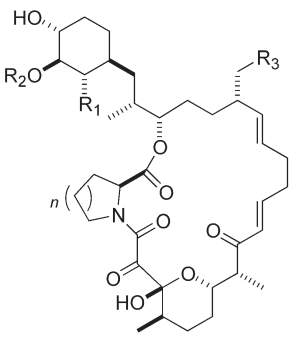
Received 6 April 2004; revised 26 April 2004; accepted 28 April 2004

Abstract—Stereoselective synthesis of the C18–C34 fragment of antascomicin A is described. Construction of the C27–C34 carbocycle moiety was achieved via catalytic Ferrier carbocylization and Johnson–Claisen rearrangement, which was converted to iodide **2** by use of asymmetric alkylation and Sharpless epoxidation as key transformations. Coupling of iodide **2** and sulfone **3** furnished the C18–C34 fragment.

1. Introduction

FK506 (tacrolimus)[1] and rapamycin (sirolimus)[2] are potent immunosuppressive agents in human clinical organ transplantation. The biological mode of action of these promising natural products have been extensively investigated over the past decade.[3] For example, FK506 is known to form an active complex with the cytosolic immunophilin FKBP12, which subsequently binds to the secondary proteinous target calcineurin. The latter interaction is responsible for potent immunosuppressive activity of FK506. On the other hand, it has recently been discovered that FKBP is present in the brain at levels 10–40 times higher than in the immune system, suggesting the possibility of nervous system roles for immunophilins.[3b,4] Subsequently, FK506 has been reported to elicit neurite outgrowth and neuroprotective effects in neuronal cultures at picomolar concentrations.[5] Although the mechanism of neuronal activity of FKBP has not yet been clarified, it has been shown that the neurotrophic properties of FKBP ligands are independent of calcineurin-mediated effects.[3b,6] Thus, FKBP ligands are now considered as potential lead compounds for the development of drugs for treatment and cure of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. With regard to clinical use, efforts have been devoted to the design of neurotrophic FKBP ligands that are non-immunosuppressive.[5,6]

Macrolide antibiotics antascomicin A–E were found in a fermentation broth of a strain of *Micromonospora*, which was isolated from a soil sample collected in China (Fig. 1).[7] The molecular architecture of antascomicin A was determined by extensive NMR studies and X-ray crystallographic analysis. Antascomicin A exhibits potent binding affinity to FKBP12 (IC_{50} 2.0 nM) and antagonize the immunosuppressive effect of FK506 and rapamycin but interestingly it does not show immunosuppressive activity. Given its intriguing biological activity, we became interested in the potential utility of antascomicin A as a lead compound for the generation of novel class of non-immunosuppressive neurotrophic molecules. Here, we describe a stereoselective synthesis of the C18–C34[8] fragment of antascomicin A that is an important key intermediate toward the total synthesis.



antascomicin A: R_1 = H, R_2 = H, R_3 = H, n = 2
B: R_1 = OH, R_2 = H, R_3 = H, n = 2
C: R_1 = OH, R_2 = Me, R_3 = H, n = 2
D: R_1 = H, R_2 = H, R_3 = H, n = 1
E: R_1 = H, R_2 = H, R_3 = OH, n = 2

Figure 1. Structures of antascomicin A–E.

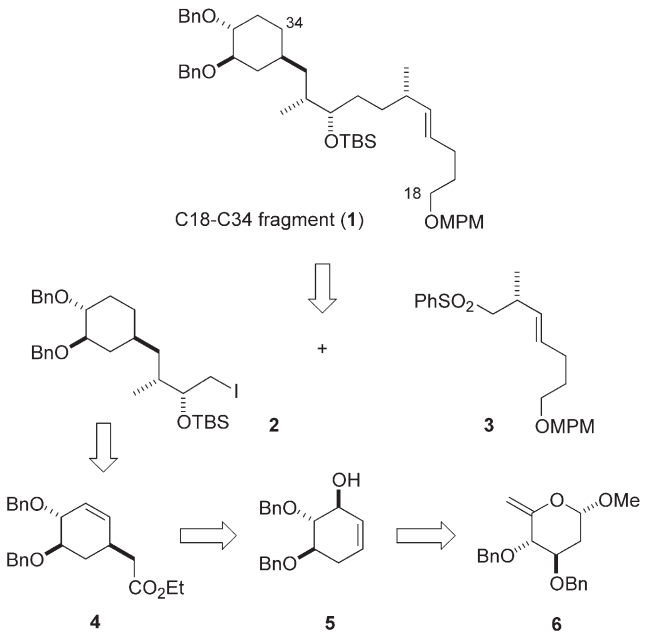
Keywords: Ferrier carbocyclization; Johnson–Claisen rearrangement; Asymmetric alkylation; Sulfone anion coupling.
* Corresponding authors. Tel./fax: +81-3-5841-4775;
e-mail addresses: hfuwa@mol.f.u-tokyo.ac.jp;
natsu@mol.f.u-tokyo.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.072

2. Results and discussions

2.1. Synthetic planning

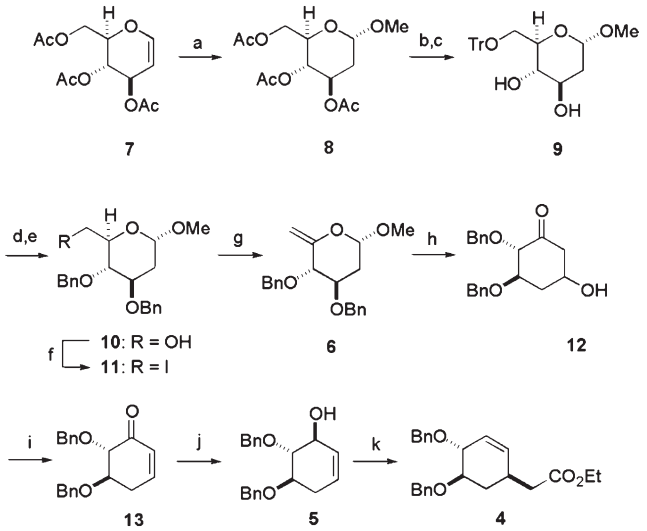
Our synthetic planning for the synthesis of the C18–C34 fragment **1** is outlined in Scheme 1. We divided **1** into iodide **2** and sulfone **3** by retro-sulfone anion coupling. The former segment was traced back to ester **4**, which could be obtained from allylic alcohol **5** by Johnson–Claisen rearrangement.[9] In turn, **5** should be available from exocyclic enol ether **6** via Ferrier carbocyclization.[10]



Scheme 1. Synthetic planning toward the C18–C34 fragment **1**.

2.2. Synthesis of the C29–C34 carbocycle

Synthesis of the C18–C34 fragment was commenced with tri-*O*-acetyl-D-glucal **7** (Scheme 2). Treatment of **7** with methanol in the presence of a catalytic amount of triphenylphosphine hydrogen bromide complex (Ph_3P·HBr) gave methyl glucoside **8** in 89% yield (α/β=ca. 9:1). Deacetylation of **8** followed by selective protection of the primary alcohol led to trityl ether **9** (81% yield for two steps). Benzylation of the remaining hydroxyls and deprotection of the trityl group delivered alcohol **10** in 91% yield (two steps). Iodination of **10** under the standard conditions delivered **11** in 84% yield. Conversion of **11** to **6** was best achieved by treatment of **11** with sodium hydride in DMF, affording exocyclic enol ether **6** in high yield.



Scheme 2. Reagents and conditions: (a) Ph_3P·HBr, MeOH, MeCN, rt, 89%; (b) NaOMe, MeOH, rt; (c) TrCl, pyridine, CH_2Cl_2, rt, 81% (two steps); (d) BnBr, NaH, DMF, 50 °C; (e) *p*-TsOH·H_2O, MeOH/$CHCl_3$ (5:1), rt, 91% (two steps); (f) I_2, PPh_3, imidazole, benzene, rt, 84%; (g) NaH, DMF, rt, 94%; (h) $Hg(OCOCF_3)_2$, acetone/H_2O (2:1), rt, 95%; (i) MsCl, Et_3N, CH_2Cl_2, rt, quant.; (j) $LiBH_4$, $CeCl·7H_2O$, THF/MeOH (1:1), 0 °C, 98% (dr 5.3:1); (k) *n*-$EtCO_2H$, $CH_3C(OEt)_3$, 140 °C, 76%.

Employing other bases such as KO*t*-Bu (THF, 0 °C) and DBU (toluene, 100 °C), **6** was obtained in only moderate yield. Catalytic Ferrier carbocyclization[11] was smoothly carried out by exposure of **6** to $Hg(OCOCF_3)_2$ (10 mol%) in acetone/H_2O, leading to hydroxyketone **12** in 95% yield as a 10:1 mixture of diastereomers. Treatment of **12** with MsCl in the presence of Et_3N gave enone **13**. Stereoselective 1,2-reduction of **13** turned out to be rather problematic than anticipated. The results of several attempts to optimize the reaction are summarized in Table 1. Under the standard Luche reduction conditions,[12] we obtained an inseparable mixture of **5** and its epimer in a ratio of 3.7:1 in 88% combined yield (entry 1). Use of THF as a co-solvent slightly improved the stereochemical outcome (entry 2). We found that the use of much reactive $LiBH_4$ in MeOH/THF at 0 °C resulted in an improved 5.3:1 diastereomer ratio (entry 3). An attempt to conduct the reaction at low temperature caused a significant decrease in the stereoselectivity (entry 4). We have also examined several aluminum hydride reagents such as $LiAlH_4$, $LiAlH(Ot\text{-}Bu)_3$ and DIBALH, but these reductants were found to be uniformly ineffective for the present case (entries 5–7). With satisfactory reaction conditions established, we then conducted Johnson–Claisen rearrangement of **5**. Thus, treatment of **5** with a catalytic amount of *n*-propionic acid in $CH_3CH(OEt)_3$ at 140 °C cleanly delivered ester **4**. For the major isomer, the

Table 1. Reduction of **13** under a variety of conditions

Entry	Reagents and conditions	dr (**5**/*epi*-**5**)[a]	Yield (%)
1	$NaBH_4$, $CeCl_3·7H_2O$, MeOH, 0 °C	3.7:1	97
2	$NaBH_4$, $CeCl_3·7H_2O$, MeOH/THF (1:1), 0 °C	4.0:1	88
3	$LiBH_4$, $CeCl_3·7H_2O$, MeOH/THF (1:1), −78 °C	2.8:1	86
4	$LiBH_4$, $CeCl_3·7H_2O$, MeOH/THF (1:1), 0 °C	5.3:1	98
5	$LiAlH_4$, THF 0 °C	1:1	Quant.
6	$LiAlH(Ot\text{-}Bu)_3$ THF, 0 °C	1:1	84
7	DiBALH, CH_2Cl_2, −78 °C	1:1.1	96

[a] Estimated by ^1H NMR (400 MHz).

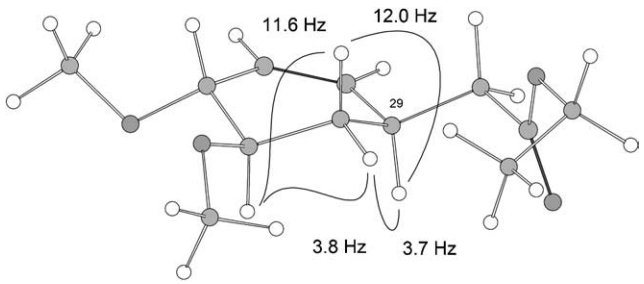
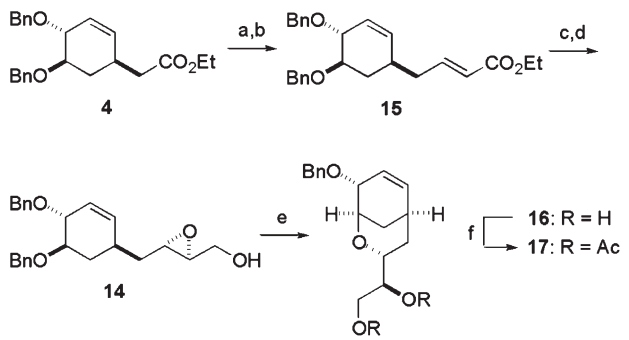


Figure 2. Stereochemical confirmation of **4** based on ^{1}H NMR analysis. The benzyl groups were replaced with methyl groups for clarity.

stereochemistry at C29 was unambiguously confirmed by ^{1}H NMR analysis (Fig. 2).

2.3. Initial attempt to construct the C26 and C27 stereocenters

Stereoselective incorporation of the C26 hydroxyl and C27 methyl groups is seemingly challenging because they locate remote from other stereocenters. Our initial strategy toward the construction of the C26 and C27 stereocenters is summarized in Scheme 3. Reduction of ester **4** with DIBALH followed by Wittig reaction gave enoate **14**. After reduction of **14**, the resultant allylic alcohol was



Scheme 3. Reagents and conditions: (a) DIBALH, CH_2Cl_2, −78 °C; (b) $Ph_3P{=}CHCO_2Et$, benzene, rt, 80% (two steps); (c) DIBALH, CH_2Cl_2, −78 °C, 93%; (d) Ti(O*i*-Pr)$_4$, (+)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 65%; (e) $AlMe_3$, hexane/CH_2Cl_2 (2:1), −78 to 0 °C; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 67% (two steps).

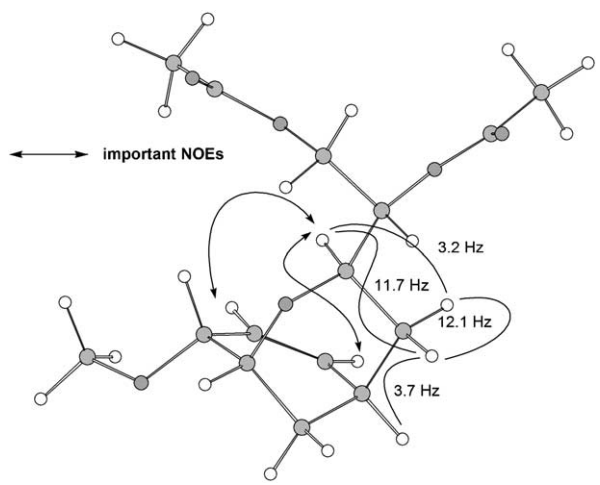


Figure 3. Confirmation of the structure of **17**. The benzyl group was replaced with a methyl group for clarity.

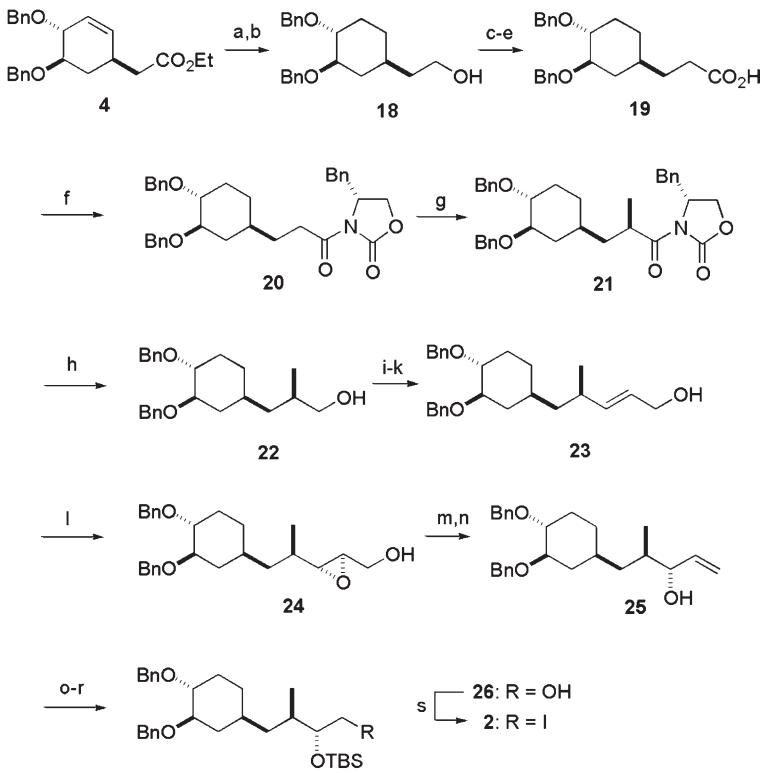
subjected to Sharpless asymmetric epoxidation using (+)-diethyl tartarate as a chiral auxiliary to afford hydroxyl epoxide **15**. The minor C29 epimer was readily separated during these transformations. To install the C27 methyl group, hydroxyl epoxide **15** was exposed to trimethylaluminum ($AlMe_3$) in hexane/CH_2Cl_2.[13] Surprisingly, however, the only isolatable product was strained bicyclic compound **16**, whose structure was confirmed by ^{1}H NMR analysis and NOE experiments on the corresponding bis(acetate) **17** (Fig. 3). This outcome can be explained by an intramolecular S_N2 attack of the C31 benzyloxy group to the oxirane activated by $AlMe_3$. Although such reaction is undesirable in this case, it is interesting that the strained bicycle **16** was constructed in a relatively simple manner.

2.4. Elaboration of the C26 and C27 stereocenters via asymmetric reactions

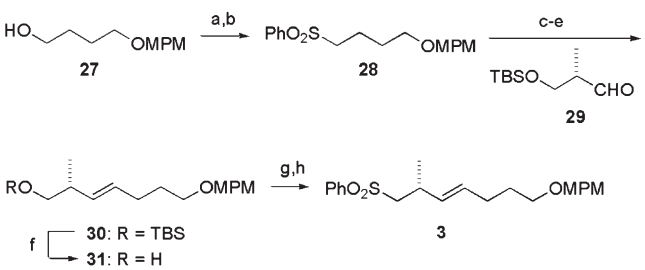
With the above result in mind, we intended to elaborate the C26 and C27 stereocenters using asymmetric alkylation and epoxidation. To this end, ester **4** was reduced with $LiAlH_4$ and the double bond was saturated by diimde reduction using *p*-toluenesulfonyl hydrazide (*p*-$TsNHNH_2$) and aqueous sodium acetate to afford alcohol **18** (Scheme 4). At this stage, the undesired C29 epimer was easily separated by flash chromatography. Tosylation, displacement with sodium cyanide, and hydrolysis under basic conditions led to carboxylic acid **19** in 84% overall yield from **18** (Scheme 4). Coupling[14] of **19** with (*R*)-(+)-4-benzyl-2-oxazolidinone furnished oxazolidinone **20** in 92% yield. The C27 methyl group was successfully incorporated by asymmetric alkylation[15] of **20** under the standard conditions (NaHMDS, MeI, THF, −78 °C), affording **21** in 93% yield as a single isomer by ^{1}H NMR (400 MHz). The chiral auxiliary was reductively removed with $LiAlH_4$ to give alcohol **22**. Oxidation, Wittig reaction of the derived aldehyde, and subsequent DIBALH reduction gave allylic alcohol **23** (98% yield for the three steps). Sharpless epoxidation of **23** afforded hydroxyl epoxide **24** as a single stereoisomer, which was iodinated and reduced with zinc, giving rise to allylic alcohol **25**, thereby establishing the C26 stereocenter. Protection of the resultant hydroxyl group with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and Et_3N, oxidative cleavage of the double bond, and subsequent reduction of the derived aldehyde led to alcohol **26** (83% yield for the four steps). Finally, iodination of **26** under standard conditions furnished iodide **2** in 97% yield.

2.5. Synthesis of the C18–C24 sulfone

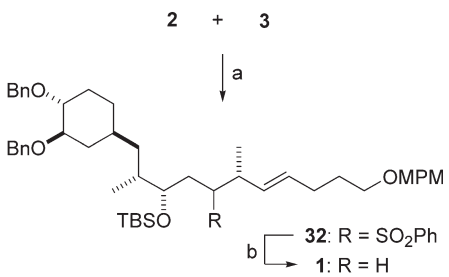
Synthesis of the C18–C24 sulfone **3** was performed based on Julia coupling as a key step, which is delineated in Scheme 5. Iodination of alcohol **27** followed by treatment with $PhSO_2Na$ gave sulfone **28** in 75% yield for the two steps. Coupling of sulfone anion derived from **28** with known aldehyde **29**[1b] (89% yield), acylation and the ensuing exposure to Na(Hg) in buffered methanol afforded olefin **30** (*E*/*Z*=ca. 8:1) in 83% yield for the two steps. Deprotection of the silyl group with TBAF gave alcohol **31**. Treatment of **31** with PhSSPh in the presence of *n*-Bu_3P followed by mCPBA oxidation of the resultant phenyl sulfide afforded sulfone **3** in 75% yield for the two steps.



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, quant.; (b) *p*-TsNHNH$_2$, aq. NaOAc, DME, 95 °C, 80%; (c) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 92%; (d) NaCN, DMSO, 60 °C, 91%; (e) KOH, aq. EtOH, reflux, quant.; (f) PivCl, Et_3N, THF, −78 to 0 °C; LiCl, (*R*)-(−)-4-benzyl-2-oxazolidinone, rt, 92%; (g) NaHMDS, MeI, THF, −78 °C, 93%; (h) $LiAlH_4$, THF, 0 °C, 91%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (j) $Ph_3P{=}CHCO_2Et$, toluene, 80 °C; (k) DIBALH, CH_2Cl_2, −78 °C, 98% (three steps); (l) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 99%; (m) I_2, PPh_3, imidazole, THF, rt; (n) Zn, AcOH, EtOH/CH_2Cl_2, rt, 97% (two steps); (o) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (p) OsO_4, NMO, THF/H_2O, rt; (q) $NaIO_4$, THF/pH 7 buffer, rt; (r) $NaBH_4$, MeOH, 0 °C, 83% (four steps); (s) I_2, PPh_3, imidazole, benzene, rt, 97%.



Scheme 5. Reagents and conditions: (a) I_2, PPh_3, imidazole, THF, rt; (b) $PhSO_2Na$, DMF, rt, 75% (two steps); (c) **28** (2 equiv.), *n*-BuLi, THF, −78 °C; **29**, −78 °C, 89%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt; (e) 5% Na(Hg), Na_2HPO_4, MeOH, 0 °C, 83% (two steps), *E*/*Z*=ca. 8:1; (f) TBAF, THF, rt, quant.; (g) PhSSPh, *n*-Bu_3P, DMF, rt; (h) mCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 75% (two steps).



Scheme 6. Reagents and conditions: (a) **3**, LiHMDS, THF, −78 to 0 °C; **2**, HMPA, rt, 90%; (b) 5% Na(Hg), Na_2HPO_4, THF/MeOH, 0 °C to rt, 71%.

2.6. Completion of the synthesis

With requisite segments in hand, we then turned our attention to the crucial coupling stage. Gratifyingly, union of iodide **2** and sulfone **3** could be efficiently and conveniently achieved (Scheme 6). Thus, sulfone **3** with LiHMDS followed by addition of HMPA and iodide **2** delivered coupling product **32** in 90% yield. The resultant phenylsulfonyl group was removed by treatment with Na(Hg) in buffered methanol, leading to **1** in 71% yield.

3. Conclusion

We have completed the stereoselective synthesis of the C18–C34 fragment of antascomicin A. The key features of the present synthesis are (i) an efficient and stereoselective construction of the C29–C34 cyclohexyl moiety based on catalytic Ferrier carbocyclization and Johnson–Claisen rearrangement and (ii) a convergent assembly of the C25–C34 and C18–C24 segments via sulfone anion coupling. Further efforts toward the total synthesis of antascomicin A are currently underway and will be reported in due course.

4. Experimental

4.1. General methods

All reactions sensitive to air and/or moisture were carried

out under an atmosphere of argon in oven-dried glassware with anhydrous solvents. All anhydrous solvents were purchased from Wako Pure Chemicals Co. Inc. and used without further drying. Triethylamine were distilled from calcium hydride under argon atmosphere. Lithium chloride was dried with heating under high vacuum prior to use. All other reagents purchased were of the highest commercial quality and used as received unless otherwise stated. Analytical thin layer chromatography was carried out using E. Merck silica gel 60 F_{254} plates (0.25 mm thickness). Column chromatography was performed on Kanto Chemical silica gel 60N (spherical, neutral). Flash chromatography was carried out using Fuji Silysia silica gel BW300 (200–400 mesh). Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter. Infrared spectra spectra were recorded on a JASCO FT/IR-420 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA400 or JNM-LA500 spectrometer. Chemical shifts are reported in ppm and tetramethylsilane was used as the internal standard. Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate the multipilicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. Low- and high-resolution mass spectra were recorded on a JEOL SX-102A mass spectrometer under fast atom bombardment (FAB) contions using *m*-nitrobenzyl alcohol (NBA) as a matrix.

4.1.1. Trityl ether 9. To a stirred solution of tri-*O*-acetyl-D-glucal **7** (10.0 g, 36.7 mmol) in acetonitrile (90 mL) were added MeOH (2.30 mL, 56.8 mmol) and $Ph_3P{\cdot}HBr$ (2.53 g, 7.37 mmol). After being stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 25→40% ethyl acetate/hexane) gave methyl glucoside **8** (10.05 g, 90%) as a 10:1 mixture of anomers. Data for major anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (ddd, *J*=11.8, 9.8, 5.9 Hz, 1H), 5.02 (dd, *J*=10.7, 9.8 Hz, 1H), 4.85 (br s, 1H), 4.32 (dd, *J*=12.7, 4.9 Hz, 1H), 4.08 (dd, *J*=12.7, 1.9 Hz, 1H), 3.95 (ddd, *J*=10.7, 4.9, 1.9 Hz, 1H), 3.35 (s, 3H), 2.25 (ddd, *J*=12.7, 5.9, <1 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.82 (ddd, *J*=12.7, 11.8, 3.9 Hz, 1H).

To a solution of the above methyl glucoside **8** (10.05 g, 33.1 mmol) in MeOH (100 mL) was added NaOMe (1 M in MeOH, 3.30 mL, 0.330 mmol). After being stirred at room temperature for 1 h, the reaction was quenched by addition of Amberlyst® and the mixture was filtered and concentrated under reduced pressure to give crude triol, which was used in the next reaction without further purification.

To a solution of the above triol in CH_2Cl_2/pyridine (4:1, v/v, 100 mL) were added DMAP (0.40 g, 3.27 mmol) and triphenylmethyl chloride (11.06 g, 39.7 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 40→50% ethyl acetate/hexane) gave trityl ether **9** (11.82 g, 85% for the two steps) as a colorless clear oil. **9**: $[\alpha]_D^{30}$=+79 (*c* 0.42, $CHCl_3$); IR (film) 3411, 2931, 1490, 1446, 1209, 1128, 1050, 986, 955, 900, 764, 747, 705, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.26 (m, 15H), 4.77 (br s, 1H), 3.92 (m, 1H), 3.61 (m, 1H), 3.44–3.37 (m, 3H), 3.31 (s, 3H), 2.76 (br, 1H), 2.50 (br, 1H), 2.11 (m, 1H), 1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 128.6, 128.3, 128.0, 127.2, 98.5, 87.3, 74.9, 69.4, 68.9, 64.9, 54.7, 36.7; HRMS (FAB) calcd for $C_{26}H_{28}O_5Na$ [(M+Na)$^+$] 443.1834, found 443.1791.

4.1.2. Primary alcohol 10. To a solution of trityl ether **9** (11.82 g, 28.14 mmol) in DMF (100 mL) was added NaH (60% in oil, 5.30 g, 132.5 mmol). The mixture was heated at 50 °C for 20 min and then treated with BnBr (11.8 mL, 99.2 mmol). After being stirred at 50 °C for 50 min, the reaction was cooled to 0 °C and quenched with methanol. The resultant mixture was diluted with ethyl acetate, washed with water, saturated aqueous ammonium chloride and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude bis(benzyl)ether, which was used in the next step without further purification.

To a solution of the above bis(benzyl)ether in MeOH/$CHCl_3$ (5:1, 180 mL) was added *p*-TsOH·H_2O (1.61 g, 8.46 mmol). After being stirred at room temperature overnight, the reaction was quenched with triethylamine and the mixture concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→40% ethyl acetate/hexane) gave primary alcohol **10** (9.55 g, 95% for the two steps) as a colorless clear oil. **10**: $[\alpha]_D^{30}$=+69 (*c* 0.43, $CHCl_3$); IR (film) 3446, 2925, 1453, 1365, 1206, 1097, 1049, 738, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 4.95 (d, *J*=10.7 Hz, 1H), 4.81 (br s, 1H), 4.71–4.62 (m, 3H), 3.99 (ddd, *J*=11.7, 8.8, 4.9 Hz, 1H), 3.85–3.72 (m, 2H), 3.64 (m, 1H), 3.50 (m, 1H), 3.30 (s, 3H), 2.29 (ddd, *J*=14.6, 4.9, <1 Hz, 1H), 1.80 (br, 1H), 1.66 (ddd, *J*=14.6, 11.7, 3.9 Hz, 1H); HRMS (FAB) calcd for $C_{21}H_{26}O_5Na$ [(M+Na)$^+$] 381.1678, found 381.1659.

4.1.3. Iodide 11. To a solution of primary alcohol **10** (9.50 g, 26.5 mmol) in THF (150 mL) were added imidazole (3.61 g, 53.0 mmol), triphenylphosphine (12.5 g, 47.7 mmol) and iodine (12.8 g, 50.4 mmol). After being stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous Na_2SO_3. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10% ethyl acetate/hexane) gave iodide **11** (11.39 g, 92%) as a colorless clear oil. **11**: $[\alpha]_D^{30}$=+49 (*c* 1.12, $CHCl_3$); IR (film) 2930, 2901, 1452, 1366, 1213, 1131, 1108, 1048, 738, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 10H), 5.00 (d, *J*=10.7 Hz, 1H), 4.82 (br s, 1H), 4.72 (d, *J*=10.7 Hz, 1H), 4.63 (d, *J*=11.7 Hz, 1H), 4.60 (d, *J*=11.7 Hz, 1H), 4.00 (ddd, *J*=11.7, 8.8, 4.9 Hz, 1H), 3.53 (m, 1H), 3.46–3.30 (m, 6H), 2.31 (ddd, *J*=12.7, 4.9, <1 Hz, 1H), 1.69 (ddd, *J*=12.7, 11.7, 3.9 Hz, 1H); HRMS (FAB) calcd for $C_{21}H_{25}IO_4Na$ [(M+Na)$^+$] 491.0695, found 491.0728.

4.1.4. Exocyclic enol ether 6. To a solution of iodide **11** (4.96 g, 10.6 mmol) in DMF (100 mL) at 0 °C was added NaH (60% in oil, 2.12 g, 53.0 mmol). After being stirred at room temperature overnight, the reaction was quenched with water at 0 °C. The resultant mixture was diluted with

ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10% ethyl acetate/hexane) gave exocylic enol ether **6** (3.41 g, 94%) as a colorless clear oil. **6**: $[\alpha]_D^{25}=+24$ (*c* 2.63, $CHCl_3$); IR (film) 2931, 2857, 1657, 1452, 1361, 1211, 1111, 1039, 734, 697 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.32 (d, *J*=6.8 Hz, 1H), 7.22 (d, *J*=8.0 Hz, 1H), 7.17–7.05 (m, 8H), 4.95 (apparently s, 1H), 4.86 (apparently s, 1H), 4.68 (d, *J*=11.8 Hz, 1H), 4.65–4.60 (m, 3H), 4.51 (d, *J*=12.7 Hz, 1H), 4.38 (d, *J*=12.7 Hz, 1H), 4.03 (ddd, *J*=9.7, 7.8, 3.9 Hz, 1H), 3.90 (d, *J*=7.8 Hz, 1H), 3.19 (s, 3H), 2.20 (ddd, *J*=13.6, 4.8, 3.9 Hz, 1H), 1.73 (ddd, *J*=13.6, 9.7, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 155.7, 139.3, 139.1, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 100.1, 96.7, 79.9, 76.4, 73.3, 72.2, 55.0, 35.6; HRMS (FAB) calcd for $C_{21}H_{24}O_4Na$ [$(M+Na)^+$] 363.1572, found 363.1530.

4.1.5. Hydroxy ketone 12. To a solution of exocyclic enol ether **6** (507.7 mg, 1.493 mmol) in acetone/water (2:1, v/v, 15 mL) was added $Hg(OCOCF_3)_2$ (64 mg, 0.15 mmol). After being stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure to remove acetone. The resultant mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 50% ethyl acetate/hexane) gave hydroxy ketone **12** (460.1 mg, 95%) as a 10:1 mixture of diastereomers. **12**: $[\alpha]_D^{30}=-22$ (*c* 0.61, $CHCl_3$); IR (film) 3439, 2926, 1727, 1453, 1359, 1207, 1107, 1026, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.39–7.25 (m, 10H), 4.82 (d, *J*=11.7 Hz, 1H), 4.74 (d, *J*=11.7 Hz, 1H), 4.61 (d, *J*=11.7 Hz, 1H), 4.54 (d, *J*=11.7 Hz, 1H), 4.33 (br, 1H), 4.04 (m, 1H), 3.98 (m, 1H), 2.68–2.53 (m, 2H), 2.32 (m, 1H), 2.02 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 206.1, 138.2, 137.6, 128.41, 128.39, 128.0, 127.8, 127.7, 85.7, 77.3, 76.7, 72.9, 65.9, 47.7, 36.5; HRMS (FAB) calcd for $C_{20}H_{22}O_4Na$ [$(M+Na)^+$] 349.1416, found 349.1454.

4.1.6. Enone 13. To a solution of hydroxy ketone **12** (7.87 g, 24.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added Et_3N (20.0 mL, 143.5 mmol) and MsCl (5.60 mL, 72.4 mmol). After being stirred at room temperature for 90 min, the reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→30% ethyl acetate/hexane) gave enone **13** (7.42 g, quantitative) as a colorless clear oil. **13**: IR (film) 3032, 2930, 2870, 1688, 1621, 1496, 1453, 1387, 1360, 1115, 1025, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.27 (m, 10H), 6.83 (ddd, *J*=9.7, 5.8, 2.9 Hz, 1H), 6.04 (d, *J*=9.7 Hz, 1H), 5.02 (d, *J*=11.7 Hz, 1H), 4.80 (d, *J*=11.7 Hz, 1H), 4.73 (d, *J*=11.7 Hz, 1H), 4.65 (d, *J*=11.7 Hz, 1H), 4.05 (d, *J*=8.8 Hz, 1H), 3.94 (m, 1H), 2.78 (ddd, *J*=18.5, 5.8, 4.9 Hz, 1H), 2.51 (ddd, *J*=18.5, 7.8, 2.9 Hz, 1H); HRMS (FAB) calcd for $C_{20}H_{20}O_3Na$ [$(M+Na)^+$] 331.1310, found 331.1336.

4.1.7. Allylic alcohol 5. To a solution of enone **13** (2.10 g, 6.82 mmol) in THF/MeOH (1:1, v/v, 70 mL) at 0 °C were added $CeCl_3{\cdot}7H_2O$ (5.08 g, 13.6 mmol) and $LiBH_4$ (594 mg, 27.3 mmol). After being stirred at 0 °C for 1 h, the reaction was quenched with saturated NH_4Cl. The resultant mixture was diluted with ethyl acetate, washed with water and brine. The combined aqueous layer was back extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20% ethyl acetate/hexane) gave an inseparable 5.3:1 mixture of allylic alcohol **5** and its epimer (2.07 g, 98%) as a colorless clear oil. **5**: $[\alpha]_D^{30}=+18$ (*c* 0.55, $CHCl_3$); IR (film) 3437, 2919, 2864, 1453, 1383, 1362, 1101, 1041, 737, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.36–7.27 (m, 10H), 5.69–5.65 (m, 2H), 4.92 (d, *J*=11.8 Hz, 1H), 4.71 (d, *J*=11.8 Hz, 1H), 4.67 (d, *J*=11.7 Hz, 1H), 4.63 (d, *J*=11.7 Hz, 1H), 4.17 (m, 1H), 3.80 (dd, *J*=8.0, 6.0 Hz, 1H), 3.65 (m, 1H), 2.52 (m, 1H), 2.40 (d, *J*=5.9 Hz, 1H), 2.25 (m, 1H); HRMS (FAB) calcd for $C_{20}H_{22}O_3Na$ [$(M+Na)^+$] 333.1467, found 333.1501.

4.1.8. Ester 4. To a solution of allylic alcohol (6.16 g, 19.9 mmol) in $CH_3C(OEt)_3$ (200 mL) was added *n*-propionic acid (0.200 mL) and the resultant mixture was heated at 140 °C for 1 day. After cooling, the mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5→8% ethyl acetate/hexane) gave an inseparable mixture of ester **4** and its C29 epimer (5.78 g, 76%) as a colorless clear oil. **4**: $[\alpha]_D^{30}=-66$ (*c* 0.57, $CHCl_3$); IR (film) 2924, 2871, 1732, 1453, 1371, 1159, 1094, 1028, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.37–7.25 (m, 10H), 5.67 (dt, *J*=10.3, 2.3 Hz, 1H), 5.61 (dd, *J*=10.3, 1.4 Hz, 1H), 4.76–4.66 (m, 4H), 4.18–4.08 (m, 3H), 3.70 (ddd, *J*=11.9, 7.3, 3.7 Hz, 1H), 2.75 (m, 1H), 2.36 (dd, *J*=15.3, 7.1 Hz, 1H), 2.27 (dd, 1H, *J*=15.3, 7.8 Hz), 2.20 (ddd, *J*=12.8, 3.7, 3.7 Hz, 1H), 1.56 (ddd, *J*=12.8, 11.9, 11.9 Hz, 1H), 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 172.1, 138.8 (×2), 132.1, 128.4 (×2), 128.3, 127.8, 127.73, 127.70, 127.67, 127.5, 127.3, 79.2, 79.0, 72.0, 71.8, 60.5, 40.5, 33.3, 33.0, 14.3; HRMS (FAB) calcd for $C_{24}H_{28}O_4Na$ [$(M+Na)^+$] 403.1885, found 403.1882.

4.1.9. Enoate 14. To a solution of ester **4** (1.37 g, 3.61 mmol) in CH_2Cl_2 (36 mL) at −78 °C was added DIBALH (1.01 M solution in hexane, 3.93 mL, 3.97 mL). After being stirred at −78 °C for 30 min, the reaction was quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with ethyl acetate and stirred vigorously at room temperature until the layers became clear. The organic layer was separated and washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was passed through a pad of silica gel to give aldehyde (0.97 g) as a colorless clear oil, which was used in the next step without further purification.

To a solution of the above aldehyde (0.97 g) in benzene (30 mL) was added $Ph_3P{=}CHCO_2Et$ (1.51 g, 4.33 mmol). After being stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% ethyl acetate/hexane) gave enoate **14** (1.17 g, 80%

for the two steps) as a colorless clear oil. **14**: $[\alpha]_D^{26}=-100$ (*c* 0.46, $CHCl_3$); IR (film) 2861, 1717, 1654, 1452, 1365, 1310, 1267, 1202, 1158, 1094, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 6.90 (dt, *J*=15.6, 7.8 Hz, 1H), 5.85 (d, *J*=15.6 Hz, 1H), 5.64 (d, *J*=9.8 Hz, 1H), 5.60 (d, *J*=9.8 Hz, 1H), 4.77–4.62 (m, 4H), 4.19 (q, *J*=6.8 Hz, 2H), 4.11 (m, 1H), 3.67 (ddd, *J*=11.7, 7.8, 3.9 Hz, 1H), 2.40 (m, 1H), 2.28–2.11 (m, 3H), 1.36–1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 146.1, 138.8 (×2), 132.1, 128.40, 128.37, 128.35, 127.8, 127.7, 127.52, 127.47, 123.4, 79.6, 79.3, 72.1, 71.8, 60.3, 38.5, 35.3, 33.6, 14.3; HRMS (FAB) calcd for $C_{26}H_{30}O_4Na$ [(M+Na)$^+$] 429.2042, found 429.2036.

4.1.10. Hydroxy epoxide 15. To a solution of enoate **14** (1.28 g, 3.15 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added DIBALH (1.01 M solution in hexane, 8.75 mL, 8.84 mmol). After being stirred at −78 °C for 2 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with ethyl acetate and stirred vigorously at room temperature until layers became clear. The organic layer was separated and washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 30⟶40% ethyl acetate/hexane) gave allylic alcohol (1.07 g, 93%) as a colorless clear oil: $[\alpha]_D^{26}=-101$ (*c* 0.62, $CHCl_3$); IR (film) 3435, 2917, 2858, 1452, 1094, 1028, 972, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H), 5.70–5.61 (m, 4H), 4.77–4.68 (m, 4H), 4.12–4.08 (m, 3H), 3.67 (ddd, *J*=11.7, 7.8, 3.9 Hz, 1H), 2.32 (m, 1H), 2.16–2.03 (m, 3H), 1.35–1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 132.9, 131.4, 129.8, 128.4, 128.3, 127.8, 127.7, 127.5, 127.0, 79.9, 79.6, 72.0, 71.8, 63.6, 38.6, 36.0, 33.6; HRMS (FAB) calcd for $C_{24}H_{28}O_3Na$ [(M+Na)$^+$] 387.1936, found 387.1966.

To a solution of allylic alcohol (1.00 g, 2.75 mmol) in CH_2Cl_2 (30 mL) were added 4 Å molecular sieves (1.00 g) and (+)-diethyl tartrate (0.100 mL, 0.584 mmol). The mixture was cooled to −20 °C and treated with titanium isopropoxide (0.120 mL, 0.407 mmol). After being stirred at −20 °C for 30 min, *t*-butyl hydroperoxide (5 M solution in decane, 0.830, 4.15 mL) was introduced. After being stirred at −20 °C overnight, the reaction was quenched with saturated aqueous Na_2SO_4. The resultant mixture was filtered through Celite® and the filtrate was extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 40⟶50% ethyl acetate/hexane) gave hydroxy epoxide **15** (674.8 mg, 65%) as a colorless clear oil. **15**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H), 5.69–5.67 (m, 2H), 4.77–4.67 (m, 2H), 4.12 (dd, *J*=7.8, 2.9 Hz, 1H), 3.91 (ddd, *J*=12.7, 4.9, 2.0 Hz, 1H), 3.72–3.61 (m, 2H), 3.02 (m, 1H), 2.91 (m, 1H), 2.49 (m, 1H), 2.01 (ddd, *J*=12.6, 4.0, 3.9 Hz, 1H), 1.73 (m, 1H), 1.69–1.51 (m, 2H), 1.41 (ddd, *J*=12.6, 11.7, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (×2), 132.2, 128.4, 127.8, 127.7, 127.5, 127.3, 79.5, 79.3, 72.1, 71.7, 61.4, 58.4, 53.9, 37.9, 34.3, 33.9.

4.1.11. Bicyclic compound 16. To a solution of hydroxy epoxide **15** (674.8 mg, 1.78 mmol) in CH_2Cl_2/hexane (1:2, v/v, 30 mL) at −78 °C was added $AlMe_3$ (1.00 M solution in hexane, 5.34 mL, 5.34 mmol). The reaction mixture was allowed to warm to 0 °C over 3 h and the reaction was quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with ethyl acetate and stirred vigorously at room temperature until layers became clear. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 60⟶75% ethyl acetate/hexane) gave bicyclic compound **16** (491.2 mg, 95%) as a pale yellow oil. **16**: $[\alpha]_D^{26}=-127$ (*c* 0.79, $CHCl_3$); IR (film) 3423, 2925, 2877, 1452, 1398, 1059, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 6.08–6.06 (m, 2H), 4.66 (d, *J*=11.7 Hz, 1H), 4.58 (d, *J*=11.7 Hz, 1H), 4.17 (br s, 1H), 3.80–3.55 (m, 5H), 2.62 (d, *J*=4.9 Hz, 1H), 2.55 (br s, 1H), 2.35 (m, 1H), 1.83–1.73 (m, 2H), 1.64 (ddd, *J*=12.7, 11.7, 3.9 Hz, 1H), 1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.9, 128.8, 128.4, 128.3, 127.7, 127.6, 73.9, 73.7, 71.5, 70.9, 70.6, 63.4, 29.3, 27.8, 26.7; HRMS (FAB) calcd for $C_{17}H_{22}O_4Na$ [(M+Na)$^+$] 313.1416, found 313.1381.

4.1.12. Bis(acetate) 17. To a solution of bicyclic compound **16** (491.2 mg, 1.69 mmol) in CH_2Cl_2 (15 mL) 0 °C were added Et_3N (1.90 mL, 13.6 mmol), DMAP (62 mg, 0.507 mmol) and Ac_2O (1.00 mL, 10.6 mmol). After being stirred at room temperature for 2 h 15 min, the reaction was quenched with MeOH at 0 °C. The resultant mixture was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 20⟶30% ethyl acetate/hexane) gave bis(acetate) **17** (421.4 mg, 67%) as a colorless clear oil. **17**: $[\alpha]_D^{25}=-139$ (*c* 0.61, $CHCl_3$); IR (film) 2927, 2850, 1743, 1451, 1370, 1225, 1059, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 6.07–6.05 (m, 2H), 5.00 (ddd, *J*=7.1, 6.0, 2.5 Hz, 1H), 4.68 (d, *J*=12.1 Hz, 1H), 4.56 (d, *J*=12.1 Hz, 1H), 4.41 (dd, *J*=12.1, 2.5 Hz, 1H), 4.15 (br, 1H), 4.14 (ddd, *J*=12.1, 7.1 Hz, 1H), 3.78 (ddd, *J*=11.7, 6.0, 3.2 Hz, 1H), 3.69 (br, 1H), 2.55 (br, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.76 (br, 2H), 1.58 (ddd, *J*=12.6, 12.1, 3.7 Hz, 1H), 1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.3, 138.4, 133.6, 129.0, 128.4, 127.7, 127.64, 127.60, 73.75, 73.70, 71.5, 70.5, 67.7, 62.9, 30.0, 27.5, 26.8, 21.0, 20.8; HRMS (FAB) calcd for $C_{21}H_{26}O_6Na$ [(M+Na)$^+$] 397.1627, found 397.1613.

4.1.13. Alcohol 18. To a solution of ester **4** (5.78 g, 15.2 mmol) in THF (120 mL) at 0 °C was added $LiAlH_4$ (692 mg, 18.2 mmol). After being stirred at 0 °C for 1 h, the mixture was successively treated with 15% aqueous NaOH and water, and the precipitate formed was removed by filtration. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 40% ethyl acetate/hexane) gave an inseparable mixture of alcohol and its C29 epimer (5.13 g, quantitative) as a colorless clear oil: $[\alpha]_D^{30}=-82$ (*c* 0.35, $CHCl_3$); IR (film) 3436, 2924, 2862, 1452, 1072, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.37–7.26 (m, 10H), 5.64 (br, 2H), 4.77–4.68 (m, 4H), 4.12

(m, 1H), 3.78–3.65 (m, 3H), 2.43 (m, 1H), 2.17 (ddd, J=11.9, 4.6, 3.7 Hz, 1H), 1.72–1.63 (m, 2H), 1.53 (m, 1H), 1.31 (ddd, J=11.9, 11.9, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 138.9 (×2), 133.3, 128.38, 128.36, 128.34, 127.77, 127.75, 127.69, 127.5, 126.6, 79.8, 79.6, 72.0, 71.8, 60.3, 40.3, 33.7, 32.8; HRMS (FAB) calcd for $C_{22}H_{26}O_3Na$ [(M+Na)$^+$] 361.1780, found 361.1738.

A solution of the above alcohol (5.13 g, 15.2 mmol) and *p*-toluenesulfonyl hydrazide (28.3 g, 152 mmol) in DME (80 mL) was heated at 95 °C. To this solution was added dropwise aqueous NaOAc (19.9 g, 243 mmol) in water (80 mL) over a period of 4 h, and the resultant mixture was heated at 95 °C for further 1 h. After cooling, the resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 35→40% ethyl acetate/hexane) gave alcohol **18** (4.10 g, 80%) as a colorless clear oil. **18**: IR (film) 3435, 2925, 2863, 1453, 1100, 1070, 1027, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H), 4.77–4.68 (m, 4H), 3.69–3.67 (m, 2H), 3.43–3.36 (m, 2H), 2.13–2.07 (m, 2H), 1.73 (m, 1H), 1.62–1.42 (m, 5H), 1.32 (m, 1H), 1.05 (ddd, J=11.7, 11.4, 11.4 Hz, 1H), 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (×2), 128.3 (×2), 127.7 (×2), 127.4 (×2), 82.5, 81.9, 72.4, 72.3, 60.7, 39.2, 37.7, 32.5, 30.6, 30.3; HRMS (FAB) calcd for $C_{22}H_{28}O_3Na$ [(M+Na)$^+$] 363.1936, found 363.1890.

4.1.14. Carboxylic acid 19. To a solution of alcohol **18** (4.10 g, 12.1 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (6.75 mL, 48.4 mmol), DMAP (0.44 g, 3.60 mmol) and *p*-toluenesulfonyl chloride (5.77 g, 30.3 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10→20% ethyl acetate/hexane) gave tosylate (5.46 g, 92%) as a colorless clear oil: $[\alpha]_D^{28}$=−9 (*c* 0.45, $CHCl_3$); IR (film) 2925, 2864, 1452, 1360, 1175, 1097, 738, 697, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J=8.4 Hz, 2H), 7.36–7.26 (m, 12H), 4.73–4.62 (m, 4H), 4.05 (t, J=6.41 Hz, 2H), 3.35–3.30 (m, 2H), 2.43 (s, 3H), 2.06–1.97 (m, 2H), 1.59–1.55 (m, 3H), 1.43 (m, 1H), 1.24 (m, 1H), 0.96 (ddd, J=12.1, 12.1, 11.0 Hz, 1H), 0.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 139.1, 139.0, 133.0, 129.9, 128.3, 127.9, 127.6, 127.43, 127.40, 82.2, 81.6, 72.4, 72.3, 68.4, 37.2, 35.1, 32.1, 30.1, 30.0, 21.6; HRMS (FAB) calcd for $C_{29}H_{34}O_5SNa$ [(M+Na)$^+$] 517.2025, found 517.2017.

To a solution of the above tosylate (5.28 g, 10.7 mmol) in DMSO (100 mL) was added NaCN (2.62 g, 53.5 mmol). After being stirred at 60 °C for 4 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 25% ethyl acetate/hexane) gave nitrile (3.40 g, 91%) as a colorless clear oil: $[\alpha]_D^{28}$=−9 (*c* 0.51, $CHCl_3$); IR (film) 2925, 2862, 1452, 1100, 1068, 1028, 737, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 4.79–4.67 (m, 4H), 3.44–3.36 (m, 2H), 2.35 (t, J=7.3 Hz, 2H), 2.14–2.07 (m, 2H), 1.74 (m, 1H), 1.60 (q, J=7.3 Hz, 2H), 1.51 (m, 1H), 1.34 (m, 1H), 1.03 (ddd, J=12.6, 12.1, 11.2 Hz, 1H), 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.04, 138.99, 128.34, 128.32, 127.7, 127.6, 127.5, 127.4, 119.6, 82.2, 81.4, 72.6, 72.3, 37.0, 34.8, 31.6, 29.9, 29.8, 15.0; HRMS (FAB) calcd for $C_{23}H_{27}NO_2Na$ [(M+Na)$^+$] 372.1939, found 372.1942.

To a solution of the above nitrile (3.40 g, 9.74 mmol) in EtOH/water (1:1, v/v, 100 mL) was added KOH (5.47 g, 97.5 mmol) and the resultant mixture was heated under reflux overnight. After cooling to room temperature, the resultant mixture was acidified with 1 M aqueous HCl and extracted with $CHCl_3$. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5% methanol/chloroform) gave carboxylic acid **19** (3.58 g, quantitative) as a colorless clear oil. **19**: $[\alpha]_D^{29}$=−13 (*c* 0.36, $CHCl_3$); IR (film) 3446, 2927, 2863, 1707, 1453, 1100, 1071, 737, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 10H), 4.77–4.67 (m, 4H), 3.42–3.35 (m, 2H), 2.38 (t, J=7.6 Hz, 2H), 2.12–2.08 (m, 2H), 1.73 (m, 1H), 1.59 (q, J=7.6 Hz, 2H), 1.42–1.24 (m, 2H), 1.02 (ddd, J=12.4, 12.4, 11.0 Hz, 1H), 0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 139.1 (×2), 128.3 (×2), 127.7 (×2), 127.4 (×2), 82.4, 81.7, 72.4, 72.3, 37.3, 35.3, 31.6, 31.0, 30.20, 30.18.

4.1.15. Oxazolidinone 20. To a solution of carboxylic acid **19** (1.30 g, 3.53 mmol) in THF (30 mL) was added Et_3N (0.980 mL, 7.03 mmol) and cooled to −78 °C. The reaction mixture was treated with pivaloyl chloride (0.520 mL, 4.22 mmol) and gradually warmed to 0 °C over 90 min. The reaction mixture was then treated with (*R*)-4-benzyl-2-oxazolidinone (626 mg, 3.53 mmol) and LiCl (450 mg, 10.6 mmol) and stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→30% ethyl acetate/hexane) gave oxazolidinone **20** (1.68 g, 92%) as a colorless clear oil. **20**: $[\alpha]_D^{27}$=−43 (*c* 0.36, $CHCl_3$); IR (film) 2925, 2861, 1780, 1699, 1452, 1386, 1354, 1211, 1098, 738, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 15H), 4.77–4.66 (m, 5H), 4.20–4.16 (m, 2H), 3.42–3.38 (m, 2H), 3.29 (dd, J=13.4, 3.4 Hz, 1H), 3.02–2.87 (m, 2H), 2.76 (dd, J=13.4, 9.4 Hz, 1H), 2.18–2.09 (m, 2H), 1.77 (m, 1H), 1.66–1.61 (m, 2H), 1.41 (m, 1H), 1.32 (m, 1H), 1.07 (ddd, J=12.5, 12.5, 11.0 Hz, 1H), 0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 153.5, 139.2 (×2), 135.3, 129.4, 129.0, 128.34, 128.30, 127.68, 127.66, 127.39, 127.36, 82.5, 81.9, 72.34, 72.28, 66.2, 55.2, 37.9, 37.6, 35.4, 33.3, 30.7, 30.4, 30.3; HRMS (FAB) calcd for $C_{33}H_{37}NO_5Na$ [(M+Na)$^+$] 550.2569, found 550.2576.

4.1.16. Alkylated product 21. To a solution of oxazolidinone **20** (4.54 g, 8.82 mmol) in THF (80 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 12.3 mL, 12.3 mmol). The reaction mixture was stirred at −78 °C for 1 h before methyl iodide (1.21 mL, 19.4 mmol) was introduced. The resultant mixture was stirred at −78 °C for

6 h and the reaction was quenched with saturated aqueous NH_4Cl at −40 °C. The resultant mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 20% ethyl acetate/hexane) gave alkylated product **21** (4.38 g, 94%) as a colorless clear oil. **21**: $[\alpha]_D^{29}=-51$ (*c* 1.15, $CHCl_3$); IR (film) 2926, 2864, 1780, 1697, 1453, 1386, 1351, 1235, 1210, 1099, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 15H), 4.75–4.66 (m, 5H), 4.22–4.16 (m, 2H), 3.82 (m, 1H), 3.42–3.32 (m, 2H), 3.26 (dd, *J*=13.3, 2.7 Hz, 1H), 2.77 (dd, *J*=13.3, 9.6 Hz, 1H), 2.15–2.06 (m, 2H), 1.83–1.69 (m, 2H), 1.31–1.21 (m, 6H), 1.08–0.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 153.0, 139.2 (×2), 135.2, 129.4, 128.9, 128.32, 128.27, 127.64, 127.59, 127.4, 127.34, 127.32, 82.4, 81.8, 72.3, 72.2, 66.1, 55.3, 39.8, 37.9, 37.7, 35.3, 33.7, 30.7, 30.3, 18.3; HRMS (FAB) calcd for $C_{34}H_{39}NO_5Na$ [$(M+Na)^+$] 564.2726, found 564.2744.

4.1.17. Primary alcohol 22. To a solution of alkylated product **21** (1.35 g, 2.55 mmol) in THF (30 mL) at 0 °C was added $LiAlH_4$ (116 mg, 3.06 mmol). After being stirred at 0 °C, the reaction was quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with ethyl acetate and stirred at room temperature until the layers became clear. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 30% ethyl acetate/hexane) gave primary alcohol **22** (858.4 mg, 91%) as a colorless clear oil. **22**: $[\alpha]_D^{25}=-4$ (*c* 0.85, $CHCl_3$); IR (film) 3437, 2924, 2864, 1452, 1383, 1367, 1101, 1068, 1028, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 4.77–4.68 (m, 4H), 3.49–3.36 (m, 4H), 2.13–2.07 (m, 2H), 1.75–1.65 (m, 2H), 1.41 (m, 1H), 1.37–1.23 (m, 3H), 1.06 (ddd, *J*=13.7, 8.2, 5.5 Hz, 1H), 0.99–0.87 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (×2), 128.3 (×2), 127.7 (×2), 127.4, 82.6, 82.0, 72.32, 72.26, 68.5, 40.1, 37.4, 33.2, 33.0, 31.5, 30.4, 16.9; HRMS (FAB) calcd for $C_{24}H_{32}O_3Na$ [$(M+Na)^+$] 391.2249, found 391.2249.

4.1.18. Allylic alcohol 23. To a solution of oxalyl chloride (0.400 mL, 4.59 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DMSO (0.480 mL, 6.76 mmol). After being stirred at −78 °C for 15 min, a solution of primary alcohol **22** (830.4 mg, 2.257 mmol) in CH_2Cl_2 (10 mL+5 mL rinse) was introduced. After being stirred at −78 °C for further 15 min, the reaction mixture was treated with Et_3N (1.26 mL, 9.04 mmol) and allowed to warm to room temperature over 30 min. The resultant mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude aldehyde, which was immediately used in the next reaction without further purification.

To a solution of the above aldehyde in CH_2Cl_2 (30 mL) was added $Ph_3P{=}CHCO_2Et$ (1.10 g, 3.16 mmol). After being stirred at room temperature overnight, the resultant mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% ethyl acetate/hexane) gave enoate (1.059 g) as a colorless clear oil, which was used in the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H), 6.81 (dd, *J*=15.6, 8.4 Hz, 1H), 5.77 (d, *J*=15.6 Hz, 1H), 4.77–4.68 (m, 4H), 4.19 (q, *J*=7.3 Hz, 2H), 3.42–3.32 (m, 2H), 2.39 (m, 1H), 2.11–2.00 (m, 2H), 1.71 (m, 1H), 1.38–1.19 (m, 7H), 1.07–0.94 (m, 4H), 0.85 (m, 1H).

To a solution of the above enoate (1.059 g) in CH_2Cl_2 (20 mL) at −78 °C was added DIBALH (0.95 M solution in hexane, 7.13 mL, 7.51 mmol). After being stirred at −78 °C for 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with ethyl acetate and stirred vigorously at room temperature until layers became clear. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 30% ethyl acetate/hexane) gave allylic alcohol **23** (872.1 mg, 98% for the three steps) as a colorless clear oil. **23**: $[\alpha]_D^{25}=-38$ (*c* 0.20, $CHCl_3$); IR (film) 3436, 2924, 2864, 1452, 1370, 1098, 1075, 971, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H), 5.59 (dt, *J*=15.3, 5.3 Hz, 1H), 5.52 (dd, *J*=15.3, 7.3 Hz, 1H), 4.77–4.68 (m, 4H), 4.09 (dd, *J*=5.5, 5.3 Hz, 2H), 3.42–3.32 (m, 2H), 2.23 (m, 1H), 2.12–2.02 (m, 2H), 1.73 (m, 1H), 1.40–1.10 (m, 5H), 1.04–0.92 (m, 4H), 0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.7, 128.3, 127.64, 127.62, 127.33, 127.27, 82.7, 81.9, 72.3, 72.2, 63.8, 43.7, 38.1, 33.7, 33.4, 30.4, 30.3, 20.9; HRMS (FAB) calcd for $C_{26}H_{34}O_3Na$ [$(M+Na)^+$] 417.2406, found 417.2399.

4.1.19. Hydroxy epoxide 24. To a solution of allylic alcohol **23** (842.1 mg, 2.137 mmol) in CH_2Cl_2 (20 mL) were added 4 Å molecular sieves (1.00 g) and (−)-diethyl tartrate (0.550 mL, 3.21 mmol). The reaction mixture was cooled to −20 °C and treated with titanium isopropoxide (0.760 mL, 2.57 mmol). After being stirred at −20 °C for 30 min, *t*-butyl hydroperoxide (5 M solution in decane, 1.28 mL, 6.40 mmol) was introduced. After being stirred at −20 °C for 4 h, the reaction mixture was treated with 0.5 M tartaric acid and stirred at room temperature for 1 h. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was taken up in ether (30 mL) and treated with 1 M aqueous NaOH (20 mL) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 40% ethyl acetate/hexane) gave hydroxy epoxide **24** (870.5 mg, 99%) as a colorless clear oil. **24**: $[\alpha]_D^{26}=-6$ (*c* 0.21, $CHCl_3$); IR (film) 3438, 2924, 2864, 1616, 1453, 1383, 1102, 1070, 1028, 902, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 4.77–4.68 (m, 4H), 3.91 (ddd, *J*=12.5, 5.5, 2.4 Hz, 1H), 3.62 (ddd, *J*=12.5, 7.3, 4.3 Hz, 1H), 3.45–3.34 (m, 2H), 2.92 (m, 1H), 2.73 (dd, *J*=7.4, 2.2 Hz, 1H), 2.12–2.05 (m, 2H), 1.74 (m, 1H), 1.63–1.39 (m, 3H), 1.33 (m, 1H), 1.23 (m, 1H), 1.02–0.85 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (×2), 128.3, 127.7, 127.6, 127.3, 82.6, 81.9, 72.3, 72.2, 61.8, 60.7, 56.8, 41.7, 37.7, 33.3, 32.8, 31.1, 30.4, 16.5; HRMS (FAB) calcd for $C_{26}H_{34}O_4Na$ [$(M+Na)^+$] 433.2355, found 433.2400.

4.1.20. Secondary allylic alcohol 25. To a solution of hydroxy epoxide **24** (756.1 mg, 1.844 mmol) in THF (20 mL) were added imidazole (377 mg, 5.538 mmol), triphenylphosphine (1.45 g, 5.528 mmol) and iodine (937 mg, 3.689 mmol). After being stirred at room temperature for 90 min, the reaction was quenched with saturated aqueous Na_2SO_3. The resultant solution was diluted with ethyl acetate, washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give iodoepoxide, which was used in the next reaction without further purification.

To a solution of the above crude iodoepoxide in EtOH/CH_2Cl_2 (2:1, v/v, 24 mL) were added zinc dust (1.21 g, 18.5 mmol) and acetic acid (0.210 mL, 3.67 mmol). After being stirred at room temperature for 2 h, the reaction mixture was filtered through Celite®, and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 15→30% ethyl acetate/hexane) gave secondary allylic alcohol **25** (706.8 mg, 97% for the two steps) as a colorless clear oil. **25**: $[\alpha]_D^{26}=-19$ (*c* 1.32, $CHCl_3$); IR (film) 3442, 2925, 2868, 1453, 1373, 1100, 1027, 993, 920, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H), 5.84 (ddd, *J*=17.1, 10.4, 6.4 Hz, 1H), 5.22 (dd, *J*=17.1, ~1 Hz, 1H), 5.18 (dd, *J*=10.4, ~1 Hz, 1H), 4.76–4.67 (m, 4H), 3.93 (m, 1H), 3.42–3.33 (m, 2H), 2.15–2.07 (m, 2H), 1.75–1.63 (m, 2H), 1.50 (m, 1H), 1.47–1.28 (m, 3H), 1.06 (m, 1H), 1.02–0.86 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 139.0, 128.3, 127.6, 127.3, 115.9, 82.6, 82.1, 80.5, 72.3, 72.2, 38.9, 37.0, 35.8, 33.3, 31.9, 30.5, 15.2; HRMS (FAB) calcd for $C_{26}H_{34}O_3Na$ [$(M+Na)^+$] 417.2406, found 417.2399.

4.1.21. Primary alcohol 26. To a solution of secondary allylic alcohol **25** (127.9 mg, 0.3246 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added Et_3N (0.180 mL, 1.29 mmol) and TBSOTf (0.220 mL, 0.958 mmol). After being stirred at 0 °C for 40 min, the reaction was quenched with MeOH. The resultant mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude silyl ether, which was used in the next reaction without further purification.

To a solution of the above crude silyl ether in THF/water (1:1, v/v, 6 mL) were added NMO (190 mg, 1.622 mmol) and a small crystal of OsO_4. After being stirred at room temperature for 3.5 h, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude diol, which was used in the next reaction without further purification.

To a solution of the above crude diol in THF/pH 7 buffer (1:1, v/v, 6 mL) at 0 °C was added $NaIO_4$ (208 mg, 0.972 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude aldehyde, which was used in the next reaction without further purification.

To a solution of the above crude aldehyde in MeOH (6 mL) at 0 °C was added $NaBH_4$ (15 mg, 0.397 mmol). After being stirred at 0 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10→20% ethyl acetate/hexane) gave primary alcohol **26** (138.2 mg, 83% for the four steps) as a colorless clear oil. **26**: $[\alpha]_D^{29}=-9$ (*c* 0.43, $CHCl_3$); IR (film) 3446, 2928, 2856, 1455, 1383, 1362, 1252, 1097, 835, 775, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 10H), 4.78–4.67 (m, 4H), 3.60–3.49 (m, 3H), 3.42–3.33 (m, 2H), 2.11–2.07 (m, 2H), 1.80–1.70 (m, 2H), 1.65 (m, 1H), 1.42–1.24 (m, 3H), 1.06–0.83 (m, 15H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.22, 139.20, 128.3, 127.64, 127.62, 127.34, 127.32, 82.6, 82.0, 76.8, 72.4, 72.2, 63.4, 39.5, 37.0, 33.7, 33.4, 31.9, 30.4, 25.9, 18.1, 15.2, −4.4, −4.5; HRMS (FAB) calcd for $C_{31}H_{48}O_4SiNa$ [$(M+Na)^+$] 535.3220, found 535.3235.

4.1.22. Iodide 2. To a solution of primary alcohol **26** (644.7 mg, 1.259 mmol) in benzene (20 mL) were added imidazole (257 mg, 3.775 mmol), triphenylphosphine (826 mg, 3.149 mmol) and iodine (640 mg, 2.520 mmol). After being stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous Na_2SO_3. The resultant mixture was diluted with ethyl acetate, washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% ethyl acetate/hexane) gave iodide **2** (741.5 mg, 96%) as a colorless clear oil. **2**: $[\alpha]_D^{29}=-1$ (*c* 0.40, $CHCl_3$); IR (film) 2926, 2855, 1453, 1384, 1254, 1101, 1071, 836, 775, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 10H), 4.78–4.68 (m, 4H), 3.42–3.36 (m, 3H), 3.18–3.26 (m, 2H), 2.15–2.08 (m, 2H), 1.86 (m, 1H), 1.65 (m, 1H), 1.37–1.30 (m, 2H), 1.25 (ddd, *J*=13.4, 9.7, 3.7 Hz, 1H), 1.06 (m, 1H), 1.00–0.86 (m, 11H), 0.82 (d, *J*=7.0 Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3 (×2), 128.30 (×2), 128.29 (×2), 127.69 (×2), 127.65 (×2), 127.3 (×2), 82.6, 82.0, 76.1, 72.3, 72.2, 38.1, 37.0, 35.4, 33.5, 32.1, 30.5, 25.9, 18.1, 15.7, 11.2, −4.1, −4.6; HRMS (FAB) calcd for $C_{31}H_{47}IO_3SiNa$ [$(M+Na)^+$] 645.2237, found 645.2272.

4.1.23. Sulfone 28. To a solution of alcohol **27** (4.17 g, 19.9 mmol) in toluene (100 mL) were added imidazole (4.06 g, 59.6 mmol), triphenylphosphine (10.4 g, 39.7 mol) and iodine (10.1 g, 39.8 mmol). After being stirred at room temperature for 25 min, the reaction was quenched with saturated aqueous Na_2SO_3. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5% ethyl acetate/hexane) gave iodide (6.00 g, 94%) as a colorless clear oil.

To a solution of the above iodide (6.00 g, 18.8 mmol) in DMF (100 mL) was added $PhSO_2Na$ (15.5 g, 94.4 mmol).

After being stirred at room temperature for 4 h, the resultant mixture was diluted with ethyl acetate, washed with water (×2) and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 30% ethyl acetate/hexane) gave sulfone **28** (4.99 g, 80%) as a colorless clear oil. **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=7.6 Hz, 2H), 7.67–7.54 (m, 3H), 7.19 (d, J=7.6 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 4.40 (s, 2H), 3.81 (s, 3H), 3.41 (t, J=6.8 Hz, 2H), 3.11 (t, J=8.0 Hz, 2H), 1.86–1.78 (m, 2H), 1.69–1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 139.1, 133.6, 130.3, 129.2, 128.1, 113.8, 72.6, 68.9, 56.0, 55.3, 28.2, 20.0.

4.1.24. (*E*)-Olefin 30. To a solution of sulfone **28** (4.55 g, 13.8 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (1.58 M solution in hexane, 7.30 mL, 11.5 mmol). After being stirred at −78 °C for 30 min, a solution of aldehyde **29** (1.73 g, 8.56 mmol) in THF (40 mL) was introduced. Stirring was continued for 1 h at −78 °C before the reaction was quenched with saturated aqueous NH_4Cl. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→40% ethyl acetate/hexane) gave coupling product (3.93 g, 89%) as a colorless clear oil.

To a solution of the above coupling product (3.93 g) in CH_2Cl_2 (80 mL) at 0 °C were added Et_3N (2.00 mL, 14.3 mmol), DMAP (88 mg, 0.720 mmol) and Ac_2O (10.7 mmol). The reaction mixture was allowed to warm to room temperature over 90 min. The reaction was quenched with MeOH at 0 °C and the resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→30% ethyl acetate/hexane) gave acetate (4.08 g, 96%) as a colorless clear oil.

To a solution of the above acetate (4.08 g) in MeOH (70 mL) at 0 °C were added Na_2HPO_4 (19.6 g, 138 mmol) and Na(Hg) (5%, 31.8 g, 69.0 mmol). After being stirred at room temperature overnight, the reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5→10% ethyl acetate/hexane) gave (*E*)-olefin **30** (2.21 g, 83% for the two steps) as a colorless clear oil. **30**: $[\alpha]_D^{28}$=−1 (*c* 0.36, $CHCl_3$); IR (film) 2954, 2929, 2855, 1613, 1513, 1464, 1249, 1101, 1038, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 2H), 6.89–6.86 (m, 2H), 5.42 (dt, J=15.6, 6.8 Hz, 1H), 5.32 (dd, J=15.6, 6.8 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.48–3.42 (m, 3H), 3.34 (dd, J=9.7, 6.8 Hz, 1H), 2.26 (m, 1H), 2.10–2.03 (m, 2H), 1.70–1.62 (m, 2H), 0.95 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 133.3, 130.8, 129.3, 129.2, 113.8, 72.5, 69.5, 68.3, 55.3, 39.3, 29.6, 29.3, 26.0, 18.4, 16.8, −5.27, −5.31; HRMS (FAB) calcd for $C_{22}H_{38}O_3SiNa$ [(M+Na)$^+$] 401.2488, found 401.2472.

4.1.25. Alcohol 31. To a solution of (*E*)-olefin **30** (1.94 g, 5.13 mmol) in THF (40 mL) was added TBAF (1.0 M solution in THF, 15.4 mL, 15.4 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 20→40% ethyl acetate/hexane) gave alcohol **31** (1.35 g, quant.) as a colorless clear oil. **31**: IR (film) 3436, 2929, 2860, 1612, 1513, 1460, 1247, 1175, 1097, 1035, 971, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 2H), 6.89–6.87 (m, 2H), 5.53 (dt, J=15.5, 6.7 Hz, 1H), 5.37 (dd, J=15.5, 7.9 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.47 (m, 1H), 3.38 (t, J=6.3 Hz, 2H), 3.33 (ddd, J=10.3, 7.9, 4.2 Hz, 1H), 2.29 (m, 1H), 2.13–2.08 (m, 2H), 1.70–1.65 (m, 2H), 1.45 (dd, J=7.9, 4.2 Hz, 1H), 0.97 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 132.8, 131.6, 130.7, 129.3, 113.8, 72.5, 69.3, 67.3, 55.3, 39.7, 29.5, 29.3, 16.6; HRMS (FAB) calcd for $C_{16}H_{24}O_3Na$ [(M+Na)$^+$] 287.1623, found 287.1642.

4.1.26. Sulfone 3. To a solution of alcohol **31** (1.80 g, 6.82 mmol) in DMF (50 mL) were added diphenyl disulfide (2.98 g, 13.6 mmol) and *n*-Bu_3P (3.40 mL, 13.6 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5→10% ethyl acetate/hexane) gave phenyl sulfide (2.23 g, 92%) as a colorless clear oil: $[\alpha]_D^{28}$=+22 (*c* 0.43, $CHCl_3$); IR (film) 2927, 2853, 1612, 1585, 1513, 1480, 1456, 1439, 1364, 1301, 1247, 1173, 1097, 1037, 969, 820, 739, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 6H), 7.15 (m, 1H), 6.88–6.86 (m, 2H), 5.43 (dt, J=15.3, 6.0 Hz, 1H), 5.35 (dd, J=15.3, 7.1 Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.44 (t, J=6.4 Hz, 2H), 2.91 (dd, J=12.4, 6.9 Hz, 1H), 2.80 (dd, J=12.4, 7.1 Hz, 1H), 2.38 (m, 1H), 2.10–2.05 (m, 2H), 1.69–1.61 (m, 2H), 1.09 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.9, 137.3, 134.4, 130.8, 129.6, 129.5, 129.3, 128.9, 128.8, 125.6, 113.8, 103.1, 72.5, 69.3, 55.3, 40.9, 36.4, 29.4, 29.0, 20.0; HRMS (FAB) calcd for $C_{22}H_{28}O_2SNa$ [(M+Na)$^+$] 379.1708, found 379.1730.

To a solution of the above phenyl sulfide (1.90 g, 5.34 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added $NaHCO_3$ (2.24 g, 26.7 mmol) and mCPBA (75% purity, 3.07 g, 13.3 mmol). After being stirred at room temperature for 45 min, the reaction mixture was cooled to 0 °C and the reaction was quenched with saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1:1, v/v). The resultant mixture was diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20→25% ethyl acetate/hexane) gave sulfone **3** (1.67 g, 81%) as a colorless clear oil. **3**: $[\alpha]_D^{30}$=+2 (*c* 1.15, $CHCl_3$); IR (film) 2929, 2854, 1611, 1512, 1446, 1301, 1246, 1146, 1087, 1033, 821, 745, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.88 (m, 2H), 7.63–7.53 (m, 3H), 7.26–7.24 (m, 2H), 6.90–6.86 (m, 2H), 5.38 (dt, J=15.2, 6.7 Hz, 1H), 5.22 (dd, J=15.2, 7.3 Hz, 1H), 4.40 (s, 2H), 3.80 (s, 3H), 3.39 (t, J=6.7 Hz, 2H), 3.10 (dd, J=14.0, 6.1 Hz, 1H), 3.01 (dd, J=14.0, 6.7 Hz, 1H), 2.74 (m, 1H),

2.00–1.96 (m, 2H), 1.63–1.56 (m, 2H), 1.12 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 140.1, 133.5, 132.8, 130.7, 130.1, 129.24, 129.18, 128.0, 113.8, 113.7, 72.5, 69.2, 62.4, 55.3, 32.0, 29.2, 28.9, 20.7; HRMS (FAB) calcd for $C_{22}H_{28}O_4SNa$ [(M+Na)$^+$] 411.1606, found 411.1599.

4.1.27. C18–C34 fragment 1. To a solution of sulfone **3** (216.1 mg, 0.5570 mmol) in THF (2 mL) at −78 °C was added LiHMDS (1.0 M solution in THF, 0.480 mL, 0.480 mmol). After being stirred at −78 °C for 25 min, the reaction mixture was warmed to 0 °C and treated with HMPA (0.400 mL) and iodide **2** (141.5 mg, 0.2312 mmol) in THF (2 mL). After being stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl at 0 °C. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5→10% ether/hexane) gave coupling product (184.2 mg, 90%) as a colorless clear oil.

To a solution of the above coupling product (184.2 mg, 0.2088 mmol) in MeOH/THF (4:1, v/v, 5 mL) at 0 °C were added Na_2HPO_4 (593 mg, 4.177 mmol) and Na(Hg) (5%, 1.00 g, 2.17 mmol). After being stirred at room temperature overnight, the reaction mixture was filtered through Celite®. The filtrate was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% ether/hexane) gave C18–C34 fragment **1** (110.5 mg, 71%) as a colorless clear oil. **1**: $[\alpha]_D^{29}$=−9 (c 0.36, $CHCl_3$); IR (film) 2928, 2855, 1613, 1513, 1456, 1383, 1363, 1249, 1099, 1068, 1035, 835, 773, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 12H), 6.86 (d, J=8.8 Hz, 2H), 5.38–5.22 (m, 2H), 4.80–4.65 (m, 4H), 4.42 (s, 2H), 3.79 (s, 3H), 3.46–3.30 (m, 5H), 2.20–1.95 (m, 5H), 1.70–1.57 (m, 4H), 1.40–0.72 (m, 25H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 139.3, 136.9, 130.8, 129.2, 128.32, 128.28, 127.8, 127.64, 127.62, 127.3, 113.7, 82.7, 82.1, 76.5, 72.5, 72.4, 72.2, 69.5, 55.2, 39.1, 37.1, 36.9, 35.3, 33.5, 33.0, 32.1, 30.5, 30.1, 29.7, 29.1, 26.0, 20.9, 18.1, 15.1, −4.2, −4.4; HRMS (FAB) calcd for $C_{47}H_{70}O_5SiNa$ [(M+Na)$^+$] 765.4890, found 765.4857.

References and notes

1. Isolation and structure determination: (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. Total syntheses : (b) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. (c) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583. (d) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856.
2. Isolation and structure determination: (a) Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (b) Sehgal, S. N.; Baker, H.; Vézina, C. *J. Antibiot.* **1975**, *28*, 728. Total syntheses: (c) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318. (d) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906. (e) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (f) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947. (g) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 962.
3. For reviews, see: (a) Schreiber, S. L. *Science* **1991**, *251*, 283. (b) Hamilton, G. S.; Steiner, J. P. *J. Med. Chem.* **1998**, *41*, 5119.
4. Steiner, J. P.; Dawson, T. M.; Fotuhi, M.; Glatt, C. E.; Snowman, A. M.; Cohen, N.; Snyder, S. H. *Nature* **1992**, *358*, 584.
5. For reviews, see: (a) Guo, X.; Dillman, J. F.; Dawson, V. L.; Dawson, T. M. *Ann. Neurol.* **2001**, *50*, 6. (b) Gold, B. G.; Villafranca, J. E. *Curr. Top. Med. Chem.* **2003**, *3*, 1368.
6. (a) Steiner, J. P.; Hamilton, G. S.; Ross, D. T.; Valentine, H. L.; Guo, H.; Connolly, M. A.; Liang, S.; Ramsey, C.; Li, J.-H.; Huang, W.; Howorth, P.; Soni, R.; Fuller, M.; Sauer, H.; Nowotnick, A.; Suzdak, P. D. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2019. (b) Hamilton, G. S.; Huang, W.; Connolly, M. A.; Ross, D. T.; Guo, H.; Valentine, H. L.; Suzdak, P. D.; Steiner, J. P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1785. (c) Hamilton, G. S.; Wu, Y. Q.; Limburg, D.; Wilkinson, D.; Vaal, M.; Li, J.-H.; Thomas, C.; Huang, W.; Sauer, H.; Ross, D. T.; Soni, R.; Chen, Y.; Guo, H.; Howorth, P.; Valentine, H.; Liang, S.; Spicer, D.; Fuller, M.; Steiner, J. P. *J. Med. Chem.* **2002**, *45*, 3549. (d) Wu, Y. Q.; Wilkinson, D.; Limburg, D.; Li, J.-H.; Sauer, H.; Ross, D. T.; Liang, S.; Spicer, D.; Valentine, H.; Fuller, M.; Guo, H.; Howorth, P.; Soni, R.; Chen, Y.; Steiner, J. P. *J. Med. Chem.* **2002**, *45*, 3550.
7. Fehr, T.; Sanglier, J.-J.; Schuler, W.; Gschwind, L.; Ponelle, M.; Schilling, W.; Wioland, C. *J. Antibiot.* **1996**, *49*, 230.
8. The carbon numbering in this paper corresponds to that of antascomicin A.
9. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. Nicolaou and co-workers have successfully utilized Johnson–Claisen rearrangement in their total synthesis of rapamycin (Ref. 2e). On the other hand, Ireland ester enolate rearrangement has been employed by Danishefsky and his colleagues in their rapamycin synthesis. See: Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826.
10. For reviews, see: (a) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.
11. Chida, N.; Ohtsuka, M.; Ogura, K.; Ogawa, S. *Bull. Chem. Soc. Jpn* **1991**, *64*, 2118.
12. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
13. Suzuki, T.; Saimoto, H.; Tomioka, H.; Ohshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
14. Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775.
15. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5353–5355
Tetrahedron

A one-pot assembly of 4-allyl-3-pyridinecarboxaldehyde. A new synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine, an annulated nicotine analogue

Shengjun Luo,[a] Fang Fang,[a] Mingyue Zhao[b] and Hongbin Zhai[a,*]

[a]*Laboratory of Modern Synthetic Organic Chemistry and State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Zhengzhou Tobacco Research Institute, Zhengzhou, Henan 450000, China*

Received 8 March 2004; revised 22 April 2004; accepted 23 April 2004

Abstract—This paper describes a two-step synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine, a conformationally constrained nicotine analogue. The target molecule was effectively assembled by an intramolecular azomethine ylide-alkene [3+2] cycloaddition. The cyclization precursor, 4-allyl-3-pyridinecarboxaldehyde, was formed efficaciously in a single step from 3-pyridinecarboxaldehyde via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.

1. Introduction

(−)-Nicotine (**1**, Fig. 1), an alkaloid present in tobacco at 0.2–5% levels, targets and activates nicotinic acetylcholine receptors (nAChRs).[1] The nAChRs provide ligand-gated ion channels in the human brain and participate in various biological processes related to numerous nervous system disorders.[2] Due to the therapeutic potential of (−)-nicotine for central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, and Tourette's diseases, nicotine analogues have received much attention from both synthetic and medicinal chemists.[2] In particular, conformationally constrained nicotinoids have become attractive candidates for new selective nAChRs-targeting ligands.[2a,3,4] On one hand, this is because of the discovery of epibatidine, an alkaloid with a rigid structure, which displays strong activity despite of its toxicity.[5] On the other hand, molecular modeling studies have demonstrated that the two heterocyclic rings of nicotine are skewed and approximately perpendicular to one another to secure low energy conformations.[3,6]

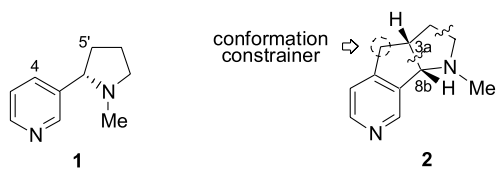


Figure 1.

Our laboratory has been fascinated in the chemistry of nicotine analogues aimed to develop new selective nAChRs-targeting ligands. A tricyclic nicotine analogue, 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (**2**, Fig. 1), was previously designed and synthesized in six steps from 3-bromopyridine.[4b] The conformational rigidity of **2** was achieved as a result of a methylene bridge erected between C-4 and C-5′ of nicotine (**1**).

2. Results and discussion

Herein we wish to report a new synthesis of **2** with high efficiency, featuring the construction of the hexahydropyrrolo[3,2-*f*]pyrindine tricyclic framework via intramolecular azomethine ylide-alkene [3+2] cycloaddition.[4b,7] The apparent precursor for the cycloaddition would be 4-allyl-3-pyridinecarboxaldehyde (**3**, Fig. 2), whose efficient synthesis itself represents one of the challenges for the current project. In principle, aldehyde **3** might be obtainable from 4-allyl-3-bromopyridine (**4**) by sequential treatment with BuLi and *N*,*N*-dimethylformamide (DMF). Alkene **4** was reportedly[8] synthesized from 3-bromopyridine in only

Keywords: Annulated nicotine analogue; Intramolecular azomethine ylide-alkene [3+2] cycloaddition; Synthesis.
* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail address: zhaih@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.069

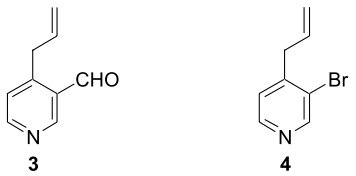
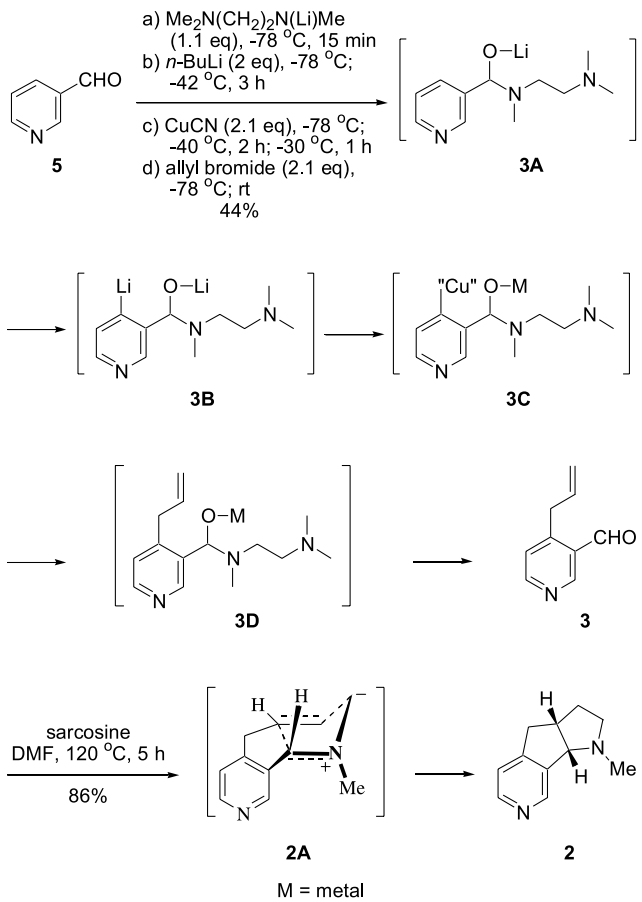


Figure 2.

40% yield. The unsatisfactory yield for this transformation resulted mainly from the further alkylatability because of the enhanced acidity of the benzylic hydrogens. By the same token, the conversion of **4** to **3** could not be a clean reaction.

Ortho lithiation of aromatic aldehydes with prior in situ aldehyde protection, first introduced by Comins and co-workers,[9] has proved to be a convenient and versatile technique having considerable potential in organic synthesis.[10] We envisaged that this protocol might be modified to synthesize enal **3** by a one-pot reaction from 3-pyridinecarboxaldehyde (**5**, Scheme 1). Indeed, the desired 4-allyl-3-pyridinecarboxaldehyde **3** was afforded when aldehyde **5** was protected in situ with LTMDA [$Me_2N(CH_2)_2N(Li)Me$, prepared by mixing *N*,*N*,*N*′-trimethylethylenediamine and *n*-BuLi], *ortho* lithiated with *n*-BuLi, converted to a high-order cuprate with CuCN, alkylated with allyl bromide, and finally hydrolyzed. The yield for this step was 44%, which amounted to an average yield of 85% for each of the five operations (**3A**–**3D** were the four plausible intermediates). We have not been able to further optimize this reaction so far. However, the current protocol should be acceptable considering the fact that such a useful intermediate as **3** can be assembled in a one-pot fashion. The absence of CuCN resulted simply in a complex reaction mixture because **3D** (an 4-allylpyridine derivative) was prone to further allylation due to the presence of the highly acidic benzylic/allylic hydrogens. Replacement of CuCN with CuBr led to less satisfactory results.



Scheme 1.

Having the enal in hand set the stage for intramolecular azomethine ylide-alkene [3+2] cycloaddition.[7] Treatment[4b] of **3** with sarcosine (120 mol%) in DMF at 120 °C for 5 h effected the desired cycloaddition (see the transition state **2A**) to produce in 86% yield the tricycle **2**, an annulated nicotine analogue. The spectroscopic data of the sample were in accord with those reported previously.[4b] Currently pharmacological studies of **2** are under way.

3. Conclusion

In summary, a two-step synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (**2**), a conformationally constrained nicotine analogue, has been accomplished. The target molecule was effectively assembled by an intramolecular azomethine ylide-alkene [3+2] cycloaddition. The cyclization precursor, 4-allyl-3-pyridinecarboxaldehyde (**3**), was formed efficaciously in a single step from 3-pyridinecarboxaldehyde (**5**) via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz), using TMS as the internal standard when appropriate. Column chromatography was performed on silica gel. THF were distilled over sodium benzophenone ketyl under N_2 prior to use. DMF was distilled over calcium hydride under N_2 prior to use.

4.1.1. 4-Allyl-3-pyridinecarboxaldehyde (3). *n*-BuLi (2.08 M, 5.6 mL, 12 mmol) was added to a stirred solution of *N*,*N*,*N*′-trimethylethylenediamine (1.62 mL, 12.5 mmol) in THF (40 mL) at −78 °C. After 15 min, 3-pyridinecarboxaldehyde (1.0 mL, 10.6 mmol) was added at −78 °C, and the stirring was continued for 15 min. *n*-BuLi (2.08 M, 10 mL, 21 mmol) was added at −78 °C and the stirring was continued at −42 °C for 3 h. After cooling to −78 °C, CuCN (1.99 g, 22.2 mmol) was added as a solid and the temperature was maintained at −40 °C for 2 h and then at −30 °C for 1 h. After cooling to −78 °C, a solution of allyl bromide (1.9 mL, 22 mmol) in THF (10 mL) was added at −78 °C. The reaction mixture was allowed to warm to rt, diluted with saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column

chromatography to afford **3** (686 mg, 44%) as a colorless oil: FT-IR (KBr, cm^{-1}): 2861, 2754, 1702, 1639, 1592, 1556, 1489, 1400, 1222, 1058, 997, 923, 839, 735, 690, 658; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (d, 2H, J=5.2 Hz), 4.97 (dd, 1H, J=17.2, 2.8 Hz), 5.06 (dd, 1H, J=10.5, 2.7 Hz), 5.81–5.96 (m, 1H), 7.18 (d, 1H, J=4.8 Hz), 8.58 (d, 1H, J=4.8 Hz), 8.87 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.9, 117.7, 125.2, 129.0, 134.3, 150.5, 153.6, 153.7, 191.2; MS (EI): 147 (M^+, 30), 146 (M−1, 100); HRMS (EI) calcd for C_9H_9NO, 147.0684, found 147.0687.

4.1.2. 1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (2). A mixture of aldehyde **3** (686 mg, 4.66 mmol) and sarcosine (495 mg, 5.56 mmol) in DMF (40 mL) was heated under N_2 at 120 °C for 5 h, cooled to rt, and concentrated in vacuo. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with isopropanol/$CHCl_3$ (1/3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, CH_2Cl_2–MeOH, 40/1) to give **2** (700 mg, 86%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.74 (m, 1H), 2.15–2.25 (m, 1H), 2.44–2.55 (m, 1H), 2.55 (s, 3H), 2.77–2.86 (m, 1H), 2.99–3.21 (m, 3H), 3.80 (d, J=7.6 Hz, 1H), 7.13 (d, J=5.2 Hz, 1H), 8.42 (d, J=5.2 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.23, 39.23, 40.50, 41.92, 57.59, 73.45, 120.34, 139.25, 145.78, 148.34, 152.95. MS (EI): 174 (M^+). Anal. calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.69; H, 7.84; N, 16.38.

Acknowledgements

We thank National Natural Science Foundation of China (No. 20372073), The Bureau of Tobacco, PRC, and Science and Technology Commission of Shanghai Municipality ('Venus' Program) for financial support.

References and notes

1. (a) Decker, M. W.; Meyer, M. D.; Sullivan, J. P. *Exp. Opin. Invest. Drugs* **2001**, *10*, 1819. (b) Nordberg, A. *Biol. Psychiat.* **2001**, *49*, 200. (c) Paterson, D.; Nordberg, A. *Prog. Neurobiol.* **2000**, *61*, 75. (d) Clementi, F.; Fornasari, D.; Gotti, C. *Eur. J. Pharmacol.* **2000**, *393*, 3.
2. (a) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41. (b) Decker, M. W.; Aneric, S. P. *Neuronal Nicotinic Recept.* **1999**, 395.
3. Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, 465.
4. (a) Meijler, M. M.; Matsushita, M.; Altobell, L. J., III.; Wirsching, P.; Janda, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 7164. (b) Zhai, H.; Liu, P.; Luo, S.; Fang, F.; Zhao, M. *Org. Lett.* **2002**, *4*, 4385. (c) Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177. (d) Lennox, J. R.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **2001**, *66*, 7078. (e) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861. (f) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (g) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506. (h) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381. (i) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492.
5. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.
6. Elmore, D. E.; Dougherty, D. A. *J. Org. Chem.* **2000**, *65*, 742.
7. (a) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559. (b) Bolognesi, M. L.; Andrisano, V.; Bartolini, M.; Minarini, A.; Rosini, M.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **2001**, *44*, 105.
8. Hong, C. Y.; Overman, L. E.; Romero, A. *Tetrahedron Lett.* **1997**, *38*, 8439.
9. (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69. (b) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.
10. (a) Schultz, A. G.; Antoulinakis, E. G. *J. Org. Chem.* **1996**, *61*, 4555. (b) Bjork, P.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, *31*, 1161.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5357–5366
Tetrahedron

Efficient preparation of 2-azulenylboronate and Miyaura-Suzuki cross-coupling reaction with aryl bromides for easy access to poly(2-azulenyl)benzenes

Shunji Ito,[a,*] Tomomi Terazono,[b] Takahiro Kubo,[b] Tetsuo Okujima,[b] Noboru Morita,[b] Toshihiro Murafuji,[c] Yoshikazu Sugihara,[c] Kunihide Fujimori,[d] Jun Kawakami[a] and Akio Tajiri[a]

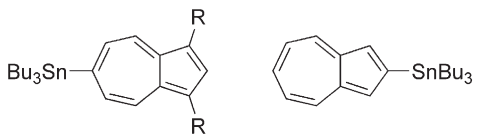
[a]*Department of Materials Science and Technology, Faculty of Science and Technology, Hirosaki University, Bunkyocho 3, Hirosaki 036-8561, Japan*
[b]*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*
[c]*Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi 753-8512, Japan*
[d]*Department of Chemistry, Faculty of Science, Shinshu University, Matsumoto 390-8621, Japan*

Received 9 February 2004; revised 22 April 2004; accepted 23 April 2004

Abstract—This paper describes an efficient preparation of 2-azulenylboronate (**6**) starting from 2-iodoazulene by halogen–metal exchange reaction using *n*-BuLi and subsequent quenching with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The boronate **6** has been found to undergo Pd-catalyzed Miyaura-Suzuki cross-coupling reaction with a range of aryl bromides including aromatic poly bromides utilizing $Pd_2(dba)_3$–P(*t*-Bu)$_3$ as a catalyst and establishes a strategy to produce novel poly(2-azulenyl)benzenes, some of which are found to be insoluble in common organic solvents, however. The redox behavior of 2-arylazulenes and poly(2-azulenyl)benzenes was examined by cyclic voltammetry (CV) and compared with those of 6-azulenylbenzene derivatives reported previously.

1. Introduction

In recent years, there has been vital interest in transition-metal catalyzed cross-coupling reaction that can be used for carbon–carbon bond formation.[1] Several applications of the palladium-catalyzed reaction in the chemistry of azulene have appeared in the literature, for example, palladium-catalyzed vinylation,[2] arylation,[3] ethynylation,[4] and alkylation[5] of azulenyl halides or triflate. We have recently developed the first versatile organometallic reagents of azulenes, 6-(tri-*n*-butylstannyl)azulene (**1a**) and its 1,3-diethoxycarbonyl derivative (**1b**), which have been subjected to the Pd(0)-catalyzed Stille cross-coupling reaction with aryl, acyl, and/or azulenyl halides (Chart 1).[6] The study made up for the deficiency of the organometallic reagent for the transition-metal catalyzed reaction of azulene itself. Especially, application of the reagents is highly advantageous for multiple functionalization by azulenyl groups because the method does not require the troublesome preparation of a polymetallic species.[7] However, extension of the methodology to the functionalization of azulenes at the 2-position was so far hampered by the inefficiency of the



1a: R = H
1b: R = COOEt
2

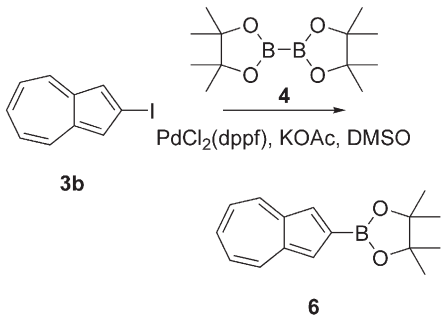
Chart 1.

preparation of 2-(tri-*n*-butylstannyl)azulene (**2**) utilizing Pd-catalyzed direct stannylation of 2-bromoazulene (**3a**).[6b]

Boronate reagents also represent an important class of synthetic intermediates for the transition-metal catalyzed reaction. Miyaura-Suzuki cross-coupling of organoborane compounds with a variety of organic electrophiles, catalyzed by palladium, provides an efficient method for carbon–carbon bond formation.[8] Synthesis of the boronate reagents consists of conventional Pd-catalyzed cross-coupling of aryl bromides, iodides, or triflates with either alkoxyboron derivatives such as bis(pinacolato)diboron (**4**) or pinacolborane (**5**).[9,10] The direct boronate formation of 2-iodoazulene (**3b**) utilizing Pd-catalyst has been revealed to be a convenient method for preparing 2-azulenylboronate (**6**) (Scheme 1).[11] However, the yield of the boronate **6** remains so far at most 42%. More recently, Ir-catalyzed reaction of azulene (**7**) with bis(pinacolato)diboron (**4**) has

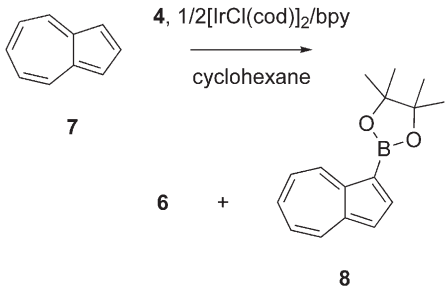
Keywords: Azulenylboronate; Palladium-catalyzed reaction; Miyaura-Suzuki cross-coupling; Redox property; Violene-cyanine hybrid.
* Corresponding author. Tel.: +81-172-39-3568; fax: +81-172-39-3541; e-mail address: itsnj@cc.hirosaki-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.057



Scheme 1.

improved the yield of the desired 2-azulenylboronate (**6**) to 70%, in spite of the formation of undesirable 1-azulenylboronate (**8**) in a certain amount (10%) (Scheme 2).[12]



Scheme 2.

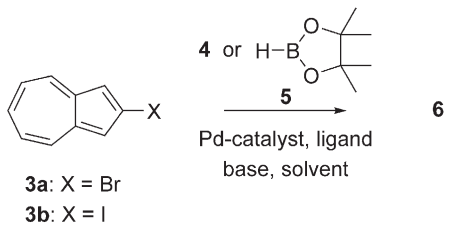
Herein, we report an efficient preparation of 2-azulenylboronate (**6**) and an efficient catalytic system for the Miyaura-Suzuki cross-coupling reaction of **6** with aryl bromides and the successful application to the Pd(0)-catalyzed cross-coupling reaction of **6** with aromatic poly bromides to afford poly(2-azulenyl)benzenes. We have recently proposed that the poly(6-azulenyl)benzene derivatives are considered to be a novel model compound of the violene-cyanine hybrid recently reported by Hünig et al.[13] Depending on the number and position of the 6-azulenyl substituents, the benzene derivatives provide a closed-shell cyanine-type substructure by an overall two-electron transfer.[14] The poly(2-azulenyl)benzenes might also provide a closed-shell system as a cyanine dye by an overall two-electron transfer, although the system does not provide a formal cyclopentadienide substructure in the closed-shell form. Herein, we also report the redox behavior of several 2-arylazulenes and poly(2-azulenyl)benzenes prepared by the cross-coupling reaction of **6**.

2. Results and discussion

2.1. Efficient synthesis of 2-azulenylboronate (6)

Employment of the reaction of 2-bromoazulene (**3a**)[15] with diboron **4** did not improve the yield of the desired 2-azulenylboronate (**6**) under the conditions originally described by Miyaura et al. (entry 1) (Table 1).[9] A slightly larger amount of the Pd-catalyst (5 mol%) in the reaction of 2-iodoazulene (**3b**)[15] with **4** was found to improve somewhat the yield of the desired 2-azulenylboronate (**6**) (entry 2), whereas a modified catalytic system of $PdCl_2$(dppf) with Et_3N in dioxane in the reaction of 2-haloazulenes (**3a** and **3b**) with pinacolborane (**5**) could not alter the situation (entries 3 and 4).[9,10]

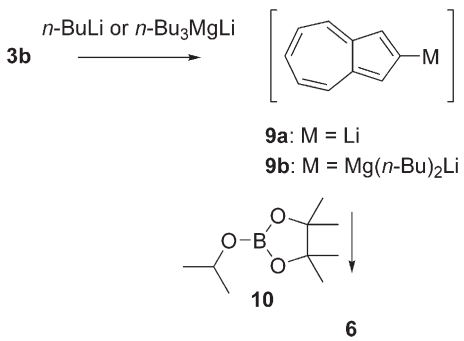
Table 1. Pd-catalyzed syntheses of 2-azulenylboronate (**6**)[a]



Entry	X	Boron reagent	Catalyst	Base	Solvent	Yield (%)[b]	
						6	**3**
1	Br	**4**	$PdCl_2$(dppf)[c]	KOAc	DMSO	40	
2	I	**4**	$PdCl_2$(dppf)	KOAc	DMSO	53	
3	Br	**5**	$PdCl_2$(dppf)	Et_3N	Dioxane	5	52
4	I	**5**	$PdCl_2$(dppf)	Et_3N	Dioxane	38	

[a] Reactions of **3a** and **3b** (1 mmol) with bis(pinacolato)diboron (**4**) (1.1 mmol) were carried out at 80 °C for 5 h by using Pd-catalyst (5 mol%) and KOAc (3 mmol) in DMSO (6 mL). Reactions of **3a** and **3b** (1 mmol) with pinacolborane (**5**) (1.5 mmol) were carried out at 80 °C for 4 h by using Pd-catalyst (5 mol%) and triethylamine (3 mmol) in dioxane (6 mL).
[b] All yields are isolated yields.
[c] $PdCl_2$(dppf): [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

The aryl boronate reagents could be also prepared by transmetalation between aryllithium or arylmagnesium reagents and boron compounds which have a good leaving group such as a halogen or an alkoxy group.[16] Synthetic inaccessibility of the metalated azulene due to the high reactivity of azulenes with organolithium and magnesium reagents to give dihydroazulene derivatives[17] hampered application to the transmetalation procedure. However, recently, generation of 2-azulenyllithium and magnesium reagents (**9a** and **9b**) has been accomplished by the transmetalation between 2-iodoazulene (**3b**) and *n*-BuLi or $(n\text{-Bu})_3MgLi$.[18] The 2-azulenylmagnesium reagent (**9b**) has been revealed to exhibit the envisaged borylation with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**10**) in 53% yield.[19,20] We found the borylation was much more effective by the use of 2-azulenyllithium reagent (**9a**) prepared by halogen–metal exchange reaction of 2-iodoazulene (**3b**) using *n*-BuLi at low temperature. Subsequent quenching of the reagent by **10** afforded the



Scheme 3.

desired 2-azulenylboronate reagent (**6**) in 78% yield as a single product (Scheme 3).

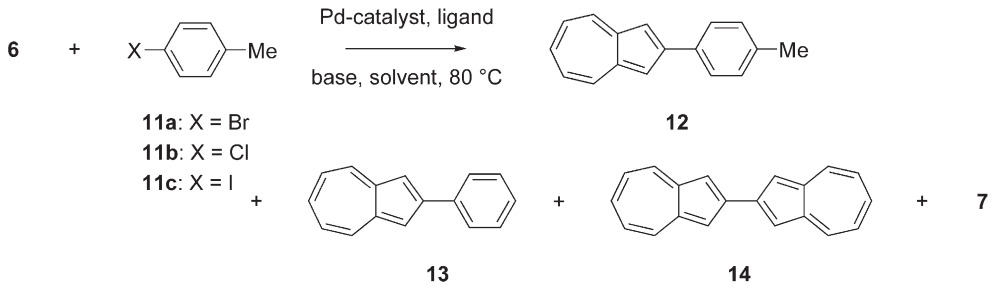
2.2. Miyaura-Suzuki cross-coupling reaction

To demonstrate the transformations utilizing **6**, the reaction with diethyl 2-amino-6-bromoazulene-1,3-dicarboxylate has been conducted under the Miyaura-Suzuki cross-coupling reaction conditions.[11] However, in our initial experiments in the cross-coupling reaction with aryl halides, **6** was found to be inefficient under similar conditions to Miyaura-Suzuki's (Table 2). Concretely, the reaction of **6** with **11a** in the presence of $PdCl_2(PPh_3)_2$ catalyst produced the desired 2-(4-tolyl)azulene (**12**)[21] in mediocre yield (39%) together with undesired 2-phenylazulene (**13**)[21,22] (entry1) (Chart 1). The choice of the catalytic system was the key to the success of the reaction of **6** with aryl halides. The use of $Pd(PPh_3)_4$ as a catalyst instead of $PdCl_2(PPh_3)_2$ was also ineffective in this reaction (entry 2). Formation of the by-product **13** could be rationalized by an aryl–aryl exchange in the intermediate palladium(II) complex and subsequent coupling with the 2-azulenylboronate (**6**).[23] Indeed, substitution of the $Pd(PPh_3)_4$ catalyst with $Pd_2(dba)_3$–P(*t*-Bu)$_3$ in the catalytic protocol resulted in a significant increase of the desired cross-coupling product **12** in 73% yield (entry 3). The $Pd(OAc)_2$–P(*t*-Bu)$_3$ catalytic system was also effective in this reaction (entry 6). However, the use of P(*o*-Tol)$_3$ or PCy_3 as a ligand did not afford satisfactory results either with $Pd_2(dba)_3$ or $Pd(OAc)_2$ as a Pd-catalyst (entries 4, 5, 7 and 8). The addition of KF as a base in the catalytic protocol decreased significantly the conversion ratio of the catalytic reaction (entry 9).[24] Using the chloride **11b** or iodide **11c** instead of the bromide **11a** decreased the yield of the desired cross-coupling product **12** (entries 10 and 11). The formation of 2,2′-biazulene in significant amounts in the case of the reaction with chloride **11b** should be attributed to the homocoupling of **6** under the reaction conditions.[25]

2.3. Generality

To examine the generality of the reaction conditions, the cross-coupling reaction with several aryl bromides (**15a–c**) was conducted under the $Pd_2(dba)_3$–P(*t*-Bu)$_3$ reaction conditions. The results of the cross-coupling reaction of **6** with the aryl bromides are summarized in Table 3. The electron-deficient aryl bromide, 4-bromonitrobenzene (**15a**), was efficiently reacted with **6** to afford the coupled product **16a** in high yield (entry 1). However, the reaction of **6** with 4-bromoacetophenone (**15b**) afforded the desired coupled product **16b** in moderate yield (entry 2). The product **16b** contains enolizable keto-group. The relatively low yield of the product **16b** should be attributed to the side reaction arising from undesired aldol condensations. The yield of **16b** was slightly improved by the use of $Pd(PPh_3)_4$ as a catalyst (42%). In the case of the reaction of **6** with electron-rich bromide, 4-bromoanisole (**15c**), the reaction also proceeded smoothly to give the cross-coupling product **16c** in good yield (entry 3). On the whole, **6** reacted with several aryl bromides including an electron-rich one under the Pd-catalyzed conditions and the isolated yields of the cross-coupling product were generally high, except for **16b**.

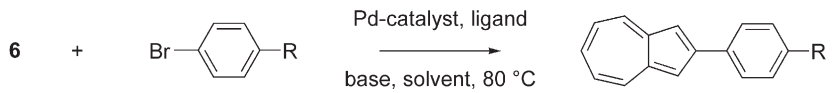
Table 2. Miyaura-Suzuki cross-coupling reaction of **6** with 4-tolyl halides **11a–c**[a]



Entry	X	Catalyst	Ligand	Base	Solvent	Yield (%) [b]				
						12	**13**	**14**	**7**	**6**
1[c]	Br	$PdCl_2(PPh_3)_2$		$Ba(OH)_2{\cdot}8H_2O$	DME/H_2O	39	21			
2	Br	$Pd(PPh_3)_4$		Cs_2CO_3	Dioxane	27	19			
3	Br	$Pd_2(dba)_3$[d]	P(*t*-Bu)$_3$	Cs_2CO_3	Dioxane	73				
4	Br	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	Cs_2CO_3	Dioxane	54		5		5
5	Br	$Pd_2(dba)_3$	PCy_3	Cs_2CO_3	Dioxane	25				
6	Br	$Pd(OAc)_2$	P(*t*-Bu)$_3$	Cs_2CO_3	Dioxane	72			5	
7	Br	$Pd(OAc)_2$	P(*o*-Tol)$_3$	Cs_2CO_3	Dioxane	27		3	32	
8	Br	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	Dioxane	42				
9	Br	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	KF	Dioxane	7				74
10	Cl	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	Cs_2CO_3	Dioxane	12		40	4	3
11	I	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	Cs_2CO_3	Dioxane	51			4	22

[a] Reactions of **6** with 4-halotoluene (2 equiv.) were carried out at 80 °C for 24 h using Pd-catalyst (5 mol%), ligand (Pd:P=1:2–3), and 1.5 equiv. of base in solvent (6 mL/**6** (1 mmol)).
[b] All yields are isolated yields.
[c] Pd-catalyst (10 mol%) and 2.0 equiv. of base in DME:H_2O (50:1) (10 mL/**6** (0.4 mmol)) were used.
[d] $Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0).

Table 3. Cross-coupling reaction of **6** with aryl bromides **15a**–**c**[a]



15a: R = NO_2
15b: R = COMe
15c: R = OMe

16a: R = NO_2
16b: R = COMe
16c: R = OMe

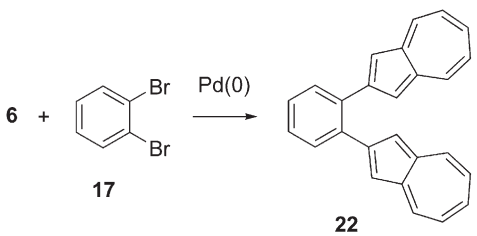
Entry	R	Catalyst	Ligand	Time (h)	Product (yield (%))[b]
1	NO_2	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	6	**16a** (80)
2	COMe	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	24	**16b** (34)
3	OMe	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	19	**16c** (72)

[a] Reaction conditions: aryl bromides (2 equiv.), Cs_2CO_3 (1.5 equiv.), Pd-catalyst (5 mol%), ligand (Pd:P=1:3–4) in dioxane (3 mL/**6** (0.4 mmol)) at 80 °C.
[b] All yields are isolated yields.

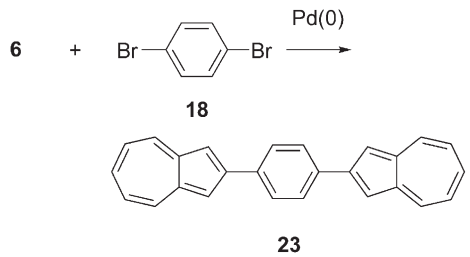
2.4. Polysubstitution

Finally, we demonstrated the intended use of the 2-azulenylboronate (**6**) in the synthesis of poly(2-azulenyl)benzenes. The scope of this methodology for multiple substitution was demonstrated utilizing the reaction of **6** with 1,2-di-, 1,4-di-, 1,3,5-tri-, 1,2,4-tri-, and 1,2,4,5-tetrabromobenzenes (**17**–**21**). The reaction of **6** with 1,2-dibromobenzene (**17**) afforded the desired coupling product, 1,2-bis(2-azulenyl)-benzene (**22**) in 33% yield (Scheme 4). Likewise, the reaction of **6** with 1,4-dibromobenzene (**18**) gave the expected 1,4-bis(2-azulenyl)benzene (**23**) in 44% yield, although the product **23** does not show any solubility in common organic solvents (Scheme 5). Sublimation could be used for the purification of the product **23** under reduced pressure. The insoluble material exhibited an ion peak at *m*/*z* 330 upon mass spectrum, which corresponds to the correct M^+ ion peak of 1,4-di(2-azulenyl)benzene (**23**).

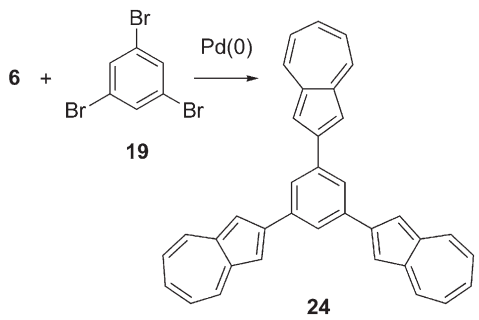
In the case of the reaction of **6** with 1,3,5-tri- and 1,2,4-tribromobenzenes (**19** and **20**), the desired *tris*-adducts **24** and **25** were obtained in 18 and 36% yields, respectively, (Schemes 6 and 7). The reaction of **6** with 1,2,4,5-tetrabromobenzenes (**21**) afforded an insoluble material (13%) in a common organic solvent along with 1,2,4-tris-adduct **25** in 13% yield (Scheme 8). The mass spectrum of the insoluble material showed the correct M^+ ion peak at *m*/*z* 582, which indicated the formation of the expected tetrakis-adduct **26**. The elimination of bromide was a side reaction for the multi-functionalization of benzene with 2-azulenyl substituents.



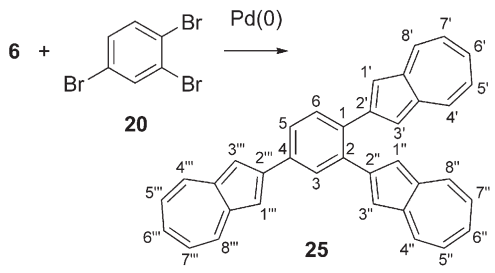
Scheme 4.



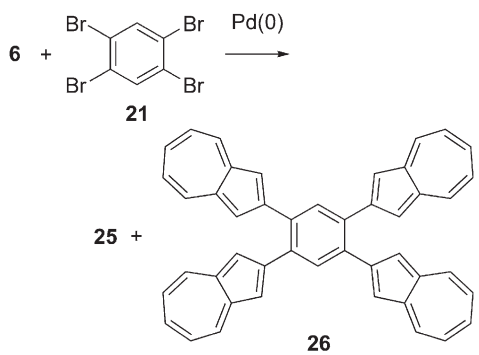
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

2.5. Redox behavior

The redox potentials (V vs Ag/Ag^+) of 2-arylazulenes (**12**, **13**, and **16a**–**c**) and poly(2-azulenyl)benzenes (**22**, **24**, and **25**) measured by CV along with those of 6-azulenylbenzene derivatives (**27**, **28**, and **29**)[14] are summarized in Table 4 (Chart 2). Insolubility of the products **23** and **26** in common organic solvents hampered the CV measurement of these compounds.

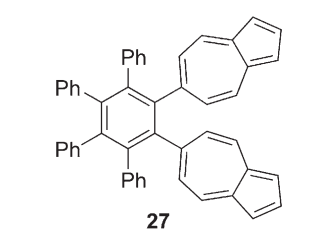
Table 4. Redox potentials[a] of 2-arylazulenes and poly(2- and 6-azulenyl)benzenes

Sample	E_1^{ox} (V)	E_2^{ox} (V)	E_1^{red} (V)	E_2^{red} (V)	E_3^{red} (V)	Ref.
12	(+1.07)	(+1.34)	(−1.85)			
13	(+1.07)	(+1.39)	(−1.82)			
16a	(+1.05)	(+1.38)	−1.33	−1.68		
16b	(+1.04)	(+1.33)	−1.65	(−2.17)		
16c	(+0.76)	(+1.02)	−1.87			
22	(+0.52)	(+0.89)	−1.82	−2.02		
24	(+0.69)	(+1.11)	(−1.72)[b]	(−1.85)[b]	(−2.01)[b]	
25	(+0.42)	(+1.10)	−1.71	−1.87	−2.11	
27[c]	(+0.81)		(−2.00)	(−2.20)		14
28[c]	(+0.73)	(+1.23)	(−1.75)[b]	(−1.87)[b]	(−2.00)[b]	14
29[c]	(+0.78)	(+1.29)	−1.74 (2e)	−2.15		14

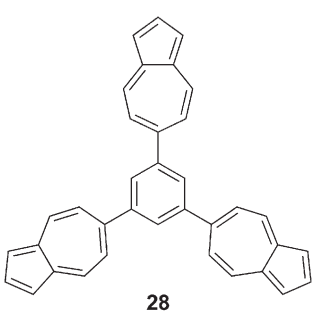
[a] The redox potentials were measured by CV (0.1 M n-Bu_4NBF_4 in o-dichlorobenzene, Pt electrode, scan=100 mV s^{-1}, and F_c^+/F_c=0.27 V). In the case of irreversible waves, which are shown in parentheses, E_{ox} and E_{red} were calculated as E_{pa} (anodic peak potential)−0.03 and E_{pc} (cathodic peak potential)+0.03 V, respectively.

[b] The values are peak potentials measured by DPV.

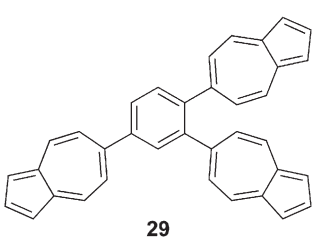
[c] The potentials have been measured in 0.1 M n-Bu_4NBF_4 tetrahydrofuran solution (F_c^+/F_c=0.19 V).



27



28



29

Chart 2.

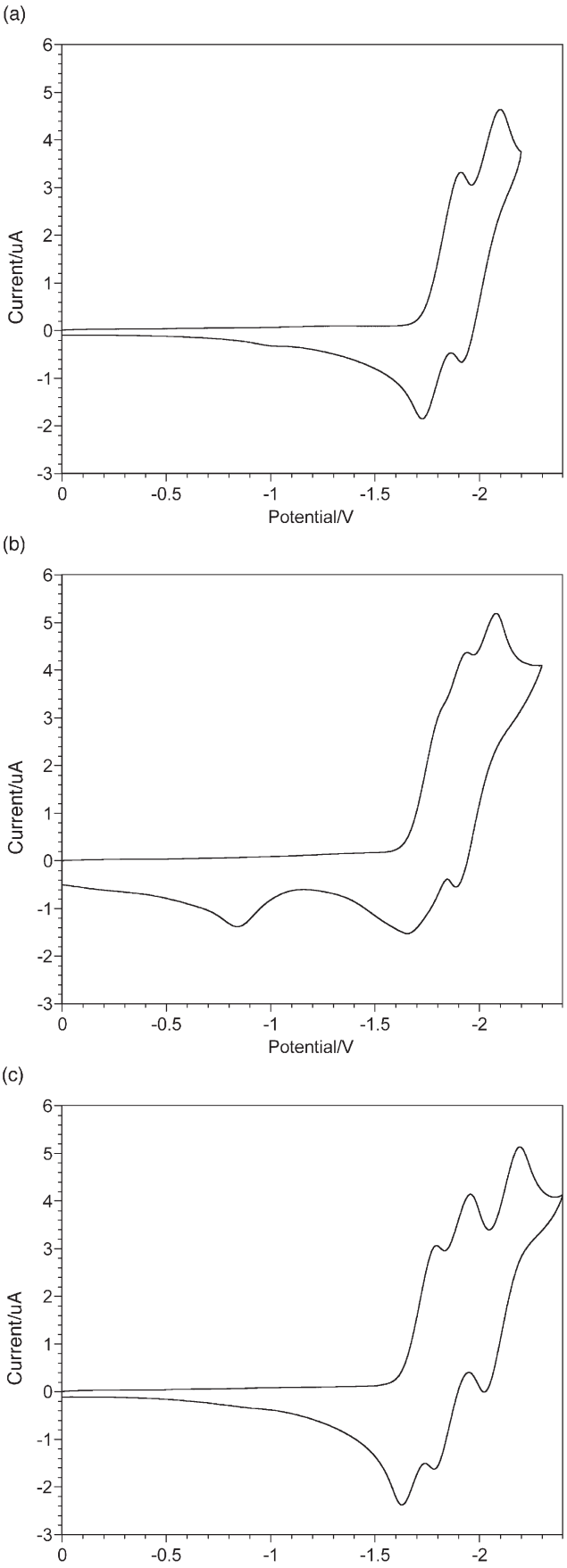
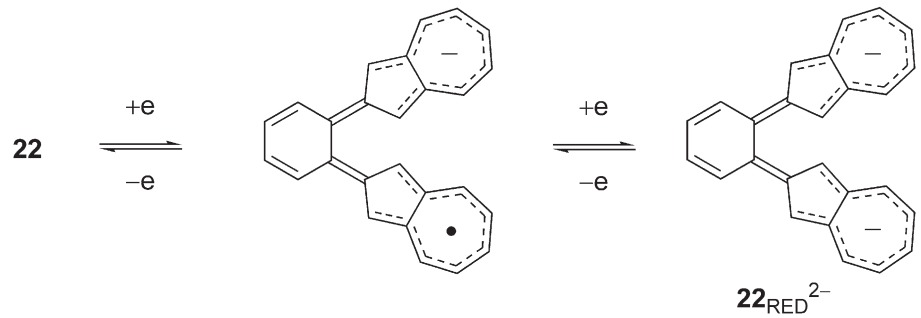


Figure 1. Cyclic voltammograms of (a) **22**, (b) **24**, and (c) **25** in o-dichlorobenzene containing n-Bu_4NBF_4 (0.1 M) as a supporting electrolyte; scan rate, 100 mV s^{-1}.



Scheme 9.

As seen from Table 4, 2-phenylazulene (**13**) showed an irreversible one-electron transfer at −1.82 V upon CV. As expected, the electron-donating group on the phenyl group, that is, 4-methyl (**12**) and 4-methoxy (**16c**), slightly decreases the electron affinity of the azulene ring. In contrast to the one-electron transfer of **12**, **13**, and **16c**, compounds **16a** and **16b** showed two-stage, one-electron reductions due to the redox reaction of the electron-withdrawing substituents such as 4-nitro and 4-acetyl groups. In addition to the two-stage reductions, compounds **16a** and **16b** showed improvement of the reversibility of the CV waves due to the stabilization of the radical anionic state.

Poly(2-azulenyl)benzenes (**22**, **24**, and **25**) revealed multi-electron redox properties. 1,2-Di(2-azulenyl)benzene (**22**) exhibited a well-resolved two-step reduction wave at $E_{1/2}$=−1.82 and −2.02 V, upon CV (Fig. 1(a)). The first reduction potential and even the second one of **22** are almost comparable with those of **12**, **13**, and **16c**. Therefore, the two 2-azulenyl substituents on a benzene ring exhibit multiple electron affinity similarly to the reduction of 6-azulenyl derivative (**27**). Thus, the redox system of **22** could be considered to be that of violene as illustrated in Scheme 9. 1,3,5-Tri(2-azulenyl)benzene (**24**) exhibited a quasi-reversible three-step reduction wave at around −1.90 V, upon CV (Fig. 1(b)). The wave was identified as the superimposition of three independent waves at −1.72, −1.85, and −2.01 V, by differential pulse voltammetry (DPV) (Fig. 2) similarly to the reduction of 6-azulenyl derivative (**28**). Therefore, the three 2-azulenyl substituents on the benzene ring are concluded to result in an increase of the multiplicity of electron affinity due to the reduction of the respective azulene chromophore. The three-step reduction exhibits the existence of the redox interaction among the three 2-azulenyl groups. Similarly to the three-step reduction of **24**, 1,2,4-tri(2-azulenyl)benzene (**25**) also showed a three-step reduction wave with excellent reversibility upon CV (Fig. 1(c)), although the reduction of **25** is expected to show a one-step, two-electron transfer as observed in the reduction of 6-azulenyl derivative (**29**). Consequently, the redox property of tri(2-azulenyl)-benzenes (**24** and **25**) does not depend on the position of the 2-azulenyl substituents on the benzene ring and the redox system of **25** could be depicted in Scheme 10.

3. Conclusion

We have demonstrated an efficient preparation of 2-azulenylboronate reagent (**6**) which has been found to undergo Pd-catalyzed coupling with a range of aryl halides, and herein established a strategy to produce novel poly(2-azulenyl)benzene derivatives. The reaction of **6** with 1,2-di-, 1,4-di-, 1,3,5-tri-, 1,2,4-tri-, and 1,2,4,5-tetrabromobenzenes afforded 1,2-di-, 1,4-di-, 1,3,5-tri-, 1,2,4-tri-, and 1,2,4,5-tetra(2-azulenyl)benzene derivatives (**22**, **23**, **24**, **25** and **26**). These results provide a straightforward methodology for the carbon–carbon bond formation at the 2-position of azulene. Although 2-azulenyl substituents do not possess the formal cyclopentadienide substructure in the electrochemically reduced form, the redox behaviors examined by CV of these compounds clarified the presumed multiple-electron transfer under the electrochemical conditions.

4. Experimental

4.1. General

Melting points were determined on a Yanagimoto micro melting apparatus MP-S3 and are uncorrected. Mass spectra were obtained with a JEOL HX-110, a Hitachi M-2500, or a Bruker APEX II instrument, usually at 70 eV. IR and UV spectra were measured on a Shimadzu FTIR-8100M and a Hitachi U-3410 spectrophotometer, respectively. ^{1}H NMR spectra (^{13}C NMR spectra) were recorded on a JEOL GSX 400 at 400 MHz (100 MHz), a JEOL JNM A500 at 500 MHz (125 MHz), or a Bruker AM 600 spectrometer at 600 MHz (150 MHz). Gel permeation chromatography (GPC) purification was performed on a TSKgel G2000H$_6$. Voltammetry measurements were carried out with a BAS 100B/W electrochemical workstation equipped with Pt working and auxiliary electrodes, and a reference electrode formed from Ag/AgNO$_3$ (0.01 M, 1 M=1 mol dm^{-3}) in a tetrabutylammonium perchlorate (0.1 M) acetonitrile solution. Elemental analyses were performed at the Instrumental Analysis Center of Chemistry, Faculty of Science, Tohoku University.

4.1.1. 2-(2-Azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6). To a solution of *n*-butyllithium (1.5 mL, 1.6 M solution in hexane, 2.4 mmol) in ether (10 mL) was added dropwise at −100 °C a solution of 2-iodoazulene (**3b**) (256 mg, 1.01 mmol) in ether (20 mL). The mixture was allowed to react at −80 °C for 30 min. A solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**10**) (563 mg, 3.03 mmol) in ether (5 mL) was added dropwise to the cooled mixture. The mixture was allowed to warm to

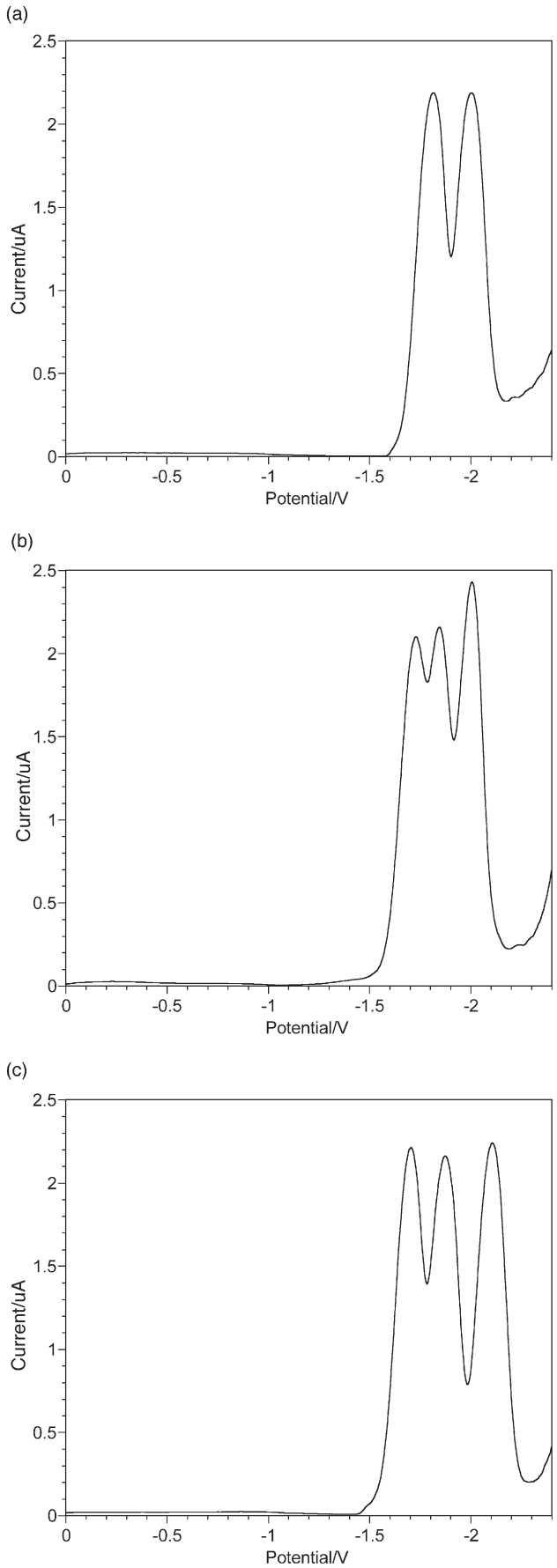


Figure 2. Differential pulse voltammograms of (a) **22**, (b) **24**, and (c) **25** in *o*-dichlorobenzene containing *n*-Bu_4NBF_4 (0.1 M) as a supporting electrolyte; scan rate, 20 mV s^{-1}.

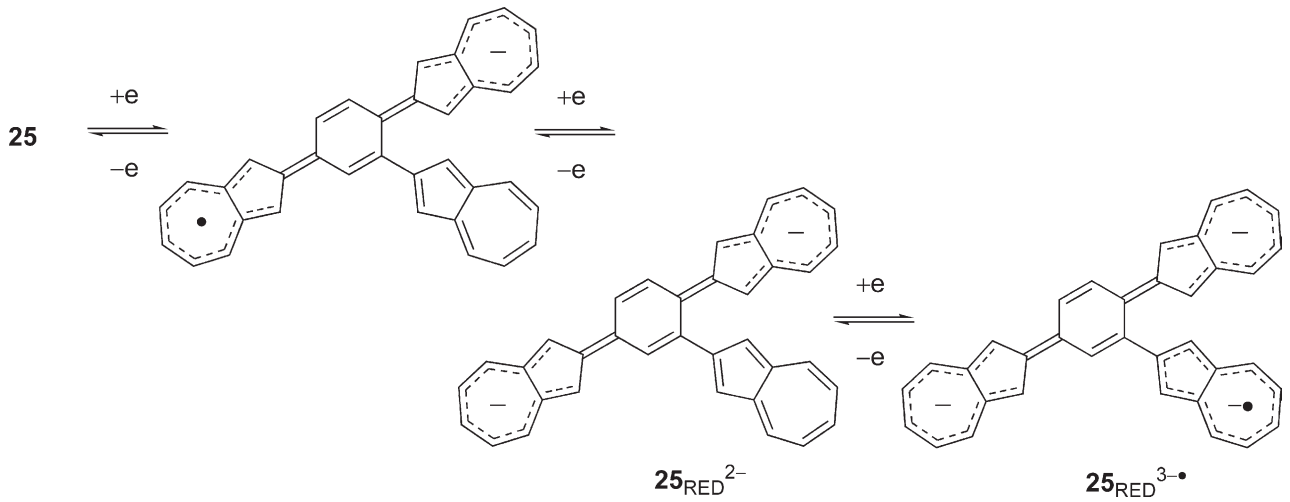
room temperature to react for 1.5 h. The reaction was quenched with water, and the organic layer was separated, washed with brine, and dried with $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2 and GPC with $CHCl_3$ to afford **6** (201 mg, 78%). blue prisms; mp 97–100 °C (sublimation) [lit.[11] mp 99–101 °C].

4.1.2. General procedure for the Pd-catalyzed reaction of 2-azulenylboronate (6). To a degassed solution of **6**, aryl halides, and base in solvent was added Pd-catalyst and ligand. The resulting mixture was heated at 80 °C under an Ar atmosphere. The reaction mixture was poured into water and then extracted with toluene or CH_2Cl_2. The organic layer was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The products were isolated by column chromatography on silica gel and/or gel permeation chromatography (GPC) with $CHCl_3$.

4.1.3. 2-Tolylazulene (12). The general procedure was followed by using 2-azulenylboronate (**6**) (252 mg, 0.992 mmol), 4-bromotoluene (**11a**) (340 mg, 1.99 mmol), Cs_2CO_3 (479 mg, 1.47 mmol), $Pd_2(dba)_3$ (45 mg, 0.049 mmol), and P(*t*-Bu)$_3$ (57 mg, 0.28 mmol) in dioxane (6 mL). Column chromatography on silica gel with 10% ethyl acetate/hexane and GPC afforded **12** (157 mg, 73%). blue plates; mp 216–217 °C [lit.[21] mp 214 °C]; MS (70 eV) *m*/*z* (relative intensity) 218 (M^+, 100%); IR (KBr disk) ν_{max} 1406, 806, 723 and 505 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 246 (4.18), 275 sh (4.37), 288 sh (4.56), 301 (4.79), 312 (4.83), 345 sh (3.68), 361 (3.90), 378 (4.17), 397 (4.23), 435 (2.26), 534 sh (2.47), 573 (2.62), 613 (2.60), and 666 sh (2.25); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.24 (d, *J*=9.9 Hz, 2H, H-4,8), 7.85 (d, *J*=8.3 Hz, 2H, H-2′,6′), 7.64 (s, 2H, H-1,3), 7.47 (t, *J*=9.9 Hz, 1H, H-6), 7.26 (d, *J*=8.3 Hz, 2H, H-3′,5′), 7.13 (dd, *J*=9.9 Hz, 2H, H-5,7), and 2.40 (s, 3H, 4′-Me).

4.1.4. 2-(4-Nitrophenyl)azulene (16a). The general procedure was followed by using 2-azulenylboronate (**6**) (100 mg, 0.393 mmol), 4-bromonitrobenzene (**15a**) (161 mg, 0.797 mmol), Cs_2CO_3 (198 mg, 0.608 mmol), $Pd_2(dba)_3$ (18 mg, 0.020 mmol), and P(*t*-Bu)$_3$ (35 mg, 0.17 mmol) in dioxane (3 mL) at 80 °C for 6 h. Column chromatography on silica gel with CH_2Cl_2 afforded **16a** (78 mg, 80%). green needles; mp 249–255 °C decomp. (hexane wash) [lit.[21] mp 248–249 °C]; MS (70 eV) *m*/*z* (relative intensity) 249 (M^+, 100%) and 202 (57); IR (KBr disk) ν_{max} 1514, 1509, 1347, 1331, 808 and 756 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 237 (4.27), 265 (4.16), 296 sh (4.50), 312 (4.58), 368 sh (4.26), 381 (4.45), 399 (4.46), 544 sh (2.54), 587 (2.70), 627 (2.70), and 683 sh (2.39); ^{1}H NMR (600 MHz, $CDCl_3$) δ=8.36 (d, *J*=9.9 Hz, 2H, H-4,8), 8.32 (d, *J*=9.0 Hz, 2H, H-3′,5′), 8.08 (d, *J*=9.0 Hz, 2H, H-2′,6′), 7.71 (s, 2H, H-1,3), 7.61 (t, *J*=9.9 Hz, 1H, H-6), and 7.22 (dd, *J*=9.9, 9.9 Hz, 2H, H-5,7); ^{13}C NMR (150 MHz, $CDCl_3$) δ=147.2 (C-1′), 146.5 (C-2), 143.0 (C-4′), 141.4 (C-3a,8a), 138.2 (C-6), 137.7 (C-4,8), 128.0 (C-2′,6′), 124.4 (C-5,7), 124.3 (C-3′,5′), and 115.0 (C-1,3). Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.83; H, 4.65; N, 5.55.

4.1.5. 2-(4-Acetylphenyl)azulene (16b). The general



Scheme 10.

procedure was followed by using 2-azulenylboronate (**6**) (110 mg, 0.433 mmol), 4-bromoacetophenone (**15b**) (150 mg, 0.754 mmol), Cs_2CO_3 (195 mg, 0.598 mmol), and $Pd(PPh_3)_4$ (27 mg, 0.023 mmol) in dioxane (3 mL) at 80 °C for 24 h. Column chromatography on silica gel with CH_2Cl_2 afforded **16b** (45 mg, 42%). blue plates; mp 247–256 °C decomp. (ethyl acetate); MS (70 eV) *m*/*z* (relative intensity) 246 (M^+, 100%); IR (KBr disk) ν_{max} 1647 (C=O), 1271, and 808 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 242 (4.16), 303 sh (4.80), 314 (4.91), 360 sh (4.14), 376 (4.38), 396 (4.40), 542 sh (2.57), 582 (2.70), 623 (2.68), and 676 sh (2.39); ^1H NMR (600 MHz, $CDCl_3$) δ=8.34 (d, *J*=9.9 Hz, 2H, H-4,8), 8.05 (m, 2H, H-3′,5′), 8.05 (m, 2H, H-2′,6′), 7.72 (s, 2H, H-1,3), 7.56 (t, *J*=9.9 Hz, 1H, H-6), 7.20 (dd, *J*=9.9, 9.9 Hz, 2H, H-5,7), and 2.66 (s, 3H, 4′-COMe); ^{13}C NMR (150 MHz, $CDCl_3$) δ=197.7 (s, 4′-COMe), 148.0 (C-2), 141.3 (C-3a,8a), 141.0 (C-4′), 137.4 (C-6), 136.9 (C-4,8), 136.3 (C-1′), 129.0 (C-2′,6′), 127.6 (C-3′,5′), 124.1 (C-5,7), 114.9 (C-1,3), and 26.7 (q, 4′-COMe). Anal. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 87.38; H, 5.92.

4.1.6. 2-(4-Methoxyphenyl)azulene (16c). The general procedure was followed by using 2-azulenylboronate (**6**) (100 mg, 0.393 mmol), 4-bromoanisole (**15c**) (164 mg, 0.877 mmol), Cs_2CO_3 (193 mg, 0.592 mmol), $Pd_2(dba)_3$ (18 mg, 0.020 mmol), and P(*t*-Bu)$_3$ (20 mg, 0.099 mmol) in dioxane (3 mL) at 80 °C for 19 h. Column chromatography on silica gel with CH_2Cl_2 and GPC afforded **16c** (66 mg, 72%). blue plates; mp 229–234 °C decomp.; MS (70 eV) *m*/*z* (relative intensity) 234 (M^+, 100%); IR (KBr disk) ν_{max} 1605, 1478, 1258, 1183, 1030 and 810 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 248 sh (4.16), 275 (4.40), 307 (4.74), 317 (4.81), 369 sh (4.01), 388 (4.25), 405 (4.29), 533 sh (2.53), 569 (2.64), 608 (2.60), and 658 sh (2.29); ^1H NMR (500 MHz, $CDCl_3$) δ=8.25 (d, *J*=9.8 Hz, 2H, H-4,8), 7.92 (d, *J*=8.9 Hz, 2H, H-2′,6′), 7.62 (s, 2H, H-1,3), 7.47 (t, *J*=9.8 Hz, 1H, H-6), 7.15 (dd, *J*=9.8, 9.8 Hz, 2H, H-5,7), 7.01 (d, *J*=8.9 Hz, 2H, H-3′,5′), and 3.88 (s, 3H, 4′-OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ=160.0 (C-4′), 149.8 (C-2), 141.4 (C-3a,8a), 135.7 (C-6), 135.2 (C-4,8), 129.2 (C-1′), 128.9 (C-2′,6′), 123.7 (C-5,7), 114.4 (C-3′,5′), 113.8 (C-1,3), and 55.4 (4′-OMe). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.85; H, 6.17.

4.1.7. 1,2-Di(2-azulenyl)benzene (22). The general procedure was followed by using 2-azulenylboronate (**6**) (203 mg, 0.799 mmol), 1,2-dibromobenzene (**17**) (95 mg, 0.40 mmol), Cs_2CO_3 (394 mg, 1.21 mmol), $Pd_2(dba)_3$ (42 mg, 0.046 mmol), P(*t*-Bu)$_3$ (65 mg, 0.32 mmol), and dioxane (5 mL) at 80 °C for 24 h. Chromatographic purification on silica gel with CH_2Cl_2 and GPC afforded **22** (43 mg, 33%), 2-phenylazulene (**13**) (11 mg, 7%), and azulene (**7**) (4 mg, 4%).

Compound **22**. Blue crystals; mp 188–189 °C; MS (70 eV) *m*/*z* (relative intensity) 330 (M^+, 88%), 329 (53), 327 (69), 326 (M^+−4H, 100), 314 (49), and 313 (57); IR (KBr disk) ν_{max} 1456, 1401, 826, 762 and 731 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 238 sh (4.44), 281 (4.93), 314 sh (4.60), 322 (4.62), 393 (4.14), 544 sh (2.65), 579 (2.88), 621 (2.75), and 673 sh (2.42); ^1H NMR (500 MHz, $CDCl_3$) δ=8.07 (d, *J*=9.9 Hz, 4H, H-4′,8′), 7.71 (m, 2H, H-3,6), 7.44 (m, 2H, H-4,5), 7.43 (t, *J*=9.9 Hz, 2H, H-6′), 7.18 (s, 4H, H-1′,3′), and 7.03 (dd, *J*=9.9, 9.9 Hz, 4H, H-5′,7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ=151.3 (C-2′), 140.2 (C-3a,8a), 136.9 (C-1,2), 136.3 (C-6′), 135.9 (C-4′,8′), 131.8 (C-3,6), 127.8 (C-4,5), 123.0 (C-5′,7′), and 118.5 (C-1′,3′); HRMS Calcd for $C_{26}H_{18}$—e 330.1403, found 330.1401. Anal. Calcd for $C_{26}H_{18}$: C, 94.51; H, 5.49. Found: C, 94.23; H, 5.65.

4.1.8. 1,4-Di(2-azulenyl)benzene (23). Following the general procedure, the reaction of 2-azulenylboronate (**6**) (204 mg, 0.803 mmol) of 1,4-dibromobenzene (**18**) (93 mg, 0.39 mmol) in dioxane (5 mL) at 80 °C for 24 h in the presence of Cs_2CO_3 (400 mg, 1.23 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), and P(*t*-Bu)$_3$ (47 mg, 0.23 mmol) afforded an insoluble material in CH_2Cl_2. Mass spectrum of the insoluble material showed a peak at *m*/*z* 330, which corresponded to a correct M^+ ion peak of **23** (57 mg, 44%). After the insoluble material was removed by filtration, the organic layer was worked up. Column chromatography on silica gel with CH_2Cl_2 and GPC with $CHCl_3$ afforded

2-phenylazulene (**13**) (2 mg, 2%) and azulene (**7**) (2 mg, 2%).

Compound **23**. Green crystals; mp >300 °C; MS (70 eV) *m/z* (relative intensity) 330 (M^+, 100%); IR (KBr disk) ν_{max} 1410 and 808 cm^{-1}; HRMS Calcd for $C_{26}H_{18}$—e 330.1403, found 330.1409. Anal. Calcd for $C_{26}H_{18}\cdot 1/4H_2O$: C, 93.24; H, 5.57. Found: C, 93.53; H, 5.63.

4.1.9. 1,3,5-Tri(2-azulenyl)benzene (24). The general procedure was followed by using 2-azulenylboronate (**6**) (301 mg, 1.18 mmol), 1,3,5-tribromobenzene (**19**) (128 mg, 0.407 mmol), Cs_2CO_3 (596 mg, 1.83 mmol), $Pd_2(dba)_3$ (66 mg, 0.072 mmol), P(*t*-Bu)$_3$ (49 mg, 0.24 mmol), dioxane (7 mL) at 80 °C for 24 h. Chromatographic purification on silica gel with CH_2Cl_2 and GPC afforded **24** (32 mg, 18%), azulene (**7**) (46 mg, 30%), and the recovered **6** (22 mg, 7%).

Compound **24**. Greenish blue microneedles; mp >300 °C; MS (70 eV) *m/z* (relative intensity) 456 (M^+, 100%); IR (KBr disk) ν_{max} 1505, 1453, 1399 and 801 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 245 (4.54), 301 (5.16), 314 (5.16), 381 (4.69), 399 (4.73), 541 sh (2.92), 575 (3.05), 615 (3.03), and 664 sh (2.67); ^{1}H NMR (600 MHz, $CDCl_3$) δ=8.54 (s, 3H, H-2,4,6), 8.39 (d, *J*=9.8 Hz, 6H, H-4′,8′), 7.89 (s, 6H, H-1′,3′), 7.57 (t, *J*=9.8 Hz, 3H, H-6′), and 7.23 (dd, *J*=9.8, 9.8 Hz, 6H, H-5′,7′); ^{13}C NMR (150 MHz, $CDCl_3$) δ=149.8 (C-2′), 141.4 (C-3′a,8′a), 137.8 (C-1,3,5), 136.6 (C-6′), 136.2 (C-4′,8′), 126.9 (C-2,4,6), 123.9 (C-5′,7′), and 114.8 (C-1′,3); HRMS Calcd for $C_{36}H_{24}$—e 456.1873, found 456.1874. Anal. Calcd for $C_{36}H_{24}\cdot 1/2H_2O$: C, 92.87; H, 5.41. Found: C, 92.73; H, 5.40.

4.1.10. 1,2,4-Tri(2-azulenyl)benzene (25). The general procedure was followed by using 2-azulenylboronate (**6**) (254 mg, 1.00 mmol), 1,2,4-tribromobenzene (**20**) (105 mg, 0.334 mmol), Cs_2CO_3 (587 mg, 1.80 mmol), $Pd_2(dba)_3$ (59 mg, 0.064 mmol), P(*t*-Bu)$_3$ (72 mg, 0.36 mmol), and dioxane (7 mL) at 80 °C for 24 h. Chromatographic purification on silica gel with CH_2Cl_2 and GPC afforded **25** (55 mg, 36%) and azulene (**7**) (3 mg, 2%).

Compound **25**. Green crystals; mp 238.5–239 °C decomp.; MS (70 eV) *m/z* (relative intensity) 456 (M^+, 100%) and 439 (49); IR (KBr disk) ν_{max} 1455, 1401 and 810 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (log ε) 236 (4.58), 274 (4.80), 316 (5.04), 386 sh (4.53), 408 (4.61), 430 sh (4.53), 537 sh (2.94), 579 (3.05), 618 (3.01), and 670 sh (2.68); ^{1}H NMR (600 MHz, $CDCl_3$) δ=8.32 (d, *J*=9.7 Hz, 2H, H-4‴,8‴), 8.30 (d, *J*=1.9 Hz, 1H, H-3), 8.18 (d, *J*=9.7 Hz, 2H, H-4″,8″), 8.11 (d, *J*=9.7 Hz, 2H, H-4′,8′), 8.06 (dd, *J*=8.1, 1.9 Hz, 1H, H-5), 7.86 (d, *J*=8.1 Hz, 1H, H-6), 7.79 (s, 2H, H-1‴,3‴), 7.53 (t, *J*=9.9 Hz, 1H, H-6‴), 7.51 (t, *J*=9.9 Hz, 1H, H-6″), 7.46 (t, *J*=9.9 Hz, 1H, H-6′), 7.32 (s, 2H, H-1″,3″), 7.22 (s, 2H, H-1′,3′), 7.18 (dd, *J*=9.9, 9.7 Hz, 2H, H-5‴,7‴), 7.11 (dd, *J*=9.9, 9.7 Hz, 2H, H-5″,7″), and 7.07 (dd, *J*=9.9, 9.7 Hz, 2H, H-5′,7′); ^{13}C NMR (150 MHz, $CDCl_3$) δ=151.5 (C-2″), 150.8 (C-2′), 149.3 (C-2‴), 141.4 (C-3‴a,8‴a), 140.3 (C-3′a,8′a or C-3″a,8″a), 140.2 (C-3′a,8′a or C-3″a,8″a), 137.7 (C-2), 136.7 (C-1), 136.5 (2C, C-6′, C-6″, and/or C-6‴), 136.3 (C-6′, C-6″, or C-6‴), 136.1 (2C, C-4′,8′, C-4″,8″, and/or C-4‴,8‴), 136.0 (C-4′,8′, C-4″,8″, or C-4‴,8‴), 135.9 (C-4), 132.5 (C-6), 131.2 (C-3), 126.9 (C-5), 123.8 (C-5‴,7‴), 123.2 (C-5′,7′ or C-5″,7″), 123.1 (C-5′,7′ or C-5″,7‴), 118.6 (C-1″,3″), 118.4 (C-1′,3′), and 114.6 (C-1‴,3‴); HRMS Calcd for $C_{36}H_{24}$—e 456.1873, found 456.1874. Anal. Calcd for $C_{36}H_{24}\cdot 1/2H_2O$: C, 92.87; H, 5.41. Found: C, 92.78; H, 5.64.

4.1.11. 1,2,4,5-Tetra(2-azulenyl)benzene (26). Following the general procedure, the reaction of 2-azulenylboronate (**6**) (417 mg, 1.64 mmol) with 1,2,4,5-tetrabromobenzene (**21**) (147 mg, 0.374 mmol) in dioxane (10 mL) at 80 °C for 24 h in the presence of Cs_2CO_3 (802 mg, 2.46 mmol), $Pd_2(dba)_3$ (74 mg, 0.081 mmol), and P(*t*-Bu)$_3$ (96 mg, 0.47 mmol) afforded an insoluble material in CH_2Cl_2. Mass spectrum of the insoluble material showed a peak at *m/z* 582, which corresponded to a correct M^+ ion peak of **26** (29 mg, 13%). After the insoluble material was removed by filtration, the organic layer was worked up. Column chromatography on silica gel with CH_2Cl_2 and GPC afforded 1,2,4-tri(2-azulenyl)benzene (**25**) (23 mg, 13%) and azulene (**7**) (9 mg, 4%).

Compound **26**. Green microneedles; mp >300 °C; MS (70 eV) *m/z* (relative intensity) 582 (M^+, 66%), 565 (45), 490 (41), 489 (55), 466 (49), 465 (100), 454 ($M^+-C_{10}H_8$, 69), 453 (47), 439 (41), 328 ($M^+-2C_{10}H_7$, 51), 291 ($M^+/2$, 53), and 265 (78); IR (KBr disk) ν_{max} 1574, 1453, 1399, 1383, 820 and 812 cm^{-1}; HRMS Calcd for $C_{46}H_{30}$—e 582.2342, found 582.2358. Anal. Calcd for $C_{46}H_{30}\cdot 2/3H_2O$: C, 92.90; H, 5.31. Found: C, 92.75; H, 5.36.

Acknowledgements

The present work was supported by a Grant-in-Aid for Scientific Research (No. 14540486 to S. I.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. See e.g.: (a) Billington, D. C. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.1. (b) Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.2. (c) Knight, D. W. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.3. (d) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.4.
2. Horino, H.; Asao, T.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 183–190.
3. (a) Dyker, G.; Borowski, S.; Heiermann, J.; Körning, J.; Opwis, K.; Henkel, G.; Köckerling, M. *J. Organomet. Chem.* **2000**, *606*, 108–111. (b) Balschukat, D.; Dehmlow, E. V. *Chem. Ber.* **1986**, *119*, 2272–2288. (c) Otani, H.; Tsunoda, Y. Presented at 79th CSJ National Meeting, Kobe, March 31, 2001, Abstr., No. 4B2 10.
4. (a) Ito, S.; Inabe, H.; Okujima, T.; Morita, N.; Watanabe, M.; Imafuku, K. *Tetrahedron Lett.* **2000**, *41*, 8343–8347.

(b) Fabin, K. H. H.; Elwahy, A. H. M.; Hafner, K. *Tetrahedron Lett.* **2000**, *41*, 2855–2858.
5. Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2001**, *3*, 1081–1084.
6. (a) Okujima, T.; Ito, S.; Morita, N. *Tetrahedron Lett.* **2002**, *43*, 1261–1264. (b) Ito, S.; Okujima, T.; Morita, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1896–1905.
7. Fujita, M.; Oka, H.; Ogura, K. *Tetrahedron Lett.* **1995**, *36*, 5247–5250.
8. See e.g.: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (c) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49–97. (d) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic: London, 1988.
9. For reviews: (a) Ishiyama, T.; Miyaura, N. *J. Syn. Org. Chem.* **1999**, *57*, 503–511. (b) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392–402.
10. (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164–168.
11. Kurotobi, K.; Tabata, H.; Miyauchi, M.; Murafuji, T.; Sugihara, Y. *Synthesis* **2002**, 1013–1016.
12. Kurotobi, K.; Miyauchi, M.; Takakura, K.; Murafuji, T.; Sugihara, Y. *Eur. J. Org. Chem.* **2003**, 3663–3665.
13. (a) Hünig, S.; Kemmer, M.; Wenner, H.; Perepichka, I. F.; Bäuerle, P.; Emge, A.; Gescheid, G. *Chem. Eur. J.* **1999**, *5*, 1969–1973. (b) Hünig, S.; Kemmer, M.; Wenner, H.; Barbosa, F.; Gescheidt, G.; Perepichka, I. F.; Bäuerle, P.; Emge, A.; Peters, K. *Chem. Eur. J.* **2000**, *6*, 2618–2632. (c) Hünig, S.; Perepichka, I. F.; Kemmer, M.; Wenner, H.; Bäuerle, P.; Emge, A. *Tetrahedron* **2000**, *56*, 4203–4211. (d) Hünig, S.; Langels, A.; Schmittel, M.; Wenner, H.; Perepichka, I. F.; Peters, K. *Eur. J. Org. Chem.* **2001**, 1393–1399.
14. (a) Ito, S.; Inabe, H.; Okujima, T.; Morita, N.; Watanabe, M.; Harada, N.; Imafuku, K. *Tetrahedron Lett.* **2001**, *42*, 1085–1089. (b) Ito, S.; Inabe, H.; Okujima, T.; Morita, N.; Watanabe, M.; Harada, N.; Imafuku, K. *J. Org. Chem.* **2001**, *66*, 7090–7101.
15. (a) McDonald, R. N.; Richmond, J. M.; Curtis, J. R.; Petty, H. E.; Hoskins, T. L. *J. Org. Chem.* **1976**, *41*, 1811–1821. (b) Ito, S.; Nomura, A.; Morita, N.; Kabuto, C.; Kobayashi, H.; Maejima, S.; Fujimori, K.; Yasunami, M. *J. Org. Chem.* **2002**, *67*, 7295–7302.
16. (a) Vaultier, M.; Carboni, B. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 191–276. (b) Miyaura, N.; Maruoka, K. *Synthesis of Organometallic Compounds*; Komiya, S., Ed.; Wiley: New York, 1997; pp 345–390.
17. Zeller, K.-P.; 4th ed. *Houben-Weyl; Methoden der Organischen Chemie*; Georg Thieme: Stuttgart, 1985; Vol. V, Part 2C, pp 127–418.
18. (a) Ito, S.; Kubo, T.; Morita, N.; Matsui, Y.; Watanabe, T.; Ohta, A.; Fujimori, K.; Murafuji, T.; Sugihara, Y.; Tajiri, A. *Tetrahedron Lett.* **2004**, *45*, 2891–2894. (b) Kurotobi, K.; Tabata, H.; Miyauchi, M.; Mustafizur, A. F. M. R.; Migita, K.; Murafuji, T.; Sugihara, Y.; Shimoyama, H.; Fujimori, K. *Synthesis* **2003**, 30–34.
19. (a) Andersen, M. W.; Hildebrandt, B.; Köster, G.; Hoffmann, R. W. *Chem. Ber.* **1989**, *122*, 1777–1782. (b) Mohanakrishnan, A. K.; Lakshmikantham, M. V.; McDougal, C.; Cava, M. P.; Baldwin, J. W.; Metzger, R. M. *J. Org. Chem.* **1998**, *63*, 3105–3112.
20. 2-(Tri-*n*-butylstannyl)azulene (**2**) has been also obtained by the reaction of 2-azulenylmagnesium reagent (**9b**) with tri-*n*-butylstannyl chloride in high yield.[18a]
21. Nefedov, V. A.; German, N. A.; Lutsenko, A. I.; Nikishin, G. I. *J. Org. Chem. U.S.S.R.* **1987**, *23*, 154–162.
22. (a) Plattner, P. A.; Sandrin, R.; Wyss, J. *Helv. Chim. Acta* **1946**, *29*, 1604–1608. (b) Morita, T.; Abe, N.; Takase, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3063–3070.
23. O'Keeefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679–6680.
24. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097.
25. (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351. (b) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Maruccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131–132.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5367–5372

Synthesis of mesoionic[1,2,3]triazolo[5,1-*d*][1,2,5]triazepines

Elena A. Savel'eva,[a] Yury A. Rozin,[a] Mikhail I. Kodess,[b] Luc Van Meervelt,[c] Wim Dehaen,[c] Yury Yu. Morzherin[a] and Vasiliy A. Bakulev[a,*]

[a]*Department of Technology and Organic Synthesis, The Urals State Technical University, 19 Mira str., 620002 Ekaterinburg, Russian Federation*
[b]*Institute of Organic Synthesis, Ural Division of Russian Academy of Sciences, 20 ul. Kovalevskoi, 620219 Ekaterinburg, Russian Federation*
[c]*Department of Chemistry, Laboratory of Organic Synthesis, University of Leuven, B-3001 Leuven, Belgium*

Received 17 December 2003; revised 2 April 2004; accepted 23 April 2004

Abstract—Intramolecular cyclization of 1-amino-3-phenacyl-4-carbohydrazido-1,2,3-triazolium-5-olates has been shown to take place via selective interaction of the carbonyl group with the terminal amino function of the hydrazido group to form a 1,2,5-triazepine ring. Minor products, resulting from the interaction of the α-nitrogen atom of the hydrazido group with the carbonyl function, having a N-amino-pyridazine structure were also detected and isolated. A general method for the synthesis of novel mesoionic 2-amino-7-aryl-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo[5,1-*d*][1,2,5]triazepin-9-ium-3-olates was developed.

1. Introduction

Fused 1,2,5-triazepines with a bridgehead nitrogen atom in the molecule exhibit interesting biological properties.[1] At the same time, there are no examples of mesoionic compounds among publications concerning the synthesis of fused triazepines,[2] although mesoionic 1,2,3-triazoles fused to six-membered rings are known to exhibit various biological effects.[3] The latter prompted M. Furber and colleagues[4] to elaborate an efficient method to prepare 1,2,3-triazoles of mesoionic structure fused to quinazoline, quinoxaline and benzotriazine rings. However, this method did not give access to 1,2,3-triazoles fused to triazepine ring.

In this connection, we would like to report our recent results of a new synthetic approach towards novel mesoionic [1,2,3]triazolo[5,1-*d*][1,2,5]triazepines.

2. Results and discussion

The basic idea of our approach consists in the synthesis of 3-phenacyl-4-carbohydrazido-1,2,3-triazolium-5-olates which in subsequent cyclization of carbonyl and hydrazide groups should form the 1,2,5-triazepine ring. Earlier we have shown,[5] that alkylation of 1-aryl- and 1-amino-5-hydroxy-1*H*[1,2,3]triazoles with substituted phenacyl bromides leads solely to *N*-3 alkylated products of type **1** (Scheme 1). We proposed that triazolotriazepines **4** could be obtained in cyclization of mesoionic hydrazides of 3-phenacyl-1,2,3-triazolio-5-olate-4-carboxylic acid **3** (Scheme 1). However, it was found that the ester group at the position 4 of the triazole ring did not react with hydrazine hydrate. An attempt to obtain 1,2,3-triazole-4-carbonyl chloride **2** starting from esters **1** completely failed. Unfortunately, in both experiments the ethyl 1-substituted 5-hydroxy-1,2,3-triazole-4-carboxylate **1** was recovered unchanged, demonstrating the low reactivity of the ester group due to extensive conjugation with the olate function.

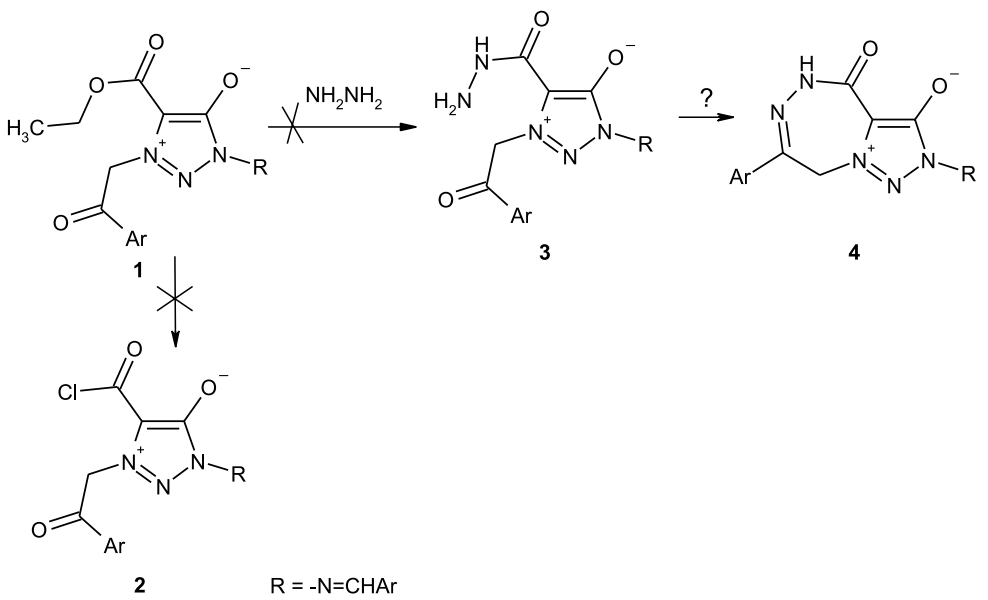
Therefore, the preparation of the desired hydrazide of type **3** was performed by a three-step synthesis starting from the protected hydrazide **5** (Scheme 2). A diazo group transfer reaction with hydrazide **5** allowed us prepare sodium 1*H*-1,2,3-triazole-5-olate **6** in good yield by adapting a literature protocol.[5]

When the triazolate **6** was reacted with substituted phenacyl bromides (Scheme 3), *N*-3 alkylated products **7** were generated. After dilution with water, the hydrolysis of one of the azomethine groups took place to form 1-amino-3-(*p*-*R*-phenacyl)-4-(*iso*-propylidencarboxamido)-1,2,3-triazolium-5-olate **8**. We managed to isolate intermediate **7e** (R=CH_3O), in good yield and then transformed this compound to 1-aminotriazolium-5-olate **8e** by subsequent hydrolysis.

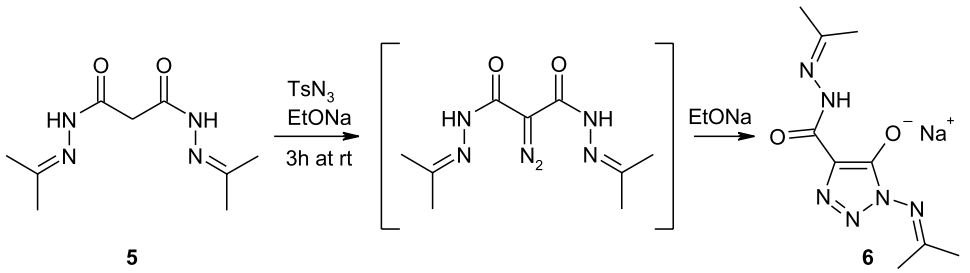
Heating of compounds **8a**-**e** in a 0.1 N HCl solution leads to the removal of the second isopropylidene group to result in

Keywords: Fused mesoionic heterocycles; 1-Amino-1,2,3-triazolium-5-olate; [1,2,3]Triazolo[5,1-*d*][1,2,5]triazepine; [1,2,3]Triazolo[1,5-*a*]-pyrazine; Diazo group transfer; Alkylation.
* Corresponding author. Fax: +7-3432-745483;
e-mail address: vasiliy.bakulev@toslab.com

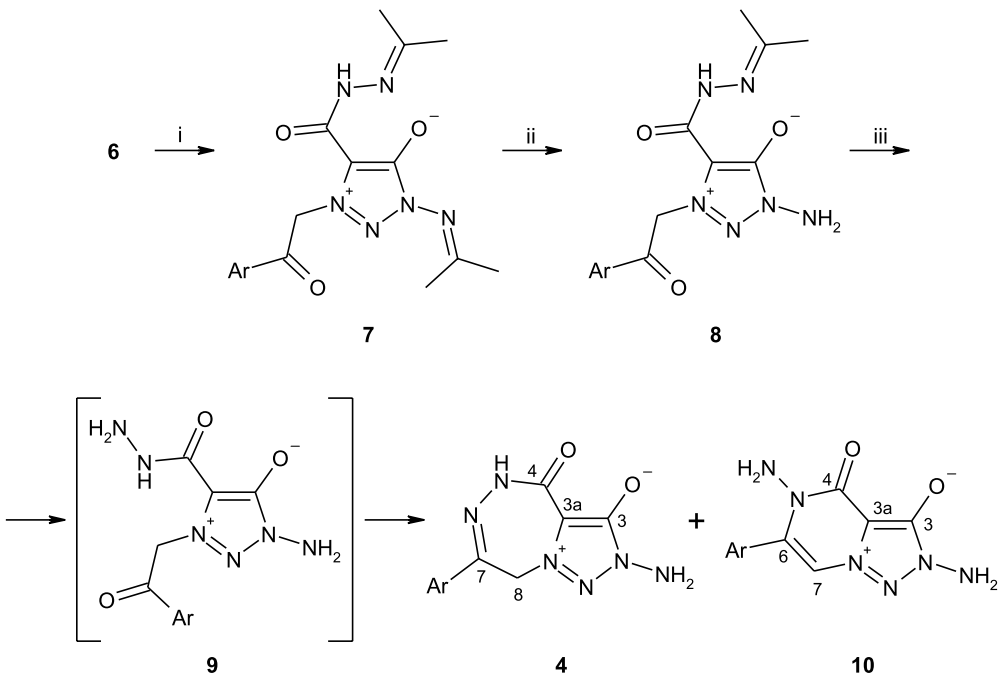
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.067



Scheme 1.



Scheme 2.



4, 7, 8, 9, 10	a	b	c	d	e
Ar	C_6H_5	p-$CH_3C_6H_4$	p-ClC_6H_4	p-BrC_6H_4	p-$CH_3OC_6H_4$

Scheme 3. Reagents and conditions: (i), $ArCOCH_2Br$, DMF, 70 °C, 5 h; (ii) H_2O, rt, 1 h; (iii) 0.1 N HCl, 100 °C, 15 h.

Table 1. ^{13}C NMR (at 100 MHz in DMSO-d_6) chemical shifts (ppm) and coupling constants (J (Hz))

δ (J (Hz))	Compound				
	4a	**4b**	**4c**	**4d**	**4e**
C_3	153.9 d ^3J=1.2	153.8 br. s $\omega_{1/2}$=2.4 Hz	153.9 d ^3J=1.2	153.9 d ^3J=1.3	153.8 s
C_{3a}	109.9 t ^3J=2.8	109.8 quintet ^3J=2.7	109.9 quintet ^3J=2.8	109.9 dt ^3J=3.1, ^3J=3.5	109.9 quintet ^3J=3.1
C_4	156.5 s	156.5 s	156.4 s	156.3 s	156.6 s
C_7	152.5 quintet ^2J=4.2	152.5 quintet ^2J=4.5	151.3 quintet ^2J=4.2	151.3 quintet ^2J=3.6	152.6 quintet ^2J=4.0
C_8	48.9 t ^1J=147.4	48.8 t ^1J=147.5	48.8 t ^1J=147.5	48.7 ^1J=148	48.8 t ^1J=147.5
Arom.	126.6, 128.9, 130.7, 133.9	126.5, 129.4, 131.0, 140.7	128.5, 128.9, 132.8, 135.5	128.6, 124.3, 124.3, 133.5	114.3, 126.0, 128.4, 161.4
Subs. (CH_3)	—	20.8 qt ^1J=126.6	—	—	55.4 q ^1J=144.8

the triazolohydrazides **9**, which undergo smooth cyclization in situ to the desired 2-amino-7-aryl-4-oxo-2,4,5,8-tetrahydro-[1,2,3]triazolo[5,1-*d*][1,2,5]triazepinium-3-olates **4a-e** in good yields. The ^1H and ^{13}C NMR spectral data for compound **4** corroborate the formation of the triazepine ring and are in a good accordance with its mesoionic structure[6] (Table 1).

Thus, for compounds **4**, splitting of signal C_{3a} due to coupling with protons of the methylene group C_8 is observed. The carbon signals for the methylene group C_8 and C_7 of the triazepines **4** are shifted upfield in comparison with the signals of similar atoms of precursors **8**. The final structural proof for the compounds **4** prepared was given by X-ray diffraction data for crystals of **4d** grown from DMF (Fig. 1).[7]

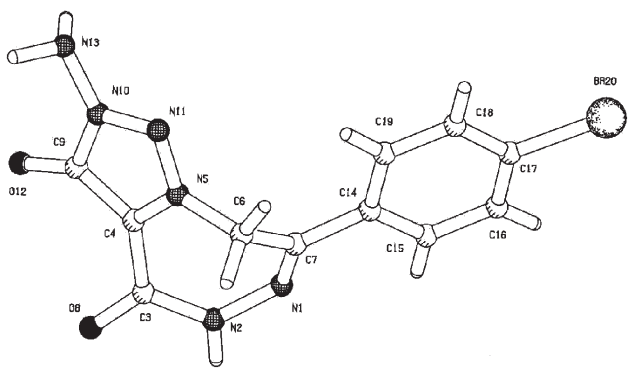


Figure 1. X-ray structure of **4d**.

The shape of molecule **4d** is determined by the boat conformation of the 7-membered ring. The phenyl ring makes an angle of 46.12(11)° with the 5-membered ring. The angle between the best planes through the 5- and 7-membered ring is 27.96(10)°. The asymmetric unit consists of one molecule **4d**, one DMF and one water molecules. These solvent molecules are involved in a hydrogen bond network with atoms N2, O8, N11, O12 and N13 (as numbered in Fig. 1).

It should be noted that the reaction described here represents the first example of the formation of the 1,2,5-triazepine ring due to intramolecular interaction of carbohydrazide and phenacyl functionalities.

It is known that both α- and β-nitrogen atoms of thiocarbohydrazide group can react with the phenacyl moiety leading to the formation of both seven- and six-membered heterocyclic compounds.[8] Careful study of the mother liquid of the reaction of compound **8** with HCl allowed us also to detect the presence of by-products, that were isolated in two cases. On the basis of elemental analyses and ^1H and ^{13}C NMR data (Table 2) the structures of the minor products were assigned as 2,5-diamino-6-aryl-4-oxo-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazinium-3-olates **10c** and **10e**.

It is known that 1,4-dihydro-5*H*-[1,3,4]-benzo- and azolotriazepin-5-ones are capable of rearranging to isomeric benzopyrimidin-4(3*H*)-ones.[9] To determine the formation mechanism of triazolo[1,5-*a*]pyrazinium-3-olates **10**, we have treated triazepines **4** with diluted

Table 2. ^1H, ^{13}C NMR (at 400 and 100 MHz in DMSO-d_6) chemical shifts (ppm) and coupling constants (J (Hz))

Atom/group	^{13}C		^1H	
	10c	**10e**	**10c**	**10e**
C_3	154.4 s	154.4 s	—	—
C_{3a}	107.3 d, ^3J=5.3	107.2 d, ^3J=4.3	—	—
C_4	151.7 d, ^3J=0.8	151.7 br. s, $\omega_{1/2}$=2.4	—	—
C_6	139.1 dt, ^2J=6.8 ^3J=3.4	139.9 dt, ^2J=6.3 ^3J=3.2	—	—
C_7	104.5 d, ^1J=200.4	103.6 d, ^1J=200	7.61, s	7.52, s
Arom.	127.7, 129.9, 131.6, 134.1	113.2, 123.2, 131.2, 160.1	7.53, d (J=8.7), 7.6, d (J=8.7)	7.01, d (J=8.7), 7.53, d (J=8.7)
CH_3	—	55.3 q, ^1J=144.6	—	3.81, s
NH_2	—	—	5.21, s[a]	5.23, s[a]
NH_2	—	—	6.28, s[a]	6.26, s[a]

[a] Disappeared after adding of D_3CCOOD.

HCl. Triazepines **4** were found to be stable even after prolonged heating at reflux in a solution of 0.1 N HCl, and this confirms the formation of compounds **10** directly from hydrazide **9** and rejects the rearrangement mechanism for their formation.

In conclusion, intramolecular cyclization of 1-amino-3-phenacyl-4-carbohydrazido-1,2,3-triazolium-5-olates has been shown to take place via selective interaction of the carbonyl group with the terminal amino function of the hydrazido group to form a 1,2,5-triazepine ring. Minor products resulting from the interaction of the α-nitrogen atom of the hydrazido group with the carbonyl function, namely the N-amino-pyridazines were also detected. A general method for the synthesis of novel mesoionic 2-amino-7-aryl-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo [5,1-*d*][1,2,5]triazepin-9-ium-3-olates was developed.

3. Experimental

3.1. General

Melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution with Bruker DRX-400, 400 MHz or Bruker WM-250, 250 MHz for ^{1}H and 100 MHz for ^{13}C, using TMS as internal standard. Infrared spectra were recorded in KBr on a UR-20 spectrometer. Mass spectra were recorded using Finnigan MAT 8200 instrument.

3.1.1. Bis(1-methylethylidene)malonhydrazide (5). A suspension of 10 g (0.76 mol) of malonhydrazide in 100 ml of acetone was refluxed for 2 h. The solid compound **5** was filtered off and washed with 15 ml of ethanol and dried in vacuum. Yield 15.5 g (98%); mp 163–5 °C. [Found C, 50.85, H, 7.53, N, 26.15. $C_9H_{16}N_4O_2$ requires: C, 50.93, H, 7.60, N, 26.40].

3.1.2. Synthesis of sodium 1-[(1-methylethylidene) amino]-4-{[2-(1-methylethylidene) hydrazino]carbonyl}-1*H*-1,2,3-triazol-5-olate (6). The N′^{1},N′^{3}-bis(1-methylethylidene)-malonohydrazide **5** (9.96 g, 0.047 mol) was suspended in a solution of sodium ethoxide (3.196 g, 0.047 mol) in 20 ml of dry ethanol, and tosyl azide (9.26 g, 0.047 mol) was added in a dropwise manner at 0–5 °C. The reaction mixture was stirred for 2 h. After cooling, the precipitate **6** was filtered off, washed with chloroform and dried. Yield 11.45 g (75%); mp 202–204 °C; ν (cm^{-1}): 1650, 1610 (CO). [Found: C 40.17, H 5.33, N 32.84. $C_9H_{13}N_6NaO_2$. requires: C 41.54, H 5.04, N 32.29]; ^{1}H NMR (250 MHz) δ: 11.27 (1H, br. s, NH), 2.13 (3H, s, Me), 1.96 (3H, s, Me), 1.94 (3H, s, Me), 1.84 (3H, s, Me).

3.2. Synthesis of 1-amino-3-(*p*-*R*-phenacyl)-4-{[2-(1-methylethylidene)hydrazino]carbonyl}-[1,2,3]-triazolium-5-olates (8a-d)

General procedure. A solution of sodium salt **6** (16 mmol) and an equivalent amount of the corresponding phenacyl bromide in 10 ml of DMF was heated at 70° for 3 h, cooled to room temperature and diluted with 15 ml of water. After 1 h, the solid of **8a-d** was filtered off, washed with water, dried and crystallized from chloroform (**8b**), from toluene (**8c**, **d**) or from ethanol (**8a**).

3.2.1. 1-Amino-4-{[2-(1-methylethylidene)hydrazino]-carbonyl}-3-phenacyl-1*H*-1,2,3-triazol-3-ium-5-olate (8a). Yield 2.28 g (45%); mp 234–236 °C; MS, *m*/*z*: 316 (54%, M$^+$). [Found: C 53.10, H 4.97, N 26.55. $C_{14}H_{16}N_6O_3$. requires: C 53.16, H 5.10, N 26.57]; ^{1}H NMR (250 MHz) δ: 1.92 (3H, s, CH_3), 1.98 (3H, s, CH_3), 6.2 (2H, s, $COCH_2$), 6.4 (2H, s, NH_2), 7.57 (2H, t, *J*=7.3 Hz, Ph), 7.67 (1H, t, *J*=7.3 Hz, Ph), 8.04 (2H, d, *J*=7.3 Hz, Ph), 10.89 (1H, s, NH).

3.2.2. 1-Amino-4-{[2-(1-methylethylidene)hydrazino]-carbonyl}-3-(4-methylphenacyl)-1*H*-1,2,3-triazol-3-ium-5-olate (8b). Yield 2.96 g (56%); mp 225–228 °C; MS, *m*/*z*: 330 (16%, M$^+$); ν (cm^{-1}): 3272, 3175 (NH), 3060, 3030, 2990, 2940 (CH), 1660, 1640 (CO), 1600, 1550. [Found: C 54.27, H 5.38, N 25.64. $C_{15}H_{18}N_6O_3$. requires: C 54.53, H 5.49, N 25.44]; ^{1}H NMR (250 MHz) δ: 1.90 (3H, s, CH_3), 1.95 (3H, s, CH_3), 2.43 (3H, s, CH_3Ar), 6.22 (2H, s, CH_2), 6.54 (2H, s, NH_2), 7.42 (2H, d, *J*=8.1 Hz, ArH), 7.94 (2H, d, *J*=8.1 Hz, ArH), 10.93 (1H, br. s., NH). ^{13}C NMR (100 MHz) δ: 16.5 (qq, CH_3, *J*=127 Hz), 21.2 (q, CH_3-*p*, *J*=131 Hz), 24.4 (qq, CH_3, *J*=127.5 Hz), 58.7 (t, CH_2, *J*=144.9 Hz), 110.1 (quint, C(4), *J*=1.7 Hz), 128.3 (dd, Ar, *J*=161.8 ,6.4 Hz), 129.4 (dm, Ar, *J*=161.4, 5.8 Hz), 131.5 (t, Ar, *J*=7.4 Hz), 144.9 (m, Ar), 153.6 (d, NCO, *J*=6.8 Hz), 154.2 (s, C(5)), 154.3 (m, C=N), 189.9 (d, CO, *J*=4.2 Hz).

3.2.3. 1-Amino-3-(4-chlorophenacyl)-4-{[2-(1-methylethylidene)hydrazino]-carbonyl}-1*H*-1,2,3-triazol-3-ium-5-olate (8c). Yield 4.32 g (77%); MS, *m*/*z*: 350 (36%, M$^+$). [Found: C 47.90, H 5.08, N 23.88. $C_{14}H_{15}ClN_6O_3$. requires: C 47.94, H 4.31, Cl 10.11, N 23.96]; ^{1}H NMR (250 MHz) δ: 1.91 (3H, s, CH_3), 1.97 (3H, s, CH_3), 6.19 (2H, s, CH_2), 6.46 (2H, s, NH_2), 7.63 (2H, d, *J*=8.5 Hz, ArH), 8.05 (2H, d, *J*=8.5 Hz, ArH), 10.88 (1H, br. s., NH). ^{13}C NMR (100 MHz) δ: 16.5 (q, CH_3, *J*=127.7, 3.1 Hz), 24.8 (q, CH_3, *J*=127.5, 2.9 Hz), 58.8 (t, CH_2, *J*=144.8 Hz), 109.9 (m, C(4), *J*=1.4 Hz), 129.1 (dd, Ph, *J*=169.1, 5.1 Hz), 130.1 (dd, Ph, *J*=164.5, 6.9 Hz), 132.8 (t, Ph, *J*=7.4 Hz), 139.2 (t, Ar, *J*=10.9, 3.03 Hz), 153.5 (d, NCO, *J*=7.1 Hz), 154.2 (s, C(5)), 154.3 (m, C=N, *J*=6.6, 3.7 Hz), 189.8 (t, CO, *J*=4.2 Hz).

3.2.4. 1-Amino-3-4-bromophenacyl)-4-{[2-(1-methylethylidene)hydrazino]-carbonyl}-1*H*-1,2,3-triazol-3-ium-5-olate (8d). Yield 4.43 g (79%); MS, *m*/*z*: (%, M$^+$). [Found: C, 42.58, H, 3.84, N, 21.22. $C_{14}H_{15}BrN_6O_3$. requires: C, 42.55, H, 3.83, N, 21.26]; ^{1}H NMR (250 MHz) δ: 1.92 (3H, s, CH_3), 1.97 (3H, s, CH_3), 6.17 (2H, s, CH_2), 6.45 (2H, s, NH_2), 7.66 (2H, d, *J*=8.3 Hz, ArH), 8.12 (2H, d, *J*=8.3 Hz, ArH), 10.87 (1H, br. s., NH). ^{13}C NMR (100 MHz) δ: 16.5 (q, CH_3, *J*=127.7, 3.1 Hz), 24.8 (q, CH_3, *J*=127.5, 2.9 Hz), 58.8 (t, CH_2, *J*=144.8 Hz), 109.9 (m, C(4), *J*=1.4 Hz), 129.1 (dd, Ph, *J*=169.1, 5.1 Hz), 130.1 (dd, Ph, *J*=164.5, 6.9 Hz), 132.8 (t, Ph, *J*=7.4 Hz), 139.2 (t, Ar, *J*=10.9, 3.03 Hz), 153.5 (d, NCO, *J*=7.1 Hz), 154.2 (s, C(5)), 154.3 (m, C=N, *J*=6.6, 3.7 Hz), 189.8 (t, CO, *J*=4.2 Hz).

3.3. Synthesis of 7e, 8e

A solution of sodium salt **6** (9.03 g, 35 mmol) and *p*-methoxyphenacyl bromide (8.15 g, 35 mmol) in DMF (5 ml) was heated at 70° for 3 h, cooled to room temperature and **7e** was filtered off from the reaction mixture, washed with DMF, dried and crystallized from ethanol. The filtrate was mixed with of water (20 ml). After 1 h, the solid **8e** was filtered off, washed with water, dried and crystallized from chloroform (Method A). Alternatively, a suspension of **7e** (6.02 g) in 50 ml water was heated at reflux for 0.5 h and evaporated under reduced pressure (Method B). The crude **8e** was purified as for method A.

3.3.1. 3-[(3-Methoxyphenacyl)-1-[(1-methylethylidene) amino]-4-{[2-(1-methylethylidene)hydrazino]carbonyl}-1*H*-1,2,3-triazol-3-ium-5-olate (7e). Yield 6.62 g (49%); mp 165–168 °C; MS, *m*/*z*: 386 (34%, $M^{+\cdot}$). [Found: C, 56.02, H, 5.56, N, 21.59. $C_{18}H_{22}N_6O_4$ requires: C, 55.96, H, 5.70, N, 21.76]; ^{1}H NMR (250 MHz) δ: 1.91 (3H, s, CH_3), 1.98 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 6.20 (2H, s, CH_2), 7.06 (2H, d, ArH, *J*=8.8 Hz), 8.1 (2H, d, ArH, *J*=8.8 Hz), 10.83 (1H, s, NH).

3.3.2. 1-Amino-3-(4-methoxyphenacyl)-4-{[2-(1-methylidene)hydrazino]-carbonyl}-1*H*-1,2,3-triazol-3-ium-5-olate (8e). Yield 4.34 g (36%); mp 200–205 °C (subl.); MS, *m*/*z*: 346 (32%, M^+). [Found: C, 52.16, H, 5.06, N, 24.20. $C_{15}H_{18}N_6O_4$ requires: C, 52.02, H, 5.20, N, 24.28]; ^{1}H NMR (250 MHz) δ: 1.91 (3H, s, CH_3), 1.97 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 6.14 (2H, s, CH_2), 6.40 (2H, s, NH), 7.04 (2H, d, ArH, *J*=8.9 Hz), 7.95 (2H, d, ArH, *J*=8.9 Hz), 10.90 (1H, s, NH). ^{13}C NMR (100 MHz) δ: 16.5 (q, CH_3, *J*=127.5 Hz), 24.8 (q, CH_3, *J*=127.3 Hz), 55.7 (q, OCH_3, *J*=145.6 Hz), 58.5 (t, CH_2, *J*=144.8 Hz), 110.2 (s, C(4)), 114.2 (dd, C(m), *J*=162.8, 4.6 Hz), 126.8 (t, C(i), *J*=7.3 Hz), 130.6 (dd, C(o), *J*=161.6, 7.1 Hz), 153.5 (d, NCO, *J*=6.9 Hz), 154.3 (m, C=N), 154.8 (s, C(5)), 188.7 (q, CO).

3.4. Synthesis of triazolotriazepines 4a-e

General procedure. A suspension of hydrazone **8** (1.0 mmol) in diluted HCl (100 ml, 0.1 N) was heated at reflux for 15 h, and then the reaction mixture was concentrated at reduced pressure to 5 ml. After cooling, product **4** was filtered off and washed with water up to neutral pH.

3.4.1. 2-Amino-4-oxo-7-phenyl-2,4,5,8-tetrahydro[1,2,3]-triazolo[5,1-*d*][1,2,5]triazepin-9-ium-3-olate (4a). Yield 0.24 g (93%); mp 273–276 °C (decomp.); MS, *m*/*z*: 258 (57%, M^+). [Found: C, 51.13, H, 3.88, N, 32.52. $C_{11}H_{10}N_6O_2$ requires: C, 51.16, H, 3.90, N, 32.54]; ^{1}H NMR (250 MHz) δ: 5.57 (2H, s, CH_2), 6.06 (2H, br. s, NH_2), 7.45 (3H, m, Ph), 7.86 (2H, m, Ph), 11.01 (1H, s, NH).

3.4.2. 2-Amino-7-(4-methylphenyl)-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo[5,1-*d*][1,2,5]-triazepin-9-ium-3-olate (4b). Yield 0.30 g (88%); mp 294–296 °C; MS, *m*/*z*: 272 (49%, M^+); ν (cm^{-1}): 3440, 3330, 3225, 3122 (NH), 3070, 3047, 3010, 2917 (CH), 1690, 1641 (CO), 1600. [Found: C, 52.72, H, 4.53, N, 30.78. $C_{15}H_{18}N_6O_4$ requires: C, 52.94, H, 4.44, N, 30.87]; ^{1}H NMR (250 MHz) δ: 2.35 (3H, s, CH_3), 5.59 (2H, s, CH_2), 6.16 (2H, s, NH_2), 7.30 (2H, d, *J*=8.2 Hz, ArH), 7.77 (2H, d, *J*=8.2 Hz, ArH), 11.04 (1H, s, NH).

3.4.3. 2-Amino-7-(4-chlorophenyl)-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo[5,1-*d*][1,2,5]-triazepin-9-ium-3-olate (4c). Yield 0.26 g (90%); mp 268–271 °C (decomp.); MS, *m*/*z*: 292 (54%, M^+). [Found: C, 45.08, H, 3.08, N, 28.68. $C_{11}H_9ClN_6O_2$ requires: C, 45.14, H, 3.10, N, 28.71]; ^{1}H NMR (250 MHz) δ: 5.58 (2H, s, CH_2), 6.09 (2H, s, NH_2), 7.47 (2H, d, *J*=8.5 Hz, ArH), 7.88 (2H, d, *J*=8.5 Hz, ArH), 11.07 (1H, s, NH).

3.4.4. 2-Amino-7-(4-bromophenyl)-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo[5,1-*d*][1,2,5]-triazepin-9-ium-3-olate (4d). Yield 0.27 g (93%); mp 272–274 °C (decomp.); MS, *m*/*z*: 336 (59%, M^{-1}), 338 (58%, M^{+1}). [Found: C, 39.15, H, 2.66, N, 24.90. $C_{11}H_9BrN_6O_2$ requires: C, 39.19, H, 2.69, N, 24.93]; ^{1}H NMR (250 MHz) δ: 5.57 (2H, s, CH_2), 6.07 (2H, br. s, NH_2), 7.61 (2H, d, *J*=8.8 Hz, ArH), 7.81 (2H, d, *J*=8.8 Hz, ArH), 11.07 (1H, s, NH).

3.4.5. 2-Amino-7-(4-methoxyphenyl)-4-oxo-2,4,5,8-tetrahydro[1,2,3]triazolo[5,1-*d*][1,2,5]-triazepin-9-ium-3-olate (4e). Yield 0.25 g (87%); mp 283–286 °C (decomp.); MS, *m*/*z*: 288 (89%, M^+). [Found: C, 49.98, H, 4.12, N, 29.13. $C_{12}H_{12}N_6O_3$ requires: C, 50.00, H, 4.20, N, 29.15]; ^{1}H NMR (250 MHz) δ: 3.82 (3H, s, OCH_3), 5.50 (2H, s, CH_2), 5.98 (2H, br. s, NH_2), 6.97 (2H, d, *J*=9.0 Hz, ArH), 7.80 (2H, d, *J*=9.0 Hz, ArH), 10.71 (1H, s, NH).

3.5. Isolation of triazolopyrazines 10c,e

The water filtrate from **4c**,**e** was concentrated under reduced pressure to yield crude **10c**,**e**, which was than purified by crystallization from ethanol.

3.5.1. 2,5-Diamino-6-(4-chlorophenyl)-4-oxo-4,5-dihydro-2*H*-[1,2,3]triazolo[1,5-*a*]pyrazin-8-ium-3-olate (10c). Yield 0.022 g (7%); mp >250 °C (decomp.); MS, *m*/*z*: 292 (27%, M^+). [Found: C, 45.17, H, 3.14, N, 28.64. $C_{11}H_9ClN_6O_2$ requires: C, 45.14, H, 3.10, N, 28.71].

3.5.2. 2,5-Diamino-6-(4-methoxyphenyl)-4-oxo-4,5-dihydro-2*H*-[1,2,3]triazolo[1,5-*a*]pyrazin-8-ium-3-olate (10e). Yield 0.015 g (5%); mp >250 °C (decomp.); MS, *m*/*z*: 288 (30%, M^+). [Found: C, 50.11, H, 4.29, N, 29.13. $C_{12}H_{12}N_6O_3$ requires: C, 50.00, H, 4.20, N, 29.15].

Acknowledgements

We thank the Russian Foundation for Basic Research (Grant 040332926), CRDF (Award No. RC1-2393-EK-02) the K. U. Leuven, the Ministerie voor Wetenschapsbeleid and INTAS for financial support of this work.

References and notes

1. (a) Groszkowski, S.; Wrona, J. *Pol. J. Pharmacol. Pharm.* **1978**, *5*, 713–715. (b) Szadowska, A.; Mazur, M.; Kamińska, A.;

Kusowska, J.; Winer, A. *Acta Pol. Pharm.* **1982**, *39*, 463–467. (c) Lenman, M.; Ingham, S.; Gani, D. *J. Chem. Soc., Chem. Commun.* **1996**, *1*, 85–88. (d) Lenman, M.; Lewis, A.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2297–2312.

2. (a) Rossi, S.; Pirola, O.; Selva, F. *Tetrahedron* **1968**, *21*, 6395–6409. (b) Stefancich, G.; Artico, M.; Corelli, F.; Massa, S. *Synthesis* **1983**, *9*, 757–759. (c) Peet, N. P.; Sunder, S. *Heterocycles* **1986**, *24*, 3213–3221. (d) Hamer, R.; Effland, R.; Klein, J.; Huger, F.; Wilker, J. *J. Heterocycl. Chem.* **1988**, *25*, 517–521. (e) Lancelot, J.-Ch.; Robba, M. *Chem. Pharm. Bull.* **1988**, *7*, 2381–2385. (f) Stefancich, G.; Silvestri, R. *J. Heterocycl. Chem.* **1989**, *26*, 745–746. (g) Effland, R.; Davis, L.; Kapples, K.; Olsen, G. *J. Heterocycl. Chem.* **1990**, *27*, 1015–1019. (h) Katritzky, A. R.; Fan, W.-Q.; Greenhill, J. V. *J. Org. Chem.* **1991**, *3*, 1299–1301. (i) Bouteau, B.; Imbs, J.-L.; Lancelot, J.-Ch.; Barthelmebs, M.; Robba, M. *Chem. Pharm. Bull.* **1991**, *39*, 81–85. (j) Artico, M.; Massa, S.; Mai, A.; Silvestri, R.; Stefancich, G. *J. Heterocycl. Chem.* **1992**, *29*, 241–245. (k) Kibal'nyi, A. V.; Nikolyukin, Yu. A.; Dulenko, V. I. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1994**, *8*, 895–900. (l) Marchalin, S.; Decroix, B. *Heterocycles* **1995**, *41*, 689–696. (m) El-Saghier, A. M. M.; Maihub, A. A.; Al-Shirayda, H. *Synth. Commun.* **1997**, *27*, 142433–142444.

3. (a) Abu-El-Haj, M. J.; McFarland, J. W. 7 pp. US Patent 3933843, 1976. (b) Abu-El-Haj, M. J.; McFarland, J. W. 6 pp. US Patent 4002636, 1977. (c) Nagano, E.; Yoshida, R. 17 pp. EP 0116928, 1984.

4. (a) Cooke, A.; Bonnert, R.; Cage, P.; Donald, D.; Furber, M.; Withnall. J. PCT Int. Appl., 169 pp. WO 9902528, 1999. (b) Abbott, P. A.; Bonnert, R. V.; Caffrey, M. V.; Cage, P. A.; Cooke, A. J.; Donald, D. K.; Furber, M.; Hill, S.; Withnall, J. *Tetrahedron* **2002**, *58*, 3185.

5. Rozin, Yu. A.; Savel'eva, E. A.; Morzherin, Yu. Yu.; Dehaen, W.; Toppet, S.; Van Meervelt, L.; Bakulev, V. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *2*, 211.

6. (a) Begtrup, M. *Acta Chem. Scand.* **1974**, *28*, 61. (b) Bocian, W.; et al. *Magn. Reson. Chem.* **1996**, *34*, 453.

7. Crystal structure determination of triazolotriazepine **4d**. The compound $C_{11}H_9BrN_6O_2$ was recrystallized from DMF. Crystal data: crystal dimensions 0.30×0.20×0.10 mm, triclinic, *P*-1, a=6.6964(5), b=9.0098(6), c=15.6736(9) Å, α=78.936(4), β=79.551(6), γ=76.967(6)°, V=894.68(11) Å^3, Z=2, ρ_{calcd}=1.590 g cm^{-3}, $2\theta_{max}$=142.2°, μ(Cu $_{K\alpha}$)=3.464 cm^{-1}, Bruker SMART 6000 detector, $Cu_{K\alpha}$ (λ=1.54178 Å), crossed Göbel mirrors, T=100 K, 7789 measured reflections, 3242 independent reflections. The data were corrected for Lorentz and polarization effects. Structure solved by direct methods, asymmetric unit contains also one DMF and one water molecule. Full-matrix least-squares refinement based on $|F^2|$, 252 parameters, OH and NH hydrogen atoms located from difference density map, other hydrogen atoms placed at calculated positions and refined in riding mode with temperature factors 20% higher than parent atom, $R1$=0.0467 (for 2901 data with $I>2\sigma(I)$), $wR2$=0.1264, max./min. residual electron density 0.61/−0.84 e$^-$ Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-227138. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

8. Molina, P.; Tàrraga, A.; Serrano, C. *Tetrahedron* **1984**, *40*, 4901.

9. (a) Scheiner, P.; Frank, L.; Giusti, I.; Arwin, S.; Pearson, Sh. A.; Excellent, F.; Harper, A. P. *J. Heterocycl. Chem.* **1984**, *21*, 1817. (b) Scheiner, P.; Arwin, S.; Eliacin, M.; Tu, J. *J. Heterocycl. Chem.* **1985**, *22*, 1435. (c) Raboisson, P.; Norberg, B.; Casimir, J. R.; Bourguignon, J.-J. *Synlett* **2002**, *3*, 519.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5373–5382
Tetrahedron

Synthesis of 4,5-diarylquinazolines: a system with cofacial aromatic rings. Diazines. Part 39

Alexandrine Busch, Valérie Gautheron Chapoulaud, Jérôme Audoux, Nelly Plé* and Alain Turck

Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF-INSA, B.P. 08, 76131 Mont Saint Aignan Cedex, France

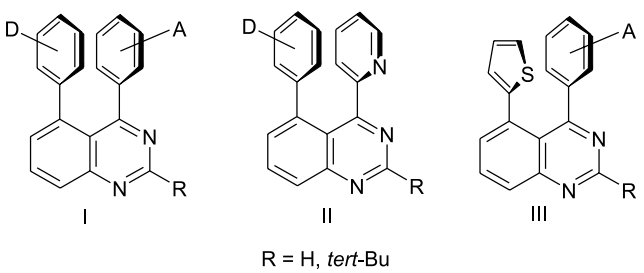
Received 24 February 2004; revised 21 April 2004; accepted 22 April 2004

Abstract—Using metallation reactions and Pd-catalyzed coupling, we report here two synthetic routes leading to eight new 4,5-di(hetero)-arylquinazolines. Non-linear activity has been highlighted for some of these compounds with stacked aromatic rings.

Stacked or cofacial aromatic or heteroaromatic rings appear in a number of natural products, the most important being nucleic acids where the rings are offset to each other.[1] Furthermore, several studies dealing with 1,8-diaryl[2–10] and 1,8-dihetarylnaphthalenes,[11–13] where the aromatic rings are π-stacked, have been developed. In such naphthalenes, the two aromatic rings are held cofacial but are splayed out from each other and are able to rotate about the bonds attaching them to the rigid naphthalene frame. Crystal structures show that the aryl rings in such naphthalenes are not parallel to each other but are tilted away in order to increase separation and thereby minimize electrostatic repulsion.

Among the 1,8-di(hetero)arylnaphthalenes previously described in the literature, some of them have highlighted interesting non-linear optic (NLO) activities.[14] These results urged us to synthesize aza-analogues of such structures which could present potential applications in NLOs.

In the context of our studies on the synthesis of benzodiazines using metallation and cross-coupling reactions, we report here the synthesis of various di(hetero)aryl-quinazolines I–III (Scheme 1).



Scheme 1.

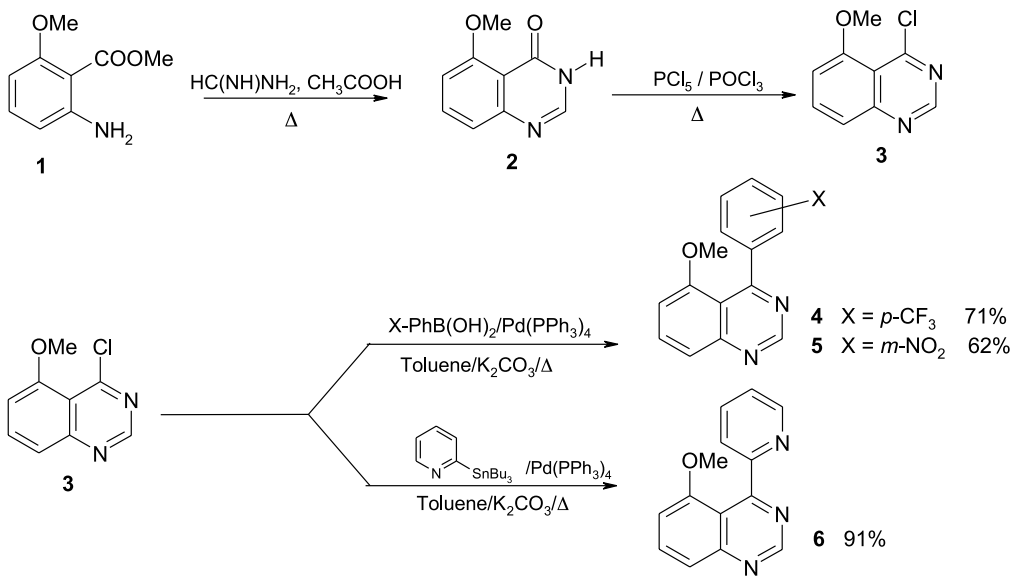
In these structures, one aryl substituent is rendered electron-rich by an electron-donor (D) or an heteroarene while the other has reduced density as a result of an electron-withdrawing group (A) or heteroarene, it could also be noticed that position of aryl or hereroarene at the C_4 and C_5 positions avoid a direct conjugation between the donor (D) and acceptor (A). So compounds of this type offer potential non-covalent interactions between the opposite faces of the D/A π-electron systems.[15] To improve this through-space effect which is defined as Coulombic (electrostatic) interactions, we have synthesized compounds with The (A) π-electron system on the pyrimidine moiety which is a π-deficient ring and the (D) π-electron system on the benzene ring.

Using cross-coupling reactions and metallations, we report here two synthetic routes for compounds of type I–III (Scheme 1), the first one involves cyclization of substituted benzene derivatives to obtain 4(3*H*)-quinazolinone derivatives, whereas the second one uses in a first step metallation reaction of 4(3*H*)-quinazolinone to functionalize the benzene moiety.

In the first synthetic route, the starting material was the methyl 2-amino-6-methoxybenzoate **1** prepared according to the procedure previously described in the literature.[16] Reaction of **1** with formamidine acetate at 180 °C led to 5-methoxy-4-(3*H*)-quinazolinone **2** which has been converted with a mixture of phosphorus pentachloride and phosphorus oxychloride to 4-chloro-5-methoxy-4-(3*H*)-quinazolinone **3**. This last compound underwent cross-coupling reactions under Suzuki or Stille conditions allowing formation of the first aryl–aryl bond at the C_4 position (Scheme 2).

Keywords: Metallation; Cross-coupling reactions; 4,5-Di(hetero)-arylquinazolines; Non-linear optics.
* Corresponding author. Tel.: +33-2-35-52-29-02; fax: +33-2-35-52-29-62; e-mail address: nelly.ple@insa-rouen.fr

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.04.065



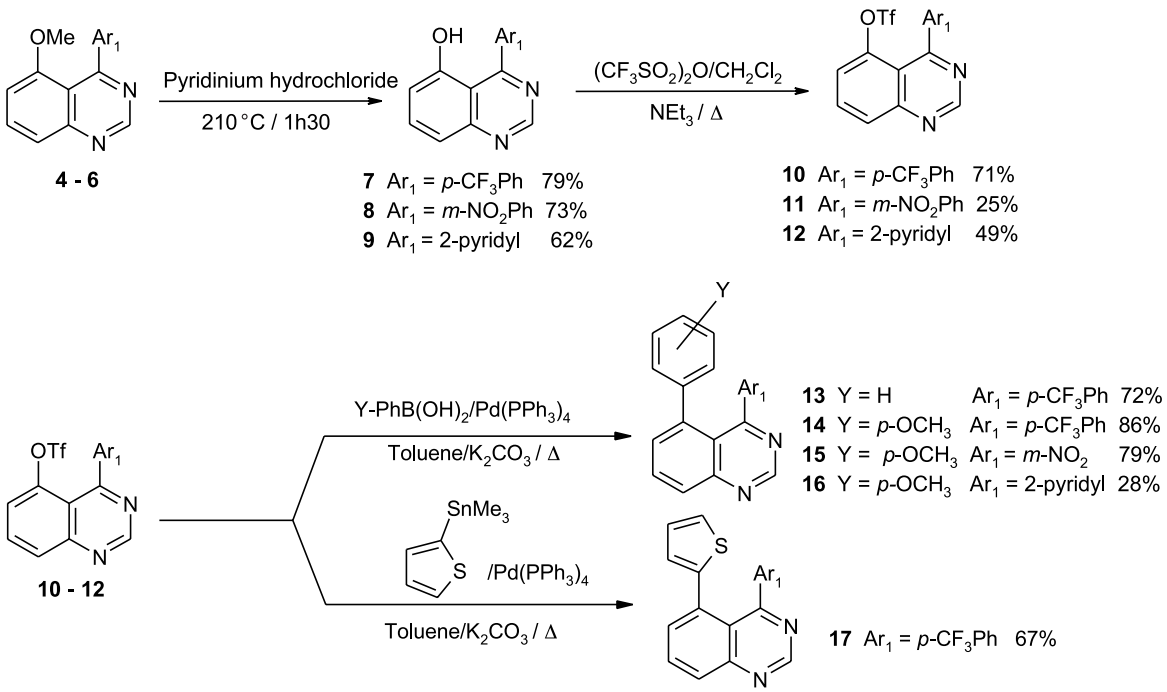
Scheme 2.

In a second time, cleavage of the methoxy group has been achieved with pyridinium hydrochloride under reflux leading to corresponding hydroxy compounds **7**–**9** which were reacted with trifluoromethanesulfonic anhydride to obtain triflate derivatives **10**–**12**. A subsequent cross-coupling reaction with various arylboronic acids was used to obtain the unsymmetrical diarylquinazolines **13**–**17** (Scheme 3).

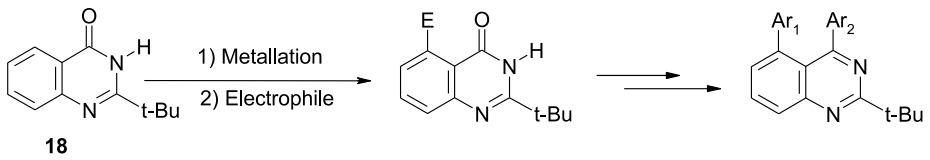
In the second synthetic route, the starting material was 2-*tert*-butyl-4(3*H*)-quinazolinone **18**. In a first step, lithiation and functionalization of the benzene moiety of **18** have been performed regioselectively at the C_5 position, then further cross-coupling reactions allowed us to access to new 4,5-di(hetero)arylquinazolines (Scheme 4).

In a previous paper,[18] we have mentioned the metallation of substituted 4-(3*H*)-quinazolones with 1 equiv. of *n*-BuLi at −78 °C, followed by reaction of LTMP in excess (4 equiv.). Under these conditions, lithiation was observed at the C_8 position, *péri* to the ring nitrogen atom N_1. We have reinvestigated the conditions of metallation with compound **18**,[21] which presents a *tert*-butyl group on the C_2 position. This group avoids a nucleophilic attack of the metallating agent at this position[19–20] and prevents deprotonation on the carbon C_α of the lateral chain.[22–24] It could be noticed that with such a product, alkyllithiums could be used as metallating agent.

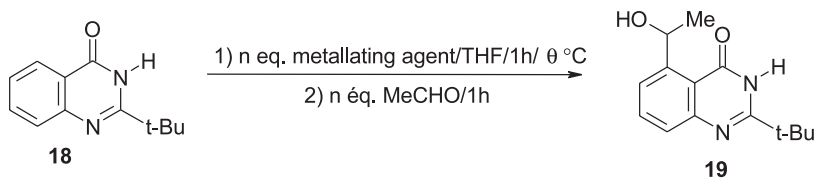
Treatment of **18** with n equivalents of LTMP (*n*=4 to 8) at 0 °C for 1 h and acetaldehyde as electrophile did not allow



Scheme 3.



Scheme 4.



Scheme 5.

Table 1. Metallation of compound **18**

Entry	Metallating agent	nequiv.	Temperature (°C)	Time, *t* (h)	Starting material (%)	
					18	**19**
1	*n*-BuLi	3	−78	1	64	36
2	*n*-BuLi	3	0	1	60	40
3	*n*-BuLi	4	0	1	28	72
4	(*n*-BuLi/TMEDA)	4	−20	2	22	78
5	(*s*-BuLi/TMEDA)	4	−78	1	62	38
6	(*s*-BuLi/TMEDA)	4	−20	1	6	94

any reaction and starting material has been recovered. So, use of alkyllithiums was performed under various conditions with acetaldehyde as electrophile, leading to compound **19** (Scheme 5, Table 1).

The results given in Table 1 revealed that the best results were obtained with 4 equiv. of *s*-BuLi and TMEDA at −20 °C for 1 h (entry 6), under these conditions, **19** was obtained in good yield (94%) beside small amounts of starting material.

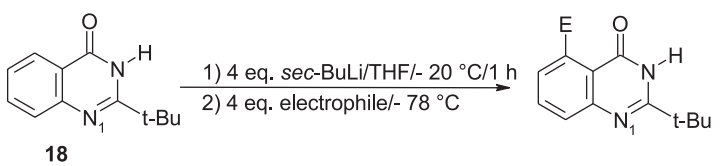
Structure of compound **19** was established unambigously by NMR experiments highlighting a regioselective metallation at the C_5 position. These conditions were used with other electrophiles (Scheme 6).

Starting from compound **24**, cross-coupling reactions were performed under Suzuki conditions leading to 2-*tert*-butyl-5-aryl-4-(3*H*)-quinazolones **25**–**27**. These 4-oxo derivatives were converted with phosphorus oxychloride to their 4-chloro derivatives **28**–**29**. In a last step compounds **28** and **29** reacted with arylboronic acids to give the expected compounds **30**–**31**. Compound **28** was also reacted with 2-tributylstannylpyridine following Stille cross-coupling conditions and afforded **32** (Scheme 7).

The X-ray structure analysis of **14** (Fig. 1) shows that both phenyl rings subtend angles of 62 and 68° with the plane of quinazoline. Similarly high torsion angles are observed in other diarylnaphthalenes[14,17] and lead to face–face arrangement of such π-electron systems. The very close approach of the two phenyl rings is noteworthy: the value of 297.1 pm observed for C_9–C_{15} is slightly smaller than in the other 1,8-diphenylnaphthalenes and markedly smaller than the van der Waals distance for parallel aromatic systems (about 345 pm).[17b]

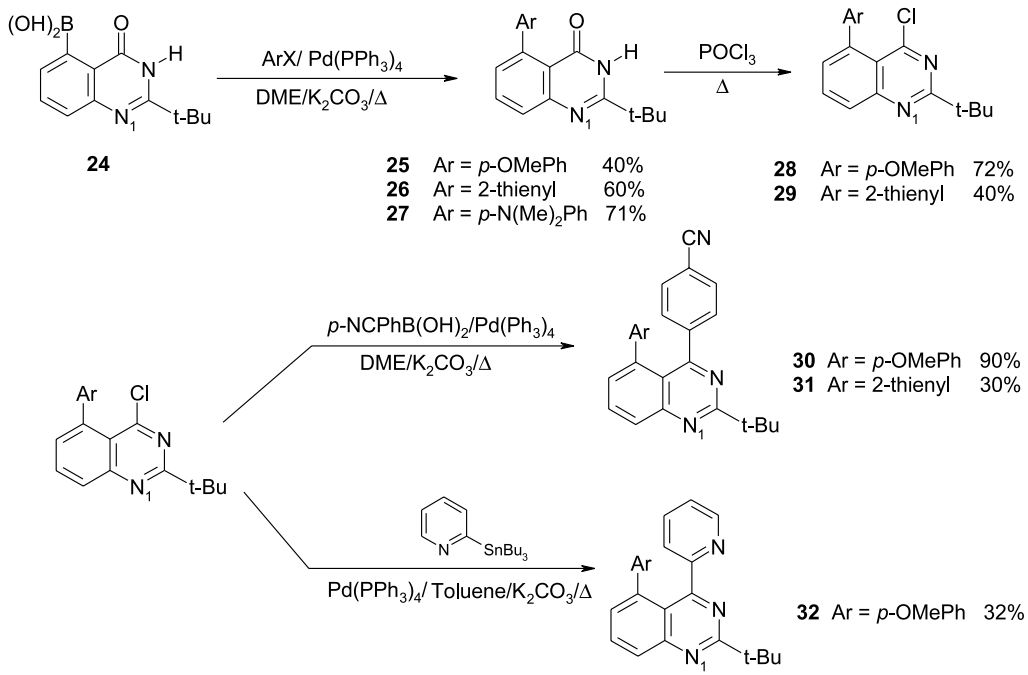
As it has been previously mentioned in the literature,[14] through-space interaction and lack of D/A conjugation with possible D–A/D–A stacking, tend to favor the formation of acentric structures. Thus **14** crystallizes in the non-centrosymmetric space group $P2_1$, which renders such a structure candidate to non-linear activity for a frequency-doubling function.

The NLO measurements of the $\mu\beta$ values of compounds **15**



19 E = MeCH(OH) 94% **22** E = Bu_3Sn 50%
20 E = PhCH(OH) 92% **23** E = I 37%
21 E = PhS 17% **24** E = $B(OH)_2$ 68%

Scheme 6.



Scheme 7.

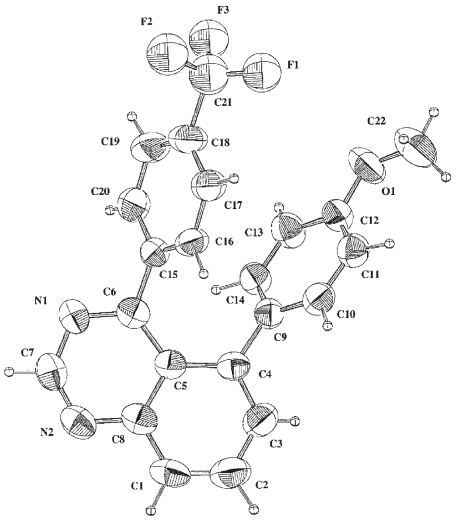


Figure 1. Crystal structure of **14**. Selected distances (ppm): C4–C6 256.5; C9–C15 297.1; N2–C1 241.9; C18–C12 435.6. Planar angles (°): C4–C5–C6: 126.4. Interplanar angles (°) C5–C6/C15–C20: 61.7; C4–C5/C9–C14: 68.0.

and **17** have been performed by means of the EFISH method (Table 2). The values μ_{calc} are the computed ground-state dipole moments calculated by AM1.

The high β values of these compounds **15**, **17**, compared to paranitroanilin (PNA) (17×10^{-30} esu)[14a] indicate that 4,5-diarylquinazolines may have appreciable non-linear optical properties. Further and complete measurements will be performed with the other compounds.

Table 2. μ_{calcd} (D): computed ground state dipole moments, experimental $\mu\beta$ values determined by EFISH measurements and evaluated first-order hyperpolarizability β of compounds **15**, **17**

Compound	μ_{calcd} (D)	$\mu\beta\times10^{-48}$ esu	$\beta\times10^{-30}$ esu
15	6.62	22.4	547
17	3.42	11.6	169

1. Conclusion

We have synthesized eight new 4,5-di(hetero)aryl quinazolines using cross-coupling reactions. The regioselective functionalization of the C_5 position of the 2-*tert*-butyl-4(*3H*)-quinazolinone **18** allowed us to develop a second synthetic route to access to compounds **29**–**31**. The non-linear optical properties of two compounds of these series have been measured and interesting and promising results have been observed. Synthesis of other new 4,5-di(hetero)-aryl quinazolines and measurement of their first-order hyperpolarizability β are in progress.

2. Experimental

Melting points were determined on a Kofler hot-stage. The ^{1}H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC 300 (300 MHz ^{1}H, 75 MHz ^{13}C, 282 MHz ^{19}F) instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin–Elmer Paragon 500 spectrophotometer.

All reagents were of commercial quality and were purchased from Acros, Aldrich Chemical Co. or Avocado. The Pd(0)-catalyst $Pd(PPh_3)_4$ was prepared according to the literature.[25] 4-Trifluoromethyl-, 4-methoxyphenyl-, 4-*N*,*N*-dimethylaminophenyl- and 4-cyanophenylboronic acids were synthesized by halogen–metal exchange followed by reaction with trimethylborate or triisopropylborate from the commercially available 1-bromo-4-trifluoromethylbenzene,

4-bromoanisole, 4-bromo-*N*,*N*-dimethylaniline or 4-bromobenzonitrile.

2.1. Procedure A for direct lithiation by lithium alkylamide (LTMP)

A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−50 °C), stirred and anhydrous tetrahydrofuran (15 mL) under an atmosphere of dry nitrogen. Then 2,2,6,6-tetramethylpiperidine (TMPH) was added. The mixture was warmed to 0 °C. After 20 min, the temperature was lowered to −78 °C and the substrate dissolved in 5 mL of THF was added. After a time t_1 at temperature T_1, iodine was introduced and stirring was continued for a time t_2 at T_2. Hydrolysis was then carried out using a mixture of ethanol and water (5/5). At room temperature, the solution was decolorized with sodium thiosulphate. After concentration, the residue was extracted with dichloromethane or ethyl acetate (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.2. Procedure B for direct lithiation by *sec*-butyllithium/tetramethylethylenediamine (*sec*-butyllithium/TMEDA

A solution of *sec*-butyllithium (1.3 M in hexane) was added to cold stirred and anhydrous tetrahydrofuran (20 mL) under an atmosphere of dry nitrogen. Then tetramethylethylenediamine (TMEDA) was added. The mixture was cooled to −78 °C and added to a solution of 2-*tert*-butylquinazolin-4(*3H*)-one **18** in THF. After a time t_1 at temperature T_1, the electrophile was introduced and the mixture was keeped at T_2 for a time t_2. Hydrolysis was then carried out using a solution of ethanol and water (5/5) at −78 °C. At room temperature, water (10 mL) was added to the mixture and THF was removed under reduced pressure. The aqueous layer was extracted with dichloromethane or ethyl acetate (3×20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.3. Procedure C for cross-coupling of arylboronic acids with heteroaryl halide under Suzuki conditions

A mixture of the heteroaryl halide (2 mmol), the arylboronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aqueous 2 M potassium carbonate (2 equiv.) and DME (12 mL) and H_2O (3 mL) or ethanol (1 mL) in degassed toluene (15 mL) was heated under reflux and under nitrogen for 15–48 h. The reaction mixture was cooled, diluted with 15 mL of water and dichloromethane (1/1) and the organic layers separated. The aqueous layer was extracted with dichloromethane (3×15 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2.4. Procedure D for cross-coupling of heteroaryl halides with tributylstannylheteroarene under Stille conditions

A solution of tributylstannylheteroarene, arylhalide (0.8 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in degassed toluene (15 mL) was heated under reflux under nitrogen atmosphere for a time *t*. After cooling, a mixture of water (10 mL) and dichloromethane (10 mL) was added. The organic phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel.

2.4.1. 4-Chloro-5-methoxyquinazoline (3). Reaction of **2** (1.5 g, 8.5 mmol) with phosphorus pentachloride (1.5 equiv.) in $POCl_3$ (30 mL) under reflux for 15 h, followed by removal of excess of $POCl_3$ under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), then poured on ice and neutralized by an aqueous Na_2CO_3 solution. The aqueous phase was extracted with dichloromethane (3×20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2/8) gave after purification 1.1 g (66%) of **3** as a white solid, mp 113–114 °C; ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H, H_2); 7.73 (dd, J=8.3, 7.9 Hz, 1H, H_7); 7.52 (d, J=8.3 Hz, 1H, H_{Ph}); 7.08 (d, J=7.9 Hz, 1H, H_{Ph}); 3.94 (s, 3H, OCH_3). Anal. calcd for $C_9H_7ClN_2O$ (194.62): C, 55.54; N, 14.39; H, 3.63. Found: C, 55.53; N, 14.40; H, 3.89.

2.4.2. 5-Methoxy-4-(4′-trifluoromethylphenyl)quinazoline (4). Cross-coupling reaction of 4-trifluoromethylphenylboronic acid (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure C (t=40 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 445 mg (71%) of **4** as a pale yellow solid, mp 94–95 °C; ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, H_2); 7.88–7.61 (m, 5H, $5H_{ar}$); 6.95 (d, J=7.7 Hz, 2H, $2H_{PhCF3}$); 3.64 (s, 3H, OCH_3); ^{19}F NMR ($CDCl_3$): −62.8; IR: ν 1614, 1573, 1331, 1122, 1067, 831 cm^{-1}. Anal. calcd for $C_{16}H_{11}F_3N_2O$ (304.27): C, 63.16; N, 9.21; H, 3.63. Found: C, 62.81; N, 9.52; H, 3.99.

2.4.3. 5-Methoxy-4-(3′-nitrophenyl)quinazoline (5). Cross-coupling reaction of 3-nitrophenylboronic acid (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure C (t=62 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 348 mg (62%) of **5** as a white solid, mp 172–173 °C; ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, H_2); 8.40 (s, 1H, H_{PhNO2}); 8.34 (d, J=8.2 Hz, 1H, H_{Ph}); 7.89 (m, 2H, $2H_{Ph}$); 7.77–7.64 (m, 2H, $2H_{Ph}$); 6.97 (d, J=7.7 Hz, 1H, H_{ar}); 3.65 (s, 3H, OCH_3); IR: ν 1571, 1525, 1350, 691 cm^{-1}. Anal. calcd for $C_{15}H_{11}N_3O_3$ (281.27): C, 64.05; N, 14.94; H, 3.94. Found: C, 63.74; N, 14.86; H, 4.32.

2.4.4. 5-Methoxy-4-(2′-pyridyl)quinazoline (6). Cross-coupling reaction of (2-pyridyl)-tributylstannane (1.3 equiv.) with **3** (390 mg, 2 mmol) according to the general procedure D (t=50 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 2/1) 431 mg (91%) of **6** as a pale yellow solid, mp 115–116 °C; ^{1}H NMR ($CDCl_3$): δ 9.24 (s, 1H, H_2); 8.61 (dd, J=4.9, 0.75 Hz, 1H, $H_{6'}$); 7.75 (m, 2H, $H_{7/4'}$); 7.62 (d, J=8.3 Hz, 1H, H_8); 7.45 (m, 1H, $H_{3'}$); 7.29 (m, 1H, $H_{5'}$); 6.82 (d, J=7.9 Hz, 1H, H_6); 3.49 (s, 3H, OCH_3)); ^{13}C NMR ($CDCl_3$): δ 165.5, 159.4, 156.2, 154.4 (C_2), 152.7, 148.6

(CH), 136.0 (CH), 134.8 (CH), 123.1 (CH), 122.8 (CH), 120.9 (CH), 115.6, 107.3 (CH), 55.9 (OCH_3). Anal. calcd for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; N, 17.71; H, 4.67. Found: C, 71.32; N, 18.12; H, 4.56.

2.4.5. 5-Hydroxy-4-(4′-trifluoromethylphenyl)quinazoline (7). A mixture of **4** (625 mg, 2.1 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (5×20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was washed with dichloromethane and **7** (488 mg, 79%) was obtained as a brown solid, mp 230–231 °C; ^{1}H NMR (d_6-DMSO): δ 10.83 (1H, OH); 9.22 (s, 1H, H_2); 7.75 (m, 5H, $4H_{PhCF3}$ and H_7); 7.52 (d, J=8.3 Hz, 1H, H_{ar}); 7.03 (d, J=7.7 Hz, 1H, H_{ar}); IR: ν 3052, 1572, 1498, 1329, 1169, 1068, 850, 828 cm^{-1}. Anal. calcd for $C_{15}H_9F_3N_2O$ (290.24): C, 62.07; N, 9.65; H, 3.13. Found: C, 62.10; N, 9.84; H, 3.44.

2.4.6. 5-Hydroxy-4-(3′-nitrophenyl)quinazoline (8). A mixture of **5** (400 mg, 1.4 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (3×20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was washed with dichloromethane and **8** (277 mg, 73%) was obtained as a brown solid, mp >260 °C; ^{1}H NMR (d_6-DMSO): δ 9.23 (s, 1H, H_2); 8.34 (m, 2H, $2H_{PhNO2}$); 8.02 (m, 1H, H_{PhNO2}); 7.85 (dd, J=8.4, 8 Hz, 1H, $1H_{PhNO2}$); 7.74 (dd, J=8, 7.6 Hz, 1H, H_7); 7.54 (d, J=8 Hz, 1H, H_{ar}); 7.02 (d, J=7.6 Hz, 1H, H_{ar}); IR: ν 3070, 1526, 1502, 1347, 830, 692 cm^{-1}. Anal. calcd for $C_{14}H_9N_3O_3$ (267.24): C, 62.92; N, 15.72; H, 3.39. Found: C, 63.16; N, 15.77; H, 3.65.

2.4.7. 5-Hydroxy-4-(2′-pyridyl)quinazoline (9). A mixture of **6** (200 mg, 0.84 mmol) and pyridinium chloride (5 g) was heated to 210 °C for 1 h 30 min. After cooling, the mixture was poured onto with ice and neutralized with a 10% ammoniac solution. The aqueous layer was extracted with ethyl acetate (3×50 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (neutral alumina, eluent: petroleum ether/ethyl acetate (5/5)) afforded 116 mg (62%) of **77** as an orange solid, mp 120–121 °C; ^{1}H NMR ($CDCl_3$): δ 15.57 (1H, OH); 9.20 (s, 1H, H_2); 8.83 (dd, J=8.3, 0.75 Hz, 1H, $H_{3'}$); 8.61 (dd, J=4.9, 0.75 Hz, 1H, $H_{6'}$); 8.03 (m, 1H, $H_{4'}$); 7.76 (dd, J=8.3, 7.9 Hz, 1H, H_7); 7.55–7.51 (m, 2H, $H_{5'/8}$); 7.10 (dd, J=7.9, 1.1 Hz, 1H, H_6) ^{13}C NMR ($CDCl_3$): δ 160.3, 155.1, 154.9, 153.0, 152.0 (C_2), 144.4 ($C_{3'}$), 138.9 ($C_{5'}$), 134.7 (C_7), 126.5 ($C_{6'}$), 125.1 (CH), 118.6 (CH), 115.3 (C_{4a}), 114.3 (CH); IR: ν 3059, 1564, 1522, 1480, 1418, 1352, 1274, 831, 796 cm^{-1}. HRMS(IC) calculated for $C_{13}H_{10}N_3O$: 224.0824. Found: 224.0829.

2.4.8. 4-(4′-Trifluoromethylphenyl)-5-trifluoromethylsulfonyloxyquinazoline (10). A mixture of **7** (460 mg, 1.59 mmol), triethylamine (0.67 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.53 mL, 2 equiv.) dissolved in 12 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate (5/5)) afforded 476 mg (71%) of **10** as a brown solid, mp 98–99 °C; ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 1H, H_2); 8.26 (d, J=8.4 Hz, 1H, H_8); 8.01 (dd, J=8.4, 7.7 Hz, 1H, H_{ar}); 7.89 (m, 4H, $4H_{PhCF3}$); 7.62 (d, J=7.7 Hz, 1H, H_{ar}); ^{19}F NMR ($CDCl_3$): δ −63.2, −73.1; IR: ν 1543, 1402, 1332, 1220, 1131, 1064, 838, 822 cm^{-1}. Anal. calcd for $C_{16}H_8F_6N_2SO_3$ (422.31): C, 45.51; N, 6.63; H, 1.91; S, 7.59. Found: C, 45.32; N, 6.39; H, 2.03; S, 7.56.

2.4.9. 4-(3′-Nitrophenyl)-5-trifluoromethylsulfonyloxyquinazoline (11). A mixture of **8** (270 mg, 1.01 mmol), triethylamine (0.43 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.34 mL, 2 equiv.) dissolved in 10 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate (5/5)) afforded 110 mg (25%) of **11** as an orange oil; ^{1}H NMR ($CDCl_3$): δ 9.46 (s, 1H, H_2); 8.50–8.40 (m, 2H, $2H_{PhNO2}$); 8.28 (d, J=8.5 Hz, 1H, $1H_{ar}$); 8.04 (m, 2H, $H_{7/PhNO2}$); 7.74 (t, J=8 Hz, 1H, $1H_{PhNO2}$); 7.64 (d, J=7.8 Hz, 1H, H_{ar}); ^{19}F NMR ($CDCl_3$): δ −73.0; IR: ν 3418, 1623, 1532, 1428, 1350, 1217, 1136 cm^{-1}. Anal. calcd for $C_{15}H_8N_3SO_5$ (399.31): C, 45.12; N, 10.52; H, 2.02; S, 8.01. Found: C, 45.38; N, 10.25; H, 2.38; S, 7.97.

2.4.10. 4-(2′-Pyridyl)-5-trifluoromethylsulfonyloxyquinazoline (12). A mixture of **9** (120 mg, 0.54 mmol), triethylamine (0.22 mL, 3 equiv.) and trifluromethanesulfonic anhydride (0.19 mL, 1 equiv.) dissolved in 10 mL of anhydrous dichloromethane was heated under reflux for 15 h. After cooling and hydrolysis with 10 mL of water and neutralization with saturated aqueous sodium carbonate solution, the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. Purification by column chromatography (neutral alumina, eluent: ethyl acetate) afforded 95 mg (49%) of **12** as a brown solid, mp 74–75 °C; ^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H, H_2)); 8.66 (dd, J=4.9, 1.1 Hz, 1H, $H_{6'}$); 8.14 (dd, J=8.7, 1.1 Hz, 1H, H_{ar}); 7.97–7.86 (m, 3H, $H_{3',4',7}$); 7.54 (d, J=7.9 Hz, 1H, H_{ar}); 7.41 (m, 1H, $H_{5'}$); ^{19}F NMR ($CDCl_3$): δ −73.2; ^{13}C NMR ($CDCl_3$): δ 164.7, 156.9, 154.8 (CH), 153.1, 149.5 (CH), 144.2, 137.5 (CH), 133.6 (CH), 130.3 (CH), 125.1 (2×CH), 121.5 (CH), 117.5, 30.1 (CF_3). HRMS(IC) calculated for $C_{14}H_8F_3N_3O_3S$: 356.0317. Found: 356.0319.

2.4.11. 5-Phenyl-4-(4′-trifluoromethylphenyl)quinazoline (13). Cross-coupling reaction of phenylboronic acid (1.3 equiv.) with **10** (200 mg, 0.47 mmol) according to the general procedure C (t=38 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 120 mg (72%) of **13** as a white solid, mp 133–134 °C; ^{1}H NMR ($CDCl_3$): δ 9.41 (s, 1H, H_2); 8.20

(dd, J=8.4, 1.2 Hz, 1H, H_8); 8.00 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.67 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.28 (m, 4H, $H_{2'/3'/5'/6'}$); 7.01 (m, 5H, $5H_{Ph}$); ^{19}F NMR ($CDCl_3$): δ −63.4; IR: ν 1537, 1324, 1108, 1065, 836, 762, 699 cm^{-1}. Anal. calcd for $C_{21}H_{13}F_3N_2$ (350.34): C, 72.00; N, 8.00; H, 3.74. Found: C, 72.30; N, 7.73; H, 3.82.

2.4.12. 5-(4″-Methoxyphenyl)-4-(4′-trifluoromethylphenyl)quinazoline (14). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **10** (200 mg, 0.47 mmol) according to the general procedure C (t=38 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 155 mg (86%) of **14** as a pale yellow solid, mp 45–46 °C; ^{1}H NMR ($CDCl_3$): δ 9.40 (s, 1H, H_2); 8.18 (dd, J=8.4, 1.2 Hz, 1H, H_8); 7.99 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.66 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.32 (m, 4H, $H_{2'/3'/5'/6'}$); 6.90 (d, J=6.7 Hz, 2H, $2H_{PhOCH3}$); 6.54 (d, J=6.7 Hz, 2H, $2H_{PhOCH3}$); ^{19}F NMR ($CDCl_3$): δ −63.3; IR: ν 1611, 1514, 1324, 1164, 1066, 831 cm^{-1}. Anal. calcd for $C_{22}H_{15}F_3N_2O$ (380.37): C, 69.47; N, 7.36; H, 3.97. Found: C, 69.35; N, 7.17; H, 3.58.

2.4.13. 5-(4″-Methoxyphenyl)-4-(3′-nitrophenyl)quinazoline (15). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **11** (100 mg, 0.25 mmol) according to the general procedure C (t=86 h) gave after purification by column chromatography (silica gel, eluent: ethyl acetate) 70 mg (79%) of **15** as a pale yellow solid, mp 136–137 °C; ^{1}H NMR ($CDCl_3$): δ 9.42 (s, 1H, H_2); 8.20 (d, J=7.9 Hz, 1H, H_{ar}); 8.03 (m, 2H, $2H_{ar}$); 7.68 (d, J=7.3 Hz, 1H, H_{ar}); 7.36 (t, J=7.9 Hz, 1H, H_{ar}); 6.94 (d, J=8.5 Hz, 2H, $H_{2''/6''}$); 6.53 (d, J=8.5 Hz, 2H, $H_{3''/5''}$); 3.70 (s, 3H, OCH_3); IR: ν 1529, 1511, 1351, 1241, 1028, 806, 692 cm^{-1}. Anal. calcd for $C_{21}H_{15}N_3O_3$ (357.37): C, 70.59; N, 11.76; H, 4.20. Found: C, 70.95; N, 11.41; H, 4.55.

2.4.14. 5-(4″-Methoxyphenyl)-4-(2′-pyridyl)quinazoline (16). Cross-coupling reaction of 4-methoxyphenylboronic acid (1.3 equiv.) with **12** (125 mg, 0.35 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 31 mg (28%) of **16** as a yellow solid, mp 106–107 °C; ^{1}H NMR ($CDCl_3$): δ 9.35 (s, 1H, H_2); 8.20 (d, J=3.8 Hz, 1H, $H_{6'}$); 8.07 (dd, J=8.7 and 1.1 Hz, 1H, H_8); 7.90 (dd, J=8.7, 7.1 Hz, 1H, H_7); 7.56 (dd, J=7.1, 1.5 Hz, 1H, H_6); 7.42–7.32 (m, 2H, $H_{3'}$ /$_{4'}$); 6.94–6.91 (m, 3H, $H_{2''/6''/5'}$); 6.49 (d, J=8.7 Hz, 2H, $H_{3''/5''}$); 3.71 (s, 3H, OCH_3); IR: ν 1606, 1565, 1512, 1465, 1359, 1246, 1031, 799 cm^{-1}. Anal. calcd for $C_{20}H_{15}N_3O$ (313.36): C, 76.46; N, 13.41; H, 4.82. Found: C, 76.22; N, 12.98; H, 4.44.

2.4.15. 5-(2″-Thienyl)-4-(4′-trifluoromethylphenyl)quinazoline (17). Cross-coupling reaction of (2-thienyl)-trimethylstannane (1.3 equiv.) with **10** (150 mg, 0.36 mmol) according to the general procedure D (t=24 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 5/5) 85 mg (67%) of **17** as a pale yellow solid, mp 137–138 °C; ^{1}H NMR ($CDCl_3$): δ 9.41 (s, 1H, H_2); 8.19 (dd, J=8.4, 1.2 Hz, 1H, H_8); 7.98 (dd, J=8.4, 7.2 Hz, 1H, H_7); 7.77 (dd, J=7.2, 1.2 Hz, 1H, H_6); 7.43 (m, 4H, $H_{2'/3'/5'/6'}$); 7.09 (dd, J=5, 1 Hz, 1H, $H_{5''}$); 6.56 (dd, J=5, 3.6 Hz, 1H, $H_{4''}$); 6.39 (dd, J=3.6, 1 Hz, 1H, $H_{3''}$); ^{19}F NMR ($CDCl_3$): δ −63.3; IR: ν 1537, 1325, 1108, 1065, 828, 706 cm^{-1}. Anal. calcd for $C_{19}H_{11}F_3N_2S$ (394.48): C, 64.04; N, 7.86; H, 3.11. Found: C, 64.31; N, 7.59; H, 3.46.

2.4.16. 2-*tert*-Butyl-5-(1-hydroxyethyl)quinazolin-4(3*H*)-one (19). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with acetaldehyde (5 equiv., 0.07 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: dichloromethane/ethyl acetate (1/1)) 49 mg (82%) of **19** as a white solid, mp 189–190 °C; ^{1}H NMR ($CDCl_3$): δ 10.94 (s, 1H, NH); 7.64 (m, 2H, H_7 and H_8); 7.46 (dd, J_{H6-H7}=6.41 Hz and J_{H6-H8}=2.26 Hz, 1H, H_6); 5.45 (quint, J=6.78 Hz, 1H, C*H*OH); 5.07 (d, J=7.54 Hz, 1H, OH); 1.57 (d, J=6.78 Hz, 3H, Me); 1.43 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 165.4 (C_{qui}), 161.8 (C_{qui}), 152.1 (C_{qui}), 147.3 (C_{qui}), 134.9 (CH_{qui}), 128.3 (CH_{qui}), 125.4 (CH_{qui}), 117.9 (C_{qui}), 69.66 (CHOH), 37.5 (*C*Me_3), 28.6 ($3Me_{tert\text{-butyl}}$), 23.8 (Me). Anal. calcd for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.99. Found: C, 67.97; H, 7.31; N, 11.61.

2.4.17. 2-*tert*-Butyl-5-(1-hydroxyphenyl)quinazolin-4(3*H*)-one (20). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with benzaldehyde (5 equiv., 0.126 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: dichloromethane/ethyl acetate (8/2)) 70 mg (92%) of **20** as a white solid, mp 163–164 °C; ^{1}H NMR ($CDCl_3$): δ 10.76 (s, 1H, NH); 7.61 (m, 2H, H_7 and H_8); 7.24 (m, 5H, Ph); 7.13 (dd, J_{H6-H7}=7.16 Hz and J_{H6-H8}=1.51 Hz, 1H, H_6); 6.39 (d, J=7.91 Hz, 1H, C*H*OH); 5.73 (d, J=7.91 Hz, 1H, OH); 1.34 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 165.2 (C_{qui}), 161.9 (C_{qui}), 152.2 (C_{qui}), 145.1 (C_{qui}), 143.3 (C_{Ph}), 134.7 (CH_{qui}), 128.8 (CH_{qui}), 128.4 ($2CH_{Ph}$), 128.3 (CH_{Ph}), 127.5 (CH_{qui}), 127.2 ($2CH_{Ph}$), 118.5 (C_{qui}), 75.1 (CHOH), 37.5 (*C*Me_3), 28.5 ($3Me_{tert\text{-butyl}}$). Anal. calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.13; H, 6.56; N, 8.69.

2.4.18. 2-*tert*-Butyl-5-phenylsulfanylquinazolin-4(3*H*)-one (21). Metallation of 18. (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with benzaldehyde (5 equiv., 0.126 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: petromeum ether/ethyl acetate (7/3)) 13 mg (17%) of **21** as a white solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 10.85 (s, 1H, NH); 7.57 (m, 2H, H_7 and H_8); 7.42 (m, 3H); 7.29 (d, J=4.52 Hz, 2H); 6.51 (dq, J=4.53 Hz, 1H); 1.42 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 164.2 (C_{qui})162.5 (C_{qui}), 151.3 (C_{qui}), 144.2 (C_{qui}), 136.7 ($2CH_{Ph}$), 133.9 (CH_{qui}), 132.5 (C_{qui}), 130.3 ($2CH_{Ph}$), 129.8 (CH_{qui}), 123.7 (CH),123.3 (CH), 37.7 (*C*Me_3), 28.6 ($3Me_{tert\text{-butyl}}$). Anal. calcd for $C_{18}H_{18}N_2OS$ (310.42): C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.37; H, 5.93; N, 8.87; S, 10.58.

2.4.19. 2-*tert*-Butyl-5-(tri-*n*-butylstannyl)quinazolin-4(3*H*)-one (22). Metallation of **18** (50 mg, 0.24 mmol)

according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with tri-*n*-butylstannyl chloride (5 equiv., 0.34 mL), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: petroleum ether/ethyl acetate (7/3)) 13 mg (17%) of **22** as a vitrous solid, mp 54–55 °C; ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H, NH); 7.59 (m, 3H, $H_{6/7/8}$); 1.48 (m, 6H, CH_2); 1.34 (s, 9H, *tert*-butyl); 1.13 (2m, 12H, CH_2); 0.79 (t, J=7.16–7.54 Hz, 9H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.2 (C_{qui}), 160.5 (C_{qui}), 149.5 (C_{qui}), 145.1 (C_{qui}), 135.8 (CH_{qui}), 134.0 (CH_{qui}), 127.9 (CH_{qui}), 125.5 (C_{qui}), 37.4 ($C_{tert\text{-}butyl}$), 29.6 (CH_2), 28.7 (3×$CH_{3\,tert\text{-}butyl}$), 27.8 ($CH_2$), 14.1 ($CH_3$), 11.8 ($CH_2$). Anal. calcd for $C_{24}H_{40}N_2OSn$ (491.30): C, 58.67; H, 8.21; N, 5.70. Found: C, 58.68; H, 8.23; N, 5.27.

2.4.20. 2-*tert*-Butyl-5-iodoquinazolin-4(3*H*)-one (23). Metallation of **18** (50 mg, 0.24 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 0.80 mL), TMEDA (4.0 equiv., 0.149 mL), T_1=−78 °C, followed by reaction with iodine in THF (5 equiv., 314 mg), t_1=1 h, gave after purification by column chromatography (silicagel, eluent: ethyl ether/dichloromethane (1/9)) 30 mg (37%) of **23** as a white solid, mp 245–246 °C; ^{1}H NMR ($CDCl_3$): δ 11.40 (s, 1H, NH); 7.99 (dd, J_{H6-H7}=7.53–7.53 Hz and J_{H6-H8}=0.75–1.13 Hz, 1H, H_6); 7.63 (dd, J_{H8-H7}=7.91–8.29 Hz and J_{H8-H6}=0.75–1.13 Hz, 1H, H_8); 7.24 (t, J=7.9 Hz, H_7); 1.44 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 162.7 (C_{qui}), 162.6 (C_{qui}), 151.0 (C_{qui}), 140.9 (CH_{qui}), 135.0 (CH_{qui}), 129.2 (CH_{qui}), 120.4 (C_{qui}), 91.3 (C_{qui}), 38.0 ($C_{tert\text{-}butyl}$), 28.6 (3×$CH_{3\,tert\text{-}butyl}$). Anal. calcd for $C_{12}H_{13}N_2OI$ (328.15): C, 43.92; H, 3.99; N, 8.54. Found: C, 43.98; H, 3.97; N, 8.35.

2.4.21. 2-*tert*-Butyl-4-oxo-3,4-dihydroquinazolin-5-boronic acid (24). Metalation of **18** (100 mg, 0.5 mmol) according to the procedure B with *sec*-BuLi 1.3 M (4.2 equiv., 1.6 mL), TMEDA (4.0 equiv., 0.3 mL), T_1=−20 °C, t_1=1 h, followed by reaction with tri-*iso*propylborate (6 equiv., 564 mg), T_2=−78 °C to rt, t_2=15 h, gave after purification by washing with DCM 84 mg (68%)of **24**, mp °C; ^{1}H NMR (d_6-DMSO): δ 11.88 (s, 1H, NH), 9.35 (s, 2H, 2×OH), 7.72 (t, J=7.9 Hz, 1H, H_7), 7.54 (dd, J=7.9, 1.1 Hz, 1H, H_{Ar}), 7.42 (dd, J=7.9, 1.1 Hz, 1H, H_{Ar}), 1.37 (s, 9H, *tert*-butyl); IR: ν 3346, 3173, 3069, 2973, 2922, 1640, 1583, 1409, 1375 cm^{-1}.

2.4.22. 2-*tert*-Butyl-5-(4′-methoxyphenyl)quinazolin-4(3*H*)-one (25). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 4-iodoanisole (468 mg, 2 mmol) according to the general procedure C (DME, t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 6/4) 246 mg (40%) of **25** as a white solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 11.17 (s, 1H, NH); 7.66 (m, 2H, $H_{6/8}$); 7.22 (d, J=8.7 Hz, 2H, $H_{2'/6'}$); 7.19 (t, 1H, H_7); 6.89 (d, J=8.7 Hz, 2H, $H_{3'/5'}$); 3.86 (s, 3H, OCH_3); 1.18 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.9 (C_4), 162.8 (C_2), 158.8 ($C_{4'}$), 151.0 (C_{8a}), 143.5 (C_5), 135.0 ($C_{1'}$), 133.4 (C_6), 130.1 ($C_{2'}$, $C_{6'}$), 129.9 (C_7), 127.6 (C_8), 118.1 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.5 (OCH_3), 37.2 ($C_{tert\text{-}butyl}$), 28.4 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 3173, 3090, 3053, 2973, 2951, 2832, 1669, 1616, 1592, 1515, 1465, 1286, 1238, 827 cm^{-1}. MS (IC): 309 $(MH)^+$. Anal. calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; N, 9.08; H, 6.54. Found: C, 73.88; N, 8.82; H, 6.34.

2.4.23. 2-*tert*-Butyl-5-(2′-thienyl)quinazolin-4(3*H*)-one (26). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 2-iodothiophene (421 mg, 2 mmol) according to the general procedure F (DME, t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 7/3) 341 mg (60%) of **26** as a beige solid, mp 242–243 °C; ^{1}H NMR ($CDCl_3$): δ 11.87 (s, 1H, NH); 7.70 (m, 2H, $H_{6/8}$); 7.35 (m, 2H, $H_{2'/7}$); 7.03 (m, 2H, $H_{3'/4'}$); 1.25 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.7 (C_4), 163.1 (C_2), 150.9 (C_{8a}), 142.8 (C_5), 135.5 ($C_{1'}$), 133.0 (C_6), 131.1 (C_7), 128.7 (C_8), 126.8 ($C_{3'}$ or $C_{4'}$), 126.6 ($C_{3'}$ or $C_{4'}$), 125.2 ($C_{2'}$), 118.8 (C_{4a}), 37.2 ($C_{tert\text{-}butyl}$), 28.3 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 3175, 1660, 1614, 1592, 1570, 1310, 976, 822, 786 cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2OS$ (284.38): C, 67.58; N, 9.85; H, 5.67. Found: C, 67.23; N, 9.37; H, 5.13.

2.4.24. 2-*tert*-Butyl-5-(4′-*N*,*N*-dimethylaminophenyl)-quinazolin-4(3*H*)-one (27). Coupling of heteroarylboronic acid **24** (640 mg, 1.3 equiv.) with 4-bromo-*N*,*N*-dimethylaniline (400 mg, 2 mmol) according to the general procedure F (DME, t=60 h) gave after purification by recrystalization in diethyl ether 454 mg (71%) of **27** as a solid, mp >250 °C; ^{1}H NMR ($CDCl_3$): δ 11.33 (s, 1H, NH); 7.64 (m, 2H, $H_{6/8}$); 7.20 (m, 3H, $H_{2'/6'/7}$); 6.74 (d, J=8.7 Hz, 2H, $H_{3'/5'}$); 3.00 (s, 6H, $N(CH_3)_2$); 1.22 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 163.9 (C_4), 162.6 (C_2), 151.0 (C_{8a}), 144.2 (C_5), 133.4 (C_6), 130.6 (C_7), 129.9 ($C_{1'}$), 129.8 ($C_{2'}$, $C_{6'}$), 126.9 (C_8), 118.0 (C_{4a}), 111.9 ($C_{3'}$, $C_{5'}$), 40.9 (2×CH_3), 37.2 ($C_{tert\text{-}butyl}$), 28.5 (3×$CH_{3\,tert\text{-}butyl}$). Anal. calcd for $C_{20}H_{23}N_3O$ (321.43): C, 74.74; N, 13.07; H, 7.21. Found: C, 74.52; N, 12.60; H, 6.98.

2.4.25. 2-*tert*-Butyl-4-chloro-5-(4′-methoxyphenyl)quinazoline (28). Reaction of **25** (900 mg, 2.9 mmol) with $POCl_3$ (50 mL) under reflux for 6 h, followed by removal of excess of $POCl_3$ under reduced pressure and partitionning of the residue between CH_2Cl_2 and cold aqueous K_2CO_3 solution, gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 6/4) 682 mg (72%) of **28** as a yellow solid, mp 98–99 °C; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, J=8.3 Hz, 1H, H_8); 7.82 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.47 (d, J=7.2 Hz, 1H, H_6); 7.24 (d, J=8.3 Hz, 2H, $H_{2'/6'}$); 6.96 (d, J=8.3 Hz, 2H, $H_{3'/5'}$); 3.89 (s, 3H, OCH_3); 1.50 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.9 (C_2), 160.7 (C_4), 159.2 ($C_{4'}$), 152.8 (C_{8a}), 140.2 (C_5), 133.5 ($C_{1'}$), 132.7 (C_6), 131.0 ($C_{2'}$, $C_{6'}$), 130.5 (C_8), 128.3 (C_7), 120.1 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.3 (OCH_3), 39.2 ($C_{tert\text{-}butyl}$), 29.3 (3×$CH_{3\,tert\text{-}butyl}$); IR: ν 1608, 1563, 1510, 1460, 1290, 1240, 1170, 881, 832, 744 cm^{-1}. Anal. calcd for $C_{19}H_{19}ClN_2O$ (326.83): C, 69.83; N, 8.57; H, 5.86. Found: C, 69.87; N, 8.49; H, 5.98.

2.4.26. 2-*tert*-Butyl-4-chloro-5-(2′-thienyl)quinazolin-4(3*H*)-one (29). Reaction of **26** (284 mg, 1 mmol) with $POCl_3$ (15 mL) under reflux for 6 h, followed by removal of excess of $POCl_3$ under reduced pressure and partitionning of the residue between CH_2Cl_2 and cold aqueous K_2CO_3 solution, gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 7/3) 121 mg

(40%) of **29** as a yellow solid, mp 134–135 °C; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, J=8.3 Hz, 1H, H_8); 7.83 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.63 (d, J=7.2 Hz, 1H, H_6); 7.44 (d, J=5.3 Hz, 1H, $H_{2'}$); 7.11 (m, 1H, $H_{3'}$); 7.02 (m, 1H, $H_{4'}$); 1.49 (s, 9H, 3×$CH_{3\,tert\text{-butyl}}$); ^{13}C NMR ($CDCl_3$): δ 172.3, 160.6, 152.9, 141.2, 132.6 (C_7), 132.5 (C_6), 132.4, 129.9 (C_8), 128.9 ($C_{4'}$), 127.1 ($C_{3'}$), 126.4 ($C_{2'}$), 121.2 (C_{4a}), 39.5 ($C_{tert\text{-butyl}}$), 29.5 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 1563, 1444, 1280, 827, 744, 712 cm^{-1}. Anal. calcd for $C_{16}H_{15}ClN_2S$ (302.83): C, 63.46; N, 9.25; H, 4.99. Found: C, 63.96; N, 8.93; H, 5.09.

2.4.27. 2-*tert*-Butyl-4-(4′-cyanophenyl)-5-(4″-methoxyphenyl)quinazoline (30). Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **28** (474 mg, 2 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 8/2)) 618 mg (90%) of **30** as a yellow solid, mp 149–150 °C; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J=8.3 Hz, 1H, H_8); 7.89 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.53 (d, J=7.2 Hz, 1H, H_6); 7.33 (m, 4H, $H_{2'/3'/5'/6'}$); 6.92 (d, J=8.7 Hz, 2H, $H_{2''/6''}$); 6.56 (d, J=8.7 Hz, 2H, $H_{3''/5''}$); 3.73 (s, 3H, OCH_3); 1.54 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.8 (C_2), 165.4 (C_4), 159.1 ($C_{4''}$), 153.1 (C_{8a}), 144.9 ($C_{1'}$), 139.9 (C_5), 132.8 (C_7), 131.1 ($C_{2''}$, $C_{6''}$), 131.0 ($C_{2'}$, $C_{6'}$), 130.7 ($C_{3'}$, $C_{5'}$), 130.0 (C_6), 128.4 (C_8), 119.2 (CN), 118.8 (C_{4a}), 113.6 ($C_{3'}$, $C_{5'}$), 111.5 ($C_{4'}$), 55.6 (OCH_3), 39.5 ($C_{tert\text{-butyl}}$), 29.7 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 3073, 3008, 2966, 2931, 2863, 2230, 1609, 1538, 1513, 1470, 1368, 1296, 1249, 1175, 1035, 827, 812 cm^{-1}. Anal. calcd for $C_{26}H_{23}N_3O$ (343.49): C, 79.36; N, 5.89; H, 10.68. Found: C, 78.99; N, 10.33; H, 6.13.

2.4.28. 2-*tert*-Butyl-4-(4′-cyanophenyl)-5-(2″-thienyl)quinazoline (31). Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **29** (mg, 2 mmol) according to the general procedure C (t=60 h) gave after purification by column chromatography (silica gel, eluent petroleum ether/ethyl acetate)) 221 mg (30%) of **31** as a yellow solid, mp 120–121 °C; ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J=8.3 Hz, 1H, H_8); 7.87 (dd, J=8.3, 7.2 Hz, 1H, H_7); 7.63 (d, J=7.2 Hz, 1H, H_6); 7.46 (d, J=8.3 Hz, 2H, $2H_{PhCN}$); 7.39 (d, J=8.3 Hz, 2H, $2H_{PhCN}$); 7.08 (d, J=5.3 Hz, 1H, $H_{2''}$); 6.56 (m, 1H, $H_{3''}$); 6.38 (m, 1H, $H_{4''}$); 1.54 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 172.1 (C_2), 165.2 (C_4), 153.1 (C_{8a}), 145.0 ($C_{1'}$), 142.0 ($C_{1''}$), 132.7 (C_5), 132.4 (C_7), 131.2 (2×CH_{PhCN}), 131.0 (C_6), 130.0 (2×CH_{PhCN}), 129.7 ($C_{4''}$), 129.4 (C_8), 127.5 ($C_{3''}$), 126.4 ($C_{2''}$), 119.7 (CN), 119.0 (C_{4a}), 111.9 ($C_{2''}$), 39.6 ($C_{tert\text{-butyl}}$), 29.8 (3×$CH_{3\,tert\text{-butyl}}$). HRMS(IC) calculated for $C_{23}H_{20}N_3S$: 370.1378. Found: 370.1380.

2.4.29. 2-*tert*-Butyl-5-(4″-methoxyphenyl)-4-(2′-pyridyl)-quinazoline (32). Coupling of (2-pyridyl)-tributylstannane (1.3 equiv.) with **28** (474 mg, 2 mmol) according to the general procedure D (t=48 h) gave after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate 8/2) 236 mg (32%) of **32** as a yellow solid, mp 107–108 °C; ^{1}H NMR ($CDCl_3$): δ 8.11 (d, J=4.9 Hz, 1H, $H_{3'}$); 8.05 (d, J=8.3 Hz, 1H, H_8); 7.86 (dd, J=8.3, 7.5 Hz, 1H, H_7); 7.66 (d, J=7.9 Hz, 1H, $H_{6'}$); 7.53 (m, 2H, $H_{6/5'}$); 6.95 (m, 3H, $H_{2''/6''/4'}$); 6.54 (d, J=8.3 Hz, 2H, $H_{3''/5''}$); 3.72 (s, 3H, OCH_3); 1.56 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$): δ 171.6 (C_2), 165.8 (C_4), 158.4 ($C_{4''}$ or $C_{1'}$), 158.3 ($C_{4''}$ or $C_{1'}$),153.1 (C_{8a}), 148.6 ($C_{3'}$), 140.4 (C_5), 135.8 ($C_{5'}$), 134.6 ($C_{1''}$), 132.6 (C_7), 130.6 ($C_{2''}$, $C_{6''}$), 129.9 (C_6), 128.0 (C_8), 124.9 ($C_{6'}$), 122.5 ($C_{4'}$), 119.3 (C_{4a}), 113.2 ($C_{3'}$, $C_{5'}$), 55.4 (OCH_3), 39.4 ($C_{tert\text{-butyl}}$), 29.8 (3×$CH_{3\,tert\text{-butyl}}$); IR: ν 3058, 3014, 2960, 2926, 2864, 2837, 1610, 1550, 1512, 1470, 1368, 1348, 1292, 1245, 1183, 1026, 827, 804, 790, 744 cm^{-1}. MS (EI): 369 $(M)^+$. Anal. calcd for $C_{24}H_{23}N_3O$ (369.47): C, 78.02; N, 11.37; H, 6.27. Found: C, 77.69; N, 10.97; H, 6.51.

Acknowledgements

We thank Dr. C. Andraud (ENS Lyon) for her collaboration and the determination of the μ_{calcd} and $\mu\beta$ values by the EFISH method, and L. Toupet (GMCM, CNRS 6626, Rennes) for the X-ray diffraction study.

References and notes

1. Puglisi, J. D.; Wyatt, J. R.; Tinoco, Jr. I. *Acc. Chem. Res.* **1991**, *24*, 152.
2. Cozzi, F.; Siegel, J. *Pure Appl. Chem.* **1995**, *67*, 683.
3. Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018.
4. House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815.
5. Cozzi, F.; Ponzini, F.; Annuziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019.
6. Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330.
7. Cozzi, F.; Cinquini, M.; Annuziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729.
8. Nugent, H. M.; Rosenblum, M. *J. Am. Chem. Soc.* **1993**, *115*, 3848.
9. Cosmo, R.; Sternell, S. *Aust. J. Chem.* **1987**, *40*, 1107.
10. Komatsu, K.; Tsuji, R.; Inoue, Y.; Takeuchi, K. *Tetrahedron Lett.* **1993**, *34*, 99.
11. Kuroda, M.; Nakayama, J.; Hoshino, M.; Furusho, N.; Kawata, T.; Ohba, S. *Tetrahedron* **1993**, *49*, 3735.
12. Iovine, P. M.; Kellet, M. A.; Redmore, N. P.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 8717.
13. (a) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 3215. (b) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 2763. (c) Zoltewicz, J. A.; Maier, N. M.; Lavieri, S.; Ghiviriga, I.; Abboud, K. A.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 5379. (d) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1996**, *61*, 7018. (e) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703. (f) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1998**, *63*, 4985. (g) Lavieri, S.; Zoltewicz, J. A. *J. Org. Chem.* **2001**, *66*, 7227.
14. (a) Bahl, A.; Grahn, W.; Stadler, S.; Feiner, F.; Bourhill, G.; Bräuchle, C.; Reisner, A.; Jones, P. G. *Angew. Chem. Int., Ed. Engl.* **1995**, *34*, 1485. (b) Di Bella, S.; Fragala, L.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc.* **1993**, *115*, 682.
15. Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584.
16. Warrener, R. N.; Russell, R. A.; Marcuccio, S. M. *Aust. J. Chem.* **1980**, *33*, 2777.
17. (a) Jones, P. G.; Grahn, W.; Bahl, A.; Reisner, A. *Z. Kristallogr.* **1995**, *210*, 229. (b) Clough, R. L.; Kung,

W. J.; Marsh, R. E.; Roberts, J. D. *J. Org. Chem.* **1976**, *41*, 3603.
18. Gautheron-Chapoulaud, V.; Salliot, I.; Plé, N.; Turck, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 5389.
19. Sugimoto, O.; Yamauchi, Y.; Tanji, K. I. *Heterocycles* **2002**, *57*, 323.
20. Plé, N.; Turck, A.; Chapoulaud, V.; Quéguiner, G. *Tetrahedron* **1997**, *53*, 2871.
21. Connoly, D. J.; Guiry, P. J. *Synlett* **2001**, *11*, 1707.
22. Armarego, W. L. F. *Fused Pyrimidines, Part 1, Quinazolines*^{II}, *Chemistry of Heterocyclic Compounds*; Wiley: New York, 1967.
23. (a) Murray, T. P.; Hay, J. V.; Portlock, D. E.; Wolfe, J. F. *J. Org. Chem.* **1974**, *39*, 595. (b) Rathman, T. L.; Sleevi, M. C.; Krafft, M. K.; Wolfe, J. F. *J. Org. Chem.* **1980**, *45*, 2169.
24. (a) Srinivasan, A.; Broom, A. D. *J. Org. Chem.* **1979**, *44*, 435. (b) Anderson, G. L.; Shim, J. L.; Broom, A. D. *J. Org. Chem.* **1977**, *42*, 993. (c) Oakes, V.; Rydon, H. N. *J. Chem. Soc.* **1956**, 4433. (d) Oakes, V.; Rydon, H. N.; Undheim, K. *J. Chem. Soc.* **1962**, 4678. (e) Oakes, V.; Rydon, H. N. U.S. Patent No 2,924, 599, 1960; *Chem. Abstr.* **1960**, *54*, 9964..
25. Coulson, D. R. *Inorg. Synth.* **1972**, *18*, 121.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5383–5392

About the stereoselectivity control in reactions of chiral *ortho*-sulfinyl benzyl carbanions with aldehydes

José L. García Ruano,* M. Teresa Aranda and José M. Aguirre†

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

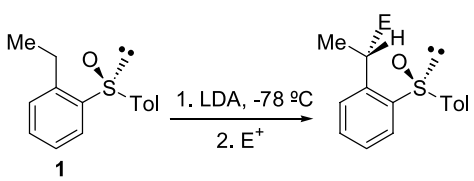
Received 13 February 2004; revised 20 April 2004; accepted 22 April 2004

Abstract—Reactions of aliphatic and aromatic aldehydes with the benzyllithium derived from 2-*p*-tolylsulfinyl ethylbenzene yield mixtures of mainly two compounds, *anti*-**3** and *syn*-**4**, epimers at hydroxylic carbon, easily separated by chromatography and desulfinylated into enantiomerically pure 1-alkyl (or aryl)-2-phenyl-1-propanols. The observed stereoselectivity at C(1) and C(2) is analyzed to the light of the steric and electronic effects of the substituents.

1. Introduction

Enantioselective deprotonation/substitution processes of benzylic positions[1] have been widely investigated in the last years. Chiral auxiliaries have allowed the sterocontrolled functionalization of remote positions[2] and the use of sparteine as a chiral ligand[3] has provided significant success in the generation of chiral benzylic carbons. We have recently reported the highly stereoselective generation of benzylic stereocenters mediated by a remote sulfinyl group.[4] The reactions of benzyl carbanions derived from enantiomerically pure *ortho*-*p*-tolylsulfinyl compounds with different electrophiles, yielded compounds with an almost complete control at the configuration of the benzylic centers (Scheme 1).

In the case of reactions with prochiral carbonyl compounds, we demonstrated that the influence of the sulfinyl group on the stereoselectivity control at the electrophilic center was also significant and, apparently, dependent on the relative size of those substituents joined to the carbonyl group. Thus, the reactions of compound **1** with 2-butanone in the presence of LDA yielded almost equimolecular mixtures of only two compounds, epimers at the hydroxylic carbon, whereas with benzaldehyde the observed stereoselectivity is clearly higher (around 70% de). Only one diastereoisomer was obtained in reactions with enantiomerically pure (2*S*,*SR*)-2-*p*-tolylsulfinyl cyclohexanone, which could be the result of a double asymmetric induction process.[4] A similar situation was also observed in reactions of **1** with optically pure *N*-sulfinyl imines, where the presence of the chiral sulfoxide at the electrophile allowed the complete control of the stereoselectivity when the proper matched pair of the reagents was used.[5] All the compounds obtained in these reactions have the same configuration at the benzylic carbon, which evidences the high stability that the sulfinyl group confers to one of the two diastereomeric *ortho* benzyl carbanions. The importance of this question in asymmetric synthesis, which would provide an entry to many fragments with two joined chiral centers (one of them benzylic) supporting a variety of heteroatoms, prompted us to check the validity of the stereochemical model so far proposed.[4] With this aim and to know the scope of reactions of **1** with aldehydes for synthesizing optically pure 1,2-disubstituted-1-propanols, we have studied and described in this paper the behavior of a series of aromatic and aliphatic aldehydes, containing substituents of different electronic character and size.



Scheme 1.

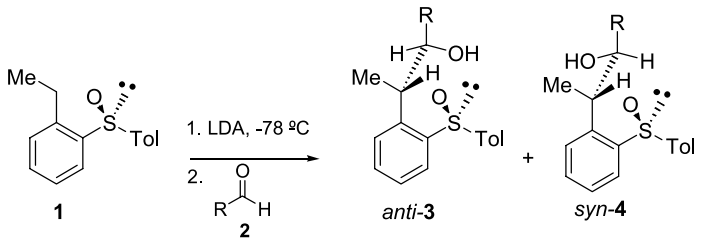
2. Results and discussion

The synthesis of the compound **1** was performed starting from *ortho*-bromoethylbenzene according to the procedure previously reported.[4] The results obtained in reactions with

Keywords: Benzylic stereocenter; Chiral benzyllithium; Sulfoxide; Remote stereocontrol; 1-Alkyl-2-phenyl-1-propanol; 1-Aryl-2-phenyl-1-propanol.
* Corresponding author. Tel.: +34-914974701; fax: +34-914973966; e-mail address: joseluis.garcia.ruano@uam.es
† Present address: Departamento de Ciencias Básicas, Universidad Nacional de Luján, Luján, Argentina.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.051

Table 1. Reactions of **1** with different aldehydes



Entry	Aldehyde (R)	Diastereomer ratio *anti*-**3**:*syn*-**4**	Isolated yield (%)	
			3	**4**
1[a]	**2a** (Ph)	85:15	65	—
2	**2b** (*p*-$OMeC_6H_4$)	84:16	68	12
3	**2c** (*p*-$NO_2C_6H_4$)	—[b]		
4	**2d** (*p*-CNC_6H_4)	—[b]		
5	**2e** (*p*-$CO_2MeC_6H_4$)	—[b]		
6	**2f** (2-Naphtyl)	85:15[c]	62	—
7	**2g** (1-Naphtyl)	88:12	73	—
8	**2h** (2,6-$DiMeC_6H_3$)	67:33	44	26
9	**2i** (*n*-Bu)	37:63	32	55
10	**2j** (*i*-Pr)	29:71	21	54
11	**2k** (*t*-Bu)	24:76	14	44

[a] Data taken from Ref. 4.
[b] Complex mixture (see text).
[c] See text.

different aromatic (**2a**–**h**) and aliphatic (**2i**–**k**) aldehydes are collected in Table 1.

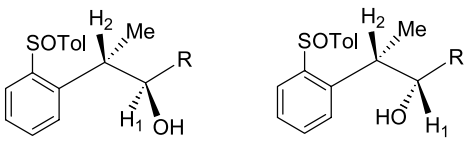
We first investigated the behavior of the aromatic aldehydes **2a**–**f** differing in the electronic density of the rings, and **2g**–**h** with different sizes. When compound **1** was treated with LDA in THF at −78 °C and then added compounds **2a**–**h**, we observed that starting material disappears after a few minutes. Aldehydes containing activated rings (**2b**, **2g** and **2h**) afforded mixtures of only two alcohols *anti*-**3** and *syn*-**4**, whereas the less activated **2f** yielded a 78:13:9 mixture of three alcohols (only **3f** and **4f** have been indicated in entry 6). We have used the notation *anti* and *syn* to design compounds **3** and **4**, respectively (Table 1). A detailed study of the reaction crude from **2a** also revealed the presence of a third stereoisomer[‡] that it had not been previously reported.[4] The **3**:**4** ratio is almost identical (85:15) for **2a**, **2b** and **2f**, all of them with a similar size of the aromatic ring, slightly increases to 88:12 for **2g** but significantly decreases (67:33) for **2h**, which is the bulkiest ring. This behavior will be later commented. The adducts were easily isolated, purified by chromatography and therefore completely characterized. Compounds **2c**–**e**, presumably the most reactive because they contain electron-withdrawing groups, yielded complex mixtures whose complete analysis was not possible in our hands. Nevertheless, the ^{1}H NMR spectra of their crudes suggest the presence of more than two alcohols.[6] Finally, the reaction of **1** with aliphatic aldehydes **2i**–**k** yielded mixtures only containing adducts **3** and **4** (entries 9–11). The stereoselectivity is lower than that observed from the aromatic aldehydes and it slightly increases when size of the R group become larger.

[‡] The ^{1}H NMR signals presumably due to the forth diastereoisomer in less than 3% ratio can also be detected.

2.1. Configurational assignment

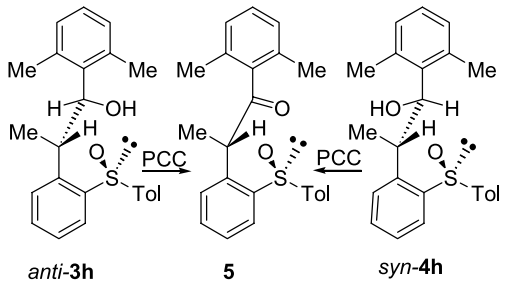
The ^{1}H NMR parameters, which are significant for the configurational assignment of both diastereomers, are depicted in Table 2. In general, *anti* isomers exhibit higher

Table 2. Significant ^{1}H NMR parameters for the configurational assignment of *syn* and *anti* epimers



Entry	Isomer	$J_{1,2}$[a]	$J_{1,OH}$[a]	δ_{OH}[b]	δ_{Me}[b]
1[c]	*anti*-**3a**	9.7	7.0	3.81	0.75
2[c]	*syn*-**4a**	4.9	—	3.26	1.10
3	*anti*-**3b**	9.7	6.5	3.66	0.75
4	*syn*-**4b**	5.6	2.4	3.27	1.10
5	*anti*-**3f**	9.7	7.3	4.14	0.76
6	*syn*-**4f**	5.3	2.0	3.50	1.14
7	*anti*-**3g**	9.3	6.5	3.75	0.75
8[d]	*syn*-**4g**	5.6	2.7	2.86	1.27
9	*anti*-**3h**	10.1	4.4	3.09	0.79
10	*syn*-**4h**	10.1	2.4	2.52	1.61
11	*anti*-**3i**	8.9	7.3	2.38	1.01
12[e]	*syn*-**4i**	5.2	4.4	1.88	1.20
13[e]	*anti*-**3j**	10.1	7.7	2.83	0.84
14	*syn*-**4j**	4.8	—	1.71	1.21
15	*anti*-**3k**	8.9	7.7	2.65	1.01
16	*syn*-**4k**	2.4	6.5	1.59	1.25

[a] Values of *J* measured in Hz.
[b] Values of δ expressed in ppm.
[c] Data taken from Ref. 4.
[d] Data taken from a mixture **3g**+**4g**.
[e] The values of *J* were measured by double resonance experiments.



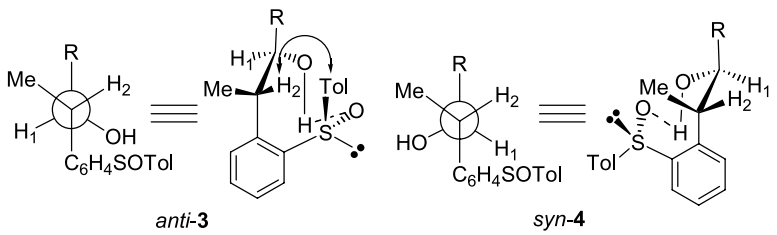
Scheme 2.

$J_{1,2}$, $J_{1,OH}$ and δ_{OH} but lower δ_{Me} values than their corresponding *syn* epimers.

We first established that both epimers had identical configuration at C(2). This had been previously demonstrated for *anti*-**3a** and *syn*-**4a**.[4] We have now checked the same for the epimeric pair *anti*-**3h** and *syn*-**4h**. Their independent oxidation with PCC afforded the same ketone **5** (Scheme 2), indicating both epimers only differs in the configuration at hydroxylic carbon C(1). The reaction of *ortho*-sulfinyl benzyl carbanions with any aldehyde followed of the PCC oxidation of the resulting epimeric mixture provides a very simple synthetic route to prepare optically pure benzylic ketones.

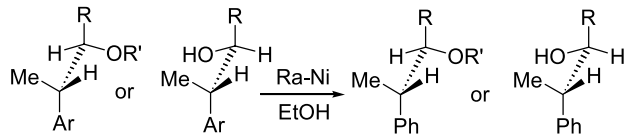
The configurational assignment of the other epimeric pairs was made from the parameters collected in Table 2. As we can see, the main difference between both diastereomers is the value of their vicinal coupling constants between the protons of the fragment H–C(1)–C(2)–H ($J_{1,2}$). They are usually ≥8.9 Hz for the isomers we have named as *anti*, but ≤5.6 Hz for the *syn* ones. Taking into account that the steric interactions must be the main factor controlling the conformational stability of these compounds around the C(1)–C(2) bond, the most populated rotamers for both diastereoisomers must be those avoiding the *gauche* interaction between the bulkiest substituents R and 2-*p*-tolylsulfinylphenyl (except in the case of *t*-Bu[7]) as they have been depicted in Scheme 3. According to this, the *syn* isomers must exhibit the lower values of $J_{1,2}$ (≤5.6 Hz) because they display the protons in a *gauche* arrangement, whereas the *anti* isomers will be those with higher $J_{1,2}$ values (≥8.9 Hz). The unequivocal configurational assignment of compounds **3k** and **4k** by X-ray diffraction analysis supports the validity of these criteria.[8]

The only pair of diastereoisomers than cannot be unequivocally assigned from their vicinal coupling constant values is that formed by *anti*-**3h** and *syn*-**4h**. These compounds have identical value of $J_{1,2}$ (10.1 Hz) suggesting that both exhibit an *anti* relationship between the protons in their most populated rotamers. Two different possibilities could explain this result: (a) the two aryl groups adopt a *gauche* arrangement in one of the epimers,[9] and (b) both isomers differ in the configuration at their two chiral carbons. To clarify this point it was necessary to perform their oxidation



Scheme 3.

Table 3. Desulfinylation of alcohols or their derivatives with Ra-Ni



Entry	Starting compound	Reaction time (h)	Product (yield, %)
1	*anti*-**8a**	1	*anti*-**9a** (70)[a] (66)[b]
2	*anti*-**8f**	24	*anti*-**9f** (48)[a] (41)[b]
3	*anti*-**8g**	24	*anti*-**9g** (60)[a] (35)[b]
4	*anti*-**3i**	0.75	*anti*-**6i** (89)
5	*syn*-**4i**	6	*syn*-**7i** (95)
6	*anti*-**3j**	1.75	*anti*-**6j** (45)
7	*syn*-**4j**	3	*syn*-**7j** (47)
8	*anti*-**3k**	3.5	*anti*-**6k** (69)
9	*syn*-**4k**	4	*syn*-**7k** (75)

[a] Isolated yield.
[b] Overall yield from *anti*-**3a**,**f**,**g** (protection+desulfinylation).

(see above), which unequivocally disregarded the second possibility.

Other significant spectroscopic value clearly different for both epimers is the $J_{1,OH}$ parameter, which is higher for the *anti* epimers (Table 2). Values lower than 4 Hz are indicative of a predominance of rotamers exhibiting a *gauche* arrangement between the involved protons. This is only possible for intramolecularly associated species.[10] Values around 5–7 Hz indicate free rotation around C–O bonds and suggest the absence of intramolecular hydrogen bonds.[11] As it can be seen from Table 2, *anti* epimers show $J_{1,OH}$ values of 7 ± 1 Hz, whereas *syn* epimers have always smaller values that, in the case of 1,2-diaryl propanols, are even lower than 3 Hz. These are the expected results on the basis that intramolecular association of the OH and the sulfinylic oxygen must be easier for the *syn*-**4** epimers than *anti*-**3**, because it is strongly hindered by the steric (Tol/CH_2)$_{1,3\text{-parallel}}$ interaction (Scheme 3).

The relationship of δ_{OH} and δ_{Me} values with the relative configuration of the epimers, which is evident from the data collected in Table 2, is more difficult to rationalize. Anyway, it must be related to the anisotropic effects exerted by the sulfinyl and aryl groups, which display a different orientation in each diastereoisomer. The combined use of all these criteria allows the assignment of compounds *syn*-**4h** and *anti*-**3h** (the first one exhibits lower $J_{1,OH}$ and δ_{OH} but higher δ_{Me} values), which have identical $J_{1,2}$ values.

2.2. Desulfinylation reactions

Desulfinylation of compounds **3** and **4** was required to obtain the corresponding 1-aryl (or alkyl)-2-phenyl 1-propanols in optically pure form. In order to illustrate this process we have studied the reactions of several sulfinyl alcohols derived from both aromatic and aliphatic aldehydes with Raney nickel and the results are indicated in Table 3.

The reactions of alcohols derived from aliphatic aldehydes evolve at room temperature in EtOH for those times indicated in Table 3 towards the expected enantiomerically pure propanols **6** and **7**. The yields ranged between moderate and very good although they have not been optimized. The alcohols derived from aromatic aldehydes (*anti*-**3a**, *anti*-**3g** and *anti*-**3f**) react with Ra-Ni yielding a 65:35 mixture of epimers at hydroxylic carbon. This epimerization, which had been previously observed in the desulfinylation of similar alcohols,[12] can be avoided by protecting the hydroxy groups as silyl derivatives before their treatment with Raney nickel. Compounds *anti*-**3a**, *anti*-**3f** and *anti*-**3g** were thus converted into their silyl derivatives *anti*-**8a**, *anti*-**8f** and *anti*-**8g**, previous to their desulfinylation. Enantiomerically pure compounds *anti*-**6** can be easily obtained from *anti*-**9** with TBAF.

2.3. Stereochemical discussion

The stereochemical results deduced from Table 1 can be summarized as follows.

Stereoselectivity at C(2). It is complete from aliphatic (**2i**–**k**) and activated aromatic (**2b**, **2g**, **2h**) aldehydes, high but incomplete for aromatic aldehydes lacking of electron donating groups (**2a** and **2f**), and low for deactivated aryl aldehyde **2d** (and probably **2e**).

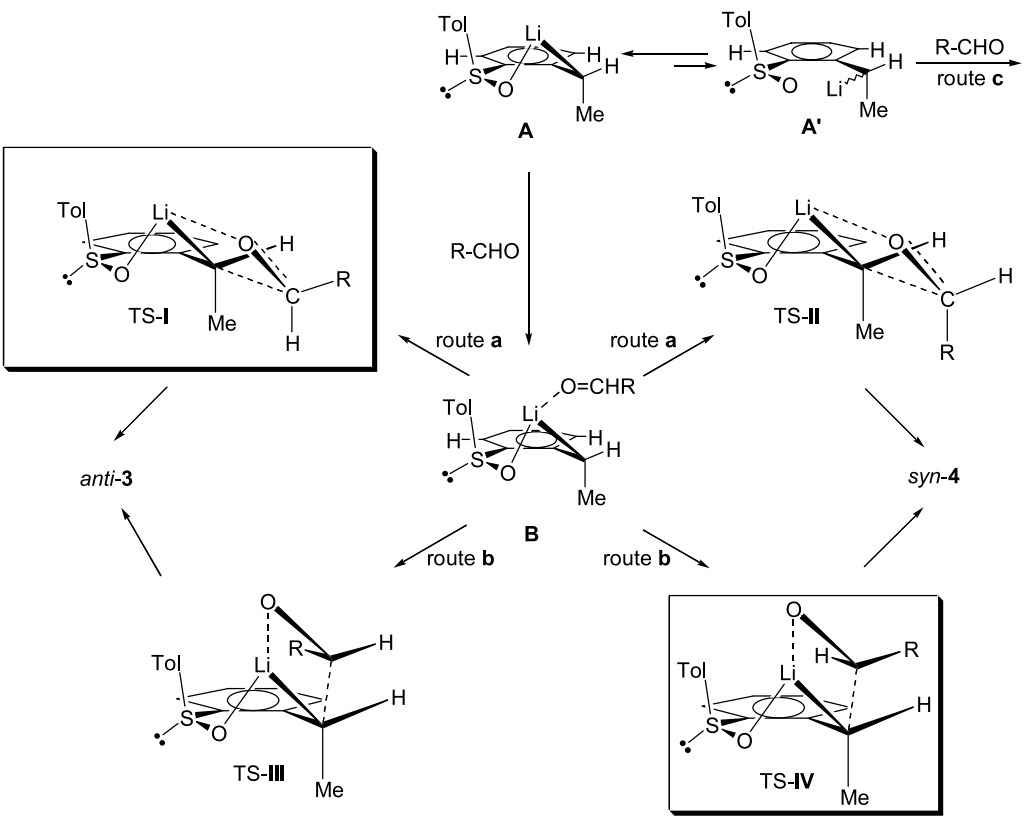


Figure 1. Stereochemical course of the reaction.

Stereoselectivity at C(1). The sense of the stereoselectivity depends on the nature of the aldehyde. *anti*-**3** Epimers are predominant from Ar–CHO, whereas *syn*-**4** are the major ones from R–CHO. The small variation of the de's obtained from aliphatic (**2i–k**) and aromatic (**2a**, **2b**, **2f–h**) aldehydes suggests a scarcely significant role of the steric effects on the stereoselectivity.

These two facts are difficult to explain from the stereochemical model proposed previously.[4] This one suggested that the reaction of **1** with LDA yields the chelated species **A** (Fig. 1), with tolyl and methyl groups adopting a pseudoaxial arrangement in order to avoid their interactions with the *ortho* protons (allylic strain). In the reactions of these species with aldehydes, the carbonyl oxygen is associated with the lithium (**B** in Fig. 1) as a previous step to the nucleophilic attack, which makes easier the reaction. Therefore it takes place intramolecularly with complete retention of the configuration at the benzylic carbon that becomes C(2) in the resulting propanol. The formation of more than two isomers, observed in reactions with aldehydes **2a**, **2f**, and **2d** (and perhaps **2e** too), means the lost of configurational integrity at such a carbon during the nucleophilic addition which must therefore take place with partial racemization.[§] The lost of stereoselectivity at C(2) may be explained by assuming that they are less efficient in the formation of the species **B** and a variable fraction of their molecules (very low in **2a** and **2f**) evolves by association to the less stable, but more reactive, species **A′** (route **c**, Fig. 1) without defined configuration. This fact would explain the partial racemization observed at benzylic carbon.[¶]

Concerning the stereoselectivity at C(1), the initial proposal established that the intramolecular evolution of **B** occurred via four-membered transition states (route **a**, Fig. 1). The higher stability of TS-**I** with respect to TS-**II**, determined by their steric interactions, was invoked to justify the 85:15 ratio of *anti*-**3a**:*syn*-**4a** observed in reaction with benzaldehyde. According to this model, steric interactions would be responsible of the observed de. The fact that similar de (70%) were obtained from **2a** (entry 1), **2b** (entry 2), and **2f** (entry 6) accounts for this proposal and suggests that electronic grounds have scarce relevance in the stereochemical course of the reaction. The slight improvement of the stereoselectivity observed for **2g** (76% de, entry 7) is also consistent although a higher increase in de should be expected on the basis of the quite higher size of the 1-naphtyl group with respect to the phenyl one. However, the decrease of the de obtained from the bulkiest aldehyde **2h** (34% de, entry 8) suggests something wrong in the initial proposal. This failure is even more evident from the results obtained with aliphatic aldehydes **2i–k**. They show a very low variation in their de despite the large differences in the size of the aliphatic residues (*n*-Bu<*i*-Pr<*t*-Bu). Moreover, they also show opposite stereoselectivity to that observed with aromatic aldehydes. This inversion in the sense of the stereoselectivity is not compatible with the initial model, which always predicts the predominance of the *anti*-**3** isomers due to steric reasons. Moreover, the small differences in de observed for the aliphatic aldehydes are not compatible with any explanation based on steric effects. These results indicate that the stereochemical course must account for the fact that aliphatic or aromatic nature of the aldehydes is more important than their size in the control of the stereoselectivity.[‖]

According to the expected tetrahedral structure of the lithium, the species **A** has two coordinating vacancies, which could be identified as pseudoequatorial (TS-**I** and TS-**II**) and pseudoaxial (TS-**III** and TS-**IV**). As we can see, from a steric point of view, TS-**I** and TS-**IV** are presumably the most stable ones, respectively yielding *anti*-**3** and *syn*-**4** isomers. From the obtained results it seems that aliphatic aldehydes prefer evolve through the axial vacancy (mainly affording the *syn* isomers), whereas the association of the aromatic aldehydes takes place mainly to the pseudoequatorial vacancy (the *anti* adducts are the mayor ones). The reasons determining the preference of the aldehydes for the pseudoaxial or pseudoequatorial approaches are not clear.[**] Taking into account that steric interactions are quite important in the four-membered rings, they could determine that TS-**I** and TS-**IV** were the only evolution ways through the routes **a** and **b**, respectively. However, they must have scarce significance in determining the pseudoequatorial or pseudoaxial approach to the organolithium, which in its term would be responsible of the stereoselectivity.

3. Conclusion

We have described the synthesis of enantiomerically pure 1-alkyl (or aryl)-2-pheny-1-propanols by reaction of different aldehydes with the lithium 2-*p*-tolylsulfinyl benzyl carbanions and further desulfinylation. Reactions from aliphatic and aromatic aldehydes containing electron donating groups are completely stereoselective at C(2), but exhibit a moderate stereoselectivity at C(1) which is mainly related to the aliphatic or aromatic character of the aldehydes.

4. Experimental

4.1. General experimental methods

Solvents and aldehydes were purified according to standard procedures. Reactions were monitored by TLC on commercially available precoated plates (Merck silica gel 60 F_{254}). Flash chromatography was performed with Merck silica gel

[§] The aldehydes showing this behavior are those with the lowest basicity at the carbonyl group, that is, with the lowest ability to be associated with the lithium.

[¶] It could also be explained by assuming the intermolecular attack of the species **A** to these aldehydes (without previous association to the metal) with inversion of the configuration at the benzylic carbon.

[‖] Toru *et al.* (see Ref. 13 observed a similar situation in the reaction of aldehydes with benzyllithium in the presence of bixoxazolines as chiral ligands. The authors do not give any explanation about this fact.

[**] We have investigated the stabilizing π-stacking interactions as a possible cause of the different behavior of aromatic and aliphatic aldehydes. TS-**III** is less stable than TS-**IV** from a steric point of view, but this situation can be inverted with aromatic aldehydes if we assume that π-stacking interactions could stabilize TS-**III** (R=Ar) with respect to TS-**IV**. This assumption could not be strictly supported by the experimental results because the stereoselectivity is scarcely modified (de ranged between 60 and 70%) by the substituent of the aromatic ring.

60 (230–400 mesh ASTM). Melting points were measured using a Gallemkamp apparatus in open capillary tubes. Specific rotations were measured at room temperature on a Perkin–Elmer 241 MC polarimeter and concentrations are expressed in g/100 mL. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-300 spectrometer (300 and 75 MHz, respectively) or Bruker WP-200-SY (200 and 50 MHz, respectively). Chemical shifts are reported in ppm and *J* values are given in Hz. The attributions are supported by double resonance experiments. IR spectra were obtained in film with a Bruker Vector 22 spectrometer (4000–400 cm^{-1}). Mass spectra were measured by electron impact (EI, 70 eV) or FAB with a VG AutoSpec spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 CHNS/O series II. Diffractions of X-rays were taken with a Siemens P4RA diffractometer.

4.2. General procedure for the reactions summarized in Table 1

A solution of *n*-BuLi 2.3 M in hexane (260 μL, 0.60 mmol, 1.2 equiv.) was added over *i*-Pr_2NH (126 μL, 0.90 mmol, 1.8 equiv.) in THF (3 mL) at 0 °C. After 45 min stirring, the mixture was cooled at −78 °C and a solution of the sulfoxide **1** (122 mg, 0.50 mmol, 1.0 equiv.) in THF (2 mL) was then added. After 1 h stirring, the electrophile (0.75 mmol, 1.5 equiv.) was added at −78 °C. When the reaction was completed (15 and 30 min for aromatic and aliphatic aldehydes, respectively) the mixture was hydrolyzed at that temperature (saturated NH_4Cl), extracted (CH_2Cl_2), dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash column chromatography.

4.2.1. (1*S*,2*S*,(*S*)*S*)-1-(*p*-Methoxyphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (3b). Eluant for chromatography: hexane/Et_2O/EtOAc 1:1:1. Yield: 68%. Mp 134–135 °C (Et_2O–hexane). $[\alpha]_D^{20}=-45.9$ (*c* 1, $CHCl_3$). IR: 3373, 2969, 1612, 1512, 1248, 1082, 1030 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, *J*=7.7 Hz), 7.55 (m, 2H), 7.46 (part of AA′BB′ system, 2H), 7.38 (m, 1H), 7.30 (part of AA′BB′ system, 2H), 7.22 (part of AA′BB′ system, 2H), 6.89 (part of AA′BB′ system, 2H), 4.41 (dd, 1H, *J*=6.5, 9.7 Hz, –C*H*–OH), 3.81 (s, 3H, –OCH_3), 3.73 (dq, 1H, *J*=6.9, 9.7 Hz, CH_3–C*H*–), 3.66 (d, 1H, *J*=6.5 Hz, –O*H*), 2.34 (s, 3H, CH_3–Ar), 0.75 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 145.7, 142.9, 141.5, 140.6, 135.8, 132.5, 129.7, 128.5, 127.9, 127.0, 124.9, 113.7, 79.5, 55.2, 41.5, 21.2, 18.2. Anal. calcd for $C_{23}H_{24}O_3S$: C, 72.60; H, 6.36; S, 8.43. Found: C, 72.66; H, 6.25; S, 8.21.

4.2.2. (1*R*,2*S*,(*S*)*S*)-1-(*p*-Methoxyphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (4b). Eluant for chromatography: hexane/Et_2O/EtOAc 1:1:1. Yield: 12%. Mp 162–163 °C (Et_2O–hexane). $[\alpha]_D^{20}=-84.2$ (*c* 0.5, $CHCl_3$). IR: 3383, 2931, 1611, 1512, 1247, 1083, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, 1H, *J*=1.6, 7.7 Hz), 7.34 (d quint, 2H, *J*=1.6, 7.7 Hz), 7.19 (s, 4H), 7.02 (dd, 1H, *J*=1.6, 7.3 Hz), 6.97 and 6.72 (AA′BB′ system, 4H), 4.80 (dd, 1H, *J*=2.4, 5.6 Hz, –C*H*–OH), 3.81 (quint, 1H, *J*=6.9 Hz, CH_3–C*H*–), 3.75 (s, 3H, –OCH_3), 3.27 (d, 1H, *J*=2.4 Hz, –O*H*), 2.37 (s, 3H, CH_3–Ar), 1.10 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 143.7, 142.5, 141.1, 140.8, 133.9, 131.3, 129.6, 128.0, 127.9, 127.2, 125.4, 113.0, 76.7, 55.0, 41.0, 21.2, 17.0. Anal. calcd for $C_{23}H_{24}O_3S$: C, 72.60; H, 6.36; S, 8.43. Found: C, 72.03; H, 6.29; S, 8.30. *m*/*z* (EI$^+$): 363 (M$^+$−OH, 27), 225 (30), 152 (44), 135 (100), 91 (32), 77 (40). HRMS calcd for $C_{23}H_{23}O_2S$: 363.1419, found 363.1427.

4.2.3. (1*S*,2*S*,(*S*)*S*)-1-(2-Naphthyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (3f). Eluant for chromatography: hexane/Et_2O/CH_2Cl_2 1:2:1. Yield: 62%. Mp 190–191 °C (Et_2O–hexane). $[\alpha]_D^{20}=+58.9$ (*c* 1, $CHCl_3$). IR: 3433, 2961, 1473, 1085, 1029 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88–7.73 (m, 5H), 7.64–7.56 (m, 3H), 7.53–7.37 (m, 5H), 7.19 (part of AA′BB′ system, 2H), 4.61 (dd, 1H, *J*=7.3, 9.7 Hz, –C*H*–OH), 4.14 (d, 1H, *J*=7.3 Hz, –O*H*), 3.87 (dq, 1H, *J*=6.9, 9.7 Hz, CH_3–C*H*–), 2.32 (s, 3H, CH_3–Ar), 0.76 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 142.8, 141.4, 141.1, 140.6, 133.1, 133.0, 132.6, 129.7, 128.7, 128.3, 128.1, 127.9, 127.6, 127.1, 126.0, 125.7, 124.7, 124.5, 80.2, 41.2, 21.2, 18.1. Anal. calcd for $C_{26}H_{24}O_2S$: C, 77.97; H, 6.04; S, 8.01. Found: C, 77.82; H, 5.82; S, 7.92.

4.2.4. (1*R*,2*S*,(*S*)*S*)-1-(2-Naphthyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (4f). Eluant for chromatography: hexane/Et_2O/CH_2Cl_2 1:2:1. $[\alpha]_D^{20}=-66.8$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (m, 1H), 7.73–7.63 (m, 3H), 7.55 (m, 1H), 7.48–7.42 (m, 2H), 7.38–7.29 (m, 2H), 7.19 (dd, 1H, *J*=1.6, 8.5 Hz), 7.13–7.05 (m, 5H), 5.00 (dd, 1H, *J*=2.0, 5.3 Hz, –C*H*–OH), 3.97 (dq, 1H, *J*=5.3, 6.9 Hz, CH_3–C*H*–), 3.50 (m, 1H, –O*H*), 2.33 (s, 3H, CH_3–Ar), 1.14 (d, 3H, *J*=6.9 Hz, CH_3–CH–).

4.2.5. (1*R*,2*R*,(*S*)*S*)-1-(2-Naphthyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (3′f). Eluant for chromatography: hexane/Et_2O/CH_2Cl_2 1:2:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–7.81 (m, 4H), 7.73 (d, 1H, *J*=8.1 Hz), 7.59 (dd, 1H, *J*=1.6, 8.5 Hz), 7.54–7.38 (m, 7H), 7.25 (part of AA′BB′ system, 2H), 4.83 (dd, 1H, *J*=4.4, 8.9 Hz, –C*H*–OH), 3.76 (dq, 1H, *J*=6.9, 8.9 Hz, CH_3–C*H*–), 2.71 (d, 1H, *J*=4.4 Hz, –O*H*), 2.36 (s, 3H, CH_3–Ar), 0.84 (d, 3H, *J*=6.9 Hz, CH_3–CH–).

4.2.6. (1*S*,2*S*,(*S*)*S*)-1-(1-Naphthyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (3g). Eluant for chromatography: hexane/Et_2O/CH_2Cl_2 1:1:1. Yield: 73%. Mp 186–187 °C (Et_2O–hexane). $[\alpha]_D^{20}=-50.8$ (*c* 1, $CHCl_3$). IR: 3436, 2968, 1595, 1474, 1266, 1085, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, 1H, *J*=8.1 Hz), 7.88–7.67 (m, 5H), 7.61 (dt, 1H, *J*=1.2, 7.7 Hz), 7.54–7.39 (m, 4H), 7.46 and 7.22 (AA′BB′ system, 4H), 5.37 (dd, 1H, *J*=6.5, 9.3 Hz, –C*H*–OH), 4.13 (dq, 1H, *J*=6.9, 9.3 Hz, CH_3–C*H*–), 3.75 (d, 1H, *J*=6.5 Hz, –O*H*), 2.33 (s, 3H, CH_3–Ar), 0.75 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 143.1, 141.3, 140.5, 139.3, 133.6, 132.4, 131.2, 129.5, 128.7, 128.3, 128.0, 127.9, 127.2, 125.8, 125.3, 124.8, 124.6, 123.5, 76.2, 41.4, 21.1, 18.5. *m*/*z* (EI$^+$): 383 (M$^+$−OH, 3), 244 (44), 225 (34), 152 (70), 135 (100), 129 (63), 91 (38), 77 (22). HRMS calcd for $C_{26}H_{23}OS$: 383.1470, found 363.1457.

4.2.7. (1*S*,2*S*,(*S*)*S*)-1-(2,6-Dimethylphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (3h). Eluant for

chromatography: hexane/EtOAc 3:1. Yield: 44%. Mp 158–159 °C (Et_2O–hexane). $[\alpha]_D^{20}=-138.3$ (*c* 1, $CHCl_3$). IR: 3343, 2972, 1474, 1264, 1084, 1008 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 1H, *J*=8.5 Hz), 7.64–7.57 (m, 2H), 7.52 and 7.24 (AA′BB′ system, 4H), 7.38 (ddd, 1H, *J*=2.4, 6.1, 8.5 Hz), 7.10–6.98 (m, 3H), 5.31 (dd, 1H, *J*=4.4, 10.1 Hz, –C*H*–OH), 4.29 (dq, 1H, *J*=6.9, 10.1 Hz, CH_3–C*H*–), 3.09 (d, 1H, *J*=4.4 Hz, –O*H*), 2.61 (bs, 3H, CH_3–Ph), 2.47 (bs, 3H, CH_3–Ph), 2.36 (s, 3H, CH_3–Ar), 0.79 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 143.8, 141.8, 140.5, 137.9, 137.0, 136.4, 132.6, 130.7, 129.6, 128.6, 128.3, 127.5, 127.4, 127.3, 124.9, 76.4, 38.8, 21.5, 21.2, 21.1, 18.3. Anal. calcd for $C_{24}H_{26}O_2S$: C, 76.15; H, 6.92; S, 8.47. Found: C, 76.11; H, 6.96; S, 8.57.

4.2.8. (1*R*,2*S*,(*S*)*S*)-1-(2,6-Dimethylphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-1-propanol (4h). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 26%. Mp 180–181 °C (Et_2O–hexane). $[\alpha]_D^{20}=-196.2$ (*c* 1, $CHCl_3$). IR: 3418, 2974, 1473, 1083, 1009 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (dd, 1H, *J*=1.2, 7.7 Hz), 7.41 (dt, 1H, *J*=1.2, 8.1 Hz, 1H), 7.14 (dt, 1H, *J*=1.2, 7.1 Hz), 7.01 (m, 4H), 6.85 (part of AA′BB′ system, 2H), 6.46 (d, 2H, *J*=8.1 Hz), 5.32 (dd, 1H, *J*=2.4, 10.1 Hz, –C*H*–OH), 4.61 (dq, 1H, *J*=6.9, 10.1 Hz, CH_3–C*H*–), 2.52 (d, 1H, *J*=2.4 Hz, –O*H*), 2.32 (s, 3H, CH_3–Ar), 2.27 (bs, 6H, 2×CH_3–Ph), 1.61 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 140.2, 138.4, 137.0, 131.5, 129.6, 129.3, 128.2, 128.1, 127.9, 127.4, 124.9, 75.2, 39.0, 21.2, 20.9, 19.5. Anal. calcd for $C_{24}H_{26}O_2S$: C, 76.15; H, 6.92; S, 8.47. Found: C, 76.10; H, 6.91; S, 8.53.

4.2.9. (2*S*,3*R*,(*S*)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-3-heptanol (3i). Eluant for chromatography: hexane/EtOAc 3:1. Yield 32%. $[\alpha]_D^{20}=-53.3$ (*c* 0.5, $CHCl_3$). IR: 3406, 2957, 2931, 1595, 1440, 1083, 1024, 1011 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, *J*=7.7 Hz), 7.52–7.42 (m, 2H), 7.44 and 7.23 (AA′BB′ system, 4H), 7.34 (m, 1H), 3.53 (m, 1H, –C*H*–OH), 3.42 (dq, 1H, *J*=6.9, 8.9 Hz, CH_3–C*H*–), 2.38 (d, 1H, *J*=7.3 Hz, O*H*), 2.36 (s, 3H, CH_3–Ar), 1.60–1.25 (m, 6H, (–CH_2–)$_3$), 1.01 (d, 3H, *J*=6.9 Hz, CH_3–CH–), 0.89 (t, 3H, *J*=7.3 Hz, CH_3–CH_2–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 142.9, 141.8, 140.8, 132.2, 129.7, 127.9, 127.8, 126.9, 125.1, 76.1, 40.0, 34.6, 27.0, 22.7, 21.3, 18.2, 14.0. *m*/*z* (FAB^+): 331 (MH^+, 100), 313 (71), 154 (59), 139 (16), 107 (22), 91 (28), 77 (22). HRMS calcd for $C_{20}H_{27}O_2S$: 331.1732, found 331.1739.

4.2.10. (2*S*,3*S*,(*S*)*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]-3-heptanol (4i). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 55%. Mp 114–115 °C (Et_2O–hexane). $[\alpha]_D^{20}=-52.0$ (*c* 0.5, $CHCl_3$). IR: 3396, 2956, 2931, 1440, 1083, 1006 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): (7.93 (dd, 1H, *J*=2.4, 6.9 Hz), 7.43 and 7.21 (AA′BB′ system, 4H), 7.41–7.32 (m, 3H), 3.30 (m, 1H, –C*H*–OH), 3.23 (m, 1H, CH_3–C*H*–), 2.36 (s, 3H, CH_3–Ar), 1.88 (d, 1H, *J*=4.4 Hz, O*H*), 1.35–0.88 (m, 6H, (–CH_2–)$_3$), 1.20 (d, 3H, *J*=6.9 Hz, CH_3–CH–), 0.79 (t, 3H, *J*=7.3 Hz, CH_3–CH_2–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 142.0, 141.7, 131.3, 129.9, 128.1, 127.1, 126.5, 126.0, 74.7, 40.0, 34.2, 28.4, 22.4, 21.3, 16.4, 13.9. *m*/*z* (FAB^+): 331 (MH^+, 100), 313 (84), 154 (13), 136 (15), 91 (11). HRMS calcd for $C_{20}H_{27}O_2S$: 331.1732, found 331.1730.

4.2.11. (3*R*,4*S*,(*S*)*S*)-2-Methyl-4-[2-(*p*-tolylsulfinyl)-phenyl]-3-pentanol (3j). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 21%. $[\alpha]_D^{20}=-52.4$ (*c* 0.5, $CHCl_3$). IR: 3396, 2930, 1469, 1129, 1082 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (dd, 1H, *J*=1.2, 7.7 Hz), 7.53–7.30 (m, 3H), 7.40 and 7.23 (AA′BB′ system, 4H), 3.47 (m, 1H, CH_3–C*H*–), 3.42 (m, 1H, –C*H*–OH), 2.83 (d, 1H, *J*=7.7 Hz, O*H*), 2.35 (s, CH_3–Ar), 1.88 (d quint, 1H, *J*=2.0, 6.9 Hz, –C*H*–(CH_3)$_2$), 0.98 (d, 3H, *J*=6.9 Hz, CH_3–CH–CH_3), 0.86 (d, 3H, *J*=6.9 Hz, CH_3–CH–CH_3), 0.84 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 141.8, 140.6, 132.7, 129.6, 128.7, 128.1, 126.7, 124.7, 80.4, 37.5, 29.7, 21.3, 20.5, 17.5, 13.5. *m*/*z* (FAB^+): 317 (MH^+, 100), 299 (39), 154 (41), 136 (30), 91 (11), 77 (13).

4.2.12. (3*S*,4*S*,(*S*)*S*))-2-Methyl-4-[2-(*p*-tolylsulfinyl)-phenyl]-3-pentanol (4j). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 54%. $[\alpha]_D^{20}=-75.7$ (*c* 0.5, $CHCl_3$). IR: 3415, 2962, 1469, 1083, 1041 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (dd, 1H, *J*=1.2, 7.3 Hz), 7.45–7.32 (m, 3H), 7.40 and 7.22 (AA′BB′ system, 4H), 3.53 (dq, 1H, *J*=4.8, 6.9 Hz, CH_3–C*H*–), 3.13 (m, 1H, –C*H*–OH), 2.34 (s, 3H, CH_3–Ar), 1.71 (bs, 1H, O*H*), 1.57 (sx, 1H, *J*=6.5 Hz, –C*H*–(CH_3)$_2$), 1.21 (d, 3H, *J*=6.9 Hz, CH_3–CH–), 0.83 (d, 3H, *J*=6.9 Hz, CH_3–CH–CH_3), 0.71 (d, 3H, *J*=6.5 Hz, CH_3–CH–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 142.1, 141.6, 141.3, 131.4, 129.9, 128.4, 127.4, 126.7, 126.3, 79.3, 36.9, 31.2, 21.3, 19.6, 17.8, 15.4. *m*/*z* (FAB^+): 317 (MH^+, 100), 299 (49), 154 (69), 136 (49), 91 (20), 77 (22).

4.2.13. (3*S*,4*S*,(*S*)*S*)-2,2-Dimethyl-4-[2-(*p*-tolylsulfinyl)-phenyl]-3-pentanol (3k). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 14%. Mp 127–128 °C. $[\alpha]_D^{20}=-51.2$ (*c* 0.5, $CHCl_3$). IR: 3406, 2956, 1471, 1131, 1082, 1007 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.66 (d, 1H, *J*=7.5 Hz), 7.51 (m, 2H), 7.43 and 7.25 (AA′BB′ system, 4H), 7.32 (m, 1H), 3.64 (dq, 1H, *J*=6.9, 8.9, Hz, CH_3–C*H*–), 3.30 (dd, 1H, *J*=7.7, 8.9 Hz, –C*H*–OH), 2.65 (d, 1H, *J*=7.7 Hz, O*H*), 2.38 (s, CH_3–Ar), 1.01 (d, 3H, *J*=6.5 Hz, CH_3–CH–), 0.97 (s, 9H, (CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 141.8, 141.3, 140.5, 132.4, 129.5, 128.6, 128.5, 126.5, 124.8, 83.2, 37.6, 36.1, 27.0, 21.2, 20.7. *m*/*z* (FAB^+): 331 (MH^+, 100), 313 (40), 154 (84), 139 (23), 91 (30), 77 (23), 57 (94). HRMS calcd for $C_{20}H_{27}O_2S$: 331.1732, found 331.1725.

4.2.14. (3*R*,4*S*,(*S*)*S*)-2,2-Dimethyl-4-[2-(*p*-tolylsulfinyl)-phenyl]-3-pentanol (4k). Eluant for chromatography: hexane/EtOAc 3:1. Yield: 44%. Mp 163–164 °C (Et_2O–hexane). $[\alpha]_D^{20}=-95.8$ (*c* 1, $CHCl_3$). IR: 3443, 2953, 1487, 1305, 1147, 1089, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (ddd, 2H, *J*=1.6, 8.1, 12.5 Hz), 7.42 (m, 1H), 7.39 and 7.22 (AA′BB′ system, 4H), 7.32 (dt, 1H, *J*=1.2, 7.7 Hz), 3.70 (dq, 1H, *J*=2.4, 7.3 Hz, CH_3–C*H*–), 3.35 (dd, 1H, *J*=2.4, 6.5 Hz, –C*H*–OH), 2.35 (s, CH_3–Ar), 1.59 (d, 1H, *J*=6.5 Hz, O*H*), 1.25 (d, 3H, *J*=7.3 Hz, CH_3–CH–), 0.82 (s, 9H, (CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 141.4, 141.3, 141.1, 131.8, 129.9, 128.4, 127.3, 126.7,

126.2, 81.3, 36.5, 35.4, 26.6, 21.3, 16.9. Anal. calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93; S, 9.70. Found: C, 72.55; H, 7.74; S, 9.39. *m/z* (FAB$^+$): 331 (MH$^+$, 100), 313 (45), 243 (15), 154 (7), 139 (5), 91 (8), 77 (51), 57 (11).

4.2.15. (2*S*,(*S*)*S*)-1-(2,6-Dimethylphenyl)-2-[2-(*p*-tolylsulfinyl)phenyl)]-propanone (5). The alcohol **3h** or **4h** was dissolved in dry CH_2Cl_2 and PCC (1.5 equiv.) was added. The mixture was stirred at room temperature during 4 h. The solvent was partially evaporated and the residue was chromatographed (hexane/EtOAc 1:1). Yield: 71%. Mp 106–107 °C (Et_2O–hexane). $[\alpha]_D^{20}=-48.2$ (*c* 0.75, $CHCl_3$). IR: 1698, 1466, 1085, 1033 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.51 (m, 2H), 7.47 (dt, 1H, *J*=1.6, 8.1 Hz), 7.35 (dt, 1H, *J*=1.6, 8.1 Hz), 7.15 (t, 1H, *J*=7.7 Hz), 7.03 and 6.92 (AA′BB′ system, 4H), 6.84 (d, 2H, *J*=8.1 Hz), 5.16 (q, 1H, *J*=6.9 Hz, CH_3–C*H*–), 2.32 (s, 3H, CH_3–Ar), 2.00 (s, 6H, 2×CH_3–Ph), 1.64 (d, 3H, *J*=6.9 Hz, CH_3–CH–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 144.7, 141.4, 140.9, 140.6, 138.1, 133.4, 131.6, 129.7, 128.9, 128.6, 128.0, 127.3, 124.7, 48.1, 21.3, 19.5, 18.5. Anal. calcd for $C_{24}H_{24}O_2S$: C, 76.56; H, 6.42; S, 8.52. Found: C, 76.73; H, 6.27; S, 8.06. *m/z* (EI$^+$): 376 (M$^+$, 5), 243 (10), 225 (24), 133 (100), 105 (36), 91 (10), 77 (13). HRMS calcd for $C_{24}H_{24}O_2S$: 376.1497, found 376.1491.

4.3. General procedure for desulfynilation of *p*-tolylsulfoxides with Raney Nickel summarized in Table 3

The sulfoxide was dissolved in a minimal amount of ethanol and excess of Raney Nickel was added. The reaction mixture was vigorously stirred at room temperature and was monitored by TLC. When no starting material remained, stirring was stopped and the solvent was carefully decanted and filtered on Celite. The solvent was evaporated and the product was obtained from the residue in high purity.

4.3.1. (1*S*,2*S*,(*S*)*S*)-1-Phenyl-2-[2-(*p*-tolylsulfinyl)-phenyl]-1-trimethylsilyloxypropane (8a). This compound was obtained employing the alcohol **3a**, trimethylsilyl triflate (2.0 equiv.), 2,6-lutidine (2.5 equiv.) and dichloromethane as solvent at 0 °C during 20 min. Yield: 94%. $[\alpha]_D^{20}=-21.1$ (*c* 1.68, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, 1H, *J*=7.6 Hz), 7.58–7.20 (m, 12H), 4.78 (d, 1H, *J*=7.0 Hz, –C*H*–OTMS), 3.85 (m, 1H, CH_3–C*H*–), 2.40 (s, 3H, CH_3–Ar), 1.13 (d, 3H, *J*=7.0 Hz, CH_3–CH–), −0.75 (s, 9H, (CH_3)$_3$–Si). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 144.5, 143.5, 142.1, 140.7, 131.1, 129.6, 128.1, 127.5, 126.9, 125.9, 125.6, 79.8, 43.1, 21.3, 19.8, −0.1.

4.3.2. (1*S*,2*S*)-1,2-Diphenyl-1-trimethylsilyloxypropane (9a). Yield: 70%. $[\alpha]_D^{20}=-82.5$ (*c* 0.71, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.15 (m, 10H), 4.60 (d, 1H, *J*=7.0 Hz, –C*H*–OTMS), 3.02 (quint, *J*=7.0 Hz, 1H, CH_3–C*H*–), 1.12 (d, 3H, *J*=7.0 Hz, CH_3–CH–), −0.20 (s, 9H, (CH_3)$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 143.7, 128.4, 127.6, 126.9, 126.8, 126.0, 82.2, 48.1, 17.5, −0.3.

4.3.3. (1*S*,2*S*,(*S*)*S*)-1-(2-Naphthyl)-2-[2-(*p*-tolylsulfinyl)-phenyl)]-1-trimethylsilyloxypropane (8f). This compound was obtained employing the alcohol **3f**, trimethylsilyl chloride (2.0 equiv.), 2,6-lutidine (2.5 equiv.) and dichloromethane as solvent at room temperature during one hour. Eluant for chromatography: hexane/AcOEt 1:1. Yield: 86%. $[\alpha]_D^{20}=-237.2$ (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86–7.27 (m, 13H), 7.13 (part of AA′BB′ system, 2H), 4.98 (d, 1H, *J*=8.1 Hz, –C*H*–OTMS), 3.97 (quint, 1H, *J*=7.0 Hz, CH_3–C*H*–), 2.35 (s, 3H, CH_3–Ar), 1.19 (d, 3H, *J*=6.9 Hz, CH_3–CH–), −0.22 (s, 9H, (CH_3)$_3$–Si).

4.3.4. (1*S*,2*S*)-1-(2-Naphthyl)-2-phenyl-1-trimethylsilyloxypropane (9f). Yield: 48%. $[\alpha]_D^{20}=-71.9$ (*c* 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.76 (m, 3H), 7.63 (bs, 1H), 7.48–7.45 (m, 2H), 7.40 (dd, *J*=1.6, 8.5 Hz, 1H) 7.30–7.18 (m, 5H), 4.75 (d, 1H, *J*=7.7 Hz, –C*H*–OTMS), 3.08 (quint, 1H, *J*=7.3 Hz, CH_3–C*H*–), 1.11 (d, 3H, *J*=6.9 Hz, CH_3–CH–), −0.19 (s, 9H, (CH_3)$_3$–Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 141.3, 133.0, 132.9, 128.5, 127.9, 127.7, 127.6, 127.5, 126.1, 125.8, 125.6, 125.5, 125.1, 80.5, 48.1, 17.6, −0.2.

4.3.5. (1*S*,2*S*)-1-(2-Naphthyl)-2-phenyl-1-propanol (6f). This compound was obtained employing **9f**, *n*-$Bu_4N^+F^-$ (2 equiv.) and THF as solvent, under inert atmosphere, at room temperature during 4 h. Eluant for chromatography: hexane/EtOAc 6:1. Yield: 78%. $[\alpha]_D^{20}=-41.7$ (*c* 0.9, $CHCl_3$). IR: 3423, 2961, 1451, 1020 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88–7.80 (m, 4H), 7.55–7.46 (m, 3H), 7.38–7.28 (m, 5H), 4.83 (d, 1H, *J*=8.6 Hz –C*H*–OH), 3.13 (dq, 1H, *J*=6.9, 8.6 Hz, CH_3–C*H*–), 1.96 (bs, 1H, O*H*), 1.10 (d, 3H, *J*=6.9 Hz, CH_3–CH–). *m/z* (EI$^+$): 262 (M$^+$, 2), 157 (100), 129 (61), 105 (13), 91 (8), 77 (12). HRMS calcd for $C_{19}H_{18}O$: 262.1358, found 262.1354.

4.3.6. (1*S*,2*S*,(*S*)*S*)-1-(1-Naphthyl)-2-[2-(*p*-tolylsulfinyl)-phenyl)]-1-trimethylsilyloxypropane (8g). This compound was obtained employing the alcohol **3g**, trimethylsilyl chloride (2.0 equiv.), 2,6-lutidine (2.5 equiv.) and dichloromethane as solvent at room temperature during one hour. Eluant for chromatography: hexane/AcOEt 1:1. Yield: 59%. $[\alpha]_D^{20}=-273.6$ (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (m, 1H), 7.87–7.22 (m, 14H), 5.65 (m, 1H, –C*H*–OTMS), 4.23 (m, 1H, CH_3–C*H*–), 2.38 (s, 3H, CH_3–Ar), 1.15 (m, 3H, CH_3–CH–), −0.23 (s, 9H, ((CH_3)$_3$–Si).

4.3.7. (1*S*,2*S*,(*S*)*S*)-1-(1-Naphthyl)-2-phenyl-1-trimethylsilyloxypropane (9g). Yield: 60%. $[\alpha]_D^{20}=-134.8$ (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.32 (m, 1H), 7.88 (dd, 1H, *J*=1.6, 7.7 Hz), 7.75 (dd, 1H, *J*=2.8, 6.5 Hz), 7.52 (dquint, 2H, *J*=1.6, 6.5 Hz), 7.39–7.33 (m, 2H), 7.26–7.16 (m, 5H) 5.36 (m, 1H, –C*H*–OTMS), 3.30 (m, 1H, CH_3–C*H*–), 1.15 (m, 3H, CH_3–CH–), −0.19 (s, 9H, ((CH_3)$_3$–Si). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.0, 139.6, 133.7, 130.7, 128.8, 128.6, 127.5, 126.0, 125.4, 125.1, 123.8, 77.6, 47.4, 18.3, −0.4.

4.3.8. (1*S*,2*S*)-1-(1-Naphthyl)-2-phenyl-1-propanol (6g).[14] This compound was obtained employing **9g**, *n*-$Bu_4N^+F^-$ (2 equiv.) and THF as solvent, under inert atmosphere, at room temperature during 4 h. Eluant for chromatography: hexane/EtOAc 6:1.Yield: 89%. $[\alpha]_D^{20}=-82.0$ (*c* 0.7, $CHCl_3$). IR: 3443, 2964, 1494, 1453, 1026 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.34 (dd, 1H, *J*=2.1, 7.5 Hz), 7.92–7.79 (m, 2H), 7.60–7.25 (m, 9H), 5.47 (dd, 1H, *J*=3.2, 8.1 Hz –C*H*–OH), 3.40 (quint, 1H,

J=7.0 Hz, CH_3–CH–), 1.97 (d, 1H, J=2.7 Hz, OH), 1.14 (d, 3H, J=7.0 Hz, CH_3–CH–). m/z (EI^+): 262 (M^+, 3), 157 (100), 129 (66), 105 (15), 91 (9), 77 (13). HRMS calcd for $C_{19}H_{18}O$: 262.1358, found 262.1355.

4.3.9. (2*S*,3*R*)-2-Phenyl-3-heptanol (6i).[15] Yield: 89%. $[\alpha]_D^{20}=-5.2$ (c 0.5, $CHCl_3$). IR: 3423, 2958, 1641, 1453, 1007 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H), 3.64 (m, 1H, –CH–OH), 2.73 (quint, 1H, J=7.3 Hz, CH_3–CH–), 1.63–1.25 (m, 7H, (–CH_2–)$_3$ and OH), 1.27 (d, 3H, J=7.3 Hz, CH_3–CH–), 0.89 (t, 3H, J=7.3 Hz, CH_3–CH_2-). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 128.5, 128.2, 126.6, 76.0, 46.1, 34.2, 27.9, 22.8, 18.0, 14.0. m/z (FAB^+): 175 (MH^+-H_2O, 52), 154 (69), 137 (55), 105 (100), 91 (63), 77 (19).

4.3.10. (2*S*,3*S*)-2-Phenyl-3-heptanol (7i).[15] Yield: 95%. $[\alpha]_D^{20}=-10.1$ (c 0.5, $CHCl_3$). IR: 3386, 2958, 1602, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.21 (m, 5H), 3.68 (m, 1H, –CH–OH), 2.79 (quint, 1H, J= 6.9 Hz, CH_3–CH–), 1.47–1.25 (m, 7H, (–CH_2–)$_3$ and OH), 1.32 (d, 3H, J=6.9 Hz, CH_3–CH–), 0.88 (t, 3H, J=7.3 Hz, CH_3–CH_2–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 128.5, 127.8, 126.4, 76.2, 45.5, 34.4, 28.2, 22.6, 15.3, 14.0. m/z (FAB^+): 175 (MH^+-H_2O, 75), 154 (18), 137 (22), 105 (100), 91 (53), 77 (11).

4.3.11. (3*R*,4*S*)-2-Methyl-4-phenyl-3-pentanol (6j).[16] Yield: 45%. $[\alpha]_D^{20}=-16.9$ (c 0.5, $CHCl_3$). IR: 3474, 2963, 1494, 1453 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.21 (m, 5H), 3.44 (m, 1H, –CH–OH), 2.85 (quint, 1H, J=7.3 Hz, CH_3–CH–), 1.80 (d sx, 1H, J=4.4, 6.9 Hz, –CH–(CH_3)$_2$), 1.26 (d, 3H, J=6.9 Hz, CH_3–CH–), 1.20 (d, 1H, J=4.4 Hz, OH), 1.03 (d, 3H, J=6.9 Hz, CH_3–CH–CH_3), 0.95 (d, 3H, J=6.9 Hz, CH_3–CH–CH_3,). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 128.6, 128.1, 126.6, 80.4, 43.4, 29.9, 20.4, 18.6, 15.3. m/z (EI^+): 178 (M^+, 4), 160 (10), 145 (27), 135 (10), 106 (100), 91 (88), 77 (27), 57 (79). HRMS calcd for $C_{12}H_{18}O$: 178.1358, found 178.1358.

4.3.12. (3*S*,4*S*)-2-Methyl-4-phenyl-3-pentanol (7j).[16] Yield: 47%. $[\alpha]_D^{20}=+11.5$ (c 0.5, $CHCl_3$). IR: 3426, 2963, 1494, 1453 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H), 3.41 (m, 1H, –CH–OH), 2.90 (quint, 1H, J=6.9 Hz, CH_3–CH–), 1.60 (m, 1H, –CH–(CH_3)$_2$), 1.40 (bs, 1H, OH), 1.31 (d, 3H, J=6.9 Hz, CH_3–CH–), 0.94 (d, 3H, J=6.5 Hz, CH_3–CH–CH_3); 0.91 (d, 3H, J=6.5 Hz, CH_3–CH–CH_3,). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 128.5, 127.7, 126.2, 81.1, 42.7, 30.1, 19.9, 16.7, 15.6. m/z (EI^+): 178 (M^+, 4), 160 (15), 145 (41), 106 (100), 91 (86), 77 (28), 57 (45). HRMS calcd for $C_{12}H_{18}O$: 178.1358, found 178.1360.

4.3.13. (3*S*,4*S*)-2,2-Dimethyl-4-phenyl-3-pentanol (6k).[17] Yield: 69%. $[\alpha]_D^{20}=+8.0$ (c 0.5, $CHCl_3$). IR: 3451, 2958, 1642, 1453, 1365 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.18 (m, 5H), 3.41 (m, 1H, –CH–OH), 3.05 (dq, 1H, J=4.0, 7.3 Hz, CH_3–CH–), 1.43 (bs, 1H, OH), 1.39 (d, 3H, J=7.3 Hz, CH_3–CH–), 0.86 (s, 9H, (CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 128.9, 128.3, 126.4, 83.4, 41.7, 35.9, 26.7, 22.4. m/z (EI^+): 192 (M^+, <1), 149 (43), 105 (25), 91 (23), 77 (18), 57 (100).

4.3.14. (3*R*,4*S*)-2,2-Dimethyl-4-phenyl-3-pentanol (7k).[17] Yield: 75%. $[\alpha]_D^{20}=+41.5$ (c 0.5, $CHCl_3$). IR: 3442, 2957, 1640, 1453, 1364 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.13 (m, 5H), 3.44 (dd, 1H, J=3.8, 5.4 Hz –CH–OH), 3.03 (dq, 1H, J=3.8, 7.0 Hz, CH_3–CH–), 1.49 (d, 1H, J=5.4 Hz, OH), 1.31 (d, 3H, J=7.0 Hz, CH_3–CH–), 0.94 (s, 9H, (CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 128.4, 127.4, 126.0, 83.0, 41.1, 36.1, 26.8, 16.4. m/z (EI^+): 192 (M^+, <1), 149 (8), 135 (12), 106 (100), 91 (62), 77 (22), 57 (91).

Acknowledgements

We thank CAICYT (Grant BQU2003-04012) for financial support.

References and notes

1. Ahlbrecht, H. *Methods of Organic Chemistry (Houben-Weyl). Additional and Supplementary Volumes to the 4th Edition*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, pp 664–695.
2. (a) Linnane, P.; Magnus, N.; Magnus, P. *Nature* **1997**, *385*, 799–801. (b) Magnus, N.; Magnus, P. *Tetrahedron Lett.* **1997**, *38*, 3491–3494. (c) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. (d) For recent review, see: Mikami, K.; Shimizu, M.; Zhang, H. C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917–2951.
3. (a) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, A. *Acc. Chem. Res.* **1996**, *29*, 552–560. For recent uses of (−)-sparteine, see: (c) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698. (d) Jang, D. O.; Kim, D. D.; Pyun, D. K.; Beak, P. *Org. Lett.* **2003**, *5*, 4155–4157.
4. García Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fisher, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2736–2737.
5. (a) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677–680. (b) García Ruano, J. L.; Alemán, *J. Org. Lett.* **2003**, *5*, 4513–4516.
6. In the crude obtained from **2c**, the identification of any compound was not possible. The signals of several alcohols, probably more than two, could be recognized in the ^1H NMR spectrum of the crude came from **2e**. They are not the major components and the products could not be isolated. Only the crude obtained from nitrile **2d** showed the presence of an 18:22:9:51 mixture of the four possible alcohols, according to eluting order, as major components (72%). Their relative stereochemistry was established by ^1H NMR (ratio *anti*–*syn*, 69:31). Nevertheless, their complete configurational assignment was not established because only the first and the last compounds could be separated.
7. Hirota, M.; Sekiya, T.; Abe, K.; Tashiro, H.; Karatsu, M. *Tetrahedron* **1983**, *39*, 3091–3099.
8. Crystallographic data (excluding structure factors) for the structures **3k** and **4k** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 221162 and 221163. Copies of the data can be

obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

9. The fact that the preferred conformation of one of these epimers displays the high sterically demandant 2,6-dimethylphenyl ring in *gauche* arrangement with respect to the sulfinylated ring suggests some kind of π-stacking interaction between the aromatic rings exhibiting complementary electronic density (donor–acceptor interaction).
10. Abraham, R. J.; Bakke, J. M. *Tetrahedron* **1978**, *34*, 2947–2951.
11. Moniz, W. B.; Poranski, Jr. C. F.; Hall, T. N. *J. Am. Chem. Soc.* **1966**, *88*, 190–192.
12. García Ruano, J. L.; García Paredes, C.; Hamdouchi, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2935–2944.
13. (a) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340–11347. (b) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 353–355.
14. Piazza, C.; Millot, N.; Knochel, P. *J. Organomet. Chem.* **2001**, *624*, 88–95.
15. Reetz, M. T.; Stanchev, S.; Haning, H. *Tetrathedron* **1992**, *48*, 6813–6820.
16. Alonso, E.; Guijarro, D.; Yus, M. *Tetrahedron* **1995**, *51*, 11457–11464.
17. Alonso, E.; Guijarro, D.; Martínez, P.; Ramón, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027–11038.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5393–5405

Synthesis, NMR, X-ray structural analyses and complexation studies of new Ag+ selective calix[4]arene based dipodal hosts—a co-complexation of neutral and charged species☆,☆☆

Narinder Singh, Manoj Kumar and Geeta Hundal*

Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, Punjab, India

Received 6 February 2004; revised 31 March 2004; accepted 22 April 2004

Abstract—New podands based on the *p-tert*-butylcalix[4]arene unit with substitution at the lower rim incorporating imine units, have been synthesized in high yield by simple condensation method. These podands have been shown to extract and transport Ag^+ selectively over alkali, alkaline earth metal cations, Zn^{2+}, Pb^{2+} and Hg^{2+} ions, from neutral aqueous phase to organic phase. In all the ligands the calix unit has been found to be present in a cone conformation except for the one having pyridine as end group, at the *ortho* position. It has been isolated in two conformations; cone and 1,2-alternate. To the best of our knowledge, this may be the first 1,3-lower rim substituted calix[4]arene to exist in a 1,2-alternate conformation and is among a few known compounds with this conformation in the general class of calix[4]arenes. A complex of this ligand, which happens to be the highest extractant of Ag^+ has been isolated and characterized using mass, ^1H and ^{13}C NMR spectroscopy's and elemental analysis. The spectroscopic evidence and molecular modelling studies performed on the complex suggest a participation of the imine and pyridine nitrogens and two of the ether oxygens in coordination to the metal ion. The X-ray crystal structures of three of the ligands establish the formation of inclusion complexes with polar acetonitrile solvent molecules. The ^1H and ^{13}C NMR spectra of all the compounds, taken in $CDCl_3$, show the presence of acetonitrile molecules in the cavity of the calix[4]arene, indicating inclusion of the neutral guest molecules in the solution phase as well. For one of the podands X-ray crystal structure has shown a formation of clatharate complex of chloroform with the ligand which has rarely been found in the case of calix[4]arenes.

1. Introduction

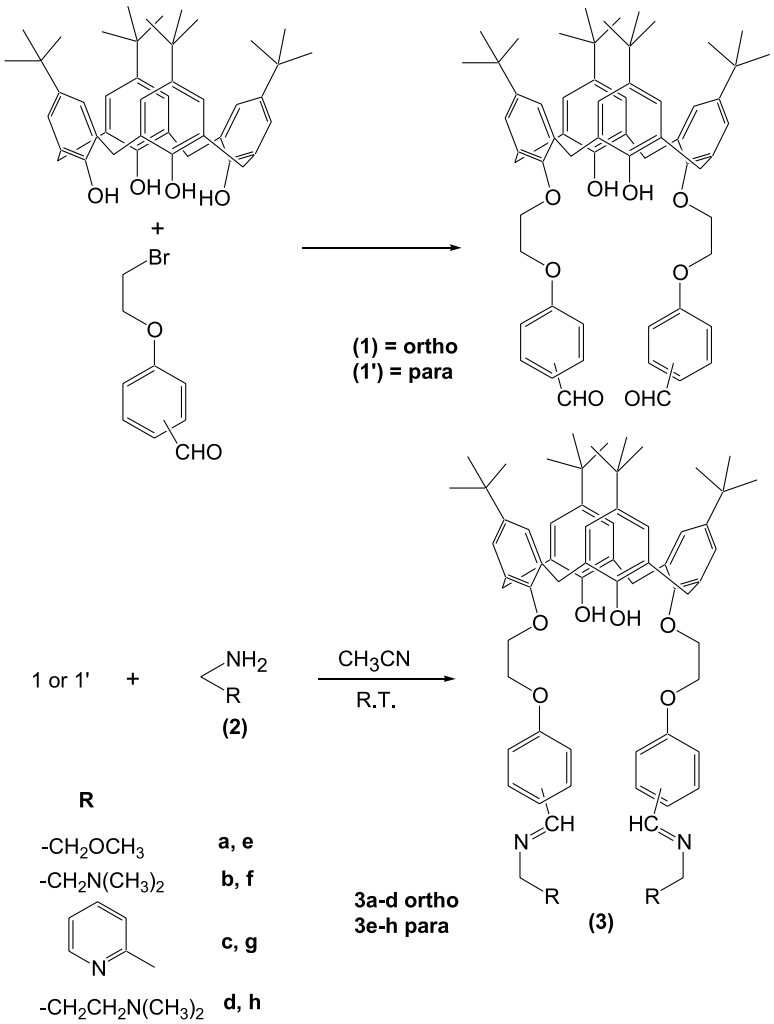
Modified calixarene derivatives having additional binding sites at the lower rim enhance the binding ability of the parent calixarene.[1] Synthesis of such polytopic receptors employs the organizing ability of calix[4]arene platform to bring together various binding subunits in a single molecule.[2] A number of receptors based on calix[4]arenes having selectivity for the alkali metals,[3] alkaline earth metals,[4] lanthanides[5] and actinides[5] have been reported. An area of increasing interest is the search for ligands, which are selective towards soft metal ions like mercury, lead, cadmium and silver. Calix[4]arene based polythia compounds have been seen to show very high Ag^+ selectivities against alkali and alkaline earth metals, lead and most of the transition metal cations.[6] In this context N and S atoms as soft donors are also expected to interact selectively with the soft Ag ion. An sp^2 hybridised N included in the host system, makes available a planar lone pair which is directional and can also be present as a part of the aromatic ring. Recently, Regnouf-de-Vains et al. have reported a new calix[4]arene based podand incorporating the 2,2′-bipyridyl moiety, where the preorganised disposal of four sp^2 nitrogens of the bipyridyl moiety plays an important role in extraction of silver ion from neutral aqueous phase to organic phase.[7] These results prompted us to synthesize new calix[4]arene based podands where apart from having other potential donors, the lower rim modifications use two imine sp^2 nitrogens (Scheme 1). Cyclic ligands, containing Schiff's bases formed on a calix[4] arene platform, have been used to some extent for cation recognition[8] but their open chained analogues are not very common[9,10] and have not been used for extraction of metal ions. As one of the factors on which cation binding by calix[4]arenes depends is the function of the substituents attached to the lower rim,[11] the podands have been synthesized with various end groups. The ligands provide a hard site (ether/hydroxyl O) for the hard alkali and alkaline earth metal cations and soft site (imine/amine N) for the soft Ag^+ ion. Thus they may behave as acyclic compartmental ligands with two differentiated sites for heterodinuclear complexes. At the soft site, the ligands provide an opportunity to compare the complexation behaviour of four aromatic sp^2 nitrogens of Regnouf's design with two imine nitrogens/two oxygens, two imine/

☆ CDRI Communication No. 6414.

☆☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2004.04.050.

Keywords: Calix[4]arene; Dipodal calix[4]arenas; Metal ion selectivities.
* Corresponding author. Tel.: +91-183-2258803x3196; fax: +911832258820; e-mail address: geeta.hundal@angelfire.com

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.04.050



Scheme 1.

two sp^3 nitrogens and two imine/two aromatic nitrogens. At the same time an effect on the complexation behavior may be studied by increasing the chain length between two kinds of nitrogens as in **3b**, **3d** and **3f**, **3h**.

2. Results and discussion

2.1. NMR data

The spectroscopic data for **3a**-**h** could be assigned fully. The conformations of the compounds were mainly derived from the signals of the bridging methylene protons in ^{1}H NMR as is usually done. A pair of doublets in ^{1}H NMR with J=12–13 Hz and peaks at ~δ 31 in ^{13}C NMR for $ArCH_2Ar$ protons and carbons, respectively, in **3a**,**d**-**h** shows that the calix[4]arenes exist in a cone conformation in all cases.[12] Imine linkages in these six compounds were determined from signals at 8.83, 8.82, 8.24, 8.24, 8.56 and 8.22 in ^{1}H NMR and 159, 168, 161, 161, 161 and 160 in ^{13}C NMR, respectively.[13] The $-CH_3$ protons of *t*-butyl groups appeared as two sharp singlets. These are well characterized from their mass spectra and C, H, N analysis as well. Compound **3b** in its ^{1}H NMR, however, showed a broad singlet for eight bridging methylene protons indicating the conformation to be 1,3 alternate. However, the peak for the methylene carbons in ^{13}C NMR did not appear at low field (~δ 38) as is required for the conformation to be 1,3-alternate[14] and was seen rather at δ 31.6. So the conformation may be cone or 1,3-alternate. The mass spectra for **3b** shows a base peak at $[2M+1]^+$ along with the parent ion peak at M^+ which indicates the possibility of a dimeric structure for this compound. The solubility behaviour of **3b** is also different than other *ortho* substituted compounds (**3a**,**c**-**d**) which readily dissolve in $CHCl_3$ whereas, **3b** takes about ten minutes to dissolve to give a clear solution. The fragmentation pattern of the latter is also different from the rest. However, no X-ray crystal structure is available to support a dimeric structure.

Compound **3c** was obtained in two different conformations, that is, cone and 1,2-alternate, in two separate preparations. These two conformers were recognized on the basis of ^{1}H and ^{13}C NMR, mainly from the signals of the bridging methylene groups. The cone conformer has two doublets at δ 3.27 and 4.33 with J=12 Hz for the bridging methylene groups and a singlet at δ 4.30 for OCH_2CH_2O protons in the ^{1}H NMR. The ^{13}C has two peaks at δ 31.5 and 31.8 corresponding to two types of bridging methylene carbons. The aromatic protons appeared as two singlets at δ 6.95 and

7.00 for four protons each. In the 1,2-alternate conformer, the bridging methylene groups gave two doublets at δ 3.28 and 4.35 with J=12 Hz and a singlet at δ 4.02 in the ^{1}H NMR. In the ^{13}C NMR the methylene carbon groups appear at δ 31.7 and 47.6 (as confirmed by DEPT-135 experiment). This value of δ 47.6 is different from what has been reported[14] for the 1,2-alternate conformation in the case of *p-tert*-butyl-*O*-acetylcalix[4]arene where the methylene carbons appeared as two signals at δ 30.2 and 38.7. It is reported there that when the phenol rings beside each methylene are in the cone conformation, the methylene signals appear around δ 31, whereas they appear around δ 38 and 31 in the 1,2-alternate and partial cone conformation and around δ 38 in the 1,3-alternate conformation. The origin of the ca. 6 ppm difference in the chemical shifts for the *syn* and *anti* orientations of the phenol rings has been reported to be steric in nature.[14] In the present case this difference has been seen to have increased considerably because of greater steric effects, owing to the fact that here the lower rim is 1,3-disubstituted by much longer and rigid substituents compared to the reported case of *p-tert*-butyl-*O*-acetylcalix[4]arene which is symmetrically substituted at all four lower oxygens with acetyl group. It is well known that the replacement of phenolic hydrogens with sufficiently large groups makes the calix[4]arenes conformationally inflexible and they exist in one discrete conformation.[15,16] Although complete conformational interconversion in a calix[4]arene is stopped the moment an R group larger than ethyl group is introduced, partial conformational change remains possible until the fourth R group is added. Thus, in spite of the fact that the preferred conformation for the ligands is a cone, the possibility of the conversion cannot be denied when there are two unsubstituted hydroxyl groups still present, which can undergo inversion. The formation of different conformations is interpreted in terms of a competition between the rate of conformational interconversion and rate of derivatization. The formation of the 1,3-substituted aldehyde (**1**) from the basic *t*-butylcalix[4]-arene may be considered a stepwise reaction. After the substitution at one of the hydroxyl groups, the stabilizing cyclic network of intramolecular H-bonding interactions is disrupted. At this stage, if two of the –OH groups invert and the second substitution takes place after the inversion, then there is a possibility of the formation of a 1,2-alternate conformer as well. It is to be noted that the number of intramolecular H-bonding interactions is two, both in the case of a cone and 1,2-alternate conformation and one and zero in the case of partial cone and 1,3-alternate conformations for a 1,3-disubstituted calix[4]arene, respectively. Thus there is a fair possibility of formation of 1,2-alternate conformation for **3c** if (**2**) reacts with (**1**) in this conformation. Although it is yet not clear how the 1,2-alternate conformer is formed, it has been formed in good yield and its NMR is unambiguous. To the best of our knowledge **3c** becomes the first 1,3-disubstituted calix[4]-arene in this conformation and among a few compounds with this conformation, in the general class of calix[4] arenes.[12,14,15,17] The remaining signals appear at almost the same positions in both the conformers. The CH_2 group which is flanked by the imine group on one side and *o*-pyridine on the other (marked as NCH_2) appears as a singlet at δ 4.64. Two *ortho* protons in two py groups appeared as a broad singlet at δ 8.55. The imine protons appeared at a low field (δ 9.03). So as to ascertain the assignment, a ^{1}H NMR with D_2O exchange was taken in the case of 1,2-alternate conformer which showed that the peak present at δ 7.83 in the previous ^{1}H NMR was absent in D_2O while the peaks at δ 8.54 and 9.02 remained. Therefore, δ 7.83 and 7.87 were marked as ArO in the 1,2-alternate and cone conformer, respectively. Two singlets at δ 2.30 and 1.61 also shifted on D_2O exchange to 1.85 and 1.43, respectively, hence these are assigned as solvent peaks for the entrapped acetonitrile molecules in 1,2-alternate conformer. Similar peaks occurred at δ 1.78 and 1.42 in the cone conformation. A low field shift of the imine proton here may be due to the combined effects of the attached py group and H-bonding interactions of imine protons with the $-OCH_2$ group and pyridine N, simultaneously. Such dual H bonding interactions would be absent in the *para* compound **3g** and the imine proton appears at δ 8.56 in the latter. In the IR spectra; peaks at 1640–1645 cm^{-1} for all the compounds correspond to the imine linkage and a broad peak (half band width ~180 cm^{-1}) around 3350–3400 cm^{-1} shows the presence of the OH group.

The stoichiometry of the air sensitive complex of the cone conformer of **3c** was confirmed to be **3c**·$AgNO_3$ by elemental analysis and mass spectrum which showed a base peak at 1232 due to [**3c**·Ag]$^+$ (Fig. 1). The complex was sparingly soluble in $CDCl_3$. The ^{1}H NMR of the complex showed significant differences from that of **3c** itself. The imine protons split into two signals and shifted to a much lower field appearing at δ 10.38, 10.49. Similarly two protons at *ortho* position to the py also appeared separately at δ 8.58 and 8.72. The conformation of the calix[4]arene seems to have changed from a cone in the free ligand to an unsymmetrical conformation, which is more likely to be a partial cone as is evident from the $ArCH_2Ar$ signals appearing as four doublets. Three of them lie at δ 3.23 (J=16 Hz), 3.30 (J=12 Hz) and 4.00 (J=16 Hz), whereas the fourth one is masked under the signal for $-OCH_2CH_2O-$ protons in the range δ 4.28–4.40. The splitting of *t*-butyl group resonances into three also reveals that Ag^+ is perturbing the conformational architecture of calixarene to make it more unsymmetrical. The CH_2 group lying between imine N and py group shifts upfield and splits into two signals, one of which lies at δ 3.38 and the second appears at δ 4.43. The inequivalence of these two methylene groups is also evident from ^{13}C spectra of the complex which shows two peaks at δ 50.9 and 61.2, these are significantly shifted upfield from being a single peak at δ 73.9 in **3c**. Similarly the $-OCH_2CH_2O-$ carbons also

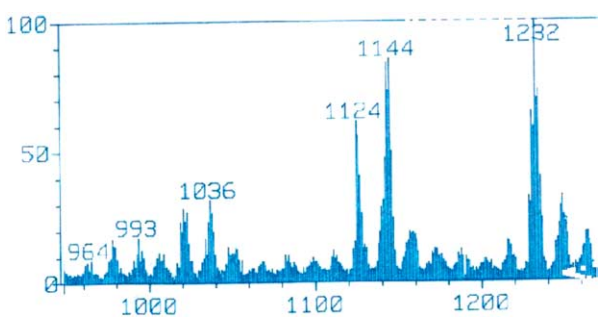


Figure 1. Showing the [**3c**+Ag]$^+$ peak in the partial Mass spectrum of the Ag^+ complex.

Table 1. Showing the changes in chemical shift values on complexation of Ag^+ with **3c**. ($\Delta\delta$) in ppm

	$-NCH_2$	OCH_2CH_2O-	$-CH{=}N$	*o*-H-Py
^{1}H NMR	−0.21, −1.26	−0.02, 0.10	1.35, 1.44	0.02, 0.17
^{13}C NMR	−12.6, −23.0	−6.9, −12.4	10.6, 10.4	0.1, 6.9

appear shifted to δ 54.2 and 59.9. The participation of the imine group in coordination to Ag^+ is also supported by a downfield shift of imine carbons to two peaks at δ 170.2 and 171.0 from δ 159.6 in **3c**. From the downfield shift and splitting of imine protons, splitting and downfield shift of one of the pyridine protons (*ortho* to N of py), accompanied by the splitting and upfield shifting of two NCH_2 signals, splitting of $-OCH_2CH_2O-$ protons and carbons (Table 1), it can be inferred that the ligand binds the Ag^+ ion through both the imine nitrogens and two ether oxygens *ortho* to the imine group and through one or both of the pyridine nitrogens giving a 5–6 coordinated Ag^+ complex. There is not any significant shift in the ArOH signal, which shows its non-participation in the bonding. An energy minimized computer generated structure calculated by using SPARTAN'02, with MMFF94 force field calculations[18] for the equilibrium conformation (Fig. 2) also supports this mode of binding. The most stable conformation has been found to be an inward flattened partial cone conformation[19] from these calculations. The NMR spectrum of a 1:1 complex of **3c** with Na^+ showed absolutely no shifts for imine, NCH_2 and py groups, a shift $\Delta\delta$ −0.02 and −0.03 for $ArCH_2Ar$ and OCH_2CH_2O- protons, respectively and a downfield shift $\Delta\delta$ 1.1 for the −OH protons was seen. This indicates that the ligand has very small affinity for Na^+ which prefers to go to the hard site constituted by the ether and hydroxyl oxygens.

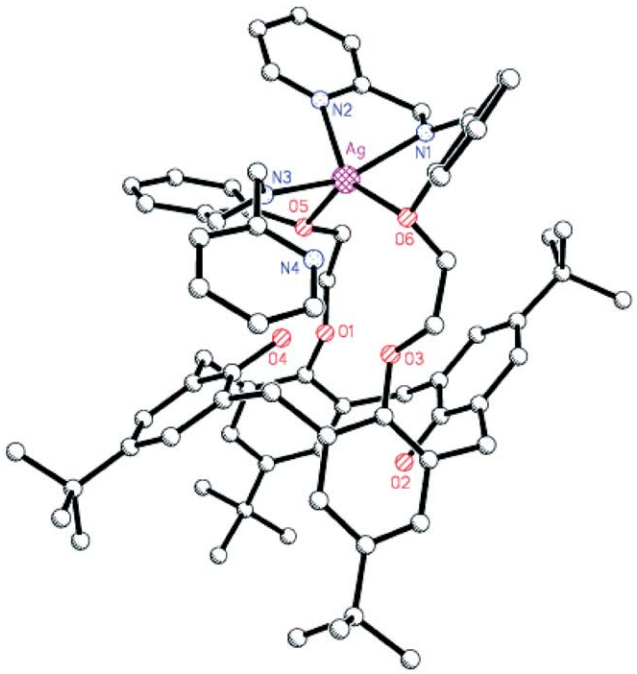


Figure 2. Showing energy minimized structure of the Ag^+ complex of **3c**.

2.2. X-ray crystallographic studies

Table 2 gives the crystal data and refinement parameters for the three structures. In the solid state **3a** crystallizes as a 1:3 complex of calix[4]arene acetonitrile. The final molecular structure is shown in Figure 3. The calix[4]arene is present in a symmetrical cone conformation with a two fold axis passing through the center of the cone. The torsion angles χ, φ about the bridgehead methylene carbons C7 and C14 alternate between + and − (82.1(5), −92.1(5) and 86.7(5), −76.6(5)°, respectively) confirming a cone conformation of the calix.[1c] The bridgehead methylene groups lie in an approximate plane (dev. from the plane being ±0.08 Å) and the phenyl ring 'A' (C1–C6) and ring 'B' (C8–C13) are making dihedral angles 114.2(1) and 124.6(1)°, respectively with this plane. The torsion angles and the dihedral angles

Table 2. Showing crystal data and refinement parameters

	3a	**3d**	**3e**
Empirical formula	$C_{74}H_{95}N_5O_8$	$C_{76}H_{101}Cl_6N_5O_6$	$C_{70}H_{89}N_3O_8$
Formula weight	1182.55	1393.32	1100.44
Temperature	293(2) K	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic	Triclinic
Space group	*C*2/*c*	*Pbcn*	*P*−1
Dimensions	*a*=12.402(6) Å, α=90°	*a*=27.639(5) Å, α=90°	*A*=11.732(5) Å, α=86.07(5)°
	b=29.743(9) Å, β=104.21(5)°	*b*=15.741(5) Å, β=90°	*b*=12.024(5) Å, β=85.24(5)°
	c=19.944(6) Å, γ=90°	*c*=18.367(5) Å, γ=90°	*C*=24.266(5) Å, γ=72.32(5)°
	V=7132(5) Å^3	*V*=7991(4) Å^3	*V*=3247(2) Å^3
	Z=4	*Z*=4	*Z*=2
Density (calc)	1.101 mg/m^3	1.158 mg/m^3	1.126 mg/m^3
μ	0.071 mm^{-1}	0.265 mm^{-1}	0.073 mg/m^3
F(000)	2552	2968	1188
Crystal size	0.20×0.10×0.10 mm	0.15×0.12×0.1 mm	0.25×0.15×0.15 mm
Range for data collection (θ)	1.73–24.99°	1.47–24.99°	1.69–22.55°
Reflections collected	6495	3915	7992
Independent reflections	6195	3915	7487
Data/restraints/parameters	6195/0/395	3915/6/233	7487/18/808
Goodness-of-fit	1.016	1.370	1.037
Final *R* indices [$I>2\sigma(I)$]	*R*1=0.0838, *wR*2=0.2250	*R*1=0.1664, *wR*2=0.4098	*R*1=0.0827, *wR*2=0.2034
R indices (all data)	*R*1=0.1930, *wR*2=0.3058	*R*1=0.3129, *wR*2=0.4984	*R*1=0.1728, *wR*2=0.2793
Largest diff. peak and hole	0.339 and −0.289 e Å^{-3}	1.190 and −0.517 e Å^{-3}	0.517 and −0.343 e Å^{-3}
Deposition number	CCDC 200395	CCDC 225240	CCDC 225239

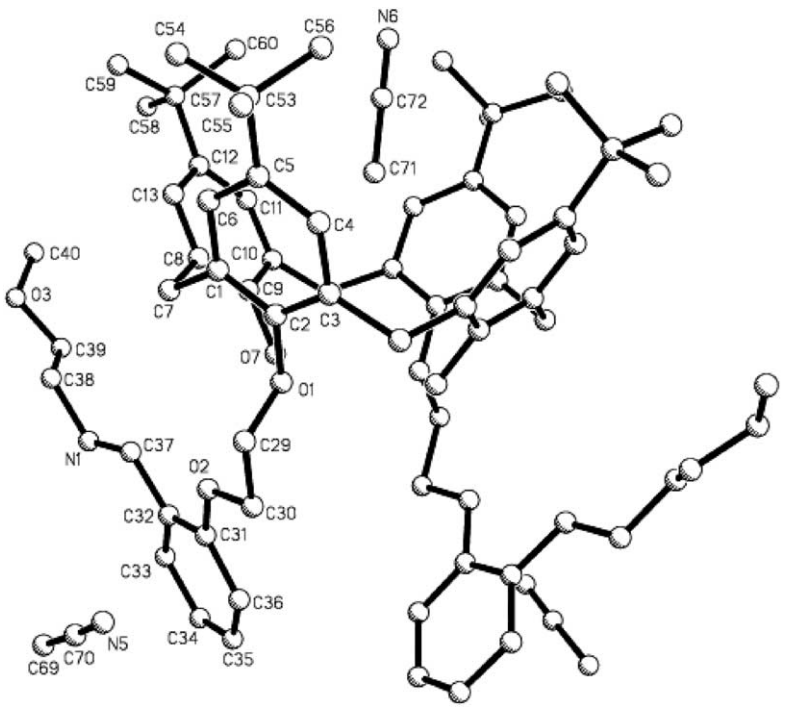


Figure 3. Showing a perspective view of the crystal structure of **3a** and its labelling scheme. The hydrogen atoms have been omitted for clarity.

found are comparable to ±90° and 123°, respectively, found in the structure of *p-tert*-butylcalix[4]arene compound (LBC).[20] The cone conformation is further stabilized by the two intramolecular H-bonds (Table 1) between the hydroxyl oxygen O7 and the substituted oxygen O1 (O7···O1 2.793(4) Å, H7C···O1 1.97 Å, ∠O7–H7C···O1 177°). It indicates that the substitution has brought up only slight changes in the open cone conformation of the basic calix unit. This cone conformation helps in the formation of an intracavity inclusion complex of **3a** with one acetonitrile molecule. This solvent molecule lies at the two fold axis of rotation and thus is truly in the center of the cavity. The hydrophobic end of the solvent molecule enters into the hydrophobic annulus provided by the calix[4]arene unit and its polar end remains outside the cavity. Inside the cavity the solvent molecule is held by C–H···π interactions[21] between the methyl hydrogens of the acetonitrile and the centroids of phenyl rings of the calix (C71···A) and C71···B) being 3.58 and 3.75 Å, respectively). The nitrogen N6 of this solvent molecule is interacting intramolecularly with the methyl protons of the *t*-butyl groups having C56···N6 3.720(9) Å, H56C···N6 2.81 Å and ∠C56–H6C···N6 158°). The remaining two solvent molecules are exhibiting multimolecular inclusion behavior whereby the guest solvent molecule is accommodated in the continuous channels within the crystal lattice. The two solvent molecules are being held in the lattice by weak C–H···N5 interactions. An intramolecular interaction exists with methylene C30 (C30···N5 3.507(11) Å, H30B···N5 2.7 Å, ∠C30–H30B···N5 138°) and three intermolecular interactions with phenyl C4 and C11 and methyl C55 (C4···N5^{i} 3.591(9) Å, H4A···N5^{i} 2.68 Å, ∠C4–H4A···N5^{i} 166°, C11···N5^{ii} 3.643(9) Å, H11A···N5^{ii} 2.72 Å, ∠C11–H11A···N5^{ii} 171°, C55···N5^{i} 3.882(13) Å, H55C···N5^{i} 2.94 Å, ∠C55–H55C···N5^{i} 167°, where i=$-x+2$, $-y$, $-z+2$ and ii=x, $-y$, $z-0.5$). These lattice solvent molecules are also showing intermolecular H-bonding interactions from their methyl hydrogens to N6 of the solvent molecule inside the cavity with C69···N6^{iii,iv} 3.378(13) Å, H69C···N6^{iii,iv} 2.93 Å, ∠C69–H69C···N6^{iii,iv} 110° (where iii=$x-0.5$, $y-0.5$, z and iv=$-x+0.5+1$, $y-0.5$, $-z+0.5+1$). There are also C–H···π interactions present between the methyl hydrogens of these acetonitrile molecules and the phenyl ring 'C ' (C31–C36) of the podand C69···C being 3.74 Å and H···C being 3.26 Å). The ring C is parallel to A and perpendicular to B while C30–O2–C31–C32 is *trans* and O2–C31–C32–C37 is *cis*. This conformation of the substituents at the lower rim makes the two ends of this dipodal molecule diverge from each other and provides two independent pseudo-cavities for the metal ion with low coordination number. There is no π–π interaction between two C phenyl rings as the minimum centroid to centroid distance between them is 5.48 Å.

Compound **3d** in the solid state crystallizes as a ternary complex 3d:acetonitrile:chloroform in the ratio 1:1:2. The final molecular structure is shown in Figure 4. It is also a symmetrical molecule with a two fold axis passing through the cavity of the calix, similar to **3a**. Here also the calix[4]arene is present in a symmetrical cone conformation as indicated by the torsion angles about the bridgehead methylene carbons C7 and C14 being −92, 81 and −70, 86°, respectively. The bridgehead methylene groups lie in an approximate plane (dev. from the plane being ±0.13 Å) and the phenyl rings A and B are making dihedral angles 126, and 111°, respectively with this plane. A strong intramolecular H-bonding is found between the hydroxyl oxygens O1 and ether oxygen O2 with O1···O2 2.736(11) Å, H1A···O2 1.92 Å, ∠O1–H1A···O2 172°. An acetonitrile molecule forms an intracavity inclusion complex with the calix, thereby lying in its cavity exactly at

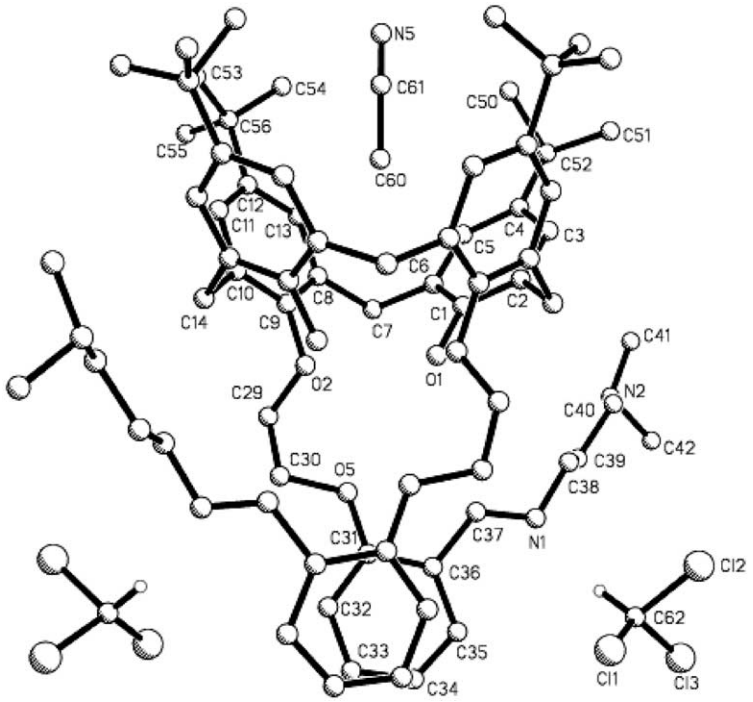


Figure 4. Showing a perspective view of the crystal structure of **3d** and its labelling scheme. The hydrogen atoms have been omitted for clarity.

the center as it is present on a symmetry element The solvent molecule is held in place by two intramolecular C54–H54C···N5 interactions with (C54···N5 3.92 (2) Å, H54C···N5 2.97 Å, ∠C54–H54C···N5 167°) and eight intermolecular C–H···N5 interactions with carbons of phenyl ring C, (C34···N5^{i,ii} 3.36(3) Å, H34A···N5^{i,ii} 2.86 Å, ∠C34–H34A···N5^{i,ii} 115°, and C33–H33A···N5^{i,ii} 3.30(2) Å, H33A···N5^{i,ii} 2.75 Å, ∠C33–H33A···N5^{i,ii} 118°, where i=x, y+1, z and ii=−x+1, y+1, −z+1+1/2). The hydrophobic end of acetonitrile faces the hydrophobic cavity of the calix[4]arene and is stabilized by C–H···π interactions between the methyl group and the phenyl rings of the calix. The distances of the centroids of ring A and B to methyl carbon C60 are 3.81 and 3.49 Å, respectively. Thus this solvent molecule is held strongly inside the cavity forming a true intracavity inclusion complex like **3a**. Formation of a clatharate complex of **3d** with $CHCl_3$ is a unique feature of the compound. Two molecules of $CHCl_3$ are held in the voids in the crystal structure of the compound. These are bonded to the molecule by an inter-molecular C–H···N interaction. Thus the $CHCl_3$ molecule is donating a H-bond to the imine nitrogen with C62···N1 3.21 (2) Å, H62A···N1 2.24 Å and ∠C62–H62A···N1 169°. There exists an intermolecular C32–H32A···Cl1 H-bonding interaction with C32···Cl1 3.79 (3) Å, H32A···Cl1 2.94 Å and ∠C32–H32A···Cl1 153°. Intermolecular H-bonding is also present between methylene C29 and secondary amine N2 and bridge head methylene C7 and ether oxygen O5. There is an intramolecular π···π interaction present between two C phenyl rings with a centroid to centroid distance of 3.75 Å. The latter brings the two ether oxygens, present *ortho* to the imine group, close to each other with O···O non-bonding distance between them as 4.11 Å.

In the solid state **3e** crystallizes as a 1:1 complex of calix[4]arene acetonitrile. The final molecular structure is shown in Figure 5. The calix[4]arene is present in a symmetrical cone conformation as indicated by the torsion angles χ, φ about the bridgehead methylene carbons C7,

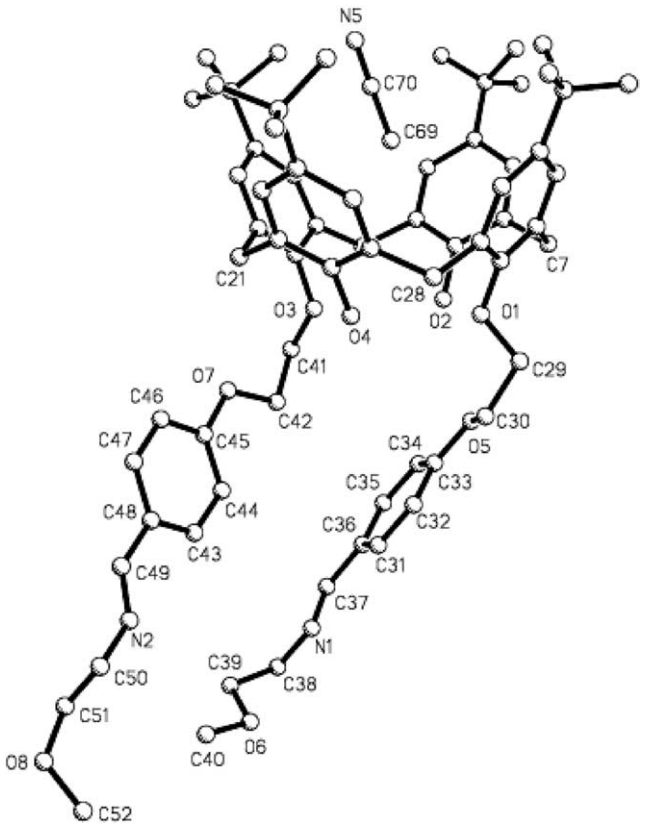


Figure 5. Showing a perspective view of the crystal structure of **3e** and its labelling scheme. The hydrogen atoms have been omitted for clarity.

C14, C21 and C28. They alternate between + and − being −84.1(8), 86.8(8), −78.1(9), 77.4(9), 86.0(8), 91.9(8), −82.1(9) and 74.4(8)°, respectively. The bridgehead methylene groups lie in an approximate plane (dev. from the plane being ±0.12 Å) and the phenyl rings A, B, E (C15–C20) and F (C22–C27) are making dihedral angles 114.5(2), 117.1(2), 116.2(1) and 123.0(2)°, respectively with this plane. The cone conformation is further stabilized by the two strong intramolecular H-bonds between the hydroxyl oxygens O2, O4 and the substituted oxygens O1 and O3. O2 is H-bond donor to O1 with O2···O1 2.817 (7) Å, H2A···O1 1.99 Å, ∠O2–H2A···O1 176° and O4 is donating to O3 with O4···O3 2.747(6) Å, H4A···O3 1.93 Å and ∠O4–H4A···O3 177°. The cone conformation facilitates formation of an intracavity inclusion complex of **3e** with an acetonitrile molecule. This solvent molecule lies in the center of the cavity of the calix with its hydrophobic end pointing towards the cavity. Inside the cavity it is held by C–H···π interactions between the methyl group of the acetonitrile and the phenyl rings A, B and E, with centroids to H distances as H69A···A 2.76 Å, H69B···B 2.76 Å, H69C···E 2.85 Å and ∠C69–H69···centroids as 152, 152 and 139°, respectively. Nitrogen of the solvent N5 is having H-bonded to methyl group C67 (C67···N5 3.76(2) Å, H67A···N5 2.82 Å and ∠C67–H67A···N5 167°) and methyl group C56 (C56···N5^{i} 3.57 (4) Å, H56B···N5^{i} 2.80 Å and ∠C56–H56B···N5^{i} 138°, i=−x+1, −y+1, −z+1). In the pendant arms ring C and ring D (C43–C48) are planar with a dihedral angle of 68.4(2)° between them. The shortest centroid to centroid distance between C and D is 4.74 Å which is longer than expected for a π···π interaction. However, there is a C–H···π interaction between ring C and methylene C42 with centroid C···C42 3.816 Å, C···H42B 3.08 Å and ∠C···H42B–C42 133°. The torsion angles for the two 1,4-dioxa units in the pendant arms are in the sequence *aga* and are slightly different in the two chains. C16–O3–C41–C42 −140.0° (7) is smaller than C2–O1–C29–C30 158.6° (7) whereas, O3–C41–C42–O7 71.6° (8) is larger than O1–C29–C30–O5 65.8° (9) which brings C42 under the influence of π cloud of ring C and rotates ring D with respect to ring C. The $-NCH_2CH_2OCH_3$ terminus of the two pendant arms also show different torsion angles. N1–C38–C39–O6 −70° (1) and C38–C39–O6–C40 is 170.9° (9) but N2–C50–C51–O8 is 168° (1) and C50–C51–O8–C52 is −87° (1) showing that they have opposite conformations which may be due to the steric hindrance. It gives a short intramolecular C40–H40C···N2 contact (C40···N2 3.63 (1) Å,

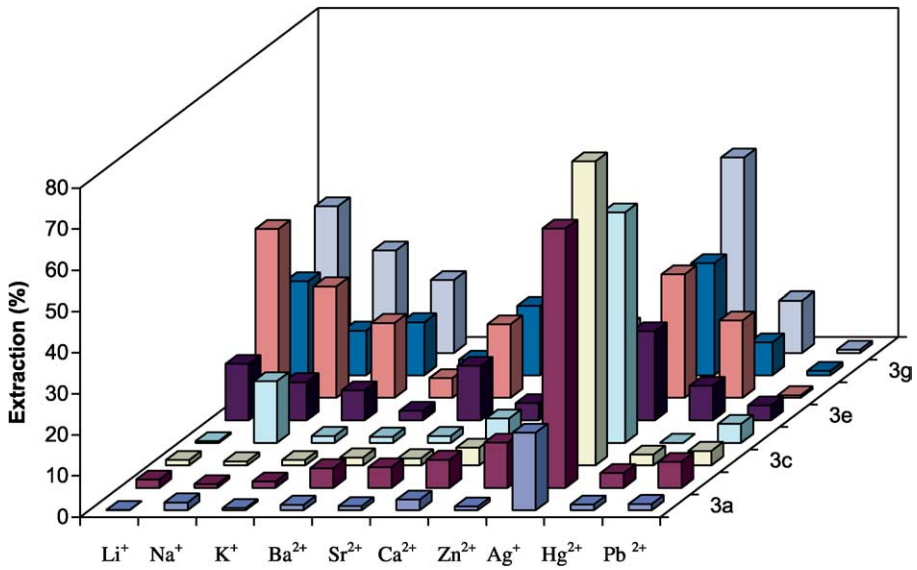


Figure 6. Showing a plot of extraction (%) of various ions versus ligands.

Table 3. Showing extraction[a] (%) and (Transport rate[b] (×10^8 mol/24 h)

	3a	3b	3c	3d	3e	3f	3g	3h
Li^+	0.1 (10)	2 (17)	1.3 (16)	0.4 (20)	13.7 (150)	41 (130)	22.8 (120)	35.6 (160)
Na^+	1.9 (26)	0.9 (52)	1 (49)	15 (37)	9.3 (460)	27 (540)	10.9 (530)	24.8 (360)
K^+	0.5 (31)	1.5 (34)	1.3 (49)	1.7 (37)	7.3 (470)	18.2 (420)	12.9 (480)	17.6 (360)
Ba^{2+}	1.3 (800)	4.8 (600)	1.9 (700)	1.5 (657)	2.3 (713)	4.8 (735)	3.8 (658)	3.9 (748)
Sr^{2+}	1 (560)	5 (430)	1.7 (467)	1.7 (487)	13.3 (556)	17.9 (587)	16.9 (414)	17.8 (597)
Ca^{2+}	2.6 (487)	6.8 (502)	4.3 (587)	5.9 (537)	4.2 (497)	6.1 (501)	1.3 (489)	6.4 (515)
Zn^{2+}	0.9 (—)	11 (—)	4.3 (—)	9.8 (—)	15.4 (—)	10.96 (—)	6.7 (—)	11.7 (—)
Ag^+	18.9 (2840)	63 (1870)	73.9 (2550)	56 (2130)	21.7 (2325)	29.97 (2120)	27.2 (1936)	47.4 (2408)
Hg^{2+}	1.4 (—)	3.6 (—)	2.6 (—)	0 (—)	8.4 (—)	18.87 (—)	8 (—)	12.7 (—)
Pb^{2+}	1.5 (—)	6.3 (—)	3.5 (—)	4.6 (—)	3.6 (—)	0.6 (—)	1.1 (—)	0.8 (—)

[a] Extraction=(concentration of extracted metal)/(concentration of the ligand)×100.
[b] Transportation=since there was a considerable amount of leakage of lead, zinc and mercury picrates in the blank determination so these values have not been taken for comparison.

H40C···N2 2.7 Å, ∠C40–H40C···N2 161°). Apart from this there are other intermolecular C–H···N and C–H···O weak H-bonding interactions as well.

2.3. Extraction studies

The ionophoric properties of compounds **3a**-**h** towards alkali, alkaline earth, Hg^{2+}, Pb^{2+} and Ag^{+} were evaluated by the picrate extraction method developed by Pedersen.[22] Solvent extraction of aqueous metal cations into water saturated organic host solutions were performed at 25 °C. An aqueous solution containing metal picrates was extracted with the host solution ($CHCl_3$, 1.0 mM). The percentage extraction (Ex%) was calculated by measuring the picrate concentration in the aqueous phase. The results are summarized in Figure 6 and Table 3, which shows that all the *ortho*-Schiff bases **3a**-**d** have maximum affinity for Ag^{+} in comparison to other metal ions and are thus highly selective for Ag^{+}. The *para*-Schiff bases **3e**-**h** also have high extractabilities for Ag^{+} but are less selective as they show good affinity for alkali metal ions too. The remarkably high selectivity of pyridinyl-*ortho*-Schiff base **3c** for Ag^{+}over all other metal ions and molecular modelling studies suggest that the four lone pairs of sp^2 nitrogens converge to form a soft binding site for Ag^{+} cation. A comparatively low affinity for Ag^{+} shown by the pyridyl-*para*-Schiff base **3g** indicates an important role in binding played by the ether oxygens present at the *ortho* position to the imine group in **3c**. The high selectivities for Ag^{+} over other metal ions shown by all the *ortho*-Schiff bases, irrespective of the end groups, may be due to the fact that coordination to Ag^{+} through this ether oxygen and imine nitrogen gives rise to a six membered chelate ring. Thus this N_2O_2 chromophore of the dipodal ligands offers an ideal tetrahedral coordination site for Ag^{+} along with the inherent stability of a six membered chelate ring. The exceptionally high selectivity exhibited by **3c** indicates a further participation by one or both of the Py nitrogens in the bonding, taking into account the tendency of Ag^{+} to form 2–6 coordinated complexes.[23] The lowest extraction percentage of **3a** out of these four ligands hints towards a preference for N over O at the additional coordination sites. As the efficiency of interaction with cations also depends on the number of donor sites[24] therefore, **3a** surrounds Ag^{+} in a less efficient way by providing lesser donor sites. Receptors **3b** and **3d** both have two amine nitrogens which may take the fifth and sixth coordinating sites around Ag^{+} but they are more flexible than the pyridyl N of **3c**, more so in **3d** which has the lowest affinity for Ag^{+} out of these three ligands. The four nitrogens (2 imine/2 amine) in **3b**-**d** must adopt a face to face orientation to coordinate with Ag^{+} in solution although the two nitrogens are in a nearly opposite orientation in the solid state structure of **3d**. Out of the four *para*-Schiff bases, **3h** shows the highest affinity for Ag^{+} which may be due to the extra stability caused by the formation of a six membered chelate ring on coordination through the N_4 chromophore.

The lower percentages found for the alkali and alkaline earth metal cations may be due to the fact that hard cations possessing high hydration energies cannot interact strongly with nitrogen moieties in the ionophore while less hydrated Ag^{+} ion coordinates to soft nitrogen donors. The four ether oxygens constituting the hard site, offer less number of donors for the alkali and alkaline earth cations with high hydration number of 6 and 8 respectively, in the absence of donation by hydroxyl groups in the neutral solution or in the present conditions.[25] The lack of donor sites will have a greater effect on divalent cations as is also seen in the extraction data.

2.4. Transport studies

Experiments testing ion transport across a liquid membrane were carried out using apparatus similar to Lamb et al.[26a] and are given in Table 3. All the ligands show high transport rates for Ag^{+}. The transport rates are determined either by the rate of diffusion or by the rate of complexation and decomplexation at the interfaces.[26b] Comparing the lowest extractant **3a** and the highest extractant **3c**, it is seen that the former has the highest transport rate (Fig. 7). As **3a** shows a weaker affinity for Ag^{+}, it is expected that it releases the

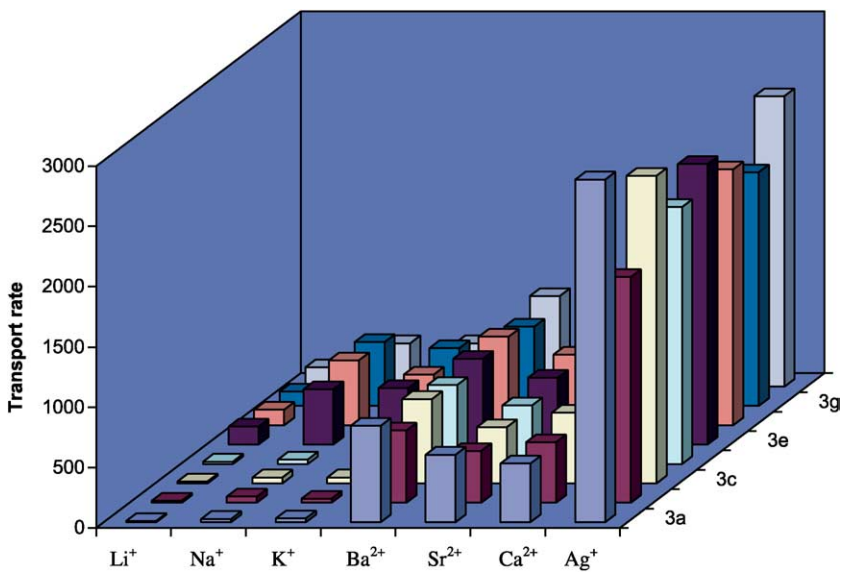


Figure 7. Showing a plot of rates of transportation of various metal ions by different ligands.

cation at the interface easily. As all the ligands show comparable transport rates for Ag^+ it indicates that the transport rates are more influenced by the diffusion of the species rather than by the rate of complexation and decomplexation and the ligands act as good receptors and carriers of silver ion. For the alkali metal ions, **3a**-**d** show poor transport rates as well showing thereby that they are both poor receptors and carriers for them. For alkaline earth metals they behave as better carriers than receptors, owing to their relatively higher rates of transport. Compounds **3e**-**h** transport alkali (except for Li^+) and alkaline earth metal cations almost equally hence behaving as reasonably good carriers for them. Li^+, which shows the highest extraction with **3e**-**h**, among all alkali and alkaline earth metal cations exhibits lower transport rates. This may be due to stronger complexation of Li^+ by them which leads to slower release at the second interface. Thus **3e**-**h** behave as better receptors and poor carriers for Li ion.

2.5. Inclusion of neutral guest molecules

Compounds **3a**, **3c**-**h** and the Ag^+ complex, show the presence of acetonitrile molecules at $\sim\delta$ 2.1–1.6 in their ^1H NMR and $\sim\delta$ 116 in ^{13}C NMR, respectively, taken in $CDCl_3$. These upfield shifted peaks for methyl protons and –CN of acetonitrile in ^1H and ^{13}C NMR suggest the presence of acetonitrile in the centre of the calix cavity which is a highly shielded region for the acetonitrile molecule, more so for the methyl group. The signal for the methyl carbon is also expected to be upfield shifted from its usual place[13] δ 0.3 to the negative side of the δ scale and is hence not reported in most of the cases. But in the case of the cone conformer of **3c** and its Ag^+ complex, peaks at δ −0.09 and −1.03 could be seen in the ^{13}C NMR. As acetonitrile was the solvent used in synthesis it indicates a possibility of the formation of stable inclusion complexes with solvent in the solution form as well. Two different peaks found in **3a** and **3c** for two types of acetonitrile solvent molecules, were sharp and well defined. This indicates that chemical exchange, if any between free and included solvent molecules is slow compared with the time scale of the NMR analysis. A larger upfield shift for the included solvent molecule may be due to the diamagnetic ring current effect of the aromatic calixarene moieties. Such diamagnetic effects on the chemical shift values of the included solvent molecules, in the solution phase have been reported earlier[27] also. However, the shifts found in the present case are much less as compared to δ −0.80 found in the literature.[27a–c] In those reports the acetonitrile molecule penetrates deep into the hydrophobic cavity with its N end reaching into the hydrophilic cavity of the lower rim substituted calix[6]arenes. In there, the N of the aetonitrile coordinates with the metal ion and the methyl group remains under the effect of the diamagnetic ring currents of the hydrophobic cavity of the calixarene framework. In the title compounds however, the methyl end of the acetonitrile enters into the hydrophobic cavity of the calixarene, but not too deep and its polar N end remains outside it. The presence of acetonitrile molecules has been confirmed in the solid state structures of three of these compounds as given above. As suggested by the crystal structures, these solvent molecules are held in the calix cavity by CH/π interactions. It has been known from a study of the data base[28] that in case of the inclusion compounds held by CH/π interactions, the spectral data show the maintenance of the crystal structure in the solution as well. The presence of the acetonitrile molecule in the Ag^+ complex hints towards co-complexation of a neutral and a charged species by the host.

2.6. Reducing properties

Surprisingly we found that in the presence of Cu(II) perchlorate in acetonitrile, **3a**-**c** gave colorless crystals which gradually turned to greenish-blue in air, losing crystallinity on removal from the solvent. They were proved to be of a Cu(I) complex with formula $[Cu(CH_3CN)_4]ClO_4$ by X-ray diffraction studies. In the case of **3c** the filtrate also yielded purple crystals of a Cu(II) complex $[Cu(NH_2CH_2\text{-}o\text{-}py)_2](ClO_4)_2$, the crystal structure of which has been solved (to be reported separately). The formation of the former complex of Cu(I) indicates a strong reductive activity of the ligand(s), which is still under investigation. Such reductive activity has earlier also been reported in the literature in the case of calix[4]arene based podands having pyridine and bipyridine as substituents.[10]

3. Conclusions

Eight new 1,3-dipodal hosts based on calix[4]arenes and having imine/two amine or two imine/two ether oxygen end groups with cavities having ether oxygens as potential donors were synthesized and characterized. The ligands have the cone conformation except for **3c** that also appears in a 1,2-alternate conformation which is known only in two or three cases of calix[4]arenes. The sp^2 nitrogens of the Schiff's bases have been seen as potential donors towards soft Ag^+ metal ion because all ligands have behaved as good extractants for Ag^+. The largest selectivity of pyridyl-*ortho*-Schiff's base **3c** for Ag^+ strongly supports a high intrinsic affinity of imine and aromatic sp^2 nitrogens[29] for Ag^+. The complexation is being further augmented here by the favourable disposition of the ether oxygens at the *ortho* position to the imine group. Two of them together form a stable six membered chelate ring with Ag^+ which seems to be crucial to achieve a high selectivity for Ag^+. The ligands give intra-cavity inclusion complexes with acetonitrile and thus may act as hosts for co-complexation of neutral and ionic guests. A clatharate complex of chloroform has been formed by its inclusion in the inter-molecular spaces in **3d**, which is quite rare.

4. Experimental

Melting points are uncorrected. Most chemicals were purchased from Aldrich Co. and used as received without further purification. Organic solvents were purified by standard procedures. The elemental analyses and FAB mass spectra were done at RSIC at Central Drug Research Institute, Lucknow. The ^1H and ^{13}C NMR were taken on a 200 MHz Bruker Instrument. TMS was used as standard reference. IR were recorded on Pye Unicam IR spectrometer as KBr pellets for the compounds in the solid state and as neat samples for the semisolid compounds.

4.1. Synthetic procedure

The *p-tert*-butylcalix[4]arene aldehydes **1** and **1′** having *ortho* and *para*-hydroxy benzaldehyde, respectively were prepared according to already reported procedures.[8]

4.1.1. Compound 3a. The *ortho* substituted dialdehyde compound **1** (0.5 mmol, 472 mg) and 2-methoxyethylamine **2a** (1.0 mmol, 75 mg) were dissolved in warm acetonitrile (20 ml). The reaction mixture was stirred at room temperature for 1 h when white colored compound separated out. The material was filtered and washed with cold acetonitrile, recrystallized from acetonitrile and was vacuum dried. Yield=85%. Mp=130 °C; IR 1640 cm^{-1}; FAB-MS $[M+1]^+$=1059, $[M-C(CH_3)_3]^+$=1003 (base peak), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.06 (s, 18H, Me_3C), 1.24 (s, 18H, Me_3C), 1.59, 1.62 (Me of acetonitrile guest), 3.29 (s, 6H, $-OCH_3$), 3.35 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 3.46 (t, 4H, $-NCH_2$), 4.28–4.36 (m, 16H, $-OCH_2CH_2O$, $-OCH_2$, $ArCH_2Ar$), 6.92–7.34 (m, 14H, Ar), 7.91 (s, 2H, −OH), 8.01 (d, 2H, J=8 Hz, *ortho*-H −OAr), 8.83 (s, 2H, CH=N), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.1, 31.6 (Me_3C), 33.8, 34.1 (Me_3C), 31.8 ($ArCH_2Ar$), 58.7 ($-OCH_3$), 60.9 (NCH_2), 66.7 (OCH_2), 72.5, 73.9 (OCH_2CH_2O), 111.3 (Ar), 116.3 (CN of acetonitrile guest), 120.9 (Ar), 124.7 (Ar), 125.7 (Ar), 127.5 (Ar), 131.8 (Ar), 133.4 (Ar), 142.1 (Ar), 147.9 (Ar), 149.5 (C_{ipso}–ArO–), 149.9 (C_{ipso}–ArOH), 158.9 (–CH=N). Anal. Calcd $C_{68}H_{86}N_2O_8$, C 77.13; H 8.13; N 2.65; found: C 77.26, H 8.20; N 2.73.

4.1.2. Compound 3b. A solution of compound **1** (0.5 mmol, 472 mg) and *N*,*N*-dimethylethylamine **2b** (1.0 mmol, 88 mg) acetonitrile (20 ml) was stirred at room temperature for 1.5 h. The stirring was stopped on the separation of a white colored product. The white material was filtered and washed and recrystallized from acetonitrile and vacuum dried. Yield=90%. Mp=180 °C; IR 1640 cm^{-1}; FAB-MS $[M+1]^+$=1085, $[2M+1]^+$=2169, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04 (s, 18H, Me_3C), 1.17 (s, 18H, Me_3C], 2.16 (s, 4H, $-NCH_3$), 2.48 (t, 4H, $-NCH_2$, J=6 Hz), 3.41 (t, 4H, $-NCH_2$, J=6 Hz), 3.93 (broad s, 8H, $ArCH_2Ar$), 4.25 (broad t, 8H, $-OCH_2CH_2O-$), 6.86–7.27 (m, 14H, Ar), 7.87 (s, 2H, ArOH), 7.89 (d, 2H, *ortho*-H −OAr, J=8 Hz), 8.63 (s, 2H, CH=N], ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.0, 31.2 (Me_3C), 31.6 ($ArCH_2Ar$), 33.9, 34.0 (Me_3C), 45.6 ($-NCH_3$), 59.3 ($-NCH_2$), 60.1 ($-NCH_2$), 67.3 ($-OCH_2$), 72.8 (OCH_2), 112.1, 121.1, 124.9, 125.9, 126.1, 127.4, 131.6, 132.2, 142.1, 147.3 (Ar), 150.0 (C_{ipso}–ArO–), 150.2 (C_{ipso}–ArOH), 157.5 (–CH=N). Anal. Calcd $C_{70}H_{92}N_4O_6$, C 74.89; H 8.49; N 5.17; found: C 74.96, H 8.39; N 5.23.

4.1.3. Compound 3c. (i) Cone conformer. Compound **1** (472 mg, 0.5 mmol) and 2-(aminomethyl)pyridine **2c** (108 mg, 1.0 mmol) were taken in warm and dry acetonitrile (25 ml). The reaction mixture was stirred for 2 h and the progress of the reaction was monitored by TLC. When all the aldehyde was consumed, then half of the solvent was evaporated and the reaction mixture was kept in the refrigerator. A white colored material separated on cooling. This was filtered, recrystallized from acetonitrile and dried under vacuum. Yield=92%. Mp=135 °C; IR 1645 cm^{-1}; FAB-MS $[M+1]^+$=1125, $[M-CH_2Py]$=1035 (base peak). (i) Cone conformer ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04 (s, 18H, Me_3C), 1.19 (s, 18H, Me_3C), 1.78, 1.42 (acetonitrile guest), 3.27 (d, 4H, $ArCH_2Ar$, J=12 Hz), 4.33 (d, 4H, $ArCH_2Ar$, J=12 Hz), 4.30 (s, OCH_2CH_2O, 8H), 4.64 (s, 4H, NCH_2-) 6.95 (s, 4H, ArH), 7.00 (s, 4H, ArH), 7.14 (d, J=8 Hz, 2H, OAr), 7.36–7.56 (m, 10H, −OArH and *meta*, *para* of pyridine), 7.87 (s, 2H, −OH, absent in D_2O), 8.09 (d, 2H, −OArH, J=8 Hz), 8.55 (bs, 2H, *ortho*-pyridine), 9.03 (s, 2H,–CH=N), ^{13}C NMR, DEPT-135 ($CDCl_3$, 50 MHz): δ 30.8, 30.9 (Me_3C), 33.7, 34.0 (Me_3C, absent), 31.5, 31.8 ($ArCH_2Ar$), 66.7, 66.8 ($-OCH_2CH_2O$), 73.9 ($-NCH_2$), 116.5 (–CN of acetonitrile, absent), 111.4, 120.7, 120.9, 121.7, 122.1, 124.7, 125.1 (quaternery C of Ar, absent in DEPT-135), 125.7, 127.3, 127.5, 127.6, 132.0, 132.8, 133.2, 136.4, 142.0, 147.4, 147.7 (Ar), 149.02 (C_{ortho} Py), 149.5 (*i*-Ar-imine, absent), 149.9 (C_{ortho} Py, absent), 157.8 (*i*-ArOH, absent in DEPT-135), 159.6 (*i*-$ArOCH_2$, absent in DEPT-135), 159.7 (imine C). Anal. Calcd $C_{74}H_{84}N_4O_6$, C 79.00; H 7.47; N 4.98; found: C 79.14, H 7.38; N 5.02. (ii) 1,2-Alternate conformer. The reaction was set up as given above for the cone conformer but the reaction mixture was stirred overnight and a white solid was separated in the same manner as above. Yield=90%, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04 (s, 18H, Me_3C), 1.19 (s, 18H, Me_3C), 2.30, 1.61 (Me of acetonitrile guest), 3.28 (d, 2H, $ArCH_2Ar$, J=12 Hz), 4.02 (s, 4H, $ArCH_2Ar$), 4.32 (bs, 8H, OCH_2CH_2O), 4.35 (2H, $ArCH_2Ar$, J=12 Hz), 4.65 (s, 4H, NCH_2-) 6.72–7.40 (14H, Ar), 7.83 (s, 2H, −OH, absent in D_2O), 8.10 (d, 2H, *ortho*-H −OAr, J=8 Hz), 8.55 (broad s, 2H, *ortho*-Py), 9.03 (s, 2H,–CH=N), ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT-135): δ 31.0, 31.4 (Me_3C), 33.7, 34.0 (Me_3C, absent in DEPT-135), 31.7, 47.6 ($ArCH_2Ar$), 66.6, 66.7 ($-OCH_2CH_2O$), 73.9 ($-NCH_2$), 116.4 (–CN of acetonitrile, absent in DEPT-135), 111.4, 120.9, 121.2, 121.7, 122.0, 125.0 (quaternery C of Ar, absent in DEPT-135), 125.6, 127.5, 127.7, 127.7, 132.0, 133.5, 136.4, 136.5, 142.3, 148.9 (Ar), 149.1 (C_{ortho} Py), 149.4 (*i*-Ar-imine, absent in DEPT-135), 149.6 (C_{ortho} Py, absent in DEPT-135), 157.7 (*i*-ArOH, absent in DEPT-135), 159.6 (*i*-$ArOCH_2$, absent in DEPT-135), 159.6 (imine C), 161.6 (*i*-$ArOCH_2$, absent).

4.1.4. Compound 3d. The compound was prepared and separated by the same method as described above for **3b** except that the amine *N*,*N*-dimethypropyldiamine **2d** (102 mg, 1.0 mmol) was taken. White solid compound was obtained. Yield=88%. Mp=187 °C; IR=1640 cm^{-1}; FAB-MS $[M+2]^+$=1114 (65), $[M+1]^+$=1113 (30), $[M]^+$=1112, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.07 (s, 18H, Me_3C), 1.25 (s, 18H, Me_3C), 1.65–1.69 (m, 4H, $-CH_2$), 1.84 (Me of acetonitrile guest), 2.14 (s, 12H, $-NCH_3$), 2.22 (t, 4H, $-NCH_2$, J=7 Hz), 2.73 (t, 4H, $-NCH_2$, J=6.8 Hz), 3.33 (d, 4H, $ArCH_2Ar$, J=13 Hz), 4.28–4.37 (m, 12H, $-ArCH_2Ar$ and $-OCH_2$), 6.94–7.01 (m, 14H, Ar), 7.27 (s, 2H, ArOH), 7.90 (m, 2H, Ar), 7.94 (d, 2H, *ortho*-H −OAr, J=8 Hz), 8.82 (s, 2H, CH=N), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.0, 31.5 (Me_3C), 33.7, 34.1 (Me_3C), 31.7 ($ArCH_2Ar$), 45.4 ($-NCH_3$), 57.5 ($-NCH_2$), 59.4 ($-NCH_2$), 66.6 ($-OCH_2$), 74.0 (OCH_2), 117.8 (CN of acetonitrile guest), 111.3, 120.9, 124.8, 125.0, 125.7, 127.2, 127.6, 131.6, 133.4, 142.1, 147.9, 149.4 (Ar), 149.8 (C_{ipso}–ArO–), 157.4 (C_{ipso}–ArOH), 157.7 (CH=N). Anal. Calcd

$C_{72}H_{96}N_4O_6$, C 77.70; H 8.63; N 5.04; found: C 77.82, H 8.59; N 5.12.

4.1.5. Compound 3e. The *para* substituted dialdehyde compound **1′** (0.5 mmol, 472 mg) and 2-methoxyethylamine **2a** (1.0 mmol, 75 mg) were stirred for 2 h in warm acetonitrile (20 ml). The reaction was followed by TLC. At the completion of the reaction the mixture was left undisturbed for a few hours when the white material separated out. The white solid product was isolated as described above and dried under vacuum. Yield=75%. Mp=162 °C; IR=1630 cm^{-1}; FAB-MS $[M+2]^+$=1060 (40), $[M+1]^+$=1059 (20), $[M]^+$=1058 (20), base peak 242, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.07 (s, 18H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$), 1.67 (Me of acetonitrile guest), 3.32 (d, 4H, $ArCH_2Ar$, J=13.0 Hz), 3.83 (s, 6H, $-OCH_3$), 3.70–3.77 (m, 8H, $-NCH_2$ and $-OCH_2$), 4.25–4.27 (8H, $-OCH_2$), 4.38 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 6.93–7.03 (m, 12H, Ar), 7.64 (s, 2H, ArOH), 7.69 (d, 4H, Ar, J=4 Hz), 8.24 (s, 2H, $-CH{=}N$), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.0, 31.7 (Me_3C), 33.7 ($ArCH_2Ar$), 33.8, 34.0 (Me_3C), 58.5 ($-OCH_3$) 58.9 ($-NCH_2$), 61.0 ($-CH_2OCH_3$), 66.6 ($-OCH_2$), 72.3 (OCH_2), 114.8 (–CN of acetonitrile guest), 114.5, 114.6, 114.8, 115.1, 15.3, 118.8, 124.8, 125.1, 125.7, 127.7, 129.1, 129.8, 130.1, 132.8, 141.5, 147.1 (Ar), 149.6 (*i*-ArO–), 150.4 (*i*-ArOH), 160.6 (CH=N). Anal. Calcd $C_{68}H_{86}N_2O_8$, C 77.13; H 8.13; N 2.65; found: C 77.28, H 8.27; N 2.78.

4.1.6. Compound 3f. The reaction was performed under similar conditions as in the case of **3b**. Completion of the reaction was indicated by TLC. Further stirring by another hour did not yield any solid material. The solvent was partially evaporated and the mixture was cooled but no solid separated out. So the whole solvent was evaporated leaving a semisolid material. It was triturated with ether, which was decanted later on. The pale yellow semisolid product was washed with methanol and vacuum dried. Yield=65%; IR 1640 cm^{-1}, $C_{70}H_{92}N_4O_6$, FAB-MS $[M+2]^+$1086 (base peak), $[M+1]^+$=1085 (25), $[M]^+$=1084 (30), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.06 (s, 18H, Me_3C), 1.24 (s, 18H, Me_3C), 2.03 (Me of acetonitrile guest), 2.33 (d, 12H, $-NCH_3$), 2.63 (t, 4H, $-NCH_2$, J=6.2 Hz), 3.31 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 3.71 (t, 4H, $-NCH_2$, J=6.8 Hz), 4.08–4.29 (m, 8H, $-OCH_2$), 4.38 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 6.92–7.03 (m, 10H, Ar), 7.64 (s, 2H, ArOH), 7.69 (d, 4H, J=4 Hz), 8.24 (s, 2H, CH=N), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.0, 31.6 (Me_3C), 33.9, 34.1 (Me_3C), 33.7 ($ArCH_2Ar$), 45.7 ($-NCH_3$), 59.4 ($-NCH_2$), 60.1 ($-NCH_2$), 66.5 (OCH_2), 72.8 (OCH_2), 114.2 (–CN of acetonitrile guest), 114.4, 114.5, 114.8, 125.0, 125.6, 126.8, 127.7, 128.9, 129.2, 129.6, 131.6, 132.2, 141.4, 147.1, 149.6, 150.4 (Ar), 150.7, 160.5 (ArOH), 161.3 ($-CH{=}N$).

4.1.7. Compound 3g. The compound was prepared as given for **3c**. The material obtained as a viscous mass which was treated as given for **3f**. Yield=78%; IR=1650 cm^{-1}, $C_{74}H_{84}N_4O_6$, FAB-MS $[M+2]^+$=1126 (base peak), $[M+1]^+$=1125 (48), $[M]^+$=1124, 1036 (98) due to loss of CH_2Py, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.03 (s, 18H, Me_3C), 1.27 (s, 18H, Me_3C), 2.14 (acetonitrile guest), 3.30 (d, 4H, $ArCH_2Ar$, J=13 Hz), 4.29 (s, 8H, $-OCH_2$), 4.38 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 4.83–4.91 (b, 4H, $-NCH_2$), 6.84–7.66 (m, 14H, Ar), 7.59 (s, 2H, ArOH), 7.60, 7.67, 8.54 (8H, *meta*, *para*, *ortho* H of Py), 8.56 (s, 2H, $-CH{=}N$), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 30.9, 31.0 (Me_3C), 33.8, 34.0 (Me_3C), 31.5, 31.7 ($ArCH_2Ar$), 58.5 ($-NCH_2$), 66.4 ($-OCH_2$), 66.5 (OCH_2), 116.5 (–CN of acetonitrile), 111.5, 120.9, 121.7, 122.1, 124.7, 125.1, 125.7, 127.6, 132.1, 133.3, 136.4, 142.2 (Ar), 149.5, 149.3 (*para*, *meta*-C of Py) 149.8, 151.3 (*i*-C ArOH), 159.2, 159.7 (*ortho* C of Py), 160.9 (CH=N).

4.1.8. Compound 3h. Prepared as given for **3d**. The product was obtained as a pale yellow semisolid. Yield=73%; IR=1640 cm^{-1}; $C_{72}H_{96}N_4O_6$, FAB-MS $[M+2]^+$=1114 (base peak), $[M+1]^+$=1113 (35), $[M]^+$=1112 (40), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.07 (s, 18H, Me_3C), 1.26 (s, 18H, Me_3C), 1.62 (q, 4H, $-CH_2$, J=8 Hz), 1.87 (Me of acetonitrile guest), 2.21 (s, 12H, $-NCH_3$), 2.31 (t, 4H, $-NCH_2$, J=8 Hz), 2.74 (t, 4H, $-NCH_2$, J=7.4 Hz), 3.33 (d, 4H, $ArCH_2Ar$, J=13.2 Hz), 4.28 (s, 8H, $-OCH_2$), 4.39 (d, 4H, $ArCH_2Ar$, J=12.8 Hz), 6.95 (d, 4H, Ar, J=6 Hz), 7.05 (m, 8H, Ar), 7.65 (s, 2H, ArOH), 7.67 (d, 4H, Ar, J=6 Hz), 8.22 (s, 2H, CH=N), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.1, 31.6 (Me_3C), 33.9, 34.1 (Me_3C), 31.9 ($ArCH_2Ar$), 58.8 ($-NCH_3$), 60.9 ($-NCH_2$), 66.8 ($-NCH_2$), 72.6, 73.9 ($-OCH_2$), 111.4 (CN of acetonitrile guest), 120.9. 124.7, 125.1, 126.7, 1274, 127.6, 131.7, 133.0, 141.7, 147.5, 149.6 (Ar), 150.0 (*i*-ArO), 157.6, (*i*-ArOH), 159.0 ($-CH{=}N$).

4.1.9. Silver (I) complex of 3c. For the preparation of the complex, $AgNO_3$ (0.5 mmol, 85 mg) was dissolved in methanol (10 ml) and mixed with **3c** (0.5 mmol, 562 mg) taken in chloroform (20 ml) in a round bottomed flask, in the dark. The mixture was stirred for 2 h and then refluxed for another 2 h. The reaction was followed by TLC. At the end half of the solvent was evaporated and the remaining solution was left for evaporation. Light yellow colored complex which tends to become dark in light, separated after a few hours. The compound was sparingly soluble in chloroform. It was filtered and washed with methanol and dried under vacuum. Yield=60%. Mp >240°; IR=1620(s), 3360(b) cm^{-1}; FAB-MS $[Ag+\mathbf{3c}]^+$=1232 (base peak), 1124 (65) due to $[M]^+$ of **3c**, $[M-(CH_2Py)]^+$ 1036 (35), ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90, 1.00, 1.26, 1.40 (Me_3C), 1.64 (Me of acetonitrile solvent), 3.23 (d, 2H, J=16 Hz, $ArCH_2Ar$), 3.30 (d, 2H, $ArCH_2Ar$, J=12 Hz), 3.38 (s, 2H, NCH_2), 4.00 (d, 2H, J=16 Hz, $ArCH_2Ar$), 4.28–4.40 (b, 10H, OCH_2CH_2O, $ArCH_2Ar$), 4.43 (s, 2H, NCH_2) 6.85–7.74 (Ar), 7.84 (ArOH), 8.57, 8.72 (1H, *ortho*-H of py), 10.38, 10.47 (s, 1H, $-CH{=}N$), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.9, 22.2 (Me_3C), 25.6, 29.7 ($ArCH_2Ar$), 33.2, 36.2 (Me_3C), 50.9, 61.2 (NCH_2), 54.2, 59.9 (OCH_2), 109.1 (–CN acetonitrile), 119.1, 123.0, 125.0, 125.3, 130.6, 132.6, 140.9, 144.1, 147.3 (Ar), 150.12 (*ortho*-C of py), 151.2 (*i*-ArOH), 155.7 (*ortho*-C of py), 155.9 (*i*-ArO–), 170.1, 170.9 (CH=N). Anal. Calcd $C_{74}H_{84}N_5O_9Ag$, C 68.62; H 6.49; N 5.41; found: C 68.26, H 6.33; N 5.27.

4.2. Extraction, transport and complexation experiments

The %E of metallic picrates (1.0×10^{-3} M, 2 ml) extracted from water to chloroform containing ligand (1.0×10^{-3} M, 2 ml) was determined at 25 °C; Transport conditions: Source phase (aqueous solution of metal picrate 3 ml,

1.0×10^{-2} M); membrane phase (chloroform, 15 ml, 1.0×10^{-3} M); receiving phase (water, 10 ml); internal diameter of glass vial=20 mm, Average value of three independent determinations and results are reproducible, %E=(concentration of extracted metal)/(concentration of organic ligand)×100, the average value of three independent determinations is reported.

4.3. X-ray diffraction data

The crystals of **3a**, **3d** and **3e** were grown from a mixture of $CH_3CN/CHCl_3$ by method of slow evaporation. The data were collected on a Siemens P4 single crystal diffractometer using graphite monochromatized Mo K_α radiation (0.71073 Å). The structures were solved by direct methods and subsequently completed by difference Fourier synthesis. They were refined by full-matrix least-squares on F^2 with SHELXTL.[30] No absorption correction was applied. The crystals were highly air sensitive and were studied after coating them with oil meant for this purpose. That explains for relatively high values of the *R*-factor achieved for them. However, overall geometry and bonding parameters are not much affected by this. The quality of the crystals of compound **3d** was exceptionally poor. A number of trials were made to grow better quality crystals and many crystals were tried for data collection. The final data set used for structure elucidation was the best out of these. Anisotropic refinement of all atoms led to a very low data to parameter ratio and the atoms tend to become non-positive definites therefore, only three oxygens, two nitrogens and two bridging methylenes were refined anisotropically. All other atoms were refined isotropically only. Phenyl rings were refined as rigid groups. The chloroform solvent molecules showed disorder, which could be resolved only for one of the chlorine atoms. All these factors contributed towards a high R index. All non-hydrogen atoms of structures **3a** and **3e** were refined anisotropically. All the hydrogens atoms were fixed geometrically as riding atoms with a displacement parameter equal to 1.2 (CH, CH_2) or 1.5 (CH_3) times that of the parent atom. Crystal data for **3a**,**e** and **3d** have been deposited with the Cambridge Crystallographic Data Center, under reference CCDC 200395, 225239 and 225240, respectively.

Acknowledgements

G.H. thanks the CSIR (New Delhi, India) for research grant vide grant No. 01(1796)/02/EMR—II and N.S. is thankful to the CSIR for research fellowship.

References and notes

1. (a) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933–8968. (b) Shinkai, S.; Takeshifa, M. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1088–1097. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–743. (d) Shinkai, S.; Ikeda, A. *Chem. Rev.* **1997**, *97*, 1713–1734.
2. Lehn, J. M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, 1995.
3. (a) Jin, T. *J. Chem. Soc., Chem. Commun.* **2000**, 1379–1380. (b) Namor, A. D.; Pugliese, A.; Casal, A. R.; Llerena, M. B.; Aymonino, P. J.; Velarde, F. J. S. *Phys. Chem. Chem. Phys.* **2000**, 4355–4360.
4. (a) Chung, T. D.; Park, J.; Ki, J.; Lim, H.; Choi, M. J.; Kim, J. R.; Chang, S. K.; Kim, H. *Anal. Chem.* **2001**, *73*, 3975–3980. (b) Barboso, S.; Casnati, A.; Dozol, J. F.; Neu, F. A.; Rouquette, H.; Weill, M. S.; Ungaro, R. *J. Am. Chem. Soc.* **2001**, *123*, 12182–12190. (c) Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Lyssenko, K.; Ogden, M. I. *J. Chem. Soc., Chem. Commun.* **1995**, 929–930.
5. (a) Wolbers, P. O.; van Veggel, F. C. J. M.; Snellink-Ruël, B. H. M.; Hofstrat, J. W.; Geurts, F. A. J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2141–2150. (b) Araki, P.; Hashimoto, N.; Otsuka, H.; Nagasaki, T.; Shinkai, S. *Chem. Lett.* **1993**, 829–832.
6. Zeng, X.; Weng, L.; Chen, L.; Leng, X.; Zhang, Z.-Z.; He, X. *Tetrahedron Lett.* **2000**, *41*, 4917–4921.
7. Regnouf-de-Vains, J.-B.; Dalbavie, J.-O.; Lamartine, R.; Fenet, B. *Tetrahedron Lett.* **2001**, *42*, 2681–2684.
8. Seangprasertkji, R.; Asfari, Z.; Arnand, F.; Vicons, *J. Org. Chem.* **1994**, *59*, 1741–1744.
9. (a) Liu, Y.; Zhao, B.-T.; Zhang, H.-Y.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1219–1223. (b) Zeng, X.; Weng, L.; Chen, L.; Leng, X.; Ju, H.; He, X.; Zhang, Z.-Z. *J. Chem. Soc., Perkin Trans. 2* **2001**, 545–549.
10. Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R.; Fenet, B. *Inorg. Chem. Commun.* **1999**, *2*, 44–47.
11. Casnati, A.; Pocini, A.; Ungaro, R.; Ugozzoli, F.; Arnand, F.; Fanni, S.; Schwig, M.-J.; Egberink, R. J. M.; Jong, E. de; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767–2777.
12. Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955–4962.
13. Kemp, W. *Organic Spectroscopy*; Macmillan: London, 1991.
14. Jaime, C.; Mendoza, J. de; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372–3376.
15. Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783–4791.
16. Shinkai, S. *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI: England, 1993; Vol. 3, p 97.
17. Bott, S. W.; Coleman, A. W.; Atwood, J. L. *J. Inclusion Phenom.* **1987**, *5*, 747–751.
18. Spartan'02, Wavefunction, Inc. Irvine, CA.
19. (a) Dave, P. R.; Doyle, G. *J. Org. Chem.* **1995**, *60*, 6946–6952. (b) Dave, P. R.; Doyle, G. *Tetrahedron Lett.* **1992**, *33*, 1021–1024.
20. Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005–1007.
21. Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, 1999.
22. Pedersen, C. *J. Am. Chem. Soc.* **1970**, *92*, 391–394.
23. Munakata, M.; Wu, L. P.; Kuroda-Sowa, T. *Adv. Inorg. Chem.* **1999**, *46*, 173–303.
24. Dietrich, B. *J. Chem. Educ.* **1985**, *62*, 954–964.
25. (a) Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 63–66. (b) Ye, Z. F.; Wang, Y. P.; Liu, Y. S.; Jiang, Z. L.; Shen, X.; Zhu, L. G.; Shi, X. F. *J. Membr. Sci.* **1999**, *163*, 367–371.
26. (a) Lamb, J. D.; Christensen, J. J.; Izatt, S. R.; Bedke, K.; Astin, M. S.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 3399–3403. (b) Kirch, M.; Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 555–556.
27. (a) Sénéque, O.; Rondelez, Y.; Clainche, L. Le; Insian, C.;

Rager, M.-N.; Giorgi, M.; Reinaud, O. *Eur. J. Inorg. Chem.* **2001**, 2597–2604. (b) Sénéque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183–6189. (c) Blanchard, S.; Clainche, L. Le; Rager, M.-N.; Chansou, B.; Tuchagues, J.-P.; Duprat, A. F.; Mest, Y. Le; Reinaud, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2732–2735. (d) Arena, G.; Casnati, A.; Contino, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1997**, *38*, 4685–4688.

28. Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185–6191.
29. (a) Vöegtle, F.; Ibach, S.; Nieger, M.; Chartroux, C.; Kruger, T.; Stephan, H.; Gloe, K. *Chem. Commun.* **1997**, 1809–1810. (b) Paek, K.; Yoon, J.; Suh, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 916–922.
30. Sheldrick, G. M. SHELXTL, version 5.1, University of Göttingen: Germany.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 5407–5412
Tetrahedron

Regio- and stereoselective reactions of a rhodanine derivative with optically active 2-methyl- and 2-phenyloxirane

Changchun Fu,[a] Marie V. Thrane,[b,†] Anthony Linden[a] and Heinz Heimgartner[a,*]

[a]*Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland*
[b]*Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark*

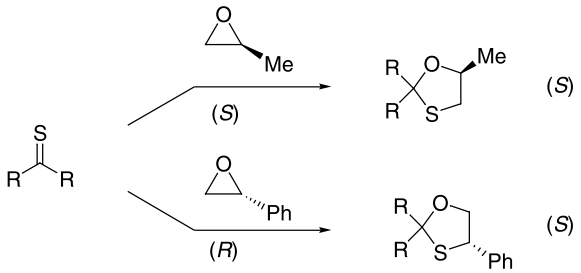
Received 3 February 2004; revised 5 April 2004; accepted 22 April 2004

Abstract—The reaction of a rhodanine derivative (=(*Z*)-5-benzylidene-3-phenyl-2-thioxo-1,3-thiazolidin-4-one; **1**) with (*S*)-2-methyloxirane (**2**) in the presence of SiO_2 in dry CH_2Cl_2 for 10 days led to two diastereoisomeric spirocyclic 1,3-oxathiolanes **3** and **4** with the Me group at C(2) (Scheme 2). The analogous reaction of **1** with (*R*)-2-phenyloxirane (**5**) afforded also two diastereoisomeric spirocyclic 1,3-oxathiolanes **6** and **7** bearing the Ph group at C(3) (Scheme 3). The structures of **3**, **4**, **6**, and **7** were confirmed by X-ray crystallography (Figs. 1 and 2). These results show that oxiranes react selectively with the thiocarbonyl group (C=S) in **1**. Furthermore, the nucleophilic attack of the thiocarbonyl S-atom at the SiO_2-activated oxirane ring proceeds with high regio- and stereoselectivity via an S_N2-type mechanism.

1. Introduction

The reaction of thiocarbonyl compounds with oxiranes in the presence of a Lewis acid to give 1,3-oxathiolanes has been investigated thoroughly in recent years.[1–7] All results reported indicate that the reactions proceed with high regio- and stereoselectivity via an S_N2-type mechanism. In the case of alkyl-substituted oxiranes, the thiocarbonyl S-atom attacks preferably at C(3) leading to the 5-substituted 1,3-oxathiolanes with retention of the configuration. On the other hand, the nucleophilic attack occurs mainly at C(2) of phenyloxirane to yield the 4-phenyl-substituted products via inversion of the configuration (Scheme 1). Furthermore, it has been shown that enolized thioketones react with oxiranes under similar conditions to give enesulfanyl alcohols.[7]

The previously reported reactions have been carried out mainly with aromatic and cycloaliphatic thioketones,[2–7] in which the sulfur atom was the only nucleophile. Furthermore, similar results were obtained with 1,3-dithiolane-2-thione, a cyclic trithiocarbonate,[8] and 4,4-disubstituted 1,3-thiazole-5(4*H*)-thiones,[1,9] which are analogues of dithiolactones. In both cases, the reaction occurred selectively at the thiocarbonyl S-atom.‡



Scheme 1.

With the aim of establishing the scope and limitation of the formation of 1,3-oxathiolanes, we decided to extend our studies to additional heterocyclic C=S compounds, thiolactones, thioesters, etc.[10] The rhodanine derivative **1**, that is, (*Z*)-5-benzylidene-3-phenyl-2-thioxo-1,3-thiazolidin-4-one,[11] which contains different heteroatoms and π-systems, was chosen to study the chemoselectivity of the reaction with oxiranes. In the present paper, the results with the optically active (*S*)-2-methyloxirane (**2**) and (*R*)-2-phenyloxirane (**5**) are described.

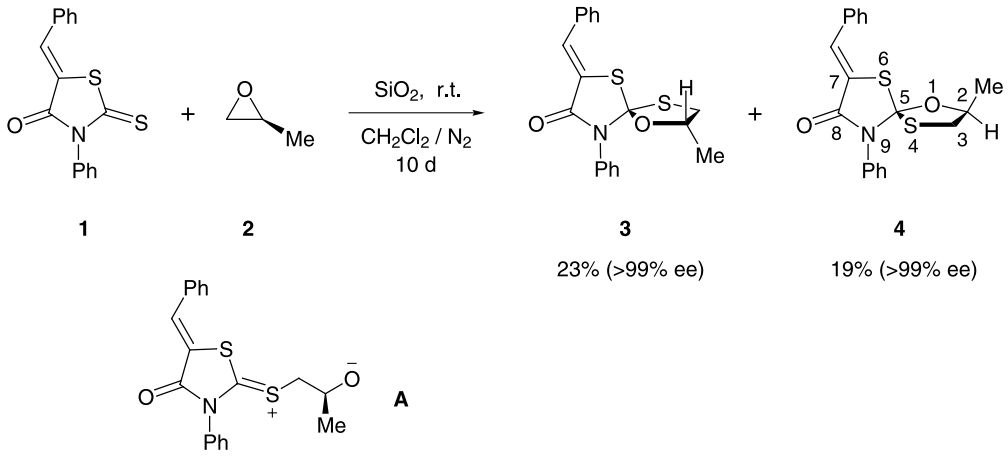
2. Results

2.1. Reaction of the rhodanine derivative 1 with (*S*)-2-methyloxirane (2)

The reaction of **1** with **2** in a molar ratio of 1:4 was carried out in dry CH_2Cl_2 at rt under an N_2 atmosphere in the

Keywords: Rhodanine; Oxiranes; 1,3-Oxathiolanes; Thiocarbonyl group; SiO_2; S_N2-type reaction.
* Corresponding author. Tel.: +41-1-6354282; fax: +41-1-6356812; e-mail address: heimgart@oci.unizh.ch
† Stay at the University of Zurich, 10. 2002-01. 2003.
‡ In some experiments with *trans*-2,3-dimethyloxirane and 1,3-thiazole-5(4*H*)-thiones, a minor product with a fused bicyclic structure was obtained, which has been formed via nucleophilic attack of the imine N-atom.[3]

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.066



Scheme 2.

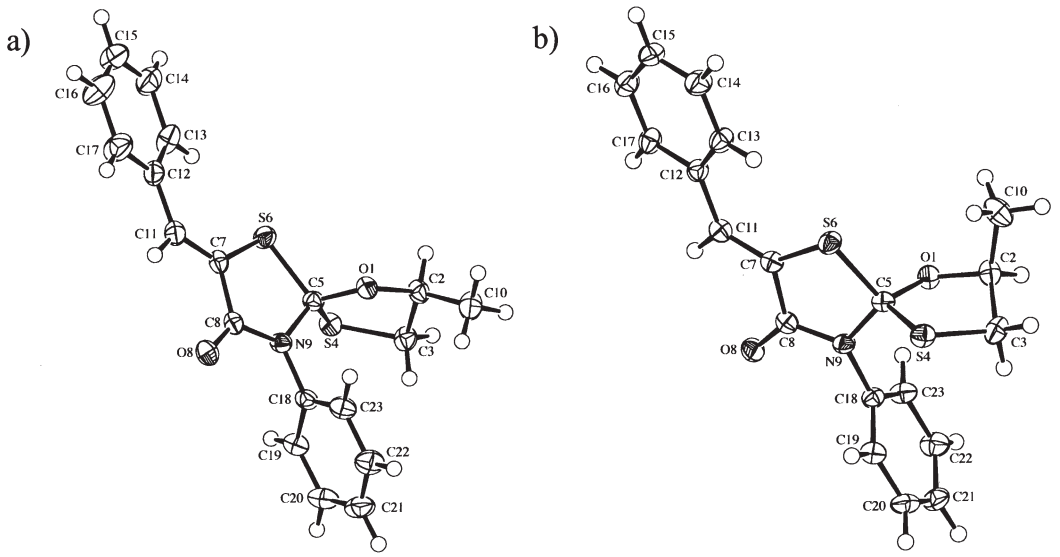


Figure 1. ORTEP Plots[12] of the molecular structures of (a) **3** and (b) **4** (displacement ellipsoids with 50% probability).

presence of SiO_2.[§] After stirring for 10 days, filtration and the usual workup by means of column chromatography (CC) and preparative TLC (PLC) gave two diastereoisomeric spirocyclic 1,3-oxathiolanes **3** and **4** in 23 and 19% yield, respectively.[¶] The starting material **1** was recovered in 52% yield (Scheme 2). The enantiomeric excess (ee) of the products was determined by analytical HPLC ((*S*,*S*)-Whelk-O 1, hexane/AcOEt 3:1).

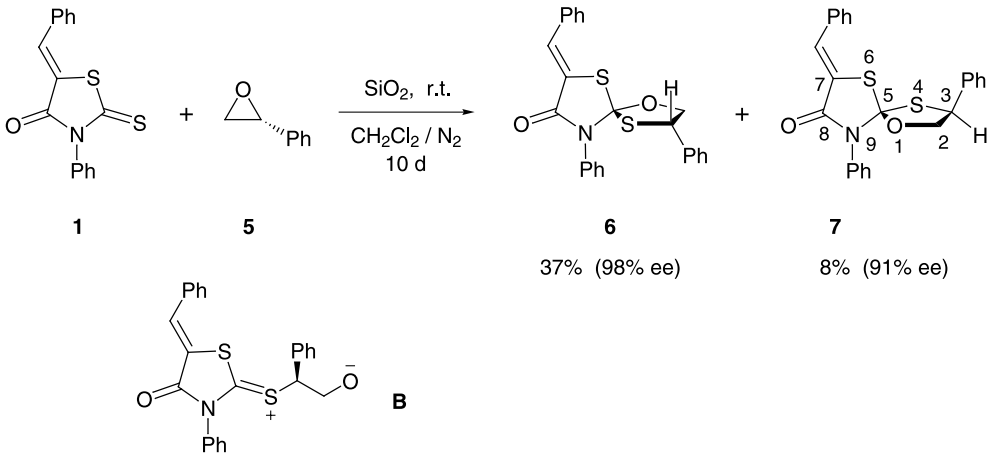
The structures of **3** and **4** were assigned on the basis of the elemental analyses, MS, IR, ^{1}H- and ^{13}C NMR, 1D-NOESY, HSQC, HSQC-TOCSY, and HMBC spectra, which clearly indicated the relative configurations of the products. For example, on irradiation of H–C(2) at 4.50 ppm, the 1D-NOESY spectrum of **4** showed one NOE-signal for two *ortho* H-atoms of the PhN residue at 7.40–7.38 ppm, whereas this signal was missing in the analogous experiment with **3**. Finally, the structures were established by X-ray crystallography (Fig. 1).

The crystals of **3** and **4** were enantiomerically pure and the absolute configurations of the molecules were determined independently by the diffraction experiments. Therefore, **3** has the (2*S*,5*R*)-configuration, whereas **4** is the (2*S*,5*S*)-diastereoisomer. In the case of **3**, the oxathiolane ring has an envelope conformation with C(3) as the envelope flap. The other five-membered ring shows a half-chair conformation twisted on S(6)–C(5), although the puckering is quite shallow and distorted towards an envelope. Both five-membered rings of **4** have a half-chair conformation twisted on C(2)–C(3) and S(6)–C(5), respectively.

The formation of **3** and **4** proceeded with retention of the configuration at C(2) of the oxirane **2** because the nucleophilic attack of the thiocarbonyl S-atom took place at C(3), leading to the intermediate **A**. Ring closure via nucleophilic addition of the O-atom at the thiocarbonylium group from the *si*- or *re*-side leads to **3** and **4**, respectively.

[§] The analogous reaction with racemic 2-methyloxirane leading to racemic products of type **3** and **4** was also carried out. No reaction took place in the absence of SiO_2.

[¶] In competition with the reaction with **1**, the oxirane was consumed by a pronounced oligomerization. Furthermore, the formed products were slowly decomposed under the reaction conditions.



Scheme 3.

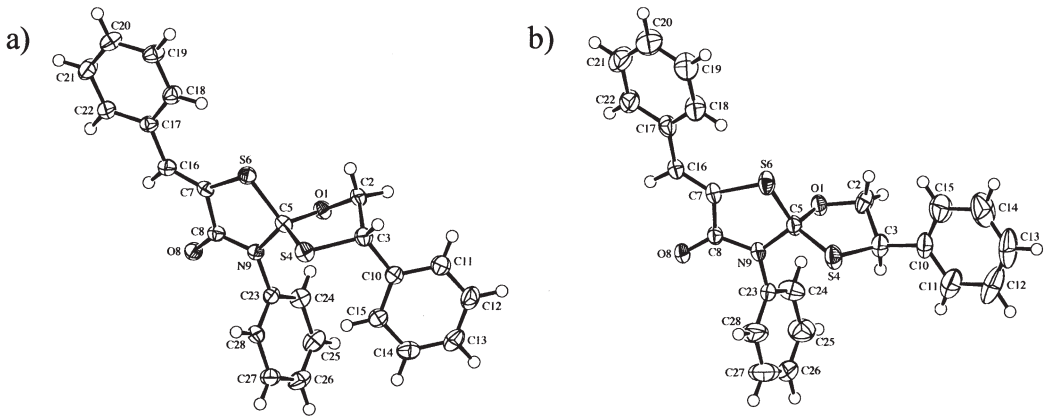


Figure 2. ORTEP Plots[12] of the molecular structures of (a) one of the two symmetry-independent molecules of **6** and (b) of **7** (displacement ellipsoids with 50% probability).

2.2. Reaction of the rhodanine derivative 1 with (*R*)-2-phenyloxirane (5)

The analogous reaction of **1** with **5** (molar ratio 1:2, dry CH_2Cl_2, rt, 10 days, N_2 atmosphere) in the presence of SiO_2 gave two diastereoisomeric spiroheterocycles **6** and **7** in 37 and 8% yield, respectively. In addition, **1** was recovered in 51% yield (Scheme 3). A likely intermediate is **B**. The determination of the ee-values by means of HPLC showed that **6** was formed via inversion of the configuration at C(2) of **5**. The formation of **7** proceeded with lower stereoselectivity and partial racemization (9%) was observed.[‖] The structures of **6** and **7** were assigned on the basis of their elemental analyses and spectroscopic data, particularly 2D-NOESY, HSQC, HSQC-TOCSY, and HMBC spectra, and they were confirmed by X-ray crystallography (Fig. 2).

The examination of a Dreiding-model of **6** shows that the distances between the *ortho*-H atoms of Ph–C(3) and those of Ph–N are small, in agreement with the 2D-NOESY spectrum of **6**, which shows one cross-signal between the *ortho*-H atoms of Ph–N at 7.33–7.30 ppm and those of Ph–C(3) at 6.55 ppm. Therefore, the configuration of **6** should be 3*S*,5*S*. Similarly, the 2D-NOESY spectrum of **7** shows one relevant cross-signal between the *ortho*-H atoms of Ph–N at 7.49–7.45 ppm and H–C(3) at 4.20 ppm, which, on the assumption that the reaction proceeded again with inversion of the configuration of **5**, indicates the (3*S*,5*R*)-configuration of **7**.

The crystals of **6** are enantiomerically pure and the absolute configuration of the molecule has been determined independently by the diffraction experiment and found to have the (3*S*,5*S*)-configuration. There are two symmetry-independent molecules in the asymmetric unit. Both are of the same enantiomer and differ primarily in the orientations of the phenyl rings, particularly the Ph–C(3), which in molecule A is rotated by 70° with respect to its orientation in molecule B. The 1,3-thiazolidine ring in molecule A has a flattened envelope conformation with the spiro C(5)-atom, as the envelope flap, while in molecule B, this ring is planar. The other five-membered ring in each molecule has an envelope conformation with C(2) acting as the envelope flap.

Although the ee of **7** amounted to 91% according to the analytical HPLC and the isolated product was optically active, the crystal used for the crystal-structure determination was racemic since the space group is centrosymmetric. The oxathiolane ring has a half-chair conformation twisted on C(2)–C(3). The other

[‖] The analogous reaction with racemic 2-phenyloxirane gave the corresponding racemic products.

five-membered ring has a distorted shallow envelope conformation with S(6) as the envelope flap. The distortion is towards a half-chair twisted on S(6)–C(5).

3. Discussion and conclusion

The five-membered ring of the rhodanine derivative **1** has been shown to be planar and the bond lengths involving S(1) indicate significant delocalization of the lone-pair electrons of S(1) with the adjacent C(2)=S and C(5)=C(1′) systems.[11] Therefore, the nucleophilic attack of **1** at the Lewis acid-complexed oxiranes could occur, in principle, either at the thiocarbonyl group (C(2)=S) or at the C(5)=C(1′) double bond. A third possibility is the reaction with the carbonyl group (C(4)=O).[3,4,13] However, the results presented show that the reactions of **1** with **2** and **5** take place chemoselectively at the thiocarbonyl group (C(2)=S) to yield the spirocyclic 1,3-oxathiolanes with high regio- and stereoselectivity. The results show that the C=S group is the most reactive nucleophile in **1**. We assume that the reactions proceed via an S_N2-type mechanism, whereby the nucleophilic thiocarbonyl S-atom favorably attacks the C(3)-atom (O–C(3) cleavage) of the activated (*S*)-2-methyloxirane (**2**) leading to intermediate **A** with retention of the configuration (Scheme 2). On the other hand, the addition to (*R*)-2-phenyloxirane (**5**) occurs selectively at the C(2)-atom (O–C(2) cleavage) with inversion of the configuration leading to intermediate **B** (Scheme 3). The partial loss of the stereochemical integrity of the phenyloxirane moiety in the formation of **7** may be interpreted by a competing reaction in which the oxirane ring-opening occurs prior to the nucleophilic attack (S_N1-type).

4. Experimental

4.1. General

See Ref. 14. Optical rotations: Perkin–Elmer 241 polarimeter (c=1 in THF). IR spectra: KBr, cm^{-1}. ^1H- and ^{13}C NMR Spectra: in $CDCl_3$. Enantiomeric excesses were determined by anal. HPLC on a (*S*,*S*)-Whelk-O 1 column (hexane/AcOEt 3:1).

4.2. Reactions of (*Z*)-5-benzylidene-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (1) with (*S*)-2-methyloxirane (2) and (*R*)-2-phenyloxirane (5)

General procedure. To a solution of **1** (ca. 1 mmol), prepared according to Ref. 15, and oxirane **2** or **5** (2–4 mmol) in dry CH_2Cl_2 (10–15 mL) under an N_2 atmosphere, 4.5 g of silica gel (SiO_2, Uetikon–Chemie Chromatographiegel C-560) were added at rt. After stirring the suspension for 10 days at rt, the mixture was filtered and the residue was washed with ethyl acetate (AcOEt, 4×). Then, the combined filtrate was evaporated i.v. The products were separated by chromatography (SiO_2, hexane/AcOEt; CC, MPLC, or prep. TLC (PLC)).

4.2.1. Reaction of 1 with (*S*)-2-methyloxirane (2). Reaction of **1** (446 mg, 1.5 mmol) with **2** (348 mg, 6 mmol) and 4.5 g of SiO_2 at rt, 10 days; CC and prep. TLC (hexane/AcOEt 20:1) yielded 120 mg (23%) of **3** and 103 mg (19%) of **4**, and 230 mg (52%) of the starting material (**1**) was recovered.

Compound (*Z*)-(2*S*,5*R*)-7-benzylidene-2-methyl-9-phenyl-1-oxa-4,6-dithia-9-azaspiro-[4.4]nonan-8-one (**3**). Colorless crystals. Mp 161.4–162.5 °C. $[\alpha]_D^{24}=-9.3$ (>98% ee). IR: 3061w, 3043w, 3026w, 3012w, 2979w, 2925w, 2815w, 1703s, 1611m, 1594w, 1493m, 1447w, 1377w, 1356s, 1337m, 1222m, 1194m, 1171w, 1143m, 1131m, 1081m, 1020s, 986s, 926m, 897w, 870w, 806w, 758m, 733m, 697m, 687m. ^1H NMR (300 MHz): 7.66 (s, PhC*H*); 7.52–7.30 (m, 10 arom. H); 4.41–4.30 (m, H–C(2)); 2.89 (dd, J=10.4, 3.9 Hz, 1H–C(3)); 2.15 (t-like, $J\approx$10.5 Hz, 1H–C(3)); 1.34 (d, J=6.0 Hz, Me). ^{13}C NMR (75.5 MHz): 164.9 (s, C=O); 135.4, 134.7 (2s, 2 arom. C); 130.5, 129.8, 128.84, 128.77, 128.73 (5d, 10 arom. CH); 127.8 (d, Ph*C*H); 124.7 (s, C(7)); 109.9 (s, C(5)); 80.1 (d, C(2)); 40.8 (t, C(3)), 18.2 (q, Me). ESI-MS (MeOH+NaI): 733 (15, $[2M+Na]^+$), 378 (100, $[M+Na]^+$). Anal. calcd for $C_{19}H_{17}NO_2S_2$ (355.48): C 64.20, H 4.82, N 3.94, S 18.04; found: C 64.27, H 4.90, N 3.93, S 17.97. Crystals of **3** suitable for an X-ray crystal-structure analysis were grown from Et_2O/hexane.

Compound (*Z*)-(2*S*,5*S*)-7-benzylidene-2-methyl-9-phenyl-1-oxa-4,6-dithia-9-azaspiro-[4.4]nonan-8-one (**4**). Colorless crystals. Mp 155.0–156.6 °C. $[\alpha]_D^{24}=+114.6$ (>98% ee). IR: 3076w, 3055w, 3039w, 3023w, 2989w, 2970w, 2943w, 2928w, 2862w, 2853w, 1679s, 1609m, 1594w, 1493m, 1447w, 1436w, 1373m, 1360s, 1312w, 1289w, 1238w, 1219w, 1191m, 1178w, 1170w, 1135m, 1104m, 1074w, 1058w, 1014s, 982s, 931s, 806w, 761s, 732s, 694s. ^1H NMR (500 MHz): 7.65 (s, PhC*H*); 7.50–7.41 (m, 7 arom. H); 7.40–7.38 (m, 2 arom. H); 7.35–7.32 (m, 1 arom. H); 4.51–4.47 (m, H–C(2)); 2.77 (dd, J=10.6, 3.6 Hz, 1H–C(3)); 2.65 (dd, J=10.7, 5.7 Hz, 1H–C(3)); 1.41 (d, J=6.3 Hz, Me). ^{13}C NMR (125.8 MHz): 164.4 (s, C=O); 135.3, 134.7 (2s, 2 arom. C); 130.7, 129.7, 129.1, 129.0, 128.73, 128.70 (6d, 10 arom. CH); 127.3 (d, Ph*C*H); 124.5 (s, C(7)); 110.6 (s, C(5)); 81.8 (d, C(2)); 41.0 (t, C(3)), 19.5 (q, Me). ESI-MS (MeOH+NaI): 733 (25, $[2M+Na]^+$), 378 (100, $[M+Na]^+$). Anal. calcd for $C_{19}H_{17}NO_2S_2$ (355.48): C 64.20, H 4.82, N 3.94, S 18.04; found: C 64.18, H 4.94, N 3.91, S 18.02. Crystals of **4** suitable for an X-ray crystal-structure analysis were grown from Et_2O/hexane.

4.2.2. Reaction of 1 with (*R*)-2-phenyloxirane (5). Reaction of **1** (297 mg, 1 mmol) with **5** (240 mg, 2 mmol) and 4.5 g of SiO_2 at rt, 10 days; CC and MPLC (hexane/AcOEt 15:1) yielded 153 mg (37%) of **6** and 32 mg (8%) of **7**, and 151 mg (51%) of the starting material (**1**) was recovered (Scheme 3).

Compound (*Z*)-(3*S*,5*S*)-7-benzylidene-3,9-diphenyl-1-oxa-4,6-dithia-9-azaspiro[4.4]no-nan-8-one (**6**). Colorless crystals. Mp 218.6–222.9 °C (partially decomposed). $[\alpha]_D^{24}=-12.3$ (98% ee). IR: 3058w, 3032w, 2970w, 2926w, 2871w, 1690vs, 1608m, 1594w, 1493s, 1453w, 1446m, 1358vs, 1347vs, 1291w, 1280w, 1243m, 1234s, 1201s, 1185w, 1171m, 1155m, 1080w, 1072w, 1053vs, 1041vs, 1002w, 967m, 940w, 914w, 898m, 864w, 797m, 774w, 762m, 754m, 735m, 728m, 702s, 693s, 687s. ^1H NMR (600 MHz):

7.62 (s, PhC*H*); 7.45 (d, *J*=7.5 Hz, 2 arom. H); 7.42–7.27 (m, 8 arom. H); 7.02 (t, *J*=7.4 Hz, 1 arom. H); 6.92 (t-like, *J*≈7.7 Hz, 2 arom. H); 6.55 (d, *J*=7.4 Hz, 2 arom. H); 4.72 (dd, *J*=5.8, 2.5 Hz, H–C(3)); 4.37 (dd, *J*=9.8, 5.8 Hz, 1H–C(2)); 4.17 (dd, *J*=9.8, 2.6 Hz, 1H–C(2)). ^{13}C NMR (150.9 MHz): 165.7 (s, C=O); 139.3, 135.3, 134.7 (3s, 3 arom. C); 131.6, 129.9, 129.1, 128.9, 128.8, 128.4 (6d, 12 arom. CH); 127.9 (d, Ph*C*H); 127.5, 127.0 (2d, 3 arom. CH); 124.0 (s, C(7)); 112.9 (s, C(5)); 75.9 (t, C(2)); 54.3 (d, C(3)). ESI-MS (MeOH/CH_2Cl_2+NaI): 859 (8), 858 (15), 857 (26, $[2M+Na]^+$), 442 (14), 441 (30), 440 (100, $[M+Na]^+$). CI-MS (NH_3): 418 (12, $[M+H]^+$), 301 (12), 300 (21), 299 (100), 282 (17), 256 (7). Anal. calcd for $C_{24}H_{19}NO_2S_2$ (417.55): C 69.04, H 4.59, N 3.35, S 15.36; found: C 68.86, H 4.50, N 3.29, S 15.20. Crystals of **6** suitable for an X-ray crystal-structure analysis were grown from CH_2Cl_2.

Compound (*Z*)-(3*S*,5*R*)-7-benzylidene-3,9-diphenyl-1-oxa-4,6-dithia-9-azaspiro[4.4]no-nan-8-one (**7**). Colorless crystals. Mp 150.3–153.7 °C. $[\alpha]_D^{24}=-152.8$ (91% ee). IR: 3057w, 3028w, 2926w, 2863w, 1697vs, 1611m, 1595w, 1492s, 1453m, 1447m, 1345vs, 1227m, 1196s, 1150m, 1078m, 1052vs, 1040s, 944w, 900w, 866w, 801w, 761s, 736w, 692vs. ^{1}H NMR (500 MHz, at 240 K): 7.73 (s, PhC*H*); 7.58–7.31 (m, 15 arom. H); 4.49 (dd, *J*=9.7, 5.4 Hz, 1H–C(2)); 4.20 (dd, *J*=10.7, 5.4 Hz, H–C(3)); 4.03 (*t*-like, *J*≈10.2 Hz, 1H–C(2)). ^{13}C NMR (125.8 MHz, at 240 K): 165.3 (s, C=O); 135.0, 134.21, 133.19 (3s, 3 arom. C); 130.1, 129.9, 129.2, 129.13, 129.05, 128.85, 128.83, 128.7, 128.33 (9d, 15 arom. CH); 128.26 (d, Ph*C*H); 123.8 (s, C(7)); 111.4 (s, C(5)); 76.5 (*t*, C(2)); 55.2 (d, C(3)). ESI-MS (MeOH+NaI): 859 (6), 858 (15), 857 (25, $[2M+Na]^+$), 442 (15), 441 (30), 440 (100, $[M+Na]^+$). Anal. calcd for $C_{24}H_{19}NO_2S_2$ (417.55): C 69.04, H 4.59, N 3.35, S 15.36; found: C 69.21, H 4.76, N 3.31, S 15.21. Crystals of *rac*-**7** suitable for an X-ray crystal-structure analysis were grown from Et_2O/hexane.

4.3. X-ray crystal-structure determination of 3, 4, 6, and 7

See Figures 1 and 2.[16] All measurements were made at 160 K on a Nonius KappaCCD diffractometer[17] using graphite-monochromated Mo K_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reductions were performed with HKL Denzo and Scalepack.[18] The intensities were corrected for Lorentz and polarization effects, and, in the cases of **3**, **4**, and **7**, an absorption correction based on the multi-scan method[19] was applied. Equivalent reflections, other than the Friedel pairs in 3, 4 and 6, were merged. The structures were solved by direct methods using SIR92,[20] which revealed the positions of all non-H-atoms. In the case of **6**, there were 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,[21] but none could be found, although there is a pseudo-inversion centre relating 89% of the atoms. 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 atom ($1.5U_{eq}$ for methyl groups). Refinements of the structures were carried out on F^2 using full-matrix least-squares procedures, which minimised the function $\sum w(F_o^2-F_c^2)^2$. A correction for secondary extinction was applied in the cases of **3**, **6**, and **7**. In **4** and **6**, one and two reflections, respectively, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Refinements of the absolute structure parameter[22] yielded values of −0.04(5), −0.04(7), and 0.00(4) for **3**, **4**, and **6**, respectively, which confidently confirm that the refined coordinates represent the true enantiomorph in each case. For **7**, the largest peak of residual electron density lies within the oxathiolane ring in the vicinity of O(1) and C(2), but is inappropriately positioned to be correlated with disorder. Neutral atom scattering factors for non-H-atoms were taken from[23a] and the scattering factors for H-atoms were taken from.[24] Anomalous dispersion effects were included in F_c;[25] the values for f' and f'' were those of Ref. 23b. The values of the mass attenuation coefficients are those of Ref. 23c. All calculations were performed using the SHELXL97[26] program.

Crystal data for **3**. $C_{19}H_{17}NO_2S_2$, M=355.48, colorless, prism, crystal dimensions 0.12×0.15×0.28 mm^3, orthorhombic, space group $P2_12_12_1$, Z=4, reflections for cell determination 57014, 2θ range for cell determination 4–60°, a=5.6543(1) Å, b=12.0695(2) Å, c=25.3032(4) Å, V=1726.81(5) Å^3, D_X=1.367 g cm^{-3}, μ(Mo K_α)=0.319 mm^{-1}, transmission factors (min; max) 0.876; 0.966, $2\theta_{(max)}$=60°, total reflections measured 30374, symmetry independent reflections 5021, reflections with $I>2\sigma(I)$ 4222, parameters refined 219, R (on F; $I>2\sigma(I)$ reflections)=0.0338, $wR(F^2)$[all reflections]=0.0777 (w=$(\sigma^2(F_o^2)+(0.0323P)^2+0.3459P)^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.032, secondary extinction coefficient 0.005(1), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)=0.34; −0.25 e Å^{-3}.

Crystal data for **4**. $C_{19}H_{17}NO_2S_2$, M=355.48, colorless, tablet, crystal dimensions 0.07×0.15×0.25 mm^3, orthorhombic, space group $P2_12_12_1$, Z=4, reflections for cell determination 35017, 2θ range for cell determination 4–60°, a=5.5855(1) Å, b=7.8820(1) Å, c=39.0360(6) Å, V=1718.56(5) Å^3, D_X=1.374 g cm^{-3}, μ(Mo K_α)=0.321 mm^{-1}, transmission factors (min; max) 0.863; 0.979, $2\theta_{(max)}$=60°, total reflections measured 25282, symmetry independent reflections 4973, reflections with $I>2\sigma(I)$ 3564, parameters refined 218, R (on F; $I>2\sigma(I)$ reflections)=0.0425, $wR(F^2)$[all reflections]=0.0871 ($w=(\sigma^2(F_o^2)+(0.0318P)^2+0.2116P)^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.040, final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)=0.41; −0.33 e Å^{-3}.

Crystal data for **6**. $C_{24}H_{19}NO_2S_2$, M=417.55, colorless, tablet, crystal dimensions 0.12×0.15×0.18 mm^3, monoclinic, space group $P2_1$, Z=4, reflections for cell determination 4714, 2θ range for cell determination 4–55°, a=8.5993(1) Å, b=14.2768(2) Å, c=16.5468(2) Å, β=103.5458(6)°, V=1974.95(4) Å^3, D_X=1.404 g cm^{-3}, μ(Mo K_α)=0.291 mm^{-1}, $2\theta_{(max)}$=55°, total reflections measured 45245, symmetry independent reflections 9001, reflections with $I>2\sigma(I)$ 7665, parameters refined 524;

restraints 1, R (on F; $I>2\sigma(I)$ reflections)=0.0402, $wR(F^2)$[all reflections]=0.0970 ($w=(\sigma^2(F_o^2)+(0.0421P)^2+0.2619P)^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.053, secondary extinction coefficient 0.0052(9), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)=0.38; −0.41 e Å^{-3}. The structure of *rac*-**6** was also determined and the data have been deposited.[16]

Crystal data for rac-**7**. $C_{24}H_{19}NO_2S_2$, M=417.55, colorless, prism, crystal dimensions 0.10×0.18×0.18 mm^3, triclinic, space group $P\bar{1}$, Z=2, reflections for cell determination 29642, 2θ range for cell determination 4–60°, a=8.5150(2) Å, b=11.0168(2) Å, c=12.1739(4) Å, α=112.9576(9)°, β=92.4883(9)°, γ=95.597(2)°, V=1042.40(5) Å^3, D_X=1.330 g cm^{-3}, μ(Mo K$_\alpha$)=0.275 mm^{-1}, transmission factors (min; max) 0.859; 0.980, $2\theta_{(max)}$=60°, total reflections measured 28717, symmetry independent reflections 6086, reflections with $I>2\sigma(I)$ 4405, parameters refined 263, R (on F; $I>2\sigma(I)$ reflections)=0.0568, $wR(F^2)$[all reflections]=0.1580 ($w=(\sigma^2(F_o^2)+(0.0615P)^2+0.8250P)^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.024, secondary extinction coefficient 0.015(4), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min)=1.06; −0.49 e Å^{-3}. Crystals of a second polymorph of *rac*-**7** were obtained from CH_2Cl_2. The structure of this polymorph was also determined and the data have been deposited.[16]

Acknowledgements

We thank the analytical services of our institute for NMR and mass spectra and elemental analyses, Mr. B. Bürgi for his assistance with the determination of the crystal structures and the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, for financial support.

References and notes

1. Blagoev, M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1999**, *82*, 1458.
2. Blagoev, M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1999**, *82*, 2316.
3. Blagoev, M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 3163.
4. Fu, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2001**, *84*, 3319.
5. Fu, C.; Linden, A.; Heimgartner, H. *Heterocycles* **2002**, *58*, 333.
6. Fu, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 2258.
7. Fu, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 2833.
8. Oremus, V.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1991**, *74*, 1500.
9. Tromm, P. C.; Heimgartner, H. *Helv. Chim. Acta* **1990**, *73*, 2287.
10. Planned PhD thesis of C. Fu, University of Zurich..
11. Linden, A.; Awad, E. M. A. H.; Heimgartner, H. *Acta Crystallogr. Sect. C* **1999**, *55*, 1877.
12. Johnson, C. K., ORTEP II. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
13. Torok, D. S.; Figueroa, J. J.; Scott, W. J. *J. Org. Chem.* **1993**, *58*, 7274.
14. Moya Argilagos, D.; Kunz, R. W.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1998**, *81*, 2388.
15. Andreasch, R.; Zipser, A. *Monatsh. Chem.* **1903**, *24*, 499.
16. CCDC-225511-225516 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 CB2 1EZ, U.K. (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
17. Hooft, R. *KappaCCD Collect Software*; Nonius BV: Delft, The Netherlands, 1999.
18. Otwinowski, Z.; Minor, W. In *Methods in Enzymology. Macromolecular Crystallography Part A*; Carter, C. W. Jr, Sweet, R. M., Eds.; Academic: New York, 1997; Vol. 276, p 307.
19. Blessing, R. H. *Acta Crystallogr. Sect. A* **1995**, *51*, 33.
20. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. SIR92. *J. Appl. Crystallogr.* **1994**, *27*, 435.
21. Spek, A. L. *PLATON, Program for the Analysis of Molecular Geometry*; University of Utrecht: The Netherlands, 2002.
22. (a) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr. Sect. A* **1999**, *55*, 908. (b) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.
23. (a) Maslen, E. N.; Fox, A. G.; O'Keefe, M. A. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992; Vol. C, p 477 Table 6.1.1.1. (b) Creagh, D. C.; McAuley, W. J. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992; Vol. C, p 219 Table 4.2.6.8. (c) Creagh, D. C.; Hubbell, J. H. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992; Vol. C, p 200 Tables 4.2.4.3.
24. Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
25. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
26. Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5413–5421
Tetrahedron

Vicarious nucleophilic substitution of hydrogen versus vinylic substitution of halogen in the reactions of carbanions of halomethyl aryl sulfones with dialkyl halofumarates and halomaleates

Mieczysław Mąkosza,* Shamil Nizamov and Andrzej Kwast

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland

Received 2 January 2004; revised 30 March 2004; accepted 22 April 2004

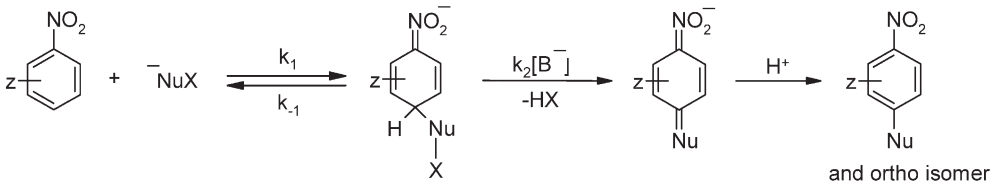
Abstract—Reaction of halomethyl aryl sulfone carbanions with dialkyl halofumarates and halomaleates results in nucleophilic substitution of hydrogen and/or of the halogen. The reaction with halofumarates proceeds via addition of the carbanions to the vinylic carbon atom connected with hydrogen, followed by base promoted β-elimination of hydrogen halide in which the halogen originates from the carbanion moiety or from the alkene. In the case of halomaleates the reaction proceeds via an elimination–addition sequence.

1. Introduction

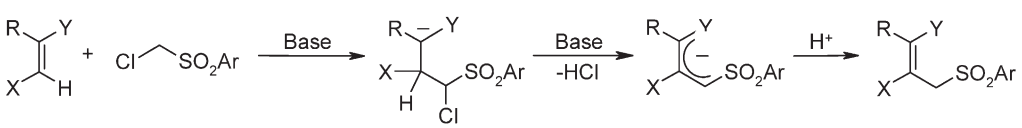
Vicarious nucleophilic substitution of hydrogen, VNS, in nitroarenes is presently a well established tool for the introduction of a variety of carbon, nitrogen and oxygen substituents into aromatic rings.[1–7] The reaction proceeds via addition of nucleophiles containing leaving groups X such as α-halocarbanions,[2] anions of alkyl hydroperoxides,[3] derivatives of sulfenamide,[4] hydrazine[5] or hydroxylamine[6] to the nitroaromatic rings with formation of the σ^H adducts, followed by base induced β-elimination of HX. The most important characteristic feature of this process is that nucleophilic replacement of hydrogen proceeds faster than halogen, even fluorine, located in a similarly activated position of the nitroaromatic ring[1–7] (Scheme 1).

The VNS reaction can be also executed in electrophilic alkenes although in these cases its scope is much limited because of the strong tendency for formation of cyclopropane rings via intramolecular nucleophilic substitution of halogen in the initial adducts of α-halocarbanions to these alkenes. Nevertheless, α-halocarbanions generated from halomethyl aryl sulfones and some other precursors react with benzylidene cyanoacetates, nitroalkenes, dimethyl fumarate, quinones etc. via the VNS pathway[8,9] (Scheme 2).

A similar process was reported to occur in activated aldimines[10] and immonium salts.[11] However, reports on VNS in electrophilic alkenes are not numerous, and very little is known concerning mechanistic features of this reaction.



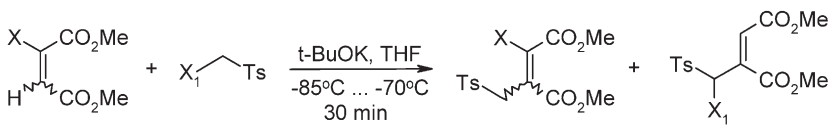
Scheme 1.



Scheme 2.

Keywords: Vicarious nucleophilic substitution; Halo esters; Sulfones; Elimination reactions; Vinylic substitution.
* Corresponding author. Tel.: +48-22-6318788; fax: +48-22-6326681; e-mail address: icho-s@icho.edu.pl

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.049



3 X = Cl **1** X_1 = Cl **5** X = Cl **7*E*** X_1 = Cl
4 X = Br **2** X_1 = Br **6** X = Br **8*E*** X_1 = Br

Scheme 3.

Nucleophilic substitution of halogen located at an electron-deficient double carbon–carbon bond (C=C)—vinylic nucleophilic substitution, S_NV—was the subject of thorough investigations. Although many mechanistic schemes are discussed for this reaction, it is commonly accepted that majority of S_NV reactions of halogen in electron-deficient alkenes proceed via irreversible addition of nucleophiles to the carbon bearing halogen, followed by elimination of the halide anion from the intermediate β-halocarbanion.[12] Not much is known, however, about relations of rates of nucleophilic addition to electron-deficient alkenes in similarly activated positions occupied with hydrogen and halogen. We have already shown that in 2-chloro-1,4-naphthoquinone, carbanions add predominantly in position 3—occupied by hydrogen.[8c] We could expect, that the VNS reaction, which in aliphatic systems also involves an irreversible addition step can be an efficient tool to study this question.

2. Results and discussion

For studies of the VNS reaction with carbanions of chloromethyl *p*-tolyl sulfone (**1**) and bromomethyl *p*-tolyl sulfone (**2**), typically used in this process, dimethyl chloromaleate (**3*E***) and chlorofumarate (**3*Z***) as well as dimethyl bromomaleate (**4*E***) and bromofumarate (**4*Z***) were chosen as model electrophilic alkenes in which positions occupied by hydrogen and by halogen are similarly activated.

Reactions of these electron-deficient alkenes **3** and **4** with carbanions of **1** and **2** were carried out using *t*-BuOK/THF base–solvent system at low temperature. As we reported earlier, dimethyl fumarate and maleate readily undergo VNS with these sulfones under similar reaction conditions.[8a,b]

Table 1. Reactions of haloesters **3** and **4** with carbanions of halosulfones **1** and **2**

Entry	Ester	X	Sulfone	X_1	Products and yields (%)			
					VNS[a]		S_NV[b]	
1	**3*E***	Cl	**1**	Cl	**5**	5	**7*E***	57
2	**3*E***	Cl	**2**	Br	**5**	7	**8*E***	57
3	**4*E***	Br	**1**	Cl	**6**	3	**7E**	64
4	**4*E***	Br	**2**	Br	**6**	6	**8*E***	52
5[c]	**3*Z***	Cl	**1**	Cl	**5**	37	**7*E***	29
6	**3*Z***	Cl	**2**	Br	**5**	41	**8*E***	15
7	**4*Z***	Br	**1**	Cl	**6**	8	**7*E***	55
8	**4*Z***	Br	**2**	Br	**6**	17	**8*E***	37

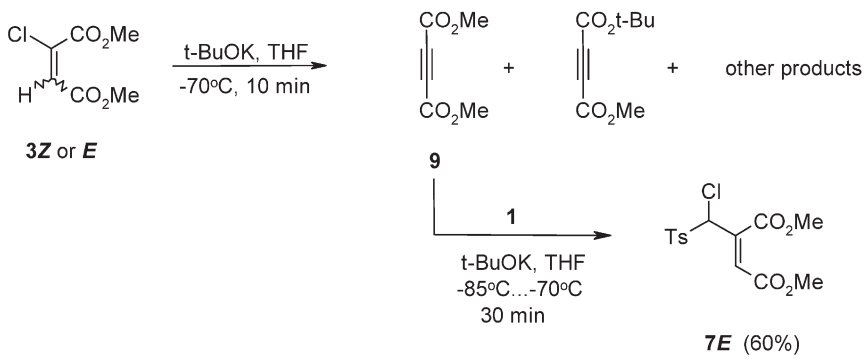
[a] One isomer. Geometry not determined.
[b] One isomer *E*.
[c] The reaction was continued for additional 60 min at −70 °C (under standard conditions also isomer **7*Z*** was obtained and the proportion of products was following: **5** (38%), **7*E*** (23%), **7*Z*** (15%)).

Results of the reaction of **1** and **2** with **3** and **4** are presented in Scheme 3 and Table 1. It is an important observation that the reaction course is a function of both halogens X in the haloester and X_1 in the carbanion and also of the geometry of the starting haloesters. The results of the reactions with the haloesters that differ in geometry indicate, that the VNS competes with the S_NV reaction only in the cases of halofumarates (**3*Z***, **4*Z***), while the reaction of these carbanions with halomaleates (**3*E***, **4*E***) give almost exclusively products of the S_NV substitution of halogen.

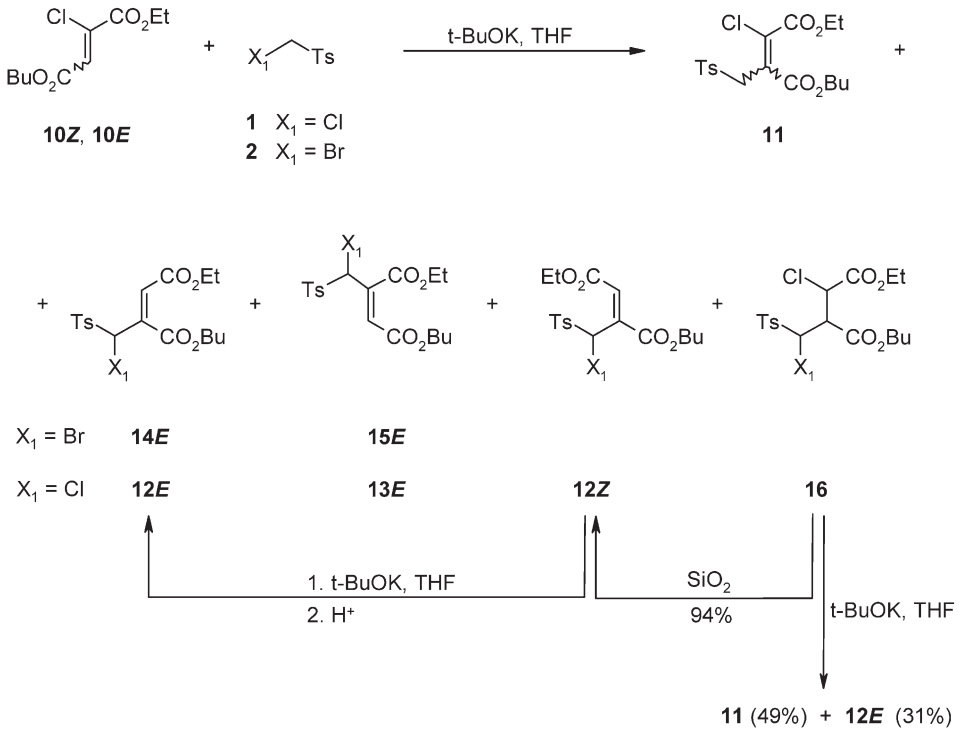
The course of the reaction of halofumarates depends strongly on the kind of the halogen. When X=X_1 the results are somewhat similar for Cl and Br (entry 5 versus 8), but when X and X_1 are different the reaction proceeds predominantly with elimination of hydrogen bromide (entry 6 and 7). The reactions of halomaleates **3*E***, **4*E*** with **1** and **2** give roughly the same results regardless of the kind of halogens (entry 1–4).

These observations, especially that the ratio of the VNS and S_NV products in certain cases depends on the kind of halogen in both reaction partners, are inconsistent with the initial assumption, that the competing reactions VNS and S_NV occur via addition of the carbanion to =C–H and to =C–X, respectively, and that the product ratio is a function of the relative rates of these two competing addition processes. There is no doubt that the VNS reaction proceeds via addition to =CH, which is obvious from the structures of **5** and **6**, on the other hand substitution of the halogen can proceed along a few mechanistic pathways. Besides the common addition–elimination mechanism, two other pathways should be considered: elimination–addition with intermediate formation of the acetylenic compounds and an addition-β-elimination pathway proceeding via addition of the carbanion to =CH and subsequent β-elimination of HX—in a kind of 'cine' substitution.

In the system studied, the elimination–addition pathway and intermediacy of acetylenedicarboxylates appears quite reasonable. Under the reaction conditions, but in the absence of the carbanion precursors, both **3*E*** and **3*Z*** undergo facile base-promoted β-elimination of HCl yielding dimethyl acetylenedicarboxylate (**9**) and products of its further transformations (Scheme 4). In a competitive experiment we found, that expectedly, formation of the acethylenic products was much faster from **3*Z*** than from **3*E***. Furthermore, independently prepared **9** reacts with the carbanion of **1** to form **7*E***, identical to the product of



Scheme 4.



Scheme 5.

substitution of the halogen in chloroester **3**. Thus, one can assume that the competition between VNS and S_NV is, in fact, a competition between addition of $\mathbf{1}^-$ to **3** and base-induced conversion of **3** to **9** followed by addition of $\mathbf{1}^-$ to the later.

The elimination–addition mechanism is also in accordance with the observation that in the reaction of **1** with chloroester **3*Z*** a mixture of products of VNS and S_NV is produced, whereas the same carbanion reacting with bromoester **4*Z***—which is more susceptible to β-elimination to form acetylenic derivative—gave predominantly the S_NV product **7*E***.

There are, however, a few observations, which seem to contradict such a competition scheme. The S_NV reaction is a dominant process in the reactions of the maleate, which was found to form acethylenic intermediates much slower than the fumarate. These observations could be explained by the hypothesis that in the case of the halofumarates, the addition of carbanion to the double bond is faster than β-elimination, whereas in the case of the halomaleates such a rate relationship is reversed.

The unique feature of the elimination–addition mechanism, as far as the substrates under investigation are concerned, is formation of the symmetrical intermediate (**9**), hence, addition of the carbanion should take place with equal rate to the both acetylenic carbons. One can expect, therefore, that using the haloester of two different alcohols in the reaction with **1** should allow to differentiate the reaction pathways. For this purpose ethyl *n*-butyl chloroesters **10*E*** and **10*Z***—in which the halogen atom is located in a defined position—were synthesized,[†] and subjected to the reaction with **1** and **2** (Scheme 5, Table 2).

In the reactions of chloromaleate **10*E*** with **1** at −90 °C subsequently warmed to −70 °C only minute amount of the

[†] The structure of **10*Z*** has been determined on the basis of ^{13}C spectra of the (2*Z*)-3-chloro-4-ethoxy-4-oxobut-2-enoic acid, compared with the isomeric ethyl ester (see Section 3).

Table 2. Reactions of ethyl butyl chloroesters **10*E*** and **10*Z*** with carbanions of halosulfones **1** and **2**

Entry	**10**	Sulfone	X_1	Reaction conditions[a]	Products and yields (%)			
					VNS[b] **11**	S_NV		other
1	***E***	**1**	Cl	−90→−70 °C	2	**12*E*/13*E*** 1:1	76	
2	***E***	**2**	Br	−90-→-70 °C	4	**14*E*/15*E*** 1:1	62	
3	***E***	**2**	Br	−90→−70 °C[c]	37	**14*E*/15*E*** 1:1	13	
4	***Z***	**1**	Cl	−90 °C	12	**12*E***	23	**12*Z*** 23, **16** 22
5	***Z***	**2**	Br	−90 °C	57	**14*E*/15*E*** 1:1	11	

[a] A mixture of both reagents was added to a solution of *tert*-BuOK.
[b] One isomer, geometry not determined.
[c] The carbanion of **2** was generated first, then **10** was added.

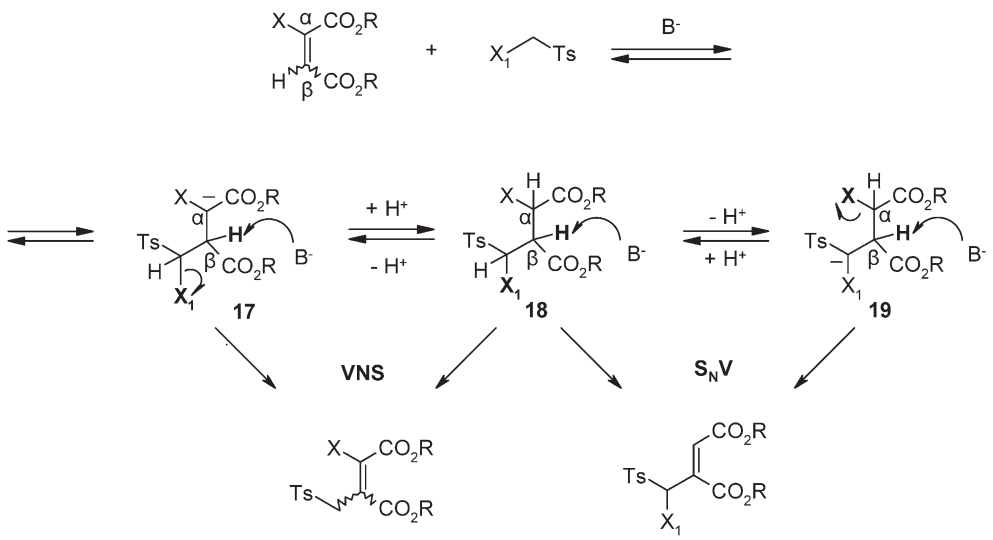
VNS product **11** was produced (Table 2, entry 1). The main reaction course was an S_NV process giving two isomeric products **12*E*** and **13*E*** as a 1:1 mixture, apparently being a result of statistical rather than selective addition of the carbanion to the mixed acetylenedicarboxylic diester.

The reaction of **10*E*** with bromosulfone **2** gave a similar picture (Table 2, entry 2). However, when the changed procedure was used—the carbanion of **2** was generated first, then **10*E*** was added—**11** became the main product of the reaction (Table 2, entry 3). This result demonstrates the role of a competition between addition of the carbanion to the alkene and the base-promoted elimination resulting in formation of the acetylene derivative.

Different results were obtained in the reactions of chlorofumarate **10*Z***. The reaction with **1** was carried out and finished at −90 °C. The usual work-up and chromatographic separation on silica gel furnished four products in roughly equal yields (Scheme 5). Two of them, **11** and **12*E***, were the expected products of nucleophilic substitution of hydrogen (VNS) and chlorine (S_NV), respectively. The stereoisomer of the latter (**12*Z***) was not found in the crude product mixture, thus it is not an original reaction product. A similar observation was made in the reaction of **3*Z*** with **1** (Table 1, entry 5 (table footnote 'c')). The additional experiments showed that protonation of the initially formed anion of **12** gives exclusively **12*E***, while **12*Z*** is produced from the adduct **16** during the column chromatography. Therefore, the combined amounts of **12*Z*** and **16** should be considered as the original yield of the latter.

The most essential observation is that in all the products of the reaction of **10*Z*** a new C–C bond was formed between the nucleophile and the β-carbon atom of the α-chloroalkene. Since it seems unlikely, that in this case, nucleophilic addition of the carbanion to the acetylene dicarboxylic acid diester proceeds selectively in the vicinity of the COOBu group, the elimination–addition mechanism of the chlorine substitution in **10*Z***and consequently also in **3*Z*** can be rejected. The adduct **16**, in the form of an anion, appears to be a common intermediate in the both substitution reactions—VNS of the hydrogen and S_NV of the halogen. The separate experiment in which **16** was treated with base under similar reaction conditions revealed that both products of substitution **11** and **12*E*** were formed, hence definitely confirmed this supposition (Scheme 6).

In the analogous reaction of **10*Z*** with bromosulfone **2** neither the adduct nor the product of its transformation on SiO_2 were observed, instead VNS product **11** was isolated in substantial yield (Table 2, entry 5). The product of chlorine substitution, which was obtained in a minor amount, consisted of a 1:1 mixture of regioisomers which means that it was formed exclusively in the elimination–addition process and also, that the addition of **2** to the fumarate resulted solely in the formation of the VNS product. Selective elimination of HBr from the intermediate adduct



Scheme 6.

reflects the higher rate of this process, compared to that of elimination of HCl. Noteworthy competition of the elimination–addition pathway suggests, that the addition of the bromomethyl sulfone to the fumarate occurs slower, than that of chloromethyl sulfone.

Thus, in the system studied, the real competition is not that between the addition of the α-halocarbanions at different sites of electrophilic alkene **3** and **4** or **10**, but first of all between elimination of HX from the haloester and addition of the carbanion to its double bond. The former process dominates in halomaleate esters resulting in non-regioselective formation of the halogen substitution products. The latter is much faster in halofumaric esters. The addition takes place exclusively at the carbon connected with H of the double bond so only one regioisomer of the intermediate adduct is formed. At this point another competition takes place, namely between two pathways of further conversion of the anionic adduct: β-elimination of HX, which leads to substitution of the vinylic halogen, or that of HX_1 resulting in VNS of hydrogen. In fact, the mechanistic picture is more complicated (Scheme 6).

While the base-promoted elimination of HX_1, in the course of the VNS reaction, can occur directly from the initially formed carbanion of the adduct **17**, the elimination of HX leading to substitution of the halogen requires protonation of **17** at C-α to form neutral intermediate **18** or—after further deprotonation at C-γ—its anionic form **19**. One can suppose, that elimination of hydrogen halide is much faster from **18** than from any negatively charged derivative. The question is, however, whether—under strongly basic conditions—sufficient concentration of the neutral adduct is present. Thus, the acid–base equilibrium between all forms of the adduct may play an important role in the final VNS–S_NV products distribution. This can probably explain the differences in VNS/S_NV ratio of the products obtained in particular cases.

Although the actual mechanism of the vinylic halogen substitution appeared to be different from that initially assumed, the obtained results provide conclusive information about relative rates of nucleophilic addition to the vinylic carbon atoms connected with hydrogen and halogen, in strongly electrophilic alkenes. Since we have not observed any product resulting from nucleophilic addition to the carbon atom bonded to a halogen, this addition must be a relatively slow process. Verification of this conclusion was obtained from an attempted substitution of the halogen in dimethyl dichloromaleate **20*Z*** and dichlorofumarate **20*E*** with potassium salt of **1** (Scheme 7).

Under the typical reaction conditions both isomers reacted differently. The only observed process in the case of **20*Z*** was slow nucleophilic addition of the carbanion to the carbonyl group leading to acylation of **1**, whereas in **20*E*** substitution of the chlorine took place as well with a comparable rate. Since the addition of the halosulfone carbanions to the carbonyl group of the monohaloesters **3** or **4** was not observed, also direct substitution of chlorine should be considered as a slow process, which does not contribute to the formation of the S_NV products in the monohaloesters. The results of Scheme 7 show also, that the addition of the carbanion to the fumarate double bond is faster than that to the maleate, which is what was suggested above and what allows a comparison of the rates of the processes involved for halofumarates (***Z***) and maleates (***E***)

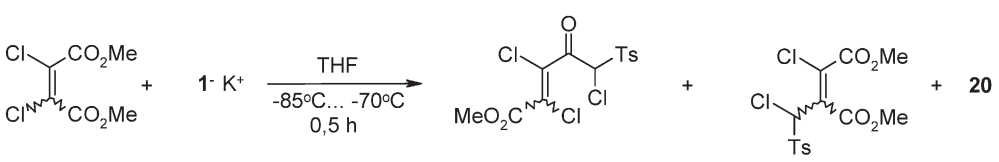
$$\boldsymbol{Z}_{\text{addition}} > \boldsymbol{Z}_{\text{elimination}} > \boldsymbol{E}_{\text{elimination}} > \boldsymbol{E}_{\text{addition}}$$

Concluding, we have shown that the S_NV reaction in halomaleate and halofumarate proceeds not via addition of the nucleophile to =CX, but along two different pathways depending on the geometry of the haloester. While the reactions of halomaleate esters proceed via an elimination–addition pathway, in halofumarates the substitution occurs mainly according to the addition-β-elimination (cine) mechanism. In this case the addition proceeds rapidly at =CH to produce carbanionic adduct being the common intermediate for the S_NV and the VNS reactions. Its further conversion depends on the relative rates of the elimination processes. We have also shown, that the halogen substituent, although it activates the β position of the vinylic system towards nucleophilic addition, protects a position it occupies against nucleophilic attack, as was observed earlier for 2-chloro-1,4-naphthoquinone.[8d]

3. Experimental

3.1. General

Melting points are uncorrected. NMR spectra were taken in $CDCl_3$ on Varian Gemini 200 (200 MHz) spectrometer operating at 200 MHz for ^1H and at 50 MHz for ^{13}C. Chemical shifts are given in δ ppm referred to TMS as an internal standard, coupling constants are given in Hertz. Mass spectra were recorded on AMD 604 apparatus.



	21(*E*,*Z*)	**22(*E*,*Z*)**
20*Z*	20 %	0 %
20*E*	8 %	14 %

Scheme 7.

IR spectra were recorded in KBr on Beckmann IR-4240 spectrometer. Column chromatography was performed using silica gel 230–400 mesh (E. Merck). Commercial *t*-BuOK was sublimed before use. All reactions were performed under argon.

The following starting materials were prepared according to the published procedures: chloromethyl *p*-tolyl sulfone (**1**),[13] bromomethyl *p*-tolyl sulfone (**2**),[13] dimethyl chlorofumarate (**3*Z***),[14,15] dimethyl chloromaleate (**3*E***),[17] dimethyl bromofumarate (**3*Z***),[14,15] dimethyl bromomaleate (**4*E***),[16,17] potassium (2*E*)-3-chloro-4-ethoxy-4-oxobut-2-enoate,[18] dimethyl dichloromaleate (**20*Z***),[19,20] dimethyl dichlorofumarate (**20*E***).[21]

3.1.1. (2*Z*)-3-Chloro-4-ethoxy-4-oxobut-2-enoic acid. The titled compound was obtained according to the described procedure.[22] Colourless prisms, mp 50–52 °C (hexane) [lit.[22] mp 52–53 °C (petr. ether)], ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.7 (bs, 1H), 7.18 (s, 1H), 4.32 (q, J=7.2 Hz, 2H), 1.34 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4, 161.3, 137.1, 125.6, 63.6, 13.9; IR (KBr) 3250, 3070, 2987, 1736, 1712, 1631, 1407, 1397, 1370, 1253, 1221, 1045, 862 cm^{-1}; Anal. Calcd for $C_6H_7ClO_4$: C, 40.35; H, 3.96. Found: C, 40.01; H 4.01.

The other regioisomer, (2*Z*)-2-chloro-4-ethoxy-4-oxobut-2-enoic acid, was also observed as a minor product of the reaction. It was not obtained in the pure state, however, but characterized by NMR spectra of a sample contaminated with the major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.7 (bs, 1H), 7.26 (s, 1H), 4.28 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1, 163.2, 133.6, 128.6, 61.8, 13.7. Comparison of the spectra of both isomers allows to conclude their structures.

3.1.2. 4-Butyl 1-ethyl (2*Z*)-2-chlorobut-2-enedioate (10*Z*). To a stirred mixture of (2*Z*)-3-chloro-4-ethoxy-4-oxobut-2-enoic acid (1.78 g, 10 mmol), BuOH (1.48 g, 20 mmol) and PPh_3 (3.93 g, 15 mmol) in dry THF (20 mL) DEAD (2.61 g, 15 mmol) was added slowly at −70 °C. The cooling bath was removed and progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with hexane/ethyl ether 1:1 (100 ml) and passed trough a small amount of silica gel. After evaporation of the solvent the crude product was purified by short column chromatography (hexane/ethyl ether 30:1 eluent), followed by distillation on the Kugelrohr apparatus (110–120 °C, 20 Torr). Yield 1.83 g (78%). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17 (s, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.22 (t, J=6.6 Hz, 2H), 1.78–1.60 (m, 2H), 1.52–1.33 (m, 2H), 1.35 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.3, 161.6, 134.5, 126.8, 65.3, 63.3, 30.4, 19.0, 14.0, 13.6; IR (KBr) 2963, 2936, 2875, 1744, 1724, 1629, 1470, 1369, 1312, 1255, 1184, 1045, 1023, 771 cm^{-1}; MS (EI,) *m*/*z* 235 [0.7, $(M+H)^+$], 189 (20), 179 (100), 161 (96), 151 (56), 133 (59), 56 (61); Anal. Calcd for $C_{10}H_{15}ClO_4$: C, 51.18; H, 6.44; Cl, 15.11. Found: C, 51.10; H, 6.33; Cl, 15.36.

3.1.3. (2*E*)-3-Chloro-4-ethoxy-4-oxobut-2-enoic acid. Potassium (2*E*)-3-chloro-4-ethoxy-4-oxobut-2-enoate[18] (3.7 g, 17.1 mmol) was dissolved in water (20 mL) and acidified with 2 M HCl up to pH=1. The solution was extracted with ether, dried ($MgSO_4$) and the solvent was evaporated to furnish the title compound as a colourless oil, yield 2.71 g (89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.6 (bs, 1H), 6.30 (s, 1H), 4.32 (q, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 162.6, 140.4, 122.0, 63.1, 13.6; IR (KBr) 3500, 3075, 2987, 1737, 1719, 1631, 1397, 1373, 1333, 1270, 1186, 1019, 870 cm^{-1}; Anal. Calcd for $C_6H_7ClO_4$: C, 40.35; H, 3.96. Found: C, 39.53, H, 4.23.

3.1.4. 4-Butyl 1-ethyl (*E*)-2-chlorobut-2-enedioate (10*E*). This compound was prepared by the Mitsunobu reaction in the same manner, as **10Z**. Yield 1.67 g (71%). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.29 (s,1H), 4.33 (q, J=7.2 Hz, 2H), 4.14 (t, J=6.6 Hz, 2H), 1.68–1.56 (m, 2H), 1.46–1.30 (m, 2H), 1.34 (t, J=7.2 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.0, 162.6, 137.3, 123.3, 65.4, 62.8, 30.4, 19.0, 13.8, 13.6; IR (KBr) 2963, 2935, 2874, 1750, 1722, 1632, 1392, 1370, 1336, 1254, 1215, 1180, 1160, 1031, 865, 738 cm^{-1}; Anal. Calcd for $C_{10}H_{15}ClO_4$: C, 51.18; H, 6.44. Found: C, 51.34; H, 6.50.

3.2. General procedure for the reactions of halomethyl *p*-tolyl sulfones 1 or 2 with dimethyl halofumarate or dimethyl halomaleate

To a stirred solution of *t*-BuOK (280 mg, 2.5 mmol) in THF (8 mL) a mixture of halomethyl *p*-tolyl sulfone (1 mmol) and the alkene (1 mmol) in THF (2 mL) was added dropwise at −90 to −85 °C. The reaction mixture was stirred for 30 min without cooling to allow the temperature to reach −70 °C. The mixture was then poured into cold, saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was chromatographed (hexane/AcOEt/CH_2Cl_2 20:2:1 eluent) to isolate the products (yields are given in Table 1).

3.2.1. Dimethyl (*E* or *Z*)-2-chloro-3-{[(4-methylphenyl)-sulfonyl]methyl}but-2-enedioate (5). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.72 (m, 2H), 7.42–7.31 (m, 2H), 4.38 (s, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.6, 162.9, 145.4, 137.9, 135.3, 129.9, 128.7, 125.0, 56.8, 53.8, 53.1, 21.7; IR (KBr) 1745, 1731, 1436, 1326, 1271, 1153, 1085, 1037 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{15}$ $^{35}ClSO_6$: 346.0278. Found: 346.0283; Anal. Calcd for $C_{14}H_{15}ClSO_6$: C, 48.48; H, 4.36; Cl, 10.23; S, 9.25. Found: C, 48.33; H, 4.49; Cl, 10.11; S, 9.31.

3.2.2. Dimethyl (*E*)-2-{chloro[(4-methylphenyl)sulfonyl]-methyl}but-2-enedioate (7E). Colourless crystals, mp 82 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84–7.75 (m, 2H), 7.44–7.34 (m, 2H), 6.48 (d, J=1.0 Hz, 1H), 5.87 (d, J=1.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 163.7, 146.5, 133.8, 133.4, 130.8, 130.4, 129.7, 71.2, 53.2, 52.5, 21.8; IR (KBr) 2945, 1731, 1327, 1276, 1156 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{15}$ $^{35}ClSO_6$ 346.0278. Found: 346.0279; Anal. Calcd for $C_{14}H_{15}ClSO_6$: C, 48.48; H, 4.36; Cl, 10.23; S, 9.25. Found: C, 48.54; H, 4.40; Cl, 10.18; S, 9.40.

3.2.3. Dimethyl (*Z*)-2-{chloro[(4-methylphenyl)sulfonyl]-methyl}but-2-enedioate (7*Z*). Colourless crystals, mp 129–130 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2H), 7.44–7.35 (m, 2H), 7.18 (s, 1H), 7.03 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 163.3, 145.7, 137.3, 134.3, 133.2, 129.8, 129.6, 67.1, 53.1, 52.7, 21.7. HRMS (EI) Calcd for $C_{14}H_{15}{}^{35}ClSO_6$: 346.0278. Found: 346.0287; Anal. Calcd for $C_{14}H_{15}ClSO_6$: C, 48.48; H, 4.36; Cl, 10.23; S, 9.25. Found: C, 48.47; H, 4.54; Cl, 10.26; S, 9.21.

3.2.4. Dimethyl (*E* or *Z*)-2-bromo-3-{[(4-methylphenyl)-sulfonyl]methyl}but-2-enedioate (6). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85–7.75 (m, 2H), 7.46–7.34 (m, 2H), 4.44 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.9, 163.2, 145.4, 135.2, 130.0, 129.9, 128.7, 127.2, 58.8, 53.5, 53.1, 21.6; IR (KBr) 2960, 1744, 1438, 1330, 1153, 1085, 1037, 819 cm^{-1}; Anal. Calcd for $C_{14}H_{15}BrSO_6$: C, 42.98; H, 3.86; Br, 20.43; S, 8.20. Found: C, 42.93; H, 3.84; Br, 20.38; S, 8.16.

3.2.5. Dimethyl (*E*)-2-{bromo[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (8*E*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85–7.75 (m, 2H), 7.42–7.32 (m, 2H), 6.69 (d, J=0.7 Hz, 1H), 5.87 (d, J=0.7 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 2.46 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 163.2, 146.4, 135.9, 133.2, 130.9, 130.6, 129.7, 59.6, 53.1, 52.5, 21.7; Anal. Calcd for $C_{14}H_{15}BrSO_6$: C, 42.98; H, 3.86; Br, 20.43; S, 8.20. Found: C, 42.89; H, 3.86; Br, 20.22; S, 8.33.

3.3. Reaction of 1 with dimethyl acetylenedicarboxylate (9)

To a stirred solution of *t*-BuOK (280 mg, 2.5 mmol) in THF (8 mL) a mixture of chloromethyl *p*-tolyl sulfone (**1**) (204.5 mg, 1 mmol) and **9** (142 mg, 1 mmol) in THF (2 mL) was added dropwise at −90 to −85 °C. The reaction mixture was stirred for 30 min without cooling to allow the temperature to reach −70 °C, then poured into cold saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was subjected to short column chromatography (hexane/AcOEt/CH_2Cl_2 10:2:1 eluent) to give product **7*E***, 209 mg (60%).

3.4. Reaction of halomethyl *p*-tolyl sulfones (1 or 2) with 10*E*

To a stirred solution of *t*-BuOK (280 mg, 2.5 mmol) in THF (8 mL) a mixture of halomethyl *p*-tolyl sulfone (1 mmol) and **10*E*** (234.5 mg, 1 mmol) in THF (2 mL) was added dropwise at −90 to −85 °C. The reaction mixture was stirred for 30 min to achieve −70 °C then poured into cold saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (hexane/AcOEt/CH_2Cl_2 50:2:1 eluent) to separate the products. In the reaction of **1** were isolated: **11**, 9 mg (2%) and the mixture of **12*E*/13*E***, 306 mg (76%) in ratio 1:1. In the reaction of **2** were isolated: **11**, 17 mg (4%) and a mixture of **14*E*/15*E***, 279 mg (62%) in the ratio 1:1. Samples of pure isomers **12*E***, **13*E*** and also **14*E***, **15*E*** were obtained after additional chromatography.

3.4.1. 4-Butyl 1-ethyl (*E* or *Z*)-2-chloro-3-{[(4-methyl-phenyl)sulfonyl]methyl}but-2-enedioate (11). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81–7.70 (m, 2H), 7.42–7.30 (m, 2H), 4.38 (s, 2H), 4.28 (q, J=7.2 Hz, 2H), 4.10 (t, J=6.6 Hz, 2H), 2.46 (s, 3H), 1.72–1.23 (m, 7H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.1, 162.5, 145.3, 138.1, 135.3, 129.9, 128.6, 124.6, 66.4, 62.9, 56.8, 30.1, 21.6, 18.9, 13.7, 13.6; IR (KBr) 2962, 1752, 1731, 1622, 1697, 1262, 1155, 1086, 1036, 734 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{23}{}^{35}ClSO_6$: 402.0904. Found: 402.0908; Anal. Calcd for $C_{18}H_{23}ClSO_6$: C, 53.66; H, 5.75; Cl, 8.80, S, 7.96. Found: C, 53.59; H, 5.75; Cl, 8.98; S, 8.07.

3.4.2. 1-Butyl 4-ethyl (*E*)-2-{chloro[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (12*E*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84–7.75 (m, 2H), 7.44–7.33 (m, 2H), 6.45 (d, J=0.9 Hz, 1H), 5.86 (d, J=0.9 Hz, 1H), 4.45–4.05 (m, 4H), 2.45 (s, 3H), 1.78–1.20 (m, 7H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 163.2, 146.4, 134.2, 132.7, 130.7, 130.4, 129.6, 71.0, 66.4, 61.6, 30.2, 21.7, 19.0, 13.9, 13.6; IR (KBr) 1745, 1731, 1336, 1270, 1156, 1085, 1027 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{23}{}^{35}ClSO_6$: 402.0904. Found: 402.0903; Anal. Calcd for $C_{18}H_{23}ClSO_6$: C, 53.66; H, 5.75; Cl, 8.80; S, 7.96. Found: C, 53.30; H, 5.93; Cl, 8.89; S, 8.01.

3.4.3. 4-Butyl 1-ethyl (*E*)-2-{chloro[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (13*E*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.72 (m, 2H), 7.41–7.31 (m, 2H), 6.43 (d, J=1.0 Hz, 1H), 5.87 (d, J=1.0 Hz, 1H), 4.38–4.00 (m, 4H), 2.44 (s, 3H), 1.75–1.20 (m, 7H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 163.1, 146.4, 134.2, 132.7, 130.8, 130.3, 129.6, 71.1, 65.5, 62.5, 30.3, 21.7, 19.0, 13.7, 13.6; IR (KBr) 2962, 2934, 2874, 1745, 1716, 1647, 1596, 1470, 1397, 1371, 1336, 1275, 1186, 1156, 1084, 1028, 817 cm^{-1}; Anal. Calcd for $C_{18}H_{23}ClSO_6$: C, 53.66; H, 5.75. Found: C, 53.54; H, 5.53.

3.4.4. 1-Butyl 4-ethyl (*E*)-2-{bromo[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (14*E*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.35 (m, 2H), 6.71 (d, J=0.5 Hz, 1H), 5.90 (d, J=0.5 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 4.10 (t, J=6.6 Hz, 2H), 2.45 (s, 3H), 1.72 1.20 (m, 7H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8, 162.7, 146.2, 136.4, 132.6, 131.0, 130.7, 129.6, 66.4, 61.6, 59.6, 30.2, 21.7, 18.9, 13.9, 13.6; IR (KBr) 2961, 2933, 2873, 1742, 1718, 1596, 1370, 1333, 1273, 1256, 1154, 1084, 1027, 819, 736 cm^{-1}; Anal. Calcd for $C_{18}H_{23}BrSO_6$: C, 48.32; H, 5.19. Found: C, 48.57; H, 4.96.

3.4.5. 4-Butyl 1-ethyl (*E*)-2-{bromo[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (15*E*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.35 (m, 2H), 6.69 (d, J=0.5 Hz, 1H), 5.91 (d, J=0.5 Hz, 1H), 4.25–4.03 (m, 4H), 2.45 (s, 3H), 1.78–1.20 (m, 7H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 162.6, 146.2, 136.4, 132.6, 130.9, 130.7, 129.6, 65.5, 62.5, 59.7, 30.3, 21.7, 19.0, 13.9, 13.7; IR (KBr) 2961, 2933, 2873, 1743, 1717, 1596, 1372, 1331, 1274, 1258, 1155, 1084, 819,

730 cm^{-1}; MS (EI) (**14*E*/15*E*** mixture) *m*/*z* 448 (6) [446 (6)], 375 (5) [373 (5)], 367 (5), 347 (8) [345 (8)], 293 (14) [291 (14)], 265 (8) [263 (8)], 248 (10) [246 (10)], 237 (24) [235 (24)], 235 (24), 220 (50) [218 (50)], 192 (40) [190 (40)], 155 (64), 139 (46), 111 (32), 91 (100), 65 (30), 57 (48), 41 (28); Anal. Calcd for $C_{18}H_{23}BrSO_6$ (**14*E*/15*E*** mixture): C, 48.32; H, 5.19. Found: C, 48.72; H, 5.05.

3.5. Reaction of halomethyl *p*-tolyl sulfone (1 or 2) with 10*Z*

To a stirred solution of *t*-BuOK (280 mg, 2.5 mmol) in THF (8 mL) a mixture of halomethyl *p*-tolyl sulfone (1 mmol) and **10*Z*** (234.5 mg, 1 mmol) in THF (2 mL) was added dropwise at −90 °C. The reaction mixture was stirred for 30 min at this temperature then poured into cold saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (hexane/AcOEt/CH_2Cl_2 50:2:1 eluent) to separate the products. In the reaction of **1** were isolated: **11**, 50 mg (12%); **12*E***, 93 mg (23%); **12*Z***, 93 mg (23%) and **16**, 95 mg (22%). In the reaction of **2** were isolated: **11**, 230 mg (57%) and a **14*E*/15*E***mixture, 50 mg (11%).

3.5.1. 1-Butyl 4-ethyl (*Z*)-2-{chloro[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (12*Z*). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96–7.85 (m, 2H), 7.46–7.34 (m, 2H), 7.22 (s, 1H), 7.02 (s, 1H), 4.45–4.15 (m, 4H), 2.49 (s, 3H), 1.82–1.23 (m, 7H), 0.98 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.3, 163.0, 145.6, 137.4, 134.5, 133.3, 129.7, 129.6, 67.1, 66.4, 61.9, 30.3, 21.7, 19.1, 13.9, 13.7; IR (KBr) 1735, 1716, 1341, 1297, 1209, 1157 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{23}{}^{35}ClSO_6$: 402.0904. Found: 402.0911; Anal. Calcd for $C_{18}H_{23}ClSO_6$: C, 53.66, H, 5.75; Cl, 8.80; S, 7.96. Found: C, 53.66; H, 5.77; Cl, 8.95; S, 7.82.

3.5.2. 4-Butyl 1-ethyl 2-chloro-3-{chloro[(4-methylphenyl)sulfonyl]methyl}]succinate (16). Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.85 (m, 2H), 7.46–7.34 (m, 2H), 5.18 (d, *J*=2.9 Hz, 1H), 4.70 (d, *J*=10.4 Hz, 1H), 4.34–4.06 (m, 5H), 2.48 (s, 3H), 1.76–1.21 (m, 7H), 0.94 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 167.3, 146.7, 134.0, 130.5, 130.3, 72.3, 66.9, 63.4, 54.8, 49.0, 30.7, 22.3, 19.5, 14.4, 14.2; HRMS (EI) Calcd for $C_{18}H_{24}{}^{35}Cl_2SO_6$: 438.0671. Found: 438.0671; IR (KBr) 2962, 1745, 1731, 1344, 1280, 1226, 1158, 1085, 1019, 662; Anal. Calcd for $C_{18}H_{24}Cl_2SO_6$: C, 49.20; H, 5.51; Cl, 16.14; S, 7.30. Found: C, 49.52; H, 5.72; Cl, 16.94; S, 7.10.

3.6. Reaction of 16 with *tert*-BuOK

To a stirred solution of *t*-BuOK (56 mg, 0.5 mmol) in THF (2 mL) a solution of **16** (79 mg, 0.18 mmol) in THF (1 mL) was added at −85 °C. The reaction mixture was stirred for 30 min at this temperature, then poured into cold saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvents were evaporated in vacuo. The residue was chromatographed (hexane/AcOEt/CH_2Cl_2 20:2:1 eluent) to separate the products: **11**, 35.5 mg (49%) and **12*E***, 22.5 mg (31%).

3.7. Reaction of dimethyl dichloromaleate (20*Z*) with potassium salt of 1

A solution of the potassium salt of **1**, generated from chloromethyl *p*-tolyl sulfone (204.5 mg, 1 mmol) and *t*-BuOK (124 mg, 1.1 mmol) in THF (1 mL), was added slowly to a stirred solution of dimethyl dichloromaleate (**20*Z***) (213 mg, 1 mmol) in THF (8 mL) at −90 to −85 °C. The reaction mixture was stirred for 30 min without cooling to allow the temperature to reach −70 °C, then poured into cold saturated NH_4Cl_{aq} and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was subjected to chromatography (SiO_2 pre-washed with AcOH/hexane 1:100, hexane/AcOEt/CH_2Cl_2 20:2:1 eluent) to obtain recovered substrates: **1** (48 mg, 23%), **20** (46 mg, 21%) and product **21** (75 mg, 20%) as a mixture of isomers.

3.7.1. Methyl (*E*,*Z*)-2,3,5-trichloro-5-[(4-methylphenyl)-sulfonyl]-4-oxopent-2-enoate (21*E*,*Z*). White solid, mp 137–143 °C (hexane/ether), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96–7.87 (m, 2H, isomer **I**), 7.85–7.77 (m, 2H, isomer **II**), 7.47–7.38 (m, 2H, isomers **I** and **II**), 5.13 (s, 1H), 5.11 (s, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.52 (s, 3H, isomers **I** and **II**); IR (KBr) 2957, 1792, 1635, 1337, 1228, 1157, 999, 918 cm^{-1}; Anal. Calcd for $C_{13}H_{11}Cl_3SO_5$: C, 40.48; H, 2.88; Cl, 27.58; S, 8.32. Found: C, 40.44; H, 2.92; Cl, 27.39; S, 8.52.

3.8. Reaction of dimethyl dichlorofumarate (20*E*) with potassium salt of 1

The reaction was performed analogously to the above procedure. After chromatography (SiO_2 pre-washed with AcOH/hexane 1:100, hexane/AcOEt/CH_2Cl_2 20:2:1 eluent) two products were identified: **21*E*,*Z*** (31 mg, 8%) and **22*E*,*Z*** (54 mg, 14%) as a mixture of *E*/*Z* isomers in ratio 83/17 according to ^{1}H NMR.

3.8.1. Dimethyl (*E*,*Z*)-1-chloro-2-{chloro[(4-methylphenyl)sulfonyl]methyl}but-2-enedioate (22*E*,*Z*). Colourless oil. Major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92–7.83 (m, 2H), 7.43–7.34 (m, 2H), 5.92 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.4, 161.4, 146.5, 135.6, 132.9, 131.0, 130.0, 129.9, 70.6, 53.9, 53.3, 21.8. Minor isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.80 (m, 2H), 7.42–7.34 (m, 2H), 6.89 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.46 (s, 3H); IR (KBr) 2956, 1746, 1597, 1453, 1343, 1301, 1271, 1237, 1159, 1085, 1041, 821, 735, 659 cm^{-1}; Anal. Calcd for $C_{14}H_{14}Cl_2SO_6$ (**22*E*,*Z***): C, 44.10; H, 3.71. Found: C, 44.44; H, 3.67.

References and notes

1. (a) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282–289. (b) Mąkosza, M. *Synthesis* **1991**, 103–111.
2. Mąkosza, M.; Wojciechowski, K. *Liebigs Ann./Recueil* **1997**, 1805–1816.
3. Mąkosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979–4981.

4. Mąkosza, M.; Białecki, M. *J. Org. Chem.* **1998**, *63*, 4878–4888.
5. (a) Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039–5040. (b) Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1988**, *53*, 3978–3982. (c) Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **1996**, *61*, 2934–2935.
6. Seko, S.; Kawamura, N. *J. Org. Chem.* **1996**, *61*, 442–443.
7. Mąkosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, *11*, 341–349.
8. (a) Mąkosza, M.; Kwast, A. *J. Chem. Soc., Chem. Commun.* **1984**, *11*, 1195–1196. (b) Mąkosza, M.; Kwast, A. *Tetrahedron* **1991**, *47*, 5001–5018. (c) Jończyk, A.; Owczarczyk, Z.; Mąkosza, M.; Winiarski, J. *Bull. Soc. Chim. Belg.* **1987**, *96*, 303–310. (d) Mąkosza, M.; Nizamov, S. *Tetrahedron* **2001**, *57*, 9615–9621.
9. (a) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213–4222. (b) Ballini, R.; Rinaldi, A. *Tetrahedron Lett.* **1994**, *35*, 9247–9250. (c) Aldersley, M. F.; Dean, F. M.; Nayyir-Mazhir, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1753–1757.
10. Mąkosza, M.; Nizamov, S.; Kwast, A. *Mendeleev Commun.* **1996**, 43–44.
11. Mąkosza, M.; Kozhevnikov, D. N. *Russ. Chem. Bull.* **2001**, *50*, 2236–2238.
12. (a) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474–479. (b) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942–973. (c) Rappoport, Z. *Recl. Trav. Chim. Pay-Bas* **1985**, *104*, 309–349. (d) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7–15. (e) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211–1218. (f) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73–80.
13. Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711–715.
14. Baudrowski, E. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2694–2698.
15. Gershon, H.; Shanks, L. *J. Pharm. Sci.* **1978**, *67*, 578.
16. Walden, P. *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 2883–2888.
17. Jones, G., II; Fantina, M. E.; Pachtman, A. H. *J. Org. Chem.* **1976**, *41*, 329–333.
18. Veibel, S.; Pedersen, C. *Acta Chem. Scand.* **1955**, *9*, 1674–1684.
19. McDonald, R. N.; Krueger, R. A. *J. Org. Chem.* **1963**, *28*, 2542–2544.
20. Eldred, S.; Young, L. *J. Am. Chem. Soc.* **1953**, *75*, 4338–4339.
21. (a) Serguchev, Y.; Britsun, V. N.; Il'chenko, N. N. *Zh. Org. Chem.* **1998**, *34*, 199–202. (b) Serguchev, Y.; Britsun, V. N.; Il'chenko, N. N. *Russ. J. Org. Chem.* **1998**, *34*, 171–174.
22. Patterson, T. S.; Todd, A. R. *J. Chem. Soc.* **1929**, 1768–1771.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 5423–5431

Synthesis of 13-acylamino-huprines: different behavior of diastereomeric 13-methanesulfonamido-huprines on PPA-mediated hydrolysis

Pelayo Camps,* Elena Gómez and Diego Muñoz-Torrero*

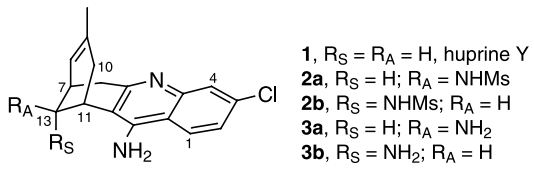
Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal, 643, E-08028 Barcelona, Spain

Received 5 December 2003; revised 23 March 2004; accepted 22 April 2004

Abstract—Two diastereomeric pairs of rationally designed huprines additionally substituted at position 13 with a formamido or an acetamido group have been synthesized as potential high affinity acetylcholinesterase inhibitors. The synthetic sequence involves hydrolysis of two diastereomeric 13-methanesulfonamido-huprines, followed by acylation of the resulting diastereomeric amines. In the hydrolysis reaction, carried out with PPA under harsh conditions, significant amounts of cyclized or rearranged by-products were also formed, depending on the stereochemistry of the starting compound.

1. Introduction

Huprines have recently emerged as a novel class of high affinity central acetylcholinesterase (AChE) inhibitors of interest for the treatment of Alzheimer's disease, which have shown to be superior in terms of affinity, potency and selectivity to most of the currently approved drugs for this disorder. This is probably due to their extended binding near the active site of AChE.[1–5] By the moment, the most powerful huprines are the so-called huprine Y [(−)-**1**, Fig. 1] and its 9-ethyl analogue, huprine X. The last one binds to the human enzyme with one of the highest affinities yet reported for a reversible AChE inhibitor (inhibition constant K_I 26 pM).



1, $R_S = R_A = H$, huprine Y
2a, $R_S = H$; $R_A = NHMs$
2b, $R_S = NHMs$; $R_A = H$
3a, $R_S = H$; $R_A = NH_2$
3b, $R_S = NH_2$; $R_A = H$

Figure 1. Structures of huprine Y, 13-methanesulfonamido-huprines **2a**,**b** and 13-amino-huprines **3a**,**b**.

On the basis of molecular modeling studies[1–3,6] and the 3D X-ray diffraction analysis of a complex of *Torpedo californica* AChE-huprine X,[7] we designed a new series of huprines, functionalized at position 13 with a formamido or acetamido group as new AChE inhibitors. These compounds, with more extended binding near the active site of AChE are expected to have higher AChE affinities. We recently described the synthesis of compounds **2a**,**b** (Fig. 1) as advanced intermediates for the synthesis of these new 13-acylamino-huprines,[8] which requires cleavage of the methanesulfonamido group of **2a**,**b** followed by acylation of the resulting primary amines **3a**,**b**.

Although arene- and alkane-sulfonyl groups have been used to protect amines, removal of these protective groups is not an easy task, and usually requires drastic conditions that may not be compatible with other functional groups present in the substrate. To solve this problem, many alternative deprotection procedures have been developed. However, most of them are not general, strongly depending on the nature of the aryl or alkyl rest bound to the sulfur atom and on the degree of substitution of the nitrogen atom.[9–26] Thus, most methods allow the cleavage of arenesulfonamides, mainly *p*-toluenesulfonamides, while very few methods have been reported for the cleavage of methanesulfonamides. Regarding the degree of substitution at the nitrogen atom, most methods allow the deprotection of sulfonamides of secondary amines (usually aromatic), while they completely fail to cleave sulfonamides of primary amines (especially aliphatic). To the best of our knowledge, only three examples of cleavage of methane- or alkanesulfonamides derived from aliphatic primary amines (the substitution pattern of compounds **2a**,**b**) have been reported, involving acidic conditions (Zn/HOAc at room temperature[12] or $MeSO_3H/H_2O$ at 135 °C[11]) or photolytic

Keywords: Huprines; Cleavage of primary aliphatic methanesulfonamides; PPA; Rearrangement; Cyclization reaction.
* Corresponding authors. Tel.: +34-93-4024536; fax: +34-93-4035941; e-mail addresses: camps@farmacia.far.ub.es; dmunoztorrero@ub.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.054

cleavage,[26] the amines being always obtained in low to moderate yields (20–66%).

In this paper, we report the unprecedented hydrolysis of the *N*-monosubstituted methanesulfonamides **2a** and **2b** using PPA to the corresponding amines **3a** and **3b**, as well as the formation of important amounts of cyclized or rearranged by-products, depending on the configuration at position 13 of the starting methanesulfonamides, and the conversion of the amines **3a** and **3b** into the rationally designed new huprines **18a**, **18b**, **19a** and **19b**.

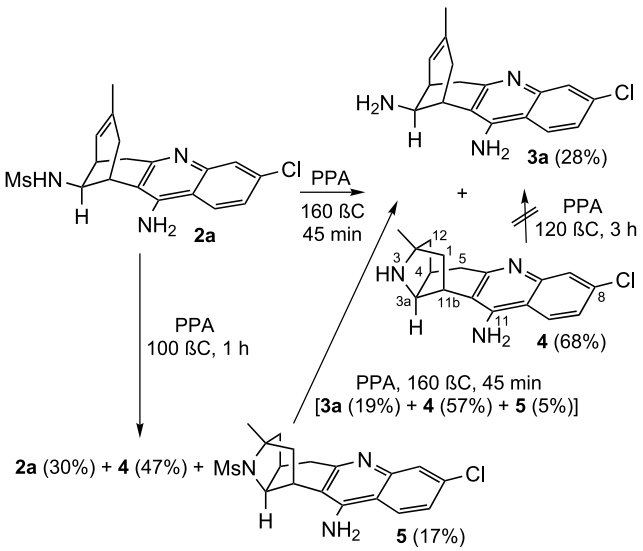
2. Results and discussion

Initial attempts to hydrolyze **2b**, on reaction with $MeSO_3H/H_2O$ at 135 °C or with Zn/HOAc under different reaction conditions, left the starting material unchanged. In view of these disappointing results and the low yield of the above mentioned photolytic deprotection method, we tried other methodologies. HBr has proved to be efficient in the deprotection of methanesulfonamides derived from primary aromatic amines.[9] Unfortunately, reaction of **2b** with 48% aq. HBr under reflux led to a complex mixture of products. Sulfuric acid has been commonly used to cleave many methanesulfonamides of primary aromatic amines.[9] However, reaction of a 1:1 diastereomeric mixture of **2a** and **2b** with a 1:1 mixture H_2SO_4/H_2O for 30 min under reflux left the starting material unchanged. Fortunately, the use of polyphosphoric acid (PPA) for the hydrolysis of **2a** afforded better results. Under the best reaction conditions (**2a** and PPA, 160 °C, 45 min), amine **3a** was obtained in 28% yield together with the pentacyclic amine **4** (68% yield) (entry 5, Table 1), which were separated by column chromatography (Scheme 1).

Table 1. Conditions and products in the reaction of methanesulfonamides **2a** and **5** with PPA

Entry	Compound	Conditions		Reaction products (%)			
		T (°C)	*t* (h)	**2a**	**3a**	**4**	**5**
1	**2a**	100	1	30		47	17
2	**2a**	115	2		13	56	6
3	**2a**	140	1.5		22	72	
4	**2a**	140	15			61	
5	**2a**	160	0.75		28	68	
6	**2a**	200	0.33		23	57	
7	**5**	160	0.75		19	57	5

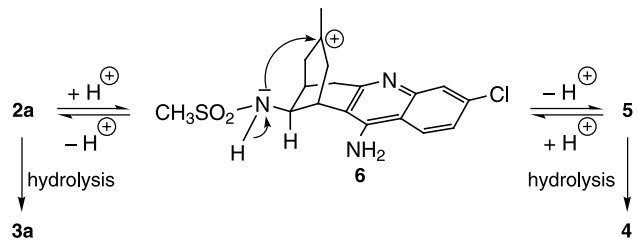
Interestingly, when this reaction was carried out at 100 °C for 1 h, **4** was again the main product (47% yield), and no amine **3a** was obtained, pentacyclic methanesulfonamide **5** (17% yield) and starting **2a** (30%) being isolated instead (entry 1, Table 1). The increase in temperature (115 °C) and reaction time (2 h) led to a total consumption of **2a** and to the formation of the desired amine **3a** (13% yield), while the yield of amine **4** increased and that of **5** greatly decreased (entry 2, Table 1). When the reaction was carried out at 140 °C for 1.5 h, **3a** and **4** were obtained in 22 and 72% yield, respectively, while increasing the reaction time to 15 h, **4** was the only isolated product (entries 3 and 4, Table 1). Finally, when the reaction was carried out at



Scheme 1. Reaction of methanesulfonamides **2a** and **5** with PPA.

200 °C for 20 min, **3a** and **4** were obtained in 23 and 57% yield, respectively (entry 6, Table 1).

When methanesulfonamide **5** was reacted with PPA at 160 °C for 45 min, the amines **3a** and **4** were obtained in 19 and 57% yield, respectively, after column chromatography, together with a small amount of unreacted **5** (entry 7, Table 1) (Scheme 1). However, **4** could not be converted into the desired amine **3a** under similar reaction conditions. From these results, we can conclude that methanesulfonamide **5** is formed from **2a** in a reversible process under the reaction conditions. The conversion of **2a** to **5** can take place by protonation of the C=C double bond at the less substituted carbon atom to give a tertiary carbocation followed by intramolecular addition of the sulfonamido nitrogen atom and deprotonation (Scheme 2).



Scheme 2. Possible mechanistic pathway for the formation of **4** and **5** from **2a**.

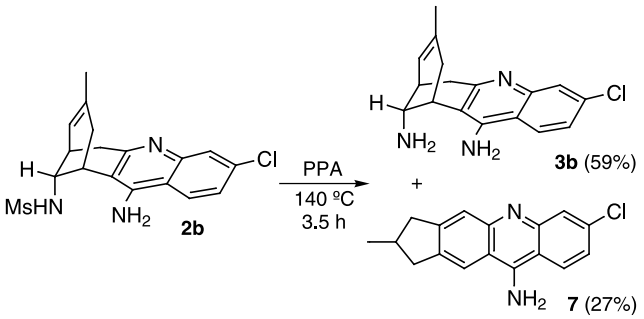
Hydrolysis of methanesulfonamides **2a** and **5** would lead to amines **3a** and **4**, respectively. The interconversion of **5** and **2a** under the reaction conditions explains the formation of both amines **3a** and **4** in the reactions of sulfonamides **2a** or **5** with PPA at 160 °C. The failure of amine **4** to give amine **3a** on reaction with PPA supports the intermediacy of sulfonamide **2a** in the formation of amine **3a** from sulfonamide **5**.

The conversion of **2a** to **5** seems to be faster than its hydrolysis to **3a**, since **5** is formed from **2a** at temperatures around 100 °C, while formation of **3a** from **2a** requires higher temperatures (around 115 °C). Also, not

unexpectedly, hydrolysis of the *N*,*N*-disubstituted methanesulfonamide **5** to **4** (47% yield from **2a** and PPA at 100 °C) appears to be faster than hydrolysis of the *N*-monosubstituted methanesulfonamide **2a** to **3a** (not formed under the same reaction conditions, entry 1, Table 1).

Contrary to **2b**, the reaction of **2a** with 48% aq. HBr (using phenol as solvent under reflux for 7 h)[27] afforded the amines **3a** and **4** in 24 and 53% yield, after column chromatography.

A completely different behavior towards PPA was exhibited by the diastereomeric methanesulfonamide **2b**. Thus, treatment of **2b** with PPA at 100 °C for 1–4 h left the starting material unchanged, but the increase in the reaction time to 15 h led to the formation of the desired amine **3b** in 46% yield, together with a by-product, which was characterized as aminocyclopentaacridine **7** (Scheme 3, entries 1 and 2, Table 2).



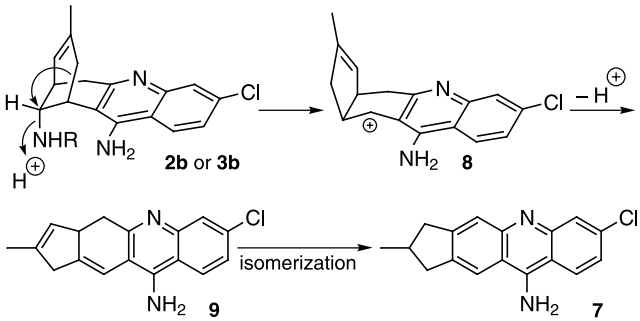
Scheme 3. Reaction of methanesulfonamide **2b** with PPA.

Table 2. Conditions and products in the reaction of methanesulfonamide **2b** with PPA

Entry	Conditions		Reaction products		
	T (°C)	*t* (h)	**2b**	**3b**	**7**
1	100	1 (4)	100 (84)		
2	100	15		46	12
3	130	3.75	7	37	21
4	130	4.5		57	26
5	140	3.5		59	27
6	150	1.75		50	33

Increasing the reaction temperature to 130–140 °C with reaction times of 3.5–4.5 h higher yields of both **3b** and **7** were obtained (entries 3–5, Table 2). Under the best reaction conditions (**2b** and PPA, 140 °C, 3.5 h), **3b** and **7** were obtained in 59 and 27% yield, respectively (Scheme 3 and entry 5, Table 2). When the reaction was carried out at 150 °C, a slightly lower yield of **3b** and a slightly higher yield of **7** were obtained (entry 6, Table 2).

In this case, the *anti*-arrangement of the 13-methanesulfonamido group and the propeno bridge of **2b** prevents any transannular reaction. However, the *antiperiplanar* arrangement of the C10–C11 sigma bond and the methanesulfonamido group favors the formation of by-product **7**, which can be rationalized on the basis of a concerted 1,2-migration of C10 from C11 to the vicinal position 13 of **2b**, which becomes electron poor by the departure of the protonated sulfonamido group. Deprotonation of the resulting carbocation **8** and C=C double bond isomerization would give the more stable compound **7**, containing a more extended aromatic system (Scheme 4).

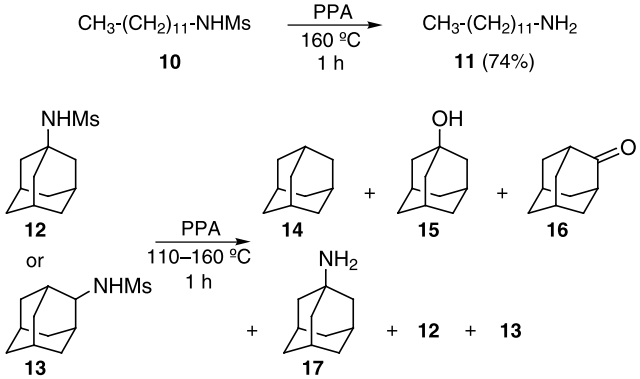


Scheme 4. Possible mechanistic pathway for the formation of **7** from **2b** or **3b**.

In sharp contrast with the results obtained in the **a** series, in this case, the hydrolysis product **3b** was always the main reaction product, thus indicating that hydrolysis is easier than rearrangement to **7**.

The increase in the yield of **7** together with the decrease in the yield of **3b** when this reaction was carried out at 150 °C (compare entries 5 and 6, Table 2) may be indicative of the alternative formation of **7** from **3b**, a transformation that could take place through the mechanism shown in Scheme 4, being R=H.

To assess the scope of this procedure of hydrolysis of methanesulfonamides derived from aliphatic primary amines, three known methanesulfonamides with different degree of substitution at the α-nitrogen position were submitted to the PPA hydrolysis conditions: *N*-dodecyl-,[28] *N*-(1-adamantyl)-,[29] and *N*-(2-adamantyl)-methanesulfonamide,[29] **10**, **12**, and **13**, respectively. Reaction of **10** with PPA at 160 °C for 1 h proceeded efficiently, affording the expected amine in 74% yield (Scheme 5). Lower reaction temperatures (110 or 140 °C) left significant amounts of starting material unchanged (89 and 30%, respectively). In sharp contrast, reaction of adamantylmethanesulfonamides **12** and **13** with PPA at 110 °C for 1 h gave similar mixtures not containing the expected amines. Thus, GC–MS and ^{13}C NMR analysis of the mixtures obtained from **12** and **13** revealed the presence of adamantane,

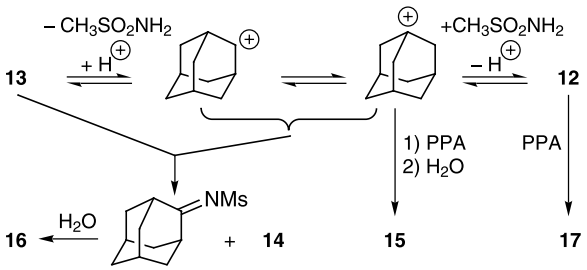


Scheme 5. Reaction of methanesulfonamides **10**, **12**, and **13** with PPA.

1-adamantanol, 2-adamantanone, **12**, and **13** (the area ratios by GC–MS are shown in Table 3) (Scheme 5). The presence of sulfonamides **12** and **13** in both mixtures indicates that these compounds may be interconverting under the reaction conditions, probably through the intermediacy of 1- and 2-adamantyl carbocations (Scheme 6). Formation of adamantane could be explained from 1- or 2-adamantyl cations by hydride abstraction, while 2-adamantanone could be formed from **13** by transfer of a hydride from position 2 to an adamantyl carbocation, followed by hydrolysis of the resulting imino derivative (Scheme 6). The ratio adamantane/2-adamantanone in these reactions is not significant since part of the volatile adamantane could have been lost during the isolation step. 1-Adamantanol could arise from 1-adamantyl carbocation on reaction with PPA followed by hydrolysis during the basic aqueous work-up (Scheme 6).

Table 3. Conditions and products in the reaction of methanesulfonamides **12** and **13** with PPA

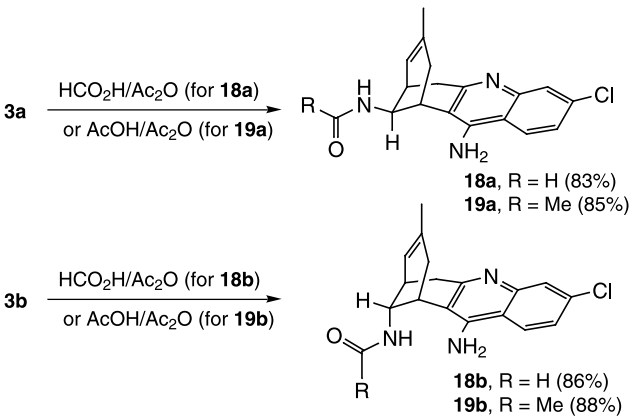
Entry	Compound	Conditions	Reaction products (relative areas by GC–MS)					
		T (°C)	**12**	**13**	**14**	**15**	**16**	**17**
1	**12**	110	36.0	10.8	8.5	15.8	28.8	
2	**13**	110	13.4	3.9	12.2	17.8	52.7	
3	**12**	160			2.2		43.7	19.4
4	**13**	160			11.8		49.6	11.4



Scheme 6. Possible mechanistic pathways for the formation of compounds **12**–**17** from **12** or **13**.

Under more forcing conditions (160 °C), **12** and **13** were fully transformed to give as before similar mixtures containing adamantane and 2-adamantanone, as well as 1-adamantylamine (Scheme 5 and Table 3). In these cases, the formation of 1-adamantanol was not detected, although other unidentified minor by-products were also formed. Although the formation of 1-adamantylamine from **13** is in accord with the previously mentioned interconversion between **12** and **13**, it is not clear why formation of 2-adamantylamine is not observed.

With the diastereomeric amines **3a** and **3b** in hand, we carried out their conversion in good yields into the corresponding 13-formamido (**18a** and **18b**) and 13-acetamido (**19a** and **19b**) derivatives on reaction with HCO_2H/Ac_2O or $AcOH/Ac_2O$ mixtures, respectively (Scheme 7). While the acetamido derivatives were routinely transformed into the corresponding hydrochlorides by treating them with a methanolic solution of HCl, partial hydrolysis of the formamido derivatives was observed when they were submitted to the same reaction conditions.



Scheme 7. Synthesis of 13-formamido and 13-acetamido-huprines **18a**, **18b**, **19a** and **19b** from the diastereomeric amines **3a** and **3b**.

Consequently, the formamido derivatives were characterized as the free base instead of the corresponding hydrochlorides as usual for other huprines.

All of the new compounds have been fully characterized on the basis of IR, ^1H NMR, ^{13}C NMR and MS spectra, and elemental analysis and/or HRMS. Assignment of the NMR spectra was performed with the aid of COSY $^1H/^1H$ and HETCOR $^1H/^{13}C$ experiments and by comparison with related compounds.[1,2,8]

3. Conclusion

In conclusion, we have carried out for the first time a PPA-mediated hydrolysis of *N*-alkyl methanesulfonamides (**2a** and **2b** to amines **3a** and **3b**) in low to moderate yields. Under the strong acidic reaction conditions, competitive side-reactions involving the sulfonamido group at position 13 occur, whose course depends on the stereochemistry of the starting sulfonamides **2a**,**b**. Also, hydrolysis of the *N*,*N*-dialkylmethanesulfonamide **5** took place in medium yield. The method was successfully applied to the hydrolysis of *N*-dodecylmethanesulfonamide, while it failed with *N*-(1-adamantyl)- and *N*-(2-adamantyl)-methanesulfonamide. Thus, the scope of the PPA hydrolysis of methanesulfonamides derived from aliphatic amines seems to be limited by the tendency of the starting sulfonamides to give carbocationic intermediates, from which by-products may be easily derived.

Also, we have prepared the 13-formamido-huprines **18a** and **18b** and the 13-acetamido-huprines **19a** and **19b**, the first examples of a new class of rationally designed huprines with a potentially increased binding near the active site of the enzyme AChE relative to the parent 13-unsubstituted huprines. The AChE inhibitory activity of these compounds, together with that of huprines **2a** and **2b** will be evaluated and reported elsewhere.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with

a MFB 595010M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra, and 75.4 and 100.6 MHz ^{13}C NMR spectra were recorded on Varian Inova 500, Varian Gemini 300 and Varian Mercury 400 spectrometers, respectively. The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in Hertz (Hz). Assignments given for the NMR spectra of the new compounds are based on the following experiments: DEPT and COSY ^{1}H/^{1}H (standard procedures), COSY ^{1}H/^{13}C (HMQC sequence with an indirect detection probe). In the case of **7**, also a COSY ^{1}H/^{13}C (gHMBC sequence) was performed. The *syn* (*anti*) notation of the amino or acylamino group at position 13 of compounds **3b** (**3a**), **18b** (**18a**) and **19b** (**19a**) means that the substituent at position 13 is on the same (different) side of the quinoline moiety with respect to the cyclohexene ring. Routine MS spectra were taken on ThermoQuest Trace MS and Hewlett–Packard 5988A spectrometers using the chemical ionization (CH_4) or the electron impact techniques (70 eV, for **7**), respectively: only significant ions are given. HRMS were performed on a Micromass Autospec spectrometer. GC–MS spectra of the crude products of the hydrolyses of compounds **12** and **13** were performed on a Hewlett–Packard 5988A spectrometer, introducing the samples through a gas chromatograph Hewlett–Packard model 5890 Series II, equipped with a 30-meter HP-5 (5% diphenyl-95% dimethyl-polysiloxane) column [10 psi, initial temperature: 50 °C (2 min), then heating at a rate of 10 °C/min till 320 °C, then isothermic for 5 min], and using the electron impact technique (70 eV). IR spectra were run on a FT/IR Perkin–Elmer model 1600 spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only the most intense absorption bands are given. Flash column chromatography was performed on silica gel 60 AC.C (35–70 mesh, SDS, ref 2000027). Thin-layer chromatography (TLC) was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. PPA (H_3PO_4 equivalent approx. 115%) was purchased from Aldrich. Analytical grade solvents were used for crystallization, while pure for synthesis solvents were used in the reactions, extractions and column chromatography. NMR spectra of all of the new compounds and routine mass spectra of **7** were performed at the Serveis Científico-Tècnics of the University of Barcelona, while routine and high resolution mass spectra of the rest of new compounds were carried out at the Mass Spectrometry Laboratory of the University of Santiago de Compostela (Spain) and the elemental analyses of compounds **7**, **18a**, **18b**, **19a** and **19b** were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.1.1. 12,*anti*-13-Diamino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline dihydrochloride (3a·2HCl) and 11-amino-8-chloro-2,3,3a,4,5,11b-hexahydro-2-methyl-1*H*-2,4-methanopyrrolo[3,2-*a*]-acridine dihydrochloride (4·2HCl). Methanesulfonamide **2a** (240 mg, 0.64 mmol) was added in portions over a 5 min period to stirred PPA (3.65 g) at 160 °C. The reaction mixture was thoroughly stirred at this temperature for 45 min, cooled to room temperature and treated with ice up to a total volume of 10 mL. The resulting suspension was alkalinized with NaOH pellets (pH=12) and extracted with AcOEt (4×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated at reduced pressure, to give a yellowish solid residue (194 mg) which was submitted to flash column chromatography (SiO_2, 8.0 g, hexane/AcOEt/MeOH mixtures, containing 0.3% of Et_3N). On elution with AcOEt/MeOH 96:4, 94:6 and 90:10, pure amine **3a** (33 mg) and mixture of amine **3a**/amine **4** in an approximate ratio of 6:4 (^{1}H NMR, 13 mg), a mixture of **3a/4** in an approximate ratio of 15:85 (82 mg, 28% total yield of **3a**), and pure amine **4** (55 mg, 68% total yield of **4**), were successively isolated.

Dihydrochloride of **3a**. A solution of pure **3a** (18 mg, 60 μmol) in MeOH (3 mL) was treated with a solution of HCl in MeOH (0.48 M, 0.8 mL, 0.38 mmol), heated at 70 °C for 30 min and evaporated at reduced pressure, to give **3a**·2HCl (22 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**3a**, free base) 0.09 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3384, 3176 and 2910), 1654, 1630, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.67 (s, 3H, 9-CH_3), 2.12 (d, J=19.5 Hz, 1H, 10-H_{endo}), 2.56 (broad dd, J=19.5 Hz, J'=5.5 Hz, 1H, 10-H_{exo}), 2.92 (m, 1H, 7-H), 3.10 (dd, J=18.0 Hz, J'=1.5 Hz, 1H, 6-H_{endo}), 3.44 (dd, $J\approx$18.0 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.59 (m, 1H, 11-H), 3.79 (m, 1H, 13-H), 4.84 (s, NH^++NH_2+NH_3^+), 5.55 (broad d, J=4.5 Hz, 1H, 8-H), 7.64 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.78 (d, J=2.0 Hz, 1H, 4-H), 8.39 (d, $J\approx$9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 23.3 (CH_3, 9-CH_3), 30.1 (CH, C11), 30.6 (CH_2, C10), 31.6 (CH, C7), 35.7 (CH_2, C6), 49.2 (CH, C13), 113.0 (C, C11a), 115.3 (C, C12a), 119.2 (CH, C4), 120.1 (CH, C8), 126.5 (CH, C1), 128.0 (CH, C2), 135.9 (C, C9), 139.7 (C, C4a), 141.0 (C, C3), 151.0 (C) and 156.8 (C) (C5a and C12); *m/z* (CI) 328 [$(M+C_2H_5)^+$, 20], 302 (39) and 300 (100) [$(M+H)^+$], 301 (34), 299 (40), 285 (13) and 283 (32) [$(M-NH_2)^+$], 264 [$(M-Cl)^+$, 64]. HRMS calcd for $C_{17}H_{19}ClN_3$ [$(M+H)^+$]: 300.1268. Found: 300.1253.

Dihydrochloride of **4**. A solution of pure **4** (200 mg, 0.67 mmol) in MeOH (10 mL) was treated with a solution of HCl in MeOH (0.48 M, 8.4 mL, 4.03 mmol), heated at 70 °C for 30 min and evaporated at reduced pressure, to give **4**·2HCl (229 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**4**, free base) 0.02 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3360, 3190 and 2867), 1654, 1635, 1594 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.54 (dd, $J\approx$12.5 Hz, $J'\approx$3.0 Hz, 1H, 1-H_{endo}), 1.62 (s, 3H, 2-CH_3), superimposed in part 1.64 (dd, J=13.5 Hz, J'=6.0 Hz, 1H, 12-H_{endo}), 2.28 (ddd, J=13.5 Hz, J'=12.0 Hz, J''=3.0 Hz, 1H, 12-H_{enx}), 2.70 (ddd, $J\approx J'\approx$12.5 Hz, J''=3.5 Hz, 1H, 1-H_{exo}), 3.09 (m, 1H, 4-H), 3.23 (broad dd, $J\approx$19.0 Hz, $J'\approx$1.5 Hz, 1H, 5-H_{exo}), 3.41 (dd, J=19.0 Hz, J'=6.0 Hz, 1H, 5-H_{endo}), 3.72 (dm, J=11.5 Hz, 1H, 11b-H), 4.36 (dd, $J\approx J'\approx$5.0 Hz, 1H, 3a-H), 4.85 (s, NH^++NH_2+NH_2^+), 7.63 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 9-H), 7.82 (d, J=2.0 Hz, 1H, 7-H), 8.40 (d, $J\approx$9.0 Hz, 1H, 10-H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 18.5 (CH_3, 2-CH_3), 29.6 (CH_2, C5), 32.0 (CH, C11b), 32.9 (CH, C4), 39.2 (CH_2, C12), 42.9 (CH_2, C1), 60.1 (CH, C3a), 70.6 (C, C2), 111.8 (C, C11a), 115.3 (C, C10a), 119.3 (CH, C7), 126.5 (CH, C10),

128.1 (CH, C9), 139.9 (C, C6a), 141.1 (C, C8), 149.1 (C) and 157.5 (C) (C5a and C11); *m/z* (CI) 328 [(M+C_2H_5)$^+$, 18], 302 (34) and 300 (100) [(M+H)$^+$], 301 (30), 299 (35), 283 [(M−NH_2)$^+$, 12], 264 [(M−Cl)$^+$, 56]. HRMS calcd for $C_{17}H_{19}ClN_3$ [(M+H)$^+$]: 300.1268. Found: 300.1257.

4.1.2. 11-Amino-8-chloro-2,3,3a,4,5,11b-hexahydro-3-methanesulfonyl-2-methyl-1*H*-2,4-methanopyrrolo[3,2-*a*]-acridine hydrochloride (5·HCl). This reaction was carried out as described for **3a**, from methanesulfonamide **2a** (220 mg, 0.58 mmol) and PPA (3.50 g), heating at 120 °C for 1 h. A yellowish solid (200 mg) was obtained, which was submitted to flash column chromatography (SiO_2, 6.4 g, hexane/AcOEt/MeOH mixtures, containing 0.3% of Et_3N). On elution with hexane/AcOEt 40:60, pure **5** (31 mg) and mixture **5/2a** in an approximate ratio of 3:7 (^{1}H NMR, 21 mg, 17% total yield of **5**) were successively isolated. On elution with hexane/AcOEt 30:70, sulfonamide **2a** (52 mg, 30% total yield) was isolated. Finally, on elution with AcOEt/MeOH 90:10, pure amine **4** (82 mg, 47% yield) was isolated.

Hydrochloride of **5**. A solution of pure **5** (44 mg, 0.12 mmol) in MeOH (3 mL) was treated with a solution of HCl in MeOH (0.48 M, 0.75 mL, 0.36 mmol), heated at 60 °C for 30 min and evaporated at reduced pressure, to give **5**·HCl (45 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**5**, free base) 0.59 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3373, 3227 and 2931), 1669, 1636, 1591, 1308, 1140, 1086 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.28 (dd, J=11.5 Hz, J'=3.0 Hz, 1H, 1-H$_{endo}$), 1.36 (dd, J=12.5 Hz, J'=6.0 Hz, 1H, 12-H$_{endo}$), 1.65 (s, 3H, 2-CH_3), 2.28 (ddd, $J\approx J'\approx$12.5 Hz, J''=3.0 Hz, 1H, 12-H$_{enx}$), 2.66 (ddd, J=J'=11.5 Hz, J''=3.0 Hz, 1H, 1-H$_{exo}$), 2.92 (m, 1H, 4-H), 3.12 (s, 3H, CH_3SO_2), 3.15 (broad d, $J\approx$19.0 Hz, 1H, 5-H$_{exo}$), 3.36 (dd, $J\approx$19.0 Hz, $J'\approx$6.0 Hz, 1H, 5-H$_{endo}$), 3.47 (dm, J=11.5 Hz, 1H, 11b-H), 4.38 (dd, $J\approx J'\approx$5.0 Hz, 1H, 3a-H), 4.86 (s, NH^++NH_2), 7.61 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 9-H), 7.77 (d, J=2.0 Hz, 1H, 7-H), 8.36 (d, J=9.0 Hz, 1H, 10-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 19.2 (CH_3, 2-CH_3), 30.7 (CH_2, C5), 33.4 (CH, C11b), 34.7 (CH, C4), 43.5 (CH_2, C12), 44.1 (CH_3, CH_3SO_2), 47.1 (CH_2, C1), 62.8 (CH, C3a), 69.9 (C, C2), 114.2 (C, C11a), 115.0 (C, C10a), 119.1 (CH, C7), 126.3 (CH, C10), 127.7 (CH, C9), 139.6 (C, C6a), 140.6 (C, C8), 149.4 (C) and 157.3 (C) (C5a and C11); *m/z* (CI) 406 [(M+C_2H_5)$^+$, 15], 380 (35) and 378 (96) [(M+H)$^+$], 379 (31), 377 (33), 344 (30) and 342 (47) [(M−Cl)$^+$], 300 (17) and 298 (34) [(M−CH_3SO_2)$^+$], 285 (35) and 283 (100) [(M−CH_3SO_2NH)$^+$], 249 [(M−CH_3SO_2NH−Cl+H)$^+$, 29]. HRMS calcd for $C_{18}H_{21}ClN_3O_2S$ [(M+H)$^+$]: 378.1043. Found: 378.1028.

4.1.3. 12,*syn*-13-Diamino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline dihydrochloride, (3b·2HCl) and 10-amino-7-chloro-2,3-dihydro-2-methyl-1*H*-cyclopenta[*b*]acridine (7). This reaction was carried out as described for **3a**, from methanesulfonamide **2b** (285 mg, 0.75 mmol), added over a 30 min period and PPA (3.75 g), heating at 140 °C for 3.5 h. A yellowish solid (234 mg) was obtained, which was submitted to flash column chromatography (SiO_2, 7.5 g, hexane/AcOEt/MeOH mixtures containing 0.3% of Et_3N). On elution with hexane/AcOEt 60:40 and AcOEt/MeOH 95:5, compound **7** (58 mg, 27% yield) and amine **3b** (132 mg, 59% yield) were isolated, respectively, as yellowish solids.

Dihydrochloride of **3b**. A solution of pure **3b** (206 mg, 0.69 mmol) in MeOH (10 mL) was treated with a solution of HCl in MeOH (0.48 M, 8.6 mL, 4.13 mmol), and the solvent was evaporated at reduced pressure, to give **3b**·2HCl (245 mg) as a yellowish solid. The analytical sample was obtained by precipitation in AcOEt/MeOH 1:2.5 followed by drying of the solid material at 80 °C/1 Torr for 2 days: mp>300 °C (dec.) (AcOEt/MeOH 1:2.5); R_f (**3b**, free base) 0.08 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3379, 3190 and 2926), 1654, 1635, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.63 (s, 3H, 9-CH_3), 2.18 (broad d, J=18.0 Hz, 1H, 10-H$_{endo}$), 2.75 (broad dd, J=18.0 Hz, J'=4.5 Hz, 1H, 10-H$_{exo}$), 3.01 (m, 1H, 7-H), 3.09 (d, J=19.0 Hz, 1H, 6-H$_{endo}$), 3.23 (dd, J=19.0 Hz, J'=5.5 Hz, 1H, 6-H$_{exo}$), 3.57 (m, 1H, 11-H), 3.92 (dd, J=3.5 Hz, J'=2.5 Hz, 1H, 13-H), 4.85 (s, NH^++NH_2+NH_3^+), 5.62 (broad d, J=6.0 Hz, 1H, 8-H), 7.64 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.82 (d, J=2.0 Hz, 1H, 4-H), 8.40 (d, $J\approx$9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 22.7 (CH_3, 9-CH_3), 30.1 (CH_2, C6), 30.8 (CH, C7), 31.2 (CH, C11), 36.7 (CH_2, C10), 50.4 (CH, C13), 109.7 (C, C11a), 115.5 (C, C12a), 119.3 (CH, C4), 123.4 (CH, C8), 126.5 (CH, C1), 128.0 (CH, C2), 135.4 (C, C9), 139.8 (C, C4a), 141.0 (C, C3), 150.7 (C) and 157.8 (C) (C5a and C12); *m/z* (CI) 328 [(M+C_2H_5)$^+$, 17], 302 (35) and 300 (100) [(M+H)$^+$], 301 (33), 299 (37), 285 (16) and 283 (38) [(M−NH_2)$^+$], 264 [(M−Cl)$^+$, 60]. HRMS calcd for $C_{17}H_{19}ClN_3$ [(M+H)$^+$]: 300.1268. Found: 300.1253.

Compound **7**. Mp 248–250 °C (dec.) (isopropanol); R_f 0.38 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3473, 2953, 2927, 1654, 1607, 1561, 1474, 1453, 1249 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.18 (d, J=7.0 Hz, 3H, 2-CH_3), 2.60 (ddq, J=J'=J''=7.0 Hz, 1H, 2-H), 2.66 (dd, $J\approx$16.0 Hz, $J'\approx$7.5 Hz, 1H, 1-H$_\alpha$), 2.68 (dd, $J\approx$15.5 Hz, $J'\approx$7.5 Hz, 1H, 3-H$_\alpha$), 3.19 (dd, $J\approx$16.0 Hz, J'=4.5 Hz, 1H, 1-H$_\beta$), 3.20 (dd, $J\approx$15.5 Hz, $J'\approx$4.5 Hz, 1H, 3-H$_\beta$), 4.85 (s, NH_2), 7.22 (dd, $J\approx$9.5 Hz, $J'\approx$2.0 Hz, 1H, 8-H), 7.57 (s, 1H, 4-H), 7.75 (d, $J\approx$2.0 Hz, 1H, 6-H), 7.98 (s, 1H, 11-H), 8.19 (d, J=9.5 Hz, 1H, 9-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.6 (CH_3, 2-CH_3), 36.4 (CH, C2), 41.4 (CH_2, C1), 42.0 (CH_2, C3), 112.0 (C, C9a), 113.1 (C, C10a), 117.3 (CH, C11), 120.9 (CH, C4), 123.2 (CH, C8), 125.2 (CH, C6), 125.6 (CH, C9), 137.3 (C, C7), 141.4 (C, C11a), 147.9 (C, C5a), 148.6 (C, C4a), 151.1 (C, C3a), 152.5 (C, C10); *m/z* (EI) 284 (34) and 282 (100) (M$^{\cdot+}$), 283 (26), 281 (19), 269 (13) and 267 (39) [(M−CH_3)$^+$], 268 (13), 266 (21), 232 [(M−Cl−CH_3)$^{\cdot+}$, 13]; *m/z* (CI) 285 (37) and 283 (100) [(M+H)$^+$], 284 (37), 282 (56), 247 [(M−Cl)$^+$, 47]. Anal. calcd for $C_{17}H_{15}ClN_2$·3/5H_2O: C, 69.55; H, 5.56; N, 9.54; Cl, 12.08. Found: C, 69.31; H, 5.34; N, 9.35; Cl, 12.37.

4.1.4. PPA hydrolysis of *N*-dodecylmethanesulfonamide. This reaction was carried out as described for **3a**, from methanesulfonamide **10** (200 mg, 0.76 mmol) and PPA

(3.80 g), heating at 160 °C for 1 h, obtaining pure *N*-dodecylamine (105 mg, 74% yield) as a brown oil.

4.1.5. PPA hydrolysis of *N*-(1-adamantyl)methanesulfonamide, 12, and *N*-(2-adamantyl)methanesulfonamide, 13. *Conditions 1*. This reaction was carried out as described for **3a**, from methanesulfonamide **12** or **13** (200 mg, 0.87 mmol) and PPA (4.47 g), heating at 110 °C for 1 h. GC–MS and ^{13}C NMR analysis of the crude products obtained from **12** and **13** (80 and 74 mg, respectively) revealed that they consisted of a mixture of adamantane, **14** (t_R=8.3 min), 1-adamantanol, **15** (t_R=11.1 min), 2-adamantanone, **16** (t_R=12.1 min), methanesulfonamide **12** (t_R=19.9 min), and methanesulfonamide **13** (t_R=20.1 min). For the GC–MS relative areas of these compounds see Table 3.

Conditions 2. This reaction was carried out as described for **3a**, from methanesulfonamide **12** (200 mg, 0.87 mmol) or **13** (179 mg, 0.78 mmol) and PPA (3.60 and 3.45 g, respectively), heating at 160 °C for 1 h. GC–MS and ^{13}C NMR analysis of the crude products obtained from **12** and **13** (43 and 67 mg, respectively) revealed that they consisted mainly of a mixture of adamantane, **14**, 1-adamantylamine, **17** (t_R=10.7 min), and 2-adamantanone, **16**. For the GC–MS relative areas of these compounds see Table 3.

4.1.6. 12-Amino-3-chloro-*anti*-13-formamido-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline (18a). Ac_2O (682 μL, 738 mg, 7.23 mmol) was added to a solution of amine **3a** (108 mg, 0.36 mmol) in HCO_2H (1 mL, 1.22 g, 26.5 mmol), and the reaction mixture was heated under reflux for 45 min, allowed to reach room temperature and concentrated in vacuo. The resulting residue was taken in MeOH (5 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic solvent was evaporated at reduced pressure, and the resulting aqueous suspension was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure, to give formamide **18a** (98 mg, 83% yield) as a white solid: mp 254–256 °C (AcOEt); R_f 0.51 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3424, 3386, 3151, 2876, 1694, 1671, 1606, 1566, 1488 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 3H, 9-CH_3), 1.97 (d, J=18.0 Hz, 1H, 10-H_{endo}), 2.46 (ddm, J≈18.0 Hz, J'=4.5 Hz, 1H, 10-H_{exo}), 2.64 (m, 1H, 7-H), 3.10 (dm, J=17.5 Hz, 1H, 6-H_{endo}), 3.32 (dd, J=17.5 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.42 (m, 1H, 11-H), 4.42 (m, 1H, 13-H), 4.76 (broad s, 2H, NH_2), 5.48 (dm, J=5.0 Hz, 1H, 8-H), 5.88 (broad d, J=6.5 Hz, 1H, HCON*H*), 7.34 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.63 (d, J=9.0 Hz, 1H, 1-H), 7.87 (broad s, 1H, 4-H), 8.28 (s, 1H, *H*CONH), a very small signal at δ 5.30 ppm corresponding to CH_2Cl_2 was also observed; ^{13}C NMR (75.4 MHz, $CDCl_3$+CD_3OD) δ 23.0 (CH_3, 9-CH_3), 30.0 (CH, C11), 30.4 (CH_2, C10), 32.9 (CH, C7), 38.5 (CH_2, C6), 46.2 (CH, C13), 113.1 (C, C11a), 115.0 (C, C12a), 121.1 (CH, C1), 122.4 (CH, C8), 124.8 (CH, C2), 125.2 (CH, C4), 133.7 (C, C9), 135.4 (C, C4a), 145.8 (C, C3), 148.3 (C) and 155.4 (C) (C5a and C12), 161.7 (C, HCONH); *m*/*z* (CI) 356 [(M+C_2H_5)$^+$, 17], 330 (37) and 328 (100) [(M+H)$^+$], 329 (28), 327 (20), 294 (17), 292 [(M−Cl)$^+$, 16]. HRMS calcd for $C_{18}H_{19}ClN_3O$ [(M+H)$^+$]: 328.1217. Found: 328.1217. Anal. calcd for $C_{18}H_{18}ClN_3O$·1/2H_2O·0.07CH_2Cl_2: C, 63.32; H, 5.63; N, 12.26; Cl, 11.79. Found: C, 63.34; H, 5.46; N, 12.10; Cl, 11.84.

4.1.7. 12-Amino-3-chloro-*syn*-13-formamido-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline (18b). It was prepared as described for **18a**. Starting from a solution of amine **3b** (121 mg, 0.40 mmol) in HCO_2H (1 mL, 1.22 g, 26.5 mmol) and Ac_2O (756 μL, 818 mg, 8.01 mmol) with a reaction time of 1 h, formamide **18b** (113 mg, 86% yield) was obtained as a yellowish solid: mp 252–253 °C (dec.) (hexane/AcOEt 1:1); R_f 0.17 (SiO_2, CH_2Cl_2/MeOH 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3351, 3246, 2903, 1637, 1560, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 3H, 9-CH_3), 2.08 (broad d, J=17.0 Hz, 1H, 10-H_{endo}), 2.70 (dm, J≈17.0 Hz, 1H, 10-H_{exo}), 2.86 (m, 1H, 7-H), 2.96 (broad d, J≈19.0 Hz, 1H, 6-H_{endo}), superimposed in part 3.14 (dd, J=19.0 Hz, J'=6.0 Hz, 1H, 6-H_{exo}), 3.16 (m, 1H, 11-H), 4.58 (m, 1H, 13-H), 4.75 (broad s, 2H, NH_2), 5.54 (dm, J=4.0 Hz, 1H, 8-H), 5.7–6.0 (broad signal, 1H, HCON*H*), 7.34 (m, 1H, 2-H), 7.60 (m, 1H, 1-H), 7.83 (broad s, 1H, 4-H), 8.16 (s, 1H, *H*CONH), signals corresponding to AcOEt were also observed; ^{13}C NMR (75.4 MHz, $CDCl_3$+CD_3OD) δ 22.7 (CH_3, 9-CH_3), 31.3 (CH, C7), 32.2 (CH, C11), 33.0 (CH_2, C6), 35.8 (CH_2, C10), 46.5 (CH, C13), 111.0 (C, C11a), 115.1 (C, C12a), 122.2 (CH, C1), 124.2 (CH, C8), 124.9 (CH, C2), 125.0 (CH, C4), 132.5 (C, C9), 135.5 (C, C4a), 145.4 (C, C3), 149.4 (C) and 155.4 (C) (C5a and C12), 161.9 (C, HCONH); *m*/*z* (CI) 356 [(M+C_2H_5)$^+$, 16], 330 (35) and 328 (100) [(M+H)$^+$], 329 (25), 294 (55), 292 [(M−Cl)$^+$, 22]. HRMS calcd for $C_{18}H_{19}ClN_3O$ [(M+H)$^+$]: 328.1217. Found: 328.1215. Anal. calcd for $C_{18}H_{18}ClN_3O$·2/5H_2O·1/2AcOEt: C, 63.37; H, 6.06; N, 11.09; Cl, 9.35. Found: C, 63.66; H, 5.74; N, 11.40; Cl, 8.93.

4.1.8. *anti*-13-Acetamido-12-amino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (19a·HCl). It was prepared as described for **18a**, but using AcOH instead of HCO_2H. Thus, starting from a solution of amine **3a** (100 mg, 0.33 mmol) in AcOH (1 mL, 1.05 g, 17.5 mmol) and Ac_2O (62 μL, 67 mg, 0.66 mmol), acetamide **19a** (96 mg, 85% yield) was obtained as a brown solid.

Hydrochloride of **19a**. A solution of pure **19a** (96 mg, 0.28 mmol) in MeOH (2 mL) was treated with a solution of HCl in MeOH (0.48 M, 1.95 mL, 0.94 mmol), stirred at room temperature for 5 min and evaporated at reduced pressure, to give the corresponding hydrochloride (110 mg) as a yellowish solid: mp>300 °C (dec.) (AcOEt/MeOH 4:1); R_f (**19a**, free base) 0.37 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3323, 3150 and 2923), 1675, 1589, 1541 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.63 (s, 3H, 9-CH_3), 1.92 (broad d, J=18.5 Hz, 1H, 10-H_{endo}), 2.02 (s, 3H, C*H*$_3$-CONH), 2.53 (broad dd, J=18.5 Hz, J'=5.0 Hz, 1H, 10-H_{exo}), 2.68 (m, 1H, 7-H), 2.98 (dd, J=18.0 Hz, J'=1.5 Hz, 1H, 6-H_{endo}), 3.39 (dd, J=18.0 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.49 (m, 1H, 11-H), 4.16 (m, 1H, 13-H), 4.84 (s, NH^++NH_2), 5.51 (dm, J=4.5 Hz, 1H, 8-H), 7.60 (dd,

J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.74 (d, J=2.0 Hz, 1H, 4-H), 8.13 (d, J=7.5 Hz, 1H, CH_3CONH), 8.35 (d, J=9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 22.6 (CH_3, CH_3CONH), 23.4 (CH_3, 9-CH_3), 30.6 (CH, C11), 31.1 (CH_2, C10), 32.8 (CH, C7), 36.5 (CH_2, C6), 48.3 (CH, C13), 114.7 (C, C11a), 115.1 (C, C12a), 119.1 (CH, C4), 121.9 (CH, C8), 126.3 (CH, C1), 127.7 (CH, C2), 135.4 (C, C9), 139.6 (C, C4a), 140.6 (C, C3), 151.8 (C) and 156.9 (C) (C5a and C12), 173.5 (C, CH_3CONH); *m/z* (CI) 344 (13) and 342 (32) [$(M+H)^+$], 306 [$(M-Cl)^+$, 9]. HRMS calcd for $C_{19}H_{21}ClN_3O$ [$(M+H)^+$]: 342.1373. Found: 342.1361. Anal. calcd for $C_{19}H_{20}ClN_3O{\cdot}HCl{\cdot}2.65H_2O$: C, 53.57; H, 6.22; N, 9.86; Cl, 16.64. Found: C, 53.18; H, 6.06; N, 9.48; Cl, 17.03.

4.1.9. *syn*-13-Acetamido-12-amino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (19b·HCl). It was prepared as described for **18a**, but using AcOH instead of HCO_2H. Thus, starting from a solution of amine **3b** (101 mg, 0.34 mmol) in AcOH (1 mL, 1.05 g, 17.5 mmol) and Ac_2O (62 μL, 67 mg, 0.66 mmol) with a reaction time of 1.25 h, acetamide **19b** (101 mg, 88% yield) was obtained as a brown solid.

Hydrochloride of **19b**. A solution of pure **19b** (101 mg, 0.30 mmol) in MeOH (2 mL) was treated with a solution of HCl in MeOH (0.48 M, 2 mL, 0.96 mmol), stirred at room temperature for 1 h and evaporated at reduced pressure, to give the corresponding hydrochloride (121 mg) as a yellowish solid: mp>300 °C (dec.) (isopropanol/AcOEt/MeOH 3:2:0.5); R_f (**19b**, free base) 0.22 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3351, 3190 and 2922), 1654, 1646, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.60 (s, 3H, 9-CH_3), 1.91 (s, 3H, CH_3CONH), 2.09 (broad d, J=18.0 Hz, 1H, 10-H_{endo}), 2.69 (ddm, J=18.0 Hz, J'=4.5 Hz, 1H, 10-H_{exo}), 2.84 (broad d, J=18.5 Hz, 1H, 6-H_{endo}), 2.88 (m, 1H, 7-H), 3.22 (dd, J=18.5 Hz, J'=5.0 Hz, 1H, 6-H_{exo}), 3.30 (m, 1H, 11-H), 4.31 (m, 1H, 13-H), 4.84 (s, $CH_3CONH+NH_2+NH^+$), 5.57 (broad d, J=6.0 Hz, 1H, 8-H), 7.61 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.77 (d, J=2.0 Hz, 1H, 4-H), 8.37 (d, J=9.0 Hz, 1H, 1-H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 22.5 (CH_3, CH_3CONH), 22.9 (CH_3, 9-CH_3), 30.9 (CH_2, C6), 31.7 (CH, C7), 32.5 (CH, C11), 36.9 (CH_2, C10), 48.9 (CH, C13), 112.4 (C, C11a), 115.5 (C, C12a), 119.2 (CH, C4), 124.8 (CH, C8), 126.4 (CH, C1), 127.9 (CH, C2), 135.0 (C, C9), 139.7 (C, C4a), 140.8 (C, C3), 152.1 (C) and 157.8 (C) (C5a and C12), 173.6 (C, CH_3CONH); *m/z* (CI) 344 (7) and 342 (19) [$(M+H)^+$], 306 [$(M-Cl)^+$, 6]. HRMS calcd for $C_{19}H_{21}ClN_3O$ [$(M+H)^+$]: 342.1373. Found: 342.1361. Anal. calcd for $C_{19}H_{20}ClN_3O{\cdot}HCl{\cdot}H_2O$: C, 57.58; H, 5.85; N, 10.60; Cl, 17.89. Found: C, 57.88; H, 5.72; N, 10.15; Cl, 17.64.

Acknowledgements

Financial support from the Dirección General de Investigación of Ministerio de Ciencia y Tecnología and FEDER (project PPQ2002-01080) and Comissionat per a Universitats i Recerca of the Generalitat de Catalunya (project 2001-SGR-00085) are gratefully acknowledged.

References and notes

1. Camps, P.; El Achab, R.; Görbig, D. M.; Morral, J.; Muñoz-Torrero, D.; Badia, A.; Baños, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **1999**, *42*, 3227–3242.
2. Camps, P.; El Achab, R.; Morral, J.; Muñoz-Torrero, D.; Badia, A.; Baños, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **2000**, *43*, 4657–4666.
3. Camps, P.; Cusack, B.; Mallender, W. D.; El Achab, R.; Morral, J.; Muñoz-Torrero, D.; Rosenberry, T. L. *Mol. Pharmacol.* **2000**, *57*, 409–417.
4. Camps, P.; Gómez, E.; Muñoz-Torrero, D.; Badia, A.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **2001**, *44*, 4733–4736.
5. Camps, P.; Muñoz-Torrero, D. *Mini Rev. Med. Chem.* **2001**, *1*, 163–174.
6. Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **1999**, *42*, 5110–5119.
7. Dvir, H.; Wong, D. M.; Harel, M.; Barril, X.; Orozco, M.; Luque, F. J.; Muñoz-Torrero, D.; Camps, P.; Rosenberry, T. L.; Silman, I.; Sussman, J. L. *Biochemistry* **2002**, *41*, 2970–2981.
8. Camps, P.; Gómez, E.; Muñoz-Torrero, D.; Font-Bardia, M.; Solans, X. *Tetrahedron* **2003**, *59*, 4143–4151.
9. Review article on the cleavage of sulfonamides: Searles, S.; Nukina, S. *Chem. Rev.* **1959**, *59*, 1077–1103. For selected examples of methods for cleavage of sulfonamides see Refs. 10–26.
10. With H_2SO_4: Carpenter, P. D.; Lennon, M. *J. Chem. Soc., Chem. Commun.* **1973**, 664–665.
11. With $MeSO_3H/H_2O$: Feit, P. W.; Nielsen, O. T. *J. Med. Chem.* **1970**, *13*, 447–452.
12. With Zn/HOAc: Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1970**, 345–348.
13. With HBr/HOAc/phenol: Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367–2371.
14. With Mg/MeOH: Nyasse, B.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S.; Ragnarsson, U. *J. Org. Chem.* **1999**, *64*, 7135–7139.
15. With metal/naphthalene: Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355–14368.
16. With Na/alcohol: Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691–1694.
17. With Na/NH_3: see Ref. 13.
18. With SmI_2: Goulaouic-Dubois, C.; Guggisberg, A.; Hesse, M. *Tetrahedron* **1995**, *51*, 12573–12582.
19. With Bu_3SnH/AIBN: Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1996**, *37*, 1667–1670.
20. With $LiAlH_4$ or Red-Al: Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 3839–3842.
21. With $PhMe_2SiLi$: Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229–1235.
22. With KF/Al_2O_3/microwave: Sabitha, G.; Abraham, S.; Reddy, B. V. S.; Yadav, J. S. *Synlett* **1999**, 1745–1746.
23. With PhSH/DIPEA: Wuts, P. G. M.; Northuis, J. M. *Tetrahedron Lett.* **1998**, *39*, 3889–3890.
24. With TMSCl/NaI: Sabitha, G.; Reddy, B. V. S.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569–1570.
25. With TBAF: Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595–596.
26. By photolysis: D'Souza, L.; Day, R. A. *Science* **1968**, *160*, 882–883.

27. Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006–2009.
28. Vanden Heuvel, W. J. A.; Gardiner, W. L.; Horning, E. C. *Anal. Chem.* **1964**, *36*, 1550–1560.
29. Satyamurthy, N.; Bida, G. T.; Phelps, M. E.; Barrio, J. R. *Appl. Radiat. Isot.* **1990**, *41*, 733–738.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5433–5438
Tetrahedron

Enantioselective synthesis of indolizidine and quinolizidine derivatives from chiral non-racemic bicyclic lactams

Claude Agami, Luc Dechoux,* Séverine Hebbe and Cécilia Ménard

Laboratoire de Synthèse Asymétrique (UMR 7611), Université P. et M. Curie, 4 place Jussieu, 75005 Paris, France

Received 21 November 2003; revised 24 March 2004; accepted 22 April 2004

Abstract—Chiral non-racemic bicyclic lactams **2b**,**c**, derived from (*R*)- and (*S*)-phenylglycinol, were used in the enantioselective synthesis of (−)-lupinine and 5-epitashiromine, respectively. The efficiency of the synthesis relied on the high diastereoselectivities of formation and reduction of compounds **2b**,**c**.

Regarding the enantioselective synthesis of polysubstituted piperidines,[1] chiral non-racemic bicyclic lactams[2] derived from homochiral β-amino alcohols are commonly considered as the most useful starting material. In these syntheses, the bicyclic ring system is usually generated by cyclocondensation of δ-oxoacid derivatives with suitable β-amino alcohols.

In previous papers, we described the enantioselective synthesis of 2,3-disubstituted piperidines[3] **4** and **5** (R=Me) from the chiral non-racemic bicyclic lactams[4] **2** and **3**. These bicyclic compounds were obtained by aza-annulation[5] of β-enaminoesters **1** derived from (*S*)-phenylglycinol with acryloyl chloride (Scheme 1).

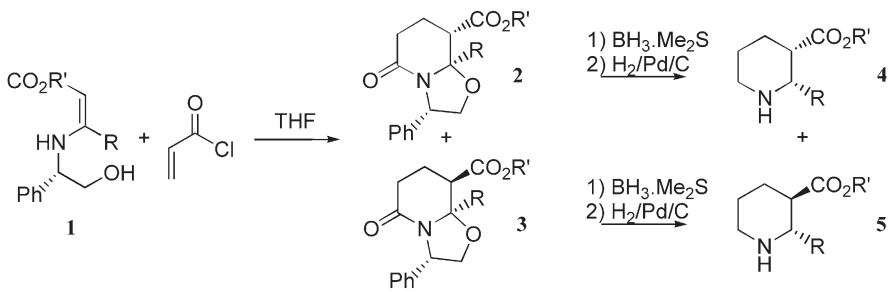
To the best of our knowledge, the synthesis of bicyclic lactams bearing an ester or a ketone moiety on C5 have not been reported so far. The efficiency of these transformations, that is the synthesis of enantiopure 2,3-disubstituted piperidines, rely on a simple introduction in the bicyclic systems of the C5 substituent and on a high stereocontrol of the reductive opening of the oxazolidine ring.

More recently, we described the diastereoselective synthesis of the *cis* bicyclic lactams **2**.[6]

Here, we wish to report full experimental details of this work, as well as two applications directed towards the enantioselective synthesis of (−)-lupinine and 5-epitashiromine. These two compounds possess the quinolizidine and indolizidine structural skeletons widely found in natural alkaloids.[7] Whereas a quite large number of enantioselective syntheses of chiral non-racemic lupinine have been described,[8] one publication only reported the synthesis of enantiopure 5-epitashiromine.[9]

1. Results and discussion

A possible precursor of (−)-lupinine **10b** (*n*=2) is the



Scheme 1.

Keywords: Bicyclic lactams; Lupinine; Epitashiromine; Quinolizidine; Indolizidine.
* Corresponding author. Tel.: +33-1-44-26-26-20; fax: +33-1-44-27-26-20; e-mail address: dechoux@ccr.jussieu.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.055

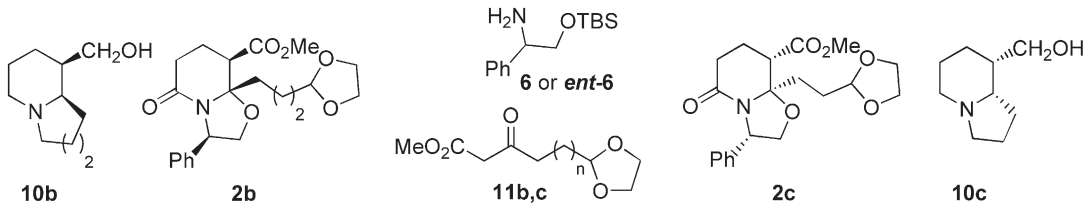


Figure 1.

bicyclic lactam **2b**, which already bears the two stereogenic centers present in **10b**. The compound **2b** could be obtained from the TBS-protected (*R*)-phenylglycinol ent-**6** and β-ketoester **11b** (*n*=2). Using the same strategy, bicyclic lactam **2c**, arising from TBS-protected (*S*)-phenylglycinol **6** and β-ketoester **11c** (*n*=1), should be a valuable precursor for the synthesis of 5-epitashiromine **10c** (Fig. 1).

In order to prepare enaminoesters **9a**,**b**,**c** (Scheme 2) by an aza-annulation process, condensation of TBS-protected (*R*)-phenylglycinol **6** with β-ketoester (*n*=2)[10] **11b** and of TBS-protected (*S*)-phenylglycinol ent-**6** with β-ketoester (*n*=1) **11c** and methylacetoacetate, in methanol, yielded β-enaminoesters **7a**,**b**,**c**. Silica gel chromatography afforded purified enaminoesters **7b** and **7c** (respective yields: 39 and 42%). These low yields resulted from the instability of β-enaminoesters on silica gel. Nevertheless, unpurified enaminoesters **7a**,**b**,**c** were obtained in nearly quantitative yields and they were used as such in the next step.

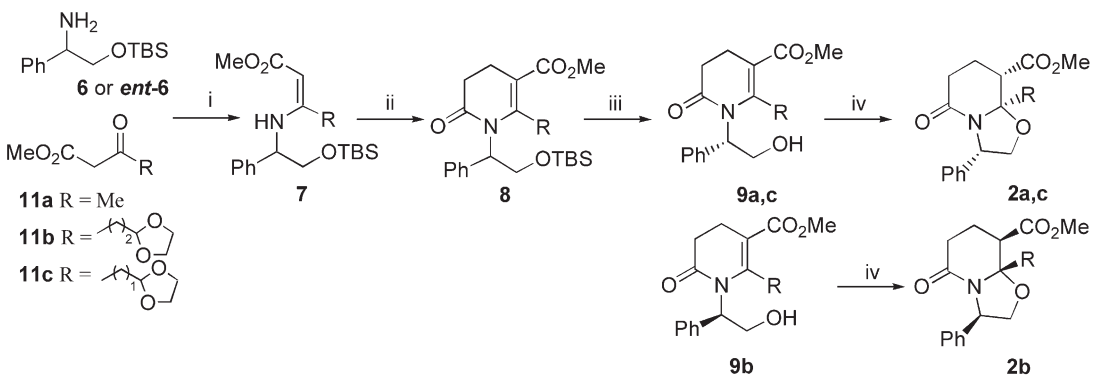
The aza-annulation reaction was performed by adding 1.2 equiv. of acryloyl chloride derivatives to β-enaminoesters **7a**,**b**,**c** in THF at 0 °C. Cyclization with acryloyl chloride was successful and yielded fair amounts of the expected TBS-protected 3,4-dihydro-2-pyridones **8a**,**b**,**c**. Deprotection of compounds **8a**,**b**,**c** with HF-pyridine at 0 °C worked properly and excellent yields of compounds **9a**,**b**,**c** were obtained if the crude materials were used without purification by silica gel chromatography. It is noteworthy that, the bicyclic lactams **2a**,**b**,**c** were formed directly with low diastereoselectivities (d.e.<20%) when using basic deprotection conditions involving tetrabutylammonium-fluoride (TBAF).

At this stage, the alcohols **9a**,**b**,**c** were purified by silica gel chromatography. Intramolecular Michael addition was performed in basic media using 0.1 mol equiv. of LiHMDS in THF, at 0 °C, during 40 min. Under these conditions, the expected bicyclic lactams **2a**,**b**,**c** were obtained in quantitative yields and excellent diastereoselectivities (>95%). Overall yields starting from (*R*)-or (*S*)-phenylglycinol were higher than 80%.

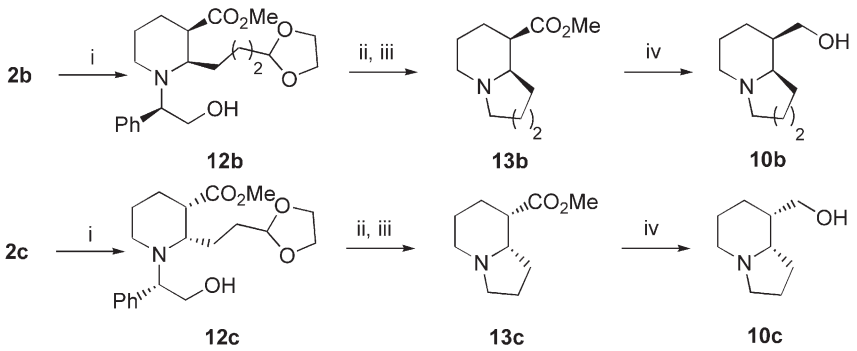
Absolute configurations of *cis* lactams **2b**,**c** and *trans* lactams **3b**,**c** were deduced from the structures of compounds **2a** (R=Me) and **3a** (R=Me) which have been previously established by NOE ^{1}H NMR experiments and X-ray analysis.[4] It was in particular observed that the chemical shift of the proton α to the ester moiety in the major *cis* lactams diastereoisomers **2b**,**c** were found up field (2.6–2.7 ppm) from that of *trans* isomers **3b**,**c** (3.1–3.2 ppm).

Reduction of the oxazololactams **2b**,**c** using 4 equiv. of BH_3·THF yielded the piperidines **12b** and **12c**, respectively, with a high facial selectivity (d.e.>95%) and in a quantitative manner (Scheme 3). We have already shown that the stereoselectivity was not governed by the stereogenic center bearing the ester moiety but by the more remote phenyl-bearing stereocenter adjacent to the nitrogen.[3] Meyers[11] reduced similar bicyclic lactams with BH_3·THF and noted that the reduction occurred also with retention of configuration. More recently, Amat[12] presented a more exhaustive study showing that the diastereoselectivity of the reduction of 2-aryloxazolidino-δ-lactams are dependent on the nature of the reducing agent.

The final steps of the two syntheses were similar to those of the previously reported synthesis of (−)-Coniceine (Meyers[13e]). Both our syntheses included cylization by reductive amination.[13] The aldehydes were deprotected by heating the piperidines **12b**,**c** in a 4:1 mixture of acetone and water with 2 mol equiv. *p*-toluenesulfonic acid. Hydrogenation of the resulting aminoaldehyde, in methanol containing a 0.3 mol equiv. of Pd/C, removed the *N*-benzyl group and allowed the reductive amination leading to



Scheme 2. (i) MeOH, reflux; (ii) acryloyl chloride, THF; (iii) HF.pyridine, THF; (iv) LiHMDS, THF.



Scheme 3. (i) BH_3·THF, THF; (ii) *p*-toluenesulfonic acid, acetone, H_2O; (iii) Pd/C, H_2, MeOH; (iv) $LiAlH_4$, THF.

quinolizidine **13b** and indolizidine **13c** with 60 and 29% yield, respectively, for the two steps. The reduction of compounds **12b**,**c** with $LiAlH_4$ in THF for 24 h gave (−)-lupinine **10b** and 5-epitashiromine **10c** in 60% yield. The products were purified by silica gel chromatography. Comparison of the ^1H NMR and ^{13}C NMR of (−)-**10b**[8d] and **10c**[9] confirmed the structures of the compounds. The value of the optical rotation of (−)-**10c** $[\alpha]_D=-21.5$ [lit[14] $[\alpha]_D$ for (−)-lupinine −21] confirmed the absolute stereochemistry and the optical purity of (−)-lupinine. For 5-epitashiromine, a very low absolute value was found (around 0). An equivalent low value was obtained for the same stereoisomer **10b** $[\alpha]_D=-1.3$ [lit[9] $[\alpha]_D$ for 5-epitashiromine +1.1].

2. Conclusion

Chiral non-racemic *cis* bicyclic lactams **2**, starting from (*R*)- and (*S*)-phenylglycinol, allow an easy access to indolizidine and quinolizidine heterocycles. As a result, (−)-lupinine **10b** and 5-epitashiromine **10c** were synthezised in 19 and 7% overall yield, respectively. The efficiency of these syntheses relied on the direct introduction in the lactam ring of the carbonyl function and on the high stereoselectivities of formation and reduction of bicyclic lactams **2**. We are currently working on enantioselective syntheses of matrine[15] and its stereoisomers.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 250 spectrometer at 250 and 62.9 MHz, respectively; chemical shifts are reported in ppm from TMS. All reaction with organometallic were conducted under argon. Column chromatography was performed on silica gel, 230–400. TLC were run on Merck Kieselgel $60F_{254}$ plates. THF was distilled from sodium/benzophenone ketyl.

3.2. General procedure for the synthesis of bicyclic lactams 2

Synthesis of (3*S*)-(8*S*)-(8a*R*)-8a-Methyl-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester **2a**. To a solution of compound **9a** (0.50 g, 1.73 mmol) in THF (17.5 mL) at 0 °C was added a solution of LiHMDS (0.173 mL, 1 M in THF). After 2 h at 0 °C (40 min for substrates **9b**,**c**), the reaction was quenched with an saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used without further purification in the next step (white crystal, 0.50 g, 100%).

3.2.1. (3*S*)-(8*S*)-(8a*R*)-8a-Methyl-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (2a).[3] White crystal, 100%. ^1H NMR ($CDCl_3$): δ=1.47 (s, 3H), 2.12–2.24 (m, 2H), 2.49 (m, 1H), 2.65 (m, 1H), 2.76 (dd, *J*=8.5, 9 Hz, 1H), 3.78 (s, 3H), 3.99 (dd, *J*=7.8, 9.2 Hz, 1H), 4.55 (dd, *J*=8.2, 9 Hz, 1H), 5.33 (t, *J*=8 Hz, 1H), 7.19–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ= 20.3, 20.5, 29.8, 50.1, 52.4, 58.7, 70.2, 93.9, 125.5, 127.4, 128.7, 139.2, 168.4, 171.4. Mp: 115 °C. $[\alpha]_D^{20}=+137$ (*c* 0.68, $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_4$: C: 66.42, H: 6.62, N: 4.84. Found: C: 66.37, H: 6.78, N: 4.77. IR ($CHCl_3$) 1734, 1655, 1395 cm^{-1}.

3.2.2. (3*R*)-(8*R*)-(8a*S*)-8a-(3-[1,3]Dioxolan-2-yl-propyl)-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (2b).[3] White crystal, 100%. ^1H NMR ($CDCl_3$): δ=1.12–2.74 (m, 11H), 3.66–3.72 (m, 2H), 3.72 (s, 3H), 3.75–3.79 (m, 2H), 4.05 (dd, *J*=6.7, 9 Hz, 1H), 4.44 (dd, *J*=8.2, 9 Hz, 1H), 4.64 (t, *J*=4.2 Hz, 1H), 5.33 (t, *J*=7 Hz, 1H), 7.17–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=17.9, 19.7, 29.5, 33.5, 33.8, 49.1, 52.4, 58.5, 64.8, 69.4, 95.8, 103.9, 125.8, 127.3, 128.5, 139.2, 169.4, 171.5. Mp: 138 °C. $[\alpha]_D^{20}=-100$ (*c* 0.78, $CHCl_3$). Anal. Calcd for $C_{21}H_{27}NO_6$: C: 64.77, H: 6.99, N: 3.60. Found: C: 63.51, H: 7.12, N: 3.47.

3.2.3. (3*S*)-(8*S*)-(8a*R*)-8a-(2-[1,3]Dioxolan-2-yl-ethyl)-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (2c). White solid, 100%. ^1H NMR ($CDCl_3$): δ=1.35–2.73 (m, 9H), 3.59–3.84 (m, 4H), 3.69 (s, 3H), 4.03 (dd, *J*=6.75, 9.25 Hz, 1H), 4.43 (dd, *J*=8.25, 9 Hz, 1H), 4.63 (t, *J*=4 Hz, 1H), 5.32 (t, *J*=7.5 Hz, 1H), 7.13–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=19.3, 27.2, 27.3, 29.2, 48.8, 52.2, 58.3, 64.6, 64.7, 69.0, 95.4, 103.3, 125.8, 127.1, 128.3, 138.3, 169.2, 171.2. Mp: 95 °C. $[\alpha]_D^{20}=+88$ (*c* 1.23, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99, H: 6.71, N: 3.73. Found: C: 64.27, H: 7.06, N: 3.63.

3.2.4. (3*S*)-(8*R*)-(8a*R*)-8a-Methyl-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (3a).[3] White crystal, obtained by epimerisation of **2a**

with 0.5 mol equiv. NaHMDS in THF. ^{1}H NMR ($CDCl_3$): δ=1.48 (s, 3H), 2.04–2.12 (m, 2H), 2.39–2.68 (m, 2H), 3.10 (t, J=4 Hz, 1H) 3.65 (s, 3H), 3.87 (dd, J=7.8, 9 Hz, 1H), 4.33 (dd, J=8.2, 8.7 Hz, 1H), 5.24 (t, J=7.7 Hz, 1H), 7.11–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=19.9, 25.9, 27.5, 47.0, 51.9, 59.4, 70.1, 93.8, 125.7, 127.3, 128.6, 139.6, 169.2, 171.5. Mp: 57 °C. $[\alpha]_D^{20}$=+106 (c 0.87, $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_4$: C: 66.42; H: 6.62; N: 4.84. Found: C: 66.25; H: 6.78; N: 4.66. IR ($CHCl_3$) 1736, 1655, 1399 cm^{-1}.

3.2.5. (3*R*)-(8*S*)-(8a*S*)-8a-(3-[1,3]Dioxolan-2-yl-propyl)-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (3b). Oil, obtained by epimerisation of **2b** with 0.5 mol equiv. NaHMDS in THF. ^{1}H NMR ($CDCl_3$): δ=1.35–2.05 (m, 8H), 2.40–2.70 (m, 2H), 3.26 (t, J=4 Hz, 1H), 3.64 (s, 3H), 3.70–3.88 (m, 5H), 4.31 (t, J=8.75 Hz, 1H), 4.74 (t, J=4 Hz, 1H), 5.21 (t, J=8 Hz, 1H), 7.15–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=18.1, 19.5, 27.5, 33.2, 36.5, 42.5, 51.9, 59.4, 64.8, 70.0, 95.7, 103.9, 125.6, 127.2, 128.5, 139.6, 169.4, 171.7.

3.2.6. (3*S*)-(8*R*)-(8a*R*)-8a-(2-[1,3]Dioxolan-2-yl-ethyl)-5-oxo-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-8-carboxylic acid methyl ester (3c). Oil, obtained by epimerisation of **2c** with 0.5 mol equiv. NaHMDS in THF. ^{1}H NMR ($CDCl_3$): δ=1.50–2.25 (m, 6H), 2.37–2.66 (m, 2H), 3.21 (t, J=4 Hz, 1H), 3.64 (s, 3H), 3.65–3.90 (m, 5H), 4.32 (t, J=8.5 Hz, 1H), 4.80 (dd, J=3.0, 4.75 Hz, 1H), 5.20 (t, J=8.2 Hz, 1H), 7.14–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=19.3, 27.3, 28.0, 30.1, 42.5, 51.8, 59.4, 64.8, 64.9, 69.8, 95.5, 103.2, 125.6, 127.1, 128.4, 139.3, 169.4, 171.5.

3.3. General procedure for the synthesis of β-enaminoesters 7

Synthesis of {3(1*S*)}-(2*Z*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-but-2-carboxylic acid methyl ester **7a**. To a TBS-protected (*S*)-phenylglycinol **6** (3 g, 11.9 mmol) in methanol (59 mL), methylacetoacetate (1.42 mL, 13.1 mmol) was added. After refluxing for 24 h (10 days for the synthesis of β-enaminoester **7b** and **7c**), the solvent was evaporated under reduced pressure to yield enaminoesters **7a** (oil, 4.17 g, 100%) Compounds **7b** and **7c** were chromatographed on silica gel (AcOEt/cyclohexane: 5/95).

3.3.1. {3(1*S*)}-(2*Z*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-carboxylic acid methyl ester (7a). Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.14 (s, 3H), −0.09 (s, 3H), 0.76 (s, 9H), 1.74 (s, 3H), 3.59 (s, 3H), 3.67 (dd, J=6.5, 10 Hz, 1H), 3.78 (dd, J=4.8, 10 Hz, 1H), 4.42 (s, 1H), 4.48–4.56 (m, 1H), 7.11–7.30 (m, 5H), 9.09 (brd, J=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=−5.8, 18.2, 19.8, 25.7, 49.9, 59.1, 67.9, 83.0, 126.6, 127.4, 128.5, 140.4, 161.8, 170.6.$[\alpha]_D^{20}$=−261 (*c* 1.46, $CHCl_3$). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C: 65.29, H: 8.94, N: 4.01. Found: C: 65.15, H: 8.85, N: 4.15.

3.3.2. {3[1*R*]}-(2*Z*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-6-[1,3]dioxolan-2-yl-hex-2-carboxylic acid methyl ester (7b). Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.19 (s, 3H), −0.15 (s, 3H), 0.72 (s, 9H), 1.40–1.57 (m, 4H), 1.99–2.15 (m, 2H), 3.55 (s, 3H), 3.59–3.87 (m, 6H), 4.41 (s, 1H), 4.45–4.53 (m, 1H), 4.66 (t, J=4 Hz, 1H), 7.11–7.24 (m, 5H), 9.06 (brd, J=9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=−5.8, 18.2, 22.2, 24.7, 32.3, 33.1, 49.9, 58.6, 64.8, 68.0, 82.4, 104.0, 126.6, 127.4, 128.5, 140.6, 164.9, 170.9. $[\alpha]_D^{20}$=+179 (*c* 0.85, $CHCl_3$). Anal. Calcd for $C_{24}H_{39}NO_5Si$: C: 64.11, H: 8.74, N: 3.11. Found: C, 63.77, H: 8.98, N: 3.19.

3.3.3. {3[1*S*]}-(2*Z*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-5-[1,3]dioxolan-2-yl-pent-2-carboxylic acid methyl ester (7c). Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.17 (s, 3H), −0.13 (s, 3H), 0.73 (s, 9H), 1.66–1.72 (m, 2H), 2.09–2.17 (m, 2H), 3.55 (s, 3H), 3.59–3.81 (m, 6H), 4.44 (s, 1H), 4.52–4.60 (m, 1H), 4.74 (t, J=4.25 Hz, 1H), 7.10–7.25 (m, 5H), 9.08 (brd, J=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=−5.7, 18.1, 25.7, 26.5, 32.1, 49.9, 58.5, 64.9, 68.0, 82.3, 103.1, 126.6, 127.4, 128.4, 140.4, 164.6, 170.8. $[\alpha]_D^{20}$=−176 (*c* 1.08, $CHCl_3$). Anal. Calcd for $C_{23}H_{37}NO_5Si$: C: 63.41, H: 8.56, N: 3.22. Found: C: 63.45, H: 8.41, N: 3.09.

3.4. General procedure for the synthesis of 3,4-dihydro-2-pyridones 8

Synthesis of {[1(1*S*)]}-1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethyl]-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester **8a**. To a solution of β-enaminoester **7a** (4 g, 11.5 mmol) in THF (57 mL) was added at 0 °C acryloyl chloride (1.03 mL; 12.6 mmol). After 15 min at 0 °C, the mixture was quenched with an aqueous solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic phase was concentrated at reduced pressure. The residue was chromatographed on silica gel (AcOEt/Cyclohexane: 15/85) to furnish 4.6 g of compound **8a**. Yellow oil, 100%.

3.4.1. {[1(1*S*)]}-1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethyl]-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (8a). Yellow oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.05 (s, 3H), −0.02 (s, 3H), 0.78 (s, 9H), 2.32 (s, 3H), 2.34–2.60 (m, 4H), 3.64 (s, 3H), 4.21–4.27 (m, 1H), 4.35–4.42 (m, 1H), 5.17 (t, J=7 Hz, 1H), 7.09–7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=−5.6, 17.6, 18.0, 21.0, 25.7, 32.4, 51.4, 60.4, 63.3, 110.1, 126.3, 127.0, 128.3, 138.8, 150.3, 167.8, 171.3. $[\alpha]_D^{20}$=+30.4 (*c* 0.91, $CHCl_3$). Calcd for $C_{22}H_{33}NO_4Si$: C: 65.47, H: 8.24, N: 3.47. Found: C: 65.20, H: 7.97, N: 3.72.

3.4.2. {1[1*R*]}-1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethyl]-2-(2-[1,3]dioxolan-2-yl-ethyl)-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (8b). Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.04 (s, 3H), −0.02 (s, 3H), 0.78 (s, 9H), 1.41–2.90 (m, 10H), 3.63 (s, 3H), 3.66–3.81 (m, 4H), 4.23–4.36 (m, 2H), 4.63 (t, J=4.25 Hz, 1H), 5.17 (t, J=6.75 Hz, 1H), 7.12–7.22 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=−5.6, 18.0, 21.0, 23.9, 25.7, 29.6, 33.3, 34.2, 51.4, 60.0, 63.5, 64.6, 103.9, 110.2, 126.2, 126.9, 128.3, 139.0, 154.7, 167.3, 171.8. $[\alpha]_D^{20}$=−5.6 (*c* 0.65, $CHCl_3$).

3.4.3. {1[1*S*]}-1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethyl]-2-(2-[1,3]dioxolan-2-yl-ethyl)-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester

(8c). Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=−0.03 (s, 3H), −0.05 (s, 3H), 0.80 (s, 9H), 1.75–3.04 (m, 8H), 3.65 (s, 3H), 3.68–3.82 (m, 4H), 4.24–4.31 (dd, *J*=6, 10 Hz, 1H), 4.34–4.41 (dd, *J*=7.75, 10 Hz, 1H), 4.71 (t, *J*=4.5 Hz, 1H), 5.21 (t, *J*=7 Hz, 1H), 7.11–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=−5.5, 18.0, 21.0, 24.3, 25.7, 32.5, 32.8, 51.4, 60.0, 63.4, 64.8, 103.5, 110.1, 126.3, 126.9, 128.3, 138.9, 154.2, 167.2, 171.7. $[\alpha]_D^{20}$=+3.5 (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{26}H_{39}NO_6Si$: C: 63.77, H: 8.03, N: 2.86. Found: C, 63.61, H: 8.22, N: 2.92.

3.5. General procedure for the synthesis of 3,4-dihydro-2-pyridones 9

Synthesis of [1(1*S*)]-1-(2-Hydroxy-1-phenyl-ethyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester **9a**. To a solution of β-enaminoester **8a** (1.14 g; 2.82 mmol) in THF (29 mL) was added, at 0 °C, 0.80 mL of HF.pyridine (70% solution of HF). After 30 min at 0 °C, the mixture was allowed to reach room temperature. After 20 h the reaction was quenched with an aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic phase was concentrated at reduced pressure. The residue was chromatographed on silica gel (AcOEt/Cyclohexane: 30/70) to furnish 0.719 g of compound **9a**. Oil, 88%.

3.5.1. [1(1*S*)]-1-(2-Hydroxy-1-phenyl-ethyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (9a). Oil, 88%. ^{1}H NMR ($CDCl_3$): δ=2.23 (s, 3H), 2.40–2.58 (m, 4H), 3.65 (s, 3H), 4.17–4.35 (m, 2H), 5.24 (t, *J*=6 Hz, 1H), 7.14–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=17.3, 20.9, 32.3, 51.5, 60.8, 63.7, 111.5; 126.3, 127.2, 128.5, 137.8, 149.5, 167.6, 172.9. $[\alpha]_D^{20}$=+15.7 (*c* 1.87; $CHCl_3$).

3.5.2. [1(1*R*)]-2-(3-[1,3]Dioxolan-2-yl-propyl)-1-(2-hydroxy-1-phenyl-ethyl)-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (9b). Oil, 53%. ^{1}H NMR ($CDCl_3$): δ=1.40–1.50 (m, 4H), 2.38–2.41 (m, 2H), 2.48–2.61 (m, 3H), 2.77–2.83 (m, 1H), 3.64 (s, 3H), 3.68–3.82 (m, 4H), 4.26 (d, *J*=6 Hz, 2H), 4.66 (t, *J*=4.2 Hz, 1H), 5.20 (t, *J*=6 Hz, 1H), 7.11–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=20.8, 23.6, 29.2, 32.4, 32.9, 51.3, 60.2, 63.5, 64.5, 103.7, 111.6, 126.2, 127.0, 128.3, 138.2; 153.8, 167.0, 173.0. $[\alpha]_D^{20}$=+19 (*c* 0.96, $CHCl_3$). Calcd for $C_{21}H_{27}NO_6$: C: 64.77, H: 6.99, N: 3.60. Found: C: 64.46, H: 7.30, N: 3.44.

3.5.3. [1(1*S*)]-2-(2-[1,3]Dioxolan-2-yl-ethyl)-1-(2-hydroxy-1-phenyl-ethyl)-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (9c). Oil, 43%. ^{1}H NMR ($CDCl_3$): δ=1.76–1.84 (m, 2H), 2.41–2.48 (m, 2H), 2.51–2.59 (m, 2H), 2.62–2.74 (m, 1H), 2.82–2.94 (m, 1H), 3.01 (brs, OH), 3.66 (s, 1H), 3.68–3.85 (m, 4H), 4.28–4.35 (m, 2H), 4.76 (t, *J*=4.2 Hz, 1H), 5.29 (t, *J*=5.7 Hz, 1H), 7.11–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=21.1, 23.9, 32.6, 51.7, 60.6, 64.2, 64.9, 103.4, 112.1, 126.4, 127.3, 128.6, 137.9, 153.3, 167.4, 173.5. $[\alpha]_D^{20}$=−12 (*c* 2.32, $CHCl_3$).

3.6. General procedure for the synthesis of alkaloids 10

Synthesis [(1*R*)-(2*R*)]-(Octahydro-quinolizin-1-yl)-methanol **10b**. To a solution of quinolizidine **13b** (0.032 g, 0.162 mmol) in THF (1.7 mL), at 0 °C, was added $LiAlH_4$ (0.013 g, 0.32 mmol). After 15 h at reflux, the reaction was quenched successively with H_2O (0.3 mL), a solution of NaOH (0.2 mL of 15% aqueous solution) and H_2O (0.9 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic phase was concentrated at reduced pressure. The residue was chromatographed on silica gel ($MeOH/CH_2Cl_2$: 20/80) to furnish 16.5 mg of compound **10b** (oil, 60%).

3.6.1. [(1*R*)-(2*R*)]-(Octahydro-quinolizin-1-yl)-methanol (10b). Oil, 60%. ^{1}H NMR ($CDCl_3$): δ=1.15–1.81 (m, 11H), 1.97–2.12 (m, 3H), 2.75–2.80 (m, 2H), 3.63 (d, *J*=10.5 Hz, 1H), 4.09 (dd, *J*=2.5, 11 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=22.9, 24.6, 25.6, 29.7, 31.4, 38.1, 57.0, 65.1, 66.0. $[\alpha]_D^{20}$=−21.5 (*c* 0.36, EtOH).

3.6.2. [(8*S*)-(8a*S*)]-(Octahydro-indolizin-8-yl)-methanol 10c. Oil, 60%. ^{1}H NMR ($CDCl_3$): δ=1.30–1.85 (m, 9H), 1.92–2.10 (m, 3H), 2.30 (brs, OH), 2.90–3.05 (m, 2H), 3.65 (d, *J*=10 Hz, 1H), 4.06 (dd, *J*=5, 10 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=20.7, 23.2, 25.6, 29.7, 35.3, 53.2, 54.4, 65.6, 66.7.

3.7. General procedure for the synthesis of piperidines 12

Synthesis of [1(1*S*)]-(2*S*)-(3*S*)-1-(2-Hydroxy-1-phenyl-ethyl)-2-methyl-piperidine-3-carboxylic acid methyl ester **12a**.[3] To a solution of bicyclic lactam **2a** (230 mg, 0.79 mmol) in THF (8 mL) was added at room temperature a solution of $BH_3{\cdot}Me_2S$ in THF (1.58 mL, 3.17 mmol). The mixture was stirred for 24 h at room temperature and quenched with 10 mL H_2O. The aqueous phases was extracted with CH_2Cl_2. The organic phase was evaporated under reduced pressure and the residue was chromatographed on silica gel (AcOEt/Cyclohexane: 30/70) to furnish 134 mg of piperidine **12a** (oil, 61%).

3.7.1. [1(1*S*)]-(2*S*)-(3*S*)-1-(2-Hydroxy-1-phenyl-ethyl)-2-methyl-piperidine-3-carboxylic acid methyl ester 12a.[3] Oil, 61%. ^{1}H NMR ($CDCl_3$): δ=0.90 (d, *J*=6.5 Hz, 3H), 1.30–1.69 (m, 4H), 2.25–2.40 (m, 1H), 2.56–2.64 (m, 2H), 3.04–3.08 (m, 1H), 3.48 (s, 3H), 3.62–3.82 (m, 3H), 7.12–7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.9, 23.5, 23.8, 43.7, 46.3, 51.4, 52.7, 61.8, 64.1, 127.6, 128.2, 128.5, 138.7, 174.0. HRMS Calcd for $C_{16}H_{24}NO_3$: 278.1756. Found: 278.1761. IR ($CHCl_3$): 3440, 1731 cm^{-1}.

3.7.2. [1(1*R*)]-(2*R*)-(3*R*)-2-(3-[1,3]Dioxolan-2-yl-propyl)-1-(2-hydroxy-1-phenyl-ethyl)-piperidine-3-carboxylic acid methyl ester (12b).[3] Oil, 100%. ^{1}H NMR ($CDCl_3$): δ=1.22–1.95 (m, 10H), 2.35 (m, 1H), 2.60–2.76 (m, 2H), 3.15 (m, 1H), 3.59 (s, 3H), 3.71–3.90 (m, 6H), 3.99 (t, *J*=5.75 Hz, 1H), 4.77 (t, *J*=4.5 Hz, 1H), 7.24–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=21.3, 21.4, 22.8, 27.3, 33.8, 41.7, 41.9, 51.5, 57.9, 62.7, 64.5, 64.8, 104.4, 127.6, 128.3, 128.5, 140.1, 174.5. $[\alpha]_D^{20}$=−58.5 (*c* 0.48, $CHCl_3$). HRMS Calcd for $C_{21}H_{32}NO_5$: 378.2280. Found: 378.2287. IR ($CHCl_3$) 3448, 1728 cm^{-1}.

3.7.3. [1(1*S*)]-(2*S*)-(3*S*)-2-(2-[1,3]Dioxolan-2-yl-ethyl)-1-(2-hydroxy-1-phenyl-ethyl)-piperidine-3-carboxylic

acid methyl ester (12c). Oil, 91%. ^{1}H NMR ($CDCl_3$): δ=1.18–1.99 (m, 8H), 2.35–2.85 (m, 3H), 3.22–3.29 (m, 1H), 3.58 (s, 3H), 3.73–3.90 (m, 6H), 3.98 (t, J=5.5 Hz, 1H), 4.77 (t, J=4.5 Hz, 1H), 7.23–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=21.0, 21.2, 22.1, 30.6, 41.1, 41.3, 51.4, 56.8, 63.1, 64.7, 64.8, 104.4, 127.5, 128.2, 128.4, 140.5, 174,4. $[\alpha]_D^{20}$=+44 (*c* 1.17, $CHCl_3$).

3.8. General procedure for the synthesis of quinolizidine and indolizidine 13

Synthesis of (1*R*)-(2*R*)-Octahydro-quinolizine-1-carboxylic acid methyl ester **13b**. To a solution of piperidine **12b** (0.155 g, 0.41 mmol) in acetone (3.2 mL) and water (0.8 mL) was added *p*-toluenesulfonic acid (0.156 g, 0.82 mmol). After 6 h, the solvents were evaporated under reduced pressure. At the crude product in methanol (4 mL) and under an atmosphere of hydrogen was added Pd/C 10% (130 mg, 0.123 mmol). The reaction mixture was stirred 24 h at room temperature and then filtered over celite. The reaction was then quenched with an aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was chromatographed on silica gel (MeOH/CH_2Cl_2: 10/90) to furnish 49 mg of quinolizidine **13b** (oil, 60%).

3.8.1. (1*R*)-(2*R*)-Octahydro-quinolizine-1-carboxylic acid methyl ester (13b). Oil, 60%. ^{1}H NMR ($CDCl_3$): δ=1.14–2.04 (m, 13H), 2.48–2.50 (m, 1H), 2.78–2.84 (m, 2H), 3.56 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=22.0, 24.3, 24.8, 26.9, 28.9, 44.4, 51.1, 54.9, 57.0, 62.6, 173.8. $[\alpha]_D^{20}$=−18 (*c* 0.42, $CHCl_3$).

3.8.2. (8*S*)-(8a*S*)-Octahydro-indolizine-8-carboxylic acid methyl ester (13c). Oil, 29%. ^{1}H NMR ($CDCl_3$): δ=1.34–2.19 (m, 11H), 2.75–2.77 (m, 1H), 2.95–3.01 (m, 2H), 3.60 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=20.0, 22.1, 23.7, 24.7, 41.1, 50.9, 51.6, 54.3, 63.0, 172.7.

References and notes

1. For recent applications see: (a) Amat, A.; Canto, M.; Llor, N.; Ponzo, V.; Perez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (b) Amat, M.; Perez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787. (c) Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (d) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661. (e) Amat, M.; Perez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611.
2. For reviews see: (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (b) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.
3. Agami, C.; Dechoux, L.; Ménard, C.; Hebbe, S. *J. Org. Chem.* **2002**, *67*, 7573.
4. Agami, C.; Dechoux, L.; Hebbe, S. *Tetrahedron Lett.* **2002**, *43*, 2521.
5. (a) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc., C* **1971**, 1358. (b) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc., C* **1971**, 2112.
6. Agami, C.; Dechoux, L.; Hebbe, S. *Tetrahedron Lett.* **2003**, *44*, 5311.
7. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic: San Diego, 2000; Vol. 54.
8. (a) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349. (b) Tate, E. W.; Zard, S. Z. *Tetrahedron Lett.* **2002**, *43*, 4683. (c) Ledoux, S.; Marchalant, E.; Celerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397. (d) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903, and references cited herein.
9. Ha, D. C.; Park, S. H.; Choi, K. S.; Yun, C. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 728.
10. Compound **11b** and **11c** were prepared by alkylation of the di-anion of methylacetoacetate with 2-(2-bromoethyl)-1,3-dioxolane and 2-bromomethyl-1,3-dioxolane, respectively.[16]
11. (a) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (b) Meyers, A. I.; Price, D. A. *Chirality* **1998**, *10*, 88. (c) Meyers, A. I.; Price, D. A.; Andre, C. J. *Synlett* **1997**, 533.
12. Amat, M.; Canto, M.; Llor, N.; Bosch, J. *Chem. Commun.* **2002**, 526.
13. (a) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515. (b) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094. (c) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *42*, 5889. (d) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625. (e) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084. (f) Wong, Y. S.; Gnecco, D.; Marazano, C.; Chiaroni, A.; Riche, C.; Billion, A.; Das, B. C. *Tetrahedron* **1998**, *54*, 9357.
14. Podkowinska, H.; Skolik, J. *Org. Magn. Res.* **1984**, *22*, 379.
15. For total syntheses of racemic matrine see: (a) Chen, J.; Brown, L. J.; Gonnela, N. C. *J. Chem. Soc., Chem. Commun.* **1986**, 905. (b) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 1128.
16. (a) Kato, M.; Kamat, V. P.; Yoshikoshi, A. *Synthesis* **1988**, 699. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5439–5451

Total synthesis of (±) maculalactone A, maculalactone B and maculalactone C and the determination of the absolute configuration of natural (+) maculalactone A by asymmetric synthesis

Geoffrey D. Brown[a,b,*] and Ho-Fai Wong[b]

[a]*School of Chemistry, The University of Reading, Whiteknights Rd., Reading RG6 6AD, UK*
[b]*The Department of Chemistry, The University of Hong Kong, Pokfulam Rd., Hong Kong, People's Republic of China*

Received 7 November 2003; revised 2 April 2004; accepted 22 April 2004

Abstract—Maculalactones A, B and C from the marine cyanobacterium *Kyrtuthrix maculans* are amongst the only compounds based on the tribenzylbutyrolactone skeleton known in nature and (+) maculalactone A from the natural source possesses significant biological activity against various marine herbivores and marine settlers. We now report a concise synthesis of racemic maculalactone A in five steps from inexpensive starting materials. Maculalactones B and C were synthesized by a minor modification to this procedure, and the synthetic design also permitted an asymmetric synthesis of maculalactone A to be achieved in around 85% ee. The (+) and (−) enantiomers of maculalactone A were assigned, respectively, to the *S* and *R* configurations on the basis of the chiral selectivity expected for catecholborane reduction of an unsymmetrical ketone in the presence of Corey's oxazoborolidine catalyst. Surprisingly, it appeared that natural (+) maculalactone A was biosynthesized in *K. maculans* in a partially racemic form, comprising ca. 90–95% of the (*S*) enantiomer and 5–10% of its (*R*) enantiomer. Coincidentally therefore, the percentage enantiomeric excess of the product obtained from asymmetric synthesis almost exactly matched that found in nature.

1. Introduction

Kyrtuthrix maculans Umezaki (*Brachytrichia maculans* Gomont; Stigonemataceae)[1] is a marine cyanobacterium found growing on moderately exposed rocky shores in Hong Kong and elsewhere in the world.[2,3] We first became interested in investigating the chemistry of *K. maculans* following the observation that this species normally survived as pure colonies, which were uncontaminated by other marine bacteria and were also apparently exempt from settling of barnacles and foraging by marine herbivores.

Maculalactone A (**1**),[4] a secondary metabolite with the highly unusual tribenzylbutyrolactone skeleton, was the first natural product to be reported from a preliminary chemical investigation of *K. maculans* made in 1996. Compound **1** was by far the most abundant secondary metabolite to be found in this species, although—following subsequent more extensive investigations—we have since described three further tribenzylbutyrolactones, maculalactones B (**2**),[5] C (**3**)[5] and L,[6] as well as the dibenzyldiphenyl-4,5,6,7-tetrahydrobenzofuranones,[5] maculalactones D (**4**), E, F, G, H, I, J and K, and the *seco*-dibenzyldiphenyl-4,5,6,7-tetrahydrobenzofuranone, maculalactone M,[7] as minor secondary metabolites (Fig. 1). *K. maculans* is still the only known natural source for all three classes of secondary metabolite. Our suspicions that some at least of these unusual metabolites might be responsible for providing the chemical defense which *K. maculans* seemed to enjoy against other marine organisms had been recently confirmed by experiments, in which samples of maculalactone A from the natural source were tested against a generalist marine herbivore (*Chlorostoma argyrostoma*) and the larvae of several barnacle species (*Balanus amphitrite*, *Ibla cumingii* and *Tetraclita japonica*). These experiments clearly demonstrated that compound **1** was a potent inhibitor of both herbivory and barnacle settling.[8–10]

Thus, there were now reasonable grounds to suppose that maculalactone A (**1**) might have some potential for development as a novel marine anti-fouling agent;[9,10] and also that the biological activity of some of the other unusual metabolites from *K. maculans* might be worthy of further investigation. Accordingly, we set out to devise a concise and inexpensive synthesis of compound **1** which would allow its preparation on a multi-gram scale for future

Keywords: Marine metabolites; Asymmetric synthesis; Grignard reactions/reagents; NMR.
* Corresponding author. Tel.: +44-118-3787418; fax: +44-118-9316331; e-mail address: g.d.brown@reading.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.060

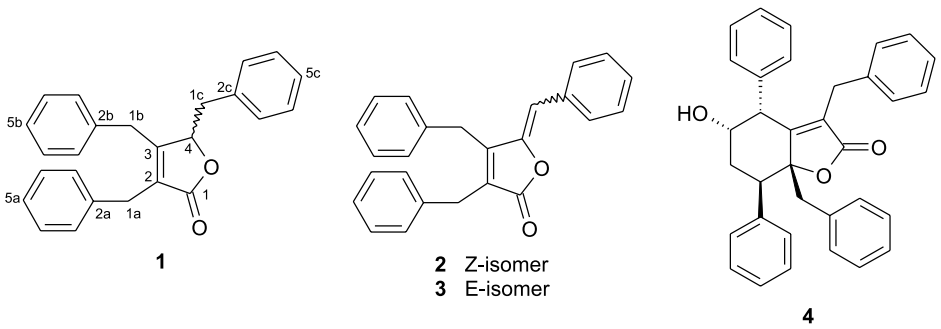


Figure 1. Maculalactones A, B, C and D (**1**–**4**), which have been reported as natural products from *Kyrtuthrix maculans* (the absolute configuration at the 4-position of compound **1** was not determined in the original report of this secondary metabolite; only relative stereochemistry is shown for compound **4**).

evaluation in field trials, when formulated as a paint[9,10] (the extracted yield of maculalactone A from *K. maculans* is of the order of 1 mg/g and it is very tedious and time-consuming to scrape even small amounts of the biological source material from the rocks on which it grows, making it almost impossible to obtain sufficiently large amounts of this compound from the natural source to permit further biological evaluation). A secondary goal of this project was to synthesize some of the other tribenzylbutyrolactones from *K. maculans*, which have not-as yet-been subjected to biological evaluation, due to their low natural abundance. Finally, we also sought to determine the absolute configuration of maculalactone A at the 4-position, an issue which was not addressed in the original report of this compound as a natural product from *K. maculans*.[4] The synthetic strategy described below, which is based on a well known route to the dibenzylbutyrolactone lignans that are commonly found in terrestial plants,[11] has resulted in the realization of all three of these goals.

2. Results and discussion

2.1. Synthesis of racemic maculalactone A ((±)-1)

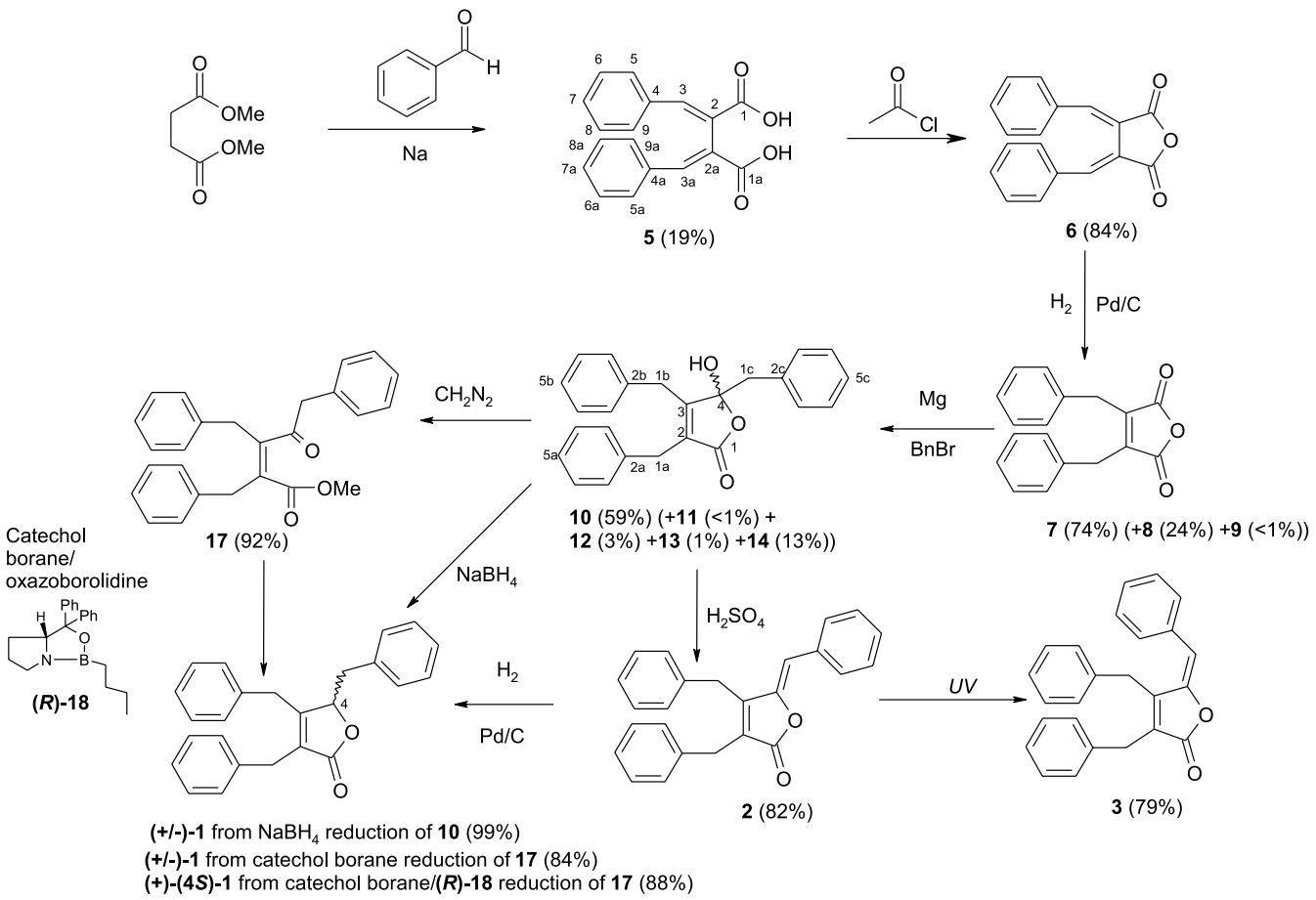
Our synthesis of the tribenzylbutyrolactone skeleton of maculalactone A (**1**) (Scheme 1) was based on previously reported syntheses of the 2,3-aryl di-substituted butyrolactone ring system, from the acid anhydride **7**.[11] 2,3-Dibenzylidenesuccinic acid (**5**), which was employed as the starting material for this synthesis, is commercially available (Section 3.2.1) although this source is rather costly for a large-scale synthesis of maculalactone A; alternatively, it can be prepared much more economically (albeit in low yield) from the Stobbe condensation of dimethyl succinate with benzaldehyde, as is shown in Scheme 1.[12,13] Treatment of the dicarboxylic acid **5** with acetyl chloride resulted in cyclization to the symmetrical acid anhydride **6**,[14,15] and the conjugated diene functional group in **6** then underwent preferential 1,4-hydrogenation to yield the tetra-substituted alkene **7**. Compound **8**, a minor side-product from this reaction, in which the diene has been completely reduced, probably arose via an initial 1,2-reduction, forming intermediate **9** (Fig. 2).† The ratio of the desired product **7** to the unwanted product **8** increased as the loading of palladium catalyst was reduced in the ethyl acetate solution, although the rate of reaction also became slower: a 5% catalyst loading was found to provide the best compromise for obtaining good yields of **7** (74%) in a reasonable time (18 h). Fully assigned NMR data for all of the compounds **5**–**9** (assigned using the 2D NMR techniques HSQC, HMBC, $^{1}H-^{1}H$ COSY and NOESY) are reported in Table 1; all other NMR data that is reported in Table 2 was also rigorously assigned by these same 2D NMR techniques.

The third aromatic substituent in the completed tribenzylbutyrolactone skeleton of **1** was introduced by the addition of a Grignard reagent derived from benzyl bromide (BnBr) to the symmetrically-substituted anhydride **7**. The optimum conditions for forming the key intermediate, tribenzyl-substituted compound **10**, were somewhat unusual and considerable experimentation was required in order to arrive at them. First of all, reflux should be avoided as this leads to dimerization of the Grignard reagent, forming stilbene (**11**). At lower temperatures (0 °C), concentrated solutions of the anhydride **7** and the ethereal Grignard reagent reacted rapidly to give the tetra-substituted addition compounds **12** and **13** (Fig. 2) as the favored products, in which 2 equiv. of Grignard reagent have participated in both 1,2- and 1,4-additions to the carbonyl group of the anhydride. Approximately half of the starting material **7** was recovered unchanged when these reactions were performed under stoichiometric conditions, which suggested that the desired compound **10** was perhaps being formed as an intermediate, but was then preferentially participating in the second addition of a Grignard reagent to yield the corresponding tetra-substituted products (this situation is analogous to the alkylation of an ester by a Grignard reagent, which, as is well known, commonly results in a di-substituted tertiary alcohol product).‡

The optimum conditions for formation of the desired addition product, compound **10**, required that both reactants were present as very dilute solutions, and in order to make compound **10** the dominant product over compound **12**, it

† Compound **9** was isolated in substantial amounts when the duration of the hydrogenation reaction was decreased from 18 to 2 h (see Section 3.2.3).

‡ The lactol group in the intermediate **10** arising from the first nucleophilic addition can reversibly interconvert in situ with its ring-opened keto/acid tautomer; the reactivity of the ketone group in this tautomer towards a second nucleophilic attack would then be greater than that of the starting material, acid anhydride **7**, thereby favoring a second Grignard addition reaction.



Scheme 1. Synthesis of maculalactones A–C (**1**–**3**) from 2,3-dibenzylidenesuccinic acid (**5**).

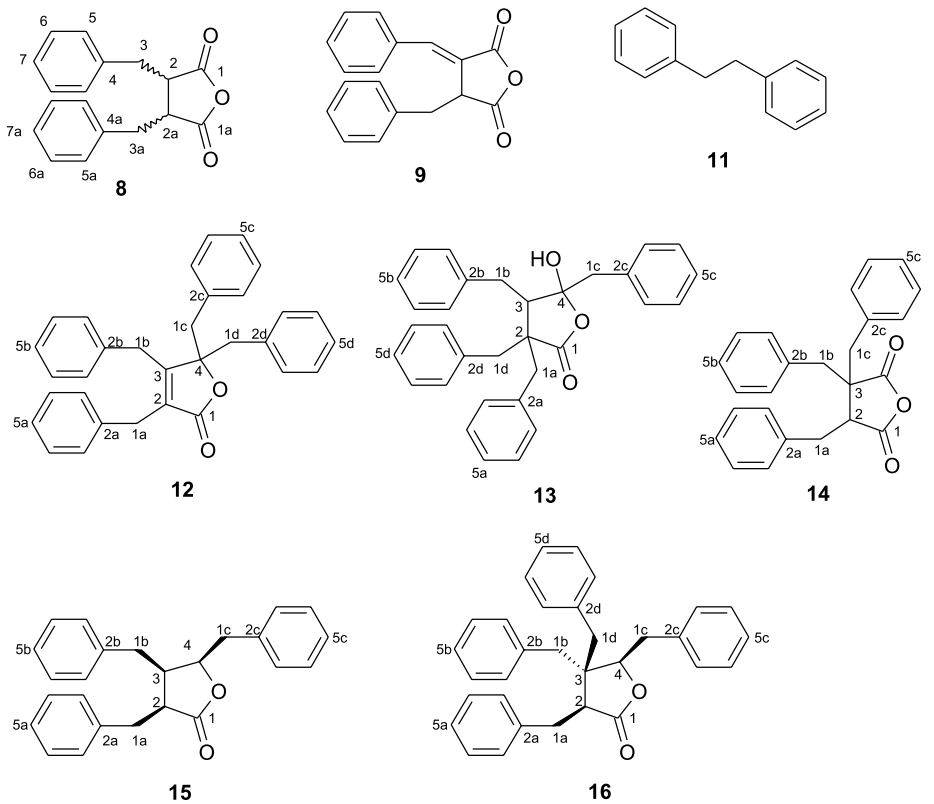


Figure 2. Minor products (**8**, **9** and **11**–**16**) obtained during the syntheses of maculalactones A–C which are described in Scheme 1.

Table 1. ^{13}C and ^{1}H NMR assignments ($CDCl_3$) for compounds **5**–**9**

		δ_C					δ_H				
Position	Mult.[a]	**5**[b]	**6**	**7**	**8**	**9**	**5**[b]	**6**	**7**	**8**	**9**
1	C	170.4	166.1	165.8	171.7	165.7	—	—	—	—	—
2	C	129.6	119.5	143.0	45.7 (CH)	123.5	—	—	—	3.50	—
3	CH	143.9	139.7	30.3 (CH_2)	32.0 (CH_2)	141.1	7.91	7.94	3.79, 3.79	3.10, 3.12	7.80
4	C	136.5	134.0	135.0	136.3	132.7	—	—	—	—	—
5=9	CH	130.9	130.1	129.1	129.0	130.4	7.35	6.83	7.13	7.14	7.58
6=8	CH	129.8	127.3	128.8	128.5	129.5	7.50	6.85	7.28	7.33	7.56
7	CH	130.8	130.8	127.5	127.4	131.4	7.35	7.15	7.31	7.28	7.53
1a	C	170.4	166.1	165.8	171.7	171.7	—	—	—	—	—
2a	C	129.6	119.5	143.0	45.7 (CH)	45.6 (CH)	—	—	—	3.50	4.38
3a	CH	143.9	139.7	30.3 (CH_2)	32.0 (CH_2)	33.7 (CH_2)	7.91	7.94	3.79, 3.79	3.10, 3.12	3.35, 3.28
4a	C	136.5	134.0	135.0	136.3	134.8	—	—	—	—	—
5a=9a	CH	130.9	130.1	129.1	129.0	129.3	7.35	6.83	7.13	7.14	6.89
6a=8a	CH	129.8	127.3	128.8	128.5	128.7	7.50	6.85	7.28	7.33	7.19
7a	CH	130.8	130.8	127.5	127.4	127.7	7.35	7.15	7.31	7.28	7.19

[a] Multiplicity determined from DEPT.
[b] Values recorded in d_4-MeOH solution.

was necessary to transfer the Grignard reagent to the solution of anhydride via a canula, rather than to perform the addition in the reverse sense (as is conventional and was practiced in the earlier trials). This procedure resulted in yields of up to 65% of **10** in the crude product (as judged by ^{1}H NMR analysis); its success may be the result of always maintaining the concentration of benzyl magnesium bromide in solution at a low level, thereby allowing compound **10**, which is the initial product of the Grignard reaction, sufficient time to precipitate out of solution before the lactol functional group undergoes a second Grignard reaction. The 1,4-adduct, compound **14**, consistently accounted for around 15% of the reaction product under all conditions that were assayed, and even under optimized conditions it was still necessary to separate compounds **10** and **14** chromatographically before proceeding to the next step.

The final step in the synthesis of maculalactone A, reduction of the lactol functionality in **10** by sodium borohydride, was straightforward, resulting in the preparation of compound **1** as a racemic mixture in almost quantitative yield. It is worth noting that although sodium borohydride was found to be a very effective reducing agent for converting compound **10** into compound **1**, reducing agents derived from neutral boranes (such as catechol borane) were completely unreactive. This may be a consequence of the ability of sodium borohydride to act also as a base, first removing the proton of the lactol hydroxy group in **10**, and thereby promoting ring opening to a keto/carboxylate tautomer, in which the carbonyl group of the ketone is more readily reduced to a secondary alcohol (this alcohol then condenses with the carboxylic acid group to recyclize the butyrolactone ring of **1**). The spectral properties (NMR, IR and MS) of (±)-**1** obtained from synthesis were identical with those of the natural product, (+) maculalactone A.[4] The two enantiomers of racemic **1** could be separated by HPLC using a semi-preparative Daicel chiral OD-column (Fig. 3). This procedure was then routinely automated so as to yield several 10 s of milligrams of each optical antipode, which were then used in making the further investigations into the absolute stereochemistry of **1** that are described at the start of Section 2.3.

2.2. Synthesis of maculalactones B (2) and C (3)

By making a slight modification to the above procedure, it was found that the key intermediate **10** could be quantitatively converted into compound **2**, which had identical physical properties to those of the natural product maculalactone B from *K. maculans*.[5] Since only the *Z*-geometric isomer was obtained from the dehydration of **10** in the presence of sulfuric acid[16] it appeared that maculalactone B must therefore be the thermodynamically more stable product (perhaps as a result of the decreased steric interaction between the benzyl and benzylidene substituents at the 3- and 4-positions in this isomer). However, synthetic maculalactone B (**2**) could be simply converted into the thermodynamically less favored *E*-isomer, with physical properties identical to those of maculalactone C (**3**) from nature,[5] by irradiation with UV light.[17] This reaction proceeded in good yield, always producing a mixture which consisted predominantly of compound **3** together with some unreacted starting material (**2**), that could only be separated by preparative normal phase HPLC. The ratio of maculalactone C (**3**) to maculalactone B (**2**) (approximately 4:1) that was obtained remained quite constant when UV irradiation was performed in a variety of solvents (e.g. benzene, dichloromethane or tetrahydrofuran) and it seems therefore to represent a photochemical equilibrium state.

An alternative synthesis of racemic maculalactone A from maculactone B was also devised by effecting hydrogenation of the diene functional group in maculalactone B (**2**) over a palladium catalyst (Scheme 1). This resulted preferentially in reduction at the tri-substituted double bond of **2**, yielding racemic **1** together with small amounts of the fully reduced tribenzylbutyrolactone **15** (trace amounts of a second fully reduced tetrabenzyl-substituted butyrolactone, compound **16** (Fig. 2), which may have arisen from a very minor

Table 2. ^{13}C and ^{1}H NMR assignments ($CDCl_3$) for compounds **10** and **12**–**17**

		δ_c							δ_H						
Position	Mult.[a]	**10**	**12**	**13**	**14**	**15**	**16**	**17**	**10**	**12**	**13**	**14**	**15**	**16**	**17**
1	C	171.0	172.7	176.9	171.8	177.3	177.6	167.6	—	—	—	—	—	—	—
2	C	130.4	130.2	52.4	47.6 (CH)	48.1 (CH)	50.3 (CH)	153.1	—	—	—	3.16	3.16	2.75	—
3	C	159.7	162.9	49.0 (CH)	56.9	42.8 (CH)	51.8	129.3	—	—	2.48	—	2.96	—	—
4	C	106.4	90.1	104.8	173.1	83.7 (CH)	84.7 (CH)	204.5	—	—	—	—	4.59	4.24	—
1a	CH_2	29.1	29.3	41.2	30.0	31.0	30.7	33.9	3.29, 3.48	3.23, 3.23	2.97, 3.56	3.03, 3.35	2.80, 3.28	2.65, 3.11	3.86, 3.86
2a	C	137.0	137.0	136.1	137.7	138.6	139.9	138.2	—	—	—	—	—	—	—
3a=7a	CH	128.4	127.8	131.0	129.2	128.5	129.0	128.2	6.69	6.25	7.22	7.28	7.09	7.21	7.14
4a=6a	CH	128.6	128.9	128.5	128.9	128.7	128.6[b]	128.7	7.11	6.98	7.31	7.37	7.27	7.26	7.30
5a	CH	126.2	125.8	126.8	128.1	126.4	126.5	126.5	7.11	7.04	[c]	7.35	7.19	[c]	7.22
1b	CH_2	32.3	33.2	30.4	39.4	29.6	39.6	37.3	3.65, 3.81	3.68, 3.68	2.91, 3.10	2.54, 3.42	2.82, 2.94	3.07, 3.07	3.70, 3.70
2b	C	135.9	135.3	139.4	135.1	139.4	135.5	135.9	—	—	—	—	—	—	—
3b=7b	CH	129.1	128.9	129.7	130.5	128.7	130.8	129.0	7.11	6.99	7.25	6.78	7.02	6.84	7.07
4b=6b	CH	128.8	128.2	128.7	128.7	128.6	128.6[b]	128.9	7.26	7.23	7.35	7.18	7.25	7.18	7.28
5b	CH	127.1	127.2	128.8	127.2	126.7	127.1	127.1	7.26	7.23	7.29	7.18	7.19	[c]	7.24
1c	CH_2	43.3	42.8	45.8	42.1	37.5	35.3	49.6	3.06, 3.23	2.90, 3.09	2.10, 2.25	3.11, 3.27	2.55, 2.96	2.86, 3.08	3.52, 3.52
2c	C	133.1	134.5	132.9	133.6	137.4	137.9	133.4	—	—	—	—	—	—	—
3c=7c	CH	130.5	130.3	130.8	130.3	129.0	128.9	130.0	7.17	7.16	6.85	7.22	7.06	7.23	7.03
4c=6c	CH	128.2	128.4	128.0	128.9	128.4	128.5[b]	128.3	7.26	7.23	7.18	7.35	7.25	7.28	7.26
5c	CH	127.6	127.2	127.5	127.6	126.6	126.8	126.9	7.35	7.23	7.23	7.31	7.19	[c]	7.20
1d	CH_2	—	42.8	40.1	—	—	37.6	—	—	2.90, 3.09	2.65, 3.26	—	—	3.11, 3.11	—
2d	C	—	134.5	136.9	—	—	137.1	—	—	—	—	—	—	—	—
3d=7d	CH	—	130.3	130.2	—	—	131.5	—	—	7.16	7.07	—	—	7.45	—
4d=6d	CH	—	128.4	128.5	—	—	128.4[b]	—	—	7.23	7.24	—	—	7.37	—
5d	CH	—	127.2	127.1	—	—	127.2	—	—	7.23	[c]	—	—	7.32	—
–OMe	CH_3	—	—	—	—	—	—	52.4	—	—	—	—	—	—	3.67

[a] Multiplicity determined from DEPT.
[b] Interchangeable within column.
[c] Not assigned.

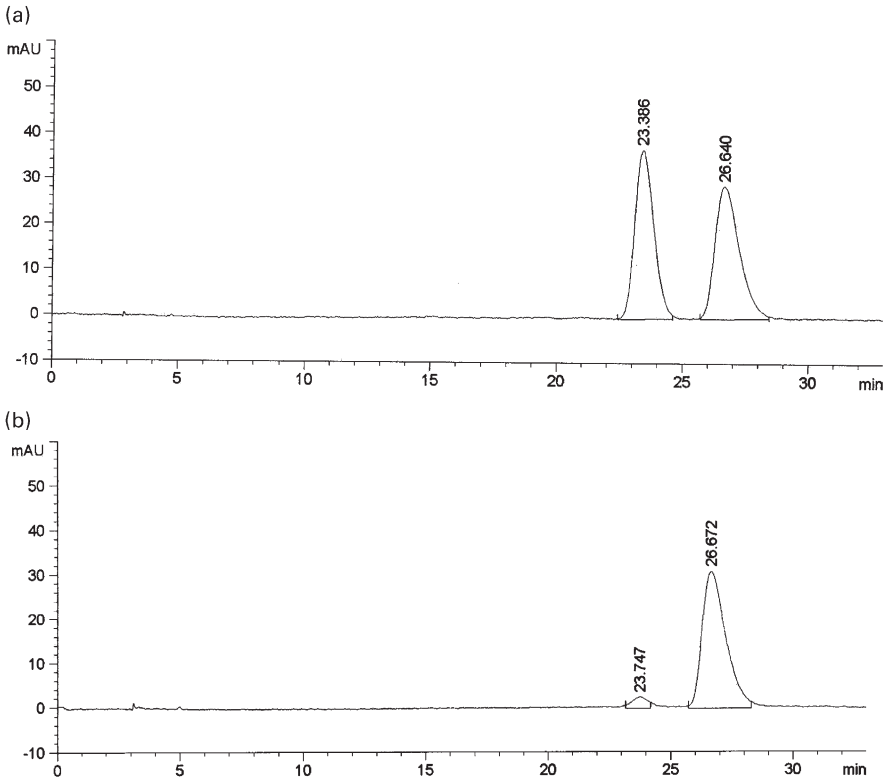


Figure 3. Analytical chiral HPLC chromatograms (Chiracel OD–H column) of: a) racemic (±) maculalactone A from synthesis; and b) natural (+) maculalactone A from *K. maculans*.

product carried through the synthesis from the preceding Grignard reaction, were also isolated).

2.3. Asymmetric synthesis of 1

Having developed two routes to racemic **1**—firstly, by borohydride reduction of the key intermediate **10** (Section 2.1) and, secondly, by hydrogenation of the diene **2** (Section 2.2)—we next attempted to perform an enantioselective synthesis of the 4*R* and 4*S* forms of **1**. As noted in the Introduction, the absolute stereochemistry of natural maculalactone A had yet to be determined, and the need to achieve an asymmetric synthesis became particularly pressing following on from the failure of all of the three most commonly used physical techniques: CD,[18] X-ray (Fig. 4) and NMR[19–21] (Mosher esterification of the secondary alcohol obtained from reductive opening of the butyrolactone ring of **1**) to define the absolute stereochemistry of the (+) and (−) enantiomorphs of **1** which had been obtained from semi-preparative chiral HPLC of the synthetic racemate (Section 2.1).

Accordingly, it was decided to modify the strategy for preparing **1** that has been reported in Sections 2.1 and 2.2 in order to effect an enantioselective synthesis of maculalacatone A. The high yield that had been recorded for the preparation of maculalactone A (**1**) from hydrogenation of maculalactone B (**2**) (Section 2.2) suggested that it might be possible to achieve an efficient enantioselective synthesis of maculalactone A by employing a chiral rhodium(I)-DuPhos catalyst[22–24] in place of the palladium-on-charcoal hydrogenation catalyst. In the event, although the overall yield of maculalactone A (**1**) from the reduction of **2** remained high

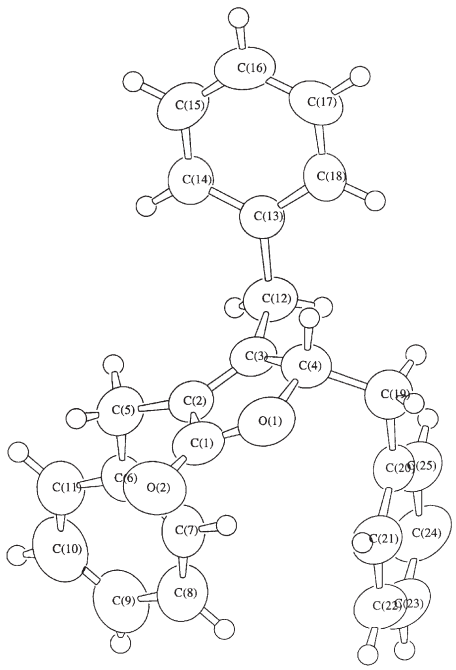


Figure 4. ORTEP diagram of the X-ray structure for synthetic (+) maculalctone A (which was separated from its enantiomer by semi-preparative chiral HPLC). The stereochemistry shown at the 4-position was suggested, but not conclusively established, by X-ray crystallographic analysis (similarly, the absolute stereochemistry could not be definitively established for synthetic (−) maculalactone A which was also obtained from semi-preparative chiral HPLC).

in the presence of this catalyst, this strategy yielded maculalactone A with an enantiomeric excess (% ee) very close to zero. However, it did prove possible to achieve a much more enantioselective synthesis of **1** by modifying the synthetic procedure that was described in Section 2.1 in order to enable reduction by a neutral borane-derivative rather than by a borohydride reducing agent. As noted in Section 2.1, the key lactol intermediate **10** was unaffected by borane reduction and it was therefore necessary to first convert this compound to its methyl ester derivative,[25] compound **17** (Scheme 1). Catecholborane reduction of the ketone group in this ring-opened substrate, in the presence of either the *R*- or *S*- enantiomer of the chiral oxazoborolidine catalyst **18** which has been developed by Corey,[26–31] then resulted in either (+) or (−) maculalactone A, respectively, in high chemical yield (85–90%) and with a reproducibly good-to-high enantiomeric excess (80–85% ee), as determined by analytical chiral HPLC (see Section 3.2.6 in the Experimental).

Based on the mechanism which has been proposed for the enantiomeric induction by the Corey catalyst (Fig. 5),[32] it is possible to infer that the (+) form of **1**-which was obtained when using the *R*- enantiomer of the oxazoborolidine catalyst (*R*)-**18**—should correspond to the (4*S*) enantiomer of maculalactone A, and that the (−)-form of maculalactone A must therefore be the (4*R*) enantiomer. Hence, it appeared that the first fraction obtained from chiral HPLC in Figure 3, i.e. (−) maculalactone A with $[\alpha]_D=-156.7$ [*c* 1.0], was the enantiomeric form of **1** with the *R* configuration at the 4-position, while the second fraction, (+) maculalactone A ($[\alpha]_D=+153.1$ [*c* 1.4]), corresponded to the 4*S* absolute configuration.

2.4. The absolute stereochemistry of natural maculalactone A from *K. maculans*

Intriguingly, although all the samples of natural maculalactone A that we had ever isolated[4,8–10] were dextroratory, none had ever exhibited such a large positive optical rotation as that recorded from the second fraction which had been obtained from semi-preparative chiral HPLC of the synthetic racemate, which should correspond to (+)-(4*S*)-**1**. Rather, samples of natural maculalactone A collected at different times from *K. maculans* growing in different localities seemed to vary quite substantially in their specific optical rotation, with an $[\alpha]_D$ averaging around +120–130. When we subjected samples of natural maculalactone A isolated from *K. maculans* to analytical chiral HPLC (as in Section 3.2.6), the chromatograms consistently demonstrated that the natural form of **1** was a mixture of two compounds, with retention times that were consistent with the contamination of the more predominant (4*S*) enantiomer by a little of the (4*R*) form of the metabolite (see Fig. 3(b)) for a representative chromatogram). These analytical HPLC studies typically indicated an 'enantiomeric excess' for naturally occurring (+) maculalactone A of the order of 85–95% ee.

Final confirmation that natural maculalactone A was, in fact, a partially racemic mixture of the two enantiomorphs of **1**, was obtained by performing ^{1}H NMR experiments with maculalactone A isolated from *K. maculans* in the presence of a chiral shift reagent (europium tris[3-heptafluoropropylhydroxymethylene]-(+)-camphorate). The effects of making successive additions of this shift reagent to a $CDCl_3$ solution of maculalactone A (**1**) from the natural

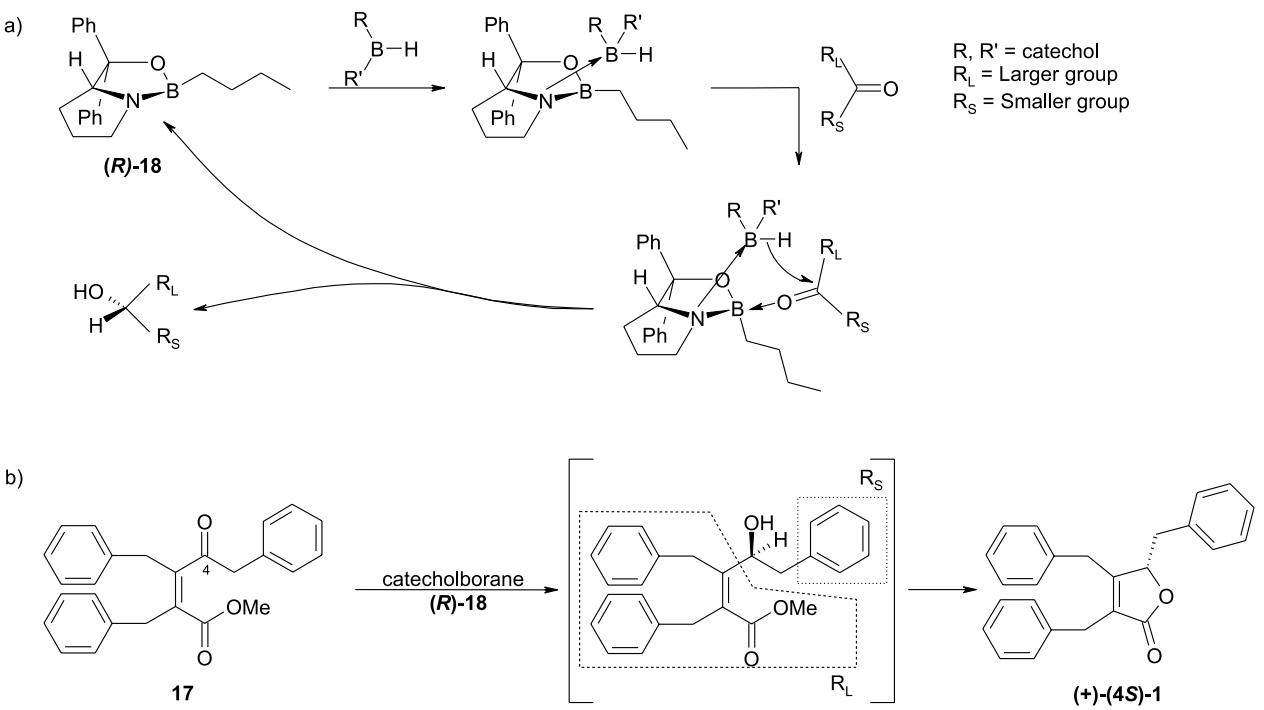


Figure 5. (a) The transition state assembly of the chiral oxazoborolidine (*R*)-**18** with a generalized prochiral ketone, and the resulting absolute configuration of the secondary alcohol product from catecholborane reduction, that has been proposed in the literature to account for the enantioselectivity of the Corey catalyst.[32] (b) The predicted absolute configuration of (+) maculalactone A (**1**) from the enantioselective reduction of the ketone **17** in the presence of (*R*)-**18**, based on this proposed mechanism.

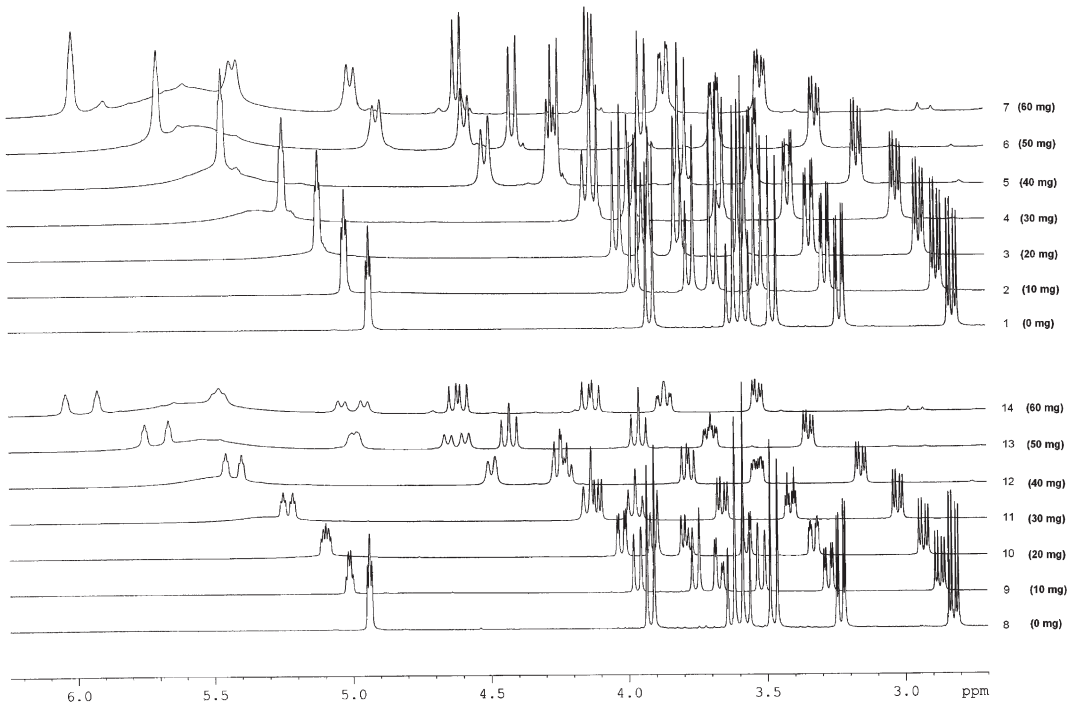


Figure 6. Expanded ^{1}H NMR spectra of natural (+)-maculalactone A from *K. maculans* (expts. 1–7); and racemic (±) maculalactone A from synthesis (Section 2.1; expts. 8–14) following successive additions (10 mg) of a europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate] chiral shift reagent.

source are shown in the upper seven ^{1}H NMR spectra in Figure 6 (experiments 1–7). Several peaks (most obviously the H-4 proton at δ_H 4.94 ppm)[§] appeared to resolve into two components in an approximately 9:1 ratio in this experiment (this is particularly evident in the ^{1}H NMR spectrum shown in entry 7 of Figure 6, which contained the largest amount of added chiral shift reagent). As demonstrated by experiments 8–14 in Figure 6, the H-4 proton of synthetic (±)-**1** (Section 2.1) was also observed to separate into two components, in the same manner as for experiments 1–7, although in this case equal intensities were observed for the two sets of peaks due to the two enantiomers of **1**, as the sample was, of course, racemic. The inescapable conclusion is therefore that natural samples of (+)-**1** are, in fact, partially racemic at the 4-position.

To summarize, the results from measurements of optical rotation, chiral HPLC and ^{1}H NMR in the presence of a chiral shift reagent all confirmed that natural maculalactone A (**1**) was present in *K. maculans* as a mixture of approximately 85–95% of the (4*S*) enantiomer with 5–15% of the (4*R*) enantiomer. This is a very unusual situation, as most natural products are normally isolated either in enantiomerically pure form (if their biosynthesis is entirely enzymic) or as completely racemic mixtures (if non-enzymic chemical processes are also involved in their biogenesis). It is rare to find intermediate cases, involving partially racemic metabolites, in natural product chemistry. Although this phenomenon has been reported on a few occasions for terpenoids (e.g. (+)-α-pinene, which is very often found as an admixture with lesser amounts of its (−)-enantiomer),[34] it seems to be extremely rare for lignans,[35] to which biogenetic class maculalactone A presumably belongs.[4,5] We were therefore rather concerned that the apparent partial racemization of **1** might be an artifact of the extraction and chromatographic procedures which were employed in the isolation of maculalactone A from *K. maculans*, especially as it is quite easy to propose a mechanism which would account for such racemization: if a trace of acid (or base) were present at either or both of the extraction and purification stages for the isolation of maculalactone A, then an extended enol could be generated by tautomerization, involving a movement of the H-4 proton to the carbonyl group; reprotonation from either side of the resulting 2-hydroxyfuran π-system would then result in racemization.

In order to test this possibility, the length of the extraction procedure that was routinely used for obtaining maculalactone A from *K. maculans*was varied from 20 h to 10 days. The effect of including a second column chromatographic step in the purification of **1** was also investigated. However, neither procedure appeared to affect the % ee of natural **1**, as determined by chiral analytical HPLC, to any significant extent. Additionally, when a sample of partially racemic **1** (from synthesis) was dissolved in organic solvent (1 mg/10 mL EtOAc) and shaken with HCl (1 M, 10 mL) for 15 min-in an attempt to induce racemization via the proposed enolic form of **1**-there was, once again, no

[§] The shifts induced by the chiral lanthanide for the proton resonances at H-1a (δ_H 3.56 and 3.64 ppm) in (±)-**1** showed the most significant changes in chemical shift as the amount of chiral shift reagent added to the $CDCl_3$ solution was gradually increased. These two protons are closest to the carbonyl functional group in **1**, suggesting that it is the non-bonding pairs of electrons in the carbonyl group which are donated to the europium ion of the shift reagent,[33] thereby producing the greatest downfield shifts at the 1a-position. The proton resonance at the 4-position (δ_H 4.94 ppm) exhibited the largest separation in chemical shifts between the 4*R*- and 4*S*- forms of **1**, as the amount of chiral shift reagent was increased, perhaps because it is this proton which is directly attached to the chiral center.

significant effect. It therefore appeared that the variation in the % ee found for (+)-**1** from the natural source was not an artifact that had been introduced by either the extraction or purification procedures. Hence, we are forced to conclude that maculalactone A is indeed naturally present in *K. maculans* in a partially racemized form.

In closing, it is worth pointing out that-quite by chance-the ratio of the two enantiomers found for natural maculalactone A (**1**) was almost identical with that which was obtained from the asymmetric synthesis described in Section 2.3. Perhaps uniquely in natural product chemistry, it appears that the asymmetric synthesis of **1** via the Corey procedure has yielded a target compound of similar enantiomeric composition to that of the natural material, and that even though the enantioselectivity of this synthetic procedure is perhaps relatively modest by the standards of the current day-at 85% ee-there is little incentive to attempt to improve the chiral selectivity of the enantiomeric step, as the product obtained from asymmetric synthesis is already almost identical with the natural product!

3. Experimental

3.1. General methods

General experimental procedures were similar to those described recently in: Brown, G.D.; Sy, L.-K., *Tetrahedron* **2004**, *60*, 1125–1138.

3.1.1. Isolation of natural (+) maculalactone A (2,3,4-tribenzyl-γ-butyro-2,3-en-lactone) (1) from *Kyrtuthrix maculans*. *K. maculans* (132.8 g wet wt., 78.6 g after freeze drying overnight) was collected from the shores at Shek Mei Tau, New Territories, Hong Kong in March. Taxonomic identification was made by Dr Williams of the Department of Ecology and Biodiversity, The University of Hong Kong. Following lyophilization, the sample was pulverized to a fine powder under liq. N_2, repeatedly extracted with CH_2Cl_2, dried ($MgSO_4$) and solvent was removed under reduced pressure to yield a dark brown gum (1.09 g; 0.82 w/w % [fresh wt]). The extract was subjected to gradient CC (*n*-hexane→EtOAc) followed by HPLC to obtain compound **1** (115.2 mg, 0.09% w/w [fresh wt.]; R_f 0.35 in 5% EtOAc/*n*-hexane) which was recrystallized from 10% *i*-PrOH/*n*-hexane, to obtain maculalactone A (**1**) as a solid, mp 88–89 °C; $[\alpha]_D$=+130.2 (*c*=2.4, $CHCl_3$)-see Ref. 4 for other physical properties.

3.2. Synthesis of (±) maculalactone A

3.2.1. Preparation of 2*E*,3*E*-Dibenzylidenesuccinic acid (5). A solution of dimethyl succinate (5.0 g, 34.2 mmol), benzaldehyde (7.3 g, 68.4 mmol) and Na (1.7 g, 75.3 mmol) in anhyd. Et_2O (50 mL) was stirred under N_2 at 0 °C and allowed to warm to room temperature over 12 h. MeOH (10 mL) was added to destroy any remaining excess Na, followed by H_2O (10 mL) and the mixture was then acidified with HCl (6 M, 10 mL), and extracted with Et_2O (2×10 mL). The combined organic layers were re-extracted with sat. $NaHCO_3$ (aq.) (3×20 mL) and the combined sat. $NaHCO_3$ (aq.) extracts were acidified and extracted with Et_2O (3×20 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a residue consisting predominantly of compound **5**, which was purified by washing with Et_2O.

2E,3E-Dibenzylidenesuccinic acid (**5**). Solid, mp 213–215 °C, (1.87 g, 6.4 mmol, 19%). ν_{max}/cm^{-1} (KBr disc): 3435 (v br), 3069, 1680, 1638, 1611; δ_H (CD_3OD)-7.91 (2H, s), 7.50 (4H, m), 7.35 (6H, m)—see also Table 1; ^{13}C NMR—see Table 1; ESI-MS *m/z* (rel. int.): 317 (M^+ $[C_{18}H_{14}O_4]+Na^+$) (100).

Note that compound **5** was also commercially available from the Aldrich Chemical Company (Cat. No. S-300187) but that this source was judged to be too costly as a starting material for performing a synthesis of maculalactone A on a gram scale, such as that described in Sections 3.2.1–3.2.5.

3.2.2. Conversion of 5 to 2*E*,3*E*-dibenzylidenesuccinic anhydride (6). To 2*E*,3*E*-dibenzylidene succinic acid (**5**) (1.5 g, 5.1 mmol) was added excess acetyl chloride (1.5 mL) and the reaction was refluxed for 2 h. After completion, as determined by TLC, the reaction mixture was cooled in an ice bath and the anhydride **6** was separated by filtration as yellow crystals, which were washed with a small amount of cold Et_2O to yield the pure product.

2E,3E-Dibenzylidenesuccinic anhydride (**6**). Solid, mp 202–204 °C (1.18 g, 4.3 mmol, 84%). ν_{max}/cm^{-1}: 3030, 1823, 1771, 1618, 1595; δ_H-7.94 (2H, s), 7.15 (2H, tt, *J*=7.1, 1.6 Hz), 6.85 (4H, dd, *J*=7.1, 7.1 Hz), 6.83 (4H, dd, *J*=7.1, 1.6 Hz)—see also Table 1; ^{13}C NMR—see Table 1; HREIMS *m/z* (rel. int.): 276.0786 (M^+, calcd 276.0786 for $C_{18}H_{12}O_3$) (60), 232 (40), 203 (80), 199 (100).

3.2.3. Reduction of 6 to 2,3-dibenzylbut-2-en-dioic anhydride (7) and 2*R*/*S*,3*S*/*R*-dibenzylbutanedioic anhydride (8). A solution of 2*E*,3*E*-dibenzylidene succinic anhydride (**6**) (1.0 g, 3.62 mmol) in EtOAc (10 mL) was charged with 5% (w/w) Pd/C (50 mg) and stirred under H_2 (1 atm) at room temperature for 18 h. The resultant colorless solution was filtered and rotary evaporated to give a crude product consisting of the anhydrides **7** and **8** in an approximately 3:1 ratio (as determined by ^1H NMR spectroscopy). Anhydride **8** precipitated out of solution after thoroughly mixing the crude product with 10% EtOAc/*n*-hexane, while compound **7** remained largely in the supernatant and was further purified by semi-preparative HPLC (10% EtOAc/*n*-hexane).

2,3-Dibenzylbut-2-en-dioic anhydride (**7**). Oil (R_t 19.1 min, 756 mg, 2.71 mmol, 74%). ν_{max}/cm^{-1}: 3032, 2928, 1825, 1767, 1603, 1497, 1456; δ_H 7.31 (2H, t, *J*=7.5 Hz), 7.28 (4H, dd, *J*=7.5, 7.5 Hz), 7.13 (4H, d, *J*=7.5 Hz) 3.79 (4H, s)—see also Table 1; ^{13}C NMR—see Table 1; HREIMS *m/z* (rel. int.): 278.0948 (M^+, calcd 278.0943 for $C_{18}H_{14}O_3$) (100), 260 (14), 233 (49), 205 (21).

2(R/S),3-Dibenzylbutanedioic anhydride (**8**). Solid, mp 105–106° C (R_t 30.0 min, 254 mg, 0.95 mmol, 24%). ν_{max}/cm^{-1}: 3032, 2926, 1863, 1786, 1605, 1496, 1456; δ_H-7.33 (4H, dd, *J*=7.3, 7.3 Hz), 7.28 (2H, t, *J*=7.3 Hz), 7.14 (4H, d, *J*=7.3 Hz), 3.50 (2H, m), 3.12 (2H, m), 3.10

(2H, m)—see also Table 1; ^{13}C NMR—see Table 1; HREIMS *m/z* (rel. int.): 280.1102 (M^+, calcd 208.1099 for $C_{18}H_{16}O_3$) (70), 125 (100).

When incomplete reduction of 2*E*,3*E*-dibenzylidene-succinic anhydride (**6**) (20.0 mg, 0.07 mmol) was performed in an EtOAc (1 mL) solution charged with 10% Pd/C (1 mg, 5% w/w) and stirred under H_2 (1 atm) at room temperature for 2 h, the resulting crude product consisted of the three anhydrides **7**–**9**, which were separated by semi-preparative HPLC (10% EtOAc/*n*-hexane): **7** (4.1 mg, 0.015 mmol, 20%; R_t 19.1 min); **8** (3.3 mg, 0.012 mmol, 16%; R_t 30.0 min); and **9** (5.5 mg, 0.020 mmol, 27%; R_t 32.3 min).

2-Benzylidene,3(R/S)-benzyl-butanedioic anhydride (**9**). Solid, mp 138–140 °C. ν_{max}/cm^{-1}: 3030, 2930, 1771, 1709, 1636, 1603, 1496, 1454, 1447 cm^{-1}; δ_H-7.80 (1H, d, *J*=2.4 Hz), 7.58–7.53 (5H, m), 7.19 (3H, m), 6.89 (2H, m), 4.38 (1H, ddd, *J*=5.7, 4.1, 2.4 Hz), 3.35 (1H, dd, *J*=13.7, 5.7 Hz), 3.25 (1H, dd, *J*=13.7, 4.1 Hz)—see also Table 1; ^{13}C NMR—see Table 1; HREIMS *m/z* (rel. int.): 278.0944 (M^+, calcd 278.0943 for $C_{18}H_{14}O_3$) (50), 233 (20), 205 (25), 178 (15), 153 (100).

3.2.4. Synthesis of 2,3,4-tribenzyl-4(*R/S*)-hydroxy-γ-butyro-2-en-lactone (10). A Grignard reagent, freshly prepared from the addition of Mg (52.4 mg, 2.16 mmol) to benzyl bromide (0.26 mL, 2.16 mmol) in anhyd. Et_2O (50 mL) at room temperature for 1 h, was transferred to a solution of anhydride **7** (500 mg, 1.80 mmol) in anhyd. Et_2O (50 mL) at 0 °C via a cannula. The reaction mixture was stirred under N_2 at 0 °C for 30 min, quenched by H_2O (15 mL) and then acidified with HCl (1 M, 15 mL). The aqueous layer was extracted with Et_2O (2×50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and rotary evaporated to give a crude product consisting predominantly of the butyrolactone **10** together with small amounts of **11**–**14**, which was purified by CC (10% EtOAc/*n*-hexane).

2,3,4-Tribenzyl-4(R/S)-hydroxy-γ-butyro-2-en-lactone (**10**). Solid, mp 107–109 °C (394 mg, 1.06 mmol, 59%; R_f 0.20). ν_{max}/cm^{-1}: 3527, 3392 (br), 3026, 2928, 1759, 1602, 1497, 1454; δ_H-7.35 (1H, m), 7.26 (5H, m), 7.17 (2H, m), 7.11 (5H, m), 6.69 (2H, dd, *J*=7.1, 1.8 Hz), 3.81 (1H, d, *J*=14.7 Hz), 3.65 (1H, d, *J*=14.7 Hz), 3.48 (1H, d, *J*=15.3 Hz), 3.29 (1H, d, *J*=15.3 Hz), 3.26 (s, –OH), 3.23 (1H, d, *J*=13.9 Hz), 3.06 (1H, d, *J*=13.9 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 352.1461 (M^+-H_2O, calcd 352.1463 for $C_{25}H_{20}O_2$) (100), 279 (55).

2,3,4,4-Tetrabenzyl-γ-butyro-2-en-lactone (**12**). Solid, mp 135–137 °C (19 mg, 0.043 mmol, 3%; R_f 0.40). ν_{max}/cm^{-1}: 3030, 3013, 2926, 1747, 1496, 1454; δ_H-7.23 (9H, m), 7.16 (4H, dd, *J*=7.5, 1.8 Hz), 7.04 (1H, t, *J*=7.0 Hz), 6.99 (2H, d, *J*=7.0 Hz), 6.98 (2H, dd, *J*=7.0, 7.0 Hz), 6.25 (2H, d, *J*=7.0 Hz), 3.68 (2H, s), 3.23 (2H, s), 3.09 (2H, d, *J*=14.3 Hz), 2.90 (2H, d, *J*=14.3 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 444.2089 (M^+, calcd 444.2089 for $C_{32}H_{28}O_2$) (30), 353 (100).

2,2,3(R/S),4(R/S)-Tetrabenzyl-4-hydroxy-γ-butyrolactone (**13**). Solid, mp 196–198 °C (7 mg, 0.016 mmol, 1%; R_f 0.31). ν_{max}/cm^{-1}: 3649, 3034, 2926, 1749, 1601, 1497, 1454; δ_H-7.35 (2H, dd, *J*=7.5, 7.5 Hz), 7.31 (2H, m), 7.29–7.14 (12H, m), 7.07 (2H, d, *J*=6.9 Hz), 6.85 (2H, dd, *J*=6.6, 1.6 Hz), 3.56 (1H, d, *J*=13.7 Hz), 3.26 (1H, d, *J*=13.9 Hz), 3.10 (1H, dd, *J*=13.9, 11.0 Hz), 3.02 (1H, s,–OH), 2.97 (1H, d, *J*=13.7 Hz), 2.91 (1H, dd, *J*=13.9, 4.2 Hz), 2.65 (1H, d, *J*=13.9 Hz), 2.48 (1H, dd, *J*=11.0, 4.2 Hz), 2.25 (1H, d, *J*=13.9 Hz), 2.10 (1H, d, *J*=13.9 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 444.2092 (M^+-H_2O, calcd 444.2089 for $C_{32}H_{28}O_2$) (45), 353 (100).

2,2,3(R/S)-Tribenzylbutanedioic anhydride (**14**). Solid, mp 145–147 °C (85 mg, 0.23 mmol, 13%; R_f 0.49). ν_{max}/cm^{-1}: 3028, 2928, 2856, 1782, 1718, 1497, 1454; δ_H-7.37 (2H, dd, *J*=7.5, 7.5 Hz), 7.35 (3H, m) 7.31 (1H, t, *J*=7.5 Hz), 7.28 (2H, d, *J*=7.5 Hz), 7.22 (2H, d, *J*=7.5 Hz), 7.18 (3H, m), 6.78 (2H, dd, *J*=7.5, 1.8 Hz), 3.42 (1H, d, *J*=14.4 Hz), 3.35 (1H, dd, *J*=14.2, 6.6 Hz), 3.27 (1H, d, *J*=13.9 Hz), 3.16 (1H, t, *J*=6.4 Hz), 3.11 (1H, d, *J*=13.9 Hz), 3.03 (1H, dd, *J*=14.2, 6.6 Hz), 2.54 (1H, d, *J*=14.4 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 370.1572 (M^+, calcd 370.1569 for $C_{25}H_{22}O_3$) (25), 352 (8), 279 (44), 251 (16), 222 (100).

3.2.5. Sodium borohydride reduction of 10 to racemic maculalactone A (4(*R/S*)-2,3,4-tribenzyl-γ-butyro-2-en-lactone) (±)-(1). To a solution of the γ-hydroxy-butyro-lactone **10** (250 mg, 0.68 mmol) in THF/H_2O (10 mL; 24:1) was added $NaBH_4$ (128 mg, 3.37 mmol) in portions at 0 °C with stirring for 2 h. The reaction mixture was quenched by HCl (1 M, 10 mL), concentrated by rotary evaporation and extracted with EtOAc (3×10 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to yield the butyrolactone **1** without the need for further purification.

4(R/S)-2,3,4-Tribenzyl-γ-butyro-2-en-lactone (**1**). Solid, mp 88–89 °C (237 mg, 0.67 mmol, 99%). ν_{max}/cm^{-1}: 3030, 3013, 2926, 1751, 1668, 1603, 1497, 1454; δ_H-7.30 (2H, m), 7.27 (1H, m), 7.25 (3H, m), 7.17 (1H, m), 7.15 (4H, m), 7.03 (2H, dd, *J*=6.6, 1.9 Hz), 6.88 (2H, dd, *J*=6.1, 2.3 Hz), 4.94 (1H, dd, *J*=6.1, 4.0 Hz), 3.92 (1H, d, *J*=15.6 Hz), 3.64 (1H, d, *J*=15.4 Hz), 3.56 (1H, d, *J*=15.4 Hz), 3.47 (1H, d, *J*=15.6 Hz), 3.23 (1H, dd, *J*=14.6, 4.0 Hz), 2.81 (1H, dd, *J*=14.6, 6.1 Hz)—see also Ref. 4; δ_C−173.5 C, 161.7 C, 137.7 C, 135.9 C, 134.8 C, 129.5 CH×2, 129.1 CH×2, 128.7 CH×2, 128.6 CH×4, 128.6 C, 128.2 CH×2, 127.3 CH, 127.2 CH, 126.4 CH, 81.6 CH, 38.0 CH_2, 33.2 CH_2, 29.4 CH_2—see also Ref. 4; HREIMS *m/z* (rel. int.): 354.1616 (M^+, calcd 354.1620 for $C_{25}H_{22}O_2$) (60), 263 (100).

3.2.6. Separation of racemic (±) maculalactone A (4(*R/S*)-2,3,4-tribenzyl-γ-butyro-2-en-lactone) (1) into its (+) and (−) enantiomers. Semi-preparative chiral HPLC separation of a sample of (±)-**1** (60 mg) was performed using a Waters chromatograph equipped with RI 410 detector and a Daicel chiral OD-column (10 mm×25 cm; 10 μm particle size; Cat. no. 14045; Chiral Technologies Inc., Exton, PA, USA) operating isocratically with 10% *i*-PrOH/ *n*-hexane at a flow rate of 8 mL min^{-1}. Typical recoveries per injection (1 mg of (±)-**1** in 100 μL) were ca. 0.35 mg of each enantiomer, yielding overall:

(−)-2,3,4-tribenzyl-γ-butyro-2-en-lactone ((−)-**1**) (15 mg, 25%; R_t=16.9 min; $[\alpha]_D$=−156.7 (*c*=1.0, $CHCl_3$); and *(+)-2,3,4-tribenzyl-γ-butyro-2-en-lactone* ((+)-**1**) (12 mg, 20%, R_t=18.3 min; $[\alpha]_D$=+153.1 (*c*=1.2, $CHCl_3$).

The analytical chiral separation shown in Figure 3 was made using a chiral stationary phase with comparable properties (Chiracel OD-H column, 4.6 mm×25 cm; 5 μm particle size; Cat. no. 14325; Chiral Technologies Inc., Exton, PA, USA). Experiments were performed with either an analytical HP 1100 series chromatogram or with an HP 2200 HPLC instrument equipped with HP 2210 UV detector (λ=245 nm), using a 20 μL injection loop (sample concentration typically 1 mg/mL) and operating isocratically with 10% *i*-PrOH/*n*-hexane at a flow rate of 1 mL min^{-1}. Under these conditions, the R_t for (−)-**1** was 23.7 min and that for (+)-**1** was 26.6 min.

3.3. Syntheses of other tribenzylbutyrolactone natural products

3.3.1. Dehydration of 10 to maculalactone B (2,3-dibenzyl-4*Z*-benzylidene-γ-butyro-2-en-lactone) (2). To a solution of the γ-hydroxy-butyrolactone **10** (100 mg, 0.27 mmol) in toluene (4 mL) was added a powder of silica gel onto which had been adsorbed H_2SO_4 (30 mg; prepared by suspending silica [100 g] in acetone [100 mL] containing H_2SO_4 [conc.; 10 g] and removing the solvent on a rotary evaporator). The mixture was heated at reflux for 5 h, and after completion of the reaction, as determined by TLC, the mixture was filtered and the solvent was removed on a rotary evaporator to yield the butyrolactone **2** without the need for further purification.

2,3-Dibenzyl-4Z-benzylidene-γ-butyro-2-en-lactone (**2**). Solid, mp 114–115 °C (78 mg, 0.21 mmol, 82%). ν_{max}/cm^{-1}: 3030, 3015, 2920, 1755, 1651, 1603, 1494, 1454; δ_H-7.70 (2H, d, *J*=7.5 Hz), 7.33 (2H, dd, *J*=7.5, 7.5 Hz), 7.28–7.20 (7H, m), 7.17 (2H, d, *J*=7.1 Hz), 7.10 (2H, d, *J*=7.4 Hz), 5.96 (1H, s), 3.92 (2H, s), 3.73 (2H, s)—see also Ref. 5; δ_C−170.3 C, 150.8 C, 148.2 C, 137.4 C, 136.6 C, 133.0 C, 130.5 CH×2, 128.9 CH×2, 128.8 CH, 128.7 CH×2, 128.6 CH×4, 128.2 CH×2, 127.8 C, 127.0 CH, 126.7 CH, 110.5 CH, 30.6 CH_2, 29.8 CH_2—see also Ref. 5; HREIMS *m/z* (rel. int.): 352.1457 (M^+, calcd 352.1463 for $C_{25}H_{20}O_2$) (100), 261 (15).

3.3.2. Photo-isomerization of maculalactone B (2) to maculalactone C (2,3-dibenzyl-4*E*-benzylidene-γ-butyro-2-en-lactone) (3). A degassed solution of the butyrolactone **2** (20 mg, 0.06 mmol) in anhyd. C_6H_6 (10 mL) was irradiated by UV light (450 W medium-pressure Hg arc lamp) at room temperature under N_2 for 1 h. Solvent was removed by rotary evaporation to give a mixture containing the butyrolactones **3** and **2**, in an approximately 4:1 ratio (by ^1H NMR of the crude product) which were separated by preparative HPLC (10% EtOAc/*n*-hexane).

2,3-Dibenzyl-4Z-benzylidene-γ-butyro-2-en-lactone (**2**). (4.0 mg, 0.011 mol, 20%; R_t 19.8 min). See Section 3.3.1 for physical properties.

2,3-Dibenzyl-4E-benzylidene-γ-butyro-2-en-lactone (**3**). Oil (15.8 mg, 0.045 mol, 79%; R_t 18.7 min). ν_{max}/cm^{-1}: 3032, 3013, 2928, 1756, 1603, 1494, 1454; δ_H-7.24–7.10 (11H, m), 7.01 (2H, d, *J*=7.3 Hz), 6.84 (1H, s), 6.60 (2H, dd, *J*=7.8, 1.7 Hz), 3.69 (2H, s), 3.66 (2H, s)—see also Ref. 5; δ_C−169.7 C, 149.3 C, 148.3 C, 137.2 C, 136.2 C, 133.0 C, 132.6 C, 129.3 CH×2, 128.7 CH×4, 128.4 CH×2, 128.2 CH×2, 128.2 CH, 127.7 CH×2, 126.7 CH, 126.4 CH, 115.3 CH, 31.5 CH_2, 29.8 CH_2—see also Ref. 5; HREIMS *m/z* (rel. int.): 352.1465 (M^+, calcd 352.1463 for $C_{25}H_{20}O_2$) (100), 261 (17).

3.3.3. Hydrogenation of maculalactone B (2) to maculalactone A (1). A solution of the butyrolactone **2** (30 mg, 0.09 mmol) in EtOAc (3 mL) was charged with 10% Pd/C (8 mg) and stirred under H_2 (1 atm) at room temperature for 18 h. The resultant mixture was filtered and rotary evaporated to give a crude product consisting predominantly of the butyrolactone **1**, which was purified from the alternative hydrogenation products **15** and **16** by preparative HPLC (10% EtOAc/*n*-hexane).

2,3,4(R/S)-Tribenzyl-γ-butyro-2-en-lactone (**1**). Solid mp 88–89 °C (23.7 mg, 0.07 mmol, 79%, R_t 31.4 min)-see Section 3.2.5 for physical properties.

2(R/S),3(S/R),4(R/S)-Tribenzyl-γ-butyrolactone (**15**). Solid, mp 145–147 °C (3.7 mg, 0.01 mmol, 12%, R_t 26.9 min). ν_{max}/cm^{-1}: 3028, 2957, 1767, 1603, 1497, 1454; δ_H-7.27 (2H, m), 7.25 (4H, m), 7.19 (3H, m), 7.09 (2H, d, *J*=7.3 Hz), 7.06 (2H, d, *J*=7.0 Hz), 7.02 (2H, d, *J*=7.3 Hz), 4.59 (1H, ddd, *J*=9.6, 4.0, 3.9 Hz), 3.28 (1H, dd, *J*=15.0, 4.8 Hz), 3.16 (1H, ddd, *J*=10.7, 6.4, 4.6 Hz), 2.96 (2H, m), 2.94 (1H, m), 2.82 (1H, dd, *J*=15.5, 4.8 Hz), 2.80 (1H, dd, *J*=15.0, 6.4 Hz), 2.55 (1H, dd, *J*=14.6, 3.9 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 356.1779 (M^+, calcd 356.1776 for $C_{25}H_{24}O_2$) (15), 265 (25), 247 (30), 229 (18), 219 (20), 208 (100).

2(R/S),3,3,4(R/S)-Tetrabenzyl-γ-butyrolactone (**16**). Solid, mp 240–242 °C (0.5 mg, 0.001 mmol, 1%; R_t 24.8 min). ν_{max}/cm^{-1}: 3026, 2926, 1773, 1497, 1454; δ_H-7.45 (2H, d, *J*=7.5 Hz), 7.37 (2H, dd, *J*=7.5 Hz), 7.32 (1H, t, *J*=7.5 Hz), 7.30–7.15 (13H, m), 6.84 (2H, m), 4.24 (1H, dd, *J*=10.7, 1.8 Hz), 3.11 (1H, dd, *J*=14.9, 10.0 Hz), 3.11 (2H, s), 3.08 (1H, m), 3.07 (2H, s), 2.86 (1H, dd, *J*=13.5, 1.8 Hz), 2.75 (1H, dd, *J*=10.0, 4.1 Hz), 2.65 (1H, dd, *J*=14.9, 4.1 Hz)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m/z* (rel. int.): 446.2245 (M^+, calcd 446.2246 for $C_{32}H_{30}O_2$) (20), 355 (30), 337 (50), 319 (10), 309 (15), 298 (35), 207 (100).

3.4. Asymmetric synthesis of (+) maculalactone A ((+)-1)

3.4.1. Attempted enantioselective hydrogenation of the trisubstituted olefin group in maculalactone B (2) in the presence of (+)-1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]-benzene-(cyclooctadiene)rhodium (I) trifluoromethanesulfonate (Et-DuPhos) catalyst. A 25 mL Schlenk tube was charged with compound **2** (25 mg, 0.071 mmol) in anhyd. MeOH (5 mL), and the solution was degassed by three freeze-thaw cycles under an atmosphere of Ar. The solution was then transferred to another 25 mL Schlenk

tube, which was pre-charged with the catalyst Rh(I)-(*S*,*S*)-Et-DuPhos (0.05 mg, 0.1 mol %; Strem chemical company, Cat. no. 45–0151), via a cannula and further degassed by two more freeze-thaw cycles. H_2 (1 atm) was introduced to the system and the reaction mixture was allowed to stir at room temperature for 3 days, after which complete conversion to product was indicated by TLC. The resulting mixture was concentrated to yield an extract consisting mostly of product **1** (22.5 mg, 0.063 mmol, 89%; R_f 0.22), following purification by CC (10% EtOAc/*n*-hexane). The enantiomeric excess (% ee) was determined as 0.5 by measurement of the optical rotation ($[\alpha]_D$=+0.70 [*c*=2.2, $CHCl_3$]), assuming $[\alpha]_D$ (+)-**1**=+153.1 and $[\alpha]_D$ (−)-**1**=−153.1.

When the same experimental procedure was employed using the catalyst Rh(I)-(*R*,*R*)-Et-DuPhos (Strem Chemical Company, Cat. no. 45–0150) in place of its (*S*) enantiomer, compound **1** (18.4 mg, 0.052 mmol, 73%; R_f 0.22) was obtained with 0.4% ee ($[\alpha]_D$=−0.67, [*c*=1.8, $CHCl_3$]).

3.4.2. Methyl esterification of compound 10 to 2,3-dibenzyl-4-oxo-5-phenyl-pent-2-en-oic acid methyl ester (17). Compound **10** (500 mg, 1.35 mmol) was dissolved in Et_2O (20 mL) and then treated with excess of a solution of CH_2N_2 in Et_2O (100 mL) at room temperature for 4 h. After the reaction was complete, excess CH_2N_2 and Et_2O were removed by gently passing N_2 gas through the solution, leaving a product consisting entirely of compound **17** (477 mg, 1.24 mmol, 92%), which could be used without the need for any further purification.

2,3-Dibenzyl-4-oxo-5-phenyl-pent-2-en-oic acid methyl ester (**17**). Solid, mp 65–67° C; ν_{max}/cm^{-1}: 3030, 3019, 2954, 1710, 1603, 1496, 1454 cm^{-1}; δ_H-7.30 (2H, dd, *J*=6.9, 6.9 Hz), 7.28 (2H, dd, *J*=7.9, 7.9 Hz), 7.26–7.20 (5H, m), 7.14 (2H, dd, *J*=8.2, 1.1 Hz), 7.07 (2H, dd, *J*=7.9, 1.1 Hz), 7.03 (2H, dd, *J*=8.1, 1.5 Hz), 3.86 (2H, s), 3.70 (2H, s), 3.67 (3H, s), 3.52 (2H, s)—see also Table 2; ^{13}C NMR—see Table 2; HREIMS *m*/*z* (rel. int.): 352.1471 (M^+−MeOH, calcd 352.1463 for $C_{25}H_{20}O_2$) (100), 293 (25), 261 (20).

3.4.3. Reduction of compound 17 to racemic maculalactone A (±)-1 by catecholborane. To a solution of **17** (10 mg, 0.026 mmol) in anhyd. toluene (0.26 mL) was added a solution of catecholborane (5.5 μL, 0.052 mmol) under an atmosphere of N_2 at −78 °C. The mixture was stirred for 6 h and then left in the freezer (at −18 °C) for 15 h. After the reaction was complete, as indicated by TLC, H_2O (1 mL) was added and the resulting mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (aq.) (5 mL), dried ($MgSO_4$) and rotary evaporated to obtain a crude product, which was purified by CC (5% EtOAc/*n*-hexane), to yield racemic (±)-**1** (7.7 mg, 0.022 mmol, 84%; R_f 0.35).

3.4.4. Asymmetric reduction of 17 by catecholborane in the presence of the chiral oxazaborolidine catalyst (*R*)-18. The oxazoborolidine catalyst (*R*)-**18** was prepared in four steps from (*R*)-proline (the more expensive unnatural enantiomer of this amino acid), according to Corey's procedure.[26,30] To a solution of (*R*)-**18** (20 μL, 0.01 mmol, 0.5 M in toluene) and compound **17** (19.2 mg, 0.05 mmol) in anhyd. toluene (0.5 mL) at −78 °C was added a solution of catecholborane (21.3 μL, 0.2 mmol) dropwise under an atmosphere of N_2. The reaction mixture was stirred at −78 °C for 6 h and then kept in the freezer (−18 °C) for 15 h. H_2O (3 mL) was added, and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (aq.) (10 mL), dried ($MgSO_4$) and rotary evaporated to obtain a crude product, which was purified by CC (5% EtOAc/*n*-hexane) to yield **1** (15.5 mg, 0.043 mmol, 88%; R_f 0.35).

The enantiomeric composition of the product was estimated at 90.7% of (+)-**1** and 9.3% of (−)-**1** by chiral HPLC analysis (Section 3.2.6), and the % ee of the reaction was therefore 81.4%.

3.4.5. Asymmetric reduction of 17 by catecholborane in the presence of the chiral oxazaborolidine catalyst (*S*)-18. The oxazoborolidine catalyst (*S*)-**18** was prepared in four steps from (*S*)-proline, according to Corey's procedure.[26,30] The same experimental procedure was employed as for the enantioselective reduction of **17** in the previous section, except that (*S*)-**18** was substituted for (*R*)-**18**. The product (15.7 mg, 0.044 mmol, 89%) consisted of 92.2% of (−)-**1**, and 7.8% of (+)-**1**, and the % ee of the reaction was therefore 84.4%.

3.5. Investigation of the extent of partial racemization in (+) maculalactone A isolated from *K. maculans*

3.5.1. Determination of the enantiomeric purity of naturally-occurring (+) maculalactone A (1) by analytical HPLC using a chiral column. See Section 3.1.1 for details of the extraction and isolation procedure for obtaining maculalactone A from *K. maculans* and Section 3.2.6 for details of the analytical chiral HPLC analysis.

3.5.2. Determination of the enantiomeric purity of naturally-occurring (+) maculalactone A (1) by ^1H NMR spectroscopy in the presence of a chiral shift reagent. The enantiomeric composition of **1** which had been isolated from *K. maculans* was determined by ^1H NMR spectroscopy in the presence of the chiral shift reagent, europium *tris*[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorate]. A sample of **1** (10 mg) from the natural source was dissolved in $CDCl_3$ (0.5 mL, containing 0.03% v/v TMS) and ^1H NMR spectra were recorded after successive additions of the chiral shift reagent (10 mg per addition) into the sample (expts. 1–7 in Fig. 6). The experiment was stopped when sufficient chiral shift reagent had been added to obtain a clear baseline separation of ^1H resonances which were considered characteristic of the two enantiomeric forms of **1**. Expts. 8–14 in Figure 6 were recorded in a similar way using racemic (±)-**1** which had been obtained from synthesis (see Section 3.2.5) in place of natural maculalactone A.

Acknowledgements

We thank the Chemistry Department of the University of Hong Kong for providing a postgraduate studentship to Mr.

Wong. This project was funded by a grant from the Committee on Research and Conference Grants (CRCG) of The University of Hong Kong.

References and notes

1. Kaehler, S. *Asian Mar. Biol.* **1994**, *11*, 41–54.
2. Kamura, S.; Choohabandit, S. *Galaxea* **1986**, *5*, 97–114.
3. Kaehler, S.; Williams, G. A. *Mar. Biol.* **1996**, *125*, 177–187.
4. Tsui, W.-Y.; Williams, G. A.; Brown, G. D. *Phytochemistry* **1996**, *43*, 1083–1085.
5. Lee, S.-C.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29–33.
6. Lee, S.-C.; Williams, G. A.; Brown, G. D. *Phytochemistry* **1999**, *52*, 537–540.
7. Wong, H.-F.; Williams, G. A.; Brown, G. D. *Phytochemistry* **2002**, *60*, 425–429.
8. Lee, S.-C. Chemical ecology of algae and the cyanobacterium *Kyrtuthrix maculans* on Hong Kong rocky shores. Ph.D. Thesis, The University of Hong Kong, 2001.
9. Brown, G. D.; Wong, H.-F.; Hutchinson, N.; Lee, S.-C.; Williams, G. A. Chemistry and biology of maculalactone A from the marine cyanobacterium *Kyrtuthrix maculans*, International Symposium Chemistry and Biology of Marine Organisms, Kolympari, Crete., 21–26 September 2003; pp. 60–61.
10. Wong, H.-F. Applications of high field nuclear magnetic resonance spectroscopy to the structure elucidation, conformational analysis and asymmetric synthesis of natural products. Ph.D. Thesis, The University of Hong Kong, 2002.
11. Ward, R. S.; Pelter, A.; Edwards, M. I.; Gilmore, J. *Tetrahedron* **1996**, *52*, 12799–12814.
12. Johnson, W. S.; Daub, G. H. *Organic Reactions*; Wiley: New York, 1951; Vol. 6. pp. 1–73.
13. Andersson, J. *Acta Chem. Scand. B* **1977**, *B31*, 340–341.
14. Fieser, L. F.; Martin, E. L. Succinic Anhydride. *Organic Synthesis*; Blatt, A. H., Ed.; Wiley: London, 1948; Collective Vol. 2, pp 560–562.
15. Davidse, P. A.; Dillen, J. L. M.; Heyns, A. M.; Modro, T. A.; van Rooyen, P. H. *Can. J. Chem.* **1990**, *68*, 741–746.
16. Chavez, F.; Suarez, S.; Diaz, M. A. *Synth. Commun.* **1994**, *24*, 2325–2339.
17. Bushan, K. M.; Rao, G. V.; Soujanya, T.; Rao, V. J.; Saha, S.; Samanta, A. *J. Org. Chem.* **2001**, *66*, 681–688.
18. Allenmark, S. G. *Nat. Prod. Rep.* **2000**, *17*, 145–155.
19. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
20. Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
21. Seco, J. M.; Quiñoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, 2781–2791.
22. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.
23. Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569–592.
24. Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653–2655.
25. Thompson, H. W.; Wong, J. K.; Lalancette, R. A.; Boyko, J. A.; Robertiello, A. M. *J. Org. Chem.* **1985**, *50*, 2115–2121.
26. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.
27. Corey, E. J.; Da Silva Jardine, P.; Mohri, T. *Tetrahedron Lett.* **1988**, *29*, 6409–6412.
28. Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672–3673.
29. Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207–5210.
30. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614.
31. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
32. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
33. Kemp, W. *Organic Spectroscopy*; MacMillan Press: New York, 1991; pp. 169–170.
34. Charlwood, B. V.; Banthorpe, D. V. Methods in Plant Biochemistry. In *Terpenoids*; Dey, P. M., Harborne, J. B., Eds.; Academic: New York; Vol. 7, pp. 33–34.
35. Sy, L.-K.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 987–992.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5453–5460
Tetrahedron

Generation of magnesium carbenoids from 1-chloroalkyl phenyl sulfoxides with a Grignard reagent and applications to alkylation and olefin synthesis

Tsuyoshi Satoh,* Atsushi Kondo and Jun Musashi

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 5 April 2004; accepted 20 April 2004

Abstract—Treatment of 1-chloroalkyl phenyl sulfoxides with a Grignard reagent at low temperature gave magnesium carbenoids in quantitative yields. The generated magnesium carbenoids were found to be stable at lower than −60 °C for long periods of time and are reactive with Grignard reagents to give alkylated products. The reaction of the generated magnesium carbenoids with various kinds of lithium α-sulfonyl carbanions gave olefins with carbon–carbon bond-formation in good to high yields. This method offers a good way for the preparation of olefins. The scope and limitations of the above-mentioned reactions are described.

New development of carbon–carbon bond-forming reactions is essential in synthetic organic chemistry and innumerable reactions have been reported.[1] Carbenes and carbenoids are known to be highly reactive intermediates and often have been recognized to be difficult to control in reactions;[2] however, this recognition is not always correct. Recently, many interesting reactions using metal carbenes have been reported.[3]

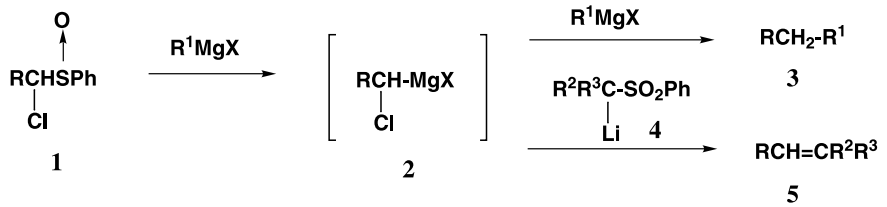
Recently, we have reported a new method for generation of magnesium carbenoids and magnesium alkylidene carbenoids,[4] magnesium cyclopropylidenes,[5] based on sulfoxide–magnesium exchange reaction[6] and application of the carbenoids in carbon–carbon bond-formation. In our study, we found that the generated magnesium carbenoids are relatively highly stable compared with the corresponding lithium carbenoids and could be used as a useful intermediate in organic synthesis.[7]

In continuation of our interest in the generation of magnesium carbenoids and their application in new synthetic methods, we recently investigated a generation of a simple magnesium carbenoids **2** from 1-chloroalkyl phenyl sulfoxides **1** with a Grignard reagent. The properties and alkylation of the generated magnesium carbenoids **2** with several Grignard reagents to give alkanes **3** are reported. A successful application of the reaction of the carbenoids **2** with lithium α-sulfonyl carbanions **4** to give olefins **5** in good to high yields is also described (Scheme 1).

1. Results and discussion

1.1. Generation of the magnesium carbenoids and their stability and the reactivity with Grignard reagents

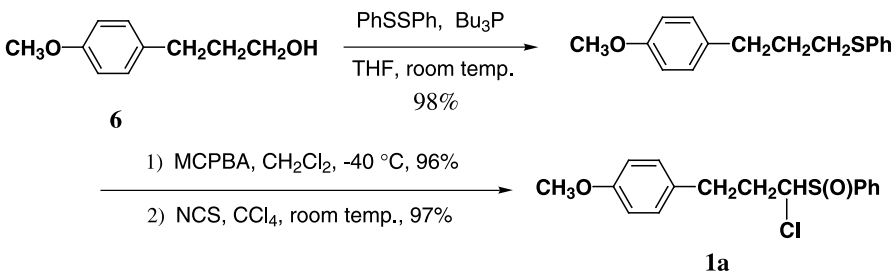
First, 1-chloro-3-(4-methoxyphenyl)propyl phenyl sulfoxide



Scheme 1.

Keywords: Magnesium carbenoid; Sulfoxide; Sulfoxide–magnesium exchange; Olefin; Sulfone.
* Corresponding author. Tel.: +81-3-5228-8272; fax: +81-3-3235-2214; e-mail address: tsatoh@ch.kagu.tus.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.063



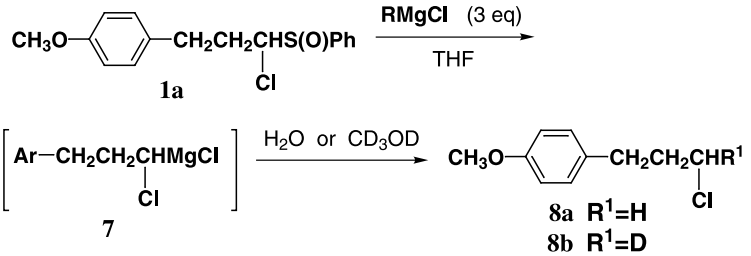
Scheme 2.

1a was selected as the representative example of the 1-chloroalkyl phenyl sulfoxide in this study and was synthesized from an alcohol **6** in three steps in 92% overall yield (Scheme 2). It is interesting to note that, although **1a** has two stereogenic centers, one isomer was obtained predominantly (over 95%) as a crystalline compound. This result indicated that the chlorination of the sulfoxide proceeded in a highly stereoselective manner. The recrystallized pure material **1a** was used throughout this study. This sulfoxide **1a** was treated with 3 equiv. of a Grignard reagent[8] at −80 °C for 10 min, and the generated magnesium carbenoid **7** was reacted with H_2O or CD_3OD to give chloroalkane **8a**[9] and **8b**. The results are summarized in Table 1.

Among the Grignard reagents examined, only ethylmagnesium chloride, isopropylmagnesium chloride, and cyclohexylmagnesium chloride were found to be highly effective for the sulfoxide–magnesium exchange reaction (entries 2–4). Methylmagnesium chloride worked; however, under these conditions, half of the starting material was recovered from the reaction mixture (entry 1). When this reaction was quenched with CD_3OD, deuterated chloride **8b** was obtained and the deuterium incorporation was found to be perfect (entries 2–4). *tert*-Butylmagnesium chloride did not react at all with **1a** under these conditions (entry 5). Almost no reaction was observed with benzylmagnesium chloride and phenylmagnesium chloride (entries 6 and 7).

Entries 8–14 show the results of the reaction of **1a** with *i*-PrMgCl under various temperature and time. When this reaction was carried out at −70 °C or at −60 °C and the reaction mixture was allowed to stand for 10 or 30 min, and the reaction was quenched with CD_3OD, the yields of **8b** and the deuterium incorporation were found to be almost the same (entries 8–11). Even when this reaction was carried out at −50 °C for 10 min, the yield of **8b** was found to be high (entry 12); however, upon standing for 30 min, slight decomposition of the carbenoid **7** was observed (entry 13). The yield of **8b** was markedly diminished when this reaction was carried out at −40 °C (entry 14). From these results, we concluded that the generated magnesium carbenoid **7** is stable at lower than −60 °C for over 30 min.

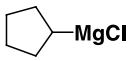
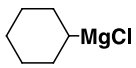
Table 1. Generation of magnesium carbenoid **7** from **1a** and quenching with water or deuterio methanol



Entry	R (RMgCl)	Conditions	8	Yield (%)
1	CH_3	−80 °C, 10 min	**8a**	44
2	CH_3CH_2	−80 °C, 10 min	**8b**	91[a]
3	$(CH_3)_2CH$	−80 °C, 10 min	**8b**	91[a]
4		−80 °C, 10 min	**8b**	89[a]
5	$(CH_3)_3C$	−80 °C, 10 min	No reaction	
6	$PhCH_2$	−80 °C, 10 min	**8a**	Trace
7	Ph	−80 °C, 10 min	**8a**	Trace
8	$(CH_3)_2CH$	−70 °C, 10 min	**8b**	92[a]
9	$(CH_3)_2CH$	−70 °C, 30 min	**8b**	92[a]
10	$(CH_3)_2CH$	−60 °C, 10 min	**8b**	89[a]
11	$(CH_3)_2CH$	−60 °C, 30 min	**8b**	87[a]
12	$(CH_3)_2CH$	−50 °C, 10 min	**8b**	89[a]
13	$(CH_3)_2CH$	−50 °C, 30 min	**8b**	76[a]
14	$(CH_3)_2CH$	−40 °C, 30 min	**8b**	51[a]

[a] Deuterium incorporation was over 99%.

Table 2. Treatment of 1-chloroalkyl phenyl sulfoxide **1a** with excess Grignard reagent

Entry	RMgX	Conditions	9	Yield (%)
1	CH_3CH_2MgCl	−80 to −30 °C, 110 min	**9a**	80
2	$CH_3(CH_2)_4CH_2MgBr$	−78 to −30 °C, 85 min	**9b**	87
3	$(CH_3)_2CHMgCl$	−80 to −30 °C, 110 min	**9c**	87
4	$CH_3(CH_2)_4CH(CH_3)MgBr$	−78 to −30 °C, 85 min	**9d**	69
5		−78 to −30 °C, 85 min	**9e**	94
6		−75 to −30 °C, 85 min	**9f**	75
7	$(CH_3)_3CMgCl$	−78 to −30 °C, 85 min		0[a]

[a] The starting material **1a** was recovered.

1.2. Alkylation of the generated magnesium carbenoids with excess Grignard reagent

In this study, we found that the reaction of **1a** with excess Grignard reagents, with warming the reaction, gave alkyated products **9** (see Table 2).[10] The mechanism of this reaction is thought to be the nucleophilic addition of the Grignard reagent to the carbon of the magnesium carbenoid **7**, which has an electrophilic nature. Both primary alkyl Grignard reagents and secondary alkyl Grignard reagents gave good yields of the alkylated products **9** (Table 2; entries 1–6). Interestingly, the Grignard reagents having a cyclic alkyl group gave **9** in good yields (entries 5 and 6). Even an acyclic secondary alkyl Grignard reagent gave good yield of the adduct (entry 4). *tert*-Butylmagnesium chloride did not react at all with **1a** even at −30 °C (entry 7).

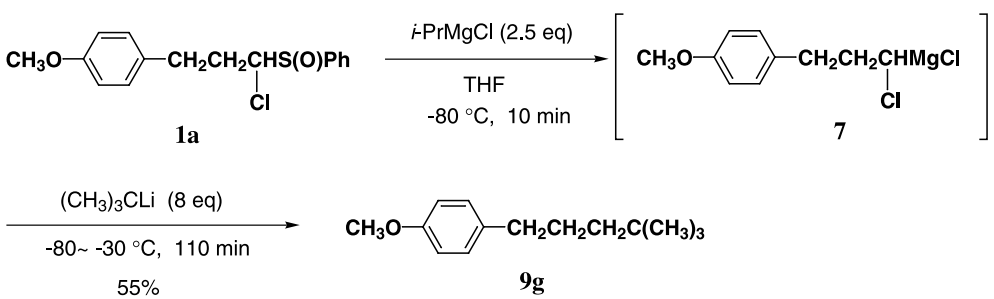
In order to synthesize *tert*-butylated compound **9g**, we tried the reaction of the magnesium carbenoid **7** with *tert*-butyllithium (Scheme 3). The magnesium carbenoid **7** was generated with 2.5 equiv. of *i*-PrMgCl in THF at −80 °C for 10 min. To this solution was added excess of *tert*-butyllithium and the temperature of the reaction mixture was allowed to warm to −30 °C for 110 min. Fortunately, this trial successfully gave the desired **9g** in 55% yield.

In conclusion, these reactions mentioned above offer an interesting method for carbon–carbon coupling, especially, with a secondary alkyl Grignard reagent.

1.3. Olefination of the magnesium carbenoids generated from 1-chloroalkyl phenyl sulfoxides with lithium α-sulfonyl carbanions

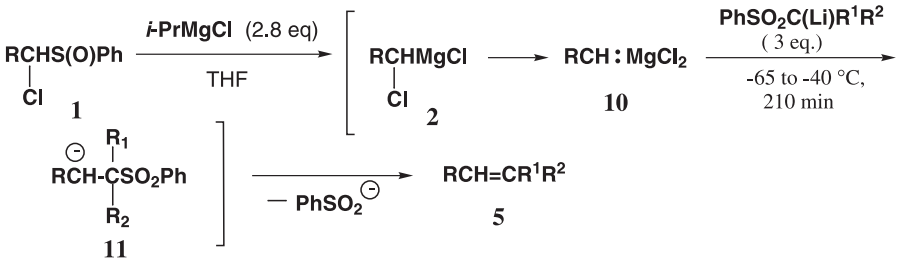
Based on the experiences described above, we studied the reaction of the magnesium carbenoids **2**, generated from 1-chloroalkyl phenyl sulfoxides **1** and isopropylmagnesium chloride, with other carbon nucleophiles than the used Grignard reagent. After some investigation, we found that the reaction of the magnesium carbenoids **2** with lithium α-sulfonyl carbanions gave olefins **5** with carbon–carbon coupling in good to high yields.[11] The results are summarized in Table 3.

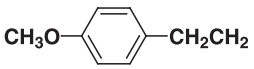
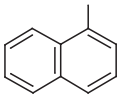
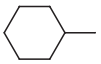
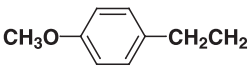
The reactions are simply conducted as follows. A representative example is described using **1a** and benzyl phenyl sulfone (Table 3, entry 1). To a flame-dried flask were added dry THF followed by *i*-PrMgCl (2.8 equiv.) at −65 °C and the solution was stirred for 10 min. A solution of **1a** in a minimum amount of THF was added dropwise to the solution of the Grignard reagent. In another flask, benzyl phenyl sulfone (3 equiv.) was treated with *n*-BuLi (3.6 equiv.) at 0 °C and the solution of the generated lithium α-sulfonyl carbanion was cooled to −65 °C and transferred to the solution of the magnesium carbenoid via a cannula. The whole mixture was stirred and slowly allowed to warm to −40 °C for about 3.5 h. After quenching the reaction with water and usual work-up, 93% of 4-(4-methoxyphenyl)-1-phenyl-1-butene (Table 3, entry 1) was obtained as a



Scheme 3.

Table 3. Treatment of 1-chloroalkyl phenyl sulfoxides **1** with isopropylmagnesium chloride followed by lithium α-sulfonyl carbanions to afford olefins **5**



Entry	**1**, R	$PhSO_2C(Li)R^1R^2$		**5**	Yield (%)	*E*/*Z*
		R^1	R^2			
1		Ph	H	**5a**	93	1/2
2	**1a**	Ph	H	**5a**	78[a]	1/2
3			H	**5b**	89	1/4
4		Ph	CH_3	**5c**	92	1/2
5		Ph	Ph	**5d**	50	—
6		CH_3	H	**5e**	78	2/3[b]
7		$CH_3(CH_2)_3$	H	**5f**	85	2/3[b]
8		$CH_3(CH_2)_8$	H	**5g**	86	2/3[b]
9		CH_3	CH_3	**5h**	88	—
10		Ph	H	**5i**	71[c]	1/2
11	**1b**	Ph	CH_3	**5j**	77[c]	2/3
12			H	**5k**	65[c]	2/3[b]
13	$PhCH_2C(CH_3)_2$ **1c**	Ph	H	**5l**	29[d]	0/1[e]

[a] The reaction temperature; −65 °C to room temperature.
[b] The stereochemistry of these products has not been determined yet.
[c] The reaction temperature; −70 to −40 °C.
[d] The reaction conditions; −70 to 0 °C for 150 min.
[e] Only *Z*-olefin was obtained.

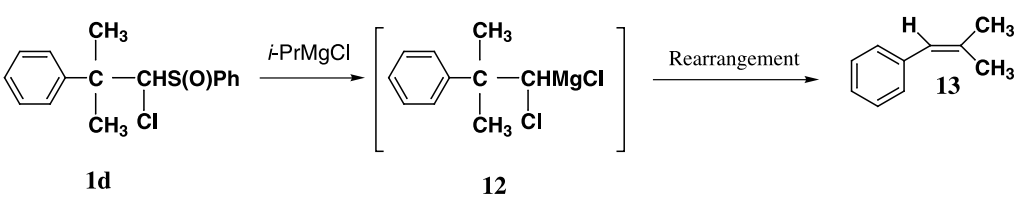
mixture of two geometrical isomers. When this reaction was allowed to warm to room temperature, marked diminishing of the yields was observed (entry 2).

1,2-Disubstituted olefins were obtained in good yields by using the sulfones having both aryl- and alkyl groups at the carbon bearing the sulfonyl group (entries 1, 3, and 6–8). Even tri-substituted olefins were obtained in good yields (entries 4 and 9) except 1,1-diphenyl olefin (50% yield, entry 5).

This olefin synthesis was investigated with other 1-chloroalkyl phenyl sulfoxides (entries 10–13). The sulfoxide **1b** has a branched chain at the 2-position. The olefination was carried out in a similar manner as described above and the desired olefins were obtained; however, the yields were found to be somewhat lower (65–77%). The sulfoxide **1c** has a quaternary carbon at the 2-position and the olefination gave markedly diminished yield. Steric hindrance is thought to be the reason for this result.

It is interesting to note that when **1d** was treated with *i*-PrMgCl followed by lithium α-sulfonyl carbanions as above, only dimethylstylene **13** was obtained in almost quantitative yield (Scheme 4). This result indicated that in the reaction of the carbenoid **12**, rearrangement[2,12] is faster than the reaction with the lithium α-sulfonyl carbanions.

In conclusion, we were able to generate magnesium carbenoids from 1-chloroalkyl phenyl sulfoxides with some Grignard reagents at lower than −60 °C, and found that the magnesium carbenoid is quite stable at below



Scheme 4.

−60 °C. A new method for carbon–carbon coupling and for olefin synthesis was realized by using the generated magnesium carbenoids. Though the selectivity is low, this reaction offers a unique and interesting method for the preparation of di- and tri-substituted olefins.

2. Experimental

2.1. General

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 300, 400 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (MERCK) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, THF was distilled from benzophenone ketyl; diisopropylamine and DMF were distilled over CaH_2 and distilled.

2.1.1. 1-Chloro-3-(4-methoxyphenyl)propyl phenyl sulfoxide (1a). A solution of 3-(4-methoxyphenyl)-1-propanol **6** (1 g; 6 mmol) and diphenyl disulfide (1.71 g; 7.8 mmol) in 20 ml of THF was cooled in an ice bath. To this solution was added with stirring 2.1 ml (8.4 mmol) of tributylphosphine. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 18 h. The reaction mixture was diluted with benzene and the solution was washed twice with 5% NaOH (50 ml) followed by sat. aq. NH_4Cl. The solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 1.53 g (98%) of 3-(4-methoxyphenyl)propyl phenyl sulfide as colorless crystals. Mp 43–44 °C (hexane); IR (KBr) 2946, 1610, 1511, 1257, 1243, 1036, 818, 738, 690 cm^{-1}; ^{1}H NMR δ 1.93 (2H, quintet, J=7.4 Hz), 2.69 (2H, t, J=7.4 Hz), 2.90 (2H, t, J=7.4 Hz), 3.78 (3H, s), 6.82 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz), 7.14–7.18 (1H, m), 7.25–7.31 (4H, m).

A solution of the sulfide (1.37 g; 5.34 mmol) in 25 ml of CH_2Cl_2 was cooled to −40 °C. To this solution was added *m*-chloroperbenzoic acid (70%; 1.37 g; 5.61 mmol) and the reaction mixture was stirred for 1 h. The reaction was quenched with sat. aq. Na_2SO_3 and was diluted with CH_2Cl_2. This solution was washed twice with 5% NaOH (50 ml) followed by sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product was purified by silica gel column chromatography to afford 1.41 g (96%) of 3-(4-methoxyphenyl)propyl phenyl sulfoxide as colorless crystals. Mp 51.5–52.5 °C (AcOEt–hexane); IR (KBr) 2937, 1613, 1515, 1440, 1260, 1044 (SO), 1031, 1007, 818, 742, 688 cm^{-1}; ^{1}H NMR δ 1.91 (1H, m), 2.06 (1H, m), 2.68 (2H, m), 2.77 (2H, t, J=7.8 Hz), 3.78 (3H, s), 6.81 (2H, d, J=8.6 Hz), 7.04 (2H, d, J=8.6), 7.48 −7.52 (3H, m), 7.58–7.60 (2H, m). MS *m*/*z* (%) 274 (M$^+$, 0.9), 258 (3), 148 (100), 121 (43), 91(8), 77(14). Calcd for $C_{16}H_{18}O_2S$: M, 274.1025. Found: *m*/*z* 274.1015.

N-Chlorosuccinimide (NCS; 716 mg; 5.36 mmol) was added to a solution of the sulfoxide (1.36 g; 5 mmol) in 25 ml of carbon tetrachloride and the suspension was stirred at room temperature for 15 h. The precipitate (succinimide) was filtered off and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 1.49 g (97%) of 1-chloro-3-(4-methoxyphenyl)propyl phenyl sulfoxide **1a** (about 95:5 diastereomeric mixture). The product was recrystallized to give single diasteromer **1a** as colorless crystals. Mp 101–102.5 °C (AcOEt–hexane); IR (KBr) 2942, 1609, 1512, 1246, 1088, 1052 (SO), 1034, 817, 749, 685 cm^{-1}; ^{1}H NMR δ 1.87 (1H, m), 2.51 (1H, m), 2.73 (1H, dt, J=14.2, 7.8 Hz), 2.88–2.95 (1H, m), 3.79 (3H, s), 4.46 (1H, dd, J=10.2, 3.6 Hz), 6.83 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz), 7.49–7.57 (3H, m), 7.59–7.65 (2H, m). MS *m*/*z* (%) 308 (M$^+$, trace), 182 (28), 121 (100). Calcd for $C_{16}H_{17}ClO_2S$: M, 308.0638. Found: *m*/*z* 308.0637. Anal calcd: C, 62.23; H, 5.55; Cl, 11.48; S, 10.38. Found: C, 62.02; H, 5.38; Cl, 11.52, S, 10.48.

2.1.2. 1-Deuterio-1-chloro-3-(4-methoxyphenyl)propane (8b). A solution of *i*-PrMgCl (0.6 mmol) in THF was added to 2 ml of dry THF in a flame-dried flask at −80 °C under Ar atmosphere. After 10 min, a solution of **1a** (62 mg; 0.2 mmol) in THF (0.4 ml) was added dropwise to the solution at −80 °C. The reaction mixture was stirred for 10 min, then quenched by CD_3OD. The whole was extracted with $CHCl_3$ and the solution was dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **8b** (34 mg; 91%) as a colorless oil; IR (neat) 2935, 1612, 1512, 1246, 1178, 1037, 832 cm^{-1}; ^{1}H NMR δ 2.04 (2H, q, J=7.0 Hz), 2.72 (2H, t, J=7.0 Hz), 3.50 (1H, t, J=7.0 Hz), 3.79 (3H, s), 6.84 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz). MS *m*/*z* (%) 185 (M$^+$, 17), 122 (10), 121 (100). Calcd for $C_{10}H_{12}DClO$: M, 185.0717. Found: *m*/*z* 185.0723. When this reaction was quenched by sat. aq. NH_4Cl, **8a** was obtained as a colorless oil; IR (neat) 2934, 1613, 1513, 1301, 1245, 1178, 1037, 831 cm^{-1}; ^{1}H NMR δ 2.05 (2H, quintet, J=6.6 Hz), 2.72 (2H, t, J=6.6 Hz), 3.52 (2H, t, J=6.6 Hz), 3.79 (3H, s), 6.84 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz).

2.1.3. 1-(4-Methoxyphenyl)pentane (9a). A solution of EtMgCl (1 mmol) in THF was added to 1.8 ml of dry THF in a flame-dried flask at −80 °C under Ar atmosphere. After 10 min, a solution of **1a** (62 mg; 0.2 mmol) in THF (0.4 ml) was added dropwise to the solution at −80 °C. The reaction mixture was stirred and slowly allowed to warm to −30 °C for 110 min, then the reaction was quenched with sat. aq. NH_4Cl. The whole was extracted with $CHCl_3$ and the solution was dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford 43 mg (80%) of **9a** as a colorless oil; IR (neat) 2956, 2928, 2856, 1613, 1512, 1465, 1300, 1245, 1176, 1039, 829 cm^{-1}; ^{1}H NMR δ 0.89 (3H, t, J=7.0 Hz), 1.29–1.34 (4H, m), 1.58 (2H, quintet, J=7.7 Hz), 2.54 (2H, t, J=7.7 Hz), 3.78 (3H, s), 6.82 (2H, d, J=8.6 Hz), 7.09 (2H, d, J=8.6 Hz). MS *m*/*z* (%) 178 (M$^+$, 19), 121 (100). Calcd for $C_{12}H_{18}O$: M, 178.1359. Found: *m*/*z* 178.1356.

2.1.4. 1-(4-Methoxyphenyl)nonane (9b). Colorless oil; IR (neat) 2926, 2854, 1613, 1512, 1465, 1246, 1040 cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.26–1.30 (12H, m),

1.53–1.60 (2H, m), 2.54 (2H, t, *J*=7.8 Hz), 3.78 (3H, s), 6.82 (2H, d, *J*=8.6 Hz), 7.09 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 234 (M^+, 25), 122 (10), 121 (100). Calcd for $C_{16}H_{26}O$: M, 234.1982. Found: *m/z* 234.1985.

2.1.5. 1-(4-Methoxyphenyl)-4-methylpentane (9c). Colorless oil; IR (neat) 2953, 2931, 2868, 1613, 1512, 1465, 1246, 1176, 1039, 827 cm^{-1}; ^1H NMR δ 0.87 (6H, d, *J*=6.4 Hz), 1.18–1.23 (2H, m), 1.54–1.59 (3H, m), 2.52 (2H, t, *J*=7.7 Hz), 3.79 (3H, s), 6.82 (2H, d, *J*=8.6 Hz), 7.09 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 192 (M^+, 21), 121 (100). Calcd for $C_{13}H_{20}O$: M, 192.1517. Found: *m/z* 192.1513.

2.1.6. 1-(4-Methoxyphenyl)-4-methylnonane (9d). Colorless oil; IR (neat) 2927, 2856, 1614, 1513, 1463, 1246, 1040 cm^{-1}; ^1H NMR δ 0.84 (3H, d, *J*=6.8 Hz), 0.88 (3H, t, *J*=7.0 Hz), 1.05–1.41 (11H, m), 1.49–1.65 (2H, m), 2.47–2.57 (2H, m), 3.79 (3H, s), 6.82 (2H, d, *J*=8.6 Hz), 7.09 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 248 (M^+, 25), 121 (100). Calcd for $C_{17}H_{28}O$: M, 248.2139. Found: *m/z* 248.2147.

2.1.7. [3-(4-Methoxyphenyl)propyl]cyclopentane (9e). Colorless oil; IR (neat) 2946, 2857, 1613, 1512, 1245, 1039 cm^{-1}; ^1H NMR δ 1.04–1.09 (2H, m), 1.30–1.35 (2H, m), 1.47–1.62 (6H, m), 1.72–1.81 (3H, m), 2.54 (2H, t, *J*=7.6 Hz), 3.79 (3H, s), 6.82 (2H, d, *J*=8.6 Hz), 7.09 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 218 (M^+, 24), 122 (11), 121 (100). Calcd for $C_{15}H_{22}O$: M, 218.1670. Found: *m/z* 218.1679.

2.1.8. [3-(4-Methoxyphenyl)propyl]cyclohexane (9f). Colorless oil; IR (neat) 2922, 2850, 1613, 1512, 1447, 1246, 1176, 1039, 828 cm^{-1}; ^1H NMR δ 0.82–0.89 (2H, m), 1.11–1.24 (6H, m), 1.56–1.70 (7H, m), 2.51 (2H, t, *J*=7.8 Hz), 3.78 (3H, s), 6.82 (2H, d, *J*=8.6 Hz), 7.09 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 232 (M^+, 31), 121 (100). Calcd for $C_{16}H_{24}O$: M, 232.1826. Found: *m/z* 232.1826.

2.1.9. 1-(4-Methoxyphenyl)-4,4-dimethylpentane (9g). A solution of *i*-PrMgCl (0.5 mmol) in THF was added to 2 ml of dry THF in a flame-dried flask at −80 °C under Ar atmosphere. After 10 min, a solution of **1a** (62 mg; 0.2 mmol) in THF (0.4 ml) was added dropwise to the solution at −80 °C to give the magnesium carbenoid **7**. To the solution of the carbenoid **7** was added *t*-BuLi (1.6 mmol) dropwise with stirring. The reaction mixture was stirred and slowly allowed to warm to −30 °C for about 110 min, then the reaction was quenched with sat. aq. NH_4Cl. The whole was extracted with $CHCl_3$ and the solution was dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **9g** (23 mg; 55%) as a colorless oil; IR (neat) 2953, 1613, 1513, 1466, 1247, 1176, 1040 cm^{-1}; ^1H NMR δ 0.86 (9H, s), 1.20–1.23 (2H, m), 1.51–1.58 (2H, m), 2.51 (2H, t, *J*=7.8 Hz), 3.79 (3H, s), 6.83 (2H, d, *J*=8.6 Hz), 7.10 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 206 (M^+, 18), 121 (100). Calcd for $C_{14}H_{22}O$: M, 206.1668. Found: *m/z* 206.1666.

2.1.10. 1-Chloro-2,2-dimethyl-3-phenylpropyl phenyl sulfoxide (1c). A solution of 2,2-dimethyl-3-phenyl-1-propanol (500 mg; 3.04 mmol) and diphenyl dilsulfide (862 mg; 3.95 mmol) in 10 ml of THF was cooled in an ice bath. To this solution was added with stirring 1.06 ml (4.26 mmol) of tributylphosphine. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 25 h. The reaction mixture was diluted with benzene and the solution was washed twice with 5% NaOH followed by sat. aq. NH_4Cl. The solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 417 mg (54%) of 2,2-dimethyl-3-phenylpropyl phenyl sulfide as a colorless oil; IR (neat) 2959, 2925, 1583, 1480, 1467, 737, 702, 690 cm^{-1}; ^1H NMR δ 1.02 (6H, s), 2.68 (2H, s), 2.87 (2H, s), 7.13–7.27 (8H, m), 7.34 (2H, d, *J*=8.0 Hz). MS *m/z* (%) 256 (M^+, 72), 165 (100), 123 (33), 91 (92). Calcd for $C_{17}H_{20}S$: M, 256.1284. Found: *m/z* 256.1274.

A solution of the sulfide (400 mg; 1.56 mmol) in 8 ml of CH_2Cl_2 was cooled to 0 °C. To this solution was added *m*-chloroperbenzoic acid (70%; 403 mg; 1.64 mmol) and the reaction mixture was stirred for 20 min. The reaction was quenched with sat. aq. Na_2SO_3 and was diluted with CH_2Cl_2. This solution was washed twice with 5% NaOH followed by sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product was purified by silica gel column chromatography to afford 374 mg (88%) of 2,2-dimethyl-3-phenylpropyl phenyl sulfoxide as a colorless oil; IR (neat) 2961, 1443, 1083, 1042 (SO), 751, 706 cm^{-1}; ^1H NMR δ 1.21 (3H, s), 1.22 (3H, s), 2.51 (1H, d, *J*=13.5 Hz), 2.79 (1H, d, *J*=13.1 Hz), 2.84 (1H, d, *J*=13.1 Hz), 2.85 (1H, d, *J*=13.5 Hz), 7.19–7.30 (5H, m), 7.46 −7.53 (3H, m), 7.58–7.63 (2H, m). MS *m/z* (%) 272 (M^+, 2), 146 (32), 126 (20), 105 (20), 91 (100). Calcd for $C_{17}H_{20}OS$: M, 272.1235. Found: *m/z* 272.1239.

N-Chlorosuccinimide (NCS; 185 mg; 1.39 mmol) was added to a solution of the sulfoxide (360 mg; 1.32 mmol) in 2 ml of carbon tetrachloride and the suspension was stirred at room temperature for 15 h. The precipitate was filtered off and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 397 mg (98%) of **1c** as colorless crystals. Mp 79.5–80 °C (AcOEt–hexane); IR (KBr) 2973, 1494, 1468, 1444, 1090, 1057 (SO), 747, 703 cm^{-1}; ^1H NMR δ 1.31 (3H, s), 1.32 (3H, s), 2.81 (1H, d, *J*=13.5 Hz), 3.01 (1H, d, *J*=13.5 Hz), 4.10 (1H, s), 7.21–7.32 (5H, m), 7.51 (5H, s). MS *m/z* (%) 306 (M^+, trace), 145 (20), 126 (39), 91 (100). Calcd for $C_{17}H_{19}ClOS$: M, 306.0845. Found: *m/z* 306.0847. Anal calcd: C, 66.54; H, 6.24; Cl, 11.55; S, 10.45. Found: C, 66.63; H, 6.06; Cl, 11.51; S, 10.40.

2.1.11. 1-Chloro-2-methyl-2-phenylpropyl phenyl sulfoxide (1d). To a solution of dry DMF (5 ml) under Ar atmosphere was added potassium hydroxide (375 mg; 5.75 mmol) and benzenethiol (634 mg; 5.75 mmol). The reaction mixture was stirred for 15 min and was added 1-chloro-2-methyl-2-phenylpropane (843 mg; 5 mmol). The reaction mixture was refluxed for 20 h. The whole mixture was diluted with ether-benzene and the solution was washed twice with 5% NaOH followed by sat. aq. NH_4Cl. The solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 1.11 g (92%) of 2-methyl-2-phenylpropyl phenyl sulfide as a colorless oil; IR (neat) 2966, 1582, 1496, 1480, 1438, 1089, 1025, 738, 697 cm^{-1}; ^1H NMR δ 1.47 (6H, s), 3.26 (2H, s), 7.10–7.14 (1H, m),

7.19–7.23 (3H, m), 7.25–7.27 (2H, m), 7.29–7.33 (2H, m), 7.37–7.39 (2H, m). MS *m/z* (%) 242 (M^+, 28), 124 (25), 119 (100), 91 (38). Calcd for $C_{16}H_{18}S$: M, 242.1127. Found: *m/z* 242.1123.

A solution of the sulfide (1.1 g; 4.54 mmol) in 25 ml of CH_2Cl_2 was cooled to 0 °C. To this solution was added *m*-chloroperbenzoic acid (70%; 1.12 g; 4.77 mmol) and the reaction mixture was stirred for 20 min. The reaction was quenched with sat. aq. Na_2SO_3 and was diluted with CH_2Cl_2. This solution was washed twice with 5% NaOH followed by sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product was purified by silica gel column chromatography to afford 1.1 g (94%) of 2-methyl-2-phenylpropyl phenyl sulfoxide as a colorless oil; IR (neat) 3057, 2966, 1497, 1475, 1443, 1083, 1041 (SO), 752, 703 cm^{-1}; ^1H NMR δ 1.56 (3H, s), 1.74 (3H, s), 3.00 (1H, d, *J*=13.4 Hz), 3.11 (1H, d, *J*=13.4 Hz), 7.23–7.26 (1H, m), 7.34–7.51 (9H, m). MS *m/z* (%) 258 (M^+, trace), 133 (33), 132 (20), 119 (18), 91 (100). Calcd for $C_{16}H_{18}OS$: M, 258.1079. Found: *m/z* 258.1074.

N-Chlorosuccinimide (583 mg; 4.37 mmol) was added to a solution of the sulfoxide (1.1 g; 4.16 mmol) in 20 ml of carbon tetrachloride and the suspension was stirred at room temperature for 20 h. The precipitate was filtered off and the solvent was evaporated. The residue was purified by silica gel column chromatography to afford 1.23 g (99%) of **1d** as colorless crystals. Mp 100–101 °C (AcOEt–hexane); IR (KBr) 3059, 2979, 1496, 1475, 1444, 1088, 1055 (SO), 748, 700 cm^{-1}; ^1H NMR δ 1.58 (3H, s), 1.75 (3H, s), 4.58 (1H, s), 7.33–7.37 (3H, m), 7.42–7.50 (7H, m). MS *m/z* (%) 292 (M^+, trace), 167 (84), 131 (100), 126 (40), 91 (92), 89 (29). Calcd for $C_{16}H_{17}ClOS$: M, 292.0689. Found: *m/z* 292.0684. Anal calcd: C, 65.63; H, 5.85; Cl, 12.11; S, 10.95. Found: C, 65.66; H, 5.78; Cl, 12.05, S, 10.89.

2.1.12. 4-(4-Methoxyphenyl)-1-phenyl-1-butene (5a). A solution of *i*-PrMgCl (0.56 mmol) in THF was added to 1.8 ml of dry THF in a flame-dried flask at −65 °C under Ar atmosphere. After 10 min, a solution of **1a** (62 mg; 0.2 mmol) in THF (0.3 ml) was added dropwise to the solution at −65 °C to give the magnesium carbenoid **7**. Benzyl phenyl sulfone (crystals; 139 mg; 0.6 mmol) was added to a solution of *n*-BuLi (0.72 mmol) in 5 ml of dry THF in another flame-dried flask at 0 °C under Ar atmosphere to give a clear yellow solution, and this solution was cooled to −65 °C. This solution was added to the solution of carbenoid **7** via a canula. The reaction mixture was stirred and slowly allowed to warm to −40 °C for about 3.5 h, then the reaction was quenched with sat. aq. NH_4Cl. The whole was extracted with $CHCl_3$ and the solution was dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford 45 mg (93%) of **5a** (a mixture of two geometrical isomers; the ratio is about *E*/*Z*=1:2) as a colorless oil; IR (neat) 3024, 3007, 2932, 2834, 1612, 1512, 1246, 1177, 1037, 826, 699 cm^{-1}; ^1H NMR δ 2.49 (0.7H, q, *J*=7.4 Hz), 2.63 (1.3H q, *J*=7.3 Hz), 2.69–2.75 (2H, m), 3.78 (2H, s), 3.79 (1H, s), 5.69 (0.65H dt, *J*=11.2, 7.1 Hz), 6.24 (0.35H, dt, *J*=15.8, 6.8 Hz), 6.40 (0.35H, d, *J*=15.8 Hz), 6.43 (0.65H, d, *J*=11.2 Hz), 6.81–6.85 (2H, m), 7.08–7.14 (2H, m), 7.17–7.33 (5H, m). MS *m/z* (%) 238 (M^+, 5), 122 (9), 121 (100). Calcd for $C_{17}H_{18}O$: M, 238.1357. Found: *m/z* 238.1371.

2.1.13. 4-(4-Methoxyphenyl)-1-(1-naphthyl)-1-butene (5b). Colorless oil (a mixture of two geometrical isomers; the ratio is about *E*/*Z*=1:4); IR (neat) 3005, 2932, 1611, 1511, 1246, 1177, 1036, 804, 782 cm^{-1}; ^1H NMR δ 2.44 (1.6H, m), 2.62 (0.4H, m), 2.65 (1.6H, t, *J*=7.6 Hz), 2.81 (0.4H, t, *J*=7.6 Hz), 3.75 (2.4H, s), 3.79 (0.6H, s), 5.95 (0.8H, dt, *J*=11.6, 7.3 Hz), 6.23 (0.2H, dt, *J*=15.6, 7.0 Hz), 6.74–7.24 (6H, m), 7.38–7.52 (3H, m), 7.72–8.02 (3H, m). MS *m/z* (%) 288 (M^+, 18), 167 (18), 165 (12), 121 (100). Calcd for $C_{21}H_{20}O$: M, 288.1513. Found: *m/z*288.1514.

2.1.14. 5-(4-Methoxyphenyl)-2-phenyl-2-pentene (5c). Colorless oil (a mixture of two geometrical isomers; the ratio is about *E*/*Z*=1:2); IR (neat) 2932, 2853, 1611, 1512, 1246, 1177, 1037, 820, 761, 701 cm^{-1}; ^1H NMR δ 1.97 (1H, s), 2.01 (2H, d, *J*=1.2 Hz), 2.25 (1.3H, q, *J*=7.4 Hz), 2.48 (0.7H, q, *J*=7.5 Hz), 2.58 (1.3H, t, *J*=7.4 Hz), 2.70 (0.7H, t, *J*=7.4 Hz), 3.77 (2H, s), 3.79 (1H, s), 5.48 (0.65H, dt, *J*=7.3, 1.2 Hz), 5.80 (0.35H, dt, *J*=7.4, 1.3 Hz), 6.77–6.85 (2H, m), 7.00–7.03 (1.3H, m), 7.10–7.15 (2H, m), 7.20–7.36 (3.7H, m). MS *m/z* (%) 252 (M^+, 8), 131 (10), 121 (100), 91 (8). Calcd for $C_{18}H_{20}O$: M, 252.1513. Found: *m/z* 252.1511.

2.1.15. 4-(4-Methoxyphenyl)-1,1-diphenyl-1-butene (5d). Colorless crystals. Mp 101–102 °C (hexane); IR (KBr) 2920, 2832, 1609, 1508, 1243, 1227, 1032, 768, 707 cm^{-1}; ^1H NMR δ 2.39 (2H, q, *J*=7.6 Hz), 2.68 (2H, t, *J*=7.6 Hz), 3.77 (3H, s), 6.09 (1H, t, *J*=7.6 Hz), 6.80 (2H, d, *J*=8.6 Hz), 7.04 (2H, d, *J*=8.6 Hz), 7.07–7.09 (2H, m), 7.18–7.34 (8H, m). MS *m/z* (%) 314 (M^+, 10), 193 (42), 178 (9) 121 (100), 91 (9). Calcd for $C_{23}H_{22}O$: M, 314.1669. Found: *m/z* 314.1665. Anal calcd: C, 87.86; H, 7.05. Found: C, 87.65; H, 6.99.

2.1.16. 5-(4-Methoxyphenyl)-2-pentene (5e). Colorless oil (a mixture of two geometrical isomers; the ratio is about 2:3); IR (neat) 3010, 2933, 1613, 1513, 1300, 1246, 1177, 1039, 824 cm^{-1}; ^1H NMR δ 1.55–1.56 (1.8H, m), 1.63–1.65 (1.2H, m), 2.23–2.35 (2H, m), 2.58–2.62 (2H, m), 3.78 (3H, s), 5.39–5.49 (2H, m), 6.81–6.83 (2H, m), 7.08–7.12 (2H, m). MS *m/z* (%) 176 (M^+, 9), 122 (10), 121 (100). Calcd for $C_{12}H_{16}O$: M, 176.1120. Found: *m/z* 176.1196.

2.1.17. 1-(4-Methoxyphenyl)-3-octene (5f). Colorless oil (a mixture of two geometrical isomers; the ratio is about 2:3); IR (neat) 3004, 2928, 1612, 1512, 1300, 1246, 1177, 1039, 824 cm^{-1}; ^1H NMR δ 0.86–0.89 (3H, m), 1.23–1.34 (4H, m), 1.97–2.00 (2H, m), 2.24–2.34 (2H, m), 2.58–2.61 (2H, m), 3.78 (3H, s), 5.37–5.43 (2H, m), 6.81–6.83 (2H, m), 7.08–7.11 (2H, m). MS *m/z* (%) 218 (M^+, 6), 122 (9), 121 (100). Calcd for $C_{15}H_{22}O$: M, 218.1670. Found: *m/z* 218.1670.

2.1.18. 1-(4-Methoxyphenyl)-3-tridecene (5g). Colorless oil (a mixture of two geometrical isomers; the ratio is about 2:3); IR (neat) 3003, 2924, 2853, 1613, 1512, 1464, 1300, 1246, 1176, 1040, 823 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7.0 Hz), 1.25–1.31 (14H, m), 1.94–1.98 (2H, m), 2.24–2.36 (2H, m), 2.58–2.61 (2H, m), 3.78 (3H, s), 5.34–5.43

(2H, m), 6.81–6.83 (2H, m), 7.08–7.11 (2H, m). MS *m/z* (%) 288 (M^+, 5), 122 (9), 121 (100). Calcd for $C_{20}H_{32}O$: M, 288.2451. Found: *m/z* 288.2460.

2.1.19. 5-(4-Methoxyphenyl)-2-methyl-2-pentene (5h). Colorless oil; IR (neat) 2927, 2855, 1612, 1509, 1300, 1245, 1177, 1039, 827 cm^{-1}; ^1H NMR δ 1.56 (3H, s), 1.68 (3H, s), 2.26 (2H, q, *J*=7.6 Hz), 2.57 (2H, t, *J*=7.6 Hz), 3.79 (3H, s), 5.16 (1H, m), 6.82 (2H, d, *J*=8.6 Hz), 7.10 (2H, d, *J*=8.6 Hz). MS *m/z* (%) 190 (M^+, 10), 121 (100), 91 (5). Calcd for $C_{13}H_{18}O$: M, 190.1355. Found: *m/z* 190.1354.

2.1.20. 1-Cyclohexyl-2-phenyl-1-ethene (5i). Colorless oil (a mixture of two geometrical isomers, the ratio is about *E*/*Z*=1:2); IR (neat) 3025, 3002, 2924, 2850, 1492, 1447, 963, 696 cm^{-1}; ^1H NMR δ 1.13–1.34 (5H, m), 1.65–1.82 (5H, m), 2.13 (0.35H, m), 2.58 (0.65H, m), 5.48 (0.65H, dd, *J*=11.6, 10.4 Hz), 6.18 (0.35H, dd, *J*=15.9, 7.1 Hz), 6.30–6.36 (1H, m), 7.16–7.35 (5H, m). MS *m/z* (%) 186 (M^+, 34), 143 (10), 129 (25), 115 (15), 104 (100), 91 (15). Calcd for $C_{14}H_{18}$: M, 186.1408. Found: *m/z* 186.1414.

2.1.21. 1-Cyclohexyl-2-phenyl-1-pentene (5j). Colorless oil (a mixture of two geometrical isomers, the ratio is about *E*/*Z*=2:3); IR (neat) 3056, 3022, 2921, 2849, 1599, 1493, 1446, 1371, 1026, 894, 757, 699 cm^{-1}; ^1H NMR δ 1.04–1.43 (5H, m), 1.58–1.76 (5H, m), 1.99–2.04 (3.6H, m), 2.31–2.38 (0.4H, m), 5.27 (0.6H, d, *J*=10.1 Hz), 5.62 (0.4H, d, *J*=8.9 Hz), 7.16–7.39 (5H, m). MS *m/z* (%) 200 (M^+, 61), 185 (20), 157 (20), 143 (35), 129 (37), 118 (100), 105 (15), 91 (19). Calcd for $C_{15}H_{20}$: M, 200.1563. Found: *m/z* 200.1558.

2.1.22. 1-Cyclohexyl-4-(4-methoxyphenyl)-1-butene (5k). Colorless oil (a mixture of two geometrical isomers; the ratio is about 2:3); IR (neat) 2998, 2922, 2849, 1613, 1513, 1447, 1300, 1245, 1177, 1040, 969, 823 cm^{-1}; ^1H NMR δ 0.96–1.29 (5H, m), 1.48–1.52 (1H, m), 1.61–1.72 (4H, m), 1.86–1.91 (0.4H, m), 2.14–2.21 (0.6H, m), 2.22–2.27 (0.8H, m), 2.31–2.35 (1.2H, m), 2.60 (2H, t, *J*=7.6 Hz), 3.78 (3H, s), 5.19–5.42 (2H, m), 6.81–6.84 (2H, m), 7.08–7.12 (2H, m). MS *m/z* (%) 244 (M^+, 8), 122 (10), 121, (100). Calcd for $C_{17}H_{24}O$: M, 244.1826. Found: *m/z* 244.1830.

2.1.23. (*Z*)-3,3-Dimethyl-1,4-diphenyl-1-butene (5l). Colorless oil; IR (neat) 3027, 2960, 2926, 1600, 1492, 1470, 1452, 721, 699 cm^{-1}; ^1H NMR δ 0.90 (6H, s), 2.62 (2H, s), 5.50 (1H, d, *J*=12.5 Hz), 6.47 (1H, d, *J*=12.5 Hz), 6.86 (2H, d, *J*=6.5 Hz), 7.14–7.29 (8H, m). MS *m/z* (%) 236 (M^+, trace), 145 (100), 130 (7), 117 (11), 91 (21). Calcd for $C_{18}H_{20}$: M, 236.1564. Found: *m/z* 236.1572.

2.1.24. 2-Methyl-1-phenyl-1-propene (13). Colorless oil; IR (neat) 3022, 2969, 2929, 1489, 1441, 1376, 740, 698 cm^{-1}; ^1H NMR δ 1.86 (3H, s), 1.90 (3H, s), 6.27 (1H, s), 7.16–7.32 (5H, m). MS *m/z* (%) 132 (M^+, 82) 117 (100), 115 (33), 91 (32). Calcd for $C_{10}H_{12}$: M, 132.0938. Found: *m/z* 132.0938.

Acknowledgements

We thank Mr Yoshihisa Konishi for his assistance. This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan to promote a multi-disciplinary research project, which is gratefully acknowledged.

References and notes

1. Mathieu, J.; Weill-Raynal, J. *Formation of C–C Bonds; Introduction of a Functional Carbon Atom*; Georg Thieme: Stuttgart, 1973. (b) Mathieu, J.; Weill-Raynal, J. *Formation of C–C Bond; Introduction of a Carbon Chain or an Aromatic Ring*; Georg Thieme: Stuttgart, 1975. (c) Mathieu, J.; Mathieu, J., J. *Formation of C–C Bonds; Introduction of an α-Functional Carbon Chain*; Georg Thieme: Stuttgart, 1979.
2. Kirmse, W. *Carbene Chemistry*; Academic: New York, 1971. (b) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.
3. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (d) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145. (e) Dorwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999. (f) Marek, I. *Tetrahedron* **2002**, *58*, 9463. (g) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477.
4. Satoh, T.; Takano, K.; Someya, H.; Matsuda, K. *Tetrahedron Lett.* **1995**, *36*, 7097. (b) Satoh, T.; Takano, K. *Tetrahedron* **1996**, *52*, 2349.
5. Satoh, T.; Kurihara, T.; Fujita, K. *Tetrahedron* **2001**, *57*, 5369. (b) Satoh, T.; Saito, S. *Tetrahedron Lett.* **2004**, *45*, 347.
6. Satoh, T. *J. Syn. Org. Chem. Jpn* **1996**, *54*, 481. (b) Satoh, T. *J. Syn. Org. Chem. Jpn* **2003**, *61*, 98.
7. Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557. (b) Satoh, T.; Sakamoto, T.; Watanabe, M. *Tetrahedron Lett.* **2002**, *43*, 2043. (c) Satoh, T.; Sakamoto, T.; Watanabe, M.; Takano, K. *Chem. Pharm. Bull.* **2003**, *51*, 966.
8. A similar study for a generation of magnesium carbenoids has independently been reported: (a) Hoffmann, R. W.; Nell, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 338. (b) Hoffmann, R. W.; Holzer, B.; Knopff, O.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3072.
9. Fronza, G.; Fuganti, C.; Serra, S.; Cisero, M.; Koziet, J. *J. Agric. Food Chem.* **2002**, *50*, 2748.
10. The alkylation of a Grignard reagent with magnesium carbenoids has been known: (a) Hahn, R.; Tompkins, J. *Tetrahedron Lett.* **1990**, *31*, 937. (b) Hoffmann, R. W.; Knopff, O.; Kusche, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1462. (c) Holzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732.
11. The reaction of lithium α-sulfonyl carbanions with magnesium carbenoids generated from chloro iodoalkanes is known: De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133.
12. Satoh, T.; Takano, K. *Tetrahedron* **1996**, *52*, 2349.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5461–5469

Stabilization of DNA duplexes by covalently-linked peptides

Vicente Marchán, Laurent Debéthune, Enrique Pedroso and Anna Grandas*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1-11, E-08028 Barcelona, Spain

Received 27 January 2004; revised 24 March 2004; accepted 20 April 2004

Abstract—The hybridization properties of various peptide–oligonucleotide hybrids were assessed from UV thermal denaturation experiments. Analysis of these and other published data suggests that peptide chains, both hydrophobic and positively charged, generally have a clear stabilizing effect on short-chain oligonucleotide duplexes.

1. Introduction

The availability of well-established methodologies for the preparation of oligonucleotides, both modified and unmodified, has made it possible to develop new therapeutic principles based on the remarkable capacity of nucleic acids for specific recognition. Oligonucleotides can be used as antisense drugs[1] or ribozymes[2] when targeted at single-stranded chains, while the target in the antigene strategy[3] is double-stranded DNA.

One of the alternatives assayed to obtain oligonucleotide analogues suitable for use as antisense drugs is to link a peptide chain to either the 3′ or the 5′ end of the oligonucleotide.[4] This modification has been shown to have beneficial effects such as rendering the oligonucleotide more resistant to exonuclease degradation[5–10] or facilitating its penetration through cell membranes.[11,12] Linking cationic peptides to oligonucleotide chains has also been described as accelerating duplex formation.[13] With respect to the contribution of peptides to the stabilization of duplexes formed by peptide–oligonucleotide conjugates and their complementary targets, the most generally accepted hypothesis, often ascertained by experimental data, is that the presence of positive charges in the peptide chain is the major duplex stabilizing factor. It is also worth mentioning that peptide–oligonucleotide conjugates have been shown not to hybridize to complementary RNA chains with the same affinity as that shown for DNA. However, the results described are contradictory.[14,15]

Here, we wish to report on the evaluation of the stability of the duplexes formed by different peptide–oligonucleotide conjugates[16–18] and their complementary oligodeoxynucleotide chains using UV melting experiments. We will also discuss, on the basis of all of the reported data, whether peptide sequences can enhance the hybridization properties of peptide–oligonucleotide conjugates.

We have investigated hybrids with both nonself- and self-complementary oligonucleotide moieties, which means that either one or two peptide chains, respectively, were attached to the ends of the duplex. Concerning the choice of the peptides, our goal was to examine the effect of peptide chains with different sequences. To the best of our knowledge, only in one case the influence of the amino acid composition on the stability of the duplex has been systematically evaluated.[19] The authors showed, in this study, that replacement of alanines by positively charged residues (lysine, ornithine, arginine or histidine) in a peptide covalently-linked to an 8-mer oligonucleotide had a greater stabilizing effect than the introduction of hydrophobic residues such as tryptophan. However, other data available in the literature suggest that hydrophobic peptides can also be stabilizing.[20–22] The purpose of this work was not to undertake a systematic study including all the natural amino acids, but to add new data to the existing ones that may be helpful not to rule out any possibility when designing peptide sequences with the aim of stabilizing oligonucleotide duplexes.

2. Results

This study was carried out using synthetic oligodeoxynucleotides to which we attached different peptide sequences. Most of the conjugates had the structure of the so-called nucleopeptides, with a phosphate diester group linked to the side chain of a hydroxylated amino acid (homoserine or tyrosine) and one of the ends of the oligonucleotide (all the nucleopeptides had a

Keywords: Nucleopeptide; Peptide–oligonucleotide conjugate; Duplex stability; Hybridization; Melting temperature.
* Corresponding author. Tel.: +34-934021263; fax: +34-933397878; e-mail address: anna.grandas@ub.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.053

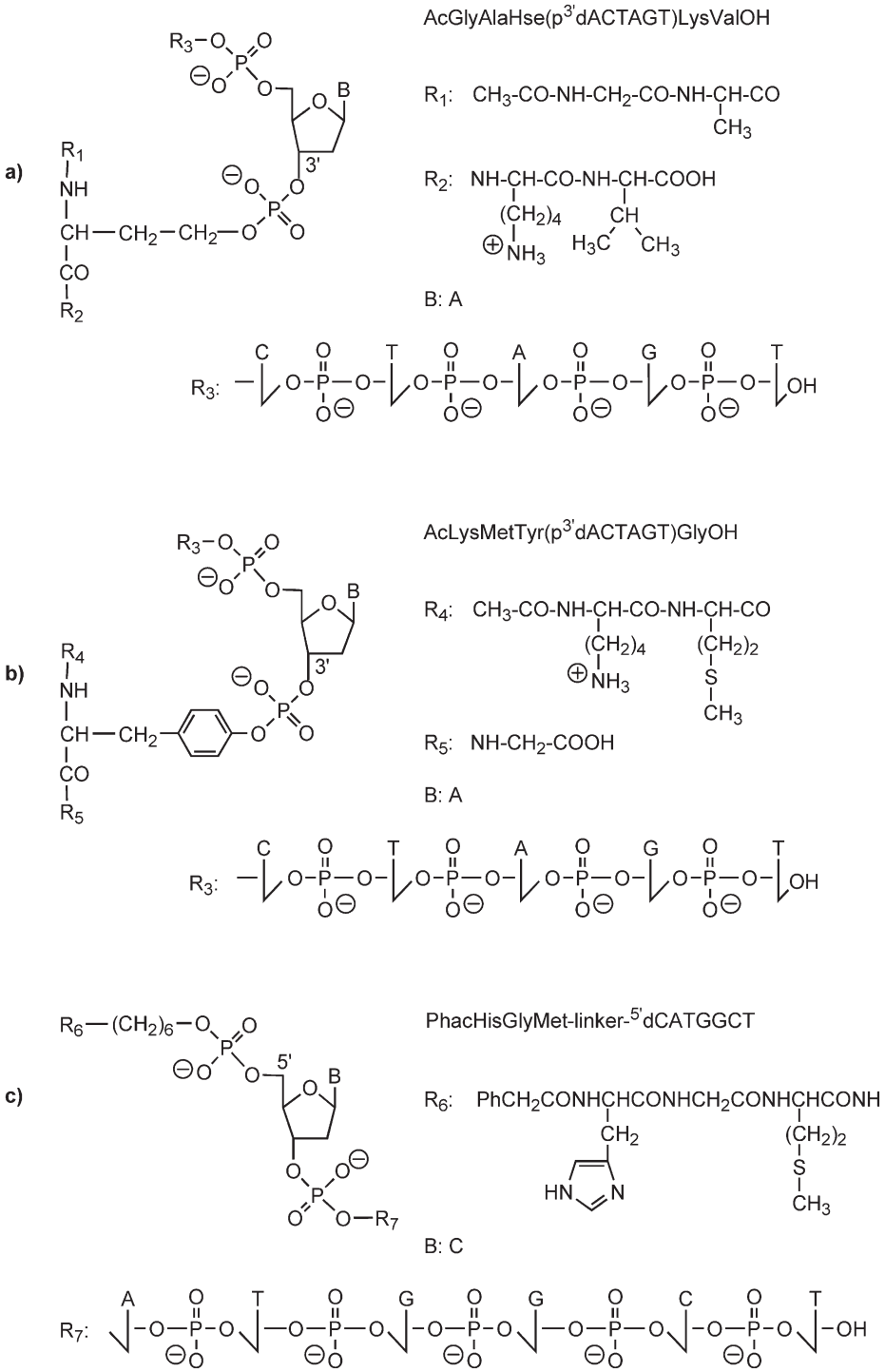


Figure 1. Structures of the nucleopeptides and peptide–oligonucleotide conjugates studied. (a) General structure of nucleopeptides with homoserine-$^{3'}$oligonucleotide phosphodiester linkages and details for one particular hybrid; (b) general structure of nucleopeptides with tyrosine-$^{3'}$oligonucleotide phosphodiester linkages and details for one particular hybrid; (c) general structure of the peptide–oligonucleotide conjugates and details for one particular hybrid.

peptide-$^{3'}$oligonucleotide linkage, in this case). In the other conjugates an aminoalkyl group linked the C-terminal amino acid and the 5′ end of the oligonucleotide. Structures of products corresponding to each of the different types of hybrids are shown in Figure 1. To help the reader follow the discussion, schemes indicating whether the duplexes were linked to one or two peptides have been included in the tables.

Both nucleopeptides and peptide–oligonucleotide conjugates were assembled on a solid matrix following stepwise procedures.[16–18] The synthesis schemes are outlined in Figure 2. All the compounds were thoroughly purified, and their identity was confirmed by electrospray or MALDI-TOF mass spectrometric analysis. The amino acid content after acid hydrolysis and/or the nucleoside composition

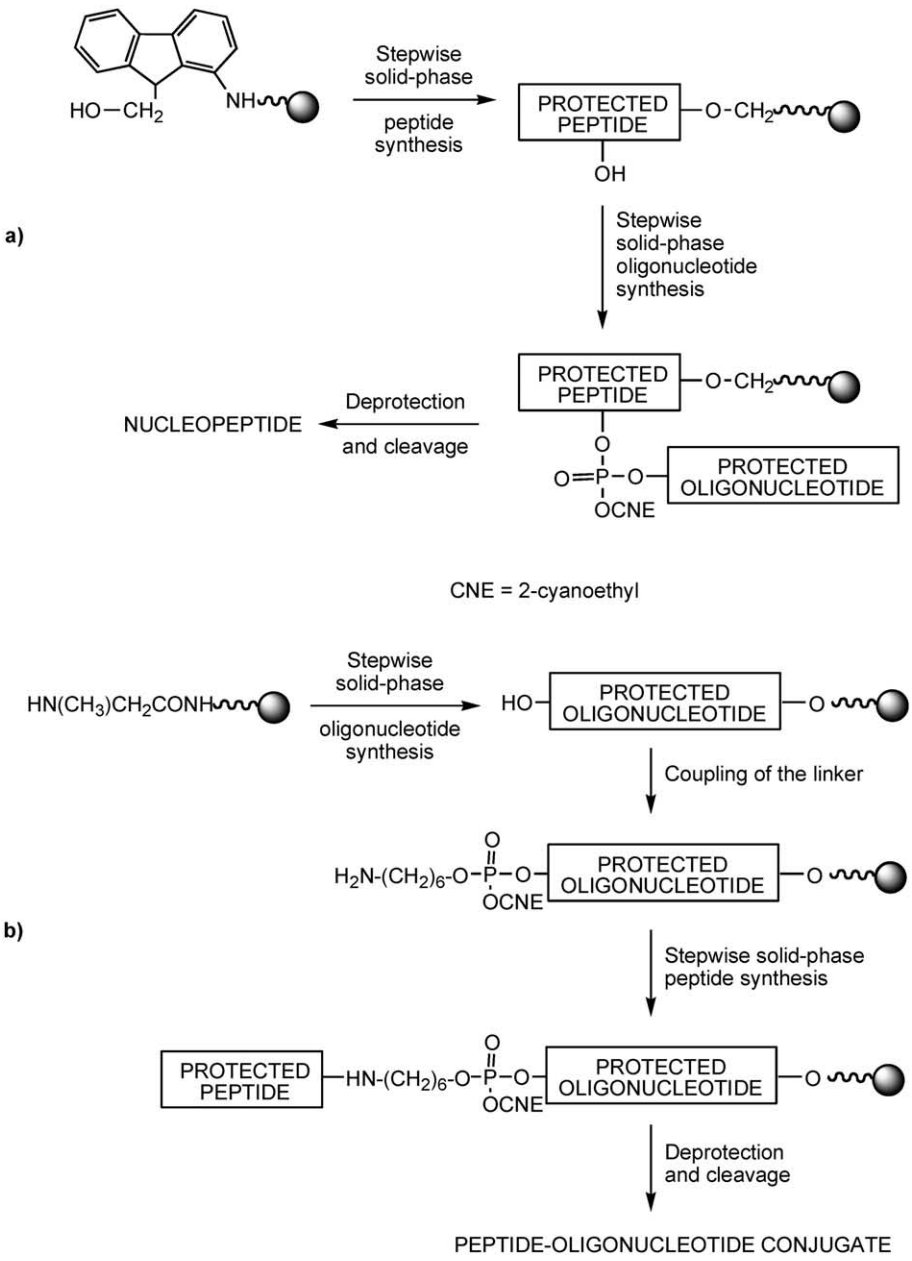


Figure 2. Synthesis schemes for the preparation of nucleopeptides (a) and peptide–oligonucleotide conjugates (b).

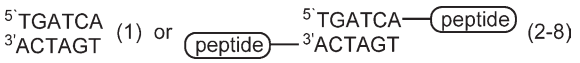
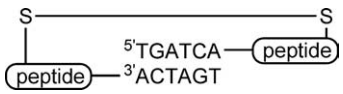
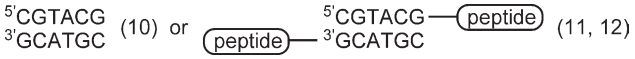
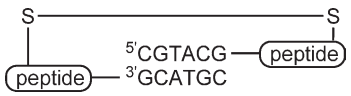
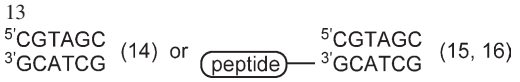
after enzymatic digestion also confirmed that the target product had been obtained.

There are no accepted standard conditions for thermal denaturation experiments. In the studies with peptide–oligonucleotide conjugates described in the literature, the samples have been dissolved in a variety of buffers such as Tris·HCl (*tris*=*tris*(hydroxymethyl)aminomethane), phosphate, acetate or pipes (pipes=piperazine-*N*,*N*′-bis-[2-ethanesulfonic acid]), with duplex concentrations ranging between 2 and 6 μM. Duplex denaturation was most often studied at pH values ranging from 6 to 7.5 in the presence of 100 mM NaCl. In spite of this variety of experimental conditions, a comparison is possible, and conclusions on general trends can be inferred from the reported values. In the present study, UV melting experiments were carried out with 2 μM duplex solutions in 10 mM pipes, 100 mM NaCl and 10 mM $MgCl_2$, pH=7 buffer, these conditions being kept in all experiments for purposes of comparison.

Magnesium was added to render the experimental conditions closer to physiological media, but this option may be subject to controversy. It has the advantage of rendering duplexes more stable, so that the formation and subsequent denaturation of short duplexes can be observed. The disadvantage is that Mg^{2+} cations may interfere with the DNA–[cationic amino acid] interaction, and thus, to some extent, mask the stabilizing effect of these amino acid side chains.

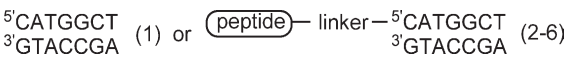
The results of the different thermal denaturation experiments have been assembled in three tables. The data from the experiments with short duplexes (6/7-mer) have been

Table 1. Melting temperatures of the duplexes formed by nucleopeptides with 6-mer oligonucleotide chains either self-complementary (entries 1–13) or nonself-complementary (entries 14–19)

Oligonucleotide or nucleopeptide duplexes (2 μM)[a]		T_m (°C)	ΔT_m
			
1	$^{3'}$dACTAGT	7.1	Par
2	PhacAlaHse(p$^{3'}$dACTAGT)GlyArgValOH[b]	9.2	+2.1
3	AcLysMetTyr(p$^{3'}$dACTAGT)GlyOH	10.0	+2.9
4	AcGlyAlaHse(p$^{3'}$dACTAGT)LysValOH	11.6	+4.5
5	AcGlyAlaHse(p$^{3'}$dACTAGT)HisValOH	7.2	+0.1
6	PhacPheValHse(p$^{3'}$dACTAGT)GlyOH[b]	11.8	+4.7
7	AcTrpValHse(p$^{3'}$dACTAGT)GlyOH	11.0	+3.9
8	HTrpValHse(p$^{3'}$dACTAGT)GlyOH	11.2	+4.1
			
9	{AcCysGlyTyr(p$^{3'}$dACTAGT)ProOH}$_2$[S–S][c]	40.0	+32.9
			
10	$^{3'}$dGCATGC	21.6	Par
11	AcLysTrpLysHse(p$^{3'}$dGCATGC)AlaOH	28.5	+6.9
12	AcAlaTrpAlaHse(p$^{3'}$dGCATGC)AlaOH	28.8	+7.2
			
13	{AcCysGlyAlaHse(p$^{3'}$dGCATGC)AlaOH}$_2$[S–S][c]	50.1	+28.5
			
14	$^{3'}$dGCATCG/$^{5'}$dCGTAGC	17.4	Par
15	AcLysTrpLysHse(p$^{3'}$dGCATCG)AlaOH/$^{5'}$dCGTAGC	21.3	+3.9
16	AcAlaTrpAlaHse(p$^{3'}$dGCATCG)AlaOH/$^{5'}$dCGTAGC	18.8	+1.8

[a] When the oligonucleotide is self-complementary only one chain is indicated, and the two chains of the duplex are shown if the oligonucleotide is nonself-complementary. Sequences are always written in the same direction for purposes of comparison. All nucleopeptides were obtained as C-terminal acids. The N-terminal amine was free in nucleopeptide of entry 8 and acetylated (Ac) in most of the others.
[b] Phac: phenylacetyl.
[c] These structures correspond to the disulfide dimers.

Table 2. Melting temperatures of duplexes formed by a nonself-complementary peptide–oligonucleotide conjugate

Oligonucleotide or conjugate duplexes[a] (2 μM)		T_m (°C)	ΔT_m
			
1	$^{5'}$dCATGGCT/$^{3'}$dGTACCGA	29.6	Par
2	HLinker-$^{5'}$dCATGGCT/$^{3'}$dGTACCGA[b]	30.0	+0.4
3	HGlyMet-linker-$^{5'}$dCATGGCT/$^{3'}$dGTACCGA	33.3	+3.7
4	BocHisGlyMet-linker-$^{5'}$dCATGGCT/$^{3'}$dGTACCGA[c]	31.5	+1.9
5	PhacHisGlyMet-linker-$^{5'}$dCATGGCT/$^{3'}$dGTACCGA[d]	34.1	+4.5
6	PhacHisGlyMet(O)-linker-$^{5'}$dCATGGCT/$^{3'}$dGTACCGA[d]	34.2	+4.6

[a] Sequences are always written in the same direction for purposes of comparison.
[b] Covalent linkage ('linker') between the C-terminal carboxyl of the peptide and the 5′ end of the oligonucleotide: –NH–$(CH_2)_6$–O–P(O)(O^-)–$^{5'}$O–. Entry 2: the N-terminal of the linker is protonated (H_3N^+–CH_2–···).
[c] Boc: *tert*-butoxycarbonyl.
[d] Phac: phenylacetyl.

separated in two different Tables, 1 and 2, only on the basis of their different structure (3′-nucleopeptides and 5′-conjugates, respectively). Table 3 illustrates the effect of peptide chains on the stability of 15- and 16-mer duplexes. Some of the melting profiles are shown in Section 5 (Figs 3–5).

Table 1 lists the melting temperatures of 6-mer oligonucleotide duplexes. Entries 1–9 correspond to the duplexes formed by the self-complementary oligonucleotide $^{5'}$TGATCA and the analogs containing this sequence, entries 10–13 to those of the self-complementary oligonucleotide $^{5'}$CGTACG, and entries 14–16 collect the data of the duplexes formed by the oligonucleotides $^{5'}$CGTAGC/$^{3'}$GCATCG.

The data in Table 2 reflect how the stability of a 7-mer duplex, $^{5'}$CATGGCT/$^{3'}$GTACCCGA is modulated by the attachment of a linker and the subsequent elongation of a tripeptide.

Finally, in Table 3, we have assembled the results of the thermal denaturation experiments carried out with

Table 3. Melting temperatures of the duplexes with 15–16 nucleobases

	Oligonucleotide or conjugate duplexes[a] (2 μM)	T_m (°C)
	(1, 3) or peptide (2, 4-6)	
1	$^{5'}$dTATAAACAATGAGACA/$^{3'}$dATATTTGTTACTCTGT[b]	54.5
2	$^{5'}$dTATAAACAATGAGACA/BocHse($p^{3'}$dATATTTGTTACTCTGT)$(Lys)_5$OH[c]	54.5
3	$^{5'}$dAAAGTCTTTTAGATC/$^{3'}$dTTTCAGAAAATCTAG	50.0
4	$^{5'}$dAAAGTCTTTTAGATC/AcTyr($p^{3'}$dTTTCAGAAAATCTAG)AlaPheGlyOH	49.0
5	$^{5'}$dAAAGTCTTTTAGATC/AcTyr($p^{3'}$dTTTCAGAAAATCTAG)LeuAspProArgIleThrValOH	48.6
6	$^{5'}$dAAAGTCTTTTAGATC/HIleAlaLeuGlyThrSerLysLeuAsnTyr($p^{3'}$dTTTCAGAAAATCTAG)LeuAspProOH	48.1

[a] Sequences are always written in the same direction for purposes of comparison. Nucleopeptides were obtained as C-terminal acids, and the N-terminal amine was either acetylated (Ac) or free (H).
[b] T_m in the absence of Mg^{2+}: 48 °C.
[c] T_m in the absence of Mg^{2+}: 50 °C. Boc: *tert*-butoxycarbonyl.

oligonucleotides and nucleopeptides forming 15- and 16-mer duplexes.

3. Discussion

The T_m values of the self-complementary $^{5'}$TGATCA duplexes were very low, as expected for a 6-mer with only two G·C base pairs. Duplexes with the self-complementary $^{5'}$CGTAGC sequence and with the $^{5'}$CGTAGC/$^{3'}$GCATCG pairing region were much more stable, as shows the comparison between the values stated in entries 1, 10 and 14 of Table 1 for the unmodified oligonucleotides. Curiously, the self-complementary unmodified oligonucleotide (entry 10) forms a duplex more stable than the nonself-complementary sequence (entry 14).

Quick inspection on the T_m and ΔT_m values included in Table 1 shows that, in all cases, the covalent linkage of a peptide to one or the two ends of the duplex did have a stabilizing effect (cf. entries 2–8 with 1, 11–12 with 10, and 15–16 with 14). The cysteine-containing nucleopeptides were a special case. These nucleopeptides (Table 1, entries 9 and 13) were obtained as dimers, with the two cysteine residues linked through a disulfide bond. Their T_m values were much higher than those of the unmodified oligonucleotides and those of the other members of their series. The covalent linkage between the two peptide units, which restricts the conformational mobility of the duplex and reduces its breathing movements, is responsible for this peculiar behavior.[23]

Since it is generally accepted that the main stabilizing factor is the presence of positive charges, it is not surprising that peptides containing residues with positively charged side chains (arginines and lysines), such as those of the nucleopeptides in entries 2–4 of Table 1, stabilized the duplex, even though the global charge of the peptide was nil (at pH=7 carboxylic acids are ionized, and amines are protonated). The difference between the T_m values of the lysine-containing nucleopeptides listed in entries 3 and 4 is significant enough to indicate that a single positive charge cannot account for the whole stabilizing effect, and that the amino acid composition and the sequence of the peptide also modulate the stability of the duplex. The histidine-containing peptide (entry 5), which only differed from nucleopeptide of entry 4 in one amino acid, lysine instead of histidine or vice versa, had a global negative charge (at pH=7 the imidazole ring is mostly unprotonated) and virtually had no effect on the duplex stability.

Interestingly, we also found duplexes more stable than those formed by the unmodified oligonucleotides in hybrids containing aromatic, hydrophobic groups such as the phenyl ring of phenylalanine and the phenylacetyl *N*-capping group, or the indole ring of tryptophan (entries 6–8). The peptides in hybrids of entries 6 and 7 were, as the histidine-containing one, negatively charged, which points up the way the negative charge was not responsible for the non-stabilizing effect of the histidine-containing peptide. Stacking interactions between the aromatic side chains and the nucleobases might possibly account for the favorable contribution of these hydrophobic peptides (see below).

Quite recently, different studies on the hybridization properties of peptide–oligonucleotide conjugates in which the peptide moiety contained tryptophan and basic amino acids[20,24] have reached common, clear conclusions with respect to the stabilizing effect of positively charged groups, but not regarding the effect of the aromatic amino acid. Harrison and Balasubramanian found little or no influence of the indole side chain on the melting temperature,[19] whereas Sarracino et al. had described a tryptophan residue, either alone or in a dipeptide, as in fact having a clear stabilizing effect.[20]

Our results, both with the $^{3'}$ACTAGT-containing nucleopeptides that we have just discussed, and with the nucleopeptides that form duplexes with four GC base pairs (entries 11, 12, 15 and 16), indicate that the role of tryptophan is not at all negligible, since all the tryptophan-containing peptides were found to stabilize the duplex. In the case of the $^{3'}$ACTAGT-containing nucleopeptides, the presence of a positive charge at the N-terminal (entry 8) seemed to have no influence on the stability of the duplex (cf. with entry 7). The stabilizing effect of additional positive charges was more pronounced in the case of the nonself-complementary oligonucleotide duplex $^{5'}$CGTAGC/$^{3'}$GCATCG than in the self-complementary one, $^{3'}$GCATGC (cf. entries 10–12 with 14–16).

The comparison between the T_ms of these tryptophan-containing nucleopeptides (cf. entries 11–12 with 15–16) also shows that the stabilizing effect of two covalently-linked peptides, one at each end of the duplex, is higher than

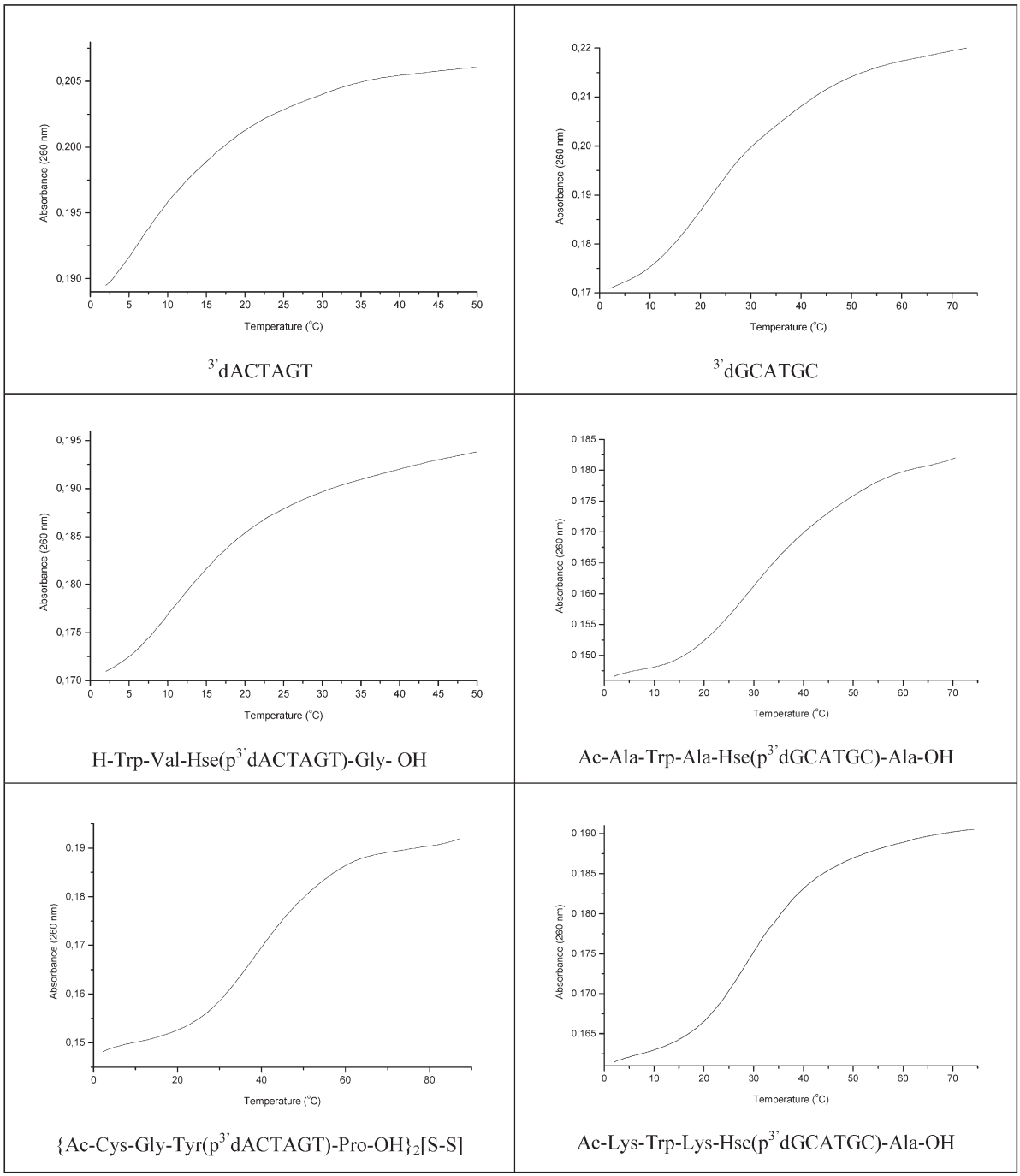


Figure 3. Melting profiles of some of the duplexes listed in Table 1.

the stabilizing effect of a single peptide chain. In duplexes with two peptide chains, the differences between the lysine- and the alanine-containing nucleopeptides of entries 11 and 12 were appreciated when the denaturation experiments were carried out at considerably higher duplex concentration and monitored by NMR.[†],[24] This and other NMR studies on the structure of tryptophan-containing conjugates[25] have shown that the tryptophan side chain can stabilize the duplex by stacking onto the terminal nucleobases.

As shown in Table 2, all the 5′-modifications of the oligonucleotide CATGGCT stabilized the duplex. The reason for this effect is, however, unclear. Attachment of the linker (entry 2) adds a hydrophobic moiety (the linker has six methylene groups), the negative charge of the phosphate, and the positive charge of the N-terminal. The overall charge was the same in the case of the Gly-Met-linker-oligonucleotide duplex (entry 3), but the higher T_m showed that the presence of the GlyMet dipeptide definitely favored base-pairing.

[†] 100 μM duplex, 100 mM NaCl, 25 mM phosphate, pH=7, T_m values: [AcLysTrpLysHse(p3′dGCATGC)AlaOH]$_2$: 34 °C, [AcAlaTrpAlaHse-(p3′dGCATGC)AlaOH]$_2$: 31 °C, [3′dGCATGC]$_2$: 28 °C.

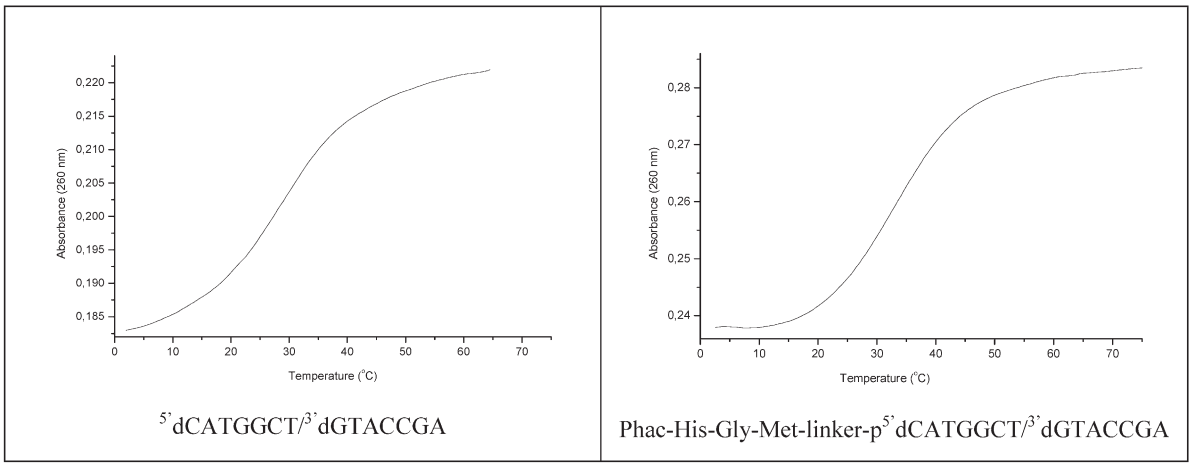


Figure 4. Melting profiles of some of the duplexes listed in Table 2.

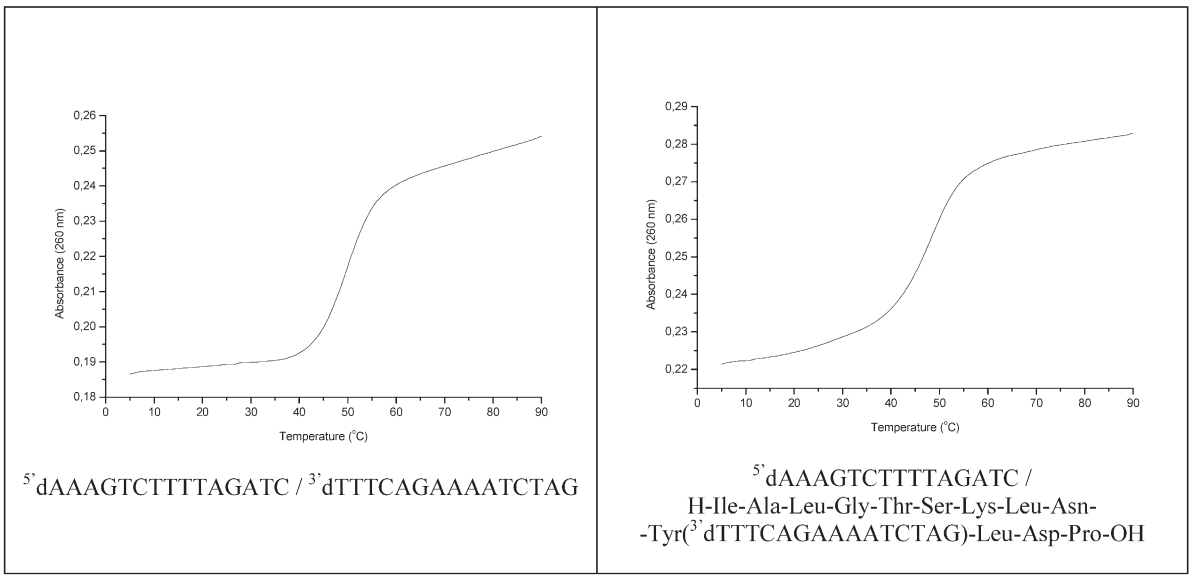


Figure 5. Melting profiles of some of the duplexes listed in Table 3.

Covalent attachment of the *N*-protected tripeptide Boc-HisGlyMet basically added hydrophobic groups, since, as previously stated, the imidazole ring is mostly unprotonated at pH=7. However, the increase in stability with respect to the unmodified oligonucleotide (cf. entries 1 and 4) was lower than that provided by the dipeptide-linker (entry 3) and replacement of the Boc group by a phenylacetyl group (entries 5 and 6). These results confirm that covalent linkage of hydrophobic moieties may be duplex-stabilizing. The difference in the effects of the Boc and phenylacetyl groups was surprising, but their differential influence might be related to the aromaticity of the latter, which might somehow favor interactions with the nucleobases. Oxidation of the methionine thioether to sulfoxide (entry 6) did not produce any substantial change in duplex stability.

The effect of a pentalysine peptide on a 16-mer blunt-end duplex was found to be virtually nil in the presence of magnesium salts (Table 3, entries 1 and 2), and only in the absence of Mg^{2+}, could we see a small favorable effect.[16] Some of the literature data on 12- to 18-mer duplexes account for a clear duplex stabilization by cationic amino acids,[15,26–29] but other authors[30] have described very small or even negative effects.

Hydrophobic peptide chains have been described as having some small, stabilizing effect on 18- to 20-mer blunt-end duplexes.[21,22] In our case, peptides with different length and composition, either with a net negative charge or uncharged, were shown to have a very slightly destabilizing effect (cf. entry 3 with 4–6), more noticeable as the length of the peptide increased.

Finally, it is interesting to keep in mind that the effect of the peptides may vary depending on whether the conjugates are targetted to DNA or RNA chains, even though no common conclusions can be drawn from the few results described. Oretskaya and co-workers[31] reported that neutral or negatively charged peptides had a stabilizing effect on hybrid DNA–RNA duplexes, but destabilized DNA–DNA duplexes. Conversely, De Napoli et al.[14] found that the peptide had virtually no effect on either DNA–DNA or DNA–RNA duplexes.

4. Conclusion

In summary, the stabilizing effect of peptides covalently-linked to oligonucleotides on the duplexes formed by these conjugates and their complementary chains is much more important in short duplexes than in duplexes with 15 or 16 nucleobases.

Both positively charged and hydrophobic peptides give rise to an increase in stability in short duplexes, the largest stabilizing effect being found in the case of conjugates with self-complementary oligonucleotides in which both ends are attached to a peptide unit.

In the case of longer duplexes, no significant destabilizing effect was found when the peptide moiety was either globally uncharged or even negatively charged, and the stabilizing effect of a positively charged peptide was relatively small.

Altogether, these results indicate that, for their use as antisense drugs, peptide–oligonucleotide conjugates should be designed mainly with the idea that the peptide chain will protect the oligonucleotide from enzymatic degradation and facilitate its transport through cell membranes. No effect of the peptide sequence on the oligonucleotide stability to exonucleases has been described so far, except in the nature of the linking amino acid in the case of nucleopeptides.[10]

5. Experimental

5.1. Oligonucleotide, nucleopeptide and peptide–oligonucleotide conjugate synthesis

The synthesis of PhacAlaHse(p$^{3'}$dACTAGT)GlyArgValOH, AcGlyAlaHse(p$^{3'}$dACTAGT)LysValOH, HTrpValHse(p$^{3'}$dACTAGT)GlyOH, $^{5'}$dTATAAACAATGAGACA, $^{3'}$dATATTTGTTACTCTGT and BocHse(p$^{3'}$dATATTTGTTACTCTGT)(Lys)$_5$OH is described in Ref. 16, that of AcGlyAlaHse(p$^{3'}$dACTAGT)HisValOH in Ref. 32, and that of AcLysTrpLysHse(p$^{3'}$dGCATGC)AlaOH, AcAlaTrpAlaHse(p$^{3'}$dGCATGC)AlaOH, $^{5'}$GCTACG, $^{5'}$dCGTAGC and AcLysTrpLysHse(p$^{3'}$dGCATCG)AlaOH in Ref. 24. The synthesis of PhacHisGlyMet-linker-$^{5'}$dCATGGCT and AcLysMetTyr(p$^{3'}$dACTAGT)GlyOH are described in Ref. 17. The preparation of {AcCysGlyTyr(p$^{3'}$dACTAGT)ProOH}$_2$[S–S], {AcCysGlyAlaHse(p$^{3'}$dGCATGC)AlaOH}$_2$[S–S], AcTyr(p$^{3'}$dTTTCAGAAAATCTAG)LeuAspProArgIleThrValOH and HIleAlaLeuGlyThrSerLysLeuAsnTyr(p$^{3'}$dTTTCAGAAAATCTAG)LeuAspProOH is described in Ref. 18, and that of AcTyr(p$^{3'}$dTTTCAGAAAATCTAG)AlaPheGlyOH in Ref. 33.

$^{5'}$dAAAGTCTTTTAGATC was purchased from Midland Certified Reagent Co (USA). Oligonucleotides synthesized in our laboratory were obtained using the phosphite triester approach, following standard procedures (stepwise elongation on controlled pore glass supports).

Methodology for the preparation of nucleopeptides is described in Refs 16 and 18. Ref. 17 describes the synthesis of peptide–oligonucleotide conjugates (Table 2). All hybrids were synthesized on polystyrene (crosslinked with 1% divinylbenzene) solid supports, and the oligonucleotide elongation was carried out using 5′-*O*-DMT-nucleoside-3′-phosphoramidite derivatives. Peptide chains were assembled using either N^{α}-Boc-protected amino acids (nucleopeptides) or N^{α}-Fmoc-protected derivatives (peptide–oligonucleotide conjugates).

MALDI-TOF mass spectrometric characterization data of the products not previously described (in the order of appearance in the tables, *M*=mass of the neutral molecule):

	M (average, calcd)	*M* (found)
$^{5'}$TGATCA	1791.2	1791.8
PhacPheValHse(p$^{3'}$dACTAGT)GlyOH	2393.8	2394.2
AcTrpValHse(p$^{3'}$dACTAGT)GlyOH	2356.7	2355.9
AcAlaTrpAlaHse(p$^{3'}$dGCATCG)AlaOH	2414.1	2413.9
$^{5'}$dGCTAGC	1792.2	1791.7
$^{5'}$dACCATTCGTAGC	3605.4	3605.8
$^{5'}$dCATGGCT	2096.4	2097.7
$^{5'}$AGCCATG	2105.4	2105.7
HLinker-$^{5'}$dCATGGCT	2275.6	2274.1
HGlyMet-linker-$^{5'}$dCATGGCT	2463.8	2462.5
BocHisGlyMet-linker-$^{5'}$dCATGGCT	2700.1	2700.0
PhacHisGlyMet(O)-linker-$^{5'}$dCATGGCT	2735.1	2733.9
$^{3'}$dTTTCAGAAAATCTAG	4574.9	4579.6

5.2. Thermal denaturation experiments

2.0 μM duplex solutions for the thermal denaturation studies were prepared by dissolving equimolar amounts of the complementary strands or the self-complementary oligomers in 10 mM Na_2pipes, pH=7, 100 mM NaCl and 10 mM $MgCl_2$ buffer. Annealing was carried out by heating at 90 °C for 5 min, and allowing the samples to cool slowly at room temperature. The samples were then kept overnight in a refrigerator (4 °C). Melting studies were carried out in 0.1 or 1 cm path length quartz cells, using a computer-interfaced Varian Cary 5E UV–Visible-NIR spectrophotometer equipped with a thermoprogrammer. Absorbance was monitored at 260 nm, and the samples were heated from 2 to 90 °C with at a constant rate of 0.5 °C/min. A high nitrogen flow was used to purge the sample compartment in order to prevent water condensation at low temperature. Mathematical analysis of the melting curves was carried out with the Microcal Origin software, and T_m values were obtained from the first derivative. From repeated experiments (at least twice), the error of the T_m data was estimated to be of ±0.5 °C. Some melting profiles are shown in Figures 3–5.

Acknowledgements

Laurent Debéthune was the recipient fellowship from of the Generalitat de Catalunya. Vicente Marchán was the recipient fellowship from the Universitat de Barcelona. This work was supported by funds from the Spanish MEC (grant BQU2001-3693-C02-01) and the Generalitat de

Catalunya (2001SGR49 and Centre de Referència de Biotecnologia).

References and notes

1. Lebedeva, I.; Stein, C. A. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 403–419.
2. Symons, R. H. *Curr. Opin. Struct. Biol.* **1994**, *4*, 322–330.
3. Praseuth, D.; Guieysse, A. L.; Hélène, C. *Biochim. Biophys. Acta* **1999**, *1489*, 181–206.
4. Tung, C.-H.; Stein, S. *Bioconjugate Chem.* **2000**, *11*, 606–618.
5. Haralambidis, J.; Duncan, L.; Tregear, G. W. *Tetrahedron Lett.* **1987**, *28*, 5199–5202.
6. Leonetti, J.-P.; Degols, G.; Lebleu, B. *Bioconjugate Chem.* **1990**, *1*, 149–153.
7. Haralambidis, J.; Duncan, L.; Angus, K.; Tregear, G. W. *Nucleic Acids Res.* **1990**, *18*, 493–499.
8. Juby, C. D.; Richardson, C. D.; Brousseau, R. *Tetrahedron Lett.* **1991**, *32*, 879–882.
9. Basu, S.; Wickstrom, R. *Tetrahedron Lett.* **1995**, *36*, 4943–4946.
10. Robles, J.; Maseda, M.; Beltrán, M.; Concernau, M.; Pedroso, E.; Grandas, A. *Bioconjugate Chem.* **1997**, *8*, 785–788.
11. Bongartz, J-P.; Aubertin, A-M.; Milhaud, P. G.; Lebleu, B. *Nucleic Acids Res.* **1994**, *22*, 4681–4688.
12. Arar, K.; Aubertin, A.-M.; Roche, A.-C.; Monsigny, M.; Mayer, R. *Bioconjugate Chem.* **1995**, *6*, 573–577.
13. Corey, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 9373–9374.
14. De Napoli, L.; Messere, A.; Montesarchio, D.; Piccialli, G.; Benedetti, E.; Bucci, E.; Rossi, F. *Bioorg. Med. Chem.* **1999**, *7*, 395–400.
15. García de la Torre, B.; Albericio, F.; Saison-Behmoaras, E.; Bachi, A.; Eritja, R. *Bioconjugate Chem.* **1999**, *10*, 1005–1012.
16. Robles, J.; Beltrán, M.; Marchán, V.; Pérez, Y.; Travesset, Y.; Pedroso, E.; Grandas, A. *Tetrahedron* **1999**, *55*, 13251–13264.
17. Marchán, V.; Rodríguez-Tanty, C.; Estrada, M.; Pedroso, E.; Grandas, A. *Eur. J. Org. Chem.* **2000**, 2495–2500.
18. Debéthune, L.; Marchán, V.; Fàbregas, G.; Pedroso, E.; Grandas, A. *Tetrahedron* **2002**, *58*, 6965–6978.
19. Harrison, J. G.; Balasubramanian, S. *Nucleic Acids Res.* **1998**, *26*, 3136–3145.
20. Sarracino, D. A.; Steinberg, J. A.; Vergo, M. T.; Woodworth, G. F.; Tetzlaff, C. N.; Richert, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2511–2516.
21. Soukchareun, S.; Tregear, G. W.; Haralambidis, J. *Bioconjugate Chem.* **1995**, *6*, 43–53.
22. Olejnik, J.; Lüdemann, H.-C.; Krzymanska-Olejnik, E.; Berkenkamp, S.; Hillenkamp, F.; Rothschild, K. J. *Nucleic Acids Res.* **1999**, *27*, 4626–4631.
23. Gómez-Pinto, I.; Marchán, V.; Gago, F.; Grandas, A.; González, C. *Chem. Commun.* **2003**, 2558–2559.
24. Gómez-Pinto, I.; Marchán, V.; Gago, F.; Grandas, A.; González, C. *ChemBioChem* **2003**, *4*, 40–49.
25. Ho, W. C.; Steinbeck, C.; Richert, C. *Biochemistry* **1999**, *38*, 12597–12606.
26. Eritja, R.; Pons, A.; Escarceller, M.; Giralt, E.; Albericio, F. *Tetrahedron* **1991**, *47*, 4113–4120.
27. Zhu, T.; Tung, C.-H.; Bresslauer, K. J.; Dickerhof, W. A.; Stein, S. *Antisense Res. Dev.* **1993**, *3*, 349–356.
28. Zhu, T.; Wei, Z.; Tung, C.-H.; Dickerhof, W. A.; Breslauer, K. J.; Georgopoulos, D. E.; Leibowitz, M. J.; Stein, S. *Antisense Res. Dev.* **1993**, *3*, 265–275.
29. Wei, Z.; Tung, C.-H.; Zhu, T.; Dickerhof, W. A.; Breslauer, K. J.; Georgopoulos, D. E.; Leibowitz, M. J.; Stein, S. *Nucleic Acids Res.* **1996**, *24*, 655–661.
30. Reed, M. W.; Fraga, D.; Schwartz, D. E.; Scholler, J.; Hinrichsen, R. D. *Bioconjugate Chem.* **1995**, *6*, 101–108.
31. Zatsepin, T. S.; Stetsenko, D. A.; Arzumanov, A. A.; Romanova, E. A.; Gait, M. J.; Oretskaya, T. S. *Bioconjugate Chem.* **2002**, *13*, 822–830.
32. Beltrán, M.; Pedroso, E.; Grandas, A. *Tetrahedron Lett.* **1998**, *39*, 4115–4118.
33. Debéthune, L.; Kohlhagen, G.; Grandas, A.; Pommier, Y. *Nucleic Acids Res.* **2002**, *30*, 1198–1204.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5471–5474
Tetrahedron

Synthesis of modulators of chloroquine resistance in *Plasmodium falciparum*, analogues of malagashanine from strychnobrasiline

François Trigalo,[a,*] Roger Joyeau,[a] Van Cuong Pham,[a] Jean Jacques Youté,[a] Philippe Rasoanaivoa[b] and François Frappier[a,†]

[a]*Laboratoire de Chimie des Substances Naturelles, ESA 8041 CNRS, Muséum National d'Histoire Naturelle, ESA 8041 CNRS, 63 rue Buffon, 75005 Paris, France*
[b]*Institut Malgache de Recherches Appliquées, BP 3833, 101 Antanarivo, Madagascar*

Received 25 October 2003; revised 22 March 2004; accepted 20 April 2004

Abstract—The syntheses of three malagashanine analogues are reported. They involve conversion of strychnobrasiline in multiple steps and obtaining (i) unsaturation of the bond 3–14, (ii) inversion of configuration on carbon C3, (iii) inversion of configuration on carbon C3 and reduction of the benzene ring.

1. Introduction

Infusion of *Strychnos myrtoïdes* Gilg. and Buss. (Loganiaceae) has been empirically used as chloroquine-adjuvant in Malagasy herbal remedies for the treatment of chronic malaria. Strychnobrasiline **1** and malagashanine **12**, (revised structure),[1] are the two major alkaloid constituents of *S. myrtoïdes*. It has been shown that **1** and **12** lacked both intrinsic anti-malarial and cytotoxic activities, but exhibited a significant chloroquine potential action against a chloroquine resistant strain of *Plasmodium falciparum*.[2] Unfortunately, strychnobrasiline **1**, which is the major alkaloid of the plant, has been found to have a lower in vivo activity than malagashanine **12**. It is therefore, of interest to convert strychnobrasiline to malagashanine and its analogues (Figure 1).

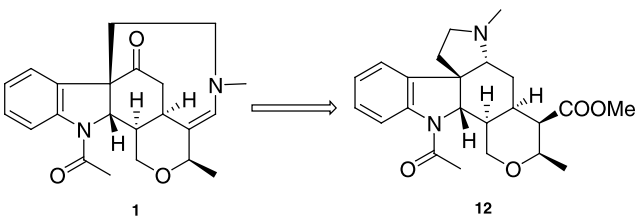


Figure 1.

Keywords: Alkaloid; Malagashanine; Strychnobrasiline; *Strychnos myrtoïdes*; Reductive amination.
* Corresponding author. Fax: +33-1-40-79-31-35;
e-mail address: trigalo@mnhn.fr
† 24th February 2003.

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.04.068

2. Results and discussion

As shown in Figure 2, the starting material **2**[3] is obtained by reduction of strychnobrasiline **1** with lithium aluminium hydride in tetrahydrofuran. The resulting indolic alkaloid, which contains an hemiacetal hydroxyl, is acetylated on the two amine groups by direct treatment with acetic anhydride without any solvent in a good yield (90%). The crystalline di-*N*-acetylated compound **3** is then oxidized by pyridinium dichromate (PDC) in methylene dichloride leading to the corresponding lactone **4**.

Further treatment of **4** with potassium hydroxide in aqueous methanolic solution at room temperature, gives the potassium carboxylate salt **5**. Unfortunately, esterification with diazomethane by a classical method[4] (acidification, then addition of a solution of diazomethane in ether), lead back to lactone **4** as the major product along with a methyl ester as minor compound. This problem is avoided by elution through a silica column with a solvent containing ammonia, to convert the potassium salt into the corresponding ammonium salt **6**, that is now dissolved in methanol and etherous diazomethane is added followed by a small quantity of silica acid (which acifidy smoothly the solution). This operation is repeated three times and the reaction, monitored by thin layer chromatography, leads to compound **7**. The hydroxyl group of **7**, formed by lactone opening is oxidized by pyridinium dichromate in methylene chloride in a good yield. Deacetylation of compound **8** by strong hydrolysis with aqueous hydrochloric and acetic acid[5] at reflux, affords the dihydrochloride **8′**. ^{1}H NMR spectra of the product before purification does not show the expected specific proton of the double bond (H14, doublet,

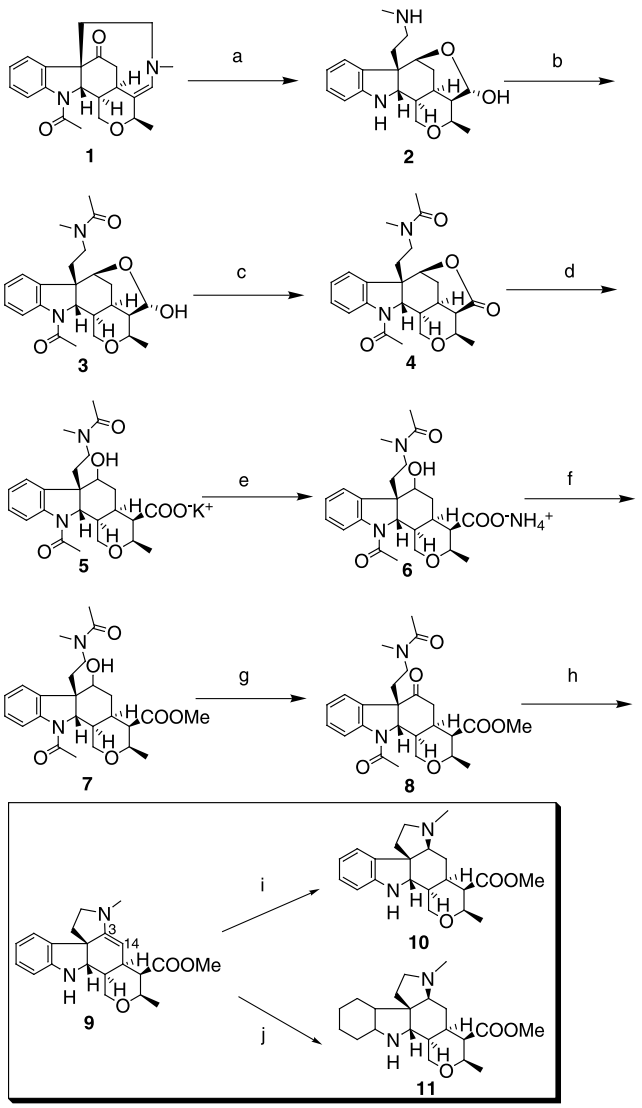


Figure 2. (a) $LiAlH_4$ 1 M/THF; (b) Ac_2O; (c) PDC/CH_2Cl_2; (d) KOH/EtOH/H_2O; (e) silicic colum 85/15/2, CH_2Cl_2/MeOH/NH_4OH 20%; (f) CH_2N_2/Et_2O/MeOH/silicic acid; (g) PDC/CH_2Cl_2; (h) H_2O/AcOH/HCl, 5 h, 120 °C; (i) $NaBH(OCOCH_3)_3/ClCH_2CH_2Cl$; (j) H_2, PtO_2, AcOH 50%.

J=4.2 Hz), but rather the presence of a singlet at 3.56 ppm specific of methyl ester, although the methyl ester in these conditions would theoretically be promptly hydrolyzed.[6] This unusual behaviour might be the result of transannular interactions between π orbitals of the ester and the carbonyl groups. Indeed C20–C21 olefin in strychnobrasiline **1** is known to be rather resistant to reductive conditions for similar reasons,[3] whereas the methyl ester of malagashanine 12, was straightforward hydrolysed in similar conditions (unpublished results). Non hydrolysis of the methyl ester during these drastic conditions suggests the lack of racemization on C20.

Filtration of the dihydrochloride **8′** (which is not isolated) through a silica column eluted with a solvent containing ammonia afforded the unsaturated C3–C14, compound **9** (Figure 3).

The free diamino intermediate **8″** is not detected because

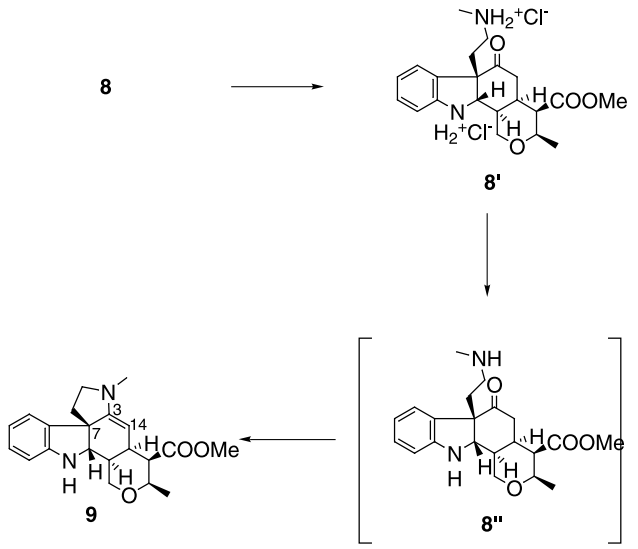


Figure 3. Reductive cyclisation.

after deprotection of the dihydrochloride **8′**, it is spontaneously transformed to unsaturated compound **9** during deanionisation through the ammonia column. Formation of this enamine is favoured by the fact that double bond can be only formed between C3 and C14, not between C3 and C7 (quaternary carbon), and not between C3 and N4 (the nitrogen cannot produce a stable imine[6] but the charged iminium). Reduction of this unsaturated compound **9** with sodium triacetoxy borohydride[7] gives mainly 3-epi-malagashamine **10**, and not malagashanine, the hydrogen proton attacks the double bond behind the plane of the molecule, due to the stereochemistry of carbon **7**. Hydrogenation of **9** in aqueous acetic acid in presence of platine oxide[8] gives the saturated compound **11**.

Compounds **3**-**8** display indescribable ^1H and ^{13}C NMR spectra with splitting due to the presence of several conformers formed by the two *N*-acetyl groups. Therefore, the six synthesized products were identified by elementary analysis or by high resolution mass spectra. However compounds **9**-**11** display clear-cut ^1H and ^{13}C NMR spectra, then confirming that not any isomerization occurred during all the successive steps of the latter synthesis.

The overall yield for the nine-step synthesis is 10% for the unsaturated compound **9**.[9]

3. Experimental

3.1. General

Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a Nermag R10-10 apparatus, while high-resolution data were measured on a Jeol MS700. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300.13 and 75.47 MHz respectively on a Bruker AC-300 spectrometer by using standard programs. The ^1H and ^{13}C chemical shifts are expressed in ppm from TMS. Coupling constant (J) ar given

in Hz. 2D NMR NOESY, HMQC and HMBC experiments were carried out on a Bruker AM-400 spectrometer using a triple resonance probe head with gradient selection of coherence transfer pathway.

Column chromatographies were carried out on 200–400 mesh silica gel 60 (Merck). Melting points (mp) were taken on a Büchi B-545 apparatus and are uncorrected.

3.1.1. Acetylation of 2. After dissolution of compound **2** (344 mg, 1 mmol) by smooth heating (40 °C) in 3 ml of acetic anhydride, compound **3** spontaneously crystallized, then it was filtered and washed with 20 ml ether. Drying in vacuo afforded pure **3** (385 mg, 90%). Mp: 203 °C; $[\alpha]_D^{20}=+84.8°$ (*c* 2.0, $CHCl_3$); HRMS (FAB): *m/z* 429.2395 $[M+H]^+$, Calcd for $C_{24}H_{33}N_2O_5$: 429.2389. Anal. Calcd for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.12; H, 7.48; N, 6.61.

3.1.2. Oxidation of 3. Compound **3** (428 mg, 1 mmol) in 3 ml methylene chloride was treated by pyridinium dichromate (PDC, 1.2 mmol, 460 mg). The above suspension was stirred overnight, then poured directly on silica gel column (CH_2Cl_2/MeOH 98:2) to give **4** (318 mg 75%), as a white powder. Mp: 126–128 °C; $[\alpha]_D^{20}=+49°$ (*c* 1.4, $CHCl_3$); HRMS (FAB): *m/z* 427.2238 $[M+H]^+$, Calcd for $C_{24}H_{31}N_2O_5$: 427.2233. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.42; H, 7.14; N, 6.50.

3.1.3. Hydrolysis of 4. To a solution of **4** (426 mg, 1 mmol) in 2 ml of methanol and 2 ml H_2O was added 560 mg of KOH (10 mmol) at room temperature. The mixture was stirred for 8 h. The volatile layer was then evaporated in vacuo and the crude was purified by chromatography (silica gel, eluted with CH_2Cl_2/MeOH/NH_4OH (*d*:0.2) 75:25:5) yielding **6** (426 mg, 70%) as a white powder. Mp: 182–183 °C; $[\alpha]_D^{20}=-19.1°$ (*c* 1.0, MeOH); HRMS (FAB): *m/z* 445.232638 (35.9%) $[M+H]^+$, Calcd for $C_{24}H_{33}N_2O_6$, 445.2339; 427.2222 (20.9%) $[M+H-H_2O]^+$, Calcd for $C_{24}H_{31}N_2O_5$: 427.2233. Anal. Calcd for $C_{24}H_{35}N_3O_6.1H_2O$: C, 60.11; H, 7.78; N, 8.76. Found: C, 60.25; H, 7.68; N, 8.65.

3.1.4. Methylation and oxidation of 6. To a solution of **6** (461 mg, 1 mmol) in methanol (5 ml) were added successively 2 ml of ethereal diazomethane[5] at 0 °C under stirring, followed 5 min later by 0.2 g of silica gel. This operation was repeated three times. After filtration of silica, the organic phase was evaporated in vacuo, the residue was dissolved in 4 ml of dichloromethane. PDC (460 mg, 1.2 mmol) were added under stirring. The above suspension was stirred overnight, then poured directly on column chromatography (CH_2Cl_2/MeOH 97:3) to give **8** (225 mg, 49%), as a yellow oil. HRMS (FAB): *m/z* 457.2339 $[M+H]^+$, Calcd for $C_{25}H_{33}N_2O_6$: 457.2339.

3.1.5. Hydrolysis and cyclisation of 8. A solution of **8** (456 mg, 1 mmol) in acetic acid (2 ml), concentrated hydrochloric acid (2 ml) and water (2 ml) was vigorously refluxed (120 °C) for 5 h. The solvent was evaporated in vacuo and the crude was purified by chromatography (silica gel, eluted with CH_2Cl_2/MeOH/NH_4OH (*d*:0.2), 90:10:1) to give **9** (223 mg, 60%) as a yellow oil. $[\alpha]_D^{20}=-42.5°$ (*c* 1.0, $CHCl_3$); HRMS (FAB): *m/z* 363.2642 $[M+H]^+$, Calcd for $C_{21}H_{35}N_2O_3$: 363.2648. ^1H NMR $CDCl_3$: δ 1.21 (d, *J*=6.5 Hz, C18H_3), 1.50 (m, C15H), 1.82 (dd.br, *J*=6.2, 11.1 Hz, C6H), 1.93 (ddd, *J*=9.0, 9.0, 11.1 Hz, C6H), 2.66 (dd, *J*=3.4, 6.5 Hz, C20H), 2.68 (s, NC23H_3), 2.73 (ddd, *J*=4.2, 4.2, 6.5 Hz, C15H), 2.82 (dd.br, *J*=9.0, 9.0 Hz, C5H), 3.50 (m, C5H), 3.55 (m, C17H), 3.56 (s, OC22H_3), 4.10 (d, *J*=4.2 Hz, C14H), 4.16 (d.br, *J*=12.3 Hz, C16H), 4.27 (d, *J*=10.6 Hz, C2H), 6.61 (dd, *J*=1.0, 7.4.0 Hz, C12H), 6.65 (dt, *J*=1.0, 7.4 Hz, C10H), 6.99 (dt, *J*=1.4, 7.4 Hz, C11H), 7.12 (dd, *J*=1.4, 7.4 Hz, C9H), ^{13}C NMR $CDCl_3$: δ 19.2 (C18), 34.7 (NC23), 34.9 (C16), 35.8 (C15), 37.0 (C6), 54.1 (C7), 61.3 (C2), 68.7 (C17), 73.7 (C19), 86.4 (C14), 110.5 (C12), 118.7 (C10), 122.9 (C9), 127.6 (C11), 136.5 (C8), 147.4 (C13), 149.3 (C3), 172.9 (C21).

3.1.6. Reduction of 9 by sodium triacetoxyborohydride. To a solution of **9** (93 mg, 0.25 mnol) in 1,2-dichloroethane (4 ml) was added sodium triacetoxyborohydride (106 mg, 0.5 mmol) under magnetic stirring at room temperature. After 18 h, the solution was evaporated in vacuo and purified by chromatography (silica gel, eluted with CH_2Cl_2/MeOH/NH_4OH (*d*:0.2), 95:5:0.5 to give **10** (50 mg, 56%) as a yellow oil. $[\alpha]_D^{20}=-25.3°$ (*c* 1.0, $CHCl_3$). HRMS (FAB): *m/z* 357.2176 $[M+H]^+$, Calcd for $C_{21}H_{29}N_2O_3$: 357.2178. ^1H NMR: δ 1.21 (d, *J*=6.6 Hz, C18H_3), 1.43 (m, C16–H), 1.48 (m, C14H), 1.80 (dd, *J*=2.3, 7.5 Hz, C6H), 1.94 (m, C14H), 2.12 (m, C6H), 2.25 (m, C15), 2.47 (s, C22H_3), 2.62 (dd *J*=7.5, 9.2 Hz), 2.70 (dd, *J*=3.8, 5.9 Hz, C20H), 2.75 (m, C3H), 2.94 (m, C5H), 3.46 (dd, *J*=4.6, 12.4 Hz, C17H), 3.65 (s, C23H_3), 3.71 (m, C19H), 4.07 (dd, *J*=3.6, 12.4 Hz, C17H), 4.09 (d, *J*=9.7 Hz, C2H), 6.60 (m, C12H), 6.69 (dd, *J*=1.2, 7.4 Hz, C10), 7.01 (dd, *J*=1.2, 7.6 Hz, C11), 7.03 (m, C9). ^{13}C NMR: δ 18.5 (C18), 28.3(C14), 32.4(C15), 35.8 (C16), 38.5 (C6), 40.3 (C22), 49.1 (C20, 51.2 (C23, 53.2 (C5), 55.8 (C7), 63.8 (C2), 66.0 (C17), 73.3 (C19), 68.8 (C3), 109.7 (C12), 118.4 (C10), 123.3 (C9), 127.7 (C11), 137.2 (C8), 148.4 (C13), 172.5 (C21).

3.1.7. Hydrogenation of 9 catalyzed by PtO_2. A solution of **9** (93 mg, 0.25 mmol) in acetic acid 0.1 M (4 ml) was hydrogenated at room temperature in the presence of platinium oxide (50 mg). After 1 h, the catalyst was removed by filtration, the solvent distilled off and compound **11** was isolated as a yellow oil (80 mg, 88%). $[\alpha]_D^{20}=-32.5°$ (*c* 2.0, $CHCl_3$); HRMS (FAB): *m/z* 363.2642 $[M+H]^+$, Calcd for $C_{21}H_{35}N_2O_3$: 363.2648. ^1H NMR: δ 1.08 (m, C9H), 1.10 (m, C12H), 1.31 (d, *J*=6.9 Hz, C18H_3), 1.49 (m, C14H), 1.54 (m, C11H), 1.58 (m, C6H), 1.58 (m, C10H), 1.65 (m, C9H), 1.71 (m, C8H), 1.93 (m, C6H), 1.77 (m, C12H), 1.89 (m, C10H), 1.98 (m, C14H), 2.41 (m, C15H), 2.45 (s, C22H_3), 2.53 (dd, *J*=5.7, 11.0 Hz, C3H), 2.56 (dd, *J*=7.4, 8.9 Hz, C5H), 2.76 (dd, *J*=2.6, 8.9 Hz, C5H), 3.03 (dd, *J*=5.2, 5.2 Hz, C20H), 3.36 (m, C2H), 3.44 (dd, *J*=4.6, 11.7 Hz, C17H), 3.59 (s, OC23H_3), 3.59 (m, C13), 3.75 (dd, *J*=11.7, 11.7 Hz, C17H), 4.35 (dq, *J*=6.9, 5.2 Hz, C19H). ^{13}C NMR: δ 16.8 (C18), 19.9 (C11), 23.1 (C9), 24.1 (C14), 24.4 (C12), 27.3 (C10) 29.3 (C6), 30.0 (C15), 40.5 (C22), 41.1 (C16), 46.3 (C8), 47.7 (C20), 51.4 (C23), 51.9 (C5), 56.1 (C13), 59.7 (C2), 59.2 (C17), 69.0 (C19), 68.8 (C3), 171.9 (C21).

References and notes

1. Caira, M. R.; Rasoanivo, P. *J. Chem. Crystallogr.* **1995**, *25*, 725–729.
2. Rasoanivo, P.; Ratsimamanga-Urverg, D.; Milijaona, R.; Rafatro, H.; Ratsimamanga, A.; Galeffi, C.; Nicoletti, M. *Planta Med.* **1994**, *27*, 2551–2552.
3. Trigalo, F.; Martin, M. T.; Blond, A.; Brouard, J. P.; Herintsoa, R.; Ramanitrahasimbola, D.; Frappier, F. *Tetrahedron* **1999**, *55*, 6139–6146.
4. Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377–5378.
5. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, H. U.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247–288.
6. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; 2nd ed. Cornell University Press: Ithaca, NY, 1969; pp 1129.
7. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
8. Boit, H. G. *Chem. Ber.* **1950**, *83*, 217–226.
9. Frappier, F.; Trigalo, A.; Ratsimamanga, S.; Rasoainavo, P. French Patent Application: No. 02/05740, 7 May, 2002.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 5475–5479

Two simple and different approaches to the synthesis of new 2,4-dialkylamino substituted 6,7-dihydro-5*H*-benzocyclohepta[1,2-*d*]pyrimidines

Antonio Herrera,[a] Roberto Martínez-Álvarez,[a,*] Rachid Chioua,[a,b] Fouad Benabdelouahab[b] and Mourad Chioua[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain*
[b]*Département de Chimie, Faculté des Sciences, Université Abdelmalek Essaâdi, Tétouan, BP: 2121, Morocco*

Received 10 February 2004; revised 26 March 2004; accepted 8 April 2004

Dedicated to Prof. José Luis Soto on the occasion of his 75th birthday

Abstract—Benzocycloheptapyrimidines are an important class of compounds because of their pharmacological properties. We report here two new synthetic procedures for the preparation of 2,4-dialkylamino substituted benzocycloheptapyrimidines. One of these methods is based on the reaction of substituted cyanamides with the vinyl triflate of the 1-benzosuberone while the other preparation relies on the nucleophilic displacement of methylsulfonyl groups by secondary amines at the 2 and 4 positions of benzocycloheptapyrimidine intermediates.

1. Introduction

The pyrimidine ring is one of the most important heterocycles because it is a component of many products involved in a large number of biological processes.[1,2] Among these, pyrimidines fused to benzocycloheptanes are compounds which are currently studied because of their interesting pharmacological properties. Thus, derivatives of the 6,7-dihydro-5*H*-benzo[6,7]cyclohepta [1,2-*d*]pyrimidine **1** (Fig. 1) are investigated for their application as blood platelet aggregation inhibitors[3] and have also shown activity against collagen-induced platelet aggregation[4] and reserpine induced hypothermia.[5] Another interesting application is their use as antidepressants.[6] Derivatives of 10,11-dihydro-5*H*-benzo[4,5]cyclohepta [1,2-*d*]pyrimidine **2** (Fig. 1) are considered cyclic analogs of diaveridin, a potent antiprotozoan.[7] On the other hand, benzocycloheptapyridines bearing nitrogen substituents are active in inhibiting the chloresterol biosynthesis and modulating blood serum lipids.[8] The inhibition of the farnesyl protein transferase, a novel approach to antitumour therapy is based on compounds such as piperazinyl substituted cycloheptapyridines.[9]

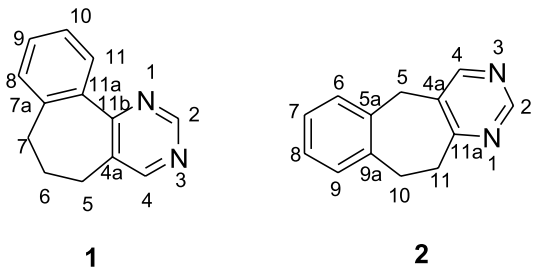


Figure 1. Structures of some benzocycloheptapyrimidines.

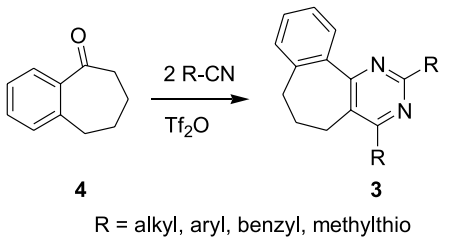
In the course of our investigation on the reaction of different carbonyl compounds with nitriles in the presence of triflic anhydride $[(CF_3SO_2)_2O](Tf_2O)$, we recently reported[10] the easy preparation of new heterocycles such as 2,4-disubstituted 6,7-dihydro-5*H*-benzo[6, 7]cyclohepta[1,2-*d*]pyrimidine **3** (Scheme 1).

The reported procedure permits the synthesis of the target molecules in a one-pot reaction with good yields. The preparation of some 2,4-disubstituted derivatives of compound **1** is based on the reaction of 1-benzosuberone **4** with the corresponding nitrile and triflic anhydride.

This procedure represents an improved extension of the well known reaction of ketones with nitriles and triflic anhydride.[11,12]

Keywords: Benzocycloheptapyrimidines; Cyanamides; 1-Benzosuberone; Triflic anhydride.
* Corresponding author. Tel.: +34-913944325; fax: +34-913944103; e-mail address: rma@quim.ucm.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.058

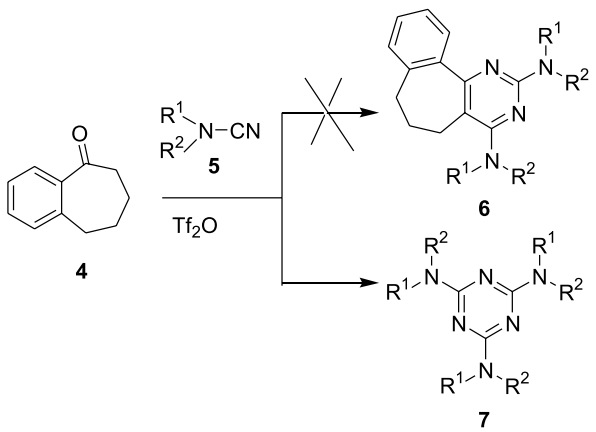


Scheme 1.

We wish to report here the synthesis of new benzocycloheptapyrimidines bearing nitrogen substituents at positions 2 and 4 (Scheme 1). Although our reported synthetic procedure[10] is simple and versatile, the attachment of nitrogen atoms at these positions requires modifications to the general approach shown in Scheme 1. Besides, on the pharmacological potential applications, this class of compounds and their uracil derivatives are also important in molecular recognition processes due to their ability in forming diverse hydrogen-bonded complexes.[13–15] To our knowledge only derivatives with one nitrogen substituent at the position 4 are reported.[4–6]

2. Results and discussion

The direct synthesis of benzocycloheptapyrimidines with nitrogen substituents at positions 2 and 4 requires the use of nitriles bearing a nitrogen atom bonded to the cyano group (Scheme 1). For this purpose, we chose different substituted cyanamides such as dimethylcyanamide **5a**, 1-piperidinecarbonitrile **5b**, 4-morpholinocarbonitrile **5c** and 1-pyrrolidinecarbonitrile **5d** to react with 1-benzosuberone **4** in the presence of triflic anhydride (Scheme 2). Surprisingly, the reaction of 1-benzosuberone (**4**) with these substituted cyanamides and Tf_2O did not lead to the expected 2,4-dialkylamino substituted benzocycloheptapyrimidines **6**. Instead, a trimerization process occurs which affords the corresponding 2,4,6-tris(dialkylamino)-1,3,5-triazines **7** even under mild reaction conditions. This side reaction constitutes a new an interesting process that can be used to easily prepare *s*-triazines.[16]



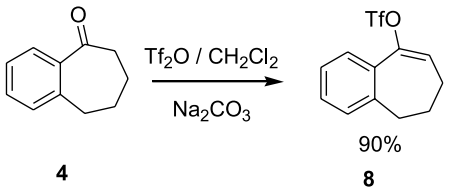
Scheme 2.

The strong electrophilic character of the triflic anhydride which acts as a powerful Lewis acid promotes the cyclotrimerization of the cyanamides at the expense of pyrimidine formation. This result suggests that 2,4-dialkylamino benzocycloheptapyrimidines might be obtained if triflic anhydride was excluded in the pyrimidine formation.

Accordingly, in order to eliminate the presence of triflic anhydride, we have used an indirect way for the preparation of nitrogen substituted pyrimidines at positions 2 and 4 based on the reaction of vinyl triflates with cyanamides.

The solvolysis of vinyl triflates derived from aliphatic ketones in presence of alkyl- or arylnitriles was reported to give alkyl- and arylpyrimidines.[17,18] This process can be considered an extension of the Ritter reaction where nitriles were used as nucleophiles.[19] Although it is a known reaction, the use of substituted cyanamides as nitriles has not yet been reported.

The vinyl triflate corresponding to the 1-benzosuberone **4** was prepared by reaction of the ketone and triflic anhydride in the presence of sodium carbonate as heterogeneous base[20] (Scheme 3).

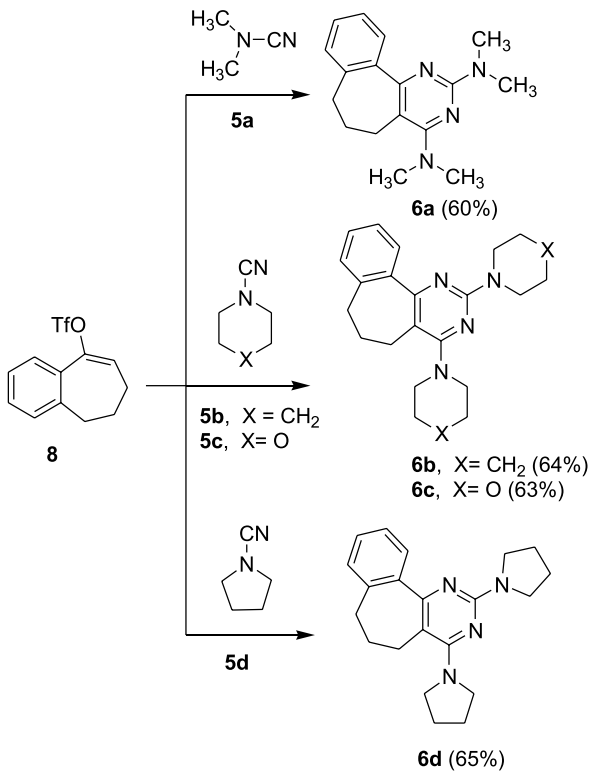


Scheme 3.

The corresponding triflate, 6,7-dihydro-5*H*-benzo[7]-annulen-9-yl trifluoromethanesulfonate **8** was isolated in excellent yield and can be used and stored without special precautions. This compound is reported to be a synthetic intermediate used in the palladium catalysed coupling reactions with carbon monoxide[21] or with trimethylstannanes derivatives.[22]

When the vinyl triflate **8** was heated in the presence of substituted cyanamides **5a–d**, the reaction affords the corresponding 2,4-dialkylamino substituted benzocycloheptapyrimidines **6** in good yield (Scheme 4). As the process is carried out in absence of a base, a large amount of triflic acid is formed as side product in the reaction. The absence of *s*-triazines **7** demonstrates that the triflic anhydride is responsible for this cyclotrimerization by-product. The triflic acid is not capable of inducing the cyclotrimerization of substituted cyanamides even when the reaction was carried out at high temperature.

These results can be explained according to the well-known mechanism of synthesis of pyrimidines[17,18] whereby the first step is a solvolytic process in which the triflate group is displaced (Scheme 5). The excellent ability of this group as leaving group allows the generation of a vinyl cation through a unimolecular process.[23] The resulting vinyl cation **9**, stabilized by the phenyl ring, is easily trapped by the nitrogen atom of the cyano group forming a nitrilium ion **10**. A second nucleophilic attack by another cyanamide molecule on the nitrilium ion followed by cyclization and loss of TfOH affords the corresponding 2,4-dialkylamino



Scheme 4.

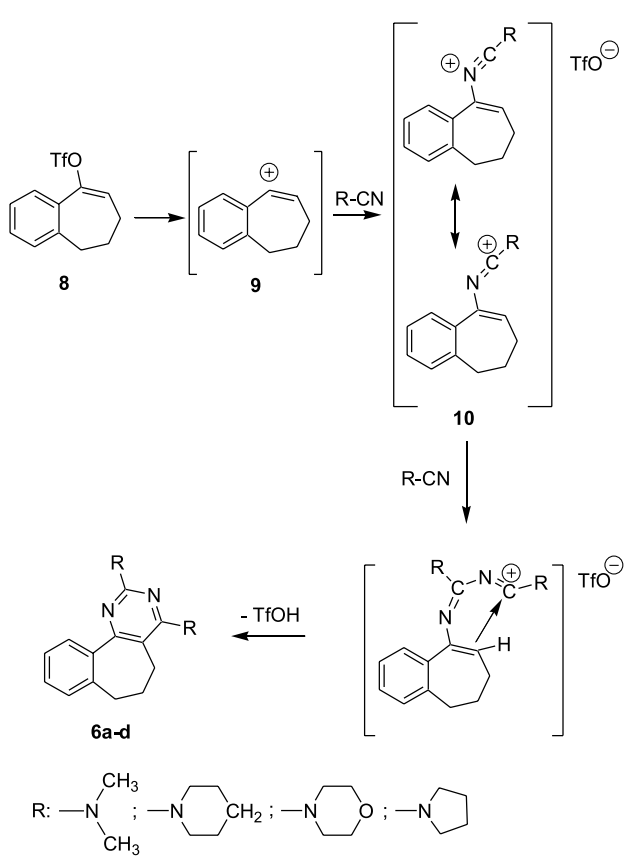
pyrimidines **6a**–**d** in good yields. No trimerization products were observed.

The drawback of this synthetic procedure is the fact that cyanamides are often unstable and hence not suitable reagents. This difficulty can be overcome by initial formation of benzocycloheptapyrimidines with easily replaceable substituents at positions 2 and 4. Nucleophilic displacement of these groups with the appropriate nitrogen reagent such as secondary amines will afford the desired 2,4-dialkylamino pyrimidines.

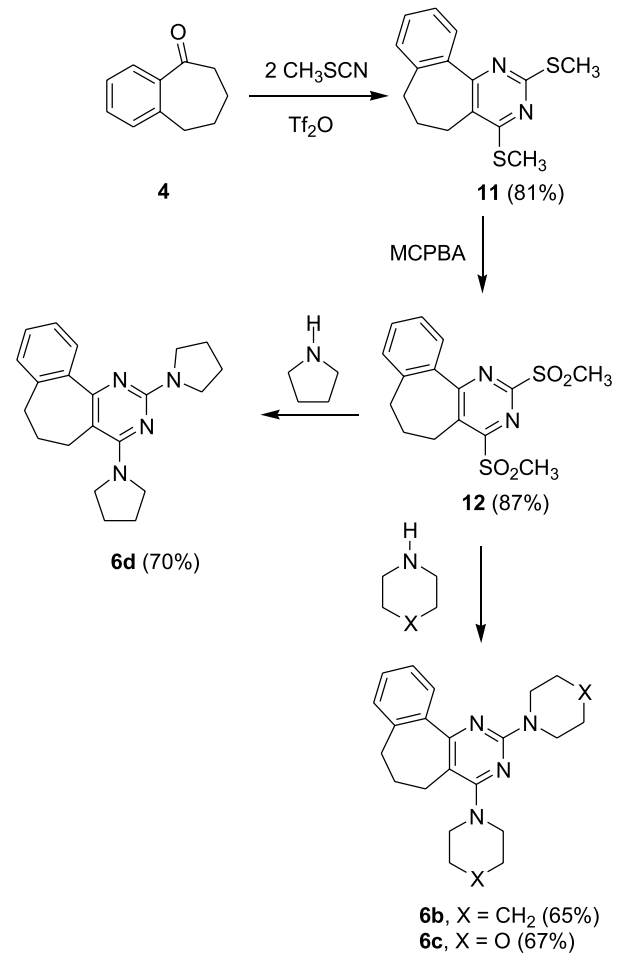
In an earlier paper we demonstrated[10] that the reaction of 1-benzosuberone **4** with methylthiocyanate in the presence of triflic anhydride affords 2,4-bis(methylthio)-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine **11** in good yield (Scheme 6). The mild oxidation of **11** produces the corresponding 2,4-bis(methylsulfonyl) derivative **12**.

Both methylsulfonyl groups can be easily replaced by aromatic nucleophilic substitution. Thus, the reaction of **12** with secondary amines such as piperidine, morpholine or pyrrolidine, affords the corresponding 2,4-dialkylamino derivatives **6b**–**d** in good yield (Scheme 6).

This second alternative also permits the preparation of the target molecules using other nucleophiles than the substituted cyanamides. The 2,4-dialkylaminoderivatives of the



Scheme 5.



Scheme 6.

benzocycloheptapyrimidines can be prepared either using substituted cyanamides and the vinyl triflate of the 1-benzosuberone or by reaction of the corresponding methylsulfonyl precursor with secondary amines.

In summary, we report that 2,4-dialkylamino derivatives of benzocycloheptapyrimidines can be easily prepared using two different synthetic strategies with similar overall yields. The first one is based on the high reactivity of vinyl triflate of 1-benzosuberone toward nucleophiles. Thus, the reaction of this triflate with substituted cyanamides affords the target molecules. The second is based on the facility to the nucleophilic displacement of the methylsulphonyl pyrimidine moiety with secondary amines. The sulfone is obtained via oxidation from the corresponding methylthio derivative obtained in a one-pot reaction from 1-benzosuberone and methylthiocyanate.

3. Experimental

3.1. General

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.[20] Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by thin-layer chromatography (TLC) using silica gel plates having $60F_{250}$. Column chromatography was performed using silica gel 60 (70–230 mesh). Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. The IR spectra were measured with a Shimadzu FTIR 8300 instrument and samples pellets were produced with potassium bromide spectroscopic grade. NMR spectra were recorded on a Bruker DPX 300 at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C. Chemical shifts are given in δ units (ppm) to residual $CHCl_3$ (7.26 and 77.0, respectively). *J* values are in Hz. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 200 °C. Elemental analysis was carried out with a Perkin–Elmer 2400 CHN apparatus.

3.1.1. Preparation of the vinyl triflate of the 1-benzosuberone: 6,7-dihydro-5*H*-benzo[7]annulen-9-yl-trifluoromethanesulfonate 8. A solution of Tf_2O (1.76 g, 6.25 mmol) in 20 mL of dichloromethane was added dropwise to a suspension containing 1-benzosuberone **4** (0.5 g, 3.12 mmol) and Na_2CO_3 (0.72 g, 6.25 mmol). The mixture was stirred overnight at room temperature. After filtration to eliminate the Na_2CO_3, the mixture was washed with saturated aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was distilled in a kugelrohr to give 0.81 g (90%) of a colourless liquid bp 80 °C (0.1 mbar). IR (film). ν=3020 (=CH), 1415, 1215 (OSO_2), 1008 (CF_3) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.08 (m, 2H, CH_2), 2.22 (m, 2H, CH_2), 2.79 (m, 2H, CH_2), 6.12 (t, 1H, *J*=6 Hz, =CH), 7.28 (m, 3H, arom.), 7.53 (m, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.25, 30.53, 33.42 (CH_2), 115.38 (C arom.), 118.56 (q, CF_3, *J*=318 Hz), 121.75 (C arom), 123.36 (C8), 126.45, 129.31, 129.49, 132.03, 141.59, 146.11 (C9) ppm. MS *m*/*z* (%)=292 [$M^{+\cdot}$] (30), 159 [$M^{+\cdot}-Tf$] (28), 131 [159-CO] (100), 91 [$C_7H_7^+$] (75), 77 [$C_6H_5^+$] (26).

3.2. Reaction of 6,7-dihydro-5*H*-benzo[7]annulen-9-yl-trifluoromethanesulfonate 8 with substituted cyanamides 5a–d: general procedure

Triflate **8** (0.3 g, 1.02 mmol) was dissolved in 5 mL of the corresponding substituted cyanamides. The solution was heated at 120 °C for 24 h. The excess of nitrile was removed in vacuo and the crude product was purified through a silica gel column with hexane/ethyl acetate (7:3) to give the corresponding pyrimidine. The pyrimidine was recrystallized twice from the appropriate solvent.

3.2.1. *N*-[2-(Dimethylamino)-6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidin-4-yl]-*N*,*N*-dimethylamine 6a. 60% yield; undistillable yellowish oil. IR (film) ν=3016 (=C–H), 2929, 2860 (C–H), 1579, 1541, 1382 {$N(CH_3)_2$} cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.28 (m, 4H, CH_2, C6 and C7), 2.67 (t, 2H, CH_2, *J*=6,3 Hz, C5), 3.06 [s, 6H, CH_3, $N(CH_3)_2$], 3.21 [s, 6H, CH_3, $N(CH_3)_2$], 7.28 (m, 3H, arom.), 787 (m, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.63 (C6), 32.32 (C7), 34.02 (C5), 36,82, 41.35 (NCH_3), 105.65, 126.49, 128.30, 128.99, 129.18, 140.18, 140.56, 160.40, 165.82, 166.78 (C arom.) ppm. MS *m*/*z* (%)=282 [$M^{+\cdot}$] (100), 267 [$M^{+\cdot}-CH_3$] (76), 253 [$M^{+\cdot}-C_2H_5$] (15), 238 [$M^{+\cdot}-N(CH_3)_2$] (13). Anal. Calcd for $C_{17}H_{22}N_2$, calc C 72.31, H 7.85, N 19.84; found C 72.12, H 7.69, N 19.75.

3.2.2. 2,4-Di(1-piperidinyl)-6,7-dihydro-5*H*-benzo[6,7]-cyclo hepta[1,2-*d*]pyrimidine 6b. 64% yield; yellow powder: mp 122–123 °C from hexane. IR (KBr) ν=3018 (=C–H), 2933, 2854, 1579, 1533 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.64 (m, 12H, CH_2 piperidine ring), 2.22 (m, 4H, CH_2, C6 and C7), 2.66 (t, 2H, CH_2, *J*=6.1 Hz, C5), 3.36 (m, 4H, CH_2-N), 3.82 (m, 4H, CH_2-N), 7.31 (m, 3H, arom.), 7.87 (m, 1H, arom.). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=24.61 (CH_2 piperidine ring), 24.88 (C6), 25.09, 25.83, 25.89, 26.04, 29.68 (CH_2 piperidine ring), 32.48(C7), 33.64 (C5) 44.11, 44.90, 50.67 (CH_2 piperidine ring), 107.76, 126.47, 128.32, 129.04, 129.21, 140.51, 167.33 (arom.) ppm. MS *m*/*z* (%)=362 [$M^{+\cdot}$] (100), 347 [$M^{+\cdot}-CH_3$] (16), 333 [$M^{+\cdot}-C_2H_5$] (57), 279 [$M^{+\cdot}-C_5H_9N$] (66). Anal. Calcd for $C_{23}H_{30}N_4$, calcd C 76.20, H 8.34, N 15.46; found C 76.09, H 8.21, N 15.33.

3.2.3. 2,4-Di(4-morpholinyl)-6,7-dihydro-5*H*-benzo[6,7]-cyclo hepta[1,2-*d*]pyrimidine 6c. 63% yield; white powder: mp 174–175 °C from ethanol. IR (KBr) ν=3020 (=C–H), 1550, 1537 (C=C), 1257, 1114 (C–O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.21 (m, 2H, CH_2, C6), 2,35 (m, 2H, CH_2, C7), 2.65 (m, 2H, CH_2, *J*=6.6 Hz, C5), 3.42 (m, 8H, CH_2-N), 3.80 (m, 8H, CH_2-O), 7.22 (m, 1H, arom.), 7.35 (m, 2H, arom.), 7.79 (m, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ=24.45 (C6), 32.30 (C7), 33 44 (C5), 44.47, 50.07 (CH_2-N), 66.88, 67.01 (CH_2-O), 108.80, 126.62, 128.48, 129.11, 129.40, 139.58, 140.28, 160.06, 166.41, 166.73 (arom.) ppm. MS *m*/*z* (%)=366 [$M^{+\cdot}$] (100), 336 [$M^{+\cdot}-CH_2O$] (58), 309 (62). Anal. Calcd for $C_{21}H_{26}N_4O_2$, calc. C 68.83, H 7.15, N 15.29; found C 68.59, H 6.97, N 15.11.

3.2.4. 2,4-Di(4-pyrrolidinyl)-6,7-dihydro-5*H*-benzo[6,7]-cyclo hepta[1,2-*d*]pyrimidine 6d. 64% yield; undistillable yellow oil; IR (film) ν=3019 (=C–H), (C–H), 1602, 1577 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz). δ=1.95 (m, 8H, CH_2 pyrrolidine ring), 2.16 (q, 2H, CH_2, J=6.6 Hz, C6), 2.34 (t, 2H, CH_2, J=6.6 Hz, C7), 2.66 (t, 2H, CH_2, J=6.6 Hz, C5), 3.59 (m, 8H, CH_2–N), 7.27 (m, 3H, arom.), 7,89 (m, 1H, arom) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.11, 25.38, 25.66, 25.82 (CH_2, pyrrolidine ring), 29.71 (C6), 31.94 (C7), 35.01 (C5), 45.72, 46.36, 49.81 (CH_2-N), 104.41, 126.48, 128.18, 128.78, 129.05, 140.53, 158.84, 163.19, 165.48 (arom.) ppm. MS: *m/z* (%)=334 [M^+] (100), 319 [$M^{+\cdot}-CH_3$] (5), 305 [$M^{+\cdot}-C_2H_5$] (30), 265 [$M^{+\cdot}-C_4H_7N$] (24). Anal. Calcd for $C_{21}H_{26}N_4$, calcd C 75.41, H 7.84, N 16.75; found 75.31, H 7.67, N 16.59.

3.2.5. 2,4-Bis-(methylsulfonyl)-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*d*]pyrimidine 12. To a stirred solution of 2,4-bis-(methylthio)-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine **11** (The synthesis of **11** is reported in the literature[10]) containing 0.3 g (1.04 mmol) in 20 mL of anhydrous dichloromethane was added slowly a solution of MCPBA 0.72 g (4.16 mmol) in 20 mL of dichloromethane. The mixture was stirred at room temperature for 2 h. An aqueous solution of $Na_2S_2O_3$ (5%) was then added, and the layers were shaken and separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and dried over sodium sulphate. The solvent was removed under reduced pressure and the crude product was purified by recrystallisation in ethanol to give 0.32 g (87%) of title compound as white solid, mp 164–165 °C from ethanol. IR (KBr) ν=1313.4, 1161, 810 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ=2.5(m, 4H, CH_2, C6, C7), 3.05(t, J=6.3 Hz, 2H, CH_2, C5), 3.43(s, 3H, CH_3SO_2), 3.53(s, 3H, CH_3SO_2), 7.34 (m, 1H arom.), 7.51 (m, 2H arom.), 7.82 (m, 1H arom.) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 24.95 (C6), 30.93 (C7), 32.72 (C5), 39.34 (CH_3SO_2), 39.87 (CH_3SO_2), 127.44, 129.28, 129.73, 132.34, 132.65, 135.36, 140.57, 162.80, 165.03, 172.82 (arom.). MS: *m/z* (%): 352 [M^+] (100), 337 [$M^{+\cdot}-CH_3$] (42), 324 (53), 289 (45), 272 (91), 209 (49), 193 (55), 181 (20), 168 (39), 166 (58), 140 (47), 115 (32), 89 (10), 79 (23), 63 (30), 39 (12). Anal. Calcd for $C_{15}H_{16}N_2O_4S_2$, calc C 51.12, H 4.58, N 7.95; found C 50.97, H 4.39, N 7.73.

3.3. Reaction of 12 with secondary cyclic amines: general procedure

Disulfone **12** (1 g, 2.8 mmol) was dissolved in 5 mL of the corresponding cyclic amine (Scheme 6) and heated at 90 °C for 24 h. The excess of amine was removed in vacuo and the residue purified through column chromatography using hexane/ethyl acetate (7:3) as eluent. The pyrimidine was recrystallised twice from the appropriate solvent. Yields: **6b**: 65%; **6c**: 67%; **6d**: 70%.

Acknowledgements

We gratefully acknowledge the DGESIC (Spain, Grant BQU2002-00406) for financial support. We also thank the CAIs of the UCM (Madrid, Spain) for determining the NMR, mass spectra and CHN analysis. R. Chioua thanks the AECI (M. AA.EE., Spain) for a fellowship. We also thank Dr. J. Almy (California State University, Stanislaus) for helpful discussions.

References and notes

1. Brown, D. J. In *The Pyrimidines*. Taylor, E. C., Weissberger, A., Eds.; Wiley: New York, 1994.
2. Katrizky, A.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 3, p 111.
3. Nakayama, T.; Takashi, H. Jpn Kokai. Tokkyo Koho JP 03167178 A2, 1991; *Chem. Abstr.* **1991**, *115*, 256204.
4. Sasaki, K.; Arimoto, Y.; Ohtomo, H.; Nakaya, T.; Takashi, H. *J. Heterocycl. Chem.* **1993**, *30*, 993.
5. Sasaki, K.; Arimoto, Y.; Ohtomo, H.; Nakayama, T.; Takashi, H. *J. Heterocycl. Chem.* **1993**, *30*, 989.
6. Sasaki, K.; Hirota, T.; Arimoto, Y.; Satoh, Y.; Ohtomo, H.; Nakayama, T. *J. Heterocycl. Chem.* **1990**, *27*, 1771.
7. Troschuetz, R. *Arch. Pharm.* **1988**, *321*, 765–766.
8. Robl, J. A.; Bang-Chi, C.; Chong-Qing, S. US Patent US 20002061901; *Chem. Abstr.*, **2001**, *136*, 401651.
9. Ganguly, A. K.; Doll, A. K.; Girijavallabhan, V. M. *Curr. Med. Chem.* **2001**, *8*, 1419.
10. Herrera, A.; Martínez-Álvarez, R.; Chioua, R.; Chioua, M. *Tetrahedron Lett.* **2003**, 2149.
11. Garcia Martinez, A.; Herrera Fernandez, A.; Moreno Jimenez, F.; Garcia Fraile, A.; Subramanian, L. R.; Hanack, M. *J. Org. Chem.* **1992**, *57*, 1627.
12. Baraznekok, L.; Nenajdenko, V. G.; Balenkova, E. *Tetrahedron* **2000**, *56*, 3077.
13. Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.
14. Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757.
15. Marczak, R.; Hoang, V. T.; Noworyta, K.; Zandler, M. E.; Kutmer, W.; D'Souza, F. *J. Chem. Mater.* **2002**, *12*, 2123.
16. Herrera, A.; Martínez-Alvarez, R.; Ramiro, P.; Chioua, R.; Chioua, M. *Synthesis* **2004**, 503.
17. García Martinez, A.; Herrera Fernández, A.; Martínez-Álvarez, R.; Teso Vilar, E.; García Fraile, A.; Osío Barcina, J.; Pargada Iglesias, L. *Tetrahedron Lett.* **1987**, 1929.
18. García Martínez, A.; Herrera Fernández, A.; Martínez-Álvarez, R.; Teso Vilar, E.; García Fraile, A.; Osío Barcina, J.; Pargada Iglesias, L.; Unanue, R.; Subramanian, L. R.; Hanack, M. *J. Heterocycl. Chem.* **1988**, *25*, 1237.
19. Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.
20. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
21. Cacchi, S.; Lupi, A. *Tetrahedron Lett.* **1992**, 3939.
22. Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114.
23. Hanack, M.; Subramanian, L. R. *Houben-Weyl, Methoden der Organischen Chemie, Carbokationen, Carbokationen-Radikale*; Georg Thieme: Stuttgart, 1990; E19c. p 98.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5481–5485
Tetrahedron

Synthesis of methylenedioxy-bearing 1-aryl-3-carboxylisoquinolines using a modified Ritter reaction procedure

Yves L. Janin,[a,*] Didier Decaudin,[b] Claude Monneret[c] and Marie-France Poupon[d]

[a]*URA 2128 CNRS-Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris cedex 15, France*
[b]*Service d'Hématologie, CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*
[c]*UMR 176 CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*
[d]*UMR 147 CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*

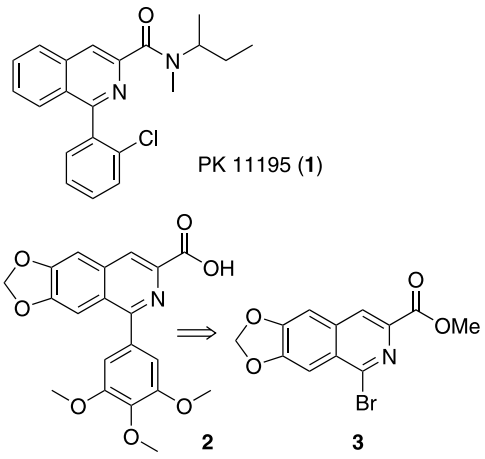
Received 12 January 2004; revised 1 April 2004; accepted 8 April 2004

Abstract—This paper describes original approaches aimed at the preparation of electron-rich 1-aryl-3-carboxylisoquinolines. Our first attempt led to an efficient preparation of 1-hydroxyisoquinoline-3-carboxylic acid methyl ester starting from bromophthalide via a rearrangement of 2-acetylamino-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-malonic acid dimethyl ester. However, as its eventual application to the synthesis of methylenedioxy-bearing substrates seemed rather long, a second approach involving an extension of the Ritter reaction to safrole was devised. We thus report that, under proper experimental settings, the use of 54% tetrafluoroboric acid in ether enables a Ritter reaction between safrole and 3,4,5-trimethoxybenzonitrile yielding 17% of 7-methyl-5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline. This acidic reagent avoids the extensive decomposition seen when using the classical Ritter reaction conditions (i.e.: concentrated sulfuric acid). Further chemical transformations of this methyl-bearing dihydroisoquinoline led to the methylenedioxy-bearing 1-aryl-3-carboxylisoquinoline. These derivatives are related to the peripheral benzodiazepine receptor ligand PK 11195 as well as falcipain-2 inhibitors and other potential antitumor agents.

1. Introduction

In the course of our work[1,2] on the synthesis of potential peripheral benzodiazepine receptor ligands[3,4] related to the phenylisoquinoline PK 11195 (**1**), we undertook the preparation of the electron-rich analogue such as **2** which are incidentally related to falcipain-2 inhibitors[5] and compounds reported for their antitumor potential.[6–8]

The first approach to such electron-rich 1-aryl-3-carboxyl-isoquinolines we envisioned is based on the Suzuki palladium-catalysed aryl coupling reaction between aryl-boronate and 1-bromo-3-carboxylisoquinoline we previously described.[1] Thus a convergent approach from electron-rich isoquinolines such as compound **3** was planned (Scheme 1).

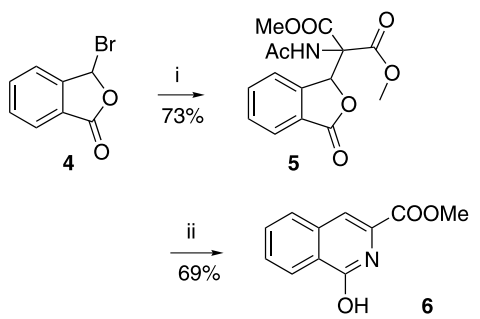


Scheme 1.

In the course of studies aimed at a simple preparation of compound **3**, we devised an original preparation of the 3-carboxyl isoquinolone **6** from bromophthalide (**4**) via lactone **5**. As depicted in Scheme 2, an alkylation of dimethyl acetamidomalonate to give lactone **5** efficiently provides a synthetic precursor bearing all the functional groups required. After various trials, we found that boiling lactone **5** in the presence of 1.1 equiv. of freshly distilled[9] boron trifluoride diethyl etherate complex in 1,2-dichloro-benzene for 30 min led to its decarboxylative rearrangement into the target isoquinolone **6** in a 69% yield.

Keywords: Ritter reaction; 1-Aryl-3-carboxylisoquinoline; PK11195.
* Corresponding author. Tel.: +33-1-45-68-83-95; fax: +33-1-45-68-84-04; e-mail address: yljanin@pasteur.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.004



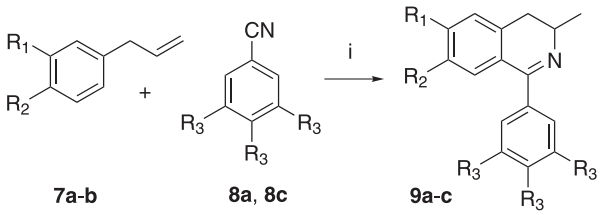
Scheme 2. (i) Dimethyl acetamidomalonate, NaH, DMF 25 °C. (ii) BF_3-OEt_2, 1,2-dichlorobenzene, 180 °C.

This method, with an overall 50% yield from commercially available material, is in fact a quite simple preparation of compound **6**.[1,10–15] However, although many bromophthalides have been described, the number of synthetic steps required to obtain target compound **2** via **3** remains important.

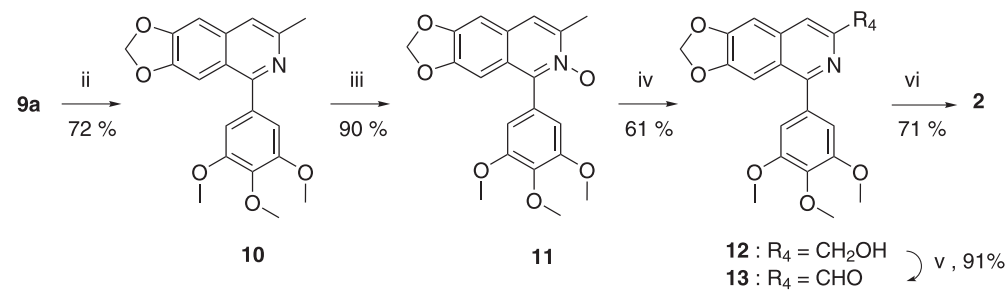
Thus we redirected our efforts to a second approach. What seems to be, in general, the quickest method to prepare the phenylisoquinoline system are the Bischler-Napieralsky reaction,[16,17] (from 2-phenylethyl benzamides) or the Pictet-Spengler reaction[18] (from 2-phenylethylamine and benzaldehyde), followed by aromatisation steps. The preparation of compound **10** has actually been reported using the Bischler-Napieralsky reaction.[19] However, if no yield is provided in that case, a more recent and remarkable work[6] reports excellent yield starting from electron-rich substrates (bearing relatively more stable 1,4-dioxane moieties). However, the fact that in our case, the synthesis of methylenedioxyphenylethylamine would have been uncomfortably close to research on the preparation of an illegal drug, we focused on a much less investigated approach based on the Ritter reaction[20,21] starting from safrole (**7a**). The initial report[22] describing the reaction between the electron-rich methyleugenol and veratronitrile mentions a 53% yield of the corresponding dihydroisoquinoline. However, the authors also state that no compound could be isolated when starting from safrole (**7a**). On the other hand, a contemporary research group described a low yield (6.5%) of an electron-rich 1-phenylisoquinoline which was obtained from safrole (**7a**) and veratricamide in boiling benzene in the presence of phosphorus oxychloride.[23] More remarkably, another group described the preparation of electron-rich 1-phenylisoquinoline from the vinylic isosafrole and piperonal oxime (or amide) under the same reaction conditions.[24,25]

Our first trials, starting from safrole (**7a**) and 3,4,5-trimethoxybenzonitrile (**8a**) in concentrated sulfuric acid, expectedly[22] only led to extensive decomposition. However, as early reports pointed out that a methylenedioxy group seems to tolerate relatively strong water-free acidic conditions,[19,23] we reasoned that the decomposition could be caused by the nature of the counter-ion of the acid used, and its water content. Accordingly, we tried other strong acids bearing a soft counter ion. Our best results were obtained with tetrafluoroboric acid in ether using a not very standard experimental setting (see Section 2). Thus a 17% yield of the isoquinoline **9a** was obtained using 1 equiv. of 3,4,5-trimethoxybenzonitrile (**8a**), 2 equiv. of safrole (**7a**) and tetrafluoroboric acid (Scheme 3). Trials with other substrates were undertaken and a yield of 36% of **9b** was obtained from methyleugenol (**7b**) and compound **8a**, whereas 16% of the corresponding dihydroisoquinoline **9c** was obtained from safrole (**7a**) and benzonitrile (**8c**). Moreover, less than 2% of dihydroisoquinoline was observed in a not quite pure chromatography fraction of the result of the reaction between allylbenzene and compound **8a**. These trials further confirmed the fragility of the safrole methylenedioxy moiety as well as the need for electron-donating groups on the allyl aryl component to obtain a cyclization reaction into dihydroisoquinoline.

From compound **9a**, an aromatisation step using palladium over charcoal gave compound **10**. This was followed by the 3-methyl oxidation[1] via the isoquinoline *N*-oxide **11** which produce compound **12** in a 61% yield. It is noteworthy that the use of acetic anhydride was necessary for the rearrangement of the *N*-oxide **11**, as the use of trifluoroacetic anhydride led to extensive acid-caused dealkylation and



	R_1	R_2	R_3	% **9**
a	OCH_2O		OCH_3	17%
b	OCH_3	OCH_3	OCH_3	36%
c	OCH_2O		H	16%



Scheme 3. (i) 54% HBF_4, Et_2O. (ii) Pd/C, decaline, reflux. (iii) 3-Chloroperoxybenzoic acid, CH_2Cl_2. (iv) (a) Ac_2O, 1,2-dichlorobenzene, reflux, (b) KOH, aqueous ethanol, 50 °C. (v) Dess–Martin periodinane, CH_2Cl_2. (vi) $AgNO_3$, NaOH, MeCN–H_2O.

subsequent decomposition. A two-stage oxidation of alcohol **12** via aldehyde **13** turned out to be necessary to obtain the target acid **2**, as no efficient method was found to oxidize directly alcohol **12** into acid **2**.

In conclusion, our first approach toward the preparation of the pentaoxygenated-1-aryl-3-carboxylisoquinoline **2** was based on a planned Suzuki reaction between 1-bromoisoquinoline **3** and arylboronates. Even if this led us to devise an original synthesis of 1-hydroxyisoquinoline-3-carboxylic acid methyl ester (**6**) an alternative to the inherently long preparations of oxygen-bearing bromophthalimides was sought. Thus a second approach, based on the Ritter reaction between safrole **7a** and 3,4,5-trimethoxybenzonitrile **8a**, was found possible by using tetrafluoroboric acid in ether under quite original reaction conditions (see Section 2). Although this synthesis provides, so far, a 17% yield of the dihydroisoquinoline **9a**, the very small number of steps following the quick preparation of this ring system provides a fast access to original electron-rich 1-arylisoquinolines bearing a functional group on carbon 3.

2. Experimental

2.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer at 300 and 75 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed on Merck silica gel 60 (0.035–0.070 mm). Low and high resolution mass spectra were obtained by Mrs Nicole Morin (ENS, 24 rue Lhomond, F-75231 Paris) on a MS 700 Jeol.

2.1.1. 2-Acetylamino-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-malonic acid dimethyl ester (5). Dry dimethyl acetamidomalonate (6.51 g, 0.034 mol) was dissolved in dry DMF (260 mL; dried over 4 Å molecular sieves). To this solution was added 60% sodium hydride (suspension in mineral oil) (1.37 g, 0.034 mol). The suspension was stirred under a moisture-protected atmosphere (calcium chloride drying tube) for 30 min and then solid bromophthalide (**4**) (6.67 g, 0.031 mol) was added. The resulting mixture was stirred at room temperature overnight and then concentrated under a reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and the suspension was washed with 1 N sodium hydroxide, water and dried over magnesium sulfate. After removal of the solvent, under reduced pressure, compound **5** was obtained as a solid (7.38 g, 73%) which could be used for the next step without further purification or recrystallized in a mixture of toluene and heptane, Mp 161 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J=7.7 Hz, 1H), 7.78 (d, J=7.7 Hz, 1H), 7.60 (t, J=7.7 Hz, 1H), 7.49 (t, J=7.7 Hz, 1H), 6.55 (s (br), 1H), 6.31 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=169.5, 168.8, 165.9, 165.6, 144.2, 133.5, 129.9, 127.4, 126.5, 124.4, 81.7, 67.6, 54.5, 53.3, 22.3. Anal. calcd for $C_{15}H_{15}NO_7$: C, 56.08; H, 4.71; N, 4.36; found C, 56.50; H, 4.72; N, 4.16.

2.1.2. 1-Hydroxyisoquinoline-3-carboxylic acid methyl ester (6). Compound **5** (1 g, 3.11 mmol) was dispersed in 1,2-dichlorobenzene (80 mL). The freshly distilled[9] boron trifluoride diethyl etherate complex (0.45 mL, 3.55 mmol) was added and the mixture was heated to reflux under a moisture-protected atmosphere (calcium chloride drying tube) for 30 min. The solution was allowed to cool, diluted in dichloromethane (100 mL), washed twice with water and dried over magnesium sulfate. After removal of the solvent under vacuum, the residue was purified by chromatography over silica gel eluting with a 99:1 mixture of dichloromethane and methanol to give compound **6** (0.44 g, 69%) which has characteristics identical with the previously reported data.[12]

2.1.3. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline (9a). In a 2.5 L thick high density polyethylene bottle, safrole (**7a**) (10.07 g, 0.062 mol) and 3,4,5-trimethoxybenzonitrile (**8a**) (6 g, 0.031 mol) were mixed together at room temperature before 54% tetrafluoroboric acid in ether (10 mL, 0.072 mol) was added and the bottle quickly (and tightly) closed. WARNING: at this stage a quite important heat evolution along with pressure build up takes places in a matter of one minute, real care should be taken in choosing (and closing) the plastic bottle used. Operating under a well-ventilated hood should be one of the safety step taken. For our part, former 2.5 L ethanol bottles (with thus a large empty volume) sold by Merck-Prolabo (article 20 820 327) with a thickness of about 2 mm underwent some shape change but never ruptured when using the amount of reagents described above. Chemists who would choose to reproduce this work should either use proper quick-closing (or featuring the means to add a reagent under pressure) plastic-coated reactors, that we lacked, or take due precautions to avoid injury and poisoning in case of a bottle 'eruption'. This bottle (which was never reused) was left to cool overnight and cautiously opened. Ethanol (500 mL) was then added followed, portion-wise, by sodium methanolate (4.3 g, 0.08 mol). The resulting dark slurry was shaken and stirred until no more solid remained attached to the bottom of the bottle. The suspension was concentrated to dryness and after its adsorption on a portion of silica, the residue was purified by chromatography over silica gel eluting first with a 1:1 mixture of ethyl acetate–cyclohexane followed by ethyl acetate and then ethyl acetate containing 2% of triethylamine. The first fraction yielded variable amounts of unreacted benzonitrile and little unreacted safrole, the second fraction gave compound **9a**. This fraction was recrystallized, with some loss, in a mixture of ethanol and water to give compound **9a** (1.81 g, 17.2%). Mp=142 °C. ^{1}H NMR ($CDCl_3$): δ=1.42 (d, 3H, J=6.6 Hz), 2.49 (dd, 1H, J=13.2, 15.4 Hz), 2.68 (dd, 1H, J=5.2, 13.2 Hz), 3.60 (m, 1H), 3.85 (s, 9H), 5.94 (s, 2H), 6.70 (s, 1H), 6.74 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=21.7, 33.8, 52.8, 56.2, 60.8, 101.2, 106.0, 108.0, 108.4, 122.6, 134.1, 138.8, 138.9, 145.9, 149.0, 153.1, 165.3. HRMS calcd for $C_{20}H_{22}NO_5$: 356.1498; found ($M+H^+$): 356.1495.

2.1.4. 6,7-Dimethoxy-3-methyl-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline (9b). Following the above procedure, using 1 equiv. of methyleugenol and 3,4,5-trimethoxybenzonitrile as well as 1.1 equiv. of 54% tetrafluoroboric acid in ether, compound **9b** was obtained in 36% yield. Mp=140 °C (ethanol–water). ^{1}H NMR

($CDCl_3$): δ=1.42 (d, 3H, J=6.5 Hz), 2.50 (dd, 1H, J=13.5, 14.6 Hz), 2.70 (dd, 1H, J=5.2, 3.5 Hz), 3.61 (m, 1H), 3.71 (s, 3H), 3.89 (s, 6H), 3.84 (s, 3H), 3.91 (s, 3H), 6.73 (s, 1H), 6.79 (s, 2H), 6.80 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=21.7, 32.2, 52.8, 56.0, 56.1, 60.8, 106.1, 110.4, 111.4, 121.2, 132.4, 134.6, 138.9, 146.9, 150.9, 152.9, 165.4. HRMS calcd for $C_{21}H_{25}NO_5$: 372.1811; found ($M+H^+$): 372.1802.

2.1.5. 7-Methyl-5-phenyl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline (9c). From 1 equiv. of benzonitrile, 2 equiv. of safrole and 2 equiv. of 54% tetrafluoroboric acid in ether, following the same procedure described for **9a**, a 16% yield of compound **9c** was obtained. In this case, the waxy chromatographic fraction obtained was re-dissolved in dichloromethane, washed with a 1 N sodium hydroxide solution, water and then dried over magnesium sulfate before concentrating to dryness. ^{1}H NMR ($CDCl_3$): δ=1.41 (d, 3H, J=7.0 Hz), 2.50 (dd, 1H, J=12.8, 15.4 Hz), 2.72 (dd, 1H, J=5.2, 15.4 Hz), 3.63 (m, 1H), 5.94 (s, 2H), 6.68 (s, 1H), 6.71 (s, 1H), 7.40 (m, 3H), 7.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=21.6, 33.8, 52.8, 101.2, 108.0, 108.5, 122.7, 128.1, 128.8, 129.1, 133.9, 138.3, 145.8, 149.9, 165.6. HRMS calcd for $C_{17}H_{15}NO_2$: 266.1181; found ($M+H^+$): 266.1184.

2.1.6. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-[1,3]-dioxolo[4,5-*g*]isoquinoline (10). Compound **9a** (1.75 g, 4.9 mmol) and 10% palladium over charcoal (0.25 g, 0.246 mmol) were heated to reflux in decaline (80 mL) for 12 h. The suspension was diluted in dichloromethane, filtered and concentrated to dryness under vacuum. The residue was purified by chromatography over silica gel eluting with a 2:3 mixture of ethyl acetate–cyclohexane to give compound **10** (1.26 g, 72%). A small portion was recrystallized in aqueous methanol. Mp=149 °C lit.[19] 152–154 °C. ^{1}H NMR ($CDCl_3$): δ=2.65 (s, 3H), 3.87 (s, 6H), 3.88 (s, 3H), 6.04 (s, 2H), 6.79 (s, 2H), 7.02 (s, 1H), 7.25 (s, 1H), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=24.1, 56.2, 60.9, 101.5, 102.2, 103.2, 106.8, 118.0, 121.8, 135.7, 136.0, 138.2, 147.7, 149.9, 150.6, 153.2, 158.3. HRMS calcd for $C_{20}H_{20}NO_5$: 354.1341; found ($M+H^+$): 354.1339.

2.1.7. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-[1,3]-dioxolo[4,5-*g*]isoquinoline *N*-oxide (11). Compound **10** (1.04 g, 2.9 mmol) was dissolved in dichloromethane (100 mL) and 70% 3-chloroperoxybenzoic acid (2.18 g, 8.8 mmol) was added. The solution was stirred overnight, further diluted in dichloromethane and washed with 1 N sodium hydroxide, water and then dried over magnesium sulfate to give compound **11** (0.98 g, 90%) pure enough for the next step. Mp=258 °C. ^{1}H NMR ($CDCl_3$): δ=2.62 (s, 3H), 3.84 (s, 6H), 3.92 (s, 3H), 6.03 (s, 2H), 6.62 (s, 2H), 6.66 (s, 1H), 6.99 (s, 1H), 7.48 (s,1H). ^{13}C NMR ($CDCl_3$): δ=18.0, 56.0, 60.8, 101.6, 101.7, 102.2, 106.8, 121.5, 125.7, 126.8, 127.6, 138.2, 144.3, 145.4, 149.0, 149.3, 153.6. HRMS calcd for $C_{20}H_{20}NO_6$: 370.1291; found ($M+H^+$): 370.1290.

2.1.8. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-7-yl]-methanol (12). Compound **11** (0.65 g, 1.76 mmol) and acetic anhydride (2 mL, 21.2 mmol) were refluxed in 1,2-dichlorobenzene (60 ml) for 4 h. The solution was concentrated to dryness and the residue was stirred in 70% aqueous ethanol (80 mL) containing sodium hydroxide (0.8 g, 0.02 mol) at 50 °C for 30 min. The resulting solution was made acid with 1 N hydrochloric acid, saturated with sodium chloride and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate before concentrating to dryness. The residue was recrystallized in toluene to give compound **12** (0.4 g, 61%). Mp=161 °C. ^{1}H NMR ($CDCl_3$): δ=3.90 (s, 6H), 3.93 (s, 3H), 4.88 (s, 2H), 6.09 (s, 2H), 6.83 (s, 2H), 7.11 (s, 1H), 7.34 (s, 1H), 7.48 (s,1H). ^{13}C NMR ($CDCl_3$): δ=56.2, 60.9, 64.7, 101.7, 102.7, 103.3, 106.8, 115.9, 123.1, 135.2, 136.0, 138.3, 148.3, 150.9, 150.95, 153.2, 158.1. HRMS calcd for $C_{20}H_{20}NO_6$: 370.1291 found ($M+H^+$): 370.1288.

2.1.9. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinoline-7-carbaldehyde (13). Compound **12** (0.35 g, 0.95 mmol) and Dess–Martin periodinane[26] (0.6 g, 1.42 mmol) were stirred in dichloromethane (50 mL) for 2 h. The solution was diluted with more dichloromethane and washed with 1 N sodium hydroxide, water and dried over magnesium sulfate before concentrating to dryness to give aldehyde **13** (0.32 g, 91%) which could be used directly for the next step or recrystallized in aqueous ethanol. Mp=145–146 °C. ^{1}H NMR ($CDCl_3$): δ=3.88 (s, 6H), 3.90 (s, 3H), 6.13 (s, 2H), 6.83 (s, 2H), 7.26 (s, 1H), 7.38 (s, 1H), 8.17 (s,1H), 10.20 (s, 2H). ^{13}C NMR ($CDCl_3$): δ=56.2, 60.9, 102.2, 103.8, 104.6, 106.8, 119.3, 126.8, 134.5, 134.8, 138.6, 145.4, 150.7, 151.2, 153.3, 159.2, 193.8. HRMS calcd for $C_{20}H_{18}NO_6$: 368.1134; found ($M+H^+$): 368.1127.

2.1.10. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinoline-7-carboxylic acid (2). Compound **13** (0.32 g, 0.87 mmol) was dissolved in acetonitrile (30 mL), water (5 mL) and silver nitrate (0.7 g, 4.12 mmol) were added to the solution followed by sodium hydroxide (0.26 g, 6.5 mmol). The blackening solution was stirred for 90 min and made acid with 1 N hydrochloric acid. This was saturated with sodium chloride and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate before concentrating to dryness. The residue was recrystallized in a mixture of toluene and heptane to give acid **2** (0.24 g, 71%). Mp=229 °C. ^{1}H NMR ($CDCl_3$): δ=3.90 (s, 6H), 3.95 (s, 3H), 6.16 (s, 2H), 6.81 (s, 2H), 7.30 (s, 1H), 7.44 (s, 1H), 8.45 (s,1H). ^{13}C NMR ($CDCl_3$): δ=54.4, 61.0, 102.4, 104.0, 104.4, 106.9, 121.0, 126.4, 133.7, 135.9, 137.8, 138.9, 150.8, 151.7, 153.4, 157.5, 165.1. HRMS calcd for $C_{20}H_{18}NO_7$: 384.1083; found ($M+H^+$): 384.1090.

References and notes

1. Janin, Y. L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M.-F. *J. Chem. Soc. Perkin Trans. I* **2002**, 529–532.
2. Decaudin, D.; Castedo, M.; Nemati, F.; Beurdeley-Thomas, A.; De Pinieux, G.; Caron, A.; Pouillart, P.; Wijdenes, J.; Rouillard, D.; Kroemer, G.; Poupon, M. F. *Cancer Res.* **2002**, *62*, 1388–1393.
3. Casellas, P.; Galiegue, S.; Basile, A. S. *Neurochemistry Int.* **2002**, *40*, 475–486.

4. Beurdeley-Thomas, A.; Miccoli, L.; Oudard, S.; Dutrillaux, B.; Poupon, M.-F. *J. Neuro-Oncol.* **2000**, *46*, 45–56.
5. Batra, S.; Sabnis, Y. A.; Rosenthal, P. J.; Avery, M. A. *Bioorg. Med. Chem.* **2003**, *11*, 2293–2299.
6. Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P. *Tetrahedron* **2001**, *57*, 8297–8303.
7. Capilla, A. S.; Sanchez, I.; Caignard, D. H.; Renard, P.; Pujol, M. D. *Eur. J. Med. Chem.* **2001**, *36*, 389–393.
8. Bermejo, A.; Andreu, I.; Suvire, F.; Léonce, S.; Caignard, D. H.; Renard, P.; Pierré, A.; Enriz, R. D.; Cortes, D.; Cabedo, N. *J. Med. Chem.* **2002**, *45*, 5058–5068.
9. Janin, Y. L.; Zoltobroda, G.; Huel, C.; Monneret, C. *J. Carbohydrate Chem.* **2002**, *21*, 275–286.
10. Hickey, D. M. B.; MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *J. Chem. Soc. Perkin Trans. I* **1987**, 921–927.
11. Gautier, N.; Dodd, R. H. *Synth. Commun.* **1998**, *28*, 3769–3777, and references cited therein.
12. Tucker, S. C.; Brown, J. M.; Oakes, J.; Thornthwaite, D. *Tetrahedron* **2001**, *57*, 2545–2554.
13. Hiebl, J.; Kollmann, H.; Levinson, S. H.; Offen, P.; Shetzline, S. B.; Badlani, R. *Tetrahedron Lett.* **1999**, *40*, 7935–7943.
14. Stiller, E. T. *J. Chem. Soc.* **1937**, 473–476.
15. Chattopadhyay, S. K.; Maity, S.; Pal, B. K.; Panja, S. *Tetrahedron Lett.* **2002**, *43*, 5079–5081.
16. Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279–1300.
17. Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150.
18. Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151–190.
19. Bruckner, V.; von Fodor, G. *Ber. Chem.* **1938**, *71*, 541–549.
20. Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213–325.
21. Ho, T.-L.; Chein, R.-J. *J. Org. Chem.* **2004**, *69*, 591–592.
22. Ritter, J. J.; Murphy, F. X. *J. Am. Chem. Soc.* **1952**, *74*, 763–765.
23. Kametani, T.; Kano, S. *J. Pharm. Soc. Jpn* **1952**, *72*, 1539–1541, *Chem. Abstr.* **1953**, 10538.
24. Madroñero, R.; Alvarez, E. F.; Lora-Tamayo, M. *An. Quim.* **1955**, *51B*, 465–468, *Chem. Abstr.* **1956**, 7805e.
25. Madroñero, R.; Fernàndez, E. A.; Lora-Tamayo, M. *An. Quim.* **1955**, *51B*, 276–282, *Chem. Abstr.* **1956**, 3445b.
26. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 5487–5493

Synthesis of monofluorinated indolizines and their derivatives by the 1,3-dipolar reaction of *N*-ylides with fluorinated vinyl tosylates

Xiang Fang,[a,b] Yong-Ming Wu,[a,*] Juan Deng[a] and Shao-Wu Wang[b,*]

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*
[b]*Department of Chemistry, Anhui Normal University, 1 Renming Road, Wuhu Anhui 241000, China*

Received 15 July 2003; revised 24 February 2004; accepted 1 April 2004

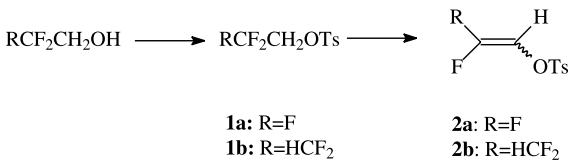
Abstract—Monofluorinated indolizines **4**, benzo[*d*]indolizines **7** and 4*H*-pyrrolo[1,2-*a*]benzimidazoles **8** were synthesized in moderate yields by 1,3-dipolar reaction between fluorinated vinyl tosylates **2a** and *N*-ylides of pyridinium, isoquinolinium and benzimidazolinium, generated in situ from their halides salts. When the same *N*-ylides were allowed to react with 2,3,3-trifluoro-1-propenyl tosylate **2b**, the unexpected product formylated indolizines and their derivatives **9** were obtained. The reaction mechanism is also proposed.

1. Introduction

Indolizine derivatives possess valuable biological activities and have been studied for their psychotropic anti-inflammatory, analgesic, antimicrobial, antiexudative and hypoglycemia activities.[1] Meanwhile, fluorinated heterocyclic compounds have received increasing attention due to their potential biological and industrial applications.[2] In the past few decades, considerable efforts have been paid to the exploitation of new and convenient synthetic routes to these compounds.[3] Comparing with direct fluorination and halo-exchange reactions, the application of fluorine-containing building blocks in organic synthesis has become a more and more important strategy for the construction of fluorinated heterocycles due to its higher selectivity and milder conditions. 1,3-Dipolar cycloaddition is one of the most important methods for constructing five-membered heterocycles.[4] Recently, it has also been used for the synthesis of fluorinated heterocyclic compounds. In 1980s, Banks reported a series of papers on the 1,3-dipolar cycloaddition reactions of pyridinium ylides with various perfluoroalkenes, perfluoroazaolefins and trifluoroacetonitrile to synthesize monofluoro- or tirfluoromethyl-substituted heterocycles, such as pyrazolo[1,2-*a*]pyridines and indolizines.[5] Huang reported the reactions of various nitrogen-containing heterocycles ylides with 2,2-dihydroperfluoroalkanoates to form perfluoroalkylated heterocycles.[6] Chen recently presented a reaction of *N*-containing heterocycles with gaseous fluoroalkenes under atmospheric pressure ylides fluorinated heterocycles.[7] Zhu reported the reactions of 4-ethoxyl-1,1,1-trifluorobut-3-ene-2-one with *N*-ylides to synthesize trifluoroacetyl substituted heterocycles.[8] In the present paper, we wish to report a new approach towards monofluorinated indolizines and 4*H*-pyrrolo[1,2-*a*]benzimidazoles via the reaction of ylides of *N*-containing heterocycles with fluorinated alkenyl tosylates.

2. Results and discussion

The starting material—fluorinated alkenyl tosylates were prepared from the corresponding fluorinated alcohol[9] (Scheme 1).



Scheme 1. Preparation of fluorinated alkenyl tosylates.

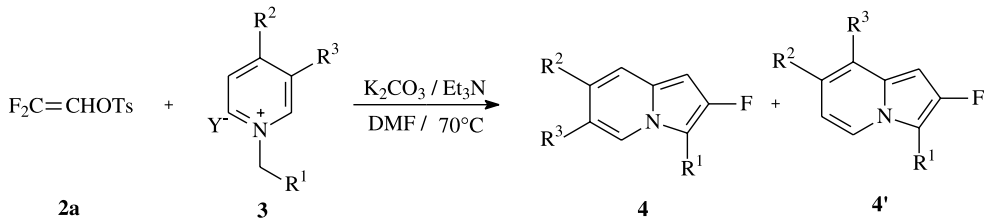
2.1. Preparation of fluorinated indolizines and 4*H*-pyrrolo[1,2-α]benzimidazoles

The fluorinated indolizines was prepared in moderate yield by heating a mixture of 2,2-difluorovinyl tosylate **2a**, pyridinium halides **3**, K_2CO_3 and Et_3N in DMF at 70 °C for 24 h (Scheme 2 and Table 1).

When R3≠H, a mixture of 6- and 8-substituted indolizine

Keywords: 1,3-Dipolar reaction; *N*-Ylides; Fluorinated vinyl tosylate; Monofluorinated indolizines and derivatives; Synthesis.
* Corresponding authors. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail address: ymwu@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.012

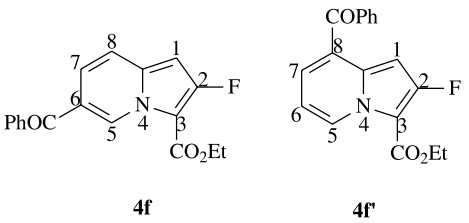


Scheme 2. Synthesis of fluorinated indolizines.

Table 1. Synthesis of fluorinated indolizines **4**

Entry	Pyridinium halides **3**			Product	Yield (%)[a] of **4**
	R^1	R^2	R^3		
1	COPh	H	H	**4a**	34
2	COPh	CH_3	H	**4b**	23
3	COPh	H	CH_3	**4c**:**4c′** (1:2)[b]	37
4	COPh	H	Br	**4d**:**4d′** (1:1.5)	27
5	CO_2Et	H	Br	**4e**:**4e′** (1:6)	40
6	CO_2Et	H	COPh	**4f**:**4f′** (1:1.5)	8
7	CN	H	H	**4g**	59
8	CN	CH_3	H	**4h**	33
9	CN	H	CH_3	**4i**:**4i′**(1:10)[b]	67
10	CN	H	Br	**4j**:**4j′** (1:1.7)	58
11	COPh	H	CN	**4k**	60

[a] Isolated yields.
[b] The mixture cannot be separated by flash chromatography.



4f **4f′**

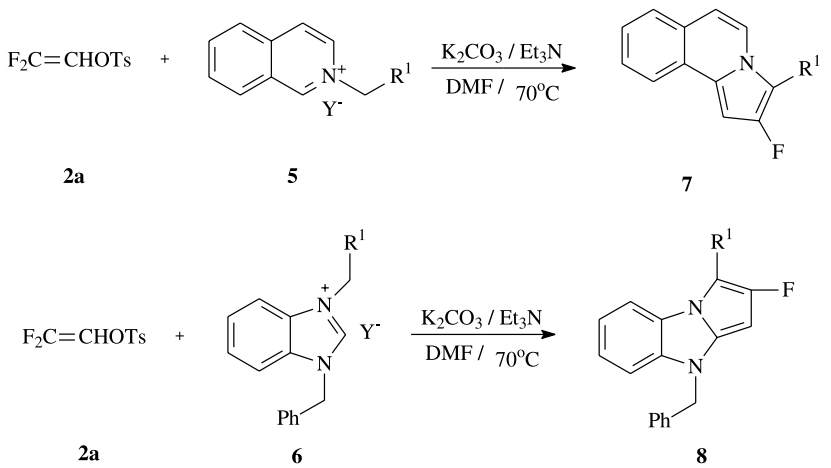
Figure 1. Structure of 6-benzoyl- and 8-benzoylindolizine derivatives **4f** and **4f′**.

derivatives **4** and **4′** were obtained in various ratio (entries 3–6,10, Table 1). The structures of products **4** and **4′** were determined on the basis of ^1H NMR spectroscopy. The proton at C-5 of product **4f** was a singlet while in product **4f′** (Fig. 1) it was a doublet, coupled with proton at C-6. According to Table 1, we find that for the same R^1 substrate, the ratio of **4** and **4′** was related to the steric hindrance of R^3 group. More **4′** (8-substituted indolizine) were formed when R^3 was a sterically hindered substitutes (Me, Br, PhCO) than a smaller group (CN) (entry 3 vs 4; entry 5 vs 6 and entry 9 vs 10, Table 1). If R^2 was an electron-withdrawing group (e.g., acetyl), then only less than 5% yield of the desired products could be obtained (from ^{19}F NMR spectra).

Under the same conditions when isoquinolinium halides **5**, benzimidazolinium halides **6** were treated with **2a**, respectively, fluorinated benzo[*d*]indolizines **7** and 4*H*-pyrrolo[1,2-α]-benzimidazoles **8** were obtained in moderate yields (Scheme 3, Table 2).

As reported by Banks,[5a] the reaction mechanism is proposed in Scheme 4. The 1,3-dipolar cycloaddition between pyridinium, isoquinolinium or benzimidazolinium *N*-ylides, generated in situ from the corresponding halides in the presence of a base, with the 2,2-difluorovinyl tosylate **2a**, gave the intermediate which aromatized by eliminating a HF and TsOH to yield the fluorinated indolizine or 4*H*-pyrrolo[1,2-*a*]benzimidazole, respectively, (Scheme 4).

It is essential to choose a suitable base for these reactions. The base should not only be able to deprotonate the pyridinium, isoquinolinium or benzimidazolinium halides to form the corresponding *N*-ylides, but also to effectively eliminate HF and TsOH to produce the indolizines or 4*H*-pyrrolo[1,2-*a*]benzimidazoles after the 1,3-dipolar cycloaddition. A mixture of organic and inorganic bases, K_2CO_3 and Et_3N, was found to give the best results. To compare the



Scheme 3. Synthesis of fluorinated benzo[*d*]indolizines **7** and 4*H*-pyrrolo[1,2-*a*]benzimidazoles **8**.

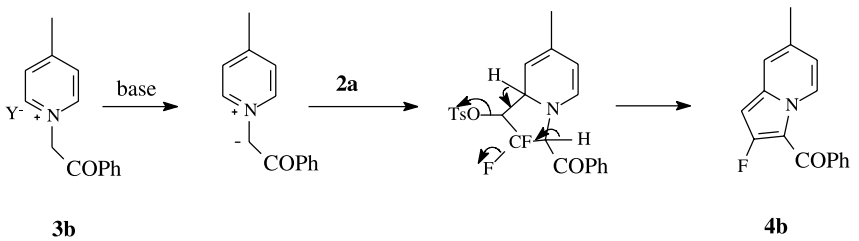
Table 2. Synthesis of fluorinated benzo[*d*]indolizines **7** and 4*H*-pyrrolo[1,2-*a*]benzimidazoles **8**

Entry	R^1	Product	Yield (%)[a] of **7**,**8**
1	COPh	**7a**	59
2	CO_2Et	**7b**	10
3	CN	**7c**	68
4	COPh	**8a**	31
5	CO_2Et	**8b**	61
6	CN	**8c**	12

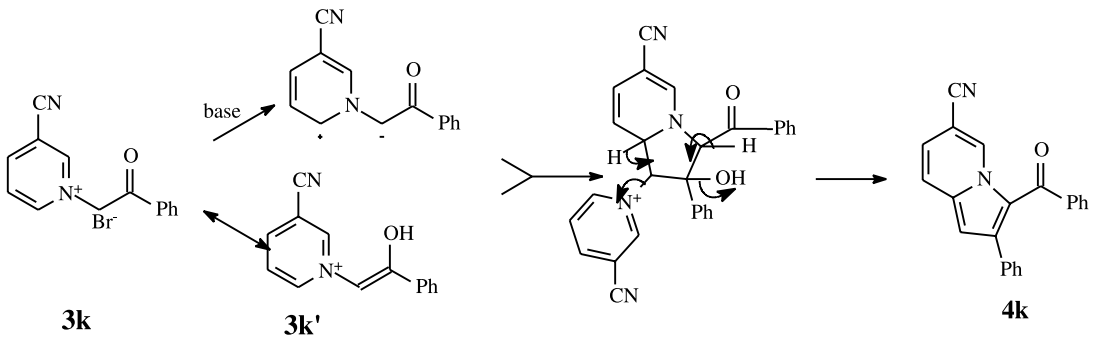
[a] Isolated yields.

2.2. Preparation of formyl indolizines and derivatives

When 2,3,3-trifluoro-1-propenyl tosylate **2b** was allowed to react with pyridinium **3** and isoquinolinium **5** *N*-ylides under similar conditions, the product obtained unexpectedly, showed no ^{19}F NMR signal. Meanwhile, its ^1H NMR spectroscopy showed a single peak at low field (ca. δ 10.2 ppm), which could be assigned to the proton of aldehyde or acid. The molecular structure was determined by a single-crystal X-ray diffraction study (Fig. 2). The selected bond lengths and bond angles of **9d** are listed in Table 3.[13]



Scheme 4.



Scheme 5.

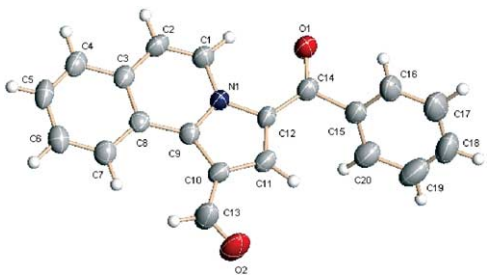


Figure 2. The X-ray crystal structure of **9d**.

solvent effect, the same reaction was also carried out in THF, 1,4-dioxane, acetonitrile. However, they all gave lower yield than DMF did.

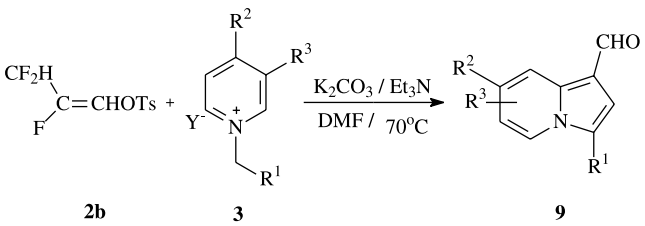
It was noticed that the cycloaddition product **3k** (entry 11, Table 1) showed no ^{19}F NMR signal. It was characterized by ^1H NMR spectroscopy, MS and micro analysis. The reaction mechanism is depicted in Scheme 5. A second molecule of pyridinium salt in enol form (**3k′**) is attacked by *N*-ylide followed by cyclization, and aromatization to give the product **4k**.

Other *N*-ylides gave similar results when they were treated with **2b**. The detailed results are listed in Scheme 6 and Table 3. When *meta*-substituted pyridinium salt **3b**, **3e** reacted with **2b**, only 8-substituted indolizines **9** could be isolated (Table 4, entries 1–3).

From these results, it was found that the *N*-ylide did not directly attack 2,3,3-trifluoro-1-propenyl tosylate **2b**. From

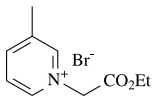
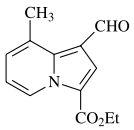
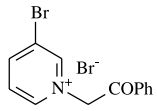
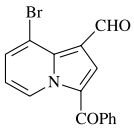
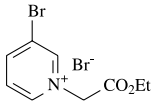
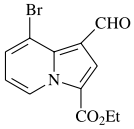
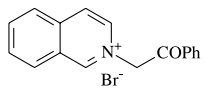
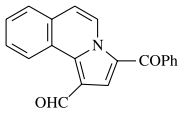
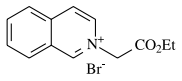
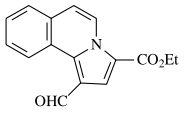
Table 3. The selected bond lengths and bond angles of **9d**

Bond lengths (Å)		Bond angles (°)	
O(1)–C(14)	1.225(3)	C(1)–N(1)–C(9)	122.8(2)
O(2)–C(13)	1.206(3)	C(1)–N(1)–C(12)	127.0(2)
N(1)–C(1)	1.385(3)	C(9)–N(1)–C(12)	110.17(19)
N(1)–C(9)	1.387(3)	C(2)–C(1)–N(1)	119.5(3)
N(1)–C(12)	1.397(3)	C(2)–C(1)–H(1)	126.6(12)
C(12)–C(14)	1.437(3)	N(1)–C(1)–H(1)	113.9(12)
C(14)–C(15)	1.495(3)	C(1)–C(2)–C(3)	121.7(2)
C(9)–C(10)	1.419(3)	C(1)–C(2)–H(2)	120.5(13)
C(10)–C(13)	1.439(3)	N(1)–C(9)–C(10)	106.0(2)
C(10)–C(11)	1.382(3)	N(1)–C(9)–C(8)	117.9(2)
C(11)–C(12)	1.373(3)	O(1)–C(14)–C(12)	123.5(2)
C(1)–C(2)	1.362(3)	O(2)–C(13)–C(10)	123.7(3)



Scheme 6. The reaction of *N*-ylides with **2b**.

Table 4. Synthesis of formyl indolizines **9**

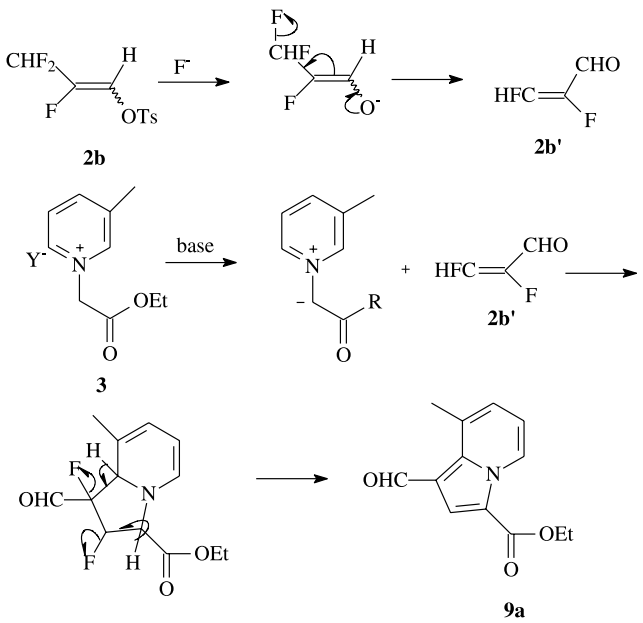
Entry	Halides	Product		Yield (%)[a] of **9**
1			**9a**	57
2			**9b**	50
3			**9c**	63
4			**9d**	65
5			**9e**	58

[a] Isolated yields.

the view point of molecular polarity (Scheme 7), *N*-ylide should attack at C2 of the tosylate **2b** and as a result the 2-substituted product should be formed. However, only 1-substituted product was obtained. Funabiki[10] reported that 2,3,3-trifluoro-1-propenyl tosylate **2b** underwent cleavage of the enol oxygen–sulfur bond with fluoride ion, followed by the loss of an allylic fluorine atom to generate α,β-difluoroacrylaldehyde **2b′** (Scheme 7).

In our experiment, a trace of fluoride ion can indeed accelerate the reaction. When a catalytic amount of tetrabutylamonium fluoride (10% mol) was added to the reaction system, the reaction temperature could be reduced to room temperature. In this way, the mechanism may be depicted as shown in Scheme 7.

In conclusion, we have developed a new method for the synthesis of monofluorinated indolizine **4**, benzo[*d*]indolizines **7**, 4*H*-pyrrolo[1,2-*a*]benzimidazoles **8** and formyl indolizines derivatives **9**. Further studies on the application of fluorinated vinyl tosylates in organic synthesis are in progress.



Scheme 7.

3. Experimental

3.1. General

Melting points and boiling points are uncorrected. IR spectra were obtained with a Perkin–Elmer 983G spectrometer on KBr disks. NMR spectra were recorded either on a Varian-360L or a Bruker AM-300 spectrometer with $CDCl_3$ as solvent. Chemical shifts were reported in parts per million relative to TMS as an internal standard ($\delta_{TMS}=0$) for ^1H NMR spectra and $CFCl_3$ as an internal standard [$\delta_{CFCl3}=0$] for ^{19}F NMR (upfield shift being designated as negative) spectra. Coupling constants are given in Hertz (Hz). Low- and high-resolution mass spectra were recorded on a Hewlett–Packard HP-5989A and a Finnigan MAT spectrometer, respectively. Elemental analyses were performed at SIOC. Single-crystal X-ray diffraction was performed by SMART APEX CCD diffractometer and the analysis software was Shelx97. Pyridinium, isoquinolinium, benzimidazolinium halides were prepared by the reported method.[11]

3.2. General procedure for the preparation of fluorinated indolizines and 4H-pyrrolo[1,2-α]benzimidazoles

To a solution of *N*-ylide halide (**3**, **5** or **6**) (1.5 mmol) in *N*,*N*-dimethylformamide (DMF, 10 mL) were added K_2CO_3 (1.5 mmol), Et_3N (1.5 mmol) and 2,2-difluorovinyl tosylate **2a** (1.0 mmol). After stirring at 70 °C for 24 h, 1 N HCl was added to neutralize the reaction mixture and the aqueous layer was extracted with diethyl ether (3×30 mL). The combined extracts were washed with brine (2×20 mL) and dried over Na_2SO_4. After removal of the solvent at reduced pressure the residue was purified by flash column chromatography on silica gel using ethyl acetate and petroleum (1:20) as eluent.

3.2.1. 2-Fluoro-3-benzoylindolizine 4a. Yield 34%; yellow solid; mp 95–97 °C, (95–97 °C[12]); ^1H NMR (300 MHz,

$CDCl_3$) δ 9.81 (1H, d, J=6.9 Hz), 7.78–7.73 (2H, m), 7.59–7.45 (4H, m), 7.24 (1H, d, J=8.4 Hz), 6.96 (1H, t, J=6.9 Hz), 6.20 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −134.60 (1F, *s*); MS (*m*/*z*) 239 (M^+, 100), 220 (4), 211(54). Anal. Calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.85; F, 7.94. Found: C, 75.19; H, 4.04; N, 5.70; F, 7.91.

3.2.2. 2-Fluoro-3-benzoyl-7-methylindolizine 4b. Yield 23%; yellow solid; mp 102–104 °C, (102–104 °C[12]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (1H, d, J=7.2 Hz), 7.76–7.71 (2H, m), 7.54–7.46 (3H, m), 7.24 (1H, s), 6.80 (1H, d, J=7.2 Hz), 6.07 (1H, s), 2.42 (3H, s); ^{19}F NMR (282 MHz, CCl_4) δ −134.22 (1F, s); MS (*m*/*z*) 253 (M^+, 13), 77 (100). Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53; F, 7.50. Found: C, 75.83; H, 4.68; N, 5.27; F, 7.45.

3.2.3. 2-Fluoro-3-benzoyl-6-methylindolizine 4c and 2-fluoro-3-benzoyl-8-methylindolizine 4c′. Yield 37%; yellow solid; mp 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68–9.63 (1H, d), 7.76–7.70 (2H, m), 7.57–7.29 (3H, m), 7.06–6.84 (2H, m), 6.17–6.12 (1H, d), 2.45–2.37 (3H, d); ^{19}F NMR (282 MHz, CCl_4) δ −135.27 (1F, s), −135.04 (1F, s); MS (*m*/*z*) 253 (M^+, 100), 234 (3); IR (cm^{-1}, KBr) 1597, 1470. Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53; F, 7.50. Found: C, 75.67; H, 4.81; N, 5.48; F, 7.48.

3.2.4. 2-Fluoro-3-benzoyl-6-bromoindolizine 4d. Yield 27%; yellow solid; mp 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (1H, s), 7.79–7.72 (5H, m), 7.41–7.28 (2H, m), 6.25 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −134.04 (1F, s); 2-fluoro-3-benzoyl-8-bromoindolizine **4d′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (1H, d, J=7.2 Hz), 7.61–7.45 (6H, m), 6.84 (1H, t, J=6.9 Hz), 6.43 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −133.42 (1F, s); MS (*m*/*z*) 319 (M+1, 21), 317 (22), 77 (100); IR (cm^{-1}, KBr) 1601, 1460. Anal. Calcd for $C_{15}H_9BrFNO$: C, 56.63; H, 2.85; N, 4.40; F, 5.97. Found: C, 56.71; H, 2.94; N, 4.16; F, 5.88.

3.2.5. 2-Fluoro-3-ethoxycarbonyl-6-bromoindolizine 4e. Yield 40%; reddish solid; mp 41–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, s), 7.83 (1H, d, J=7.8 Hz), 7.38 (1H, d, J=7.8 Hz), 6.22 (1H, s), 4.42 (2H, q, J=7.2 Hz), 1.43 (3H, t, J=7.2 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −138.39 (1F, s); 2-fluoro-3-ethoxycarbonyl-8-bromoindolizine **4e′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (1H, d, J=6.9 Hz), 7.30 (1H, d, J=7.5 Hz), 6.70 (1H, t, J=7.5 Hz), 6.39 (1H, s), 4.42 (2H, q, J=7.2 Hz), 1.43 (3H, t, J=7.2 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −137.66 (1F, s); IR (cm^{-1}, KBr) 1689, 1465. HRMS Calcd for $C_{11}H_9BrFNO_2$: 284.9801, found: 284.9792.

3.2.6. 2-Fluoro-3-ethoxycarbonyl-6-benzoylindolizine 4f. Yield 8%; yellow solid; mp 99–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (1H, s), 7.87–7.48 (7H, m), 6.34 (1H, s), 4.38 (2H, q, J=7.5 Hz), 1.38 (3H, t, J=7.5 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −124.54 (1F, s); 2-fluoro-3-ethoxycarbonyl-8-benzoylindolizine **4f′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (1H, d, J=7.5 Hz), 7.70–7.57 (4H, m), 7.46 (2H, d, J=7.5 Hz), 6.92 (1H, t, J=7.2 Hz), 6.84 (1H, s), 4.45 (2H, q, J=6.9 Hz), 1.45 (3H, t, J=7.5 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −122.33 (1F, s); MS (*m*/*z*) 311 (M^+, 100), 283 (18); IR (cm^{-1}, KBr) 1688, 1656, 1469. HRMS Calcd for $C_{18}H_{14}FNO_3$: 311.0958, found: 311.0953.

3.2.7. 2-Fluoro-3-cyanoindolizine 4g. Yield 59%; white needles; mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, J=6.9 Hz), 7.43 (1H, d, J=8.7 Hz), 7.11 (1H, t, J=8.1 Hz), 6.89 (1H, t, J=6.9 Hz), 6.19 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −143.15 (1F, s); MS (*m*/*z*) 160 (M^+, 100), 133 (20); IR (cm^{-1}, neat) 2208, 1447. Anal. Calcd for $C_9H_5FN_2$: C, 67.50; H, 3.15; N, 17.49. Found: C, 67.19; H, 3.13; N, 17.49.

3.2.8. 2-Fluoro-3-cyano-7-methylindolizine 4h. Yield 33%; white needles; mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, J=6.9 Hz), 7.19 (1H, s), 6.72 (1H, d, J=6.9 Hz), 6.04 (1H, s), 2.38 (3H, s); ^{19}F NMR (282 MHz, CCl_4) δ −143.09 (1F, s); MS (*m*/*z*) 174 (M^+, 100), 155 (4); IR (cm^{-1}, KBr) 2198, 1455. Anal. Calcd for $C_{10}H_7FN_2$: C, 68.96; H, 4.05; N, 16.08. Found: C, 68.93; H, 4.02; N, 16.28.

3.2.9. 2-Fluoro-3-cyano-6-methylindolizine 4i and 2-fluoro-3-cyano-8-methylindolizine 4i′. Yield 67%; pale red needles; mp 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, J=6.9 Hz), 6.91 (1H, d, J=6.9 Hz), 6.82 (1H, t, J=6.9 Hz), 6.16 (1H, s), 2.42 (3H, s); ^{19}F NMR (282 MHz, CCl_4) δ −143.67 (1F, s); MS (*m*/*z*) 174 (M^+, 100), 155 (5); IR (cm^{-1}, KBr) 2207, 1473. Anal. Calcd for $C_{10}H_7FN_2$: C, 68.96; H, 4.05; N, 16.08. Found: C, 68.79; H, 3.91; N, 16.22.

3.2.10. 2-Fluoro-3-cyano-6-bromoindolizine 4j. Yield 58%; yellow solid; mp 179–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.35 (1H, s), 7.18 (1H, d, J=9.3 Hz), 6.23 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −142.01 (1F, s); 2-fluoro-3-cyano-8-bromoindolizine **4j′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J=7.5 Hz), 7.33 (1H, s), 6.79 (1H, t, J=7.5 Hz), 6.39 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −141.42 (1F, s); MS (*m*/*z*) 240 (M+1, 97), 238 (100); IR (cm^{-1}, KBr) 2210, 1463. Anal. Calcd for $C_9H_4BrFN_2$: C, 45.22; H, 1.69; N, 11.72. Found: C, 45.24; H, 1.59; N, 11.63.

3.2.11. 2-Benzyl-3-benzoyl-6-cyanoindolizine 4k. Yield 60%; bright yellow solid; mp 211–212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (1H, S), 7.62 (1H, d, J=9.0 Hz), 7.44 (2H, d, J=8.1 Hz), 7.23–7.04 (9H, m), 6.75 (1H, s); MS (*m*/*z*) 322 (M^+, 100), 293 (52); IR (cm^{-1}, KBr) 2229, 1601. Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.78; H, 4.25; N, 8.52.

3.2.12. 2-F1uoro-benzoylbenzo[*d*]indolizines 7a. Yield 59%; yellow needles; mp 139–141 °C, (139–141 °C[12]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (1H, d, J=7.8 Hz), 8.11–8.06 (1H, m), 7.84–7.47 (8H, m), 7.16 (1H, d, J=7.5 Hz), 6.75 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −136.34 (1F, s); MS (*m*/*z*) 289 (M^+, 100), 261 (41). Anal. Calcd for $C_{19}H_{12}FNO$: C, 78.88; H, 4.18; N, 4.84; F, 6.57. Found: C, 78.85; H, 4.21; N, 4.65; F, 6.41.

3.2.13. 2-F1uoro-ethoxycarbonylbenzo[*d*]indolizines 7b. Yield 10%; white solid; mp 115–117 °C, (1115–117 °C[12]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (1H, d, J=7.5 Hz), 8.05–8.01 (1H, m), 7.71–7.67 (1H, m), 7.58–7.53 (2H, m), 7.06 (1H, d, J=7.2 Hz), 6.75 (1H, s), 4.44 (2H, d,

J=7.2 Hz), 1.45 (3H, t, J=7.2 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −140.49 (1F, s); MS (*m*/*z*) 257 (M^+, 100), 229 (40). Anal. Calcd for $C_{15}H_{12}FNO_2$: C, 70.03; H, 4.70; N, 5.44; F, 7.38. Found: C, 69.93; H, 4.63; N, 5.43; F, 7.15.

3.2.14. 2-F1uoro-cyanobenzo[*d*]indolizines 7c. Yield 68%; yellow needles; mp 135–137 °C, (135–137 °C[12]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, d, J=7.2 Hz), 7.91 (1H, d, J=7.2 Hz), 7.73–7.54 (3H, m), 7.11 (1H, d, J=7.2 Hz), 6.69 (1H, s); ^{19}F NMR (282 MHz, CCl_4) δ −144.28 (1F, s).

3.2.15. 1-Benzoyl-2-fluoro-4-benzyl-4*H*-pyrrolo[1,2-α]benzimidazole 8a. Yield 31%; yellow solid; mp 148–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, d, J=7.8 Hz), 7.86–7.81 (2H, m), 7.57–7.24 (11H, m), 5.46 (1H, s), 5.28 (2H, s); ^{19}F NMR (282 MHz, CCl_4) δ −127.91 (1F, s); MS (*m*/*z*) 368 (M^+, 35), 91 (100); IR (cm^{-1}, KBr) 1613, 1405. Anal. Calcd for $C_{24}H_{17}FN_2O$: C, 78.25; H, 4.65; N, 7.60; F, 5.16. Found: C, 78.22; H, 4.65; N, 7.35; F, 4.94.

3.2.16. 1-Ethoxycarbonyl-2-fluoro-4-benzyl-4*H*-pyrrolo[1,2-α]benzimidazole 8b. Yield 61%; white feather; mp 90–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (1H, d, J=9.3 Hz), 7.36–7.19 (8H, m), 5.42 (1H, s), 5.24 (2H, s), 4.43 (2H, q, J=7.2 Hz), 1.44 (3H, t, J=7.2 Hz); ^{19}F NMR (282 MHz, CCl_4) δ −133.54 (1F, s); MS (*m*/*z*) 336 (M^+, 53), 91 (100); IR (cm^{-1}, KBr) 1690, 1473. Anal. Calcd for $C_{20}H_{17}FN_2O_2$: C, 71.42; H, 5.09; N, 8.33. Found: C, 71.56; H, 4.95; N, 8.21.

3.2.17. 1-Cyano-2-fluoro-4-benzyl-4*H*-pyrrolo[1,2-α]benzimidazole 8c. Yield 12%; white solid; mp 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, d, J=7.5 Hz), 7.43–7.22 (8H, m), 5.34 (1H, s), 5.24 (2H, s); ^{19}F NMR (282 MHz, CCl_4) δ −137.27 (1F, s); MS (*m*/*z*) 289 (M^+, 29), 91 (100); IR (cm^{-1}, KBr) 2194, 1470. Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.60; H, 4.43; N, 14.36.

3.3. General procedure for the preparation of formyl indolizines

To a solution of pyridinium **3** or isoquinolinium **5** halide (1.2 mmol), K_2CO_3 (1.2 mmol), triethylamine (1.2 mmol) in *N*,*N*-dimethylformamide (DMF, 5 mL) was added a solution of 2,3,3-trifluoro-1-propenyl tosylate **2b** (1.0 mmol) in DMF (5 mL) at 70 °C. The mixture was stirred for 24 h and was then quenched with brine, followed by extraction with diethyl ether, drying over Na_2SO_4, and concentration in vacuum. The resulting residue was chromatographed on a silica-gel column with ethyl acetate and petroleum (1:10) as eluent.

3.3.1. 1-Formyl-3-ethoxycarbonyl-8-methylindolizine 9a. Yield 57%; white feather; mp 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (1H, s), 9.55 (1H, d, J=7.5 Hz), 8.16 (1H, s), 7.22 (1H, d, J=6.9 Hz), 6.97 (1H, t, J=6.9 Hz), 4.41 (2H, d, J=6.9 Hz), 2.80 (3H, s), 1.43 (3H, t, J=7.2 Hz); MS (*m*/*z*) 231 (M^+, 89), 202 (100); IR (cm^{-1}, KBr) 1688, 1645. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.22; H, 5.47; N, 5.76.

3.3.2. 1-Formyl-3-benzoyl-8-bromoindolizine 9b. Yield 50%; red solid; mp 183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (1H, s), 10.04 (1H, d, J=6.9 Hz), 8.04 (1H, s), 7.84–7.76 (3H, m), 7.63–7.49 (3H, m), 7.00 (1H, d, J=7.2 Hz); MS (*m*/*z*) 329 (M^++1, 93), 328 (M^+, 97), 327 (M^+−1, 100), 326 (86); IR (cm^{-1}, KBr) 1646, 1630. Anal. Calcd for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.27. Found: C, 58.65; H, 3.04; N, 4.17.

3.3.3. 1-Formyl-3-ethoxycarbonyl-8-bromoindolizine 9c. Yield 63%; yellow needles; mp 173–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (1H, s), 9.69 (1H, d, J=7.5 Hz), 8.21 (1H, s), 7.66 (1H, d, J=7.2 Hz), 6.89 (1H, t, J=7.2 Hz), 4.40 (2H, d, J=7.2 Hz), 1.41 (3H, t, J=7.2 Hz); MS (*m*/*z*) 297 (M^++1, 88), 295 (M^+−1, 90), 268 (99), 266 (100); IR (cm^{-1}, KBr) 1701, 1654. Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.60; H, 3.41; N, 4.51.

3.3.4. 1-Formyl-3-benzoylbenzo[*d*]indolizine 9d. Yield 65%; reddish solid; mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (1H, s), 9.76–9.68 (2H, m), 8.01–7.53 (9H, m), 7.41 (1H, d, J=7.2 Hz); MS (*m*/*z*) 299 (M^+, 100), 270 (13); IR (cm^{-1}, KBr) 1650, 1618. Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.20; H, 4.43; N, 4.68. Crystal system, space group: monoclinic, $p2(1)/c$. Unit cell dimensions: a=14.1907(15) Å, b=6.8890(7) Å, c=29.670(3) Å, α=90°, β=96.791(2)°, γ=90°; volume: 2880.2(5) Å^3; Z, 8; calculated density: 1.381 Mg/m^3; absorption coefficient: 0.090 mm^3; F(000): 1248; crystal size: 0.366×0.192×0.043 mm; theta range for data collection: 1.38–28.29°; Completeness to theta=28.32, 92.6%; data/restraints/parameters: 6624/5/520; goodness-of-fit on F^2: 0.808; final R indices[I>2sigma910]: $R1$=0.0569, $wR2$=0.1026; R indices(all data): $R1$=0.1471, $wR2$=0.1286; extinction coefficient: 0.0020(3); largest diff. Peak and hole: 0.193 and −0.215 e A^{-3}

3.3.5. 1-Formyl-3-ethoxycarbonylbenzo[*d*]indolizines 9e. Yield 58%; yellow solid; mp 210–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (1H, s), 9.73 (1H, d, J=8.4 Hz), 9.45 (1H, d, J=7.8 Hz), 8.05 (1H, s), 7.83–7.67 (3H, m), 7.32 (1H, d, J=7.5 Hz), 4.45 (2H, q, J=7.2 Hz), 1.46 (3H, t, J=7.2 Hz); MS (*m*/*z*) 267 (M^+, 89), 238 (100); IR (cm^{-1}, KBr) 1704, 1670. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.91; H, 5.01; N, 5.23.

Acknowledgements

The authors thank partial financial support by the Excellent Yong Scholars Foundation of Anhui Province.

References and notes

1. (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Flitsch, W., Ed.; Pergaman: Oxford, 1984; Vol. 4, pp 443–495. (b) Gubin, J.; Lucchetti, J.; Nisato, D.; Rosseeles, G.; Chinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1992**, *35*, 981–988. (c) Nugent, R. A.; Murphy, M. *J. Org. Chem.* **1987**, *52*, 2206–2208.

2. (a) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555–1584. (b) Resnati, G.; Soloshnok, V. A. *Tetrahedron* **1996**, *52*, 1–8.
3. Review: (a) Hudlicky, M. *Chemistry of Organofluorine Compounds*; 2nd ed. Ellis Horwood: Chichester, England, 1976. (b) Kodansha; Filler, R.; Kobayashi, Y., Eds., Biomedicinal Aspects of Fluorine Chemistry. Tokyo, 1982. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197.
4. (a) Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Tetrahedron* **1998**, *54*, 2843–3852, and references cited therein. (b) Padwa, A. *1.3-Diplomar Cycloaddition Chemistry*; Intersciences: New York, 1984; Vol. 1.
5. (a) Banks, R. E.; Hitchen, S. M. *J. Fluorine Chem.* **1982**, *20*, 373–384. (b) Banks, R. E.; Hitchen, S. M. *J. Chem. Soc., Perkin. Trans. 1* **1982**, 1593–1600. (c) Banks, R. E.; Hitchen, S. M. *J. Fluorine Chem.* **1978**, *12*, 159–166. (d) Banks, R. E.; Mohialdin, A. *J. Fluorine Chem.* **1986**, *34*, 275–279. (e) Banks, R. E.; Pritchard, R. G.; Thomson, J. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1769–1776. (f) Banks, R. E.; Hitchen, S. M.; Thomson, J. *J. Fluorine Chem.* **1982**, *20*, 127–131. (g) Banks, R. E.; Thomson, J. *J. Fluorine Chem.* **1982**, *22*, 589–592. (h) Banks, R. E.; Khaffaff, S. *J. Fluorine Chem.* **1991**, *51*, 407–418.
6. (a) Zhang, X. C.; Huang, W. Y. *Tetrahedron Lett.* **1997**, *38*, 4827–4830. (b) Zhang, X. C.; Huang, W. Y. *Tetrahedron* **1998**, *54*, 12465–12474. (c) Zhang, X. C.; Huang, W. Y. *J. Fluorine Chem.* **1998**, *87*, 57–64. (d) Zhang, X.; Huang, W. Y. *J. Fluorine Chem.* **1998**, *92*, 13–16. (e) Zhang, X. C.; Huang, W. Y. *Synthesis* **1999**, 51–54.
7. Wu, K.; Chen, Q. Y. *Synthesis* **2003**, 35–40.
8. (a) Zhu, S. Z.; Qin, C. Y.; Wang, Y. L.; Chu, Q. L. *J. Fluorine Chem.* **1999**, *99*, 183–187. (b) Peng, W. M.; Zhu, S. Z. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 3204–3210.
9. (a) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakada, K. *Synthesis* **2002**, 1917–1920. (b) Funabikim, K.; Tetsuki, I.; Hiroki, Y. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 2413–2442.
10. Funabiki, K.; Ohtsuki, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **1994**, 1075.
11. Coe, D. G. *J. Org. Chem.* **1959**, *24*, 882–884.
12. Wu, K.; Chen, Q. Y. *J. Fluorine Chem.* **2003**, *122*, 171–174.
13. The crystal data of **9d** has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number is CCDC 250572.