ELSEVIER

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Contents

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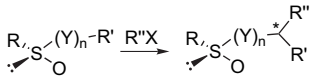
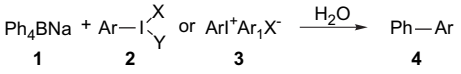
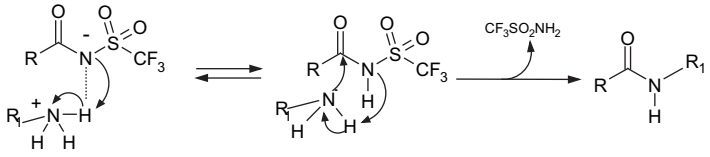
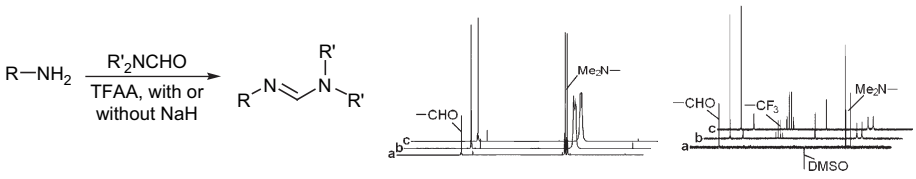


This report is intended to update the most recent advances in asymmetric synthesis using chiral sulfoxides, focusing on their use as chiral auxiliaries from 2000 to 2006 and their applications in the synthesis of biologically active products. The main purpose of this review is to demonstrate the growing potential of these chiral sulfur reagents in transmitting chirality to other centres, establishing the sulfinyl group as one of the most stereocontrolling elements in numerous asymmetric reactions.

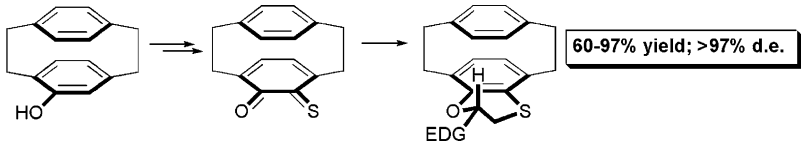
ARTICLES

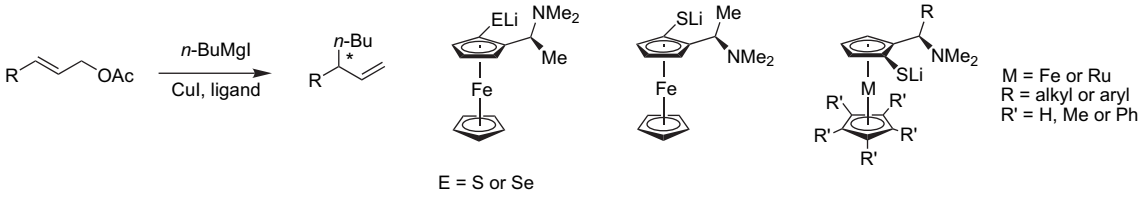


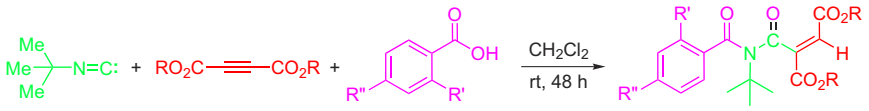


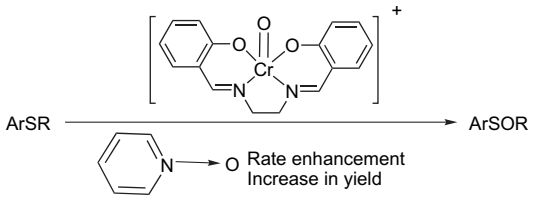


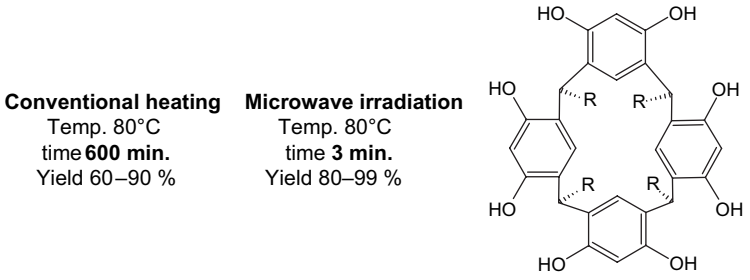
^{1}H and ^{13}C NMR studies of DMF+TFAA led to a mechanism proposal.

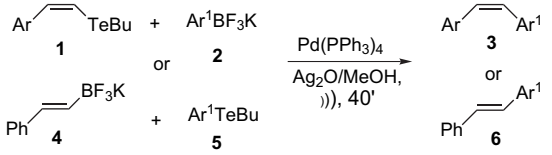


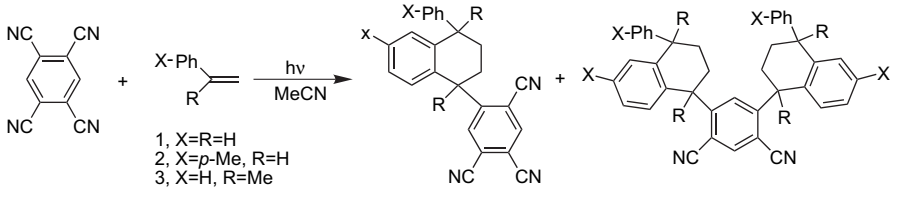


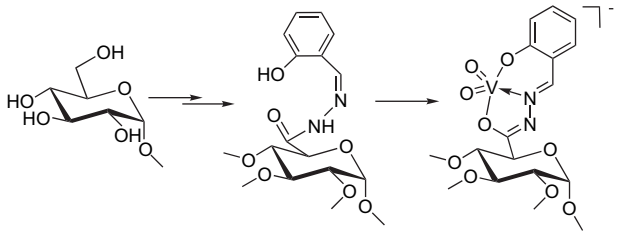


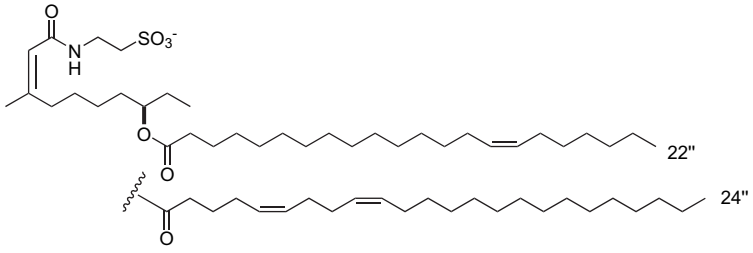


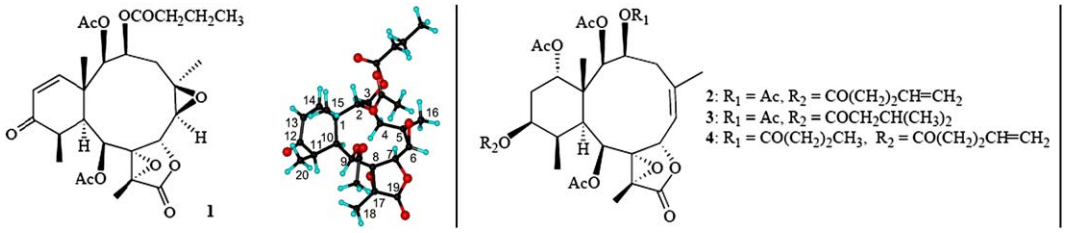


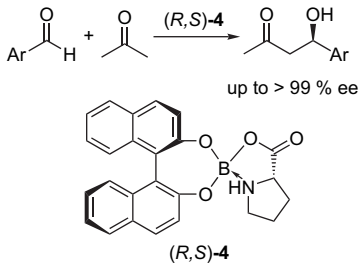


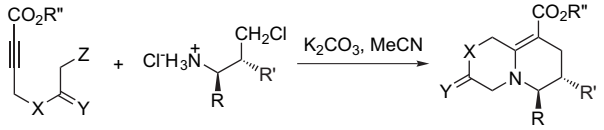




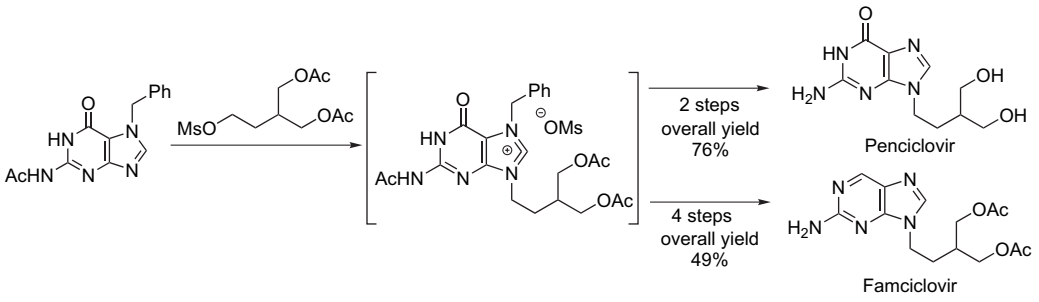


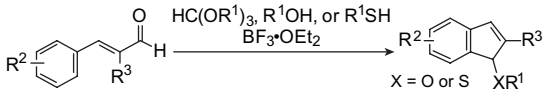


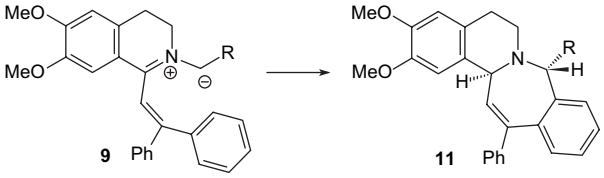


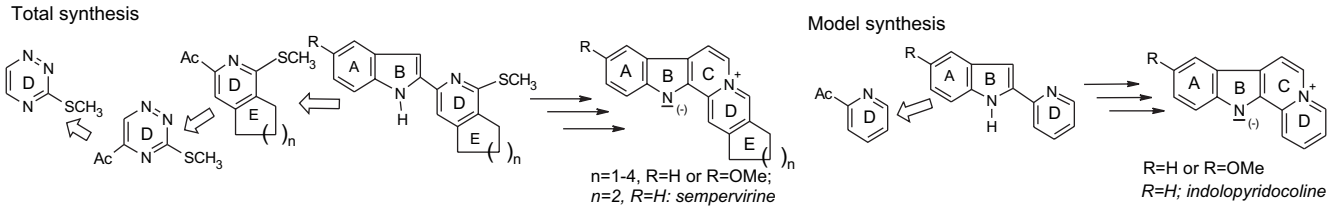


X = CH_2, O, NH, or NBn; Y = H_2 or O; Z = I or Br

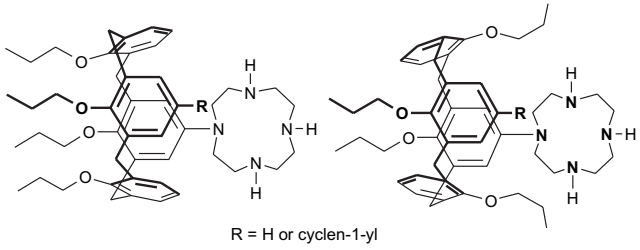




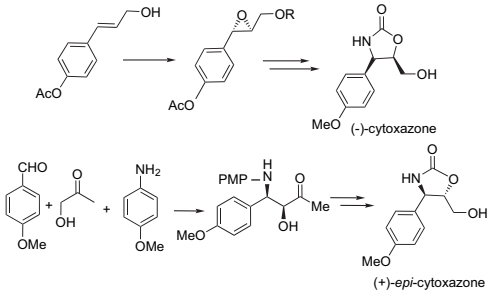


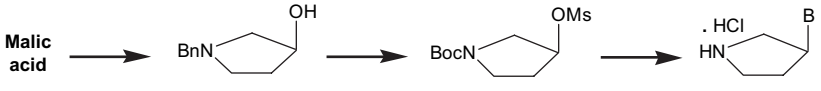


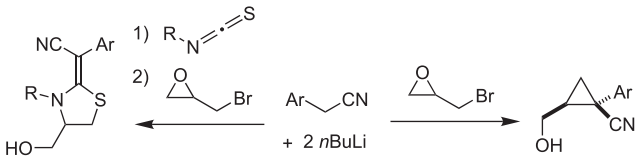
Seven new pentacyclic alkaloids sempervirine type have been synthesized via the AB–DE synthons obtainable by Fischer indolization of fused pyridines acetyl derivatives, which were formed in Diels–Alder reaction of 1,2,4-triazine precursor with cyclic enamines. New indolopyridocoline methoxy analogue has been obtained in the model synthesis from 2-acetylpyridine.

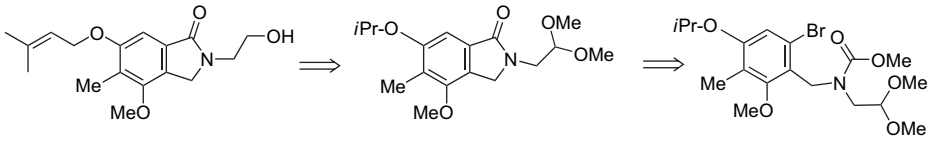


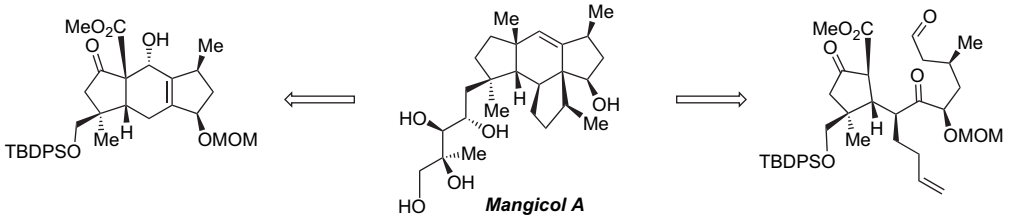
Novel calix[4]arene derivatives immobilized in the *cone* or *1,3-alternate* conformations, bearing one or two cyclen (1,4,7,10-tetraazacyclododecane) moieties directly appended to the upper rim, have been synthesized using Buchwald–Hartwig coupling reaction.

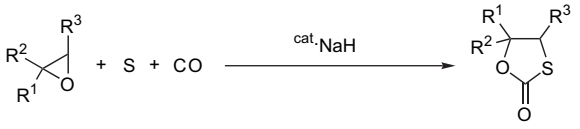


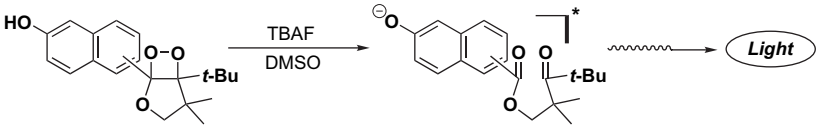












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Use of chiral sulfoxides in asymmetric synthesis

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Contents

1. Introduction

Although the first chiral organosulfur compounds were obtained at the beginning of this century, they have received more attention since the early 1960s. Initially, chiral sulfur compounds served as model compounds in studies on the mechanism and stereochemistry of nucleophilic substitution at sulfur. Quite soon, however, it was recognised

Abbreviations list: Ac, acetyl; Acac, acetylacetone; AIBN, 2,2′-azobisisobutyronitrile; Ar, aryl; $BF_3 \cdot Et_2O$, boron trifluoride etherate; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Born, borneol; Bu, butyl; Cbz, benzyloxycarbonyl; Cod, 1,5-cyclooctadiene; Cy, cyclohexyl; dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DIBAL, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DMF, dimethylformamide; Dodec, dodecyl; dppf, 1,1′-bis(diphenylphosphanyl)ferrocene; dr, diastereomeric ratio; E, electrophile; ee, enantiomeric excess; Et, ethyl; Hex, hexyl; HMDS, hexamethyldisilazide; isoB, isoborneol; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; LICA, lithium dicyclohexylamine; M, metal; MA, maleic anhydride; *m*-CPBA, 3-chloroperoxybenzoic acid; Me, methyl; Ment, menthyl; Mes, mesyl; MOM, methoxymethyl; Naph, naphthyl; NMM, *N*-methylmaleimide; NMO, *N*-methylmorpholine *N*-oxide; NPM, *N*-phenylmaleimide; Pent, pentyl; Ph, phenyl; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; Pr, propyl; PTAD, phenyltriazolinedione; Py, pyridine; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulphonyl; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIP, triisopropylphenyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Tol, tolyl; Ts, 4-toluenesulphonyl (tosyl).

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that chiral sulfur compounds are of great value in asymmetric synthesis, since many reactions may be efficiently stereocontrolled by chiral sulfur auxiliaries, which, later, are easily removable under mild conditions by reductive or eliminative methods. As a result, there has been a literature explosion in this field. On the other hand, over the last three decades, more than 40 different classes of chiral sulfur compounds have been described in the chemical literature and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed, especially of tri- and tetracoordinated sulfur structures. Every year, the literature records dozens and dozens of diverse sulfur-mediated asymmetric syntheses applied in both academic and industrial laboratories for obtaining desirable chiral materials like natural products, drugs or agrochemicals. A book that covers a wide range of chiral organosulfur compounds has been published.[1] Several other excellent reviews pertinent to this area are available.[2]

Chiral sulfoxides belong to the class of chiral organosulfur compounds which are most widely used in asymmetric synthesis. Their application as chiral synthons has now become a well-established and reliable strategy. This is mainly due to their ready availability and high asymmetric induction exerted by the chiral sulfinyl group. Moreover, the chiral sulfur groupings that induce optical activity can be removed from the molecule easily, under fairly mild conditions, thus presenting an additional advantage in the asymmetric synthesis of chiral compounds. The main advantage of sulfoxides over other sulfur functions such as sulfides and sulfones is indeed their chirality. The efficacy of a sulfoxide in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom, a lone electron pair, an oxygen, and two different carbon ligands, which are able to differentiate the diastereotopic faces of a proximal or even of a remote reaction centre. Sulfoxides are chiral groups, which are easy to introduce and easy to remove and which give high asymmetric induction in many reactions. The oxygen atom of a sulfoxide can be coordinated to a metal ion or a proton, and electronic and steric repulsions between nucleophiles and the substituents of a sulfoxide are also expected. The sulfinyl group acts as an electron-withdrawing group and activates a carbon–carbon double bond for conjugate addition and stabilises the corresponding α-carbanion. The stable pyramidal structure of a chiral sulfoxide allows a diastereoselective reaction to occur at a nearby or distant reaction centre. Complexation of the sulfoxide group with a suitable metal ion forms a rigid diastereomeric intermediate, which can undergo subsequent reactions stereoselectively.

To date, a large number of asymmetric syntheses using chiral sulfoxides[3] have been investigated in a wide range of reactions such as the reduction of β-ketosulfoxides,[3e] the Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides, C–C bond formation using sulfoxide-stabilised carbanions,[3b,4] or the Diels–Alder reaction of vinyl sulfoxides.[3e] Enantiopure sulfoxides have become one of the most important classes of chiral auxiliaries as a result of their ease of preparation, remarkable synthetic versatility, and straightforward removal.[5]

The synthesis of chiral sulfoxides has been the subject of constant interest over the past two decades.[3b,c,6] A real breakthrough occurred in the synthesis of chiral sulfoxides at the beginning of the 1990s, when various new methodologies appeared. Several methods are presently available to obtain optically active sulfoxides: optical resolution,[7] asymmetric oxidation of nonsymmetric sulfides,[8] asymmetric biological oxidation,[8] and nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates[9] such as the Andersen procedure, which is still the most important and generally used method.[10] The Andersen method consists of a substitution at the sulfur atom of commercially available (*S*)-menthyl *p*-toluenesulfinate with an appropriate organometallic reagent, which is favoured since it has the advantage that the substitution takes place with 100% inversion of configuration.[10,11] This classical method has been extensively used to prepare *p*-tolyl alkyl or aryl sulfoxides, and the use of various organometallic nucleophiles has allowed the synthesis of a wide variety of enantiomerically pure sulfoxides. The usefulness of this method is mainly due to the accessibility of the sulfinylating agent, obtained as a mixture of sulfur epimers, which are separated by repeated recrystallisations. The enantiomerically pure sulfinate is then displaced by an organomagnesium halide with complete inversion of stereochemistry at the sulfur, as first demonstrated by Mislow et al.[12] The separation of alkyl menthylsulfinate diastereomers appears to be tricky, however, and Andersen's synthesis is not efficient enough to access enantiomerically pure dialkyl sulfoxides. Other authors have developed synthetic schemes that established the enantiomeric purity at sulfur prior to addition to the organometallic reagent.[13]

Other techniques have been developed for the preparation of optically active sulfoxides such as classical resolution of racemic sulfoxides containing a resolving handle, formation and separation of optically active diastereomeric transition metal complexes, direct resolution of racemic sulfoxides by chromatography over optically activated stationary phases, optical enrichment by incorporation into inclusion compounds with a chiral host molecule, kinetic resolution by partial oxidation or reduction with chiral reagents.

Chiral sulfoxides are important intermediates in asymmetric synthesis and bioactive ingredients in the pharmaceutical industry, as demonstrated in this review. A recent industrial application of the enantioselective oxidations of sulfides using chiral metal catalysts was the development of two syntheses of sulindac, an efficient non-steroidal anti-inflammatory drug (NSAID). The first synthesis was based on an iron-catalysed sulfoxidation,[14] whereas the second involved an asymmetric Kagan sulfoxidation as the key step.[15] In addition, Matsugi et al. reported a practical synthesis of the platelet adhesion inhibitor, OPC-29030, via a catalytic asymmetric oxidation of sulfide with a titanium–mandelic acid complex.[16]

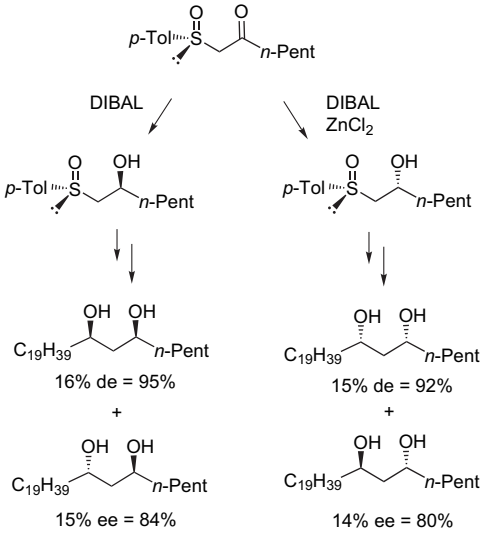
The goal of the present review is to examine recent advances in the use of chiral sulfoxides as chiral auxiliaries in asymmetric synthesis, focusing on those which have been published since 2000, the most recent review covering the literature until this latter year.[17] This review is divided into

seven sections corresponding to the different types of reactions making possible the stereoselective generation of new stereogenic centres by means of sulfoxides.

Since a recent review has focused on the preparation of chiral sulfoxides,[18] the present review only deals with the use of chiral sulfoxides as chiral auxiliaries, focusing on their applications in the synthesis of biologically active products. It is important to note that the chemistry of chiral sulfinimines[19] has recently been reported in excellent reviews by Davis et al.,[20] as well as that of chiral sulfoximines.[21,2e]

2. Reduction reactions

The reduction of chiral β-ketosulfoxides has been the most extensively investigated and used reaction involving the asymmetric induction of chiral sulfoxides. The stereochemical outcome in the reduction of either isomer of the β-ketosulfoxide can be controlled by the configuration of the sulfoxide, the reducing reagent, and the absence or presence of a Lewis acid. As an example, both diastereomers of β-hydroxysulfoxides, precursors of biologically active heptacosane-6,8-diols, could be prepared by reduction of the corresponding β-ketosulfoxide by treatment with DIBAL in the presence or absence of $ZnCl_2$ (Scheme 1).[22]



Scheme 1. Synthesis of heptacosane-6,8-diols induced by chiral sulfoxides.

This methodology was successfully applied by Stefani et al. in order to develop a total synthesis of a natural polyacetylenic product, (+)-virol C (Fig. 1).[23] Similarly, Solladié et al. have prepared the C8–C18 subunit of pamamycin 607, which has a remarkable range of biological activities, via stereoselective reduction of a chiral β,δ-diketosulfoxide (Fig. 1).[24]

In 2002, Carreno et al. described the first enantioselective total synthesis of (−)-centrolobine, based on the stereoselective reduction of a chiral β-ketosulfoxide bearing an ester as the source of chirality (Scheme 2).[25]

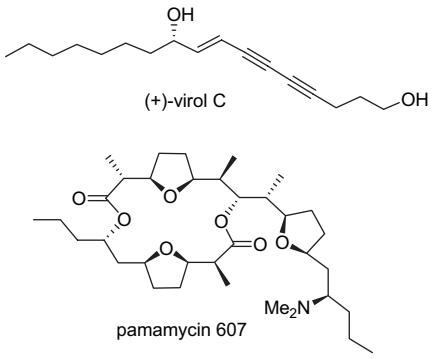
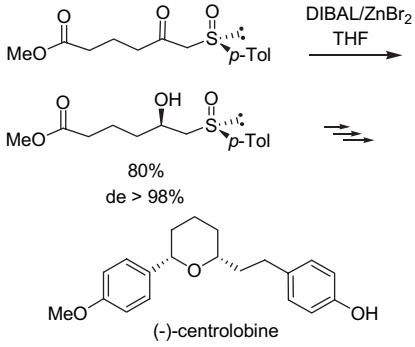
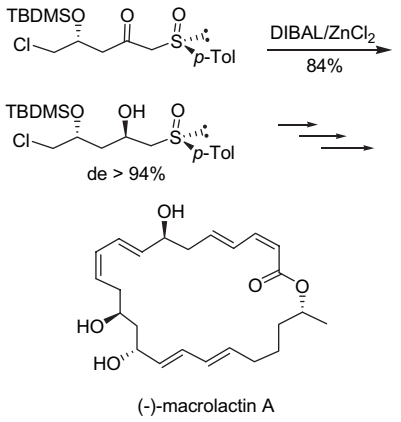


Figure 1. Structures of natural products prepared via chiral sulfoxide methodology.



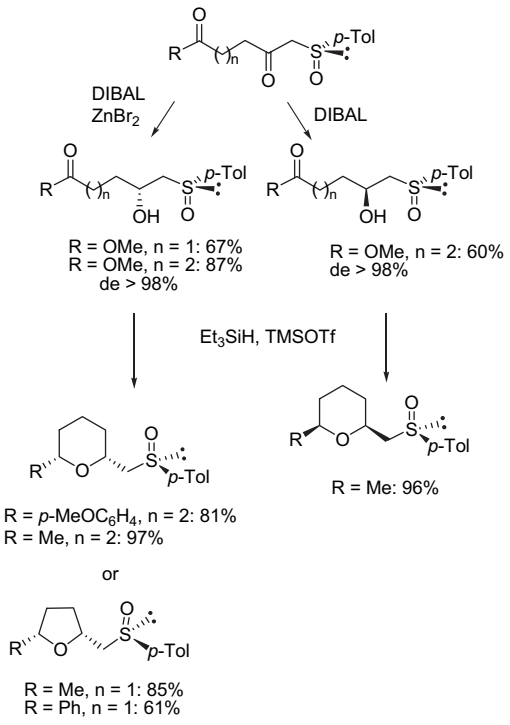
Scheme 2. Synthesis of (−)-centrolobine.

The chiral sulfoxide methodology was applied by the same group to the preparation of the C12–C24 fragment of macrolactin A, a 24-membered polyene macrolide possessing powerful antiviral activities.[26] This latter product was also prepared by Marino et al., starting from a functionalised chiral sulfoxide (Scheme 3).[27]



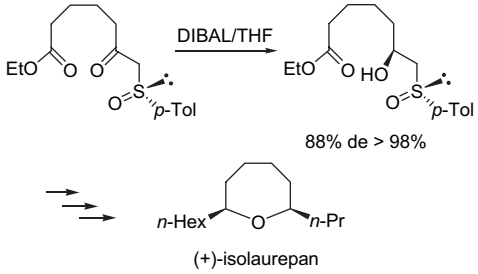
Scheme 3. Synthesis of (−)-macrolactin A.

In 2003, Carreno et al. reported the stereocontrolled formation of *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans from enantiopure ketosulfinyl esters by reduction (Scheme 4).[28] The sulfoxide bearing heterocycles were further converted into natural products.



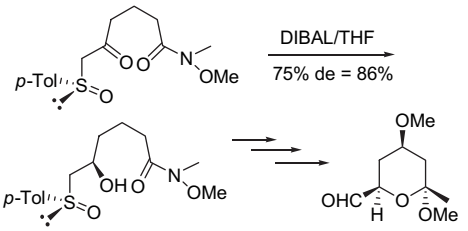
Scheme 4. Enantioselective access to tetrahydropyran and tetrahydrofuran derivatives.

In 2004, an extension of this methodology allowed a formal synthesis of (+)-isolaurepan and, more generally, an easy access to chiral 2,7-*cis*-disubstituted oxepanes (Scheme 5).[29]



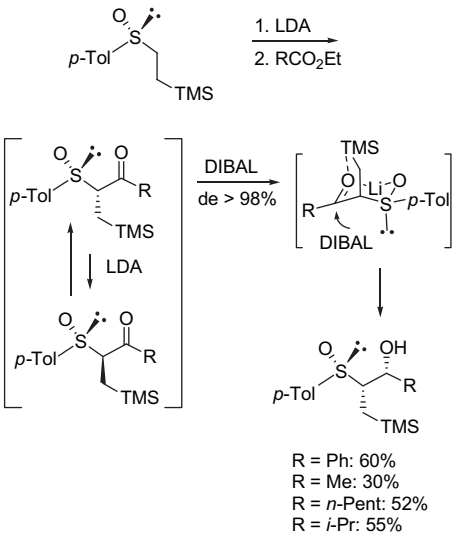
Scheme 5. Synthesis of (+)-isolaurepan.

In addition, the enantioselective construction of the tetrahydropyran ring, the C32–C38 fragment of phorboxazoles, was based on a stereoselective reduction of a chiral sulfoxide bearing a Weinreb amide (Scheme 6).[30]



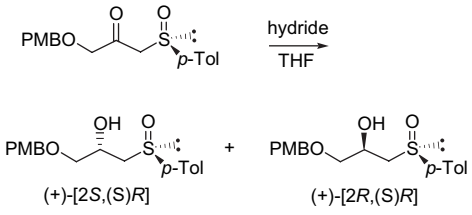
Scheme 6. Synthesis of C32–C38 THP fragment of phorboxazoles.

In 2003, Toru et al. reported an asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxide with DIBAL under basic conditions (Scheme 7). The stereoselective reaction was demonstrated to proceed through a dynamic kinetic resolution pathway via a six-membered cyclic transition state involving Si–O interaction.[31]



Scheme 7. Asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxide.

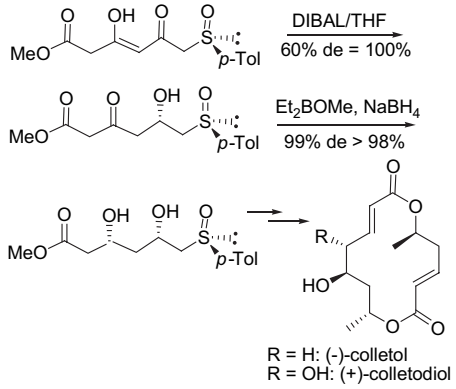
In 2004, Colobert et al. studied the use of various hydrides for the reduction of a β-ketosulfoxide bearing an oxygenated function at C1 of the β-ketosulfoxide.[32] As expected, when the reduction was carried out in the presence of DIBAL, the [2*S*,(S)*R*]-product was obtained as a single diastereomer, whereas the DIBAL/ZnX_2 (X=Cl, Br, I) reduction was poorly stereoselective and led to an almost equimolecular mixture of the two diastereomers. The presence of an oxygenated function at C1 of the β-ketosulfoxide, which could compete with the sulfinyl oxygen for chelation with the Zn atom, could be the origin of the lack of selectivity. Other hydrides such as $LiAlH_4$, $NaBH_4$, and Bu_4NBH_4 gave diastereomeric ratios that were not in the range of utility. On the other hand, the use of $Yb(OTf)_3$ and DIBAL afforded a mixture of the [2*R*,(S)*R*]-product and its epimer in a 92:8 ratio (Scheme 8).



Hydride	(+)-[2*S*,(S)*R*]/(+)-[2*R*,(S)*R*]	Yield (%)
DIBAL	100/0	98
$ZnCl_2$/DIBAL	50/50	62
$ZnBr_2$/DIBAL	67/33	65
ZnI_2/DIBAL	50/50	60
$LiAlH_4$	24/76	41
$NaBH_4$	36/64	99
Bu_4NBH_4	38/72	99
$Yb(OTf)_3$/DIBAL	8/92	96

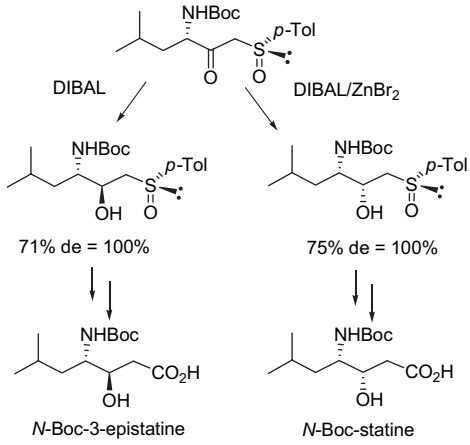
Scheme 8. Stereoselective reduction of a δ-alkoxy-β-ketosulfoxide.

In 2000, Solladié et al. reported a general synthetic strategy towards the two bis(lactones), (−)-colletol and (+)-colletodiol, based on two successive stereoselective reduction reactions induced by a chiral β,δ-diketosulfoxide.[33] Since the δ carbonyl was entirely enolised, the first reduction carried out in the presence of DIBAL yielded the corresponding β-hydroxysulfoxide as a single isomer. In the next step, the δ carbonyl group was reduced with $Et_2BOMe/NaBH_4$ to give the corresponding *syn*-diol in quantitative yield and with de>98% (Scheme 9).



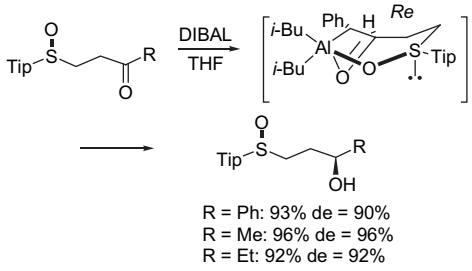
Scheme 9. Synthesis of (−)-colletol and (+)-colletodiol.

β-Hydroxy-γ-amino acids have received considerable attention, notably those acting as key components of peptidomimetic protease inhibitors such as statine. In 2003, Garcia Ruano et al. developed a unique approach to the *syn*- and *anti*-stereoisomers of *N*-Boc statine, based on the stereodivergent reduction of a chiral β-ketosulfoxide derived from *N*-Boc-L-leucine methyl ester.[34] Since *N*-Boc-D-leucine was also commercially available, the synthesis of the four stereoisomers of statine could be performed using this methodology (Scheme 10).



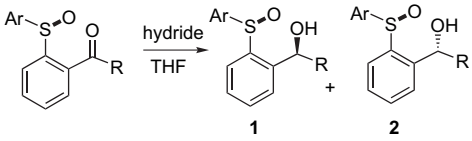
Scheme 10. Synthesis of *N*-Boc-statine and *N*-Boc-3-epistatine mediated by sulfoxides.

In 2000, Toru et al. reported a highly diastereoselective reduction of γ-ketosulfoxides having a sterically bulky aryl group such as 2,4,6-triisopropylphenyl (Scheme 11).[35] In comparison with the lower stereoselectivities obtained in the reaction of γ-ketosulfoxides bearing *p*-tolyl or 2,4,6-trimethylphenyl groups, the sterically bulky (2,4,6-triisopropylphenyl)sulfinyl group was extremely efficient in effecting high 1,4-remote asymmetric induction, irrespective of the substituent R attached to the carbonyl group, showing very weak steric or electronic effects of these substituents on the stereoselectivity. The high stereoselectivity could be ascribed to a cyclic twisted-chair transition state involving a trigonal bipyramidal structure, as depicted in Scheme 11. The bulky group was placed at the pseudoequatorial position and might constrain the cyclic transition state more efficiently than the *p*-tolyl and mesityl groups. The reduction would preferably occur from the *re* face of the carbonyl.



Scheme 11. Asymmetric reduction of γ-ketosulfoxides bearing a 2,4,6-triisopropylphenyl group.

The same authors have reported a 1,4-asymmetric induction in the stereoselective reduction of enantiomerically enriched γ-ketosulfoxides where the sulfinyl and carbonyl groups were separated by a phenyl ring (Scheme 12).[36] Thus, these authors have studied the reactions of *p*-tolylsulfinyl, (2,4,6-trimethylphenyl)sulfinyl and [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones with various reducing reagents, without, or in the presence of Lewis acids. Reduction with



Ar	R	Hydride	Yield (%)	Ratio **1**:**2**
Tol	Ph	$LiAlH_4$	80	47:53
Tol	Ph	DIBAL	80	15:85
Tol	Me	$LiAlH_4$	84	51:49
Tol	Me	DIBAL	85	37:63
Mes	Ph	$LiAlH_4$	82	21:79
Mes	Ph	DIBAL	92	2:98
Mes	Me	$LiAlH_4$	94	56:44
Mes	Me	DIBAL	94	16:84
Tip	Ph	$LiAlH_4$	81	35:65
Tip	Ph	DIBAL	96	2:98
Tip	Ph	L-selectride	86	11:89
Tip	Ph	Superhydride	86	11:89
Tip	Ph	DIBAL/LiBr	88	16:84
Tip	Ph	$DIBAL/Yb(OTf)_3$	81	19:81
Tip	Ph	$DIBAL/ZnCl_2$	92	85:15
Tip	Me	DIBAL	96	3:97
Tip	Allyl	DIBAL	94	2:98

Scheme 12. Stereoselective reduction of 2-(arylsulfinyl)phenyl ketones.

$LiAlH_4$ proceeded with low diastereoselectivity, irrespective of the bulkiness of the substituent on the sulfur. The diastereoselectivity of the products in the DIBAL reduction depended upon the substituent on the sulfur. (*p*-Tolylsulfinyl)phenyl ketones with DIBAL afforded the products with low stereoselectivity, whereas [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones gave the corresponding alcohols with high stereoselectivity, favouring isomer **2**. Other reducing agents such as L-Selectride and Superhydride gave slightly lower stereoselectivity. Solladié et al. have previously reported that the reduction of γ-ketosulfoxides with DIBAL proceeded with moderate diastereoselectivity without Lewis acids and the stereochemistry of the product was reversed in the presence of $Yb(OTf)_3$.[37] In the DIBAL reduction of [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones, the stereoselectivity was lowered in the presence of $Yb(OTf)_3$ or LiBr, but not reversed. On the other hand, $ZnCl_2$ significantly reversed the diastereoselectivity in favour of isomer **1**.

The stereochemical outcome in the reduction of 2-(arylsulfinyl)phenyl ketones with DIBAL was ascribed to a seven-membered cyclic transition state, as shown in Figure 2. The bulky 2,4,6-triisopropylphenyl group was placed away from the neighbouring acyl substituent in a preferred transition state, and intramolecular reduction occurred from the *si* face of the carbonyl to give isomer **2**. High stereoselectivity could be achieved through the cyclic transition state constrained preferably by the 2,4,6-triisopropylphenyl group rather than by the mesityl and *p*-tolyl groups. Addition of $ZnCl_2$ reversed the stereochemistry of the product, indicating that $ZnCl_2$ would form a chelate in place of DIBAL, and reduction occurred from the outside of the chelate.

In the course of developing a new access to chiral benzothiepines, which are potent apical sodium co-dependent bile acid transporter inhibitors, Lee et al. have studied the reduction of a polyfunctionalised chiral γ-ketosulfoxide carried out in the presence of $NaBH_4$, providing a 27:73 mixture of both corresponding alcohols favouring the trans-isomer (Scheme 13).[38]

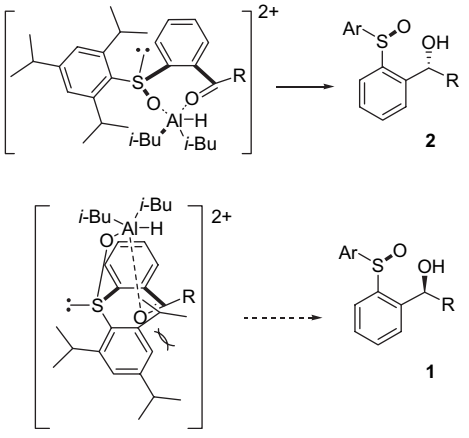
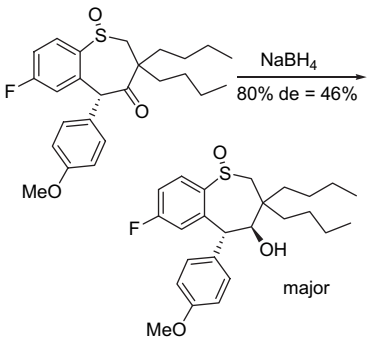
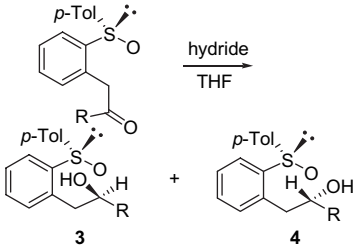


Figure 2. Assumed transition states in DIBAL reduction of 2-(arylsulfinyl)-phenyl ketones.

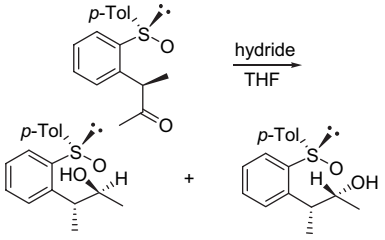


Scheme 13. Asymmetric reduction of a polyfunctionalised γ-ketosulfoxide.

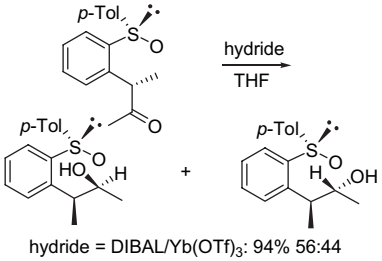
Very recently, Garcia Ruano et al. demonstrated that the reduction of δ-ketosulfoxides constituted the first evidence of the efficiency of the sulfinyl group to control the stereoselectivity of 1,5-asymmetric induction processes.[39] The use of DIBAL/$Yb(OTf)_3$ or L-Selectride as the reducing agents provided the corresponding δ-hydroxysulfoxides **3** and **4** with the opposite configuration at the hydroxylic carbon in a highly stereoselective manner (Scheme 14).



R	Hydride	3:4	Yield (%)
Me	DIBAL/$Yb(OTf)_3$	97:3	96
Me	L-Selectride	5:95	75
Ph	DIBAL/$Yb(OTf)_3$	89:11	95
Ph	L-Selectride	40:60	55
n-Pr	DIBAL/$Yb(OTf)_3$	92:8	95
n-Pr	L-Selectride	2:98	65
i-Pr	DIBAL/$Yb(OTf)_3$	92:8	97
i-Pr	L-Selectride	2:98	60



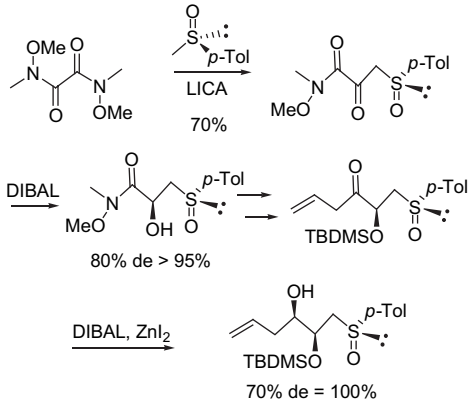
hydride = DIBAL/$Yb(OTf)_3$: 70% 100:0
hydride = L-Selectride: 65% 86:14



hydride = DIBAL/$Yb(OTf)_3$: 94% 56:44
hydride = L-Selectride: 60% 53:47

Scheme 14. Asymmetric reduction of δ-ketosulfoxides.

Solladié has considerably extended the sulfoxide-mediated enantioselective reduction of carbonyl compounds to the synthesis of enantiomerically pure diols, including C_2 symmetric diols from the corresponding diketodisulfoxides.[40] This methodology could be successfully applied to the synthesis of many biologically important compounds such as (−)-tarchonanthuslactone,[41] cladospolide,[42] solenopsins,[43] compactin analogues,[44] insect pheromones[45] and descarestrictine.[46] More recently, a formal synthesis of the 10-membered lactone core of ascidiatrienolides and didemnilactones was developed on the basis of two successive highly diastereoselective sulfoxide-directed reductions of an oxalic diamide (Scheme 15).[47]

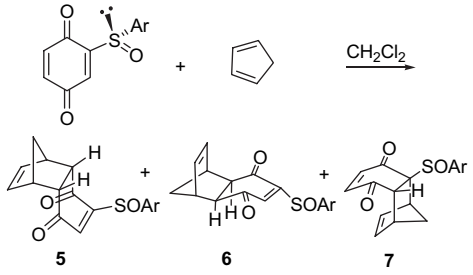


Scheme 15. Sequential DIBAL sulfoxide-directed reduction of an oxalic diamide derivative.

3. Cycloaddition reactions

3.1. Diels–Alder reactions

3.1.1. Sulfinyl dienophiles. The combination of a Diels–Alder reaction with asymmetric induction exerted by sulfoxides represents a very powerful method for C–C bond formation in a stereocontrolled manner.[48] The sulfinyl group has, equally, become one of the most interesting chiral inductors in asymmetric Diels–Alder reactions, due to: (a) its ability to differentiate between diastereotopic faces of neighbouring double bonds, (b) the ease of chemical transformations into different functional groups including its clean removal under mild conditions and (c) the existence of several efficient methods that allow the preparation of enantiomerically pure sulfoxides. The poor results obtained in the Diels–Alder reaction using unsubstituted vinylic sulfoxides (low reactivity and only moderate stereoselectivity)[49] were substantially improved by attaching additional groups to the double bond, which increased the reactivity and simultaneously restricted the conformational mobility around the C–S bond, hence improving the stereoselectivity of the dienophile. In this sense, several electron-withdrawing groups have been incorporated to vinylic sulfoxides such as carbonyl,[50] nitro,[51] sulfonyl,[52] sulfinyl[53] and cyano.[54] Nevertheless, the most widely studied is doubtlessly the ester group, the contributions by Koizumi in this field clearly being the most significant.[55] Application of optically active vinyl sulfoxides as dienophiles is a fascinating strategy, since the chiral sulfinyl auxiliary is known to exert a high asymmetric induction in the carbon–carbon bond formation. Such a strategy creates the possibility of an easy synthesis of complex products possessing several chiral centres of desired stereochemistry. This approach has been the subject of a great number of publications.[55–57] It should be emphasised that, while the *endo*/*exo* stereoselection, consisting of a different orientation of the diene with respect to the sulfoxide substituents in a dienophile is rather a consequence of steric and/or electronic interaction, the π-facial stereoselectivity arising from the approach of the diene to a different face of the dienophile is only a result of the influence of the sulfinyl group chirality.[58] Thus, the π-facial stereoselectivity can be considered as a measure of the asymmetric induction exerted by the sulfinyl group. Diels–Alder reactions of enantiomerically enriched dienophiles and dienes are highly stereoselective and efficient for the asymmetric construction of cyclic or bicyclic skeletons. In recent years, a number of examples of Diels–Alder reactions of optically active sulfinyl dienophiles have been reported.[59] Subsequent efforts focused on the design of sulfinyl dienophiles bearing additional electron-withdrawing groups on the double bond such as ketones, esters and sulfones, which allowed a serious improvement of the facial selectivity in both cases. Although quinones are among the best dienophiles traditionally used in Diels–Alder reactions, relatively few examples of chiral derivatives for use in asymmetric synthesis are known, despite their potential to construct structurally complex molecules in enantiomerically pure form. Carreno et al. have extensively studied the use of 2-(arylsulfinyl)-1,4-benzoquinones as chiral dienophiles in Diels–Alder reactions. They have shown that reactions with acyclic dienes took place through a sequential Diels–Alder cycloaddition/pyrolytic sulfoxide elimination, giving rise to chiral polycyclic dihydroquinones.[60] This process, coupled with the kinetic resolution of a chiral racemic vinylcyclohexene, which occurred simultaneously, was further applied to the enantioselective synthesis of several angucyclinones.[61] In 2000, these authors extended the same methodology to cyclic dienes such as, for the first time, cyclopentadiene (Scheme 16 and Table 1).[62] They demonstrated that the reactivity, chemoselectivity and π-facial diastereoselectivity of Diels–Alder reactions of 2-(arylsulfinyl)-1,4-benzoquinones and cyclopentadiene were related to the electron-donating or withdrawing character of the substituent at the aromatic sulfoxide, as well as the Lewis acid employed. In the presence of $BF_3 \cdot Et_2O$, the cycloadditions occurred exclusively on the unsubstituted double bond C5–C6, affording the diastereoisomers **6** as the major isomers, whereas $Eu(fod)_3$ directed the attack mainly on C5–C6 with the opposite π-facial diastereoselectivity, affording predominantly the diastereoisomers **5**. The opposite chemoselectivity (90% of the cycloaddition from the sulfinyl-substituted



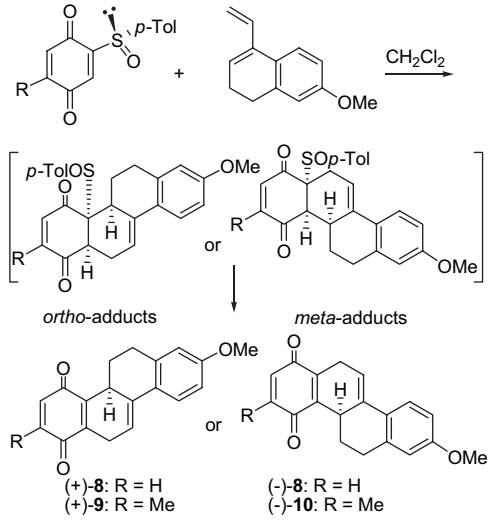
Scheme 16. Diels–Alder reaction of 2-(arylsulfinyl)-1,4-benzoquinones with cyclopentadiene.

Table 1

Ar	Lewis acid	**5**:**6** (% de)	**7** (% de)	Yield (%)
p-Tol	—	71:29 (42)	—	95
2-MeONaph	—	63:37 (26)	—	98
p-MeOPh	—	68:32 (36)	—	98
p-NO_2Ph	—	66:34 (32)	—	95
p-Tol	Eu(fod)$_3$	80:10 (70)	10 (100)	80
2-MeONaph	Eu(fod)$_3$	82:18 (64)	—	90
p-MeOPh	Eu(fod)$_3$	78:8 (70)	14 (100)	87
p-NO_2Ph	Eu(fod)$_3$	58:19 (39)	23 (100)	87
p-Tol	$BF_3{\cdot}Et_2O$	10:90 (80)	—	90
2-MeONaph	$BF_3{\cdot}Et_2O$	5:95 (90)	—	92
p-MeOPh	$BF_3{\cdot}Et_2O$	5:95 (90)	—	92
p-NO_2Ph	$BF_3{\cdot}Et_2O$	19:81 (62)	—	65
p-Tol	$ZnBr_2$	20:20 (0)	60 (100)	83
2-MeONaph	$ZnBr_2$	42:58 (16)	—	60
p-MeOPh	$ZnBr_2$	32:32 (0)	36 (100)	75
p-NO_2Ph	$ZnBr_2$	6:4 (20)	90 (100)	70

double bond C2–C3) was achieved from benzoquinone substituted by a *p*-nitrophenyl group in the presence of $ZnBr_2$, yielding exclusively the diastereoisomer **7** (de=100%).

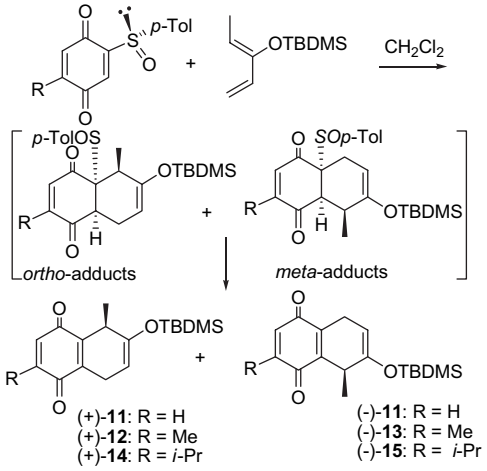
This group has reported the extension of this reaction to various 1,2-disubstituted dienes such as Dane's diene (Scheme 17) and differently substituted enantiopure (*p*-tolylsulfinyl)-1,4-benzoquinones.[63] Similar π-facial diastereoselectivities, but reversed regiochemistry under thermal conditions and in the presence of $ZnBr_2$, were observed in all dienes. After spontaneous elimination of the sulfoxide, optically active polycyclic dihydroquinones were formed with ees ranging from 36 to >97%. It was demonstrated that the regiochemistry of the process was controlled by the alkyl substituent at C1 in thermal reactions, whereas, in the presence of $ZnBr_2$, the oxygenated function at C2 became the main controller.



R	Lewis acid	Products (% Yield)	Products (% ee)
H	-	(+)-**8** (23)	(+)-**8** (80)
H	$ZnBr_2$	(-)-**8** (20)	(-)-**8** (36)
Me	-	(+)-**9** (43)	(+)-**9** (80)
Me	$ZnBr_2$	(-)-**10** (38)	(-)-**10** (> 97)

Scheme 17. Diels–Alder reaction of 2-(*p*-tolylsulfinyl)-1,4-benzoquinones with Dane's diene.

All cases of cycloadditions carried out with 3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene occurred through the sulfinyl-substituted C2–C3 double bond of the sulfinyl-quinones, affording the corresponding 5,8-dihydronaphthoquinones, which partially aromatised to the corresponding naphthoquinones during the isolation process (Scheme 18).

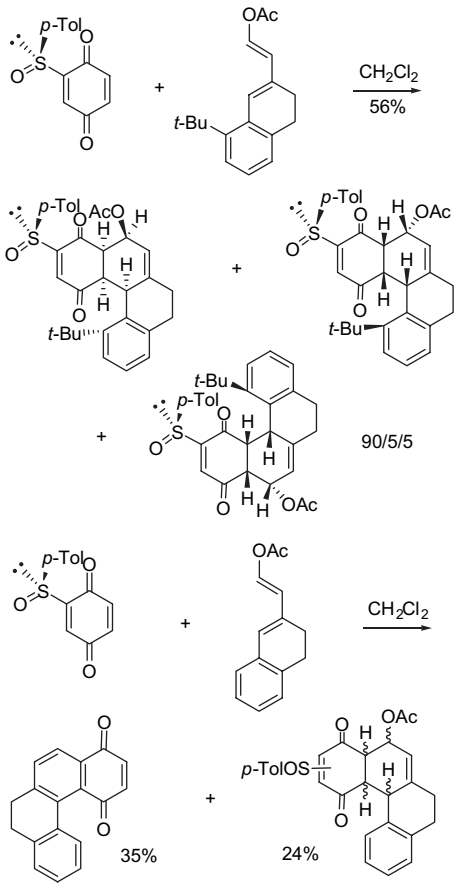


R	Lewis acid	Products (% Yield)	Products (% ee)
H	-	**11** (32)	**11** (0)
H	$ZnBr_2$	(-)-**11** (36)	(-)-**11** (36)
Me	-	(+)-**12** (25) + (-)-**13** (22)	**12** (78) + **13** (72)
Me	$ZnBr_2$	(+)-**12** (0) + (-)-**13** (100)	**13** (72)
i-Pr	-	(+)-**14** (40) + (-)-**15** (10)	**14** (>97) + **15** (74)
i-Pr	$ZnBr_2$	(-)-**15** (62)	**15** (74)

Scheme 18. Diels–Alder reaction of 3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene.

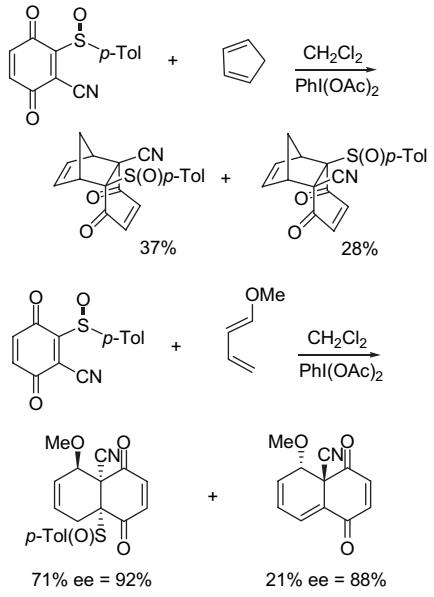
In addition, 1-methyl-2-(*tert*-butyldimethylsilyloxy)-1,3-cyclohexadiene was investigated using the same conditions as before, giving reactions, which took place chemoselectively on the sulfinyl-substituted double bond of the quinones in all cases of benzoquinones. The influence of diene substitution on Diels–Alder reactions between vinyl dihydronaphthalenes and 2-(*p*-tolylsulfinyl)-1,4-benzoquinone was studied in 2003 (Scheme 19).[64] It was shown that the reaction carried out with 2-(*E*-2-acetoxyvinyl)-8-*tert*-butyl-3,4-dihydronaphthalene took place exclusively on the unsubstituted C5–C6 double bond of the benzoquinone with a very high control of the chemo-, regio- and diastereoselectivities of the process, affording the corresponding tetracyclic sulfinyl derivative possessing five stereogenic centres. On the other hand, the analogue diene lacking the *tert*-butyl group gave a less chemoselective reaction (C2–C3/C5–C6=60:40) in favour of reaction through the sulfoxide-substituted double bond C2–C3 of benzoquinone. A balance between steric effects of a remote *tert*-butyl group and electronic factors in the diene partner was the origin of the observed chemo- and regioselectivities of the cycloadditions that occurred from the C5–C6 unsubstituted double bond of the dienophile.

In order to increase the reactivity of the C2–C3 double bond of the dienophile, thus inverting the chemoselectivity, and to avoid desulfinylation by subsequent aromatisation, Garcia Ruano et al. introduced a cyano group at C3 of the benzoquinone.[65] Thus, (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone was submitted to cycloaddition in the presence of



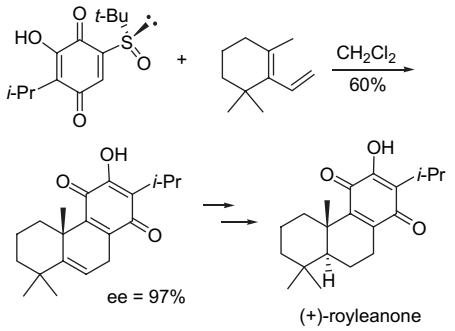
Scheme 19. Diels–Alder reaction of vinyl dihydronaphthalenes.

cyclic and acyclic dienes, affording the Diels–Alder adducts with a complete chemo- (only reaction with the sulfinyl-substituted double bond took place), regio- (controlled by the cyano group) and *endo* selectivities (with respect to the quinone moiety), whereas the π-facial selectivity was dependent on the structure of the diene (Scheme 20).



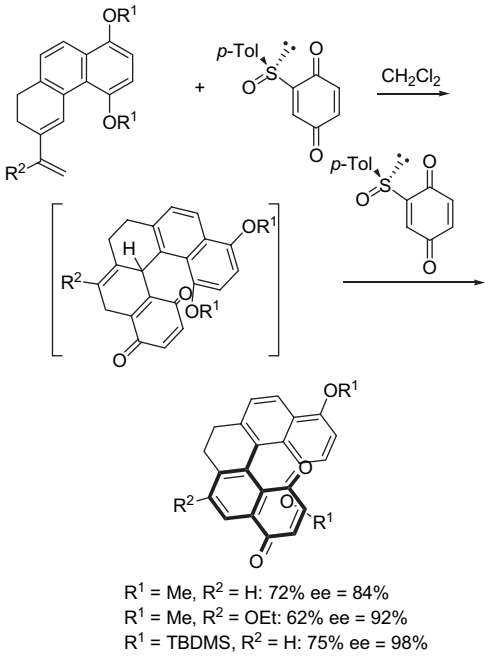
Scheme 20. Diels–Alder reaction of (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone.

An enantioselective synthesis of (+)-royleanone, an insecticide and disinfectant agent, could be developed using the sulfinylquinone methodology.[66] The key step was a tandem asymmetric Diels–Alder reaction/pyrolytic sulfoxide elimination process involving (*S*)-3-hydroxy-2-isopropyl-5-*tert*-butylsulfinyl-*p*-benzoquinone as chiral auxiliary (Scheme 21).



Scheme 21. Synthesis of (+)-royleanone.

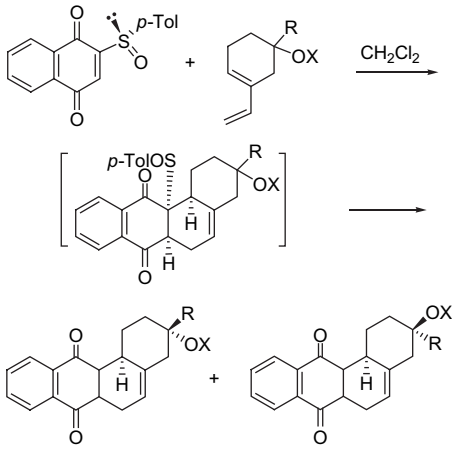
This powerful methodology was also applied to the first synthesis of chiral dihydro[5]helicenequinones and bisquinones, by reaction of 1,4-divinyl-1,3-cyclohexadiene, 5,8-dimethoxy- or *tert*-butyldimethylsilyloxy-3-vinyl-1,2-dihydrophenanthrene or 6-vinyl-7,8-dihydro-1,4-phenanthrenequinone with (*S*,*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone.[67] A domino Diels–Alder cycloaddition/sulfoxide elimination/partial aromatisation process occurred, the absolute configuration of the final helicene being defined in the aromatisation step (Scheme 22).



Scheme 22. Enantioselective synthesis of (*P*)-dihydro[5]helicenequinones and bisquinones.

In the same way, enantiomerically enriched 1,4-dihydro-9,10-anthraquinone derivatives have been prepared by reaction between (*S*,*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone and racemic acyclic dienes bearing a substituted allylic centre through a tandem cycloaddition/pyrolytic sulfoxide

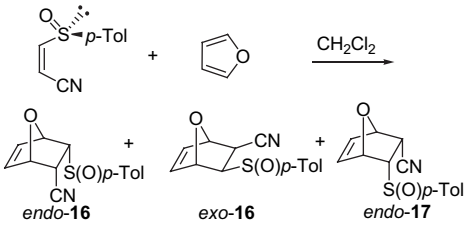
elimination.[68] When vinylcyclohexenes, bearing oxygenated substituents and/or a methyl group at the C5 position of the cyclohexene ring, were used as dienes, the asymmetric domino process led to the formation of chiral C3-oxygenated angucyclinones, which are a large group of naturally occurring quinones that display a broad range of biological properties such as antiviral, antifungal and antitumour effects, as well as enzyme-inhibitory activity (Scheme 23).[69] The process took place through a domino Diels–Alder reaction/pyrolytic sulfoxide elimination with simultaneous kinetic resolution of the racemic diene.



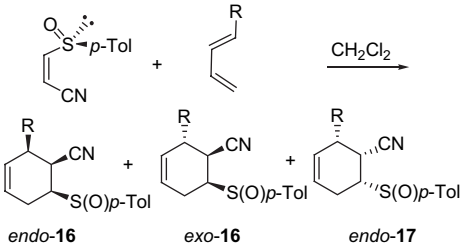
Scheme 23. Asymmetric synthesis of C3-oxygenated angucyclinones.

On the other hand, the behaviour of (*Z*)-3-*p*-tolylsulfinylacrylonitrile as a chiral dienophile has been evaluated by Garcia Ruano et al. from its reaction with furan and acyclic dienes.[54a] Electrostatic interactions of the cyano group with the sulfinyl moiety restricted the conformational mobility around the C–S bond, thus controlling the π-facial selectivity, which was almost complete in all cases, the approach of the diene from the less hindered face of the dienophile (that bearing the lone electron pair) in the predominant rotamer being favoured. The regioselectivity was also completely controlled by the cyano group. Additionally, the reactivity of (*Z*)-3-*p*-tolylsulfinylacrylonitrile, as well as its *endo* selectivity, was both higher than those observed for the corresponding (*Z*)-3-sulfinylacrylates, thus proving the potential of sulfinylnitriles as chiral dienophiles (Scheme 24). The same group has also outlined the Diels–Alder reactions of the corresponding chiral (*E*)-3-formyl-2-sulfinylacrylonitrile and its diethyl acetal derivative with cyclopentadiene.[70]

In the course of studying the stereoselectivity control in Diels–Alder reactions of 4-thiosubstituted 5-alkoxyfuranones, Martin et al. have developed the cycloaddition of (*S*)-4-phenylsulfinyl-(5*S*)-5-(*l*-menthyloxy)furan-2(5*H*)-one with cyclopentadiene.[71] They have demonstrated that the sulfur substituents at C4 inverted the trend imposed by C5 on the π-facial selectivity and the *syn*-adducts became favoured. Indeed, Scheme 25 shows that the major adduct resulted from the *exo* approach of the diene to the *syn* face bearing the menthyloxy moiety. Moreover, the π-facial selectivity,



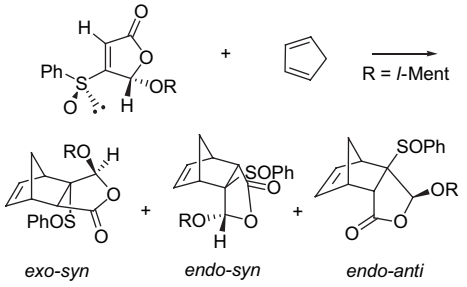
Catalyst	*endo*-**16** (%)	*exo*-**16** (%)	*endo*-**17** (%)	*endo*/*exo*	**16**/**17**
-	51	11	0	84/16	> 33
$ZnBr_2$	42	13	0	86/14	> 33
Me_2AlCl	53	10	0	87/13	> 33



Catalyst	R	*endo*-**16** (%)	*exo*-**16** (%)	*endo*-**17** (%)
-	OMe	70	12	0
$ZnBr_2$	OMe	63	13	16
-	Me	70	5	0
$ZnBr_2$	Me	57	4	13

Scheme 24. Diels–Alder reaction of (*Z*)-3-*p*-tolylsulfinylacrylonitriles.

measured as the *syn*/*anti* adduct ratio (≥3:1), indicated that the approach of the diene from the same face of the alkoxy group was favoured, and the *exo*/*endo* ratio (>1) revealed that the *exo* addition mode was slightly preferred.

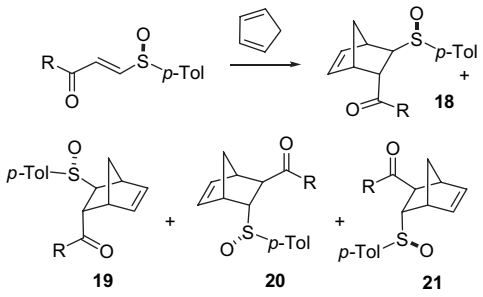


Catalyst	Yield (%)	Adduct ratio *exo-syn*	*endo-syn*	*endo-anti*
-	88	53	21	26
$ZnBr_2$	76	60	20	20

Scheme 25. Diels–Alder reaction of (*S*)-4-phenylsulfinyl-(5*S*)-5-(*l*-menthyloxy)furan-2(5*H*)-one.

In 2004, Ordonez et al. reported the Diels–Alder reaction of chiral (*E*)-γ-keto-α,β-unsaturated *p*-tolyl sulfoxides with cyclopentadiene (Scheme 26).[72] The effect of several Lewis acids on the reaction was studied, revealing a high *endo* selectivity with respect to the carbonyl group and a moderate π-diastereoselectivity using $BF_3 \cdot Et_2O$ as catalyst. The

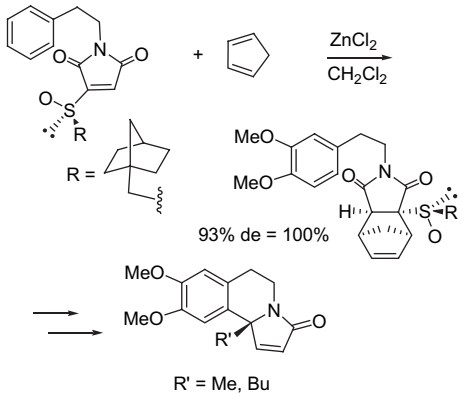
reactivity, as well as the *endo* selectivity, was both higher than those observed for the corresponding (*E*)-3-sulfinylacrylates.



Catalyst	R	Yield (%)	18/19/20/21	*endo*/*exo*	% de *endo*	% de *exo*
-	*n*-Pr	90	21/33/17/29	54/46	22	26
-	*i*-Pr	95	15/36/17/32	51/49	41	31
SiO_2	*n*-Pr	99	19/36/16/29	55/45	31	29
$LiClO_4$	*n*-Pr	95	20/35/16/29	55/45	27	29
$ZnBr_2$	*n*-Pr	97	32/45/09/14	77/23	17	23
$SnCl_4$	*n*-Pr	80	35/54/05/06	89/11	21	9
$SnCl_4$	*i*-Pr	82	37/52/06/05	89/11	17	9
$TiCl_4$	*n*-Pr	85	53/31/07/09	84/16	26	13
Et_2AlCl	*n*-Pr	86	60/25/11/04	85/15	41	47
$BF_3.Et_2O$	*n*-Pr	97	71/22/05/02	93/7	53	43
$BF_3.Et_2O$	*i*-Pr	98	60/24/10/06	86/14	42	25

Scheme 26. Diels–Alder reaction of (*E*)-γ-keto-α,β-unsaturated *p*-tolyl sulfoxides.

A stereoselective Diels–Alder reaction of a chiral sulfinylmaleimide with cyclopentadiene was one of the key steps in the enantioselective synthesis of dihydropyrrolo[2,1-*a*]isoquinolones.[73] The reaction, in the presence of $ZnCl_2$, afforded the corresponding sulfinylnorbornenimide in excellent yield and as a single diastereoisomer (Scheme 27).

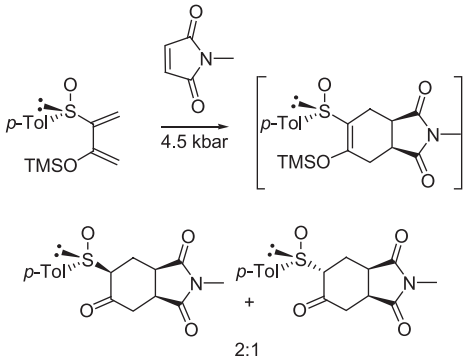


Scheme 27. Diels–Alder reaction of a chiral sulfinylmaleimide.

In addition, Aversa et al. have investigated the Diels–Alder reactivity of chiral sulfinyl dienophiles with a carbohydrate attached to the sulfoxide moiety. Unfortunately, their reactivity was very low (about 14 days were required for the reaction to be completed) and the cycloadducts spontaneously underwent regioselective elimination of sulfenic acid.[74]

Finally, among the large number of synthetic applications of chiral C_2-symmetric bis(sulfoxides) are their involvement in asymmetric Diels–Alder reactions.[75]

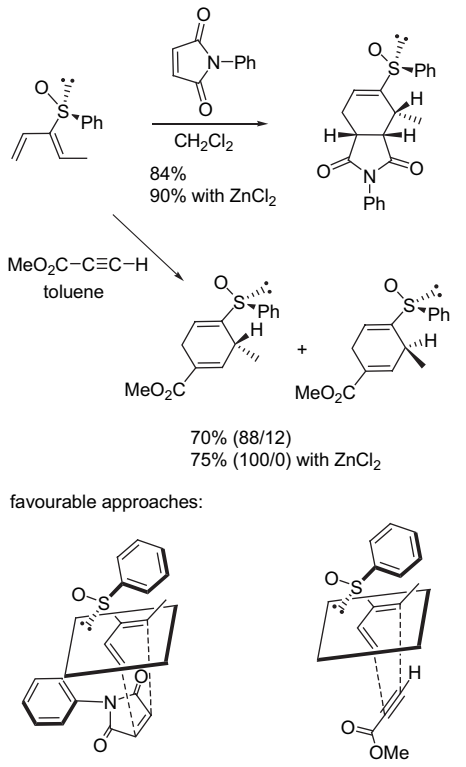
3.1.2. Sulfinyl dienes. Diels–Alder reactions of enantiomerically enriched sulfinyl dienes are less well documented in the literature, presumably due to the synthetic difficulties in preparing such molecules. Nevertheless, enantiomerically enriched sulfinyl 1,3-butadienes are frequently used to react with a variety of dienophiles that undergo Diels–Alder cycloaddition.[76] The use of a Lewis acid to restrict the rotation around the C–S bond has been used to improve the stereoselectivities. In 2000, Garcia Ruano et al. studied the behaviour of chiral 2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene in Diels–Alder reactions with cyclic dienophiles such as *N*-methylmaleimide.[77] The reaction provided a 2:1 diastereomeric mixture of cycloadducts (Scheme 28), from which the major stereoisomer was isolated in enantiomerically pure form by crystallisation. The results supported a cycloaddition occurring in a completely stereoselective manner, followed by a less diastereoselective Si–O bond cleavage.



Scheme 28. Diels–Alder reaction of (*S*)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene.

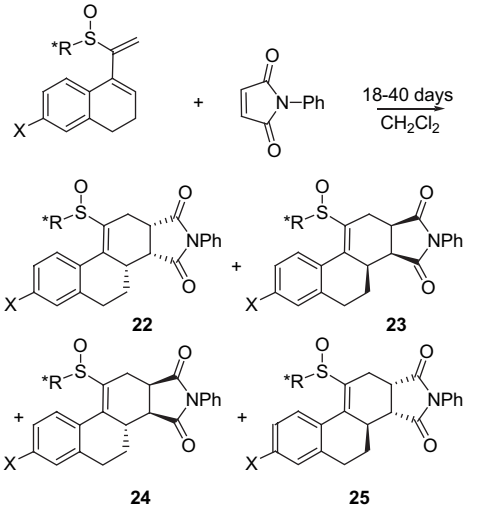
Similarly, chiral (*Z*)-1-methyl-2-(*p*-toluenesulfinyl)-1,3-butadiene has been condensed on *N*-phenylmaleimide and methyl propiolate, providing the expected corresponding cycloadducts with good to excellent regio-, stereo- and enantioselectivities, either under thermolysis or Lewis acid catalysis.[78] The stereospecific formation of a single stereoisomer from *N*-phenylmaleimide could be rationalised as shown in Scheme 29. The chiral dienyl sulfoxide preferred to adopt a conformation in which the S–O bond was parallel to the C=C bond, and *endo* addition of *N*-phenylmaleimide from the less hindered side of the diene (below the plane) would give the observed product. Since the Lewis acid-catalysed reaction gave the same product, it was assumed that similar steric arrangements were involved. The formation of two diastereoisomers from the thermal reaction with methyl propiolate indicated that the regioselectivity of the cycloaddition was dominated by the phenylsulfinyl group at C2 over the methyl group at C1. Preferential approach of methyl propiolate from the bottom face of the diene would give the major product. In the presence of the Lewis acid, this reaction led to only one stereoisomer, presumably by lowering the energy difference of HOMO (diene)−LUMO (dienophile) and thus making this reaction more stereoselective.

The use of enantiopure 2-sulfinylbuta-1,3-dienes in Diels–Alder reactions has allowed the development of a stereoselective approach to an azasteroidal skeleton.[79] Thus, Diels–Alder reactions of several chiral dihydro(vinyl)naphthalenes with *N*-phenylmaleimide occurred under thermal



Scheme 29. Diels–Alder reaction of chiral (*Z*)-1-methyl-2-(*p*-toluenesulfinyl)-1,3-butadiene.

conditions very slowly, but with notable stereoselectivity, giving, in each case, just one of the two *endo* adducts in high yield (Scheme 30). These results have opened the way for the setting up of stereocontrolled syntheses of further estrone-like compounds.

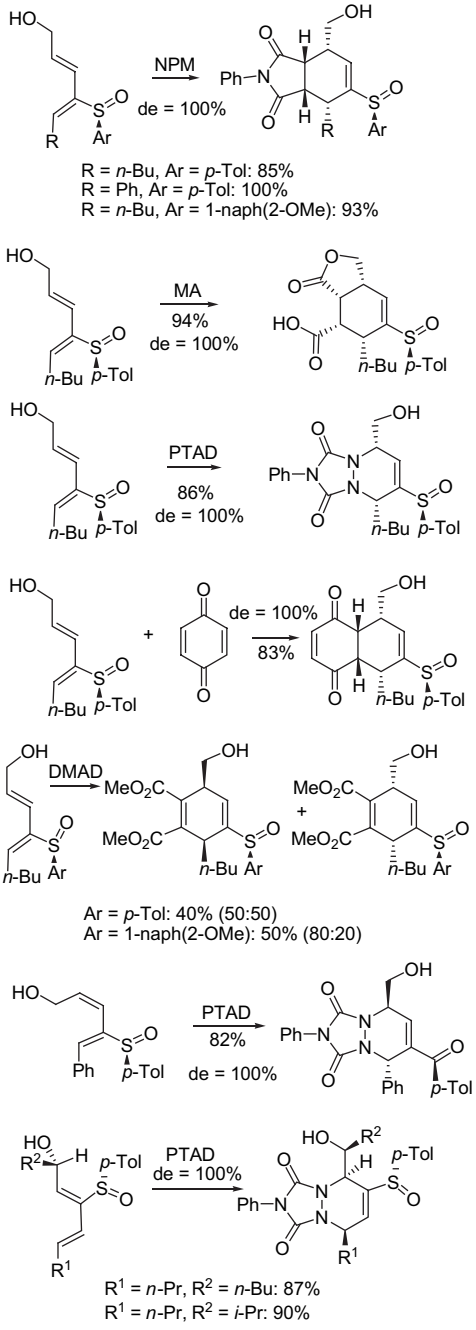


S*	R*	X	Yield (%)	*endo*	*exo*	Ratio
R	isoB	H	95	**22**	**24** + **25**	42:29:29
R	isoB	OMe	93	**22** + **23**	**24** + **25**	52:5:23:20
S	Born	OMe	95	**23**	**24** + **25**	67:19:14

S* : configuration at sulfur

Scheme 30. Synthesis of an azasteroidal skeleton via Diels–Alder reaction of chiral 2-sulfinylbuta-1,3-dienes.

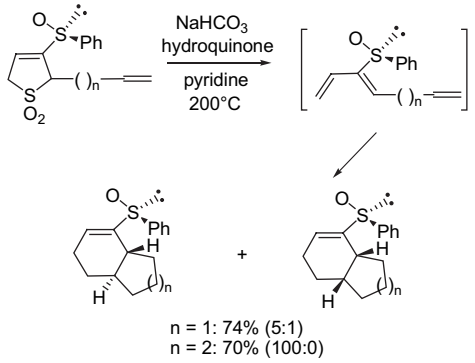
In 2005, de la Pradilla et al. reported highly diastereoselective Diels–Alder reactions of enantiopure sulfinyl-substituted 1-hydroxymethyldienes with various dienophiles.[80] Both hydroxy-2- and -3-sulfinyl dienes displayed highly π-face-selective Diels–Alder cycloadditions with dienophiles such as maleic anhydride (MA), phenyltriazolinedione (PTAD), *N*-phenylmaleimide (NPM), dimethyl acetylenedicarboxylate (DMAD) or *p*-benzoquinone, generating densely functionalised cycloadducts (Scheme 31).



Scheme 31. Diels–Alder reactions of chiral sulfinyl-substituted 1-hydroxymethyldienes.

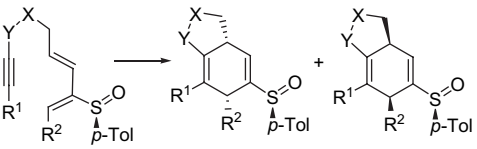
Both intermolecular and intramolecular Diels–Alder reactions involving chiral sulfoxides have been reported. As an example, Chou et al. have reported the intramolecular Diels–Alder reaction of a chiral sulfinyltriene intermediate, which

was generated in situ, providing the corresponding bicyclic products (Scheme 32).[78]



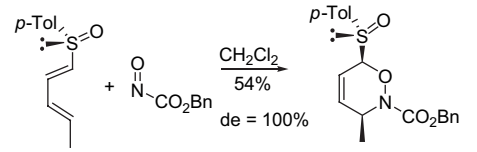
Scheme 32. Intramolecular Diels–Alder reaction of in situ-generated chiral sulfinyltrienes.

Dienynes generally require harsh thermal conditions to cycloadduct, which limit their applications in synthesis. De la Pradilla et al. have shown, however, that 2-sulfinylbutadienes tethered to unactivated alkynes underwent a facile thermal intramolecular Diels–Alder cycloaddition, often at room temperature, to produce cyclohexa-1,4-dienes with good selectivities (Scheme 33).[81] This strategy allowed the highly diastereoselective construction of a broad range of carbo- and heterocycles under exceptionally mild conditions, whilst preserving the valuable vinyl sulfoxide functionality.



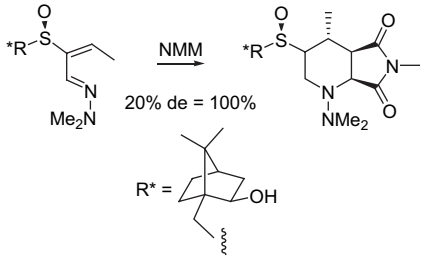
Scheme 33. Intramolecular Diels–Alder reaction of 2-sulfinylbutadienes.

Relatively few intermolecular and intramolecular hetero Diels–Alder reactions involving chiral sulfoxides give generally high stereoselectivities. Complete regioselectivity and stereoselectivity were, however, observed for the first asymmetric hetero Diels–Alder reaction of 1-sulfinyl dienes with acylnitroso derivatives such as benzyl nitrosoformate (Scheme 34).[82] The stereochemical course of the reaction could be explained by considering that the heterodienophile approached the less hindered face of diene that which supported the lone electron pair at sulfur, with the sulfinyl group in an *s*-trans arrangement with respect to C1═C2.



Scheme 34. Hetero Diels–Alder reaction of a 1-sulfinyldiene with a nitroso derivative.

In addition, a new approach towards chiral six-membered nitrogen heterocycles was developed by Aversa et al., on the basis of a hetero Diels–Alder reaction occurring between chiral (*E*,*E*)-2-[(1*S*)-isoborneol-10-sulfinyl]-2-butenal dimethylhydrazone and *N*-methylmaleimide (NMM).[83] This latter sulfoxide behaved as a 1-azabuta-1,3-diene, providing a unique cycloadduct with complete *endo* and facial selectivities (Scheme 35).

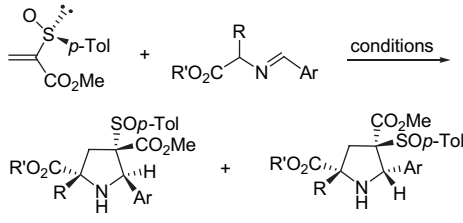


Scheme 35. Hetero Diels–Alder reaction of chiral (*E*,*E*)-2-[(1*S*)-isoborneol-10-sulfinyl]-2-butenal dimethylhydrazone.

Aversa et al. have also tested phenyl vinyl sulfide and ethyl vinyl ether as electron-rich dienophiles towards chiral (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one.[84] The reaction led to (4*S*,6*R*)-4-[(1*S*)-isoborneol-10-sulfinyl]-5,6-dihydro-2-phenyl-6-phenylthio-4*H*-pyran as the only cycloadduct among four possible diastereomers.

3.2. 1,3-Dipolar cycloaddition reactions

1,3-Dipolar cycloaddition involving a stereogenic centre or a chiral auxiliary on the dipole or the dipolarophile moiety is a useful tool for the regio- and stereoselective construction of five-membered heterocycles.[85] Most of the reported studies concern the use of acrylates as chiral dipolarophiles. Chiral vinyl sulfoxides, widely used as dienophiles, have been much less investigated as homochiral dipolarophiles.[59c] Several years ago, Garcia Ruano et al. initiated a research programme to explore the scope and limitations of vinyl sulfoxides in asymmetric 1,3-dipolar cycloadditions.[86] As an example, in 2002, this group reported the first 1,3-dipolar cycloaddition of azomethine ylides to vinyl sulfoxides such as methyl (*S*)-2-(*p*-tolylsulfinyl)acrylate (Scheme 36).[87] The

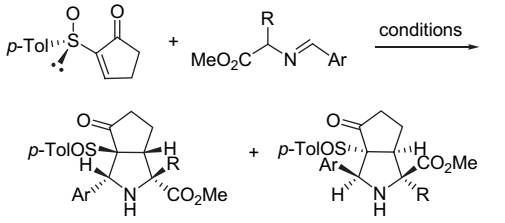


Ar	R	R'	Conditions	Yield (%)
Ph	H	Me	AgOAc/DBU/MeCN	13% + 36%
Ph	H	Me	AgOAc/DBU/THF	32% + 13%
Naph	H	Me	AgOAc/DBU/THF	50% + 8%
Naph	H	Me	AgOAc/DBU/MeCN	12% + 51%
Naph	Me	Me	AgOAc/DBU/MeCN	51% + 6%
Naph	Me	Et	AgOAc/DBU/MeCN	50% + 3%
Naph	Me	Et	AgOAc/DBU/THF	44% + 9%
Naph	Me	Et	AgOAc/NEt3/MeCN	11% + 48%

Scheme 36. Cycloaddition of azomethine ylides to sulfinylacrylates.

reaction evolved with complete regio- and *endo* selectivities, but, nevertheless, mixtures of two diastereoisomers (de 75–88%) resulting from the *anti* dipole/*s*-cis dipolarophile and *syn* dipole/*s*-trans dipolarophile approaches, respectively, were obtained. The stereoselectivity could, however, be controlled by using THF or MeCN as solvents. This new methodology represented a new entry into the synthesis of highly substituted pyrrolidines, which constitute the main building blocks of many alkaloids and pharmacologically active compounds.

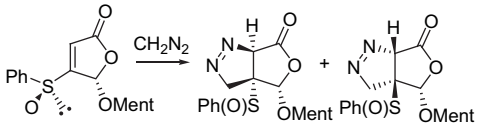
Similarly, azomethine ylides generated from imino esters could be condensed on (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone in a completely regio- and *endo* selective manner, but with a low facial selectivity, affording a mixture of two cycloadducts (Scheme 37).[88] When the ylides were prepared with LHMDS, only one diastereoisomer was obtained in almost quantitative yield. A nucleophilic addition/ring-closure process easily accounted for the stereochemical results.



Ar	R	Conditions	Yield (%)
Ph	H	AgOAc/DBU/MeCN	42% + 38%
2-Naph	H	AgOAc/DBU/MeCN	42% + 31%
2-Naph	Me	AgOAc/DBU/MeCN	34% + 33%
2-Naph	H	AgOAc/DBU/THF	19% + 19%
2-Naph	H	AgOAc/NEt_3/MeCN	20% + 18%
2-Naph	Me	LHMDS/THF	91% + < 2%
Ph	H	LHMDS/THF	89% + < 2%
Ph	Me	LHMDS/THF	91% + < 2%
2-Naph	H	LHMDS/THF	93% + < 2%

Scheme 37. Cycloaddition of azomethine ylides to (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone.

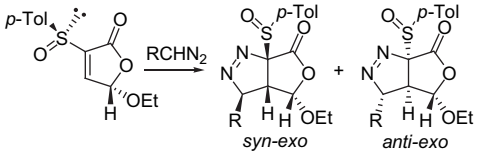
Diazoalkanes have also been submitted to asymmetric 1,3-dipolar cycloaddition in the presence of ($5S,S_S$)-5-[(1*R*)-menthyloxy]-4-phenylsulfinylfuran-2(5*H*)-ones, providing the corresponding pyrazolines resulting from the approach of the dipole to both diastereotopic faces of the dipolarophile (Scheme 38).[89] The reactions were completely regioselective, yielding only the adduct resulting from formation of the N_{dipole}–$C(3)_{furanone}$ bond.



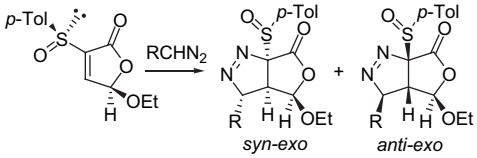
80% de = 70%
with $ZnBr_2$: 79% de = 100%

Scheme 38. Cycloaddition of ($5S,S_S$)-5-[(1*R*)-menthyloxy]-4-phenylsulfinylfuran-2(5*H*)-one to diazomethane.

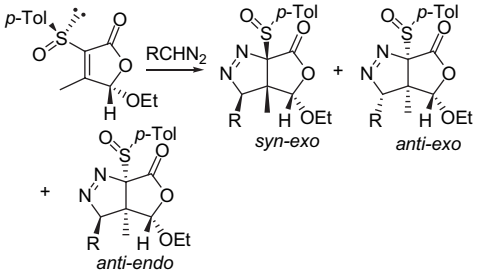
The role of steric and electronic interactions in the stereocontrol of the asymmetric 1,3-dipolar reactions of 5-alkoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones with diazoalkanes was studied in 2003 (Scheme 39).[90] It was demonstrated that these reactions evolved in high yields under mild conditions, affording bicyclic pyrazolines with complete regioselectivity, which could be modulated, becoming almost complete, with the solvent polarity. Electrostatic interactions between dipoles and the alkoxy group at C5 were, however, also significant in apolar solvents. The steric interactions between the substituents at diazoethane and at C4 of the furanone rings were the main reasons for the observed *exo* selectivity.



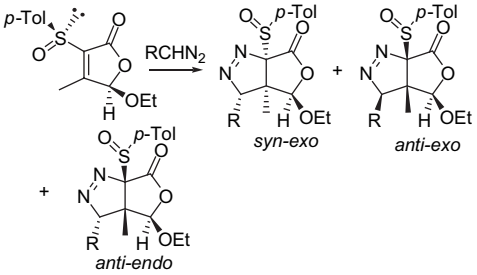
R = Me, solvent = Et_2O: *syn:anti* = 95:5
R = Me, solvent = MeCN/Et_2O: *syn:anti* = 60:40
R = H, solvent = MeCN/Et_2O: *syn:anti* = 40:60
R = H, solvent = Et_2O: *syn:anti* = 100:0



R = Me, solvent = Et_2O: *syn:anti* = 7:93
R = Me, solvent = MeCN/Et_2O: *syn:anti* = 5:95
R = H, solvent = Et_2O: *syn:anti* = 7:93
R = H, solvent = MeCN/Et_2O: *syn:anti* = 9:91



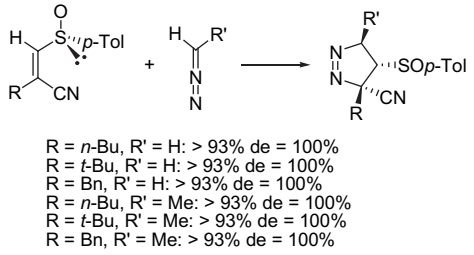
R = Me, solvent = Et_2O: *syn:anti* = 100:0
R = Me, solvent = MeCN/Et_2O: *syn:anti* = 84:16
R = H, solvent = Et_2O: *syn:anti* = 100:0
R = H, solvent = MeCN/Et_2O: *syn:anti* = 75:25



R = Me, solvent = Et_2O: *syn:anti* = 0:100
R = Me, solvent = MeCN/Et_2O: *syn:anti* = 0:100
R = H, solvent = Et_2O: *syn:anti* = 0:100
R = H, solvent = MeCN/Et_2O: *syn:anti* = 5:95

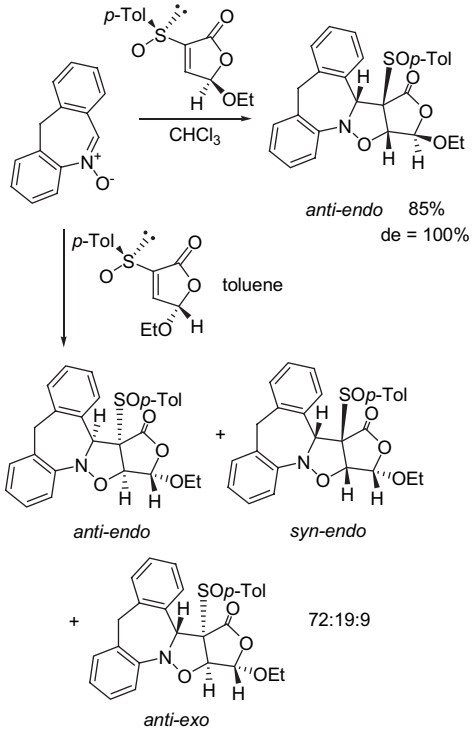
Scheme 39. Cycloaddition of chiral 5-alkoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones to diazoalkanes.

In addition, the dipolarophilic reactivity of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles has been evaluated with diazoalkanes, providing a new entry into chiral Δ^1-cyanopyrazolines, the structures of which are much less frequently reported in the literature than those of their corresponding Δ^2-analogues (Scheme 40).[91] Moreover, the asymmetric synthesis of pyrazolines has been studied mainly from cyclic and much less from acyclic alkenes. In each case, only one cycloadduct was formed in high yield under mild conditions, therefore evidencing a complete control of the regioselectivity and the *endo*/*exo* and π-facial selectivities.



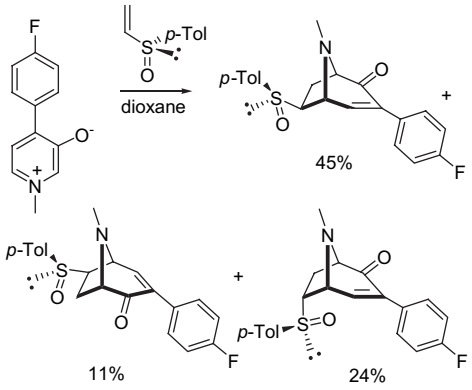
Scheme 40. Cycloaddition of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles to diazoalkanes.

The biological activity of molecules containing a modified azepine ring has been intensively tested against various diseases. In the course of preparing new chiral pyrroloazepines and isoxazoloazepines, Rosario Martin et al. have developed asymmetric 1,3-dipolar reactions of 3-sulfinylfuran-2(5*H*)-ones with 11*H*-dibenzo[*b*,*e*]azepine 5-oxide, affording the corresponding furoisoxazoloazepines (Scheme 41).[92] In one case, the regio-, π-facial and *endo* selectivities were complete, yielding only one diastereoisomer.



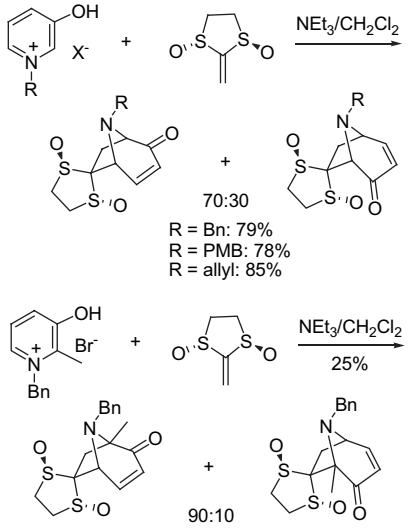
Scheme 41. Cycloaddition of 3-sulfinylfuran-2(5*H*)-ones to 11*H*-dibenzo[*b*,*e*]-azepine 5-oxide.

In 2000, the 1,3-dipolar cycloaddition methodology was applied to the synthesis of chiral 7-fluorotropanes as structural probes of the dopamine transporter.[93] The synthesis of these cocaine analogues was accomplished with complete regioselectivity through the reaction of an oxidopyridinium betaine with the chiral dipolarophile, (*R*)-*p*-tolyl vinyl sulfoxide (Scheme 42).



Scheme 42. Cycloaddition of an oxidopyridinium betaine to (*R*)-*p*-tolyl vinyl sulfoxide.

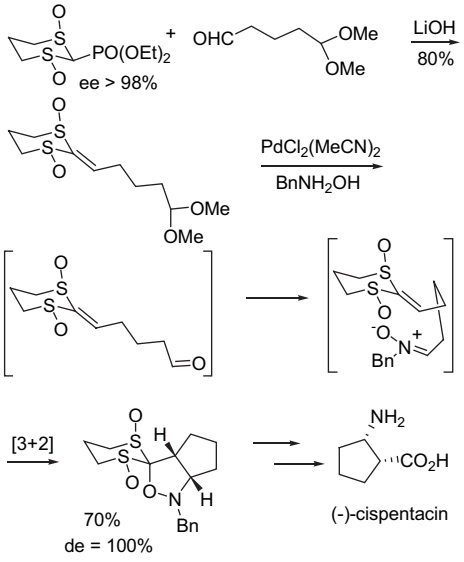
A range of 3-oxidopyridinium betaines bearing various substituents on nitrogen was found to react with the C2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, with total diastereoselectivity in the case of simple 3-oxidopyridinium betaines (Scheme 43).[94] These reactions were under kinetic control, although, over longer periods of time, the ratio of regioisomers changed, on account of the reversibility of the reaction. The regioselectivity in these reactions was moderate, although this could be improved by placing an additional substituent at the 2-position of the betaine.



Scheme 43. Cycloaddition of 3-oxidopyridinium betaines to chiral *trans*-2-methylene-1,3-dithiolane 1,3-dioxide.

In 2003, Aggarwal et al. reported the intramolecular 1,3-dipolar nitrone cycloaddition onto an enantiomerically pure ketene dithioacetal dioxide using a three-carbon tether, providing the corresponding 5,5-disubstituted isoxazolidine as a single diastereomer (Scheme 44).[95] In fact, such a process

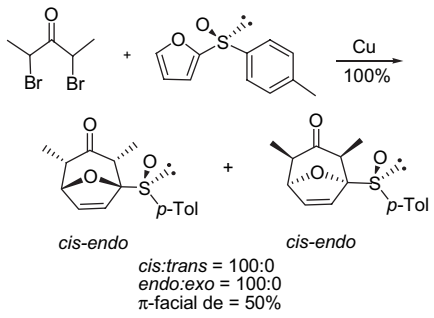
was the first example of an intramolecular cycloaddition in which a chiral ketene equivalent was employed. This reaction has been used as the key step in an asymmetric synthesis of the naturally occurring antibiotic, (−)-cispentacin. In addition, a first asymmetric synthesis of 4-amino-pyrrolidine-3-carboxylic acid has also been carried out using the intramolecular nitrone cycloaddition as the stereocontrolling step.



Scheme 44. Intramolecular nitrone cycloaddition of chiral ketene dithioacetal bis(sulfoxides).

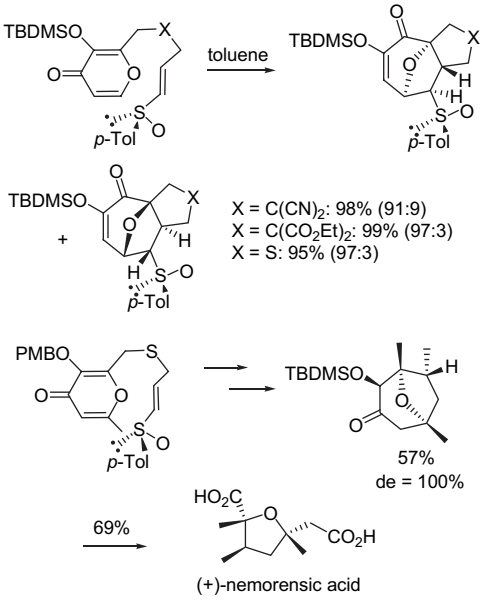
3.3. Other cycloaddition reactions

The [4+3] cycloaddition reaction between C2-functionalised furans and oxyallyl cations is an elegant and efficient method to synthesise polyfunctionalised cycloheptenes; these synthons facilitate the straightforward synthesis of molecules having a seven-membered ring. In 2002, Montana et al. reported [4+3] cycloaddition reactions of chiral C2-functionalised furans with a 2-oxyallyl cation in which the asymmetry was introduced by a chiral auxiliary such as a chiral sulfoxide on C2 of the furan (Scheme 45).[96] The process gave almost stereospecifically the cis-*endo* diastereoisomeric cycloadducts. The exclusive formation of the *endo* isomers could be due to the fact that the extended approach leading to the formation of the *exo* products was destabilised in favour of the compact approach, due to the presence of a bulky group on C2 of the diene.



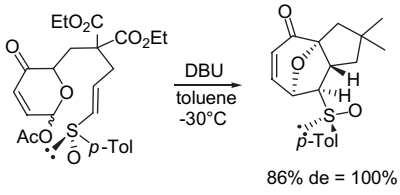
Scheme 45. [4+3] Cycloaddition of a chiral furyl sulfoxide to 2-oxyallyl cation.

A practical route to enantiopure 8-oxabicyclo[3.2.1]octane derivatives has been developed by Mascarenas et al. on the basis of a sulfinyl-directed diastereoselective [5+2] pyrone–alkene cycloaddition.[97] Thus, these authors have shown that the introduction of a homochiral *p*-tolylsulfinyl group at the trans-terminal position of an alkene accelerated its thermal [5C+2C] intramolecular cycloaddition to β-silyloxy-γ-pyrones and led to excellent levels of diastereodifferentiation (Scheme 46). The stereochemical outcome of the reaction could be rationalised by assuming that the alkenyl sulfoxide unit adopted an *s*-trans conformation in order to avoid repulsive dipole–dipole interactions with the pyrone, disfavouring the approach from the face of the sulfoxide displaying the *p*-tolyl group. In addition, these authors have shown that switching from a sulfinyl to a sulfonimidoyl group allowed the reversal of the sense of asymmetric induction.[97b] The utility of this methodology was demonstrated by its application to a concise synthesis of the naturally occurring pyrrolizidine alkaloid, (+)-nemorensic acid.[98]



Scheme 46. Sulfinyl-directed diastereoselective [5+2] pyrone-alkene cycloaddition.

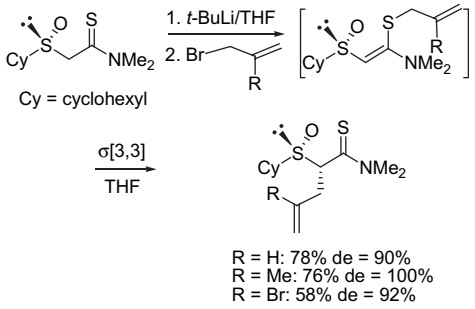
Another version of this reaction could be developed starting from the more classical oxidopyrilium-alkenes.[97c] A mild and fully diastereoselective intramolecular cycloaddition led to the formation of 6-acetoxy-3-pyranones (Scheme 47).



Scheme 47. Diastereoselective [5+2] acetoxypyrone-alkene cycloaddition.

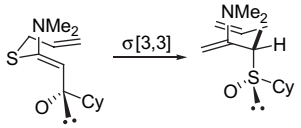
The Claisen rearrangement is a powerful reaction for the construction of complex molecules including natural products and biologically active molecules.[99] Metzner et al. have developed a new version of this reaction, in which the absolute and relative stereochemistries were directed

by a sulfinyl group, located in an adjacent position to the pericyclic [3,3] sigmatropic nucleus.[100] Thus, ketene aminothioacetals bearing an enantiopure vinylic alkylsulfinyl substituent underwent a Claisen rearrangement upon heating at THF reflux to afford α-sulfinyl γ-unsaturated thioamides (Scheme 48). In this transposition, which needed heating to be accomplished, an unexpected facile sulfenic acid elimination was often observed. In order to avoid this problem, Metzner et al. replaced the oxygen atom of the Claisen pericyclic nucleus by a sulfur atom, leading to an acceleration of the rearrangement.[100] A second way to modulate this elimination was to use a cyclohexyl group linked to sulfur. With all substrates, the asymmetric induction of the sulfinyl group was excellent (de≥90%).



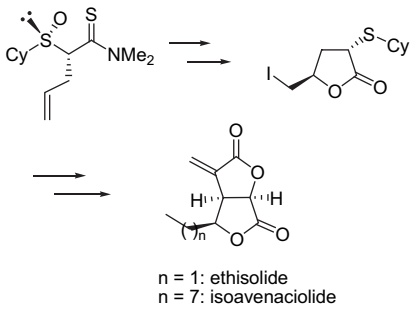
Scheme 48. Thio-Claisen rearrangement of chiral allyl ketene aminothioacetals.

In order to explain the stereochemical course of the [3,3] sigmatropic transposition, an electronic model was proposed as an extension of the Felkin Anh model (Scheme 49). The allyl moiety (electrophilic) approached the keteneaminothioacetal bond (nucleophilic) with substituents oriented on the chiral sulfur atom so that placing the most electron-donating group in an antiperiplanar position maximised the orbital overlap. The oxygen atom (linked to sulfur) occupied the inside allylic position, and the large cyclohexyl moiety the outside position.



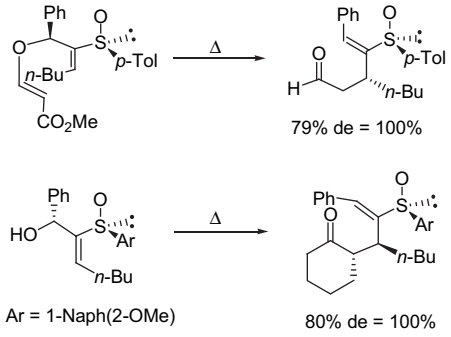
Scheme 49. Stereochemical course of the Claisen rearrangement.

The easy access to this attractive, small, functionalised chiral synthon was applied to the synthesis of natural bis(lactones) such as ethisolide and isoavenaciolide (Scheme 50).



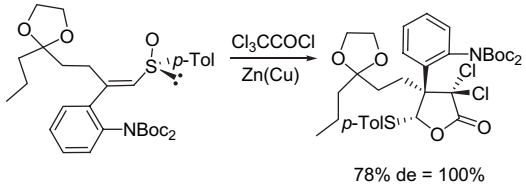
Scheme 50. Synthesis of ethisolide and isoavenaciolide.

In 2002, the first examples of Claisen rearrangements of substrates bearing a sulfinyl functionality at C5 were described, allowing for the creation of up to two asymmetric centres (Scheme 51).[101]



Scheme 51. Claisen rearrangements of substrates bearing sulfinyl functionality at C5.

A [3,3]-sigmatropic rearrangement of a chiral vinyl sulfoxide with in situ-generated dichloroketene was the key step of a total synthesis of (+)-aspidospermidine.[102] This ketene lactonisation reaction afforded the corresponding chiral dichlorolactone as a single diastereoisomer (Scheme 52).



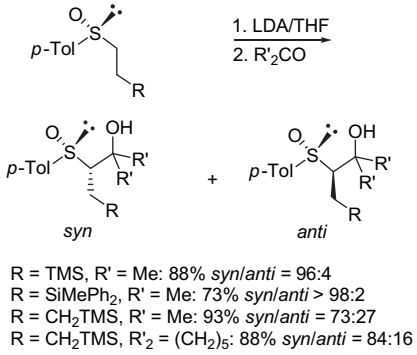
Scheme 52. Asymmetric ketene lactonisation reaction.

4. Reactions of sulfoxide-stabilised carbanions

4.1. Unconjugated addition reactions

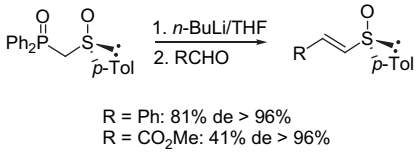
The ability of sulfoxides to stabilise a negative charge on an adjacent carbon atom has prompted the development of synthetic procedures based on optically active α-sulfinyl carbanions.[103] The use of chiral sulfoxide-stabilised carbanions for asymmetric carbon–carbon bond formation via alkylation, or addition to carbonyl and activated C=C double bonds, has been extensively studied over the past two decades. Deprotonation of the α-carbon of the sulfoxide requires a strong base such as $LiNH_2$, LDA, *n*-BuLi, LiHMDS or a Grignard reagent. High stereoselectivity usually requires steric hindrance in the vicinity of the α-carbon of the sulfoxide and the use of an electrophile with a bulky group. Condensations of α-sulfinyl carbanions with aldehydes provide a useful method for generating 1,2-asymmetry, as well as for the construction of 1,3-asymmetric relationships in acyclic systems. If optically active sulfoxides such as methyl *p*-tolyl sulfoxide give a poor diastereoselectivity when such an α-sulfinyl carbanion is added to a carbonyl, the presence of another function such as an ester, sulfide or amide, which has a chelating effect in the transition state, makes optically active α-sulfinyl esters, sulfides or amides very useful in asymmetric aldol-type condensations. In 2000, Toru et al. demonstrated the stereoselectivity of the reaction of α-sulfinyl carbanions derived from chiral 2-(trialkylsilyl)ethyl sulfoxides with ketones (Scheme 53).[104]

Interaction between the silicon in the trialkylsilyl group and the carbonyl oxygen in the nucleophiles was postulated to stabilise the transition state, leading preferably to the *syn* diastereoisomers. This novel silicon–oxygen interaction was supported by an MO calculation study.



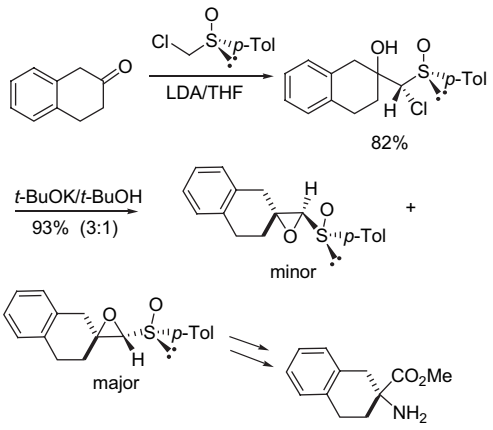
Scheme 53. Reaction of chiral 2-(trialkylsilyl)ethyl sulfoxides with ketones.

In the course of preparing new (*E*)-vinyl sulfoxides by the Horner–Wittig reaction, van der Gen et al. have shown that the use of (*S*)-diphenyl(*p*-tolylsulfinylmethyl)phosphane oxide allowed the synthesis of chiral (*E*)-vinyl sulfoxides (Scheme 54).[105]



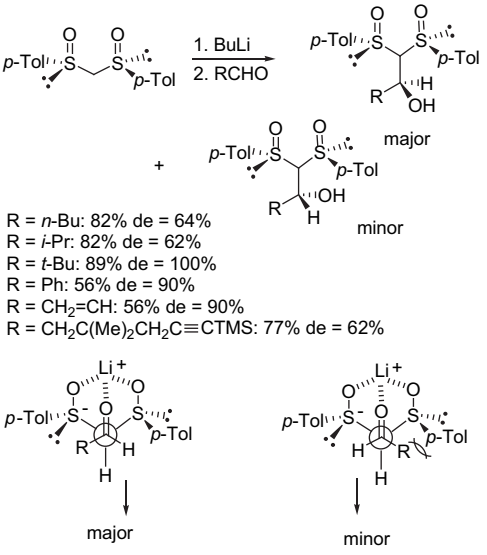
Scheme 54. Horner–Wittig synthesis of (*S*)-(*E*)-vinyl tolyl sulfoxides.

In 2005, Satoh et al. developed a novel synthesis of α-quaternary α-amino acid methyl esters from ketones via sulfinyloxiranes. Starting from β-tetralone and (*R*)-chloromethyl *p*-tolyl sulfoxide, an asymmetric synthesis of optically pure (*R*)-methyl 2-aminotetraline-2-carboxylate was performed in good overall yields.[106] As depicted in Scheme 55, the reaction of β-tetralone with the lithium α-sulfinyl carbanion generated from (*R*)-chloromethyl *p*-tolyl sulfoxide and LDA in THF gave the intermediate chloride as a mixture of two diastereomers. Without separation, this mixture was treated with *t*-BuOK to afford a 3:1 mixture of sulfinyloxiranes. The separated major product was further converted into the expected (*R*)-methyl 2-aminotetraline-2-carboxylate.



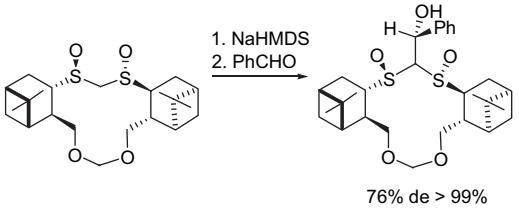
Scheme 55. Synthesis of (*R*)-methyl 2-aminotetraline-2-carboxylate.

The chemistry of C_2-symmetric bis(sulfoxides) has been widely studied by Malacria et al. and, in particular, their condensation onto carbonyl derivatives.[75] Thus, the diastereoselectivity of the alkylation of the lithium anion of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with aldehydes was examined.[107] The reaction proved to be fairly diastereoselective, even for simple alkyl aldehydes, and not only for aromatic aldehydes, as found for cyclic disulfoxides.[108] Scheme 56 depicts the most favourable approach involving a chelated transition state in which nonbonding interactions between the *p*-tolyl group of the anion and the R group of the aldehyde are minimised.



Scheme 56. Reaction of anion of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with acyclic aldehydes.

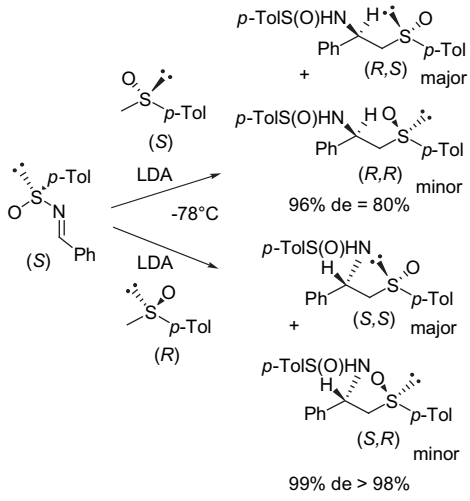
An efficient preparation of a myrtenal-derived bis-sulfoxide was reported in 2005 by Zepeda et al.[109] The utility of this *trans* bis-sulfoxide as a chiral acyl donor was explored by condensing its derived anion with benzaldehyde in THF, giving the corresponding carbinol with complete diastereoselectivity (Scheme 57). The stereochemical outcome of the reaction was explained by a reasonable chair-like six-membered transition state, in which the axial-like arrangement of the phenyl group, which minimised steric interactions with the β-oxygen of the nonchelated sulfoxide, could be appreciated. Accordingly, it could be inferred that nucleophilic addition by the *si* face was disfavoured.



Scheme 57. Reaction of anion of a myrtenal-derived bis-sulfoxide with benzaldehyde.

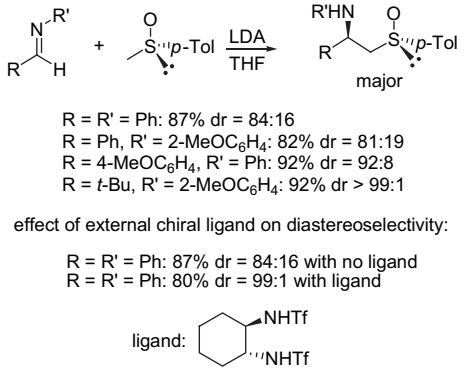
There are few reports on chiral sulfoxide anion addition to imines. The reaction of chiral α-sulfinyl anions with imines has been reported to proceed with better diastereoselectivity for simple systems than the analogous reactions

on aldehydes.[110] In 2000, Garcia Ruano et al. reported the addition of the lithium anions derived from (*R*)- and (*S*)-methyl and -ethyl *p*-tolyl sulfoxides to (*S*)-*N*-benzylidene-*p*-toluenesulfinamide, providing an easy access route to enantiomerically pure β-(*N*-sulfinyl)amino sulfoxides (Scheme 58).[111] Stereoselectivity could be achieved when the configurations at the sulfur atoms of the two reagents were opposite, thus resulting in only one diastereoisomer, even for the case in which two new chiral centres were created. The *N*-sulfinyl group primarily controlled the configuration of the carbon bonded to the nitrogen, whereas the configuration of the α-sulfinyl carbanion seemed to be responsible for the level of asymmetry induction, as well as for the configuration of the new stereogenic C–SO carbon, in the reactions with ethyl *p*-tolyl sulfoxides. This methodology constituted one of the best methods for obtaining enantiomerically pure β-amino sulfoxides.



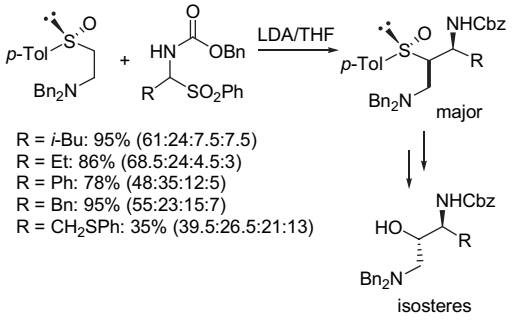
Scheme 58. Reaction of α-sulfinyl carbanions with (*S*)-*N*-sulfinimines.

In 2003, Tanner et al. revisited the diastereoselective addition of α-metallated methyl tolyl sulfoxides to imines recently studied by several groups,[112] showing that up to >98% des could be obtained under conditions of kinetic control (short reaction time, low temperature).[113] Moreover, these authors demonstrated that the use of external chiral ligands such as C_2-symmetric bis(sulfonamide) ligands enhanced the diastereoselectivity of otherwise moderately selective reactions (Scheme 59).



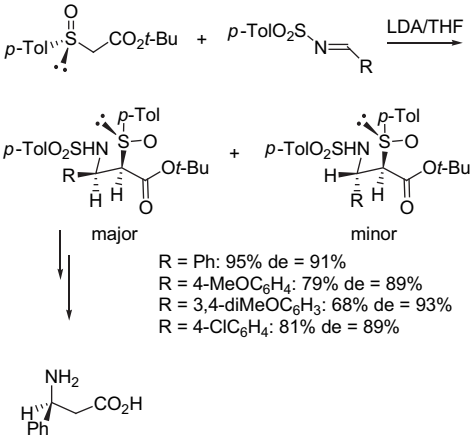
Scheme 59. Reaction of α-metallated methyl tolyl sulfoxides with imines.

In 2004, Zanda et al. reported a novel synthesis of chiral hydroxyethylamine dipeptide isosteres on the basis of the Mannich-type reaction of a lithiated β-sulfinylethylamine with *N*-Cbz-imines generated in situ from α-amino-sulfones (Scheme 60).[114] The 2-sulfinyl-1,3-diamines thus formed could be converted into an epimer of saquinavir, an inhibitor of HIV protease. In that context, a similar methodology was also applied to the synthesis of both enantiomers of natural statine, exploiting an α-lithiated alkylsulfoxide as a chiral α-hydroxyalkyl carbanion equivalent.[115]



Scheme 60. Synthesis of hydroxyethylamine isosteres.

In 2001, Bhat et al. developed an elegant synthesis of β-aminophenylpropionic acid, based on the stereoselective condensation of *tert*-butyl (*R*)-*p*-tolylsulfinylacetate with *N*-(benzylidene)toluene-4-sulfonamides in the presence of LDA (Scheme 61).[116]

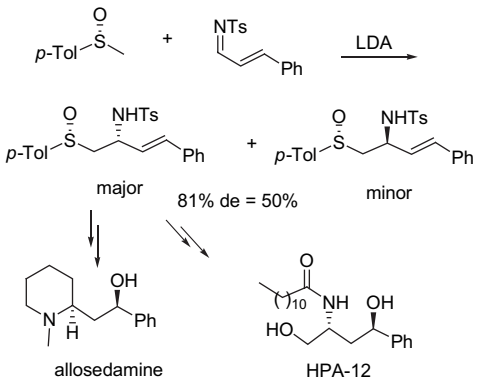


Scheme 61. Synthesis of chiral β-aminophenylpropionic acid.

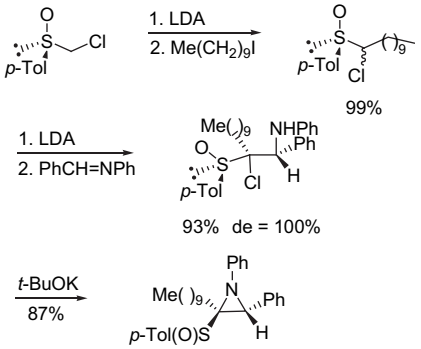
The diastereoselective addition of the carbanion derived from (*S*)-*tert*-butyl phenylmethylsulfoxide to imines derived from α,β-unsaturated aldehydes such as cinnamaldehyde was the key step of a total synthesis of biologically active (−)-allosedamine and HPA-12 (Scheme 62).[117]

In addition, Satoh et al. have prepared various chiral sulfinylaziridines by condensation of the anion of *p*-tolyl sulfoxides onto imines, followed by treatment with potassium *tert*-butoxide, as depicted in Scheme 63.[118]

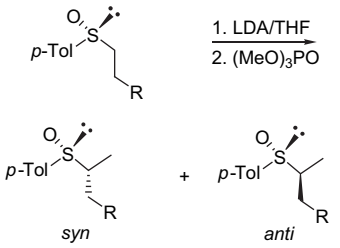
α-Sulfinyl carbanions have been condensed onto various other electrophiles such as trimethyl phosphate, which gave excellent diastereoselectivities in the case of carbanions derived from chiral 2-(trialkylsilyl)ethyl sulfoxides (Scheme 64).[104]



Scheme 62. Reaction of anion of (*S*)-*tert*-butyl phenylmethylsulfoxide with unsaturated imine.



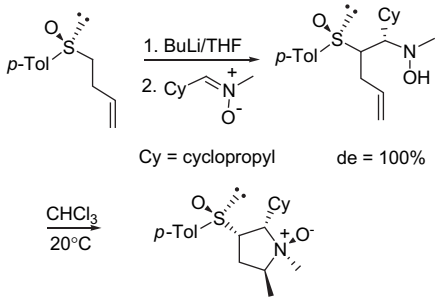
Scheme 63. Synthesis of a chiral sulfinylaziridine.



R = TMS: 94% *syn*/*anti* = 96:4
R = $SiMePh_2$: 69% *syn*/*anti* = 94:6
R = $SiMePh_2$: 69% *syn*/*anti* = 94:6
R = Me: 64% *syn*/*anti* = 88:12
R = CH_2TMS: 80% *syn*/*anti* = 83:17
R = *t*-Bu: 68% *syn*/*anti* = 19:81

Scheme 64. Methylation reaction of chiral *p*-tolyl sulfoxides.

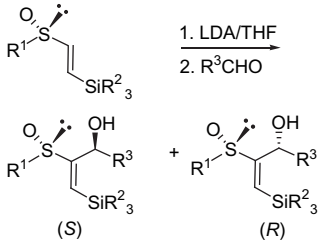
Knight et al. have shown that the chiral lithiated homoallylic sulfoxide depicted in Scheme 65 added smoothly to an aldonitrone to give a single diastereoisomer of the corresponding



Scheme 65. Synthesis of a chiral pyrrolidine-*N*-oxide.

unsaturated hydroxylamine, which then underwent a reverse Cope cyclisation to give the corresponding highly substituted pyrrolidine-*N*-oxide in a stereocontrolled manner.[119]

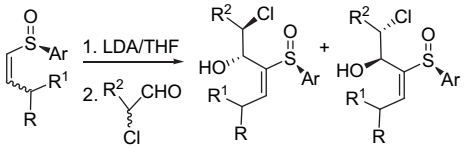
Nucleophilic addition of α-carbanions of enantiomerically enriched vinyl sulfoxides is also useful in the construction of new stereogenic centres. Several authors have studied the reaction of the α-vinyl anions derived from chiral vinyl sulfoxides with aldehydes. As an example, Toru et al. have prepared chiral alcohols by condensation of lithiated silylvinyl sulfoxides onto aldehydes (Scheme 66).[120]



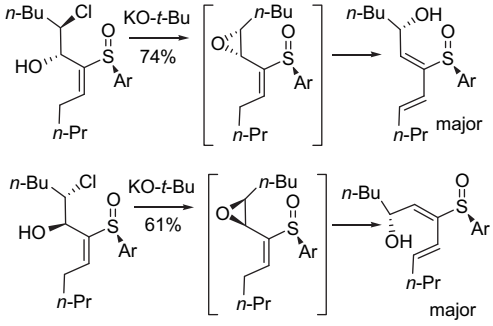
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = Ph: 88% (*S*):(*R*) = 45:55
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = Me: 82% (*S*):(*R*) = 68:32
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 93% (*S*):(*R*) = 73:27
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = *i*-Pr: 92% (*S*):(*R*) = 68:32
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = *t*-Bu: 71% (*S*):(*R*) = 76:24
R^1 = *p*-Tol, SiR^2_3 = $SiPh_2Me$, R^3 = n-C_5H_{11}: 77% (*S*):(*R*) = 69:31
R^1 = *p*-Tol, SiR^2_3 = $SiPh_3$, R^3 = n-C_5H_{11}: 70% (*S*):(*R*) = 66:34
R^1 = *p*-Tol, SiR^2_3 = $SiPh_3$, R^3 = *t*-Bu: 74% (*S*):(*R*) = 67:33
R^1 = *t*-Bu, SiR^2_3 = TMS, R^3 = Ph: 88% (*S*):(*R*) = 34:66
R^1 = *t*-Bu, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 82% (*S*):(*R*) = 29:71
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 70% (*S*):(*R*) = 37:63
R^1 = *p*-Tol, SiR^2_3 = $SiPh_2Me$, R^3 = n-C_5H_{11}: 65% (*S*):(*R*) = 32:68

Scheme 66. Reaction of chiral silylvinyl sulfoxides with aldehydes.

Similar stereoselectivities were observed for the preparation of chiral α′-hydroxy vinyl sulfoxides through lithiation followed by addition to aldehydes of various alkylvinyl sulfoxides.[121] In the same context, sulfur-directed synthesis of enantiopure hydroxy 2-sulfinylbutadienes was reported in 2004.[122] It was shown that the treatment of sulfinyl



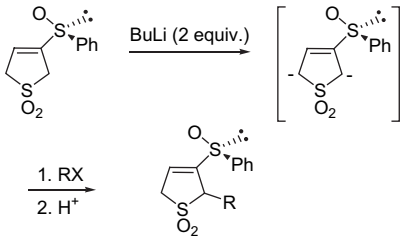
Ar = *p*-Tol, R = *n*-Pr, R^1 = H, R^2 = *n*-Bu: 74% (46:54)
Ar = *p*-Tol, R = Me, R^1 = H, R^2 = Bn: 58% (48:52)
Ar = *p*-Tol, R = *i*-Pr, R^1 = H, R^2 = Bn: 58% (58:42)
Ar = *p*-Tol, R = Me, R^1 = Me, R^2 = *n*-Bu: 73% (52:48)
Ar = *p*-Tol, R = *n*-Pr, R^1 = H, R^2 = *i*-Pr: 75% (56:44)



Scheme 67. Sulfur-directed synthesis of chiral hydroxy 2-sulfinylbutadienes.

chlorohydrins with KO-*t*-Bu in THF generated epoxy vinyl sulfoxides that underwent an efficient base-induced rearrangement to generate chiral hydroxy 2-sulfinyl dienes (Scheme 67). This novel process took place with high chemo- and stereoselectivity. The chirality at sulfur effectively controlled the geometry of the trisubstituted alkene.

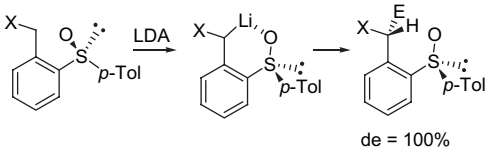
On the other hand, the deprotonation of the cyclic chiral 3-phenylsulfinyl-3-sulfolene depicted in Scheme 68 and its subsequent reaction with alkyl halides gave regiospecifically the C2-alkylated products.[78] The regiospecific alkylation could be explained by a first deprotonation at the most acidic C5 position, followed by a second deprotonation at C2. The reaction with allyl bromide yielded only one enantiomer, whereas the reactions with other electrophiles gave a mixture of two diastereomers.



RX = MeI: 88% (*S*,*S*)/(*S*,*R*) = 6:1
RX = allylBr: 84% (*S*,*S*)/(*S*,*R*) = 100:0
RX = BnBr: 75% (*S*,*S*)/(*S*,*R*) = 5:1
RX = CH_2=$CH(CH_2)_3$I: 80% (*S*,*S*)/(*S*,*R*) = 4:1
RX = CH_2=$CH(CH_2)_4$I: 82% (*S*,*S*)/(*S*,*R*) = 4:1

Scheme 68. Reaction of a chiral 3-phenylsulfinyl-3-sulfolene with alkyl halides.

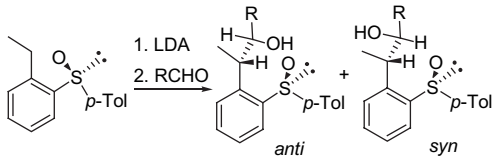
Garcia Ruano et al. have demonstrated that enantiopure *ortho*-sulfinyl groups could stabilise benzyllithium carbanions and promote diastereoselective reactions with electrophiles by a 1,4-induction.[123] This possibility was firstly evaluated for (*S*)-2-ethylphenyl *p*-tolyl sulfoxide and (*S*)-2-(triisopropylsiloxymethyl)phenyl *p*-tolyl sulfoxide, the corresponding carbanions of which were alkylated with various electrophiles (Scheme 69). With simple electrophiles such as ethyl chloroformate or acetone, the new benzylic stereogenic centres were always generated in a highly diastereoselective manner and with the same induction, independent of the electrophile.



Electrophile = $ClCO_2Et$, E = CO_2Et, X = Me: 75%
Electrophile = $ClCO_2Et$, E = CO_2Et, X = OTIPS: 75%
Electrophile = MeCOMe, E = CO_2Et, X = Me: 81%
Electrophile = MeCOMe, E = CO_2Et, X = OTIPS: 78%

Scheme 69. Enantioselective generation of benzylic stereocentres mediated by a remote sulfoxide.

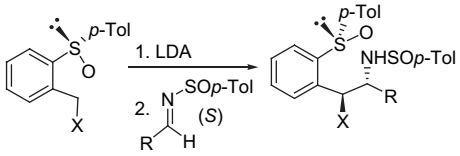
In contrast, when additional stereogenic centres were created, the stereoselectivity of the latter process was electrophile dependent. Thus, when aldehydes were used as electrophiles, the diastereoselectivity of the reaction was dependent upon the nature of the aldehyde.[124] Reactions from aliphatic and aromatic aldehydes containing electron-donating groups were completely stereoselective at C2, but exhibited a moderate stereoselectivity at C1, which was mainly related to the aliphatic or aromatic character of the aldehydes (Scheme 70). After separation by chromatography, a further desulfinylation allowed the obtention of enantiomerically pure 1-alkyl (or aryl)-2-phenyl-1-propanols.



R = Ph: 65% *anti*:*syn* = 85:15
R = (p-$OMeC_6H_4$): 80% *anti*:*syn* = 84:16
R = (2-Naph): 62% *anti*:*syn* = 85:15
R = (1-Naph): 73% *anti*:*syn* = 88:12
R = (2,6-$Me_2C_6H_3$): 70% *anti*:*syn* = 67:33
R = *n*-Bu: 87% *anti*:*syn* = 37:63
R = *i*-Pr: 75% *anti*:*syn* = 29:71
R = *t*-Bu: 58% *anti*:*syn* = 24:76

Scheme 70. Reaction of chiral *ortho*-sulfinyl benzyl carbanions with aldehydes.

The scope of this reaction could be extended to other electrophiles such as *N*-*p*-toluenesulfinylimines. Addition of lithium (*R*)-*ortho*-(*p*-toluenesulfinyl)benzylic carbanions took place with complete stereoselectivity, yielding useful chiral 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines (Scheme 71).[125] Similarly, enantiomerically pure *anti*-1,2-amino alcohol derivatives could be achieved by the reaction of prochiral oxygenated 2-*p*-tolylsulfinylbenzyl carbanions with *N*-sulfinylimines bearing the same configuration at sulfur (Scheme 71).[126]

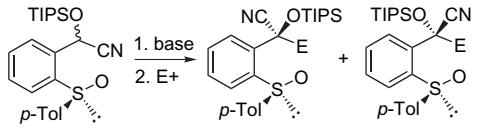


X = OTIPS, R = Ph: 81% de > 98%
X = OTIPS, R = *o*-BrC_6H_4: 71% de > 98%
X = OTIPS, R = *p*-$MeOC_6H_4$: 78% de > 98%
X = OTIPS, R = *p*-CNC_6H_4: 74% de > 98%
X = OTIPS, R = *p*-ClC_6H_4: 76% de > 98%
X = OTIPS, R = 2-py: 77% de > 98%
X = OTIPS, R = 2-Naph: 68% de > 98%
X = OTIPS, R = *n*-Bu: 74% de > 98%
X = OTIPS, R = *i*-Pr: 72% de > 98%
X = Me, R = Ph: 82% de > 98%
X = Me, R = *o*-BrC_6H_4: 87% de > 98%
X = Me, R = *p*-$MeOC_6H_4$: 84% de > 98%
X = Me, R = *p*-CNC_6H_4: 60% de > 98%
X = Me, R = 2-Naph: 75% de = 78%
X = Me, R = *n*-Bu: 85% de > 98%
X = Me, R = *i*-Pr: 88% de > 98%
X = Me, R = *t*-Bu: 89% de > 98%
X = Me, R = Bn: 88% de > 98%

Scheme 71. Reaction of chiral *ortho*-sulfinyl benzyl carbanions with *N*-sulfinylimines.

Finally, optically pure functionalised cyanohydrins derived from 1-[2-(*p*-tolylsulfinyl)phenyl] ethanone could be obtained by the reaction of 2-*p*-tolylsulfinylbenzaldehyde-derived cyanohydrins with bases and further treatment with suitable electrophiles.[127] Thus, this remote 1,4-asymmetric

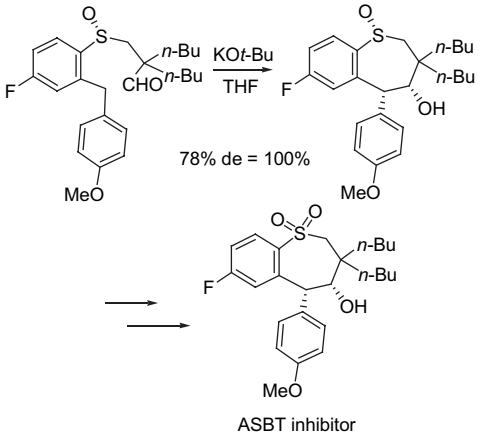
induction process constituted a new strategy for preparing chiral ketone-derived cyanohydrins, starting from the much more readily available aldehyde-derived cyanohydrins (Scheme 72).



Base	Electrophile	dr (Yield %)
KHMDS	$ClCO_2Me$	> 98:2 (85)
KHMDS	ClCOMe	> 98:2 (83)
KHMDS	allylBr	> 98:2
LiHMDS	$ClCO_2Me$	> 98:2
LiHMDS	ClCOMe	> 98:2
LiHMDS	$CH_2{=}N^+Me_2\ I^-$	> 98:2 (74)
LiHMDS	BnBr	> 98:2 (77)
LiHMDS	allylBr	> 98:2 (89)
K/18-crown-6	MeI	88:12 (76)
K/18-crown-6	EtOTf	87:13 (73)

Scheme 72. Quaternisation of cyanohydrins derived from 2-*p*-tolylsulfinylbenzaldehyde.

Stereoselective intramolecular additions of α-sulfinyl carbanions are also present in the literature such as intramolecular aldol condensation involved in the formation of a benzothiepine ring, in which the chirality of the sulfoxide controlled the configurations of two new stereogenic centres.[38] This strategy was applied to the synthesis of the apical sodium co-dependent bile acid transporter (ASBT) inhibitor depicted in Scheme 73. The cyclisation providing a single diastereomer was shown to be thermodynamically controlled. A metal chelate between the sulfoxide oxygen and the alkoxide oxygen was proposed to rationalise the configuration of the newly formed stereogenic centre at C4. The cis configuration was lower in energy, due to unfavourable steric interactions berween the C5-aryl and C3-butyl groups in the trans configuration. Thus, the configuration of the chiral sulfoxide determined the absolute configuration at both of the newly formed stereogenic centres.

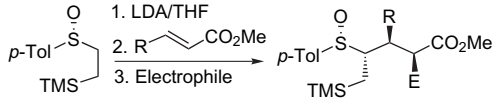


Scheme 73. Synthesis of an ASBT inhibitor via intramolecular aldol reaction.

Other intramolecular reactions of α-sulfinyl vinylic carbanions have also been reported such as those described by Tanaka et al., allowing a novel route to chiral 1-cycloalkenyl sulfoxides.[128]

4.2. Conjugated addition reactions

Michael addition of enantiomerically enriched sulfinyl carbanions to α,β-unsaturated carbonyl compounds is a very useful method for stereoselective C–C bond formation. Toru et al. have discovered that the reaction of chiral *p*-tolyl 2-(trimethylsilyl)ethyl sulfoxide with LDA and acetone gave the *syn*-isomer in high yield and 92% de.[104] It was postulated that a novel Si–O interaction between the trimethylsilyl and the carbonyl group, which stabilised the transition state of the nucleophilic addition, accounted for the *syn*-isomer formation. Conjugated addition reactions of the carbanion of a chiral β-silylethyl sulfoxide with α,β-unsaturated esters afforded the conjugate addition products as a single diastereoisomer. Moreover, high diastereoselectivities were also observed for the Michael addition reactions of the same carbanion with α,β-unsaturated esters, where the enolate intermediates were subsequently trapped with alkyl halides or aldehydes (Scheme 74).[129] In general, the trapping reactions took place in good yields, except for the reaction involving methyl acrylate, because of polymerisation.

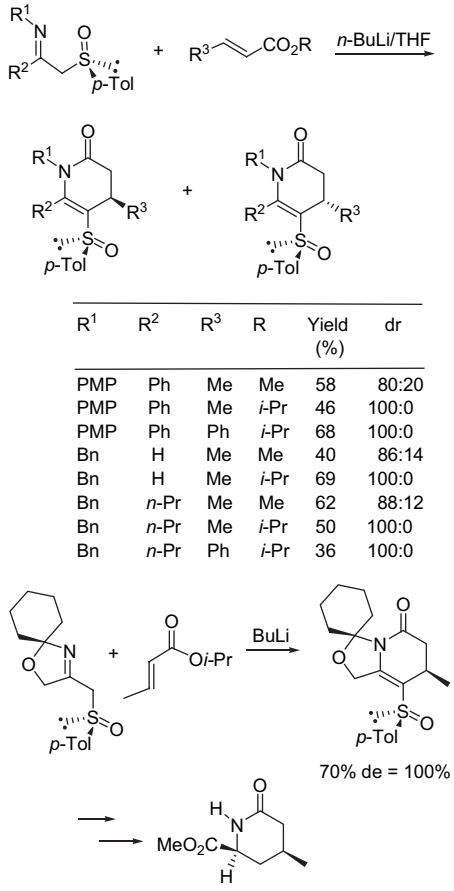


R	Electrophile	Yield (%)	de (%)
H	MeI	21	> 96
Me	MeI	59	> 96
Ph	MeI	75	> 96
Ph	BnBr	74	> 96
Ph	*i*-PrCHO	90	> 96
Ph	PhCHO	98	> 96

Scheme 74. Conjugate addition and subsequent trapping reactions of a chiral β-silylethyl sulfoxide.

As an extension of this work, the asymmetric conjugate addition reactions of polymer-supported highly enantioenriched β-(trimethylsilyl)ethyl sulfoxides were reported. Thus, chiral β-(trimethylsilyl)ethyl sulfoxides supported on Merrifield resin could be treated with LDA and subsequently with methyl cinnamate.[130] Thermal treatment or reaction with TBAF liberated the optically active methyl 3-phenyl-5-trimethylsilylpent-4-enoate or methyl 3-phenylpent-4-enoate, respectively, in good yields with high enantioselectivity.

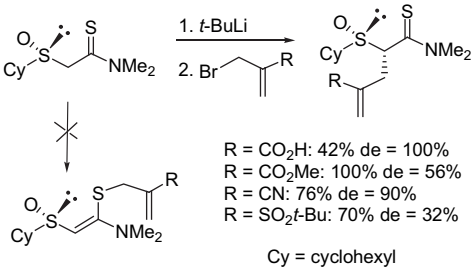
Alvarez-Ibarra et al. have explored the sulfoxide-mediated diastereoselective Michael reaction of chiral α-sulfinylketimines and β-substituted ene esters (Scheme 75).[131] Straightforward cyclisation of the open-chain adducts took place under the reaction conditions, to provide the corresponding 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones, the stereochemistry of which was formed in the prior step. Furthermore, the role of the metal ion of the aza-enolate reagents, and the steric demands of the *O*-alkyl ester group have been examined. It appeared that the *anti*-diastereoselectivity depended upon metal chelation by the oxygen of the ester, as well as the oxygen of the sulfinyl group and the nitrogen in the aza-enolate ((*Z*)-configuration). These results could be applied to the synthesis of methyl L-(2*S*,4*S*)-4-methyl-6-oxopipecolate.



R^1	R^2	R^3	R	Yield (%)	dr
PMP	Ph	Me	Me	58	80:20
PMP	Ph	Me	*i*-Pr	46	100:0
PMP	Ph	Ph	*i*-Pr	68	100:0
Bn	H	Me	Me	40	86:14
Bn	H	Me	*i*-Pr	69	100:0
Bn	*n*-Pr	Me	Me	62	88:12
Bn	*n*-Pr	Me	*i*-Pr	50	100:0
Bn	*n*-Pr	Ph	*i*-Pr	36	100:0

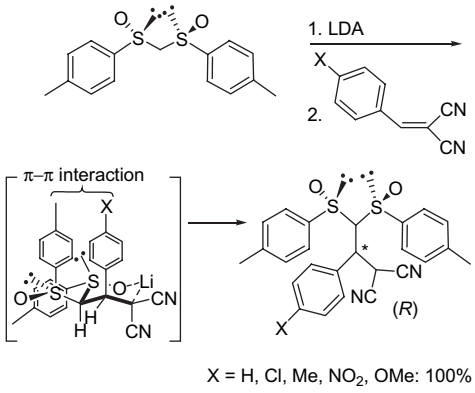
Scheme 75. Michael reaction of chiral α-sulfinylketimines with β-substituted ene esters.

In 2002, Metzner et al. showed that the alkylation of the lithium enolate of a chiral α-cyclohexylsulfinyl thioacetamide with allyl bromides possessing an electron-withdrawing group at the vinyl position did not occur at the sulfur centre, as expected in the sulfur series, but at the carbon centre through conjugate addition, followed by bromide elimination (Scheme 76).[132]



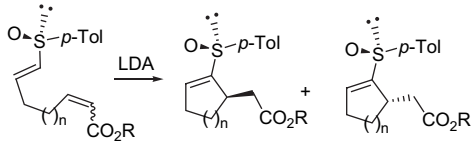
Scheme 76. C-allylation of a chiral α-sulfinyl thioacetamide.

Highly diastereoselective 1,4-additions to stabilised Michael acceptors have also been carried out by Fernandez et al. with carbanions of C_2-symmetric bis-sulfoxides such as (*S*,*S*)-bis-*p*-tolylsulfinylmethane (Scheme 77).[133] These authors claimed thermodynamic control and proposed a Zimmerman–Traxler-type model, which disclosed a favourable π–π interaction between the two aromatic rings, one belonging to the Michael acceptor, and the other to the anion.



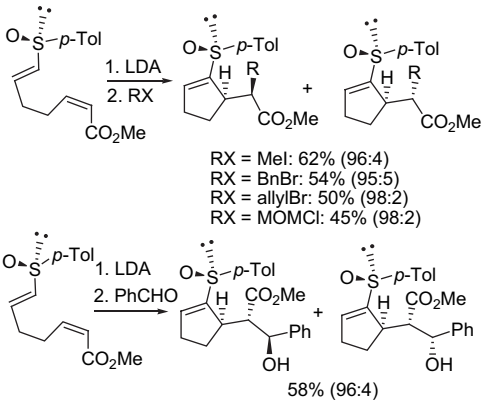
Scheme 77. Reaction of a C_2-symmetric bis-sulfoxide with stabilised Michael acceptors.

The first example of an asymmetric intramolecular Michael addition reaction using an α-lithiated vinylic sulfoxide as a Michael donor was reported by Tanaka et al.[134] Michael addition of the α-lithiated vinylic sulfoxide to (*Z*)-enoates proceeded with high diastereoselectivity to give the adducts having a stereogenic centre with (*R*)-configuration at the β-position of the ester in the cyclopentene ring formation (Scheme 78). The diastereoselectivity was dependent upon the geometry of the enoate, since low des were systematically obtained with the corresponding (*E*)-enoates. Moreover, the selectivity was reversed in the six-membered ring formation.



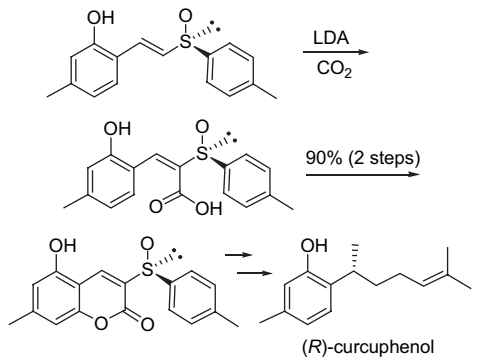
Scheme 78. Intramolecular Michael addition of α-sulfinyl vinylic carbanion to enoates.

The intramolecular Michael addition of the α-sulfinyl vinyl carbanion generated a new anion species, which was expected to react diastereoselectively with electrophiles such as alkyl halides or benzaldehyde, providing two stereocentres in a one-pot operation reaction (Scheme 79).



Scheme 79. Intramolecular Michael addition followed by alkylation or aldol reaction.

In 2005, Pan et al. reported an enantioselective synthesis of (*S*)- and (*R*)-curcuphenol, showing, respectively, potent antifungal and antitumour activity, and antibacterial activity. The key step was an asymmetric conjugate addition using a chiral sulfoxide (Scheme 80).[135]



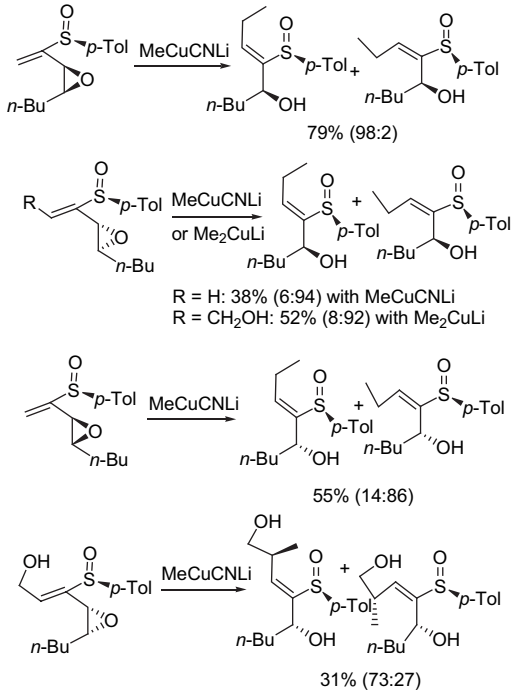
Scheme 80. Synthesis of (*R*)-curcuphenol.

5. Conjugated additions to α,β-unsaturated sulfoxides

α,β-Unsaturated sulfoxides have been extensively used in asymmetric synthesis as versatile chiral reagents with the sulfinyl group playing the role of chiral auxiliary.[136]

5.1. C–C bond formation

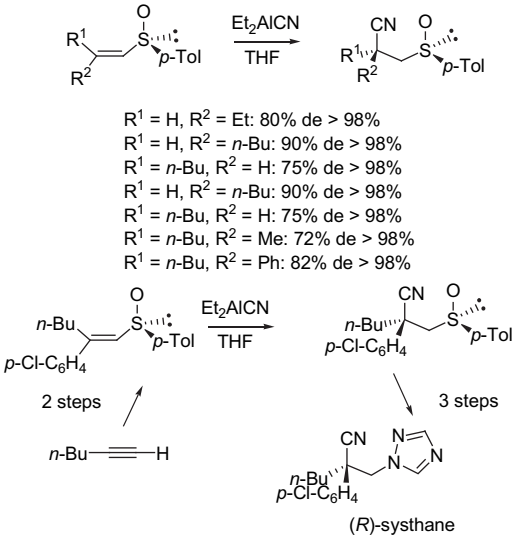
The conjugate addition of carbon nucleophiles to chiral α,β-unsaturated α-arylsulfinyl carbonyl compounds was studied by Posner et al., giving the best results in the case of cyclic systems.[137] In 2000, Marino et al. demonstrated that chiral acyclic epoxy vinyl sulfoxides underwent highly regio- and stereoselective S_N2' displacements with lithium cyanocuprates to give the corresponding α′-alkylated, γ-oxygenated



Scheme 81. S_N2' displacements between cyanocuprates and vinyl and alkynyl epoxy sulfoxides.

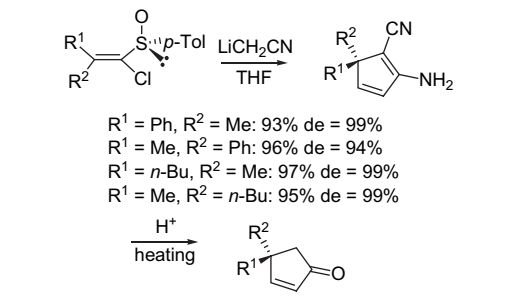
Z α,β-unsaturated sulfoxides in good yields and with good to excellent diastereoselectivities.[138] In order to extend this study, the readily available vinyl epoxy sulfoxides depicted in Scheme 81 were submitted to S_N2' displacement with organocopper reagents, producing the corresponding chiral α-hydroxy vinyl sulfoxides with high *anti* selectivity and a good degree of *E*/*Z* stereocontrol.

In 2001, Garcia Ruano et al. showed that the hydrocyanation of alkenyl sulfoxides with Et_2AlCN took place in a completely stereoselective manner (Scheme 82).[139] This methodology was applied for the synthesis of the fungicide, systhane, in which the sulfinyl group controlled the two key steps of the synthetic sequence, the highly stereoselective hydrocyanation of vinyl sulfoxides and the further introduction of the proper functionality into the molecule (Scheme 82).[140]



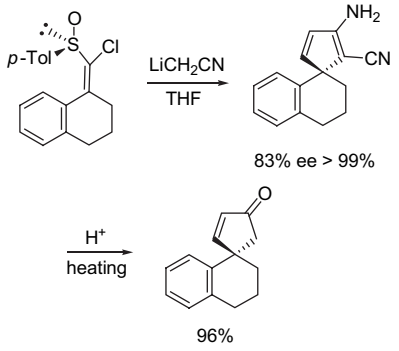
Scheme 82. Stereoselective hydrocyanation of alkenyl sulfoxides.

Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides having two different substituents at the 2-position, which were synthesised from unsymmetrical ketones and (*R*)-chloromethyl *p*-tolyl sulfoxide, with cyanomethyllithium was shown to give chiral 2-amino-1-cyano-5,5-disubstituted-1,3-cyclopentadienes with very high asymmetric induction.[141] The products were further converted into the corresponding chiral 4,4-disubstituted 2-cyclopentenones by heating with phosphoric acid (Scheme 83). This novel reaction was successfully applied to the total synthesis of (+)-α-cuparenone,[142] and 2,4,4-trisubstituted cyclopent-2-enones.[143]



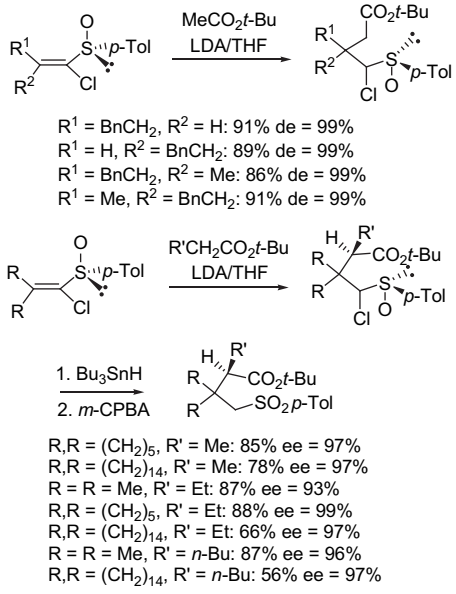
Scheme 83. Reaction of cyanomethyllithium with 1-chlorovinyl *p*-tolyl sulfoxides.

This methodology was extended to cyclic 1-chlorovinyl *p*-tolyl sulfoxides, providing under the same conditions the corresponding spirocyclic enaminonitriles, the acidic treatment of which afforded the corresponding chiral spiro[4,*n*]alkenones (Scheme 84).[144] By using an unsymmetrical cyclic ketone such as α-tetralone and chiral chloromethyl *p*-tolyl sulfoxide, this procedure afforded chiral spiro[4,5]decenone with excellent induction. This method was applied to a formal synthesis of a spirocyclic sesquiterpene, acorone.



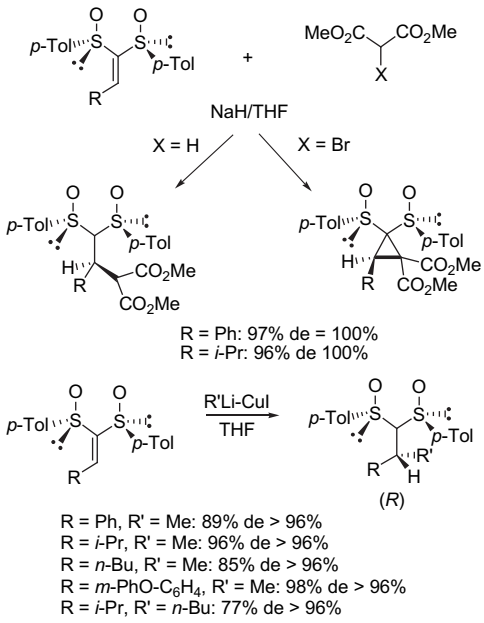
Scheme 84. Synthesis of chiral spiro[4,5]decenone.

Similarly, lithium ester enolates were condensed onto chiral 1-chlorovinyl *p*-tolyl sulfoxides, leading to the formation of chiral esters and lactones having a tertiary or a quaternary stereogenic centre at the γ-position (Scheme 85).[145]



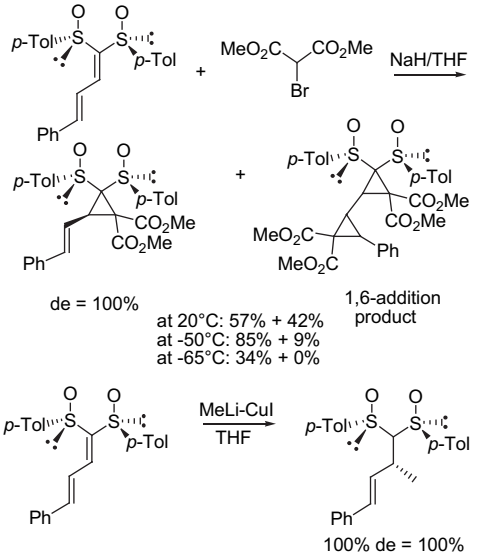
Scheme 85. Reaction of lithium ester enolates with 1-chlorovinyl *p*-tolyl sulfoxides.

Malacria et al. have shown that alkylidene bis(sulfoxides) were exceptional partners in high yielding and totally diastereoselective Michael additions, as well as with heteronucleophiles (Section 5.2) or carbon nucleophiles such as sodium dimethylmalonate or copper reagents, which both gave complete stereoselectivity when reacting with alkylidene bis(sulfoxides) (Scheme 86).[146]



Scheme 86. Reaction of carbon nucleophiles with chiral alkylidene bis(sulfoxides).

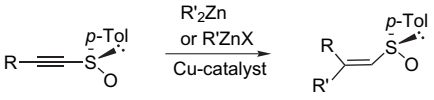
In 2005, this methodology was extended to a dienyl bis-sulfoxide derived from cinnamaldehyde, which gave stereoselective conjugate additions with the same carbon nucleophiles, providing the corresponding 1,4-addition products (Scheme 87).[147] When the reaction was carried out at low temperature, the formation of the 1,6-addition products could be avoided. The use of this outstanding Michael acceptor with a methylcopper reagent gave an access to an enantiopure precursor of cryptophycin.



Scheme 87. Michael additions onto dienyl bis-sulfoxides.

A new synthetic method for chiral β,β-disubstituted vinylic sulfoxides bearing various functionalities has been developed by employing Cu-catalysed conjugate addition of an organozinc reagent to a chiral 1-alkynyl sulfoxide.[148] Since the reaction proceeded with very high *syn*-selectivity, both geometric β,β-disubstituted vinylic sulfoxides were

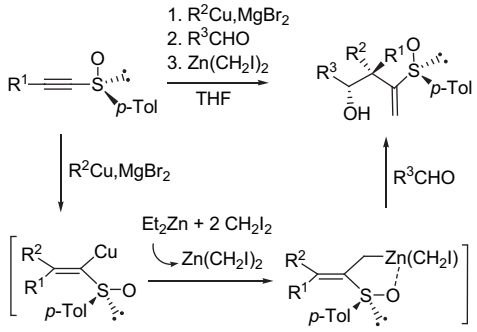
stereoselectively synthesised by changing the combination of the 1-alkynyl sulfoxide and the organozinc reagent (Scheme 88). The scope of the reaction could be extended to the synthesis of trisubstituted vinylic sulfoxides by trapping the resulting intermediate α-sulfinyl vinylic carbanion with electrophiles such as alkyl halides. Moreover, highly diastereoselective THF and THP ring formations were accomplished by means of this methodology, followed by an intramolecular Michael addition.[149]



R	R'_2Zn or R'ZnX	Cu-cat.	Yield (%)
n-Bu	Et_2Zn	CuI	97%
$TBDMSO(CH_2)_2$	Et_2Zn	CuI	78%
$AcO(CH_2)_2$	Et_2Zn	CuI	84%
$I(CH_2)_4$	Et_2Zn	CuI	84%
H	Et_2Zn	CuI	24%
n-Bu	Me_2Zn	CuI	67%
H	Et_2Zn	CuI	24%
n-Bu	allylZnBr	CuI	72%
n-Bu	allylZnBr	$Cu(OTf)_2$	81%
n-Bu	$PivOCH_2ZnI$	$Cu(OTf)_2$	75%

Scheme 88. Addition of organozinc reagents to 1-alkynyl sulfoxides.

On the other hand, chiral alkynyl sulfoxides were involved in a new four-component reaction, leading to the creation of three new carbon–carbon bonds and two new chiral centres, including a quaternary centre.[150] First, the regio- and stereospecific carbocupration reactions of the alkynyl sulfoxide with an organocopper derivative, easily prepared from the corresponding alkylmagnesium halide and CuBr, provided the corresponding metallated β,β-dialkylated α,β-ethylenic sulfoxide in quantitative yield. The reaction mixture was then treated with an aldehyde or an imine, followed by bis(iodomethyl)zinc carbenoid (Scheme 89).

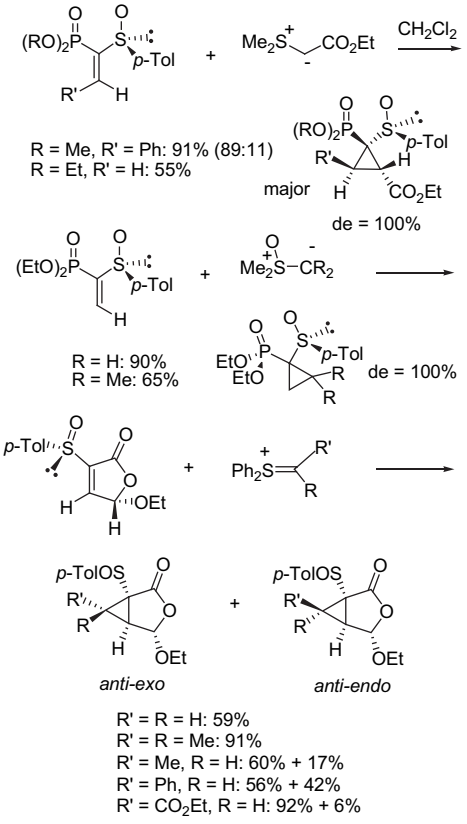


R^1 = *n*-Bu, R^2 = Et, R^3 = Ph: 78% de > 98%
R^1 = Et, R^2 = *n*-Bu, R^3 = Ph: 68% de > 98%
R^1 = *n*-Bu, R^2 = Me, R^3 = Ph: 66% de > 98%
R^1 = Et, R^2 = Me, R^3 = Ph: 66% de > 98%
R^1 = H, R^2 = Et, R^3 = Ph: 78% de = 60%

Scheme 89. Four-component reactions with chiral alkynyl sulfoxides.

In 2004, Midura et al. showed that chiral α-phosphorylvinyl sulfoxides were effective acceptors in conjugate additions of various nucleophiles such as alkoxides, amines or malonates. In all cases, a 2:1 mixture of two (from four possible) diastereoisomers was obtained.[151]

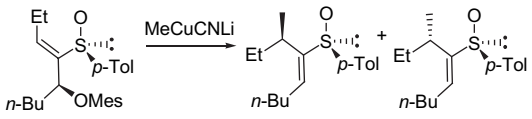
Enantiomerically enriched cyclopropanes are widely used as building blocks for the synthesis of complex molecules. In this context, Mikolajczyk et al. have studied the asymmetric cyclopropanation of chiral (1-dialkoxyphosphoryl)vinyl *p*-tolyl sulfoxides with sulfur ylides, opening a new access to chiral 2-amino-1-cyclopropane-phosphonic acid derivatives (Scheme 90).[152] A constrained analogue of the GABA antagonist, phaclofen and cyclopropylphosphonate analogues of nucleotides could be synthesised using this methodology. The extension of this method to (5*S*,*S*)-3-*p*-tolylsulfinyl-5-ethoxyfuran-2(5*H*)-one led to a very high π-facial selectivity.



R' = R = H: 59%
R' = R = Me: 91%
R' = Me, R = H: 60% + 17%
R' = Ph, R = H: 56% + 42%
R' = CO_2Et, R = H: 92% + 6%

Scheme 90. Cyclopropanation of (1-dialkoxyphosphoryl)vinyl *p*-tolyl sulfoxides.

De la Pradilla et al. have reported that an α′-alkylated γ-mesyloxy-(*Z*)-α,β-unsaturated sulfoxide depicted in Scheme 91 could readily undergo stereoselective S_N2' displacement with lithium methyl cyanocuprate to yield the corresponding vinyl sulfoxide with high diastereoselectivity.[153]

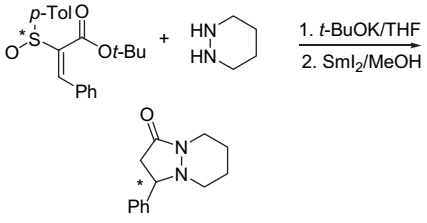


Scheme 91. Reaction of an α′-alkylated γ-mesyloxy-(*Z*)-α,β-unsaturated sulfoxide with MeCuCNLi.

5.2. C–N, C–O and C–S bond formations

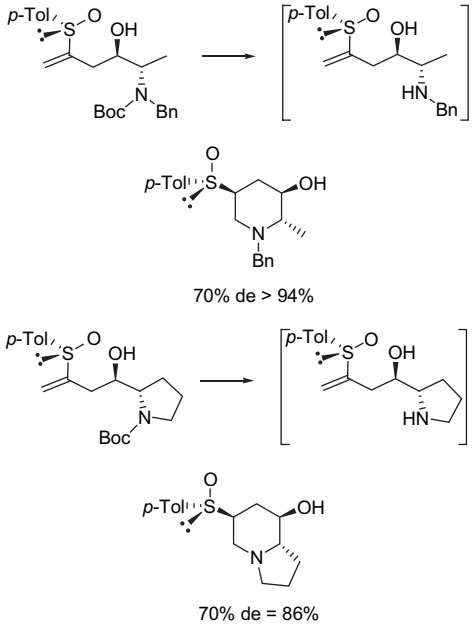
Asymmetric induction in the conjugate addition of nitrogen nucleophiles to chiral vinyl sulfoxides has proved to be a useful methodology for the synthesis of chiral compounds.[2c]

The intermolecular conjugate addition of nitrogen nucleophiles to chiral α,β-unsaturated-sulfoxides has not been widely applied in synthesis, probably due to the low reactivity of these simple Michael acceptors. Matsuyama et al. have, however, developed the conjugate addition of a six-membered hydrazine to chiral *tert*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamates.[154] The asymmetric conjugate addition–cyclisation of piperidazine with *tert*-butyl (*E*)-2-[(*R*)- or (*S*)-*p*-tolylsulfinyl]cinnamate gave diastereoselectively the corresponding bicyclic lactam after the subsequent removal of the *p*-tolylsulfinyl group with SmI_2 (Scheme 92). Next, the reductive cleavage of the N–N bond of the bicyclic lactam gave rise to the corresponding nine-membered azalactam, (*S*)- or (*R*)-4-phenyl-1,5-diazacyclononan-2-one, which was a potent precursor for the synthesis of the natural 13-membered alkaloid, celacinnine.



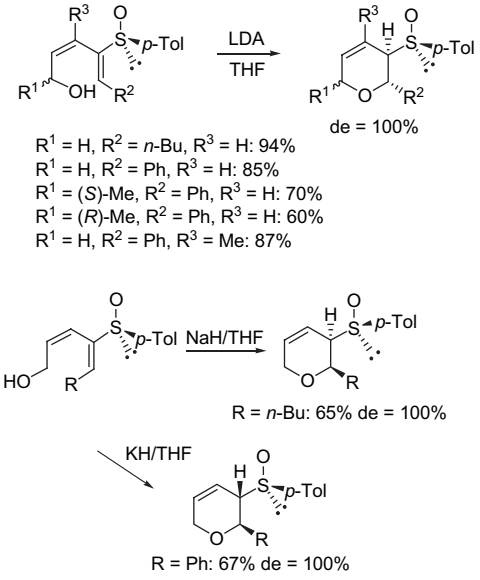
Scheme 92. Conjugate addition of piperidazine to *tert*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamate.

On the other hand, the intramolecular version of the Michael addition of nitrogen nucleophiles, which took place at a lower temperature, was used in the development of a new diastereoselective route to piperidine and indolizidine scaffolds from chiral vinylsulfinyl-containing amino alcohols (Scheme 93).[155] In addition, pyrolytic elimination of the resulting cycloadducts resulted in the regioselective formation of the corresponding tetrahydropyridines and indolizidines.



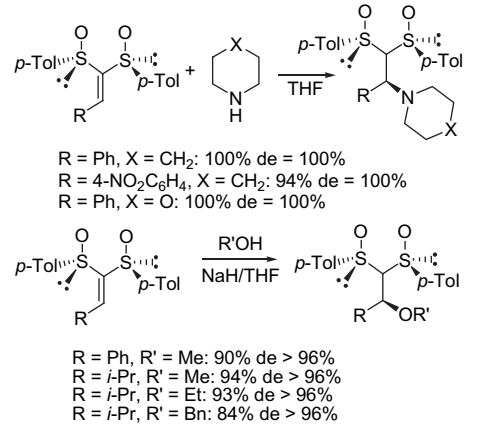
Scheme 93. Intramolecular addition–cyclisation of vinylsulfinyl-containing amino alcohols.

It is known that alcohols add to α,β-unsaturated sulfoxides in the presence of bases in a reversible, thermodynamically controlled process.[156] In some cases, however, particularly when the conjugate addition proceeds in an intramolecular fashion, it is possible to isolate the kinetically controlled product usually formed with a very high stereoselectivity. Thus, the first examples of base-promoted intramolecular cyclisation of 2-sulfinyl dienols affording sulfinyl dihydropyrans have been reported (Scheme 94).[157] This new strategy allowed the creation of two asymmetric centres within a synthetically useful dihydropyran framework in an expedient manner.



Scheme 94. Intramolecular addition–cyclisation of 2-sulfinyl dienols.

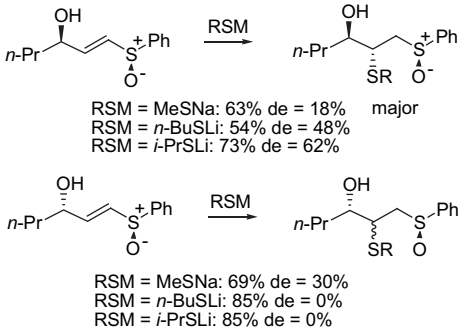
In Section 5.1, it was shown that alkylidene bis(sulfoxides) were appealing candidates for asymmetric conjugate additions to carbon nucleophiles. In addition, Malacria et al. were able to extend their methodology to amines, the reaction of which gave the corresponding amino adducts in a completely diastereoselective manner.[146] Moreover, oxygenated nucleophiles such as sodium alkoxides also gave the conjugate addition in high yields and with total stereoselectivity (Scheme 95).



Scheme 95. Addition of amines and alkoxides to alkylidene bis(sulfoxides).

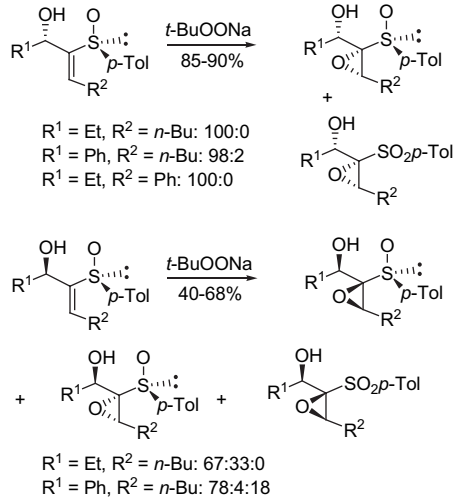
Other heteronucleophiles such as dimethylamine, ethyl mercaptan in the presence of Et_3N, and methanol in the presence of KOH could also form adducts with α-phosphorylvinyl sulfoxides, affording the desired products as a mixture of diastereomers in around a 2:1 ratio.[151] In addition, Ma et al. have reported a short synthesis of the HIV protease inhibitor, nelfinavir, via a diastereoselective 1,4-addition of ammonia to an α,β-unsaturated sulfoxide derived from (*R*)-glyceraldehyde acetonide.[158]

There has been considerable interest in the development of novel methodologies for the 1,4-additions of other heteroatom nucleophiles to vinyl sulfoxides. With this aim in view, Forristal et al. have reported the first stereoselective conjugate addition of thiolate nucleophiles to chiral (*E*)-γ-hydroxy α,β-unsaturated sulfoxides, as depicted in Scheme 96.[159] Moderate levels of diastereoselectivity were observed, with the two stereocontrolling elements, the hydroxyl group and the sulfoxide moiety, showing reinforcing and nonreinforcing control of stereoselectivity, depending upon their relative configuration.



Scheme 96. Reaction of (*E*)-γ-hydroxy α,β-unsaturated sulfoxides with thiolates.

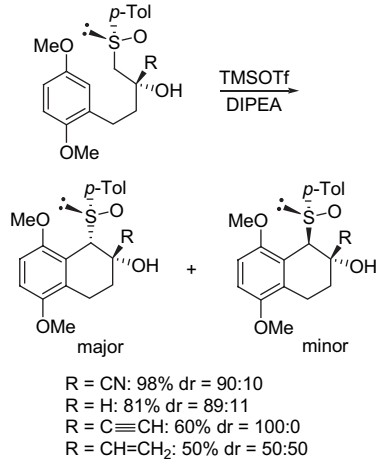
There continues to be considerable interest in the stereoselective preparation of heterosubstituted oxiranes using the nucleophilic epoxidation of vinyl sulfoxides. Diastereoselective nucleophilic epoxidation takes place when enantiomerically enriched sulfoxides are treated with MOO*t*-Bu (M: Li, Na, K) in ether or THF at 0 °C, to afford α,β-epoxy sulfoxides in good yield. As an example, de la Pradilla et al. have studied the epoxidation of a variety of α′-(1-hydroxyalkyl)vinyl sulfoxides.[121] As shown in Scheme 97, a highly *syn*-selective epoxidation–oxidation was observed with the (S,S_S)-sulfoxide, whereas the (R,S_S)-diastereoisomer showed diminished reactivities and a very substrate-dependent stereochemical outcome. The same group also reported that the nucleophilic epoxidation of simple (γ-silyloxy)vinyl sulfoxides took place with complete stereocontrol in high yields.[160] For substrates bearing an additional substituent at the γ-position, once again a reinforcing/nonreinforcing scenario was operative.



Scheme 97. Nucleophilic epoxidation of α′-(1-hydroxyalkyl)vinyl sulfoxides.

6. Pummerer reactions

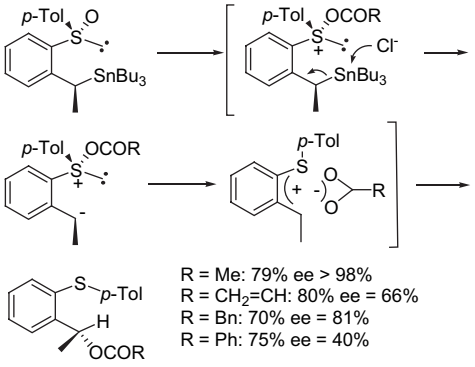
The reaction discovered by Pummerer consists of the transformation of sulfoxides bearing α-hydrogens in α-acyloxy sulfides by treatment with acid anhydrides and has been widely used in synthesis.[161] From a stereochemical point of view, this is a self-immolative asymmetric process where the chirality at sulfur is transferred to the α-carbon. The asymmetric Pummerer reaction of chiral, nonracemic sulfoxides[162] is of significant interest, since it allows the synthesis of enantiomerically pure α-substituted sulfides.[163] Intramolecular Pummerer cyclisation is especially useful for building chiral heterocyclic compounds.[164] As an example, highly stereoselective Pummerer reactions were observed on reaction of the β-hydroxysulfoxides depicted in Scheme 98 with TMSOTf.[165] Sulfenium intermediates were captured intramolecularly by the electrophilic aromatic ring, thus yielding bicyclic structures with a *p*-tolylsulfenyl group at the benzylic position in a cis arrangement with respect to the hydroxyl group. The stereogenicity transfer seemed to be mainly controlled by the hydroxylated chiral carbon. The resulting compounds could be used as bicyclic precursors of different anthracyclinones.



Scheme 98. Intramolecular Pummerer reaction of β-hydroxysulfoxides.

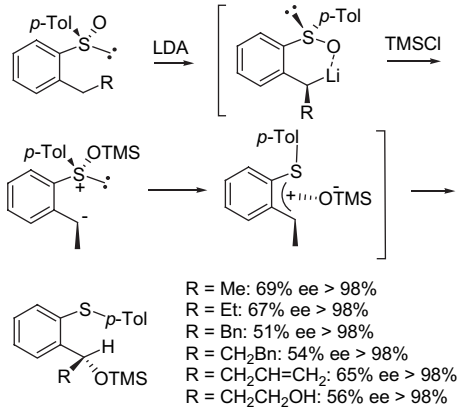
In general, better results are obtained for the additive Pummerer-type reaction, which occurs on vinylic sulfoxides. In 2004, Garcia Ruano et al. reported a new type of vinylogous

tin-Pummerer rearrangement reaction, which was observed when benzyltin derivatives containing a sulfinyl group at the *ortho* position were allowed to react with acyl chlorides (Scheme 99).[166] The reaction was thought to proceed by nucleophilic attack of the leaving carboxylate at the γ-position of the conjugated thionium ion and gave ees of up to 98%, constituting a new route to chiral benzyl alcohols.



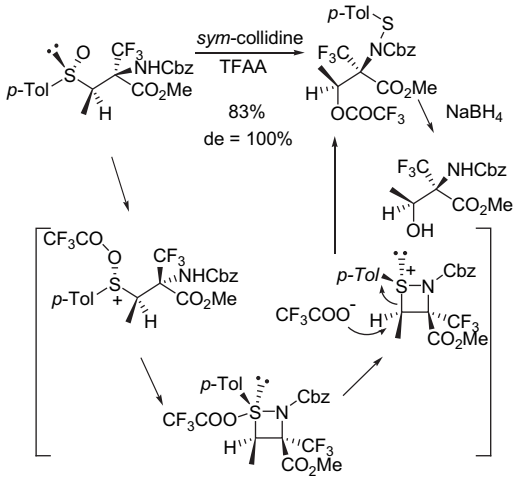
Scheme 99. Vinylogous tin-Pummerer rearrangement reaction.

Another highly stereoselective vinylogous Pummerer reaction mediated by Me_3SiX was developed by the same group in 2005.[167] This reaction involving 1,4-migration of the sulfinyl oxygen atom occurred when *ortho*-sulfinyl benzyl carbanions were treated with trimethylsilyl halides with good yield and high enantioselectivity (Scheme 100).



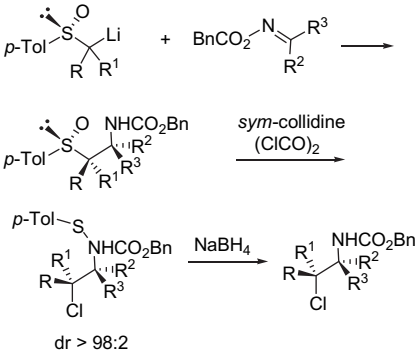
Scheme 100. Sila-Pummerer reaction.

In the course of investigating the synthesis of a new statine dipeptide isostere, Zanda et al. have discovered the non-oxidative Pummerer reaction.[168] When the chiral sulfoxide depicted in Scheme 101 was treated with 5 equiv of trifluoroacetic anhydride (TFAA) and 3 equiv of *sym*-collidine in acetonitrile, the normal Pummerer rearrangement did not take place. Instead, the trifluoroacetoxy group displaced the sulfinyl group in an S_N2 manner to afford a sulfenamide intermediate, treatment of which with aqueous K_2CO_3 and $NaBH_4$ provided the corresponding β-amino alcohol in high yield and with high diastereoselectivity. The authors have proposed an explanation for this transformation that involves the formation of an intermediate acylated sulfoxide, followed by a cyclisation to give the corresponding σ-sulfurane. The dissociation of the trifluoroacetoxy group and the subsequent S_N2 displacement gave the final sulfenamide with inversion of configuration at the α-sulfinyl carbon.



Scheme 101. Non-oxidative Pummerer reaction.

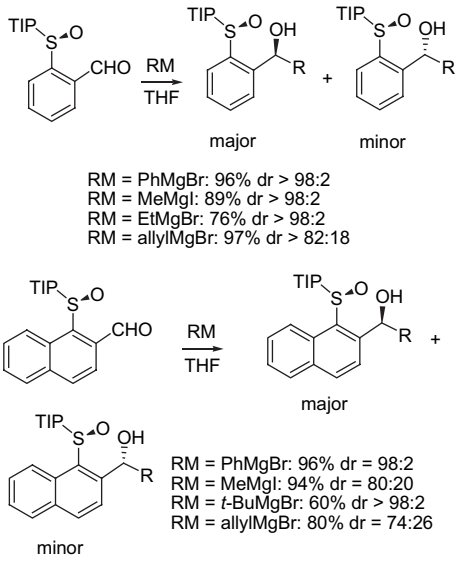
An extension of this methodology was the non-oxidative chloro-Pummerer reaction, providing a highly stereoselective entry into β-chloro amines and aziridines.[169] Thus, chiral α-Li alkyl sulfoxides could be used as chiral α-chloroalkyl carbanions with *N*-protected imines by means of the non-oxidative chloro-Pummerer reaction (Scheme 102). This methodology allowed a one-pot displacement of a sulfinyl group by chlorine from *N*-alkoxycarbonyl β-sulfinylamines derived from aryl, fluoroalkyl and alkyl imines, with clean stereoinversion at carbon. In addition, several 1,2-chloroamines produced by this method could be converted into the corresponding aziridines.



Scheme 102. Non-oxidative chloro-Pummerer reaction.

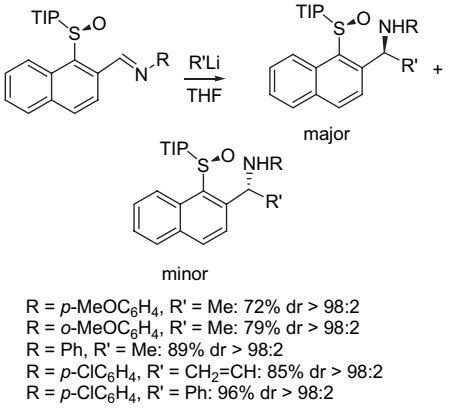
7. Miscellaneous reactions

The asymmetric approach to enantiopure carbinols based on the simplest addition of the widely used Grignard reagents or other organometallic compounds to benzaldehydes bearing a chiral auxiliary has been studied only recently. In 2001, Toru reported the Grignard reaction of benzaldehydes bearing a bulky (2,4,6-triisopropylphenyl)-sulfinyl group at the 2-position occurring with high 1,4-remote asymmetric induction (Scheme 103).[36] As an extension, this methodology could be applied to naphthalenic systems (Scheme 103).



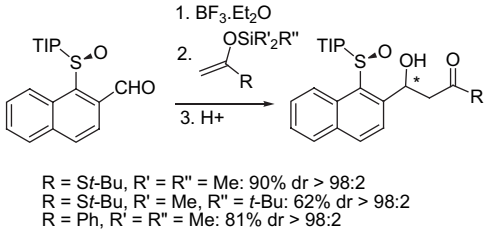
Scheme 103. Addition of Grignard reagents to bulky 2-(arylsulfinyl)benzaldehydes.

Another extension of this work was the reaction of alkyllithium reagents with (1-sulfinyl-2-naphthyl)methanimines bearing a 2,4,6-triisopropylphenylsulfinyl group, leading to the corresponding products as a single diastereomer (Scheme 104).[170] It was demonstrated that the high diastereoselectivity was due to the restricted rotation about the C_{naphth}–S bond having the bulky 2,4,6-triisopropylphenylsulfinyl group. The subsequent elimination of the sulfinyl group allowed an easy access to chiral 1-(2-naphthyl)ethylamines.



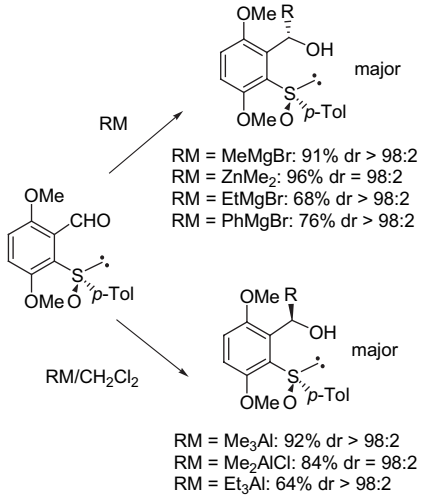
Scheme 104. Addition of alkyllithium reagents to 1-sulfinyl-2-naphthylmethanimines.

High stereoselectivity was also observed during the Mukaiyama aldol reactions of naphthaldehydes having a 2,4,6-triisopropylphenylsulfinyl group (Scheme 105).[171] In addition, the aldol reaction of a chiral sulfinyl furaldehyde with 1-phenoxy-1-trimethylsilyloxyethene was the basis of an asymmetric synthesis of (+)-dihydrokawain-5-ol, having anxiolytic and analgesic properties. The Mukaiyama reaction provided the expected chiral functionalised furylpropanoate with 91% yield and 90% diastereoisomeric excess.[112a]



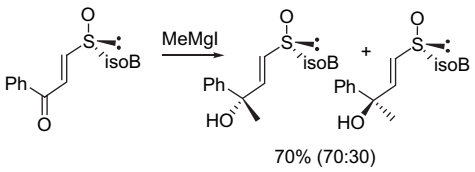
Scheme 105. Mukaiyama aldol reactions of a 1-sulfinyl-2-naphthaldehyde.

In 2003, Carreno et al. demonstrated that it was not necessary to use a bulky group such as (2,4,6-triisopropylphenyl)-sulfinyl to obtain good results.[172] Thus, the common *p*-tolylsulfinyl group proved to be very efficient in directing the nucleophilic addition of different organometallic derivatives onto the carbonyl group of [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde, allowing the diastereodivergent synthesis of the corresponding sulfinyl-substituted (*S*) or (*R*) alkyl aryl or diaryl carbinols, by simply choosing the appropriate organometallic reagent (Scheme 106).



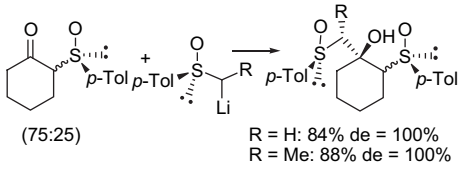
Scheme 106. Addition of organometallic reagents to 3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde.

Moreover, an unsaturated sulfoxide such as chiral (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one has confirmed its expected value as a nucleophile acceptor, giving useful stereochemical results in 1,2-additions of Grignard reagents (Scheme 107).[84] It was demonstrated that the chiral sulfur atom exerted a remote stereocontrol if assisted by the hydroxyl group being part of the isoborneol substituent.



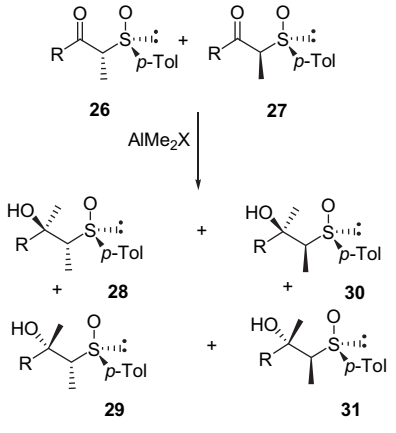
Scheme 107. Addition of MeMgI to (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one.

In 2000, Garcia Ruano et al. described the addition reaction of α-thiocarbanions derived from sulfoxides to 2-(*p*-tolylsulfinyl)cyclohexanone, which occurred with a total control of the stereoselectivity at the hydroxylic carbon (Scheme 108).[173]



Scheme 108. Reaction of α-thiocarbanions with 2-(*p*-tolylsulfinyl)cyclohexanone.

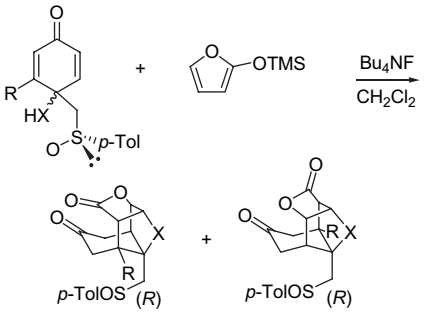
In order to stereoselectively methylate α-methyl-β-ketosulfoxides, other nucleophiles such as aluminium reagents could be successfully employed (Scheme 109).[174] The induced configuration at the hydroxylic carbon was mainly controlled by the configuration at C-α. The resulting hydroxysulfoxides could be used in the synthesis of optically pure tertiary methyl carbinols.



X	R (**26**:**27**)	Yield	**28**:**29**:**30**:**31**
Me	*n*-Pr (39:61)	72%	13:10:67:10
Me	*i*-Pr (36:64)	58%	29:0:71:0
Me	Ph (44:56)	89%	33:10:38:19
Me	*t*-Bu (100:0)	40%	70:30:0:0
Me	*t*-Bu (0:100)	43%	0:0:100:0
Me	*n*-Pr (40:60)	90%	18:9:69:4
Me	*i*-Pr (36:64)	98%	35:0:65:0
Me	Ph (44:56)	77%	23:3:74:0
Me	*t*-Bu (100:0)	0%	-
Me	*t*-Bu (0:100)	0%	-

Scheme 109. Reaction of Me_2AlX with α-methyl-β-ketosulfoxides.

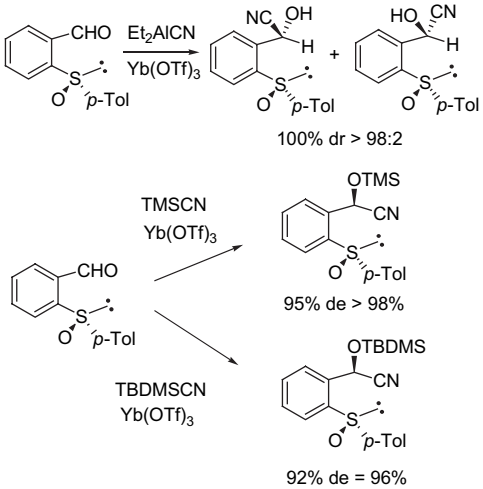
With the aim of preparing new chiral tetracyclic cage compounds, Carreno et al. have developed new domino conjugate additions of 2-(trimethylsilyloxy)furan with enantiopure 4-amino- or 4-hydroxy-3-methyl-4-[(*p*-tolylsulfinyl)-methyl]cyclohexa-2,5-dienones in the presence of Bu_4NF (Scheme 110).[175] The method was particularly valuable, not only because of the stereochemical control, but also because the reactions occurred in an experimentally simple one-pot procedure through a domino sequence of three consecutive conjugate additions.



Starting material	R	X	Ratio (products)	Yield (%)
[(S)*R*]	H	NH	50:50	67
[4*R*(S)*R*]	Me	NH	100:0	56
[4*S*(S)*R*]	Me	NH	0:100	70
[(S)*R*]	H	O	50:50	67
[4*S*(S)*R*]	Me	O	100:0	67

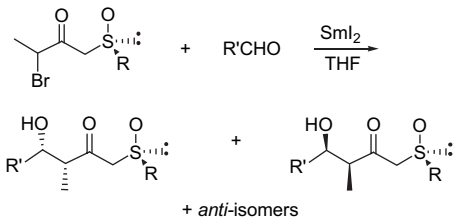
Scheme 110. Synthesis of chiral cage compounds via domino conjugate additions.

The hydrocyanation of (*S*)-2-*p*-tolylsulfinylbenzaldehyde with Et_2AlCN and R_3SiCN was reported in 2005 (Scheme 111).[176] A high stereoselectivity was observed in the presence of Lewis acids such as $Yb(OTf)_3$ as a consequence of cyanide attack on a chelate involving aldehyde and sulfoxide coordination with the metal.



Scheme 111. Hydrocyanation of 2-*p*-tolylsulfinylbenzaldehyde.

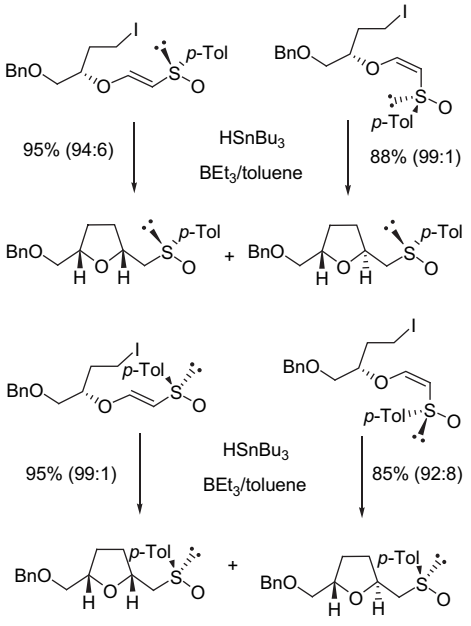
In 2003, Colobert et al. reported a highly stereoselective Reformatsky addition of chiral α-bromo-α′-sulfinyl ketones with various linear aliphatic aldehydes promoted by samarium(II) diiodide (Scheme 112).[177] The corresponding adduct was obtained with excellent *syn* diastereoselectivity and could be converted by further reduction into the corresponding *anti*- and *syn*-2-methyl-1,3-diol moieties.



R = *p*-Tol, R' = Ph: 47% 80:20 *syn:anti* = 75:25
R = *t*-Bu, R' = Ph: 61% 96:4 *syn:anti* = 96:4
R = *t*-Bu, R' = Et: 85% 95:5 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-Pr: 85% 95:5 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-Pent: 75% 92:8 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-C_7H_{15}: 77% 95:5 *syn:anti* = 98:2

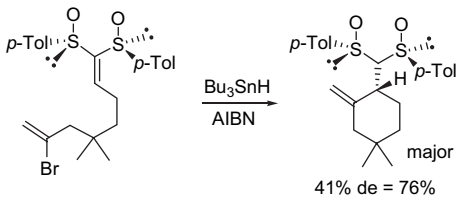
Scheme 112. Reformatsky-type reaction of α-bromo-α′-sulfinyl ketones with aldehydes.

Radical-mediated asymmetric reactions have been extensively studied.[178] This is due, in part, to the high compatibility of radical reactions with a large number of interesting functionalities, notably present on chiral auxiliaries. Chiral sulfoxides have been used to control the configuration of newly formed stereogenic centres in free radical reactions. The addition of radicals to prochiral alkenes bearing a chiral centre is an important radical-mediated asymmetric process.[179–182] High diastereoselectivities were obtained by Malacria et al. for the Michael addition of a vinyl radical onto β-alkoxy vinyl sulfoxides.[183] This radical cyclisation was more recently revisited by Lee et al. and applied to the stereoselective synthesis of chiral tetrahydrofuranyl allyl carbinols after subsequent Pummerer rearrangement and allylstannane reaction (Scheme 113).[184]



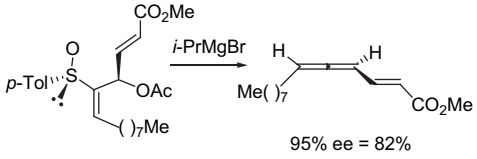
Scheme 113. Radical cyclisation of β-alkoxy vinyl sulfoxides.

In 2003, Malacria et al. introduced enantiopure alkylidene-1,1-bis-*p*-tolyl sulfoxides as new partners in diastereoselective radical cyclisations.[185] In particular, good diastereoselectivities could be observed for the 6-*exo-trig* precursor, as depicted in Scheme 114, whereas, in the 5-*exo* precursor case, rather frustrating results were obtained (de≤15%).



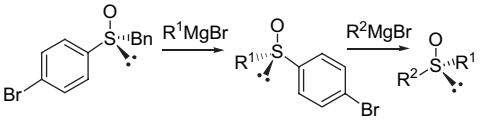
Scheme 114. Radical cyclisation of alkylidene-1,1-bis-*p*-tolyl sulfoxides.

The sulfoxide–metal exchange reaction of β-acetoxy or β-mesyloxy sulfoxides with a Grignard or alkyllithium reagent at low temperature gave allenes in good yields. Enantiomerically pure allenes were synthesised from enantiopure 2-substituted ethenyl *p*-tolyl sulfoxides. A short asymmetric synthesis of (*R*)-(−)-methyl tetradeca-2,4,5-trienoate, depicted in Scheme 115, a male bean weevil sex attractant, from an enantiopure alkenyl sulfoxide was developed by using this method.[186]



Scheme 115. Synthesis of (*R*)-(−)-methyl tetradeca-2,4,5-trienoate.

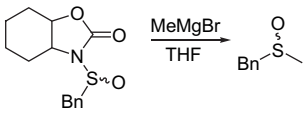
In 2000, Naso et al. demonstrated that displacement of leaving groups by Grignard reagents on sulfinyl compounds constituted an efficient route to chiral dialkyl sulfoxides.[187] An extension of this work was the development of a sequence of two stereocontrolled carbon-for-carbon substitution reactions (Scheme 116).[188]



R^1 = *n*-Pent, R^2 = *n*-dodec: 62% ee > 98%
R^1 = *n*-dodec, R^2 = *n*-Pent: 69% ee > 98%
R^1 = *n*-dodec, R^2 = *i*-Pr: 91% ee > 98%

Scheme 116. Two carbon-for-carbon substitution sequences.

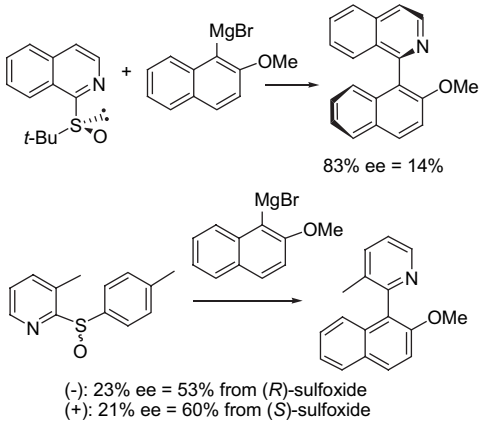
Other enantioselective chiral sulfinyl-transfer reactions have been performed by Juaristi et al., using *N*-(thiobenzylsulfinyl)hexahydrobenzoxazolidin-2-ones as recoverable chiral auxiliaries (Scheme 117).[189]



Substrate configuration	Yield (%)	Product configuration	ee (%)
(4*S*,5*S*,R_S)	70	(R_S)	> 98
(4*R*,5*R*,S_S)	70	(S_S)	> 98
(4*S*,5*R*,S_S)	75	(S_S)	> 98
(4*R*,5*S*,R_S)	75	(R_S)	> 99

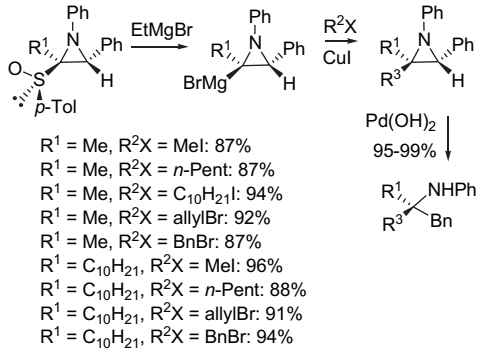
Scheme 117. *N*-(Thiobenzylsulfinyl)hexahydrobenzoxazolidin-2-ones as chiral sulfinyl-transfer reagents.

In 2005, Baker et al. reported an enantioselective synthesis of axially chiral 1-(1-naphthyl)isoquinolines and 2-(1-naphthyl)pyridines through sulfoxide ligand coupling reactions.[190] Good selectivities were obtained for the coupling between 2-methoxy-1-naphthylmagnesium bromide and (*R*)- and (*S*)-2-[(4′-methylphenyl)sulfinyl]-3-methylpyridines, whereas the same Grignard reagent gave low ees when reacting with (*S*)-1-(*tert*-butyl-sulfinyl)isoquinoline, because of partial racemisation of the starting material (Scheme 118).



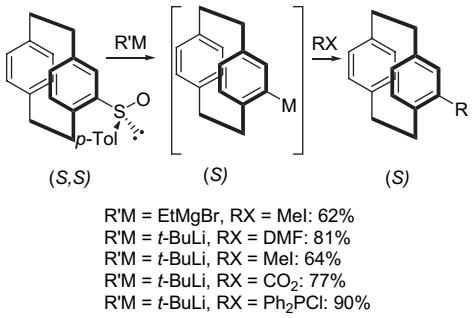
Scheme 118. Sulfoxide ligand coupling reactions.

On the other hand, Satoh et al. have reported a new synthesis of chiral amines bearing a quaternary chiral centre on the basis of a sulfoxide–magnesium exchange reaction.[191,118] Treatment of sulfinylaziridines with ethylmagnesium bromide gave the corresponding nonstabilised aziridinylmagnesium derivatives by sulfoxide–magnesium exchange reactions, and the organomagnesium compounds were then cross-coupled with various alkyl halides (Scheme 119). The resulting alkylated aziridines were further converted into amines bearing a quaternary chiral centre by hydrogenation.



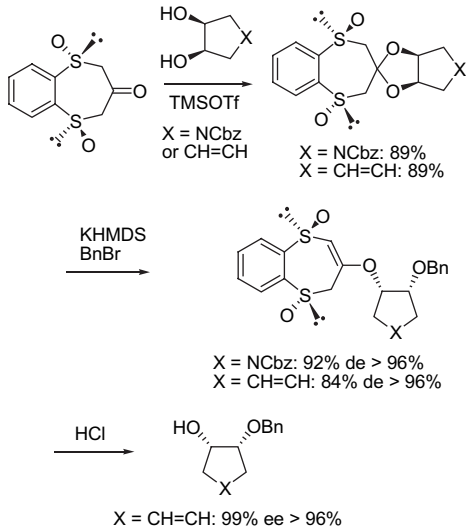
Scheme 119. Sulfoxide–magnesium exchange from sulfinylaziridines.

In 2005, the sulfoxide–metal exchange methodology was applied to the development of a general strategy for the synthesis of chiral 4-substituted [2.2]paracyclophane derivatives.[192] The sulfoxide moiety was able to both resolve planar chirality and act as a precursor to the formation of 4-metallo[2.2]paracyclophanes (Scheme 120).



Scheme 120. Synthesis of 4-substituted [2.2]paracyclophanes.

C_2-symmetric bis-sulfoxides have proved to be efficient chiral auxiliaries for asymmetric desymmetrisation of various diols such as *meso*-erythritol derivatives,[193] or cyclic *meso*-1,2-diols (Scheme 121).[194] These reactions were applied to the synthesis of two natural biologically active products, (+)-aspicilin and mosin B.[195]



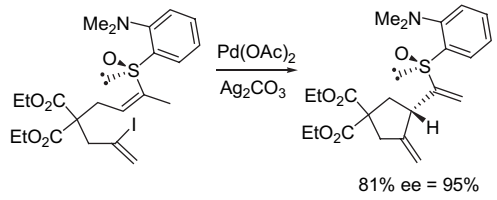
Scheme 121. Desymmetrisation of cyclic *meso*-1,2-diols.

8. Diastereoselective processes promoted by transition metals

Significant advances have been made in the use of chiral sulfoxides in processes catalysed by transition metals.[18] In order to combine the stereodirecting effect of the sulfinyl group with the chemistry of transition metals,[196] various groups started programmes in the mid-1990s directed towards this end. The contributions in this specific area can be divided into two approaches, those using the transition metal as a part of the molecule, and those using the metal as a reagent in a key asymmetric bond event. Only the second approach will be developed in this report.

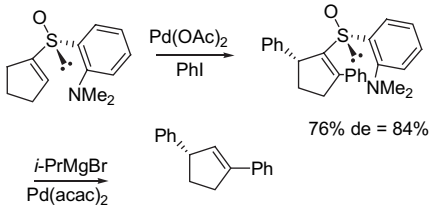
The Heck reaction is widely used for C–C bond formation that couples a vinyl or aryl halide (or anhydride) with an alkene in the presence of an appropriate palladium catalyst. Stereoselective Heck reactions usually involve the use of palladium complexes with chiral ligands. Carretero et al. successfully used chiral 2-iodo-1,6- and 1,7-dienes bearing an (*N*,*N*-dimethylamino)phenylsulfinyl group as chiral

auxiliaries in intramolecular Heck reactions to construct five-membered rings (Scheme 122).[197]



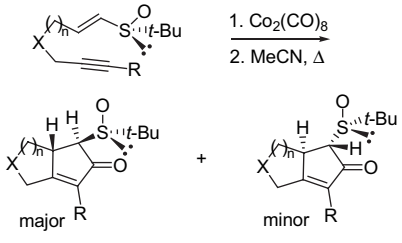
Scheme 122. Intramolecular Heck reaction of a 2-(*N*,*N*-dimethylamino)-phenylsulfinyl derivative.

These authors have reported the asymmetric synthesis of tetrahydrofurans from the Heck reaction of chiral 3-arylsulfinyl-2,3-dihydrofurans with aryl iodides.[198] An application of this methodology was the asymmetric synthesis of (*S*)-1,3-diphenylcyclopentene, depicted in Scheme 123, via a double Heck reaction of the corresponding chiral 1-sulfinylcyclopentene with iodobenzene, followed by palladium-catalysed reductive desulfurisation of the corresponding sulfoxide.[199] This work illustrated that sulfoxides were excellent stereochemical controllers in intermolecular Heck reactions. It should be noted that the 2-(*N*,*N*-dimethylamino)phenyl substituent was necessary in order to obtain high stereoselectivity, presumably via coordination of the Pd atom with the nitrogen.



Scheme 123. Double Heck reaction of a chiral 1-sulfinylcyclopentene.

Over the past few decades, the Pauson–Khand reaction, in which a cyclopentenone framework is constructed, has received great attention, due to its potential application in complex-molecule synthesis.[200] In 2001, Carretero reported an intramolecular version of the Pauson–Khand reaction involving enantiopure 1-sulfinyl-1,6-enynes (Scheme 124).[201]

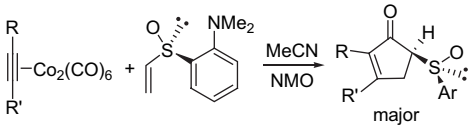


X = CH_2, n = 1, R = H: 50% de > 96%
X = CMe_2, n = 1, R = H: 65% de > 96%
X = $C(CO_2Et)_2$, n = 1, R = H: 60% de > 96%
X = $C(CO_2Et)_2$, n = 2, R = H: 60% de > 96%
X = NBoc, n = 1, R = H: 30% de > 96%

Scheme 124. Intramolecular Pauson–Khand reaction of 1-sulfinyl-1,6-enynes.

As the final desulfinylation step was high yielding, this procedure constituted an efficient alternative to the synthesis of chiral bicyclo[3.3.0]oct-1-en-3-ones. Complete diastereoselectivities were obtained using the *tert*-butylsulfinyl group as a chiral auxiliary.

The same group has also explored the capability of sulfoxide-based chiral auxiliaries in the much less thermodynamically favourable intermolecular processes. These workers reported the first asymmetric version of intermolecular Pauson–Khand reactions of acyclic alkenes.[202] Thus, chiral vinyl sulfoxides, depicted in Scheme 125, reacted under very mild conditions with terminal alkynes to yield the corresponding 5-sulfinylcyclopente-2-enones with complete regioselectivity and high stereoselectivity. A recent application of this methodology allowed the enantioselective synthesis of natural cyclopentanoids such as (−)-pentenomycin I and the (−)-aminocyclopentitol moiety of a hopane triterpenoid.[203]

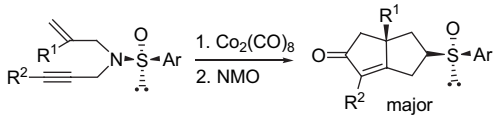


R = *n*-Bu, R' = H: 74% de = 86%
R = *t*-Bu, R' = H: 55% de > 96%
R = Bn, R' = H: 58% de = 86%
R = *p*-Tol, R' = H: 49% de = 86%
R = TMS, R' = H: 59% de > 96%
R = $(CH_2)_3Br$, R' = H: 68% de > 96%
R = $(CH_2)_2OTIPS$, R' = H: 66% de > 96%
R = R' = Me: 33% de = 84%

NMO = *N*-methylmorpholine *N*-oxide

Scheme 125. Pauson–Khand reaction of chiral acyclic vinyl sulfoxides with terminal alkynes.

In 2001, Hiroi et al. reported the first example of the use of a chiral sulfinamide functionality in Pauson–Khand reactions.[204] The cobalt-catalysed reaction of chiral *N*-allyl-*N*-propargyl-*N*-arylsulfinamide derivatives, however, gave the corresponding chiral 3-azabicyclo[3.3.0]oct-5-en-7-ones with only moderate or low enantioselectivity (Scheme 126).

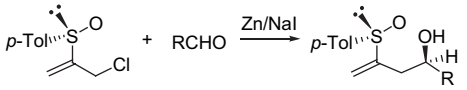


Ar = *p*-Tol, $R^1 = R^2$ = H: 79% de = 38%
Ar = *p*-Tol, R^1 = H, R^2 = Me: 87% de = 10%
Ar = *p*-Tol, R^1 = H, R^2 = TMS: 81% de = 18%
Ar = *p*-Tol, R^1 = Me, R^2 = TMS: 42% de = 10%
Ar = *p*-Tol, R^1 = Me, R^2 = H: 55% de = 11%
Ar = 2-MeOnaph, $R^1 = R^2$ = H: 13% de = 15%

Scheme 126. Pauson–Khand reaction of chiral sulfinamide derivatives.

The allylation of carbonyl derivatives to afford homoallylic alcohols is a useful synthetic transformation that has attracted considerable attention over the past few years. In this context, Delgado et al. have described a simple, efficient and diastereoselective zinc-promoted allylation of aldehydes with enantiopure 3-chloro-2-(*p*-tolylsulfinyl)-1-propene

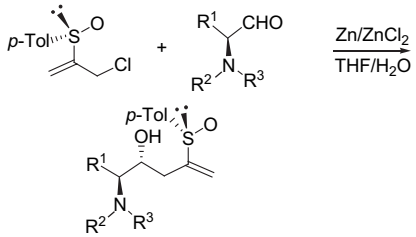
under aqueous Barbier conditions (Scheme 127).[205] Tin-promoted, palladium-catalysed carbonyl allylation was also studied as a suitable alternative to this Barbier-type process.[206] Although, in general, Barbier-type Zn-promoted allylations afforded the expected sulfinyl alcohols in higher yields at lower temperatures and with shorter reaction times than the Sn/Pd system, the Sn/Pd methodology proved to be superior in terms of diastereoselectivity. The sense of diastereoselectivity was identical in both allylation systems. A total synthesis of natural (*S*)-nicotine was elaborated using this methodology.



R = Ph: 80% de = 72%
R = Cy: 60% de = 66%
R = *n*-Bu: 67% de = 50%
R = *t*-Bu: 60% de = 66%
R = *p*-(OCH_3)Ph: 70% de = 66%
R = 2-furyl: 60% de = 60%
R = $BnOCH_2$: 75% de = 44%

Scheme 127. Zinc-promoted allylation of aldehydes with a 2-sulfinylallyl halide.

A similar methodology was applied to the use of a series of α-amino aldehydes, providing the corresponding chiral sulfinylamino alcohols in good yields and diastereoselectivities.[207] Particularly high levels of diastereoselectivity could be achieved from α-amino aldehydes configurationally related to natural α-amino acids such as serine, glycine or alanine (Scheme 128).

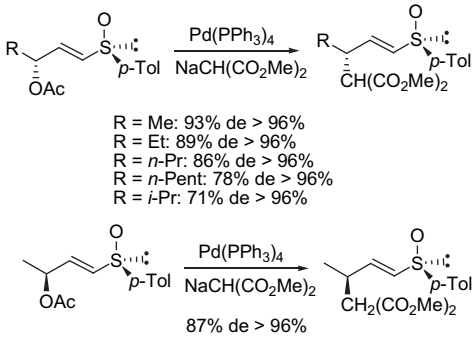


R^1 = H, R^2 = Boc, R^3 = Bn: 90% de = 50%
R^1 = Me, R^2 = H, R^3 = Boc: 82% de = 50%
R^1 = Me, R^2 = Bn, R^3 = Boc: 70% de = 86%
R^1 = *i*-Pr, R^2 = Bn, R^3 = Boc: 75% de = 76%
R^1 = R^2 = Bn, R^3 = Boc: 75% de = 86%

R = Me: 75% de = 20%
R = H: 79% de = 82%

Scheme 128. Allylation of α-amino aldehydes.

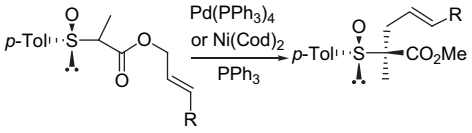
In 2001, Llera et al. reported the first example of palladium-mediated allylic substitution on chiral γ-oxygenated α,β-unsaturated sulfoxides.[208] Excellent regio- and stereoselectivities were observed using sodium dimethylmalonate. The reactivity of these substrates was controlled by both the chiral sulfinyl group and the size of the alkyl group attached to the terminus of the allylic system (Scheme 129). This process constituted an example of palladium-mediated resolution of a 50:50 mixture of the two starting acetates.



R = Me: 93% de > 96%
R = Et: 89% de > 96%
R = *n*-Pr: 86% de > 96%
R = *n*-Pent: 78% de > 96%
R = *i*-Pr: 71% de > 96%

Scheme 129. Palladium-mediated allylic substitution of chiral γ-oxygenated α,β-unsaturated sulfoxides.

The stereochemistry of palladium- or nickel-catalysed asymmetric intramolecular allyl transfer in chiral α-sulfinyl allylic esters has been studied by Hiroi et al.[209] Participation of the catalyst and the chiral sulfinyl functionality in these reactions, presumably by the coordination of the sulfinyl group to the catalyst, allowed the achievement of good diastereoselectivities (Scheme 130).

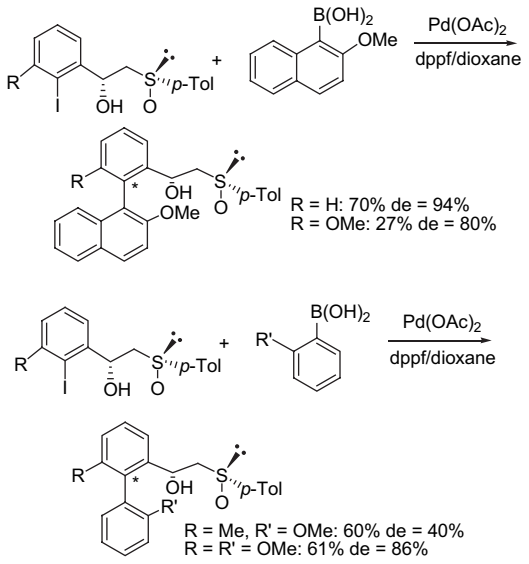


R = H, with $Pd(PPh_3)_4$: 54% de = 94%
R = H, with $Ni(Cod)_2$: 18% de = 87%
R = Me, with $Pd(PPh_3)_4$: 73% de = 98%

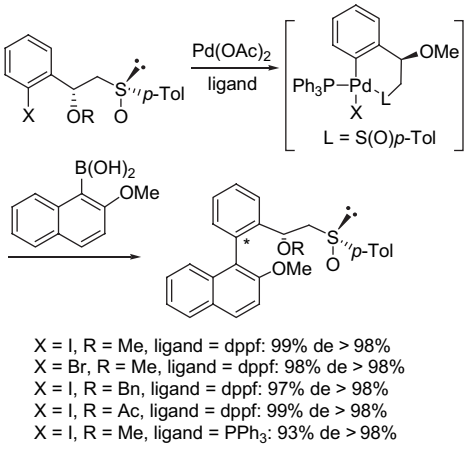
Scheme 130. Transition metal-catalysed intramolecular allyl transfer in α-sulfinyl allylic esters.

Axially chiral biaryls are of importance, not only as chiral ligands in asymmetric reactions, but also as biologically active natural products. Among the few successful methods allowing the asymmetric synthesis of this biaryl subunit are the asymmetric Suzuki reactions, which have been reported only in the past few years. Thus, Colobert et al. have involved enantiopure β-hydroxysulfoxide derivatives as novel chiral auxiliaries in asymmetric biaryl Suzuki reactions in the presence of aryl- or naphthylboronic acids (or esters).[210] High yields were obtained associated with an excellent control of the axial chirality (Scheme 131).

In 2005, the best results were obtained when the chiral sulfoxide was bearing an alkoxy group in the β-position.[211] A plausible mechanism responsible for the high selectivity might reasonably invoke the formation of a palladacycle during the oxidative addition, in which the palladium was coordinated to the internal chelating ligand such as the *p*-tolyl sulfoxide group (Scheme 132).

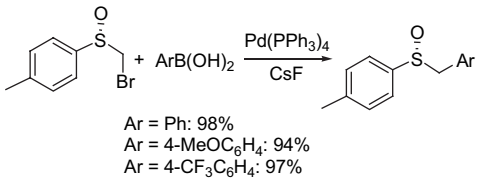


Scheme 131. Biaryl Suzuki coupling reactions of β-hydroxysulfoxide derivatives with aryl- or naphthylboronic acids.



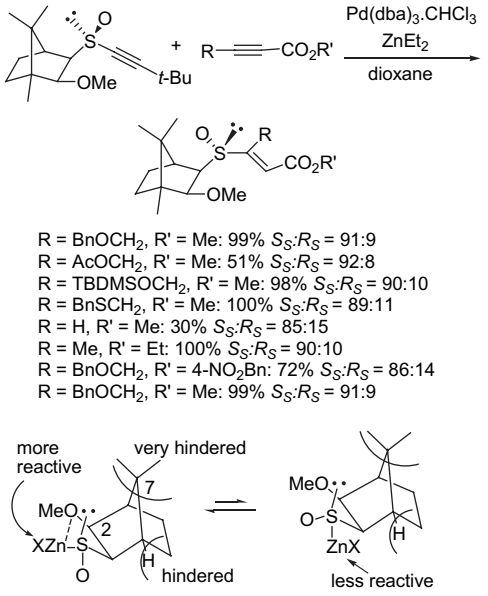
Scheme 132. Suzuki reactions of phenyl halide-containing protected β-hydroxysulfoxide derivatives with 2-methoxynaphthylboronic acid.

On the other hand, palladium-catalysed cross-coupling reactions of chiral α-bromo sulfoxides with arylboronic acids were reported in 2004 allowing the formation of a new C sp^3–sp^2 bond (Scheme 133).[212] The corresponding chiral aryl benzyl sulfoxides were isolated in high yields despite the previously reported racemisation of the chiral sulfur centre in chiral α-sulfinyl–palladium(II) complexes.[213]



Scheme 133. Palladium-catalysed reaction of boronic acids with α-bromo sulfoxides.

In 2003, Tanaka et al. accomplished a novel asymmetric sulfinylzincation of alkynoates via a palladium-catalysed sulfinylzincation using 1-alkynyl sulfoxides bearing chiral auxiliaries such as isoborneol as a sulfinylating reagent.[214] The reaction proceeded in a highly *syn*-selective fashion, giving the (*E*)-β-sulfinyl α,β-unsaturated ester exclusively (Scheme 134). The diastereoselectivity of the reaction could be interpreted (Scheme 134) by postulating that, in the preferred conformer of the sulfinylzinc species, the smallest lone pair electron would situate at the most crowded space near one of the C_7–Me and C_2–MeO groups.

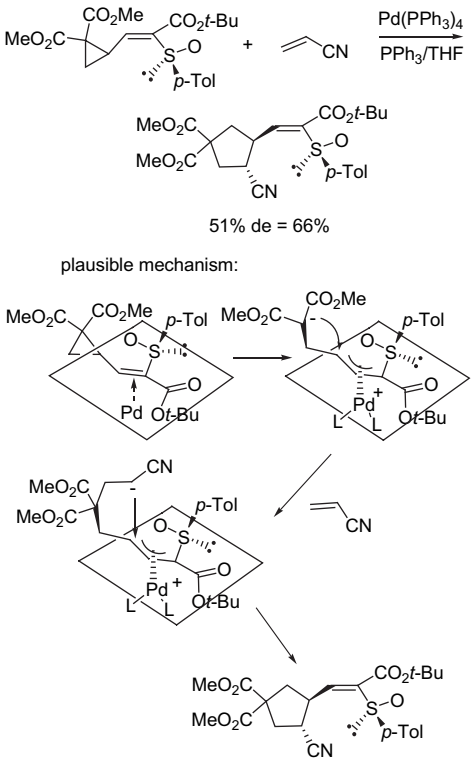


Scheme 134. Asymmetric sulfinylzincation of 1-alkynoates with chiral 1-alkynyl sulfoxides.

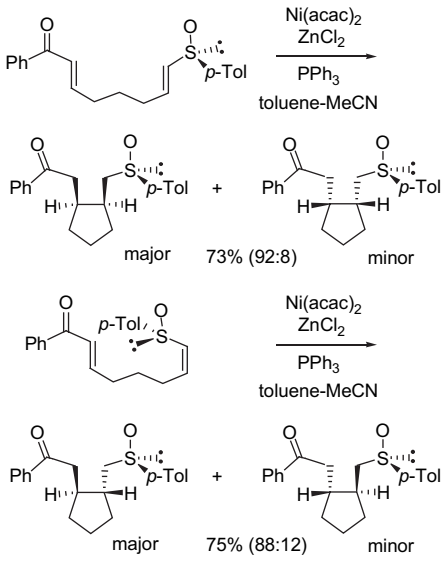
Asymmetric synthesis of a cyclopentane derivative using a chiral sulfinyl functionality as the chiral source has been successfully executed by a transition metal-catalysed asymmetric cycloaddition reaction of a chiral (β-sulfinyl) vinylcyclopropane derivative to acrylonitrile.[215] A plausible mechanism is depicted in Scheme 135, involving an intermediary π-allylpalladium complex formed by the effect of the chiral sulfinyl group, without steric control by the racemic carbon centre. The palladium catalyst would react from the sterically less crowded downward direction on the same side as the sterically smallest lone pair side of the chiral sulfinyl group in the conformationally most stable conformer having coplanarity between the olefinic bond and the sulfur–oxygen bond of the sulfinyl group, affording a chiral π-allylpalladium complex possessing a chiral sulfinyl group at the α-site. The carbanion formed would undergo a conjugate addition to acrylonitrile. The thus-formed α-carbanion to the cyano group would react from the back side of the palladium catalyst at the sterically less crowded γ-site in the π-allylpalladium system, to afford the final product.

In 2005, Tanaka et al. reported the diastereoselective Ni(0)-catalysed carbocyclisation of enone to chiral vinylic sulfoxide, in which two stereogenic centres were constructed simultaneously to give cis- and trans-disubstituted cyclopentanes from (*E*)- and (*Z*)-vinylic sulfoxides, respectively (Scheme 136).[216]

Sato et al. have developed a new tandem asymmetric reaction constituted by a titanium-promoted cyclisation and a Pummerer reaction involving a chiral enyne bearing a vinylic sulfoxide moiety as chiral starting material (Scheme 137).[217]

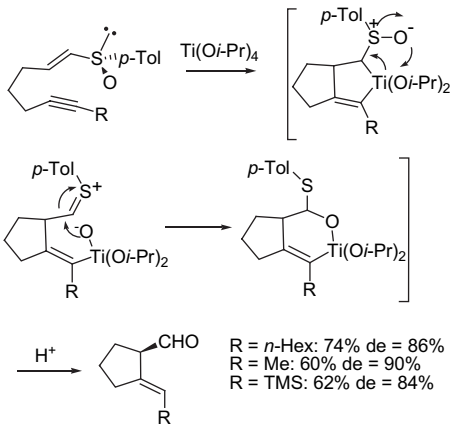


Scheme 135. Palladium-catalysed asymmetric cycloaddition.

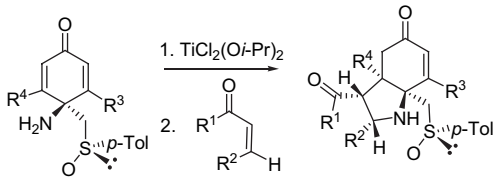


Scheme 136. Ni(0)-catalysed carbocyclisation to chiral vinylic sulfoxide.

In addition, a titanium-promoted stereoselective synthesis of hydroindolones, commonly found in alkaloids, from *p*-quinamines bearing a chiral sulfoxide was accomplished by Carreno et al. on the basis of a domino conjugate reaction.[218] Thus, the reaction of chiral 4-[(*p*-tolylsulfinyl)methyl]-*p*-quinamines with α,β-unsaturated ketones in the presence of $TiCl_2(O\textit{i}\text{-}Pr)_2$ yielded stereoselectively the corresponding hydroindolones as a single diastereoisomer (Scheme 138). The method allowed quaternary centres to be created efficiently with a single configuration through consistent asymmetric induction.



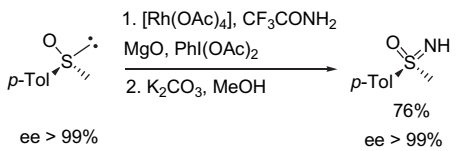
Scheme 137. Asymmetric tandem titanium-promoted cyclisation/Pummerer reactions.



$R^1,R^2 = (CH_2)_2$, $R^3 = R^4 = H$: 60%
$R^1,R^2 = (CH_2)_3$, $R^3 = R^4 = H$: 60%
$R^1 = Et$, $R^2 = R^3 = R^4 = H$: 51%
$R^1 = Et$, $R^2 = H$, $R^3 = Me$, $R^4 = H$: 54%
$R^1,R^2 = (CH_2)_2$, $R^3 = Me$, $R^4 = H$: 50%
$R^1,R^2 = (CH_2)_3$, $R^3 = Me$, $R^4 = H$: 54%
$R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Me$: 68%
$R^1 = Et$, $R^2 = R^3 = H$, $R^4 = Me$: 62%

Scheme 138. Asymmetric domino titanium-promoted conjugate reactions.

Various sulfoxides have been converted into their corresponding sulfoximines using $[Rh(OAc)_4]$ as a catalyst with trifluoroacetamide in combination with iodobenzene diacetate and magnesium oxide.[219] Synthetically valuable *NH*-sulfoximines could easily be obtained by cleavage of the *N*-acyl bond of the resulting *N*-trifluoroacetyl-protected derivatives. The imination reaction was stereospecific and proceeded with retention of configuration at the stereogenic centre. Consequently, enantiomerically pure sulfoximines were accessible by starting from chiral sulfoxides (Scheme 139).



Scheme 139. Rhodium-catalysed imination of chiral sulfoxides.

9. Conclusions

The main purpose of this review has been to demonstrate the growing potential of enantiomerically pure sulfur reagents in transmitting chirality to other centres, establishing the sulfinyl group as an excellent stereocontrolling element in various asymmetric reactions.

The chiral sulfinyl group clearly appears to be one of the most efficient and versatile chiral controllers in C–C and C–X bond formations.

The key to success is related to the steric and electronic differences between the substituents at sulfur, as well as to the conformational behaviour of the sulfinyl group, which is able to react in a rigid conformation. The presence in the reaction medium of metal atoms in the reagents or in an added catalyst, which may undergo a bonding interaction with the sulfinyl oxygen, can dramatically modify the nature of the reactive conformation, in many cases being able to achieve products of opposite configuration from a common starting material by changing the reaction conditions.

An advantage of using chiral sulfinyl auxiliaries is that they can be readily introduced to effect the diastereomeric induction and subsequently can be removed to afford the molecule of interest. Moreover, the stereochemical course can be successfully navigated by the configuration of the sulfoxide and the reaction conditions.

This review amply demonstrates that new examples and methodologies using chiral sulfoxides for asymmetric syntheses continue to emerge in the literature. In particular, the utility of chiral sulfoxides in asymmetric syntheses of biologically interesting compounds is well documented.

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Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr. G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K.P.C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.

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Metal catalyst-free Suzuki-type coupling reaction in water

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Abstract—The catalyst-free Suzuki-type coupling reaction of sodium tetraphenylborate with iodanes was achieved in good yields in water at room temperature. Similarly, the coupling of sodium tetraphenylborate with iodonium salts easily occurred in aqueous water medium at 50 °C in good yields. Both coupling reactions were also promoted by microwave irradiation in water in short time.

1. Introduction

The Suzuki reaction is one of the most versatile and utilized reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls.[1] For the development of improved conditions for the Suzuki reaction, a wide range of metal complexes have been used as catalysts in these coupling reactions, attention has particularly been focused on palladium. Recently, N. E. Leadbeater and M. Marco first reported a catalyst-free Suzuki coupling reaction,[2] in which aryl halides reacted with aryl boronic acids under microwave irradiation without catalyst and afforded biaryls in good yields (Fig. 1). It was also reported sodium tetraphenylborate could be used in place of phenylboronic acid as a phenylating agent in the reaction. Due to the development of pressure and the need for specialized sealed vessels for this method, the development of mild and efficient catalyst-free reaction conditions are required.

In order to improve and extend the scope of this reaction, especially to improve the coupling reaction using sodium tetraphenylborate as a phenylating agent, we focused our attention on hypervalent iodonium compounds. As powerful electrophilic reagents, hypervalent iodine compounds, in particular, iodonium salts have found synthetic application in the reaction with various nucleophiles,[3] they have also been used in Suzuki reaction to replace aryl halides and triflates affording products in excellent yields under mild reaction conditions.[4] Using hypervalent iodonium compounds as alternative for aryl halides and triflates, we investigated the coupling reaction of them with sodium tetraphenylborate. Here we would like to report the metal catalyst-free Suzuki-type coupling reaction of sodium tetraphenylborate with hypervalent iodonium compounds in water.

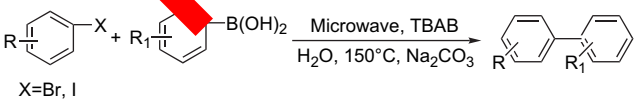
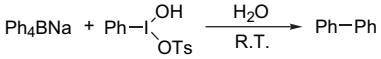


Figure 1.

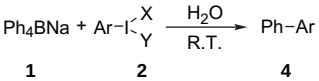
2. Results and discussion

2.1. The coupling reaction of sodium tetraphenylborate with iodanes in water

At the beginning, a readily available iodane, hydroxy(tosyloxy)iodobenzene,[5] referred to as Koser's reagent was used to couple with sodium tetraphenylborate in water at room temperature, the product of a biphenyl in good yield was obtained after the mixture was stirred for a short period of time (Scheme 1). To determine suitable reaction conditions, a series of experiments were performed on the coupling of sodium tetraphenylborate (**1**) with Koser's reagent (**2a**) to form biphenyl (**4a**), we found that when 2 equiv of **1** were used to react with **2a** in water for 0.5 h at room temperature, nearly quantitative **4a** was formed. Under the optimal reaction conditions, we checked the reactions of a series of typical iodanes stable in water with sodium tetraphenylborate (Scheme 2), the results were summarized in Table 1.[6]



Scheme 1.



Scheme 2.

Keywords: Suzuki-type reaction; Sodium tetraphenylborate; Iodanes; Iodonium salts; Microwave irradiation.
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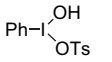
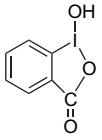
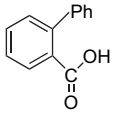
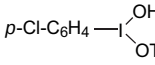
Table 1. The results of the Suzuki reaction of sodium tetraphenylborate with iodanes

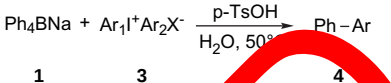
Entry	Iodane	Product	Yield (%)[a]
1	**2a** 	**4a** Ph–Ph	97
2	**2b** $PhI(OAc)_2$	**4a**	78
3	**2c** $PhI(OCOCF_3)_2$	**4a**	90
4	**2d** $Ph–I^+–O–I^+–Ph$ $2BF_4^-$	**4a**	91
5	**2e** PhI=O	**4a**	55[b]
6	**2f** p-MeO–$C_6H_4I(OAc)_2$	**4b** p-MeO–C_6H_4–Ph	99
7	**2g** p-Cl–$C_6H_4I(OAc)_2$	**4c** p-Cl–C_6H_4–Ph	47
8	**2h** 	**4d** 	90
9	**2i** 	**4c**	84

[a] Isolated yields.
[b] The reaction was run with sodium tetraphenylborate (4 equiv), iodosylbenzene (1 equiv), and p-TsOH (2 equiv) in water for 0.5 h.

It was shown that when Ar was a phenyl with electron-donating group, the yield of **4b** was almost quantitative (entry 6) and when Ar was a phenyl with electron-withdrawing group, the yields of **4c** were somewhat lower (entries 7 and 9) compared to **4b** (entry 6) and **4a** (entry 1), respectively. When iodosylbenzene (**2e**) was treated with **1** under the same reaction conditions, the reaction did not occur even when the reaction mixture was stirred for longer time at room temperature or in heating conditions, but after adding 2 equiv of p-TsOH and stirred for 5 h, product **4a** was obtained in 55% yield.[7]

2.2. The coupling reaction of sodium tetraphenylborate with iodonium salts in acidic water

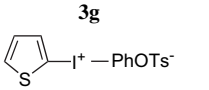
Analogous to iodanes, iodonium salts have high reactivity to sodium tetraphenylborate. However, we found that the catalyst-free Suzuki reaction did not occur when iodonium salts were used to react with sodium tetraphenylborate in water in the presence or absence of base at room temperature or higher temperatures. Then, we explored the coupling reaction in acidic conditions, a quite different result was obtained: the mixture of diphenyliodonium chloride (**3a**) with **1** was only stirred for a short time at 50 °C in acidic water, a product of biphenyl (**4a**) was obtained in good yield. Prompted by the result, a series of experiments were performed on the coupling of **1** with **3a** to determine the suitable reaction conditions. It was found that p-TsOH was the most efficient acid and the reaction of 4 equiv of sodium tetraphenylborate, 2 equiv of p-TsOH, and 1 equiv of diphenyliodonium chloride in water at 50 °C for 30 min afforded biphenyl in 95% yield. We extended this protocol to other iodonium salts, the symmetrical and unsymmetrical biaryls were readily available in high yields as shown in Scheme 3 and the results were summarized in Table 2.



Scheme 3.

From Table 2, it was shown that excellent iodonium salt **3c** (entry 3), all iodonium salts worked well in the reaction providing products in good to excellent yields. Iodonium salt **3f** with electron-withdrawing substituent in phenyl gave a somewhat lower yield product **4g** (entry 6) than electron-rich phenyliodonium salts **3d** and **3e** (entries 2, 4, and 5). It was also observed that the anions of iodonium salts affected the yield greatly: with **3b** the reaction was complete after only 0.5 h affording **4e** in 92% yield (entry 2); when **3h** was used in place of **3b** under the same reaction conditions, the reaction was not completed even after 28 h and the product was obtained in poor 29% yield. To try to improve the yield, we increased the amount of acid to 6 equiv and found that the coupling reaction was completed after 1 h, giving the desired product in a much improved 78% yield (entry 8). Similarly, **3i** was also mixed with 6 equiv of p-TsOH and 4 equiv of **1**, the reaction could give 72% product (entry 9), compared to a yield of 20% after a reaction time of 35 h under the standard conditions. With a tosylate iodonium salt **3g**, the reaction time was somewhat longer

Table 2. The results of the coupling reaction of sodium tetraphenylborate with iodonium salts

Entry	Iodonium salt	Product	Time (h)	Yield (%)[a]
1	**3a** $Ph_2I^+Cl^-$	**4a**	0.5	95
2	**3b** $(p$-Me–$C_6H_4)_2I^+Br^-$	**4e** p-Me–C_6H_4–Ph	0.5	92
3	**3c** $(p$-Br–$C_6H_4)_2I^+Br^-$	**4f** p-Br–C_6H_4–Ph	1	61
4	**3d** p-Me–$C_6H_4–I^+–PhBr^-$	**4e**	1	94
5	**3e** p-MeO–$C_6H_4–I^+–PhBr^-$	**4b**	1	92
6	**3f** $(m$-NO_2–$C_6H_4)_2I^+Br^-$	**4g** m-NO_2–C_6H_4–Ph	1	80
7	**3g** 	**4h** 	2	81
8	**3h** $(p$-Me–$C_6H_4)_2I^+BF_4^-$	**4e**	1	78[b]
9	**3i** $(p$-MeO–$C_6H_4)_2I^+BF_4^-$	**4b**	2	72[b]

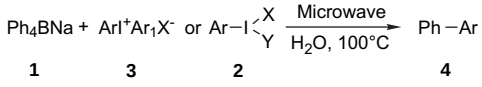
[a] Isolated yields.
[b] The reaction was run with sodium tetraphenylborate (4 equiv), iodonium salt (1 equiv), and p-TsOH (6 equiv) in water.

and the yield was somewhat lower compared with **3a** due to the influence of the anion (entry 7).

2.3. The coupling reaction of sodium tetraphenylborate with iodonium salts and iodanes under microwave irradiation in water

Taking advantage of the above results, we further checked the coupling reaction under microwave irradiation because microwave-assisted organic syntheses have some advantages such as fast reaction rates, high purity of products, and ease of manipulation.[8] In particular, the microwave-irradiated procedures in water medium for organic synthesis have attracted considerable interest in recent years due to their efficient and environmentally benign conditions.[9]

We used diphenyliodonium chloride (**3a**) to investigate the coupling reaction with sodium tetraphenylborate (**1**) under microwave irradiation in water, we found that the coupling was easy to be carried out and when the molar ratio of **1** to **3a** reached 2:1, the best result of 90% biphenyl was afforded under microwave irradiation for 4 min at 100 °C. Under the optimized conditions, the coupling reactions of iodonium salts **3** with **1** were shown in Scheme 4 and the good results were given in Table 3.



Scheme 4.

It was shown that most reactions could be completed in 4 min affording products in good to excellent yields (entries 1–6). However, iodonium salt **3f** with electron-withdrawing substituent in phenyl only provided **4g** in 37% yield after 5 min (entry 7). We also observed that the anions of iodonium salts affected the yield strongly: with **3b** the reaction was completed after only 3 min and afforded **4e** in 93% yield (entry 2); when **3h** was used in place of **3b** under the same reaction conditions, even after a prolonged reaction time of 15 min, **4e** was obtained in a poor 41% yield (entry 8).

Under the same reaction conditions, we found that iodanes (**2**) could react with sodium tetraphenylborate (**1**) and afforded products **4** in good yields only in 2 min (Scheme 4, Table 3).

The reaction with iodanes needed shorter reaction time than with iodonium salts meant that iodanes had more activity towards sodium tetraphenylborate. However, it may be due to their stability in water, in particular, under microwave irradiation part of them could be decomposed.

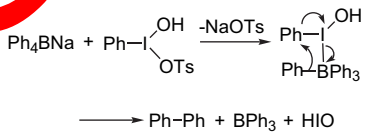
Table 3 The results of the Suzuki reaction under microwave irradiation

Entry	Reaction salt and iodanes	Product	Time (min)	Yield (%)[a]
1	**3a**	**4a**	4	90
2	**3b**	**4e**	3	93
3	**3c**	**4f**	3	91
4	**3d**	**4e**	2	74
5	**3e**	**4b**	4	77
6	**3g**	**4h**	3	80
7	**3f**	**4g**	5	37
8	**3h**	**4e**	15	41
9	**2a**	**4a**	2	83
10	**2b**	**4a**	2	87
11	**2c**	**4a**	1	82
12	**2d**	**4a**	1	80
13	**2e**	**4a**	1	65
14	**2g**	**4c**	2	73
15	**2h**	**4d**	1	67

[a] Isolated yield.

3. Conclusions

In summary, we have presented the our observations that the metal catalyst-free Suzuki-type coupling reaction of sodium tetraphenylborate with hypervalent iodonium compounds can be performed in water. The mechanism probably involved first a nucleophilic substitution of acid radical of iodonium salts or iodanes by Ph_4B^-, then an intramolecular coupling reaction was accompanied to yield biaryls as shown by the coupling of sodium tetraphenylborate with Koser's reagent (Scheme 5). This coupling reaction provided fast and efficient method for preparation of biaryls, it had the advantages such as mild reaction conditions, simple procedure, and good yields. Furthermore, the scope of the catalyst-free Suzuki coupling reactions could be extended.



Scheme 5.

4. Experimental

4.1. General

Mps were determined on a digital mp apparatus and were not corrected. IR spectra were recorded on a FT-170 SX instrument, ^{1}H NMR spectra were measured on a Bruker AM-400 FT-NMR spectrometer, and Mass spectra were determined on HP5989A mass spectrometer. Microwave reaction was carried out with a single-mode cavity Sanle WHL70S-01 Microwave Synthesizer (Nanjing Sanle Microwave Equipment Corporation). Iodonium salts were prepared according to the literature procedures.[10] Iodanes were prepared according to the literature procedures.[5,11] Sodium tetraphenylborate is commercially available.

4.2. The general procedure for reaction of sodium tetraphenylborate with iodanes in water

Sodium tetraphenylborate (**1**) (342 mg, 1.0 mmol) and iodane (**2**) (0.5 mmol) were added in 5 mL of H_2O. The mixture was stirred for 0.5 h at room temperature and quenched with brine (5 mL). The mixture was extracted with diethyl ether (20×3 mL), and the organic layer was dried over anhydrous $MgSO_4$, and then evaporated in vacuo. The crude product was separated by a silica gel plate using hexane as developer to afford the pure product **4** in good yields.

4.3. The general procedure for reaction of sodium tetraphenylborate with iodonium salts in water

Sodium tetraphenylborate (**1**) (137 mg, 0.4 mmol, 4.0 equiv), iodonium salt (**3**) (0.1 mmol), and *p*-TsOH (38 mg, 0.2 mmol, 2.0 equiv) were added in 5 mL of H_2O. The mixture was stirred at 50 °C until it was complete. After cooling to room temperature the mixture was extracted with diethyl ether (20×3 mL), and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by a silica gel plate using hexane as developer to afford the pure product **4** in good yields.

4.4. The general procedure for reaction of sodium tetraphenylborate with iodonium salts and iodanes under microwave irradiation in water

Sodium tetraphenylborate (**1**) (513 mg, 1.5 mmol), iodonium salt (**3**) or iodane (**2**) (0.75 mmol), and 5 mL of water were added to a 50 mL flask with a condenser. The vessel was placed inside the center of the microwave synthesizer and then exposed to microwave irradiation (250 W) to heat it at reflux for 1–15 min at 100 °C. After irradiation, the reaction mixture was cooled to room temperature and extracted with diethyl ether (20×3 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by a silica gel plate using hexane as eluent and the pure product **4** was afforded.

4.4.1. Biphenyl (4a). Mp 68–69 °C (lit.[12] 69–72 °C). ^{1}H NMR ($CDCl_3$): δ=7.32–7.36 (m, 2H), 7.42–7.46 (m, 4H), 7.58–7.61 (m, 4H); IR (KBr): ν=3035, 1469, 1481, 730 cm^{-1}; MS (70 eV, EI) *m/z* (%): 154 (M$^+$, 100).

4.4.2. *p*-Methoxybiphenyl (4b). Mp 86–87 °C (lit.[13] 88 °C). ^{1}H NMR ($CDCl_3$): δ=3.83 (s, 3H), 6.96–6.99 (m, 2H), 7.27–7.31 (m, 1H), 7.38–7.42 (m, 2H), 7.51–7.55 (m, 4H); IR (KBr): ν=3068, 3033, 1262, 1035, 835, 761 cm^{-1}; MS (70 eV, EI) *m/z* (%): 184 (M$^+$, 100).

4.4.3. *p*-Chlorobiphenyl (4c). Mp 74–77 °C (lit.[14] 77 °C). ^{1}H NMR ($CDCl_3$): δ=7.32–7.34 (m, 1H), 7.36–7.39 (m, 2H), 7.40–7.43 (m, 2H), 7.46–7.50 (m, 2H), 7.51–7.55 (m, 2H); IR (KBr): 3067, 3035, 1479, 1099,1005, 833, 760 cm^{-1}; MS (70 eV, EI) *m/z* (%): 188 (M$^+$, 100).

4.4.4. *p*-Biphenylcarboxylic acid (4d). Mp 108–110 °C (lit.[15] 112 °C). ^{1}H NMR ($CDCl_3$): δ=7.30–7.39 (m, 7H), 7.53 (m, 2H), 7.93 (m, 1H), 11.0 (br, 1H); IR (KBr): ν=3400–2400 (br), 1700, 1685, 1306, 1296 cm^{-1}; MS (70 eV, EI) *m/z* (%): 198 (M$^+$, 100).

4.4.5. *p*-Methylbiphenyl (4e). Mp 43–46 °C (lit.[16] 44–47 °C). ^{1}H NMR ($CDCl_3$): δ=2.39 (s, 3H), 7.23–7.26 (m, 2H), 7.30–7.34 (m, 1H), 7.40–7.44 (m, 2H), 7.48–7.51 (m, 2H), 7.56–7.59 (m, 2H); IR (KBr): ν=3067, 3033, 1488, 1007, 823, 766, 690 cm^{-1}; MS (70 eV, EI) *m/z* (%): 168 (M$^+$, 100).

4.4.6. *p*-Bromobiphenyl (4f). Mp 83–85 °C (lit.[16] 85–87 °C). ^{1}H NMR ($CDCl_3$): δ=7.33–7.37 (m, 1H), 7.42–7.46 (m, 4H), 7.52–7.57 (m, 4H); IR (KBr): ν=3064, 3031, 1477, 1393, 1080, 830, 767, 691 cm^{-1}; MS (75 eV, EI) *m/z* (%): 234 (M+1), 233 (M$^+$, 13.3), 232 (100).

4.4.7. *m*-Nitrobiphenyl (4g). Mp 56–58 °C (lit.[16] 58–60 °C). ^{1}H NMR ($CDCl_3$): δ=7.40–7.67 (m, 6H), 7.83–7.95 (m, 1H), 8.11–8.23 (m, 1H), 8.40–8.45 (m, 1H); IR (KBr): ν=3064, 3036, 1536, 1362, 877, 772, 733 cm^{-1}; MS (75 eV, EI) *m/z* (%): 199 (M$^+$, 100).

4.4.8. 2-Phenylthiophene (4h). Oil.[4a] ^{1}H NMR ($CDCl_3$): δ=7.10–7.13 (m, 1H), 7.30–7.34 (m, 2H), 7.37–7.40 (m, 1H), 7.46–7.49 (m, 2H), 7.62–7.66 (m, 2H); IR (KBr) ν=3103, 3062, 3036, 1496, 1451, 747 cm^{-1}; MS (70 eV, EI) *m/z* (%): 160 (M$^+$, 100).

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N-Acyltrifluoromethanesulfonamides as new chemoselective acylating agents for aliphatic and aromatic amines

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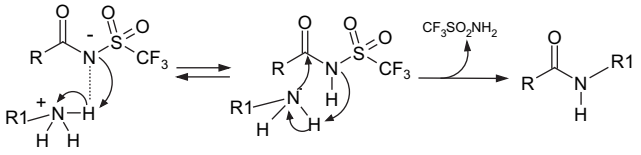
Abstract—This work describes advances in the study of the internal condensation of ammonium salts of *N*-acylsulfonamides. *N*-Acyltrifluoromethanesulfonamides show considerable advantages over the non fluorinated analogues by virtue of their higher reactivity and acidity. The reaction chemoselectivity has been investigated using a wide range of amines. The sensitivity of the reaction to steric and electronic effects confirms the potential application of these reagents in chemoselective acylation of polyamines.

1. Introduction

We have recently reported[1] that alkylammonium salts of acylmethanesulfonamides undergo internal condensation to give the corresponding amide derivatives under thermal conditions (T=120 °C, 3 h, 80 mmHg). The proposed reaction mechanism is depicted in Scheme 1.



Scheme 1.

The ionic interaction between the reagents is the crucial reaction step and, furthermore, methanesulfonamide harvesting by sublimation strongly contributes to drive the reaction equilibrium. These preliminary reactivity studies clearly demonstrate that the proximity of the reactive centres strongly influences the steric requirements of the reaction. In fact, secondary ammonium salts do not evolve to the corresponding amides and selective monoacylation of mixed primary–secondary amines has been reported to proceed in good yields.

Chemoselective acylation of mixed primary–secondary amines is a synthetic challenge and, to date, a wide range of strategies have been used to address this problem;[2–6] the observed chemoselectivity suggests promising applications of this process, but the relatively harsh conditions strongly limit the scope of the reaction. Here we report the efforts at extending the reactivity studies with the aim to select optimised conditions for the process.

2. Results and discussion

The aim of the present study is to evaluate acyltrifluoromethanesulfonamides in comparison with related acylmethanesulfonamides as novel acylating reagents for the amino group (Fig. 1).

The rationale behind this choice is based on the following considerations: (1) the marked acidity of the amide hydrogen should favour the acid–base interaction with low-basicity amines; (2) the electron-withdrawing effect of the fluorine atoms should enhance the reactivity of the electrophilic centre and (3) the higher vapour tension of trifluoromethanesulfonamide as compared to methanesulfonamide should positively influence the reaction course.

In Table 1, a comparison between the reactivity of 2-(4-isobutylphenyl)-*N*-(methylsulfonyl)acetamide **1** and its trifluoromethyl analogue **2** is described. As previously reported, **1** significantly undergoes internal condensation only when heated under vacuum in the absence of solvent (entries 1 and 2). On the contrary, comparable yields are obtained when **2** is heated either neat (entry 3) or in toluene

Keywords: Alkylammonium salts; *N*-Acyltrifluoromethanesulfonamides; Chemoselective acylation; Mixed primary–secondary amines.
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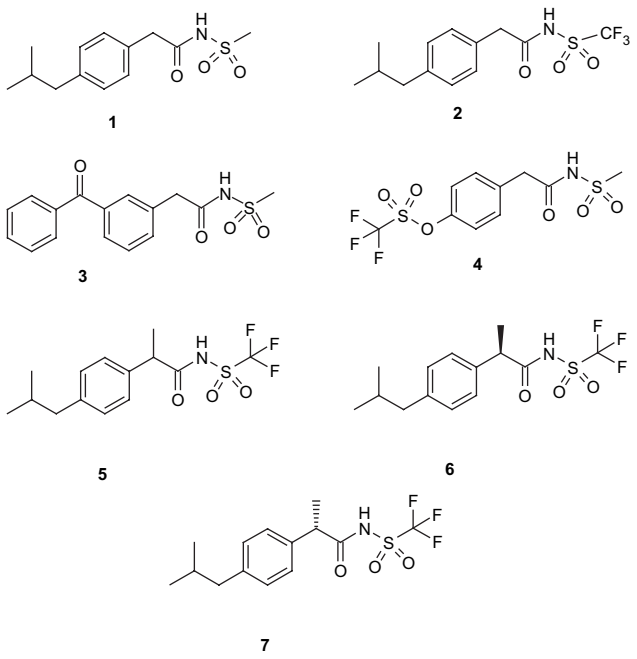


Figure 1. Substrates used as acylating agents.

Table 1. Reactivity of **1** and **2** with butylamine in various reaction conditions

Entry	Reagent	Amine	Reaction conditions	Yield (%)
1	**1**	H_2N	Neat/T=120 °C/4 h, 80 mmHg	90
2	**1**	H_2N	Toluene/reflux/8 h	0
3	**2**	H_2N	Neat/T=120 °C/4 h, 80 mmHg	90
4	**2**	H_2N	Toluene/reflux/8 h	80
5	**2**	H_2N	Toluene/rt/3 d	10
6	**2**	H_2N	Toluene/T=30 °C/1 h	Traces[a]
7	**2**	H_2N	Toluene/T=30 °C/1 h	10[a]

[a] The different yield is due to different work-up procedure (see text).

solution (entry 4). A low but significant conversion is obtained by stirring a toluene solution of the salt at room temperature for several days (entry 5). The results in entries 6 and 7 confirm the sublimation of the trifluoromethanesulfonamide as the crucial event for the reaction proceeding. In fact, after 1 h at T=30 °C (entry 6) only traces of the product are detected (GC–MS analysis) in the crude reaction mixture, whereas a subsequent analysis after simple solvent evaporation shows a consistent increase of yield (entry 7).

To explore the reactivity of acyltrifluoromethanesulfonamides, several ammonium salts, prepared by mixing **2** with the desired amine in toluene, have been treated under the selected conditions (Table 2).

Primary amines (entries 1–4) afford the corresponding amides in moderate to good yields. In our previous paper, we reported the lack of reactivity of secondary ammonium salts of **1**, but further experiments revealed that by prolonging the reaction time under the fusion conditions, small amount of the condensation product occurs. On the contrary, **2** shows a marked reactivity towards secondary amines; in fact, the reactions with pyrrolidine (entry 5) and *N*-butylmethylamine (entry 6) proceed in appreciable yield. The higher reactivity of **2** is in agreement with the increased electrophilic character of the carbonyl group.

On the basis of the mechanistic hypothesis, the acid–base interaction between the reagents is a crucial step for the reaction course (Table 3). Accordingly, low-basicity amines, such as anilines, fail to react with **1** since the formation of the ion-pair is highly disfavoured (entries 1 and 2). Heating a 1:1 mixture of the reagents does not lead to appreciable amounts of the amide products. The modest acidity increase caused by electron-withdrawing ring substituents, in compounds **3** and **4**, does not significantly enhance the reactivity of the substrates (entries 3 and 4).

Unlike the corresponding methanesulfonamide, **2** reacts with aniline to give the corresponding anilide (entry 5). This result is in agreement with the higher acidity and reactivity of the substrate. Substitution in the *para* position of the aniline ring with electron-withdrawing or electron-releasing groups does not markedly influence the reaction outcome (entries 6–8), whereas substituents in the *ortho* position clearly depress the aniline reactivity (entries 9–11). The observed trend highlights the importance of steric hindrance. The absolute unreactivity of 2,6-difluoroaniline (entry 12) could be explained by the low basicity and nucleophilicity of the amino group. 2,6-Difluoroaniline is, in fact, significantly less basic than the other tested anilines (pK_a=2.47). As reported for dialkyl amines, *N*-methylaniline is moderately reactive in our conditions (entry 13), while the more sterically congested 2-methyl-*N*-methylaniline fails to afford the desired condensation product (entry 14).

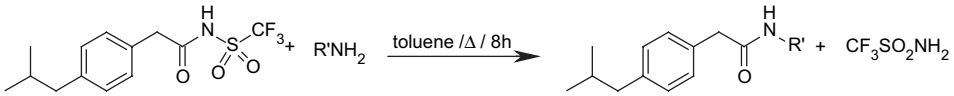
The above results confirm the hypothesis that acyltrifluoromethanesulfonamides, due to their increased reactivity, may constitute a valuable alternative to acylmethanesulfonamides as an activated intermediates for amide synthesis.

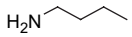
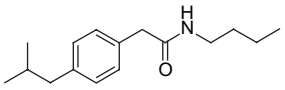
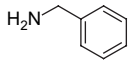
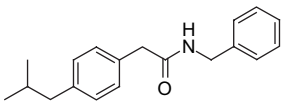
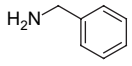
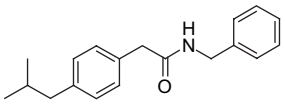
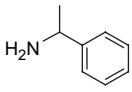
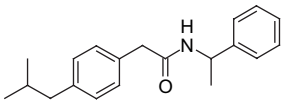
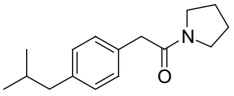
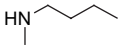
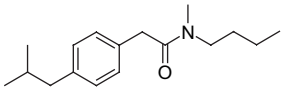
As a next step, we have verified if the enhanced reactivity of the substrate could be detrimental to the chemoselectivity of the reaction (Table 4).

When a two-fold molar excess of **2** reacts with *N*-propylaminoethylamine, the amine reagent is efficiently transformed (90% conversion yield) to give a 70:30 mixture of the amide products 2-(4-isobutylphenyl)-*N*-[2-(propylamino)ethyl]-acetamide **A** and *N*-(2-aminoethyl)-2-(4-isobutylphenyl)-*N*-propylacetamide **B**. Using a 1:1 ratio of the reagents, the reaction proceeds with high chemoselectivity (**A**/**B** ratio=97:3) although in lower yield (60%) (entries 1 and 2).

No traces of the diacylated compound are detectable. The surprising lack of reactivity of the primary amino group of **B** could be due to the engagement of a stable intramolecular interaction with the electrophilic carbonyl group. In fact, the only product detected in the reaction mixture is **C** (Fig. 2). Prolonging the reaction time to 24 h a 70:30 mixture of the

Table 2. Reactivity of **2** with alkylamines in the selected conditions



Entry	Amine	Product	Yield (%)
1			80
2			90
3			95[a]
4			35
5			40
6			45

[a] Reaction conditions: xylene/reflux/8 h.

products **A/C** is obtained. This result supports the hypothesis, confirming a marked tendency of **B** to the cyclisation.

The lower reactivity of α-branched-amines (Table 2, entry 4) suggests an additional steric effect induced by the hindrance on the α-carbon of the amine reagent. To explore this hypothesis, **2** has been reacted with a 1:1 mixture of butylamine and racemic α-methylbenzylamine. The 80:20 ratio between the products confirms the high sensitivity of the reaction to steric effects (Table 4, entry 3).

Keeping this in mind we have reasoned that the steric hindrance at the carbon next to the carbonyl group could also play a role on the substrate reactivity. With the aim to address this issue, 2-(4-isobutylphenyl)propionyltrifluoromethanesulfonamide **5** has been synthesised and reacted with several amines. Interestingly, a dramatic decrease in reactivity has been observed on moving from linear (entry 4) to branched primary amines (entry 5), whereas pyrrolidine proves unreactive under our standard conditions (entry 6). The same competition experiment described in entry 3 has been performed with **5** and higher chemoselectivity has been observed (entry 7). The results of the experiments in Table 4 confirm that steric hindrance at both the α-carbons next to the reactive centres strongly affects the reactivity of the substrate.

As a final step of this work, we have investigated the diastereodifferentiation of the process reacting racemic α-methylbenzylamine with the enantiopure substrates **6** and **7** (Table 5).

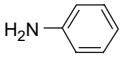
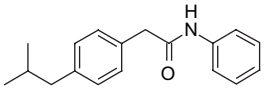
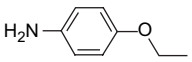
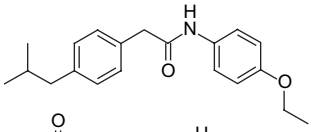
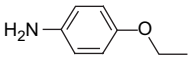
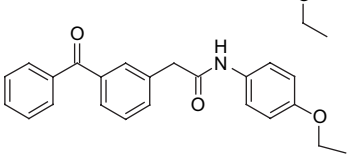
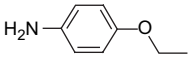
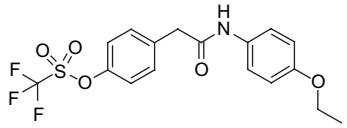
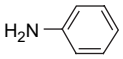
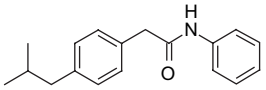
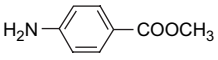
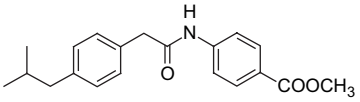
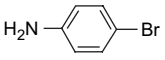
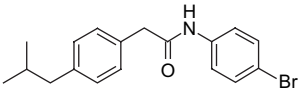
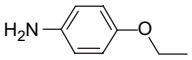
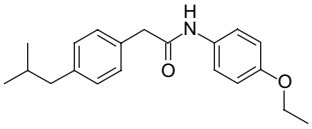
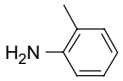
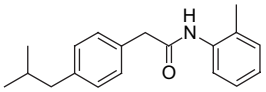
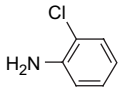
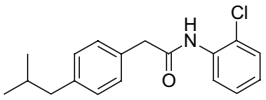
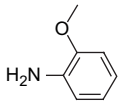
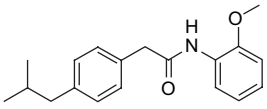
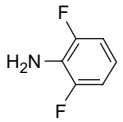
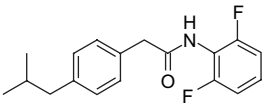
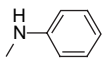
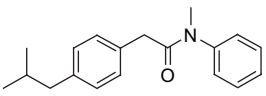
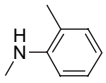
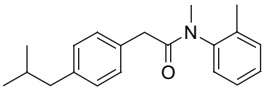
On the basis of the described steric effect, it was conceivable to expect a different reactivity of the *R* and *S* enantiomers. The four pure diastereomers have been singularly synthesised, as reference compounds for the following reaction products, by reacting **6** and **7** with the commercially available pure (*R*)(+) and (*S*)(−)-α-methylbenzylamines. Starting material **6** and the final diastereomeric product have been proved stable to epimerisation in the reaction conditions (reflux, toluene, 48 h, triethylamine as non reactive amine).

The reaction of **6** with racemic α-methylbenzylamine affords the diastereoisomers (2*R*,1*R*) with 80% diastereomeric excess but with a modest conversion yield (20%) and high recovery of the starting material (Table 5, entry 1). Prolonging the reaction time to 24 h (entry 2) the yield increases up to 82% without significant change in the enantiodiscrimination of the reaction. Analogous results have been obtained when substrates **7** and **5** have been, respectively, reacted with racemic and enantiopure α-methylbenzylamines (entries 4–6).

3. Conclusions

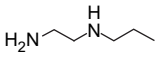
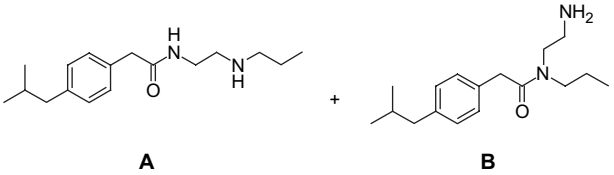
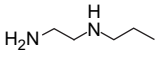
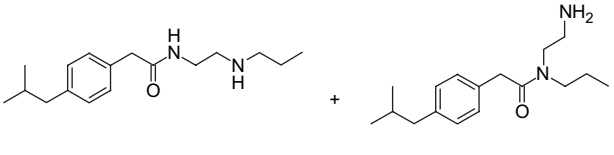
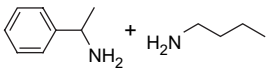
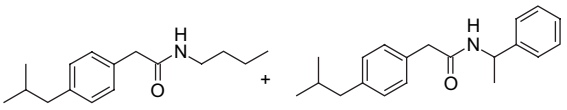
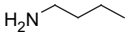
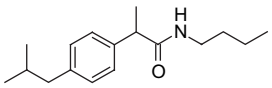
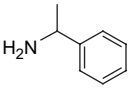
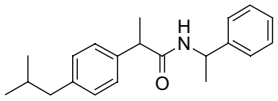
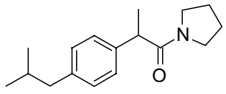
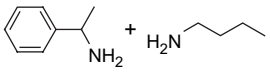
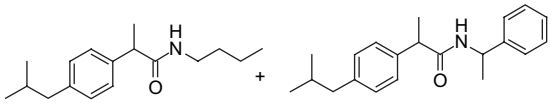
Summarizing, this work describes our advances in the study of the internal condensation of ammonium salts of

Table 3. Reaction of acylsulfonamides with aniline derivatives

Entry	Reagent	Amine	Product	Yield (%)
1	**1**			N.d.[a]
2	**1**			N.d.
3	**3**			Traces[b]
4	**4**			Traces[b]
5	**2**			70
6	**2**			80
7	**2**			75
8	**2**			71
9	**2**			59
10	**2**			37
11	**2**			Traces[b]
12	**2**			Traces[b]
13	**2**			30
14	**2**			N.d.

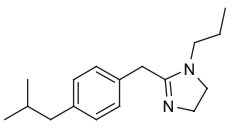
[a] N.d.: not detected.
[b] Detected by GC–MS analysis.

Table 4. Reactivity of acyltrifluoromethanesulfonamides with amines in standard conditions

Entry	Reagent	Amine	Ratio	Products[a]	Conversion yield (%)[b]
1	**2**		2:1	 **A** + **B** (70:30)	90
2	**2**		1:1	 **A** + **B** (97:3)	60
3	**2**		1:1	 (80:20)	89
4	**5**		1:1		92
5	**5**		1:1		20
6	**5**		1:1		N.d.[c]
7	**5**		1:1	 (95:5)	73

[a] Yields of isolated products are calculated after purification by flash chromatography.
[b] Conversion yields are calculated on recovered starting materials.
[c] N.d.: not detected.

N-acylmethanesulfonamides. *N*-Acyltrifluoromethanesulfonamides show considerable advantages over their non fluorinated analogues by virtue of their higher reactivity and acidity. The results in Table 5 are not optimal in terms of stereoselectivity, but they are encouraging and further studies on more hindered substrates could provide access to interesting synthetic applications.



C

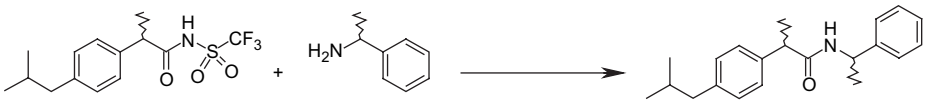
Figure 2. 2-(4-Isobutylbenzyl)1-propyl-4,5-dihydro-1*H*-imidazole (**C**).

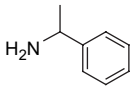
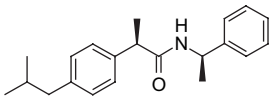
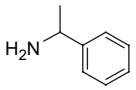
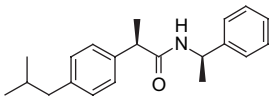
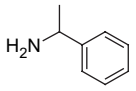
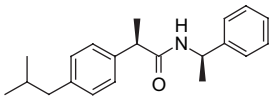
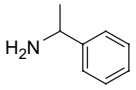
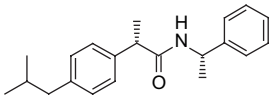
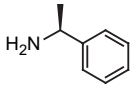
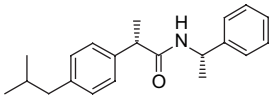
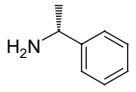
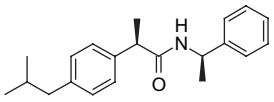
4. Experimental

4.1. General

Thin-layer chromatography was carried out with Macherey-Nagel-DURASIL-25 silica gel plates. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 MHz spectrometer. Column chromatography was performed on silica gel (300–400 mesh). IR spectra were recorded on Perkin–Elmer Spectrum One FTIR Spectrometer. GC–MS analysis was performed using a Thermo-Finnigan Trace 2030 UP MS chromatograph (analytical column: RTX-5MS) and a ThermoFinnigan DSQ 250 spectrometer. Uncorrected melting points were performed on a Buchi 530 apparatus. Elemental analyses were within ±0.4% of the theoretical values calculated for C, H and N

Table 5. Stereoselective reaction of *N*-acyltrifluoromethanesulfonamides with racemic and chiral α-methylbenzylamine



Entry	Reagent	Amine	Reaction conditions	Products	de (%)[a]	Yield (%)
1	**6**		Toluene/reflux/8 h	 (2*R*, 1*R*)	80	20
2	**6**		Toluene/reflux/24 h	 (2*R*, 1*R*)	40	82
3	**6**	 (2 eq.)	Toluene/reflux/24 h	 (2*R*, 1*R*)	30	85
4	**7**		Toluene/reflux/24 h	 (2*S*, 1*S*)	40	78
5	**5**		Toluene/reflux/24 h	 (2*S*, 1*S*)	40	74
6	**5**		Toluene/reflux/24 h	 (2*R*, 1*R*)	40	70

[a] Diastereoisomeric excess is calculated by chromatography purification of the products.

and is reported only with symbols. Commercially available reagents and solvents were used as received.

4.1.1. 2-(4-Isobutylphenyl)-*N*-(methylsulfonyl)acetamide (1). 1,1′-carbonyldiimidazole (CDI) (0.930 g, 5.73 mmol) was added to a solution of 4-isobutylphenyl acetic acid[7] (1.00 g, 5.21 mmol) in dry CH_2Cl_2 (25 mL) and the resulting solution was stirred for 30 min. Triethylamine (1.5 mL, 10.42 mmol) and methanesulfonamide (0.850 g, 10.42 mmol) were consecutively added and the solution stirred for 12 h at room temperature. After cooling to 0 °C, a KH_2PO_4 buffer solution (pH 2.4, 20 mL) was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL) and the collected organic extracts washed with brine (2×15 mL) and dried over Na_2SO_4. Solvent removal under reduced pressure afforded a crude residue, which after purification by flash chromatography (eluent mixture $CHCl_3$/MeOH 9:1), afforded the pure compound **1** (1.05 g, yield 75%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.20–7.10 (m, 4H), 3.80 (s, 2H), 3.18 (s, 3H), 2.00 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1680, 1500, 1380, 1130; EIMS *m*/*z* 269 (M+). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 57.96; H, 7.09; N, 5.21; S, 11.89.

4.1.2. 2-(4-Isobutylphenyl)-*N*-[trifluromethylsulfonyl]-acetamide (2). Following the same procedure described for **1** and starting from 4-isobutylphenyl acetic acid (1.00 g, 5.21 mmol), compound **2** was prepared using commercial trifluoromethanesulfonamide. The pure compound **2** was obtained (0.84 g, yield 50%) as a pale yellow solid. Mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.20–7.10 (m, 4H), 3.80 (s, 2H), 2.00 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.60–1.50 (br s, 1H, CON*H*), 0.90 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1680, 1500, 1380, 1130; EIMS *m*/*z* 323 (M^+). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 58.00; H, 7.08; N, 5.19; S, 11.91.

4.1.3. 2-(3-Benzoylphenyl)-*N*-(methylsulfonyl)acetamide (3). Following the same procedure as described for **1** and starting from commercial 2-(3-benzoylphenyl)acetic acid (1.00 g, 4.16 mmol), compound **3** was prepared. The pure compound **3** (1.05 g, yield 75%) was obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 8.20 (d, J=7 Hz, 1H), 8.02 (d, J=7 Hz, 1H), 7.80–7.67 (m, 4H+N*H*), 7.50 (m, 2H), 3.38 (m, 5H); IR (neat, cm^{-1}) ν 3150, 3000, 1650, 1450, 750; EIMS m/z 317 (M$^+$). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.56; H, 4.73; N, 4.45; S, 10.09.

4.1.4. 4-{2-[(Methylsulfonyl)amino]-2-oxoethyl}phenyl trifluoromethanesulfonate (4). Following a synthetic procedure as already described[8] compound **4** was prepared from commercially available 4-hydroxyphenylacetic acid. The pure compound **4** (1.48 g, yield 78%) was obtained as colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J=7 Hz, 2H), 7.18 (d, J=7 Hz, 2H), 4.95 (br s, 1H+CON*H*), 3.80 (s, 2H), 3.18 (s, 3H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1685, 1500, 1380, 1130; EIMS m/z 361 (M$^+$). Anal. Calcd for $C_{10}H_{10}F_3NO_6S_2$: C, 33.24; H, 2.79; F, 15.77; N, 3.88; S, 17.75. Found: C, 33.25; H, 2.76; F, 15.79; N, 3.87; S, 17.78.

4.1.5. 2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (5). Following the same procedure as described for **1** and starting from the commercially available reagents 4-isobutylphenyl propionic acid (1.00 g, 4.85 mmol) and trifluoromethanesulfonamide (1.44 g, 9.7 mmol), compound **5** (1.26 g, yield 80%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.86; H, 5.36; F, 16.91; N, 4.14; S, 9.52.

4.1.6. (2*R*)-2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (6). Compound **6** was synthesised as described in Ref. 9. $[\alpha]_D^{20}$ −80.5 (c 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.85; H, 5.35; F, 16.92; N, 4.16; S, 9.48.

4.1.7. (2*S*)-2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (7). Compound **7** was synthesised following the same procedure as described for **6** and starting from the commercially available reagent (2*S*)-2-(4-isobutylphenyl)propionic acid. $[\alpha]_D^{20}$ +79 (c 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.87; H, 5.35; F, 16.91; N, 4.17; S, 9.48.

4.2. General procedure for the preparation of amides

The selected amine (1.0 mmol) was added to a solution of *N*-acylmethanesulfonamide (compounds **1–4**, 1.0 mmol) or *N*-acyltrifluoromethanesulfonamide (compounds **5–7**, 1.0 mmol) in toluene (5 mL). The resulting solution was refluxed for 8 h. After cooling to room temperature, toluene was removed under reduced pressure and the residue diluted with CH_2Cl_2 (10 mL) and washed with a KH_2PO_4 buffer solution (pH 2.4, 3×10 mL). After drying over Na_2SO_4 the organic phase was evaporated under reduced pressure and pure arylamides were obtained by flash chromatography of the crude residue.

4.2.1. *N*-Butyl-2-(4-isobutylphenyl)-*N*-acetamide (Table 1, entry 4). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 80%; mp 57–58 °C; ^{1}H NMR ($CDCl_3$) δ 7.20–7.05 (m, 4H), 5.30 (br s, 1H, CON*H*), 3.55 (s, 2H), 3.21–3.14 (m, 2H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.44–1.35 (m, 2H), 1.25 (m, 2H), 0.97–0.85 (m, 9H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 247 (M$^+$). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.70; H, 10.15; N, 5.68.

4.2.2. *N*-Benzyl-2-(4-isobutylphenyl)acetamide (Table 2, entry 2). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 90%; mp 100–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 4H), 7.15–7.05 (m, 5H), 5.60 (br s, 1H, CON*H*), 4.40 (d, J=5 Hz, 2H), 3.55 (s, 2H), 2.55 (d, J=7 Hz, 2H), 1.90–1.82 (m, 1H), 0.85 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 281 (M$^+$). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.11; H, 8.19; N, 5.01.

4.2.3. 2-(4-Isobutylphenyl)-*N*-(1-phenylethyl)acetamide (Table 2, entry 4). White solid (eluent mixture $CHCl_3$/CH_3OH 98:2); yield 35%; mp 89–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.20 (m, 4H), 7.18–7.05 (m, 5H), 5.55 (br s, 1H, CON*H*), 5.15–5.04 (m, 1H), 3.50 (s, 2H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.35 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 295 (M$^+$). Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.34; H, 8.49; N, 4.70.

4.2.4. 1-[(4-Isobutylphenyl)acetyl]pyrrolidine (Table 2, entry 5). Colourless oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 40%; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J=7 Hz, 2H), 7.05 (d, J=7 Hz, 2H), 3.63 (s, 2H), 3.49 (t, J=7 Hz, 2H), 3.43 (t, J=7 Hz, 2H), 2.45 (d, J=7 Hz, 2H), 1.70–1.76 (m, 5H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 2950, 1670, 1460; EIMS m/z 245 (M$^+$). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.33; H, 9.48; N, 5.73.

4.2.5. *N*-Butyl-2-(4-isobutylphenyl)-*N*-methylacetamide (Table 2, entry 6). Colourless oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 80%; ^{1}H NMR ($CDCl_3$) δ 7.20–7.05 (m, 4H), 3.55 (s, 2H), 3.15–3.10 (m, 5H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.44–1.35 (m, 2H), 1.30–1.20 (m, 2H), 0.97–0.85 (m, 9H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 261 (M$^+$). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.13; H, 10.39; N, 5.38.

4.2.6. 2-(4-Isobutylphenyl)-*N*-phenylacetamide (Table 3, entry 5). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 70%; mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 4H), 7.15–7.05 (m, 5H), 6.90 (br s, 1H, CON*H*), 3.36 (s, 2H), 2.51 (d, *J*=7 Hz, 2H), 1.90 (m, 1H), 0.93 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 267 (M^+). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.89; H, 7.88; N, 5.27.

4.2.7. Methyl 4-{[(4-isobutylphenyl)acetyl]amino}benzoate (Table 3, entry 6). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); yield 80%; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J*=7 Hz, 2H), 7.50 (d, *J*=7 Hz, 2H), 7.28–7.15 (m, 4H), 3.90 (s, 3H), 3.80 (br s, 1H, CON*H*), 3.65 (s, 2H), 2.55 (d, *J*=7 Hz, 2H), 1.85–1.78 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3300, 2950, 1680, 1460; EIMS *m*/*z* 325 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.83; H, 7.10; N, 4.31.

4.2.8. *N*-(4-Bromophenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 7). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 75%; mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 4H), 7.27–7.12 (m, 4H), 7.00 (br s, 1H, CON*H*), 3.65 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3300, 2950, 1680, 1460; EIMS *m*/*z* 345/347 ([$^{79/81}$Br] M^+). Anal. Calcd for $C_{18}H_{20}BrNO$: C, 62.44; H, 5.82; Br, 23.08; N, 4.05. Found: C, 62.46; H, 5.79; Br, 23.10; N, 4.04.

4.2.9. *N*-(4-Ethoxyphenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 8). Yellow oil (eluent mixture *n*-hexane/EtOAc 85:15); yield 71%; ^{1}H NMR ($CDCl_3$) δ 8.00 (br s, 1H, CON*H*), 7.55 (d, *J*=7 Hz, 2H), 7.10–7.01 (m, 4H), 6.95 (d, *J*=7 Hz, 2H), 3.75 (q, *J*=7 Hz, 2H), 3.65 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.45 (t, *J*=7 Hz, 3H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 311 (M^+). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.15; H, 8.13; N, 4.48.

4.2.10. 2-(4-Isobutylphenyl)-*N*-(2-methylphenyl)acetamide (Table 3, entry 9). White solid, (eluent mixture *n*-hexane/EtOAc 9:1); yield 59%; mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J*=7 Hz, 1H), 7.23–7.00 (m, 7H), 6.85 (br s, 1H, CON*H*), 3.70 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.85–1.80 (m, 4H), 0.85 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 281 (M^+). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.12; H, 8.21; N, 4.95.

4.2.11. *N*-(2-Chlorophenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 10). Yellow oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 37%; ^{1}H NMR ($CDCl_3$) δ 8.05 (br s, 1H, CON*H*), 7.58 (d, *J*=7 Hz, 1H), 7.35 (d, *J*=7 Hz, 1H), 7.25–7.00 (m, 6H), 3.68 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 300/302 ([$^{35/37}$Cl] M^+). Anal. Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; Cl, 11.75; N, 4.64. Found: C, 71.63; H, 6.68; Cl, 11.75; N, 4.64.

4.2.12. 2-(4-Isobutylphenyl)-*N*-methyl-*N*-phenylacetamide (Table 3, entry 13). Light brown oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 30%; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 3H), 7.15 (d, *J*=7 Hz, 2H), 7.05–6.90 (m, 4H), 3.45 (s, 2H), 3.30 (s, 3H), 2.42 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.85 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 281 (M^+). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.20; N, 5.01.

4.2.13. 2-(4-Isobutylphenyl)-*N*-[2-(propylamino)ethyl]-acetamide (Table 4, compound A). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.18–7.12 (m, 4H), 6.05 (br s, 1H, CON*H*), 3.50 (s, 2H), 3.30–3.25 (m, 2H), 2.74–2.66 (m, 2H), 2.45–2.52 (m, 4H), 1.92–1.83 (m, 1H), 1.62 (br s, 1H, N*H*), 1.48–1.30 (m, 2H), 0.95–0.80 (m, 9H); IR (neat, cm^{-1}) ν 3360, 3060, 1914, 1643, 1456, 1233, 650; ESIMS *m*/*z* 276 (M^+). Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.88; H, 10.23; N, 10.15.

4.2.14. *N*-(2-Aminoethyl)-2-(4-isobutylphenyl)-*N*-propylacetamide (Table 4, compound B). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.02 (m, 4H), 3.50 (t, *J*=7 Hz, 2H), 3.45 (s, 2H), 3.35 (m, 2H), 3.20 (t, *J*=7 Hz, 2H), 2.50 (d, *J*=7 Hz, 2H), 2.05 (br s, 2H, NH_2), 1.85 (m, 1H), 1.50 (m, 2H), 1.02–0.92 (m, 9H); IR (neat, cm^{-1}) ν 3345, 2950, 1670, 1460; ESIMS *m*/*z* 276 (M^+). Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.89; H, 10.24; N, 10.09.

4.2.15. 2-(4-Isobutylbenzyl)-1-propyl-4,5-dihydro-1*H*-imidazole (compound C). Colourless oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.19 (d, *J*=7 Hz, 2H), 7.09 (d, *J*=7 Hz, 2H), 3.78 (t, *J*=10 Hz, 2H), 3.62 (s, 2H), 3.35 (t, *J*=10 Hz, 2H), 2.97 (t, *J*=7 Hz, 2H), 2.48 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.35–1.28 (m, *J*=7 Hz, 2H), 0.90 (d, *J*=7 Hz, 6H), 0.75 (t, *J*=7 Hz, 3H); IR (neat, cm^{-1}) ν 2957, 1605, 1460, 1125; ESIMS *m*/*z* 258 (M^+). Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 79.05; H, 10.12; N, 10.83.

4.2.16. (2*R*)-2-(4-Isobutylphenyl)-*N*-[(1*R*)-1-phenylethyl]propanamide (Table 5, entry 1). White solid (eluent mixture *n*-hexane/EtOAc 7:3); mp 107–109 °C; $[\alpha]_D^{20}$ +22.6 (*c* 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.30–7.05 (m, 9H), 5.50 (br s, *J*=7 Hz, 1H, CON*H*), 5.14–5.07 (m, 1H), 3.55 (q, *J*=7 Hz, 1H), 2.47 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.51 (d, *J*=7 Hz, 3H), 1.39 (d, *J*=7 Hz, 3H), 0.91 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3286, 2950, 2864, 1642, 1540, 1447; EIMS *m*/*z* 309 (M^+). Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.55; H, 8.77; N, 4.51.

4.2.17. (2*S*)-2-(4-Isobutylphenyl)-*N*-[(1*S*)-1-phenylethyl]-propanamide (Table 5, entry 4). White solid (eluent mixture *n*-hexane/EtOAc 7:3); mp 108–110 °C; $[\alpha]_D^{20}$ −23.2 (*c* 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.30–7.05 (m, 9H), 5.50 (br s, *J*=7 Hz, 1H, CON*H*), 5.14–5.07 (m, 1H), 3.55 (q, *J*=7 Hz, 1H), 2.47 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.51 (d, *J*=7 Hz, 3H), 1.39 (d, *J*=7 Hz, 3H), 0.91 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3286, 2950, 2864, 1642, 1540, 1447; EIMS *m*/*z* 309 (M^+). Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.52; H, 8.81; N, 4.50.

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Unexpected formation of *N*,*N*-disubstituted formamidines from aromatic amines, formamides and trifluoroacetic anhydride

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Abstract—An intriguing selectivity towards the formation of the formamidine was observed upon the reaction of an amine with sodium hydride and trifluoroacetic anhydride in dimethyl formamide. Various aromatic amines were reacted with a series of *N*,*N*-disubstituted formamides as a solvent under the influence of trifluoroacetic anhydride to thoroughly probe this behaviour. A trend in selectivity is discussed and a proposed mechanism for the reaction is also presented.

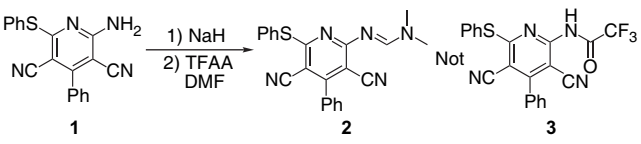
1. Introduction

The preparation of nitrogen-containing compounds such as amidines has been studied extensively owing to their importance as biologically active compounds.[1,2] Classes of compounds containing amidine substructures have found additional application as building blocks in polymer synthesis,[3] bleaching agents for paper,[4] ultraviolet light absorbers[5] and ligands in transition metal catalysis.[6] In the field of organic synthesis, formamidines serve as protecting groups for primary amines,[7] support linkers in solid phase synthesis[8] and auxiliaries in asymmetric synthesis.[9]

In the literature, a great many procedures are reported for the condensation of *N*,*N*-dialkylformamides with primary amines employing $POCl_3$, P_2O_5, PCl_5, $(COCl)_2$, $SOCl_2$ and acyl chlorides as coupling agents.[10–13] However, most of these methods have drawbacks such as low yields,[11] long reaction times,[12] harsh reaction conditions and difficulties in work up.[13] *N*,*N*-Dialkylformamide dimethylacetals are also utilised as the main reagent, in dimethylformamide (DMF), for the direct protection of primary aliphatic and aromatic amines under mild conditions.[14] Recently, Cai and co-workers reported the use of a set of sulfonylchloride coupling agents for DMF, which provided a one-step procedure for the preparation of formamidines from primary amines.[15] Delarue and Sergheraert have found that PyBOP, a well known reagent in peptide synthesis, is a convenient coupling reagent in the synthesis of formamidines from aliphatic and aromatic primary amines and DMF.[11] In this paper, we wish to add to this substantial known body of work a novel, convenient and highly efficient synthesis of a variety of formamidines using trifluoroacetic anhydride (TFAA) as the coupling agent.

2. Results and discussion

During our recent studies on the modification of the amino group present in 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1**,[16] we observed that treatment of this amine with sodium hydride (*CAUTION* reacts violently with a proton source and can ignite spontaneously) in DMF, followed by addition of an equimolar amount of TFAA, provided the corresponding *N*′-(3,5-dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethylformamidine **2**, instead of the expected *N*-(3,5-dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-2,2,2-trifluoroacetamide **3**, in high yield (Scheme 1).



1 2 3

Scheme 1.

We found that the optimal reaction protocol was to add sodium hydride to a solution of the amine in a minimum volume of anhydrous DMF at room temperature, followed by addition of an equimolar amount of TFAA. Once the

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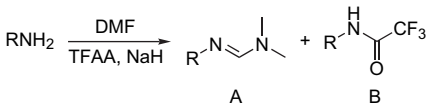
Table 1. Reaction of aromatic and aliphatic amines with DMF in the presence of TFAA



Entry	R	Molar ratio (A:B)[a]	Yield (%)
1	Phenyl	1:5	100
2	Pyrid-2-yl	1:4	100
3	3-Nitropyrid-2-yl	10:7	96
4	4-Methoxyphenyl	B only	100
5	6-Methoxypyrimidin-4-yl	B only	93
6	*C*-Pyridin-3-ylmethyl	B only	95

[a] Molar ratio determined from ^{1}H NMR data.

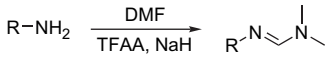
reaction was complete, cold water was added effecting precipitation of the product. Using this protocol the *N*,*N*-dimethylformamidine **2** was isolated in 95–99% yield with >95% purity.

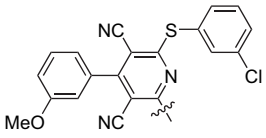
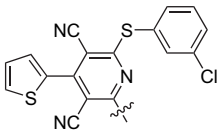
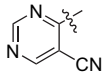
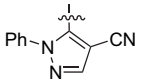
In an attempt to see whether these conditions were applicable to a broader range of starting materials, reactions of a variety of aryl and alkyl amines with DMF under similar conditions were examined (Table 1). The reactions either afforded a mixture of the corresponding formamidine together with the amide (entries 1–3), or gave only the amide (entries 4–6). For example, the reaction of aniline gave a 1:5 mixture of the *N*,*N*-dimethyl-*N*′-phenylformamidine and the *N*-phenyltrifluoroacetamide, respectively (entry 1). When using 2-aminopyridine, a mixture of *N*,*N*-dimethyl-*N*′-2-pyridinylformamidine and 2,2,2-trifluoro-*N*-2-pyridinylacetamide was produced in a 1:4 ratio, respectively (entry 2). However, the use of 2-amino-3-nitropyridine showed the presence of an electron-withdrawing group on the aromatic ring promoted formamidine formation, as a 10:7 ratio of the *N*′-(3-nitropyridinyl)-*N*,*N*-dimethylformamidine/*N*-(3-nitropyridinyl)-trifluoroacetamide mixture was obtained in this case (entry 3). Interestingly, the presence of an electron-donating group bound to the aromatic ring was found to endorse the formation of amide, as in the case of 4-methoxyaniline and 4-amino-6-methoxypyrimidine (entries 4 and 5). 3-(Aminomethyl)-pyridine was also converted into the trifluoroacetamide in excellent yield under identical conditions (entry 6).

To investigate the role of the 3-cyano functionality of amine **1** upon the observed selectivity (Scheme 1), a series of amines having similar structural features were reacted with DMF under optimised conditions (Table 2). In all cases, the corresponding *N*,*N*-dimethyformamidines were obtained in high yield with no detectable formation of the *N*-trifluoroacetamides. The reactions of 4-aminopyrimidine-5-carbonitrile and 5-amino-1-phenylpyrazole-4-carbonitrile (entries 3 and 4), not possessing the pyridine-3,5-dicarbonitrile core, also resulted in exclusive formamidine formation.

In an attempt to broaden the scope of this condensation reaction, we supposed that condensation of amines with various *N*,*N*-dialkylformamides and *N*-alkyl-*N*-arylformamides would also give rise to a range of *N*,*N*-disubstituted amidines (Table 3). Reaction of **1** with *N*,*N*-diethylformamide, pyrrolidine-1-carbaldehyde and piperidine-1-carbaldehyde, proceeded efficiently to afford the corresponding formamidines in excellent yields (entries 2–4). For the more viscous *N*-methyl-*N*-phenyl formamide the reaction also proceeded, producing the corresponding formamidine in satisfactory yield (entry 5).

Table 2. Condensation of aromatic amines with DMF using TFAA

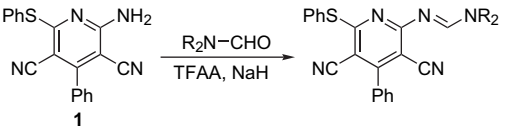


Entry	R	Yield (%)
1		96
2		95
3		99
4		82

The amino group of analogues of **1** also underwent coupling with pyrrolidine-1-carbaldehyde and piperidine-1-carboxaldehyde by this procedure, providing the desired formamidines in good to excellent yields (Table 4, entries 1–4). 4-Aminopyrimidine-5-carbonitrile reacted with *N*,*N*-diethylformamide and pyrrolidine-1-carbaldehyde to give the corresponding formamidines in 77 and 78% yield (Table 5, entries 1 and 2). Additionally, reaction of 5-amino-1-phenylpyrazole-4-carbonitrile with pyrolidine-1-carboxaldehyde furnished the corresponding formamidine in 73% yield (Table 5, entry 4).

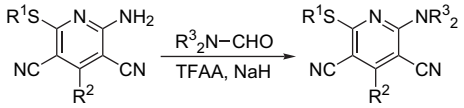
There is considerable experimental evidence indicating that the electrophilic intermediate formed in situ may be attacked by neutral amines as well as by the deprotonated forms. Therefore, we expected that free amines would condense directly with formamides in the presence of TFAA, without the need for deprotonation by NaH, to afford the corresponding

Table 3. Synthesis of formamidines by condensing **1** with various formamides



Entry	R	Yield (%)
1	Me	95–99
2	Et	93
3	–$(CH_2)_4$–	97
4	–$(CH_2)_5$–	90
5	PhMe	67

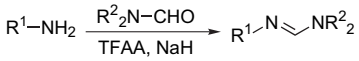
Table 4. Condensation of aromatic amines with various formamides using TFAA

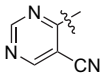
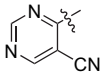
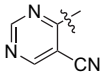
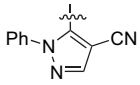


Entry	R^1	R^2	R^3	Yield (%)
1	3-Chlorophenyl	3-Methoxyphenyl	$-(CH_2)_4-$	94
2	3-Chlorophenyl	3-Methoxyphenyl	$-(CH_2)_5-$	77
3	3-Chlorophenyl	Thiophenyl	$-(CH_2)_4-$	93
4	Benzyl	Thiophenyl	$-(CH_2)_4-$	94
5	Phenyl	Phenyl	Methyl	96[a]
6	Benzyl	Thiophenyl	Methyl	91[a]
7	*p*-Benzoic acid methyl ester	*p*-Benzoic acid methyl ester	Methyl	86[a]
8	*p*-Benzoic acid methyl ester	*p*-Benzoic acid methyl ester	$-(CH_2)_4-$	78[a]

[a] Reaction without NaH.

Table 5. Condensation of aromatic amines with various formamides using TFAA



Entry	R^1	R^2	Yield (%)
1		Ethyl	77
2		$-(CH_2)_4-$	78
3		Methyl	79[a]
4		$-(CH_2)_4-$	73

[a] Reaction without NaH.

formamidines preferentially. Examination of the reaction of a variety of amines under such conditions proved this to be correct. We initially examined the reaction of **1** with DMF, in the absence of NaH, as a model system. When the amine (1 equiv) was treated with TFAA (1 equiv) at room temperature in DMF for 20 min, the corresponding *N*,*N*-dimethylformamidine was produced in excellent yield (Table 4, entry 5). The reaction of three other analogues of **1** with DMF under identical conditions afforded the expected formamidines in good to excellent yields (Table 4, entries 6–8). Interestingly, the presence of methyl ester groups in the substrates was found to be well-tolerated under these conditions. 4-Aminopyrimidine-5-carbonitrile could also be converted smoothly into the *N*,*N*-dimethylformamidine using these conditions in good yield (Table 5, entry 3). In all cases, the reaction proceeded without complication, typically taking 20 min to reach completion and producing no detectable amount of *N*-trifluoroacetamide.

These experimental results raise intriguing questions regarding the reaction mechanism. There is evidence that an amide is the only product formed in the reaction of aromatic amines with TFAA in DMF,[7] and the Vilsmeier–Haack like intermediate is the only key intermediate formed in the amidination of certain aromatic amines in DMF using PyBOP[11] and sulfonylchloride[15] coupling agents. It was decided therefore to carry out ^{1}H and ^{13}C NMR spectroscopic experiments to investigate the course of the reaction.

Inspection of the ^{1}H NMR spectrum of DMF in chloroform revealed three sharp singlets at δ=2.60, 2.80 and 7.80 ppm. These signals were due to the two methyl groups attached to the nitrogen atom and the formamide proton, respectively (Fig. 1). After an equimolar amount of TFAA was added, the peaks at δ_H=2.60 and δ_H=2.80 ppm were observed to have begun to merge together. When 2 equiv of TFAA were added, the methyl groups showed as a broad singlet at δ_H=2.65 ppm. It was very interesting to note however, that when this simple investigation was repeated with an equimolar amount or excess of Ac_2O or TFA the three sharp singlets at δ_H=2.60, 2.80 and 7.80 ppm remained unchanged (spectra not shown). Similarly, when observing the ^{13}C NMR spectrum of DMF in chloroform, three sharp peaks at δ_C=30.8, 35.9 and 161.9 ppm were observed (Fig. 2). These signals are due to the two methyl groups attached to the nitrogen atom and formamide carbon, respectively. Again, when TFAA was added, the two peaks corresponding to the methyl carbons broadened and appeared at δ_C=30.5 and 35.7 ppm. From these results it can be concluded that addition of TFAA makes the methyl groups equivalent, indicating an increase in rotational freedom.

Based on experimental results and the ^{1}H and ^{13}C NMR spectroscopic studies reported above, a mechanism for this reaction is proposed (Scheme 2). The condensation seemingly involves in situ generation of a Vilsmeier–Haack like intermediate **4**, which is in equilibrium with the

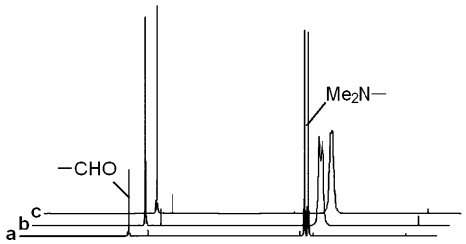


Figure 1. Changes in ^{1}H NMR spectra of (a) DMF, (b) DMF+TFAA (1:1) and (c) DMF+TFAA (1:2) in $CDCl_3$ at room temperature.

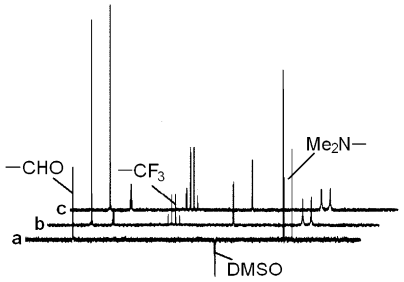
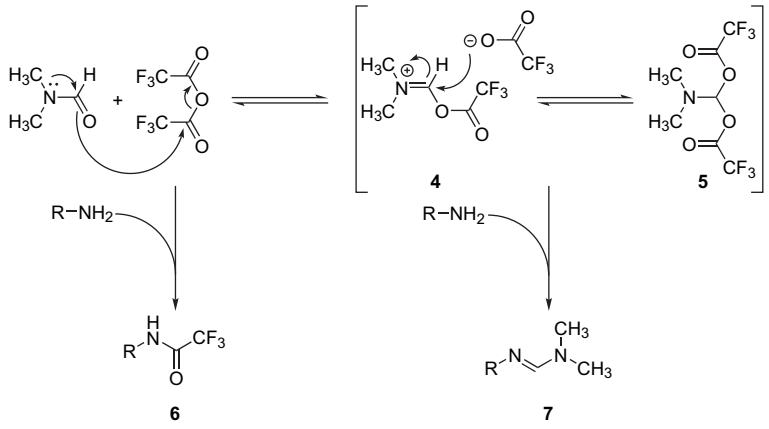


Figure 2. Changes in ^{13}C NMR spectra of (a) DMF, (b) DMF+TFAA (1:1) and (c) DMF+TFAA (1:2) in $CDCl_3$ at room temperature.



Scheme 2.

corresponding trifluoroacetyl acetal intermediate **5**, resulting from attack by a trifluoroacetic anion.[15] This would allow the two methyl groups to equilibrate through free rotation, as observed in the NMR studies. Condensation of these intermediates with an amine gives rise to a single-step synthesis of the corresponding trifluoroacetamide **6**, formamidine **7**, or a mixture of both. As found, the character of the amine nitrogen as well as the nature of the substituents on the body of the amine has a marked effect on the outcome of the reaction. Electron-withdrawing groups, especially carbonitriles in the *ortho*-position, yield amidines preferentially.

3. Conclusion

We have described a simple, convenient and efficient preparation of formamidines from various primary aromatic amines and a series of *N*,*N*-disubstituted formamides in the presence of TFAA. Advantages of the reactions presented include operational simplicity, ease of product isolation, elimination of the use of highly toxic reagents, and excellent product yields. Both the presence of the electron-withdrawing cyano group at the *ortho*-position of the amine and a nitrogen in the aromatic system have a marked effect on the outcome of the final product. However, it appears that DMF is not the solvent of choice if the trifluoroacetamide is the desired product.

4. Experimental

4.1. General details

Melting points were measured with a Bibby-Sterilin SMP10 melting point apparatus and are uncorrected. Infrared analyses were recorded using neat compounds on a Perkin–Elmer Spectrum RX1 FT-IR system equipped with a Dura Sampl*IR* II™—diamond ATR solid sample unit, measuring from 4000 to 400 cm^{-1}. Accurate mass and nominal mass measurements were measured using Waters-Micromass LCT electrospray mass spectrometer. ^1H and ^{13}C NMR analyses were performed on a Bruker AC-250 instrument in DMSO-d_6 or $CDCl_3$; chemical shifts are quoted in parts per million relative to TMS, with coupling constants quoted in Hertz. Analytical thin layer chromatography was performed on pre-coated Macherey–Nagel glass backed silica gel 60 plates (0.25 mm layer), or Merck silica gel 60 F_{254} aluminium backed plates, and visualised by ultraviolet light and potassium permanganate, or ninhydrin stains as appropriate. Commercially available reagents (including dry solvents) were used as received without further purification. Pyridine dicarbonitriles were prepared according to previously reported procedures.[16] All reactions were carried out under a nitrogen atmosphere. Isolated compounds were >95% pure by ^1H NMR analysis unless otherwise stated.

4.2. Synthesis of formamidines

4.2.1. *N*′-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (2). To a solution of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1** (50.0 mg, 0.15 mmol) in dry DMF (1.0 mL) was cautiously added sodium hydride (*CAUTION* reacts violently with a proton source and can ignite spontaneously) (7.4 mg, 0.31 mmol) in portions under nitrogen at room temperature. After 1 h stirring at room temperature, trifluoroacetic anhydride (50.0 mg, 0.24 mmol) was added, and the reaction was stirred at room temperature for 10 min until the reaction was deemed complete by TLC. The reaction mixture was poured into cold water (10 mL) and stirred for 5 min, the suspension formed was filtered and the crude product washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave **2** (55.6 mg, 95% yield) as white powder; mp 216–218 °C; IR (neat) ν_{max} 2217 (s), 1624 (s), 1579 (s), 1525, 1513, 1488, 1140, 1422, 1369, 1299, 1250, 1208, 1135, 1110, 1014, 997, 916, 863, 809 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.95 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 7.40–7.60 (m, 10H, ArH), 8.00 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 35.3, 41.3, 95.6, 95.6, 115.2, 115.7, 128.3, 128.6 (2C), 128.8 (2C), 129.0 (2C), 129.5, 130.5, 133.7 (2C), 136.4, 136.4, 158.2, 163.4, 165.0 ppm; ESMS *m*/*z*: 384 $(M+H)^+$; HRMS found, 384.1283, $C_{22}H_{18}N_5S$ requires 384.1284.

4.2.2. Reaction of aniline (Table 1, entry 1). Upon completion, the reaction mixture was concentrated under reduced pressure. The resultant oily residue was taken up in chloroform, filtered and all volatiles then removed under reduced pressure. Drying in vacuo gave a mixture of *N*,*N*-dimethyl-

N′-phenyl-formamidine and 2,2,2-trifluoro-*N*-phenyl-acetamide (745.8 mg, 1:5, 100%) as a white solid. *N,N-dimethyl-N′-phenyl-formamidine*: mp 87–90 °C; IR (neat) ν_{max} 3316, 3206, 1694, 1601, 1547, 1497, 1451, 1347, 1305, 1283, 1235, 1143, 1070, 1030, 1003, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.90 (s, 3H, NCH_3), 2.99 (s, 3H, NCH_3), 7.20–7.36 (m, 5H, ArH), 8.01 (s, 1H, N═CHN) ppm; ESMS *m/z*: 149 $(M+H)^+$; HRMS found, 149.1074, $C_9H_{12}N_2$ requires 149.1079. *2,2,2-Trifluoro-N-phenyl-acetamide*: mp 87–90 °C (lit.[17] for acetamide 88–89 °C); IR (neat) ν_{max} 3317, 1700, 1601, 1548, 1497, 1451, 1347, 1307, 1283, 1233, 1169, 1141, 1078, 1030, 1003 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.20–7.36 (m, 3H, ArH), 7.55 (m, 2H, ArH), 8.77 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.2 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.5, 118.10, 121.0, 125.5, 128.9, 129.3, 136.3, 154.1 ppm; EIMS *m/z*: 189 $(M)^+$; HRMS found, 189.041059, $C_8H_6F_3NO$ requires 189.040149.

4.2.3. Reaction of pyridin-2-yl amine (Table 1, entry 2). A mixture of *N,N*-dimethyl-*N*′-pyridin-2-yl-formamidine and 2,2,2-trifluoro-*N*-pyridin-2-yl-acetamide (136.0 mg, 1:4, 100%) was obtained as a colourless oil. *N,N-Dimethyl-N′-pyridin-2-yl-formamidine*: IR (neat) ν_{max} 3331, 3078, 2723, 1670, 1638, 1551, 1486, 1434, 1383, 1329, 1256, 1196, 1176, 1125, 989, 939 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.85 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 6.69 (m, 1H, ArH), 6.79 (m, 1H, ArH), 7.68 (m, 2H, ArH), 8.98 (s, 1H, N═CHN) ppm; ESMS *m/z*: 150 $(M+H)^+$; HRMS found, 150.1034, $C_8H_{12}N_3$ requires 150.1031. *2,2,2-Trifluoro-N-pyridin-2-yl-acetamide*: IR (neat) ν_{max} 3331, 3078, 2723, 1670, 1638, 1551, 1486, 1434, 1383, 1329, 1256, 1196, 1176, 1125, 989, 939 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 1H, ArH), 7.95 (m, 1H, ArH), 8.26 (m, 1H, ArH), 8.35 (d, 1H, *J*=11.2 Hz, ArH), 13.49 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.9, 113.4, 135.90, 143.8, 143.8, 154.5, 159.6 ppm; ESMS *m/z*: 191 $(M+H)^+$; HRMS found, 191.0435, $C_8H_6F_3N_2O$ requires 191.0432.

4.2.4. Reaction of 3-nitro-pyridin-2-yl amine (Table 1, entry 3). A mixture of *N,N*-dimethyl-*N*′-(3-nitro-pyridin-2-yl)-formamidine and 2,2,2-trifluoro-*N*-(3-nitro-pyridin-2-yl)-acetamide (94.3 mg, 10:7, 96% yield) was obtained as a yellowish oil. *N,N-Dimethyl-N′-(3-nitro-pyridin-2-yl)-formamidine*: IR (neat) ν_{max} 3305, 3086, 2843, 1691, 1602, 1545, 1511, 1466, 1444, 1349, 1289, 1223, 1150, 1110, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.01 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 7.07 (m, 1H, ArH), 7.65 (m, 1H, ArH), 8.50 (m, 1H, ArH), 8.51 (s, 1H, N═CHN) ppm; ESMS *m/z*: 195 $(M+H)^+$; HRMS found, 195.0873, $C_8H_{10}N_4O_2$ requires 195.0882. *2,2,2-Trifluoro-N-(3-nitro-pyridin-2-yl)-acetamide*: ^1H NMR (250 MHz, $CDCl_3$) δ 8.08 (m, 1H, ArH), 8.37 (m, 1H, ArH), 8.61 (d, 1H, *J*=11.0 Hz, ArH), 13.50 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (235 MHz, $CDCl_3$) δ 123.6, 134.9, 140.3, 140.7, 152.8, 153.5, 158.1 ppm; ESMS *m/z*: 236 $(M+H)^+$; HRMS found, 236.0288, $C_7H_5F_3N_3O_3$ requires 236.0283.

4.2.5. 2,2,2-Trifluoro-*N*-(4-methoxy-phenyl)-acetamide (Table 1, entry 4). Obtained as white crystals (171.7 mg, 100%); mp 112–114 °C (lit.,[18] 113–115 °C); IR (neat) ν_{max} 3305, 3086, 2843, 1691, 1602, 1545, 1511, 1466, 1444, 1349, 1289, 1223, 1150, 1110, 1022 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 6.88 (d, 2H, *J*=9.16 Hz, ArH), 7.45 (d, 2H, *J*=9.16 Hz, ArH), 7.92 (br s, 1H, $NHCOCF_3$) ppm (lit.[19] (400 MHz, $CDCl_3$) 3.80 (s, 3H, OCH_3), 6.90 (d, 2H, *J*=8.8 Hz, ArH), 7.46 (d, 2H, *J*=8.8 Hz, ArH), 7.87 (br s, 1H, $NHCOCF_3$)) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.4, 113.5, 114.4 (2C), 122.3 (2C), 127.95, 155.0, 157.8 ppm; EIMS *m/z*: 219 $(M)^+$; HRMS found, 219.050654, $C_9H_8F_3NO_2$ requires 219.050713.

4.2.6. 2,2,2-Trifluoro-*N*-(6-methoxy-pyrimidin-4-yl)-acetamide (Table 1, entry 5). Obtained as a yellowish solid (193.0 mg, 93% yield); mp 121–122 °C; IR (neat) ν_{max} 3441, 3388, 3296, 3148, 3011, 1636, 1589, 1544, 1493, 1468, 1410, 1364, 1297, 1275, 1212, 1029, 988 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.99 (s, 3H, OCH_3), 7.55 (s, 1H, ArH), 8.51 (s, 1H, ArH), 10.18 (br s, 1H, $NHCOCF_3$) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 54.5, 97.0, 107.5, 112.8, 117.4, 155.9, 171.8 ppm; ESMS *m/z*: 222 $(M+H)^+$; HRMS found, 222.0499, $C_7H_6F_3N_3O_2$ requires 222.0481.

4.2.7. 2,2,2-Trifluoro-*N*-pyridin-3-ylmethyl-acetamide (Table 1, entry 6). Obtained as a white solid (113.4 mg, 95%); mp 110–111 °C; IR (neat) ν_{max} 3299, 3171, 3008, 2854, 1706, 1559, 1480, 1432, 1367, 1206, 1182, 1146, 1037, 975 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.50 (d, 2H, *J*=6.1 Hz, $ArCH_2$), 7.28 (m, 1H, ArH), 7.66 (m, 1H, ArH), 8.29 (br s, 1H, $NHCOCF_3$), 8.42 (s, 1H, ArH), 8.44 (m, 1H, ArH) ppm; ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.1 ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.2, 113.5, 123.9, 132.3, 136.1, 148.8, 141.1, 157.9 ppm; EIMS *m/z*: 204 $(M)^+$; HRMS found, 204.050552, $C_8H_7F_3N_2O$ requires 204.051048.

4.2.8. *N*′-[6-(3-Chloro-phenylsulfanyl)-3,5-dicyano-4-(3-methoxy-phenyl)-pyridin-2-yl]-*N,N*-dimethyl-formamidine (Table 2, entry 1). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a white powder (95.0 mg, 96%); mp 212–214 °C; IR (neat) ν_{max} 3605, 3531, 3076, 2924, 2222, 2206, 1625, 1602, 1578, 1519, 1488, 1456, 1415, 1372, 1327, 1308, 1260, 1228, 1205, 1187, 1170, 1132, 1106, 1038, 1018, 995, 926 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.05 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 7.65–6.95 (m, 8H, ArH), 8.16 (s, 1H, N═CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 35.4, 41.4, 55.4, 96.5, 97.1, 113.8, 115.0, 115.5, 116.6, 120.8, 129.6, 130.0, 130.0, 130.2, 133.8, 134.1, 134.6, 136.2, 157.9, 158.8 (2C), 163.4, 165.1 ppm; ESMS *m/z*: 448 $(M+H)^+$; HRMS found, 448.1005, $C_{23}H_{18}ClN_5OS$ requires 448.0999.

4.2.9. *N*′-[6-(3-Chloro-phenylsulfanyl)-3,5-dicyano-4-thiophen-2-yl-pyridin-2-yl]-*N,N*-dimethyl-formamidine (Table 2, entry 2). Yellowish powder (308.0 mg, 95%); mp 152–161 °C; IR (neat) ν_{max} 3322, 3082, 2918, 2207 (s),

1617, 1495, 1445, 1417, 1398, 1368, 1349, 1310, 1287, 1245, 1223, 1169, 1123, 1099, 1084, 1055, 1029, 994, 910 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.04 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3), 7.28–7.98 (m, 7H, ArH), 8.07 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 34.9, 41.2, 101.1, 106.8 (2C), 115.1, 115.5, 127.9, 129.1, 129.9, 130.9, 131.4, 132.5, 133.3, 134.2, 135.1, 158.0, 163.2, 164.6 ppm; ESMS *m/z*: 424 $(M+H)^+$; HRMS found, 424.0450, $C_{20}H_{15}N_5SCl$ requires 424.0457.

4.2.10. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-dimethyl-formamidine (Table 2, entry 3). Upon completion the reaction mixture was concentrated under reduced pressure, before ice-water (10 mL) was added and the resultant mixture extracted with EtOAc (2×10 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. Drying the solid in vacuo overnight gave the product as pale yellowish crystals (86.9 mg, 99%); mp 128–132 °C; IR (neat) ν_{max} 3269, 3099, 2869, 2811, 27.05, 2224, 1668, 1585, 1549, 1505, 1412, 1364, 1309, 1236, 1202, 1136, 1037, 946, 913 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.15 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 8.80 (s, 1H, ArH), 8.85 (s, 1H, ArH), 8.90 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 34.9, 41.0, 81.0, 100.0, 106.8, 115.6, 157.9, 161.3 ppm; ESMS *m/z*: 176 $(M+H)^+$; HRMS found, 176.0937, $C_8H_9N_5$ requires 176.0936.

4.2.11. 1-Phenyl-5-[(pyrrolidin-1-ylmethylene)-amino]-1*H*-pyrazole-4-carbonitrile (Table 2, entry 4). White solid (104.0 mg, 78% yield); mp 156 °C; IR (neat) ν_{max} 3317, 3104, 3049, 2967, 2872, 2211, 1638, 1609, 1562, 1530, 1502, 1492, 1478, 1455, 1416, 1385, 1325, 1252, 1200, 1174, 1063, 959, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95 (m, 4H, NCH_2CH_2), 3.45 (t, 2H, *J*=9.5 Hz, NCH_2), 3.55 (t, 2H, *J*=9.5 Hz, NCH_2), 7.25–7.90 (m, 6H, ArH), 8.41 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.3, 25.1, 45.8, 49.2, 116.2, 123.7, 123.9, 126.9, 128.4, 129.5, 129.9, 141.2, 141.8, 152.5, 154.5 ppm; EIMS *m/z*: 266 $(M+H)^+$; HRMS found, 266.1394, $C_{15}H_{17}N_5$ requires 266.1406.

4.2.12. *N′*-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-diethyl formamidine (Table 3, entry 2). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a white powder (139.7 mg, 93%); mp 213–215 °C; IR (neat) ν_{max} 3361, 2932, 2748, 2688, 2448, 2270, 2210 (s), 1782, 1720, 1614, 1581, 1537, 1514, 1487, 1451, 1360, 1326, 1255, 1217, 1171, 1121, 1051, 1035, 1018, 997 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (2t, 6H, *J*=8.0 Hz, $N(CH_2CH_3)_2$), 3.25 (q, 2H, *J*=8.0 Hz, NCH_2CH_3); 3.50 (q, 2H, *J*=8.0 Hz, NCH_2CH_3); 7.45–7.65 (m, 10H, ArH), 8.05 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.0, 14.4, 38.5, 40.9, 46.7, 75.0, 98.5, 99.0, 112.6, 115.1, 115.4, 125.0, 127.0, 128.5, 128.7, 129.3, 129.9, 130.3, 133.8, 136.0, 157.1, 158.5, 163.1, 165.1 ppm; ESMS *m/z*: 412 $(M+H)^+$; HRMS found, 412.1606, $C_{24}H_{22}ClN_5S$ requires 412.1596.

4.2.13. 4-Phenyl-2-phenylsulfanyl-6-[(pyrrolidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 3, entry 3). Pale yellowish powder (123.0 mg, 97%); mp 228–231 °C; IR (neat) ν_{max} 3056, 2965, 2872, 2350, 2340, 2205, 1612, 1578, 1514, 1489, 1450, 1408, 1370, 1328, 1305, 1247, 1220, 1183, 1157, 1111, 1031, 1010, 986, 963 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.85 (t, 4H, *J*=7.5 Hz, CH_2CH_2), 3.50 (t, 4H, *J*=7.5 Hz, NCH_2), 7.55 (m, 10H, ArH), 8.15 (s, 1H, N=CH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.8, 46.5, 49.7, 97.7 (2C), 107.4, 115.3, 115.8, 128.3, 128.6 (2C), 128.8 (2C), 128.9, 129.4, 130.5, 133.7, 136.3 (2C), 154.8, 158.8, 163.4, 166.3 ppm; ESMS *m/z*: 410 $(M+H)^+$; HRMS found, 410.1446, $C_{24}H_{20}N_5O_2S$ requires 410.1439.

4.2.14. 4-Phenyl-2-phenylsulfanyl-6-[(piperidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 3, entry 4). A mixture of two isomers was obtained as a white powder (139.0 mg, 90%); mp 196–197 °C; IR (neat) ν_{max} 3060, 2943, 2856, 2211 (s), 1721, 1664 (s), 1603, 1578, 1517, 1485, 1468, 1435, 1407, 1380, 1358, 1295, 1247, 1223, 1202, 1131, 1111, 1078, 1026, 997, 951, 921, 852 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) major isomer δ 1.65 (m, 6H, $CH_2CH_2CH_2$), 3.15 (t, 2H, *J*=6.4 Hz, NCH_2), 3.75 (t, 2H, *J*=6.4 Hz, NCH_2), 7.50–7.60 (m, 10H, ArH), 8.50 (s, 1H, N=CHN) ppm; (minor isomer) δ 1.60 (m, 6H, $CH_2CH_2CH_2$), 3.27 (t, 2H, *J*=6.4 Hz, NCH_2), 3.50 (t, 2H, *J*=6.4 Hz, NCH_2), 7.50–7.60 (m, 10H, ArH), 8.50 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 24.7, 25.0, 26.6, 40.6, 44.5, 46.8, 52.0, 97.6 (2C), 115.3, 115.8, 128.0, 128.3, 128.6, 128.8, 128.9, 129.4, 130.5, 133.7, 136.4, 136.4, 156.6, 158.8, 163.7, 166.3 ppm; ESMS *m/z*: 424 $(M+H)^+$; HRMS found, 424.1581, $C_{25}H_{22}N_5S$ requires 424.1596.

4.2.15. *N′*-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*-methyl-*N*-phenyl-formamidine (Table 3, entry 5). Yellowish solid (91.6 mg, 68%); mp 245–247 °C; IR (neat) ν_{max} 3051, 2216 (s), 1621, 1606 (s), 1584, 1546, 1515, 1488, 1441, 1419, 1349, 1309, 1283, 1252, 1211, 1117, 1039, 1017, 998, 979, 912, 823, 800, 790, 761 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 3H, NCH_3), 7.15–7.60 (m, 15H, ArH), 8.55 (s, 1H, N=CHN) ppm; ^{13}C NMR (250 MHz, $CDCl_3$) δ 15.2, 35.2, 65.8, 98.8, 98.9, 114.9, 115.5, 121.0, 126.5, 127.7, 128.6, 128.7, 128.9, 129.0, 129.2, 129.3, 129.5, 129.6, 129.9, 130.7, 130.9, 133.4, 135.7, 136.3, 143.4, 156.7, 163.3 ppm; ESMS *m/z*: 468 $(M+Na)^+$; HRMS found, 468.1240, $C_{27}H_{19}N_5SNa$ requires 468.1259.

4.2.16. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-diethyl-formamidine (Table 5, entry 1). Upon completion the reaction mixture was concentrated under reduced pressure, before ice-water (10 mL) was added and the resultant mixture extracted with EtOAc (2×10 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. Drying the solid in vacuo overnight gave the product as yellowish crystals (156.0 mg, 77%); mp 152–154 °C; IR (neat) ν_{max} 3060, 2943, 2211 (s), 1664, 1603 (s), 1517, 1485, 1468, 1380, 1326, 1295, 1247, 1223, 1202, 1131, 1111, 1078, 1026, 997, 951 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (m, 6H, $N(CH_3)_2$), 3.45 (q, 2H, *J*=7.5 Hz, NCH_2), 3.70 (q, 2H, *J*=7.5 Hz, NCH_2), 8.55 (s, 1H, ArH), 8.70 (s, 1H, ArH), 8.80 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.2, 14.4, 41.0, 47.1,

101.6, 115.5, 156.3, 160.8, 167.6 ppm; ESMS *m/z*: 204 $(M+H)^+$; HRMS found, 204.1244, $C_{10}H_{14}N_5$ requires 204.1249.

4.2.17. 4-[(Pyrrolidin-1-ylmethylene)-amino]-pyrimidine-5-carbonitrile (Table 5, entry 2). Yellowish solid (81.4 mg, 78%); mp 164–166 °C; IR (neat) ν_{max} 3276, 3098, 2872, 2705, 2225, 1668, 1586, 1550, 1506, 1412, 1366, 1310, 1236, 1201, 1136, 1037, 946, 914, 833 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85 (m, 4H, CH_2CH_2), 3.60 (t, 2H, J=6.5 Hz, NCH_2), 3.75 (t, 2H, J=6.5 Hz, NCH_2), 8.85 (s, 1H, N=CHN), 8.90 (s, 1H, ArH), 9.04 (s, 1H, ArH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.8, 24.4, 89.8, 99.6, 113.7, 115.3, 155.2, 158.1, 159.2, 166.8 ppm; ESMS *m/z*: 202 $(M+H)^+$; HRMS found, 202.1091, $C_{10}H_{12}N_5$ requires 202.1093.

4.2.18. *N*′-(4-Cyano-2-phenyl-2*H*-pyrazol-3-yl)-*N*,*N*-dimethyl-formamidine (Table 5, entry 4). White solids (98.6 mg, 82%); mp 144–147 °C; IR (neat) ν_{max} 3229, 3008, 2919, 2207, 1749, 1624, 1591, 1526, 1509, 1492, 14.52, 14.16, 1406, 1309, 1340, 1259, 1200, 1155, 1116, 1087, 1062, 1022, 991, 958 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.95 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 7.25–7.80 (m, 5H, ArH), 8.00 (s, 1H, ArH), 8.25 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 35.7, 40.1, 78.2, 115.6, 123.2, 123.8, 126.8, 128.6, 129.5, 138.5, 141.8, 154.8, 156.6 ppm; EIMS *m/z*: 239 $(M)^+$; HRMS found, 239.1175, $C_{13}H_{13}N_5$ requires 239.1170.

4.2.19. 2-(3-Chloro-phenylsulfanyl)-4-(3-methoxy-phenyl)-6-[(pyrrolidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 4, entry 1). Upon completion the reaction mixture was poured into cold water (10 mL) and stirred for 5 min. The precipitate formed was recovered by suction filtration and washed sequentially with water (10 mL) and petroleum ether (10 mL). Drying the solid in vacuo gave the product as a pale yellowish powder (115.9 mg, 96%); mp 172–175 °C; IR (neat) ν_{max} 3082, 2973, 2221 (s), 1610 (s), 1575 (s), 1520, 1508, 1488, 1450, 1428, 1369, 1328, 1307, 1289, 1236, 1214, 1186, 1154, 1118, 1037, 994, 964 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65–2.15 (m, 4H, CH_2CH_2), 3.35–3.70 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 6.90–7.50 (m, 7H, ArH), 7.65 (s, 1H, ArH), 8.34 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 24.3, 24.9, 43.1, 46.7, 49.9, 97.3, 97.8, 115.4, 115.9, 127.8, 129.2, 129.6, 130.0 (2C), 130.1, 131.2, 133.0, 133.7, 134.1, 136.2, 137.8, 151.1, 154.6, 163.7, 165.5 ppm; ESMS *m/z*: 474 $(M+H)^+$; HRMS found, 474.1138, $C_{25}H_{21}ClN_5OS$ requires 374.1155.

4.2.20. 2-(3-Chloro-phenylsulfanyl)-4-(3-methoxy-phenyl)-6-[(piperidin-1-ylmethylene)-amino]-pyridine-3,5-dicarbonitrile (Table 4, entry 2). A mixture of two isomers was obtained as a white powder (95.1 mg, 77%); mp 185–186 °C; IR (neat) ν_{max} 3480, 3330, 3213 (s), 2215, 1635 (s), 1610, 1518, 1384, 1243, 994, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 1.60 (m, 6H, $CH_2CH_2CH_2$), 3.22 (t, 2H, J=4.8 Hz, NCH_2), 3.72 (t, 2H, J=4.8 Hz, NCH_2), 7.60 (m, 8H, ArH), 8.10 (s, 1H, N=CHN) ppm; (minor isomer) δ 1.74 (m, 6H, $CH_2CH_2CH_2$), 3.40 (t, 2H, J=4.8 Hz, NCH_2), 3.66 (t, 2H, J=4.8 Hz, NCH_2), 7.60 (m, 8H, ArH), 7.92 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 25.6, 26.7, 40.0, 44.7, 46.8, 52.2, 55.4, 97.6, 113.8, 115.0, 115.6, 116.6, 120.8, 129.5, 130.0, 130.2, 133.8, 134.1, 134.7, 136.1, 156.3, 158.8, 159.5, 163.7, 165.0 ppm; ESMS *m/z*: 488 $(M+H)^+$; HRMS found, 488.1300, $C_{26}H_{23}ClN_5OS$ requires 488.1312.

4.2.21. 2-(3-Chloro-phenylsulfanyl)-6-[(pyrrolidin-1-ylmethylene)-amino]-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile (Table 4, entry 3). Pale yellow powder (95 mg, 77%); mp 214–216 °C; IR (neat) ν_{max} 3083, 2966, 2870, 2204 (s), 1660, 1606 (s), 1574, 1527, 1439, 1399, 1367, 1350, 1323, 1300, 1245, 1229, 1152, 1113, 1070, 1029, 993, 965 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.88 (m, 4H, CH_2CH_2); 3.48 (m, 4H, NCH_2), 7.29 (m, 1H, ArH), 7.62 (m, 4H, ArH), 7.78 (m, 1H, ArH), 7.89 (d, 1H, J=6.5 Hz, ArH), 8.24 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.8, 43.1, 46.0, 98.9, 90.0, 114.9, 115.4, 124.0, 128.8, 128.8, 130.2, 130.3, 130.6, 131.5, 133.0, 133.8, 134.7, 135.4, 150.0, 159.5, 160.9 ppm; ESMS *m/z*: 450 $(M+H)^+$; HRMS found, 450.0609, $C_{22}H_{17}ClN_5S_2$ requires 450.0614.

4.2.22. 2-Benzylsulfanyl-6-[(pyrrolidin-1-ylmethylene)-amino]-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile (Table 4, entry 4). Greenish powder (113.0 mg, 94%); mp 164–166 °C dec; IR (neat) ν_{max} 3317, 3092, 2981, 2876, 2485, 2208, 1608, 1531, 1490, 1462, 1448, 1397, 1366, 1324, 1301, 1278, 1228, 1204, 1152, 1073, 1052, 1029, 1009, 977 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.90 (m, 4H, NCH_2CH_2), 3.55 (t, 2H, J=5.5 Hz, NCH_2), 3.70 (t, 2H, J=5.5 Hz, NCH_2), 4.60 (s, 2H, $ArCH_2$), 7.15–7.50 (m, 6H, ArH), 7.55 (d, 1H, J=6.5 Hz, ArH), 7.95 (d, 1H, J=6.5 Hz, ArH), 9.00 (s, 1H, N=CHN) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 23.7, 24.5, 33.9, 46.4, 49.8, 96.3, 96.6, 115.3, 115.8, 127.2, 128.4, 128.5, 128.7, 130.8, 131.3, 132.6, 136.9, 150.4, 155.0, 160.5, 163.3, 165.6 ppm; ESMS *m/z*: 430 $(M+H)^+$; HRMS found, 430.1167, $C_{23}H_{20}N_5S$ requires 430.1160.

4.3. Synthesis of formamidines without NaH

4.3.1. *N*′-(3,5-Dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 5). To a stirred solution of 2-amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile **1** (50.0 mg, 0.22 mmol) in dry DMF (1.0 mL) was added TFAA (50.0 mg, 0.24 mmol) under nitrogen at room temperature. After the mixture was stirred for 20 min at room temperature it was poured into cold water (10 mL) and stirred for 5 min, the suspension was filtered and the precipitated crude product washed with water (10 mL). Drying the solid in vacuo overnight gave **2** (57.3 mg, 96%).

4.3.2. *N*′-(6-Benzylsulfanyl-3,5-dicyano-4-thiophen-2-yl-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 6). Yellowish powder (256.0 mg, 89%): mp 202–204 °C; IR (neat) ν_{max} 3440, 3318, 3216, 2212, 1719, 1619, 1518, 1491, 1449, 1419, 1397, 1367, 1340, 1314, 1286, 1245, 1222, 1124, 1098, 1055, 1008, 982 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.15 (s, 3H, NCH_3), 3.25 (s, 3H, NCH_3), 4.60 (s, 2H, $ArCH_2$), 7.10–7.65 (m, 7H, ArH), 7.95 (d, J=7.5 Hz, ArH), 8.90 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 33.9, 35.0, 41.1, 96.4, 96.7, 115.3, 115.8, 127.3,

127.8, 128.5, 129.3, 130.7, 130.8, 131.2, 131.3, 132.6, 136.9, 150.4, 158.2, 163.3, 165.7 ppm; ESMS *m/z*: 404 $(M+H)^+$; HRMS found, 404.0998, $C_{21}H_{18}N_5S_2$ requires 404.1004.

4.3.3. *N′*-[3,5-Dicyano-4-(phenyl-4-carboxylic acid methyl ester)-6-(phenylsulfanyl-4-carboxylic acid methyl ester)-pyridin-2-yl)-*N*,*N*-dimethyl-formamidine (Table 4, entry 7). A mixture of two isomers was obtained as a faint yellowish solid (203.4 mg, 78%); mp 145–147 °C; IR (neat) ν_{max} 2935, 2217 (s), 1723, 1624 (s), 1569, 1527, 1494, 1437, 1401, 1371, 1275, 1251, 1182, 1135, 1105, 1014, 987, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 3.05 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 3.94 (s, 3H, $COOCH_3$), 3.95 (s, 3H, $COOCH_3$), 7.58 (d, 2H, *J*=8.5 Hz, ArH), 7.70 (d, 2H, *J*=8.5 Hz, ArH), 8.01 (s, 1H, N=CHN), 8.10 (d, 2H, *J*=8.5 Hz, ArH), 8.20 (d, 2H, *J*=8.5 Hz, ArH) ppm; (minor isomer) δ 2.92 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 3.88 (s, 3H, $COOCH_3$), 3.91 (s, 3H, $COOCH_3$), 7.40 (d, 2H, *J*=9.2 Hz, ArH), 7.50 (d, 2H, *J*=9.2 Hz, ArH), 7.89 (s, 1H, N=CHN), 8.04 (d, 2H, *J*=9.2 Hz, ArH), 8.07 (d, 2H, *J*=9.2 Hz, ArH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.4, 40.9, 52.5 (2C), 97.8, 98.0, 114.7, 115.2, 128.6, 129.8, 130.1, 130.4, 130.6, 131.1, 132.0, 132.2, 133.8, 136.1, 137.7, 156.2, 157.8, 157.9, 163.4, 165.4, 166.1, 166.3 ppm; ESMS *m/z*: 500 $(M+H)^+$; HRMS found, 522.1192, $C_{26}H_{21}N_5O_4NaS$ requires 522.1212.

4.3.4. 4-{3,5-Dicyano-2-[(pyrrolidin-1-ylmethylene)-amino]-6-*p*-methylcarboxylester sulfanyl-pyridin-4-yl}-benzoic acid methyl ester (Table 4, entry 8). A mixture of two isomers was obtained as a pale yellowish solid (194.2 mg, 78%); mp 187–190 °C dec; IR (neat) ν_{max} 2954, 2876, 2216, 1714, 1613, 1519, 1503, 1449, 1363, 1329, 1274, 1245, 1192, 1157, 1106, 1013, 965 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 1.83 (m, 4H, $2NCH_2CH_2$), 3.42 (t, 2H, *J*=6.5 Hz, NCH_2), 3.57 (t, 2H, *J*=6.5 Hz, NCH_2), 3.88 (s, 3H, $COOCH_3$), 3.89 (s, 3H, $COOCH_3$), 7.52 (d, 2H, *J*=9.2 Hz, ArH), 7.60 (d, 2H, *J*=9.2 Hz, ArH), 8.01 (s, 1H, N=CHN), 8.04 (d, 2H, *J*=9.2 Hz, ArH), 8.12 (d, 2H, *J*=9.2 Hz, ArH); (minor isomer) δ 1.83 (m, 4H, $2NCH_2CH_2$), 3.42 (t, 2H, *J*=6.5 Hz, NCH_2), 3.46 (t, 2H, *J*=6.5 Hz, NCH_2), 3.85 (s, 3H, $COOCH_3$), 3.88 (s, 3H, $COOCH_3$), 7.31 (d, 2H, *J*=9.2 Hz, ArH), 7.38 (d, 2H, *J*=9.2 Hz, ArH), 7.94 (d, 2H, *J*=9.2 Hz, ArH), 8.00 (d, 2H, *J*=9.2 Hz, ArH), 8.01 (s, 1H, N=CHN) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 24.2, 24.9, 46.7, 49.8, 52.5, 97.7, 98.0, 114.8, 115.3, 125.9, 127.4, 128.8, 129.8, 130.2, 130.8, 131.1, 132.0, 134.0, 135.8, 137.8, 153.1, 154.6, 157.9, 161.0, 163.4, 165.3, 166.2, 166.4 ppm; ESMS *m/z*: 526 $(M+H)^+$; HRMS found, 526.1550, $C_{28}H_{24}N_5O_4S$ requires 526.1549.

4.3.5. *N′*-(5-Cyano-pyrimidin-4-yl)-*N*,*N*-dimethyl-formamidine (Table 5, entry 3). Pale yellowish solid (83.4 mg, 79%).

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o-Thioquinones on [2.2]paracyclophanes: an example of totally stereocontrolled hetero Diels–Alder reactions

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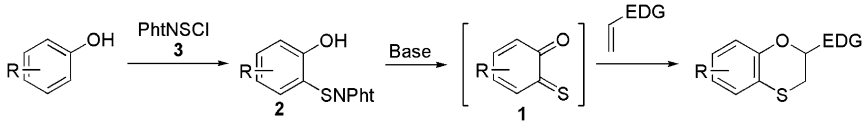
Abstract—The reaction of 4-hydroxy[2.2]paracyclophane with phthalimidesulfenyl chloride allowed the preparation of a suitable precursor for a paracyclophane-*o*-thioquinone. This species participates in an inverse electron demand hetero Diels–Alder reaction with different electron-rich alkenes to give the expected benzoxathiin cycloadducts with complete control of regio- and stereochemistry.

1. Introduction

Normal electron demand Diels–Alder reaction of [2.2]paracyclophane-based dienes is a well documented process that allowed the preparation of a variety of cyclophanes, especially chiral [2.2]paracyclophanes containing helical condensed aromatic subunits.[1] Helicenophanes, and more generally planar chiral cyclophanes are promising ligands to prepare catalysts for asymmetric processes, and are interesting for their potential applications as new materials.[2] There is now an increasing attention for paracyclophanes condensed with heterocyclic rings, and the hetero Diels–Alder reaction represents an useful tool for this task.[3] Mono-*o*-thioquinones,[4] of general formula **1**, are reactive intermediates potentially useful in this chemistry. As recently reported,[5] they can be obtained under very mild conditions by reacting the corresponding *o*-hydroxy-*N*-thiophthalimides **2** with bases (Scheme 1).

Compounds **2**, in turn, are the products of the *ortho* regiospecific S_EAr of phthalimidesulfenyl chloride **3** (PhtNSCl, Pht=Phthaloyl) with phenols, the key step of this procedure.[5] *o*-Thioquinones **1** are efficient electron-poor dienes with a plethora of electron-rich dienophiles[6] (Scheme 1), thus we envisaged their development with [2.2]paracyclophane substrates.

This paper reports the results of the study of (i) the sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (**4**) with **3** (Scheme 2); (ii) the inverse electron demand Diels–Alder reaction of a [2.2]paracyclophane-*o*-thioquinone (**8**) obtained by this procedure.



Scheme 1. General procedure for the generation and trapping of *o*-thioquinones **1**.

Keywords: [2.2]Paracyclophanes; *o*-Thioquinones; Hetero Diels–Alder reactions; Stereoselectivity; Sulfur heterocycles.
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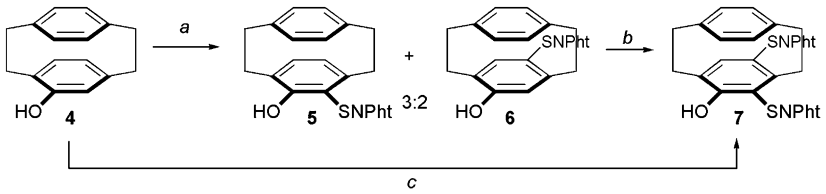


Scheme 2. Products formed on the phthalimide sulfenylation of 4-hydroxy[2.2]paracyclophane (**4**). Reagents: (a) **3** (1 equiv), $CHCl_3$, 0 °C, 2 h; (b) **3** (1 equiv), $CHCl_3$, rt, 1 h; (c) **3** (2.2 equiv), $CHCl_3$, rt, 2 h.

2. Results and discussion

2.1. Sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (4)

The sulfenylation reaction of 4-hydroxy[2.2]paracyclophane (**4**) with **3** turned out to be a nontrivial extension of previously reported chemistry. After several attempts we realized that by carrying out the sulfenylation by adding 1 equiv of **3**, over 2 h at 0 °C, the expected *o*-hydroxy substituted derivative **5** could be isolated by flash chromatography on silica gel in 58% yield (Scheme 2). ^{1}H NMR spectroscopy of the crude reaction mixture showed (see Section 4) the contemporary formation of *para* isomer **6** (**5**:**6**=3:2), which was not isolated due to its poor stability and sensitivity to silica gel (Scheme 2).

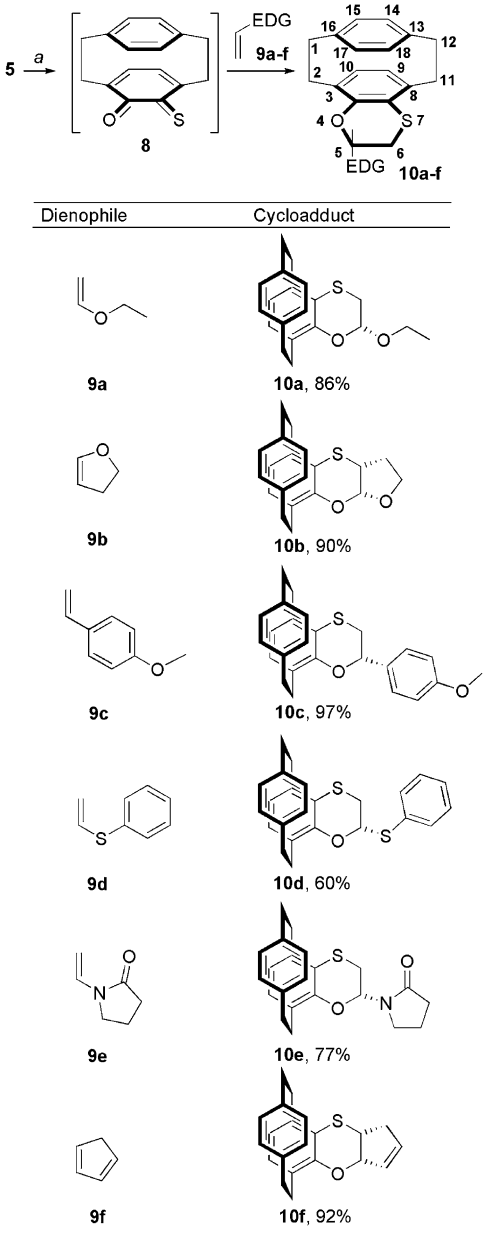
Carrying out the sulfenylation at rt, and/or using 2.2 equiv of **3**, led to the bis-sulfenylated thiophthalimide **7**, isolated as the sole reaction product in 82% yield (Scheme 2).

The sulfenylation of more than 50 different substituted phenols reported in the last decade,[5,6] afforded the *o*-monosubstituted *N*-thiophthalimide as the sole reaction product. However, the reaction of **3** with 2,5-dimethyl phenol, chosen as a simplified model of **4**, gave, after 3 h at rt, a 2:1 mixture of the corresponding *o*- and *p*-*N*-thiophthalimides indicating that a 2,5-dialkyl substitution can cause the lack of *ortho* regioselectivity. On the other hand, the possibility of bis-sulfenylation, with formation of **7**, is peculiar of this system. It has been demonstrated that a *N*-thiophthalimide substituent strongly depletes the nucleophilicity of aromatic rings[7] avoiding poly-substitution even with high reactive aromatics, like resorcin or 2,7-dihydroxynaphthalene. The isolation of **7**, that is formed even under very mild conditions, suggested that the paracyclophane system, due to the particular stereo-electronic situation offered by the proximity of the two aromatic rings, is able to overcome the withdrawing effect of the first thiophthalimide group. As a matter of fact, 2,5-dimethyl phenol or the corresponding *o*- and *p*-thiophthalimides, did not undergo bis-substitution neither using excess amounts of **3**, nor carrying out the reaction at 60 °C for several hours.

2.2. Inverse electron demand Diels–Alder reaction of the [2.2]paracyclophane-*o*-thioquinone (8)

Having derivative **5** in hand we decided to verify the possibility to generate the corresponding *o*-thioquinone **8** as a new interesting electron-poor diene possessing diastereotopic faces.

Reacting *o*-hydroxy-*N*-thiophthalimide **5** with 1 equiv of Et_3N in the presence of 5 equiv of ethyl vinyl ether (**9a**), after 20 h at 60 °C in $CHCl_3$, the expected benzoxathiin **10a** was obtained in 86% yield (Scheme 3).



Scheme 3. Generation and [4+2] cycloadditions of *o*-thioquionone **8**. Reagents: (a) Et_3N (1 equiv), dienophile **9** (2–5 equiv), $CHCl_3$, 60 °C, 20 h.

This confirms that *o*-thioquinone **8** is formed in situ and participates in an inverse electron demand cycloaddition with **9a** to give cycloadduct **10a** with complete regio- and stereocontrol (Scheme 3).

The cycloadditions occurred with different electron-rich alkenes **9b–e** and with cyclopentadiene (**9f**). In all cases, the expected cycloadducts **10b–f** were isolated in very good yield as single regio- and stereoisomers (Scheme 3).[8]

Although the Diels–Alder reactions were highly diastereoselective and occurred with good to high yields, we also tried to carry out the cycloadditions under high pressure conditions. It is well-known that pressure not only accelerates the cycloadditions, but also can affect the diastereoselectivity and the regioselectivity of the reactions. Surprisingly, when we performed the cycloadditions under high pressure (7–9 kbar) at 25–60 °C the reaction yield dropped dramatically.

2.3. Structure analysis

The structures of the isolated benzoxathiins were assigned by analysis of their ^{1}H and ^{13}C NMR spectra, in some cases confirmed by X-ray analysis. In all cycloadducts **10a–e**, the proton on C-5 appears as a doublet of doublets with a small and a high ^{3}J coupling constant with the diastereotopic C(6)H protons (see Section 4). This clearly indicates that the C(5)H proton lies in the pseudo-axial position and the EDG lies in the pseudo-equatorial position. However, this is not enough to attribute the relative stereochemistry to the diastereoisomer achieved from the cycloaddition.

For example oxathiin **10a**, isolated in the reaction of **8** with vinyl ether **9a**, could possess either structure ***A*** or ***B*** as reported in Figure 1. The attribution of the structure ***A*** to **10a** was determined by extensive ^{1}H and ^{13}C NMR investigations, especially ^{1}H–{^{1}H} NOE experiments.

Selective pre-irradiation of the C(17)H resonance resulted in signal enhancement of the resonances attributed to C(5)H, C(18)H, and C(1)H. This indicated a cis-relationship between C(5)H and the unsubstituted benzene ring of the paracyclophane unit (i.e., structure ***A***), confirming either a totally *anti* (with respect to the unsubstituted benzene ring of the paracyclophane unit)–*endo*- or *syn*–*exo*-diastereoselectivity in the cycloaddition reaction between **8** and **9a** (Fig. 1). Further support for such assignment was given by the NOE's observed between C(6)H and C(18)H, C(10)H and C(15)H, and C(9)H and C(14). Definitive confirmation for the structure ***A*** of oxathiin **10a** was obtained by X-ray analysis as showed in Figure 1.

The complete stereoselectivity[8] obtained in these reactions can be probably justified considering the matching situation of the *anti*-approach, favorite for the lack of steric interaction between the dienophile and the paracyclophane bridge, and the *endo* mode, preferred for the possibility of secondary orbital interactions. Similar considerations and spectroscopic evidences were convincing for the attribution of the same relative structure to oxathiins **10b–e**.

However, NMR considerations were less helpful for the attribution of the structure to derivative **10f**, first of all since the unique ^{3}J coupling constant is less supportive, and secondly for the modifications of the twisted-chair conformations produced on such oxathiin by the cis-fused cyclopentene ring.

Gratifyingly, it was possible to obtain an X-ray structure of derivative **10f**. As reported in Figure 2 the oxathiin ring of **10f** adopts an almost boat conformation and, as in the case of derivative **10a**, it is formed through a complete regio- and stereoselective *endo–anti* (or *exo–syn*) cycloaddition between paracyclophane derived *o*-thioquinone **8** and dienophile **9f** (Fig. 2).

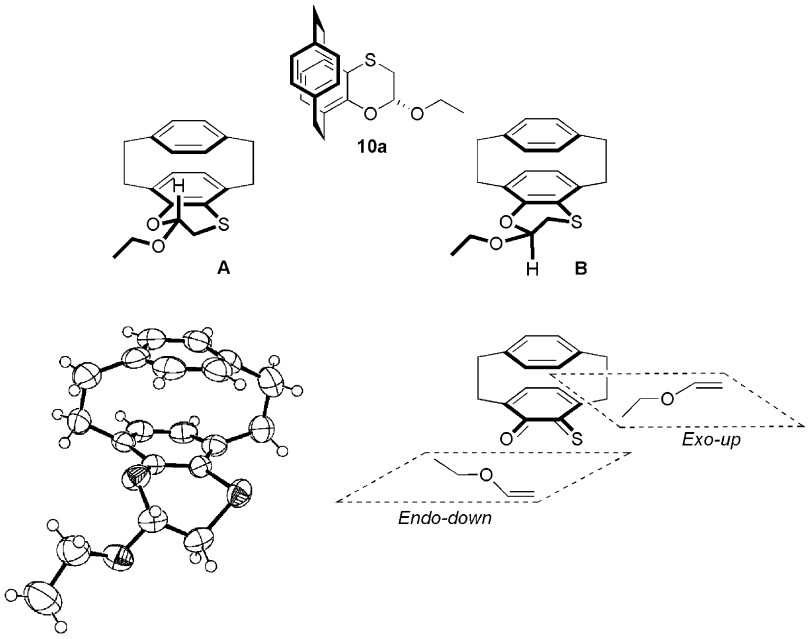


Figure 1. Relative structures ***A*** and ***B*** for **10a**, front view X-ray ORTEP of **10a**, and possible approaches leading to structure ***A***.

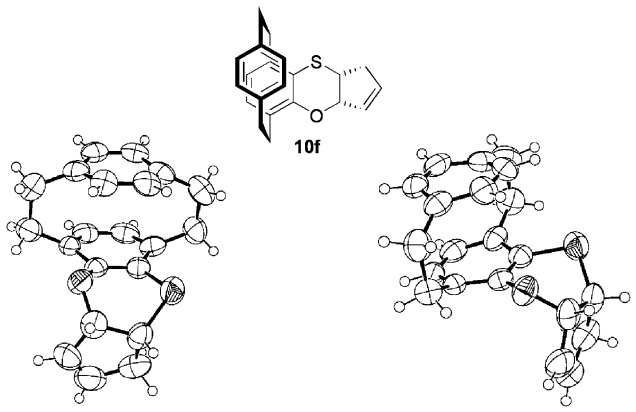


Figure 2. Front and side view of X-ray ORTEP of **10f**.

3. Conclusions

The application of the phthalimidesulfenyl chloride chemistry to 4-hydroxy-[2.2]paracyclophane **4** allowed the preparation of the precursor for the new chiral *o*-thioquinone **8** as well as furnished the first example of bis-sulfenylation. The cycloaddition of several electron-rich alkenes with the heterodiene **8** generated in situ occurred with a complete stereo differentiation between the diastereotopic faces of diene **8**. Further application of this chemistry as well as the opportunities disclosed by the preparation of **7** are under investigations in these labs.

4. Experimental

4.1. General

All reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F_{254}) and the products were visualized with acid vanillin solution. Silica gel 60, 230–400 mesh, was used for column chromatography. Petrol refers to light petroleum, bp 40–60 °C. Melting points were measured on a microscopic apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solutions. Residual $CHCl_3$ was used as reference at 7.26 and 77.00 ppm, respectively. FTIR spectra were recorded in KBr pellets. Mass spectra were measured with a Shimadzu QP5050. Phthalimidesulfenyl chloride[6c] (**3**) and 4-hydroxy[2.2]paracyclophane[9] (**4**) were prepared as reported elsewhere.

4.1.1. X-ray crystallography. These were carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at rt. In both cases KM4 CCD/SAPPHIRE detectors were used for cell parameter determination and data collection; in the case of cycloadduct **10a**, a graphite-monochromated Cu Kα radiation (40 mA/−40 KV) was used, whereas for cycloadduct **10f** a graphite-monochromated Mo Kα radiation (40 mA/−40 KV) was used. The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarization effects.[10] The substantial redundancy in data allows empirical absorption corrections (SADABS[11]) to be applied using multiple measurements of symmetry-equivalent reflections. These structures were solved by direct methods of SIR97[12] and refined using the full-matrix least squares on F^2 provided by SHELXL97.[13] The nonhydrogen atoms were refined anisotropically, whereas hydrogen atoms were refined as isotropic. In both cases hydrogens were assigned in calculated positions.

The X-ray CIF files for these structures have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition numbers *CCDC 294833* for cycloadduct **10a** and *CCDC 294834* for cycloadduct **10f**. Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk; internet: www.ccdc.cam.ac.uk).

4.1.2. 5-*N*-Thiophthalimide-4-hydroxy[2.2]paracyclophane (5). To a solution of 4-hydroxy[2.2]paracyclophane (**4**) (0.400 g, 1.78 mmol) in dry $CHCl_3$ (25 mL), at 0 °C, a solution of sulfenyl chloride (**3**) (0.409 g, 1.78 mmol) in dry $CHCl_3$ (20 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h, then diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ solution (2×100 mL) and H_2O (2×100 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give *ortho-N*-thiophthalimide (**5**) and *para-N*-thiophthalimide substituted derivatives (**6**) in a 3:2 ratio (δ OH_{ortho}= 8.23 ppm, δ OH_{para}=5.59 ppm). After column chromatography (eluent: CH_2Cl_2), the major product **5** was isolated pure as a white solid (0.420 g, 1.05 mmol, 58% yield), mp 205–207 °C; ^{1}H NMR δ 8.23 (1H, s), 7.85–7.78 (2H, m), 7.73–7.67 (2H, m), 7.0 (1H, dd, *J*=7.8, 1.8 Hz), 6.58 (1H, dd, *J*=8.0, 1.8 Hz), 6.51 (1H, d, *J*=7.8 Hz), 6.43–6.35 (2H, m), 6.32 (1H, d, *J*=8.0 Hz), 4.40–4.27 (1H, m), 3.54–3.41 (1H, m), 3.27–3.06 (4H, m), 3.03–2.88 (1H, m), 2.68–2.53 (1H, m); ^{13}C NMR δ 168.2, 157.5, 146.7, 139.7, 138.9, 138.6, 134.6, 134.3, 132.7, 131.9, 129.5, 127.9, 127.54, 127.53, 125.1, 123.9, 120.6, 34.8, 34.7, 33.6, 30.9; MS *m*/*z* (%) 401 ($M^{\bullet+}$, 34), 297 (57), 254 (44), 150 (88), 104 (100); IR ν_{max} 3355 (O–H stretching), 1776+1731+1703 (C═O stretching PhtN), 1283 (C–OH stretching) cm^{-1}; Anal. Calcd for $C_{24}H_{19}NO_3S$: C 71.80, H 4.77, N 3.49. Found: C 71.64, H 4.75, N 3.42.

4.1.3. 5,7-Bis(*N*-thiophthalimide)-4-hydroxy[2.2]paracyclophane (7). To a solution of 4-hydroxy[2.2]paracyclophane (**4**) (0.100 g, 0.44 mmol) in dry $CHCl_3$ (4 mL), a solution of sulfenyl chloride (**3**) (0.215 g, 1.01 mmol) in dry $CHCl_3$ (4 mL) was added. The reaction mixture was stirred at rt for 2 h, then diluted with CH_2Cl_2 (15 mL), and washed with saturated $NaHCO_3$ solution (2×25 mL) and H_2O (2×25 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (eluent: CH_2Cl_2), to give compound **7** as a yellow solid (0.210 g, 0.36 mmol, 82% yield), mp 199 °C decomp.; ^{1}H NMR δ 8.63 (1H, s), 7.84–7.81 (2H, m), 7.79–7.77 (2H, m), 7.69–7.65 (4H, m), 7.12 (1H, s), 6.92 (1H, dd, *J*=8.0, 2.0 Hz), 6.61 (1H, dd, *J*=8.0, 2.0 Hz), 6.38 (1H, dd, *J*=8.0, 2.0 Hz), 6.34 (1H, dd, *J*=8.0, 2.0 Hz), 4.40–4.28 (2H, m), 3.43–3.34 (2H, m), 3.25–3.17 (1H, m), 3.15–3.05 (2H, m), 2.63–2.55 (1H, m); ^{13}C NMR δ 168.2, 167.8, 159.9, 151.3, 145.9, 139.6, 139.4, 134.8, 134.5, 133.9, 132.1, 131.9, 131.2, 129.5, 128.4, 128.3, 126.2, 124.2, 123.9, 122.2, 34.7, 33.4, 32.4, 30.6; IR ν_{max} 3344 (O–H stretching), 1781+1731+1703 (C═O stretching PhtN), 1278 (C–OH

stretching) cm^{-1}; Anal. Calcd for $C_{32}H_{22}N_2O_5S_2$: C 66.42, H 3.83, N 4.84. Found: C 66.30, H 3.70, N 4.71.

4.1.4. General procedure for Diels–Alder cycloadditions of *o*-thioquinone 8 with dienophiles 9. To a solution of 5-*N*-thiophthalimide-4-hydroxy[2.2]paracyclophane (**5**) (0.40 g, 1.0 mmol) in dry $CHCl_3$ (10 mL), Et_3N (0.14 mL, 1.0 mmol) and dienophile **9a–f** (2–5 mmol) were added in sequence. The mixture was heated at 60 °C for 20 h and then concentrated under reduced pressure. The crude material was purified by column chromatography to give cycloadduct **10a–f**. Data are as it follows:

4.1.4.1. Cycloadduct 10a. General procedure was followed to afford, after column chromatography (eluent: CH_2Cl_2/petroleum ether 1:1), the title product **10a** as a yellow solid (86% yield), mp 108–110 °C (from acetone); ^1H NMR δ 7.05 (1H, ddd, J=7.9, 1.1, 1.1 Hz, H-18), 6.67 (1H, d, J=7.9, 1.1, 1.1 Hz, H-17), 6.51 (2H, t, J=1.1 Hz, H-14, H-15), 6.31 (1H, d, J=7.7 Hz, H-10), 6.14 (1H, d, J=7.7 Hz, H-9), 5.46 (1H, dd, J=4.9, 2.6 Hz, H-5), 3.88–3.70 (2H, m, OCH_2), 3.30 (1H, ddd, J=13.0, 9.9, 2.9 Hz, H-2), 3.15 (1H, m, H-11), 3.12 (1H, dd, J=12.7, 2.6 Hz, H-6), 3.08–2.94 (4H, m, H-1, H-12), 2.81 (1H, dd, J=12.7, 4.9 Hz, H-6), 2.71 (1H, m, H-11), 2.55 (1H, ddd, J=13.0, 10.4, 5.6 Hz, H-2), 1.22 (3H, t, J=7.1 Hz, CH_3). ^{13}C NMR δ148.2 (C-3), 139.7+138.4 (C-13, C-16), 138.2 (C-8), 133.4+132.9 (C-14, C-15), 130.9 (C-10), 128.8 (C-3), 128.0 (C-17), 127.4 (C-18), 126.5 (C-9), 119.9 (C-7a), 94.2 (C-5), 64.2 (OCH_2), 34.3+33.2 (C-1, C-12), 32.9 (C-3a), 30.5 (C-2), 28.4 (C-6), 15.2 (CH_3). MS m/z (%) 326 ($M^{\bullet+}$, 85), 222 (63), 176 (88), 163 (100); IR ν_{max} 2997, 2963, 2918, 1574, 1412, 1054, 1015 cm^{-1}; Anal. Calcd for $C_{20}H_{22}O_2S$: C 73.58, H 6.79. Found: C 73.88, H 6.91.

X-ray structural analysis of **10a**: formula $C_{20}H_{22}O_2S$, M_r=326.44, Monoclinic, space group Cc, a=9.165(1), b=23.026(2), c=8.052(1) Å, β=93.166(7), V=1696.6(3) Å^3, Z=4, D_c=1.278, μ=1.742 mm^{-1}, $F(000)$=696. Reflections (6201) were collected with a $7.38<\theta<58.68$ range with a completeness to theta 98.3%; 1783 were independent, the parameters were 284, and the final R index was 0.0388 for reflections having $I>2\sigma I$, and 0.0470 for all data.

4.1.4.2. Cycloadduct 10b. General procedure was followed to afford, after column chromatography (eluent: petroleum ether/EtOAc 15:1), the title product **10b** as a yellow solid (90% yield), mp 108–110 °C; ^1H NMR δ 6.96 (1H, d, J=8.0 Hz), 6.72 (1H, d, J=8.0 Hz), 6.49 (2H, s), 6.38 (1H, d, J=8.0 Hz), 6.24 (1H, d, J=7.6 Hz), 5.91 (1H, d, J=6.0 Hz), 3.81–3.70 (2H, m), 3.64 (1H, dt, J=9.0, 5.6 Hz), 3.38 (1H, ddd, J=13.0, 9.8, 3.2 Hz), 3.09–2.91 (5H, m), 2.83–2.76 (1H, m), 2.56 (1H, ddd, J=15.6, 10.4, 5.1 Hz), 2.20–2.11 (1H, m), 1.69–1.58 (1H, m); ^{13}C NMR δ 150.2, 139.5, 139.4, 137.6, 132.7, 132.3, 131.1, 129.1, 128.1, 127.4, 126.6, 122.8, 101.6, 68.1, 41.7, 34.1, 33.6, 32.3, 31.4, 30.2; MS m/z (%) 324 ($M^{\bullet+}$, 68), 220 (100), 104 (78), 70 (60); IR ν_{max} 3000, 2924, 2845, 1567, 1409, 1040, 1006 cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_2S$: C 74.04, H 6.21. Found: C 73.84, H 6.49.

4.1.4.3. Cycloadduct 10c. General procedure was followed to afford, after column chromatography (eluent: petroleum ether/EtOAc 100:1), the title product **10c** as a yellow solid (97% yield), mp 98–100 °C; ^1H NMR δ 7.38–7.34 (2H, m), 7.31 (1H, d, J=7.4 Hz), 6.98–6.94 (2H, m), 6.67 (1H, d, J=8.0 Hz), 6.56 (2H, s), 6.36 (1H, d, J=7.6 Hz), 6.19 (1H, d, J=7.6 Hz), 5.41 (1H, dd, J=9.4, 2.2 Hz), 3.85 (3H, s), 3.43–3.36 (1H, m), 3.17–3.08 (3H, m), 3.06–3.01 (3H, m), 2.95 (1H, dd, J=13.4, 9.4 Hz), 2.83–2.75 (1H, m), 2.62–2.55 (1H, m); ^{13}C NMR δ 159.4, 149.5, 139.9, 138.3, 138.1, 133.4, 133.0, 132.4, 130.5, 128.8, 128.5, 127.2, 127.0, 126.0, 118.7, 113.9, 74.3, 55.3, 34.2, 33.0, 32.5, 31.6, 30.3; MS m/z (%) 388 ($M^{\bullet+}$, 39), 163 (62), 134 (62), 121 (100); IR ν_{max} 3008, 2918, 2840, 1608, 1580, 1513, 1250, 1020 cm^{-1}; Anal. Calcd for $C_{25}H_{24}O_2S$: C 77.28, H 6.23. Found: C 77.22, H 6.25.

4.1.4.4. Cycloadduct 10d. General procedure was followed to afford, after column chromatography (eluent: petroleum ether/CH_2Cl_2 7:3), the title product **10d** as a white solid (60% yield), mp 130–132 °C; ^1H NMR δ 7.53 (2H, m, H-2′+H-6′), 7.34 (3H, m, H-3′, H-4′, H-5′), 7.02 (1H, dd, J=8.0, 1.6 Hz, H-18), 6.58 (1H, dd, J=8.0, 1.6 Hz, H-17), 6.51 (2H, d, J=1.6 Hz, H-14, H-15), 6.34 (1H, d, J=7.7 Hz, H-10), 6.21 (1H, d, J=7.7 Hz, H-9), 5.86 (1H, dd, J=5.2, 3.1 Hz, H-5), 3.47 (1H, dd, J=13.0, 3.1 Hz, H-6), 3.25–3.16 (3H, m, H-2, H-12, H-11), 3.06 (1H, dd, J=13.0, 5.2 Hz, H-6), 3.02–2.95 (2H, m, H-1, H-12), 2.85 (1H, ddd, J=13.1, 10.3, 5.1 Hz, H-1), 2.72 (1H, m, H-11), 2.55 (1H, ddd, J=13.0, 11.0, 5.5 Hz, H-2). ^{13}C NMR δ 147.7 (C-3a), 139.8+138.4+138.3 (C-8, C-16, C-13), 133.7 (C-1′), 133.3 (C-2′, C-6′), 133.4+133.0 (C-15, C-14), 131.25 (C-2), 129.6 (C-1), 129.2 (C-3′, C-5′), 128.2 (C-4′), 127.9 (C-17), 127.6 (C-18), 127.0 (C-9), 119.2 (C-7a), 81.3 (C-5), 34.2+33.1 (C-1, C-12), 32.9 (C-11), 30.5 (C-2), 29.3 (C-6); MS m/z (%) 390 ($M^{\bullet+}$, 100), 281 (38), 177 (93), 163 (66), 136 (29); IR ν_{max} 3042, 2918, 2851, 1580, 1401, 1048 cm^{-1}; Anal. Calcd for $C_{24}H_{22}OS_2$: C 73.81, H 5.68. Found: C 73.87, H 5.67.

4.1.4.5. Cycloadduct 10e. General procedure was followed to afford, after column chromatography (eluent: petroleum ether/EtOAc 1:1), the title product **10e** as a white solid (77% yield), mp 175–177 °C; ^1H NMR δ 7.22 (1H, dd, J=8.0, 1.6 Hz), 6.87 (1H, dd, J=8.0, 1.6 Hz), 6.52–6.47 (2H, m), 6.33 (1H, d, J=7.6 Hz), 6.25 (1H, dd, J=7.6, 4.0 Hz), 6.17 (1H, d, J=7.6 Hz), 3.52–3.46 (1H, m), 3.36–3.30 (1H, m), 3.25 (1H, ddd, J=12.8, 9.2, 3.2 Hz), 3.10–2.97 (5H, m), 2.94–2.92 (2H, m), 2.80–2.71 (1H, m), 2.57–2.47 (3H, m), 2.12–2.0 (2H, m); ^{13}C NMR δ 175.5, 149.7, 139.7, 138.4, 137.6, 133.2, 132.3, 130.8, 128.9, 128.5, 127.3, 126.2, 118.9, 75.9, 42.2, 33.9, 33.0, 32.4, 31.2, 30.4, 27.2, 18.1; MS m/z (%) 365 ($M^{\bullet+}$, 32), 280 (12), 176 (100), 56 (25); IR ν_{max} 3002, 2918, 2851, 1686 (C=O str.), 1401, 1283, 1032 cm^{-1}; Anal. Calcd for $C_{22}H_{23}NO_2S$: C 72.30, H 6.34, N 3.83. Found: C 71.97, H 6.37, N 3.64.

4.1.4.6. Cycloadduct 10f. General procedure was followed to afford, after column chromatography (eluent: petroleum ether/CH_2Cl_2 7:3), the title product **10f** as a white solid (92% yield), mp 105–107 °C (from $CHCl_3$); ^1H NMR δ 6.92 (1H, dd, J=7.6, 1.6 Hz), 6.74 (1H, dd, J=7.8, 1.8 Hz), 6.51–6.45 (2H, m), 6.33 (1H, d, J=8.0 Hz), 6.21 (1H, d, J=7.6 Hz), 5.77–5.73 (1H, m), 5.67–5.62 (1H, m),

5.56–5.51 (1H, m), 3.94 (1H, dt, J=8.4, 5.6 Hz), 3.26 (1H, ddd, J=13.0, 9.8, 3.4 Hz), 3.13–3.03 (1H, m), 3.02–2.89 (4H, m), 2.80–2.73 (1H, m), 2.66 (1H, ddt, J=17.6, 8.4, 2.4 Hz), 2.54 (1H, ddd, J=15.6, 10.3, 5.4 Hz), 2.20–2.12 (1H, m); ^{13}C NMR δ 152.2, 140.0, 139.3, 137.8, 136.4, 132.6, 132.2, 130.7, 130.2, 129.7, 128.2, 127.7, 127.2, 126.4, 86.3, 42.3, 41.9, 34.3, 33.9, 32.3, 29.9; MS m/z (%) 320 ($M^{\bullet+}$, 64), 216 (100), 183 (39), 104 (42), 66 (26); IR ν_{max} 3036, 2924, 2845, 1611, 1577, 1404, 1029 cm^{-1}; Anal. Calcd for $C_{21}H_{20}OS$: C 78.71, H 6.29. Found: C 78.65, H 6.13.

X-ray structural analysis of cycloadduct **10f**: formula $C_{21}H_{20}OS$, M_r=320.43, Orthorhombic, space group $Pc2_1b$, a=8.020(2), b=11.423(3), c=17.745(3) Å, V=1625.7(6) Å^3, Z=4, D_c=1.309, μ=0.201 mm^{-1}, $F(000)$=680. Reflections (13,642) were collected with a $4.24<\theta<25.78$ range with a completeness to theta 88.9%; 2692 were independent, the parameters were 208, and the final R index was 0.0590 for reflections having $I>2\sigma I$.

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Screening of ligands in the asymmetric metallocenethiolatocopper(I)-catalyzed allylic substitution with Grignard reagents

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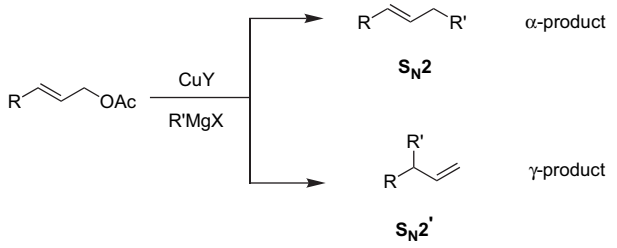
Abstract—Screening of metallocenethiolate ligands for copper(I)-catalyzed substitution of allylic acetates with Grignard reagents has been carried out. The previously used ligand, lithium (R,S_p)-2-(1-dimethylaminoethyl)ferrocenylthiolate (**4a**), possessing both central and planar chirality, was the starting point for the screening. It was found that the diastereomeric ligand lithium (R,R_p)-2-(1-dimethylaminoethyl)ferrocenylthiolate (**4b**) exhibiting reversed planar chirality gave increased enantioselectivity in the allylic substitution, at least when cinnamyl acetate was used as a substrate. The ruthenocene-based ligand lithium (R,S_p)-2-(1-dimethylaminoethyl)ruthenocenylthiolate (**4c**) gave an enhanced reaction rate, but lower chiral induction. The use of disulfide bis[(R,S_p)-2-(1-dimethylaminoethyl)ferrocenyl]disulfide (**7a**) as a ligand precursor worked well but resulted in lower enantioselectivity.

1. Introduction

Metal-mediated carbon–carbon bond formation has become a versatile synthetic method.[1] Organocopper(I) reactions are frequently used for carbon–carbon bond formation, and excellent results have been obtained in stoichiometric, as well as in catalytic reactions with zinc- or Grignard reagents.[2] The allylic substitution reaction has attracted considerable attention and several methods have been developed for the control of regio- and stereochemistry in these type of reactions. Copper-catalyzed reactions of allylic acetates with Grignard reagents were reported in 1977 by Schlosser,[3] and this reaction proceeds with high α-selectivity. Subsequently, Goering[4] and our group[5] showed that the regioselectivity of the copper-catalyzed Grignard reaction can be controlled toward either α- or γ-selectivity. In particular, our group showed that by careful choice of solvent, copper catalyst, and temperature, and by tuning the time of addition of the Grignard reagent, full control of regioselectivity can be obtained and the reaction of allylic acetates can be directed to give either an S_N2-type reaction (α-product) or an S_N2'-type reaction (γ-product), Scheme 1.[5] With dialkylcuprates only one alkyl group is transferred and often a large excess of the cuprate is required to obtain full conversion. By using non-transferable ligands, for example, alkoxy, aryloxy, alkylthio, or arylthio groups on copper, an efficient use of the alkyl group is achieved.[6] In a collaboration between our group and the group of van Koten, the allylic substitution of acetate with Grignard reagents was studied using catalytic amounts of copper(I)-arylthiolate (*rac*)-**1** (Scheme 2), where the arenethiolato group acts as a non-transferable group on copper. This reaction gave an even more pronounced γ-selectivity, than the previously used copper catalysts.[7]



Scheme 1. Allylic substitution of acetate with Grignard reagent performed either by an S_N2-type reaction to give the α-product or an S_N2'-type reaction to give the γ-product.

The need for efficient methods to prepare enantiomerically pure compounds has led to a continuously growing interest in asymmetric synthesis, especially asymmetric catalysis. In metal-catalyzed asymmetric synthesis the chirality can be introduced by the coordination of an enantiomerically pure ligand to the metal, assuming that the chirality is in near proximity to the reaction center. Ferrocene ligands have gained much interest in asymmetric catalysis, as numerous structural variations are possible.[8] Furthermore, ferrocenes may possess two kinds of chirality: (i) the central chirality of substituents and (ii) the element of planar chirality in

Keywords: Asymmetric induction; Copper catalysis; Allylic substitution; Cross-coupling; Ferrocene ligands.
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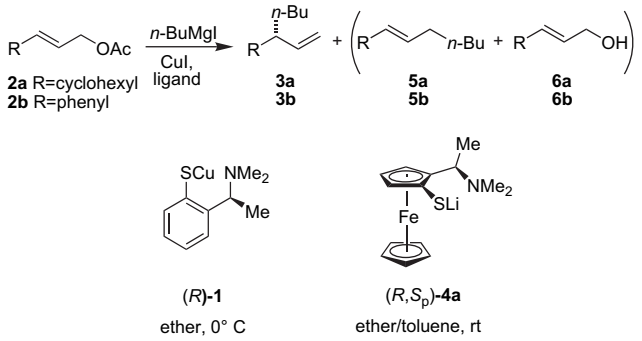


Scheme 2. Enantioselective substitution of allylic acetates with Grignard reagents and copper thiolate complexes.

unsymmetrical 1,2- and 1,3-substituted ferrocenes. Ferrocene is, by far, the metallocene most frequently used for chiral ligands. However, some examples of ruthenocene ligands have also been reported.[9]

The scope of the allylic substitution of acetate using Grignard reagents was extended to asymmetric catalysis, by using enantiomerically pure non-transferable ligands on copper; in this way the chiral ligand is in close proximity to the metal. Indeed, the use of copper(I)-arylthiolate **1** in the allylic substitution of **2a** with Grignard reagent gave the γ-product **3a** with an enantiomeric excess of 42%, Scheme 2.[10] Using the corresponding ferrocenylthiolate ligand **4a** gave the highest enantioselectivity obtained thus far with allylic acetates (64% ee).[11] Only traces of the α-product **5a** were formed and no alcohol **6a** could be detected. Substrate **2b** gave a lower enantiomeric excess (42%) with ligand **4a**.

Other groups have reported on asymmetric allylic substitution using external ligands.[12] Knochel, for example, has obtained an excellent result with 1-ferrocenylethylamines in reactions of allylic chlorides with dialkylzinc reagents, and Hoveyda has recently with success employed heterocyclic carbene ligands with allylic phosphates.[12g]

Arenethiols are susceptible to oxidation, forming the disulfide in the presence of oxygen.[13] This tendency is more pronounced for the electron-rich ferrocenylthiols.[14] Hence, protonation of lithium thiolate **4a** led to disulfide formation. Therefore, the copper(I) complex was generated in situ, by mixing lithium thiolate **4a** and a copper salt.[11]

A systematic screening of ligands was pursued in order to gain an insight into the factors governing the copper-catalyzed substitution of allylic acetates. We also investigated plausible background reactions that may lead to a less enantioselective formation of product. In order to obtain more robust reaction conditions, disulfide **7a** was tested as a ligand precursor.

2. Results and discussion

2.1. Ligand selection

Since a change of the steric and electronic properties of the ligand affected the enantioselectivity of the allylic substitution, by exchanging ligand **1** for ligand **4a**, ligand screening

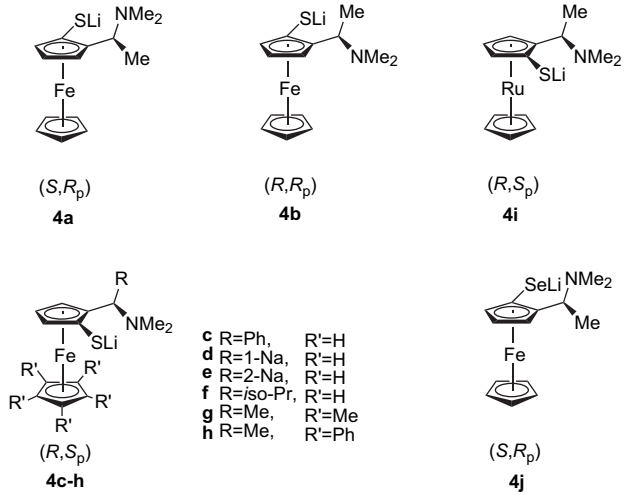


Figure 1. Ligands for the copper(I)-catalyzed allylic substitution.

based on the ferrocene structure was pursued, Figure 1. Due to the choice of method of preparation the ligands depicted in Figure 1 are of different absolute configuration. In one case also the relative stereochemistry is different (**4b**).

We wanted to study the effect of changing the substituent R and chose aliphatic, as well as, aromatic substituents in target compounds **4c–f**. Knochel and co-workers have shown that increased bulk of the R-group, led to higher enantioselectivity in the asymmetric copper-catalyzed reaction of allylic chloride with diorganozinc compounds.[12a,b]

The increase in enantioselectivity when changing from copper(I) complex **1** to the corresponding ferrocene ligand **4a** might be explained by a shielding effect of the lower cyclopentadienyl (Cp) ring. By introducing substituents on the lower Cp-ring the shielding effect would be even more pronounced. Furthermore, introducing substituents on the lower Cp-ring provides ligands that are assumed to exhibit different electronic properties, which in turn might affect the stability of the ligand. Hence, target compounds **4g** and **4h** were selected, possessing different steric and electronic properties.

Ruthenocene ligands have recently gained some interest. Fu reported on an accelerated reaction rate with ruthenocene over ferrocene but less chiral induction in most cases.[9a] According to Fu the lower enantioselectivity could be explained by the ruthenocene being less chiral than the corresponding ferrocene, due to the greater distance between the Cp-rings and thereby enhanced flexibility. Togni and co-workers reported on a slight decrease in enantioselectivity with ruthenocene over ferrocene ligands in palladium-catalyzed alkylation and rhodium-catalyzed hydroboration reactions.[9b] On the other hand, Hayashi and co-workers showed that in the case of bidentate ligands with coordination sites on both Cp-rings, the bite angle of the ligand changed, due to the difference in distance between the Cp-rings in ferrocene and ruthenocene. This did in fact have a positive effect on the enantioselectivity.[9c] Bolm reported that a very small difference in selectivity was observed between C_2-symmetric 1,1′-bis(oxazolinyl)metallocenes of Fe and Ru in asymmetric phenyl transfer from organozincs to aldehydes.[9d]

In our case, a change of the metal might have an impact on the stability of the copper complex, and therefore target compound **4i** was selected.

Arylthiolates are known to be excellent non-transferable ligands on copper due to the strong copper–sulfur bond. One approach to further increase the stability of the copper complex would be to make the ligand bind even more strongly to copper. This effect might be achieved by employing selenium instead of sulfur. Target compound **4j** was therefore selected.

As there might be a matched or mismatched situation in terms of chiral induction, ligand **4b** with reversed relative stereochemistry, in comparison to ligand **4a**, was prepared.

2.2. Ligand synthesis

The thiolate ligand **4a** has previously been prepared by stereoselective *ortho*-lithiation of enantiopure amine (*S*)-**8a**, followed by addition of elemental sulfur.[11] Amine (*S*)-**8a** was prepared according to a literature procedure, where resolution of (*rac*)-**8a**, which is known as Ugi's amine, with tartaric acid afforded enantiomerically pure (*S*)-amine, Figure 2.[15] The same procedure was used for the preparation of ligands **4c–g** and **4i**, except that the intermediate alcohol was obtained via enantioselective CBS-reduction, omitting the resolution step.[16,17] In these cases, the products with (*R*)-configuration were formed. Ligand **4b** was prepared from (*R*)-**8a** obtained from the mother liquor in the resolution step.

The chirality of the ligands was created in two key steps, enantioselective reduction to the alcohol and stereoselective *ortho*-lithiation of the amine (vide infra). The enantiomeric purity of the ligands was governed by the outcome of both these two reactions.

Ferrocene and ruthenocene were subjected to standard Friedel–Craft acylation conditions to give acylmetallocenes **9c–f** and **9i**, Scheme 3. Acylation of the pentasubstituted ferrocenes was not straightforward and an alternative method for the preparation of acetyl ferrocenes **9g** and **9h** was developed by mixing $FeCl_2$, sodium acetylcyclopentadienide and pentasubstituted lithium cyclopentadienide in good yields, which we have reported elsewhere.[18]

Enantioselective CBS-reduction of the ferrocenyl ketones has been performed previously.[17] We had problems in reproducing the published results and tried both commercially available methyl-oxazaborolidine and in situ prepared oxazaborolidine catalyst.[19] The difficulties encountered with the CBS-reduction may be ascribed to the purity of the catalyst and solvents used. Alcohols **10c** and **10f–h** were obtained in high enantiomeric excess, Scheme 3. Naphthyl

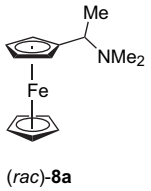
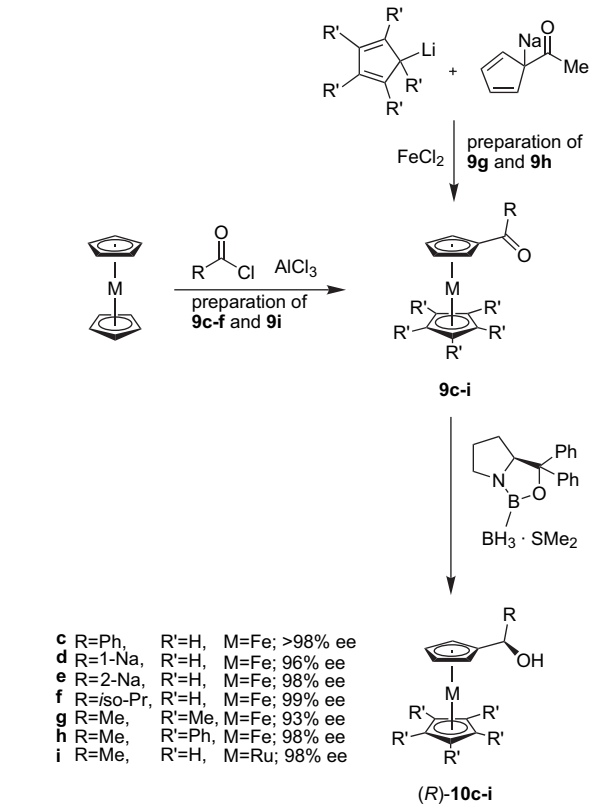


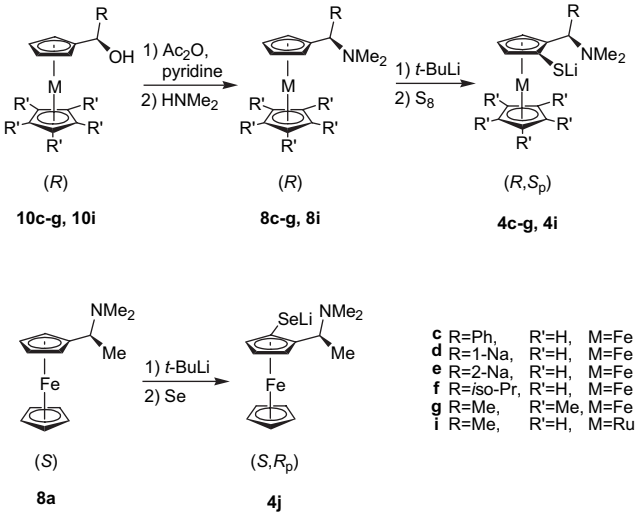
Figure 2. Ugi's amine.



Scheme 3. Preparation of chiral alcohols **10c–i**.

alcohols **10d** and **10e**, on the other hand, had to be recrystallized to give satisfactory enantiomeric excess. Hayashi has prepared the enantiomerically pure alcohol **10i** by treating ruthenocenecarboxaldehyde with dimethylzinc in the presence of a chiral ligand for an extensive period of time.[9c] As we had experience of CBS-reduction, this method was used instead and yielded alcohol **10i** in 45 min with excellent results.

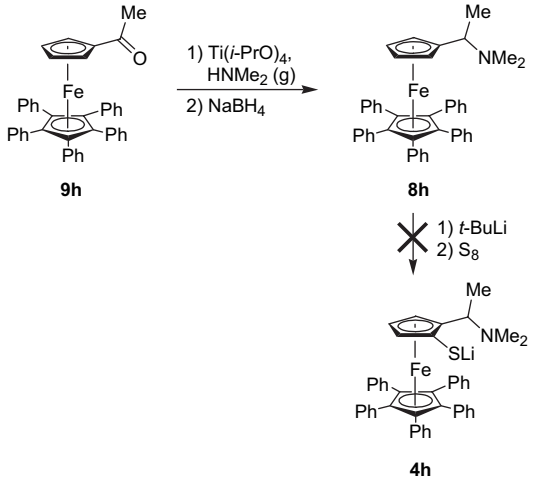
Alcohols **10c–i** were transformed to the corresponding acetates, which were substituted by dimethylamine to give amines **8c–g** and **8i**, in high yields (Scheme 4). Substitution



Scheme 4. Preparation of ligands **4c–g**, **4i**, and **4j**.

of an acetate group, at the α-carbon to ferrocene, proceeds via an S_N1-type of reaction, by anchimeric assistance from the metal with retention of the configuration at the carbon.[20] Hence, the enantiomeric excess of the alcohols is transferred to the amines.

The phenyl groups on the pentaphenyl-substituted ferrocene affected the reactivity of the ferrocene structure to a large extent. Alcohol **10h** was transformed into the corresponding acetate. No substitution of acetate by amine was observed when the acetate was treated with dimethylamine. This might be a consequence of the steric properties of the lower Cp-ring, but it may also be due to electronic effects. The racemic amine **8h** was instead prepared by reductive amination of the ketone **9h** employing a modified Ti(*i*-PrO)$_4$/HNMe$_2$/NaBH$_4$-system, Scheme 5.[21]

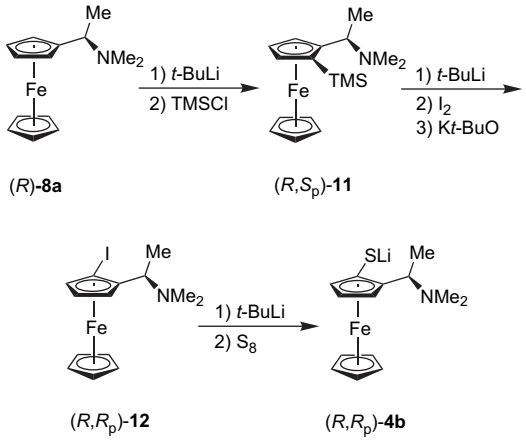


Scheme 5. Attempted preparation of ligand **4h**.

The amines **8c–g** and **8i** were *ortho*-lithiated by *t*-BuLi in ether and treated with elemental sulfur, Scheme 4.[11] Ligand **4j** was obtained by treating Ugi's amine with *t*-BuLi and selenium. For ligands **4b–e**, **4g**, and **4j** the lithium salts precipitated. Depending on the solubility of the product the precipitate was washed either with diethyl ether or hexane. In the case for ligand **4f** no material was precipitated and the solvent was removed by evaporation. The crude ligand was used in the allylic substitution without further purification. The purity of the ligands depended in this step on the selectivity of the *ortho*-lithiation, which was governed by the steric properties of the amine,[22] and the purification obtained in the precipitation of the lithium salts.

Attempts to *ortho*-lithiate the pentaphenyl-substituted amine **8h** by a variety of lithium sources in different solvents and at different temperatures were unsuccessful, Scheme 5. Unsuccessful lithiation of pentaphenyl-substituted ferrocenes has also been reported by others.[23]

The diastereomer with reversed planar chirality **4b** was obtained by treating (*R*)-**8a** with *t*-BuLi and TMS–Cl, blocking the *ortho*-position, which is preferably lithiated, Scheme 6.[24] The resulting compound **11** was subjected to an additional lithiation in the remaining *ortho*-position, followed by treatment with iodine as electrophile and removal of the TMS-group by base,[25] acquiring the diastereomer with reversed planar chirality, compound **12**. The lithium thiolate **4b** was subsequently obtained by halogen–metal exchange employing *t*-BuLi[26] and treatment with elemental sulfur. The bulky *t*-BuLi was used to prevent alkylation of the ferrocene by attack on the alkyl iodide formed during the reaction.



Scheme 6. Preparation of the diastereomeric ligand **4b** with reversed planar chirality.

2.3. The stereochemical purity of the ligands

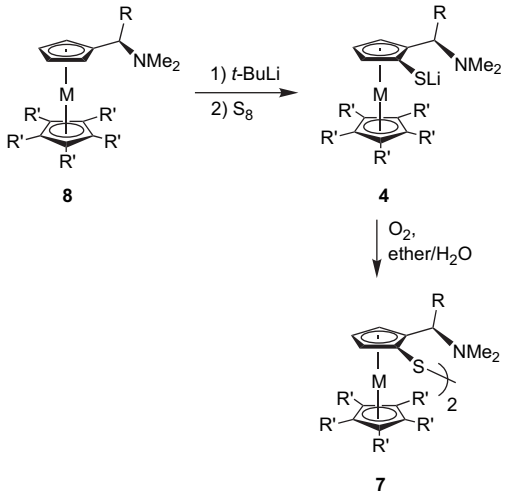
The enantiomeric and diastereomeric purity of the ligands is essential for the enantioselectivity of the allylic substitution reaction. As the copper complexes often are trimers or tetramers the relationship between the purity of the ligand and the enantiomeric excess obtained in the allylic substitution might be nonlinear.[27] Both van Koten and Pfaltz report on negative nonlinear effects when using copper(I)thiolates in conjugate addition of Grignard reagents to cyclic enones.[28] In theory even small amounts of a fast reacting isomer, yielding racemic product might hamper the reaction and give low enantiomeric excess. When using a ligand contaminated with stereoisomers, low enantiomeric excess may be caused by the contamination. Hence, to be able to compare the results obtained with different ligands the purity has to be considered.

The alcohols **10c–i**, obtained in the enantioselective CBS-reduction, had very high enantiomeric excess. Since the conversion to the amines, via the acetate, proceeds with retention of configuration, it can be assumed that no racemization took place.

It is well established that the *ortho*-lithiation of amine **8a** is selective, with a diastereoselectivity of around 95%.[24a,29] The diastereoselectivity of the *ortho*-lithiation of similar amines is not so well studied, but can be assumed to be highly affected by the structure of the amine. However, the selectivity could only be measured by indirect methods as the lithium chalcogenides **4a–g**, **4i**, and **4j** degrade in the presence of oxygen. As the *ortho*-protons for amines **8d**, **8e**, and **8i** were separated in the ^{1}H NMR spectra the selectivity of the *ortho*-lithiation could easily be determined by treating the lithiated amines with methanol-d_4. This revealed that *ortho*-lithiation of naphthylamines **8d** and **8e** was highly selective and none of the diastereomer with reversed planar chirality could be detected, probably due to the bulky naphthyl-substituent. *Ortho*-lithiation of ruthenocene-derived amine **8i** on the other hand, gave a diastereomeric ratio of 80:20.

The lower selectivity for **8i** can be a result of the larger distance between the Cp-rings, thus allowing for a nitrogen-assisted lithiation on both sides of the substituent.

To determine the selectivity of the *ortho*-lithiation in the cases when the *ortho*-protons overlap and to determine the purity of the lithium thiolates, the lithium thiolates **4** were transformed to disulfide **7** by treatment with oxygen according to a known procedure, Scheme 7.[13] In those cases where the thiolates **4** obtained according to Scheme 4 would consist of diastereomeric mixtures, disulfide formation would lead to a diastereomeric mixture of disulfides, hence the ratio between the stereoisomeric disulfides **7** should be possible to analyze by ^{1}H NMR.



Scheme 7. Disulfide formation.

Disulfide and diselenide formation worked well for Ugi's amine-derived ligands **4a** and **4j** and showed that the crystallization of the lithium salts improved the diastereomeric purity, as only one diastereomer could be detected. In the case of **4c**, **4f**, and **4g** disulfide formation was sluggish and the diastereomeric purity could not be determined. For ligands **4d** and **4e** there was no need for disulfide formation as the *ortho*-lithiation was highly selective. Disulfide formation with ruthenocene-derived **4i** showed an 80:20 relationship between the two major disulfide diastereoisomers, which shows that the diastereomeric ratio of the monomeric sulfide **4i** was 89:11.

Despite the fact that some of the ligands had unsatisfactory stereochemical purity we intended to try them as ligands in the allylic substitution reaction.

2.4. Allylic substitution

The allylic substitution reactions were performed in diethyl ether with ligands **4b–g**, **4i**, and **4j** (0.3 equiv), CuI (0.15 equiv), and substrates **2a** or **2b**. Higher temperatures and a slow addition of the Grignard reagents are required for high regio- and stereoselectivities.[5,7,30] Thus the reactions were performed at either 0 °C or rt and *n*-BuMgI (1.5 equiv) was added over 2 h. The results were compared with those previously published of ligand **4a** (entries 1 and 3, Table 1).[11] Although somewhat higher enantioselectivity had been obtained in ether/toluene 3:1 than in ether, we decided to use ether as solvent, since the product is volatile and hence difficult to isolate from toluene.

Increasing the bulk of the R-group, as in ligands **4c–f** gave very low enantioselectivity in the allylic substitution reaction (entries 5–9, Table 1). In the case of ligand **4f**, purification of the lithium thiolate by crystallization was not possible. The allylic substitution was performed using the crude ligand prepared in situ, which may have affected the outcome of the reaction. It can anyhow be concluded that other groups than methyl on the α-carbon are detrimental to the chiral induction.

With the pentamethyl substituted ligand **4g** 33% ee was obtained (entry 8, Table 1). The ruthenocene ligand **4i** also

Table 1. Reactions between allylic acetates and *n*-BuMgl catalyzed by Cul and ligands **4a–g**, **4i**, and **4j**[a]

Entry	Substrate	Ligand	Product	ee (%)[b]	γ:α Ratio	**6** (%)	Conversion (%)	Isolated yield (%)
1[c]	**2a**	(S,R_p)-**4a**	**3a**	64 (*S*)-(+)	98:2	—	100	88
2	**2a**	(S,R_p)-**4a**	**3a**	62 (*S*)-(+)	97:3	0	100	88
3[d]	**2b**	(S,R_p)-**4a**	**3b**	42 (+)	94:6	—	100	78
4	**2b**	(S,R_p)-**4a**	**3b**	40 (+)	96:4	5	100	82
5	**2a**	(R,S_p)-**4c**	**3a**	14 (*R*)-(−)	95:5	8	100	52
6[e]	**2a**	(R,S_p)-**4d**	**3a**	6 (*R*)-(−)	95:5	3	100	65
7[e]	**2b**	(R,S_p)-**4e**	**3b**	0	92:8	2	100	64
8	**2b**	(R,S_p)-**4e**	**3b**	14 (−)	89:11	0	100	60
9	**2b**	(R,S_p)-**4f**	**3b**	2 (−)	100:0	60	85	25
10	**2a**	(R,S_p)-**4g**	**3a**	33 (*R*)-(−)	94:6	6	99	80
11	**2b**	(R,S_p)-**4i**	**3b**	20 (−)	92:8	2	100	89
12[f]	**2b**	(R,S_p)-**4i**	**3b**	20 (−)	93:7	0	100	83
13[f]	**2b**	(S,R_p)-**4a**	**3b**	31 (+)	86:14	2	100	90
14	**2a**	(S,R_p)-**4j**	**3a**	42 (*S*)-(+)	93:7	2	98	67
15	**2b**	(S,R_p)-**4j**	**3b**	41 (+)	94:6	3	100	78
16	**2b**	(R,R_p)-**4b**	**3b**	52 (+)	94:6	38	100	60

[a] Reaction conditions: The allylic acetate **2**, ligand **4** (0.30 equiv), and CuI (0.15 equiv) were mixed in diethyl ether at rt for 30 min. *n*-BuMgI (1.5 equiv) was added via a syringe pump over 2 h to maintain a low concentration. The reaction mixture was kept at rt for 1 h.
[b] Enantioselectivity was measured by chiral GC, except for entries 2 and 6, which were measured by optical rotation.
[c] The reaction was performed in diethyl ether/toluene 3:1, with 13% CuI, and a ligand/CuI ratio of 2.7:1.
[d] The reaction was performed at 0 °C, with 13% CuI, and a ligand/Cu ratio of 1.3:1.
[e] The reaction was performed at 0 °C.
[f] *n*-BuMgI was added over 3 min.

gave lower enantioselectivity (20%) than ligand **4a** (entries 11 and 12, Table 1). However, the reaction was considerably faster. The same γ:α selectivity and enantioselectivity were obtained when the Grignard reagent was added over 2 h (standard conditions) or over 3 min. In the case of ligand **4a** the γ:α selectivity and the enantioselectivity dropped considerably when adding the Grignard reagent over 3 min (entry 13, Table 1). The faster reaction rate can be explained by the stronger coordinating ability of the ruthenocene ligand, compared to the ferrocene equivalent. The lower chiral induction can be a consequence of the lower diastereomeric purity (78% de) of **4i**, but it is more likely caused by the fact that the planar chirality is less pronounced, due to the greater distance between the Cp-rings in ruthenocene and therefore enhanced flexibility compared to ferrocene.[9a]

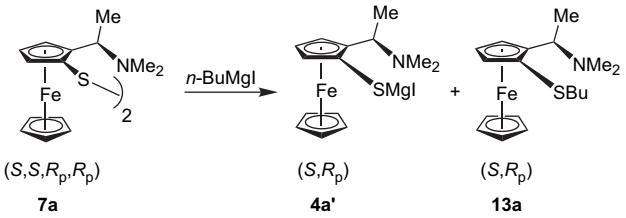
The lithium selenide **4j** gave the same enantioselectivity with cinnamyl acetate **2b** as ligand **4a**. However, for substrate **2a** ligand **4j** gave lower enantioselectivity in the allylic substitution than ligand **4a** (entries 14 and 15, Table 1), which is not the case for ligand **4a**.

Allylic substitution with the diastereomer of reversed planar chirality **4b**, compared to ligand **4a**, gave 52% ee with substrate **2b** (entry 16, Table 1). This is higher than the chiral induction obtained with ligand **4a**. It may therefore be that the chiral induction obtained with ligand **4a** is a mismatched situation, while a matched situation exists for ligand **4b**. It is interesting to note that the absolute configuration in the allylic substitution is governed by the planar chirality.

2.5. The disulfide as a ligand precursor

The difficulty in purifying the lithium thiolate and the susceptibility toward degradation prompted us to investigate the possibility of preparing a ligand precursor that would generate the ligand in situ. Disulfide formation worked cleanly for ligand **4a** resulting in disulfide **7a**, Scheme 7. It is known that disulfide bridges can be cleaved reductively.[31] Uemura showed that $LiAlH_4$ in THF could cleave the corresponding diselenide.[13] For the copper(I)-catalyzed substitution of allylic acetates, the cleavage of the disulfide in situ requires a reagent that does not affect the allylic substitution reaction. Alkali metal hydrides were therefore ruled out. Cleavage with alkali metal was attempted but so far this has been without success.

Dichalcogenides have previously been reported as ligand precursors, heterolytically cleaved in situ.[32] We decided to cleave the disulfide with the Grignard reagent employed in the allylic substitution reaction. Addition of 1 equiv of *n*-BuMgI to the disulfide resulted in heterolytic cleavage generating 1 equiv of magnesium thiolate **4a′** and 1 equiv of the corresponding butyl thioether **13a** in situ, Scheme 8. If the butyl thioether **13a** does not affect the allylic substitution negatively the disulfide **7a** can be used as a ligand precursor, generating the desired ligand with the Grignard reagent.



Scheme 8. Disulfide **7a** used as a ligand precursor, generating the desired ligand **4a′** in situ.

Allylic substitution with substrate **2a** under standard conditions gave 62% ee (entry 1, Table 2). Performing the allylic substitution on substrate **2a** without any ligand present gave almost only the alcohol by-product **7** (entry 2, Table 2). Employing the disulfide **7a** as a ligand afforded the desired product in high yield with 50% ee (entry 3, Table 2). The decrease in enantioselectivity can be explained by the presence of 1 equiv of butyl thioether **13a**. In a control experiment it was shown that the latter compound, when used as ligand in the same reaction afforded the product, though with a very low yield and in an almost racemic form (entry 4, Table 2). When the free amine **8a** was used as ligand in the allylic substitution with substrate **2b** racemic material was obtained (entry 5, Table 2). Employing substrate **2b** showed an even larger difference between the reactions using the thiolate ligand **4a** and the disulfide **7a**, 38 versus 18% ee (entries 6 and 7, Table 2). This can be explained by a higher reaction rate observed for the butyl thioether **13a** with substrate **2b**, compared to substrate **2a** (entry 8, Table 2). Furthermore, the butyl thioether **13a** gave the opposite enantiomer in the allylic substitution.

In conclusion, when using the disulfide **7a** as a ligand precursor the reaction catalyzed by the butyl thioether **13a** has to

Table 2. Reactions between allylic acetates and *n*-BuMgI catalyzed by CuI in the presence of ligand **4a**, ligand precursor **7a**, or **13a**[a]

Entry	Substrate	Ligand	Product	ee (%)[b]	γ:α Ratio	**7** (%)[c]	Conv (%)[c]	Yield (%) (**3**+**5**)[c]
1	**2a**	(S,R_p)-**4a**	**3a**	62 (*S*)-(+)	97:3	0	100	98
2	**2a**	—	**3a**	Not det.	Not det.	91	94	3
3[d]	**2a**	(S,S,R_p,R_p)-**7a**	**3a**	50 (*S*)-(+)	96:4	0	97	94
4	**2a**	(S,R_p)-**13a**	**3a**	3 (*R*)-(−)	80:20	25	32	6
5	**2b**	(*S*)-**8a**	**3b**	2 (+)	96:4	14	93	55
6	**2b**	(S,R_p)-**4a**	**3b**	38 (+)	96:4	5	100	90
7[d]	**2b**	(S,S,R_p,R_p)-**7a**	**3b**	18 (+)	96:4	10	100	84
8	**2b**	(S,R_p)-**13a**	**3b**	11 (−)	97:3	14	92	61

[a] Reaction conditions: The allylic acetate **2**, ligands (0.30 equiv) and CuI (0.15 equiv) were mixed in diethyl ether at rt for 30 min. *n*-BuMgI (1.5 equiv) was added via a syringe pump over 2 h to maintain a low concentration. The reaction mixture was kept at rt for 1 h.
[b] Enantioselectivity was measured by chiral GC, except for entry 1, which was measured by optical rotation.
[c] Determined by GC with 2-decanol as internal standard, for entries 1–3 and by ^{1}H NMR with 2-decanol as internal standard, for entries 4–8.
[d] The ligand/metal ratio was 1.2.

be suppressed, otherwise a decrease in enantioselectivity compared to the lithium thiolate catalyzed reaction will be observed. For substrate **2a** this might be possible, as the reaction catalyzed by the butyl thioether is slow, but not for substrate **2b**.

3. Conclusions

A systematic variation of the structure of thiolate ligands for the copper(I)-catalyzed substitution of allylic acetates was conducted. Eight different ligands (**4b–g**, **4i**, and **4j**) were prepared and employed in the allylic substitution reaction. Ligands **4c–g**, **4i**, and **4j** gave lower enantioselectivity than ligand **4a**. In agreement with Fu's observations, ruthenocene ligand **4i** gave a lower chiral induction than the corresponding ferrocene ligand, but an enhanced reaction rate. Ligand **4b** with reversed planar chirality (in comparison to ligand **4a**) gave a slightly better enantioselectivity than diastereomer **4a**.

A more robust system was investigated, employing disulfide **7a** as a ligand precursor. Generating the ligand **4a′** in situ by the reaction with the Grignard reagent would be useful if the butyl thioether **13a** did not catalyze the reaction. In the case of substrate **2a** this might be possible as only a small decrease of the enantioselectivity was observed with **7a** as a ligand precursor, compared to **4a** (64 versus 50% ee). Indeed, for substrate **2a** the butyl thioether did not catalyze the reaction. On the other hand, for substrate **2b** the butyl thioether did catalyze the racemic reaction and a substantial decrease of enantioselectivity was observed (38 versus 18% ee).

4. Experimental

4.1. General

^{1}H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were recorded on a Varian Mercury spectrometer. Chemical shifts (δ) are reported in parts per million, using residual solvent proton resonance or tetramethylsilane as internal standard. IR-spectra were obtained using a Perkin–Elmer 1600 FTIR instrument and the samples were examined on NaBr plates. Only the strongest/structurally most important peaks (cm^{-1}) are listed. Optical rotation was obtained on a Perkin–Elmer 241 Polarimeter. Merck silica gel 60 (240–400 mesh) was used for flash chromatography and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Unless otherwise noted, all the materials were obtained from commercial suppliers and used without further purification. All the reactions were performed under argon, using freshly distilled solvents. Ether was distilled from sodium benzophenone ketyl radical, hexane was distilled from sodium, and pentane was distilled from calcium hydride prior to use. Ruthenocene was prepared according to a published procedure.[33] Compounds **2a**,[5c] **7a**,[13] **8a**,[15] **8f**,[34] **8g**,[17] **8i**,[9c] **10c**,[35] and **12**,[25] were prepared according to published procedures and analytical data were in agreement with the literature. The enantiomeric excess of the intermediate alcohol **10f** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 95:5; rt_{major}=11.5 min, rt_{minor}=12.3 min. Compound **13a** was prepared by treating **4a** with *n*-BuI and analytical data were in agreement with the literature.[36]

The allylic substitution reactions were performed as previously reported, unless stated in Tables 1 or 2.[10b,11] Analytical and spectroscopic data for products **3a** and **5a**,[5c] **3b** and **5b**[37] were in agreement with those in the literature. The absolute configuration of **3a** was assigned from the optical rotation, accordingly to previously reported data.[10b,38]

4.1.1. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-phenylmethylamine 8c.[39] The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10c** was determined to be 98% by chiral HPLC, using an AD-column with 0.5 ml/min of hexane/isopropanol 95:5; rt_{major}=37.5 min, rt_{minor}=48.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J=7.4 Hz, 2H), 7.40 (t, J=7.4 Hz, 2H), 7.30 (t, J=7.4 Hz, 1H), 4.22–4.17 (m, 2H), 4.16–4.12 (m, 1H), 4.12–4.05 (m, 1H), 3.78 (s, 1H), 3.73 (s, 3H), 2.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 128.6, 128.0, 127.1, 90.5, 72.4, 70.6, 68.8, 68.6, 67.3, 66.5, 44.6; $[\alpha]_D^{21}$ +108 (*c* 1.88, $CHCl_3$).

4.1.2. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-1-naphthylmethylamine 8d. The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10d** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 90:10; rt_{major}=29.2 min, rt_{minor}=41.1 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.67 (d, J=8.7 Hz, 1H), 7.91 (dd, J=7.8, 1.5 Hz, 1H), 7.85–7.80 (m, 2H), 7.61–7.48 (m, 3H), 4.57 (s, 1H), 4.28 (m, 1H), 4.24 (m, 1H), 4.12 (m, 1H), 4.10 (m, 1H), 3.45 (s, 5H), 2.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.4, 134.0, 132.2, 129.1, 127.5, 125.7, 125.6, 125.5, 125.4, 124.5, 91.2, 70.8 (2C), 68.6, 68.5, 67.5, 66.4, 45.1; $[\alpha]_D^{21}$ −96.6 (*c* 0.550, $CHCl_3$).

4.1.3. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-2-naphthylmethylamine 8e. The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10e** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 90:10; rt_{major}=30.1 min, rt_{minor}=48.6 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92–7.88 (m, 3H), 7.86 (d, J=2.1 Hz, 1H), 7.69 (dd, J=8.7, 1.8 Hz, 1H), 7.53–7.44 (m, 2H), 4.26 (m, 1H), 4.23 (m, 1H), 4.15 (m, 1H), 4.12 (m, 1H), 3.97 (s, 1H), 3.68 (s, 5H), 2.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1, 133.3, 132.9, 128.0, 127.8, 127.7, 127.11, 127.06, 126.10, 125.7, 90.5, 72.5, 70.5, 68.8, 68.6, 67.5, 66.6, 44.7; $[\alpha]_D^{21}$ +73.6 (*c* 0.635, $CHCl_3$).

4.1.4. (*rac*)-*N*,*N*-Dimethyl-1-pentaphenylferrocenylethylamine 8h. Titanium isopropoxide (0.469 ml, 1.59 mmol) was added to acetyl-pentaphenylferrocene (0.483 g, 0.794 mmol) dissolved in dichloromethane (5 ml). The solution was cooled to −15 °C and dimethylamine gas (1.27 g, 57 mmol) was condensed into the solution. The cooling bath was removed and the reaction mixture was kept at rt over night. An additional 5 ml of dichloromethane was added. The imine-solution was added dropwise to a suspension of sodium borohydride (126 mg, 3.32 mmol) in 10 ml of ethanol at rt. After 3 h the reaction had gone to completion. Saturated ammonium chloride was added and material

was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and evaporated. The material was purified by chromatography dichloromethane/MeOH 95:5 and 0.384 g of **8h** (76%) was obtained as an orange colored solid. ^1H NMR ($CDCl_3$) δ 7.03–7.14 (m, 25H), 4.62 (m, 1H), 4.12 (dt, J=2.4, 1.5 Hz, 1H), 4.08 (dt, J=2.4, 1.2 Hz, 1H), 4.04 (m, 1H), 3.55 (q, J=6.6 Hz, 1H), 2.04 (s, 6H), 0.93 (d, J=6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 135.9, 132.4, 127.1, 126.0, 95.1, 87.3, 75.0, 74.8, 74.4, 72.0, 54.7, 39.8, 10.8; IR (neat): 3056, 2933, 2821, 1601, 1502, 1443, 1089, 1074, 1028, 908, 739, 700 cm^{-1}. HRMS (m/z) calculated for $C_{44}H_{39}FeN$ (M^+), 637.2432; found, 637.2488.

4.1.5. General procedure for the preparation of thiolates 4a, 4c–g, 4i, and selenoate 4j. Amine **8** was added to a dry Schlenk tube, dissolved in ether and cooled to −15 °C. *t*-BuLi (1.05 equiv, 1.7 M in pentane) was added. The reaction mixture was stirred at −15 °C for 15 min and thereafter for 1 h at rt. In another Schlenk tube, sulfur or selenium (0.97 equiv) was suspended in ether and cooled to −15 °C. The lithiated amine was transferred to the sulfur or selenium suspension. The resulting mixture was stirred at −15 °C for 15 min and thereafter at rt for 1 h and worked up as described below for each case.

4.1.5.1. Thiolate 4a. Amine **8a** (532 mg, 2.07 mmol in 7 ml ether) was lithiated with *t*-BuLi (2.28 mmol), followed by treatment with S_8 (63 mg, 1.97 mmol), according to the general procedure. About half of the solvent was evaporated from the precipitate formed. The residing mother liquor was withdrawn from the product, which was subsequently washed with ether (3×3 ml). Ligand **4a** was isolated in 482 mg (79%) as an orange colored solid.

4.1.5.2. Thiolate 4c. Amine **8c** (159 mg, 0.498 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.525 mmol), followed by treatment with S_8 (16.0 mg, 0.499 mmol in 2 ml of ether), according to the general procedure. The product precipitated after the addition of 1.5 ml pentane. After removal of the mother liquor, the product was washed with pentane (3×1.5 ml). Ligand **4c** was isolated in 143 mg (80%) as an orange colored solid.

4.1.5.3. Thiolate 4d. Amine **8d** (190 mg, 0.520 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.566 mmol), followed by treatment with S_8 (16.0 mg, 0.499 mmol in 2 ml of ether), according to the general procedure. The product precipitated. After removal of the mother liquor, the product was washed with ether (2×1 ml). Ligand **4d** was isolated in 29 mg (14%) as an orange colored solid.

4.1.5.4. Thiolate 4e. Amine **8e** (200 mg, 0.542 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.704 mmol), followed by treatment with S_8 (17.3 mg, 0.542 mmol in 2 ml of ether), according to the general procedure. The product precipitated after the addition of 3.0 ml pentane. After removal of the mother liquor, the product was washed with pentane (2×1.5 ml). Ligand **4e** was isolated in 126 mg (57%) as an orange colored solid.

4.1.5.5. Thiolate 4f. Amine **8f** (255 mg, 0.895 mmol in 3 ml ether) was lithiated with *t*-BuLi (1.164 mmol), followed by treatment with S_8 (28.7 mg, 0.895 mmol in 2 ml of ether), according to the general procedure. The product did not precipitate; instead the solvent was removed in vacuo obtaining **4f** as an orange colored solid.

4.1.5.6. Thiolate 4g. Amine **8g** (345 mg, 1.05 mmol in 4 ml ether) was lithiated with *t*-BuLi (1.10 mmol), followed by treatment with S_8 (32.7 mg, 1.02 mmol in 3 ml of ether), according to the general procedure. All the solvent was evaporated and hexane (3 ml) was added. The precipitate, which then formed, was washed with hexane (3×3 ml). Ligand **4g** was isolated in 258 mg (67%) as an orange colored solid.

4.1.5.7. Thiolate 4i. Amine **8i** (262 mg, 0.868 mmol in 3 ml ether) was lithiated with *n*-BuLi (1.128 mmol), followed by treatment with S_8 (27.9 mg, 0.868 mmol in 3 ml of ether), according to the general procedure. The product precipitated after the addition of 1.5 ml pentane. After removal of the mother liquor, the product was washed with pentane (3×1.5 ml). Ligand **4i** was isolated in 133 mg (45%) as white solid.

4.1.5.8. Selenoate 4j. Amine **8a** (545 mg, 2.12 mmol in 7 ml ether) was lithiated with *t*-BuLi (2.23 mmol), followed by treatment with Se (159 mg, 2.01 mmol in 5 ml ether), according to the general procedure. About half of the solvent was evaporated from the precipitate formed. The residing mother liquor was withdrawn and the product was subsequently washed with ether (3×3 ml). Ligand **4j** was isolated in 361 mg (50%) as an orange colored solid.

4.1.5.9. Thiolate 4b. (R,R_p)-1-iodo-2-(1-*N*,*N*-dimethylaminoethyl) ferrocene (**12**) (331 mg, 0.864 mmol in 3 ml ether) was treated with *t*-BuLi (0.907 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, followed by 30 min at rt. The reaction mixture was transferred to another Schlenk tube containing S_8 (27 mg, 0.838 mmol in 3 ml ether). The product precipitated after evaporation of half the ether, followed by addition of 2 ml of hexane. The crude product was washed with hexane (3×3 ml). Ligand **4b** was isolated in 84 mg (33%) as an orange colored solid.

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Reaction between *tert*-butyl isocyanide, dialkyl acetylenedicarboxylates, and aromatic carboxylic acids: an efficient method for the synthesis of dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives

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Abstract—Protonation of the reactive intermediates produced in the reaction between *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates by aromatic carboxylic acids leads to vinylnitrilium cations, which undergo nucleophilic reaction with conjugate bases of the carboxylic acids to produce dialkyl (*E*)-2-[(benzoyloxy)(*tert*-butylimino)methyl]-2-butenedioates and this intermediate rearranges to the dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives.

1. Introduction

Within the last decade, the resurgence of interest in multicomponent reactions (MCRs) has been considered, not only because of their inherent atom efficiency and ease of implementation, but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies or parallel synthesis.[1,2] The ability of an isonitrile to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs.[3–9]

In the context of our on going studies on heterocyclic construction mediated by zwitterionic intermediates,[10] the possibility of trapping the 1:1 intermediate formed between dialkyl acetylenedicarboxylate and isocyanides with suitable O–H acids appeared attractive from the viewpoint of devising a novel MCR.[11]

Although the trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with O–H, N–H, and C–H acids has been widely studied,[10–14] trapping of the initially formed 1:1 intermediate with carboxylic acids has not been reported.

We wish to report a simple one-pot three-component reaction between dialkyl acetylenedicarboxylates and *tert*-butyl isocyanide in the presence of aromatic carboxylic acids leading to yield dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives **3**.

2. Results and discussion

The reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylates **1** in the presence of aromatic carboxylic acids **2** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature, to produce dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives **3** in 61–98% yields (Scheme 1).

The structures of compounds **3a–g** were deduced from their elemental analysis, IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion (MC) peak at 376 *m*/*z*, which is consistent with the 1:1:1 adduct of dimethyl acetylenedicarboxylate, *tert*-butyl isocyanide, and benzoic acid. The ^{1}H NMR spectrum of **3a** exhibited four single sharp singlets readily recognized as arising from *tert*-butyl group (δ=1.62 ppm), methoxy (δ=3.65 and 3.84 ppm) protons along with an vinylic CH (δ=6.44 ppm). The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 14 distinct resonances in agreement with the dimethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate structure. Partial assignment of these resonances is given in Section 4.

Keywords: Alkyl isocyanide; Dialkyl acetylenedicarboxylate; Aromatic carboxylic acid; Multicomponent reaction.
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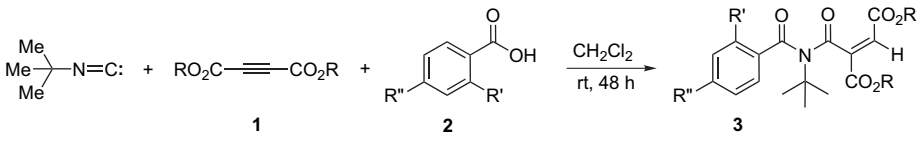


3	R	R'	R"	% Yield of 3
a	Me	H	H	95
b	Et	H	H	98
c	^{i}Pr	H	H	97
d	^{t}Bu	H	H	97
e	Me	H	NO_2	61
f	Me	OCOMe	H	74
g	Et	OCOMe	H	95

Scheme 1.

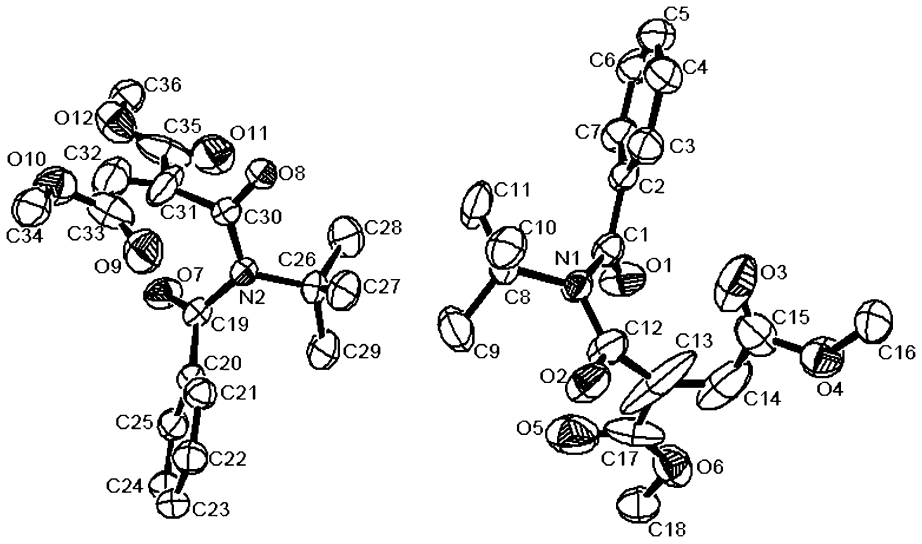
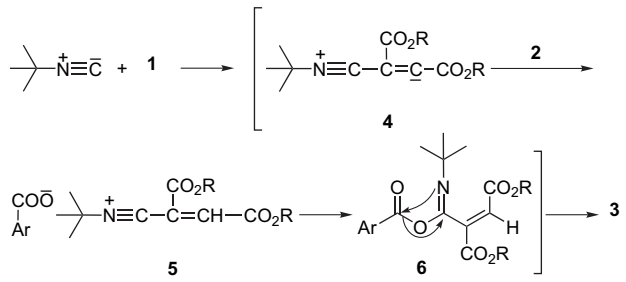


Figure 1. The molecular structure of compound **3a**.

Finally, **3a** was further confirmed by a single crystal X-ray diffraction analysis (Fig. 1).

The ^{1}H and ^{13}C NMR spectra of compounds **3b–g** are similar to those of **3a**, except for the aromatic moiety, and the ester groups, which exhibit characteristic signals with appropriate chemical shifts (see Section 4).

Although we have not established the mechanism of the reaction between the isocyanides and the acetylenic esters in the presence of the carboxylic acid derivatives **2** in an experimental manner, a possible explanation is proposed in Scheme 2.



Scheme 2.

On the basis of the well-established chemistry of isocyanides,[15–20] it is reasonable to assume that the compound **3** apparently results from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **4** by compound **2**, followed by attack of the carboxylate anion on the positively charged ion **5** to form imidoyl carboxylate **6**, which undergoes rearrangement[21–23] under the reaction condition employed, to produce the compound **3** (Scheme 2).

3. Conclusion

In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of carboxylic acids is a regioselective reaction and provides a simple one-pot entry into the synthesis of dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)-amino]carbonyl}-2-butenedioate derivatives of potential synthetic. The present method carries the advantage that, not only is the reaction performed under neutral condition, but also the substances can be mixed without any activation or modification.

4. Experimental

Dimethyl, diethyl and di(*tert*-butyl) acetylenedicarboxylates, and *tert*-butyl isocyanides were obtained from Merck

(Germany) and Fluka (Switzerland) and were used without further purification. Diisopropyl acetylenedicarboxylate was prepared according to the literature procedure.[24,25] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O– Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

4.1. General procedure for preparation of compound 3a–d, exemplified on 3a

To a magnetically stirred solution of 0.14 g of dimethyl acetylenedicarboxylate (1 mmol) and 0.12 g of benzoic acid (1 mmol) in 5 mL dry CH_2Cl_2 was added dropwise a solution of 0.083 g of *tert*-butyl isocyanide (1 mmol) in 3 mL dry CH_2Cl_2 at room temperature over 10 min. The reaction mixture was then allowed to stir for 48 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–ethyl acetate mixture (5:2) as eluent.

4.1.1. Dimethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3a. Colorless crystals, mp 130–132 °C, solvent of crystallization ethyl acetate, yield 0.33 g, 95%. IR (KBr) (ν_{max} cm^{-1}): 1716 (OCNCO), 1680 (CO_2Me), 1650 (C=C), 1586 and 1435 (Ph), 1368, 1296, 1263, 1210, and 1178 (C–O). MS, *m*/*z* (%): 347 (M^+, 2), 233 (1), 232 (7), 226 (1), 171 (20), 105 (100), 77 (55), 57 (12), 41 (8). Anal. Calcd for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03%. Found: C, 62.21; H, 6.10; N, 4.00%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.62 (9H, s, C*Me*$_3$), 3.65 (3H, s, OMe), 3.77 (3H, s, OMe), 6.44 (1H, s, CH), 7.42 (2H, dd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2CH$_{meta}$ of C_6H_5), 7.50 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.80 (2H, d, $^3J_{HH}$=7.4 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=28.46 (C*Me*$_3$), 52.45 (OMe), 52.86 (OMe), 59.88 (*C*Me$_3$), 128.48 (2CH$_{meta}$ of C_6H_5), 128.64 (2CH$_{ortho}$ of C_6H_5), 130.64 (C=*C*H), 134.29 (CH$_{para}$ of C_6H_5), 135.81 (C$_{ipso}$ of C_6H_5), 141.20 (*C*=CH), 162.27 (PhCON*C*O), 162.99 (*C*O$_2$Me), 163.78 (*C*O$_2$Me), 175.21 (Ph*C*ON).

Crystal data for **3a** $C_{18}H_{21}NO_6$ (CCDC 288926): M_W=347.36, monoclinic, space group $P2_1/n$, a=10.6670(6) Å, b=12.5163(7) Å, c=26.5532(14) Å, β=99.2400(10)°, V=3499.2(3) Å^3, Z=8, D_c=1.319 mg/m^3, $F(000)$=1472, crystal dimension 0.28×0.23×0.12 mm, radiation, Mo Kα (λ=0.71073 Å), $1.55\leq 2\theta\leq 25.00$, intensity data were collected at 293 K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-12\leq h\leq 12$, $-14\leq k\leq 14$, $-31\leq l\leq 31$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 33076 observed reflections with R(int)=0.0255 by a full-matrix least-squares technique converged to R=0.1069 and Rw=0.3149.

4.1.2. Diethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3b. Colorless crystals, mp 79–81 °C, yield 0.36 g, 98%. IR (KBr) (ν_{max} cm^{-1}): 1716 (OCNCO), 1690 (CO_2Et), 1661 (C=C), 1589 and 1443 (Ph), 1365, 1287, 1248, and 1182 (C–O). MS, *m*/*z* (%): 375 (M^+, 1), 329 (4), 319 (2), 302 (4), 279 (10), 246 (21), 224 (1), 199 (12), 190 (1), 176 (18), 167 (26), 149 (58), 113 (6), 105 (100), 77 (25), 71 (14), 57 (26), 43 (10), 41 (15). Anal. Calcd for $C_{20}H_{25}NO_6$ (375.42): C, 63.99; H, 6.71; N, 3.73%. Found: C, 64.00; H, 6.80; N, 3.70%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.26 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.28 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.62 (9H, s, C*Me*$_3$), 4.11 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 4.23 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 6.40 (1H, s, CH), 7.40 (2H, dd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2CH$_{meta}$ of C_6H_5), 7.57 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.83 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.8 (*C*H$_3$CH$_2$), 14.08 (*C*H$_3$CH$_2$), 28.49 (C*Me*$_3$), 59.97 (*C*Me$_3$), 61.52 (O*C*H$_2$CH$_3$), 62.14 (O*C*H$_2$CH$_3$), 128.45 (C=*C*H), 128.57 (2CH$_{meta}$ of C_6H_5), 130.57 (2CH$_{ortho}$ of C_6H_5), 134.12 (CH$_{para}$ of C_6H_5), 136.08 (C$_{ipso}$ of C_6H_5), 141.80 (*C*=CH), 162.56 (PhCON*C*O), 162.61 (*C*O$_2$Et), 163.45 (*C*O$_2$Et), 175.25 (Ph*C*ON).

4.1.3. Diisopropyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3c. Yellow oil, yield 0.40 g, 97%. IR (KBr) (ν_{max} cm^{-1}): 1713 (OCNCO), 1700 (CO_2^iPr), 1661 (C=C), 1590 and 1440 (Ph), 1286, 1258, 1248, and 1182 (C–O). MS, *m*/*z* (%): 403 (M^+, 2), 280 (2), 179 (12), 168 (3), 167 (35), 149 (100), 132 (2), 113 (11), 104 (4), 71 (31), 57 (57), 43 (36), 41 (32). Anal. Calcd for $C_{22}H_{29}NO_6$ (403.47): C, 65.49; H, 7.24; N, 3.47%. Found: C, 65.50; H, 7.30; N, 3.50%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.20 (6H, d, $^3J_{HH}$=6.3 Hz, CH*Me*$_2$), 1.22 (6H, d, $^3J_{HH}$=6.3 Hz, CH*Me*$_2$), 1.58 (9H, s, CMe$_3$), 4.91 (1H, hept, $^3J_{HH}$=6.2 Hz, *CH*Me$_2$), 5.03 (1H, hept, $^3J_{HH}$=6.2 Hz, *CH*Me$_2$), 6.31 (1H, s, C=CH), 7.36 (2H, t, $^3J_{HH}$=7.9 Hz, 2CH$_{meta}$ of C_6H_5), 7.53 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.82 (2H, d, $^3J_{HH}$=7.6 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=21.43 (OCH*Me*$_2$), 21.66 (OCH*Me*$_2$), 28.50 (C*Me*$_3$), 59.66 (*C*Me$_3$), 69.09 (O*C*HMe$_2$), 70.16 (O*C*HMe$_2$), 128.52 (4CH of C_6H_5), 130.49 (C=*C*H), 133.98 (CH$_{para}$ of C_6H_5), 136.24 (C$_{ipso}$ of C_6H_5), 142.28 (*C*=CH), 162.10 (PhCON*C*O), 162.73 (*C*O$_2^i$Pr), 162.99 (*C*O$_2^i$Pr), 175.18 (Ph*C*ON).

4.1.4. Di(*tert*-butyl) (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3d. Yellow oil, yield 0.42 g, 97%. IR (KBr) (ν_{max} cm^{-1}): 1709 (OCNCO), 1685 (CO_2^tBu), 1660 (C=C), 1590 and 1465 (Ph), 1399, 1364, 1270, and 1191 (C–O). MS, *m*/*z* (%): 431 (M^+, 2), 274 (12), 258 (14), 218 (16), 162 (24), 142 (16), 123 (14), 105 (100), 77 (24), 57 (83), 41 (24). Anal. Calcd for $C_{24}H_{33}NO_6$ (431.52): C, 66.80; H, 7.71; N, 3.25%. Found: C, 66.75; H, 7.60; N, 3.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.44 (9H, s, OCMe$_3$), 1.47 (9H, s, OCMe$_3$), 1.60 (9H, s, NCMe$_3$), 6.25 (1H, s, CH), 7.38 (2H, t, $^3J_{HH}$=7.8 Hz, 2CH$_{meta}$ of C_6H_5), 7.55 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.89 (2H, d, $^3J_{HH}$=7.4 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=27.71 (OC*Me*$_3$), 28.01 (OC*Me*$_3$), 28.60 (NC*Me*$_3$), 59.49 (N*C*Me$_3$), 81.97 (O*C*Me$_3$), 83.01 (O*C*Me$_3$), 128.57

(C=*C*H), 129.93 (2CH$_{meta}$ of C_6H_5), 130.56 (2CH$_{ortho}$ of C_6H_5), 133.88 (C_{ipso} of C_6H_5), 136.39 (CH$_{para}$ of C_6H_5), 142.57 (*C*=CH), 161.67 (PhCON*C*O), 162.73 (*C*O$_2^t$Bu), 163.06 (*C*O$_2^t$Bu), 175.32 (Ph*C*ON).

4.1.5. Dimethyl (*E*)-2-{[*tert*-butyl(4-nitrobenzoyl)amino]-carbonyl}-2-butenedioate 3e. Yellow oil, yield 0.24 g, 61%. IR (KBr) (ν_{max} cm^{-1}): 1717 (OCNCO), 1664 (CO_2Me), 1660 (C=C), 1596 and 1429 (Ar), 1521 and 1351 (NO_2), 1300, 1266, 1210, and 1190 (C–O). MS, *m*/*z* (%): 392 (M$^+$, 2), 260 (1), 228 (6), 171 (100), 150 (57), 138 (71), 121 (10), 104 (24), 84 (576), 59 (57), 41 (38). Anal. Calcd for $C_{18}H_{20}N_2O_8$ (392.36): C, 55.10; H, 5.14; N, 7.14%. Found: C, 5; H, 5.10; N, 7.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.60 (9H, s, C*Me*$_3$), 3.74 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 6.48 (1H, s, C*H*), 8.02 (2H, d, $^3J_{HH}$=8.8 Hz, 2CH of C_6H_4), 8.27 (2H, d, $^3J_{HH}$=8.9 Hz, 2CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=28.73 (C*Me*$_3$), 52.62 (O*Me*), 53.11 (O*Me*), 60.69 (*C*Me$_3$), 123.73 (2CH of C_6H_4), 128.44 (C=*C*H), 131.34 (2CH of C_6H_4), 141.17 (*C*=CH), 141.61 (*C*–CON), 150.74 (*C*–NO_2), 162.75 (ArCON*C*O), 162.97 (*C*O$_2$Me), 163.94 (*C*O$_2$Me), 174.11 (Ar*C*ON).

4.1.6. Dimethyl (*E*)-2-{[[2-(acetyloxy)benzoyl](*tert*-butyl)-amino]carbonyl}-2-butendioate 3f. Colorless crystals, mp 150–151 °C, yield 0.30 g, 74%. IR (KBr) (ν_{max} cm^{-1}): 1764 (OCOMe), 1718 (OCNCO), 1663 (CO_2Me), 1650 (C=C), 1593 and 1469 (Ar), 1365, 1300, 1259, and 1184 (C–O). MS, *m*/*z* (%): 405 (M$^+$, 2), 358 (2), 326 (1), 307 (6), 291 (3), 270 (7), 248 (8), 214 (8), 171 (71), 121 (100), 92 (16), 57 (12), 43 (14), 41 (6). Anal. Calcd for $C_{20}H_{23}NO_8$ (405.40): C, 59.25; H, 5.72; N, 3.46%. Found: C, 59.10; H, 5.80; N, 3.35%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.69 (9H, s, C*Me*$_3$), 2.29 (3H, s, OCO*Me*), 3.58 (3H, s, OMe), 3.84 (3H, s, O*Me*), 6.53 (1H, s, C*H*), 7.17 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4), 7.30 (1H, dd, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.60 (1H, t, $^3J_{HH}$=7.7 Hz, CH of C_6H_4), 7.64 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=20.55 (*C*H$_3$COO), 28.58 (C*Me*$_3$), 52.41 (O*Me*), 52.65 (O*Me*), 60.47 (*C*Me$_3$), 124.87, 125.22, and 134.45 (4CH of C_6H_4), 128 (C_{ipso}–CON), 129.31 (C=*C*H), 131.47 (*C*=CH), 150.25 (C_{ipso}–OCOMe), 162.53 (ArCON*C*O), 163.77 (*C*O$_2$Me), 168.95 (2*C*O$_2$Me), 172.00 (Ar*C*ON).

4.1.7. Diethyl (*E*)-2-{[[2-(acetyloxy)benzoyl](*tert*-butyl)-amino]carbonyl}-2-butendioate 3g. Yellow oil, yield 0.40 g, 95%. IR (KBr) (ν_{max} cm^{-1}): 1766 (OCOMe), 1714 (OCNCO), 1663 (CO_2Et), 1650 (C=C), 1594 and 1468 (Ar), 1366, 1300, 1248, and 1178 (C–O). MS, *m*/*z* (%): 433 (M$^+$, 2), 344 (2), 335 (1), 318 (2), 298 (4), 262 (8), 241 (8), 215 (2), 199 (7), 163 (40), 143 (22), 121 (100), 92 (14), 57 (12), 41 (6). Anal. Calcd for $C_{22}H_{27}NO_8$ (433.45): C, 60.96; H, 6.28; N, 3.23%. Found: C, 60.80; H, 6.10; N, 3.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.22 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3CH_2), 1.31 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3CH_2), 1.64 (9H, s, CMe_3), 2.25 (3H, s, OCOMe), 3.98 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 4.25 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 6.45 (1H, s, CH), 7.13 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4), 7.24 (1H, t, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.56 (1H, t, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.67 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.74 (*C*H$_3$CH$_2$), 14.15 (*C*H$_3$CH$_2$), 20.54 (*C*H$_3$COO), 28.54 (C*Me*$_3$), 60.29 (*C*Me$_3$), 61.54 (O*C*H$_2$CH$_3$), 61.94 (O*C*H$_2$CH$_3$), 124.70 (CH of C_6H_4), 125.31 (CH of C_6H_4), 128.13 (C=*C*H), 128.23 (C_{ipso}–CON), 129.35 (CH of C_6H_4), 131.54 (*C*=CH), 134.30 (CH of C_6H_4), 150.22 (C_{ipso}–OCOMe), 162.12 (ArCON*C*O), 162.72 (CO_2Et), 163.47 (CO_2Et), 168.86 (ArO*C*OMe), 172.21 (Ar*C*ON).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.102.

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Effect of added donor ligands on the selective oxygenation of organic sulfides by oxo(salen)chromium(V) complexes

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Abstract—Oxo(salen)chromium(V) complexes, $[(salen)Cr^{V}{=}O]^{+}$, oxidize organic sulfides selectively to sulfoxides in high yield. This oxygenation reaction is catalyzed by ligand oxides (LO's), pyridine *N*-oxide, 4-picoline *N*-oxide, 4-phenyl pyridine *N*-oxide and triphenylphosphine oxide. The rate is accelerated by 10–20 times with an increase in yield of sulfoxide in less reaction time. This catalytic activity is highly sensitive to the nature of the substituent in the phenyl ring of ArSMe and in the 3- and 5-position of the salen ligand. The reaction constant (ρ) value obtained with the ligand oxide catalyzed reaction is low compared to the value in the absence of LO. The strong binding and catalytic activity of ligand oxides on the oxo(salen)chromium(V) ion oxygenation is explained in terms of binding constants and a mechanism involving the electrophilic attack of $[(salen)Cr^{V}{=}O]^{+}$–LO adduct on the sulfur centre of phenyl methyl sulfide.

1. Introduction

The use of metal–salen complexes as efficient catalysts in oxygenation reactions, particularly epoxidation and sulfoxidation, has been widespread in recent years.[1–10] Though the catalytic role of many metal–salen complexes is reported in the literature, most of the work is concerned with Fe(III)–salen, Mn(III)–salen and Cr(III)–salen complexes. Among these metal complexes, Cr(III)–salen has the advantage that the oxo(salen)chromium(V) ion, $[(salen)Cr^{V}{=}O]^{+}$, generated from Cr(III)–salen complex and PhIO, is stable and can be isolated unlike the oxo(salen)manganese and oxo(salen)Iron ion, which has a fleeting existence.[1,2,8,9,11] The $[(salen)Cr^{V}{=}O]^{+}$ ion has been characterized definitely by spectroscopic techniques and by single crystal X-ray structure determination. Consequently, there is no ambiguity concerning the identity of the active oxidizing agent. Thus the use of the isolated oxo(salen)chromium(V) complex allows reactions to be carried out stoichiometrically, in the absence of co-oxidants, facilitating kinetic studies and mechanistic evaluation. Recently Venkataramanan et al.[13] have studied the oxygenation reaction of organic sulfides and sulfoxides with 10 oxo(salen)chromium(V) complexes by varying the substituents on the salen ligand electronically and sterically. This redox reaction is highly sensitive to the change in structure of the ligand in the Cr(V)–salen complex and of the substrate. In recent years, Gilheany and co-workers[14–17] in a series of publications have shown that the stereoselectivity in the epoxidation of alkenes with oxo(salen)chromium(V) complexes is substantially changed on the addition of certain oxygen containing donor ligands such as phosphine oxide and amine *N*-oxides. In most cases the presence of ligand oxides (LO's) has a significant effect, increasing the ee by 30%. It is known that such additives are coordinated to the metal atom at the axial position through the oxygen atom of LO's, which weakens the Cr=O bond in $[(salen)Cr^{V}{=}O]^{+}$ ion and thereby increases the reactivity.[1,14–17] Though the effect of such additives on the reactivity of oxo(salen)metal complexes has been studied on the epoxidation reaction, no attempt has been made to look at such an effect on the sulfoxidation reaction. Moreover, the addition of ligand oxides was found to change the reaction mechanism.[18] To get a clear picture we have attempted a study, on the oxidation of sulfides with several oxo(salen)-chromium(V) in the presence of donor ligands, like triphenylphosphine oxide (TPPO), pyridine *N*-oxide (PyO), 4-picoline *N*-oxide (PicNO) and 4-phenyl pyridine *N*-oxide (PPNO). These were studied using spectrophotometric and EPR techniques and the observed results are presented in this article.

2. Results

2.1. Spectral studies

The selective oxidation of several substituted phenyl methyl sulfides with 10 oxo(salen)chromium(V) complexes was

Keywords: Cr(III)–salen; Sulfide; Sulfoxide oxygenation; Ligand oxides; Rate enhancement.
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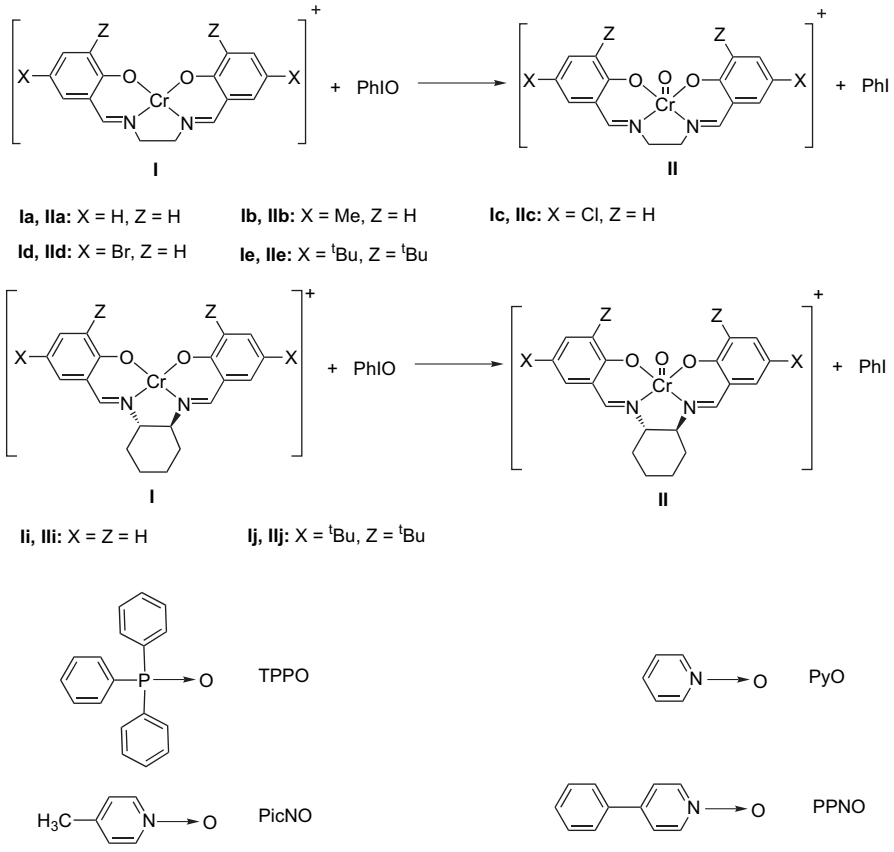


Scheme 1. Structure of complexes **IIa**–**IIg** and the ligand oxides (LO's).

well studied.[10b,13] A mechanism involving an electrophilic attack of the oxygen of the oxidant at the electron-rich sulfur centre of the substrate has been proposed. Realizing the importance of donor ligands on the oxygenation reaction with oxo-metal complexes[10b,14–19] we have investigated the effect of LO's on the sulfoxidation reaction with oxo (salen)chromium(V) complexes and the structures of Cr(III) and Cr(V) complexes and the donor ligands used in the present study are shown in Scheme 1.

The parent oxo(salen)chromium(V) ion has an absorption maximum (λ_{max}) at 560 nm in CH_3CN. When the ligand oxide, LO, is added to the Cr(V) ion a substantial red shift is noticed in the absorption maximum. This shift in the λ_{max} depends on the nature of the LO and is in the range of 15–100 nm. The λ_{max} values of all substituted oxo (salen)chromium(V) complexes in the absence and presence of additives are given in Table 1. Further, an increase in the concentration of additive increases the absorbance of Cr(V)–LO adduct. A sample spectrum to show the increase of absorption with [LO] is given in Figure 1.

Table 1. Absorption maxima, λ_{max}, of $[(salen)Cr^{V}{=}O]^{+}$ complexes in the presence and absence of LO

Serial number	Complex	λ_{max} (nm) in the absence of LO	λ_{max} (nm) in the presence of LO			
			TTPO	PyO	PicNO	PPNO
1.	**IIa**	560	627	612	608	615
2.	**IIb**	557	640	620	642	655
3.	**IIc**	584	645	630	630	630
4.	**IId**	590	645	632	630	625
5.	**IIe**	595	610	671	650	654
6.	**IIf**	600	620	615	610	615
7.	**IIg**	610	630	685	664	665

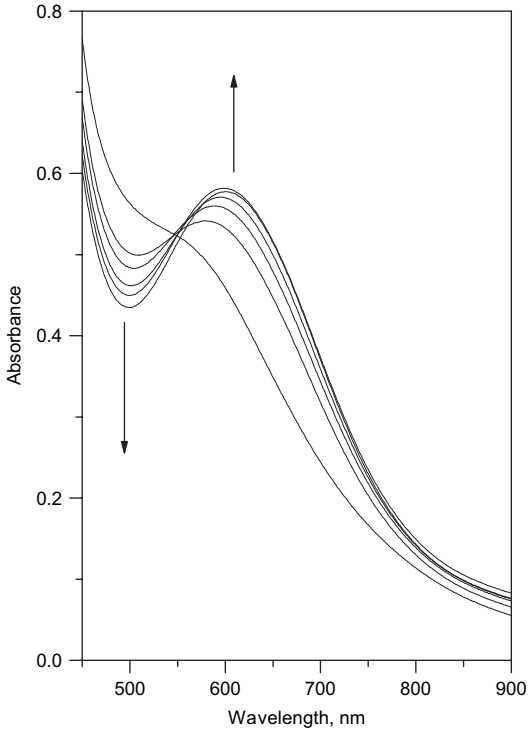


Figure 1. Absorption spectra of **IIa** in the absence of PyO and at 0.025 M, 0.05 M, 0.075 M, 0.1 M and 0.125 M PyO. [**IIa**]=3×10^{-4} M.

Table 2. Binding constants for the complex formed between **IIa–IIg** and ligand oxides

Serial number	Complex	Ligand oxides (LO's)			
		TPPO	PyO	PicNO	PPNO
1.	**IIa**	44±11	125±21	165±32	183±41
2.	**IIb**	32±11	140±14	146±42.0	150±31.5
3.	**IIc**	71±19	123±24.2	241±34.1	192±21.4
4.	**IId**	84±31	184±44	321±48	230±36
5.	**IIe**	24±9	73±14.4	112±21.4	156±15
6.	**IIf**	41±10	101±12.2	185±16.4	646±51
7.	**IIg**	27±11	69±18.8	142±34.8	150±29

From these spectral changes we have estimated the binding constants by using the Benesi–Hildebrand equation and the values of binding constants are given in Table 2.

The binding constant depends on the nature of the LO's as well as the substituents in the salen ligand. Furthermore, the metal ion containing electron donating groups in the 5-position of the salen ligands has a low binding constant value compared to those carrying electron withdrawing groups. This is expected as the electrophilicity of metal centre is decided by the nature of the substituents in the salen ligand. The low binding constant values for the complexes **IIe** and **IIg** can be accounted for on the basis of the presence of the bulky *tert*-butyl group at the 3-position, which may hinder the binding of the LO's to the metal centre.

Kochi and co-workers[1] have isolated the oxo(salen)chromium(V) ion and its adduct with PyO and determined their structure by X-ray analysis. The authors have shown that the Cr(V) ion and the Cr(V)–LO adduct have roughly the square pyramidal and octahedral geometries in which the Cr atom is displaced 0.53 and 0.26 Å units above the mean-salen plane, respectively. Thus the LO binds strongly with metal centre and affects the strength of Cr–O bond. In the present study the enormous shift observed in the λ_{max} value of [(salen) Cr^{V}═O]$^{+}$ on the addition of LO and large binding constants support the strong binding of LO to the metal resulting in the formation of O═Cr–O–L.

2.2. Kinetics

The progress of the title reaction is followed by measuring the change in OD of the Cr(V)–LO adduct at the wavelength given in Table 1. A sample run to show the decrease in OD of Cr(V)–LO adduct with time is shown in Figure 2.

The reaction is of first order for both the oxidant and the substrate. The first order dependence in the oxidant is evident from the linear log OD versus time plot (figure not shown) and in the substrate is confirmed from the linear k_1 versus [substrate] plot (Fig. 3).

To know the effect of LO's on reaction rates, experiments were carried out with different [LO]. At low concentration, the k_1 values vary linearly and at high [LO] the rate reaches the maximum. Further increase in [LO] has no profound influence on the rate of the reaction. Thus the reaction follows saturation kinetics with respect to the added LO's.

The rate constants for the oxygenation of several *para*-substituted phenyl methyl sulfides with oxo(salen) chromium(V) complexes (**IIa–IIg**) in the absence and presence of donor ligands are presented in Tables 3–7. These kinetic data show that the reaction is highly sensitive to the change of substituents in the phenyl ring of ArSMe, and in the 5,5′-positions of the salen ligand. The kinetic data in Tables 3–7 have been analyzed using the Hammett equation, and the reaction constant (ρ) values obtained for the substituent variation in ArSMe are given at the bottom of the tables and for the substituent variation in the salen ligand of oxo(salen)chromium(V) complexes in the 7th column of the tables. Though the ρ value is highly sensitive to the structure of the salen ligand and nature of the LO it is not very sensitive to the change of the substituent in the aryl moiety of ArSMe. The important point to be noted regarding ρ value is that the ρ value is always small in the presence of LO's compared to the ρ value in the absence of LO.

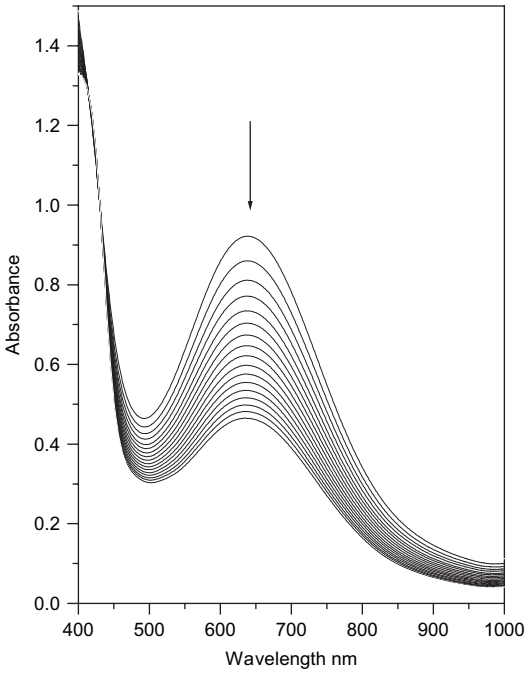


Figure 2. Sample run showing the change in OD of **IIc**–TPPO adduct with time in the presence of PhSMe. [**IIc**]=5×10^{-4} M, [MPS]=0.01 M and [TPPO]=0.01 M.

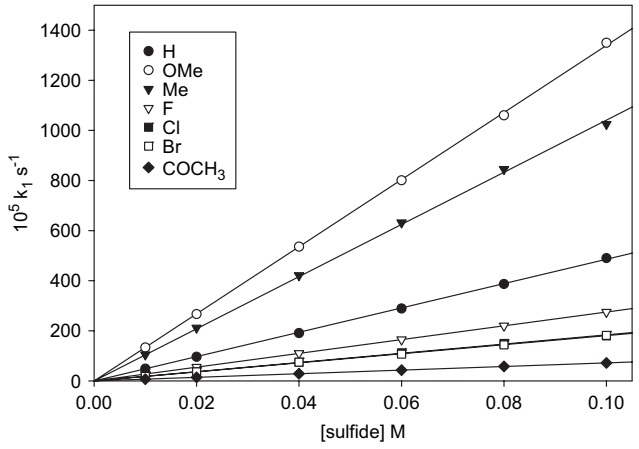


Figure 3. Plot of k_1 versus [sulfide] for the oxidation of sulfides by **IIa** in the presence of TPPO at 298 K. [TPPO]=0.01 M and [**IIa**]=5×10^{-4} M.

Table 3. Second-order rate constant (k_2) and reaction constant (ρ) values for the **IIa–IIg** oxygenation of X–C_6H_4SMe in the absence of LO

X–$C_6H_4SCH_3$ (*p*-X=)	$k_2\times10^3$ M^{-1} s^{-1}							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	ρ	**IIf**	**IIg**
H	1.31±0.03	1.15±0.04	36.4±0.9	45.8±1.4	0.11±0.00	2.2(0.980)	1.20±0.03	0.19±0.01
OMe	25.9±0.60	4.60±0.13	320±9.6	526±14	0.36±0.01	2.6(0.995)	5.10±0.15	0.37±0.01
Me	11.4±0.23	2.60±0.52	114±2.4	140±4.2	0.17±0.00	2.4(0.988)	2.20±0.06	0.28±0.00
F	1.58±0.08	0.59±0.10	26.9±0.4	61.0±1.3	0.06±0.00	2.4(0.995)	1.10±0.04	0.15±0.00
Cl	0.93±0.01	0.32±0.01	21.6±0.4	43.8±1.0	0.06±0.00	2.4(0.995)	0.65±0.02	0.13±0.00
Br	0.93±0.01	0.28±0.06	18.8±0.8	24.2±0.4	0.04±0.00	2.4(0.998)	0.42±0.01	0.09±0.00
$COCH_3$	0.16±0.01	0.23±0.01	7.40±0.22	8.80±0.2	0.02±0.00	2.3(0.965)	0.22±0.00	0.06±0.00
ρ	−2.8	−1.9	−2.0	−2.2	−1.8		−1.8	−1.1
r	0.965	0.980	0.972	0.953	0.970		0.988	0.990

Table 4. Second-order rate constant (k_2) and reaction constant (ρ) values for the **IIa–IIg** oxygenation of X–C_6H_4SMe in the presence of TPPO

X–$C_6H_4SCH_3$ (*p*-X=)	$k_2\times10^3$ M^{-1} s^{-1}							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	ρ	**IIf**	**IIg**
H	48.8±1.5	10.4±0.4	184±5.4	207±7.4	0.20±0.01	2.3(0.934)	8.98±0.3	0.23±0.01
OMe	133±4.1	24.2±0.8	561±17	744±27	0.60±0.02	2.2(0.979)	21.9±0.7	0.60±0.02
Me	105±3.3	16.4±0.5	499±14	702±23	0.35±0.01	2.4(0.981)	18.9±0.6	0.37±0.01
F	27.4±0.8	5.75±0.1	190±4.2	145±4.5	0.13±0.00	2.2(0.980)	6.91±0.2	0.18±0.01
Cl	18.5±0.4	3.92±0.0	142±2.4	147±3.4	0.11±0.00	2.3(0.987)	5.30±0.1	0.13±0.00
Br	18.1±0.3	3.22±0.0	137±1.5	122±2.1	0.08±0.00	2.3(0.985)	4.63±0.08	0.10±0.00
$COCH_3$	7.21±0.1	2.76±0.0	72.8±0.7	69.4±1.0	0.05±0.00	2.2(0.983)	3.68±0.00	0.07±0.00
ρ	−1.8	−1.4	−1.2	−1.5	−1.5		−1.2	−1.3
r	0.994	0.989	0.965	0.967	0.996		0.984	0.991

Table 5. Second-order rate constant (k_2) and reaction constant (ρ) values for the **IIa–IIg** oxygenation of X–C_6H_4SMe in the presence of PyO

X–$C_6H_4SCH_3$ (*p*-X=)	$k_2\times10^3$ M^{-1} s^{-1}							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	ρ	**IIf**	**IIg**
H	37.3±1.2	5.6±0.21	64.9±2.5	140±5.5	0.48±0.02	1.9(0.950)	18.9±0.72	0.30±0.02
OMe	90.9±2.7	35.5±1.4	334±11	677±23	0.88±0.02	2.2(0.942)	31.6±1.23	0.55±0.02
Me	38.5±1.5	21.2±0.72	230±9	527±15	0.65±0.01	2.2(0.958)	26.7±0.65	0.37±0.02
F	17.2±0.35	4.3±0.13	39.6±1.6	120±2.7	0.42±0.01	1.8(0.965)	12.2±0.26	0.19±0.01
Cl	10.4±0.17	3.3±0.08	30.2±0.91	93.5±1.8	0.29±0.00	1.9(0.967)	8.5±0.12	0.14±0.00
Br	9.77±0.14	3.1±0.05	27.4±0.55	86.1±1.2	0.25±0.00	1.9(0.966)	8.2±0.09	0.12±0.00
$COCH_3$	4.69±0.06	1.6±0.02	13.1±0.14	38.0±0.40	0.20±0.00	1.7(0.974)	3.2±0.01	0.07±0.00
ρ	−1.7	−1.8	−2.0	−1.7	−0.90		−1.3	−1.2
r	0.989	0.975	0.988	0.972	0.990		0.980	0.994

Table 6. Second-order rate constant (k_2) and reaction constant (ρ) values for the **IIa–IIg** oxygenation of X–C_6H_4SMe in the presence of PicNO

X–$C_6H_4SCH_3$ (*p*-X=)	$k_2\times10^3$ M^{-1} s^{-1}							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	ρ	**IIf**	**IIg**
H	16.6±0.7	10.4±0.3	99.72±3.1	146±5.5	0.63±0.02	1.8(0.966)	3.91±0.12	0.25±0.01
OMe	45.2±1.5	20.5±0.5	338.6±11	518±20	0.86±0.03	2.1(0.971)	14.5±0.28	0.48±0.02
Me	27.2±0.5	15.9±0.4	192.3±7	304±9.2	0.75±0.03	2.0(0.967)	9.44±0.29	0.37±0.01
F	15.3±0.3	6.72±0.1	64.3±1.8	103.6±3.0	0.44±0.01	1.8(0.966)	3.68±0.10	0.23±0.00
Cl	14.3±0.3	3.45±0.07	38.5±1.1	72.8±1.8	0.33±0.01	1.8(0.968)	3.22±0.07	0.19±0.00
Br	13.8±0.2	2.76±0.03	37.5±0.53	69.8±1.3	0.32±0.01	1.8(0.973)	2.99±0.06	0.19±0.00
$COCH_3$	7.27±0.08	1.61±0.02	21.2±0.30	40.5±0.45	0.22±0.00	1.8(0.979)	2.19±0.03	0.17±0.00
ρ	−0.95	−1.6	−1.7	−1.5	−0.89		−1.1	−0.65
r	0.963	0.984	0.997	0.994	0.992		0.960	0.977

Table 7. Second-order rate constant (k_2) and reaction constant (ρ) values for the **IIa–IIg** oxygenation of X–C_6H_4SMe in the presence of PPNO

X–$C_6H_4SCH_3$ (*p*-X=)	$k_2\times10^3$ M^{-1} s^{-1}							
	IIa	**IIb**	**IIc**	**IId**	**IIe**	ρ	**IIf**	**IIg**
H	12.9±0.4	12.6±0.5	152±5.3	186±7.4	0.65±0.01	1.9(0.964)	29.4±1.0	0.51±0.02
OMe	35.2±1.3	26.1±0.8	522±18	488±17	0.99±0.03	2.2(0.962)	111±3.9	0.99±0.04
Me	24.0±0.9	23.6±0.5	310±12	304±11	0.71±0.02	2.1(0.952)	56.1±2.3	0.78±0.02
F	9.93±0.3	9.2±0.3	94.9±2.9	129±4.8	0.58±0.01	1.9(0.966)	31.6±1.0	0.45±0.01
Cl	7.60±0.16	8.7±0.2	68.4±2.0	88.2±2.7	0.46±0.01	1.8(0.953)	20.6±0.7	0.39±0.00
Br	6.68±0.08	8.4±0.2	65.8±1.4	63.8±1.3	0.45±0.01	1.7(0.945)	20.5±0.6	0.35±0.00
$COCH_3$	4.38±0.05	3.7±0.01	29.9±0.5	28.5±1.0	0.35±0.00	1.6(0.964)	12.0±0.2	0.23±0.00
ρ	−1.3	−1.1	−1.7	−1.6	−0.59		−1.2	−0.85
r	0.995	0.972	0.997	0.989	−0.986		0.976	0.989

This trend is expected based on the reactivity–selectivity principle (RSP).[10,11,21–23,25] As the reactivity in the presence of LO is more than that in the absence of LO, we expect that the ρ value, an empirical term representing the selectivity of the reaction, should be less than what is actually observed.

2.3. EPR studies

The added advantage of Cr(V) complexes is that they are EPR active and hence EPR spectra were recorded at room temperature for the complexes and they show a strong signal at ca. $\langle g\rangle$=1.987 and possess nitrogen and ^{53}Cr hyperfine splitting. Upon addition of LO to the oxo(salen) chromium(V) ion, the g value shifts from 1.987 to 1.975 with the disappearance of the hyperfine splitting, indicating the binding of the LO to the metal centre.[1] The kinetics of the reaction can also be followed by this EPR technique. The change in the intensity of the EPR signal of [O═Cr(V) salen]$^+$ ion with time is used to follow the kinetics of the reaction. A sample run to show the change in the EPR signal intensity with time obtained during the reaction of **IIc** with MPS in the presence of TPPO as the additive is shown in Figure 4. The rate constant obtained by EPR technique is found to be in close agreement with the values obtained by the spectrophotometric method.

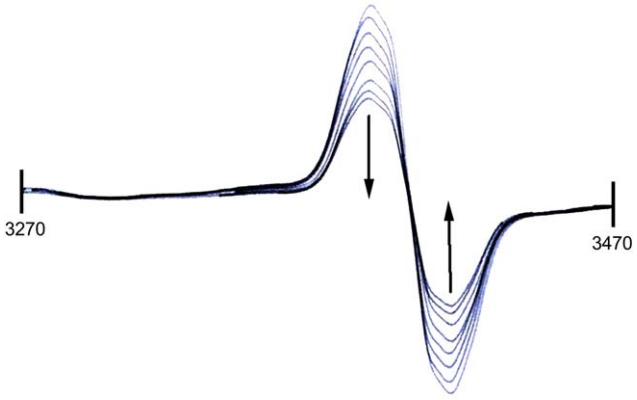


Figure 4. EPR spectra showing the change in the intensity with time for the oxidation of MPS by **IIc** in the presence of TPPO as ligand oxide.

2.4. Effect of donor ligand on product yield

Table 8 shows the effect of added donor ligands on the yield of sulfoxide formed in the stoichiometric oxidation of organic sulfides. From the data given in Table 8 we can understand that the added LO's have a small effect on the product yield. All the LO's increase the percentage of product formed with less reaction time. Thus the data indicate that in the presence of ligand oxides, product yield is improved along with the increase in the rate of the reaction. When we compare the analogous epoxidation reactions with similar complexes, Gilheany and co-workers found that yields did not exceed 50%. Furthermore the rates of oxidation in the presence LO's for sulfides are in the range of 10^{-3} M^{-1} s^{-1} and that of epoxidation are in 10^{-2} M^{-1} s^{-1}.[1b] Thus both the kinetic data and percentage of sulfoxide formed support the catalytic role of all LO's used in the reaction.

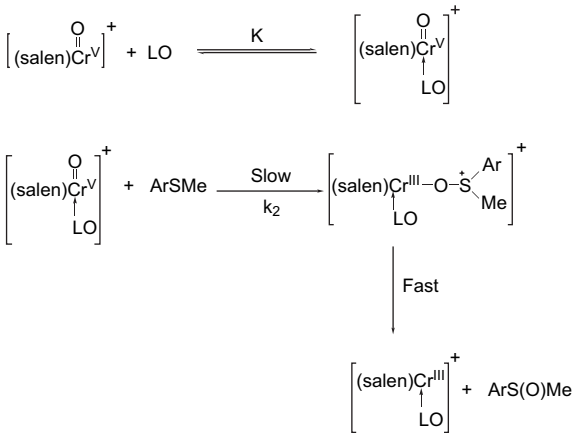
3. Discussion

The spectral and kinetic data given in Figures 1–4 and Tables 1–8 show the catalytic role of the added ligand oxide, LO. The addition of LO shifts the λ_{max} of **IIa–IIg** enormously and accelerates the reaction rate by 10–20 times. The coordination of the LO occurs at the axial position to complete the octahedral coordination of chromium. The infrared spectrum of the LO bound chromium(V) complex indicates that significant bond weakening occurs upon axial coordination.[1a,2b] Among the five LO's used, triphenylphosphine oxide was known to have a better binding ability, but 4-phenyl pyridine *N*-oxide was found to have highest binding constant and the maximum rate. This unusual behaviour may be attributed to the steric hinderance created by TPPO during the binding with the metal centre.[12a]

The spectral, kinetic and product yield data presented above confirm the formation of oxidant–ligand oxide adduct as the first step, which in turn acts as a more powerful oxidant than the oxo(salen)chromium(V) ion. At least two different modes of oxidation may be envisaged to account for the type of reactivity observed: (i) a bimolecular electrophilic oxygen transfer from [O═Cr^V(salen)]$^+$ to the substrate and (ii) a bimolecular electrophilic oxidation performed by [O═Cr^V(salen)–LO]$^+$. As the binding constant of LO with Cr(V) ion is high and the rate of oxidation in the presence of LO is 10–20 times more than that in the absence of LO; the bimolecular electrophilic oxidation of the complex alone is less important compared to bimolecular electrophilic oxidation of the adduct complex under the present experimental conditions. Hence a mechanism involving electrophilic attack of [(salen)Cr^V═O]$^+$–LO adduct on the sulfur centre of ArSMe (Scheme 2) can be proposed.

Table 8. Percentage of sulfoxide formed from the selective oxidation of *p*-X–$C_6H_4SCH_3$ with **IIa** in CH_3CN in the presence and absence of ligand oxides at 298 K

X–$C_6H_4SCH_3$ X=	Without LO			TTPO	PyO	PicNO
	Reaction time (min)	% of sulfoxide	Reaction time (min)	% of sulfoxide	% of sulfoxide	% of sulfoxide
H	240	96	90	97	96	94
OMe	60	95	60	99	98	97
Me	75	93	60	94	98	98
F	200	78	90	81	72	76
Cl	240	60	90	76	68	72
Br	240	61	90	56	65	64
$COCH_3$	240	40	90	55	48	49



Scheme 2.

The ligand oxide binds strongly with the oxo(salen)chromium(V) ion via oxygen atom of the ligand oxide(LO) to chromium. The binding of the oxygen of the LO to the metal weakens the Cr=O bond in the oxo(salen)chromium(V) complex and facilitates the removal of oxygen atom from the oxo complex to form sulfoxide as the product. When the Cr(III) complex is formed as the product, the ligand oxide occupies two coordination sites making the product octahedral. It is pertinent to recall that Kochi and co-workers[1] have isolated the Cr(III) complex, $[Cr^{III}(salen)(OPEt_3)_2]^+$, which indicates that the one molecule of ligand oxide entered the coordination sphere of oxo(salen)chromium(V) ion prior to oxygen transfer to the substrate since the rate of incorporation of ligand oxide into the substitutionally inert Cr(III)–salen is slow.[1]

When we compare the rate constant and product yield data carefully, we realize that the rate constant in the presence of ligand oxides is 10–20 times more than that in the absence of ligand oxides. An increase in the product yield in the presence of LO is also observed. This was because the rates of oxidation of sulfides are much higher compared to that of epoxides. Therefore the formation of an unreactive μ-oxo dimer by the reaction between $[O{=}Cr^{V}(salen)]^+$ and $[Cr^{III}(salen)]^+$ in sulfoxidation has less effect compared to the epoxidation reaction.[16,17] On the other hand, in the case of oxo(salen)manganese complexes the μ-oxo dimer, Mn(IV)–O–Mn(IV) formed is an alternative source of $[(salen)Mn^{V}{=}O]^+$ for the epoxidation and sulfoxidation reactions.[11,26–28]

4. Experimental

4.1. Materials

Chromium(III)–salen [salen=*N*,*N*-bis(salicylidine) ethylenediaminato] complex was synthesized[1,2] using the established procedure. Iodosylbenzene was prepared by alkaline hydrolysis of iodosobenzene diacetate according to the reported method.[20] The purity of ligands was checked by ^{1}H NMR spectroscopy and that of Cr(III) complexes was checked by IR and ESI-MS spectroscopy. The oxo(salen)-chromium(V) complexes **IIa–IIg** were obtained from chromium(III) complexes **Ia–Ig** by the general procedure described below. A slight excess of iodosylbenzene is added to Cr^{III}–salen complex dissolved in ~25 mL of CH_3CN. The colour of the reaction mixture has turned from orange to dark green. This slurry is stirred for 20 min and then filtered to remove the unreacted iodosylbenzene. Ether is slowly added to the dark filtrate in order to precipitate crystals of oxo(salen)chromium(V) salts. The ligand oxides used as donor ligands are commercial samples from Aldrich and they were used as such without further purification. Various substituted phenyl methyl sulfides were prepared[29,30] and their purity checked by established methods. The solvents used in the study were of HPLC grade.

4.2. Estimation of binding constants

The complexation/adduct formation of LO with the oxo (salen)chromium(V) cation was monitored by UV–vis spectroscopy. A 5×10^{-4} M solution of oxo(salen)chromium(V) ion in acetonitrile, taken in a quartz cuvette with 1 cm path length, was treated with successive aliquots of concentrated solution of LO in the same solvent. The absorption spectrum of the oxo(salen)chromium(V) ion exhibited a red shift upon the addition of LO. The formation of complex/adduct was evident from the colour change (dark green to emerald green) and the shift in the λ_{max}. By measuring the OD at different concentration of a particular LO at the appropriate λ_{max}, the binding constant has been calculated by using the modified Benesi–Hildebrand (double reciprocal plot) equation.[24]

$$\frac{[\text{oxid}][\text{LO}]}{\Delta\text{OD}} = \frac{[\text{oxid}]+[\text{LO}]}{\Delta\varepsilon} + \frac{1}{K_f\Delta\varepsilon}$$

In the above equation ΔOD is the difference in the absorption intensities of $[(salen)Cr^{V}{=}O]^+$ in the presence and absence of LO and K_f is the equilibrium constant for the formation of adduct or complex. The plot of [oxid][LO]/ΔOD versus [oxid]+[LO] is linear and from the values of slope and intercept, K_f values for the complex formation with LO have been calculated.

4.3. Kinetic measurements

An analytik-jena Specrod-diode array photometer (Specord S100) was employed to record the absorption spectra of Cr(III) and oxo(salen)chromium(V) complexes used in the present study and to follow the kinetics.

The kinetic studies of oxidation of *para*-substituted phenyl methyl sulfides with oxo(salen)chromium(V) complexes were carried out in acetonitrile under pseudo first order conditions using excess of substrate over the oxidant (10:1). The rate of oxygenation of organic sulfides in the presence of donor ligands was followed by measuring the change in the absorbance of Cr^{V}–ligand oxide adduct at the wavelength given in Table 1. The concentration of the ligand oxides was chosen in such a way that the OD of the oxo(salen)chromium(V) complexes was unaffected by the further addition of the donor ligand.

4.4. Product analysis

In a typical experiment involving the selective oxidation of sulfides to sulfoxides, 2 mM oxo(salen)chromium(V)

complex, and the same equivalent of ligand oxides, LO (triphenylphosphine oxide, pyridine oxide, 4-picoline *N*-oxide and 4-phenyl pyridine *N*-oxide) are taken in 5 mL of solvent. To this is added the 2 mM *p*-substituted phenyl methyl sulfide. The solution was stirred at 298 K for 60–240 min depending on the nature of the sulfide. After the removal of the solvent under reduced pressure, the organic product was extracted with dry ether, dried and the solvent removed. The resulting residue was analyzed by GC. Product yields were determined by comparison with authentic samples and sulfoxide was the only product under the present experimental conditions.

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Microwave-assisted synthesis of calix[4]resorcinarenes

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Abstract—Microwave-assisted synthesis of calix[4]resorcinarenes by cyclocondensation of various aldehydes and resorcinol catalysed by 12-tungstophosphoric acid type Keggin ($H_3PW_{12}O_{40}\cdot 13H_2O$) or concentrated HCl is described. Excellent isolated yields (up to 90%) were attained within short reaction times (typically, 3–5 min) when the reaction was performed under microwaves irradiation.

1. Introduction

Interest in the chemistry of calixarenes has increased in recent years. Of particular significance has been the preparation of a range of calix[4]resorcinarene derivatives in high yields.[1] Self-assembled monolayers of resorcinarene derivatives on gold surfaces provide an important starting point for fabricating and operating nanoscale devices for advanced information technologies. Resorcinarene derivatives have also been used as stationary phase in achiral capillary gas chromatography for the separation of positional isomers of substituted benzenes.[2]

Recently, Robert et al.[1] and Cave et al.[1] obtained the *C*-methylcalix[4]resorcinarene and five arylcalix[4]resorcinarenes by simply grinding together resorcinol and aldehydes in the presence of catalytic quantities of *p*-toluenesulfonic acid. The final product partition was carried out either at room temperature (for aromatic aldehydes) or at −78 °C (for acetaldehyde). These 'green' approaches to synthetize resorcinarenes were convincing and efficient but it seems that their application to both aromatic and aliphatic aldehydes was not claimed by the authors. The use of aliphatic aldehydes as starting material in these approaches was unsuccessful since the longer the alkyl chain of aldehydes, the lower the reaction yield. For this purpose, we searched for a simple and rapid synthesis pathway that applies most of the green chemistry principles and that is efficient for both aromatic and aliphatic aldehydes.

Tungstophosphoric acid (TPA), an effective catalyst in the series of Keggin-structure HPAs, is believed to have extensive prospects of application in synthesis chemistry, analysis chemistry, biology, medicine, catalysis and materials science. Especially, its utility and versatility in catalysis and various medical applications would thereby be increased. Their significantly higher Brønsted acidity, compared with the acidity of traditional mineral acid catalysts, is of great importance for catalysis because HPA-based catalysts have higher activity than known traditional catalysts. Using HPA-based catalysts, it is frequently possible to obtain higher selectivity and successfully solve ecological problems.[3]

In recent decades microwave technology has taken an undeniable place in chemical laboratory practise as a very effective and non-polluting method for activating reactions. Examples of this technology in organic synthesis and to organo-metallic chemistry are numerous. The greater successes achieved have been to perform reactions very efficiently in closed vessels or in the reduction or absence of organic solvents. The uses of microwaves provide fast volumetric heating of the chemicals thus enhancing reaction rates and dramatically shortening preparation times.[4]

Herein, we report the first synthesis of calix[4]resorcinarenes using aldehydes and resorcinol catalysed by 12-tungstophosphoric acid type Keggin ($H_3PW_{12}O_{40}\cdot 13H_2O$)

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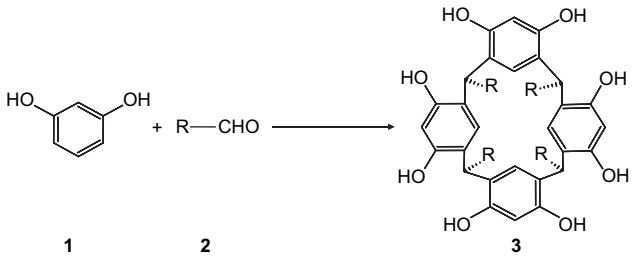
or concentrated HCl under microwave irradiations. The reaction takes place in excellent yield (>90%) with short reaction times (<3–5 min) and does not require harsh conditions. The reaction allows the presence of some functional groups thanks to the rather mild acidic conditions.

2. Results and discussion

Scheme 1 represents the general procedure for the formation of calix[4]resorcinarenes **3** by acid-catalysed cyclocondensation of resorcinol **1** and aldehydes **2**. Selected reaction data obtained from model compounds **2a–i** were illustrated in Table 1 according to different experimental procedures. The process involves microwave irradiation (modified domestic microwave oven) of a mixture containing the resorcinol **1** and aldehydes **2** with a catalytic amount of TPA (procedure D) for 5 min or HCl (procedure B) for 3 min. The corresponding thermal reaction takes 5 h with TPA catalyst (procedure C) and 10 h with concentrated HCl (procedure A).

Products (**3a–i**) were dried at 70 °C under vacuum. Microanalyses, ^{1}H and ^{13}C NMR spectra confirmed their good purity. We carefully analyzed ^{1}H NMR spectra of **3a**, **3i** (aromatic) and **3c**, **3d**, **3f**, **3g** (aliphatic). All of them exhibited an equivalent single resonance for the four *ortho* protons of resorcinol rings. It was also the case for the four *meta* protons. These NMR data were consistent with those previously reported for the C_{4v} isomer.[1] Thus, using our procedure, we obtained the **3a–i** products with high yield, purity and stereoselectivity. This synthesis route can fruitfully used to expand possibilities of molecular recognition in solution of resorcinarenes.[1]



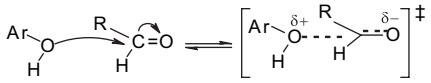
Scheme 1. Synthesis of calix[4]resorcinarenes by cyclocondensation of resorcinol and aldehydes.

Table 1. Microwave-assisted cyclocondensation of resorcinol **1** and aldehydes **2a–i**

Product	R–	Procedures	Conditions			Yield (%)	Mp (°C)
			Power (W)	Time (min)	*T* (°C)		
3a	*p*-But-*O*-C_6H_4	A	—	600	80	86	>300
		B	100	3	80	96	
		C	—	300	80	78	
		D	300	5	108	91	
3b	CH_3	A	—	600	80	60	>300
		B	100	3	80	88	
		C	—	300	80	67	
		D	300	5	108	89	
3c	$CH_3(CH_2)_3$	A	—	600	80	69	>300
		B	100	3	80	82	
		C	—	300	80	91	
		D	300	5	108	88	
3d	$CH_3(CH_2)_4$	A	—	600	80	87	>300
		B	100	3	80	95	
		C	—	300	80	88	
		D	300	5	108	91	
3e	$CH_3(CH_2)_6$	A	—	600	80	79	>300
		B	100	3	80	93	
		C	—	300	80	84	
		D	300	5	108	91	
3f	$CH_3(CH_2)_7$	A	—	600	80	82	280
		B	100	3	80	96	
		C	—	300	80	91	
		D	300	5	108	90	
3g	$CH_3(CH_2)_8$	A	—	600	80	84	295
		B	100	3	80	93	
		C	—	300	80	87	
		D	300	5	108	89	
3h	$CH_3(CH_2)_{10}$	A	—	600	80	85	285
		B	100	3	80	93	
		C	—	300	80	—	
		D	300	5	108	90	
3i	C_6H_5	A	—	600	80	88	300
		B	100	3	80	94	
		C	—	300	80	78	
		D	300	5	108	95	

Analysis of selected reaction data (see Table 1) obtained from model compounds **2a–i** shows the following outstanding facts:

(a) Comparison between conventional heating and microwave irradiation (same temperature, same reagents) revealed a strong specific effect of microwaves because, under conventional heating, the reaction occurred in a very limited extension. After 30 min, thermal reaction did not allow to produce any calix[4]resorcinarenes using 2-ethoxyethanol as solvent with procedures B or C. A possible explanation for the favourable effect of microwaves is that they enhance dipole–dipole interaction in the transition state (Scheme 2).



Scheme 2. Dipolar transition state.

However, a crucial role for the acid during the dehydratation step cannot be excluded since we obtained very low yields in all reactions carried without acid.

(b) Calix[4]resorcinarenes **3** have been synthesised after 5–10 h by conventional heating with fairly moderate yields between 60 and 90%. Under microwave irradiation, excellent yields (between 80 and 99%) were obtained after 3–5 min.
(c) The power range was set to 100 W for HCl catalyst and 300 W for TPA catalyst, since an excessive power could cause the degradation of the product.
(d) When microwave irradiation is applied, less solvent is necessary for conducting cyclocondensation acid-catalysed by HCl or TPA. One of the goals of the 'green chemistry' is to avoid or to reduce the use of solvents in organic chemistry.
(e) In general, the cyclocondensation worked well with alkyl or aryl aldehydes with or without functional groups.

Microwaves are used as a useful tool for preparative organic synthesis: reactions can be carried with less solvent under monitored temperature. There is a fundamental difference between microwave irradiation and conventional heating; conventional heating is an inward heat transfer (from the heating device, e.g., the walls of the reactor for jacketed tanks, to the medium); in microwave irradiation, thermal energy is generated in situ due to the interaction of polar molecules or ionic species with the electric field. Physical acceleration (higher temperature) or chemical activation (enhancement in dipole moment) could be happened using microwaves, which reduce reaction times and enhance yields in comparison with conventional reflux reaction conditions.

3. Conclusion

An extremely simple method for the preparation of calix[4]-resorcinarenes **3** by acid-catalysed cyclocondensation of aldehydes **2** and resorcinol **1** has been perfected using microwave technology. The reaction can be carried out in environmentally friendly conditions: less solvent, less added acid and less reaction time, which means less energy consumed for heating. This 'green' procedure for cycloaddition reaction may set the basis for its application assisted by microwaves in a near future.

4. Experimental

Procedure A: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of ethyl alcohol (25 mL, 95%) and concentrated HCl (7 mL). This mixture was heated by conventional heated jacket for 10 h. The reaction mixture was cooled in an ice bath and the solid material formed was filtered off and washed by water to eliminate acid trace. The filtrate was dried at 70 °C and analysed by ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ or acetone-d_6 solutions, on a VARIAN spectrometer operating at 300 MHz. Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope. Procedure B: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of 2-ethoxyethanol (2 mL) and concentrated HCl (2 mL). This mixture was heated by microwaves for 3 min with a fixed power of 100 W. Procedure C: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of ethyl alcohol (12 mL, 95%) and TPA (0.31 g, 1% molar). This mixture was heated by conventional heated jacket for 5 h. Procedure D: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of 2-ethoxyethanol (2 mL) and TPA (0.31 g; 1% molar). This mixture was heated by microwaves for 5 min with affixed power of 300 W.

^{1}H and ^{13}C NMR spectroscopic data example of calix[4]-resorcinarene (300 MHz): 2,8,14,20-tetra(*p*-butoxyphenyl)-pentacyclo[19,3,1,1,1]octacosa-1(25),3,5,7,(28),9,11,13(27) 15,17,19(26),21,23, dodecanene-4,6,10,12,16,22,24-octol (**3a**); ^{1}H NMR (acetone-d_6) δ_H (ppm): 0.98 (12H, t, J=6.72 Hz,CH_3), 1.50 (8H, m, CH_2), 1.75 (8H, m, CH_2), 4.00 (8H, t, J=7.8 Hz, OCH_2), 5.75 (4H, s, CH), 6.30 (4H, s, ArH *meta* of OH), 6.34 (4H, s, ArH *ortho* OH), 6.69 (8H, m, ArH *meta* of *O*-alkyl), 6.78 (8H, m, ArH *ortho* of *O*-alkyl), 7.51 (8H, s, ArOH); ^{13}C NMR (acetone-d_6) δ_C (ppm): 14.26, 20.00, 32.38, 42.00, 67.87, 102.00, 114.00, 122.26, 130.39, 132.06, 137.30, 153.70, 157.42.

The multimode microwave reactor (a modified microwave oven candy mga20m) has a single magnetron (2450 MHz) with a maximum delivered power of 800 W. It was directly graduated in W (from 100 to 800 W). Experiments were carried out in a Pyrex reactor fitted with a condenser. During experiments, time, temperature and power were monitored. Temperature was monitored with the aid of an external infrared IR thermometer (Flashpoint FZ400).

Resorcinol, aldehydes, ethyl alcohol, 2-ethoxyethanol and HCl, were purchased from Aldrich and TPA synthesized by authors following literature procedures.[5]

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Ultrasound-assisted synthesis of *Z* and *E* stilbenes by Suzuki cross-coupling reactions of organotellurides with potassium organotrifluoroborate salts

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Abstract—Palladium (0)-catalyzed cross-coupling reactions between potassium aryl- and vinyltrifluoroborate salts and aryl- and vinylic tellurides proceeds readily to afford the desired stilbenes in good to excellent yields. Stilbenes containing a variety of functional groups can be prepared.

1. Introduction

The palladium-catalyzed cross-coupling reaction of an organometallic (R^1M) with an organic electrophile (R^2X) has emerged over the past 30 years as one of the most general and selective methods for carbon–carbon bond formation. Currently, it appears to be generally superior to related methods involving the use of Ni, Cu, or Fe catalysts in its scope and stereo-, regio-, and chemoselectivities.[1] The R^1 group of R^1M can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, cyano, or enoxy; while the R^2 group of R^2X can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, or acyl. The use of other related carbon groups as R^1 and/or R^2 is not only conceivable, but also known in the literature. The direct cross-coupling of alkenes with aryl and alkenyl halides is the most widely used and well known cross-coupling procedure.[2]

Boronic acids and boronate esters are the most commonly used derivatives in Suzuki cross-coupling reactions. Recently, Molander et al.[3] have explored the use of potassium organotrifluoroborate salts as an alternative to these boron reagents in Suzuki cross-coupling reactions. These salts are readily prepared from organoboronic acids or esters by the treatment with an aqueous solution of inexpensive and widely available KHF_2.[4] The potassium organotrifluoroborates are monomeric solids and indefinitely stable in the air.

The interest for chemistry of organotellurium compounds has increased and has been extensively explored in the last 20 years. As a consequence of these studies, many methods employing tellurium compounds have been developed.[5] Some metal-catalyzed cross-coupling reactions employing organotellurium reagents as the electrophilic reagent[6] have been successfully demonstrated, among this cross-coupling reactions we can mention the Sonogashira,[7] Negishi,[8] Heck,[9] and Suzuki–Miyaura.[10]

Ultrasound has been utilized recently to accelerate a number of synthetically useful reactions.[11] The use of ultrasound in chemistry is called sonochemistry and the ultrasound effects observed on organic reactions are due to cavitation, a physical process that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer.

Although stilbene itself (1,2-diphenylethene) is not a natural product, a large number of its derivatives has been isolated from various plant species. Among these naturally occurring stilbenoid compounds, polyhydroxystilbenes, and their glucosides are currently attracting considerable attention, because of their wide range of biological activities and potential therapeutic value.[12] Stilbenes, the target of this paper, exhibit some activities such as antineoplastic, antimicrobial, multi-drug-resistant, antiangiogenesis, cytotoxic, and inhibit cell proliferation.[13]

Since these early days, several catalytic approaches have been proposed and investigated for the synthesis of

Keywords: Stilbenes; Suzuki; Tellurium compounds; Potassium organotrifluoroborate salt.
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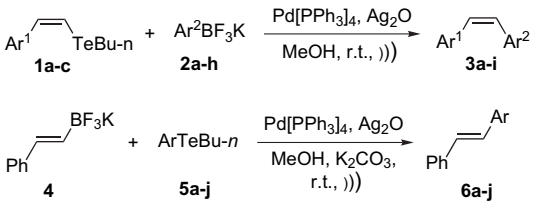
stilbenoid compounds. Among them, methods based on the Heck and Suzuki reactions stand out for their synthetic versatility and efficiency.[14]

By taking advantage of the attractive features of sonochemistry and of potassium organotrifluoroborate salts and the organotellurium compounds in cross-coupling reactions, we report herein an efficient ultrasound-assisted method for the synthesis of *Z* and *E* stilbene compounds by the palladium-catalyzed cross-coupling reaction of aryl- and vinyl tellurides and potassium aryl- and vinyltrifluoroborate salts (Scheme 1).



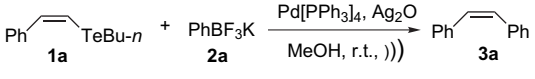
Scheme 1. Cross-coupling reaction between potassium organotrifluoroborate salts and the organotellurium compounds.

2. Results and discussion

The ultrasound-assisted cross-coupling reaction between the *Z*-styryl *n*-butyltellurides (**1a**) and potassium phenyltrifluoroborate (**2a**) in presence of silver oxide was chosen as the model reaction and a variety of conditions were screened (Table 1). Palladium (II) and (0) species were employed in the cross-coupling reaction, and the best results were reached with the catalysts of palladium (0) (Table 1, entries 3 and 6). $Pd(PPh_3)_4$ was chosen as the source of palladium. When the reaction was performed without the silver oxide, no reaction was observed (Table 1, entry 7). Other additives were used in the reaction, like AgOAc and CuI (Table 1, entries 9 and 10), however the results were worse. A base, triethylamine was also used in combination of $Pd(PPh_3)_4$ (Table 1, entry 8), but the yield decreased.

The catalyst loadings were analyzed (Table 1, entries 11–13), and the reaction yield decreased as the catalyst loadings were lowered. The best result was achieved when 8 mol % of catalyst was used. Thus, the careful analysis of the optimized reactions revealed that the optimum conditions for the coupling was found to be the use of *Z*-styryl *n*-butyltelluride (**1a**, 1 mmol), potassium organotrifluoroborate (**2a**, 1.2 equiv), $Pd(PPh_3)_4$ (8 mol %), and silver oxide (2 equiv) diluted in methanol (4 mL), under irradiation of ultrasound waves for 40 min at room temperature. Using this reaction condition we were able to prepare the *Z*-stilbene (**3a**) in 82% yield. The homocoupling reaction of phenyltrifluoroborate **2a** under these conditions was observed on a small scale. Because of this, the phenyltrifluoroborate **2a** is used in a little excess.

Table 1. Study of catalyst effect on cross-coupling reaction using vinylic telluride **1a** and potassium phenyltrifluoroborate salt **2a**



Entry	Catalyst	Additive	Base	Yield (%)
1	$Pd(acac)_2$ 10%	Ag_2O (2 equiv)	—	10
2	$PdCl_2$ 10%	Ag_2O (2 equiv)	—	60
3	$Pd_2(dba)_3$ 10%	Ag_2O (2 equiv)	—	72
4	$PdCl_2(BnCN)_2$ 10%	Ag_2O (2 equiv)	—	64
5	$Pd(dppf)Cl_2$ 10%	Ag_2O (2 equiv)	—	68
6	$Pd(PPh_3)_4$ 10%	Ag_2O (2 equiv)	—	79
7	$Pd(PPh_3)_4$ 10%	—	—	Nr
8	$Pd(PPh_3)_4$ 10%	Ag_2O (2 equiv)	TEA	50
9	$Pd(PPh_3)_4$ 10%	CuI (2 equiv)	—	Nr
10	$Pd(PPh_3)_4$ 10%	AcOAg (2 equiv)	—	15
11	$Pd(PPh_3)_4$ 8%	Ag_2O (2 equiv)	—	82
12	$Pd(PPh_3)_4$ 5%	Ag_2O (2 equiv)	—	73
13	$Pd(PPh_3)_4$ 1%	Ag_2O (2 equiv)	—	60

This optimal condition was employed under conventional reaction (magnetic stirring), but it was necessary a prolonged time reaction (18 h) at reflux temperature. The product *Z*-stilbene (**3a**) was obtained in medium yield, 63%. When the reaction was carried out at room temperature after 24 h, it remained many starting materials.

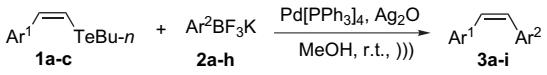
With the optimized cross-coupling conditions at hand, we examined the *Z*-stilbene derivates (**3**) formation with a range of potassium aryltrifluoroborate salts and *Z*-styryl tellurides, as shown in Table 2. The Pd (0)-catalyzed Suzuki reaction proved to be active. It is clear that this is a general method that tolerates the presence of functional groups. In addition, even an *ortho*-substituted aryltrifluoroborate salt afforded the corresponding stilbene compound in medium yield (Table 2; entry 5). However, when the potassium heteroaryltrifluoroborate was used as a nucleophilic partner no reaction was observed (Table 2, entries 9 and 10) and all of the starting material was recovered.

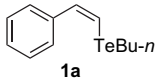
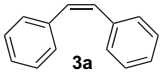
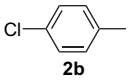
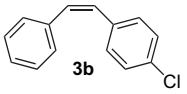
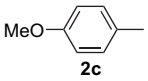
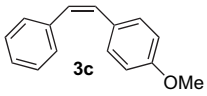
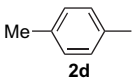
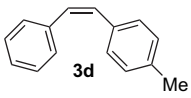
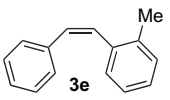
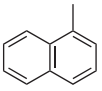
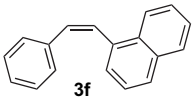
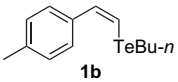
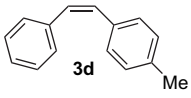
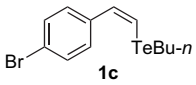
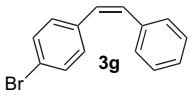
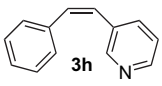
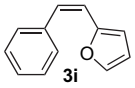
In a next step of this report, we synthesized *E*-stilbenes from the palladium (0)-catalyzed Suzuki–Miayura cross-coupling reaction between the potassium *E*-styryltrifluoroborate (**4**) and *n*-butyl(aryl)tellurides (**5**). Initially, we used the protocol above, which describe the synthesis of *Z*-stilbenes. However, the protocol described before to prepare Z-stilbenes did not demonstrate to be efficient for this case, remaining many starting material, under this condition. Using the *E*-styrylfluoroborate **4** and the aryl telluride **5a** we observed that just by addition of 1 equiv of potassium carbonate all starting material was consumed and the stilbene **6a** (Table 3, entry 1) was obtained in 90% yield.

As shown in Table 3, a variety of aryl tellurides (**5**) were subjected to the optimized palladium-catalyzed cross-coupling reaction conditions with the *E*-styryltrifluoroborate (**4**). When heteroaryl tellurides were employed, the products were obtained in moderate yields (Table 3, entries 10 and 11), while in the other case (Table 2, entries 9 and 10), the starting materials were unreactive.

When aryl tellurides (**5**) containing halides attached to the ring were used under the optimal conditions for Suzuki cross-coupling, the reaction demonstrated high chemoselectivity, with the substitution occurring only in the tellurium group leaving the halide moiety intact. The *E*-1-chloro-4-styryl-benzene (**6g**) (Table 3, entry 7), *E*-1-bromo-4-styryl-benzene (**6h**) (Table 3, entry 8), and *E*-1-iodo-4-styryl-benzene (**6i**) (Table 3, entry 9) were obtained in good yields. We described similar results in a previous report,[10a] but

Table 2. Reaction of *Z*-vinylic tellurides with potassium aryltrifluoroborate salts



Entry	Ar^1	Ar^2	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	82
2	**1a**	 **2b**	 **3b**	70
3	**1a**	 **2c**	 **3c**	60
4	**1a**	 **2d**	 **3d**	78
5	**1a**	 **2e**	 **3e**	62
6	**1a**	 **2f**	 **3f**	70
7	 **1b**	 **2a**	 **3d**	76
8	 **1c**	 **2a**	 **3g**	78
9	**1a**	 **2g**	 **3h**	Nr
10	**1a**	 **2h**	 **3i**	Nr

[a] Isolated product yield.

here in this report we did not observe reaction when the aryl telluride containing iodo (Table 3, entry 9) was used. With these results at hand, we can rule that the general order of reactivity for Suzuki cross-coupling is as follows: BuTe>I>Br≥OTf≫Cl.

3. Conclusion

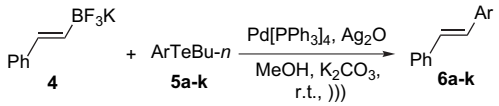
In summary, we have developed general and good yielding methods for accomplishing Suzuki cross-coupling reactions between aryl- and vinylic tellurides and potassium aryl- and vinyltrifluoroborate salts. The use of potassium organotrifluoroborate salts, as well as the use of ultrasound energy makes this method useful, fast and attractive for the synthesis of stilbenes and derivative compounds. One feature of this method was the tolerance of functional groups in both substrates. The Suzuki–Miyaura cross-coupling reaction was highly chemoselective, and we have demonstrated that aryl tellurides are more reactive than aryl halides under these conditions.

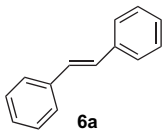
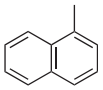
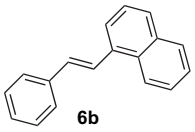
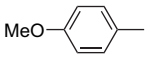
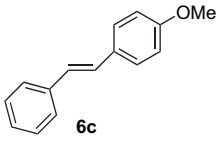
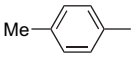
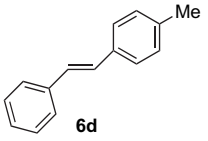
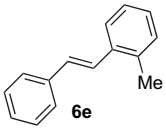
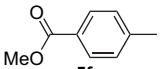
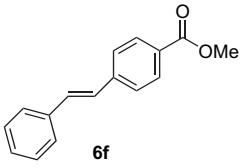
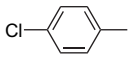
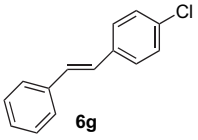
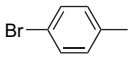
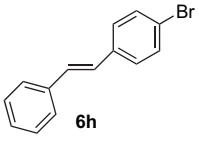
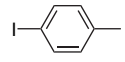
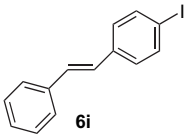
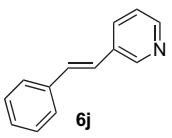
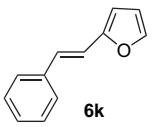
4. Experimental

4.1. General

IR spectra were recorded on Varian 3100 FTIR (ν in cm^{-1}). NMR spectra were performed on a Bruker DPX 300, chemical shifts δ in parts per million, the following abbreviations are used: singlet (s), doublet (d), multiplet (m). Low-resolution mass spectra were determined on a Shimadzu GCMS-QP5050A. Chromatographic purifications were performed by flash silica gel Merck. Palladium catalyst, potassium carbonate and silver (I) oxide were obtained from commercial sources. The methanol was distilled from sodium methoxide and kept over molecular sieves. THF was distilled from sodium benzophenone. Vinylic tellurides (**1**),[15] aryl tellurides

Table 3. Reaction of potassium *E*-vinylic trifluoroborates with aryl tellurides



Entry	Ar	Product	Yield (%)[a]
1	 **5a**	 **6a**	90
2	 **5b**	 **6b**	87
3	 MeO **5c**	 OMe **6c**	75
4	 Me **5d**	 Me **6d**	83
5	 Me **5e**	 Me **6e**	91
6	 O MeO **5f**	 O OMe **6f**	72
7	 Cl **5g**	 Cl **6g**	77
8	 Br **5h**	 Br **6h**	91
9	 I **5i**	 I **6i**	71
10	 N **5j**	 N **6j**	69
11	 O **5k**	 O **6k**	59

[a] Isolated product yield.

(**5**),[10a,b] aryltrifluoroborate (**2**), and vinyltrifluoroborate (**4**)[3,4] were prepared according to literature procedures.

4.2. Representative procedure of *Z*-stilbenes (3a–g) synthesis by Suzuki–Miyaura cross-coupling reaction

A suspension of *Z*-(2-butyltellanyl-vinyl)-benzene (**1a**) (0.144 g, 0.5 mmol), potassium phenyltrifluoroborate (**2a**) (0.110 g, 0.6 mmol), $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) and silver (I) oxide (0.232 g, 1 mmol) in 4 mL of methanol was irradiated in a water bath of an ultrasonic cleaner for 40 min. Then, the reaction was diluted with ethyl acetate (30 mL). The organic layer was washed with saturated solution of NH_4Cl (2×10 mL) and water (2×10 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by silica gel chromatography (eluting with hexane/ethyl acetate 9.5:0.5) yielded *Z*-stilbene (**3a**).[16] This product was obtained in 82% yield with data identical to a commercial sample.

4.2.1. *Z*-1-Chloro-4-styryl-benzene (3b).[17] This product was obtained as a colorless oil in 70% yield from **1a** and **2b** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.18–7.10 (m, 9H), 6.58 (d, J=12.2 Hz, 1H), 6.48 (d, J=12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.0; 135.8; 131.1; 130.3; 129.1; 128.9; 128.6; 128.5; 128.4; 127.47. MS: *m*/*z* (%) 216 (21); 214 (65); 179 (91); 178 (100); 76 (41). IR (neat): 3099, 1268, 937, 749 cm^{-1}.

4.2.2. *Z*-1-Methoxy-4-styryl-benzene (3c).[17] This product was obtained as a colorless oil in 60% yield from **1a** and **2c** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.27–7.15 (m, 7H), 7.72 (d, J=9.7 Hz, 2H), 6.50 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 158.8; 137.8; 130.3; 129.9; 129.0; 128.9; 128.4; 127.9; 127.0; 113.7; 55.4. MS: *m*/*z* (%) 210 (100); 209 (18); 195 (18); 179 (15); 76 (8). IR (neat): 3016, 1512, 1267, 925, 747 cm^{-1}.

4.2.3. *Z*-1-Methyl-4-styryl-benzene (3d).[17] This product was obtained as a colorless oil in 78% and 76% yield from **1a** and **2d** or from **1b** and **2a**, respectively, by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.37–7.10 (m, 7H), 7.00–6.98 (m, 2H), 6.52 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.7; 137.1; 134.5; 130.4; 129.8; 129.2; 129.1; 129.0; 128.4; 127.2; 21.5. MS: *m*/*z* (%) 194 (100); 193 (32); 179 (99); 76 (13). IR (neat): 2982, 1453, 820, 668 cm^{-1}.

4.2.4. *Z*-1-Methyl-2-styryl-benzene (3e).[17] This product was obtained as a colorless oil in 62% yield from **1a** and **2e** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.19–7.08 (m, 8H), 7.05–7.00 (m, 1H), 6.64 (d, J=12.4 Hz, 1H), 6.59 (d, J=12.1 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.1; 137.0; 136.1; 130.5; 130.0; 129.5; 128.9; 128.8; 128.0; 127.2; 127.0; 125.5; 19.8. MS: *m*/*z* (%) 194 (83); 193 (14); 179 (100); 178 (70). IR (neat): 3059, 2989, 1324, 816, 666 cm^{-1}.

4.2.5. *Z*-1-Styryl-naphthalene (3f).[18] This product was obtained as a colorless oil in 70% yield from **1a** and **2f** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.11–8.08 (m, 1H), 7.90–7.86 (m, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.53–7.47 (m, 2H), 7.40–7.28 (m, 4H), 7.10–7.04 (m, 4H), 6.84 (d, J=12.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.0; 129.0; 128.6; 128.5; 128.4; 128.3; 128.0; 127.5; 127.0; 126.6; 126.5; 126.4; 126.0; 125.9; 125.6; 124.9. MS: *m*/*z* (%) 230 (90); 229 (100); 152 (27); 128 (7); 101 (25). IR (neat): 3062, 1383, 987, 790, 672 cm^{-1}.

4.2.6. *Z*-1-Bromo-4-styryl-benzene (3g).[19] This product was obtained as a colorless oil in 78% yield from **1c** and **2a** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.40 (d, J=9.8 Hz, 2H), 7.20–7.13 (m, 5H), 7.07 (d, J=6.4 Hz, 2H), 6.60 (d, J=12.2 Hz, 1H), 6.46 (d, J=13.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.0; 136.3; 131.6; 131.3; 130.8; 129.2; 129.0; 128.6; 127.6; 121.2. MS: *m*/*z* (%) 259 (10); 258 (59); 179 (79); 178 (100); 76 (48). IR (neat): 2986, 1479, 1266, 1064, 751 cm^{-1}.

4.3. Representative procedure of *E*-stilbenes (6a–k) synthesis by Suzuki–Miyaura cross-coupling reaction

A suspension of potassium *E*-styryltrifluoroborate (**4**) (0.126 g, 0.5 mmol), butyl(phenyl)tellane (**5a**) (0.131 g, 0.5 mmol), $Pd(Ph_3P)_4$ (0.046 g, 0.04 mmol), potassium carbonate (0.138 g, 1 mmol), and silver (I) oxide (0.232 g, 1 mmol) in 4 mL of methanol was irradiated in a water bath of an ultrasonic cleaner for 40 min. Then the reaction was diluted with ethyl acetate (30 mL). The organic layer was washed with saturated solution of NH_4Cl (2×10 mL) and water (2×10 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by silica gel chromatography (eluting with hexane/ethyl acetate 9.5:0.5) yielded *E*-stilbene (**6a**).[20] This product was obtained in 90% yield with data identical to a commercial sample.

4.3.1. *E*-1-Styryl-naphthalene (6b).[21] This product was obtained as a white solid in 87% yield from **4** and **5b** by the general method. Mp 68–72 °C (lit., 70 °C). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (d, J=8.3 Hz, 1H), 7.88–7.69 (m, 4H), 7.58–7.32 (m, 7H), 7.25 (q, J=7.6 Hz, 1H), 7.07 (d, J=10.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.6; 135.0; 133.7; 131.7; 131.4; 129.2; 128.7; 128.6; 128.0; 127.7; 127.5; 126.7; 126.4; 126.0; 125.8; 125.7; 123.8; 123.6. MS: *m*/*z* (%) 230 (100); 229 (40); 152 (24); 101 (29). IR (neat): 3070, 1368, 967, 863, 651 cm^{-1}.

4.3.2. *E*-1-Methoxy-4-styryl-benzene (6c).[20] This product was obtained as a white solid in 75% yield from **4** and **5c** by the general method. Mp 133–136 °C (lit., 135 °C). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.46–7.39 (m, 4H), 7.3 (t, J=7.9 Hz, 2H), 7.21–7.16 (m, 1H), 7.06–6.95 (m, 2H), 6.90–6.84 (m, 2H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 159.6; 137.9; 130.4; 128.9; 128.5; 128.0; 127.5; 126.9; 126.5; 114.4; 55.5. MS: *m*/*z* (%) 210 (100); 209 (22); 195 (21); 179 (15); 89 (15). IR (neat): 3067, 1416, 1046, 879, 649 cm^{-1}.

4.3.3. *E*-1-Methyl-4-styryl-benzene (6d).[20] This product was obtained as a white solid in 83% yield from **4** and **5d** by the general method. Mp 119–122 °C (lit., 120 °C). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.49 (d, J=7.6 Hz, 2H), 7.41–7.31 (m, 4H), 7.26–7.21 (m, 1H), 7.16 (d, J=8.3 Hz, 2H); 7.06 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.6; 134.6; 129.5; 129.3; 128.7; 127.8;

127.6; 127.5; 126.8; 126.5; 21.3. MS: *m/z* (%) 194 (100); 193 (32); 179 (99); 178 (96); 89 (20). IR (neat): 2991, 1421, 899, 753 cm^{-1}.

4.3.4. *E*-1-Methyl-2-styryl-benzene (6e).[20] This product was obtained as a colorless oil in 91% yield from **4** and **5e** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.67 (d, J=7.8 Hz, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.49–7.39 (m, 3H), 7.36–7.25 (m, 4H), 7.08 (d, J=16.1 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.0; 136.7; 136.1; 130.8; 130.4; 129.0; 127.9; 126.9; 126.7; 126.6; 125.7; 20.2. MS: *m/z* (%) 194 (85); 193 (15); 179 (100); 178 (66); 89 (18). IR (neat): 3027, 1268, 923, 748 cm^{-1}.

4.3.5. *E*-4-Styryl-benzoic acid methyl ester (6f).[22] This product was obtained as a white solid in 72% yield from **4** and **5f** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.20 (d, J=9.2 Hz, 2H), 7.56–7.51 (m, 4H), 7.39–7.24 (m, 3H), 7.20 (d, J=15.6 Hz, 1H), 7.10 (d, J=15.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.0; 141.9; 136.9; 131.4; 130.2; 129.0; 128.9; 128.4; 127.7; 126.9; 126.4; 52.2. MS: *m/z* (%) 238 (92); 207 (44); 179 (89); 178 (100); 89 (72); 76 (34). IR (neat): 2977, 1714, 1406, 1273, 1060, 713 cm^{-1}.

4.3.6. *E*-1-Chloro-4-styryl-benzene (6g).[20] This product was obtained as a white solid in 77% yield from **4** and **5g** by the general method. Mp 127–130 °C (lit., 128 °C). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.45–7.20 (m, 9H), 6.99 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.2; 136.0; 133.4; 129.5; 129.0; 128.9; 128.1; 127.9; 127.5; 126.8. MS: *m/z* (%) 216 (25); 214 (82); 179 (87); 178 (100); 89 (45); 76 (45). IR (neat): 3072, 1399, 1055 cm^{-1}.

4.3.7. *E*-1-Bromo-4-styryl-benzene (6h).[22] This product was obtained as a white solid in 91% yield from **4** and **5h** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.52–7.38 (m, 4H), 7.33–7.17 (m, 5H), 7.04 (d, J=16.2 Hz, 1H); 6.96 (d, J=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.2; 136.5; 132.0; 129.6; 129.0; 128.2; 128.1; 127.6; 126.8; 121.5. MS: *m/z* (%) 260 (48); 258 (49); 179 (69); 178 (100); 89 (68); 76 (45). IR (neat): 3010, 1267, 912, 746 cm^{-1}.

4.3.8. *E*-1-Iodo-4-styryl-benzene (6i).[23] This product was obtained as a white solid in 71% yield from **4** and **5i** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J=8.3 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 7.40–7.19 (m, 5H), 7.08 (d, J=16.1 Hz, 1H), 6.97 (d, J=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.9; 137.1; 137.0; 129.6; 128.9; 128.4; 128.1; 127.6; 126.8; 92.9. MS: *m/z* (%) 306 (100); 179 (52); 178 (91); 89 (63); 76 (28). IR (neat): 3068, 1415, 879 cm^{-1}.

4.3.9. *E*-3-Styryl-pyridine (6j).[24] This product was obtained as a white solid in 69% yield from **4** and **5j** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.70 (s, 1H), 8.47 (d, J=6.7 Hz, 1H), 7.79 (d, J=6.7 Hz, 1H), 7.50 (d, J=9.3 Hz, 2H), 7.39–7.23 (m, 4H), 7.14 (d, J=17.1 Hz, 1H), 7.07 (d, J=15.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.7; 136.8; 133.2; 132.8; 131.0; 129.0 (2C); 128.4; 126.9; 125.0; 123.7. MS: *m/z* (%) 181 (14); 180 (100); 89 (23); 76 (22). IR (neat): 3068, 1400, 662 cm^{-1}.

4.3.10. *E*-2-Styryl-furan (6k).[25] This product was obtained as a white solid in 59% yield from **4** and **5k** by the general method. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.45–7.19 (m, 6H), 7.02 (d, J=15.3 Hz, 1H), 6.86 (d, J=15.0 Hz, 1H), 6.40–6.38 (m, 1H), 6.31 (d, J=3.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.5; 142.3; 137.2; 128.9; 127.8; 127.4; 126.5; 116.8; 111.8; 108.8. MS: *m/z* (%) 170 (100); 169 (64); 89 (10). IR (neat): 3072, 1369, 968, 651 cm^{-1}.

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Photoreactions of 1,2,4,5-benzenetetracarbonitrile with arylethenes—photo- olefin dimerization–aromatic substitution reactions

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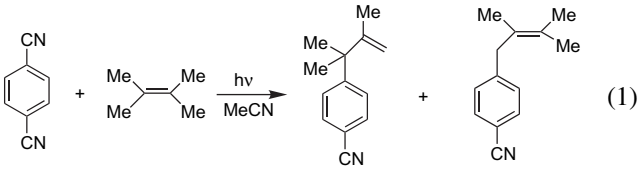
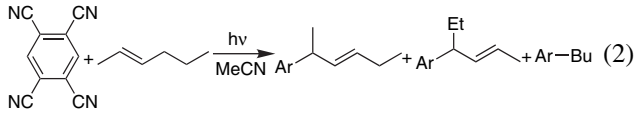
Abstract—Irradiation of 1,2,4,5-tetracyanobenzene (TCNB) with styrene derivatives **1**–**4**, respectively, leads to a photochemical olefin dimerization–aromatic substitution reaction to give the corresponding (2,4,5-tricyanophenyl)tetralin derivative (**8**, **12**, **16**, **17**, and **20**) as the main product. Further irradiation of the primary product with alkene results in substitution of the *meta*-CN group by another phenyltetralinyl to give the corresponding 4:1 (alkene–TCNB) product. According to the effect of the codonor (biphenyl) and salt (magnesium perchlorate) on reaction rate, the result of photoinduced reactions of TCNB with tetralin (**6**) and 1-phenyltetralin (**7**) and analysis of the known kinetic data for relevant processes in the cyanoarene–alkene reactions, the mechanism for the formation of the olefin dimerization–aromatic substitution products (such as **8**) is proposed to involve radical pair combination of the alkene cyclodimer radical (the corresponding 4-phenyl-1-tetralinyl radical) with $TCNB^{-\bullet}$ followed by expulsion of a CN^-. Photoreactions of TCNB with the alkene photocyclodimer (1-phenyltetralin) may also make minor contributions. Photoinduced reaction of TCNB with 1-phenylcyclohexene (**5**) takes a different pathway from **1**–**4** to afford the 1:1 (**5**–TCNB) primary product **21** by deprotonation of $\mathbf{5}^{+\bullet}$ and radical pair combination with $TCNB^{-\bullet}$ followed by elimination of HCN.

1. Introduction

Photoinduced electron transfer (PET) reactions of cyanoarenes with alkenes have been the subject of active research.[1] They have contributed a wealth of knowledge to the structures and reactivities of the cation radicals of various alkenes, and have been a source of new chemical reactions of synthetic and mechanistic value. Several typical reaction modes in this area have been studied, which depend on the structures of the cyanoarene and the alkene, as well as on reaction conditions such as solvent polarity, the presence of added nucleophile, cosensitizer (codonor), base, etc. In the photoreactions of aliphatic alkenes with cyanoarenes in the absence of ambient nucleophile, the strongly acidic cation radical of the alkene deprotonates to give an allylic type radical, which combines with the cyanoarene anion radical followed by extrusion of a cyanide anion to give an alkene–cyanoarene 1:1 *ipso* substitution product as exemplified by reactions 1 and 2.[2]

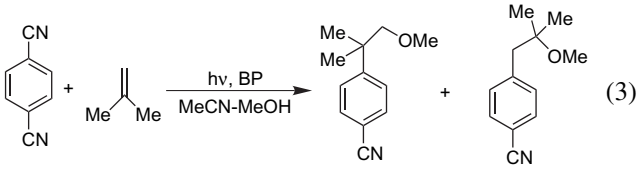


(1)



(2)

In the presence of added nucleophile such as methanol or anions (cyanide, fluoride), the aliphatic alkene cation radical is first attacked by the nucleophile regioselectively, giving a β-methoxyalkyl, β-cyano, or β-fluoroalkyl radical, which subsequently adds to the cyanoarene anion radical followed by extrusion of a cyanide anion to afford a nucleophile–olefin combination, aromatic substitution (photo-NOCAS) product (reactions 3[2c] and 4[2g]).[1h,2–5]



(3)

Keywords: Photochemistry; 1,2,4,5-Tetracyanobenzene; Arylethene.
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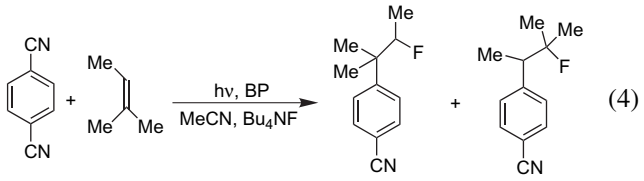
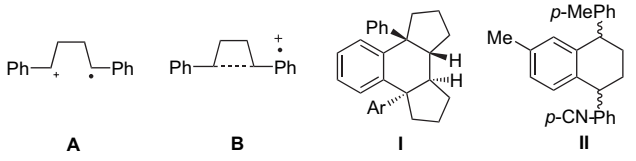


(4)

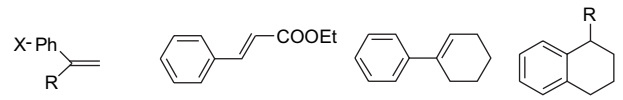
The cation radicals of arylethenes behave quite differently from their aliphatic counterparts. In PET reactions with cyanoarenes in the presence of added high concentration nucleophile, such as an alcohol as cosolvent, the arylethene cation radical is trapped by the nucleophile regioselectively and the resulting alkene–nucleophile addition radical is then reduced by the cyanoarene anion radical to a carbanion, which is protonated. The net result is an *anti*-Markovnikov addition of the nucleophile to the arylethene.[1b,6a]

In the absence of added nucleophile, the arylethene cation radical tends to attack a neutral arylalkene molecule, which is a stronger nucleophile than aliphatic alkenes, to give the dimeric cation radical as an open chain 1,4-distonic cation radical[7] or a long bond cyclobutane cation radical.[8] Transformation of **A** and **B** to the cyclobutane and hexatriene cation radicals followed by reduction by the acceptor anion radical or by the starting neutral alkene affords the cyclobutane and tetralin products.[6] This is caused by the higher electron acceptor ability of the arylalkene's dimer cation radical than the aliphatic alkene cation radical. Radical pair combination between the arylethene's dimer cation radical and the cyanoarene's anion radical is therefore largely averted. In these reactions, the cyanoarene more often serves as a sensitizer without taking part in net reactions, and alkene dimer–cyanoarene *ipso* substitution reactions are seldom reported.[9] To our knowledge, there are only two reports on such reactions, all for 1,4-dicyanobenzene (DCNB). In photoreactions of DCNB with phenylcyclopentene in MeCN, the alkene dimer–DCNB coupling product **I** was formed as a minor product together with the alkene dimer products.[9a,b] In photoreaction of DCNB with *p*-methylstyrene, the coupling product **II** was formed in low yield (30%).[9c]



A **B** **I** **II**

Tetracyanobenzene (TCNB) has a half wave reduction potential of −0.65 V (SCE, MeCN) and a singlet excited state (S_1) energy of 3.83 eV, and with an excited state reduction potential of 3.18 V, it is the strongest electron acceptor of all cyanoarenes.[1b,10] With the singlet excited TCNB as an electron acceptor, even saturated aliphatic alkanes with high oxidation potential may serve as σ-donor to take part in PET reactions to give alkane cation radicals in which the C–H σ bond is activated for ready deprotonation leading to the alkyl radicals.[11] Because of the much higher oxidation potential of TCNB anion radical (−0.65 V) than that of other cyanoarenes such as DCNB, back SET from $TCNB^{-\bullet}$ to the arylethene dimer cation radical is inhibited, it is therefore anticipated that this would open the way for efficient $TCNB^{-\bullet}$–arylalkene dimer cation radical combination, leading to an olefin dimerization–aromatic substitution reaction. However, this type of reaction has not been reported before for TCNB.[12] We report here our investigation on photoinduced reactions of TCNB with the arylalkenes **1**–**5**. In these reactions, the olefin dimerization–aromatic substitution products were formed in high yield for **1**–**4**, while **5** gave 1:1 substitution product. Photoinduced reactions of TCNB with tetralin **6** and 1-phenyltetralin **7** were also investigated to provide insight to the mechanism of the photoreactions of TCNB with **1**–**4**.



1 X=R=H
2 X=*p*-Me, R=H
3 X=H, R=Me

4 **5**

6 R=H
7 R=Ph

Chart 1.

2. Results and discussion

2.1. Results

Although styrene[13a] and α-methylstyrene[13b] form a weak charge transfer complex (CTC) with TCNB in the ground state, they cause no measurable change in the electronic spectrum of TCNB when added to a TCNB acetonitrile solution (1×10^{-3} mol L^{-1}) in concentrations up to 0.5 M. Therefore, in their photoreactions, selective excitation of TCNB without significant CTC excitation involvement can be achieved by irradiation through a glass filter, which cuts off light of $\lambda<300$ nm. Irradiation of an acetonitrile solution of TCNB (0.05 M) and **1** (0.75 M) under nitrogen atmosphere for 13 h resulted in complete consumption of TCNB and gave a single product **8**[14a] in 86% yield. We further found that, irradiation of **8** in MeCN in the presence of **1** resulted in continuous consumption of **8** and the reaction was completed in 22 h, giving two diastereomeric 4:1 products (**1**–TCNB) **10** (66%) and **11** (10%). These two products could also be formed in the photoreactions of TCNB with **1** if the irradiation was continued after the complete consumption of TCNB.

Similar irradiation of TCNB with *p*-methylstyrene **2** for 10 h gave the 4:1 adduct **13** (Fig. 1) as main product (67%) together with a small amount of a 2:1 adduct **12** (2%).

Photoreactions of TCNB with α-methylstyrene **3** in MeCN gave two diastereomeric 2:1 products **16** (36%) and **17** (31%), together with a 4:1 product **18** (18%) and an isocoumarin derivative **19** (11%).

Ethyl cinnamate **4** can also take part in similar reaction with TCNB in MeCN to give the 2:1 product **20** (45%).

In these photoreactions, different amounts of nonpolar products consisting of the alkene dimers were found, which can be eluted out by petroleum ether in column chromatography. However, due to the difficulty in separating them, these were only quantified in the case of reaction of TCNB with **3** (see Section 4).

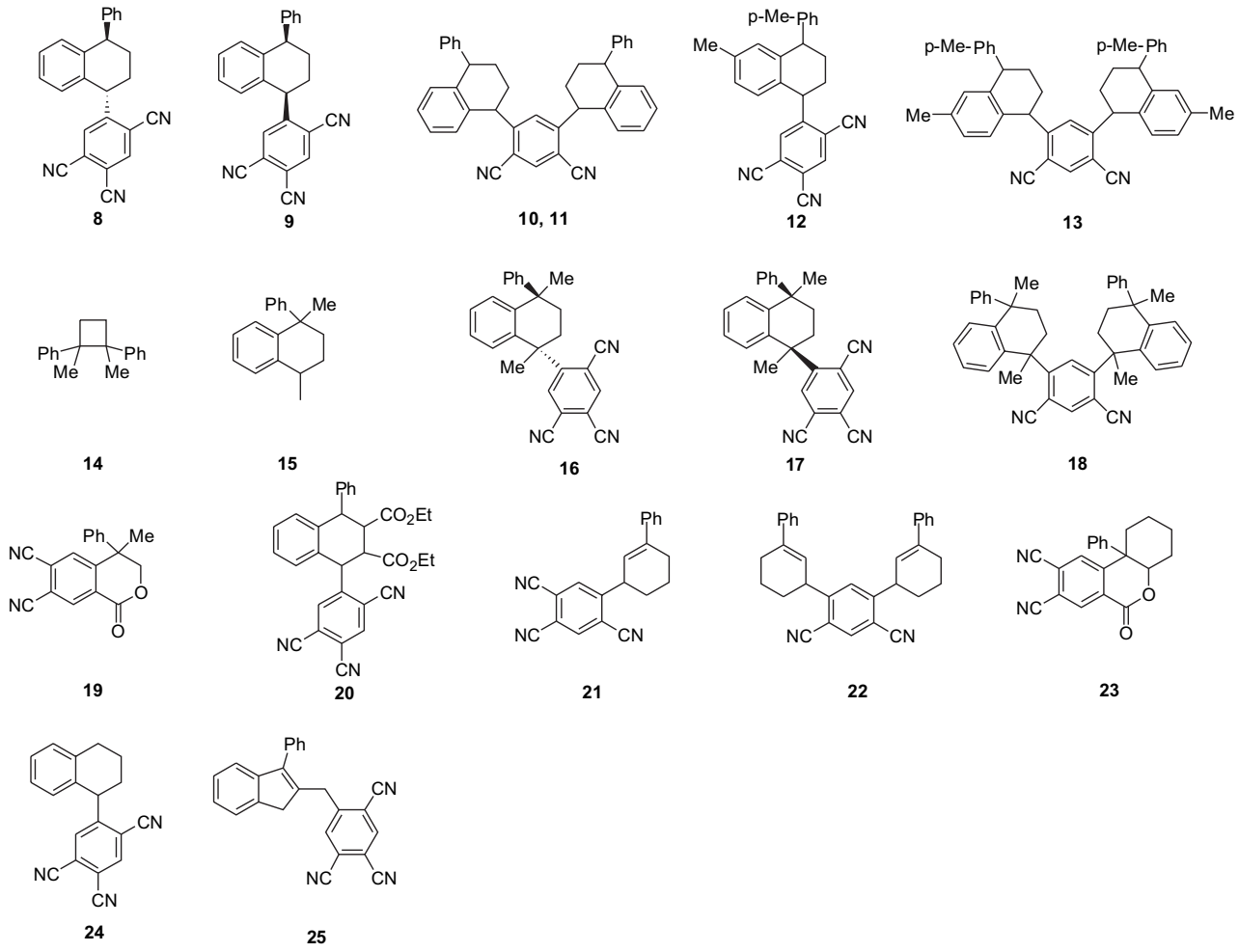


Chart 2.

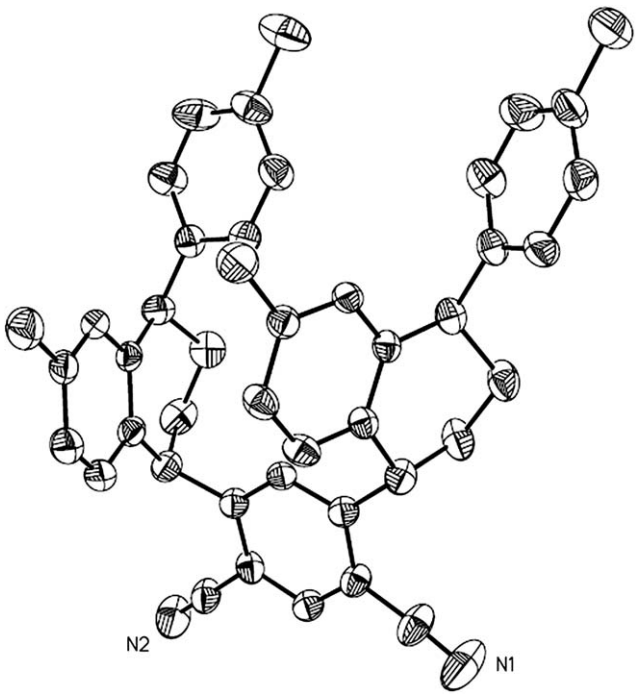


Figure 1. X-ray structure of **13**, showing 30% probability displacement ellipsoids. H-atoms have been omitted for clarity.

To help to clarify the mechanism of these reactions, photoreactions of TCNB with tetralin **6** and 1-phenyltetralin **7** were also investigated. Irradiation of TCNB (0.05 M) with **6** (0.5 M) in MeCN under similar conditions as mentioned above resulted in a sluggish reaction, and the total conversion of TCNB required 48 h irradiation to give the product **24** in 74% yield. Similar photolysis of TCNB (0.05 M) with **7** (0.5 M) in MeCN for 60 h led to the total conversion of TCNB and afforded the same 2:1 product **8** (37%) as obtained in photoreactions of TCNB with **1**, and its diastereomer **9** (21%), along with an indene product **25** (7%) obviously derived from secondary reactions.

The influence of added codonor (cosensitizer)[6d,15–18] and salt[19] on these reactions was also examined by testing the photoreactions of TCNB with **3** in the presence and absence of the added biphenyl (BP) and anhydrous $Mg(ClO_4)_2$, respectively. The results are given in Table 1 (entries 4–6). When the reactants were irradiated for 7.5 h in the absence of BP and salt, it only reached a 95% conversion of TCNB without the formation of secondary 4:1 product **18**. At the same time, parallel runs with added BP and $Mg(ClO_4)_2$, respectively, were 'overirradiated' in view of the complete conversion of TCNB and the formation of the secondary 4:1 product in significant amount by further reactions of **16*** and **17*** with **3**. These results showed that reaction rate was substantially accelerated by the added BP and $Mg(ClO_4)_2$.

Table 1. Photoreactions of TCNB with **1–7**[a]

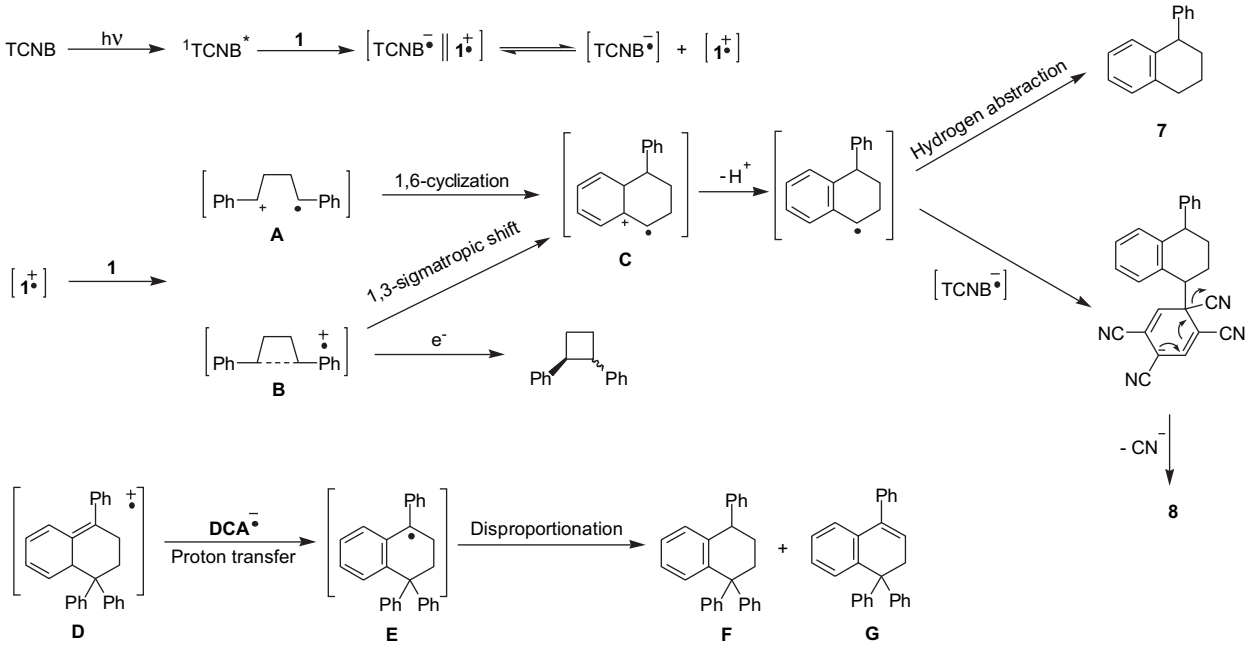
Entry	Donor	$E^{ox}_{1/2}$ [b] (V, SCE)	ΔG_{ET} (kcal mol^{-1})	K_{SV} (M^{-1})	Irrd. time (h)	Conv. (%)	Products and yield (%)
1	**1**	1.93	−30.9	299	13	100	**8** (86)
2	**2**	1.74	−35.3	215	10	100	**12** (2), **13** (66)
3[b]	**3**	1.86	−32.5	248	14	98	**16** (50), **17** (38), **18** (5), **19** (6)
4[c]	**3**				7.5	95	**16** (49), **17** (41), **19** (4)
5[d]	**3**				7.5	100	**16** (47), **17** (33), **18** (14), **19** (4)
6[e]	**3**				7.5	100	**16** (47), **17** (31), **18** (16), **19** (4)
7	**4**	2.16	−25.6	[f]	17	100	**20** (45)
8	**5**	1.61	−38.3	320	48	100	**21** (50), **22** (7), **23** (30)
9	**6**	2.10	−27.0	164	48	100	**24** (74)
10	**7**	2.08	−27.4	233	60	100	**8** (37), **9** (21), **25** (7)

[a] All the reactions were carried out in MeCN solution. For reaction conditions and scale, see Section 4.
[b] Peak potential versus SCE in MeCN.
[c] Entries 4–6 were run parallely under same irradiation conditions. In entry 4, reaction was carried out without any additive.
[d] With added $Mg(ClO_4)_2$ (0.025 M).
[e] With added BP (0.05 M).
[f] Not measured because ethyl cinnamate has absorption at the excitation wavelength.

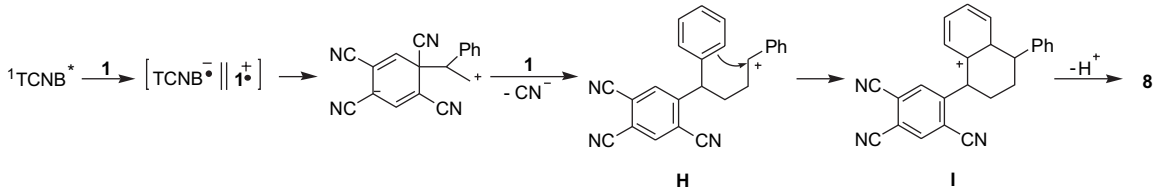
In the photoinduced reaction of TCNB with 1-phenylcyclohexene **5**, the 1:1 product **21** (50%), 2:1 product **22** (7%), and an isocoumarin product **23** (30%) were formed, no tetralin type products were found.

2.2. Mechanism in the photoreactions of TCNB with the arylethenes 1–4

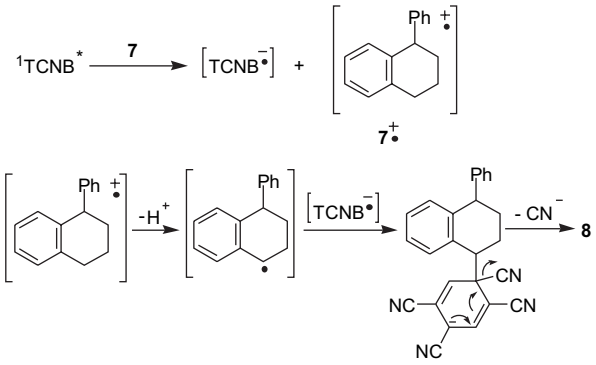
As shown in Table 1, alkenes **1–4** have large negative free energy change (ΔG_{ET}) for single electron transfer (SET) with ^{1}TCNB* and they quench the TCNB fluorescence with a diffusion controlled rate constant (2×10^{10} M^{-1} s^{-1} in MeCN). The photoreactions of TCNB with these alkenes are therefore initiated by SET between ^{1}TCNB* and the alkenes to give solvent separated ion radical pairs (SSIRP) as the primary intermediate in acetonitrile.[20] Three possible pathways for subsequent reactions of the TCNB$^{-\bullet}$–alkene$^{+\bullet}$ ion radical pairs can be envisioned, as shown in Schemes 1–3. In pathway 1 (Scheme 1), following the previously suggested mechanism for the dimerization of arylethene via



Scheme 1.



Scheme 2.



Scheme 3.

PET reactions with 1,4-dicyanobenzene (DCNB)[6a,b,9a] or 9,10-dicyanoanthracene (DCA),[7] interception of the cation radical $\mathbf{1}^{+\bullet}$ by a neutral **1** gives dimeric cation radical as an open chain distonic 1,4-cation radical **A**[6a,b,7] or as a long bond cyclobutane cation radical **B**.[8] A 1,6-cyclization in the former or a 1,3-sigmatropic shift in the later leads to the substituted hexatriene cation radical **C**. However, the fate of this cation radical is different here than that in the DCNB or DCA sensitized reactions. In DCNB sensitized reactions, the main reaction pathway for the substituted hexatriene cation radical such as **C** is to be reduced by the sensitizer anion radical ($DCNB^{-\bullet}$) to give the tetralin product **7**. In DCA sensitized reactions, beside this back SET, another pathway is also available. $DCA^{-\bullet}$ is a better proton acceptor than $DCNB^{-\bullet}$ because its protonation in would result in less loss of aromatization stabilization than in a monocyclic cyanoarene anion radical as $DCNB^{-\bullet}$. As a result, proton transfer from the hexatriene cation radical (**D** when the alkene is 1,1-diphenylethene, Scheme 1) to $DCA^{-\bullet}$ takes place, giving the tetralin radical **E**, which on disproportionation gives the tetralin **F** and the dihydronaphthalene derivative **G**. In contrast to these DCNB and DCA sensitized reactions, in the photoreactions of TCNB with the alkenes **1**–**4**, the highly stabilized $TCNB^{-\bullet}$ formed is neither a good electron donor nor a strong base. As a result, these reaction pathways might be suppressed by deprotonation of **C** to the solvent to give the tetralin radical. Combination of this radical with TCNB anion radical at the *ipso* position, which has the largest spin density in $TCNB^{-\bullet}$[21] followed by extrusion of a cyanide anion gives the product **8**.

Another possible route to product **8** (Scheme 2) invokes a prior in cage radical pair coupling of the alkene cation radical and $TCNB^{-\bullet}$ to give a zwitterionic intermediate followed by departure of a CN^- and the capture of the cationic center by a neutral alkene, yielding the carbocation **H**. A 1,6-cyclization in **H** followed by deprotonation would give product **8**. However, this reaction sequence is disfavored by consideration of known kinetic data in the cyanoarene–alkene photoreactions. The trapping of the arylethene cation radical by a neutral alkene has been identified as a fast process, taking place with a nearly diffusion controlled rate constant of 10^9–10^{10} M^{-1} s^{-1},[7,8e] and competing favorably with back electron transfer ($k_{BET}\sim10^8$ M^{-1} s^{-1})[7] and ion radical pair dissociation ($k_{dis}\sim5.5\times10^8$ M^{-1} s^{-1}),[7] while in cage ion radical pair coupling to a zwitterionic intermediate is believed to be an inherently slow process, which is not able to be competent with the former processes.[2b] Furthermore, our results using the biphenyl (BP) as a codonor in the reactions of TCNB with **1** also regards pathway 2 as unlikely. In many cases, the use of a codonor (usually an aromatic hydrocarbon) is known to enhance the PET reaction efficiency by avoiding the generation of the acceptor anion radical and the donor cation radical in a geminate pair, and therefore circumventing facile back electron transfer and possible in cage ion radical pair recombination.[15–18] In the photoreactions of TCNB with **3**, significant rate acceleration was found when the codonor BP ($E^{ox}_{1/2}$ = 1.85 V, SCE, MeCN) was added to the reaction mixture. In this case, BP as a relay intervenes the SET between ^{1}TCNB* and **3**, so that $TCNB^{-\bullet}$ and $\mathbf{D}^{+\bullet}$ were not generated geminately. This would have caused a retardation of the reaction if pathway 2 (Scheme 1) was followed because in cage recombination of the ion radical pairs should be suppressed. The profound rate acceleration effect of BP on the reaction clearly discards the mechanism in Scheme 2 but favors pathway 1 in Scheme 1. Since styrene (**1**) has an oxidation potential (1.93 V) higher than BP, this rate enhancement may be caused by taking advantage of the longer lifetime of $BP^{+\bullet}$ than ^{1}TCNB* and the continuous move of the equilibrium to the right side in the SET between $BP^{+\bullet}$ and alkene owing to the irreversible consumption of $alkene^{+\bullet}$ in subsequent reactions.

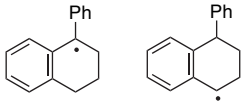
In PET reaction of cyanoarene with electron donor compounds, the addition of a salt with anion of low nucleophilicity, e.g., $Mg(ClO_4)_2$, often leads to a rate acceleration by promoting ion radical pair dissociation.[19] This is similar to the special salt effect in carbocation chemistry where the added $LiClO_4$ suppresses the external return from solvent separated ion pair (SSIP) by anion exchange in the ion pair.[22] We also observed a reaction rate enhancement in the photoreactions of TCNB with **3** by adding an equimolar amount of anhydrous magnesium perchlorate (Table 1, entry 5). This result, together with the cosensitizer effect using biphenyl, renders additional support to the out of cage mechanism in Scheme 1 and disregards a reaction pathway involving an in cage $TCNB^{-\bullet}$–$\mathbf{3}^{+\bullet}$ recombination.

A third mechanistic possibility is that the product **8** may be formed by secondary photoreaction between TCNB and the tetralin product formed in primary reactions of TCNB with the alkenes **1**–**4** (Scheme 3).

The dimer cation radical **C** formed in photoreaction of TCNB with the arylethene (Scheme 1) was deprotonated (with MeCN as proton acceptor) to give the tetralin radical, which yielded the tetralin product **7** by hydrogen abstraction. In photoreactions of TCNB with the alkenes, the neutral alkene dimers were indeed found in the reaction mixture (vide supra). In this case, the TCNB anion radicals would be accumulated in the solution. However, neutral TCNB may be regenerated by oxidation of $TCNB^{-\bullet}$ by the trace amount of oxygen remained in the solution or by disproportionation of $TCNB^{-\bullet}$.[23] Ground state oxygen has a reduction potential of −0.75 V (SCE).[24] SET between O_2 and $TCNB^{-\bullet}$ ($E^{ox}_{1/2}$ = −0.65 V) is a slightly endergonic process. Since we have not found any products that may be derived from the reduced TCNB ($TCNBH_2$) such as 1,2,4-tricyanobenzene in the reaction mixture, we envisage that the main regeneration pathway might be the oxidation by oxygen.

Further photoreaction of TCNB with the tetralin product **7** gives product **8** (Scheme 3). SET of ^{1}TCNB* with **6** and **7** are heavily exergonic (Table 1) and **6** and **7** quenched the TCNB fluorescence with diffusion controlled rate constant. The tetralin cation radical ($\mathbf{7}^{+\bullet}$) generated in the SET event is strongly acidic. Although the pK_a value for this species is not known, it would not be much different from the pK_a of toluene (pK_a~−17),[25] therefore, deprotonation to the acetonitrile solvent (pK_a~−11) should be feasible. The formed tetralin radical is then added to the $TCNB^{-\bullet}$ to give the addition anion radical, which on extrusion of a cyanide anion afforded product **8**.

We examined this mechanism by carrying out the photoreactions of TCNB with tetralin **6** and the independently synthesized 1-phenyltetralin **7**. In contrast to the prompted reactions between TCNB and **1**–**4** (Table 1), irradiation of TCNB with **6** and **7**, respectively, in MeCN under same conditions resulted in rather sluggish reactions. Therefore, while photoreaction of TCNB with **1** took 13 h to reach a complete conversion of TCNB, a lengthy photolysis of 48 h was needed for the complete conversion of TCNB in reaction with **6**. This gave product **24** in 74% yield. The photoreaction of TCNB with **7** required a 60 h irradiation for complete conversion of TCNB and furnished two diastereomeric addition–substitution products **8** (37%) and **9** (21%), and an indene product **25** (7%).



J **K**

In the reaction of TCNB with **7**, we only found coupling products with the tricyanophenyl group attached to the 4-position of **7** (products **8** and **9**) without any products that might be derived from the coupling of the $TCNB^{-\bullet}$ with the tertiary radical **J**. The diphenylmethylene radical **J** is expected to be thermodynamically more stable than the benzylic radical **K** by better spin delocalization. Also, bond dissociation energy (BDE) in the cation radical $\mathbf{7}^{+\bullet}$ for the C(1)–H should be lower than C(4)–H as estimated by Eq. 5 derived from a thermodynamic cycle.[25]

$$\mathrm{BDE}(\mathrm{RH}^{+\bullet}) = \mathrm{BDE}(\mathrm{R-H}) - \mathrm{E}^{\mathrm{ox}}_{1/2}(\mathrm{RH}) + \mathrm{E}^{\mathrm{ox}}_{1/2}(\mathrm{H}^{\bullet}) \qquad (5)$$

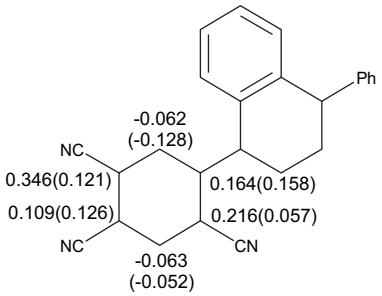
The difference in the BDEs of the relevant C–H bonds in the neutral hydrocarbon is manifested in the BDEs of the same bonds in the hydrocarbon cation radical. However, this difference in the BDE of C(1)–H (~81.8 kcal mol^{-1}, taken as the C–H BDE in Ph_2CH–H)[26a] and C(4)–H (~85 kcal mol^{-1})[26b,c] bonds in 1-phenyltetralin is quite small (~3 kcal mol^{-1}). Considering that the deprotonation of $\mathbf{7}^{+\bullet}$ is an exergonic process with an early transition state, the breaking of the C(1)–H and C(4)–H bonds would have no significant difference in activation energies. Furthermore, kinetic stability of radicals, and therefore the activity in radical coupling reactions are largely controlled by steric shielding to the radical center. Therefore, coupling of $TCNB^{-\bullet}$ with the radical **K** is much more favored and it is the predominant reaction pathway.

It is evident that although photoreactions of TCNB with **7** afford the same addition–substitution product **8** as in the photoreactions of TCNB with **1**, the reaction rate is at least four times slower than in the TCNB–**1** reaction, taking into account that the concentration of **7** formed in the TCNB–**1** reaction should be much lower than in the TCNB–**7** reaction where **7** is in a large excess amount (10 equiv vs TCNB). The low (TCNB–**7**) reaction rate is also the reason why significant amount of the cyclodimers such as **15** was accumulated in the reaction products in these TCNB–**1** photoreactions. Within the short reaction time and with the small concentration of the formed **7** in the reaction mixture, secondary (TCNB–**7**) photoreaction would not make a significant contribution for the formation of **8** in the TCNB–**1** photoreaction.

We therefore come to the conclusion that the photoreactions of TCNB with the arylethene **1**–**4** proceed predominately by the reaction pathway 1 in Scheme 1 via the tetralinyl radical–radical anion ($TCNB^{-\bullet}$) combination, although the secondary photoreaction of TCNB–**7** as shown in Scheme 3 might make a minor contribution.

2.3. Formation of the 4:1 (1:TCNB) product

A control experiment showed that products **10** and **11** was formed by secondary PET reactions of the primary product **8** with styrene **1**. This follows a mechanism similar to Scheme 1. The anion radical $\mathbf{8}^{-\bullet}$ combines with the styrene dimer radical at the *meta*-carbon atom bearing a CN group, and this is followed by loss of a cyanide anion to give **10** (**11**). Again, the coupling of the styrene dimer radical with $\mathbf{8}^{-\bullet}$ takes place at the site with the highest spin density in $\mathbf{8}^{-\bullet}$ as indicated by the result of a DFT UB3LYP/6-31G* calculation[27] on its spin and charge density distribution (Fig. 2).



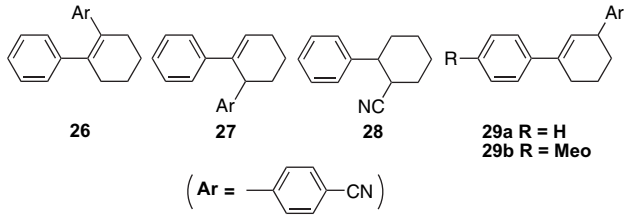
$\mathbf{8}^{-\bullet}$

Figure 2. Spin and charge (in parentheses, with the charge density at hydrogen atom summed up to their attached C atom) density in $\mathbf{8}^{-\bullet}$.

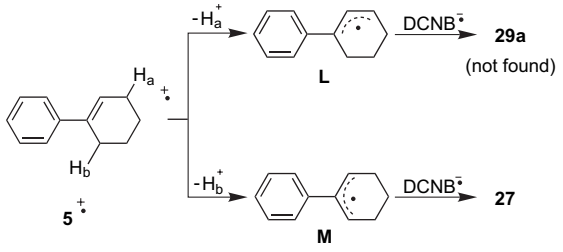
2.4. Mechanism of photoreaction of TCNB with 1-phenylcyclohexene 5

In this reaction, only the 1:1 (**5**–TCNB) product **21** was formed as the primary product. Secondary reaction of excited **21** with **5** resulted in the 2:1 product **22**. No alkene dimerization–aromatic substitution products were formed. This difference in the reactivity of $\mathbf{5}^{+\bullet}$ and the cation radicals of **1**–**4** is attributed to the special structure of $\mathbf{5}^{+\bullet}$. It was

reported that according to a semiempirical PM3 calculation, the optimized $\mathbf{5}^{+\bullet}$ has a nonplanar structure and the cyclohexene ring has a chair-like conformation, which causes a large static hindrance toward its trapping by a neutral **5**. This is supported by a laser flash photolysis (LFP) study of the (DCNB–**5**) system in MeCN, in which only transient absorption bands attributable to the monomer cation radical ($\mathbf{5}^{+\bullet}$) were detected.[9a] In accordance with this, photoinduced reactions of DCNB with **5** in MeCN gave two 1:1 adducts **26** and **27** in 34% total yield together with **28** (17%).[9a] In the photoreactions of TCNB with **5**, we found a 1:1 adduct **21** (50%), along with a 2:1 adduct **22** (7%) and an isocoumarin product **23** (30%).



As pointed out based on a PM3 computation,[9a] the deprotonation of $\mathbf{5}^{+\bullet}$ would give radicals **L** and **M**, with the former being thermodynamically more stable. Our own calculation by UB3LYP/6-31G* supports this conclusion by indicating that **L** is 5.27 kcal mol^{-1} more stable than **M**. Although product derived from coupling of **L** with DCNB$^{-\bullet}$ was not found in photoreaction of DCNB with **5** (reaction 6),[9a] in our reaction of TCNB with **5**, we obtained product **21** (which is similar to **29a**) as the only 1:1 coupling product between TCNB and **5**.



(6)

As a matter of fact, in the photoreactions of DCNB with 1-(4-methoxyphenyl)cyclohexene,[28] it was found that by adding collidine as a base, product **29b** derived from the combination of the deprotonated allyl radical similar to **L** with DCNB$^{-\bullet}$ was indeed formed. In this case, the deprotonation of 1-(4-methoxyphenyl)cyclohexene cation radical, which is less acidic than $\mathbf{5}^{+\bullet}$, was promoted by adding a base. The formation of **29b** further supports the mechanism in Scheme 4 for the formation of **21**.

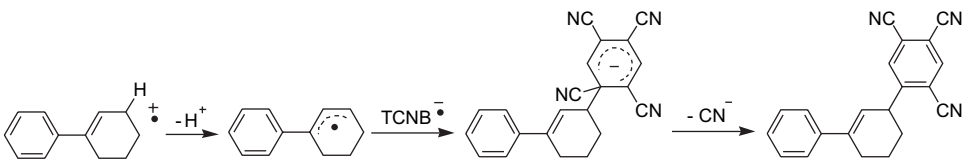
3. Conclusions

In summary, we have described the olefin dimerization–aromatic substitution reactions between singlet excited TCNB with a series of arylethenes that lead to the *ipso* substitution of one or two of the CN groups in TCNB by 1-tetralinyl as the alkene cyclodimer. These reactions gave high yield of products. Based on the codonor and salt effect on the reactions, the result of photoinduced reactions of TCNB with tetralin and 1-phenyltetralin, argument based on the analysis of known kinetic data for relevant processes and computational results on the structures of the alkene cation radicals, these reactions are proposed to follow a mechanism involving out of cage interception of the alkene cation radical by a neutral alkene, deprotonation of the cyclodimer cation radical to the solvent and coupling of the cyclodimer radical with TCNB$^{-\bullet}$. These described reaction modes serve to extend the reaction diversity and help to further clarify several delicate mechanistic issues in the cyanoarene–alkenes PET reactions depending on the structures of the alkene cation radical and cyanoarene anion radical.

4. Experimental

4.1. General

Melting points were measured on a Yanaco microscopic melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker DPX 300 spectrometer with $CDCl_3$ as internal standard and solvent. Other NMR spectra were recorded on a Bruker Avance 400 spectrometer with $CDCl_3$ as internal standard and solvent. IR spectra were taken with a Shimadzu IR 440 spectrometer for samples in KBr pellets. Mass spectra were recorded with a VG ZAB-HS spectrometer. Elemental analyses were obtained using a Perkin–Elmer 240 C analyzer. Oxidation potentials were measured by a CHI 600 electrochemical workstation (CH Instruments, USA). Quenching experiments of the fluorescence were performed on an AMINCO Bowman Series 2 fluorescence spectrophotometer. For X-ray crystallographic analysis, the X-ray diffraction intensities and the unit cell parameters were determined on an Enraf-Nonius CAD-4 diffractometer employing graphite-monochromated (MoKα) radiation (λ=0.71073 Å) and operating in the $\omega/2\theta$ scan mode. Data collection and cell refinement were performed with CAD-4 Software. Structures were solved by direct methods and refined by full-matrix least-squares on F^2 with SHELXTL. Nonhydrogen atoms were refined by anisotropic displacement parameters, and the positions of all H-atoms were fixed geometrically and included in estimated positions using a riding model.



Scheme 4.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 293776. 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].

4.2. Materials

1-Phenylcyclohexene (**5**) was synthesized according to a procedure described for the synthesis of 1-phenylcyclopentene.[29] Tetracyanobenzene and 1-phenyltetralin (**7**) were prepared by literature procedures.[30,31] Acetonitrile (AR grade) was first refluxed with phosphorus pentoxide and distilled and then refluxed with anhydrous potassium carbonate and redistilled. Other reagents were CP or AR grade and were used as received without further purification. Petroleum ether refers to the fraction with boiling point in the range 60–90 °C.

4.3. Cyclic voltammetric measurements

Oxidation potentials of the alkenes were measured at 298 K by cyclic voltammetry in dry acetonitrile with tetrabutylammonium perchlorate (0.1 M) as supporting electrolyte. Platinum electrodes were used as working electrode and auxiliary electrode, and the reference electrode was a saturated calomel electrode (SCE). The scan speed was 100 mV s^{-1}. The solutions were 0.5–1 mM in the substrate and were purged with dry nitrogen for 10 min before measurements to remove dissolved oxygen.

4.4. Fluorescence quenching

Excitation was at 313 nm. The monitoring wavelength was 333 nm. The solutions were deoxygenated by argon purging for 10 min prior to the measurements. Relative emission intensities were measured for MeCN solution containing TCNB (2.5×10^{-5} M) with electron donors at various concentrations (0–1.0×10^{-1} M) at 298 K. There was no change in the shape but there was a change in the intensity of the fluorescence spectrum by the addition of an electron donor. The Stern–Volmer relationship

$$I_0/I = 1 + K_{SV}[D]$$

was obtained from the ratio of the emission intensities in absence and presence of electron donors (I_0/I) and the concentrations of quenchers [D].

4.5. Procedures for the preparative photolysis of TCNB with alkynes

The light source was a medium-pressure mercury lamp (500 W) in a glass cooling water jacket to cut off light of wavelength shorter than 300 nm. If it was further surrounded by a layer of filter solution (10% aqueous sodium nitrate, 1 cm thick), it gave light of wavelength longer than 330 nm. The solution of tetracyanobenzene (TCNB) and an excess amount of alkene in MeCN was purged with dry argon for 15 min and then irradiated under continuous argon purging. The reaction course was monitored by TLC. At the end of the reaction, the solvent was removed under reduced pressure and the residue was separated by flash chromatography on a silica gel column with petroleum ether–ethyl acetate as eluent.

4.5.1. Photolysis of TCNB with 1. A solution of TCNB (713 mg, 4 mmol) and **1** (6.25 g, 60 mmol) in MeCN (80 mL) was photolyzed ($\lambda>300$ nm) for 13 h to reach a complete conversion of TCNB. The solvent was removed under reduced pressure and the residue was separated by flash chromatography on a silica gel column with petroleum ether–ethyl acetate as eluent to give **8** (1.23 g, 86%).

4.5.1.1. 4-Phenyl-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (8). Colorless crystals from petroleum ether–acetone, mp 221–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79–1.90 (1H, m), 1.93–2.04 (1H, m), 2.14–2.24 (1H, m), 2.39–2.49 (1H, m), 4.32 (1H, t, J=6.6 Hz), 4.87 (1H, t, J=6.7 Hz), 6.71 (1H, dd, J=6.9 and 1.6 Hz), 7.11–7.14 (2H, m), 7.17 (1H, dd, J=6.8 and 1.6 Hz), 7.21–7.25 (2H, m), 7.26–7.29 (1H, m), 7.34–7.38 (2H, m), 7.49 (1H, s), 8.13 (1H, s) ppm; IR (KBr): 3024, 2939, 2920, 2861, 2240, 1596, 1488, 1447, 1384, 1236, 1029, 1002, 912, 814, 765, 751, 705, 662 cm^{-1}; MS (EI): *m*/*z* (% base) 359 (M^+, 85), 358 (100), 341 (34), 330 (25), 302 (6), 280 (72), 226 (4), 202 (2), 180 (59), 165 (29), 152 (6), 104 (24), 91 (19), 77 (16), 63 (5), 51 (12). Anal. Calcd for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69. Found: C, 83.35; H, 4.53; N, 11.52.

4.5.2. Photolysis of 8 with 1. A solution of **8** (209 mg, 0.6 mmol) and **1** (0.94 g, 9 mmol) in MeCN (12 mL) was photolyzed ($\lambda>300$ nm) for 22 h to reach a complete conversion of TCNB. Workup as described above gave **10** (31 mg, 10%) and **11** (213 mg, 66%).

4.5.2.1. 2,4-Di(4-phenyl-1,2,3,4-tetrahydro-1-naphthyl)-1,5-benzenedicarbonitrile (10). Colorless crystals from petroleum ether–acetone, mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.92 (5H, m), 1.99–2.14 (1H, m), 2.26–2.40 (2H, m), 3.94–4.01 (1H, m), 4.11–4.22 (1H, m), 4.68 (2H, dd, J=5.9 and 9.3 Hz), 6.57–6.70 (1H, m), 6.74–6.77 (2H, m), 6.86–6.89 (3H, m), 7.03–7.25 (10H, m), 7.29–7.33 (4H, m) ppm; IR (KBr): 3059, 3023, 2934, 2860, 2228, 1599, 1490, 1448, 1238, 748, 701, 521 cm^{-1}; MS (EI): *m*/*z* (% base) 540 (M^+, 100), 180 (38), 179 (13), 165 (15), 91 (19), 70 (24). Anal. Calcd for $C_{40}H_{32}N_2$: C, 88.85; H, 5.96; N, 5.18. Found: C, 88.83; H, 5.98; N, 5.09.

4.5.2.2. 2,4-Di(4-phenyl-1,2,3,4-tetrahydro-1-naphthyl)-1,5-benzenedicarbonitrile (11). Colorless crystals from petroleum ether–acetone, mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83–2.02 (4H, m), 2.20–2.24 (2H, m), 2.35–2.43 (2H, m), 4.10–4.32 (2H, m), 4.75 (2H, t, J=6.6 Hz), 6.80–6.83 (1H, m), 6.97–7.00 (2H, m), 7.13–7.19 (7H, m), 7.24–7.41 (9H, m), 7.49 (1H, d, J=6.3 Hz) ppm; IR (KBr): 3024, 2932, 2859, 2229, 1599, 1491, 1448, 1389, 908, 748, 701, 528 cm^{-1}; MS (EI): *m*/*z* (% base) 540 (M^+, 26), 539 (26), 281 (7), 255 (6), 179 (34), 180 (100), 181 (12), 191 (19), 178 (17), 165 (45). Anal. Calcd for $C_{40}H_{32}N_2$: C, 88.85; H, 5.96; N, 5.18. Found: C, 88.81; H, 6.01; N, 5.13.

4.5.3. Photolysis of TCNB with 2. A solution of TCNB (713 mg, 4 mmol) and **2** (4.72 g, 40 mmol) in MeCN

(80 mL) was photolyzed (λ>300 nm) for 10 h to reach a complete conversion of TCNB. Workup as described above gave **12** (28 mg, 2%) and **13** (1.58 g, 66%).

4.5.3.1. 6-Methyl-4-(4-methylphenyl)-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (12). Colorless crystals from petroleum ether–acetone, mp 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81–1.90 (2H, m), 2.12–2.19 (2H, m), 2.23 (3H, s), 2.37 (3H, s), 4.23 (1H, t, J=6.7 Hz), 4.68 (1H, t, J=6.6 Hz), 6.69 (1H, d, J=7.8 Hz), 6.80 (1H, s), 6.94–7.16 (7H, m) ppm; IR (KBr): 3018, 2921, 2860, 2229, 1612, 1513, 1495, 1447, 1387, 894, 813, 518 cm^{-1}; MS (EI): *m*/*z* (% base) 295 (2), 283 (2), 234 (4), 208 (31), 193 (11), 105 (19), 104 (46), 77 (4), 64 (16), 57 (15), 55 (12), 44 (100), 43 (23). Anal. Calcd for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.61; H, 5.55; N, 10.76.

4.5.3.2. 4,6-Di(6-methyl-4-(4-methylphenyl)-1,2,3,4-tetrahydro-1-naphthyl)-1,3-benzenedicarbonitrile (13). Colorless crystals from petroleum ether–acetone, mp 252–254 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63–1.81 (4H, m), 1.90–2.24 (4H, m), 2.09 (3H, s), 2.20 (3H, s), 2.33 (3H, s), 2.42 (3H, s), 4.09–4.12 (2H, m), 4.60–4.66 (2H, m), 6.50 (2H, t, J=8.7 Hz), 6.62–6.87 (7H, m), 6.97 (1H, s), 7.00 (1H, s), 7.14 (4H, dd, J=7.5 and 5.6 Hz), 7.97 (1H, s) ppm; IR (KBr): 3020, 2927, 2856, 2230, 1607, 1513, 1501, 1447, 1382, 1111, 897, 815, 560, 537 cm^{-1}; MS (EI): *m*/*z* (% base) 597 (4), 596 (M$^+$, 23), 595 (3), 504 (4), 209 (3), 208 (100), 193 (18), 178 (3), 118 (3), 105 (10), 91 (2), 44 (2). Anal. Calcd for $C_{44}H_{40}N_2$: C, 88.55; H, 6.76; N, 4.69. Found: C, 88.51; H, 6.80; N, 4.61.

4.5.4. Photolysis of TCNB with 3. A solution of TCNB (713 mg, 4 mmol) and **3** (7.08 g, 60 mmol) in MeCN (80 mL) was photolyzed (λ>300 nm) for 14 h to reach a 98% conversion of TCNB. Workup as described above gave **14** (188 mg), **15** (586 mg), **16** (754 mg, 50%), **17** (574 mg, 38%), **18** (112 mg, 5%), and **19** (65 mg, 6%).

4.5.4.1. 1,4-Dimethyl-4-phenyl-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (16). Colorless crystals from petroleum ether–acetone, mp 277–278 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81–1.83 (1H, m), 1.87 (1H, m), 1.90 (3H, s), 2.00 (3H, s), 2.23–2.33 (1H, m), 2.40–2.49 (1H, m), 6.64 (1H, dd, J=7.7 and 1.4 Hz), 7.01 (1H, dd, J=7.7 and 1.4 Hz), 7.14 (1H, td, J=7.7 and 1.5 Hz), 7.19–7.25 (4H, m), 7.30–7.35 (2H, m), 8.01 (1H, s), 8.08 (1H, s) ppm; IR (KBr): 3052, 3020, 2985, 2931, 2240, 1734, 1598, 1490, 1450, 1383, 1280, 1226, 1028, 914, 770, 700 cm^{-1}; MS (EI): *m*/*z* (% base) 387(M$^+$, 17), 372 (100), 355 (19), 294 (12), 280 (10), 223 (7), 197 (81), 119 (19), 91 (39), 77 (15), 43 (32). Anal. Calcd for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.59; H, 5.54; N, 10.78.

4.5.4.2. 1,4-Dimethyl-4-phenyl-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (17). Colorless crystals from petroleum ether–acetone, mp 232–233 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (3H, s), 1.81–1.86 (1H, m), 1.95–2.03 (1H, m), 2.10 (3H, s), 2.09–2.20 (1H, m), 2.38 (1H, ddd, J=14.0, 8.4, and 2.9 Hz), 7.02–7.05 (1H, m), 7.16–7.22 (4H, m), 7.27–7.36 (4H, m), 7.57 (1H, s), 8.08 (1H, s) ppm; IR (KBr): 3112, 3038, 2948, 2235, 1594, 1492, 1440, 1381, 1216, 1102, 1029, 936, 766, 704 cm^{-1}; MS (EI): *m*/*z* (% base) 387(M$^+$, 15), 372 (100), 355 (18), 294 (11), 280 (7), 219 (2), 192 (6), 105 (4), 91 (25), 43 (4). Anal. Calcd for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.62; H, 5.42; N, 10.88.

4.5.4.3. 4,6-Di(1,4-dimethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthyl)-1,3-benzenedicarbonitrile (18). Colorless crystals from petroleum ether–acetone, mp>300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (3H, s), 1.77 (3H, s), 1.68–1.82 (2H, m), 1.87 (3H, s), 1.82–1.89 (2H, m), 2.11 (3H, s), 2.22–2.30 (2H, m), 2.40–2.47 (1H, m), 2.63–2.69 (1H, m), 6.66–6.69 (1H, m), 6.92–6.94 (1H, m), 7.01–7.04 (2H, m), 7.10–7.13 (1H, m), 7.15–7.16 (1H, m), 7.18–7.20 (4H, m), 7.21–7.26 (5H, m), 7.27–7.34 (4H, m), 7.98 (1H, s) ppm; IR (KBr): 3055, 2971, 2939, 2228, 1739, 1593, 1489, 1441, 1378, 1237, 1030, 918, 758, 702, 631 cm^{-1}; MS (EI): *m*/*z* (% base) 596 (M$^+$, 19), 581 (100), 503 (5), 465 (2), 331 (1), 283 (12), 176 (4), 105 (1), 91 (19), 44 (1). Anal. Calcd for $C_{44}H_{40}N_2$: C, 88.55; H, 6.76; N, 4.69. Found: C, 88.50; H, 6.49; N, 4.58.

4.5.4.4. 6,7-Dicyano-4-methyl-4-phenyl-3,4-dihydroisocoumarin (19). Colorless crystals from petroleum ether–acetone, mp 217–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (3H, s), 4.39 (1H, d, J=11.6 Hz), 4.83 (1H, d, J=11.6 Hz), 7.19–7.22 (2H, m), 7.41–7.46 (3H, m), 7.55 (1H, s), 8.59 (1H, s) ppm; IR (KBr): 3080, 3048, 2994, 2974, 2236, 1728, 1601, 1495, 1466, 1446, 1412, 1310, 1240, 1195, 1096, 1045, 942, 901, 799, 769, 744, 707 cm^{-1}; MS (EI): *m*/*z* (% base) 288 (M$^+$, 23), 258 (100), 243 (20), 215 (19), 176 (2), 165 (1), 129 (2), 77 (3), 51 (3). Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.82; H, 4.32; N, 9.59.

4.5.5. Photolysis of TCNB with 4. A solution of TCNB (534 mg, 3 mmol) and **4** (5.28 g, 30 mmol) in MeCN (60 mL) was photolyzed (λ>300 nm) for 17 h to reach a complete conversion of TCNB. Workup as described above gave **20** (677 mg, 45%).

4.5.5.1. 2,3-Di(ethoxycarbonyl)-4-phenyl-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (20). Colorless crystals from petroleum ether–acetone, mp 177–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J=7.1 Hz), 1.13 (3H, t, J=7.1 Hz), 3.40 (1H, q, J=10.5 Hz), 3.43 (1H, q, J=10.5 Hz), 3.87–3.92 (2H, m), 4.07 (2H, m), 4.53 (1H, d, J=10.3 Hz), 5.13 (1H, d, J=10.4 Hz), 6.47 (1H, d, J=6.9 Hz), 6.85 (1H, d, J=6.8 Hz), 7.09–7.13 (2H, m), 7.18–7.21 (2H, m), 7.29–7.40 (3H, m), 7.76 (1H, s), 8.12 (1H, s) ppm; IR (KBr): 3112, 3045, 2983, 2241, 1736, 1600, 1491, 1449, 1375, 1274, 1248, 1185, 1013, 915, 858, 762, 703 cm^{-1}; MS (EI): *m*/*z* (% base) 356 (0.2), 276 (3), 205 (3), 178 (100), 151 (9), 100 (12), 75 (14), 69 (7), 51 (10), 44 (8). Anal. Calcd for $C_{31}H_{25}N_3O_4$: C, 73.94; H, 5.00; N, 8.34. Found: C, 73.69; H, 4.89; N, 8.41.

4.5.6. Photolysis of TCNB with 5. A solution of TCNB (534 mg, 3 mmol) and **5** (2.84 g, 18 mmol) in MeCN (60 mL) was photolyzed (λ>330 nm) for 48 h to reach a complete conversion of TCNB. Workup as described above gave **21** (457 mg, 50%), **22** (96 mg, 7%), and **23** (297 mg, 30%).

4.5.6.1. 5-(2-Phenyl-2-cyclohexenyl)-1,2,4-benzenetricarbonitrile (21). Colorless crystals from petroleum

ether–acetone, mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57–1.61 (1H, m), 1.91–1.95 (2H, m), 2.27–2.31 (2H, m), 2.60–2.65 (1H, m), 4.18 (1H, m), 5.96 (1H, s), 7.33–7.38 (1H, m), 7.40–7.42 (2H, m), 7.45–7.48 (2H, m), 7.86 (1H, s), 8.08 (1H, s) ppm; ^{13}C NMR (100.7 MHz, $CDCl_3$): δ 21.13, 27.21, 30.94, 41.24, 113.72, 114.24, 114.53, 117.32, 119.46, 121.67, 125.32, 128.00, 128.59, 133.87, 137.17, 140.88, 142.53, 156.61 ppm; IR (KBr): 3105, 3042, 2934, 2862, 2235, 1644, 1487, 1447, 1381, 1321, 1240, 1184, 920, 792, 744, 698, 509 cm^{-1}; MS (EI): *m*/*z* (% base) 309 (M^+, 49), 280 (100), 266 (81), 230 (6), 152 (2), 128 (6), 115 (11), 91 (15), 77 (6), 51 (3). Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.32; H, 4.82; N, 13.75.

4.5.6.2. 2,4-Di(2-phenyl-2-cyclohexenyl)-1,5-benzenedicarbonitrile (22). Colorless crystals from petroleum ether–acetone, mp 187–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (2H, m), 1.88 (4H, m), 2.23 (2H, m), 2.53 (4H, m), 4.08 (2H, m), 5.94–5.97 (2H, m), 7.15–7.25 (3H, m), 7.27–7.33 (7H, m), 7.48 (1H, s), 7.95 (1H, s) ppm; IR (KBr): 3026, 2932, 2861, 2227, 1602, 1489, 1444, 1390, 1154, 1034, 757, 696 cm^{-1}; MS (EI): *m*/*z* (% base) 440 (M^+, 100), 439 (97), 422 (2), 414 (17), 383 (2), 255 (3), 227 (1), 205 (2), 191 (1), 157 (5). Anal. Calcd for $C_{32}H_{28}N_2$: C, 87.24; H, 6.41; N, 6.36. Found: C, 87.32; H, 6.62; N, 6.23.

4.5.6.3. 6,7-Dicyano-3,4-cyclohexyl-4-phenyl-3,4-dihydroisocoumarin (23). Colorless crystals from petroleum ether–acetone, mp 183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42–1.57 (2H, m), 1.69–1.77 (2H, m), 1.93–1.97 (1H, m), 2.24–2.28 (1H, m), 2.39 (1H, ddd, J=23.5, 10.4, and 4.4 Hz), 3.12 (1H, d, J=13.3 Hz), 4.75 (1H, dd, J=4.2 and 2.4 Hz), 7.23–7.28 (1H, m), 7.35 (2H, t, J=7.3 Hz), 7.60 (2H, d, J=7.6 Hz), 7.98 (1H, s), 8.45 (1H, s) ppm; IR (KBr): 3115, 3050, 2952, 2868, 2236, 1731, 1603, 1495, 1453, 1403, 1288, 1256, 1217, 1142, 1044, 788, 726 cm^{-1}; MS (EI): *m*/*z* (% base) 328 (M^+, 64), 300 (6), 257 (100), 244 (5), 228 (11), 215 (12), 202 (9), 175 (3), 151 (1), 91 (3), 77 (4), 51 (2). Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.92; H, 4.85; N, 8.43.

4.5.7. Photolysis of TCNB with 6. A solution of TCNB (534 mg, 3 mmol) and **6** (3.96 g, 30 mmol) in MeCN (60 mL) was photolyzed (λ>300 nm) for 48 h to reach a complete conversion of TCNB. Workup as described above gave **24** (686 mg, 74%).

4.5.7.1. 1-(2,4,5-Tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (24). Colorless crystals from petroleum ether–acetone, mp 134–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79–1.90 (3H, m), 2.32–2.39 (1H, m), 2.94–2.99 (2H, m), 4.71–4.75 (1H, m), 6.67 (1H, d, J=7.7 Hz), 7.11–7.16 (1H, m), 7.24–7.29 (2H, m), 7.41 (1H, s), 8.10 (1H, s) ppm; IR (KBr): 3109, 3042, 2934, 2862, 2238, 1596, 1543, 1490, 1449, 1384, 1329, 1274, 1246, 1199, 1158, 993, 911, 767, 746 cm^{-1}; MS (EI): *m*/*z* (% base) 283 (M^+, 87), 282 (100), 265 (81), 254 (21), 240 (10), 228 (135), 200 (6), 188 (2), 175 (3), 154 (2), 128 (6), 115 (10), 104 (86), 91 (8), 84 (47), 77 (5), 49 (39). Anal. Calcd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.45; H, 4.52; N, 14.75.

4.5.8. Photolysis of TCNB with 7. A solution of TCNB (713 mg, 4 mmol) and **7** (8.33 g, 40 mmol) in MeCN (80 mL) was photolyzed (λ>300 nm) for 60 h to reach a complete conversion of TCNB. Workup as described above gave **8** (536 mg, 37%), **9** (303 mg, 21%), and **25** (102 mg, 7%).

4.5.8.1. 4-Phenyl-1-(2,4,5-tricyanophenyl)-1,2,3,4-tetrahydronaphthalene (9). Colorless crystals from petroleum ether–acetone, mp 218–219 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62–1.70 (2H, m), 2.75–2.81 (1H, m), 2.93–3.09 (3H, m), 6.51 (1H, d, J=7.7 Hz), 7.10–7.14 (3H, m), 7.25–7.31 (2H, m), 7.35–7.45 (3H, m), 7.46 (1H, d, J=0.4 Hz), 8.05 (1H, d, J=0.4 Hz) ppm; IR (KBr): 3031, 2939, 2873, 2235, 1492, 1483, 1460, 1445, 1424, 1366, 1272, 1206, 927, 914, 785, 752, 742, 702, 532, 512 cm^{-1}; MS (EI): *m*/*z* (% base) 360 (23), 359 (M^+, 100), 341 (23), 331 (46), 330 (92), 329 (20), 280 (27), 265 (23), 178 (29), 165 (19), 115 (21), 104 (23), 91 (50), 77 (31), 57 (29), 55 (30), 51 (26), 43 (42), 41 (57). Anal. Calcd for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69. Found: C, 83.47; H, 4.81; N, 11.62.

4.5.8.2. 2-(2,4,5-Tricyanophenylmethyl)-3-phenylindene (25). Colorless crystals from petroleum ether–acetone, mp 219–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (2H, s), 4.22 (2H, s), 7.22–7.36 (5H, m), 7.42–7.54 (4H, m), 7.49 (1H, d, J=0.5 Hz), 8.00 (1H, d, J=0.5 Hz) ppm; IR (KBr): 3113, 2235, 1601, 1488, 1459, 1440, 1423, 1394, 1297, 1205, 905, 771, 760, 726, 703, 527, 490 cm^{-1}; MS (EI): *m*/*z* (% base) 358 (7), 357 (M^+, 26), 192 (23), 191 (100), 190 (13), 189 (33), 166 (12), 165 (23), 139 (11), 51 (6). Anal. Calcd for $C_{25}H_{15}N_3$: C, 84.01; H, 4.23; N, 11.76. Found: C, 84.02; H, 4.16; N, 11.68.

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Supplementary data

Supplementary data, including Stern–Volmer plots for the fluorescence quenching of TCNB, X-ray data and crystallographic structure for compound **13**, NMR spectra of all new compounds (**8**–**13**, **16**–**25**), computational results on $TCNB^{-\bullet}$, $\mathbf{3}^{+\bullet}$, **L**, **M**, and $\mathbf{8}^{-\bullet}$, associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.089.

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Synthesis pathway to carbohydrate-derived salicylidene hydrazides as ligands for oxovanadium complexes

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Abstract—Salicylidene hydrazides represent important ligands forming oxovanadium complexes. Carbohydrate-derived chiral salicylidene hydrazides as ligands for metal ion complexation were synthesized for the first time. The pathway of the mild and selective synthesis starts from commercial saccharides like methyl-α-D-glucopyranoside and methyl-α-D-mannopyranoside. All synthesized carbohydrate-derived salicylidene hydrazides are able to form oxovanadium complexes. The mononuclear structure proposed for the complex of 1,2,3,4-tetra-*O*-methyl-α-D-glucopyranuronic acid salicylidene hydrazide is consistent with the analytical data (NMR, IR and MS).

1. Introduction

Salicylidene hydrazides are versatile structural units that can act as mono- or dianionic ONO tridentate donors. Oxovanadium complexes of these ligands have been used as enzyme models for the active site of vanadium dependent haloperoxidases.[1–3] Similar complexes, which have an additional coordination site bound at a side chain also offer good haloperoxidase activity.[4,5]

Since haloperoxidases are known to catalyze enantioselective sulfoxidation[6–9] as well as oxovanadium complexes of tri- or tetradentate Schiff base ligands,[10–13] such complexes of salicylidene hydrazides with a chiral backbone should be a good catalysts for enantioselective sulfoxidation (Fig. 1).

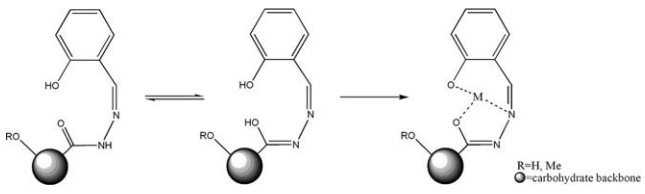

Figure 1. Salicylidene hydrazides with a chiral carbohydrate backbone.

Recently, we described the first structurally characterized prototypes of copper complexes from aminodeoxysugars and its efficient catalytic activity in catechol oxidation.[14–17] Moreover, carbohydrate-derived chiral Mn(III)–salen complexes are potent catalysts in enantiomeric epoxidation of alkenes.[18]

The aim of the present paper is to extend and to confirm the carbohydrate-based structure design of chiral transition metal complexes with catalytic activity using salicylidene hydrazides as ONO ligands and carbohydrates with or without additional free hydroxyl groups. Therefore, an important topic of the work was a concept for an easy synthesis of a large variety of carbohydrate-derived salicylidene hydrazides and its exemplification by typical examples.

Furthermore the complexation behaviour of these ligands with vanadate was investigated.

2. Results and discussion

Carbohydrates as polyfunctional and chiral natural compounds are—with growing importance—starting materials and ligands for the synthesis of catalytic active transition metal complexes.[19–26] Due to the broad variety of configurational and conformational principles of carbohydrates a tuning of the complex structure and also of its catalytic activity can be achieved by varying the carbohydrate moiety. Moreover, the introduction of substituents into the carbohydrate skeleton may influence complex properties like

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solubility and magnetic behaviour as well as the catalytic activity—even if the substituent is not directly coordinated to the metal.[16]

In order to investigate the structural design in the field of carbohydrate-based salicylidene hydrazides and their oxovanadium complexes we have synthesized a set of pyranosides and open chain analogue (Fig. 2, **11** and **23**), respectively. Besides, the stereochemistry of the ligands (glucose and mannose, see Fig. 2, **14** and **5**) and the kind and amount of functional substituents (ketal groups, ethers) at the carbohydrate have been modified.

We developed a synthetic route that allows a selective conversion to salicylidene hydrazides starting from any purchasable saccharide with a primary OH-group. Scheme 1 shows this synthetic pathway considering methyl-2,3-*O*-isopropylidene-α-D-mannuronic acid salicylidene hydrazide **5** starting from methyl-α-D-mannopyranoside **1** as an example.

First, an isopropylidene ketal **2** is formed in order to increase the solubility of the educt **1**. In the next step, which is the key step, the primary OH-group is oxidized selectively using TEMPO-reagent. The carboxyl group is transformed into the corresponding methylester **3** and then converted into the hydrazide **4**. Finally, the Schiff base **5** with salicylaldehyde is formed.

For transferring this pathway to other saccharides just the introduction of the functional substituents has to be adapted to the respective carbohydrate and its stereochemistry.

The ability of this type of ligands to form oxovanadium complexes was demonstrated primarily using the salicylidene hydrazide **20** without free OH donor groups. Therefore, a solution of the ligand and equimolar amount of KVO_3 in methanol was refluxed for 24 h. After purification potassium [1,2,3,4-tetra-*O*-methyl-α-D-glucopyranuronic acid salicylidene hydrazidato] dioxo vanadate **24** could be obtained as a yellow powder in 63% yield. The structure proposed for the vanadium complex **24**, which is consistent with the analytical data (quod infra), is shown in Figure 3. The ^{1}H NMR data of the complex verify the absence of the signals of the aromatic OH-group and of the amide N–H proton (9.19 and 10.87 ppm, respectively). The ^{51}V NMR spectrum recorded in MeOD shows a single resonance in the expected range for *cis*-dioxovanadium(v) complexes, i.e., at $\delta=-544$ ppm with a peak width at half height of $\Delta\nu_{1/2}=526$ Hz. Mass spectrometry experiments have confirmed the formation of the named complex. Infrared spectra show a deprotonation of the ligand amide function since the C=O and N–H stretches of the free ligand at 1711 and 3206 cm^{-1}, respectively, can not be observed in the complex spectrum. Instead a strong signal at 1617 cm^{-1} occurs that can be assigned to the –C=N–N=C-structural unit of the metal-bound salicylidene hydrazide. It indicates a coordination of the enolate form of the amide moiety.[2,27] Furthermore two strong bands are observed at 910 and 918 cm^{-1} belonging to the stretching vibrations of the *cis*-dioxovanadium moiety of the complex.

Attempts to form oxovanadium complexes of the ligands **5**, **11** and **23** lead to mixtures of different coordination compounds, that we were not able to separate up to now. But ^{51}V NMR experiments show a formation of two species in

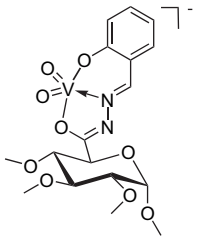


Figure 3. Proposed structure of the complex anion **24**.

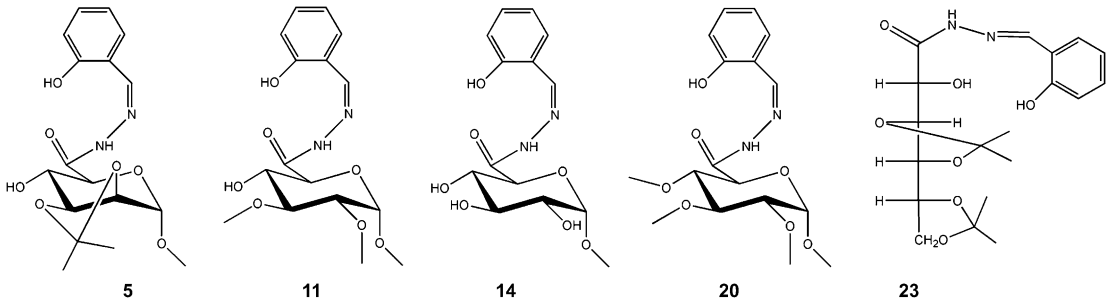
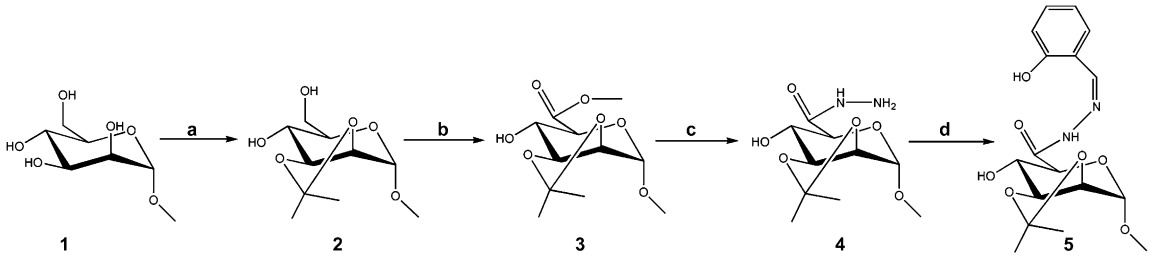


Figure 2. Set of carbohydrate-based salicylidene hydrazides.



Scheme 1. Reagents and conditions: (a) dimethoxy propane, *p*-toluene sulfonic acid, DMF, rt, 24 h; (b) TEMPO oxidation, rt, 2 h; methyl iodide, DMF, rt, 24 h; (c) hydrazine monohydrate, ethanol, reflux, 3 h and (d) salicylaldehyde, ethanol, reflux, 6 h.

each case. This suggests that the free OH-group at these carbohydrates is able to participate in the complex formation.

A first test in catalytic sulfoxidation reaction with **24** showed a complete and selective conversion of the substrate to the corresponding sulfoxide within 90 min. Therefore thioanisole was reacted with 1 mol % of **24** at room temperature in CH_2Cl_2/MeOH (7:3) with 1.2 equiv of H_2O_2 as oxidation agent. No enantioselectivity was observed, which may be caused by the use of the protic solvent methanol, as described in lit.[10]

3. Conclusion

The paper reports the preparation of the first carbohydrate-derived chiral salicylidene hydrazides and its oxovanadium complexes. An important topic of the work was the development of an easy pathway to a large variety of chiral ligands of this type starting from commercial carbohydrates. The ligands **5**, **11**, **14**, **20** and **23** form oxovanadium complexes with VO_3^-. The proposed mononuclear structure of complex **24** can be proved by NMR, IR and MS and it is an active catalyst for sulfoxidation.

Further investigations are concentrated on structure determination of the oxovanadium complexes and their catalytic activity in sulfoxidation reactions.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC-200 spectrometer. IR spectra were measured on a Perkin–Elmer 2000 spectrometer. Mass spectra were carried out on a Finnigan MAT SSQ710 or a Finnigan MAT 95XLTRAP. Elemental analyses were acquired by use of a Leco CHNS 932. The UV–vis data were recorded with a Cary 5000 from Varian. Chemicals were obtained from Fluka and Aldrich, respectively. TLC was conducted on Merck glass plates coated with silica gel 60. Chromatography was performed using silica gel 60 (Particle size 0.063–0.2 mm) from Fluka Chemie GmbH.

4.1.1. Methyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (2). Compound **2** was synthesized according to the lit.[28] starting from methyl-α-D-mannopyranoside **1**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36, 1.45 (2s, 6H, 2× –$C(CH_3)_2$), 3.36 (s, 3H, –OCH_3), 3.50–4.11 (m, 6H, H-2, H-3, H-4, H-5, H-6), 4.88 ppm (s, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.01, 27.83 (2×–$C(CH_3)_2$), 54.99 (–OCH_3), 62.28 (C-6), 69.29 (C-4), 69.54 (C-2), 75.40 (C-3), 78.25 (C-5), 98.38 (C-1), 109.65 ppm (–$C(CH_3)_2$). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.36; H, 7.60.

4.1.2. Methyl-2,3-*O*-isopropylidene-α-D-mannuronic acid methylester (3). Compound **2** 2.5 g (10.6 mmol) was dissolved in 55 ml ethyl acetate, 31 ml of a saturated aqueous solution of $NaHCO_3$, 0.3 g (1.6 mmol) TBAF trihydrate and 0.445 g (2.8 mmol) TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) were added. After cooling to 0 °C a cooled mixture of 55 ml sodium hypochloride (6% in water), 27 ml of a saturated solution of $NaHCO_3$ and 55 ml of a saturated solution of NaCl in water was added slowly. The reaction mixture was stirred vigorously for 2 h at 0 °C until completion (TLC control, eluent ethyl acetate/methanol 1:1). After evaporation in vacuum the product was dissolved in methanol and filtered over silica gel suspended in methanol in order to remove the inorganic salts. The crude acid was converted into the methylester as described.[29] Yield: 1.72 g (62%) colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.33, 1.49 (2s, 6H, 2× –$C(CH_3)_2$), 3.45 (s, 3H, –OCH_3), 3.80 (s, 3H, –$COOCH_3$), 3.95–4.35 (m, 4H, H-2, H-3, H-4, H-5), 4.94 ppm (s, 1H, H-1); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.31, 26.89 (2× –$C(CH_3)_2$), 52.22 (–$COOCH_3$), 55.33 (–OCH_3), 69.01 (C-4), 69.87 (C-2), 74.16 (C-3), 76.05 (C-5), 98.53 (C-1), 109.59 (–$C(CH_3)_2$), 170.25 ppm (–$COOCH_3$). Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92%. Found: C, 49.69; H, 6.89.

4.1.3. Methyl-2,3-*O*-isopropylidene-α-D-mannuronic acid hydrazide (4). Compound **3** 3.3 g (12.5 mmol) and 1.25 g (25 mmol) hydrazine hydrate were refluxed in dry ethanol (50 ml) for 3 h. After evaporation the crude product was crystallized from methanol/ethyl acetate/*n*-hexane. Yield: 1.91 g (58%) colourless needles.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31, 1.47 (2s, 6H, 2× –$C(CH_3)_2$), 3.40 (s, 3H, –OCH_3), 3.81 (dd, J=9.0 Hz, J=6.2 Hz, 1H, H-4), 3.89 (s, 1H, –NH_2), 4.03–4.21 (m, 3H, H-5, H-3, H-2), 4.34 (s, 1H, –OH), 4.93 (s, 1H, H-1), 7.86 ppm (s, 1H, –N*H*NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.75, 27.50 (–$C(CH_3)_2$), 55.70 (–OCH_3), 68.42 (C-4), 70.12 (C-2), 74.29 (C-3), 76.62 (C-5), 98.53 (C-1), 109.74 (–$C(CH_3)_2$), 171.18 ppm (–CO–NH–). Anal. Calcd for $C_{10}H_{18}N_2O_6$: C, 45.80; H, 6.92%; N, 10.68. Found: C, 45.81; H, 6.85; N, 10.81.

4.1.4. Methyl-2,3-*O*-isopropylidene-α-D-mannuronic acid salicylidene hydrazide (5). Compound **4** 1.0 g (3.8 mmol) was suspended in dry methanol (30 ml) and refluxed after adding 0.46 g (3.8 mmol) salicylaldehyde. After 6 h reaction was completed (TLC control ethyl acetate/methanol 1:1). The solvent was removed and the crude product was washed with ethanol. Yield: 1.25 g (90%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26, 1.36 (s, 3H, –$C(CH_3)_2$), 3.50 (s, 3H, –OCH_3), 4.00 (m, 1H, H-4), 4.17–4.32 (m, 4H, H-5, H-3, H-2, –OH), 5.03 (s, 1H, H-1), 6.87–7.03 (m, 2H, H-3_{Ar}, H-5_{Ar}), 7.21 (dd, J=7.7 Hz, J=1.7 Hz, 1H, H-4_{Ar}), 7.29–7.37 (m, 1H, H-6_{Ar}), 8.41 (s, 1H, –CH=N–), 9.54 (s, 1H, Ar–OH), 10.80 ppm (s, 1H, –CO–NH–); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.26, 27.05 (–$C(CH_3)_2$), 55.70 (–OCH_3), 69.18 (C-4), 69.48 (C-2), 73.70 (C-3), 75.86 (C-5), 98.38 (C-1), 109.87 (–$C(CH_3)_2$), 116.66 (C-3_{Ar}), 117.05 (C-1_{Ar}), 119.09 (C-5_{Ar}), 130.83 (C-6_{Ar}), 132.07 (C-4_{Ar}), 152.21 (–CH=N–), 158.41 (C-2_{Ar}), 166.17 ppm (–CO–NH–). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.74; H, 5.71; N, 7.51.

4.1.5. Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (6). Methyl-α-D-glucopyranoside was reacted as described in lit.[30] to give **6**.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.42–3.83 (m, 5H, H-2, H-3, H-5, H-6), 3.42 (s, 3H, –OCH_3), 4.27 (dd, *J*=8.8 Hz, *J*=3.0 Hz, 1H, H-4), 4.74 (d, *J*=3.8 Hz, 1H, H-1), 5.50 (s, 1H, Ph–CH), 7.34–7.37 (m, 3H, H-3$_{Ar}$, H-4$_{Ar}$, H-5$_{Ar}$), 7.47–7.53 ppm (m, 2H, H-2$_{Ar}$, H-6$_{Ar}$); ^{13}C NMR ($CDCl_3$, 60 MHz): δ 55.49 (–OCH_3), 62.35 (C-5), 68.90 (C-6), 71.53 (C-3), 72.79 (C-2), 80.93 (C-4), 99.82 (C-1), 101.90 (Ph–CH), 126.33 (C-2$_{Ar}$ C-6), 127.03 (C-3$_{Ar}$ C-5$_{Ar}$), 128.97 (C-4$_{Ar}$), 137.06 ppm (C-1$_{Ar}$). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.70; H, 6.32.

4.1.6. 4,6-*O*-Benzylidene-1,2,3-tri-*O*-methyl-α-D-glucopyranoside (7). Synthesis was carried out according to Ref. 31 starting from **6**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.23 (dd, *J*=9.1 Hz, *J*=3.6 Hz, 1H, H-2), 3.50–3.83 (m, 4H, H-6, H-5, H-3), 3.44, 3.55, 3.64 (3s, 9H, 3×–OCH_3), 4.28 (dd, *J*=9.3 Hz, *J*=4.0 Hz, 1H, H-4), 4.86 (d, *J*=3.6 Hz, 1H, H-1), 5.45 (s, 1H, Ph–CH), 7.33–7.4 (m, 3H, H-3$_{Ar}$, H-4$_{Ar}$, H-5$_{Ar}$), 7.46–7.53 ppm (m, 2H, H-2$_{Ar}$, H-6$_{Ar}$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 54.93, 59.00, 60.65 (3×–OCH_3), 61.92 (C-5), 68.74 (C-6), 79.53 (C-4), 81.11 (C-3), 81.84 (C-2), 98.10 (C-1), 101.05 (Ph–CH), 125.75 (C-2$_{Ar}$ C-6), 127.86 (C-3$_{Ar}$ C-5$_{Ar}$), 128.59 (C-4$_{Ar}$), 137.06 ppm (C-1$_{Ar}$). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.96; H, 7.15. Found: C, 62.20; H, 7.28.

4.1.7. 1,2,3-Tri-*O*-methyl-α-D-glucopyranoside (8). Compound **8** was prepared by conversion of **7** as described.[32]

^{1}H NMR (methanol-d_3, 200 MHz): δ 3.29–3.37 (m, 2H, H-2, H-3), 3.41, 3.46, 3.48 (3s, 9H, 3×–OCH_3), 3.67–3.83 (m, 4H, H-4, H-5, H-6), 4.85 ppm (d, *J*=3.4 Hz, 1H, H-1); ^{13}C NMR (methanol-d_3, 50 MHz): δ 55.34, 58.67, 61.21 (3×–OCH_3), 62.48 (C-5), 71.31 (C-6), 73.43 (C-3), 82.82 (C-2), 84.45 (C-4), 98.52 ppm (C-1). Anal. Calcd for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.72; H, 8.15.

4.1.8. 1,2,3-Tri-*O*-methyl-α-D-glucopyranuronic acid methylester (9). Oxidation of 2.0 g (9 mmol) **8** was performed like **3**. The crude acid was treated as describe to obtain the methylester.[33] Yield: 1.94 g (86%) of a colourless oil.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.21 (dd, *J*=9.2 Hz, *J*=3.4 Hz, 1H, H-2), 3.45–3.70 (m, 2H, H-3, H-4), 3.43, 3.46, 3.58 (3s, 9H, 3×–OCH_3), 3.77 (1s, 3H, –COO*C*H$_3$), 4.08 (d, *J*=9.5 Hz, 1H, H-5), 4.86 ppm (d, *J*=3.4 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 60 MHz): δ 52.64 (COO*C*H$_3$), 55.82, 58.97, 61.07 (3×–OCH_3), 70.52 (C-5), 71.63 (C-3), 80.74 (C-2), 81.67 (C-4), 97.96 (C-1), 170.69 ppm (*C*OOCH$_3$). Anal. Calcd for $C_{10}H_{18}O_7$: C, 48.00; H, 7.25. Found: C, 47.93; H, 7.00.

4.1.9. 1,2,3-Tri-*O*-methyl-α-D-glucopyranuronic acid hydrazide (10). Procedure like that of **4**. The product precipitated, was filtered and washed with ethyl acetate. Compound **9** 1.64 g (6.55 mmol) gave 1.40 g (85%) as colourless needles.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.07 (dd, *J*=9.6 Hz, *J*=3.2 Hz, 1H, H-2), 3.18–3.69 (m, 2H, H-3, H-4), 3.28, 3.31, 3.42 (3s, 9H, 3×–OCH_3), 4.27 (s 2H, –NH_2), 4.79 (d, *J*=3.2 Hz, 1H, H-5), 5.27 (d, *J*=5.6 Hz, 1H, H-1), 9.35 ppm (s, 1H, –N*H*NH$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 54.55, 57.24, 59.73 (3×–OCH_3), 70.14 (C-5), 70.27 (C-3), 80.18 (C-2), 82.14 (C-4), 97.08 (C-1), 167.51 ppm (–CO–NH–). Anal. Calcd for $C_9H_{18}O_6N_2$: C, 43.20; H, 7.25; N, 11.19. Found: C, 43.24; H, 7.34; N, 11.11.

4.1.10. 1,2,3-Tri-*O*-methyl-α-D-glucopyranuronic acid salicylidene hydrazide (11). The reaction was carried out like **5**. The crude product was purified by column chromatography (eluent: ethyl acetate). Compound **10** 0.60 g (2.4 mmol) gave 0.68 g (80%) **11**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.20 (dd, *J*=9.6 Hz, *J*=3.5 Hz, 1H, H-2), 3.47–3.75 (m, 2H, H-3, H-4), 3.47, 3.52, 3.65 (3s, 9H, 3×–OCH_3), 4.17 (d, *J*=9.8 Hz, 1H, H-5), 4.91 (d, *J*=3.6 Hz, 1H, H-1), 6.83–6.99 (m, 2H, H-3$_{Ar}$, H-5$_{Ar}$), 7.16 (dd, *J*=7.7 Hz, *J*=1.7 Hz, 1H, H-4$_{Ar}$), 7.26–7.34 (m, 1H, H-6$_{Ar}$), 8.35 (s, 1H, –CH=N–), 9.41 (s, 1H, Ar–OH), 10.75 ppm (s, 1H, –CO–NH–); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 56.10, 59.32, 61.24 (3×–OCH_3), 69.15 (C-5), 73.02 (C-3), 80.44 (C-2), 81.80 (C-4), 98.27 (C-1), 116.94 (C-3$_{Ar}$), 117.39 (C-1$_{Ar}$), 119.46 (C-5$_{Ar}$), 131.16 (C-6$_{Ar}$), 132.47 (C-4$_{Ar}$), 152.72 (–CH=N–), 158.74 (C-2$_{Ar}$), 166.99 ppm (–CO–NH–). Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.26; N, 7.91. Found: C, 53.61; H, 6.43; N, 7.46.

4.1.11. 1-*O*-Methyl-α-D-glucopyranuronic acid methylester (12). Procedure like that of **9**. Methyl-α-D-glucopyranoside 3.88 g (20 mmol) gave 3.19 g (72%) as a colourless oil.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.15 (d, *J*=5.2 Hz, 1H, H-2), 3.27 (s, 3H, –OCH_3), 3.47 (s, 1H, –OH), 3.65 (s, 3H, –COO*C*H$_3$), 3.78 (s, 1H, –OH), 3.84 (s, 1H, –OH), 4.58 (d, *J*=3.4 Hz, 1H, H-3), 4.88 (d, *J*=6.2 Hz, 1H, H-4), 4.95 (d, *J*=4.6 Hz, 1H, H-5), 5.27 ppm (d, *J*=5.8 Hz, H-1); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 51.90 (–COO*C*H$_3$), 54.97 (–OCH_3), 71.49 (H-4), 71.61 (H-2), 71.75 (H-3), 72.71 (H-5), 100.67 (H-1), 170.01 ppm (–*C*OOCH$_3$). Anal. Calcd for $C_8H_{14}O_7$: C, 43.24; H, 6.35. Found: C, 42.87; H, 6.85.

4.1.12. 1-*O*-Methyl-α-D-glucopyranuronic acid hydrazide (13). Compound **12** 3.13 g (14.1 mmol) was treated like **4**. Crystallization from methanol gave 2.29 g (73%) as colourless needles.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.16 (m, 1H, H-2), 3.36 (s, 3H, –OCH_3), 3.47, 3.65, 3.70 (3s, 3H, 3×–OH), 4.25 (s, 2H, –NH_2), 4.51 (d, *J*=3.6 Hz, 1H, H-3), 4.77 (d, *J*=6.2 Hz, 1H, H-4), 4.81 (d, *J*=4.4 Hz, 1H, H-5), 5.02 (d, *J*=4.2 Hz, H-1), 9.29 ppm (–N*H*NH$_2$); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 54.88 (–OCH_3), 70.68 (H-4), 71.24 (H-2), 71.56 (H-3), 72.98 (H-5), 100.45 (H-1), 167.88 ppm (–CO–NH–). Anal. Calcd for $C_7H_{14}N_2O_6$: C, 37.84; H, 6.35; N, 12.61. Found: C, 37.76; H, 6.38; N, 12.48.

4.1.13. 1-*O*-Methyl-α-D-glucopyranuronic acid salicylidene hydrazide (14). Procedure like that of **5**. The crude

product was crystallized from ethyl acetate/methanol (2:1). Compound **13** 0.50 g (2.3 mmol) gave 0.59 g (78%) **14**.

^{1}H NMR (acetone-d_6, 200 MHz): δ 3.31 (d, J=5.0 Hz, 1H, H-2), 3.43 (s, 3H, –OCH_3), 3.62–3.70 (m, 2H, H-3, H-4), 3.83 (d, J=7.4 Hz, 1H, –OH), 4.10 (d, J=9.2 Hz, 1H, H-5), 4.26 (d, J=3 Hz, 1H, –OH), 4.51 (d, J=3 Hz, 1H, –OH), 4.77 (d, J=3.6 Hz, 1H, H-1), 6.87–6.95 (m, 2H, H-3_{Ar}, H-5_{Ar}), 7.27–7.36 (m, 2H, H-4_{Ar}, H-6_{Ar}), 8.54 (s, 1H, –CH=N–), 10.96 (s, 1H, Ar–OH), 11.38 ppm (s, 1H, –CO–NH–); ^{13}C NMR (acetone-d_6, 50 MHz): δ 55.77 (–OCH_3), 71.06 (H-4), 72.45 (H-2), 73.22 (H-3), 74.05 (H-5), 101.14 (H-1), 117.29 (C-3_{Ar}), 118.46 (C-1_{Ar}), 119.75 (C-5_{Ar}), 131.63 (C-6_{Ar}), 132.15 (C-4_{Ar}), 151.51 (–CH=N–), 159.19 (C-2_{Ar}), 167.02 ppm (–CO–NH–). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 50.74; H, 6.61; N, 7.41.

4.1.14. 1-*O*-Methyl-6-*O*-triphenylmethyl-α-D-glucopyranose (15). Synthesized according to lit.[34]

^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.03 (t, J=8.2 Hz, 2H, H-6), 3.26 (d, J=9.6 Hz, 1H, H-4), 3.42 (d, J=9.4 Hz, 1H, H-3), 3.60 (t, J=7.6 Hz, 1H, H-2), 4.07 (m, 1H, H-5), 3.37 (s, 3H, –OCH_3), 4.61 (d, J=3.5 Hz, 1H, H-1), 7.15–7.38 (m, 15H, –$C(Ph)_3$); ^{13}C NMR ($CDCl_3$, 250 MHz): δ 55.11 (–OCH_3), 63.89 (C-6), 70.20 (C-5), 71.43 (C-3), 72.05 (C-2), 74.48 (C-4), 86.82 (–$C(Ph)_3$), 99.12 (C-1), 127.18 (C-4_{Ar}), 127.91 (C-3_{Ar}), 128.68 (C-2_{Ar}), 143.83 ppm (C-1_{Ar}). Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 72.14; H, 6.89.

4.1.15. 1,2,3,4-Tetra-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranose (16). Compound **15** 12.25 g (28.1 mmol) was treated like **7**. Crystallization of the crude product in methanol gave 10.08 g (75%) as colourless needles.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.13 (dd, J=4.4 Hz, J=10.0 Hz, 1H, H-2), 3.33–3.65 (m, 5H, H-3, H-4, H-5, H-6), 3.33, 3.48, 3.59, 3.65 (4s, 12H, 4×–OCH_3), 4.94 (d, J=3.5 Hz, 1H, H-1), 7.26–7.54 ppm (m, 15H, –$C(Ph)_3$); ^{13}C NMR ($CDCl_3$, 250 MHz): δ 54.95, 59.04, 60.38, 60.96 (4×–OCH_3), 62.44 (C-6), 70.10 (C-5), 79.98 (C-3), 81.90 (C-2), 83.74 (C-4), 86.25 (–OC(Ph)$_3$), 97.32 (C-1), 126.94 (C-4_{Ar}), 127.74 (C-2_{Ar}), 128.78 (C-3_{Ar}), 144.06 ppm (C-1_{Ar}). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.99; H, 7.30.

4.1.16. 1,2,3,4-Tetra-*O*-methyl-α-D-glucopyranose (17). Treating of **16** as shown in Ref. 35 gave **17**.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.09 (dd, J=3.6 Hz, J=9.6 Hz, 1H, H-2), 3.44–3.58 (m, 2H, H-3, H-4), 3.66 (dd, J=11.7 Hz, J=4.0 Hz, 1H, H-6), 3.76 (dd, J=11.7 Hz, J=2.9 Hz, 1H, H-5), 3.34, 3.45, 3.50, 3.56 (4s, 12H, 4×–OCH_3), 4.73 ppm (d, J=3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 250 MHz): δ 55.13, 59.02, 60.54, 60.83 (4×–OCH_3), 61.91 (C-6), 70.54 (C-5), 79.61 (C-3), 81.82 (C-2), 83.37 (C-4), 97.48 ppm (C-1). Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.84; H, 8.53. Found: C, 52.08; H, 8.93.

4.1.17. 1,2,3,4-Tetra-*O*-methyl-α-D-glucopyranuronic acid methylester (18). Oxidation of 5.00 g (21 mmol) **17** and formation of the corresponding methylester was performed like **3**. Purification of the crude product by column chromatography with ethyl acetate gave 3.91 g (70%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.15 (dd, J=14.6 Hz, J=3.4 Hz, 1H, H-2), 3.33–3.53 (m, 2H, H-3, H-4), 4.01 (d, J=12.3 Hz, 1H, H-5), 3.41, 3.47, 3.48, 3.58 (4s, 12H, 4×–OCH_3), 3.78 (s, 3H, –$COOCH_3$), 4.81 ppm (d, J=3.6 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 52.51 (–COOCH$_3$), 55.58, 59.14, 60.46, 60.94 (4×–OCH_3), 69.90 (C-5), 81.18 (C-3), 81.21 (C-2), 82.86 (C-4), 98.06 (C-1), 170.11 ppm (–COOCH$_3$). Anal. Calcd for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 50.16; H, 7.53.

4.1.18. 1,2,3,4-Tetra-*O*-methyl-α-D-glucopyranuronic acid hydrazide (19). Procedure like that of **4**. The product precipitated, was filtered and washed with ethyl acetate. Yield: 3.90 g (14.7 mmol) **18** gave 3.57 g (92%) **19**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.18 (dd, J=3.6 Hz, J=9.7 Hz, 1H, H-2), 3.24–3.36 (m, 2H, H-3, H-4), 3.87 (d, J=10.0 Hz, 1H, H-5), 3.38, 3.47, 3.47, 3.57 (4s, 12H, 4×–OCH_3), 4.82 (d, J=3.4 Hz, 1H, H-1), 7.44 ppm (s, 1H, –NHNH$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.76, 59.13, 60.62, 60.95 (4×–OCH_3), 69.47 (C-5), 81.06 (C-3), 81.63 (C-2), 83.04 (C-4), 97.87 (C-1), 169.81 ppm (–CO–NH–NH$_2$). Anal. Calcd for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.63; N, 10.60. Found: C, 44.56; H, 7.81; N, 10.37.

4.1.19. 1,2,3,4-Tetra-*O*-methyl-α-D-glucopyranuronic acid salicylidene hydrazide (20). Compound **19** 0.5 g (1.9 mmol) was treated like **5**. Crystallization in methanol/ethyl acetate (1:4) gave 0.53 g (74%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.22 (dd, J=3.4 Hz, J=6.2 Hz, 1H, H-2), 3.29–3.60 (m, 2H, H-4, H-3), 3.46, 3.54, 3.57, 3.64 (4s, 12H, 4×–OCH_3), 4.10 (d, J=12.5 Hz, 1H, H-5), 4.92 (d, J=3.4 Hz, 1H, H-1), 6.87–7.03 (m, 2H, H-3_{Ar}, H-5_{Ar}), 7.20–7.32 (m, 2H, H-4_{Ar}, H-6_{Ar}), 8.47 (s, 1H, –CH=N–), 9.19 (s, 1H, Ar–OH), 10.87 ppm (s, 1H, –CO–NH–); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.64, 58.89, 60.42, 60.71 (4×–OCH_3), 69.32 (C-5), 80.74 (C-3), 81.60 (C-2), 82.77 (C-4), 97.66 (C-1), 116.89 (C-3_{Ar}), 116.99 (C-1_{Ar}), 119.02 (C-5_{Ar}), 130.71 (C-6_{Ar}), 131.83 (C-4_{Ar}), 151.72 (–CH=N–), 158.34 (C-2_{Ar}), 164.57 ppm (–CO–NH–). Anal. Calcd for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.57; N, 7.60. Found: C, 55.51; H, 6.51; N, 7.64.

4.1.20. 3,4,5,6-Di-*O*-isopropylidene-D-gluconic acid methylester (21). Synthesis was carried out according to lit.[36] starting from D-gluconic acid-δ-lactone.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.37, 1.39 (2s, 6H, –$C(CH_3)_2$), 1.41, 1.45 (2s, 6H, –$C(CH_3)_2$), 2.44 (s, –OH), 3.86 (s, 3H, –COOCH$_3$), 3.99–4.24 (m, 5H, H-3, H-4, H-5, H-6), 4.37 ppm (dd, J=9.1 Hz, J=2.3 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 25.27, 26.53, 26.69, 27.16 (2×–C(CH$_3$)$_2$), 52.73 (–COOCH$_3$), 67.89 (C-6), 69.43 (C-5), 76.45 (C-4), 77.27 (C-3), 80.89 (C-2), 109.87, 110.09 (2×–C(CH$_3$)$_2$), 173.02 ppm (–COOCH$_3$). Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.48; H, 7.79.

4.1.21. 3,4,5,6-Di-*O*-isopropylidene-D-gluconic acid hydrazide (22). Compound **21** 4.11 g (14.2 mmol) was treated like **4**. Crystallization from ethyl acetate/*n*-hexane gave 3.81 g (92%) **22**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30, 1.35 (2s, 6H, –C(CH_3)$_2$), 1.38 (s, 6H, –C(CH_3)$_2$), 3.83–3.99 (m, 2H, H-6), 4.03–4.15 (m, 2H, H-5, H-4), 4.29 (d, J=1.4 Hz, 1H, H-3), 4.42 (dd, J=8.0 Hz, J=1.6 Hz, 1H, H-2), 7.84 ppm (s, 1H, –N*H*NH$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.14, 26.66 (–C(*C*H$_3$)$_2$), 26.82, 27.02 (–C(*C*H$_3$)$_2$), 67.71 (C-6), 69.87 (C-5), 76.89 (C-4), 76.94 (C-3), 79.72 (C-2), 109.91, 110.07 (2×–*C*(CH$_3$)$_2$), 171.75 ppm (–CO–NH–). Anal. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65. Found: C, 48.86; H, 7.77; N, 9.53.

4.1.22. 3,4,5,6-Di-*O*-isopropylidene-D-gluconic salicylidene hydrazide (23). Procedure like that of **5**. The product was washed with ethanol. The conversion of 1.14 g (4.0 mmol) **22** gave 1.12 g (70%) **23**.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.28, 1.35 (2s, 12H, 2× –C(CH_3)$_2$), 3.80–3.86 (m, 1H), 3.95–4.19 (m, 3H, H-6, H-5, H-4), 4.16 (s, 1H, H-3), 4.31 (dd, J=7.6 Hz, J=1.8 Hz, 1H, H-2), 6.08 (d, J=6.4 Hz, 1H, –OH), 6.86–6.93 (m, 2H, H-3$_{Ar}$, H-5$_{Ar}$), 7.24–7.32 (m, 1H, H-4$_{Ar}$), 7.39–7.44 (m, 1H, H-6$_{Ar}$), 8.67 (s, 1H, –CH=N–), 11.34 (s, 1H, Ar–OH), 11.59 ppm (s, 1H, –CO–NH–); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 25.25, 26.48 (–C(*C*H$_3$)$_2$), 26.74, 27.06 (–C(*C*H$_3$)$_2$), 66.59 (C-6), 69.90 (C-5), 75.1 (C-4), 76.45 (C-3), 80.32 (C-2), 108.91, 109.07 (2×–*C*(CH$_3$)$_2$), 116.41 (C-3$_{Ar}$), 118.44 (C-1$_{Ar}$), 119.29 (C-5$_{Ar}$), 129.83 (C-6$_{Ar}$), 131.32 (C-4$_{Ar}$), 149.12 (–CH=N–), 157.50 (C-2$_{Ar}$), 168.16 ppm (–CO–NH–). Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.98; H, 6.59; N, 7.13.

4.1.23. Potassium [1,2,3,4-tetra-*O*-methyl-α-D-glucopyranuronic acid salicylidene hydrazidato] dioxo vanadate (24). KVO_3 0.190 g (1.36 mmol) was added to a solution of 0.500 g (1.36 mmol) **20** in 75 ml methanol. The mixture was refluxed for 24 h and filtered hot. After removing the solvent the solid residue was washed with CH_2Cl_2. Yield: 0.42 g (63%) of a yellow powder.

MS (Micro-ESI neg. in MeOH): m/z=937 (18%, 2(VO$_2$L)$^-$+K$^+$), 921 (20%, 2(VO$_2$L)$^-$+Na$^+$), 449.3 (100%, (VO$_2$L)$^-$); FTIR (KBr): 2939 ($\nu_{as\ C-H}$ –CH_3), 2839 (ν_{C-H} –OCH_3), 1617 ($\nu_{C=N-N=C}$), 1570+1546 ($\nu_{C=C}$ Ar), 1476+1449 ($\delta_{as\ C-H}$ –CH_3), 1356+1362 ($\delta_{sy\ C-H}$ –CH_3), 1157+1093+1071+1045 ($\nu_{as\ C-O-C}$), 918+910 (ν_{VO_2}), 760 cm^{-1} (γ_{OOP} amide); UV–vis (MeOH): λ_{max} (log ε)=228 (3.19), 290 (3.07), 381 (2.63) nm; ^{1}H NMR (methanol-d_3, 400 MHz): δ 3.38–3.57 (m, 3H, H-2, H-3, H-4), 3.38, 3.39, 3.44, 3.54 (4s, 12H, 4×–OCH_3), 4.13 (d, J=9.65 Hz, 1H, H-5), 4.90 (d, J=3.36 Hz, 1H, H-1), 6.84–6.91 (m, 2H, H-3$_{Ar}$, H-5$_{Ar}$), 7.38–7.41 (m, 1H, H-4$_{Ar}$), 7.49 (dd, J=7.60 Hz, J=1.60 Hz, 1H, H-6$_{Ar}$), 8.79 ppm (s, 1H, –CH=N–); ^{13}C NMR (methanol-d_3, 100 MHz): δ 55.65, 58.78, 60.65, 60.90 (4×–OCH_3), 70.25 (C-5), 82.14 (C-3), 82.53 (C-2), 83.70 (C-4), 99.03 (C-1), 119.48 (C-3$_{Ar}$), 120.15 (C-1$_{Ar}$), 120.74 (C-5$_{Ar}$), 133.76 (C-6$_{Ar}$), 135.40 (C-4$_{Ar}$), 158.83 (–CH=N–), 165.74 (C-2$_{Ar}$), 173.31 ppm (–CO–N–); ^{51}V NMR (methanol-d_3, 105 MHz): δ −544 ppm ($\nu_{½}$=526 Hz). Anal. Calcd for $C_{17}H_{22}N_2O_9VK\cdot H_2O$: C, 40.32; H, 4.78; N, 5.53. Found: C, 40.34; H, 4.58; N, 5.95.

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Irciniasulfonic acid B, a novel taurine conjugated fatty acid derivative from a Japanese marine sponge, *Ircinia* sp.

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Abstract—Irciniasulfonic acid B (**1**) was obtained from a marine sponge, *Ircinia* sp., together with a known multi-drug resistance modulator irciniasulfonic acid (**2**). Spectroscopic and chemical analyses revealed structure consisting of common unsaturated fatty acids, a novel unsaturated branched fatty acid, and a taurine. Final separation of irciniasulfonic acid B (**1**) was achieved with its methylated derivatives. Irciniasulfonic acid B (**1**) reversed the multi-drug resistance in the same way as irciniasulfonic acid.

1. Introduction

In our continuing research for bioactive compounds from marine invertebrates, we isolated a novel fatty acid derivative, irciniasulfonic acid (ISA, **2**), which reverses multi-drug resistance (MDR) in human carcinoma cell lines caused by overexpression of membrane glycoprotein (P-gp) from a marine sponge *Ircinia* sp.[1] Further investigation has resulted in isolation of a novel taurine conjugated fatty acid derivative, irciniasulfonic acid B (ISA-B, **1**) from the same marine sponge. In this paper, we will describe the isolation, structure elucidation, and biological activity of ISA-B.

2. Results and discussion

2.1. Isolation and structure elucidation

The gray-colored sponge *Ircinia* sp., collected off Tsuzumi Island, Fukuoka Prefecture, Japan in 2004 was extracted with EtOH. The extract was partitioned between Et_2O and H_2O, and the aqueous layer was further extracted with *n*-BuOH. By means of TLC analysis, the *n*-BuOH extract was found to contain ISA, and its related compound was in the polar fraction. The *n*-BuOH extract was subjected to flash silica gel column chromatography (EtOAc/MeOH), reversed phase column chromatography (RP-18), and preparative TLC (EtOAc/MeOH) to give ISA (8.2 mg) and ISA-B (3.5 mg). ISA (17.3 mg) and ISA-B (8.4 mg) were also purified from the Et_2O extract in a similar manner as above.

The negative FABMS of ISA-B showed quasi-molecular ion peaks at *m/z* 652 and 626 $[M-H]^-$, caused by the diversity of a fatty acid moiety, and these molecular ion peaks were one mass unit, which is less than those of ISA. The HR-ESI TOFMS gave their molecular formula for $C_{37}H_{66}NO_6S$ and $C_{35}H_{64}NO_6S$. The fragment ion peaks at *m/z* 288 $[M-\text{fatty acids}]^-$ and *m/z* 80 $[SO_3]^-$ were also observed and these fragment ion peaks were the same as those for ISA. In a comparison of ^1H NMR spectral data for ISA-B and ISA, an oxygenated methylene proton at δ_H 4.32 (2H, t) in an isethionic acid moiety of ISA was upfield shifted at δ_H 3.51 (2H, t) in ISA-B. Furthermore, the ^1H NMR spectrum of ISA-B measured in CD_3OH showed an amide proton signal at δ_H 7.55 (1H, br s). These spectral data suggested that ISA-B consists of taurine in place of isethionic acid in ISA. Further structural analysis was achieved with a deacyl derivative of ISA-B (deacyl ISA-B, **3**). Methanolysis of ISA-B with 1.0% HCl/MeOH gave **3** and a mixture of fatty acid methyl esters (FAMEs).

Deacyl ISA-B (**3**) showed a quasi-molecular ion peak at *m/z* 306 $[M-H]^-$, IR absorption bands due to hydroxyl (3359 cm^{-1}), amide (1659, 1632 cm^{-1}) functionalities, and a UV absorption band due to α,β-unsaturated carbonyl functionality (λ_{max} 220 nm). These spectral features were quite similar to those of deacyl ISA (**4**). The ^1H, ^{13}C NMR, and HSQC spectral data indicated the presence of one primary methyl, one vinyl methyl, five aliphatic methylenes, one nitrogenous methylene, one sulfur-bearing methylene, one oxygenated methine, one tri-substituted olefin, and one amide carbonyl (Table 1). The ^1H–^1H COSY and TOCSY spectra of **3** afforded two partial structures A and B. The correlation from a terminal methyl (δ_H 0.83, H-10) to an allylic methylene (δ_H 2.51, H-4) gave the partial structure of A. The correlation between a nitrogenous methylene

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Table 1. ^{1}H and ^{13}C NMR data of deacyl ISA-B (**3**) and deacyl ISA (**4**) in CD_3OD

No.	3		4	
	^{1}H	^{13}C	^{1}H	^{13}C
1		169.1 (s)		166.1 (s)
2	5.55 (1H, br s)	119.7 (d)	5.60 (1H, br s)	115.1 (d)
3		155.7 (s)		161.6 (s)
4	2.51 (2H, t, 7.2)	33.9 (t)	2.54 (2H, m)	32.8 (t)
5	1.39 (2H, m)	29.4 (t)	1.39 (2H, m)	27.8 (t)
6	1.27, 1.39 (each 1H, m)	26.8 (t)	1.19 (2H, m)	29.3 (t)
7	1.29, 1.37 (each 1H, m)	37.8 (t)	1.28 (2H, m)	25.2 (t)
8	3.34 (1H, m)	73.8 (d)	1.30 (2H, m)	38.7 (t)
9	1.30, 1.39 (each 1H, m)	31.0 (t)	3.61 (1H, m)	67.1 (d)
10	0.83 (3H, t, 7.2)	10.4 (q)	1.05 (3H, d, 6.4)	22.0 (q)
11	1.74 (3H, d, 1.2)	24.8 (q)	1.80 (3H, d, 1.3)	23.8 (q)
1′	2.87 (2H, t, 6.6)	51.6 (t)	3.05 (2H, t, 7.2)	49.9 (t)
2′	3.51 (2H, t, 6.6)	36.3 (t)	4.32 (2H, t, 7.2)	59.0 (t)

(δ_H 3.51, H′-2) and a sulfur-bearing methylene (δ_H 2.87, H′-1) gave the partial structure of B. These two partial structures, a tri-substituted olefin and an amide carbonyl were merged by the aid of the HMBC experiment. The HMBC correlation between an olefinic methyl (δ_H 1.74, H-11) and an allylic methylene (δ_C 33.9, C-4) gave the connectivity of partial structure of A and the substituted olefin. The correlations from a nitrogenous methylene (δ_H 3.51, H′-1) and an olefinic proton (δ_H 5.55, H-2) to an amide carbonyl (δ_C 169.1, C-1) gave the connectivity of partial structures B and A. The geometry of the tri-substituted olefin was assigned as *Z* based on the NOESY spectral data and the ^{13}C chemical shifts with the value of olefinic methyl (δ_C 24.8, C-11)[2] as shown in Figure 1.

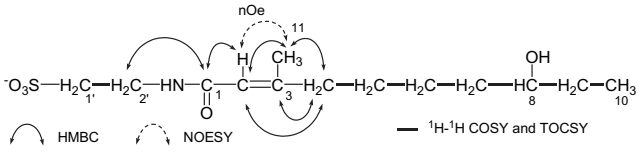

Figure 1. Plane structure of deacyl ISA-B (**3**), based on 2D NMR correlations.

The absolute configuration at C-8 was investigated by application of a modified Mosher's method.[3] Deacyl ISA-B (**3**) was esterified with (*R*)- or (*S*)-MTPA to furnish the 8-*O*-*R* (**5a**) and 8-*O*-*S*-MTPA ester (**5b**). The absolute configuration at C-8 was determined to be *R* on the basis of $\Delta\delta$ values, which were obtained from the proton signals of **5a** and **5b** as shown in Figure 2.

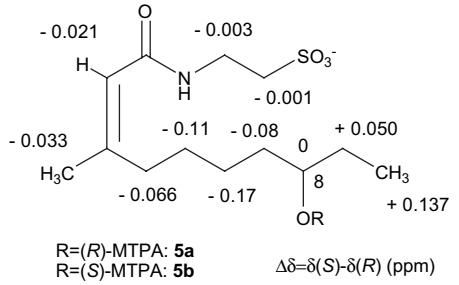

Figure 2. Application of a modified Mosher's method to **5a** and **5b**.

Fatty acid methyl esters (FAMEs) were purified by reversed phase HPLC, and each FAME was compared with those of ISA by the retention time of GC–MS and ^{1}H NMR spectra. As a result, two kinds of constituent fatty acid components were identified as (*Z*)-15-docosenoic acid for FAME-1 (**6**) and (5*Z*,9*Z*)-5,9-tetracosadienoic acid for FAME-2 (**7**). Accordingly, the structure of ISA-B (**1**) was determined to be a mixture of constituted fatty acids as shown in Figure 3.

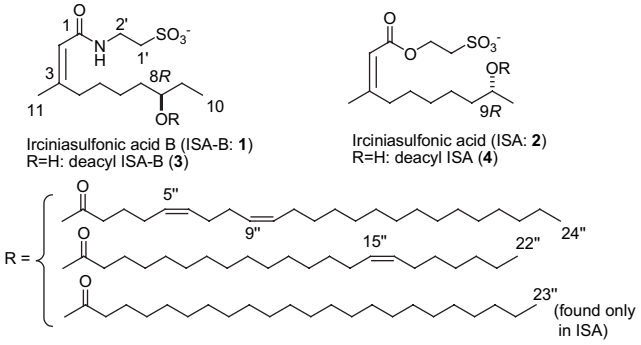

Figure 3. Structures of irciniasulfonic acids.

Because the ISA-B could not be separated into each component in an intact form, we prepared the methylated derivative of ISA-B, and applied it to HPLC separation. ISA-B was methylated with TMS–CHN_2, and successively subjected to reversed phase HPLC to give Me–ISA-B1 (**8**) and Me–ISA-B2 (**9**), respectively. The negative FABMS of **8** showed quasi-molecular ion peaks at *m/z* 666 $[M-H]^-$. The ^{1}H NMR spectrum of **8** quite resembled that of **1** except for the signals due to methoxy methyl [δ_H 3.90 (3H, s)] and the upfield shifted methylene signal [δ_H 3.31 (2H, t, H′-1)]. Me–ISA-B2 (**9**) also showed quasi-molecular ion peaks at *m/z* 640 $[M-H]^-$ in the negative FABMS and the ^{1}H NMR spectrum showed the signals due to methoxy methyl [δ_H 3.90 (3H, s)] and olefinic protons [δ_H 5.3–5.4 (2H, m)]. Thus, ISA-B (**1**) consisted of ISA-B1 and ISA-B2 (Fig. 4).

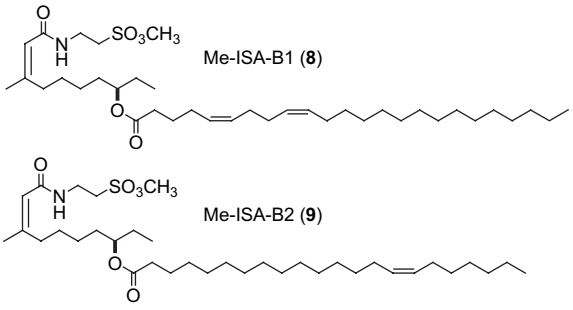

Figure 4. Structures of methylated ISA-B.

2.2. Bioactivity

ISA-B (**1**) reversed the multi-drug resistance to vincristine in KB/VJ300 cells at the concentration of 100 μM, and the reverse activity was equivalent to ISA (**2**) as shown in Figure 5.

Recently, a few taurine conjugated derivatives have been found from marine organisms.[4] Taurospongin A is the

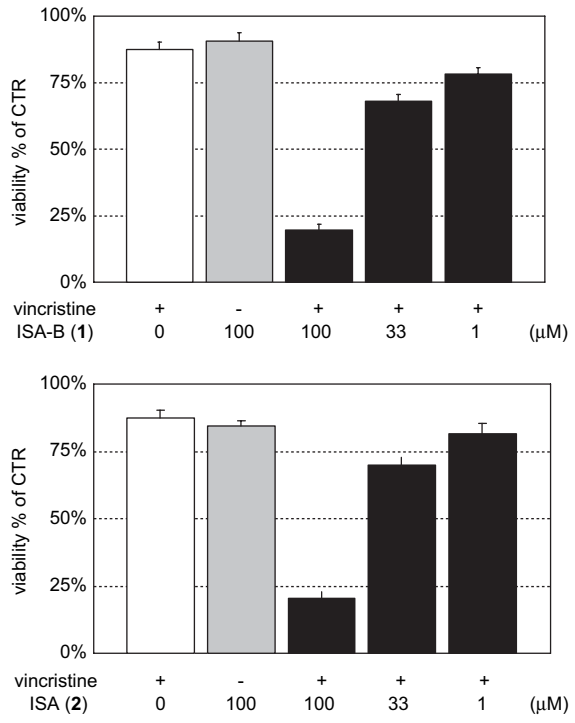

Figure 5. Reversal of MDR in KB/VJ300 cells by ISA-B (**1**) and ISA (**2**). CTR: without vincristine and testing samples, each value represents the mean±SD (n=6).

closest structural relative in the marine sponge, *Hippospongia* sp., consisting of taurine, trihydroxy fatty acid, and unsaturated fatty acid residues.[5] Taurospongin A showed a potent inhibitory activity against DNA polymerase β and HIV reverse transcriptase. Taurine is the major ingredient contained in oyster, squid, and octopus, and it is one of the free intracellular amino acids that produce oxidants and toxic substances in many tissues. It has been reported that taurine enhances cholesterol degradation and reduces serum and liver cholesterol concentrations in rats fed on a high-cholesterol diet.[6]

3. Experimental

3.1. General experimental procedures

NMR spectra including COSY, TOCSY, NOESY, HSQC, and HMBC experiments were recorded in CD_3OD or CD_3OH on a Varian INOVA 600 spectrometer at 600 MHz (^{1}H) or 150 MHz (^{13}C) NMR, and a Varian INOVA 400 spectrometer at 400 MHz (^{1}H), using tetramethylsilane (TMS) as an internal standard. FABMS data were obtained using a JEOL SX 102 mass spectrometer using triethyleneglycol (TEG) as a matrix. HR-ESI TOFMS was obtained on a Micromass Q-TOF Ultima LCMS spectrometer (Waters). UV spectra were recorded on a Jasco Ubest-30 Spectrometer in MeOH. IR spectra were obtained in $CHCl_3$ on a Jasco FTIR-410 spectrometer. The optical rotation was recorded on a Jasco DIP 370 digital polarimeter. The GC–MS was carried out on a Neutra BOND-5 capillary column (GL Science) with a Shimadzu QP5050A gas chromatograph mass spectrometer. Reversed phase high-performance liquid chromatography (HPLC) was carried out on a YMC-Pack Pro C_{18} column (YMC) and a Cosmosil $5C_{18}$ AR-II column (Nacalai tesque). Column chromatography was carried out on a silica gel 60 (70–230 mesh, Merck), and TLC was performed on precoated silica gel 60 F_{254} plates (Merck).

3.2. Collection, extraction, and isolation

Ircinia sp. (wet weight 790 g) was collected by hand at a depth of 10 m off Tsuzumi Island, Fukuoka Prefecture, Japan, in October of 2004. The sponge was homogenated and extracted with EtOH (3×1 L) and filtered. The extract was evaporated in vacuo, and the resulting aqueous suspension was diluted with H_2O (500 mL) and extracted with Et_2O (3×0.5 L) and *n*-BuOH (3×0.5 L). These organic layers were evaporated to give Et_2O extract (2.30 g) and *n*-BuOH extract (2.09 g). The *n*-BuOH extract was subjected to flash silica gel column chromatography with EtOAc/MeOH (10/0.05→10/0.5→10/1)→MeOH to give five fractions [Fr.1 (44.1 mg), Fr.2 (5.5 mg), Fr.3 (9.5 mg), Fr.4 (9.1 mg), and Fr.5 (516.8 mg)]. Fr.5 was dissolved in EtOAc/MeOH (10/1), and centrifuged. The supernatant was further chromatographed on silica gel with EtOAc/MeOH (10/1) to give three fractions [Fr.5-1 (**2**, 1.8 mg), Fr.5-2 (33.2 mg), and Fr.5-3 (124.3 mg)]. Fr.5-2 was subjected to reversed phase column chromatography (RP-18) with 90% MeOH/H_2O to give two fractions Fr.5-2-1 (15.2 mg) and Fr.5-2-2 (13.8 mg). Fr.5-2-2 was subjected to preparative TLC with EtOAc/MeOH (5/1) to give ISA (**2**, 6.4 mg) and ISA-B (**1**, 3.5 mg).

3.2.1. Irciniasulfonic acid B (1). White amorphous, IR ν_{max} ($CHCl_3$) cm^{-1}: 2928, 2855, 1721, 1658, 1461. Negative FABMS *m/z*: 652, 626, 288, 124, 80. HR-ESI TOFMS *m/z* 652.4604 [M−H]$^-$ (calcd for $C_{37}H_{66}NO_6S$, 652.4611), 626.4473 [M−H]$^-$ (calcd for $C_{35}H_{64}NO_6S$, 626.4454). ^{1}H NMR (CD_3OD) δ 0.79, 0.801 (terminal methyls), 1.11–1.60 (aliphatic methylenes), 1.73 (H-11), 1.92–2.22 (aliphatic methylenes), 2.40 (CO–CH_2), 2.52 (H-4), 2.88 (H′-1), 3.52 (H′-2), 4.88 (H-8), 5.35 (CH=CH), 5.55 (H-2), 7.58 (CO–NH, in CD_3OH). ^{13}C NMR (CD_3OD) δ 9.9 (C-10), 14.3 (terminal methyl), 23.6 (C-11), 24.0–36.0 (methylenes), 51.5 (C′-1), 76.6 (C-8), 119.6 (C-2), 129.9, 130.7, 131.2 (CH=CH), 155.6 (C-3), 169.0 (C-1), 175.1 (C=O).

3.2.2. Methanolysis of 1. ISA-B (**1**, 5.6 mg) was dissolved in 3.0 mL of 1% HCl/MeOH, and the solution was refluxed for 4 h. The reaction mixture was extracted with *n*-hexane (3×3 mL), and the remaining layer was neutralized with Ag_2CO_3, and filtrated. The *n*-hexane layer was evaporated in vacuo to give the mixture of fatty acid methyl esters (FAMEs), and subjected to reversed phase HPLC (YMC-Pack Pro C_{18}) with 100% MeOH to give FAME-1 (**6**, 0.5 mg) and FAME-2 (**7**, 1.0 mg). The filtrate was evaporated in vacuo, and subjected to silica gel column chromatography with $CHCl_3$/MeOH/H_2O (8/2/0.2) to give deacyl ISA-B (**3**, 1.6 mg).

3.2.3. Deacyl ISA-B (3). White amorphous, $[\alpha]_D$ +9.0 (*c* 0.1, MeOH). IR ν_{max} ($CHCl_3$) cm^{-1}: 3359, 2932, 2857, 1659, 1632, 1539, 1375, 1200. UV λ_{max} (MeOH) nm: 220 (ε=6490). Negative FABMS *m/z*: 306 [M−H]$^-$. ^{1}H and ^{13}C NMR, see Table 1.

3.2.4. Preparation of (*R*)- and (*S*)-MTPA esters. A solution of deacyl ISA-B (**3**, 0.7 mg, 2.3 μmol) in CH_2Cl_2 (100 μL) was added to (*R*)-α-methoxy (trifluoromethyl) phenyl acetic acid (MTPA) (5.4 mg, 23 μmol), *N*,*N*′-dicyclohexyl carbodiimide (DCC) (16.3 mg, 80 μmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP). The solution was stirred for 20 h at room temperature and filtered. The filtrate was dried with N_2, and subjected to silica gel column chromatography with *n*-hexane/EtOAc (20/1) to give (*R*)-MTPA ester (**5a**, 0.8 mg, 1.5 μmol). (*S*)-MTPA ester (**5b**, 0.9 mg, 1.7 μmol) was prepared in a similar manner as (*R*)-MTPA ester. Compound **5a**, negative FABMS *m*/*z*: 522 $[M-H]^-$. ^1H NMR (CD_3OD) δ 0.703 (H-10), 1.260 (H-6), 1.380 (H-5), 1.530 (H-9), 1.580 (H-7), 1.730 (H-11), 2.514 (H-4), 2.871 (H′-1), 3.514 (H′-2), 4.931 (H-8), 5.553 (H-2). Compound **5b**, negative FABMS *m*/*z*: 522 $[M-H]^-$. ^1H NMR (CD_3OD) δ 0.840 (H-10), 1.090 (H-6), 1.270 (H-5), 1.580 (H-9), 1.500 (H-7), 1.697 (H-11), 2.448 (H-4), 2.870 (H′-1), 3.511 (H′-2), 4.931 (H-8), 5.532 (H-2). These chemical shifts were assigned by ^1H–^1H COSY and TOCSY spectral data.

3.2.5. FAME-1 (6) and FAME-2 (7). FAME-1 (**6**): *O*-methyl (*Z*)-15-docosenoate, t_R=29.3 min, EIMS *m*/*z*: 352 $(M)^+$, 320 $(M-32)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, *J*=6.8 Hz, terminal methyl), 1.24 (aliphatic methylenes), 1.99 (4H, m, allylic methylenes), 2.28 (2H, t, *J*=7.2 Hz, CO–CH_2), 3.64(3H, s, OCH_3), 5.33 (2H, m, CH=CH). FAME-2 (**7**): *O*-methyl (5*Z*,9*Z*)-5,9-tetracosadienoate, t_R=32.7 min, EIMS *m*/*z*: 378 $(M)^+$, 346 $(M-32)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, *J*=6.8 Hz, terminal methyl), 1.24 (aliphatic methylenes), 2.00 (8H, m, allylic methylenes), 2.29 (2H, t, *J*=7.2 Hz, CO–CH_2), 3.65 (3H, s, OCH_3), 5.34 (4H, m, CH=CH).

3.2.6. Methylation of 1. A solution of ISA-B (**1**, 2.5 mg) in dried MeOH (1 mL) was added to 0.1 mL of trimethylsilyldiazomethane (TMS–CHN_2), and stirred for 1 h at room temperature. The reaction mixture was dried with N_2 and subjected to silica gel column chromatography with *n*-hexane/EtOAc (20/1), then reversed phase HPLC (Cosmosil AR-II $5C_{18}$) with 100% MeOH to give Me–ISA-B1 (**8**, 0.5 mg) and Me–ISA-B2 (**9**, 0.9 mg). Compound **8**: negative FABMS *m*/*z*: 666 $[M-H]^-$, 652 $[M-15]^-$. ^1H NMR (CD_3OD) δ 0.79, 0.80 (terminal methyl, H-10), 1.25–1.60 (aliphatic methylenes), 1.75 (H-11), 1.9–2.0 (aliphatic methylenes), 2.22 (CO–CH_2), 2.53 (H-4), 3.31 (H′-1), 3.50 (H′-2), 3.90 (O–CH_3), 5.2–5.35 (4H, CH=CH), 5.56 (H-2). Compound **9**: negative FABMS *m*/*z*: 640 $[M-H]^-$, 626 $[M-15]^-$. ^1H NMR ($CDCl_3$) δ 0.86 (terminal methyl, H-10), 1.24 (methylenes), 1.82 (H-11), 2.0–2.4 (methylenes), 2.60 (H-4), 3.32 (H′-1), 3.74 (H′-2), 3.90 (O–CH_3), 4.80 (H-8), 5.3–5.4 (2H, CH=CH), 5.50 (H-2).

4. Bioassay

Multi-drug resistant KB/VJ300 cells were maintained in an EMEM medium supplemented with 10% FBS and 100 ng/mL of vincristine. The reversing activities of ISA-B and ISA were measured by means of a CellTiter 96® aqueous colorimetric assay (Promega) performed in 96-well plates. KB/VJ300 cells were seeded at 1.0×10^4 cells/mL with 180 μL of the culture medium, then grown with or without vincristine and several dilutions of testing samples with 20 μL of culture medium for 72 h (37 °C, 5% CO_2). Thereafter, 10 μL of CellTiter 96® was added to each well and incubated for a further 2 h, and the percentage of cell growth inhibition was evaluated from the absorbance at 490 nm.

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Briaexcavatins C–F, four new briarane-related diterpenoids from the Formosan octocoral *Briareum excavatum* (Briareidae)

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Abstract—Four new briarane-related diterpenoids, designated as briaexcavatins C–F (**1**–**4**), were isolated from the Formosan octocoral *Briareum excavatum*, collected off southern Taiwan coast. The structures of these new metabolites were elucidated by the interpretation of spectroscopic and chemical methods. The configuration of **1** was further supported by molecular mechanics calculations. Briarane **1** has been shown to exhibit mild cytotoxicity toward MDA-MB-231 human breast tumor cells and briarane **3** was found to show activity to inhibit neutrophil elastase release in humans.

1. Introduction

Octocorals belonging to the genus *Briareum* (=*Solenopodium*) (Briareidae) are organisms taxonomically placed within the order Alcyonacea and Gorgonacea.[1,2] These organisms inhabit abundantly in the coral reefs of tropical and subtropical Indo-Pacific Ocean and Caribbean Sea and have been recognized as rich sources for marine natural products with novel structural features.[3–5] Since the first briarane-type natural product, briarein A, was obtained from the Caribbean octocoral *Briareum asbestinum* in 1977,[6] a number of briarane derivatives have been isolated from various marine organisms.[3,5] Briarane-related natural products continue to attract the attentions of investigators because of the structural complexity and interesting biological activity associated with numerous compounds of this type.[3,5] In previous studies, 64 new briaranes, including stecholides I–N and 16-hydroxy-stecholide C acetate,[7] excavatolides A–Z,[8] briaexcavatolides A–Z,[9] briantheins A–C,[10] and briaexcavatins A and B,[11] have been isolated from the octocoral *Briareum excavatum* (Nutting, 1911). During our continuing studies on the chemical constituents of *B. excavatum*, four new diterpenoids, briaexcavatins C–F (**1**–**4**), were isolated. We describe herein the isolation, structure elucidation, and biological activity of these new metabolites.

2. Results and discussion

Specimens of the octocoral *B. excavatum*, collected at southern Taiwan coast, were minced and extracted with EtOAc. The extract was separated on silica gel column chromatography to afford briaranes **1**–**4**. Briaexcavatin C (**1**) was obtained as a white powder. The HRESIMS data recorded at *m/z* 549.2340 established the molecular formula of **1** as $C_{28}H_{36}O_{11}$ (calcd for $C_{28}H_{36}O_{11}$+H, 549.2336). Thus, 11 degrees of unsaturation were determined for **1**. The IR spectrum showed bands at 1792, 1744, and 1688 cm^{-1}, consistent with the presence of γ-lactone, ester, and conjugated ketone groups in **1**. The conjugated ketone group was further confirmed by ^{13}C NMR signals at δ 200.7 (s), 154.5 (d), and 126.4 (d) (Table 1). The FABMS of **1** exhibited peaks at *m/z* 549 $(M+H)^+$, 489 $(M+H-AcOH)^+$, 429 $(M+H-2AcOH)^+$, and 341 $(M+H-C_3H_7CO_2H-2AcOH)^+$, which suggested the presence of a butyryloxy and two acetoxy groups. In the ^{13}C NMR spectrum, five carbonyl resonances appeared at δ 200.7 (s), 172.4 (s), 170.3 (2×s), and 169.0 (s),

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Table 1. ^{13}C NMR data for diterpenoids **1**–**4**

Carbon	**1**[a]	**2**[b]	**3**[c]	**4**[b]
1	43.3 (s)[d]	43.7 (s)	44.1 (s)	43.6 (s)
2	80.7 (d)	81.0 (d)	81.4 (d)	81.3 (d)
3	70.5 (d)	73.2 (d)	73.5 (d)	72.9 (d)
4	33.3 (t)	33.6 (t)	33.9 (t)	33.9 (t)
5	59.5 (s)	138.9 (s)	139.2 (s)	139.1 (s)
6	62.8 (d)	121.6 (d)	122.0 (d)	121.6 (d)
7	76.5 (d)	73.7 (d)	74.0 (d)	73.7 (d)
8	68.8 (s)	68.6 (s)	69.0 (s)	68.7 (s)
9	66.2 (d)	65.8 (d)	66.2 (d)	65.9 (d)
10	41.8 (d)	39.7 (d)	40.1 (d)	39.7 (d)
11	40.0 (d)	32.2 (d)	32.6 (d)	32.1 (d)
12	200.7 (s)	69.2 (d)	69.2 (d)	69.2 (d)
13	126.4 (d)	26.9 (t)	27.2 (t)	26.9 (t)
14	154.5 (d)	80.6 (d)	80.9 (d)	80.4 (d)
15	17.5 (q)	18.0 (q)	18.3 (q)	17.9 (q)
16	21.5 (q)	22.2 (q)	22.5 (q)	22.3 (q)
17	59.9 (s)	60.0 (s)	60.3 (s)	60.0 (s)
18	10.4 (q)	10.0 (q)	10.3 (q)	10.0 (q)
19	170.3 (s)	171.7 (s)	172.0 (s)	171.6 (s)
20	14.5 (q)	10.2 (q)	10.5 (q)	10.2 (q)
Acetate methyls	21.8 (q)	22.2 (q)	22.6 (q)	22.2 (q)
	21.7 (q)	22.2 (q)	22.5 (q)	22.1 (q)
		21.6 (q)	21.9 (q)	21.6 (q)
		21.0 (q)	21.3 (q)	
Acetate carbonyls	170.3 (s)	171.0 (s)	172.7 (s)	171.3 (s)
	169.0 (s)	170.3 (s)	170.7 (s)	170.9 (s)
		169.5 (s)	169.8 (s)	169.4 (s)
		169.4 (s)	169.7 (s)	
n-Butyrate	13.6 (q)			13.6 (q)
	18.1 (t)			18.1 (t)
	36.0 (t)			35.8 (t)
	172.4 (s)			171.7 (s)
3-Vinylpropionate		115.6 (t)		115.6 (t)
		136.4 (d)		136.4 (d)
		28.5 (t)		28.5 (t)
		33.2 (t)		33.3 (t)
		172.3 (s)		172.3 (s)
Isovalerate			22.7 (2×q)	
			25.8 (d)	
			43.7 (t)	
			171.3 (s)	

[a] Spectra recorded at 100 MHz in $CDCl_3$ at 25 °C.
[b] Spectra recorded at 150 MHz in $CDCl_3$ at −20 °C.
[c] Spectra recorded at 100 MHz in $CDCl_3$ at −20 °C.
[d] Multiplicity deduced by DEPT and indicated by usual symbols. The values are downfield in parts per million from TMS.

supporting the presence of a ketone, a lactone, and three esters. In the ^{1}H NMR spectrum (Table 2), an *n*-butyryloxy group (δ 2.24, 2H, t, J=7.2 Hz; 1.66, 2H, m; 0.95, 3H, t, J=7.2 Hz) and two acetate methyls (δ 2.25, 3H, s; 2.23, 3H, s) were further observed. Thus, the ^{13}C NMR data accounted for six degrees of unsaturation and required **1** to be pentacyclic. The presence of a tetrasubstituted epoxide containing a methyl substituent was elucidated from the signals of two oxygen-bearing quaternary carbons at δ 68.8 (s, C-8) and 59.9 (s, C-17), and further confirmed from the proton signal of a methyl singlet resonating at δ 1.64 (3H, s, H_3-18). In addition, a trisubstituted epoxide containing a methyl substituent was deduced from the signals of an oxymethine (δ_H 3.06, 1H, d, J=8.0 Hz, H-6; δ_C 62.8, d, C-6), an oxygen-bearing quaternary carbon (δ 59.5, s, C-5), and a methyl singlet resonating at δ 1.34 (3H, s, H_3-16). Moreover, a methyl doublet (δ 1.27, 3H, d, J=7.2 Hz, H_3-20), a methyl singlet (δ 1.08, 3H, s, H_3-15), two conjugated olefin protons (δ 6.62, 1H, d, J=10.4 Hz, H-14; 6.19, 1H, d, J=10.4 Hz, H-13), two aliphatic methine protons (δ 2.94, 1H, dd, J=9.6, 4.8 Hz, H-10; 2.93, 1H, m, H-11), a pair of methylene protons (δ 2.48, 1H, dd, J=16.0, 6.4 Hz; 2.11, 1H, d, J=16.0 Hz, H_2-4), and five oxygenated methine protons (δ 5.27, 1H, br s, H-2; 5.24, 1H, d, J=9.6 Hz, H-9; 5.08, 1H, d, J=6.4 Hz, H-3; 4.43, 1H, d, J=8.0 Hz, H-7; 3.06, 1H, d, J=8.0 Hz, H-6) were further assigned by the assistance of ^{1}H–^{1}H COSY and HSQC spectrum. From the ^{1}H–^{1}H COSY and HMBC correlations, the epoxy groups positioned at C-5/C-6 and C-8/C-17, acetoxy groups positioned at C-2 and C-9, and an *n*-butyryloxy group positioned at C-3, were established (Fig. 1).

The relative stereochemistry of **1** was elucidated from the NOE interactions observed in an NOESY experiment (Fig. 2) and by the vicinal ^{1}H–^{1}H coupling constants. As per convention while analyzing the stereochemistry of briarane-type diterpenoids, H-10 and H_3-15 were assigned to the α and β face, anchoring the stereochemical analysis because no NOE correlation was found between H-10 and H_3-15. In the NOESY experiment of **1**, H-10 gives NOE correlations to H-3 and H-11, and H-3 was found to show responses with H-2 and one proton of the C-4 methylene (δ 2.11), indicating that these protons (H-2, H-3, H-4α, H-10, and H-11) are located on the same face of the molecule and therefore are assigned as α protons, as the C-15 methyl is the β-substituent at C-1. Furthermore, H_3-16 exhibited NOE correlations with H-4α and H-6, but not with H-7, suggesting that H_3-16 and H-6 were positioned on the α face in the epoxy group and H-7 was β-oriented in the 10-membered ring. H-9 was found to show NOE correlations with H-10, H-11, and H_3-18. From the detailed consideration of molecular models, H-9 was found to be reasonably close to H-10, H-11, and H_3-18, while H-9 should be placed on the α face in **1**, and H_3-18 was β-oriented in the γ-lactone ring. The cis geometry of the C-13/C-14 double bond was indicated by a 10.4 Hz coupling constant between H-13 (δ 6.19) and H-14 (δ 6.62) and by the NOE correlation between H-13 and H-14. Based on above observations, the configurations of all chiral centers of **1** are assigned as 1*R**,2*R**,3*S**,5*R**,6*S**,7*S**,8*R**,9*S**,10*S**,11*R**,13*Z*,17*R**. Geometrical optimization of **1** was performed with DISCOVER utilizing the consistent valence force field (CVFF) calculations for energy minimization. The calculated results were visualized using INSIGHT II, running on a Silicon Graphics IRIS (SGI) Indigo XS24/4000 workstation. The conformation search suggested that the most stable conformation and the calculated distances of selected key protons of **1** are shown in Table 3.

The new briarane diterpene, briaexcavatin D (**2**), had the molecular formula of $C_{33}H_{44}O_{13}$, as determined by HRESIMS. It was found that the ^{13}C and ^{1}H NMR spectra of **2** in $CDCl_3$ revealed mostly broad peaks when measured at room temperature (25 °C). In order to make more reliable assignments of the NMR signals of briarane **2**, the ^{13}C and ^{1}H NMR spectra of **2** were measured at −20 °C in $CDCl_3$ (Tables 1 and 2). It was found that at this temperature the signals for each proton and carbon of the molecule were sharpened and could be assigned by the assistance of 1D and 2D NMR experiments. By detailed analysis, the NMR data of **2** were very similar to those of a known metabolite, excavatolide C (**5**).[8a] However, the ^{13}C and ^{1}H NMR spectra revealed that the signals corresponding to the hydroxy group in **5** (δ_C 65.8, d, C-12; δ_H

Table 2. ^{1}H NMR data for diterpenoids **1**–**4**

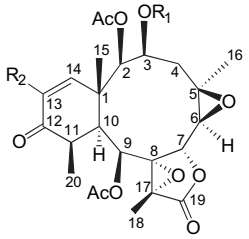
Proton	**1**[a]	**2**[b]	**3**[b]	**4**[b]
2	5.27 br s	5.13 br s	5.17 br s	5.16 br s
3	5.08 d (6.4)[c]	5.69 m	5.72 d (6.8)	5.74 m
4α	2.11 d (16.0)	1.96 m	1.96 m	1.97 m
4β	2.48 dd (16.0, 6.4)	3.67 dd (16.0, 7.2)	3.72 dd (16.0, 6.8)	3.73 dd (15.2, 6.8)
6	3.06 d (8.0)	5.33 d (6.8)	5.37 d (6.4)	5.37 d (6.8)
7	4.43 d (8.0)	5.25 d (6.8)	5.30 d (6.4)	5.29 d (6.8)
9	5.24 d (9.6)	5.28 d (10.4)	5.32 d (10.4)	5.31 d (10.0)
10	2.94 dd (9.6, 4.8)	2.97 dd (10.4, 4.8)	3.01 dd (10.4, 5.2)	3.00 dd (10.0, 6.8)
11	2.93 m	2.57 m	2.59 m	2.60 m
12		5.02 m	5.04 m	5.03 m
13/13′	6.19 d (10.4)	2.29 m; 1.86 m	2.01 m; 1.83 m	2.32 m; 1.87 m
14	6.62 d (10.4)	4.80 br s	4.82 br s	4.85 br s
15	1.08 s	0.78 s	0.82 s	0.83 s
16	1.34 s	1.88 s	1.92 s	1.93 s
18	1.64 s	1.55 s	1.58 s	1.59 s
20	1.27 d (7.2)	1.00 d (6.8)	1.04 d (7.2)	1.95 d (7.2)
Acetate methyls	2.25 s	2.43 s	2.37 s	2.37 s
	2.23 s	2.21 s	2.24 s	2.25 s
		2.13 s	2.16 s	2.17 s
		1.90 s	1.93 s	
n-Butyrate	2.24 t (7.2)			2.33 t (7.2)
	1.66 m			1.57 m
	0.95 t (7.2)			0.88 t (7.2)
3-Vinylpropionate		5.77 m		5.78 m
		5.02 m		5.03 m
		2.35 m		2.36 m
		2.30 t (7.2)		2.36 t (7.2)
Isovalerate			0.89 d (2×3H, 6.8)	
			2.03 m	
			2.12 d (7.2)	

[a] Spectra recorded at 400 MHz in $CDCl_3$ at 25 °C.
[b] Spectra recorded at 400 MHz in $CDCl_3$ at −20 °C.
[c] *J* value (in Hz) in parentheses. The values are downfield in parts per million from TMS.

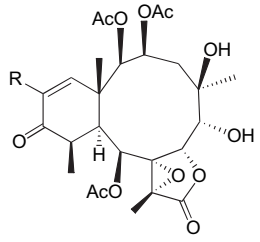
3.89, 1H, m, H-12) were replaced by those of a 3-vinylpropionyloxy group (δ_C 172.3, s; 136.4, d; 115.6, t; 33.2, t; 28.5, t; δ_H 5.77, 1H, m; 5.02, 2H, m; 2.35, 2H, m; 2.30, 2H, t, *J*=7.2 Hz) in **2**. In the HMBC experiment of **2**, the carbon signal at δ 172.3 (s), which showed a correlation with H-12 (δ 5.02) was found to be correlated with the signal of the methylene protons at δ 2.30, and was consequently assigned as the carbon atom of the 3-vinylpropionate carbonyl. Thus, the 3-vinylpropionate ester should be positioned at C-12 in **2**. Furthermore, vinylpropionylation of **5** gave a less polar product, which was found to be identical with natural product **2** by comparison of the physical and spectral data, and confirmed the structure of diterpenoid **2**.

Briaexcavatin E (**3**) had the molecular formula of $C_{33}H_{46}O_{13}$ as determined by HRESIMS, with 11 degrees of unsaturation thereby being determined for the molecule. The IR absorptions of **3** showed the presence of γ-lactone (ν_{max} 1787 cm^{-1}) and ester carbonyl groups (ν_{max} 1742 cm^{-1}). Like as those of **2**, the sharpened ^{13}C and ^{1}H NMR signals of **3** (Tables 1 and 2) were also obtained in $CDCl_3$ at −20 °C. Carbonyl resonances in the ^{13}C NMR spectrum of **3** at δ 172.7 (s), 172.0 (s), 171.3 (s), 170.7 (s), 169.8 (s), and 169.7 (s) confirmed the presence of a γ-lactone and five other esters in the molecule. In the ^{1}H NMR spectrum, four acetate methyls were observed at δ 2.37 (3H, s), 2.24 (3H, s), 2.16 (3H, s), and 1.93 (3H, s). The additional acyl group was found to be an isovaleryl group, which showed nine contiguous protons (δ 2.12, 2H, t, *J*=7.2 Hz; 2.03, 1H, m; 0.89, 2×3H, d, *J*=6.8 Hz) were observed. The ^{13}C NMR signal appeared at δ 171.3 (s) correlated with the signal of the methylene protons at δ_H 2.12 in the HMBC spectrum and was consequently assigned as the carbon atom of the isovalerate carbonyl. The ^{1}H–^{13}C long-range correlations observed in an HMBC experiment of **3** further revealed the connectivity between H-12 (δ 5.04) and the carbonyl carbon (δ 171.3) of the isovalerate unit and demonstrated the location of the isovalerate to be at C-12. The positions of the other four acetoxy groups at C-2, C-3, C-9, and C-14 were also confirmed by the connectivities between the four oxymethine protons at δ 5.17 (H-2), 5.72 (H-3), 5.32 (H-9), 4.82 (H-14) and the four ester carbonyls (δ 172.7, s; 170.7, s; 169.8, s; 169.7, s) in the HMBC spectrum of **3**. Moreover, isovalerylation of excavatolide C (**5**)[8a] yielded a compound that was found to be identical with diterpenoid **3** by physical and spectral data comparison.

Our present study has also led to the isolation of the new briarane, briaexcavatin F (**4**). The molecular formula of $C_{35}H_{48}O_{13}$ was deduced from HRESIMS with *m/z* 699.2996 (calcd for $C_{35}H_{48}O_{13}$+Na, 699.2993). This showed that briarane **4** contained 12 degrees of unsaturation. From detailed analysis, the NMR data of **4** (measured in $CDCl_3$ at −20 °C) (Tables 1 and 2) were found to be close to those of **2** and the known metabolite, excavatolide B (**6**),[8a] and showed the presence of a γ-lactone, an *n*-butyryloxy, a 3-vinylpropionyloxy, and three acetoxy groups. Comparison of the ^{1}H and ^{13}C NMR spectral data of **4** with those of



1: $R_1 = CO(CH_2)_2CH_3$, $R_2 = H$
10: $R_1 = Ac$, $R_2 = OH$ (revised)
11: $R_1 = Ac$, $R_2 = H$ (revised)



7: R = OH
8: R = H

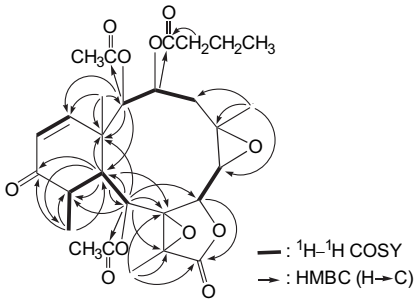
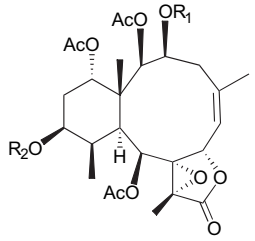
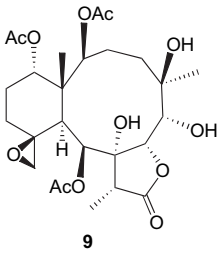


Figure 1. The ^{1}H–^{1}H COSY and selective HMBC correlations of **1**.



2: $R_1 = Ac$, $R_2 = CO(CH_2)_2CH{=}CH_2$
3: $R_1 = Ac$, $R_2 = COCH_2CH(CH_3)_2$
4: $R_1 = CO(CH_2)_2CH_3$, $R_2 = CO(CH_2)_2CH{=}CH_2$
5: $R_1 = Ac$, $R_2 = H$
6: $R_1 = CO(CH_2)_2CH_3$, $R_2 = H$



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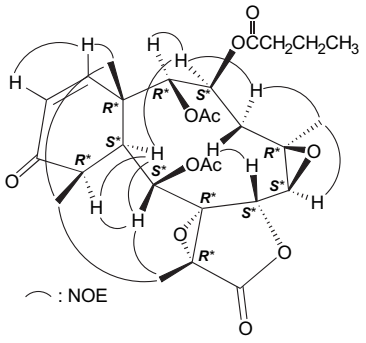


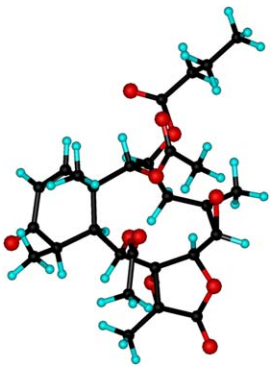
Figure 2. Selective NOESY correlations of **1**.

2 showed that the acetoxy group attached to C-3 in **2** could be replaced by an *n*-butyryloxy group in **4**. These observations were further confirmed by the correlations observed in the 2D NMR experiments of **4** including ^{1}H–^{1}H COSY, HSQC, and HMBC spectra. Similar to that of briarane **2**, vinylpropionylation of **6** gave a less polar product, which was found to be identical with natural product **4** by comparison of the physical and spectral data. Since the absolute configuration of the known briarane, excavatolide B (**6**), had been determined by modified Mosher's method,[11] we were able to assign the absolute configurations of all the chiral centers of **4** as 1*R*,2*R*,3*S*,5*Z*,7*S*,8*S*,9*S*,10*S*,11*R*,12*S*,14*S*,17*R*. Based on above findings, the structure of **4** was established unambiguously.

In a previous study, we reported the isolation and structure elucidation of two 5,6-dihydroxybriarane metabolites, briaexcavatolides X (**7**) and Y (**8**).[9f] However, based on the detailed spectral data analysis and by comparing the ^{1}H and ^{13}C NMR chemical shifts of C-5 and C-6 in briaranes **7** (δ_C 59.3, s, C-5; 62.7, d, C-6; δ_H 3.05, 1H, d, J=8.5 Hz, H-6) and **8** (δ_C 59.4, s, C-5; 62.7, d, C-6; δ_H 3.06, 1H, d, J=8.5 Hz, H-6) with those of briarane **1** (δ_C 59.5, s, C-5; 62.8, d, C-6; δ_H 3.06, 1H, d, J=8.0 Hz, H-6) and a known 5,6-dihydroxybriarane, junceellolide L (**9**) (δ_C 89.6, s, C-5; 82.7, d, C-6; δ_H 4.22, 1H, br s, H-6),[12] the 5,6-dihydroxy groups in briaranes **7** and **8** should be revised as 5β,6β-epoxy groups as presented in briaranes **10** and **11**, respectively. The spectral data (IR and MS) for briaranes **10** (briaexcavatolide X) and **11** (briaexcavatolide Y) are reassigned in this study (see Section 3).

In the biological activity testing, briaexcavatin C (**1**) exhibited mild cytotoxicity toward MDA-MB-231 human breast tumor cells (IC_{50}=17.50 μg/mL) and briaexcavatin

Table 3. The stereoview of **1** (generated from computer modeling) and the calculated distances (Å) between selected protons having key NOE correlations[a]

Briaexcavatin C (**1**)	H/H	(Å)
	H-2/H-3	2.44
	H-3/H-10	3.09
	H-3/H-4α	2.24
	H-4α/H_3-16	2.57
	H-6/H_3-16	2.40
	H-9/H-10	2.73
	H-9/H-11	2.41
	H-9/H_3-18	2.37
	H-10/H-11	2.28
	H-13/H-14	2.38

[a] The calculated distance between H-10 (α) and H_3-15 (β) is 3.91 Å.

Table 4. Inhibitory effects of briarane **3** on superoxide generation and elastase release by human neutrophil in response to fMet-Leu-Phe/cytochalasin B[a]

Compound	Concn (μM)	Superoxide generation (%)	Elastase release (%)
3	3	—	87.77±5.86
	5	—	65.96±9.94
	10	101.19±4.15	37.89±13.53

[a] Data obtained without any drugs were set to 100%. Means±SEM of three separate experiments are shown.

E (**3**) was found to show the activity to inhibit human neutrophil elastase (HNE) release but not superoxide anion generation (Table 4). To the best of our knowledge, briaexcavatin E (**3**) is the first briarane-type natural product reported to possess the activity to inhibit HNE release.

3. Experimental

3.1. General experimental procedures

Optical rotation values were measured with a JASCO P-1010 digital polarimeter at 25 °C. Infrared spectra were obtained on a VARIAN DIGLAB FTS 1000 FTIR spectrometer. EIMS and FABMS were obtained with a VG QUATTRO GC/MS spectrometer. HRMS data were recorded by ESI FT-MS on a BRUKER APEX II mass spectrometer or by EI on a JEOL JMS-700 mass spectrometer. ^{1}H NMR spectra were recorded on a VARIAN MERCURY PLUS 400 FT-NMR at 400 MHz and ^{13}C NMR spectra were recorded on a VARIAN MERCURY PLUS 400 FT-NMR at 100 MHz or on a VARIAN UNITY INOVA 600 FT-NMR at 150 MHz, in $CDCl_3$ using TMS as an internal standard. Column chromatography was performed on silica gel 60 (230–400 mesh) (Merck, Darmstadt, Germany). TLC spots (silica gel 60 F_{254}, Merck) were detected with an UV_{254} lamp and by 10% H_2SO_4 followed by heating at 120 °C for 5 min. All solvents and reagents used were analytical grade.

3.2. Animal material

Specimen of the octocoral *B. excavatum* was collected by hand using scuba off the coast of southern Taiwan in October 2003, at a depth of −10 m. Live reference specimens are being maintained in the authors' marine organism cultivating tanks and a voucher specimen was deposited in the National Museum of Marine Biology and Aquarium (NMMBA).

3.3. Extraction and isolation

The organism (wet weight 1.0 kg) was collected and freeze-dried. The freeze-dried material (0.57 kg) was minced and extracted with EtOAc. The extract was separated by silica gel column chromatography, using *n*-hexane and *n*-hexane–EtOAc mixtures of increased polarity. Briarane **3** was eluted with *n*-hexane–EtOAc (6:1→5:1), **4** with *n*-hexane–EtOAc (5:1), **2** with *n*-hexane–EtOAc (4:1), and **1** with *n*-hexane–EtOAc (5:2).

3.3.1. Briaexcavatin C (1). White powder (2.1 mg); 79–81 °C; $[\alpha]_D^{25}$ −25 (*c* 0.40, $CHCl_3$); IR (neat) ν_{max} 1792, 1744, 1688 cm^{-1}; ^{13}C ($CDCl_3$, 100 MHz) and ^{1}H ($CDCl_3$, 400 MHz) NMR data, see Tables 1 and 2; FABMS *m/z* 549 $(M+H)^+$, 489, 429, 341; HRESIMS *m/z* 549.2340 (calcd for $C_{28}H_{36}O_{11}$+H, 549.2336).

3.3.2. Briaexcavatin D (2). Colorless gum (2.4 mg); $[\alpha]_D^{25}$ +32 (*c* 0.12, CH_2Cl_2); IR (neat) ν_{max} 1792, 1737 cm^{-1}; ^{13}C ($CDCl_3$, 150 MHz) and ^{1}H ($CDCl_3$, 400 MHz) NMR data, see Tables 1 and 2; FABMS *m/z* 671 $(M+Na)^+$, 649, 589, 529, 489, 469, 429, 369, 309; HRESIMS *m/z* 671.2684 (calcd for $C_{33}H_{44}O_{13}$+Na, 671.2680).

3.3.3. Briaexcavatin E (3). White powder (2.2 mg); 251–252 °C; $[\alpha]_D^{29}$ +42 (*c* 0.40, $CHCl_3$); IR (neat) ν_{max} 1787, 1742 cm^{-1}; ^{13}C ($CDCl_3$, 100 MHz) and ^{1}H ($CDCl_3$, 400 MHz) NMR data, see Tables 1 and 2; FABMS *m/z* 673 $(M+Na)^+$, 651, 591, 549, 489, 471, 429, 369, 309; HRESIMS *m/z* 673.2834 (calcd for $C_{33}H_{46}O_{13}$+Na, 673.2836).

3.3.4. Briaexcavatin F (4). Colorless gum (1.7 mg); $[\alpha]_D^{25}$ +46 (*c* 0.09, CH_2Cl_2); IR (neat) ν_{max} 1787, 1735 cm^{-1}; ^{13}C ($CDCl_3$, 150 MHz) and ^{1}H ($CDCl_3$, 400 MHz) NMR data, see Tables 1 and 2; FABMS *m/z* 699 $(M+Na)^+$, 677 $(M+H)^+$, 617, 589, 557, 529, 517, 469, 409, 369, 309; HRESIMS *m/z* 699.2996 (calcd for $C_{35}H_{48}O_{13}$+Na, 699.2993).

3.3.5. Briaexcavatolide X (10). IR (neat) ν_{max} 3472, 1792, 1748, 1703 cm^{-1}; EIMS *m/z* 537 $(M+H)^+$, 459 $(M+H-H_2O-AcOH)^+$, 417 $(M+H-2AcOH)^+$, 399 $(M+H-H_2O-2AcOH)^+$, 357 $(M+H-3AcOH)^+$, 339 $(M+H-H_2O-3AcOH)^+$; HREIMS *m/z* 536.1894 (calcd for $C_{26}H_{32}O_{12}$, 536.1894).

3.3.6. Briaexcavatolide Y (11). IR (neat) ν_{max} 1792, 1744, 1686 cm^{-1}; FABMS *m/z* 521 $(M+H)^+$, 461 $(M+H-AcOH)^+$, 401 $(M+H-2AcOH)^+$, 341 $(M+H-3AcOH)^+$; HRESIMS *m/z* 543.1844 (calcd for $C_{26}H_{32}O_{11}$+Na, 543.1842).

3.4. Vinylpropionylation of excavatolide C (5)

Excavatolide C (**5**) (5.0 mg) was stirred with 2 mL of 3-vinylpropionic anhydride (pent-4-enoic anhydride) in 2 mL of pyridine for 96 h at room temperature. After evaporation of excess reagent, the residue was separated by column chromatography on silica gel to give pure briaexcavatin D (**2**) (*n*-hexane–EtOAc, 4:1, 4.0 mg, 70%); physical (R_f and optical rotation values) and NMR data were in full agreement with those of natural product **2**.

3.5. Isovalerylation of excavatolide C (5)

Excavatolide C (**5**) (5.0 mg) was stirred with 2 mL of isovaleric anhydride in 2 mL of pyridine for 96 h at room temperature. After evaporation of excess reagent, the residue was separated by column chromatography on silica gel to give pure briaexcavatin E (**3**) (*n*-hexane–EtOAc, 6:1→5:1, 3.9 mg, 68%); physical (mp, R_f, and optical rotation values) and NMR data were in full agreement with those of natural product **3**.

3.6. Vinylpropionylation of excavatolide B (6)

Excavatolide B (**6**) (8.0 mg) was stirred with 2.5 mL of 3-vinylpropionic anhydride (pent-4-enoic anhydride) in

2.5 mL of pyridine for 96 h at room temperature. After evaporation of excess reagent, the residue was separated by column chromatography on silica gel to give pure briaexcavatin F (**4**) (*n*-hexane–EtOAc, 5:1, 6.6 mg, 72%); physical (R_f and optical rotation values) and NMR data were in full agreement with those of natural product **4**.

3.7. Molecular mechanics calculations

The minimum energy conformation of briaexcavatin C (**1**) was determined using the MSI Insight II/DISCOVER version 95 molecular modeling package incorporating an empirical force field, the consistent valence force field (CVFF),[13] on Silicon Graphic IRIS (SGI) Indigo XS24/4000 workstation. All force field calculations were carried out in vacuo (dielectric constant=1). The conformational space of **1** was scanned using the high-temperature molecular dynamics simulation technique followed by energy minimization. A 100 ps molecular dynamics simulation at 1000 K provided a set of 500 conformations of **1**. Each conformation was used as a starting structure for the subsequent energy minimization (1000 steps, conjugated gradient algorithm). In the subsequent analysis, only 10 conformations with a reasonably low energy (at most 5 kcal/mol higher with respect to the lowest energy conformer) were used. The conformational search suggested that the most stable conformation of briarane **1** shown in Table 3 is the lowest.

3.8. Cytotoxicity assays

Compounds were assayed for cytotoxicity against MDA-MB-231 cells using the MTT method. Freshly trypsinized cell suspensions were seeded in 96-well microtitre plates at densities of 5000–10,000 cells per well with tested compounds added from DMSO-diluted stock. After 3 days in culture, attached cells were incubated with MTT (0.5 mg/mL, 1 h) and subsequently solubilized in DMSO. The absorbency at 550 nm was then measured using a microplate reader. The IC_{50} is the concentration of agent that reduced cell growth by 50% under the experimental conditions.

3.9. Human neutrophil superoxide generation and elastase release

Human neutrophils were obtained by means of dextran sedimentation and Ficoll centrifugation. Superoxide generation and elastase release were carried out according to the procedures described previously.[14,15] Briefly, superoxide anion production was assayed by monitoring the superoxide dismutase-inhibitable reduction of ferricytochrome *c*. Elastase release experiments were performed using MeO-Suc-Ala-Ala-Pro-Valp-nitroanilide as the elastase substrate.

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Chiral spiroborate esters catalyzed highly enantioselective direct aldol reaction☆

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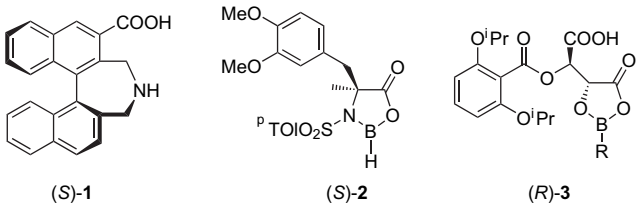
Abstract—Asymmetric catalysis of chiral spiroborate esters with an O_3BN framework toward the direct aldol reaction of acetone and aromatic aldehydes was examined, and a new, efficient chiral catalyst was discovered. In the presence of the novel catalyst, acetone was allowed to react with aromatic aldehydes at 0 °C for 50 h to afford chiral β-hydroxyketone in up to >99% ee and 92% yield. The catalyst, which is readily synthesized, is highly stable to hydrolysis, thermolysis, oxidation, and racemization, can be conveniently recovered.

1. Introduction

The asymmetric aldol reaction is considered to be one of the most powerful tools for the carbon–carbon bond formation.[1] Traditionally, catalytic asymmetric aldol reactions require pre-conversion of the carbonyl pro-nucleophile to a corresponding more active enolate or enol ether with the aid of stoichiometric Lewis acid[2] or Lewis base,[3] which plays a role in controlling stereochemistry of the aldol reaction. However, a more convenient method is direct addition of unmodified ketone to aldehyde in the presence of chiral catalyst. This is a protocol with high atom-economy.[4] The synthetic importance has continually stimulated chemists to search for highly enantioselective chiral catalysts. In the past decade, much work has been done in the direct aldol reaction, and numerous efficient catalysts have been developed. Shibasaki,[5] Evans,[6] and Trost[7] designed their own metallic chiral catalysts, and high ee was obtained. It was not until the work by List and Barbas that L-proline could act as an efficient catalyst in intermolecular direct aldol addition,[8] small organic molecules began to receive increasing attention. Now, non-metal small molecular organocatalyst has become a new focus in asymmetric synthesis.[9] Recent studies by Gong[10] demonstrated that L-prolinamide derivatives could catalyze the direct aldol reaction and the enantioselectivity was improved significantly for the aromatic aldehydes with 20 mol % catalyst loading. Several other proline derivatives have also been applied to highly enantioselective direct aldol reaction.[11] However, the preparation of those catalysts is not so easy.

The motivation for this investigation came from our recent study on borane reduction of prochiral ketones,[12] imines,[13] and oxime ethers catalyzed by tetra-coordinated chiral spiroborate esters with an O_3BN framework, which were synthesized conveniently from diol, boric acid, and L-proline,[14] and found that some α-amino acid and β-amino alcohol derivatives of 1,1′-bi-2-naphtholboric acid were high efficient chiral catalyst. We believe that the binaphthyl backbone in these chiral catalysts played an important role in the asymmetric induction.[12b] Later on, Maruoka[15a] designed a γ-amino acid based on binaphthyl backbone (*S*)-**1** (Fig. 1), which also showed high enantioselectivity in direct aldol reaction.[15] On the other hand, it was previously reported that tri-coordinated, moisture-sensitive chiral oxazaborolidinones (*S*)-**2**[16] and chiral 1,3,2-dioxaborole derivatives (*R*)-**3**[17] were employed as catalysts for the aldol addition of enol silyl ether and aldehyde. We suppose that chiral spiroborate esters (Fig. 2) could also show high asymmetric catalytic activity toward aldol reaction because the chiral spiroborate ester not only contains 1,1′-bi-2-naphthyl and (*S*)-proline moiety but also includes a boron atom and a nitrogen atom, which can act as an acidic center and a basic center under suitable conditions, respectively. If this hypothesis is



(*S*)-**1** (*S*)-**2** (*R*)-**3**

Figure 1. Tri-coordinated boron catalyst and binaphthyl backbone containing catalyst.

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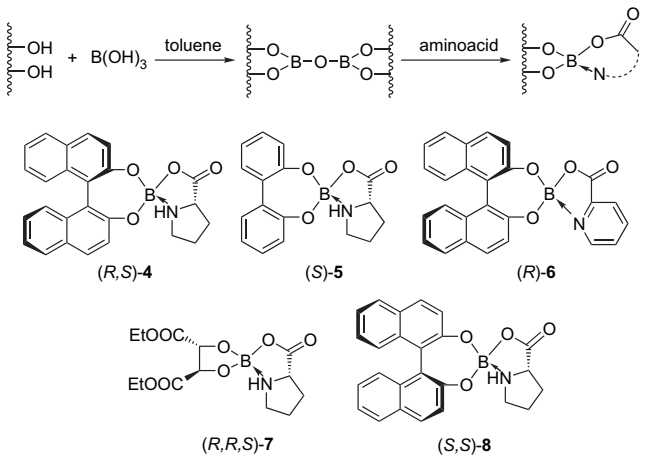


Figure 2. Chiral spiroborate esters evaluated in the aldol reaction.

validated, there will be greater merit than moisture-sensitive tri-coordinated boron compound due to their easy preparation and high stability to hydrolysis, thermolysis, oxidation, and racemization resulted from N→B coordination.[14b] Direct aldol reaction was examined under the catalysis of some chiral spiroborate esters and up to 90% ee was observed. In this paper, we will report the result of asymmetric reaction of acetone to aromatic aldehydes in the presence of some chiral borate esters with an O_3BN framework.

2. Results and discussion

2.1. Screening of chiral catalyst and optimization of the reaction condition

To explore the possibility of the catalysis, five chiral spiroborate esters (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8** were synthesized (Fig. 2) according to the literature procedure.[14] As a model experiment, we explored the direct addition of acetone to benzaldehyde in the presence of the above spiroborate esters, respectively, the influence of the catalyst loading, solvent, temperature, and reaction time on the stereoselectivity of the reaction were also examined.

Benzaldehyde was allowed to react with excess acetone at 0 °C for 50 h in the presence of chiral spiroborate esters (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8**, respectively. The reaction mixture was treated with saturated aqueous ammonium chloride, and followed by extraction with ethyl acetate. After the combined organic phase was dried and concentrated, the catalyst was recovered from the residue upon standing. The desired product was afforded after purified on column chromatography. The results were summarized in Table 1.

It was showed that the catalytic activity and the stereoselectivity were in close relationship with the composition and the loadings of the chiral spiroborate ester. The catalyst (*S*)-**5**, (*R*)-**6** showed little asymmetric induction to the aldol reaction with (*R*,*S*)-**4** an exception, which resulted in high enantioselectivity. It seemed that the stereoselectivity was influenced not only by the diol moiety (entries 2, 4) but also by the chiral carboxyl group and the secondary amine

Table 1. Exploration of various chiral spiroborates as catalyst of the direct asymmetric aldol addition of acetone to benzaldehyde

Entry	Cat.	Catalyst loading (%)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	(*R*,*S*)-**4**	20	0	50	12	81	*R*
2	(*R*,*S*)-**4**	30	0	50	44	96	*R*
3	(*R*,*S*)-**4**	40	0	50	19	89	*R*
4	(*S*)-**5**	30	0	50	18	7.4	*S*
5	(*R*)-**6**	30	0	50	48	4.4	*S*
6	(*R*,*R*,*S*)-**7**	30	0	50	Trace	—	—
7	(*S*,*S*)-**8**	30	0	50	Trace	—	—

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.

in the nitrogen containing moiety (entries 2, 5). In terms of catalytic activity, the diol moiety matters a lot. Almost no catalytic activity was observed when (*R*,*R*,*S*)-**7** or (*S*,*S*)-**8** was used. Specifically, it was quite unexpected that (*S*,*S*)-**8**, possessing the same composition as (*R*,*S*)-**4** almost did not show catalytic activity to the addition. Perhaps, this was originated from the chiral dismatching of the two chiral centers in (*S*,*S*)-**8**, which was disfavored for the catalysis. Moreover, the absolute configuration relied much on the composition of the catalyst. Little difference in the structure led to the opposite configuration (entries 4, 5).

The reaction in acetone (Table 1: entries 1–3) showed that 0.3 equiv of (*R*,*S*)-**4** was suitable for the reaction. To explore better solvent for the reaction, we examined the reaction of benzaldehyde with acetone in various solvent and at different temperatures in the presence of 0.3 equiv of (*R*,*S*)-**4**. The results were summarized in Table 2.

It was revealed that DMSO was a more appropriate solvent when the reaction was performed at 20 °C (entry 4); however, the reaction carried out in acetone at 0 °C for 50 h furnished the desired product in the highest ee and better yield (entry 5), and the enantioselectivity declines with the prolongation of reaction time (entries 9, 8, 10). It was suitable that the reaction was performed at 0 °C for 50 h in the presence of 0.3 equiv of (*R*,*S*)-**4** for the direct addition of acetone to aromatic aldehydes.

Table 2. Screening of the conditions on the direct addition of acetone to benzaldehyde in the presence of the catalyst (*R*,*S*)-**4**

Entry	Solvent	Catalyst loading (%)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	Acetone	30	20	50	11	70	*R*
2	THF	30	20	50	8	79	*R*
3	DMF	30	20	50	17	86	*R*
4	DMSO	30	20	50	48	87	*R*
5	Acetone	30	0	50	44	96	*R*
6	THF	30	0	50	23	92	*R*
7	DMF	30	0	50	35	96	*R*
8	Acetone	30	−15	50	64	83	*R*
9	Acetone	30	0	36	36	98	*R*
10	Acetone	30	0	72	44	76	*R*

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.

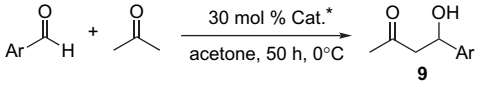
2.2. Asymmetric direct aldol addition of acetone to aromatic aldehydes catalyzed by (*R*,*S*)-4

Having established the optimal reaction conditions, the direct asymmetric aldol reaction of representative aldehydes with acetone was evaluated, and the results were summarized in Table 3.

Most of the reactions furnished good and better enantioselectivities under the experiment conditions. The addition of acetone to benzaldehyde, *p*-chlorobenzaldehyde, *m*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, and 1-naphthaldehyde gave enantioselectivity in over 90% ee; while the reactions of acetone with aromatic aldehydes bearing a methoxyl group in benzene ring exhibited only moderate stereoselectivity. That is to say, the aromatic aldehydes bearing an electron-withdrawing group in the benzene ring generally can offer the desired products of higher ee than those bearing an electron-donating group. So the electronic effect is a major factor, the existence of electron-withdrawing group in the benzene ring increases positive charge at the carbonylic carbon atom of the aldehyde, which is favorable for the attack of the α-carbon of ketone, while the existence of electron-donating group in the benzene ring does not. However, 4-nitrobenzaldehyde and 3,5-dichlorobenzaldehyde gave β-hydroxyketones of lower ee (entries 5, 7), meaning that the enantioselectivity of the aldol additions is in close relationship with the position and the number of the electron-withdrawing group in the aromatic ring. It appears that the steric and electronic effect of the substituted groups in the aromatic aldehydes considerably influence the enantioselectivity of the direct aldol addition.

Our catalyst (*R*,*S*)-**4** showed much stronger chiral inductive ability than (*S*)-proline in asymmetric catalysis toward direct aldol addition. It was assumed that (*R*,*S*)-**4** was a tetra-coordinated, polycyclic structural boron compound, in which all the atoms are in cycles except hydrogen atoms. This strong conformational rigidity and special configuration can provide a suitable quadrant and space for the attack of reactant, in other words, the attack of the reactant molecules have to occur in a limited small space due to the small size of the boron atom and steric bulk of the polycycle and 1,1′-bi-2-naphthyl moiety; as a result, the number of reaction transition states is reduced. Moreover, the catalyst can be conveniently recovered in high yield.

Table 3. Direct aldol reaction of aromatic aldehydes with acetone catalyzed by (*R*,*S*)-**1**



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Entry	Ar	Product	Yield[a] (%)	ee[b] (%)	Config.[c]
1	1-$C_{10}H_9$[d]	**9a**	34	96	*R*
2	Ph	**9b**	44	96	*R*
3	2-$NO_2C_6H_4$	**9c**	65	96	*R*
4	3-$NO_2C_6H_4$	**9d**	92	>99	*R*
5	4-$NO_2C_6H_4$	**9e**	65	75	*R*
6	4-ClC_6H_4	**9f**	55	90	*R*
7	3,5-$Cl_2C_6H_3$	**9g**	23	74	*R*
8	2-$MeOC_6H_4$	**9h**	26	nd	*R*[e]
9	3-$MeOC_6H_4$	**9i**	39	nd	*R*[e]
10	4-$MeOC_6H_4$	**9j**	42	67	*R*

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.
[d] 1-Naphthyl.
[e] Assigned by analogy.

3. Conclusion

A novel, efficient catalyst (*R*,*S*)-**4** for direct aldol addition of acetone to aromatic aldehydes was developed. In the presence of 0.3 equiv of (*R*,*S*)-**4**, acetone was allowed to react with aromatic aldehydes at 0 °C for 50 h to afford chiral 4-aryl-4-hydroxyl-2-butanone in >99% ee and 92% yield. In the catalytic addition, the aromatic aldehydes bearing an electron-withdrawing group in benzene ring generally offered the desired products in higher ee than those bearing an electron-donating group in the benzene ring. On the other hand, the position and the number of the electron-withdrawing groups in the aromatic ring influenced considerably the enantioselectivity of the direct aldol addition.

4. Experimental

4.1. General

IR spectra were recorded on a Testscan Shimadzu FTIR 8000 or a Nicolet 170 SX FTIR spectrophotometer in KBr. The ^1H and ^{13}C NMR spectra were performed on a Varian Mercury VX 300, and all chemical shifts were reported as δ values (ppm) relative to Me_4Si. Optical rotations were measured on a Perkin–Elmer 341 Mc polarimeter. Melting points were determined on a VEB Wagetechnik Rapio PHMK 05 instrument and were not corrected.

4.2. Materials

All reactions were carried out under an Ar atmosphere in freshly dried glassware. Commercially available starting materials were used without further purification if not specified. Acetone was treated successively with small portions of $KMnO_4$ under reflux, until the violet color persists, followed by distillation, and then stored over 4 Å molecular sieves. Benzaldehyde was washed successively with 10% Na_2CO_3 (until no more CO_2 is evolved), saturated Na_2SO_3 and H_2O, followed by drying with $MgSO_4$, and then distilled under Ar under reduced pressure. (*S*)-Proline and boric acid were dried prior to use.

4.2.1. General procedure for the synthesis of the catalysts.[14a] A mixture of a chiral or non-chiral diol and boric acid were allowed to dehydrate in toluene under azeotropic condition for 7–8 h, and then a chiral or non-chiral α-amino acid was added and continued to reflux for several hours to precipitate the desired optically active products (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8** in high yield. The data of (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, and (*S*,*S*)-**8** were identical with the literature.[14a] (*R*,*S*)-**4** and (*S*,*S*)-**8** can also be prepared from racemic BINOL via diastereomeric seperation.[14b]

(*R*,*R*,*S*)-**7**: yield, 82.8%; mp: 168–170 °C; $[\alpha]_D^{25}$ −12.78 (*c* 1.033, in CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz, TMS)

δ (ppm): 1.28–1.33 (m, 6H, CH_3), 1.89–1.97 (m, 2H, NCH_2CH_2), 2.20–2.28 (m, 2H, $CHCH_2$), 3.16–3.24 (m, 1H, NCHH), 3.90–3.92 (m, 1H, NCHH), 4.23 (d, J=8.0 Hz, 4H, CH_3CH_2), 4.54 (d, J=5.7 Hz, 2H, OCH), 4.68 (d, J=8.3 Hz, 1H, NCH), 6.55 (s, 1H, NH); IR (KBr): ν 3230 (s, NH), 2991 (s, CH), 1764, 1748 (COOR), 1371 (ms, B–O), 1211 (vs, N→B), 1233 (s, C–O), 1069 (vs, B–O).

4.2.2. General procedure for direct aldol reaction. In a Schlenk test tube fitted with a magnetic bar, catalyst (*R*,*S*)-**4** (0.61 g 1.5 mmol) was charged, and followed by injection of acetone (5 ml), after stirring for 15 min in ice bath, an aromatic aldehyde (5 mmol) was added and continued to stir at 0 °C for 50 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×10 ml). The combined organic phase was dried over anhydrous Na_2SO_4. After concentration, white solid isolated upon standing (recovered catalyst), filtered and the liquor was worked up through flash column chromatography on a silica gel (200–300 mesh, eluent: petroether/acetate 2:1) to give the desired product.

4.2.3. (4*R*)-Hydroxy-4-(1′-naphthyl)-butan-2-one (9a). Yield: 34%; $[\alpha]_D^{25}$ +56.30 (*c* 0.08, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.02–7.46 (m, 7H, Naph–H), 5.94 (m, 1H, CH), 3.38 (s, 1H, OH), 3.02–2.99 (m, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 207.8, 137.0, 132.5, 128.6, 127.8, 126.8, 125.0, 124.3, 121.7, 121.5, 65.5, 50.2, 29.7; IR (KBr): ν 3421 (s, OH), 3050 (w, Ph–H), 2923 (w, CH), 1687 (vs, C=O), 1614 (w, Ph–H). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=8.7 min and (*S*)-isomer, t_R=10.7 min.

4.2.4. (4*R*)-Hydroxy-4-phenyl-butan-2-one (9b). Yield: 44%; $[\alpha]_D^{20}$ +58.58 (*c* 0.39, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.34–7.26 (m, 5H, Ph–H), 5.15–5.11 (m, 1H, CH), 3.50 (s, 1H, OH), 2.92–2.75 (m, 2H, CH_2), 2.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.1, 143.0, 129.2, 128.7, 128.5, 127.9, 125.8, 70.1, 52.3, 31.1; IR (KBr): ν 3420 (s, OH), 3031 (w, Ph–H), 2902 (w, CH), 1708 (vs, C=O), 1602 (w, Ph–H). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=8.1 min and (*S*)-isomer, t_R=8.9 min.

4.2.5. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (9c). Yield: 65%; $[\alpha]_D^{27}$ −107.91 (*c* 1.11, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.95–7.39 (m, 4H, Ph–H), 5.66 (d, J=10.7 Hz, 1H, CH), 3.67 (s, 1H, OH), 3.13–2.68 (m, 2H, CH_2), 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.8, 147.2, 138.7, 134.0, 128.5, 128.4, 124.6, 65.9, 51.4, 30.8; IR (KBr): ν 3418 (s, OH), 3077 (w, Ph–H), 2920 (w, CH), 1712 (vs, C=O), 1609 (w, Ph–H), 1524, 1348 (s, NO_2). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=9.0 min and (*S*)-isomer, t_R=3.8 min.

4.2.6. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (9d). Yield: 92%; $[\alpha]_D^{27}$ +58.88 (*c* 0.45, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.24–7.50 (m, 4H, Ph–H), 5.26 (s, 1H, CH), 3.63 (d, J=3.3 Hz, 1H, OH), 2.89 (d, J=5.7 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.7, 148.6, 145.0, 132.0, 129.7, 122.8, 121.0, 69.1, 51.8, 31.0; IR (KBr): ν 3417 (s, OH), 3090 (w, Ph–H), 2917 (w, CH), 1709 (vs, C=O), 1618 (w, Ph–H), 1529, 1351 (s, NO_2). Enantiomeric excess: >99%, determined by HPLC (Daicel chiralpak OJ-H, *i*-PrOH/hexane 20:80), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=18.7 min and (*S*)-isomer, t_R=21.3 min.

4.2.7. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (9e). Yield: 65%; $[\alpha]_D^{16}$ +51.03 (*c* 0.28, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.23–7.53 (m, 4H, Ph–H), 5.27 (s, 1H, CH), 3.64 (s, 1H, OH), 2.86 (t, J=4.5 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.5, 150.2, 147.4, 129.0, 126.6, 124.4, 123.9, 69.2, 51.9, 31.1; IR (KBr): ν 3436 (s, OH), 3081 (w, Ph–H), 2902 (w, CH), 1707 (vs, C=O), 1602 (w, Ph–H), 1517, 1347 (s, NO_2). Enantiomeric excess: 75%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=10.5 min and (*S*)-isomer, t_R=13.5 min.

4.2.8. (4*R*)-Hydroxy-4-(4′-chlorophenyl)-butan-2-one (9f). Yield: 55%; $[\alpha]_D^{27}$ +46.36 (*c* 0.48, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.33–7.26 (m, 4H, Ph–H), 5.11 (q, J=4.7 Hz, 1H, CH), 3.44 (s, 1H, OH), 2.83–2.79 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.0, 141.4, 133.5, 128.9, 127.2, 69.5, 52.1, 31.1; IR (KBr): ν 3426 (s, OH), 3001 (w, Ph–H), 2902 (w, CH), 1711 (vs, C=O), 1597 (w, Ph–H). Enantiomeric excess: 90%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=10.9 min and (*S*)-isomer, t_R=12.6 min.

4.2.9. (4*R*)-Hydroxy-4-(3′,5′-dichlorophenyl)-butan-2-one (9g). Yield: 23%; $[\alpha]_D^{16}$ +39.22 (*c* 0.26, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25, 7.24 (s, 3H, Ph–H), 5.09 (s, 1H, CH), 3.58 (s, 1H, OH), 2.81 (d, J=6.7 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.6, 146.3, 135.3, 127.9, 124.4, 68.9, 51.8, 31.1; IR (KBr): ν 3430 (s, OH), 3078 (w, Ph–H), 2925 (w, CH), 1711 (vs, C=O), 1594 (w, Ph–H), 689 (s, C–Cl). Enantiomeric excess: 74%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=5.1 min and (*S*)-isomer, t_R=6.1 min.

4.2.10. (4*R*)-Hydroxy-4-(2′-methoxyphenyl)-butan-2-one (9h). Yield: 26%; $[\alpha]_D^{25}$ +61.02 (*c* 0.15, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.44–6.84 (m, 4H, Ph–H), 5.40 (t, J=10.3 Hz, 1H, CH), 3.83 (s, 1H, OCH_3), 3.43 (d, J=4.3 Hz, 1H, OH), 2.96–2.74 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.7, 156.0, 131.1, 128.6, 126.6, 121.1, 110.5, 65.8, 55.5, 50.6, 30.8; IR (KBr): ν 3442 (s, OH), 3003 (w, Ph–H), 2939 (w, CH), 1708 (vs, C=O), 1600 (w, Ph–H), 1240, 1068 (s, O–CH_3).

4.2.11. (4*R*)-Hydroxy-4-(3′-methoxyphenyl)-butan-2-one (9i). Yield: 39%; $[\alpha]_D^{25}$ +38.45 (*c* 0.53, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.27–6.79 (m, 4H,

Ph–H), 5.11 (d, J=10.0 Hz, 1H, CH), 3.80 (s, 1H, OCH_3), 3.40 (s, 1H, OH), 2.86–2.80 (m, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.0, 159.9, 144.8, 129.7, 118.1, 113.4, 111.3, 70.0, 55.5, 52.4, 31.1; IR (KBr): ν 3434 (s, OH), 3000 (w, Ph–H), 2966 (w, CH), 1708 (vs, C=O), 1602 (w, Ph–H), 1161, 1042 (s, O–CH_3).

4.2.12. (4*R*)-Hydroxy-4-(4′-methoxyphenyl)-butan-2-one (9j). Yield: 42%; $[\alpha]_D^{16}$ +25.51 (c 0.24, in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.98–6.86 (m, 4H, Ph–H), 5.10–5.07 (m, 1H, CH), 3.80 (s, 1H, OCH_3), 3.25 (s, 1H, OH), 2.93–2.74 (m, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.2, 159.3, 152.9, 127.1, 124.1, 118.1, 114.1, 69.8, 70.0, 55.6, 52.3, 31.1; IR (KBr): ν 3414 (s, OH), 3059 (w, Ph–H), 2964 (w, CH), 1703 (vs, C=O), 1616 (w, Ph–H), 1248, 1032 (s, O–CH_3). Enantiomeric excess: 67%, determined by HPLC (Daicel chiralpak AD-H, *i*-PrOH/hexane 10:90), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=6.0 min and (*S*)-isomer, t_R=4.7 min.

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A sequential reaction process to assemble polysubstituted indolizidines, quinolizidines and quinolizidine analogues

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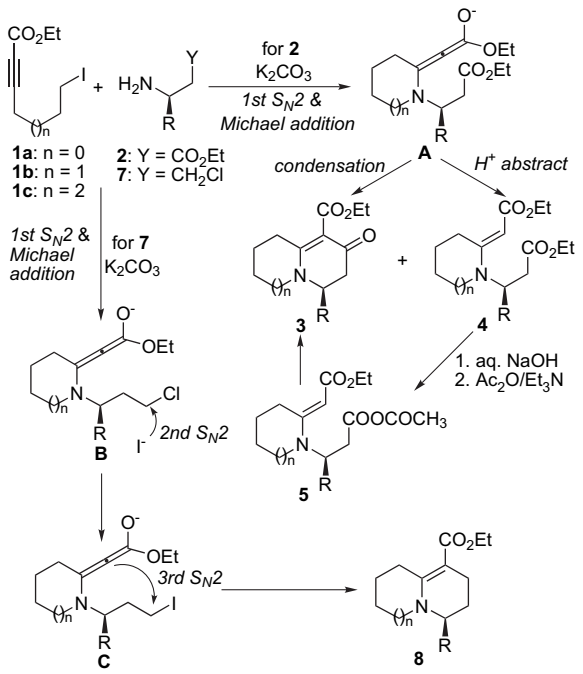
Abstract—The ω-iodo-α,β-alkynoates and their ketone, sulfone or phosphonate analogues react with δ-chloropropylamines in MeCN assisted with K_2CO_3 to undergo a sequential S_N2/Michael addition/S_N2/S_N2 reaction process, giving polysubstituted indolizidines or quinolizidines in good to excellent yields. This sequential reaction process is also compatible with three other substituted α,β-alkynoates, affording quinolizidine analogues in moderate to good yields.

1. Introduction

Fused nitrogen heterocyclic units of indolizidine and quinolizidine are found in a rather large class of alkaloids isolated from diverse natural sources and in human-made substances.[1] These compounds exhibit a considerable range of biological functions including neurological,[1–3] antiviral,[4] immunosuppressive,[5] antimalarial[6] and anti-tumor[7] activities. Because of the very limited amounts available to us from natural sources, total synthesis of natural indolizidines and quinolizidines has greatly facilitated their structural elucidation, as well as evaluation of their pharmacological profile in the past decades.[1,2] In order to assemble quickly the bicyclic skeletons of these compounds, several elegant methods have been developed and found extensive applications in the total synthesis of the targeted alkaloids.[8–13] However, more efficient protocols are still highly required to merit the increasing need for rapidly synthesizing these natural products, and their analogues for drug development and chemical biology.

During the studies aimed at synthesizing pyrrolizidine indolizidine and quinolizidine alkaloids,[14] we have developed a sequential S_N2/Michael addition/condensation reaction process[14a] to enantiopure quinolizidinones and indolizidinones **3** by refluxing enantiopure β-amino esters **2** and ω-iodo-α,β-alkynoates **1** in acetonitrile under the action of K_2CO_3 (Scheme 1). A plausible mechanism was that the amino group in a β-amino ester **2** first attacked the terminal carbon of ethyl 7-iodo-2-heptynoate **1a** or ethyl 7-iodo-2-hexynoate **1b** to form a secondary amine, which spontaneously attacked the electron-deficient triple bond to provide a heterocyclic intermediate **A**. Finally the vinylogous anion



Scheme 1.

Keywords: Sequential reaction process; Indolizidines; Quinolizidines; Michael addition, analogues.
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of **A** generated in the Michael addition step reacted with the carbonyl group of the β-amino ester **2** to give the bicyclic product **3**. Unfortunately, the efficiency of this process was greatly decreased by formation of a side product **4** through proton abstraction in intermediate **A**, although **4** could be converted into **3** through the mixed anhydrides **5**.[14a] In this article, we wish to report a new cascade process, which could deliver the desired bicyclic products exclusively in most cases.[15]

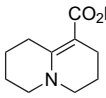
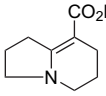
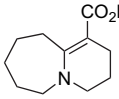
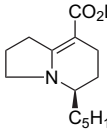
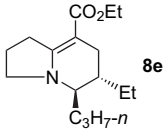
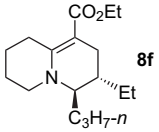
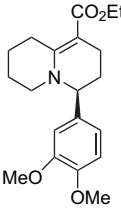
2. Results and discussion

2.1. Sequential S_N2/Michael addition/S_N2/S_N2 reaction process to indolizidines and quinolizidines

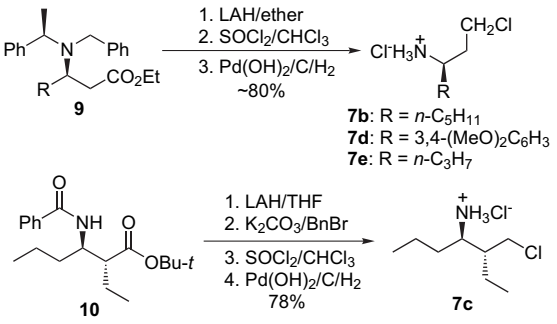
As depicted in Scheme 1, the successful transformation of **4** to **3** through the mixed anhydrides **5** implied that the lower reactivity of the ester moiety in **4** was the cause for incomplete conversion of the above sequential reaction process. One can easily think that increasing the reactivity of nucleophilic moiety of the bifunctional agents **2** would provide a cure for the above drawback. However, such substrates would probably lead to an intramolecular reaction between the amine group and this nucleophilic moiety. After careful analysis, we envisioned that if δ-amino chlorides **7** were used as the substrates, its amine group would first attack the terminal carbon of the ω-iodo-α,β-alkynoates **1** in an S_N2 reaction. Subsequently a Michael addition would occur spontaneously to form the intermediate **B** based on our previous observation.[16] At this time, the resultant iodine anion would probably undergo a halogen-exchange with the chloride, which in turn would generate a more reactive species to react with the allenolate moiety as depicted in intermediate **C**, thereby giving bicyclic products exclusively. Noteworthy is that the γ-amino chlorides have been investigated by Back and Nakajima for assembling piperidines, indolizidines and quinolizidines by reacting with acetylenic sulfones.[13e]

With the above idea in mind, a reaction of ethyl 7-iodo-2-heptynoate **1b** with 3-chloropropylamine hydrochloride **7a** was conducted in acetonitrile under the action of 3.5 equiv of K_2CO_3 and 4 Å MS. At room temperature the reaction gave only a monocyclic product **14** (see Scheme 3), which indicated that a single S_N2 and subsequent Michael reaction took place under these conditions. However, when the reaction temperature was raised to 65 °C, we were pleased to notice that indolizidine **8a** was isolated as a single product in 81% yield (Table 1, entry 1). Using acetonitrile was essential for this process because other solvents such as DMF gave relatively low yield due to formation of unidentified side products (entry 2). Further examination indicated that other iodides **1** with different length of chain also worked at different reaction temperatures to provide indolizidine **8b** (entry 3), or even a piperidinoazpine product **8c** (entry 4). Most importantly, either α-substituted or α,β-disubstituted δ-chloropropylamines was suitable for this process although higher reaction temperatures were needed (entries 5–8). Considering that these amines were readily available in enantiopure form from protected enantiopure β-amino esters **9**[17] or **10**[22c] based on the reaction sequence as outlined in Scheme 2, this method furnished an efficient protocol for synthesis of enantiopure polysubstituted indolizidines and quinolizidines.

Table 1. Reaction of ω-iodo-α,β-alkynoates **1** with δ-chloropropylamines[a]

Entry	Iodide	Amine	Temperature (°C)/time (h)	Product	Yield (%)[b]
1	**1b**	**7a**	65/36	 **8a**	81
2	**1b**	**7a**	50/24		60[c]
3	**1a**	**7a**	60/24	 **8b**	92
4	**1c**	**7a**	70/24	 **8c**	62
5	**1a**	**7b**	82/24	 **8d**	80
6	**1a**	**7c**	82/36	 **8e**	70
7	**1b**	**7c**	82/24	 **8f**	75
8	**1b**	**7d**	82/48	 **8g**	63

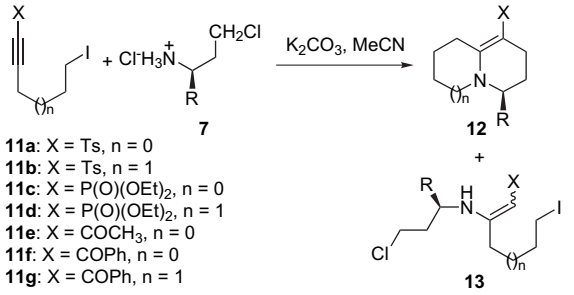
[a] Reaction conditions: **1** (0.2 mmol), **7** (0.2 mmol), K_2CO_3 (0.7 mmol) 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.
[c] Reaction was carried out in DMF.



Scheme 2.

In view of this encouraging result, other iodides **11a**–**11g** bearing different electron-withdrawing groups at the terminal of the acetylene were prepared[18] in order to further explore the scope of this process. As summarized in Table 2, it was found that reaction of tosylate **11a** or **11b** with **7** delivered corresponding indolizidines or quinolizidines **12**, but

Table 2. Reaction of iodides **11** with δ-chloropropylamines[a]



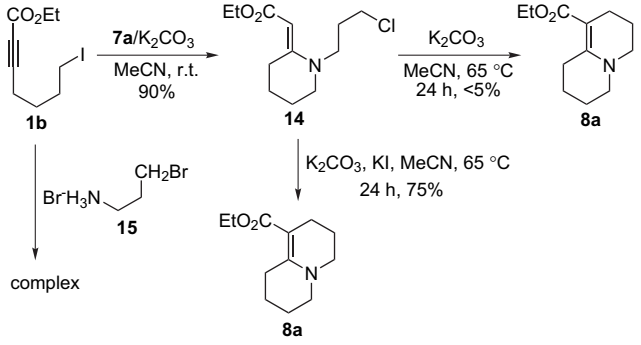
11a: X = Ts, n = 0
11b: X = Ts, n = 1
11c: X = P(O)(OEt)$_2$, n = 0
11d: X = P(O)(OEt)$_2$, n = 1
11e: X = COCH$_3$, n = 0
11f: X = COPh, n = 0
11g: X = COPh, n = 1

Entry	Iodide	Amine	Temperature (°C)/time (h)	Product	Yield (%)[b]
1	**11a**	**7a**	82/24	**12a**	87
2	**11b**	**7a**	82/18	**12b**	83
3	**11a**	**7e**	82/26	**12c**	84
4	**11c**	**7a**	82/36	**12d**	84
5	**11d**	**7a**	82/36	**12e**	77
6	**11c**	**7e**	82/48	**12f**	72
7	**11d**	**7b**	82/48	**12g**	70
8	**11e**	**7a**	30–60/24	**12h**	0 (80)[c]
9	**11f**	**7a**	30–60/24	**12i**	70 (20)[c]
10	**11g**	**7a**	30–60/24	**12j**	~10 (75)[c]
11	**11g**	**7d**	30–60/24	**12k**	55 (20)[c]

[a] Reaction conditions: **11** (0.2 mmol), **7** (0.2 mmol), K_2CO_3 (0.7 mmol), 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.
[c] Yields in parentheses are for direct Michael addition products.

refluxing temperature was required to ensure good yields (entries 1–3). Phosphonates **11c** and **11d** gave similar results under these conditions but needed longer reaction time to complete the conversion (entries 4–7). Then we moved our attention to ketone-derived iodides **11e–11g** and observed that the reaction of **11e** with **7a** only produced a direct Michael addition product **13** (entry 8). This result indicated that for **11e** the ynone moiety was the target for the first attack of the amine group, which should result from the higher electron-withdrawing ability of methyl ketone. Consequently we chose less reactive phenyl ketones as substrates and noticed that reaction of **11f** with **7a** provided the desired indolizidine **12i** in 70% yield (entry 9). In this case some direct Michael addition product was still isolated. Dramatically, when phenyl ketone **11g** was used, the reaction only gave the desired quinolizidine **12j** in less than 10% yield, together with a direct Michael addition product in 70% yield (entry 10), which illustrated that subtle change in structures of ketone substrates would greatly alter the reaction sequence. Moreover, the priority for the first nucleophilic attack site was also dependant on the nature of nucleophiles because when **11g** reacted with sterically hindered amino chloride **7d**, desired bicyclic product **12k** was obtained in 55% yield (entry 11). It is notable that for ketone substrates the reaction mixture should be heated at 30 °C for 12 h first to avoid forming more direct Michael addition products, and then 60 °C for 12 h to complete the conversion. From all the reaction results it was seen that reactivity order for this process was ketone>ester>tosylate>phosphonate, which was consistent with the order of electron-withdrawing ability for the corresponding functional groups.

As mentioned before, the reaction of iodide **1b** and δ-chloropropylamine **7a** at room temperature only gave a monocyclic product **14** (Scheme 3). This result clearly indicated that the formation of the second ring was a rate-determining step for the present process. In order to check if halogen-exchange was important for the second cyclization, controlled experiments as depicted in Scheme 3 were conducted. It was observed when **14** and K_2CO_3 were heated in acetonitrile at 65 °C for 24 h, quinolizidine **8a** was isolated in less than 5% yield. However, when catalytic amount of KI was added to this reaction system, **8a** was obtained in 75% yield. These results demonstrated that the halogen-exchange is necessary for closure of the second ring in satisfactory conversion. The additional evidence came from the fact that reaction of either **11a** or **11b** with **7** gave bicyclic products in good yields (entries 1–3, Table 2), while in a Back's report it was mentioned that addition of δ-chloropropylamines to acetylenic sulfones in several refluxed solvents did not give any cyclization products directly.[13e] On the other hand, we found that when 3-bromopropylamine hydrobromide **15** was used as the substrate, only some polar, unidentified side products and unreacted **1b** were obtained, which implied that **15** was not stable at this reaction condition. Based on these results, we concluded that both the δ-chloropropylamine substrates and the reaction sequence (S_N2/Michael addition/S_N2/S_N2) depicted in Scheme 1 are the key elements for obtaining the target molecules in high yields.



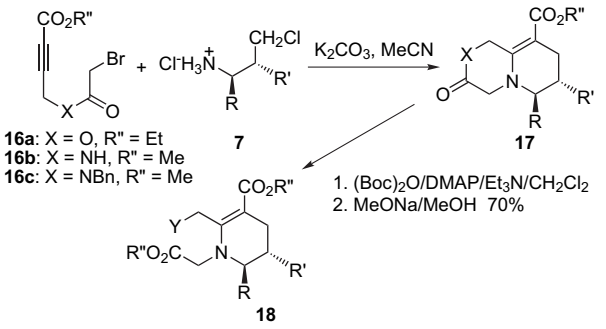
Scheme 3.

Noteworthy is that the present methodology is very useful for quickly assembling natural indolizidines and quinolizidines. For example, from products **8b**, **8d** and **12c** we could prepare tashiromine,[19] indolizidine 209B[20] and indolizidine 167B[21] following the known procedures, respectively.

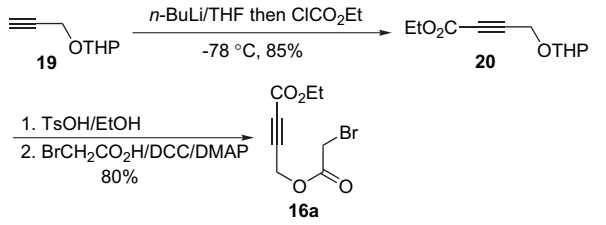
2.2. Sequential S_N2/Michael addition/S_N2/S_N2 reaction process to quinolizidine analogues

Encouraged by the above success, we decided to explore the possibility of substituted α,β-alkynoates **16** as the substrates. If they worked for the above cascade process, we would be able to obtain some quinolizidine analogues **17**. These molecules not only are of interest for further biological evaluation, but also serve as the precusors for elaborating polysubstituted piperidines **18** (Scheme 4).

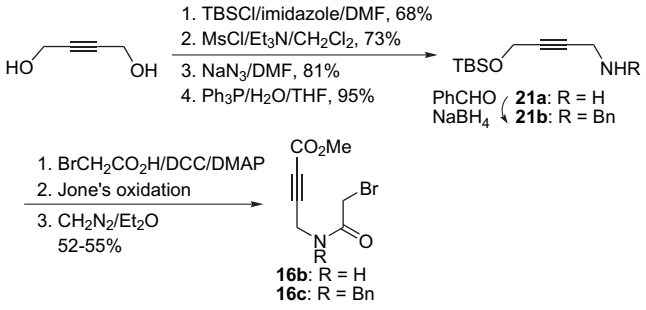
The required substrates **16** were prepared from the corresponding γ-substituted α,β-alkynoates as outline in Schemes 5 and 6. From protected propargyl alcohol **19**, ester **20** was obtained. Removal of the protecting group of **20**



Scheme 4.



Scheme 5.



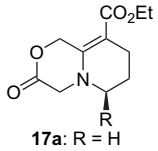
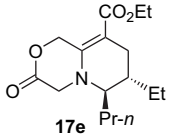
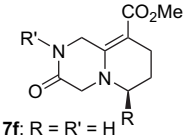
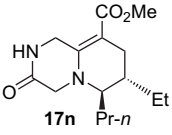
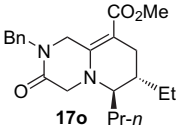
Scheme 6.

followed by coupling with bromoacetic acid provided **16a** in 80% yield.

In a parallel procedure, 2-butyn-1,4-diol was monoprotected and the left hydroxy group was converted into azide through its mesylate. This azide was reduced with triphenylphosphine and water yielded amine **21a**, which was transformed into benzyl amine **21b** via reductive amination. Coupling of amines **21** with bromoacetic acid and subsequent Jone's oxidation and esterification with diazomethane produced the desired amides **16b** and **16c**.

With the above building blocks in hand, we next explored their reaction with several δ-chloropropylamines and the results are summarized in Table 3. In all cases catalytic amount of *n*-Bu_4NI was added to facilitate all S_N2 reactions through halogen-exchange. When diester **16a** was used, its reaction with **7a** was initially carried out under our standard conditions as mentioned above. In this case low yield was observed although the desired bicyclic product **17a** was isolated (entry 1). After some experiment, we found that if a relatively weak base, $NaHCO_3$ was employed, the yield was improved (entry 2). Using these new reaction conditions some α-substituted or α,β-disubstituted δ-chloropropylamines were checked and the corresponding cyclization

Table 3. Reaction of ω-iodo-α,β-alkynoates **16** with δ-chloropropylamines[a]

Entry	Bromide	Amine	Product	Yield (%)[b]
1	**16a**	**7a**	 **17a**: R = H	22
2	**16a**	**7a**	**17a**	57
3	**16a**	**7b**	**17b**: R=*n*-C_5H_{11}	46
4	**16a**	**7d**	**17c**: R=3,4-$(MeO)_2C_6H_3$	41
5	**16a**	**7f**	**17d**: R=Me	49
6	**16a**	**7c**	 **17e** Pr-*n*	37
7	**16b**	**7a**	 **17f**: R = R' = H	74
8	**16c**	**7a**	**17g**: R=H, R′=Bn	82
9	**16b**	**7b**	**17h**: R=*n*-C_5H_{11}, R′=H	68
10	**16b**	**7d**	**17i**: R=3,4-$(MeO)_2C_6H_3$, R′=H	63
11	**16b**	**7f**	**17j**: R=Me, R′=H	71
12	**16c**	**7b**	**17k**: R=*n*-C_5H_{11}, R′=Bn	81
13	**16c**	**7d**	**17l**: R=3,4-$(MeO)_2C_6H_3$, R′=Bn	74
14	**16c**	**7f**	**17m**: R=Me, R′=Bn	78
15	**16b**	**7c**	 **17n** Pr-*n*	59
16	**16c**	**7c**	 **17o** Pr-*n*	72

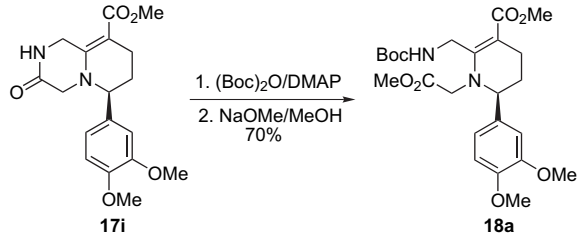
[a] Reaction conditions: **16** (0.2 mmol), **7** (0.2 mmol), Na_2CO_3 (0.7 mmol) [or $NaHCO_3$ (0.7 mmol) for entries 2–6], Bu_4NI (0.02 mmol), 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.

products were isolated in moderate yields (entries 3–6). We reasoned that unsatisfactory yields might result from the bromoacetate moiety in **16a** that was too active and some side reactions might occur. Therefore, less reactive amide **16b** was investigated. As expected, reaction of **16b** with **7a** under the action of Na_2CO_3 worked well, giving **17f** in 74% yield. Using *N*-benzyl amide **16c**, better yield was observed (entry 8).

Further studies revealed that reactions of **16b** and **16c** with some α-substituted (entries 9–14) or α,β-disubstituted (entries 15 and 16) δ-chloropropylamines all proceeded smoothly, delivering the corresponding quinolizidine analogues in good yields. These results indicated that the α-substitutents or α,β-disubstitutents only slightly alter the cascade process, and this process is reliable for elaborating polysubstituted quinolizidine analogues in reasonable diversity.

We next attempted to assemble polysubstituted piperidines using our bicyclic products. Accordingly, treatment of **17i**

with di-*tert*-butyl dicarbonate in the presence of DMAP provided a carbamate. Ring opening of this intermediate with sodium methoxide in methanol afforded tetrasubstituted piperidine **18a** in 70% overall yield (Scheme 7). Obviously, other related bicyclic products **17f**, **17h**, **17j** and **17n** could be converted into corresponding piperidines in the same procedure. Thus, combination of our cascade process and ring-opening transformation gave a facile protocol for elaboration of polysubstituted piperidines.[22]



Scheme 7.

3. Conclusions

In conclusion, we have demonstrated here a sequential S_N2/Michael addition/S_N2/S_N2 reaction process, which allows effectively assembling polysubstituted indolizidines, or quinolizidines and their analogues with a great diversity. This process should find further application in the total synthesis of natural products and designed molecules for biological evaluation.

4. Experimental

4.1. (*R*)-1-Chloro-3-octylamine hydrochloride salt (7b)

To a stirred suspension of LAH (544 mg, 14.3 mmol) in dry diethyl ether (40 mL) was added dropwise β-amino ester **9b** (5.5 g, 14.3 mmol) in dry diethyl ether (40 mL) at 0 °C. After the reaction mixture was stirred at 20 °C for 1 h, water (0.57 mL), 15% NaOH (0.57 mL) and more water (1.71 mL) was added successively. Stirring was continued until a white precipitate formed, then it was filtered through Celite, and the filtrate was dried over $MgSO_4$, concentrated and purified via chromatography to give 4.85 g (100%) of amino alcohol as a viscous oil. $[\alpha]_D^{20}$ −38.9 (*c* 1.1, $CHCl_3$); IR (film) 2931, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.20 (m, 10H), 3.95 (t, *J*=6.9 Hz, 1H), 3.85 (d, *J*=13.7 Hz, 1H), 3.68 (d, *J*=13.7 Hz, 1H), 3.52–3.46 (m, 1H), 3.22–3.15 (m, 1H), 2.80–2.76 (m, 2H), 1.71–1.67 (m, 1H), 1.57–1.50 (m, 1H), 1.46–1.26 (m, 11H), 0.91 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 140.7, 129.1, 128.4, 128.1, 128.0, 126.9, 61.9, 56.6, 55.2, 49.8, 33.7, 32.6, 32.2, 27.4, 22.7, 14.9, 14.1; HRMS calcd for $C_{23}H_{34}NO$ 340.2635 $(M+H)^+$, found 340.2624.

To a stirred solution of the above amino alcohol (339 mg, 5.5 mmol) in $CHCl_3$ (15 mL) was slowly added a solution of $SOCl_2$ (0.8 mL, 10.9 mmol) in $CHCl_3$ (3 mL) at 0 °C. The reaction mixture was refluxed for 1 h, and then evaporated. The residue was dissolved directly in methanol (40 mL), and hydrogenated over 20% $Pd(OH)_2$ (400 mg) under 50 atm hydrogen atmosphere at 30 °C for 48 h. The reaction mixture was filtered off, and the filtrate was concentrated in vacuum to afford 0.9 g (85%) of crude **7b** as a light yellow solid, which was directly used due to its instability. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.49–8.47 (m, 3H), 3.86–3.82 (m, 1H), 3.75–3.69 (m, 1H), 3.52–3.48 (m, 1H), 2.2–2.24 (m, 1H), 2.17–2.13 (m, 1H), 1.82–1.29 (m, 8H), 0.91 (t, *J*=6.6 Hz, 3H).

4.2. General procedure for reaction of ω-iodo-α,β-alkynoates 1 with δ-chloropropylamines (7)

A mixture of **1** (0.22 mmol), **7** (0.23 mmol), anhydrous K_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared as monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:10 to 1:1 ethyl acetate/petroleum ether to afford **8**.

4.2.1. 3,4,6,7,8,9-Hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8a).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, *J*=7.2 Hz, 2H), 3.13–3.06 (m, 4H), 3.01 (t, *J*=6.4 Hz, 2H), 2.38 (t, *J*=12.9 Hz, 2H), 1.80–1.73 (m, 4H), 1.63–1.59 (m, 2H), 1.24 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 209 $(M)^+$.

4.2.2. 1,2,3,5,6,7-Hexahydroindolizine-8-carboxylic acid ethyl ester (8b).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.28 (t, *J*=7.1 Hz, 2H), 3.14 (t, *J*=5.8 Hz, 2H), 3.05 (t, *J*=7.8 Hz, 2H), 2.35 (t, *J*=6.5 Hz, 2H), 1.94–1.81 (m, 4H), 1.25 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 195 $(M)^+$.

4.2.3. 2,3,4,6,7,8,9,10-Octahydropyrido[1,2-*a*]azepine-1-carboxylic acid ethyl ester (8c).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, *J*=7.2 Hz, 2H), 3.37–3.34 (m, 2H), 3.21 (t, *J*=5.8 Hz, 2H), 3.15 (t, *J*=4.7 Hz, 2H), 2.37 (t, *J*=6.3 Hz, 2H), 1.81–1.77 (m, 2H), 1.65–1.57 (m, 6H), 1.25 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 223 $(M)^+$.

4.2.4. (2*R*)-3,4,6,7,8,9-Hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8d). $[\alpha]_D^{30}$ −1.05 (*c* 1.2, EtOH); IR (film) 2932, 1680, 1593, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.51 (dt, *J*=9.3, 7.0 Hz, 1H), 3.24–3.14 (m, 2H), 3.10–3.04 (m, 2H), 2.44 (dt, *J*=15.8, 5.1 Hz, 1H), 2.27–2.16 (m, 1H), 1.97–1.85 (m, 2H), 1.86–1.75 (m, 2H), 1.68–1.55 (m, 2H), 1.38–1.23 (m, 1H), 0.89 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{16}H_{29}NO_2$ 266.2115, found 266.2119.

4.2.5. (2*R*,3*S*)-6-Ethyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid ethyl ester (8e). $[\alpha]_D^{17}$ −26.3 (*c* 0.75, $CHCl_3$); IR (film) 1678, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.56 (dt, *J*=9.3, 7.1 Hz, 1H), 3.24–3.17 (m, 1H), 3.09–3.01 (m, 3H), 2.39–2.19 (m, 2H), 1.97–1.86 (m, 2H), 1.65 (m, 1H), 1.53 (m, 1H), 1.40–1.23 (m, 6H), 1.17–1.10 (m, 2H), 0.95–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 157.2, 84.6, 58.3, 58.0, 52.4, 35.4, 34.7, 32.7, 25.3, 22.3, 21.2, 19.2, 14.8, 14.1, 12.0; MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{16}H_{28}NO_2$ 266.2115 $(M+H)^+$, found 266.2113.

4.2.6. (2*R*,3*S*)-3-Ethyl-4-propyl-3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8f). $[\alpha]_D^{18}$ −139.2 (*c* 0.5, $CHCl_3$); IR (film) 1730, 1673, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, *J*=7.0 Hz, 2H), 3.35–3.10 (m, 3H), 2.90–2.81 (m, 2H), 2.37–2.23 (m, 2H), 1.74–1.64 (m, 3H), 1.57–1.52 (m, 4H), 1.34–1.16 (m, 7H), 0.94–0.88 (m, 6H); MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{17}H_{30}NO_2$ 280.2271 $(M+H)^+$, found 280.2277.

4.2.7. (2*S*)-4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8g). $[\alpha]_D^{19}$ +44.3 (*c* 1.4, $CHCl_3$); IR (film) 2939, 1669, 1549 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.83–6.81 (m, 1H), 6.72–6.69 (m, 2H), 4.20 (br s, 1H), 4.11–4.06 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.21–3.15 (m, 4H), 2.57–2.45 (m, 1H), 2.10–1.69 (m, 7H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 156.4, 148.9, 147.9, 135.1, 118.3, 111.0, 109.3, 91.5, 62.9, 58.5, 55.9, 55.8, 49.6, 28.6, 27.6, 23.4, 20.4, 19.2, 14.7; ESI-MS *m*/*z* 346 $(M+H)^+$; HRMS calcd for $C_{20}H_{28}NO_4$ 346.2013 $(M+H)^+$, found 346.2013.

4.2.8. 1-(6-Iodohex-1-yne-1-sulfonyl)-4-methylbenzene (11b). A mixture of selenosulfonate (3.4 g, 10.8 mmol), 5-hexyn-1-ol (1.05 g, 10.8 mmol) and AIBN (80 mg) was refluxed in chloroform (100 mL) under an argon atmosphere for 24 h. The solvent was evaporated on vacuum, and the residue was chromatographed to give the addition product, which was dissolved in dichloromethane (30 mL) and *n*-hexane (180 mL). With vigorous stirring, *m*-CPBA (70%, 2.52 g) was added in small portions at room temperature. After 10 min, a white precipitate formed, which was filtered and washed with diethyl ether, and then dried on vacuum. The white solid was suspended in chloroform (100 mL) and refluxed for 3 h. The solvent was removed, and the residue was purified via chromatograph to afford 1.5 g (57%) of alcohol. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.37 (d, *J*=8.6 Hz, 2H), 3.64 (t, *J*=5.8 Hz, 2H), 2.47 (s, 3H), 2.44–2.40 (m, 2H), 1.67–1.62 (m, 4H); MS *m*/*z* 252 $(M)^+$; HRMS calcd for $C_{13}H_{16}O_3S$ 252.0820 $(M)^+$, found 252.0808.

To a solution of the above alcohol (0.58 g, 2.3 mmol) and Et_3N (0.5 mL, 3.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (0.22 mL, 2.8 mmol). The reaction mixture was stirred at room temperature for 1 h, and then quenched with methanol (0.2 mL). The mixture was washed with water and brine, dried over Na_2SO_4 and evaporated to give the crude product, which was dissolved in acetone (25 mL). Sodium iodide (0.82 g, 5.4 mmol) was added, and the reaction mixture was stirred in dark for 72 h. The solvent was removed, and the residue was diluted with dichloromethane, washed with saturated $Na_2S_2O_3$ and dried over Na_2SO_4. The organic phase was concentrated and the residue was chromatographed to give 0.7 g (84%) of **11b** as a viscous oil. IR (film) 2935, 1596, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.39–7.37 (m, 2H), 3.15 (t, *J*=6.7 Hz, 2H), 2.47 (s, 3H), 2.40 (t, *J*=6.8 Hz, 2H), 1.88–1.81 (m, 2H), 1.73–1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3, 140.0, 130.0, 127.3, 95.9, 32.1, 27.7, 21.8, 18.0, 5.1; MS *m*/*z* 362 $(M)^+$; HRMS calcd for $C_{13}H_{15}O_2SI$ 361.9838 $(M)^+$, found 361.9859.

4.2.9. 1-(5-Iodopent-1-yne-1-sulfonyl)-4-methylbenzene (11a). Following a similar procedure from 5-hexyn-1-ol to **11b**, **11a** was prepared from 4-pentyn-1-ol in 48% yield. IR (film) 2203, 1596, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 3.19 (t, *J*=7.2 Hz, 2H), 2.53 (t, *J*=7.5 Hz, 2H), 2.47 (s, 3H), 2.08–1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 138.8, 130.0, 127.3, 94.7, 79.3, 30.4, 21.8, 20.1, 4.0; MS *m*/*z* 348 $(M)^+$; ESI-HRMS calcd for $C_{12}H_{13}O_2SINa$ 370.9573 $(M+Na)^+$, found 370.9592.

4.2.10. (5-Iodopent-1-ynyl)phosphonic acid diethyl ester (11c). To a solution of 2-(4-pentyn-1-oxy)tetrahydrofuran (0.74 g, 4.4 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 2.8 mL, 4.9 mmol) dropwise at −78 °C under an argon atmosphere. The resultant solution was stirred for 30 min, and then diethylchlorophosphate (0.7 mL, 4.8 mmol) in THF (5 mL) was added slowly. After the reaction mixture was stirred for a further 1 h at −78 °C, it was quenched with brine, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in methanol (50 mL) before 20 mg of *p*-TsOH was added. After the reaction mixture was stirred at room temperature for 24 h, it was concentrated in vacuo. The residue was purified by chromatography to give 0.87 g (90%) of phosphonate as a viscous oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.10 (m, 4H), 3.79–3.73 (m, 2H), 2.54–2.47 (m, 2H), 1.89–1.81 (m, 2H), 1.36–1.33 (m, 6H); MS *m*/*z* 220 $(M)^+$; HRMS calcd for $C_9H_{17}O_4P$ 220.0865 $(M)^+$, found 220.0871.

To a solution of the above phosphonate (0.51 g, 2.3 mmol) and Et_3N (0.5 mL, 3.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (0.22 mL, 2.8 mmol). The reaction mixture was stirred at room temperature for 1 h before 0.2 mL of MeOH was added to quench the reaction. The mixture was washed with water and brine, dried over Na_2SO_4 and evaporated to give the crude product, which was dissolved in acetone (25 mL). After sodium iodide (0.82 g, 5.4 mmol) was added, the reaction mixture was stirred in dark for 72 h. The solvent was removed, and the residue was diluted with dichloromethane, washed with saturated $Na_2S_2O_3$ and dried over Na_2SO_4. The organic phase was concentrated and the residue was chromatographed to give 0.68 g (90%) of **11c** as a viscous oil. IR (film) 2208, 1259, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.11 (m, 4H), 3.29 (t, *J*=6.6 Hz, 2H), 2.55–2.49 (m, 2H), 2.11–2.02 (m, 2H), 1.38 (t, *J*=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 100.7, 100.0, 63.0, 62.9, 20.2, 20.1, 16.1, 16.0, 4.1; MS *m*/*z* 330 $(M)^+$; HRMS calcd for $C_9H_{16}O_3PI$ 329.9882 $(M)^+$, found 329.9904.

4.2.11. (6-Iodohex-1-ynyl)phosphonic acid diethyl ester (11d). Following a similar procedure from 2-(4-pentyn-1-oxy)tetrahydrofuran to **11c**, **11d** was prepared in 78% yield from 2-(5-hexyn-1-oxy)tetrahydrofuran. IR (film) 2985, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.11 (m, 4H), 3.21 (t, *J*=6.6 Hz, 2H), 2.43–2.37 (m, 2H), 1.97–1.92 (m, 2H), 1.75–1.70 (m, 2H), 1.40–1.35 (m, 6H); MS *m*/*z* 344 $(M)^+$; ESI-HRMS calcd for $C_{10}H_{19}O_3PI$ 345.0111 $(M+H)^+$, found 345.0099.

4.2.12. 6-Iodo-1-phenylhex-2-yn-1-one (11f). To a stirred solution of 2-(4-pentyn-1-oxy)tetrahydrofuran (1.51 g, 9.0 mmol) in dry THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 6.2 mL, 10.0 mmol) at −78 °C. The reaction mixture was stirred for 30 min, and then a solution of PhCHO (1.1 mL, 10.8 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred for a further 30 min before saturated NH_4Cl was added at −78 °C to quench the reaction. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and purified via chromatograph to give 2.33 g (95%) of the desired alcohol.

To a solution of oxalyl chloride (1.54 mL, 18.0 mmol) in dichloromethane (40 mL) was added methyl sulfoxide (1.9 mL, 20.9 mmol) in dichloromethane (6 mL) at −78 °C. After 15 min, a solution of the above alcohol (2.33 g, 8.57 mmol) in dichloromethane (15 mL) was added slowly. After the solution was stirred for a further 15 min at −78 °C, triethylamine (6.2 mL) was added dropwise. The reaction mixture was warmed to room temperature, and stirring was continued for 30 min. After saturated $NaHCO_3$ was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, evaporated and purified via chromatograph to give 2.1 g (90%) of ketone.

A solution of the above ketone (2.1 g, 7.72 mmol) and *p*-TsOH (10 mg) in MeOH (30 mL) and water (1.5 mL) was stirred at room temperature for 24 h. The solvent was removed under vacuum, and the residue was dissolved in ethyl acetate, washed with brine and dried over Na_2SO_4. Evaporation on vacuum followed by chromatography afforded 1.2 g (83%) of alcohol, which was converted to iodide **11f** through its mesylate in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15–8.12 (m, 2H), 7.62–7.59 (m, 1H), 7.52–7.47 (m, 2H), 3.36 (t, J=6.5 Hz, 2H), 2.69 (t, J=6.8 Hz, 2H), 2.19–2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.0, 134.1, 129.6, 128.6, 93.9, 80.4, 31.1, 20.3, 4.6; MS *m*/*z* 298 $(M)^+$.

4.2.13. 7-Iodo-1-phenylhept-2-yn-1-one (11g). Following a similar procedure from 2-(4-pentyn-1-oxy)tetrahydrofuran to **11b**, **11g** was prepared in 63% overall yield from 2-(5-hexyn-1-oxy)tetrahydrofuran. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16–8.12 (m, 2H), 7.65–7.60 (m, 1H), 7.52–7.47 (m, 2H), 3.25 (t, J=6.6 Hz, 2H), 2.56 (t, J=7.1 Hz, 2H), 2.07–1.98 (m, 2H), 1.86–1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 136.8, 134.0, 129.6, 128.6, 95.4, 80.1, 32.4, 28.5, 18.3, 5.6; ESI-HRMS calcd for $C_{13}H_{14}O_6I$ 313.0084 $(M+H)^+$, found 313.0083.

4.3. General procedure for reaction of iodides 11 with δ-chloropropylamines (7)

A mixture of **11** (0.22 mmol), **7** (0.23 mmol), anhydrous K_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared as monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:1 to 1:10 ethyl acetate/petroleum ether to afford **12**.

4.3.1. 8-(Toluene-4-sulfonyl)-1,2,3,5,6,7-hexahydroindolizine (12a). IR (film) 2847, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.68 (m, 2H), 7.28–7.23 (m, 2H), 3.28 (t, J=7.2 Hz, 2H), 3.14–3.09 (m, 4H), 2.40 (s. 3H), 2.33 (t, J=6.0 Hz, 2H), 1.98–1.88 (m, 2H), 1.86–1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 142.2, 129.7, 126.6, 93.0, 53.3, 45.0, 31.6, 22.5, 21.8, 21.7, 21.3; MS *m*/*z* 277 $(M)^+$; HRMS calcd for $C_{15}H_{19}NSO_2$ 277.1180 $(M)^+$, found 277.1158.

4.3.2. 9-(Toluene-4-sulfonyl)-1,3,4,6,7,8-hexahydro-2*H*-quinolizine (12b). IR (film) 2948, 1558, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.68 (m, 2H), 7.27–7.24 (m, 2H), 3.12–3.04 (m, 4H), 2.84 (t, J=6.5 Hz, 2H), 2.53 (t, J=6.2 Hz, 2H), 2.40 (s, 3H), 1.83–1.77 (m, 2H), 1.74–1.68 (m, 2H), 1.60–1.55 (m, 2H); MS *m*/*z* 291 $(M)^+$; HRMS calcd for $C_{16}H_{21}NSO_2$ 291.1315 $(M)^+$, found 291.1304.

4.3.3. (5*R*)-5-Propyl-8-(toluene-4-sulfonyl)-1,2,3,5,6,7-hexahydroindolizine (12c). $[\alpha]_D^{19}$ +3.0 (*c* 1.1, $CHCl_3$); IR (film) 2956, 1596, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J=8.5 Hz, 2H), 7.27–7.23 (m, 3H), 3.51 (dt, J=9.6, 6.9 Hz, 1H), 3.23–3.08 (m, 4H), 2.43 (s, 3H), 2.38–2.25 (m, 2H), 1.91 (q, J=7.3 Hz, 2H), 1.80–1.74 (m, 1H), 1.65–1.50 (m, 1H), 1.39–1.20 (m, 4H), 0.91 (t, J=6.8 Hz, 3H); MS *m*/*z* 319 $(M)^+$; HRMS calcd for $C_{18}H_{26}NSO_2Na^+$ 320.1679 $(M+Na)^+$, found 320.1682.

4.3.4. (1,2,3,5,6,7-Hexahydroindolizin-8-yl)phosphonic acid diethyl ester (12d). IR (film) 2979, 1610, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04–3.90 (m, 4H), 3.22 (t, J=6.9 Hz, 2H), 3.15 (t, J=5.8 Hz, 2H), 2.90 (t, J=7.4 Hz, 2H), 2.18 (q, J=6.1 Hz, 2H), 1.92–1.81 (m, 4H), 1.29 (t, J=7.2 Hz, 6H); MS *m*/*z* 259 $(M)^+$; HRMS calcd for $C_{12}H_{23}NPO_3$ 260.1410 $(M+H)^+$, found 260.1415.

4.3.5. (3,4,6,7,8,9-Hexahydro-2*H*-quinolizin-1-yl)phosphonic acid diethyl ester (12e). IR (film) 2939, 1577, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06–3.96 (m, 4H), 3.07–3.01 (m, 4H), 2.80 (br s, 2H), 2.27–2.21 (m, 2H), 1.85–1.73 (m, 4H), 1.64–1.58 (m, 2H), 1.34–1.28 (m, 6H); MS *m*/*z* 273 $(M)^+$; HRMS calcd for $C_{13}H_{25}NPO_3$ 274.1567 $(M+H)^+$, found 274.1565.

4.3.6. (5*R*)-(5-Propyl-1,2,3,5,6,7-hexahydroindolizin-8-yl)phosphonic acid diethyl ester (12f). $[\alpha]_D^{18}$ +2.4 (*c* 1.0, $CHCl_3$); IR (film) 2962, 1707, 1606, 1292 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04–3.91 (m, 4H), 3.47 (dt, J=9.1, 6.5 Hz, 1H), 3.27–3.20 (m, 1H), 3.12 (dt, J=8.7, 6.9 Hz, 1H), 2.94–2.88 (m, 2H), 2.17–2.07 (m, 2H), 1.92–1.82 (m, 2H), 1.75–1.54 (m, 2H), 1.37–1.25 (m, 10H), 0.96–0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.4, 60.3, 53.7, 51.1, 34.9, 31.7, 25.0, 24.9, 21.4, 19.6, 19.4, 19.0, 16.5, 16.4, 14.2; MS *m*/*z* 301 $(M)^+$; HRMS calcd for $C_{15}H_{29}NPO_3$ 302.1880 $(M+H)^+$, found 302.1886.

4.3.7. (4*R*)-(4-Pentyl-3,4,6,7,8,9-hexahydro-2*H*-quinolizin-1-yl)phosphonic acid diethyl ester (12g). $[\alpha]_D^{19}$ −26.1 (*c* 0.53, $CHCl_3$); IR (film) 2926, 1577, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03–3.93 (m, 4H), 3.21–3.15 (m, 1H), 3.09–3.03 (m, 1H), 3.01–2.99 (m, 1H), 2.92–2.84

(m, 1H), 2.68–2.61 (m, 1H), 2.28–2.08 (m, 2H), 1.79–1.47 (m, 6H), 1.36–1.25 (m, 14H), 0.89 (t, J=6.8 Hz, 3H); MS m/z 343 $(M)^+$; HRMS calcd for $C_{18}H_{35}NPO_3$ 344.2349 $(M+H)^+$, found 344.2348.

4.3.8. (1,2,3,5,6,7-Hexahydroindolizin-8-yl)phenylmethanone (12i). IR (film) 2926, 1531, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.32 (m, 5H), 3.40–3.36 (m, 2H), 3.28–3.24 (m, 2H), 2.79 (t, J=7.8 Hz, 2H), 2.46 (t, J=6.0 Hz, 2H), 1.92–1.82 (m, 4H); ESI-MS m/z 228 $(M+H)^+$; HRMS calcd for $C_{15}H_{18}NO$ 228.1383 $(M+H)^+$, found 228.1389.

4.3.9. (2*S*)-[4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2*H*-quinolizin-1-yl]-phenylmethanone 12k. $[\alpha]_D^{21}$ +144.9 (c 1.2, $CHCl_3$); IR (film) 2933, 1712, 1595, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.46 (m, 2H), 7.40–7.30 (m, 3H), 6.89–6.86 (m, 1H), 6.79–6.74 (m, 2H), 4.29 (t, J=3.9 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.29–3.00 (m, 4H), 2.32–2.19 (m, 2H), 2.03–1.96 (m, 1H), 1.88–1.64 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 158.6, 149.1, 148.2, 143.9, 135.0, 129.3 (2C), 127.9 (2C), 127.6 (2C), 118.4, 111.1, 109.3, 102.5, 63.5, 55.9, 49.5, 29.4, 28.8, 23.2, 22.6, 20.4; ESI-HRMS calcd for $C_{24}H_{28}NO_3$ 378.2070 $(M+H)^+$, found 378.2064.

4.3.10. [1-(3-Chloropropyl)piperidin-2-ylidene]acetic acid ethyl ester (14). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.56 (s, 1H), 4.06 (q, J=7.2 Hz, 2H), 3.58 (t, J=12.3 Hz, 2H), 3.35 (t, J=14.4 Hz, 2H), 3.26 (t, J=12.3 Hz, 2H), 3.10 (t, J=12.9 Hz, 2H), 2.11–2.06 (m, 2H), 1.80–1.74 (m, 2H), 1.66–1.62 (m, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 161.8, 82.0, 58.2, 50.4, 49.2, 42.5, 28.2, 26.5, 23.3, 19.5, 14.7; ESI-MS m/z 246 $(M+H)^+$; ESI-HRMS calcd for $C_{12}H_{21}NO_2Cl$ 246.1255 $(M+H)^+$, found 246.1257.

4.3.11. Ethyl 4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-ynoate (20). To a stirred solution of **19** (4.36 g, 31.2 mmol) in dry ethyl ether (100 mL) at −78 °C under N_2 atmosphere was added dropwise *n*-butyllithium (1.6 M in hexane, 20.0 mL, 32.0 mmol). The resultant solution was stirred for 30 min, and ethyl chloroformate (4.5 mL, 47.1 mmol) was added dropwise. The solution was stirred for 30 min and the solution was warmed to room temperature before it was quenched with saturated NH_4Cl. The separated organic layer was washed with brine and water, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/20 ethyl acetate/petroleum ether to give 5.62 g of **20** in 85% yield. IR (film) 2946, 2241, 1718, 1254, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (m, 1H), 4.25 (m, 2H), 4.18 (m, 1H), 3.82 (m, 1H), 3.52 (m, 1H), 2.41 (m, 1H), 1.77–1.42 (m, 6H), 1.29 (m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 144.1, 96.8, 79.8, 73.9, 67.7, 62.0, 54.0, 30.2, 25.3, 19.0, 18.9; MS m/z 212.2 $(M)^+$.

4.3.12. Ethyl 4-(2-bromoacetoxy)but-2-ynoate (16a). To a solution of **20** (2.55 g, 12.0 mmol) in ethanol (20 mL) was added TsOH (0.23 g, 1.20 mmol). The resultant solution was stirred overnight and concentrated to remove the solvent. The residue was diluted with dichloromethane and washed with saturated $NaHCO_3$, brine and water sequentially. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 1.39 g of alcohol, which was dissolved in dry CH_2Cl_2 (15 mL). To this solution were added bromoacetic acid (1.81 g, 13.0 mmol), DMAP (0.14 g, 1.10 mmol) and DCC (2.68 g, 13.0 mmol) sequentially. The resultant mixture was stirred for 3 h before it was filtered and concentrated in vacuo. The residue was purified by chromatography eluting with 1/10 ethyl acetate/petroleum ether to give 2.29 g of **16a** (80% yield for two steps). IR (film) 2987, 2252, 1752, 1716, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (s, 2H), 4.27 (q, J=6.9 Hz, 2H), 3.91 (s, 2H), 1.33 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.6, 79.5, 78.7, 62.4, 52.8, 24.8, 13.9; MS m/z 248.2 $(M)^+$.

4.3.13. *N*-Benzyl-4-(*tert*-butyldimethylsilyloxy)but-2-yn-1-amine (21b). To a stirred solution of 2-butyne-1,4-diol (17.22 g, 0.20 mol) in DMF (200 mL) were added imidazole (20.42 g, 0.30 mol) and *tert*-butyldimethylsilyl chloride (36.02 g, 0.24 mol). The resultant solution was stirred for 24 h, and then quenched with methanol (25 mL) and water (200 mL). The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 27.19 g of silyl ether in 68% yield.

To a solution of the above silyl ether (19.10 g, 98.5 mmol) in dry CH_2Cl_2 (150 mL) were added Et_3N (19.2 mL, 138 mmol) and MsCl (9.2 mL, 118 mmol) successively at 0 °C under nitrogen atmosphere. The resultant solution was stirred overnight, and then washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 19.30 g of mesylate in 73% yield.

To a stirred solution of above mesylate (8.80 g, 31.7 mmol) in DMF (50 mL) was added NaN_3 (2.47 g, 38.0 mmol) and stirred for 2 h, and then quenched with water (200 mL). The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/20 ethyl acetate/petroleum ether to give 5.78 g of azide in 81% yield.

A solution of above azide (5.78 g, 25.7 mmol), Ph_3P (7.41 g, 28.3 mmol) and water (0.70 mL, 38.9 mmol) in THF (100 mL) was stirred for 2 days at room temperature. After the solution was concentrated in vacuo, the residual oil was purified by chromatography eluting with ethyl acetate to give 4.86 g of **21a** in 95% yield.

A mixture of **21a** (0.85 g, 4.27 mmol) and PhCHO (0.44 g, 4.33 mmol) in ethanol (20 mL) was stirred for 3 h before $NaBH_4$ (0.24 g, 6.39 mmol) was added. After the resultant solution was refluxed for 3 h, it was concentrated and then diluted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/4 ethyl acetate/petroleum ether to give 0.55 g of **21b** in 45% yield. IR (film) 2930, 2858, 1472, 1255,

1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.36 (t, J=1.8 Hz, 2H), 3.90 (s, 3H), 3.46 (t, J=1.8 Hz, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.57, 128.41, 128.39, 127.10, 82.91, 82.12, 52.43, 51.86, 37.75, 25.86, 18.34, −5.11; ESI-MS *m/z* 290.2 $(M-H)^+$; HRMS calcd for $C_{17}H_{28}NOSi$ 290.1935 $(M+H)^+$, found 290.1945.

4.3.14. Methyl 4-(2-bromoacetamido)but-2-ynoate (16b). A solution of **21a** (8.1 g, 29.3 mmol), bromoacetic acid (4.07 g, 29.3 mmol), DMAP (0.30 g, 2.44 mmol) and DCC (6.03 g, 29.3 mmol) in 100 mL of CH_2Cl_2 was stirred for 3 h before it was filtered and concentrated in vacuo. The residue was purified by chromatography eluting with 1/4 ethyl acetate/petroleum ether to give 7.42 g of amide in 95% yield.

To a stirred solution of above amide (1.04 g, 3.25 mmol) in acetone (20 mL) was added Jone's reagent (5.0 mL) at −10 °C for 2 h. The resultant solution was warmed to room temperature and stirred for 4 h. After the solution was diluted with water (100 mL), it was extracted with ethyl ether. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give crude acid. The crude acid was dissolved in ethyl ether and a solution of CH_2N_2 in ethyl ether was added at 0 °C. After it was stirred for 0.5 h, the solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/2 ethyl acetate/petroleum ether to give 0.41 g of **16b** in 54% yield. IR (film) 3300, 2247, 1717, 1668, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J=5.7 Hz, 2H), 3.92 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 153.4, 82.3, 75.3, 52.9, 29.8, 28.4; MS *m/z* 234.0 $(M+H)^+$; HRMS calcd for $C_7H_9BrNO_3$ 232.9688 $(M+H)^+$, found 232.9685.

4.3.15. Methyl 4-(*N*-benzyl-2-bromoacetamido)but-2-ynoate (16c). Following the same procedure from **21b** to **16b**, **16c** was prepared from **21c** in 52% yield. IR (film) 2955, 2242, 1716, 1656, 1436, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.72 (d, J=7.8 Hz, 2H), 4.33 (s, 1H), 4.18 (s, 1H), 3.97 (s, 1H), 3.93 (s, 1H), 3.79 (d, J=8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 134.7, 129.3, 129.2, 128.9, 128.4, 82.0, 75.8, 52.8, 51.5, 34.7, 25.7; ESI-MS 324.0 $(M+H)^+$; HRMS calcd for $C_{14}H_{14}BrNO_3$ 323.0157 $(M)^+$, found 323.0157.

4.4. General procedure for reaction of iodides 16 with δ-chloropropylamines (7)

A mixture of **16** (0.22 mmol), **7** (0.23 mmol), anhydrous $NaHCO_3$ (0.7 mmol) or Na_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:0 to 1:10 ethyl acetate/petroleum ether to afford **17**.

4.4.1. 3-Oxo-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17a). IR (film) 3426, 1737, 1656, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.90 (s, 2H), 3.19 (t, J=5.4 Hz, 2H), 2.42 (t, J=6.0 Hz, 2H), 1.91 (m, 2H), 1.27 (t, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.7, 147.0, 95.4, 66.3, 59.5, 50.9, 49.2, 22.2, 20.9, 14.5; ESI-MS 226.15 $(M+H)^+$; HRMS calcd for $C_{11}H_{15}NO_4Na$ 248.0893 $(M+Na)^+$, found 248.0884.

4.4.2. (*R*)-3-Oxo-6-pentyl-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17b). $[\alpha]_D^{20}$ +0.81 (*c* 0.64, $CHCl_3$); IR (film) 2932, 1770, 1677, 1592, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, J=15.6 Hz, 1H), 5.51 (d, J=15.6 Hz, 1H), 4.13 (q, J=6.9 Hz, 2H), 4.00 (d, J=16.8 Hz, 1H), 3.89 (d, J=16.8 Hz, 1H), 3.18 (m, 1H), 2.54 (m, 1H), 2.21 (m, 1H), 1.68 (m, 1H), 1.51–1.26 (m, 8H), 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.7, 145.7, 94.5, 66.0, 59.5, 58.1, 50.4, 31.7, 31.2, 25.3, 23.2, 22.5, 18.4, 14.5, 13.9; ESI-MS 296.1 $(M+H)^+$.

4.4.3. (*S*)-6-(3,4-Dimethoxyphenyl)-3-oxo-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17c). $[\alpha]_D^{20}$ +48.8 (*c* 0.83, $CHCl_3$); IR (film) 2932, 1768, 1675, 1597, 1517, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J=8.1 Hz, 1H), 6.69–6.63 (m, 2H), 5.80 (d, J=16.2 Hz, 1H), 5.63 (d, J=15.6 Hz, 1H), 4.27 (m, 1H), 4.15 (q, J=6.9 Hz, 2H), 3.92 (s, 3H), 3.88 (m, 3H), 3.90 (d, J=16.8 Hz, 1H), 3.78 (d, J=16.8 Hz, 1H), 2.49 (m, 1H), 2.25 (m, 1H), 2.05–1.97 (m, 2H), 1.28 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.25, 167.52, 149.64, 148.91, 146.99, 132.96, 118.47, 111.56, 109.27, 95.97, 65.84, 61.74, 59.66, 56.02, 55.99, 49.33, 29.18, 19.25, 14.46; ESI-MS 362.1 $(M+H)^+$.

4.4.4. (*R*)-6-Methyl-3-oxo-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17d). $[\alpha]_D^{20}$ +48.3 (*c* 0.61, $CHCl_3$); IR (film) 2976, 1768, 1673, 1591, 1281 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (d, J=13.2 Hz, 1H), 5.40 (dd, J=15.9, 1.2 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 4.00 (d, J=16.5 Hz, 1H), 3.85 (d, J=16.5 Hz, 1H), 3.39 (m, 1H), 2.57 (m, 1H), 2.31 (m, 1H), 1.87–1.70 (m, 2H), 1.30 (t, J=7.2 Hz, 3H), 1.15 (d, J=5.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 167.7, 145.8, 94.7, 66.1, 59.5, 53.1, 49.3, 26.5, 18.4, 17.4, 14.5; ESI-MS 240.20 $(M+H)^+$; HRMS calcd for $C_{12}H_{18}NO_4$ 240.1230 $(M+H)^+$, found 240.1240.

4.4.5. (6*R*,7*S*)-7-Ethyl-3-oxo-6-propyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17e). $[\alpha]_D^{20}$ −24.2 (*c* 0.28, $CHCl_3$); IR (film) 2961, 2929, 2855, 1769, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, J=15.3 Hz, 1H), 5.55 (dd, J=15.3, 0.9 Hz, 1H), 4.13 (q, J=6.9 Hz, 2H), 4.04 (d, J=13.8 Hz, 1H), 3.91 (d, J=16.2 Hz, 1H), 2.92 (m, 1H), 2.42–2.26 (m, 3H), 1.70–1.17 (m, 6H), 1.01–0.85 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 168.2, 144.8, 92.5, 65.8, 62.6, 59.5, 51.3, 35.2, 34.1, 31.9, 25.4, 22.7, 19.2, 14.5, 11.9; ESI-MS 296.2 $(M+H)^+$; HRMS calcd for $C_{16}H_{26}NO_4$ 296.2856 $(M+H)^+$, found 296.1865.

4.4.6. 3-Oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17f). IR (film) 1702, 1676, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 4.80 (s, 2H), 3.78 (s, 2H), 3.65 (s, 3H), 3.19 (t, J=5.7 Hz, 2H), 2.40 (t, J=6.3 Hz, 2H), 1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 168.4, 148.9,

62.5, 53.2, 50.6, 50.0, 42.5, 22.4, 21.0; ESI-MS 211.3 $(M+H)^+$; HRMS calcd for $C_{10}H_{14}N_2O_3Na$ 233.0897 $(M+Na)^+$, found 233.0893.

4.4.7. 2-Benzyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido-[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17g). IR (film) 3406, 2952, 1737, 1681, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.73 (s, 2H), 4.64 (s, 2H), 3.81 (s, 2H), 3.60 (s, 3H), 3.16 (t, J=5.4 Hz, 2H), 2.36 (t, J=5.4 Hz, 2H), 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.8, 149.3, 136.0, 128.9, 128.7, 127.7, 92.4, 53.5, 50.6, 49.7, 47.6, 29.7, 22.3, 20.9; ESI-MS 301.2 $(M+H)^+$; HRMS calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366 $(M+Na)^+$, found 323.1360.

4.4.8. (*R*)-3-Oxo-6-pentyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17h). $[\alpha]_D^{20}$ −78.2 (*c* 0.25, $CHCl_3$); IR (film) 2931, 2858, 1686, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 4.85 (dd, J=18.0, 3.6 Hz, 2H), 3.90 (d, J=9.0 Hz, 1H), 3.76 (d, J=9.0 Hz, 1H), 3.63 (s, 3H), 3.17 (m, 1H), 2.50 (m, 1H), 2.24 (m, 1H), 1.90 (m, 1H), 1.72–1.30 (m, 9H), 0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.6, 147.8, 91.8, 58.8, 53.0, 50.7, 42.2, 31.07, 31.0, 25.4, 23.2, 22.5, 18.4, 14.1; ESI-MS 281.25 $(M+H)^+$; HRMS calcd for $C_{15}H_{25}N_2O_3$ 281.1860 $(M+H)^+$, found 281.1864.

4.4.9. (*S*)-6-(3,4-Dimethoxyphenyl)-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17i). $[\alpha]_D^{20}$ +30.7 (*c* 0.47, $CHCl_3$); IR (film) 3302, 2952, 1868, 1517, 1272 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J=8.1 Hz, 1H), 6.69–6.63 (m, 2H), 6.38 (m, 1H), 4.95 (m, 2H), 4.30 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (d, J=16.5 Hz, 1H), 3.68 (d, J=16.5 Hz, 1H), 3.66 (s, 3H), 2.50 (m, 1H), 2.18–1.91 (m, 2H), 1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.4, 149.5, 148.9, 148.7, 133.4, 118.4, 111.5, 109.4, 93.1, 62.3, 56.0, 52.2, 50.8, 42.0, 29.7, 28.8, 18.7; ESI-MS 347.20 $(M+H)^+$; HRMS calcd for $C_{18}H_{23}N_2O_5$ 347.1602 $(M+H)^+$, found 347.1608.

4.4.10. (*R*)-6-Methyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17j). $[\alpha]_D^{20}$ +27.7 (*c* 0.89, $CHCl_3$); IR (film) 2954, 2850, 1686, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H), 4.98 (dd, J=18.0, 3.6 Hz, 1H), 4.66 (d, J=16.8 Hz, 1H), 3.90 (d, J=16.5 Hz, 1H), 3.70 (d, J=16.5 Hz, 1H), 3.66 (s, 3H), 3.38 (m, 1H), 2.55 (m, 1H), 2.29 (m, 1H), 2.05 (m, 1H), 1.83–1.72 (m, 1H), 1.14 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.6, 147.9, 92.0, 53.7, 51.9, 50.7, 42.2, 31.9, 26.4, 18.2; ESI-MS 225.15 $(M+H)^+$; HRMS calcd for $C_{11}H_{17}N_2O_3$ 225.1234 $(M+H)^+$, found 225.1242.

4.4.11. (*R*)-2-Benzyl-3-oxo-6-pentyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17k). $[\alpha]_D^{20}$ −43.0 (*c* 0.62, $CHCl_3$); IR (film) 2956, 2931, 2858, 1739, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.81 (d, J=17.7 Hz, 1H), 4.72 (d, J=17.7 Hz, 1H), 4.67 (d, J=14.4 Hz, 1H), 4.58 (d, J=14.4 Hz, 1H), 3.94 (d, J=15.9 Hz, 1H), 3.81 (d, J=16.5 Hz, 1H), 3.60 (s, 3H), 3.16 (m, 1H), 2.47 (dd, J=16.8, 4.5 Hz, 1H), 2.16 (m, 1H), 1.86 (m, 1H), 1.68–1.29 (m, 9H), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.6, 148.3, 136.2, 128.7, 128.3, 127.7, 91.4, 58.3, 53.2, 50.5, 49.8, 47.3, 31.7, 31.0, 29.7, 25.4, 23.2, 18.3, 14.0; EIMS m/z 370 $(M)^+$.

4.4.12. (*S*)-2-Benzyl-6-(3,4-dimethoxyphenyl)-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17l). $[\alpha]_D^{20}$ +33.4 (*c* 0.89, $CHCl_3$); IR (film) 2924, 1674, 1642, 1562, 1278, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 6.80 (d, J=7.8 Hz, 1H), 6.65 (m, 2H), 4.91 (s, 2H), 4.74 (d, J=14.7 Hz, 1H), 4.58 (d, J=14.7 Hz, 1H), 4.28 (t, J=4.5 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.83 (d, J=13.8 Hz, 1H), 3.73 (d, J=13.8 Hz, 1H), 3.62 (s, 3H), 2.47 (m, 1H), 2.11–1.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 166.5, 149.5, 149.4, 148.7, 136.2, 133.5, 128.8, 128.4, 127.8, 118.4, 111.5, 109.4, 92.8, 62.0, 56.0, 52.5, 50.7, 49.8, 47.1, 31.9, 29.7, 22.7; ESI-MS 437.25 $(M+H)^+$; HRMS calcd for $C_{25}H_{29}N_2O_5$ 437.2071 $(M+H)^+$, found 437.2063.

4.4.13. (*R*)-2-Benzyl-6-methyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17m). $[\alpha]_D^{20}$ −10.3 (*c* 1.2, $CHCl_3$); IR (film) 3449, 1708, 1579, 1364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.90 (d, J=17.7 Hz, 1H), 4.70–4.57 (m, 3H), 3.94 (d, J=16.8 Hz, 1H), 3.75 (d, J=16.5 Hz, 1H), 3.61 (s, 3H), 3.38 (m, 1H), 2.49 (dt, J=15.0, 4.2 Hz, 1H), 2.28 (m, 1H), 1.72 (m, 2H), 1.13 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.6, 148.3, 136.1, 128.7, 128.3, 127.7, 91.4, 53.3, 52.1, 50.6, 49.8, 47.3, 31.9, 29.4, 22.7; ESI-MS 315.20 $(M+H)^+$; HRMS calcd for $C_{18}H_{23}N_2O_3$ 315.1703 $(M+H)^+$, found 315.1701.

4.4.14. (6*R*,7*S*)-7-Ethyl-3-oxo-6-propyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17n). $[\alpha]_D^{20}$ −30.8 (*c* 0.46, $CHCl_3$); IR (film) 2961, 2931, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 4.82 (m, 2H), 3.93–3.75 (m, 3H), 3.64 (s, 3H), 2.92 (m, 1H), 2.40–2.30 (m, 2H), 1.66 (m, 1H), 1.47–1.13 (m, 5H), 0.99–0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.8, 146.9, 89.6, 63.0, 53.8, 50.7, 42.0, 34.7, 34.1, 31.9, 29.4, 22.7, 19.2, 14.1; ESI-MS 281.25 $(M+H)^+$; HRMS calcd for $C_{15}H_{25}N_2O_3$ 281.1860 $(M+H)^+$, found 281.1866.

4.4.15. (6*R*,7*S*)-2-Benzyl-7-ethyl-3-oxo-6-propyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17o). $[\alpha]_D^{20}$ −36.8 (*c* 0.69, $CHCl_3$); IR (film) 2958, 1684, 1579, 1458, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.76 (s, 2H), 4.63 (m, 2H), 3.96 (d, J=16.8 Hz, 1H), 3.83 (d, J=16.5 Hz, 1H), 3.60 (s, 3H), 2.93 (m, 1H), 2.27 (m, 2H), 1.70–1.11 (m, 7H), 0.95–0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.6, 147.4, 136.2, 128.7, 128.2, 127.7, 89.2, 62.7, 54.2, 50.6, 49.7, 47.0, 35.0, 34.1, 31.9, 29.4, 25.3, 22.7, 14.1; ESI-MS 371.25 $(M+H)^+$; HRMS calcd for $C_{22}H_{31}N_2O_3$ 371.2329 $(M+H)^+$, found 371.2329.

4.4.16. (*S*)-2-((*tert*-Butoxycarbonyl)methyl)-6-(3,4-dimethoxyphenyl)-1-(2-methoxy-2-oxoethyl)-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (18a). To a solution of **17i** (20 mg, 0.058 mmol) in methylene chloride were added triethylamine (8 μL, 0.058 mmol), di-*tert*-butyl

dicarbonate (25 mg, 0.116 mmol) and DMAP (7 mg, 0.058 mmol). The solution was stirred for 7 h at 25 °C under an argon atmosphere. The volatiles were removed, and the residue was purified by rapid chromatography on silica gel. Elution with 1/2 ethyl acetate/petroleum ether gave 21 mg of the desired *N*-Boc derivative, which was dissolved in 0.5 mL of methanol. Under an argon atmosphere, 0.40 mL (0.080 mmol) of a 0.2 M solution of sodium methoxide in methanol was added. After 10 min the solution was poured into brine and extracted with ether. After drying (Na_2SO_4) and concentration, the residue was chromatographed on silica gel. Elution with 1/4 ethyl acetate/petroleum ether afforded 19 mg of **18a** (70% from **17i**). $[\alpha]_D^{20}$ −34.0 (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J*=8.4 Hz, 1H), 6.69–6.63 (m, 2H), 5.86 (t, *J*=5.3 Hz, 1H), 5.07 (d, *J*=18.4 Hz, 1H), 4.31 (m, 2H), 4.22 (dd, *J*=14.9, 8.1 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (d, *J*=18.7 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.50 (m, 1H), 2.09–1.93 (m, 3H), 1.43 (s, 9H); ESI-MS 479 $(M+H)^+$; HRMS calcd for $C_{24}H_{34}N_2O_8Na$ 501.2207 $(M+Na)^+$, found 501.2196.

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16. When iodides **1** were reacted with β-amino esters **2**, simple S_N2 reaction products were never determined even at low reaction temperature and only monocyclic products were determined.
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Practical syntheses of penciclovir and famciclovir from *N*2-acetyl-7-benzylguanine

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Abstract—We have established practical methods for the synthesis of penciclovir (PCV) and famciclovir (FCV) from readily available guanosine via *N*2-acetyl-7-benzylguanine. The alkylation of *N*2-acetyl-7-benzylguanine proceeded selectively at the N9 position to give the desired alkylated product in good yield in salt form. After conventional catalytic hydrogenolysis of the benzyl group and hydrolysis of the resulting acetate, pure PCV was obtained without the need for chromatography. As a side chain precursor, the mesylate was selected rather than a halide since the corresponding halides gave several impurities under the same reaction conditions. Two procedures for the synthesis of FCV from PCV and a derivative are also reported.

1. Introduction

Since Schaeffer et al. discovered that acyclovir is a potent and selective anti-herpes virus agent, several groups have undertaken intensive studies to develop still more potent and effective acyclic nucleoside analogues.[1] As a result, penciclovir (PCV) **1** and its pro-drug famciclovir (FCV) **2** were found to be potent and highly selective anti-viral agents against both the herpes simplex virus (HSV) and the varicella-zoster virus (VZV).[2] It has also been reported that **1** and **2** exhibit anti hepatitis B virus (HBV) activity.[3] PCV **1** and FCV **2** are analogues of acyclovir that have alkyl side chains at the N9 position (Fig. 1).

To synthesize **1** and **2**, 2-amino-6-chloropurine is commonly used as a starting material for coupling with alkyl halide side chains.[4] Normally, alkylation takes place at the N9 position as well as at the N7 position of the purine moiety, and the N9/N7 ratio is less than 6:1.[4a,b,g] To improve this ratio, several approaches have been reported, which involve changing the C-6 substituent of 2-aminopurine.[4h] For example, Geen et al. reported a ratio of 5.5:1 in the alkylation of 2-amino-6-chloropurine and noted that it could be improved to 9:1 using 2-amino-6-iodopurine as the starting material.[4c] On the other hand, this ratio was also improved by changing the structure of the side chains.[4d,e,k] Recently, Toyokuni et al. reported an excellent method using 2-phenyl-5-haloethyl-1,3-dioxolane to give the N9-alkylated compound in 94% yield.[4l] However, in each case the regioselectivity was not perfect, and it was difficult to eliminate N7 compounds from the desired N9 product without column chromatography. When triethyl 3-bromopropane-1,1,1-tricarboxylate was used as an alkyl side chain, the N7-alkylated compound was easily separated by crystallization of the N9-alkylated compound.[4f] Unfortunately, though, this reaction sequence required longer steps than the case of using diacetoxy alkyl halide side chain which is normally used to synthesize **1** and **2** from 2-amino-6-chloropurine. Geen et al. have further developed several interesting methods, which involve the coupling of 2-amino-6-chloropurine with an α-acetoxyfuran derivative under acidic conditions[4j] and Pd-catalyzed N9-selective allylation with an allyl acetate side chain.[4i] However, these sequences again require multiple steps to synthesize **1** and **2**. It should be noted that 2-amino-6-chloropurine is not a desirable compound for use in large-scale synthesis due to its high mutagenicity.[5]

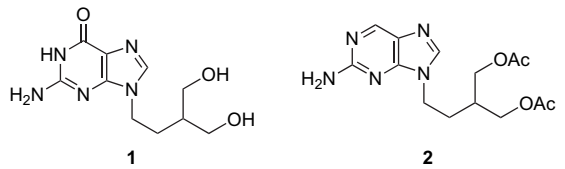

Figure 1. PCV **1** and FCV **2**.

Guanosine **3** is manufactured in very large scale by fermentation. We have previously developed practical methods to

Keywords: Penciclovir; Famciclovir; Practical synthesis; N9-selective; Alkylation.
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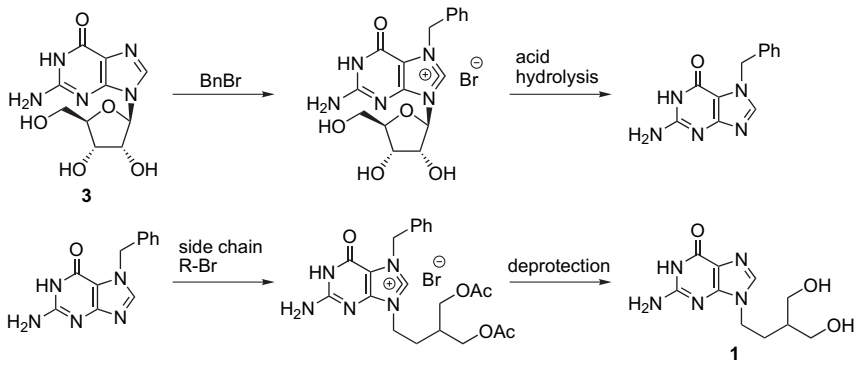
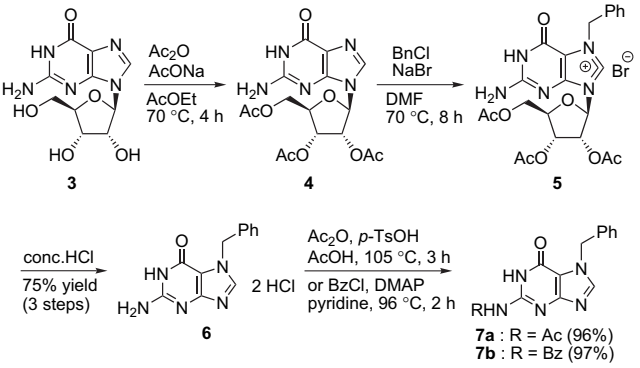


Scheme 1. Synthesis of 7-benzylguanine and selective N9-alkylation.

synthesize first acyclovir by the chemical transpurination of **3**[6a] and then d4T via the enzymatic transglycosylation of **3**.[6b] We considered that it may also be possible to use **3** as a starting material for the synthesis of **1** and **2**: in this respect, **3** may be considered an N9 ribofuranoside-protected guanine. It is known that **3** can be converted to 7-benzylguanine in two steps by conducting benzylation under neutral conditions followed by acidic deglycosylation.[7] We speculated that if 7-benzylguanine could be coupled with the side chains **8a**–**c** at the N9 position under neutral conditions, we might be able to obtain PCV **1** without the formation of the N7-alkylated byproduct after reductive removal of the N7 benzyl group (Scheme 1).[8] We reported here a practical synthesis of PCV **1** using 7-benzylguanine derivatives and also describe two methods for the synthesis of FCV **2** via **1** and its precursor.[9]

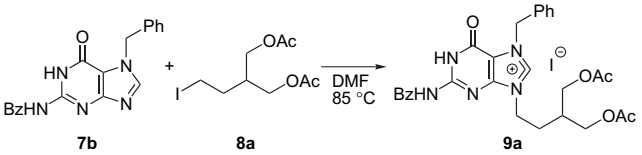
2. Results and discussion

7-Benzylguanine has previously been prepared by treating guanosine **3** with benzyl bromide followed by acid hydrolysis.[7] However, the reaction required dimethyl sulfoxide (DMSO) as a solvent due to the low solubility of **3** in other solvents. Since DMSO is not desirable for use in industrial-scale production for reasons of cost and safety, we searched for other reaction systems to prepare 7-benzylguanine. When we used readily available 2′,3′,5′-tri-*O*-acetylguanosine **4** as a starting material, the benzylation of **4** proceeded well even in *N*,*N*-dimethylformamide (DMF) to give the desired benzylated product as a bromide salt **5** in good yield. In this reaction, the combination of benzyl chloride and sodium bromide can be used instead of expensive benzyl bromide. The benzylation reaction must be carried out below 70 °C, since the deglycosylation of **5** occurs at higher temperatures to generate 7,9-dibenzylated guanine[10] as a byproduct. After the acid hydrolysis of **5**, 7BnG·2HCl **6** was obtained in 75% yield.[11] In addition to the fact that a favorable solvent and inexpensive benzyl chloride can be used, there is another advantage in this reaction sequence, although the reaction requires an additional acetylation step. Specifically, the free form of 7-benzylguanine prepared by the previous method was obtained as very low-density crystals, which were therefore difficult to filter off. On the other hand, upon formation of the HCl salt, compound **6** could be handled more easily in the isolation steps. To improve the solubility of **6** in the reaction solvent, we carried out the acetylation and benzoylation of **6** to give *N*Ac7BnG **7a** and *N*Bz7BnG **7b**, respectively, in good yield (Scheme 2). We considered using *N*-acetyl-2′,3′,5′-tri-*O*-acetylguanosine[12] as a starting material for the synthesis of **7a**, but discounted this idea because deprotection of the *N*-acetyl group is inevitable in the deglycosylation step.



Scheme 2. Preparation of *N*2-protected 7-benzylguanines from guanosine **3**.

First, we examined the coupling reactions of the 7BnG derivatives **7a**,**b** with the diacetate side chains **8a**,**b**. In the case of the coupling of *N*Bz7BnG **7b** with **8a**[4c], the coupling product **9a** could be obtained in crystalline form. After X-ray crystal structural analysis and NMR studies, compound **9a** was unequivocally identified as the N9-alkylated compound (Scheme 3). The coupling product **9a** exists as a rather stable ionic compound under neutral conditions, while acidic or basic hydrolysis produces decomposition products (Fig. 2).[13]



Scheme 3. Preparation of an N9-alkylated 7-benzylguanine derivative.

However, when we used *N*Ac7BnG **7a** and side chains **8a**,**b**, the coupling products **9b**,**c** could not be crystallized, and therefore it was difficult to purify these products in this step. Fortunately, after the debenzylation by catalytic hydrogenolysis of **9b**,**c** followed by alkaline hydrolysis of the acetate, PCV **1** was easily isolated as crystals in respective yields of 74 and 68%. This process did not require any form of chromatographic purification to give pure PCV **1** in good yield (Scheme 4).

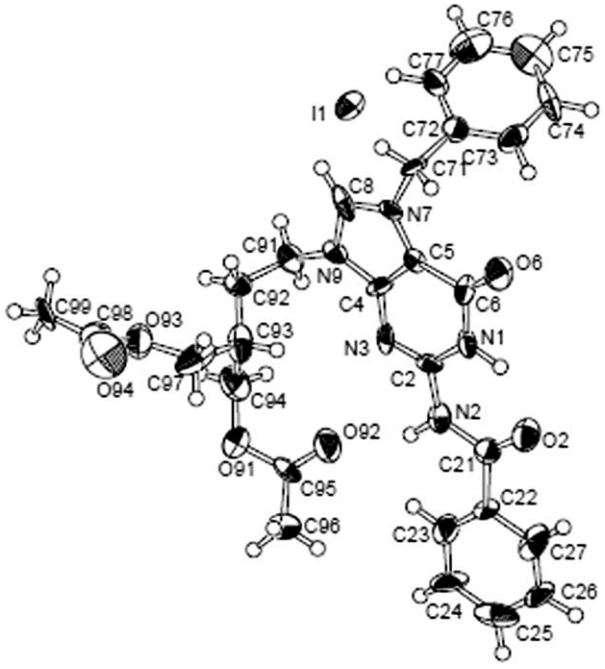
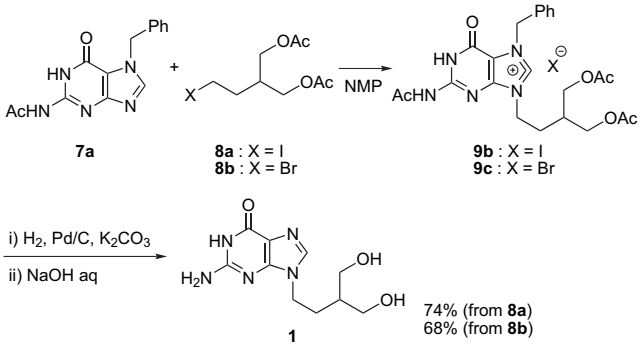


Figure 2. X-ray crystal structure of the coupling product **9a**.



Scheme 4. Preparation of PCV **1** from *N*Ac7BnG **7a**.

Next, we turned our attention to the comparative reactivities with various alkyl side chains (see Table 1). In the case of the bromide **8b**,[14] the yield of PCV **1** was lower than that of the expensive iodide **8a** (68 vs 74%) under the same reaction conditions (80 °C, 20 h). When the temperature in the reaction of *N*Ac7BnG **7a** with **8b** was raised, several byproducts such as Ac_3PCV **10**, the 7,9-dialkylated compound **11**, and NAc-Bn_2G **12**[8b] were detected by HPLC: clearly, the yield of PCV **1** could not be improved simply by raising the reaction temperature, and problematic impurities were also generated. We speculate that the mechanism of the side reaction is that shown in Scheme 5. The coupling of **7a** with the bromide **8b** gives **9c** as a bromide salt. However, the bromide anion of **9c** attacks the benzyl carbon of **9c** itself at a higher temperature to give **10** and benzyl bromide. Ac_3PCV **10** then reacts with extra **8b** to give **11**. NAc-Bn_2G **12** must arise by the reaction of benzyl bromide with remaining **7a**.

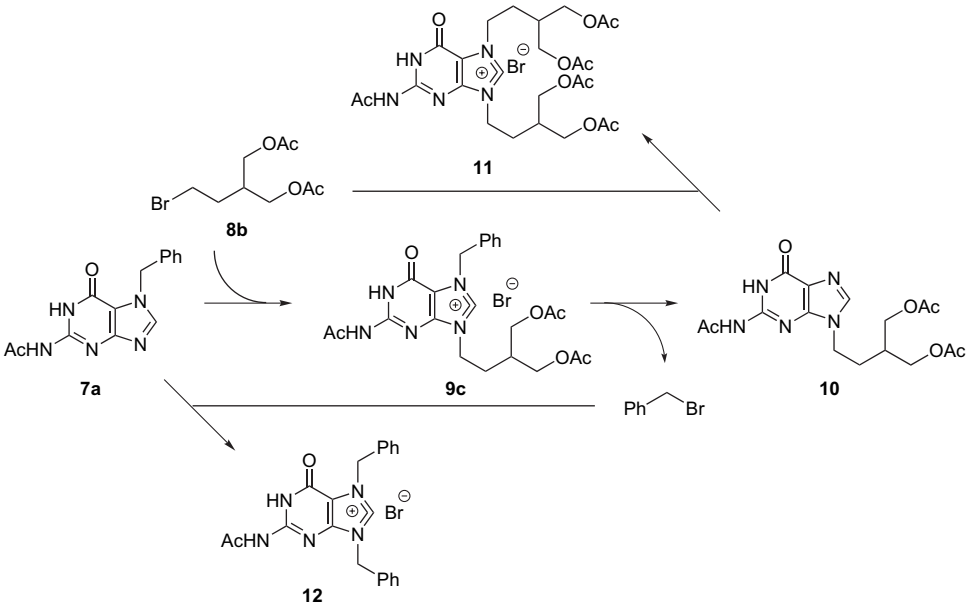
We considered that it may be possible to suppress the side reactions by changing the leaving group of the side chain from halide to the less nucleophilic sulfonate. Thus, we tried the coupling of *N*Ac7BnG **7a** with the mesylate **8c**,[4c] which is a precursor in the synthesis of iodide **8a** and bromide **8b** and therefore less expensive. As we anticipated, the mesylate **8c** was much less reactive than iodide **8a** and bromide **8b**. However, the reaction of *N*Ac7BnG **7a** with mesylate **8c** was complete within 8 h in *N*-methylpyrrolidone (NMP) when the reaction temperature was raised to 120 °C. The reaction proceeded without the formation of any impurities—even at higher temperature. PCV **1** was synthesized by coupling with *N*Ac7BnG **7a** and mesylate **8c**, followed by debenzylation and deacetylation in 76% without isolation of any intermediates from *N*Ac7BnG **7a**. In addition to the use of cheap **8c**, there was another advantage in terms of product purity, although the reaction yield was similar to that using iodide **8a** as a side chain.

6ClFCV **14** has been reported to be a key intermediate for the synthesis of FCV **2**.[4f] We investigated the transformation of PCV **1** to **2**. PCV **1** was converted to Ac_2PCV **13** by selective acetylation of the hydroxy groups.[15] Ac_2PCV **13** was then treated with phosphorus oxychloride, tetraethylammonium chloride, and triethylamine at 80 °C to give the known intermediate **14** in 70% yield, in the same manner as has been reported in the 6-chlorination of *N*-acetyl-2′,3′,5′-tri-*O*-acetyl-guanosine.[16] 6ClFCV **14** was transformed into FCV **2** in 81% yield by the procedure described in the literature (Scheme 6).[4f]

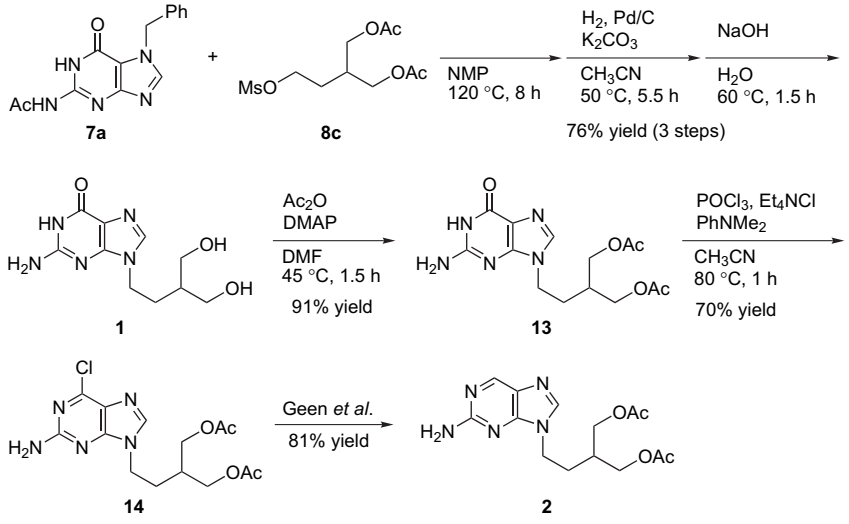
We also established another efficient synthetic route to prepare FCV **2** from **10**. Ac_3PCV **10** was synthesized by coupling with *N*Ac7BnG **7a** and **8c** followed by catalytic debenzylation at 50 °C, in 78% yield based on **7a**. Ac_3PCV **10** was then converted to *N*Ac6ClFCV **15** by chlorination in the same manner as Ac_2PCV **13**. The reaction mixture of **15** was treated under acidic conditions in MeOH, where the *N*-acetyl group of **15** was deprotected selectively to give 6ClFCV **14** (Scheme 7). The overall yield of **14** from Ac_3PCV **10** was 77%, which is better than the yield of **14** (64%) from PCV **1**. Interestingly, the *N*-selective deacetylation of *N*Ac6ClFCV **15** was accomplished under acidic conditions.

Table 1. N-Alkylation of *N*Ac7BnG **7a**

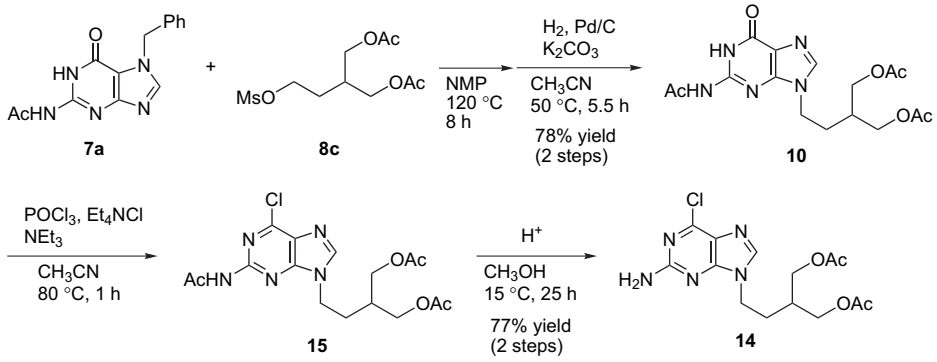
Entry	Side chain leaving group	Temp (°C)	Time (h)	HPLC (area %)				
				9-Alkyl (**9x**)	*N*Ac7BnG (**7a**)	Ac_3PCV (**10**)	7,9-Alkyl (**11**)	NAc-Bn_2G (**12**)
1	**8a** (I)	80	20	75.5	8.1	4.9	2.9	4.7
2	**8b** (Br)	80	20	70.1	20.6	1.6	1.1	2
3	**8b** (Br)	100	8	72.1	3.7	5.6	6.9	8.6
4	**8c** (OMs)	80	20	36.6	58.4	0.1	0.1	N.D.
5	**8c** (OMs)	100	20	79.2	14.8	0.1	0.2	N.D.
6	**8c** (OMs)	120	8	86.2	9.5	0.4	0.3	0.4



Scheme 5. Possible mechanism for the N9-alkylation of *N*Ac7BnG **7a**.



Scheme 6. Preparation of FCV **2** from *N*Ac7BnG **7a**.



Scheme 7. Preparation of 6ClFCV **14** from *N*Ac7BnG **7a**.

3. Conclusion

We have established practical synthetic routes to PCV **1** and FCV **2**. The yields of **1** and **2** were 76 and 49% from *N*Ac7BnG **7a**, respectively; there was no need to purify either by chromatography.

4. Experimental

4.1. General

All reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was conducted on precoated TLC plates (Merck $60F_{254}$). High-performance liquid chromatography (HPLC) was performed with a Hitachi L-6000 pump and L-4000 UV detector system using a YMC-ODS-A column. Melting points were measured with a Büchi B-545. NMR spectra were obtained on a BRUKER Advance-400 MHz spectrometer. All ^{1}H NMR spectra were measured in DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. All ^{13}C NMR spectra were measured in DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to DMSO-d_6 (δ 39.5) as an internal standard. Infrared (IR) spectra were recorded on an ASI React IR 1000 FTIR spectrometer with an ATR sampling system and are reported in wave number (cm^{-1}). Mass spectra (MS) and High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-700V (JEOL Datum Ltd).

4.1.1. 2′,3′,5′-Tri-*O*-acetylguanosine (4). A mixture of guanosine **3** sodium salt (66.58 g, 0.20 mol) in AcOEt (400 mL) was added to acetic anhydride (79.3 mL, 0.84 mol) and stirred for 2 h at 60 °C. After the mixture was cooled to room temperature, water (200 mL) was added, and the mixture was separated. The organic layer was concentrated in vacuo. To the residue was added water (1.0 L) and 1 M NaOH aq to pH 5.0. The mixture was filtered off and washed with water (1.0 L). After the residue was dried, compound **4** (74.4 g, 91%) was obtained as colorless crystals: mp 224–227 °C (lit.[17] 225–227 °C); IR (neat) 3149, 2738, 1740, 1686, 1212, 1073, 783, 675, 635 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 2.11 (3H, s, NAc), 4.26 (1H, dd, J=5.6, 11.2 Hz, H5′-a), 4.29–4.34 (1H, m, H-4′), 4.38 (1H, dd, J=3.6, 11.2 Hz, H-5′-b), 5.49 (1H, dd, J=4.1, 5.9 Hz, H-3′), 5.79 (1H, t, J=6.0 Hz, H-2′), 5.98 (1H, d, J=6.1 Hz, H-1′), 6.53 (2H, br s, NH_2), 7.93 (1H, s, H-8), 10.72 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 20.7, 20.9, 63.4, 70.7, 72.4, 79.9, 84.8, 117.2, 136.0, 151.5, 154.3, 157.0, 169.6, 169.8, 170.4; MS (FAB+) *m*/*z* 410 (MH^+), 432 ($M+Na^+$); HRMS (FAB+) calcd for $C_{16}H_{20}N_5O_8$ (MH^+): 410.1312, found, 410.1310.

4.1.2. 7-Benzylguanine dihydrochloride (6).[11] A solution of guanosine **3** (13.9 g, 48.1 mmol) in DMF (28.3 mL) was added to sodium acetate (985.6 mg, 12.0 mmol) and acetic anhydride (19.1 mL, 202 mol) and the mixture was stirred for 4 h at 70 °C. After the mixture was cooled to 30 °C, concd HCl (19.1 mL, 202 mmol), sodium bromide (8.89 g, 86.5 mmol), and benzyl chloride (6.64 mL, 57.7 mmol) were added, and the mixture was stirred for 8 h at 70 °C. After the mixture was cooled to room temperature, concd HCl (40.5 mL, 481 mmol) was added and the mixture was stirred for 3 h at 40 °C. After the mixture was cooled to 0 °C, 8 M NaOH aq (42 mL, 336 mmol) and CH_3OH (50 mL) were added. The mixture was filtered off and washed with 50% CH_3OH aq (40 mL). After the residue was dried, compound **6** (15.1 g, 75%) was obtained as colorless crystals: mp 285 °C (dec); IR (neat) 3406, 3122, 2732, 1706, 1663, 1609, 1520, 1158, 843, 706, 679, 621 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.52 (2H, s, CH_2), 7.32–7.43 (5H, m, aryl), 8.34 (2H, br s, NH_2), 8.91 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.6, 107.5, 128.2, 128.6, 129.1, 136.2, 140.5, 150.9, 153.4, 154.5; MS (FAB+) *m*/*z* 242 (7BnG-H^+); HRMS (FAB+) calcd for $C_{12}H_{12}N_5O$ (7BnG-H^+): 242.1031, found, 242.1064; Anal. Calcd for $C_{12}H_{13}Cl_2N_5O$: C, 45.88; H, 4.17; N, 22.29. Found: C, 46.17; H, 4.30; N, 22.69.

4.1.3. *N*2-Acetyl-7-benzylguanine (7a). A mixture of compound **6** (4.37 g, 13.9 mmol) in AcOH (9 mL) was added to acetic anhydride (4.44 mL, 45.1 mmol) and *p*-TsOH·H_2O (132.8 mg, 0.70 mmol) and the resulting solution was stirred for 3 h at 105 °C. After the mixture was cooled to room temperature, water (180 mL), 5% $NaHCO_3$ aq (150 mL) and 1 M NaOH aq (100 mL) were added to give pH 5.3. The slurry was filtered off and washed with water (50 mL). After the residue was dried, *N*Ac7BnG **7a** (3.77 g, 95.7%) was obtained as colorless crystals: mp 237–238 °C (lit.[18] 241 °C); IR (neat) 3141, 1713, 1686, 1619, 1546, 1424, 1364, 1246, 1216, 778, 710, 652 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (3H, s, NAc), 5.51 (2H, s, CH_2), 7.27–7.36 (5H, m, aryl), 8.34 (1H, s, H-8), 11.56 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 49.6, 111.5, 127.9, 128.2, 129.0, 137.7, 144.7, 147.4, 153.0, 157.6, 173.7; MS (FAB+) *m*/*z* 284 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{14}N_5O_2$ (MH^+): 284.1148, found, 284.1147.

4.1.4. *N*2-Benzoyl-7-benzylguanine (7b). A mixture of compound **6** (7.29 g, 23.2 mmol) in pyridine (47 mL) was added to 4-dimethylaminopyridine (145.6 mg, 1.19 mmol). Benzoyl chloride (5.5 mL, 47.4 mmol) was added dropwise and the mixture was stirred for 2 h at 96 °C. After the mixture was cooled to room temperature, AcOEt (95 mL) was added and the mixture was stirred for 0.5 h at room temperature. The precipitated crystals were collected on filter and washed with AcOEt. The crystals were added to water (95 mL) and stirred for 2 h at room temperature. The slurry was filtered off and washed with water. After the residue was dried, *N*Bz7BnG **7b** (7.79 g, 97.0%) was obtained as an off-white powder: mp 265–267 °C; IR (neat) 3089, 1684, 1657, 1609, 1534, 1370, 1268, 1233, 903, 782, 697, 658 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.55 (2H, s, CH_2), 7.28–7.39 (5H, m, aryl), 7.53–7.58 (2H, m, aryl), 7.64–7.69 (1H, m, aryl), 8.03–8.07 (2H, m, aryl), 8.39 (1H, s, H-8), 11.86 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.6, 111.9, 127.9, 128.3, 128.7, 128.9, 129.1, 132.6, 133.4, 137.7, 144.8, 147.5, 153.2, 157.6, 169.1; MS (FAB+) *m*/*z* 346 (MH^+); HRMS (FAB+) calcd for $C_{19}H_{16}N_5O_2$ (MH^+): 346.1304, found, 346.1315.

4.1.5. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-*N*2-benzoyl-7-benzylguaninium iodide (9a). A mixture of *N*Bz7BnG **7b**

(3.579 g, 10.0 mmol) in DMF (7.5 mL) was added to iodide **8a** (3.25 g, 10.0 mmol), and the mixture was stirred for 18 h at 85 °C. After the mixture was cooled to 75 °C, AcOEt (30 mL) was added and the mixture was cooled to 0 °C. The mixture was filtered off and washed with AcOEt (15 mL). After the residue was dried, compound **9a** (4.41 g, 64%) was obtained as a pale yellowish powder: mp 180–181 °C; IR (neat) 3320, 3160, 2977, 1711, 1596, 1420, 1241, 787, 710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.96–2.04 (2H, m, H-2′), 2.02 (6H, s, Ac×2), 2.06–2.12 (1H, m, H-3′), 4.06 (4H, d, J=5.7 Hz, H-4′), 4.37 (2H, t, J=7.4 Hz, H-1′), 5.73 (2H, s, CH_2), 7.38–7.47 (3H, m, aryl), 7.50–7.53 (2H, m, aryl), 7.56–7.61 (2H, m, aryl), 7.69–7.74 (1H, m, aryl), 8.03–8.06 (2H, m, aryl), 9.74 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 27.8, 34.5, 44.1, 52.0, 63.7, 111.1, 128.7, 129.0, 129.0, 129.2, 129.3, 132.1, 134.0, 134.6, 140.4, 148.0, 151.3, 152.1, 169.5, 170.7; MS (FAB+) m/z 532 ($M-I^+$); HRMS (FAB+) calcd for $C_{28}H_{29}N_5O_6$ ($M-I^+$): 532.2191, found, 532.2214.

4.1.6. Penciclovir (1) from iodide 8a. A mixture of *N*Ac7BnG **7a** (20.6 g, 70.5 mmol) in 1-methylpyrrolidone (23.5 mL) was added to iodide **8a** (22.9 g, 70.5 mmol), and the mixture was stirred for16 h at 80 °C. After the mixture was cooled to room temperature, 50% CH_3OH aq (236 mL), 5% Pd–C (50% wet, 6.34 g), and K_2CO_3 (14.9 g, 141 mmol) were added and the mixture was stirred at 45 °C under a hydrogen atmosphere (1 atm) for 21.5 h. After the mixture was cooled to room temperature, 4 M NaOH aq (35.5 mL) was added and filtered off, the residue was washed with 2 M NaOH aq (60 mL), and the filtrate was concentrated. To the residue was added water (20 mL), and this mixture was stirred for 1 h at 60 °C. After the mixture was cooled to room temperature, the pH of the solution was adjusted to 11.5 by 2 M HCl aq and the precipitated 7BnG was filtered off. The pH of the filtrate was adjusted to 6.0 by 6 M HCl aq, and then the temperature was lowered to 0 °C. The mixture was filtered off and washed with cold water (30 mL). After the residue was dried, PCV **1** (13.4 g, 74%) was obtained as colorless crystals: mp 270–272 °C (lit.[4b] 275–277 °C); IR (neat) 3411, 3128, 2881, 2667, 1675, 1602, 1397, 1196, 1054, 992, 781, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.41–1.48 (1H, m, H-3′), 1.67–1.74 (2H, m, H-2′), 3.32–3.38 (2H, m, H-4′-a), 3.39–3.46 (2H, m, H-4′-b), 4.00 (2H, t, J=7.4 Hz, H-1′), 4.41 (2H, t, J=5.2 Hz, OH×2), 6.41 (2H, br s, NH_2), 7.68 (1H, s, H-8), 10.50 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.2, 41.1, 41.4, 61.7, 116.9, 137.7, 151.5, 153.8, 157.2; MS (FAB+) m/z 254 (MH^+); HRMS (FAB+) calcd for $C_{10}H_{16}N_5O_3$ (MH^+): 254.1253, found, 254.1230.

4.1.7. Penciclovir (1) from bromide 8b. A mixture of *N*Ac7BnG **7a** (4.44 g, 15.0 mmol) in 1-methylpyrrolidone (5.0 mL) was added to bromide **8b** (4.23 g, 15.0 mmol) and this mixture was stirred for 18 h at 80 °C. After the mixture was cooled to room temperature, 50% CH_3OH aq (60 mL), 5% Pd–C (50% wet, 1.37 g), and K_2CO_3 (3.18 g, 30.0 mmol) were added and the mixture was stirred at 45 °C under a hydrogen atmosphere (1 atm) for 21.5 h. After the mixture was cooled to room temperature, 25% NaOH aq (4.85 g) was added and filtered off, the residue was washed with 50% CH_3OH aq (20 mL), and the filtrate was concentrated. To the residue was added 25% NaOH aq (1.18 g) to pH over 13.0 and the mixture was stirred for 2 h at 50 °C. After the mixture was cooled to room temperature, the pH of the solution was adjusted to 7.0 by 6 M HCl aq and the solution was cooled to 0 °C. The mixture was filtered off and washed with cold water (5 mL). After the residue was dried, PCV **1** (2.58 g, 68%) was obtained as colorless crystals.

4.1.8. Penciclovir (1) from mesylate 8c. A mixture of *N*Ac7BnG **7a** (1.67 g, 5.84 mmol) in 1-methylpyrrolidone (1.2 mL) was added to mesylate **8c** (1.68 g, 5.84 mmol) and this mixture was stirred for 8 h at 120 °C. After the mixture was cooled to room temperature, CH_3CN (29.2 mL), 5% Pd–C (50% wet, 0.515 g), and K_2CO_3 (0.485 g, 3.50 mmol) were added and the mixture was stirred at 50 °C under a hydrogen atmosphere (1 atm) for 10 h. After the mixture was cooled to room temperature, 4 M NaOH aq (4.4 mL) was added and filtered off, the residue was washed with 2 M NaOH aq (2×3 mL), and the filtrate was concentrated. To the residue was added 2 M NaOH aq (8.5 L) and the mixture was stirred for 1.5 h at 60 °C. After the mixture was cooled to room temperature, the solution was washed with CH_2Cl_2 (10 mL), and the pH of the water layer was adjusted to 6.7 by concd H_2SO_4. The mixture was stirred for 1 h at room temperature and filtered off, and the residue was washed with cold water (3 mL). After the residue was dried, PCV **1** (1.12 g, 76%) was obtained as colorless crystals.

4.1.9. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-*N*2-acetylguanine (10). A mixture of *N*Ac7BnG **7a** (2.86 g, 10.0 mmol) in 1-methylpyrrolidone (2.0 mL) was added to **8c** (2.87 g, 10.0 mmol) and the mixture was stirred for 8 h at 120 °C. After the mixture was cooled to 50 °C, CH_3CN (50 mL), 5% Pd–C (50% wet, 0.88 g), and K_2CO_3 (0.83 g, 6.02 mmol) were added and the mixture was stirred at 50 °C under a hydrogen atmosphere (1 atm) for 5.5 h. AcOH (20.0 mL) was added and filtered off at 50 °C, and the residue was washed with AcOH (10 mL). After the mixture was cooled to room temperature, the filtrate was concentrated in vacuo, and coevaporated with toluene (10 mL). To the residue was added AcOEt (20 mL), and the mixture was stirred for 1 h at room temperature, filtered off, washed with AcOEt (10 mL). The wet crystals were added to water (40 mL), and then stirred for 0.5 h at 60 °C and for 2 h at room temperature. The mixture was filtered off and washed with water. After the mixture was dried, Ac_3PCV **10** (3.03 g, 78%) was obtained as a pale yellowish powder: mp 226–227 °C (lit.[8c] 222–223 °C); IR (neat) 3267, 3085, 1729, 1663, 1603, 1540, 1262, 1233, 785, 739, 633 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.82–1.88 (2H, m, H-2′), 1.90–1.97 (1H, m, H-3′), 2.00 (6H, s, OAc×2), 2.18 (3H, s, NAc), 4.02 (4H, d, J=5.3 Hz, H-4′), 4.15 (2H, t, J=7.1 Hz, H-1′), 8.02 (1H, s, H-8), 11.66 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 24.2, 28.6, 34.8, 41.4, 63.8, 120.5, 140.1, 148.0, 148.9, 155.3, 170.7, 173.8; MS (FAB+) m/z 380 (MH^+); HRMS (FAB+) calcd for $C_{16}H_{22}N_5O_6$ (MH^+): 380.1570, found, 380.1556.

4.1.10. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)guanine (13). A mixture of PCV **1** (12.5 g, 48.8 mmol) in DMF (46 mL) was added to 4-dimethylaminopyridine (0.3 g, 2.5 mmol) and acetic anhydride (10.6 mL, 112.2 mmol), and the mixture was stirred for 1.5 h at 45 °C. After the mixture was cooled to room temperature, 2-propanol (115 mL)

was added and the mixture was stirred for 1.5 h at 0 °C. The mixture was filtered off and washed with 2-propanol (2×15 mL). The wet crystals were added to AcOEt (105 mL), warmed to 70 °C, and cooled to room temperature. The mixture was filtered off and washed with AcOEt (2×15 mL). After the residue was dried, Ac_2PCV **13** (15.3 g, 91%) was obtained as colorless crystals: mp 198–202 °C (lit.[15a] 202–205 °C); IR (neat) 3323, 3159, 2730, 1735, 1686, 1605, 1366, 1221, 1036, 785, 691, 639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.77–1.84 (2H, m, H-2′), 1.88–1.95 (1H, m, H-3′), 2.00 (6H, s, Ac×2), 4.00–4.04 (6H, m, H-1′ and H-4′), 6.40 (2H, br s, NH_2), 7.70 (1H, s, H-8), 10.52 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.5, 28.1, 34.3, 40.3, 63.3, 116.5, 137.2, 151.0, 153.4, 156.7, 170.2; MS (FAB+) *m/z* 338 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{20}N_5O_5$ (MH^+): 338.1464, found, 338.1462.

4.1.11. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (14), from Ac_2PCV 13. A mixture of Ac_2PCV **13** (5.16 g, 15.0 mmol) and tetraethylammonium chloride (4.97 g, 30.0 mmol) in CH_3CN (30 mL) was cooled to 0 °C and added to *N*,*N*-dimethylaniline (1.0 mL, 7.5 mmol) and phosphorus oxychloride (6.25 mL, 67.5 mmol). The mixture was stirred for 1 h at 70 °C and evaporated. The residue was diluted with CH_2Cl_2 (60 mL) and washed with satd $NaHCO_3$ aq (2×45 mL) and water (30 mL). The CH_2Cl_2 layer was evaporated in vacuo. To the residue was added CH_3OH (7 mL) and H_2O (3.5 mL) and the mixture was stirred for 1.5 h at −5 °C. The mixture was filtered off and washed with 75% CH_3OH aq. After the residue was dried, the crude solid of 6ClFCV **14** (3.96 g) was obtained as an off-white solid. Recrystallization from 2-propanol gave pure 6ClFCV **14** (3.74 g, 70%) as a pale yellowish powder: mp 132–134 °C (lit.[4c] 134–136 °C); IR (neat) 3485, 3301, 3195, 1744, 1729, 1623, 1559, 1472, 1239, 1023, 907, 880, 647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.83–1.89 (2H, m, H-2′), 1.90–1.95 (1H, m, H-3′), 1.99 (6H, s, Ac×2), 4.01 (4H, d, J=5.6 Hz, H-4′), 4.13 (2H, t, J=7.1 Hz, H-1′), 6.90 (2H, br s, NH_2), 8.16 (1H, s, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 28.1, 34.8, 41.2, 63.8, 123.7, 143.5, 149.7, 154.4, 160.1, 170.7; MS (FAB+) *m/z* 356 (MH^+); HRMS (FAB+) calcd for $C_{14}H_{19}ClN_5O_4$ (MH^+): 356.1126, found, 356.1131.

4.1.12. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (14), from Ac_3PCV 10. A mixture of Ac_3PCV **10** (1.93 g, 5.02 mmol) and tetraethylammonium chloride (1.66 g, 10.4 mmol) in CH_3CN (10 mL) was cooled to 0 °C, and triethylamine (0.35 mL, 2.51 mmol) and phosphorus oxychloride (2.09 mL, 22.6 mmol) were added. The mixture was stirred for 1 h at 80 °C and evaporated. The residue was diluted by CH_2Cl_2 (9 mL). After the mixture was cooled to 0 °C, 2 M NaOH aq (6 mL) and 4 M NaOH aq (3 mL) were added dropwise, and the mixture was separated. To the CH_2Cl_2 layer was added satd $NaHCO_3$ aq (4 mL) and water (2 mL), and the mixture was stirred for 0.5 h at room temperature. After layer separation, the CH_2Cl_2 layer was evaporated in vacuo. To the residue was added CH_3OH (6 mL), and the mixture was stirred 25 h at 15 °C, while the progression of deacetylation was confirmed. At that time the pH of the solution was 0.6. After deacetylation, the pH of the mixture was adjusted to 7.0 by satd $NaHCO_3$ aq, and the mixture was stirred for 1.5 h at 0 °C. The mixture was filtered off and washed with water. After the residue was dried, 6ClFCV **14** (1.42 g, 77%) was obtained as a pale yellowish powder.

5. Crystallographic data

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC600088. Copies of the data can be obtained, free of charge, on application on CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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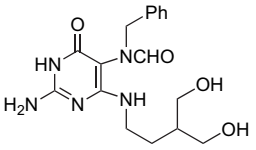

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Intramolecular electrophilic aromatic substitution of α-alkylcinnamaldehydes affording 1-alkoxy-2-alkylindenes

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Abstract—Treatment of α-alkylcinnamaldehydes with orthoesters, alcohols, or thiols in the presence of $BF_3{\cdot}OEt_2$ induces an intramolecular electrophilic aromatic substitution reaction to afford 1-alkoxy-2-alkylindenes. The reaction mechanisms of the indene formation have been elucidated on the basis of the reaction behaviors of β-deuterated α-methylcinnamaldehyde and the NMR studies of the reaction mixture. The transformation process involves successive reactions, i.e., alkoxylation of the carbonyl carbon of α-alkylcinnamaldehydes to form acetals, elimination of alkoxide from the acetals to give alkoxycarbenium ion and γ-alkoxyallyl cation, and intramolecular electrophilic arylation to afford the indene ring structure.

1. Introduction

Indene derivatives are frequently found in natural products and widely employed as medicinal compounds.[1–5] In accordance with this, indene derivatives have attracted organic and pharmaceutical chemists. One of the conventional approaches toward producing the indene framework is acid-mediated cyclodehydration reaction of aryl ketones.[6–8] Some 1-phenylallyl cations also undergo the intramolecular cyclization to afford the corresponding indenes.[9–12] In these cases, the cyclization proceeds via electrophilic aromatic substitution mechanisms. While various substituted indenes have so far been prepared by these methods, synthesis of 1-indenols and 1-alkoxyindenes through the electrophilic aromatic substitution process has not been reported. Recently, transition metal catalyzed coupling reactions of alkynes with *ortho*-carbonylated arylhalides[13] or arylboron compounds[14] have been developed as an effective method for the preparation of 1-indenols. The transition metal catalyzed annulation reaction has also been applied for the construction of indenes.[15,16] Nevertheless, an efficient and practical means to construct 1-alkoxyindene frameworks has been an ongoing challenge. Almost all of the syntheses of 1-alkoxyindenes are performed via multi step transformations[5,17] or low chemoselective one-pot preparations,[18] except for a recent report of Pd-complex catalyzed intramolecular cyclization of alkynylbenzaldehyde dialkyl acetals to form dialkoxyindenes.[19]

During the study on the acid mediated oxidative crossed aldol type reaction of aliphatic ethers with benzaldehyde dimethyl acetal giving α,β-unsaturated carbonyl compounds,[20] we have found that several ethers afford 1-alkoxy-2-alkylindenes in place of α,β-unsaturated carbonyl compounds.[21] Our preliminary study indicated that the produced α,β-unsaturated carbonyl compounds may be further transformed to 1-alkoxy-2-alkylindenes during the reaction.

In consequence, we have investigated the above reaction aiming at the development of the efficient one-pot synthesis of 1-alkoxyindenes to reveal the structural requirements and the activation process. In this paper, the reaction features, the scope and limitations, and the reaction mechanisms of the transformation of α-alkylcinnamaldehydes into 1-alkoxyindenes are discussed.

2. Results and discussion

2.1. The reaction behaviors and characterization of the products

We have recently reported that the BF_3 mediated reaction of bis(β-alkylethyl) ethers with benzaldehyde dimethyl acetal

Keywords: 1-Alkoxy-2-alkylindene; α-Alkylcinnamaldehyde; Alkoxylation; Intramolecular electrophilic arylation; Acetal.
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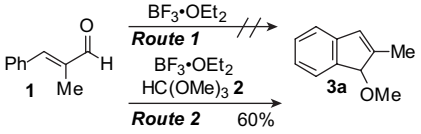
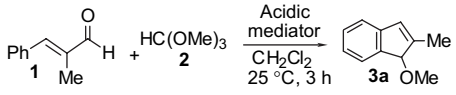
affords 1-alkoxy-2-alkylindenes.[21] As some kinds of aliphatic ethers yield α,β-unsaturated carbonyl compounds in the presence of benzaldehyde dimethyl acetal and BF_3 etherates, α,β-unsaturated carbonyl compounds were obviously regarded as the precursors for the 1-alkoxyindene formation reaction.[20,21] However, the treatment of $BF_3{\cdot}OEt_2$ against α-methylcinnamaldehyde (**1**) did not afford any indenes (Scheme 1, Route 1). In this case, aldehyde **1** was recovered. In contrast, addition of trimethyl orthoformate [$HC(OMe)_3$ (**2**)] to this reaction system has been found to accomplish the transformation affording 1-methoxy-2-methylindene (**3a**) in a good yield (Scheme 1, Route 2). These facts demonstrate that α-methylcinnamaldehyde (**1**) by itself is not the direct precursor of 1-methoxyindene **3a**, but has a capability to form 1-methoxy-2-methylindene (**3a**) with the aid of $HC(OMe)_3$ (**2**).



Scheme 1.

Table 1 shows the results of the reaction of α-methylcinnamaldehyde (**1**) with $HC(OMe)_3$ (**2**) in the presence of several acidic mediators.

Table 1. Reaction of α-methylcinnamaldehyde (**1**) with $HC(OMe)_3$ (**2**) in the presence of several acidic mediators[a]



Entry	**2**/**1** (mol/mol)	Acidic mediator	Acidic mediaor/**1** (mol/mol)	NMR yield/%[b]
1	1	$BF_3{\cdot}OEt_2$	1	60
2	2	$BF_3{\cdot}OEt_2$	1	72
3	4	$BF_3{\cdot}OEt_2$	1	79
4	4	$BF_3{\cdot}OEt_2$	0.5	37
5	4	$BF_3{\cdot}OEt_2$	2	74
6	4	$BF_3{\cdot}OMe_2$	1	57
7	4	$AlCl_3$	1	8
8	4	$SnCl_4$	1	5
9	4	$ZnCl_2$	1	32
10	4	H_2SO_4	1	35
11	4	CF_3SO_3H	1	68

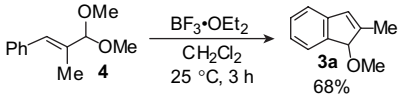
[a] Reaction conditions: α-methylcinnamaldehyde (**1**), 0.5 mmol; CH_2Cl_2, 2.5 mL; 25 °C, 3 h.
[b] Determined by ^1H NMR spectrum with the use of nitrobenzene as internal standard.

In the presence of one equimolar amount of $BF_3{\cdot}OEt_2$, the treatment of α-methylcinnamaldehyde (**1**) with four equimolar amounts of $HC(OMe)_3$ (**2**) afforded 1-methoxyindene **3a** in a high yield (79%, Entry 3). However, the reaction was retarded with the decrease in the amount of $HC(OMe)_3$ (**2**) (Entries 1 and 2). In addition, the use of catalytic amount of $BF_3{\cdot}OEt_2$ resulted in a lower yield of 1-methoxyindene **3a** (Entry 4), while the treatment with excess amount of $BF_3{\cdot}OEt_2$ afforded 1-methoxyindene **3a** in a comparative yield (Entry 5).

Among the acidic mediators employed, $BF_3{\cdot}OEt_2$ afforded 1-methoxy-2-methylindene (**3a**) in the highest yield (Entry 3). Acidic mediators except $BF_3{\cdot}OEt_2$ gave aldehyde **1** and/or unidentified products that have broad signals of aromatic ring protons and alkyl group ones in ^1H NMR spectra (Entries 6–10), though triflic acid also gave 1-methoxyindene **3a** in a good yield (Entry 11). These by-products are probably composed of some kinds of polymeric compounds formed via cationic polymerization of 1-alkoxyindene[22] and/or α-methylcinnamaldehyde (**1**)[23] produced in the early stage of the reaction.

2.2. Effect of the alkoxylating agent

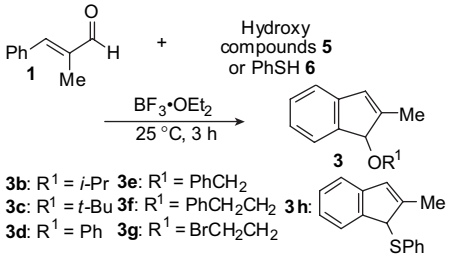
Generally, treatment of orthoester against aldehyde in the presence of acidic mediator is known to give acetal.[24] In other words, acetals of α-alkylcinnamaldehydes were considered to be the actual precursors of the 1-alkoxyindenes in this transformation. In fact, when α-methylcinnamaldehyde dimethyl acetal (**4**) was treated with $BF_3{\cdot}OEt_2$ in the absence of $HC(OMe)_3$ (**2**), 1-methoxy-2-methylindene (**3a**) was also formed in a good yield (Scheme 2). Therefore, 1-alkoxyindenes must be produced via the acetal of α-alkylcinnamaldehyde or at least its equivalent.



Scheme 2.

Acetals are also synthesized by the reaction of aldehyde with alcohol or thiol.[24] Therefore, alcohols and thiols are expected to react with aldehyde **1** affording the corresponding indenes. Table 2 shows the results of the reaction using other hydroxy compounds **5** or thiophenol (**6**). When MeOH (**5a**)

Table 2. Reaction of α-methylcinnamaldehyde (**1**) with hydroxy compounds **5** or thiophenol (**6**) in the presence of $BF_3{\cdot}OEt_2$[a]



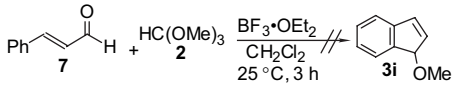
Entry	**5** or **6**	**5** or **6**/**1** (mol/mol)	$BF_3{\cdot}OEt_2$/**1** (mol/mol)	**3**	NMR yield/%[b]
1[c]	MeOH **5a**	4	1	**3a**	Trace
2	**5a**	10	10	**3a**	69
3	*i*-PrOH **5b**	10	10	**3b**	54
4	*t*-BuOH **5c**	10	10	**3c**	0
5	PhOH **5d**	10	10	**3d**	0
6	$PhCH_2OH$ **5e**	10	10	**3e**	0
7	$PhCH_2CH_2OH$ **5f**	10	10	**3f**	56
8	$BrCH_2CH_2OH$ **5g**	10	10	**3g**	30
9	PhSH **6**	10	10	**3h**	59

[a] Reaction conditions: aldehyde **1**, 0.5 mmol; 25 °C, 3 h.
[b] Determined by ^1H NMR spectrum with the use of nitrobenzene as internal standard.
[c] Reaction conditions: aldehyde **1**, 0.5 mmol; CH_2Cl_2, 2.5 mL; 25 °C, 3 h.

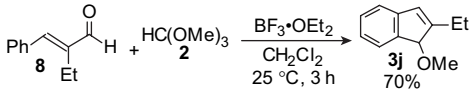
was treated with α-methylcinnamaldehyde (**1**) as an alternative alkoxylating agent under the same conditions as for orthoester **2**, 1-methoxyindene **3a** was slightly obtained (Entry 1). On the other hand, manipulation with excess amounts of $BF_3{\cdot}OEt_2$ and MeOH (**5a**) to α-methylcinnamaldehyde (**1**) without solvents gave 1-alkoxyindene **3a** in a good yield (Entry 2). Furthermore, some primary alcohols **5f** and **5g** (Entries 7 and 8) and secondary alcohol **5b** (Entry 3) also gave the corresponding 1-alkoxy-2-methylindenes (**3f**, **3g**, and **3b**) under the same conditions. However, *t*-BuOH (**5c**), phenol (**5d**), and benzyl alcohol (**5e**) did not yield 1-alkoxyindenes, which suggests that large steric hindrance and/or the low nucleophilicity of the hydroxy compounds prevent alkoxylation of the carbonyl group of α-methylcinnamaldehyde (**1**) (Entries 4–6). On the other hand, the reaction of thiophenol (**6**) with α-methylcinnamaldehyde (**1**) gave 2-methyl-1-phenylthioindene (**3h**) (Entry 9). Hence, some alcohols and thiols show lower reactivity than orthoester, but have a sufficient potential to give indene derivatives in this system.

2.3. Structural requirements of α-alkylcinnamaldehydes

To clarify the structural requirements of the starting aldehydes, simple and several substituted cinnamaldehydes were employed for the reaction with $HC(OMe)_3$ (**2**) in the presence of $BF_3{\cdot}OEt_2$ (Schemes 3 and 4). When cinnamaldehyde (**7**) was treated with $HC(OMe)_3$ (**2**), indene **3i** was not obtained at all (Scheme 3). In contrast, α-ethylcinnamaldehyde (**8**) afforded the corresponding 1-alkoxyindene (**3j**) (Scheme 4). Aldehydes **1** and **8** have an α-alkyl substituent in common, which is considered to be essential for the formation of 1-alkoxyindenes.



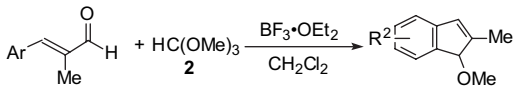
Scheme 3.

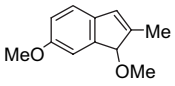
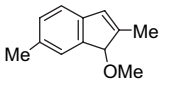
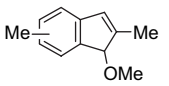
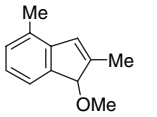
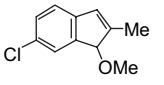
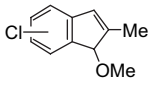
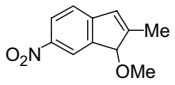


Scheme 4.

Table 3 shows the results of the reaction of several α-methylcinnamaldehydes that have a substituent in the aromatic ring in the presence of $BF_3{\cdot}OEt_2$ and $HC(OMe)_3$ (**2**). When methylated or *m*-chlorinated α-methylcinnamaldehydes (**10**–**12** and **14**) were allowed to react with $HC(OMe)_3$ (**2**), the corresponding 1-alkoxyindenes (**3l**–**3o**, **3q**, and **3r**) were obtained in high yields (Entries 2–4 and 6). In contrast, *p*-methoxylated and *p*-chlorinated α-methylcinnamaldehydes (**9** and **13**) afforded 1-alkoxyindenes **3k** and **3p**, respectively, in low yields (Entries 1 and 5). In the case of the reaction of α-methyl-*p*-nitrocinnamaldehyde (**15**) with $HC(OMe)_3$ (**2**) at room temperature, the nitrated 1-alkoxyindene (**3s**) was not obtained, while the manipulation at higher temperature gave 1-alkoxyindene **3s** in a moderate yield (Entry 7). *p*-Methoxylated aldehyde **9** is considered to be highly active against electrophilic attack on the aromatic ring moiety. This probably caused the side reactions to give unknown products resulting in diminishment of the yield of the corresponding 1-methoxyindene (**3k**) to a trace amount.

Table 3. Reaction of α-alkylcinnamaldehydes with $HC(OMe)_3$ (**2**) in the presence of $BF_3{\cdot}OEt_2$[a]



Entry	Ar=	Aldehyde	Product			NMR yield/%[b]
1	4-$MeOC_6H_4$	**9**			**3k**	Trace
2	4-MeC_6H_4	**10**			**3l**	82
3	3-MeC_6H_4	**11**		5-Me 7-Me	**3m** **3n**	75[c]
4	2-MeC_6H_4	**12**			**3o**	90
5	4-ClC_6H_4	**13**			**3p**	Trace
6	3-ClC_6H_4	**14**		5-Cl 7-Cl	**3q** **3r**	57[d]
7	4-$NO_2C_6H_4$	**15**			**3s**	0 (33)[e]

[a] Reaction conditions: aldehyde, 0.5 mmol; $HC(OMe)_3$ (**2**), 2 mmol; $BF_3{\cdot}OEt_2$, 0.5 mmol; CH_2Cl_2, 2.5 mL; 25 °C, 3 h.
[b] Determined by ^1H NMR spectrum with the use of nitrobenzene as internal standard.
[c] Indene **3m**:indene **3n**=59:16.
[d] Indene **3q**:indene **3r**=43:14.
[e] Reaction was undertaken in $ClCH_2CH_2Cl$ instead of CH_2Cl_2 at reflux.

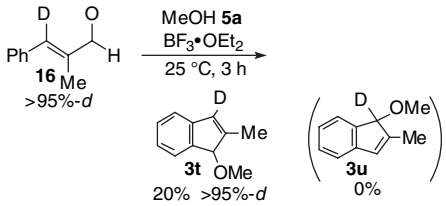
On the other hand, *m*-substituted α-methylcinnamaldehydes **11** and **14** afforded 5- and 7-substituted indenes (Entries 3 and 6). In these cases, 5-substituted ones were produced preferentially compared to 7-substituted ones. This behavior is probably due to the steric effect of the substituent of aromatic ring.

2.4. Reaction mechanisms

The plausible reaction pathway for the formation of 1-alkoxyindenes is elucidated on the basis of the results of the following two experimental approaches. First is the reaction of a partially deuterated α-methylcinnamaldehyde. Second is the analysis of the ^{13}C NMR spectral change of the reaction solution.

The reaction of β-deuterated α-methylcinnamaldehyde (**16**) with MeOH (**5a**) in the presence of $BF_3{\cdot}OEt_2$ afforded

3-deuterio-1-methoxy-2-methylindene (**3t**) (Scheme 5). In this case, 1-deuterio-1-methoxy-2-methylindene (**3u**) was not obtained at all. As the cyclization proceeds via carbon–carbon bond formation between the carbonyl carbon and the *ortho*-carbon of aromatic ring, this result indicates that the alkoxylation occurs at the carbonyl carbon of α-alkylcinnamaldehyde during the formation of 1-alkoxyindenes. In other words, this conversion does not proceed via Michael type alkoxylation product but via acetal or its equivalent. The results agree with the formation of 1-alkoxyindene **3a** from α-methylcinnamaldehyde dimethyl acetal (**4**) described in the previous section.



Scheme 5.

In addition, this result also means that the alkoxylating agent does not attack via S_N2' type displacement against the alkoxy group in the formed 1-alkoxyindene. On the other hand, Wadia's group has reported that 1-chloroindenes are formed via the reaction of α,β-unsaturated carbonyl compounds with hydrogen chloride.[7] In their paper, 1-chloroindene is proposed to be formed by S_N2' attack of the chloride ion against the hydroxy group of the indenol intermediate that is formed via intramolecular electrophilic aromatic substitution of the α,β-unsaturated carbonyl compound. In contrast, the 1-alkoxyindenes in the transformation reaction presented here are inertness against nucleophilic substitution and the alkoxy group attached on the indene ring retains throughout the transformation.

2.5. Determination of intermediates with the aid of NMR study of the reaction mixture

The intermediates of this reaction are determined as methoxycarbenium ion **17** and γ-alkoxyallyl cation **18** by NMR spectra of reaction solutions. Figure 1 shows the ^{13}C NMR spectral change of the reaction solution of α-methylcinnamaldehyde

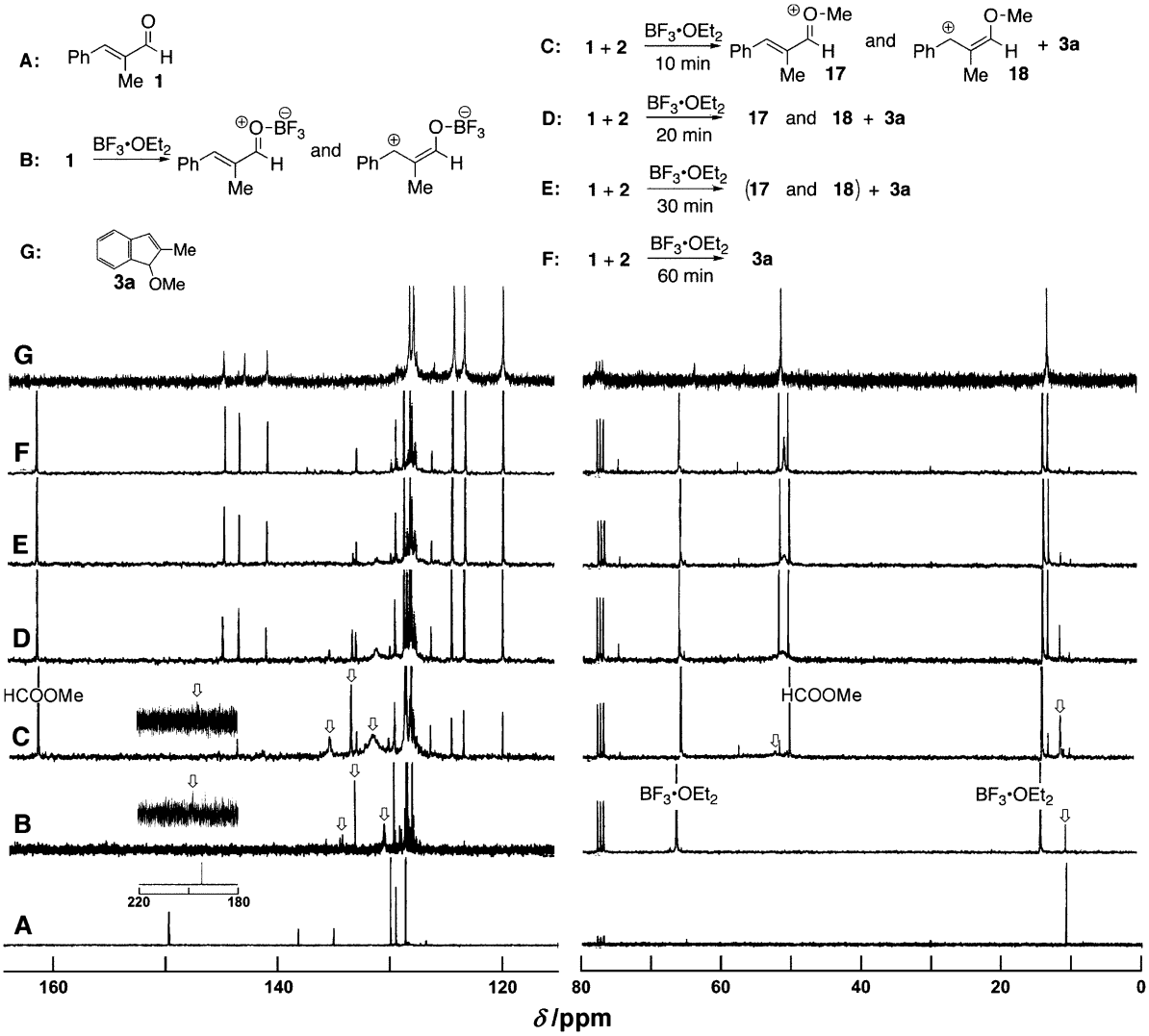
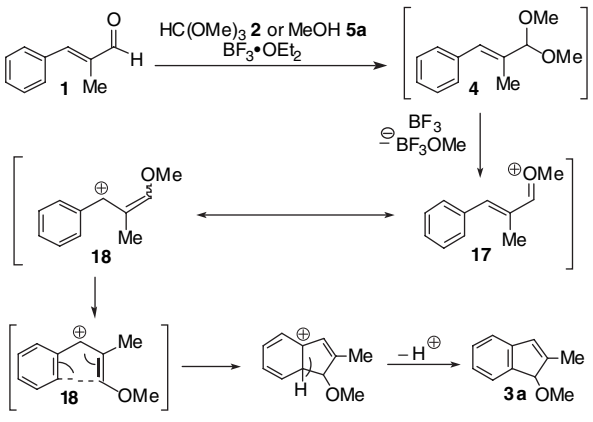


Figure 1. ^{13}C NMR spectra of the reaction solution of α-methylcinnamaldehyde (**1**) with $HC(OMe)_3$ (**2**) and $BF_3{\cdot}OEt_2$, and the related reaction solutions in $CDCl_3$ at rt.

(**1**) with $HC(OMe)_3$ (**2**) in the presence of $BF_3{\cdot}OEt_2$ and the spectra of the related solutions. After addition of an equimolar amount of $BF_3{\cdot}OEt_2$ to the solution of α-methylcinnamaldehyde (**1**) and an equimolar amount of $HC(OMe)_3$ (**2**), α-methylcinnamaldehyde (**1**) and $HC(OMe)_3$ (**2**) are rapidly consumed and an intermediate and methyl formate (HCOOMe) are generated (Fig. 1, 10 min). Then, the intermediate disappears and 1-methoxy-2-methylindene (**3a**) appears and increases with passage of time (Fig. 1, 10–60 min). The intermediate has the broad signals of methoxy, carbonyl, and two alkenyl carbons and the sharp signals of methyl and some aromatic carbons (marked by arrows in the spectrum). Those signals except that at around 50 ppm due to the methoxy carbon are essentially identical to those of the solutions of the mixture of α-methylcinnamaldehyde (**1**) and $BF_3{\cdot}OEt_2$ (Fig. 1). This behavior means that the electron structure of the reaction intermediate should be a homologue of the BF_3-coordinated complex of α-methylcinnamaldehyde (**1**). Thus, the intermediates are proposed as methoxycarbenium ion **17** and its resonance structure as γ-methoxyallyl cation **18**.

2.6. Plausible reaction pathway

The plausible pathway of the reaction of α-methylcinnamaldehyde (**1**) with alkoxylating agents to form 1-methoxy-2-methylindene (**3a**) is shown in Scheme 6 on the basis of the consideration described above. In this pathway, α-methylcinnamaldehyde (**1**) is transformed into the corresponding acetal (**4**) through the coordination of BF_3 to the carbonyl oxygen and the nucleophilic attack of alkoxylating agent, i.e., orthoester **2** and alcohol **5a**. Then, elimination of an alkoxide group from acetal **4** with the aid of BF_3 affords the resonance hybrid of alkoxycarbenium ions **17** and γ-methoxyallyl cations **18**. These cations presumably produce small amounts of the corresponding geometrical isomers. The sterically crowded geometrical isomers thus formed are certainly liable to intramolecular electrophilic aromatic substitution ring closure to yield 1-methoxy-2-methylindene (**3a**). In this ring closure transformation, the α-alkyl group of α-substituted cinnamaldehydes probably assists the formation of the precursory isomers of the alkoxycarbenium ion/γ-alkoxyallyl cation. When cinnamaldehydes have no α-alkyl groups, formation of the sterically unfavorable geometrical isomer is strictly prevented. In this consequence, cinnamaldehyde (**7**) does not afford 1-alkoxyindenes because of the lack of α-alkyl group that destabilize the precursor.



Scheme 6.

3. Conclusion

We have found the reaction of α-alkylcinnamaldehyde with alkoxylating agents to afford 1-alkoxy-2-alkylindenes. The scope and limitation and the reaction mechanisms have also been elucidated. This reaction has sufficient potential for the novel preparative synthesis of indene skeleton compounds by one pot operation.

4. Experimental

4.1. General

Trimethyl orthoformate (**2**), alcohols **5**, thiophenol (**6**), boron trifluoride etherates, nitrobenzene, CH_2Cl_2, and $ClCH_2CH_2Cl$ were purchased and purified according to the method in the literature.[25] Other acidic mediators were employed as received. α-Alkylcinnamaldehydes were synthesized by the same method as in the literature.[26] Acetal **4** was synthesized by the same method as in the literature.[27] Distillation of indene derivatives was carried out by Kügelrohr distillation. Boiling point was determined by the temperature of the furnace. ^1H NMR spectra were recorded on a JEOL JNM-LA500 (500 MHz) or a JEOL JNM-AL300 (300 MHz) spectrometer using Me_4Si (^1H, δ 0.00) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-LA500 (125 MHz) or a JEOL JNM-AL300 (75 MHz) spectrometer using $CDCl_3$ (^{13}C, δ 77.0) as an internal standard. IR spectra were recorded on a JASCO FTIR-5300. High-resolution mass spectra (HRMS) were recorded on a JEOL MStation JMS-700.

4.1.1. 3-Chloro-α-methylcinnamaldehyde (14). Aldehyde **14** was synthesized from 3-chlorobenzaldehyde and propanal by the same method of the literature.[25] Isolated yield 50% [distillation], pale yellow oil. Bp 130–132 °C (10 mmHg). ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (1H, s), 7.50 (1H, s), 7.34–7.45 (3H, m), 7.20 (1H, s), 2.07 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 147.8, 139.4, 136.7, 134.6, 129.9, 129.6, 129.4, 127.9, 10.9 ppm. IR (neat) ν 1675, 1630, 1606, 1450, 1114, 900 cm^{-1}. Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02. Found: C, 66.64; H, 4.97.

4.2. Typical procedure for the reaction of α-alkylcinnamaldehyde with alkoxylating agent in the presence of acidic mediator

Method A: $BF_3{\cdot}OEt_2$ (0.5 mmol, 0.071 g) was added to the solution of α-alkylcinnamaldehyde (0.5 mmol) and $HC(OMe)_3$ (2 mmol, 0.21 g) in CH_2Cl_2 (2.5 mL) and stirring at 25 °C for 3 h. The solution was quenched with water (20 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined extracts were washed with saturated aqueous NaCl (15 mL×3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Method B: $BF_3{\cdot}OEt_2$ (5 mmol, 0.710 g) was added to the mixture of α-alkylcinnamaldehyde (0.5 mmol) and alkoxylating agent (5 mmol) and stirring at 25 °C for 3 h. The solution was quenched with water (20 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined extracts were

washed with saturated aqueous NaCl (15 mL×3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

4.2.1. 1-Methoxy-2-methylindene (3a).[17,21] Isolated yield 45% [method A, silica gel column chromatography (hexane/ethyl acetate=5:1 v/v) and distillation], pale yellow oil. Bp 92–94 °C (8 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d, J=7.5 Hz), 7.23 (1H, t, J=7.5 Hz), 7.14 (1H, d, J=7.5 Hz), 7.12 (1H, t, J=7.5 Hz), 6.45 (1H, s), 4.86 (1H, s), 3.05 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 143.8, 141.7, 128.7, 128.3, 124.6, 123.7, 120.1, 84.8, 51.8, 14.1 ppm. IR (neat) ν 1720, 1626, 1606, 1464, 1373, 1321, 1207, 1107, 1080, 752 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}O$ $(M-H)^+$ 159.0810, found 159.0766.

4.2.2. 1-Isopropoxy-2-methylindene (3b). Isolated yield 34% [method B, silica gel column chromatography (toluene) and distillation], pale yellow oil. Bp 110–113 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, d, J=7.2 Hz), 7.18 (1H, t, J=7.2 Hz), 7.05–7.08 (2H, m), 6.34 (1H, s), 4.79 (1H, s), 3.78 (1H, sept, J=6.0 Hz), 2.04 (3H, s), 1.24 (3H, d, J=6.0 Hz), 1.18 (3H, d, J=6.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 143.8, 143.1, 127.9, 127.2, 124.3, 123.3, 119.8, 83.4, 70.2, 23.4, 23.2, 14.1 ppm. IR (KBr) ν 1720, 1618, 1460, 1381, 1302, 1107, 1070, 750, 702 cm^{-1}. HRMS m/z (EI) calcd for $C_{13}H_{16}O$ $(M)^+$ 188.1201, found 188.1201.

4.2.3. 2-Methyl-1-(2-phenylethoxy)indene (3f). Isolated yield 34% [method B, silica gel column chromatography (toluene) and distillation], yellow oil. Bp 140–145 °C (6 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–7.30 (9H, m), 6.38 (1H, s), 4.86 (1H, s), 3.53 (2H, t, J=7.5 Hz), 2.83 (2H, t, J=7.5 Hz), 1.92 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 143.6, 142.1, 139.0, 128.9, 128.8, 128.3, 128.2, 126.1, 124.5, 123.6, 120.0, 84.4, 65.3, 36.7, 14.0 ppm. IR (KBr) ν 1722, 1602, 1454, 1282, 1078, 750, 700 cm^{-1}. HRMS m/z (EI) calcd for $C_{18}H_{18}O$ $(M)^+$ 250.1358, found 250.1286.

4.2.4. 1-(2-Bromoethoxy)-2-methylindene (3g). Isolated yield 15% [method B, silica gel column chromatography (toluene) and distillation], yellow oil. Bp 123–127 °C (6 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, J=6.9 Hz), 7.24 (1H, t, J=6.9 Hz), 7.10–7.15 (2H, m), 6.45 (1H, s), 4.98 (1H, s), 3.40–3.53 (4H, m), 2.07 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 143.5, 141.5, 128.9, 128.6, 124.8, 123.7, 120.2, 84.3, 64.1, 31.3, 14.1 ppm. IR (KBr) ν 1722, 1601, 1460, 1379, 1277, 1109, 754 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{13}BrO$ $(M)^+$ 252.0150, found 252.0900.

4.2.5. 2-Methyl-1-phenylthioindene (3h). Isolated yield 41% [method B, silica gel column chromatography (toluene) and distillation], pale yellow oil. Bp 138–142 °C (6 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, d, J=7.5 Hz), 7.44 (1H, d, J=7.5 Hz), 7.27 (1H, t, J=7.5 Hz), 7.19 (1H, t, J=7.5 Hz), 7.05–7.16 (5H, m), 6.36 (1H, s), 4.43 (1H, s), 2.17 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 144.9, 143.7, 132.8, 132.5, 128.3, 128.2, 127.4, 127.3, 124.4, 123.9, 120.1, 56.3, 15.0 ppm. IR (KBr) ν 1720, 1583, 1477, 1377, 1024, 750, 700 cm^{-1}. HRMS m/z (EI) calcd for $C_{16}H_{14}S$ $(M)^+$ 238.0816, found 238.0790.

4.2.6. 2-Ethyl-1-methoxyindene (3j).[21] Isolated yield 48% [method A, column chromatography (silica gel, hexane/ethyl acetate=5:1 v/v) and distillation], pale yellow oil. Bp 100–102 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, J=7.2 Hz), 7.23 (1H, t, J=7.5 Hz), 7.14 (1H, d, J=7.5 Hz), 7.12 (1H, t, J=7.5 Hz), 6.46 (1H, s), 4.95 (1H, s), 3.07 (3H, s), 2.25–2.50 (2H, m), 1.21 (3H, t, J=6.6 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 143.8, 141.8, 128.4, 126.7, 124.6, 123.8, 120.3, 83.8, 51.8, 21.5, 12.4 ppm. IR (KBr) ν 1722, 1618, 1460, 1319, 1203, 1103, 1082, 752, 734 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{13}O$ $(M-H)^+$ 173.0966, found 173.0925.

4.2.7. 1-Methoxy-2,6-dimethylindene (3l). Isolated yield 38% [method A, column chromatography (silica gel, hexane/ethyl acetate=5:1 v/v) and distillation], pale yellow oil. Bp 99–102 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.15 (2H, m), 7.00 (1H, s), 6.39 (1H, s), 4.82 (1H, s), 3.03 (3H, s), 2.32 (3H, s), 2.00 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 142.1, 137.1, 136.8, 128.9, 128.8, 124.8, 119.7, 84.8, 51.8, 21.4, 14.0 ppm. IR (neat) ν 1722, 1610, 1512, 1450, 1377, 1091, 817 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1046, found 174.1012.

4.2.8. 1-Methoxy-2,5-dimethylindene (3m). Isolated yield 25% [method A, column chromatography (silica gel, toluene) and distillation], pale yellow oil. Bp 103–106 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J=7.5 Hz), 6.96 (1H, s), 6.93 (1H, d, J=7.5 Hz), 6.39 (1H, s), 4.83 (1H, s), 3.02 (3H, s), 2.37 (3H, s), 2.02 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 144.1, 138.8, 138.1, 128.6, 125.2, 123.5, 121.1, 84.6, 51.6, 21.5, 14.1 ppm. IR (neat) ν 1724, 1608, 1462, 1379, 1265, 1120, 808 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1046, found 174.1012.

4.2.9. 1-Methoxy-2,7-dimethylindene (3n). Isolated yield 8% [method A, column chromatography (silica gel, toluene) and distillation], colorless oil. Bp 101–102 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, t, J=7.5 Hz), 7.14 (1H, t, J=7.5 Hz), 6.95 (1H, d, J=7.5 Hz), 6.90 (1H, d, J=7.5 Hz), 6.43 (1H, s), 4.93 (1H, s), 2.91 (3H, s), 2.39 (3H, s), 2.02 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 139.0, 134.7, 133.5, 128.8, 128.6, 126.5, 117.6, 84.4, 50.4, 22.6, 14.0 ppm. IR (neat) ν 1724, 1608, 1448, 1277, 1087, 825, 704 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1046, found 174.1052.

4.2.10. 1-Methoxy-2,4-dimethylindene (3o). Isolated yield 50% [method A, column chromatography (silica gel, toluene) and distillation], pale yellow oil. Bp 104–108 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–7.20 (3H, m), 6.55 (1H, s), 4.85 (1H, s), 3.03 (3H, s), 2.33 (3H, s), 2.04 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.4, 141.7, 141.6, 129.6, 126.8, 124.6, 121.2, 85.1, 51.7, 18.0, 14.1 ppm. IR (neat) ν 1720, 1601, 1448, 1099, 761 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1046, found 174.1012.

4.2.11. 5-Chloro-1-methoxy-2-methylindene (3q). Isolated yield 19% [method A, column chromatography (silica gel, toluene) and recrystallization (hexane)], colorless needle. Mp 32.5–34 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (1H, d, J=7.2 Hz), 7.10 (1H, s), 7.08 (1H, d, J=7.2 Hz), 6.39 (1H, s), 4.82 (1H, s), 3.02 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.5, 139.9, 134.2, 127.8, 124.5, 124.4, 120.5, 84.2, 51.8, 14.1 ppm. IR (KBr) ν 1724, 1601, 1460, 1278, 1103, 898, 823, 698 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{10}ClO$ $(M-H)^+$ 193.0420, found 193.0376. Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70. Found: C, 67.66; H, 5.77.

4.2.12. 7-Chloro-1-methoxy-2-methylindene (3r). Isolated yield 5% [method A, column chromatography (silica gel, toluene)], pale yellow oil. Bp 115–118 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, t, J=8.1 Hz), 7.05 (1H, d, J=8.1 Hz), 7.01 (1H, d, J=8.1 Hz), 6.41 (1H, s), 4.97 (1H, s), 3.01 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 146.0, 142.1, 138.0, 130.2, 127.9, 125.5, 118.5, 88.4, 51.5, 13.9 ppm. IR (KBr) ν 1730, 1601, 1458, 1280, 790, 758, 702 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}ClO$ $(M)^+$ 194.0498, found 194.0470.

4.2.13. 1-Methoxy-2-methyl-6-nitroindene (3s). Isolated yield 10% [method A, column chromatography (silica gel, toluene) and distillation], yellow oil. Bp 120–123 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, s), 8.20 (1H, d, J=8.1 Hz), 7.24 (1H, d, J=8.1 Hz), 6.55 (1H, s), 4.91 (1H, s), 3.12 (3H, s), 2.13 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 147.7, 147.3, 142.8, 129.4, 123.8, 123.6, 119.7, 83.2, 51.8, 12.5 ppm. IR (neat) ν 1725, 1602, 1456, 1375, 1086, 812 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}NO_3$ $(M)^+$ 205.0739, found 205.0725.

4.2.14. 3-Deuterio-1-methoxy-2-methylindene (3t).[21] Isolated yield 8% [method B, column chromatography (silica gel, hexane/ethyl acetate=5:1 v/v) and distillation], pale yellow oil. Bp 93–96 °C (7 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, J=7.5 Hz), 7.23 (1H, t, J=7.5 Hz), 7.14 (1H, d, J=7.5 Hz), 7.12 (1H, t, J=7.5 Hz), 4.86 (1H, s), 3.05 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 143.8, 141.8, 128.6 (t, J_{CD}=28 Hz), 128.3, 124.6, 123.7, 120.1, 84.8, 51.7, 14.0 ppm. IR (KBr) ν 1720, 1626, 1606, 1464, 1373, 1321, 1207, 1107, 1080, 752 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}DO$ $(M)^+$ 161.0951, found 161.0925.

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1,7-Electrocyclization reactions of stabilized α,β:γ,δ-unsaturated azomethine ylides

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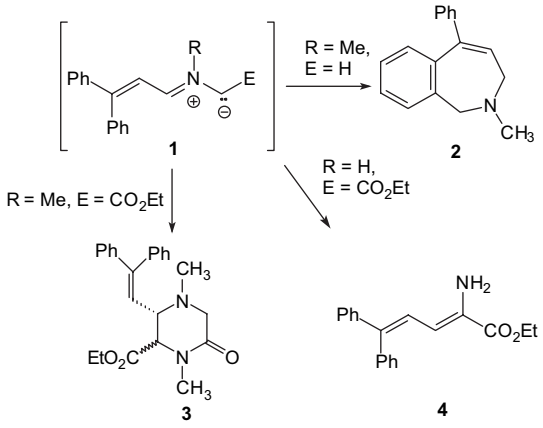
Abstract—Stabilized α,β:γ,δ-unsaturated azomethine ylides were generated by the deprotonation of isoquinolinium salts. 1,7-Electrocyclization of these dipoles, followed by a 1,5-hydrogen shift, gives tetrahydro[5,6]azepino[2,1-*a*]isoquinolines.

1. Introduction

For many years 1,3-dipoles have been used extensively in the construction of five-membered heterocyclic rings via their cycloadditions with suitable dipolarophiles[1] and by the 1,5-electrocyclization reactions of α,β-unsaturated 1,3-dipoles.[2] More recently, the electrocyclization of diene-conjugated 1,3-dipolar intermediates has provided a powerful general synthetic route to seven-membered heterocyclic ring systems.[3] We have been concerned for some years with synthetic and mechanistic aspects of these reactions and, in particular, with the cyclizations of azomethine ylides to give azepines.[4] During these studies we have found significant differences between the reactivity of α,β:γ,δ-unsaturated, non-stabilized **1** (E=H) and α,β:γ,δ-unsaturated, ester-stabilized azomethine ylides **1** (E=CO_2Et). The former dipoles react via a 1,7-electrocyclization,[5] followed by a [1,5]-hydrogen shift to give dihydroazepines **2**, while the latter give other products (**3** or **4**) via novel rearrangements (Scheme 1).[6,7]

We recently published the first examples of the 1,7-electrocyclizations of an azomethine ylide onto a nitro group, producing indazole-*N*-oxides after the ring contraction of the unstable oxadiazepine intermediates.[8] As a continuation of these studies we have now examined the reactivity of some α,β:γ,δ-unsaturated, ester-stabilized azomethine ylides generated by the deprotonation of iminium salts derived from 3,4-dihydroisoquinolines.[9]



Scheme 1.

2. Results and discussion

The synthesis of the dipole precursors was carried out according to the Bischler–Napieralski procedure[10] by cyclization of amides **6a**–**b** in the presence of $POCl_3$ and resulted in the formation of 3,4-dihydroisoquinolines **7a**–**b**. Subsequent reaction with different bromoalkyl derivatives, in anhydrous ether, gave the quaternary salts **8** (Scheme 2, Table 1).

Reacting the isoquinolinium salts **8a**–**j** with triethylamine, at ambient temperature in dry methanol, leads to the formation of 8-substituted-2,3-dimethoxy-13-phenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinolines **11a**–**j** via

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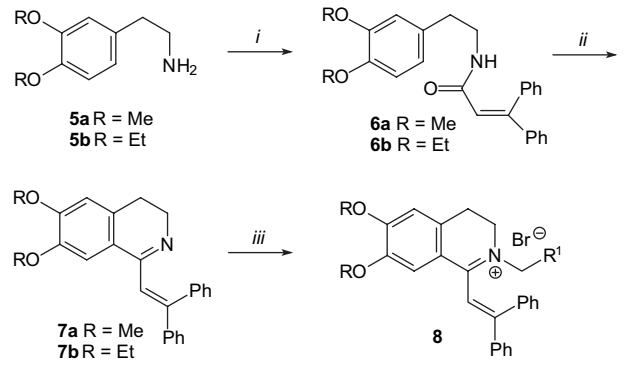
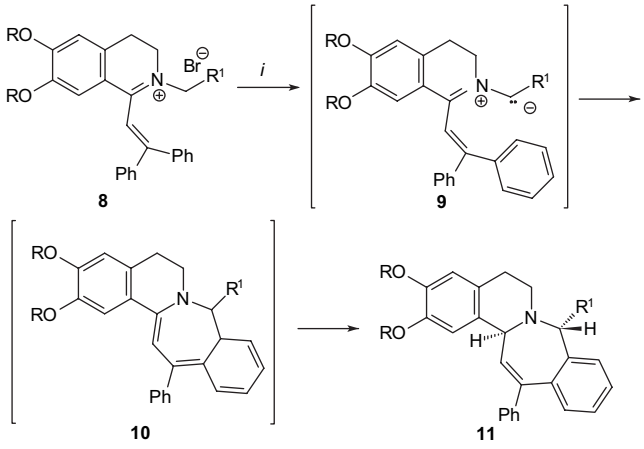


Scheme 2. Reagents and conditions: (i) $Ph_2C{=}CHCOCl$, NaOH, Et_2O, H_2O, rt; (ii) $POCl_3$, toluene, reflux and (iii) R^1CH_2Br, Et_2O, rt.

Table 1

Entry	R	R^1	Product	Yield (%)	Product	Yield (%)
1	Me	$-CO_2Me$	**8a**	100	**11a**	83
2	Et	$-CO_2Me$	**8b**	100	**11b**	86
3	Me	Ph–	**8c**	98	**11c**	77
4	Et	Ph–	**8d**	96	**11d**	82
5	Me	$CH_2{=}CH$–	**8e**	95	**11e**	53
6	Et	$CH_2{=}CH$–	**8f**	97	**11f**	50
7	Me	PhCO–	**8g**	100	**11g**	81
8	Et	PhCO–	**8h**	100	**11h**	80
9	Me	3-MeOPhCO–	**8i**	100	**11i**	85
10	Me	2-CNPh–	**8j**	99	**11j**	73

azomethine ylide intermediates **9a–j**. The benzazepinoisoquinolines could be isolated in moderate to good yields by simple filtration. In this reaction the azomethine ylides are produced by dehydrohalogenation of the isoquinolinium salts,[11] which leads, via a 1,7-electrocyclization to the azepines **10**, and finally, by a [1,5]-hydrogen shift, to the products **11a–j** (Scheme 3, Table 1). The relative stereochemistry of the tetracycles **11a–j** was deduced by NOE studies.

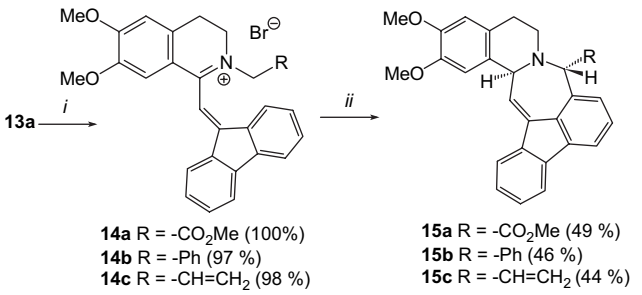


Scheme 3. Reagents and conditions: (i) Et_3N, MeOH, rt.

We next studied the influence of steric restrictions on the ethenyl side chain on the course of 1,7-electrocyclization reaction. The synthesis of the requisite precursors commenced with the conversion of the amides **12**, derived by coupling 2-(3,4-dimethoxyphenyl)ethylamine **5a** with fluorenylidene[12] and naphthoic acid chlorides, to the dihydroisoquinolines **13**.

The cyclized products **13a–b** were obtained in isolated yields greater than 70%, thus showing that the replacement of the side-chains had no affect on the outcome of the cyclization reaction (Scheme 4).

The alkylation of **13a** with three bromoalkyl derivatives, in anhydrous ether, gave the quaternary salts **14a–c**, the reaction of which, with triethylamine at room temperature in methanol, provided the expected hexacyclic products **15a–c**. These novel compounds were isolated in acceptable yields after column chromatography (Scheme 5).

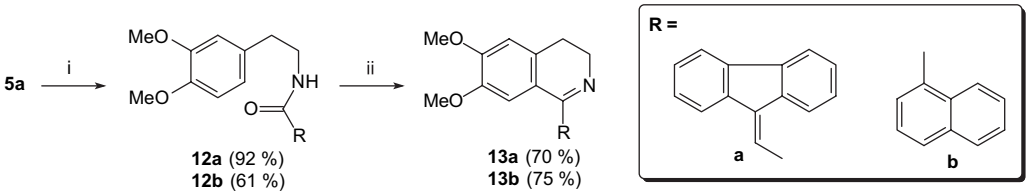


Scheme 5. Reagents and conditions: (i) R^1CH_2Br, Et_2O, rt; (ii) Et_3N, MeOH, rt.

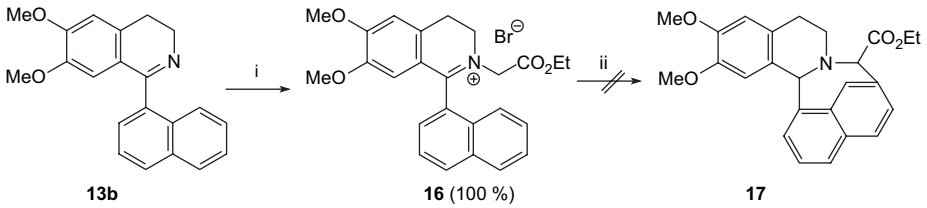
The reaction of quaternary salt **16**, prepared from isoquinoline **13b** and ethyl bromoacetate, with triethylamine or with other bases such as DBU, DABCO, or $KOBu^t$ and in different solvents, did not give the expected cyclized product—only the dihydroisoquinoline **13b** was isolated from the complex reaction mixture formed (Scheme 6).

These experiments show the scope and limitations of our strategy for the construction of the azepine ring system via the 1,7-electrocyclization of these azomethine ylides. The reactions with the diphenylethenyl side chains proceeded in good to excellent yield, depending upon the electron-withdrawing ability of the substituent on the azomethine ylide. The steric restrictions caused by the additional bond between the two phenyl groups in the dipoles derived from **14a–c** resulted in significant decrease in the yields of the electrocyclization products **15a–c** and the rigid nature of the naphthalene side chain makes the reaction of **16** impossible.

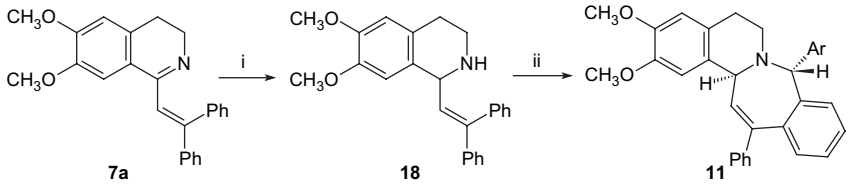
In order to extend the scope of this reaction we have used a different method for the generation of α,β:γ,δ-unsaturated



Scheme 4. Reagents and conditions: (i) RCOCl, NaOH, Et_2O, H_2O, rt and (ii) $POCl_3$, toluene, reflux.



Scheme 6. Reagents and conditions: (i) EtO_2CCH_2Br, Et_2O, rt and (ii) Et_3N, MeOH, rt.



Scheme 7. Reagents and conditions: (i) $NaBH_4$, EtOH and (ii) ArCHO, xylene, reflux.

azomethine ylides **9** where R^1 is derived from an aromatic aldehyde. This method was efficiently used by Grigg and co-workers in the synthesis of a pyrrolo[2,1-*a*]isoquinoline via a 1,5-electrocyclization.[13] The reduction of **7a** with sodium borohydride gave the tetrahydroisoquinoline **18**, which on refluxing with xylene, reacted slowly with various aromatic aldehydes furnishing tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinolines **11c**, **11k**, **11l** and **11m** in low yield (Scheme 7, Table 2).

Table 2

Entry	Ar	Reaction time (h)	Product	Yield (%)
1	Ph–	16	**11c**	24
2	4-ClPh–	12	**11k**	32
3	4-MeO–Ph–	30	**11l**	26
4	3,4-MeO–Ph–	48	**11m**	11

We have thus successfully developed a mild and efficient protocol for the convenient synthesis of tetrahydrobenz[5,6]-azepino[2,1-*a*]isoquinolines from stabilized azomethine ylides. The mechanistic course of the reaction suggests the involvment of an 8π-electrocyclization process, followed by a sigmatropic 1,5-hydrogen shift. This methodology may find application in the synthesis of the pharmacologically interesting homoprotoberberine derivatives.[14]

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using Merck Kieselgel 60, 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml concd sulfuric acid and 1 ml anisaldehyde) and heated at ca. 150 °C. IR spectra were obtained on a Bruker VECTOR 22 FTIR instrument. NMR spectra were obtained on Varian INOVA 500, Bruker DRX-500 and Bruker 250 instruments. Chemical shifts are given relative to δ_{TMS}. All solvents were purified according to standard procedures.

3.1.1. *N*-[2-(3′,4′-Dimethoxyphenyl)ethyl]-3,3-diphenyl-2-propenamide (6a). 2-(3,4-Dimethoxy-phenyl)ethyl amine **5a** (7.27 g, 40 mmol) was dissolved in ether (40 ml) and 10% aqueous sodium hydroxide (1.6 g, 40 mmol in 15 ml water) was added at 0 °C. A solution of β-phenylcinnamoyl chloride (9.97 g, 40 mmol) in ether (30 ml) was added dropwise. After 4 h stirring at room temperature the precipitated product was filtered off and washed with water then ether and dried in air to give the product as a white powder (10.70 g, 69%), mp 162–163 °C; [Found: C, 77.7; H, 6.5; N, 3.5. $C_{25}H_{25}NO_3$ requires C, 77.5; H, 6.5; N, 3.6%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.35–7.21 (m, 10H, Ar–H), 6.73 (d, 1H, *J*=8.0 Hz, H-5′), 6.57 (s, 1H, H-2′), 6.51 (d, 1H, *J*=8.0 Hz, H-6′), 6.35 (s, 1H, H-2), 5.35 (br s, 1H, NH), 3.85 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.33 (t, 2H, *J*=7.2 Hz, CH_2), 2.48 (t, 2H, *J*=7.2 Hz, NCH_2); ^{13}C NMR (63 MHz, $CDCl_3$): 166.7 (quat.), 149.4 (quat.), 148.8 (quat.), 147.5 (quat.), 140.6 (quat.), 138.3 (quat.), 131.1 (quat.), 129.3 (2×CH), 128.8 (CH), 128.4 (2×CH), 128.35 (CH), 128.3 (2×CH), 127.8 (2×CH), 122.5 (CH), 120.4 (CH), 111.6 (CH), 111.2 (CH), 55.8 (CH_3), 55.7 (CH_3), 40.4 (CH_2), 34.6 (CH_2); IR (KBr, cm^{-1}): 3286, 3057, 2962, 2925, 2835, 1639, 1614, 1547, 1518, 1464, 1442, 1417, 1386, 1356, 1287, 1270, 1225, 1160, 1151, 1137, 1028.

3.1.2. *N*-[2-(3′,4′-Diethoxyphenyl)ethyl]-3,3-diphenyl-2-propenamide (6b). Compound **6b** was prepared, in a manner analogous to that for **6a**, from amine **5b** (8.4 g, 40 mmol) and was isolated as a white powder (11.2 g, 67.5%), mp 158–159 °C; [Found: C, 77.9; H, 6.8; N, 3.5. $C_{27}H_{29}NO_3$ requires C, 78.0; H, 7.0; N, 3.4%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.35–7.18 (m, 10H, Ar–H), 6.74 (d, 1H, *J*=8.1 Hz, H-5′), 6.58 (d, 1H, *J*=1.7 Hz, H-2′), 6.45 (dd, 1H, *J*=8.1 and 1.7 Hz, H-6′), 6.35 (s, 1H, H-2), 5.40 (br s, 1H, NH), 4.08–3.98 (m, 4H, OCH_2), 3.33 (t, 2H, *J*=7.2 Hz, CH_2), 2.48 (t, 2H, *J*=7.2 Hz, NCH_2), 1.42 (t, 6H, *J*=7.0 Hz, 2×CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 166.2 (quat.), 149.4 (quat.), 148.5 (quat.), 147.0 (quat.), 140.6 (quat.), 138.2 (quat.), 132.2 (quat.), 131.1 (CH), 129.1 (2×CH), 128.6 (CH), 128.3 (2×CH), 128.1 (2×CH), 127.7 (2×CH), 122.3 (CH), 120.5 (CH), 113.7 (CH), 113.4 (CH), 64.4 (CH_2), 64.2 (CH_2), 40.3 (CH_2), 34.5 (CH_2), 14.7 (2×CH_3); IR (KBr, cm^{-1}): 3281, 3107,

2955, 2845, 1638, 1612, 1539, 1520, 1441, 1386, 1301, 1282, 1271, 1150, 1132, 1022.

3.1.3. 6,7-Dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinoline (7a). *N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-3,3-diphenyl-2-propenamide **6a** (7.0 g, 18 mmol) was dissolved in dry benzene (30 ml) and freshly distilled phosphorus oxychloride (3.67 g, 24 mmol) was added dropwise to the well-stirred mixture at 0 °C. The reaction mixture was then refluxed and stirred for 4 h, followed by cooling to room temperature. Then benzene was decanted and the semi-solid residue was stirred overnight with an excess of 10% aqueous sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate (3×25 ml) and the combined organic extracts were washed with brine (25 ml), then dried ($MgSO_4$) and the solvent evaporated in vacuo to yield the title product as a yellow solid (4.92 g, 74%), mp 171 °C (lit.[10a] 168–170 °C); ^{1}H NMR (250 MHz, DMSO-d_6): 7.40–7.30 (m, 6H, Ar–H), 7.10 (m, 4H, Ar–H), 6.85 (s, 1H, H-8), 6.79 (s, 1H, H-5), 6.57 (s, 1H, CH═), 3.82 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.59 (t, 2H, *J*=7.5 Hz, H-4), 2.55 (t, 2H, *J*=7.5 Hz, H-3); ^{13}C NMR (63 MHz, DMSO-d_6): 164.2 (quat.), 150.1 (quat.), 148.0 (quat.), 146.5 (quat.), 141.7 (quat.), 139.2 (quat.), 130.7 (quat.), 129.5 (2×CH), 128.0 (2×CH), 127.7 (CH), 127.2 (4×CH), 125.5 (2×CH), 121.2 (quat.), 109.6 (CH), 109.4 (CH), 55.5 (CH_3), 55.3 (CH_3), 46.7 (CH_2), 25.0 (CH_2); IR (KBr, cm^{-1}): 2995, 2952, 2937, 2904, 2825, 1616, 1595, 1563, 1509, 1490, 1461, 1404, 1361, 1346, 1331, 1317, 1287, 1271, 1232, 1142, 1075, 1026; (HRMS Found: *m*/*z* 369.1711. $C_{25}H_{23}NO_2$ requires *m*/*z* 369.1729).

3.1.4. 6,7-Diethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinoline (7b). Compound **7b** was prepared, in a manner analogous to that for **7a**, from **6b** (9.95 g, 24 mmol) and was isolated as a yellow semi-solid material (6.50 g, 69%); ^{1}H NMR (250 MHz, $CDCl_3$): 7.41–7.12 (m, 11H, Ar–H), 6.85 (s, 1H, H-5), 6.62 (s, 1H, CH═), 4.19 (q, 2H, *J*=7.0 Hz, OCH_2), 3.81 (m, 4H, H-4 and OCH_2), 2.89 (br s, 2H, H-3), 1.45 (t, 3H, *J*=7.0 Hz, CH_3), 1.28 (t, 3H, *J*=7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 164.2 (quat.), 150.3 (quat.), 147.7 (quat.), 146.3 (quat.), 142.0 (quat.), 139.4 (quat.), 130.95 (quat.), 129.6 (2×CH), 128.1 (2×CH), 127.9 (3×CH), 127.8 (CH), 127.3 (2×CH), 125.9 (CH), 121.6 (quat.), 112.3 (CH), 111.2 (CH), 64.6 (CH_2), 63.95 (CH_2), 47.0 (CH_2), 25.2 (CH_2), 14.5 (CH_3), 14.4 (CH_3); IR (KBr, cm^{-1}): 2955, 2947, 2911, 1612, 1599, 1567, 1514, 1488, 1462, 1404, 1388, 1342, 1337, 1319, 1277, 1233, 1200, 1144, 1075, 1033; (HRMS Found: *m*/*z* 397.2055. $C_{27}H_{27}NO_2$ requires *m*/*z* 397.2041).

3.1.5. 6,7-Dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-2-methoxycarbonylmethyl-3,4-dihydroisoquinolinium bromide (8a). Compound **8a** 6,7-dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinoline (0.5 g, 1.35 mmol) was dissolved in dry diethyl ether (30 ml) and methyl bromoacetate (0.56 ml, 0.82 g, 6 mmol) was added. The reaction mixture was stirred at room temperature overnight. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo to give a yellow powder (0.70 g, 100%), mp 260–262 °C; [Found: C, 64.5; H, 5.6; N, 2.7. $C_{28}H_{28}NO_4Br$ requires C, 64.5; H, 5.4; N, 2.7%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.52 (m, 5H, Ph–H), 7.32 (m, 6H, Ph–H and CH═), 7.00 (s, 1H, H-5), 6.91 (s, 1H, H-8), 5.58 (d, 1H, *J*=17.4 Hz, *N*CH_2), 5.17 (d, 1H, *J*=17.4 Hz, *N*CH_2), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.55 (m, 2H, H-4), 3.26 (m, 2H, H-3); ^{13}C NMR (63 MHz, DMSO-d_6): 172.1 (quat.), 166.6 (quat.), 158.2 (quat.), 155.7 (quat.), 147.0 (quat.), 139.2 (quat.), 137.6 (quat.), 134.5 (quat.), 130.4 (CH), 130.0 (2×CH), 129.9 (CH), 129.4 (2×CH), 128.7 (2×CH), 128.3 (2×CH), 117.6 (quat.), 117.1 (CH), 114.5 (CH), 110.9 (CH), 57.6 (CH_2), 56.5 (CH_3), 55.5 (CH_3), 53.1 (CH_3), 50.8 (CH_2), 27.0 (CH_2); IR (KBr, cm^{-1}): 3001, 2950, 2922, 2861, 2832, 1747, 1606, 1550, 1520, 1464, 1387, 1338, 1294, 1270, 1218, 1014.

3.1.6. 6,7-Diethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-2-methoxycarbonylmethyl-3,4-dihydroisoquinolinium bromide (8b). Compound **8b** was prepared analogously to **8a** from **7b** (0.5 g, 1.25 mmol) and was isolated as a yellow powder (0.68 g, 100%), mp 266–267 °C; [Found: C, 65.9; H, 5.7; N, 2.7. $C_{30}H_{32}NO_4Br$ requires C, 65.6; H, 5.9; N, 2.6%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.50–7.43 (m, 5H, Ar–H), 7.18 (m, 6H, Ph–H and CH═), 6.97 (s, 1H, H-5), 6.72 (s, 1H, H-8), 5.73 (d, 1H, *J*=17.9 Hz, *N*CH_2), 5.22 (d, 1H, *J*=17.9 Hz, *N*CH_2), 4.34–4.17 (4H, m, 2×OCH_2), 3.80 (s, 3H, OCH_3), 3.51 (2H, m, H-4), 3.22 (2H, m, H-3), 1.42 (3H, t, *J*=6.9 Hz, CH_3), 1.27 (3H, t, *J*=6.9 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 172.7 (quat.), 166.9 (quat.), 159.3 (quat.), 156.6 (quat.), 147.3 (quat.), 138.9 (quat.), 137.2 (quat.), 130.9 (CH), 130.4 (CH), 130.2 (2×CH), 129.4 (2×CH), 129.0 (2×CH), 128.7 (2×CH), 117.8 (quat.), 116.5 (CH), 115.7 (CH), 111.4 (CH), 65.3 (CH_2), 65.0 (CH_2), 58.7 (CH_2), 53.3 (*O*CH_3), 51.7 (CH_2), 26.2 (CH_2), 14.7 (CH_3), 14.4 (CH_3); IR (KBr, cm^{-1}): 3406, 2979, 2934, 1753, 1604, 1550, 1519, 1475, 1444, 1387, 1334, 1292, 1270, 1215, 1180, 1031.

3.1.7. 2-Benzyl-6,7-dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinolinium bromide (8c). Compound **8c** was prepared analogously to **8a** from **7a** (0.5 g, 1.35 mmol), benzyl bromide (0.36 ml, 0.50 g, 3 mmol) and was isolated as a yellow powder (0.72 g, 98%), mp 241–242 °C; [Found: C, 71.2; H, 5.7; N, 2.7. $C_{32}H_{30}NO_2Br$ requires C, 71.2; H, 5.6; N, 2.6%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.52–7.31 (m, 11H, Ph–H), 7.20 (m, 4H, Ph–H), 7.08 (s, 1H, CH═), 7.00 (s, 1H, H-5), 6.92 (s, 1H, H-8), 5.53 (br s, 2H, NCH_2), 3.78 (s, 3H, *O*Me), 3.70 (m, 2H, H-4), 3.63 (s, 3H, OMe), 3.02 (m, 2H, H-3); ^{13}C NMR (63 MHz, DMSO-d_6): 170.7 (quat.), 156.0 (quat.), 155.5 (quat.), 147.0 (quat.), 139.2 (quat.), 137.5 (quat.), 133.8 (quat.), 132.5 (quat.), 130.1 (CH), 129.6 (CH), 129.4 (2×CH), 129.0 (7×CH), 128.75 (2×CH), 128.3 (2×CH), 117.9 (quat.), 117.8 (CH), 114.4 (CH), 110.8 (CH), 59.8 (CH_2), 56.3 (CH_3), 55.6 (CH_3), 49.8 (CH_2), 24.9 (CH_2); IR (KBr, cm^{-1}): 2952, 2949, 2934, 2901, 2867, 1606, 1550, 1520, 1455, 1384, 1337, 1291, 1215, 1171, 1001.

3.1.8. 2-Benzyl-6,7-diethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinolinium bromide (8d). Compound **8d** was prepared analogously to **8c** from **7b** (0.5 g, 1.25 mmol) and was isolated as a yellow powder (0.69 g, 96%), mp 272 °C; [Found: C, 71.9; H, 6.1; N, 2.7. $C_{34}H_{34}NO_2Br$ requires C, 71.9; H, 6.0; N, 2.5%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.60 (m, 4H, Ar–H), 7.38 (m, 6H,

Ar–H), 7.12–7.08 (m, 7H, Ar–H and H-5 and CH═), 6.74 (s, 1H, H-8), 5.75 (d, 1H, J=15 Hz, NCH_2), 5.49 (d, 1H, J=15 Hz, NCH_2), 4.12 (q, 2H, J=7 Hz, OCH_2), 3.95 (q, 2H, J=7 Hz, OCH_2), 3.50 (m, 2H, H-4), 3.00 (m, 2H, H-3), 1.42 (t, 3H, J=7 Hz, CH_3), 1.36 (t, 3H, J=7 Hz, CH_3); ^{13}C NMR (63 MHz, DMSO-d_6): 170.8 (quat.), 155.6 (quat.), 155.2 (quat.), 146.3 (quat.), 139.2 (quat.), 139.1 (quat.), 137.4 (quat.), 133.8 (quat.), 132.4 (CH), 130.0 (CH), 129.5 (CH), 129.4 (2×CH), 128.9 (6×CH), 128.7 (2×CH), 128.3 (2×CH), 118.0 (CH), 117.9 (CH), 116.0 (quat.), 111.5 (CH), 64.6 (CH_2), 64.1 (CH_2), 59.7 (CH_2), 49.7 (CH_2), 24.9 (CH_2), 14.5 (CH_3), 14.3 (CH_3); IR (KBr, cm^{-1}): 2954, 2945, 2933, 2869, 1603, 1551, 1522, 1458, 1384, 1292, 1225, 1141, 1011.

3.1.9. 2-Allyl-6,7-dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinolinium bromide (8e). 6,7-Dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl]-3,4-dihydroisoquinoline (0.5 g, 1.35 mmol) was dissolved in allyl bromide (8 ml). The resulting solution was heated for 24 h under reflux, under an argon atmosphere. The excess allyl bromide was removed in vacuo and the residue was triturated with dry diethyl ether. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo. The product is a yellow powder (0.63 g, 95%), mp 233–234 °C; [Found: C, 68.8; H, 6.1; N, 2.7. $C_{28}H_{28}NO_2Br$ requires C, 68.7; H, 5.8; N, 2.9%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.46–7.25 (m, 10H, Ar–H), 7.17 (s, 2H, H-5 and H-8), 7.15 (s, 1H, CH═), 5.99 (d, 1H, J=8.1 Hz, allyl–H), 5.80 (m, 1H, allyl–H), 5.45 (m, 1H, allyl–H), 4.76 (d, 1H, J=18.8 Hz, NCH_2), 4.39 (d, 1H, J=18.8 Hz, NCH_2), 3.93 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.62 (m, 2H, H-4), 3.21 (m, 2H, H-3); ^{13}C NMR (63 MHz, DMSO-d_6): 175.6 (quat.), 157.0 (quat.), 148.2 (quat.), 144.8 (quat.), 141.2 (quat.), 139.2 (quat.), 133.5 (quat.), 130.2 (CH), 128.8 (CH), 128.5 (2×CH), 128.3 (3×CH), 127.1 (2×CH), 126.7 (2×CH), 124.6 (CH_2), 114.9 (quat.), 115.8 (CH), 113.5 (CH), 111.7 (CH), 56.6 (CH_3), 56.4 (CH_3), 44.5 (CH_2), 43.2 (CH_2), 25.2 (CH_2); IR (KBr, cm^{-1}): 3005, 2952, 2934, 2867, 1627, 1602, 1559, 1526, 1466, 1423, 1398, 1342, 1298, 1278, 1218, 1167, 1006.

3.1.10. 2-Allyl-6,7-diethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinolinium bromide (8f). Compound **8f** was prepared analogously to **8e** from **7b** (0.5 g, 1.25 mmol) and was isolated as a yellow powder (0.62 g, 97%), mp 274–278 °C; [Found: C, 69.6; H, 6.2; N, 2.7. $C_{30}H_{32}NO_2Br$ requires C, 69.6; H, 6.2; N, 2.7%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.47 (m, 6H, Ar–H), 7.26 (m, 4H, Ar–H), 7.02 (s, 1H, CH═), 6.98 (s, 1H, H-5), 6.73 (s, 1H, H-8), 5.73 (m, 1H, allyl–H), 5.45 (m, 2H, allyl–H), 5.13 (d, 1H, J=19 Hz, NCH_2), 4.90 (d, 1H, J=19 Hz, NCH_2), 4.35–4.15 (m, 4H, 2×OCH_2CH_3), 3.54 (m, 2H, H-4), 3.29 (m, 2H, H-3), 1.48 (t, 3H, J=6.9 Hz, CH_3), 1.23 (t, 3H, J=6.9 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 170.8 (quat.), 157.4 (quat.), 156.3 (quat.), 147.4 (quat.), 138.9 (quat.), 137.3 (quat.), 134.2 (quat.), 130.6 (CH), 130.2 (CH), 129.8 (2×CH), 129.2 (2×CH), 128.9 (2×CH), 128.8 (2×CH), 128.3 (CH), 122.6 (CH_2), 118.1 (quat.), 116.4 (CH), 116.1 (CH), 111.6 (CH), 65.3 (CH_2), 65.1 (CH_2), 60.1 (CH_2), 49.0 (CH_2), 26.1 (CH_2), 14.7 (CH_3), 14.4 (CH_3); IR (KBr, cm^{-1}): 2966, 2944, 2934, 2868, 1628, 1603, 1561, 1522, 1454, 1399, 1345, 1278, 1222, 1169, 1122, 1008.

3.1.11. 6,7-Dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-2-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinolinium bromide (8g). Compound **8g** was prepared analogously to **8a** from **7a** (0.5 g, 1.35 mmol) and phenacyl bromide (0.60 g, 3 mmol) and was isolated as a yellow powder (0.77 g, 100%), mp 263–264 °C; [Found: C, 70.1; H, 5.2; N, 2.7. $C_{33}H_{30}NO_3Br$ requires C, 69.8; H, 5.3; N, 2.5%]; ^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (d, 2H, J=7.4 Hz, Ph–H), 7.89 (d, 2H, J=7.5 Hz, Ph–H), 7.40 (m, 4H, Ph–H), 7.23 (m, 3H, Ph–H), 7.18 (s, 1H, H-8), 7.01 (d, 2H, J=7.4 Hz, Ph–H), 7.00 (s, 1H, H-5), 6.90 (s, 1H, CH═), 6.89 (d, 2H, J=7.5 Hz, Ph–H), 5.80 (m, 1H, H-4), 4.66 (d, 1H, J=18.4 Hz, NCH_2), 4.04 (s, 3H, OMe), 3.98 (s, 3H, OMe), 3.80 (d, 1H, J=18.4 Hz, NCH_2), 3.73 (m, 1H, H-4), 3.47 (m, 1H, H-3), 3.20 (m, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 193.1 (quat.), 177.9 (quat.), 157.2 (quat.), 148.1 (quat.), 144.0 (quat.), 136.8 (quat.), 135.2 (quat.), 134.6 (quat.), 133.2 (quat.), 128.4 (2×CH), 128.3 (5×CH), 127.6 (2×CH), 127.3 (2×CH), 127.1 (CH), 126.9 (CH), 126.6 (2×CH), 121.9 (CH), 120.0 (quat.), 114.3 (CH), 112.9 (CH), 110.8 (CH), 56.2 (CH_3), 56.1 (CH_3), 44.4 (CH_2), 44.1 (CH_2), 25.1 (CH_2); IR (KBr, cm^{-1}): 3422, 3011, 2950, 1684, 1625, 1603, 1559, 1527, 1448, 1426, 1402, 1343, 1299, 1169, 1011.

3.1.12. 6,7-Diethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-2-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinoliniumbromide (8h). Compound **8h** was prepared analogously to **8a** from **7b** phenacyl bromide (0.60 g, 3 mmol) and was isolated as a yellow powder (0.75 g, 100%); mp 260–261 °C; [Found: C, 70.5; H, 6.1; N, 2.3. $C_{35}H_{34}NO_3Br$ requires C, 70.6; H, 5.8; N, 2.3%]; ^{1}H NMR (500 MHz, $CDCl_3$): 8.07 (m, 1H, Ph–H), 7.98 (d, 2H, J=7.8 Hz, Ph–H), 7.86 (d, 2H, J=8.1 Hz, Ph–H), 7.40 (m, 3H, Ph–H), 7.24 (m, 3H, Ph–H and H-8), 7.14 (m, 2H, Ph–H), 7.00 (m, 2H, Ph–H and H-5), 6.92 (s, 1H, CH═), 6.90 (m, 2H, Ph–H), 5.77 (m, 1H, H-4), 4.63 (d, 1H, J=17.1 Hz, NCH_2), 4.25 (q, 2H, J=7.0 Hz, OCH_2), 4.15 (q, 2H, J=7.0 Hz, OCH_2), 3.72 (d, 1H, J=17.1 Hz, NCH_2), 3.70 (m, 1H, H-4), 3.49 (m, 1H, H-4), 3.17 (m, 2H, H-3), 1.51 (t, 3H, J=7.0 Hz, CH_3), 1.49 (t, 3H, J=7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 194.5 (quat.), 177.1 (quat.), 158.0 (quat.), 148.3 (quat.), 144.2 (quat.), 137.3 (quat.), 135.7 (quat.), 134.4 (quat.), 133.8 (quat.), 129.6 (2×CH), 129.3 (2×CH), 128.7 (2×CH), 128.3 (2×CH), 128.0 (2×CH), 127.8 (CH), 127.6 (3×CH), 127.5 (CH), 114.7 (CH), 114.0 (quat.), 112.1 (CH), 112.0 (CH), 65.5 (2×CH_2), 45.7 (CH_2), 44.7 (CH_2), 26.2 (CH_2), 14.6 (CH_3), 14.3 (CH_3); IR (KBr, cm^{-1}): 3031, 2969, 2943, 1670, 1629, 1599, 1587, 1557, 1527, 1464, 1456, 1446, 1426, 1399, 1340, 1298, 1228, 1169, 1093, 1010.

3.1.13. 6,7-Dimethoxy-1-(2′,2′-diphenyl-1′-ethenyl)-2-[2-(4-methoxyphenyl)-2-oxoethyl]-3,4-dihydroisoquinolinium bromide (8i). Compound **8i** was prepared analogously to **8a** from **7a** (0.5 g, 1.35 mmol) and 2′-bromo-4-methoxyacetophenone (0.69 g, 3 mmol) and was isolated as a yellow powder (0.77 g, 100%), mp 272 °C; [Found: C, 68.3; H, 5.2; N, 2.3. $C_{34}H_{34}NO_4Br$ requires C, 68.2; H, 5.4; N, 2.3%]; ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (d, 2H, J=8.3 Hz, Ar–2′ and 6′H), 7.41 (m, 4H, Ph–H), 7.30 (m, 6H, Ph–H), 7.06 (s, 1H, H-8), 6.94 (s, 1H, H-5 and CH═), 6.58 (d, 2H, J=8.3 Hz, Ar–3′ and 5′H), 5.63 (m, 1H, H-4), 4.81 (d, 1H, J=19.0 Hz, NCH_2), 4.68 (d, 1H, J=19.0 Hz, NCH_2), 4.03

(s, 3H, OMe), 3.98 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.70 (m, 1H, H-4), 3.55 (m, 1H, H-3), 3.22 (m, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 191.8 (quat.), 177.3 (quat.), 164.3 (quat.), 157.7 (quat.), 148.8 (quat.), 144.4 (quat.), 137.6 (quat.), 135.9 (quat.), 134.3 (quat.), 129.2 (2×CH), 128.8 (2×CH), 128.7 (2×CH), 128.6 (quat.), 128.5 (CH), 127.9 (2×CH), 127.6 (2×CH), 127.4 (CH), 115.1 (quat.), 114.3 (quat.), 113.6 (2×CH), 112.1 (CH), 111.3 (CH), 56.9 (CH_3), 56.7 (CH_3), 55.8 (CH_3), 45.5 (CH_2), 45.1 (CH_2), 26.0 (CH_2); IR (KBr, cm^{-1}): 2936, 2838, 1675, 1600, 1559, 1526, 1513, 1457, 1424, 1401, 1341, 1297, 1244, 1169, 1045.

3.1.14. 2-(2-Cyanobenzyl)-1-(2′,2′-diphenyl-1′-ethenyl)-6,7-dimethoy-3,4-dihydroisoquinolinium bromide (8j). Compound **8j** was prepared analogously to **8a** from **7a** (0.5 g, 1.35 mmol) and 2-bromomethyl-benzonitrile (0.39 g, 2 mmol) and was isolated as a yellow powder (0.76 g, 99%), mp 192–193 °C; [Found: C, 70.2; H, 5.2; N, 4.8. $C_{33}H_{29}N_2O_2Br$ requires C, 70.2; H, 5.2; N, 5.0%]; ^{1}H NMR (500 MHz, $CDCl_3$): 8.24 (d, 1H, J=7.8 Hz, Ar–3′H), 7.76 (d, 1H, J=7.8 Hz, Ar–6′H), 7.72 (t, 1H, J=7.8 Hz, Ar–5′H), 7.59–7.44 (m, 5H, Ph–H and Ar–4′H), 7.40 (d, 2H, J=7.5 Hz, Ph–H), 7.35 (m, 2H, Ph–H and H-8), 7.26 (t, 1H, J=7.5 Hz, Ph–H), 7.19 (d, 2H, J=7.5 Hz, Ph–H), 7.07 (s, 1H, H-5), 6.79 (s, 1H, CH═), 6.21 (d, 1H, J= 15.1 Hz, NCH_2), 5.72 (d, 1H, J=15.1 Hz, NCH_2), 3.91 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.55 (m, 1H, H-4), 3.47 (m, 1H, H-4), 2.98 (m, 1H, H-3), 2.78 (m, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 171.9 (quat.), 158.4 (quat.), 156.3 (quat.), 147.5 (quat.), 138.5 (quat.), 136.7 (quat.), 135.0 (quat.), 134.3 (quat.), 134.0 (CH), 133.3 (CH), 133.2 (CH), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.6 (2×CH), 128.8 (2×CH), 128.65 (2×CH), 128.6 (2×CH), 118.1 (quat.), 117.3 (CH), 116.7 (quat.), 113.9 (CH), 111.6 (CH), 110.3 (CH), 58.0 (CH_2), 56.5 (CH_3), 55.7 (CH_3), 48.8 (CH_2), 25.8 (CH_2); IR (KBr, cm^{-1}): 2937, 2889, 2224, 1604, 1545, 1521, 1447, 1386, 1338, 1292, 1272, 1216, 1172, 1002.

3.2. 1,7-Electrocyclizations—method A

The corresponding 1-(2′,2′-diphenyl-1′-ethenyl)-3,4-dihydroisoquinolinium bromide (0.75 mmol) was dissolved in dry methanol (10 ml) and triethylamine (0.11 ml, 1.5 mmol) was added. The reaction mixture was stirred for 24 h at room temperature under an argon atmosphere. The precipitated products were filtered off, washed with ethanol and dried in air.

3.2.1. Methyl 2,3-dimethoxy-13-phenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline-8-carboxylate (11a). White powder (0.27 g, 83%), mp 148–149 °C; [Found: C, 76.0; H, 6.2; N, 2.9. $C_{28}H_{27}NO_4$ requires C, 76.2; H, 6.2; N, 3.1%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.63 (m, 2H, Ar–H), 7.40 (m, 2H, Ar–H), 7.26 (m, 6H, Ar–H), 7.11 (s, 1H, H-1), 6.64 (s, 1H, H-14), 5.52 (s, 1H, H-14*a*), 4.82 (s, 1H, H-8), 3.89 (s, 6H, 2×OCH_3), 3.34 (s, 3H, CO_2CH_3), 3.31 (m, 2H, H-6), 2.18 (m, 2H, H-5); ^{13}C NMR (63 MHz, $CDCl_3$): 170.7 (quat.), 149.3 (quat.), 147.4 (quat.), 146.2 (quat.), 144.5 (quat.), 143.8 (quat.), 128.6 (quat.) 128.5 (CH, C-9), 128.2 (2×CH), 127.9 (CH, C-11), 127.8 (CH), 127.5 (2×CH), 126.5 (CH, C-10), 126.0 (CH, C-12), 121.1 (quat.), 119.5 (quat.), 110.4 (CH), 107.2 (CH), 102.1 (CH), 76.5 (CH, C-14*a*), 62.1 (CH), 55.8 (CH_3), 55.7 (CH_3), 51.3 (CH_3), 46.5 (CH_2), 29.0 (CH_2); IR (KBr, cm^{-1}): 2985, 2956, 2834, 1723, 1513, 1464, 1450, 1355, 1342, 1275, 1234, 1212, 1177, 1149, 1025.

3.2.2. Methyl 2,3-diethoxy-13-phenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline-8-carboxylate (11b). White powder (0.30 g, 86%), mp 157–159 °C; [Found: C, 76.7; H, 6.5; N, 2.9. $C_{30}H_{31}NO_4$ requires C, 76.7; H, 6.6; N, 3.0%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.60 (m, 2H, Ar–H), 7.37 (m, 2H, Ar–H), 7.27–7.11 (m, 7H, Ar–H), 6.63 (s, 1H, H-14), 5.46 (s, 1H, H-14*a*), 4.79 (s, 1H, H-8), 4.07 (m, 4H, 2×OCH_2), 3.31 (s, 3H, CO_2CH_3), 3.27 (m, 2H, CH_2-6), 2.78 (m, 2H, CH_2-5), 1.44 (t, 3H, J=7.1 Hz, CH_3), 1.42 (t, 3H, J=7.1 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 170.8 (quat.), 149.3 (quat.), 147.1 (quat.), 146.4 (quat.), 144.7 (quat.), 143.9 (quat.), 128.6 (CH), 128.2 (2×CH), 127.8 (CH), 127.6 (2×CH), 127.5 (CH), 127.1 (quat.), 126.5 (CH), 126.1 (CH), 121.3 (quat.), 119.6 (quat.), 112.3 (CH), 109.7 (CH), 102.0 (CH), 76.6 (CH), 64.6 (CH_2), 64.3 (CH_2), 62.2 (CH), 51.4 (CH_3), 46.6 (CH_2), 29.0 (CH_2), 14.8 (CH_3), 14.7 (CH_3); IR (KBr, cm^{-1}): 3053, 3030, 2980, 2932, 2879, 2815, 1749, 1731, 1608, 1509, 1444, 1392, 1333, 1275, 1235, 1208, 1177, 1153, 1108, 1041.

3.2.3. 2,3-Dimethoxy-8,13-diphenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11c). White powder (0.26 g, 77%), mp 140 °C; [Found: C, 83.7; H, 6.2; N, 3.0. $C_{32}H_{29}NO_2$ requires C, 83.6; H, 6.4; N, 3.0%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.53 (m, 2H, Ar–H), 7.33 (m, 2H, Ar–H), 7.20 (m, 2H, Ar–H), 7.02 (m, 7H, Ar–H), 6.87 (m, 3H, Ar–H), 6.63 (s, 1H, H-14), 5.50 (s, 1H, H-14*a*), 5.17 (s, 1H, H-8), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.08 (m, 1H, CH_2-6), 3.02 (m, 1H, CH_2-6), 2.70 (m, 2H, CH_2-5); ^{13}C NMR (63 MHz, $CDCl_3$): 147.6 (quat.), 147.4 (quat.), 145.5 (quat.), 143.6 (quat.), 138.4 (quat.), 129.9 (2×CH), 129.2 (quat.), 129.1 (CH), 128.1 (2×CH), 127.9 (3×CH), 127.7 (quat.), 127.4 (quat.), 127.0 (CH), 126.9 (3×CH), 125.7 (2×CH), 120.1 (quat.), 110.7 (CH), 107.2 (CH), 103.2 (CH), 77.8 (CH), 63.2 (CH), 55.9 (2×CH_3), 45.6 (CH_2), 29.4 (CH_2); IR (KBr, cm^{-1}): 2945, 2922, 2830, 1608, 1500, 1462, 1337, 1270, 1231, 1212, 1174, 1148, 1020.

3.2.4. 2,3-Diethoxy-8,13-diphenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11d). White powder (0.30 g, 82%), mp 142–143 °C; [Found: C, 83.8; H, 7.0; N, 2.9. $C_{34}H_{33}NO_2$ requires C, 83.7; H, 6.8; N, 2.9%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.58 (m, 2H, Ar–H), 7.37 (m, 2H, Ar–H), 7.27 (m, 2H, Ar–H), 7.12–7.01 (m, 10H, Ar–H), 6.69 (s, 1H, H-14), 5.52 (s, 1H, H-14*a*), 5.22 (s, 1H, H-8), 4.13 (m, 4H, OCH_2), 3.17 (m, 1H, CH_2-6), 2.96 (m, 1H, CH_2-6), 2.74 (m, 2H, CH_2-5), 1.51 (t, 3H, J=7.1 Hz, CH_3), 1.49 (t, 3H, J=7.1 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 149.0 (quat.), 147.2 (quat.), 145.0 (quat.), 144.4 (quat.), 143.5 (quat.), 129.8 (2×CH), 129.0 (2×CH), 127.9 (2×CH), 127.75 (2×CH), 127.7 (quat.), 127.6 (quat.), 127.4 (quat.), 127.2 (2×CH), 126.8 (CH), 125.5 (3×CH), 119.9 (quat.), 112.3 (CH), 109.4 (CH), 102.8 (CH), 77.7 (CH, C-8), 64.5 (CH_2), 64.2 (CH_2), 63.0 (CH), 45.4 (CH_2), 29.2 (CH_2), 14.6 (CH_3), 14.5 (CH_3); IR (KBr, cm^{-1}): 2963, 2955, 2932, 2811, 1609, 1508, 1488, 1463, 1338, 1270, 1233, 1210, 1179, 1166, 1141, 1011.

3.2.5. 8-Ethenyl-2,3-dimethoxy-13-phenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11e). White powder (0.16 g, 53%), mp 133 °C; [Found: C, 82.4; H, 6.5; N, 3.0. $C_{28}H_{27}NO_2$ requires C, 82.1; H, 6.6; N, 3.4%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.44 (m, 2H, Ar–H), 7.33 (m, 2H, Ar–H), 7.25–7.11 (m, 7H, Ar–H), 6.64 (s, 1H, H-14), 5.67 (s, 1H, H-14*a*), 5.46–5.33 (m, 3H, vinyl–H and H-8), 5.23 (dd, 1H, *J*=2.8 and 8.6 Hz, vinyl–H), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.20 (m, 1H, CH_2-6), 3.05 (m, 1H, CH_2-6), 2.71 (m, 2H, CH_2-5); ^{13}C NMR (63 MHz, $CDCl_3$): 149.3 (quat.), 149.2 (quat.), 145.9 (quat.), 144.6 (quat.), 136.5 (quat.), 129.7 (quat.), 129.2 (2×CH), 128.3 (CH), 128.2 (CH), 128.0 (quat.), 127.6 (CH), 127.5 (CH), 127.45 (CH), 126.2 (2×CH), 126.1 (CH_2), 126.0 (CH), 119.9 (quat.), 112.5 (CH), 109.8 (CH), 103.7 (CH), 78.5 (CH), 60.9 (CH), 55.95 (CH_3), 55.9 (CH_3), 45.2 (CH_2), 29.4 (CH_2); IR (KBr, cm^{-1}): 3052, 3011, 2980, 2921, 2811, 1611, 1514, 1478, 1437, 1417, 1389, 1333, 1234, 1184, 1177, 1155, 1111, 1021.

3.2.6. 2,3-Diethoxy-13-phenyl-8-vinyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11f). White powder (0.16 g, 50%), mp 139–140 °C; [Found: C, 82.3; H, 6.9; N, 3.0. $C_{30}H_{31}NO_2$ requires C, 82.3; H, 7.1; N, 3.2%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.44 (m, 2H, Ar–H), 7.33 (m, 2H, Ar–H), 7.25–7.11 (m, 7H, Ar–H), 6.64 (s, 1H, H-14), 5.67 (s, 1H, H-14*a*), 5.46–5.33 (m, 3H, vinyl and H-8), 5.23 (dd, 1H, *J*=2.8 and 8.6 Hz, vinyl–H), 4.09 (m, 4H, OCH_2), 3.18 (m, 1H, CH_2-6), 3.08 (m, 1H, CH_2-6), 2.76–2.55 (m, 2H, CH_2-5), 1.45 (t, 6H, *J*=6.9 Hz, 2×CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 149.3 (quat.), 149.2 (quat.), 145.8 (quat.), 144.6 (quat.), 136.8 (quat.), 129.7 (quat.), 129.2 (2×CH), 128.3 (CH), 128.1 (CH), 128.0 (quat.), 127.6 (2×CH), 127.5 (CH), 126.2 (2×CH), 126.15 (CH_2), 126.1 (CH), 120.0 (quat.), 112.5 (CH), 109.6 (CH), 103.4 (CH, C-1), 78.3 (CH, C-8), 64.8 (OCH_2), 64.4 (OCH_2), 61.1 (CH), 45.1 (CH_2-6), 29.4 (CH_2-5), 14.9 (CH_3), 14.8 (CH_3); IR (KBr, cm^{-1}): 3077, 2978, 2917, 2879, 2807, 1608, 1511, 1474, 1438, 1416, 1388, 1334, 1273, 1233, 1208, 1184, 1150, 1110, 1088, 1037.

3.2.7. 2,3-Dimethoxy-13-phenyl-8-benzoyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11g). White powder (0.31 g, 81%), mp 164–165 °C; [Found: C, 81.3; H, 6.0; N, 3.0. $C_{33}H_{29}NO_3$ requires C, 81.3; H, 6.0; N, 2.9%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.98 (d, 2H, *J*=7.7 Hz, Ph–2′ and 6′H), 7.65 (d, 2H, *J*=7.4 Hz, Ph–2′ and 6′H), 7.37–7.24 (m, 3H), 7.15–6.70 (m, 9H), 6.67 (s, 1H, H-14), 5.50 (s, 1H, H-14*a*), 5.32 (s, 1H, H-8), 4.01 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.15 (m, 1H, CH_2-6), 3.05 (m, 1H, CH_2-6), 2.72 (m, 2H, CH_2-5); ^{13}C NMR (63 MHz, $CDCl_3$): 199.8 (quat.), 148.6 (quat.), 148.3 (quat.), 147.4 (quat.), 144.1 (quat.), 139.9 (quat.), 132.0 (quat.), 130.0 (quat.), 128.8 (CH), 128.6 (2×CH), 128.4 (CH), 128.0 (2×CH), 127.8 (CH), 127.3 (2×CH), 127.2 (CH), 127.1 (2×CH), 126.9 (CH), 126.3 (CH), 125.4 (quat.), 119.3 (quat.), 111.9 (CH), 109.3 (CH), 101.6 (CH), 80.5 (CH), 56.3 (CH_3), 56.2 (CH_3), 62.5 (CH), 46.1 (CH_2), 28.8 (CH_2); IR (KBr, cm^{-1}): 2967, 2954, 2887, 1692, 1625, 1606, 1560, 1525, 1448, 1428, 1404, 1349, 1278, 1230, 1170, 1024, 1001.

3.2.8. 2,3-Diethoxy-13-phenyl-8-benzoyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11h). White powder (0.31 g, 80%); mp 167 °C; [Found: C, 81.5; H, 6.4; N, 2.7. $C_{30}H_{31}NO_2$ requires C, 81.5; H, 6.4; N, 2.7%]; ^{1}H NMR (250 MHz, $CDCl_3$): 7.95 (d, 2H, *J*=7.7 Hz, Ar–2′ and 6′H), 7.63 (d, 2H, *J*=7.4 Hz, Ph–2′ and 6′H), 7.37–7.21 (m, 3H), 7.17–6.99 (m, 6H), 6.66 (m, 3H), 6.64 (s, 1H, H-14), 5.51 (s, 1H, H-14*a*), 5.35 (s, 1H, H-8), 4.24–4.07 (m, 4H, OCH_2), 3.12 (m, 1H, CH_2-6), 3.01 (m, 1H, CH_2-6), 2.84 (m, 1H, CH_2-5), 2.73 (m, 1H, CH_2-5), 1.50 (t, 3H, *J*=7.1 Hz, CH_3), 1.47 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 200.0 (quat.), 149.1 (quat.), 148.0 (quat.), 147.0 (quat.), 144.1 (quat.), 144.0 (quat.), 129.9 (CH), 128.9 (CH), 128.6 (2×CH), 128.5 (CH), 127.9 (2×CH), 127.7 (CH), 127.3 (2×CH), 127.2 (quat.), 127.1 (2×CH), 127.0 (CH), 126.1 (CH), 125.9 (quat.), 125.5 (quat.), 119.4 (quat.), 111.8 (CH), 109.5 (CH), 101.6 (CH), 80.5 (CH), 64.5 (CH_2), 64.1 (CH_2), 62.5 (CH), 46.1 (CH_2), 28.8 (CH_2), 14.5 (CH_3), 14.4 (CH_3); IR (KBr, cm^{-1}): 2957, 2954, 2899, 2834, 1691, 1626, 1606, 1562, 1524, 1444, 1400, 1279, 1233, 1144, 1102, 1024, 1011.

3.2.9. 2,3-Dimethoxy-13-phenyl-8-(4′-methoxybenzoyl)-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11i). White powder (0.33 g, 85%), mp 179–180 °C; [Found: C, 78.9; H, 6.0; N, 2.9. $C_{34}H_{31}NO_4$ requires C, 78.9; H, 6.0; N, 2.7%]; ^{1}H NMR (500 MHz, $CDCl_3$): 7.85 (d, 2H, *J*=7.5 Hz, Ar–2′ and 6′H), 7.67 (d, 2H, *J*=6.7 Hz, Ph–2′ and 6′H), 7.35 (m, 2H, H-10 and H-12), 7.17 (m, 4H, Ph–3′, 4′ and 5′H, H-9), 6.96–6.88 (m, 3H, H-1, H-4 and H-8), 6.63 (s, 1H, H-14), 6.57 (d, 2H, *J*=7.5 Hz, Ar–3′ and 5′H), 5.55 (s, 1H, H-14*a*), 5.29 (s, 1H, H-8), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.04 (m, 2H, CH_2-6), 2.81 (m, 1H, CH_2-5), 2.70 (m, 1H, CH_2-5); ^{13}C NMR (125 MHz, $CDCl_3$): 198.4 (quat.), 162.7 (quat.), 149.5 (quat.), 147.7 (quat.), 147.3 (quat.), 144.3 (quat.), 144.0 (quat.), 131.5 (2×CH), 130.2 (quat.), 129.5 (2×CH), 128.2 (CH), 127.7 (CH), 127.4 (2×CH), 127.2 (quat.), 126.4 (CH), 125.9 (quat.), 125.85 (CH), 125.8 (CH), 119.8 (quat.), 112.4 (2×CH), 110.7 (CH), 107.5 (CH), 102.3 (CH), 81.2 (CH), 62.8 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.1 (CH_3), 46.5 (CH_2), 29.1 (CH_2); IR (KBr, cm^{-1}): 3057, 3005, 2965, 2838, 1648, 1593, 1510, 1490, 1457, 1447, 1314, 1300, 1276, 1260, 1235, 1210, 1170, 1020.

3.2.10. 2,3-Dimethoxy-8-(2-cyanophenyl)-13-phenyl-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11j). White powder (0.26 g, 73%), mp 155 °C; [Found: C, 82.0; H, 5.9; N, 5.7. $C_{33}H_{28}N_2O_2$ requires C, 81.8; H, 5.8; N, 5.8%]; ^{1}H NMR (500 MHz, $CDCl_3$): 7.57 (d, 2H, *J*=7.5 Hz, Ph–2′ and 6′H), 7.48 (dd, 1H, *J*=2.1 and 7.2 Hz, Ar–6′H), 7.37 (t, 1H, *J*=7.5 Hz, Ph–4′H), 7.35 (d, 2H, *J*=7.5 Hz, Ph–3′ and 5′H), 7.23 (d, 1H, *J*=7.2 Hz, Ar–3′H), 7.19 (m, 2H, H-10 and H-11), 7.13 (dt, 1H, *J*=2.1 and 7.2 Hz, Ar–5′H), 7.03 (m, 4H, H-1, H-4, H-12 and Ar–4′H), 6.98 (d, 1H, *J*=7.8 Hz, H-9), 6.67 (s, 1H, H-14), 5.80 (s, 1H, H-14*a*), 5.47 (s, 1H, H-8), 3.93 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.94 (m, 2H, CH_2-6), 2.88 (m, 2H, CH_2-5); ^{13}C NMR (125 MHz, $CDCl_3$): 149.4 (quat.), 147.6 (quat.), 147.0 (quat.), 144.0 (quat.), 143.2 (quat.), 142.9 (quat.), 132.1 (CH), 131.4 (CH), 130.3 (CH), 129.9 (CH), 128.1 (CH), 128.0 (2×CH), 127.5 (2×CH), 127.4 (quat.), 127.1 (2×CH), 126.0 (CH), 125.9 (CH), 125.8 (quat.), 119.8 (quat.), 118.3 (quat.), 112.9 (quat.), 110.6 (CH), 107.3 (CH), 101.3 (CH), 75.0 (CH), 64.3 (CH), 55.8

(CH_3), 55.7 (CH_3), 44.6 (CH_2), 29.4 (CH_2); IR (KBr, cm^{-1}): 3058, 2934, 2223, 1700, 1603, 1493, 1450, 1432, 1338, 1275, 1167, 1090, 1002.

3.2.11. *N*-1-(3′,4′-Dimethoxyphenethyl)-2-(9*H*-9-fluorenylidenyl)acetamide (12a). 2-(3′,4′-Dimethoxyphenyl)-ethylamine (4.54 g, 25 mmol) was dissolved in dry dichloromethane (30 ml) and triethylamine (3.6 ml, 2.5 g, 25 mmol) was added at 0 °C. Fluorylidenylcarboxylic acid chloride (6.02 g, 25 mmol), dissolved in dry dichloromethane (50 ml), was added dropwise. The reaction mixture was stirred at room temperature for 3 h and water was added (50 ml). The organic layer was washed with brine (25 ml), then dried ($MgSO_4$) and evaporated in vacuo to yield the title product as a white solid (8.87 g, 92%), mp 154–155 °C; [Found: C, 78.0; H, 5.9; N, 3.6. $C_{25}H_{23}NO_3$ requires C, 77.9; H, 6.0; N, 3.6%]; ^{1}H NMR (500 MHz, DMSO-d_6): 8.68 (d, 1H, *J*=7.6 Hz, Flu–H), 8.58 (t, 1H, *J*=5.5 Hz, NH), 7.83 (m, 2H, Flu–H), 7.77 (d, 1H, *J*=7.6 Hz, Flu–H), 7.43 (t, 2H, *J*=7.6 Hz, Flu–H), 7.34 (t, 1H, *J*=7.6 Hz, Flu–H), 7.30 (t, 1H, *J*=7.6 Hz, Flu–H), 7.08 (s, 1H, CH═), 6.80 (m, 2H, Ar–2′ and 5′H), 6.78 (dd, 1H, *J*=1.8 and 8 Hz, Ar–6′H), 3.72 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.51 (m, 2H, H-1), 2.80 (t, 2H, *J*=7.2 Hz, H-2); ^{13}C NMR (125 MHz, DMSO-d_6): 165.5 (quat.), 148.8 (quat.), 147.4 (quat.), 141.3 (quat.), 139.6 (quat.), 138.7 (quat.), 135.1 (quat.), 131.9 (CH), 130.1 (quat.), 129.9 (CH), 128.1 (CH), 127.7 (3×CH), 121.1 (CH), 120.6 (CH), 120.5 (CH), 120.2 (CH), 120.0 (quat.), 112.7 (CH), 112.1 (CH), 55.7 (CH_3), 55.5 (CH_3), 40.7 (CH_2), 34.7 (CH_2); IR (KBr, cm^{-1}): 3311, 2935, 2841, 1625, 1605, 1516, 1451, 1443, 1301, 1290, 1262, 1236, 1190, 1157, 1141, 1027.

3.2.12. 1-(3′,4′-Dimethoxyphenethyl)-1-naphthamide (12b). Compound **12b** was prepared analogously to **6a** from naphthoic-1-carboxylic acid (9.53 g, 50 mmol) and was isolated as a white powder (10.2 g, 61%), mp 137–139 °C; [Found: C, 75.0; H, 6.3; N, 4.1. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%]; ^{1}H NMR (500 MHz, DMSO-d_6): 8.56 (t, 1H, *J*=5.5 Hz, NH), 8.04 (d, 1H, *J*=8.9 Hz, Naph–4′H), 7.98 (t, 1H, *J*=8.9 Hz, Naph–6′H), 7.95 (d, 1H, *J*=8.9 Hz, Naph–8′H), 7.56–7.46 (m, 4H, Naph–2′, 3′, 5′, and 7′H), 6.89 (m, 2H, Ar–2′ and 5′H), 6.80 (dd, 1H, *J*=2.0 and 8.1 Hz, Ar–6′H), 3.73 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.57 (m, 2H, CH_2), 2.85 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): 168.6 (quat.), 148.8 (quat.), 147.5 (quat.), 135.4 (quat.), 133.3 (quat.), 132.1 (quat.), 129.9 (CH), 129.7 (CH), 128.3 (CH), 126.7 (CH), 126.5 (quat.), 126.3 (CH), 125.6 (CH), 125.0 (CH), 120.8 (CH), 112.9 (CH), 112.1 (CH), 55.7 (CH_3), 55.5 (CH_3), 40.9 (CH_2), 34.8 (CH_2); IR (KBr, cm^{-1}): 3335, 3001, 2956, 2938, 2914, 2835, 1633, 1619, 1592, 1538, 1518, 1461, 1329, 1291, 1265, 1201, 1161, 1025.

3.2.13. 6,7-Dimethoxy-1-(9*H*-9-fluorenylidenmethyl)-3,4-dihydroisoquinoline (13a). *N*-1-(3′,4′-Dimethoxyphenethyl)-2-(9*H*-9-fluorenyliden)acetamide (8.0 g, 20.8 mmol) was dissolved in dry toluene (50 ml) and freshly distilled phosphorus oxychloride (3.15 g, 21 mmol) was added dropwise to the well-stirred mixture at 0 °C. The reaction mixture was stirred at reflux for 6 h, cooled to 5–10 °C and then the mixture was stirred with an excess of 10% aqueous sodium hydroxide solution. The aqueous phase was washed with ethyl acetate (3×30 ml) and the combined organic extracts were washed with brine (30 ml), then dried ($MgSO_4$) and evaporated in vacuo to give the title product as a yellow solid (5.34 g, 70%), mp 118–119 °C; [Found: C, 82.0; H, 5.9; N, 4.0. $C_{25}H_{21}NO_2$ requires C, 81.7; H, 5.8; N, 3.8%]; ^{1}H NMR (500 MHz, $CDCl_3$): 7.78 (d, 1H, *J*=7.4 Hz, Flu–H), 7.67 (d, 1H, *J*=7.4 Hz, Flu–H), 7.64 (d, 1H, *J*=7.4 Hz, Flu–H), 7.55 (d, 1H, *J*=7.4 Hz, Flu–H), 7.38 (t, 1H, *J*=7.4 Hz, Flu–H), 7.32 (s, 1H, H-8), 7.31 (t, 1H, *J*=7.4 Hz, Flu–H), 7.28 (t, 1H, *J*=7.4 Hz, Flu–H), 7.06 (t, 1H, *J*=7.4 Hz, Flu–H), 6.96 (s, 1H, H-5), 6.77 (s, 1H, CH═), 3.96 (t, 2H, *J*=7.7 Hz, H-4), 3.92 (s, 3H, *O*Me), 3.63 (s, 3H, *O*Me), 2.82 (t, 2H, *J*=7.7 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 163.7 (quat.), 151.3 (quat.), 147.6 (quat.), 141.3 (quat.), 140.4 (quat.), 139.8 (quat.), 138.8 (quat.), 136.0 (quat.), 131.0 (quat.), 128.9 (CH), 128.8 (CH), 127.0 (CH), 126 5 (quat.), 126.9 (CH), 125.7 (CH), 122.7 (CH), 121.6 (quat.), 120.6 (CH), 119.5 (CH), 119.4 (CH), 110.4 (CH), 109.9 (CH), 56.1 (CH_3), 55.9 (CH_3), 47.4 (CH_2), 25.5 (CH_2); IR (KBr, cm^{-1}): 3426, 3001, 2933, 2830, 1714, 1603, 1562, 1512, 1463, 1450, 1357, 1317, 1277, 1207, 1151, 1140, 1024.

3.2.14. 6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydroisoquinoline (13b). 1-(3′,4′-Dimethoxyphenethyl)-1-naphthamide (10.0 g, 29.8 mmol) was dissolved in dry toluene (50 ml) and freshly distilled phosphorus oxychloride (9.12 g, 60 mmol) was added dropwise to the well-stirred mixture at 0 °C. The reaction mixture was stirred at reflux for 6 h, cooled to 5–10 °C and then the mixture was stirred with an excess of 10% aqueous sodium hydroxide solution. The aqueous phase was washed with ethyl acetate (3×30 ml) and the combined organic extracts were washed with brine (30 ml), then dried ($MgSO_4$) and evaporated in vacuo to yield the title product as a yellow solid (7.09 g, 75%), mp 105–107 °C; [Found: C, 79.2; H, 5.9; N, 4.2. $C_{21}H_{19}NO_2$ requires C, 79.5; H, 6.0; N, 4.4%]; ^{1}H NMR (500 MHz, DMSO-d_6): 8.00 (d, 1H, *J*=8.3 Hz, Naph–4′H), 7.98 (d, 1H, *J*=8.3 Hz, Naph–8′H), 7.73 (dd, 1H, *J*=1 and 8.3 Hz, Naph–5′H), 7.59 (t, 1H, *J*=8.3 Hz, Naph–6′H), 7.51 (m, 2H, Naph–7′ and 2′H), 7.42 (dt, 1H, *J*=1 and 8.3 Hz, Naph–3′H), 7.02 (s, 1H, H-8), 6.26 (s, 1H, H-5), 3.86 (m, 2H, H-3), 3.85 (s, 3H, *O*Me), 3.29 (s, 3H, *O*Me), 2.84 (m, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6): 165.6 (quat.), 151.3 (quat.), 147.1 (quat.), 137.1 (quat.), 133.3 (quat.), 131.4 (quat.), 131.2 (CH), 128.7 (CH), 128.4 (quat.), 126.5 (CH), 126.3 (CH), 126.1 (CH), 125.7 (quat.), 125.4 (CH), 122.5 (CH), 111.25 (CH), 111.2 (CH), 55.8 (CH_3), 55.7 (CH_3), 47.5 (CH_2), 25.3 (CH_2); IR (KBr, cm^{-1}): 3013, 2933, 2896, 2830, 1604, 1564, 1510, 1464, 1456, 1432, 1353, 1318, 1277, 1262, 1236, 1213, 1197, 1163, 1131, 1057, 1040, 1017.

3.2.15. 6,7-Dimethoxy-1-(9*H*-9-fluorenylidenylmethyl)-2-methoxycarbonylmethyl-3,4-dihydroisoquinolinium bromide (14a). Compound **14a** was prepared analogously to **8a** from **13a** (0.5 g, 1.36 mmol) and was isolated as a yellow powder (0.71 g, 100%), mp 222–223 °C; [Found: C, 64.6; H, 5.0; N, 2.7. $C_{28}H_{26}NO_4Br$ requires C, 64.6; H, 5.0; N, 2.7%]; ^{1}H NMR (500 MHz, $CDCl_3$): 8.12 (d, 1H, *J*=7.5 Hz, Flu–H), 7.62 (m, 3H, Flu–H), 7.46 (t, 1H, *J*=7.5 Hz, Flu–H), 7.39 (d, 1H, *J*=7.5 Hz, Flu–H), 7.28 (m, 1H, Flu–H), 7.10 (s, 1H, H-8), 7.07 (s, 1H, H-5), 7.02 (s, 1H, CH═), 6.86 (d, 1H, *J*=7.5 Hz, Flu–H), 5.64 (d, 1H *J*=17 Hz, NCH_2), 5.13 (d,

1H, J=17 Hz, NCH_2), 3.84 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.72 (m, 2H, H-3), 3.59 (s, 3H, OMe), 3.28 (m, 2H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): 179.0 (quat.), 166.1 (quat.), 158.1 (quat.), 149.0 (quat.), 145.0 (quat.), 144.6 (quat.), 142.3 (quat.), 140.6 (quat.), 140.1 (quat.), 134.4 (CH), 134.3 (quat.), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.4 (quat.), 127.5 (CH), 126.4 (CH), 123.0 (CH), 120.2 (CH), 119.7 (CH), 118.6 (quat.), 112.5 (CH), 111.5 (CH), 57.0 (CH_3), 56.4 (CH_3), 55.4 (CH_2), 52.2 (CH_3), 45.9 (CH_2), 26.7 (CH_2); IR (KBr, cm^{-1}): 3425, 2938, 2831, 1744, 1609, 1513, 1465, 1449, 1436, 1426, 1390, 1340, 1276, 1235, 1224, 1210, 1180, 1165, 1148, 1115, 1085, 1022.

3.2.16. 2-Benzyl-6,7-dimethoxy-1-(9*H*-9-fluorenylidenylmethyl)-3,4-dihydroisoquinolinium bromide (14b). Compound **14b** was prepared analogously to **8a** from **13a** (0.5 g; 1.36 mmol) and benzyl bromide (0.36 ml, 0.50 g, 3 mmol) and was isolated as a yellow powder (0.71 g, 97%), mp 239–241 °C; [Found: C, 71.3; H, 5.2; N, 2.6. $C_{32}H_{28}NO_2Br$ requires C, 71.4; H, 5.2; N, 2.6%]; ^1H NMR (500 MHz, $CDCl_3$): 8.12 (d, 1H, J=7.5 Hz, Flu–H), 7.71 (m, 3H, Flu–H), 7.52 (m, 2H, Ph–H), 7.44 (m, 3H, Ar–H and Flu–H), 7.30 (m, 2H, Ar–H), 7.22 (d, 1H, J=7.5 Hz, Flu–H), 7.05 (s, 2H, H-8 and H-5), 6.85 (d, 1H, J=7.5 Hz, Flu–H), 6.51 (s, 1H, CH═), 5.64 (d, 1H, J=17.7 Hz, NCH_2), 5.10 (d, 1H, J=17.7 Hz, NCH_2), 4.04 (s, 3H, *O*Me), 3.84 (s, 3H, *O*Me), 3.58 (m, 2H, H-4), 3.48 (m, 2H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 171.6 (quat.), 157.6 (quat.), 148.9 (quat.), 146.2 (quat.), 142.8 (quat.), 140.4 (quat.), 136.7 (quat.), 134.1 (quat.), 133.5 (quat.), 131.3 (CH), 129.5 (2×CH), 129.4 (CH), 129.2 (2×CH), 129.0 (CH), 128.5 (CH), 128.3 (quat.), 127.9 (CH), 125.5 (CH), 123.3 (CH), 120.8 (CH), 120.3 (CH), 118.7 (quat.), 115.2 (CH), 114.0 (CH), 111.5 (CH), 62.0 (CH_2), 57.2 (CH_3), 56.4 (CH_3), 49.7 (CH_2), 26.4 (CH_2); IR (KBr, cm^{-1}): 2955, 2938, 1602, 1551, 1496, 1451, 1386, 1338, 1293, 1271, 1219, 1170, 1004.

3.2.17. 2-Allyl-6,7-dimethoxy-1-(9*H*-9-fluorenylidenmethyl)-3,4-dihydroisoquinolinium bromide (14c). Compound **14c** was prepared analogously to **8e** from **13a** (0.5 g, 1.36 mmol) and was isolated as a yellow powder (0.65 g, 98%), mp 233 °C; [Found: C, 69.0; H, 5.2; N, 2.7. $C_{28}H_{26}NO_2Br$ requires C, 68.9; H, 5.4; N, 2.9%]; ^1H NMR (500 MHz, $CDCl_3$): 7.72 (d, 1H, J=7.8 Hz, Flu–H), 7.67 (m, 1H, Flu–H), 7.41 (m, 3H, Flu–H), 7.25 (t, 1H, J=7.5 Hz, Flu–H), 7.17 (m, 2H, Flu–H), 7.07 (s, 2H, H-5 and H-8), 7.00 (s, 1H, CH═), 6.05 (d, 1H, J=9.5 Hz, allyl), 5.47 (m, 1H, allyl), 5.24 (d, 1H, J=18 Hz, NCH_2), 5.13 (m, 1H, allyl), 4.85 (d, 1H, J=18 Hz, NCH_2), 4.02 (s, 3H, OMe), 3.91 (m, 1H, H-3), 3.85 (s, 3H, OMe), 3.70 (m, 2H, H-3 and H-4), 3.33 (m, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): 177.4 (quat.), 157.6 (quat.), 148.9 (quat.), 145.3 (quat.), 143.9 (quat.), 140.8 (quat.), 140.4 (quat.), 133.6 (quat.), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH_2), 125.7 (quat.), 123.0 (CH), 125.3 (CH_2), 120.8 (CH), 119.8 (CH), 116.2 (quat.), 112.4 (CH), 111.6 (CH), 80.5 (CH), 56.9 (CH_3), 56.3 (CH_3), 44.3 (CH_2), 26.4 (CH_2); IR (KBr, cm^{-1}): 2937, 1603, 1554, 1521, 1450, 1387, 1338, 1291, 1271, 1219, 1171, 1004.

3.2.18. 6,7-Dimethoxy-1-(1-naphthyl)-2-ethoxycarbonylmethyl-3,4-dihydroisoquinolinium bromide (16). Compound **16** was prepared analogously to **8a** from **13b** (0.5 g, 1.57 mmol) and was isolated as a yellow powder (0.73 g, 100%); mp 211–212 °C; [Found: C, 61.3; H, 5.2; N, 2.9. $C_{24}H_{24}NO_4Br$ requires C, 61.3; H, 5.1; N, 3.0%]; ^1H NMR (500 MHz, DMSO-d_6): 8.33 (d, 1H, J=8.0 Hz, Naph–4′H), 8.15 (d, 1H, J=8.0 Hz, Naph–8′H), 7.83 (dd, 1H, J=1.5 and 8.0 Hz, Naph–5′H), 7.80 (t, 1H, J=8.0 Hz, Naph–6′H), 7.65 (dt, 1H, J=1.5 and 8 Hz, Naph–7′H), 7.58 (dt, 1H, J=1.5 and 8.0 Hz, Naph–3′H), 7.53 (d, 1H, J=8.0 Hz, Naph–2′H), 7.47 (s, 1H, H-5), 6.17 (s, 1H, H-8), 4.80 (d, 1H, J=17.1 Hz, NCH_2), 4.64 (d, 1H, J=17.1 Hz, NCH_2), 4.59 (m, 1H, H-4), 4.48 (m, 1H, H-4), 4.03 (q, 2H, J=7.1 Hz, OCH_2), 3.98 (s, 3H, OMe), 3.61 (m, 1H, H-3), 3.50 (m, 1H, H-3), 3.21 (s, 3H, *O*Me), 1.03 (t, 3H, J=7.1 Hz, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): 174.6 (quat.), 165.8 (quat.), 157.8 (quat.), 148.0 (quat.), 135.8 (quat.), 133.0 (quat.), 132.5 (quat.), 129.1 (CH), 128.9 (CH), 128.5 (quat.), 127.6 (CH), 127.3 (CH), 126.2 (CH), 125.6 (quat.), 124.3 (CH), 119.4 (CH), 114.7 (CH), 112.1 (CH), 62.3 (CH_2), 58.4 (CH_2), 57.1 (CH_3), 55.7 (CH_3), 51.7 (CH_2), 25.2 (CH_2), 13.8 (CH_3); IR (KBr, cm^{-1}): 3020, 3002, 2985, 1747, 1602, 1551, 1520, 1506, 1473, 1403, 1376, 1342, 1292, 1276, 1224, 1178, 1120, 1007.

3.3. 1,7-Electrocyclizations—method B

The corresponding 6,7-dimethoxy-1-(9*H*-9-fluorenylidenemethyl)-3,4-dihydroisoquinolinium bromide (0.75 mmol) was dissolved in dry methanol (10 ml) and triethylamine (0.11 ml, 1.5 mmol) was added. The reaction mixture was stirred for 24 h at room temperature under an argon atmosphere. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (15 ml) and washed with water (2×10 ml) and brine (10 ml). The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was further purified by column chromatography on silica gel, eluting with hexane–acetone (3:1).

3.3.1. Methyl 14,15-dimethoxy-1,2,4,12*a*-tetrahydrofluoreno[9′,1′:4,5,6]azepino[2,1-*a*]isoquinoline-4-carboxylate (15a). Pale yellow oil, (0.16 g, 49%); ^1H NMR (500 MHz, $CDCl_3$): 7.70 (m, 2H, H-5 and H-11), 7.56 (m, 2H, H-7 and H-8), 7.37 (m, 2H, H-6 and H-16), 7.31 (dt, 1H, J=1.0 and 7.5 Hz, H-10), 7.21 (dt, 1H, J=1.0 and 7.5 Hz, H-9), 6.98 (s, 1H, H-13), 6.69 (s, 1H, H-12), 5.00 (s, 1H, H-4), 4.42 (s, 1H, H-12*a*), 3.89 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.47 (m, 2H, H-1), 3.05 (s, 3H, OMe), 2.84 (m, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): 169.8 (quat.), 150.4 (quat.), 149.7 (quat.), 148.0 (quat.), 147.8 (quat.), 147.0 (quat.), 141.0 (quat.), 139.7 (quat.), 129.1 (quat.), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.2 (quat.), 125.6 (CH), 124.3 (CH), 120.0 (quat.), 119.7 (CH), 110.8 (CH), 107.5 (CH), 99.0 (CH), 77.3 (CH), 56.0 (CH_3), 55.85 (CH_3), 53.9 (CH), 51.3 (CH_3), 47.8 (CH_2), 29.3 (CH_2); IR (neat, cm^{-1}): 2938, 2831, 1744, 1629, 1513, 1465, 1449, 1436, 1426, 1276, 1235, 1224, 1210, 1180, 1165, 1148, 1115, 1085, 1022; (HRMS Found: *m/z* 439.1747. $C_{28}H_{25}NO_4$ *m/z* 439.1783).

3.3.2. 14,15-Dimethoxy-4-phenyl-1,2,4,12*a*-tetrahydrofluoreno[9′,1′:4,5,6]azepino[2,1-*a*]isoquinoline (15b). Pale yellow oil, (0.16 g, 46%); ^1H NMR (500 MHz, $CDCl_3$): 7.82 (m, 2H, H-5 and H-11), 7.61 (m, 2H, H-7 and H-8), 7.40 (m, 5H, Ph–H and H-6, H-16), 7.21 (m, 2H, H-9

and H-10), 7.08 (m, 2H, Ph–H), 6.76 (s, 1H, H-13), 6.73 (s, 1H, H-12), 5.21 (s, 1H, H-12*a*), 4.84 (s, 1H, H-4), 3.92 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.32 (m, 2H, H-1), 2.82 (m, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): 149.9 (quat.), 148.2 (quat.), 147.7 (quat.), 147.1 (quat.), 146.2 (quat.), 142.3 (quat.), 140.0 (quat.), 133.4 (quat.), 129.7 (2×CH), 129.4 (quat.), 128.9 (2×CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.3 (quat.), 125.9 (CH), 124.8 (CH), 121.1 (CH), 119.9 (quat.), 111.0 (CH), 108.0 (CH), 101.8 (quat.), 80.2 (CH), 55.9 (CH_3), 55.85 (CH_3), 55.8 (CH), 45.9 (CH_2), 29.2 (CH_2); IR (neat, cm^{-1}): 2932, 2835, 1607, 1513, 1502, 1494, 1464, 1390, 1345, 1267, 1211, 1148, 1025; (HRMS Found: *m/z* 457.2040. $C_{32}H_{27}NO_2$ requires *m/z* 457.2042).

3.3.3. 14,15-Dimethoxy-4-ethenyl-1,2,4,12*a*-tetrahydrofluoreno[9′,1′:4,5,6]azepino[2,1-*a*]isoquinoline (15c). Pale yellow oil, (0.13 g, 44%); ^{1}H NMR (500 MHz, $CDCl_3$): 7.72 (m, 2H, H-5 and H-11), 7.41 (m, 3H, H-6, H-7 and H-8), 7.27 (s, 1H, H-16), 7.22 (m, 2H, H-9 and H-10), 7.09 (s, 2H, H-12 and H-13), 6.03 (d, 1H, *J*=9.3 Hz, H-4), 5.47 (m, 1H, vinyl–CH), 5.17 (d, 1H, *J*=18 Hz, vinyl–CH_2), 5.11 (s, 1H, H-12*a*), 4.85 (d, 1H, *J*=18 Hz, vinyl–CH_2), 4.32 (m, 1H, H-1), 4.02 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.68 (m, 2H, H-1 and H-2), 3.36 (m, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): 150.1 (quat.), 147.9 (quat.), 147.7 (quat.), 147.5 (quat.), 147.1 (quat.), 143.1 (quat.), 139.5 (quat.), 129.7 (quat.), 128.6 (CH), 127.7 (CH), 127.6 (2×CH), 127.3 (CH), 127.2 (quat.), 126.3 (CH_2), 126.1 (CH), 124.9 (CH), 121.4 (CH), 119.8 (quat.), 110.7 (CH), 107.9 (CH), 102.1 (CH), 79.2 (CH), 59.9 (CH), 55.8 (CH_3), 55.7 (CH_3), 46.0 (CH_2), 29.2 (CH_2); IR (neat, cm^{-1}): 3387, 2937, 1711, 1604, 1559, 1524, 1450, 1421, 1397, 1337, 1291, 1220, 1164, 1083, 1006; (HRMS Found: *m/z* 407.1907. $C_{28}H_{25}NO_2$ requires *m/z* 407.1885).

3.3.4. 1-(2,2-Diphenylethenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (16). 6,7-Dimethoxy-1-(2′,2′-diphenyl-1-ethenyl]-3,4-dihydroisoquinoline (3.73 g, 10 mmol) was dissolved in ethanol (50 ml) and sodium borohydride (1.89 g, 50 mmol) was added in small portions. The mixture was refluxed for 1 h, then the solvent was removed in vacuo. The residue was dissolved in dichloromethane (100 ml) and washed with water (2×50 ml) and brine (30 ml). The organic layer was dried over magnesium sulfate and evaporated in vacuo to give a white semi-solid product (3.71 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.41–7.23 (m, 10H, Ph), 6.63 (s, 1H, H-5), 6.58 (s, 1H, H-8), 6.20 (d, 1H, *J*=9.6 Hz, CH═), 4.58 (d, 1H, *J*=9.6 Hz, H-1), 3.82 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.27 (m, 1H, H_2-4), 2.90 (m, 1H, H_2-4), 2.63 (m, 2H, H_2-3); ^{13}C NMR (125 MHz, $CDCl_3$): 147.7 (quat.), 147.3 (quat.), 143.6 (quat.), 141.9 (quat.), 139.6 (quat.), 130.7 (quat.), 129.7 (2×CH), 129.6 (quat.), 128.6 (2×CH), 128.3 (2×CH), 127.6 (CH), 127.5 (3×CH), 126.9 (CH), 111.9 (CH), 110.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.5 (CH), 42.4 (CH_2), 29.2 (CH_2); IR (KBr, cm^{-1}): 3047, 3023, 3000, 2958, 2921, 2826, 1599, 1575, 1509, 1466, 1446, 1427, 1369, 1329, 1281, 1265, 1218, 1126, 1033; (HRMS: Found: *m/z* 371.1872. $C_{25}H_{25}NO_2$ requires *m/z* 371.1885).

3.4. 1,7-Electrocyclization—method C

1-(2,2-Diphenylethenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.37 g, 1 mmol) and the corresponding aldehyde (1.1 mmol) were dissolved in dry xylene (15 ml), the reaction mixture was refluxed for 11–32 h and the water formed was removed with the aid of a Dean–Stark trap. After cooling, the solvent was removed in vacuo and the resulting residue purified by column chromatography on silica, eluting with hexane–acetone (90:10 to 50:50).

3.4.1. 2,3-Dimethoxy-13-phenyl-8-(4-chlorophenyl)-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11k). Pale yellow oil (0.16 g, 32%); ^{1}H NMR (500 MHz, $CDCl_3$): 7.50 (d, 2H, *J*=7.5 Hz, Ar–H, H-2′ and 6′), 7.37–7.22 (m, 5H, Ar–H), 7.18 (s, 1H, H-1), 7.01 (d, 2H, *J*=7.5 Hz, Ar–3′ and 5′H), 6.96 (m, 2H, Ar–H), 6.85 (m, 2H, Ar–H), 6.65 (s, 1H, H-14), 5.49 (s, 1H, H-14*a*), 5.14 (s, 1H, H-8), 3.91 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.85 (m, 2H, H_2-6), 3.07 (m, 1H, H_2-5), 2.89 (m, 1H, H_2-5); ^{13}C NMR (125 MHz, $CDCl_3$): 152.7 (quat.), 150.2 (quat.), 147.9 (quat.), 144.2 (quat.), 141.2 (quat.), 140.1 (quat.), 137.8 (quat.), 136.6 (quat.), 129.5 (quat.), 129.2 (2×CH), 128.5 (CH), 128.2 (2×CH), 130.2 (2×CH), 128.5 (2×CH), 128.45 (2×CH), 128.2 (CH), 128.0 (2×CH), 120.3 (quat.), 111.0 (CH), 110.1 (CH), 104.7 (CH), 77.4 (CH), 56.2 (CH_3), 56.1 (CH_3), 45.0 (CH_2), 30.0 (CH_2); IR (KBr, cm^{-1}): 2940, 2921, 2910, 2845, 1611, 1501, 1460, 1337, 1319, 1296, 1271, 1212, 1177, 1149, 1111, 1029; (HRMS Found: *m/z* 493.1803. $C_{32}H_{28}NO_2Cl$ requires *m/z* 493.1809).

3.4.2. 2,3-Dimethoxy-13-phenyl-8-(4-methoxyphenyl)-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11l). Pale yellow oil (0.13 g, 26%); ^{1}H NMR (500 MHz, $CDCl_3$): 7.53 (d, 2H, *J*=7.5 Hz, Ar^8-2′ and 6′H), 7.34–7.15 (m, 7H, Ar–H), 7.01 (m, 3H, Ar–H), 6.90 (m, 3H, Ar–H), 6.66 (s, 1H, H-14), 5.54 (s, 1H, H-14*a*), 5.12 (s, 1H, H-8), 3.89 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.77 (m, 2H, H_2-6), 3.00 (m, 1H, H_2-5), 2.74 (m, 1H, H_2-5); ^{13}C NMR (125 MHz, $CDCl_3$): 162.8 (quat.), 149.6 (quat.), 147.3 (quat.), 144.8 (quat.), 142.5 (quat.), 141.1 (quat.), 137.6 (quat.), 133.2 (2×CH), 129.0 (2×CH), 128.2 (quat.), 128.1 (2×CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.3 (CH), 126.1 (quat.), 120.0 (quat.), 112.7 (2×CH), 110.8 (CH), 109.9 (CH), 103.0 (CH), 77.6 (CH), 56.0 (CH_3), 55.8 (CH_3), 45.3 (CH_2), 29.6 (CH_2); IR (KBr, cm^{-1}): 2963, 2836, 1604, 1559, 1513, 1464, 1399, 1258, 1168, 1113, 1028; (HRMS Found: *m/z* 489.2324. $C_{33}H_{31}NO_3$ requires *m/z* 489.2303).

3.4.3. 2,3-Dimethoxy-13-phenyl-8-(3,4-methoxyphenyl)-5,6,8,14*a*-tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline (11m). Pale yellow oil, 0.06 g (11%); ^{1}H NMR (500 MHz, $CDCl_3$): 7.52 (m, 2H, Ar–H), 7.33 (m, 2H, Ar–H), 7.24 (m, 3H, Ar–H), 7.06 (m, 4H, Ar–H), 6.88 (m, 3H, Ar–H), 6.66 (s, 1H, H-14), 6.14 (s, 1H, H-14*a*), 5.47 (s, 1H, H-8), 3.93 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.81 (s, 6H, 2×OMe), 3.39 (m, 2H, H_2-6), 3.05 (m, 1H, H_2-5), 2.63 (m, 1H, H_2-5); ^{13}C NMR (125 MHz, $CDCl_3$): 149.2 (quat.), 149.1 (quat.), 148.8 (quat.), 147.1 (quat.), 144.9 (quat.), 143.9 (quat.), 143.0 (quat.), 137.2 (quat.), 129.1 (quat.), 128.8 (2×CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.8 (2×CH), 127.5 (2×CH), 127.25 (CH), 127.2 (quat.), 120.0 (quat.), 119.3 (CH), 112.7 (CH), 112.0 (CH), 110.8 (CH), 109.9 (CH), 102.9 (CH), 77.5 (CH), 56.0 (CH_3), 55.9 (2×CH_3), 55.8 (CH_3), 45.4 (CH_2), 29.6 (CH_2); IR (KBr,

cm^{-1}): 2937, 2836, 1603, 1514, 1495, 1464, 1399, 1268, 1147, 1025; (HRMS Found: *m/z* 519.2398. $C_{34}H_{33}NO_4$ requires *m/z* 519.2409).

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Total synthesis of new indolo[2,3-*a*]quinolizine alkaloids sempervirine type, potential pharmaceuticals☆

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Abstract—Total synthesis of the two series of new pentacycilc cycloalk[*g*]indolo[2,3-*a*]quinolizine alkaloids (modified sempervirine possessing the wide range of activity), has been elaborated in five steps from 5-acetyl-3-methylthio-1,2,4-triazine (obtained from the simple acyclic materials). In the two key steps: inverse electron demand Diels–Alder reaction of precursor with cyclic enamines and the following Fischer indolization of 3-acetyl-1-methylthiocycloalka[*c*]pyridines, the AB–DE synthons, has been obtained. The final stages: desulfuration, and formation of the C-ring via the Gribble method have led to the expected zwitterionic alkaloids. Model syntheses of the indolopyridocoline and its methoxy analogue from 2-acetylpyridine have been performed for investigation of the microwave-induced Fischer synthesis of sensitive indoles and for obtaining compounds for comparative study of spectroscopic data.

1. Introduction

In recent years, there has been a growing interest in the synthesis of bioactive molecules and their non-natural analogues in the field of organic chemistry as a result of the new synthetic methods and techniques, which enable creating new medicaments. Sempervirine and other indolo[2,3-*a*]quinolizine alkaloids (alstonine, flavopereirine), were first known as cardiac species,[2] but recently their anticancer[3] (as DNA intercalating agent),[4] immunostimulative[3d,5] and anti-HIV,[3d] sedative and antipsychotic[5a,6] activities have been discovered. Just recently, it has been shown that sempervirine and other indole alkaloids (vinblastine, vincamine, ajmalicine, harmaline) can act as inhibitors of the enzyme CYP2D6 (it might exists as various polymorphic genotypes), giving a wide range of clinical effects, depending on individual organism.[7] Sempervirine, as indolo[2,3-*a*]quinolizinium type of molecule, can exist in acidic and neutral medium as a cation and in alkaline medium it has a conjugated zwitterionic structure, where one neutral canonical structure can be drawn[8,9] (Fig. 1). Since trace amounts of sempervirine exist in a natural resource, the rhizome and roots of *Gelsemium sempervirens*,[10] many methods have already been developed for its total synthesis involving various strategies for construction of the 1,2,3,4-tetrahydrobenz[*g*]indolo[2,3-*a*]quinolizine ring system.[8,11] Among them, the conception of the construction of pentacyclic ring system via a AB–DE synthon was developed,[12,13] as it is shown in Figure 2. This 2-(2-pyridyl)indole-type synthon was obtained by Stevens and co-workers[12] in the Fischer synthesis from 3-acetyl-5,6,7,8-tetrahydroisoquinoline

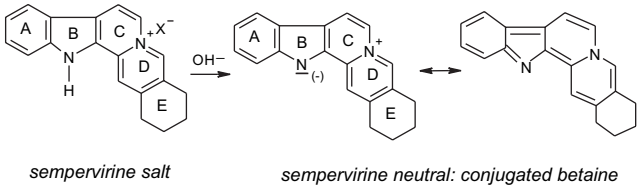

Figure 1.

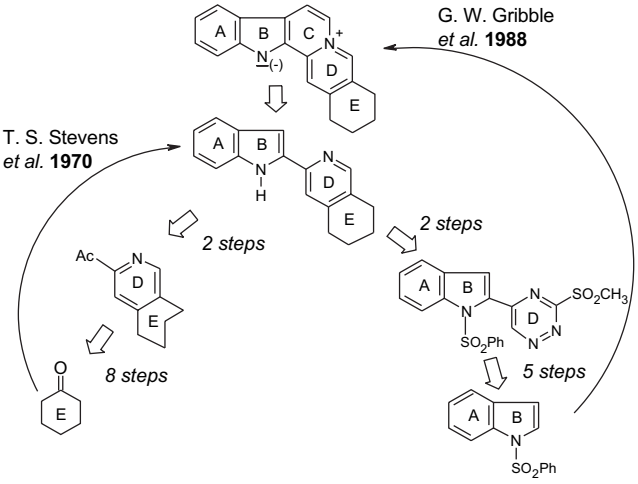

Figure 2.

☆ See Ref. 1.
Keywords: Total synthesis; Pentacyclic indole alkaloids; Zwitterions; DNA intercalators-anticancer agents.
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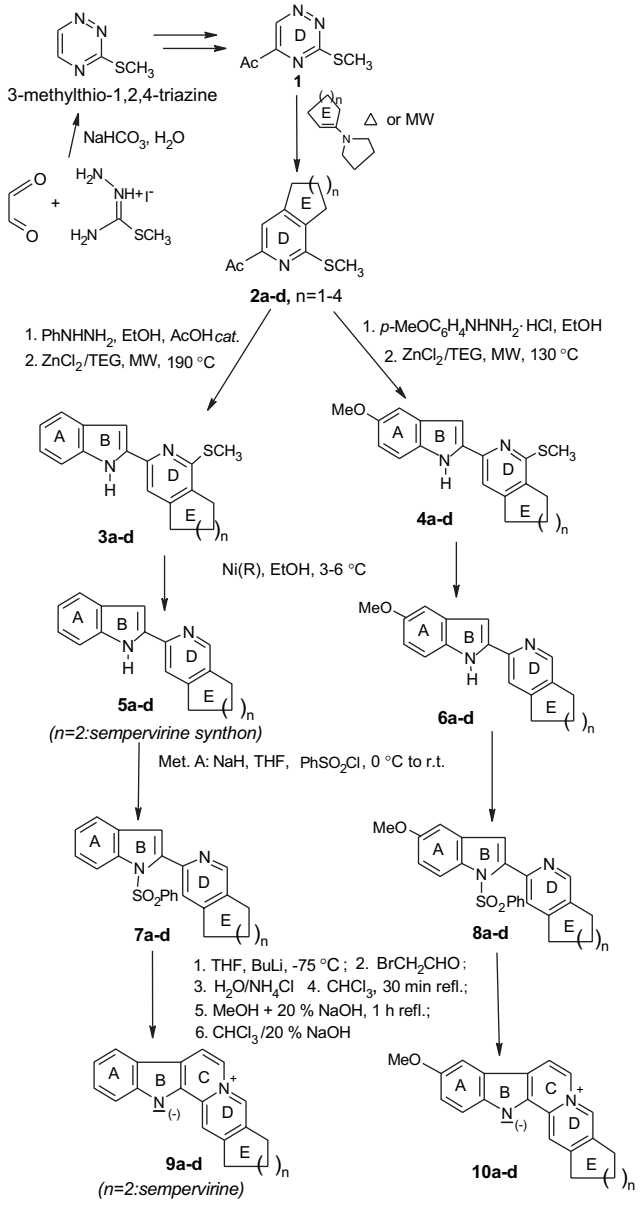
prepared in eight steps from cyclohexanone. The second synthesis by Gribble and co-workers[13] formed the AB–CD synthon in eight steps from *N*-phenylsulfonylindole, which was functionalized in C2 position for construction of the 1,2,4-triazine ring, next transformed by Diels–Alder reaction with the 1-(1-pyrrolidine)cyclohexene. The latter investigators successfully formed the middle C-ring via the indole *N*-protection, direct metalation and reaction with bromoacetaldehyde as a 1,2-dielectrophile. We took some advantage of these two developments and elaborated a novel total synthesis strategy, not only to improve the yield of sempervirine, but also to gain access to its new analogues for biological evaluation.

In present paper, we describe the scope and limitations of our method (see Scheme 1) and, report the full experimental details after optimization of its key steps and give the characterization data of the intermediates and final products.



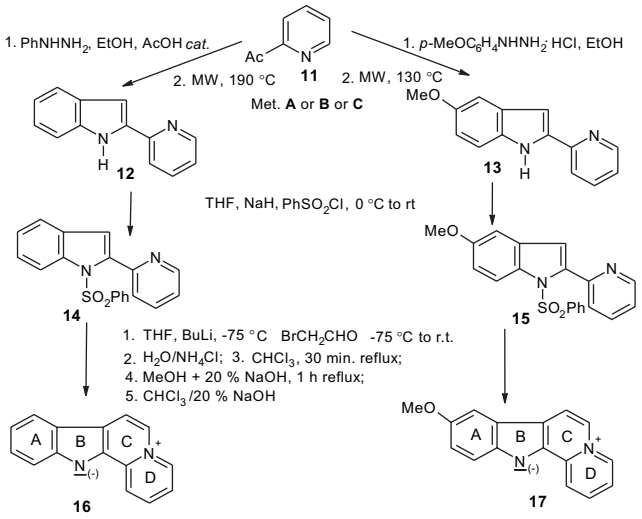
Scheme 1. Synthesis of the two series of modified sempervirine.

2. Results and discussion

2.1. Synthetic strategy

Our total synthesis strategy is based on the availability of the 5-acetyl-3-methylthio-1,2,4-triazine **1**[14] and the possibility of its transformation into 3-acetyl-1-methylthiocycloalka[*c*]pyridines **2a–d** by the Diels–Alder reaction with cyclic enamines.[15] Thus, we envisioned and discovered that the AB–DE sempervirine synthon **5b**[14b] as well as other 2-(2-pyridyl)indoles could be constructed in the Fischer indolization, thanks to the presence of the acetyl group in the molecules **2a–d** (see Scheme 1). With this perspective in mind, we planned the synthesis of **3a–d**[15b] and **4a–d**,[16] and next the AB–CD synthons **5a–d** and **6a–d**. The latter can be transformed into pentacyclic indolo[2,3-*a*]quinolizine alkaloids via the Gribble method.[13]

The starting material, 5-acetyl-3-methylthio-1,2,4-triazine **1**, was prepared in 40% yield in two-step synthesis[14] from 3-methylthio-1,2,4-triazine,[17] which can be obtained on a large laboratory-scale (up to 100 g) from the glioxal and *S*-methylthiosemicarbazide hydroiodide. Syntheses of **2a–d** via inverse electron demand Diels–Alder reaction of the **1** with cyclic enamines have been optimized recently.[18] The acetyl group remains in compounds **2a–d**, which gives access to the construction of the indole moiety via the Fischer synthesis. Initially, we obtained **3b** in conventional conditions;[14b] in a medium of excess molten zinc chloride and methylnaphthalene at temperature 200–220 °C, according to the Steven's method.[12] We chose this procedure from the two classic methods for performing the difficult Fischer synthesis. However, this procedure was inconvenient and non-ecological and gave rather low and non-reproducible 25–55% yield. The second method for performing difficult Fischer synthesis, described as efficient for transformation of 2-acetylpyridine **11** into 2-(2-pyridyl)indole **12** (see Scheme 2), involves using the polyphosphoric acid as a reaction medium.[19] However, we observed that this procedure gave the overall degradation of more complicated molecules like the **2a–d** phenylhydrazones. Having observed this, we had to search for another, more efficient



Scheme 2. Model synthesis of the indolopyridocoline **16** and its methoxy analogue **17**.

and ecological-friendly Fischer synthesis procedure, without the use of the protic acids.

2.2. Model synthesis

In order to investigate novel procedures for the difficult Fischer synthesis of sensitive indoles **3a–d** and **4a–d**, the key step in our total synthesis, we first carried out model syntheses, using the 2-acetypyridine **11** as a starting material (see Scheme 2). We investigated parallelly the syntheses towards the indolopyridocoline **16** and its unknown methoxy analogue **17**, as a model synthesis towards the methoxy analogues of sempervirine (**10a–d**). We noticed that the difference between them was only visible in the first, Fischer indolization step.[16] We confirmed that both conventional procedures were suitable for the indole **12** synthesis, they are not proper for obtaining 6-methoxy-2-(2-pyridyl)indole **13**, due to degradation processes. We investigated the three microwave-induced Fischer indolization procedures (methods *A*, *B* and *C*, see Scheme 2 and Table 1) as suitable for the difficult processes with acid-catalysis and high-temperature requirements.

The first investigated method (method *A*) involved the temperature-controlled microwave irradiation of the mixture of the 2-acetylpyridine **11** phenylhydrazone with an excess of the polyphosphoric acid (PPA) at 190 °C for 4 min. The indole **12** can be obtained in 60% yield in scale up to 5 g. However, in the case of microwave irradiation of the 2-acetylpyridine **11** *p*-methoxy-phenylhydrazone in this medium at temperature 120 °C for 4 min degradation was observed and only trace of the 6-methoxyindole was isolated **13** (see Table 1).

Next, we elaborated more ecological Fischer synthesis procedure, where the 2-acetylpyridine **11** phenylhydrazone is adsorbed on montmorillonite K10 modified by zinc chloride (MK10/$ZnCl_2$) and irradiated by microwaves without a solvent at controlled temperature (method *B*).[20] Finally, in this procedure, synthesis of 2-(2-pyridyl)indole **12** ran at 160 °C for 6 min in 45% yield. The 5-methoxy-2-(2-pyridyl)indole **13** was obtained in yield of 40–43% by this method[16] at temperature 130 °C from 2-acetylpyridine **11** via its *p*-methoxyphenylhydrazone hydrochloride.

Recently, we have discovered a new microwave-assisted procedure, where controlled microwave irradiation of the 2-acetylpyridine **11** phenylhydrazone was performed in the medium of the anhydrous zinc chloride solution (0.16 M) in dry triethylene glycol: $ZnCl_2$/TEG-mediated method *C*.[21] Only catalytic quantity of zinc chloride (0.1 equiv) was used in the reaction mixture. 2-(2-Pyridyl)indole **12** was isolated in 65% yield by column chromatography of the dichloromethane extracts, obtained by treatment with this solvent the reaction mixture, prior diluted with the cooled 5% sodium hydroxide. The Fischer synthesis of 5-methoxy-2-(2-pyridyl)indole **13** was established in yield 63% at the lower programmed temperature then the indole **12** (see, Table 1).

Table 1. Comparison of the 2-acetylpyridine **11** Fischer indolization yields into **12** and **13** via three microwave-assisted methods

Indole	Method	Conditions under MW	Yield (%)
12	*A*[a]	PPA, 190 °C, 4 min	60
12	*B*[b]	MK10/$ZnCl_2$, solvent free 190 °C, 4 min	45
12	*C*[c]	$ZnCl_2$/TEG, 190 °C, 8 min	65
13	*A*[a]	PPA, 130 °C, 4 min	Trace
13	*B*[b]	MK10/$ZnCl_2$, solvent free 130 °C, 4 min	43
13	*C*[c]	$ZnCl_2$/TEG, 130 °C, 5 min	63

[a] Irradiation of a crude phenylhydrazone with an excess PPA.
[b] Irradiation of a solid-supported phenylhydrazone without solvent.
[c] Irradiation of the mixture 0.5 mmol substrate with a 0.33 mL, 0.16 M, zinc chloride solution in triethylene glycol ($ZnCl_2$/TEG).

Comparison of the yields of **12** and **13** obtained by the Fischer transformation of the 2-acetylpyridine **11** via the methods *A*, *B* and *C* is shown in Table 1. Next, construction of the C-ring by using the Gribble method: *N*-protection of indole, direct metalation with *n*-butyllithium and reaction with dry solution of bromoacetaldehyde (Scheme 2), resulted in the formation of **16** and **17**. Both products were obtained in overall yields of 24–29% from **11**.

2.3. Synthesis of the sempervirine and its analogues

The two key steps in our total synthetic strategy (see Scheme 1) consist of the synthesis of the acetyl derivatives of cycloalka[*c*]pyridine **2a–d** and their transformation via the Fischer reaction towards the indoles **3a–d** and 5-methoxyindoles **4a–d**. Optimization of both these stages was necessary to obtain the final products in high enough quantities for biological investigations. Recently, we have published the results of the experimental and theoretical studies towards optimization of the synthesis of **2a–d**.[18] Thus, we arrived at 75% yield of **2a** (n=1), 65% of **2b** (n=2), 54% of **2c** (n=3) and 30% of **2d** (n=4) in the conventional heating of **1** and appropriate enamine with anhydrous ethanol. Better yield of **2d**, 45%, was obtained when high concentration reaction mixture **1** and 1-pyrrolidine-1-cyclooctanone in chlorobenzene was irradiated by microwaves at the controlled temperature of 110 °C. The Fischer indolization was previously performed by conventional method with an excess of zinc chloride.[14b] Next, we applied our microwave-induced solid-supported procedure (method *B*) with the use of the montmorillonite K10 modified with zinc chloride (MK10/$ZnCl_2$)[15,16] as the extension of the model reactions **11**→**12**[20] and **11**→**13**[16] (see Scheme 2). However, the yields of products were dissatisfying: 26–29% of **3a–d** and 38–43% of **4a–d**, due to overheating and following degradation processes of irradiated reactants on the solid support. Just recently, we have updated this crucial step by application of our new, $ZnCl_2$/TEG-mediated microwave-induced methodology (method *C*).[21] The Fischer transformations of the **2a–d** phenylhydrazones into **3a–d** required microwave irradiation of the reaction mixture (0.5 mmol substrate with the 0.33 mL of the 0.16 M zinc chloride solution in triethylene glycol ($ZnCl_2$/TEG)) at 180 °C the temperature programed for 7 min. The 5-methoxyindoles **4a–d** were formed at 130 °C for 5 min of irradiation of the *p*-methoxyphenylhydrazones in $ZnCl_2$/TEG medium. This one pot procedure (without isolation of phenylhydrazones) gave almost double increase in yields in comparison to method *B*. After an aqueous workup of the reaction mixture and isolation by column chromatography, the indoles **3a–d** were obtained in yields of 50–53% and the 5-methoxyindoles **4a–d** in yields of 60–63%.[21] These were good results for the difficult Fischer syntheses of the sensitive indoles.

Next step in our total synthesis, removal of the methylthio group in indoles **3a–d** and 5-methoxyindoles **4a–d**, was successfully carried out with the W2 Raney nickel in ethanol at 3–6 °C. We observed that in higher temperature the reaction ran less selectively (with reduction of the pyridine ring) and the yield of products decreased, but in lower temperature the desulfurization process was inhibited. As the crude products were partially bonded in nickel-complexed forms, the workup with EDTA was necessary. The synthons **5a–d** and **6a–d** were obtained in 60–70% yields and were converted to their *N*-phenylsulfonyl derivatives **7a–d** and **8a–d**. Subsequent formation of the C-ring according to the Gribble method[13] led to the sempervirine **9b**, its three analogues with different E-ring **9a**, **9c**,**d** and four alkaloids with methoxy group **10a–d**. Unfortunately, the yields of the two final steps were moderate. We observed incomplete conversion of the substrate in the process of *N*-protection of the indole with phenylsulfonyl chloride in the presence of sodium hydride. It resulted in troublesome isolation of **7a–d** (55–60%) and **8a–d** (52–57%) by column chromatography, because their R_f are lower then R_f of the substrates **5a–d** and **6a–d** (see, Table 2), which were recovered in 15–25% yields. The one pot process of the C ring construction, started when the excess of the bromoacetaldehyde (6 equiv) was added to the cooled (−78 °C) reaction mixture containing the substrate **7a–d** or **8a–d** and *n*-butyllithium (4 equiv). The step by step rearrangements: reaction of an indole β-carboanion with the carbonyl group of the bromoacetaldehyde, protonation with water, closure of the C ring by intramolecular alkylation of the pyridine nitrogen with methylene group from indole β-chain –CHOHCH$_2$–Br, dehydration–aromatization of the C-ring and hydrolysis of the phenylsulfonyl group (deprotection of the indole nitrogen), resulted in the formation of the final pentacyclic alkaloids **9a–d** and **10a–d**. They were extracted in their free base forms to chloroform phase during partitionating with 20% sodium hydroxide, and next purified by preparative thin-layer chromatography on silica gel plates using polar eluent, dichloromethane/methanol 5:1. Yellowish-green to orange-brown, amorphic substances were obtained in 48–58% yields. We observed that in methanolic solution the inert forms come slowly into cations, which are more polar and were visualized on TLC plates (as possessing lower R_f) together with the inert forms. This is in accordance to the investigations of other zwitterionic alkaloids, e.g., by Fujii et al.[22] Alkaloids **9a–d** and **10a–d** itself and their solutions were stored at temperature below 0 °C for several months, but they are sensitive if are exposed to the room temperature and air, when degradation processes were observed.

Chromatographic analysis (TLC) and isolation (column and thin layer preparative chromatography) were very useful in our total synthesis. Therefore, in Table 2, the R_f values for all intermediates, final alkaloids and model compound are shown. In particular, the compounds with methoxy group in indole moiety are more polar then their analogues without OMe in all steps of the synthesis. The main tendency can be observed in Table 2, relies on augmentation polarity of all compounds coming from **3a–d** and **4a–d** towards products **9a–d** and **10a–d**.

We obtained the final alkaloids **9a–d** and **10a–d** in overall yields of 4.1–10.1% in the total synthesis from the substrate **1** (five steps), the highest for **10a**,**b** and the lowest for **9d**.

2.4. Comparative study of the spectroscopic data

The structure of all intermediates and the final pentacyclic cycloalk[*g*]indolo[2,3-*a*]quinolizines, shown in Schemes 1 and 2, were determined by the spectroscopic method. As we prepared and investigated two four-membered series of the final products and three kinds of the consecutive intermediates and also appropriate model compounds, we had the ability for interpretation of their spectroscopic data by comparative study.

The UV spectra of four sempervirine methoxy analogues **10a–d** are shown in Figure 3, together with the spectrum of our synthetic model alkaloids **17**.

The structure variables of the intermediates and the final products can be well observed in their NMR spectra. Table 3 shows the data from the ^{1}H NMR spectra of the three kinds of the succeeding intermediates with the five-membered C ring only. Since differences in the chemical shifts of the two methylene group bonded with pyridine ring exist in the cases of **3a–d** and **4a–d** (as is shown in Table 3 for **3a** and **4a**), we can conclude that the presence of methylthio group gives upfield effect to the nearer one. The methylthio

Table 2. Polarity comparison of the intermediates, the final alkaloids **9a–d**, **10a–d** as well as appropriate model compounds **12–17** as their retention factors (R_f) observed on silica TLC plates with four different eluents

No. compd	R_f [a]	No. compd	R_f [b]	No. compd	R_f [c]	No. compd	R_f [d]
—	—	**12**	0.46	**14**	0.57	**16**	0.25
3a	0.51	**5a**	0.45	**7a**	0.50	**9a**	0.59
3b	0.53	**5b**	0.46	**7b**	0.57	**9b**	0.62
3c	0.54	**5c**	0.48	**7c**	0.59	**9c**	0.64
3d	0.57	**5d**	0.49	**7d**	0.60	**9d**	0.65
—	—	**13**	0.33	**15**	0.35	**17**	0.07
4a	0.18	**6a**	0.32	**8a**	0.32	**10a**	0.17
4b	0.20	**6b**	0.33	**8b**	0.36	**10b**	0.21
4c	0.21	**6c**	0.36	**8c**	0.38	**10c**	0.26
4d	0.23	**6d**	0.37	**8d**	0.41	**10d**	0.30

[a] Obtained with dichloromethane/hexane 1:1.
[b] Obtained with dichloromethane/acetone 50:1.
[c] Obtained with dichloromethane/acetone 30:1.
[d] For inert forms, obtained with dichloromethane/methanol 5:1.

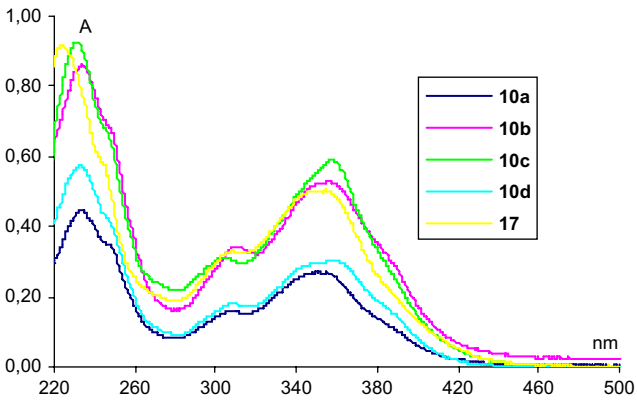
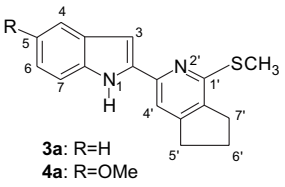
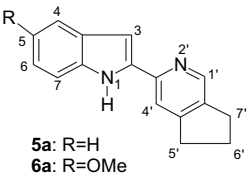
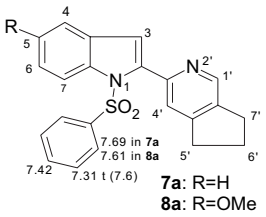


Figure 3. The UV spectra of **10a–d** and **17** in MeOH [c~10^{-4} mol/L].

Table 3. Comparison of the ^{1}H NMR data for the three kinds of consecutive intermediates with five-membered E ring: **3a** and **4a**, **5a** and **6a**, **7a** and **8a** from their simple spectra in $CDCl_3$ (400 MHz)







Position	**3a** δ_H (J in Hz)[a]	**4a** δ_H (J in Hz)[a]	**5a** δ_H (J in Hz)	**6a** δ_H (J in Hz)	**7a** δ_H (J in Hz)	**8a** δ_H (J in Hz)
1 (NH)	9.39 br s	9.24 br s	9.55 br s	9.84 br s	—	—
3	6.96 dd (2.0, 0.9)	6.86 d (2.0)	6.97 dd (2.2, 07)	6.87 d (1.8)	6.85 s	6.82 s
4	7.66 dd (7.0, 1.3)	7.09 d (2.4)	7.65 dd (7.9, 1.3)	7.07 d (2.4)	7.33 d (7.2)	6.88 d (2.4)
5	7.4 ddd (7.6, 7.0, 1.1)	OCH_3: 3.87 s, 3H	7.11 ddd (7.9, 7.6, 1.2)	OCH_3: 3.85 s, 3H	7.24 m	OCH_3: 3.80 s, 3H
6	7.21 ddd (7.9, 7.6, 1.3)	6.89 dd (8.9, 2.4)	7.20 ddd (8.2, 7.6, 1.3)	6.84 dd (8.8, 2.4)	7.44 m	6.94 dd (8.8, 2.4)
7	7.46 dd (7.9, 1.1)	7.28 d (8.9)	7.42 dd (8.2, 1.2)	7.24 d (8.8)	8.18 d (8.4)	8.07 d (8.8)
1′	SCH_3: 2.55 s, 3H	SCH_3: 2.71 s, 3H	8.42 s	8.38 s	8.54 s	8.54 s
4′	7.42 s	7.38 s	7.70 s	7.65 s	7.59 s	7.61 s
5′	2.89 t, 2H (7.5)	2.94 t (7.6)	2.97 t (7.4)	2.93 t (7.5)	3.03 t (7.6)	3.03 t (7.6)
6′	2.19 quintet, 2H (7.5)	2.19 quintet (7.6)	2.15 quintet (7.4)	2.12 quintet (7.5)	2.19 quintet (7.6)	2.19 quintet (7.6)
7′	2.74 t, 2H (7.5)	2.81 t (7.6)	2.97 t (7.4)	2.93 t (7.5)	3.03 t (7.6)	3.03 t (7.6)

[a] Compound described in Ref. 21.

group is visible in the spectra of **3a–d** and **4a–d** as a singlet at δ 2.55–2.72. After its removal, a new singlet emerges in aromatic region (at δ 8.38–8.54) in the spectra of the consecutive compounds **5a–d**, **6a–d**, **7a–d** and **8a–d**, as a signal of the C1′ proton. The spectra of all methoxy analogues in the aromatic region are more simple than the spectra of the intermediates and the final products without methoxy group. It is important, because it allows comparative interpretation of the ^{1}H NMR spectra. Figure 4 shows examples of the ^{1}H NMR data of one pair: **9c** and **10c** of the final products. They are in accordance with the earlier determined ^{1}H NMR for yohimbane anhydronium bases.[23] We can conclude that the chemical shifts of the aromatic protons of the indolo[2,3-*a*]quinolizinium ring system are higher than those observed for the protons of the AB–DE synthons **5a–d** and **6a–d** at the appropriate positions. The two vicinal protons of the new-formed bridge in the C ring of **9a–d** and **10a–d** can be observed as doublets with the J=6.8 Hz. The ^{13}C NMR spectra also show well the changes in the structure of the intermediates and the final products.

We have examined and compared the fragmentation paths of all intermediates and the final products, which are visible in their EI mass spectra. In the mass spectra of the compounds with the methylthio group (**3a–d** and **4a–d**) the removal of the SH radical $[M-33]^+$ can be observed as a tendency to

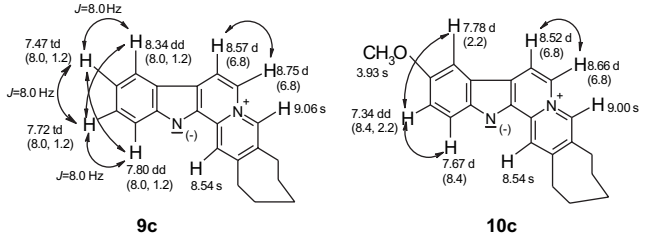


Figure 4. Comparison of the ^{1}H NMR data of the indolo[2,3-*a*]quinolizine ring system in the pair **9c** and **10c** of the final alkaloids from their simple spectra in CD_3OD (400 MHz).

an azatrophylic cation formation. Existence of the methoxy group is indicated by removal of the methyl radical and next carbon oxide from the parent cations, which give peaks $[M-15]^+$ and $[M-43]^+$ in the mass spectra of **4a–d**, **6a–d** and **8a–d** and also **10a–d**, **13**, **15** and **17**. It is interesting that the peaks corresponding to the double charged cations (M^{++}, m/z=M/2) as an ionization possibility in the two points (indole and pyridine moieties of the molecules) can be observed in the mass spectra of all compounds, apart from the *N*-protected indoles **7a–d** and **8a–d**. In the mass spectra of the *N*-protected indoles **7a–d** and **8a–d** the parent cations have been observed, but more intensive peaks: $[M-64]^+$ and $[M-141]^+$ indicate the loss of SO_2 and $PhSO_2$ by molecular cations. Molecules of the final alkaloids can be analyzed with the electron impact mass spectrometer, only in their inert (free bases) forms as they are more volatile than the salts (protonated forms). All intermediates and final products have indicated the parent peaks in their electron impact mass spectra. However, the final alkaloids are unstable during the high-temperature EIMS experiments and the high-resolution measurements of their molecular ions were carried out with an electron-spray technique.

3. Conclusions

A unified synthetic strategy for the zwitterionic indolo[2,3-*a*]quinolizine alkaloid group has been developed, allowing the total synthesis of the pentacyclic sempervirine analogues to be carried out using the same starting material and similar conditions. 5-Acetyl-3-methylthio-1,2,4-triazine has been used as azadiene in Diels–Alder reaction with cyclic enamines and the acetyl derivatives of cycloalka[*c*]pyridines (DE ring systems, differentiation of E ring) have been obtained in the first key step. In the Fischer indolization as the second crucial step, the AB–DE synthons (indole or 5-methoxyindole as AB moiety) have been prepared in satisfying yields thanks to discovery of the new procedure for performing Fischer synthesis. Anhydrous zinc chloride

solution in triethylene glycol has been used as a homogeneous Lewis acid catalytic system and the Fischer reaction has been carried out under controlled microwave irradiation for several minutes. After removal of the methylthio group, the middle C ring has been formed via indole *N*-protection, direct metalation and reaction with the bromoacetaldehyde as a 1,2-dielectrophile. In result, the sempervirine and its seven new analogues have been obtained for the biological evaluation since these structures modification can remain or change the therapeutic profile (anticancer, immunostimulating, antiviral, antipsychotic) of the sempervirine itself.

In the model synthesis, two tetracyclic alkaloids: indolopyridocoline and its new analogue, 9-methoxyindolo[2,3-*a*]quinolizine, have been obtained easily.

Comparative studies on molecular structures and spectroscopic and chemical properties of intermediates and final alkaloids have been performed and their most important results are described in this paper.

4. Experimental

4.1. General

Commercial 2-acetylpyridine **11** was used for model studies. The temperature-controlled microwave-assisted reactions were performed using a microwave reactor Synthewave 402 (Prolabo, 300 W, focused microwaves, open rotating system of reaction vessel) with software (feedback temperature monitoring). Raney nickel W2 was used for desulfurization. Anhydrous bromoacetaldehyde solution in methylene chloride/hexane was obtained by ozonolysis of (*E*)-1,4-dibromo-2-butene.[24] Other reagents were used as commercial. Anhydrous solvents were prepared via standard procedures.[25] The course of reactions was monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm Merck silica gel plates ($60F_{254}$). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Melting points were determined on Boëtius microscopic plate and were not corrected. All new compounds were determined to be >95% pure by ^{1}H NMR. The ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz), Mercury 400BB (400 MHz) or Bruker GRX (500 MHz) spectrometers. IR spectra (KBr pellets) were recorded on FTIR Magna 760 (Nicolet) apparatus. Mass spectrometer AMD 604 (Intectra, GmbH, Germany) was used for EI mass spectra and high-resolution measurements. High-resolution electron spray measurements were carried our with Mariner mass spectrometer (with methanol). The UV measurements were recorded digitally (0.5 nm step) for $c=5\times10^{-4}$ mol/dm^3 solutions in methanol with a BECKMAN DU-68 spectrophotometer using 1-cm quartz cell at a room temperature.

4.2. General procedures for the microwave-assisted Fischer synthesis of indoles 3a–d, 4a–d, 12, 13

4.2.1. Method A: Fischer synthesis in polyphosphoric acid for preparation model indole 12 only. To a solution of 2-acetylpyridine **11** (2.42 g, 20 mmol) in anhydrous ethanol (25 mL) were added phenylhydrazine (2.37 g, 2.33 mL, 22 mmol) and glacial acetic acid (four drops, ~50 mg). The mixture was refluxed under argon for 30 min: the complete disappearance of substrate was observed by TLC monitoring (dichloromethane/acetone 50:1). Solvents were removed under reduced pressure and crude phenylhydrazone was placed into cylindrical quartz vessel. Polyphosphoric acid (~10 g) was added and mixed manually. Irradiation by microwaves was performed at temperature programed at 180 °C for 4 min. Having been cooled, the reaction mixture was quenched with cooled 20% NaOH (150 mL). The aqueous layer was extracted with dichloromethane (3×50 mL), the combined organic phases were dried ($CaCl_2$) and evaporated. Purification of the crude product by flash chromatography on silica gel using hexane/dichloromethane 1:1 as eluent afforded **12** as yellow crystals (2.30 g, 60%), mp 152–153 °C, lit.[26a] mp 154–155 °C. Recrystallization with diethyl ether/hexane gives yellow crystals with mp 156.0–156.5 °C.

4.2.2. Method B: solvent-free Fischer synthesis. The first, solvent-free procedure with modified solid support MK10/$ZnCl_2$ was elaborated in model synthesis of **12** (45%),[20] next it was extended to synthesis of **3a–d** (26–29%)[15] and then was adapted to the preparation of model **13** (43%) and **4a–d** (38–43%).[16]

4.2.3. Method C: controlled microwave irradiation of phenylhydrazones with 0.16 M zinc chloride solution in triethylene glycol. This efficient procedure has been recently described.[21] Indole **12** was obtained in 65% yield and methoxyindole **13** in 63% yield from 2-acetylpyridine **11** (see Table 1). The Fischer indolization of ketones **2a–d** towards indoles **3a–d** was carried out in 50–53% yields and towards methoxyindoles **4a–d** in 60–63% yields.[21]

Model 2-(2-pyridyl)indole **12** was described earlier.[26] Additional characterization data: IR (KBr): ν_{max} 3134, 3078, 1598, 1562, 1546, 1470, 1443, 1416, 1345, 1304, 1155, 997, 758, 755, 733 cm^{-1}; GC–MS: t_R=12.3 min, *m*/*z* 194 (M^+, 100), 167 (10), 139 (6), 97 (M^{2+}, 25), 89 (11), 83 (22), 78 (10), 70 (11); ^{1}H NMR (200 MHz, CD_3OD): δ 8.56 (1H, ddd, *J*=5.0, 1.7, 1.0 Hz), 7.89 (1H, ddd, *J*=8.0, 1.5, 1.0 Hz), 7.81 (1H, ddd, *J*=8.0, 7.1, 1.7 Hz), 7.57 (1H, ddd, *J*=8.1, 1.1, 0.9 Hz), 7.43 (1H, dd, *J*=8.0, 1.1 Hz), 7.24 (1H, ddd, *J*=7.1, 5.0, 1.5 Hz), 7.14 (1H, ddd, *J*=8.1, 7.0, 1.1 Hz), 7.06 (1H, d, *J*=0.9 Hz), 7.01 (1H, ddd, *J*=8.0, 7.8, 1.1 Hz).

Model 5-methoxy-2-(2-pyridyl)indole **13** and compound **4c** were characterized in Ref. 16, compound **3b** in Ref. 14b and all compounds **3a–d** and **4a–d** in Ref. 21.

4.3. Preparation of the synthons 5a–d and 6a–d in the desulfurization process

General procedure: compound **3a** (280 mg, 1 mmol) was dissolved in anhydrous ethanol (50 mL) at room temperature and the rapidly stirred solution was cooled to 0 °C. The first portion of the W2 Raney nickel (~2 g) was added and the temperature was maintained between 3–6 °C. At this temperature next portions of Raney nickel were added. Reaction was monitored by TLC (dichloromethane), where substrate **3a** (R_f=0.87) disappeared and product **5a** (R_f=0.17) was

formed. Optimal reaction time was 45–60 min for complete desulfurization. Reaction mixture was cooled to −10 °C and quickly filtered through Celite. Reaction flask and Celite were washed with a cooled mixture of ethanol/acetone 2:1. Solvents evaporated under reduced pressure and green residue was obtained. After treatment with 5% hydrochloric acid (10 mL) the yellow precipitate was obtained, to which the cooled 10% EDTA solution in 10% ammonium hydroxide (10 mL) and diethyl ether (50 mL) were added. The mixture was shaken and organic layer separated. The aqueous phase was extracted with diethyl ether (2×50 mL), combined organic phases were washed with brine and dried with sodium sulfate. Removing the solvent led to **5a** as a white solid, which was purified by recrystallization with dichloromethane/hexane. Characterization data of **5a** are given in Section 4.3.1.

According to the general procedure mentioned above the following products were obtained: **5b–d** from **3b–d** (1 mmol) and **6a–d** from **4a–d** (1 mmol). The yields and the characterization data are given below.

4.3.1. 2-(6,7-dihydro-5*H*-[2]pyrindin-3-yl)-1*H*-indole (5a). Yield 160 mg (68%); mp 160–161 °C; IR (KBr): 3216, 2952, 2923, 2860, 1654, 1608, 1556, 1425, 1344, 1299, 1117, 1055, 873, 792, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (2H, quintet, J=7.6 Hz), 2.97 (4H, 2×t, J=7.6 Hz), 6.97 (1H, dd, J=2.2, 0.7 Hz), 7.11 (1H, ddd, J=7.9, 7.6, 1.2 Hz), 7.20 (1H, ddd, J=8.2, 7.6, 1,3 Hz), 7.42 (1H, dd, J=8.2, 1.2 Hz), 7.65 (1H, dd, J=7.9, 1.3 Hz), 7.70 (1H, s), 8.42 (1H, s), 9.55 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 30.1, 32.6, 99.4, 111.2, 115.9, 119.9, 120.9, 122.7, 129.1, 136.4, 137.4, 139.0, 144.7, 148.2, 154.6; EIMS m/z (%): 234 (M^+, 100), 204 (8), 117 (M^{++}, 12); HRMS (EI, M^+) found 234.1157, calcd for $C_{16}H_{14}N_2$ 234.1157.

4.3.2. 3-(Indol-2-yl)-5,6,7,8-tetrahydroisiquinolie (5b). Yield 174 mg (70%); mp 160–161 °C lit.[12] 158.0–158.5 °C, lit.[13a] 159.5–160.5 °C, lit.[14b] 158–159 °C; IR (KBr): 3131, 3069, 2925, 2854, 1604, 1608, 1550, 1473, 1426, 1346, 1305, 1141, 1070, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (4H, m), 2.75 (2H, m), 2.80 (2H, m), 6.93 (1H, d, J=1.6 Hz), 7.08 (1H, dd, J=8.1, 7.2 Hz), 7.17 (1H, ddd, J=7.9, 7.2, 1,3 Hz), 7.36 (1H, d, J=8.1 Hz), 7.49 (1H, s), 7.62 (1H, dd, J=7.9, 1.3 Hz), 8.25 (1H, s), 9.86 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4, 22.6, 26.2, 28.9, 99.5, 111.3, 119.9, 120.0, 120.9, 122.7, 129.2, 131.9, 136.5, 137.0, 147.1, 147.2, 149.2; EIMS m/z (%): 248 (M^+, 100), 232 (5), 220 (18), 124 (M^{++}, 6), 116 (5).

4.3.3. 3-(Indol-2-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]-pyridine (5c). Yield 172 mg (65%); mp 141–142 °C; IR (KBr): 3213, 3013, 2921, 2848, 1654, 1602, 1552, 1479, 1425, 1348, 1311, 1225, 1185, 792, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.60–180 (4H, m), 1.81–1.90 (2H, m), 2.81–2.98 (4H, m), 6.98 (1H, dd, J=2.0, 0.8 Hz), 7.09, (1H, ddd, J=7.8, 7.0, 1.1 Hz), 7.22 (1H, ddd, J=7.2, 7.0, 1.3 Hz), 7.38 (1H, dd, J=2.2, 1.1 Hz), 7.57 (1H, s), 7.65 (1H, dd, J=7.8, 1.3 Hz), 8.28 (1H, s), 9.71 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.1, 32.6, 33.1, 36.4, 99.7, 111.2, 115.8, 119.9, 120.9, 122.7, 129.1, 136.3, 137.1, 137.5, 148.4, 148.5, 152.7; EIMS m/z (%): 262 (M^+, 100), 233 (9), 221 (5), 131 (M^{++}, 5) 116 (5); HRMS (EI, M^+) found 262.14732, calcd for $C_{18}H_{18}N_2$ 262.14700.

4.3.4. 3-(Indol-2-yl)-5,6,7,8,9,10-heksahydrocyclo-octa[*c*]pyridine (5d). Yield 168 mg (61%); mp 144–145 °C; IR (KBr): 3174, 3150, 3077, 2923, 2851, 1602, 1550, 1477, 1446, 1424, 1344, 1344, 1321, 1227, 1182, 1070, 1003, 793, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.35–1.45 (4H, m), 1.67–1.79 (4H, m), 2.74–2.82 (4H, m), 6.98 (1H, d, J=1.8 Hz), 7.08, (1H, ddd, J=8.1, 7.0, 1.2 Hz), 7.17 (1H, ddd, J=7.8, 7.0, 1,2 Hz), 7.32 (1H, dd, J=8.1, 1.2 Hz), 7.56 (1H, s), 7.63 (1H, dd, J=7.8, 1.2 Hz), 8.28 (1H, s), 10.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$), δ 25.6, 25.8, 29.2, 31.4, 31.7, 32.1, 99.9, 111.4, 119.9, 120.0, 120.9, 122.7, 129.2, 135.9, 136.6, 136.9, 148.3, 148.5, 151.2; EIMS m/z (%): 276 (M^+, 100), 247 (4), 233 (9), 220 (4), 138 (M^{++}, 5), 116 (4); HRMS (EI, M^+) found 276.16234, calcd for $C_{19}H_{20}N_2$ 276.16265.

4.3.5. 2-(6,7-Dihydro-5*H*-[2]pyrindin-3-yl)-5-methoxy-1*H*-indole (6a). Yield 185 mg (70%); mp 144–145 °C; IR (KBr): 3192, 3063, 2927, 2831, 1609, 1549, 1461, 1433, 1336, 1308 1294, 1260, 1225, 1152, 1034, 856, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 3.85 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.87 (1H, d, J=1.8 Hz), 7.07 (1H, d, J=2.4 Hz), 7.24 (1H, d, J=8.8 Hz), 7.65 (1H, s), 8.28 (1H, s), 9.85 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 30.1, 32.7, 55.8, 99.5, 102.3, 112.0, 113.4, 115.9, 129.5, 131.8, 137.8, 138.9, 144.4, 148.1, 154.3, 154.8; EIMS m/z (%): 264 (M^+, 100), 249 (65), 221 (28), 192 (4), 132 (M^{++}, 6), 116 (4); HRMS (EI, M^+) found 264.12601, calcd for $C_{17}H_{16}N_2O$ 264.12626.

4.3.6. 5-Methoxy-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (6b). Yield 189 mg (68%); mp 129–130 °C; IR (KBr): 3127, 3060, 2927, 2890, 1621, 1604, 1549, 1480, 1447, 1423, 1350, 1302, 1226, 1199, 1156, 1117, 1073, 885, 839, 797 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (4H, m), 2.74 (2H, m), 2.79 (2H, m), 3.84 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.85 (1H, d, J=2.2 Hz), 7.06 (1H, d, J=2.4 Hz), 7.25 (1H, d, J=8.8 Hz), 7.45 (1H, s), 8.23 (1H, s), 9.71 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4, 22.6, 26.2, 28.9, 55.8, 99.3, 102.3, 112.0, 113.3, 119.8, 129.5, 131.8, 131.9, 137.5, 147.1, 147.2, 149.2, 154.2; EIMS m/z (%): 278 (M^+, 100), 263 (40), 235 (18), 207 (5), 139 (M^{++}, 9), 116 (4); HRMS (EI, M^+) found 278.14128, calcd for $C_{18}H_{18}N_2O$ 278.14191.

4.3.7. 5-Methoxy-2-(5,6,7,8-tetrahydro-5*H*-cyclohepta[*c*]-pyridine-3yl)-1*H*-indole (6c). Yield 192 mg (66%); mp 126–127 °C; IR (KBr): 3160, 3055, 2923, 2848, 1621, 1604, 1546, 1451, 1421, 1352, 1294, 1223, 1159, 1112, 1028, 830, 788 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.64–1.73 (4H, m), 1.89 (2H, m), 2.80 (2H, m), 2.85 (2H, m), 3.86 (3H, s), 6.86 (1H, dd, J=9.0, 2.0 Hz), 6.89–6.91 (1H, m), 7.09 (1H, d, J=2.0 Hz), 7.25 (1H, d, J=9.0 Hz), 7.53 (1H, s), 8.25 (1H, s), 9.87 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.5, 28.1, 32.5, 33.1, 36.5, 55.8, 99.7, 102.3, 112.0, 113.4, 119.9, 129.5, 131.9, 137.4, 137.5, 148.1, 148.5, 153.1, 154.3; EIMS m/z (%): 292 (M^+, 100), 277 (65), 249 (45), 219 (5), 192 (5), 146 (M^{++}, 11), 119 (6);

HRMS (ESI, $[M+H]^+$) found 293.1655, calcd for $C_{19}H_{21}N_2O$ 293.1648.

4.3.8. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-5-methoxy-1*H*-indole (6d). Yield 205 mg (68%); mp 110–111 °C; IR (KBr): 3157, 3055, 2991, 2923, 2851, 1622, 1601, 1547, 1451, 1422, 1299, 1220, 1195, 1156, 1031, 844, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.35–1.45 (4H, m), 1.67–1.79 (4H, m), 2.76–2.84 (4H, m), 3.85 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.90 (1H, d, J=1.6 Hz), 7.07 (1H, d, J=2.4 Hz), 7.23 (1H, d, J=8.8 Hz), 7.53 (1H, s), 8.26 (1H, s), 9.89 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.5, 25.8, 29.2, 31.4, 31.7, 32.1, 55.8, 99.6, 102.3, 112.0, 113.3, 120.0, 129.5, 131.9, 135.8, 137.5, 148.4, 148.8, 151.2, 154.2; EIMS *m*/*z* (%): 306 (M^+, 100), 291 (68), 263 (32), 219 (5), 207 (4), 153 (M^{++}, 6); HRMS (EI, M^+) found 306.17281, calcd for $C_{20}H_{22}N_2O$ 306.17321.

4.4. Preparation of the *N*-phenylsulfonylindoles: 7a–d, 8a–d and models 14 and 15

General procedure: Sodium hydride as a 60% dispersion (120 mg, 3.0 mmol) was washed twice with anhydrous diethyl ether (5 mL), which was decanted. Anhydrous THF (30 mL) was added immediately, and cooled to 0 °C with stirring. A solution of indole **5a** (117 mg, 0.50 mmol) in THF (10 mL) was added dropwise for 5 min and the reaction mixture was stirred at 0 °C for 1 h and next at 5–10 °C for 2 h. After cooling to 0 °C, phenylsulfonyl chloride (0.6 mL, 5 mmol) was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 1 h, next at 0–10 °C for 1.5 h and was placed in a refrigerator overnight (5 °C). Saturated aqueous $NaHCO_3$ (10 mL) was added dropwise over 10 min with vigorously stirring at 0 °C, which was continued for 30 min and then the reaction mixture was allowed to warm to ambient temperature for 1 h. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with brine (2×10 mL), dried with K_2CO_3 and concentrated under reduced pressure to give an oily residue. Isolation by column chromatography was carried out at first with dichloromethane/hexane 1:1 (phenylsulfonyl chloride was isolated), next with dichloromethane when the substrate **5a** (R_f=0.45, dichloromethane/acetone 50:1) was recovered in 18% yield and then with dichloromethane/acetone 30:1 gave **7a** (R_f=18, dichloromethane/acetone 50:1) as a white solid. Characterization data for **7a** are given in Section 4.4.1.

Following this general procedure, the products **7b–d** were also obtained from **5b–d**, **8a–d** from **6a–d** and **14** and **16** from appropriate model indoles **12** and **13**, respectively. These yields and the identification data are given below.

4.4.1. 2-(6,7-Dihydro-5*H*-[2]pyrindin-3-yl)-1-phenylsulfonyl-1*H*-indole (7a). Yield 110 mg (59%); 147–148 °C; IR (KBr): 3062, 3002, 2958, 2923, 2858, 1607, 1548, 1449, 1371, 1305, 1189, 1176, 1115, 1089, 1059, 996, 888, 829, 755, 728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 6.85 (1H, s), 7.24 (1H, m), 7.31 (2H, t, J=7.6 Hz), 7.33 (1H, d, J=7.6 Hz), 7.42 (1H, t, J=7.6 Hz), 7.44 (1H, m), 7.59 (1H, s), 7.69 (2H, d, J=7.6 Hz), 8.18 (1H, d, J=8.4 Hz), 8.54 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0, 30.2, 32.6, 114.6, 116.2, 121.2, 122.4, 124.3, 125.1, 127.0, 128.6, 130.5, 133.5, 137.1, 137.9, 140.0, 141.7, 144.6, 148.9, 153.3; EIMS *m*/*z* (%): 374 (M^+, 27), 310 (97), 233 (100), 205 (17); HRMS (EI, M^+) found 374.1088, calcd for $C_{22}H_{18}N_2O_2S$ 374.1089.

4.4.2. 1-Phenylsulfonyl-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (7b). Yield 116 mg (60%); mp 160–161 °C lit.[13a] 158.5–159.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–192 (4H, m), 2.80–2.90 (4H, m), 6.85 (1H, s), 7.23 (1H, dd, J=7.2, 1.2 Hz), 7.28–7.39 (3H, m), 7.41 (1H, s), 7.42–7.48 (2H, m) 7.69 (2H, d, J=7.2 Hz), 8.18 (1H, dd, J=8.3, 0.7 Hz), 8.39 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.5, 26.2, 28.8, 115.0, 116.3, 121.3, 122.4, 125.2, 126.5, 127.1, 128.7, 130.5, 133.1, 133.5, 137.0, 138.0, 140.0, 146.2, 147.6, 148.9; EIMS *m*/*z* (%): 388 (M^+, 20), 324 (100), 261 (17), 247 (75), 231 (7), 219 (22), 205 (6), 192 (5); HRMS (EI, M^+) found 388.12414, calcd for $C_{23}H_{20}N_2O_2S$ 388.12455.

4.4.3. 1-Phenylsulfonyl-2-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-3yl)-1*H*-indole (7c). Yield 112 mg (56%); mp 149–150 °C; IR (KBr): 3062, 2998, 2923, 2858, 1616, 1604, 1483, 1446, 1370, 1317, 1189, 1168, 1115, 1090, 1069, 995, 823, 751, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.65–1.81 (4H, m), 1.82–1.97 (2H, m), 2.85–2.92 (4H, m), 6.84 (1H, d, J=0.7 Hz), 7.24–7.48 (6H, m) 7.43 (1H, s), 7.69 (2H, dt, J=7.2, 1.4 Hz), 8.20 (1H, dd, J=8.3, 0.7 Hz), 8.39 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 27.9, 32.6, 33.2, 36.3, 114.7, 116.2, 121.2, 124.3, 125.1, 126.3, 127.0, 128.6, 130.5, 133.5, 137.0, 138.0, 138.4, 141.4, 148.3, 149.3, 151.5; EIMS *m*/*z* (%): 402 (M^+, 21), 338 (100), 275 (15), 261 (56), 245 (6), 219 (10), 205 (7), 192 (4); HRMS (EI, M^+) found 402.1382, calcd for $C_{24}H_{22}N_2O_2S$ 402.1402.

4.4.4. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-1-phenysulfonyl-1*H*-indole (7d). Yield 114 mg (55%); mp 162–163 °C; IR (KBr): 3062, 3003, 2979, 2923, 2858, 1616, 1601, 1514, 1476, 1374, 1327, 1165, 1143, 1105, 1090, 1055, 985, 845, 759, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35–1.47 (4H, m), 1.69–1.80 (4H, m), 2.76–2.83 (4H, m), 6.86 (1H, d, J=0.7 Hz), 7.22–7.44 (6H, m), 7.47 (1H, s), 7.67 (2H, dt, J=7.2, 1.4 Hz), 8.15 (1H, dd, J=8.3, 0.7 Hz), 8.33 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 25.6, 29.1, 30.6, 31.8, 32.0, 115.1, 116.1, 121.3, 124.2, 125.4, 126.7, 127.0, 128.7, 130.5, 133.1, 133.3, 137.1, 138.4, 139.9, 148.9, 148.5, 148.7; EIMS *m*/*z* (%): 416 (M^+, 15), 352 (100), 288 (15), 275 (52), 259 (5), 219 (10), 205 (7), 192 (4); HRMS (ESI, $[M+H]^+$) found 417.1637, calcd for $C_{25}H_{25}N_2O_2S$ 417.1637.

4.4.5. 2-(6,7-Dihydro-5*H*-[*c*]pyrindin-3-yl)-5-methoxy-1-phenylsulfonyl-1*H*-indole (8a). Yield 115 mg (57%); mp 101.5–102.5 °C; IR (KBr): 3063, 2930, 2859, 1604, 1552, 1466, 1447, 1370, 1292, 1214, 1181, 1157, 1090, 1029, 855, 809, 734, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 3.85 (3H, s), 6.82 (1H, s), 6.88 (1H, d, J=2.4 Hz), 6.94 (1H, dd J=8.8, 2.4 Hz), 7.30 (2H, t, J=7.6 Hz), 7.42 (1H, t, J=7.6), 7.60 (2H, d, J=7.6 Hz), 7.61 (1H, s), 8.07 (1H, d, J=8.8 Hz), 8.54 (1H, s); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 25.0, 30.2, 32.7, 55.5, 103.6, 114.2, 115.8, 117.4, 122.8, 127.0, 128.6, 131.7, 132.6, 133.5, 136.5, 140.2, 141.8, 144.0, 148.4, 154.0, 157.1; EIMS *m/z* (%): 404 (M^+, 28), 340 (65), 263 (100), 248 (14), 219 (22), 192 (5), 168 (9); HRMS (EI, M^+) found 404.11920, calcd for $C_{23}H_{20}N_2O_3S$ 404.11946.

4.4.6. 5-Methoxy-1-phenylsulfonyl-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (8b). Yield 117 mg (56%); mp 125–126 °C; IR (KBr): 3065, 3005, 2956, 2927, 2844, 1606, 1545, 1469, 1369, 1215, 1182, 1144, 1099, 1029, 865, 822, 733, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.92 (4H, m), 2.81–2.90 (4H, m), 3.79 (3H, s), 6.80 (1H, s), 6.87 (1H, d, *J*=2.4 Hz), 6.93 (1H, dd, *J*=9.2, 2.4 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.40 (1H, s), 7.42 (1H, t, *J*=7.6 Hz), 7.60 (2H, d, *J*=7.6 Hz), 8.06 (1H, d, *J*=9.2 Hz), 8.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 22.3, 22.4, 28.3, 28.8, 55.5, 103.6, 114.6, 115.6, 117.4, 122.6, 127.0, 128.6, 131.7, 132.6, 133.1, 133.5, 136.6, 141.5, 146.4, 148.8, 154.1, 157.1; EIMS *m/z* (%): 418 (M^+, 27), 354 (85), 339 (6), 291 (6), 277 (100), 262 (20), 249 (10), 234 (19), 218 (8), 182 (7); HRMS (ESI, $[M+H]^+$) found 419.1445, calcd for $C_{24}H_{23}N_2O_3S$ 419.1424.

4.4.7. 5-Methoxy-1-phenylsulfonyl-2-(5,6,7,8-tetrahydro-5*H*-cyclohepta[*c*]pyridin-3-yl)-1*H*-indole (8c). Yield 119 mg (55%); mp 132.5–133.5 °C; IR (KBr): 3063, 2998, 2923, 2850, 1605, 1550, 1471, 1447 1371, 1294, 1217, 1179, 1150, 1091, 1031, 807, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ.1.65–1.81 (4H, m), 1.82–1.97 (2H, m), 2.86–2.96 (4H, m), 3.83 (3H, s), 6.81 (1H, s), 6.87 (1H, d, *J*=2.4 Hz), 6.93 (1H, dd, *J*=9.2, 2.4 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.42 (1H, t, *J*=7.6 Hz), 7.46 (1H, s), 7.58 (2H, d, *J*=7.6 Hz), 8.07 (1H, d, *J*=9.2 Hz), 8.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 27.8, 32.6, 33.2, 36.3, 55.5, 103.6, 114.6, 115.6, 117.4, 122.7, 127.0, 128.6, 131.7, 132.7, 133.1, 133.5, 136.6, 141.8, 146.4, 148.8, 154.0, 157.1; EIMS *m/z* (%): 432 (M^+, 23), 368 (100), 353 (5), 305 (5), 291 (96), 276 (17), 263 (6), 248 (17), 219 (9), 205 (5), 196 (5); HRMS (ESI, $[M+H]^+$) found 433.1602, calcd for $C_{25}H_{25}N_2O_3S$ 433.1580.

4.4.8. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-5-methoxy-1-phenylsulfonyl-1*H*-indole (8d). Yield 116 mg (52%); mp 116–117 °C; IR (KBr): 3063, 2997, 2925, 2853, 1606, 1549, 1470, 1447, 1371, 1298, 1214, 1178, 1148, 1090, 1031, 912, 859, 809, 757, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37–1.50 (4H, m), 1.71–1.81 (4H, m), 2.80–2.90 (4H, m), 3.85 (3H, s), 6.79 (1H, s), 6.88 (1H, d, *J*=2.4 Hz), 6.92 (1H, dd, *J*=9.2, 2.4 Hz), 7.29 (2H, t, *J*=7.6 Hz), 7.41 (1H, t, *J*=7.6 Hz), 7.45 (1H, s), 7.56 (2H, d, *J*=7.6 Hz), 8.05 (1H, d, *J*=9.2 Hz), 8.36 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 25.5, 29.0, 30.3, 31.7, 31.9, 55.5, 103.6, 114.6, 115.5, 117.4, 122.5, 127.0, 128.6, 131.7, 132.6, 133.0, 133.5, 136.3, 141.6, 146.1, 148.8, 154.1, 157.1; EIMS *m/z* (%): 446 (M^+, 15), 382 (100), 367 (5), 319 (4), 305 (63), 290 (5), 290 (5), 262 (7), 247 (4), 233 (5), 219 (6), 206 (6); HRMS (EI, H^+) found 446.1673, calcd for $C_{26}H_{26}N_2O_3S$ 445.1664.

4.4.9. 1-Phenylsulfonyl-2-(pyridin-2-yl)-1*H*-indole (14). Yield 124 mg (74%); mp 113–114 °C (diethyl ether); IR (KBr): 3079, 3059, 3010, 2998, 1585, 1550, 1480, 1450, 1425, 1375, 1310, 1260, 1223, 1159, 1195, 1180, 1055, 1018, 1001, 980, 905, 838, 805, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.88 (1H, s), 7.21–7.50 (7H, m), 7.62–7.84 (4H, m), 8.20 (1H, dd, *J*=8.3, 1.5 Hz), 8.69 (1H, ddd, *J*=5.0, 1.7, 1.0 Hz); EIMS *m/z* (%): 334 (M^+, 35), 270 (100), 241 (5), 209 (4), 193 (98), 166 (80), 140 (34); HRMS (EI, M^+) found 334.0770, calcd for $C_{19}H_{14}N_2O_2S$ 334.0776; Elem. anal. Found C, 68.15; H, 4.25; N, 8.33. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38.

4.4.10. 5-Methoxy-1-phenylsulfonyl-2-(pyridin-2yl)-1*H*-indole (15). Yield 127 mg (70%); mp 92–93 °C (diethyl ether); IR (KBr): 3063, 2997, 2925, 1600, 1544, 1460, 1443, 1375, 1290, 1210, 1130, 1100, 1090, 1021, 902, 869, 803, 755, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s), 6.82 (1H, s), 6.88 (1H, d, *J*=2.2 Hz), 6.95 (1H, dd, *J*=8.7, 2.2 Hz), 7.26–7.35 (3H, m), 7.42 (1H, t, *J*=7.6 Hz), 7.56 (2H, d, *J*=7.9 Hz), 7.71–7.78 (2H, m), 8.08 (1H, d, *J*=8.3 Hz), 8.36 (1H, d, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 103.9, 114.6, 116.4, 117.7, 123.4, 126.7, 128.8, 131.8, 132.6, 133.0, 133.7, 135.8, 136.7, 142.0, 148.9, 151.5, 157.3; EIMS *m/z* (%): 364 (M^+, 55), 300 (88), 221 (100), 206 (16), 177 (27); HRMS (ESI, $[M+H]^+$) found 365.0967, calcd for $C_{20}H_{17}N_2O_3S$ 365.0954.

4.5. The final alkaloids 9a–d, 10a–d and model compounds 16 and 17 preparation in modified Gribble's procedure one pot annulation of the C ring

A solution of the protected indole **7a** (75 mg, 0.02 mmol) in THF (15 mL) was stirred under argon and cooled to −70 °C. A 1.6 M solution of *n*-butyllithium in hexane (0.63 mL, 1.0 mmol) was added dropwise for 2 min, and stirring was continued for 1 h at −70 °C and then the reaction mixture was warmed to −20 °C for 1 h. A orange solution was obtained and then it was cooled to −70 °C and a 0.62 M dry bromoacetaldehyde solution in dichloromethane/hexane[24] (2.5 mL, 1.55 mmol) was added dropwise for 5 min. The reaction mixture was stirred at −70 °C for 1 h and then it was allowed to warm to −10 °C for another hour. The reaction mixture was cooled to −70 °C and water (0.18 mL, 10 mmol) was added dropwise with stirring for 1 h, then it was allowed to warm to 0 °C over another hour, and saturated ammonium chloride (10 mL) and CH_2Cl_2 (30 mL) were added. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (30 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. A yellow oily residue was obtained, which was dissolved in $CHCl_3$ (5 mL) and was refluxed for 30 min. The solvent was removed and the residue was washed with diethyl ether (3×4 mL). The pale yellow crude powder (salt) was quenched with methanol (20 mL) and 10% sodium hydroxide (4 mL) and it was heated at reflux for 1 h. The reaction mixture was cooled and concentrated in vacuo. The residue was partitioned between $CHCl_3$ (40 mL) and 20% sodium hydroxide (5 mL). The organic layer was washed with water (15 mL) and dried with Na_2SO_4 and concentrated. Purification of the residue by preparative thin-layer chromatography on silica gel plates using dichloromethane/methanol 5:1 as an eluent afforded pure **9a** (28 mg, 55%) as a dark yellow amorphic powder, shows decomposition above 250 °C

during the measurement of the melting point. Identification data for **9a** is given in Section 4.5.1.

Following this general procedure, the products **9b–d** were obtained from **7b–d**, **10a–d** from **8a–d** and model **16** and **17** from appropriate model protected indoles **14** and **15**, respectively. These yields and the identification data are given below.

4.5.1. 2,3-Dihydro-1*H*-cyclopent[*g*]indolo[2,3-*a*]quinolizine (9a). Yellow powder, yield 28 mg (55%); mp 260–265 °C (dec); IR (KBr): 3060, 2950, 2924, 2854, 1635, 1603, 1448, 1410, 1366, 1330, 1171, 1084, 747, 570, 463 cm^{-1}; UV (MeOH) λ_{max}: 235, 302, 333, 360, 382 nm; ^1H NMR (400 MHz, CD_3OD): δ 2.20 (2H, m), 2.87 (2H, m), 3.04 (2H, m), 7.45–7.49 (1H, m), 7.69–7.73 (1H, m), 7.79 (1H, d, J=8.4 Hz), 8.33 (1H, d, J=8.0 Hz), 8.55 (1H, d, J=6.8 Hz), 8.61 (1H, s), 8.78 (1H, d, J=6.8 Hz), 9.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 30.8, 32.9, 113.3, 117.0, 118.8, 122.1, 122.0, 122.5, 125.0, 128.3, 129.1, 132.9, 133.9, 135.2, 140.5, 144.4, 156.1; EIMS (temp=306 °C: spectrum showed some products of the thermal decomposition of the product), *m/z* (%): 258 (M^+, 9), 129 (M^{++}, 15), 126 (18), 111 (25), 95 (42), 83 (49), 69 (61), 57 (100); HRMS (ESI, $[M+H]^+$) found 259.1238, calcd for $C_{18}H_{15}N_2$ 259.1213.

4.5.2. 2,3,4,13-Tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]quinolizin-6-ium inner salt (9b). Orange-red powder, yield 32 mg (58%); mp 259–262 °C (dec), lit.[11] 258–260 °C; IR (KBr): 3055, 2935, 2860, 1650, 1635, 1603, 1560, 1464, 1447, 1375, 1164, 1094, 747, 620 cm^{-1}; UV (MeOH) λ_{max}: 238.5, 294.0, 330.5, 366.0, 385.5 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.97–2.04 (4H, m), 3.08 (2H, m), 3.24 (2H, m) 7.46 (1H, td, J=8.0, 1.2 Hz), 7.70 (1H, td, J=8.0, 1.2 Hz), 7.79 (1H, dd, J=8.0, 1.2 Hz), 8.32 (1H, dd, J=8.0, 1.2 Hz), 8.50 (1H, s), 8.53 (1H, d, J=6.8 Hz), 8.72 (1H, d, J=6.8 Hz), 9.05 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 22.4, 22.5, 26.3, 28.5, 115.6, 117.7, 119.5, 120.5, 121.0, 121.7, 123.6, 125.8, 126.9, 131.3, 134.5, 134.9, 140.8, 144.1, 155.1; EIMS (temp=231 °C: spectrum showed some products of the thermal degradation), *m/z* (%): 272 (M^+, 9), 136 (M^{++}, 9), 128 (18), 111 (25), 95 (42), 83 (49), 69 (61), 57 (100); HRMS (ESI, $[M+H]^+$) found 273.1374, calcd for $C_{19}H_{17}N_2$ 273.1386.

4.5.3. 2,3,4,5-Tetrahydro-1*H*-cyclohept[*g*]indolo[2,3-*a*]quinolizine (9c). Pale brown powder, yield 30 mg (53%); mp 269–272 °C (dec); IR (KBr): 3061, 2925, 2853, 1649, 1633, 1600, 1521, 1470, 1410, 1370, 1329, 1261, 1226, 1191, 1096, 800, 775, 766, 746, 659, 599, 568, 468 cm^{-1}; UV (MeOH) λ_{max}: 238.0, 294.5, 330.5, 366.5, 385.0 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.80 (4H, m), 1.95 (2H, m), 3.06 (2H, m), 3.12 (2H, m), 7.47 (1H, td, J=8.0, 1.2 Hz), 7.72 (1H, td, J=8.0, 1.2 Hz), 7.80 (1H, dd, J=8.0, 1.2 Hz), 8.34 (1H, dd, J=8.0, 1.2 Hz), 8.54 (1H, s), 8.57 (1H, d, J=6.8 Hz), 8.75 (1H, d, J=6.8 Hz), 9.06 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 27.4, 27.8, 32.8, 33.6, 36.2, 115.1, 117.3, 121.6, 122.1, 123.0, 124.5, 125.6, 127.5, 128.1, 132.3, 133.1, 136.9, 140.5, 144.2, 155.9; EIMS (temp=298 °C: in the spectrum appeared some products of the thermal degradation), *m/z* (%): 286 (M^+, 12), 257 (13), 143 (M^{++}, 5), 128 (15), 111 (28), 95 (38), 83 (47), 69 (57), 57 (100); HRMS (ESI, $[M+H]^+$) found 287.1542, calcd for $C_{20}H_{19}N_2$ 287.1543.

4.5.4. 9,10,11,12,13,14-Hexahydrocyclooct[*g*]indolo[2,3-*a*]quinolizine (9d). Dark yellow powder, yield 33 mg (55%); mp 254–256 °C (dec); IR (KBr): 3058, 2940, 2865, 1648, 1630, 1601, 1555, 1454, 1417, 1380, 1175, 1099, 747, 620, 455 cm^{-1}; UV (MeOH) λ_{max}: 245.0, 297.0, 330.5, 360.0, 383.5 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.57–1.47 (4H, m), 1.86–2.00 (4H, m), 3.10 (2H, t, J=6.0 Hz), 3.20 (2H, t, J=6.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.70 (1H, t, J=8.0 Hz), 7.79 (1H, d, J=8.0 Hz), 8.32 (1H, d, J=8.0 Hz), 8.54 (1H, d, J=6.8 Hz), 8.58 (1H, s), 8.75 (1H, d, J=6.8 Hz), 9.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 28.1, 31.7, 32.2, 34.5, 34.6, 115.1, 118.6, 122.3, 124.1, 124.6, 125.5, 127.7, 128.8, 132.0, 133.0, 134.6, 137.4, 140.7, 144.4, 156.9; EIMS (temp=294 °C) *m/z* (%): 300 (M^+, 100), 271 (9), 256 (10), 243 (7), 218 (4), 205 (3), 150 (M^{++}, 4), 128 (6), 109 (6), 95 (9), 83 (10), 69 (13), 57 (21); HRMS (ESI, $[M+H]^+$) found 301.1718, calcd for $C_{21}H_{21}N_2$ 301.1705.

4.5.5. 9-Methoxy-2,3-dihydro-1*H*-cyclopent[*g*]indolo[2,3-*a*]quinolizine (10a). Yellow-green powder, yield 31 mg (54%); mp 275–278 °C (dec); IR (KBr): 3065, 2960, 2925, 2870, 1647, 1599, 1470, 1440, 1366, 1270, 1160, 1014, 758, 779, 555, 469 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 248.0, 307.0, 352.5, 385.5 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (2H, m), 3.01 (2H, m), 3.12 (2H, m), 3.95 (3H, s), 7.19 (1H, m), 7.47 (1H, m), 7.90 (1H, d, J=8.6 Hz), 8.00 (1H d, J=6.8 Hz), 8.07 (1H, d, J=6.8 Hz), 8.33 (1H, s), 8.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 30.1, 32.5, 55.9, 100.7, 115.7, 116.9, 119.6, 122.3, 125.2, 128.2, 129.0, 129.5, 130.5, 132.0, 137.9, 145.1, 159.1, 160.8; EIMS (temp=344 °C), *m/z* (%): 288 (M^+, 9), 273 (100), 245 (43), 216 (4), 144 (M^{++}, 12), 122 (12); HRMS (ESI, $[M+H]^+$) found 289.1344, calcd for $C_{19}H_{17}N_2O$ 289.1335.

4.5.6. 10-Methoxy-2,3,4,13-tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]quinolizin-6-ium inner salt (10b). Yellow-green powder, yield 34 mg (56%); mp 277–280 °C (dec); IR (KBr): 3065, 2960, 2925, 2855, 1646, 1600, 1449, 1360, 1310, 1220, 1117, 1017, 875, 770, 618, 554, 470 cm^{-1}; UV (MeOH) λ_{max}: 233.5, 248.0, 308.5, 354.0, 392.0 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–1.98 (4H, m), 2.90 (2H, m), 3.06 (2H, m), 3.95 (3H, s), 7.21 (1H, dd, J=8.8, 2.0 Hz), 7.53 (1H, d, J=2.0 Hz), 7.80 (1H, d, J=6.0 Hz), 7.93 (1H, d, J=8.8 Hz), 8.12 (1H, d, J=6.0 Hz), 8.17 (1H, s), 8.92 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 26.3, 28.9, 29.7, 55.9, 100.6, 115.7, 116.9, 119.6, 121.1, 126.3, 127.7, 129.4, 130.7, 132.1, 138.3, 145.2, 159.6, 160.8; EIMS (temp=353 °C), *m/z* (%): 302 (M^+, 86), 287 (100), 259 (21), 231 (4), 207 (4), 151 (M^{++}, 16), 127 (18), 112 (31); HRMS (ESI, $[M+H]^+$) found 303.1503, calcd for $C_{20}H_{19}N_2O$ 303.1492.

4.5.7. 11-Methoxy-2,3,4,5-tetrahydro-1*H*-cyclohept[*g*]indolo[2,3-*a*]quinolizine (10c). Yellow-green powder, yield 31 mg (49%); mp 270–275 °C (dec); IR (KBr): 3060, 2924, 2853, 1638, 1550, 1480, 1448, 1390, 1280, 1218, 1124, 1037, 875, 770, 696, 551, 470 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 249.0, 303.5, 355.0, 385.0 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.78–196 (6H, m), 3.04–3.08 (4H,

m), 3.87 (3H, s), 7.33 (1H, dd, J=8.4, 2.2 Hz), 7.66 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=2.2 Hz), 8.46 (1H, s), 8.52 (1H, d, J=6.8 Hz), 8.66 (d, J=6.6 Hz), 8.17, 9.00 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.8, 27.5, 28.3, 34.5, 36.2, 55.9, 100.3, 115.3, 118.9, 122.5, 123.9, 126.2, 128.4, 129.1, 129.5, 130.8, 132.5, 137.8, 145.4, 159.9, 160.0; EIMS (temp=342 °C), m/z (%): 316 (M^+, 6), 301 (7), 273 (3), 205 (4), 162 (4), 158 (M^{++}, 3), 127 (28), 110 (20), 84 (100); HRMS (ESI, $[M+H]^+$) found 317.1651, calcd for $C_{21}H_{21}N_2O$ 317.1648.

4.5.8. 3-Methoxy-9,10,11,12,13,14-hexahydrocyclooct[*g*]quinolizine (10d). Yellow-green powder, yield 36 mg (55%); mp 262–266 °C (dec); IR (KBr): 3060, 2923, 2853, 1646, 1590, 1475, 1450, 1410, 1366, 1297, 1223, 1193, 1170, 1016, 878, 813, 553, 470 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 248.0, 305.5, 340.5, 362.5, 385.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50–185 (8H, m), 2.78–2.88 (2H, m), 2.90–2.98 (2H, m), 3.95 (3H, s), 7.35 (1H, d, J=8.4 Hz), 7.46 (1H, s), 7.91 (1H, d, J=8.4 Hz), 8.03 (1H, d, J=6.8 Hz), 8.07 (d, J=6.6 Hz), 8.31 (1H, s), 8.91 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 25.6, 29.5, 29.7, 31.7, 32.3, 55.9, 100.7, 115.9, 121.4, 125.3, 127.9, 128.1, 128.8, 129.0, 129.6, 130.9, 132.2, 137.8, 145.8, 159.9, 161.1; EIMS (temp=259 °C), m/z (%): 330 (M^+, 77), 315 (100), 287 (15), 271 (4), 245 (4), 223 (11), 205 (6), 194 (27), 165 (M^{++}, 15), 121 (10); HRMS (ESI, $[M+H]^+$) found 331.1816, calcd for $C_{22}H_{23}N_2O$ 331.1805.

4.5.9. Indolo[2,3-*a*]quinolizine (16). Yellow powder, yield 28 mg (65%); mp 277–280 °C (dec); IR (KBr): 3065, 1647, 1599, 1470, 1427, 1366, 1195, 1160, 748, 770, 550, 475 cm^{-1}; UV (MeOH) λ_{max}: 236.0, 243.5, 291.5, 342.5, 385.5 nm; lit.[27] UV (perchlorate, MeOH) λ_{max}: 222, 237, 244, 293, 344, 386; lit.[27] UV (MeOH/KOH) λ_{max}: 225, 240, 287, 319, 361, 435; EIMS (temp=322 °C), m/z (%): 218 (M^+, 100), 194 (7), 143 (4), 109 (M^{++}, 18), 95 (20); HRMS (EI, M^+) found 218.08431, calcd for $C_{15}H_{10}N_2$ 218.08440.

4.5.10. 9-Methoxyindolo[2,3-*a*]quinolizine (17). Yellow-green powder, yield 30 mg (60%); mp 267–271 °C (dec); IR (KBr): 3060, 2970, 2865, 1646, 1600, 1449, 1310, 1220, 1117, 875, 770, 618, 554, 470 cm^{-1}; UV (MeOH) λ_{max}: 224.0, 243.5, 307.5, 351.5, 386.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (3H, s), 7.23 (1H, dd, J=8.6, 2.0 Hz), 7.56 (1H, d, J=2.0 Hz), 7.68 (1H, d, J=2.0 Hz), 7.80–7.95 (3H, m), 8.12 (1H, d, J=6.4 Hz), 8.33 (1H, d, J=6.4 Hz), 8.48 (1H, s), 9.12 (1H, d, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 55.9, 100.5, 113.7, 122.4, 125.2, 127.7, 127.8, 128.0, 128.8, 129.0, 131.9, 135.5, 141.8, 148.8, 159.1, 161.0; EIMS (temp=305 °C), m/z (%): 248 (M^+, 68), 233 (100), 205 (55), 177 (4), 151 (5), 124 (M^{++}, 10), 102 (8), 89 (8); HRMS (ESI, $[M+H]^+$) found 249.1035, calcd for $C_{16}H_{13}N_2O$ 249.1022.

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Synthesis of calix[4]arene–cyclen conjugates

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Abstract—Novel calix[4]arene derivatives constrained in the *cone* or *1,3-alternate* conformations, bearing one or two cyclen (1,4,7,10-tetraazacyclododecane) moieties directly connected to the upper rim, have been synthesized using Buchwald–Hartwig coupling reaction. The complexation ability and hydrolytic activities of selected Zn(II) complexes of these calixarenes were studied. Although the attempts to hydrolyze activated phosphodiester bonds were unsuccessful, the NMR titration experiments revealed binding affinity for chloride, acetate, and benzoate anions in defined stoichiometry.

1. Introduction

1,4,7,10-Tetraazacyclododecane (cyclen) and its metallated analogues have been widely used in molecular recognition[1] and supramolecular catalysis[2] as artificial metalloenzymes. The cyclen moiety is known as a good ligand possessing very high affinity towards transition metals[3] and lanthanide[4] ions. Some metal ions, such as zinc(II), behave as Lewis acids when coordinated with the ligand and offer free binding sites (depending on the nature and properties of their coordination sphere) suitable for reversible coordination of the corresponding binding partners (Lewis bases).[5] As the above metal complexes represent suitable binding sites for a variety of anionic guest molecules, the attachment of cyclen moieties to an appropriate rigid scaffold should lead to highly preorganized artificial receptors with potential applications as metalloenzymes.[6,7] Calix[4]arenes,[8,9] due to their unique three-dimensional structures, easy derivatization, and the tunable shape of the molecules, represent ideal candidates for such a molecular scaffold. While the connection of calix[4]arene and cyclen moieties via a spacer unit has been published very recently,[7] we assumed that using a rigid connection between the two subunits could result in a higher degree of preorganization and enhanced binding properties. In this paper, we report on the synthesis of novel calix[4]arene–cyclen conjugates with the cyclen moiety directly attached to the upper rim of calix[4]arene.

2. Results and discussion

2.1. Synthesis

Based on the previous results on the N-arylation of 1,4,7,10-tetraazacyclododecanes,[10] we used the Buchwald–Hartwig coupling reaction as a synthetic tool for direct *N*-aryl connection. To the best of our knowledge, this method, based on the application of recently developed palladium-catalyzed N-arylation procedures,[11,12] has never been used in calixarene chemistry so far. The synthesis of tris(Boc)cyclenylcalix[4]arenes **8** and **9** in the *cone* conformation, and consequently, the formation of their Lewis-acidic Zn(II) complexes, was accomplished according to Scheme 1. Starting calix[4]arene **3** was selectively monobrominated according to a known procedure[22] using 1 equiv of *N*-bromosuccinimide in butane-2-one at ambient temperature to give monobromocalix[4]arene **6** in 55% yield. On the other hand, dibromocalix[4]arene **7** was obtained in 83% overall yield by regioselective bromination of dipropoxycalix[4]arene **4** using bromine in chloroform at 0 °C (intermediate **5** formed in 95% yield) followed by alkylation with propyl iodide in DMF in the presence of NaH (product **7**, 87% yield) as described by Casnati et al.[23] Both bromocalix[4]arenes **6** and **7** were then subjected to the Buchwald–Hartwig Pd-catalyzed amination reaction with 1,4,7-tris(Boc)cyclen **2**. The cyclen **1** was protected before coupling reaction to avoid the connection of more calixarene molecules on its skeleton. Since the Boc (*tert*-butoxycarbonyl) group has been proven as the most effective protecting group for the synthesis of cyclic polyamines,[13] we subjected cyclen **1** to the reaction with 2.75 equiv of Boc_2O in DCM to form the protected cyclen **2** in 75% yield.[1d] The coupling reaction between bromocalixarene **6** blocked in the *cone* conformation

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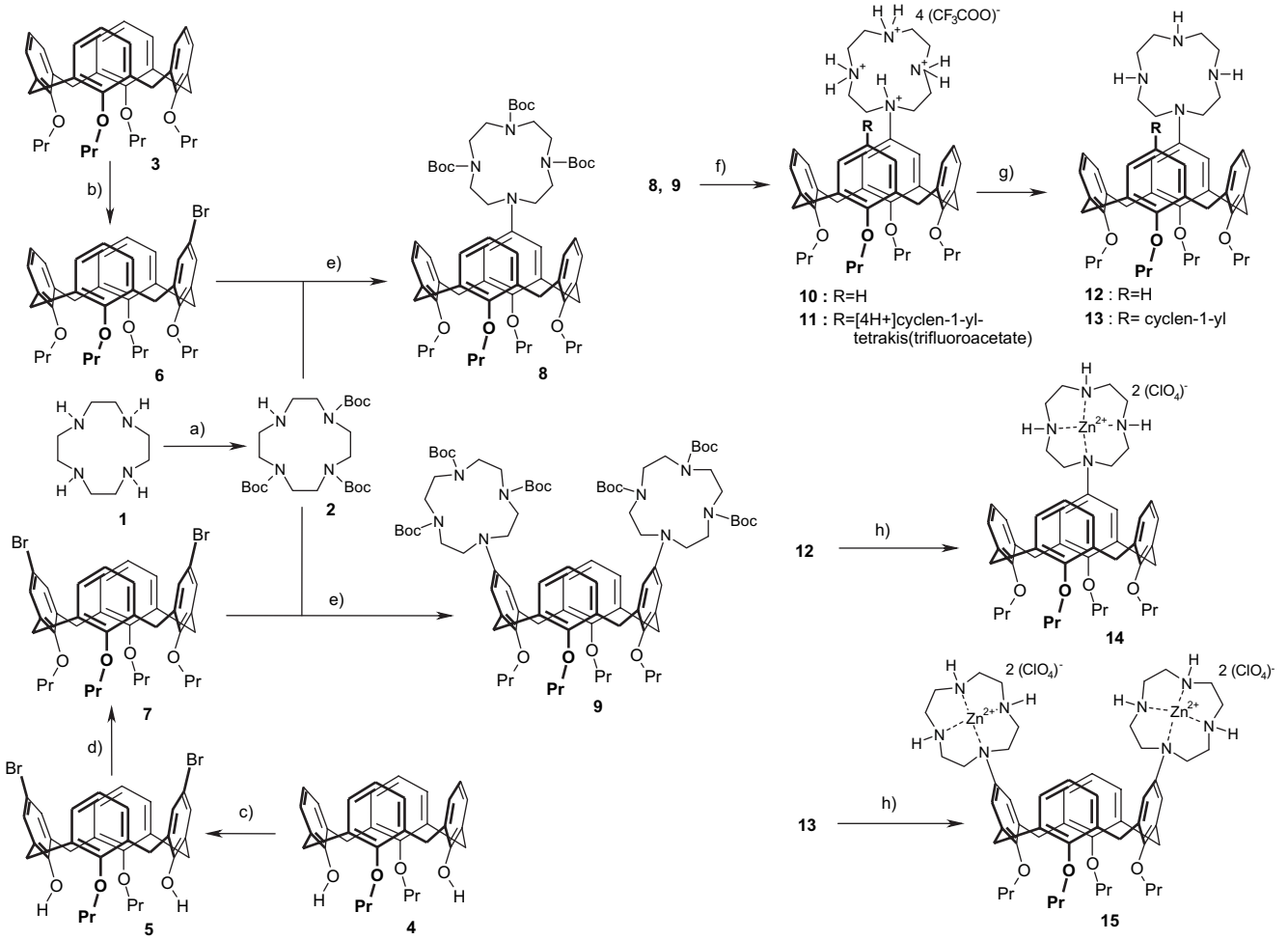


Scheme 1. (a) 2.75 equiv $(Boc)_2O$, CH_2Cl_2, rt (75%); (b) 1 equiv NBS, butane-2-one, rt (55%); (c) Br_2, $CHCl_3$, 0 °C (95%); (d) PrI, NaH, DMF, −10 °C to rt (87%); (e) $Pd(OAc)_2$, P(*t*-Bu)$_3$, *t*-BuONa, toluene, 80–90 °C (66% for **8**, 65% for **9**); (f) CF_3COOH, CH_2Cl_2, rt (quant.); (g) Ion exchanger III; Merck©, CH_3OH–H_2O 10:1 (v/v) (quant.); (h) $Zn(ClO_4)_2 \cdot 6H_2O$, CH_3OH, rt (quant.).

and threefold Boc-protected cyclen **2** was carried out in dry toluene at 80–90 °C in the presence of stoichiometric amount of base (*t*-BuONa), a catalytic amount of palladium acetate, and the corresponding phosphine ligand (see Table 1). Triphenylphosphine was described as the best ligand in the attempts of N-arylation of Boc-protected cyclen using simple aryl halides.[10] However, as shown in Table 1 (run 1), the use of Ph_3P led only to moderate conversion together with a low yield of the required calix–cyclen conjugate **8** in our case. Using a large amount of Pd-source, higher temperature, and a longer reaction time did not improve the yield (run 2). Similar results have been achieved using DPPF as a chelating ligand (Table 1, run 3).

It is known that the reaction rate of the Pd-catalyzed amination reaction is determined by the reductive elimination step in the catalytic cycle,[14] which can be considerably influenced by electronic and steric effects of phosphine ligands used. Indeed, the successful application of more bulky and electron rich phosphine ligands such as PCy_3 and P(*t*-Bu)$_3$ in Pd-catalyzed cross-coupling reactions of aryl halides and secondary amines has precedent in the literature.[15] Consequently, the use of tris(*tert*-butyl)phosphine led immediately to the dramatic improvement of both yield and conversion (run 4). The conversion of the starting bromocalix[4]arene **6** increased to 82% and tris(Boc)cyclenylcalix[4]arene **8** was isolated in 66% after column

Table 1. Yields, stoichiometry, and reaction conditions of Buchwald–Hartwig coupling reactions between calix[4]arenes **6**, **7**, and **16** and protected cyclen **2**

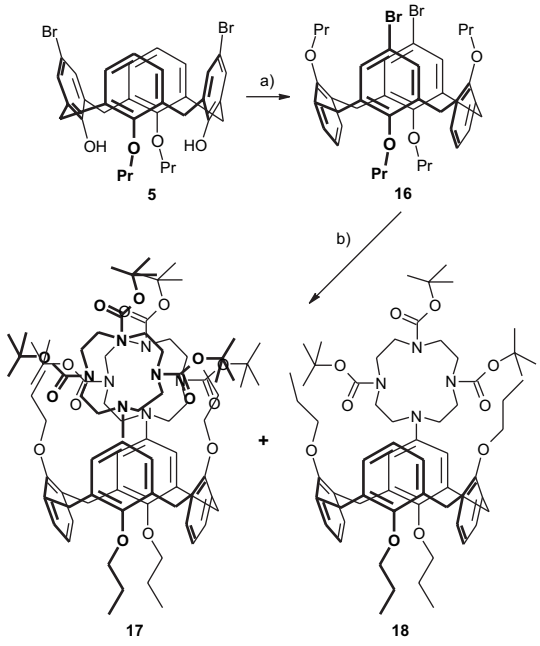
Run	Starting materials	Pd-source (mol %)	Ligand (mol %)	Base (equiv)	*T* (°C)	Time (h)	Product	Yield[a] (%)
1.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (5)	PPh_3 (10)	NaO*t*-Bu (1.3)	80	35	**8**	21 (42)
2.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (15)	PPh_3 (10)	NaO*t*-Bu (1.3)	90	48	**8**	17 (32)
3.	**2** (1.1 equiv)+**6**	$Pd(OAc)_2$ (7)	DPPF (7.5)	NaO*t*-Bu (1.3)	80	70	**8**	19 (31)
4.	**2** (1.05 equiv)+**6**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (15)	NaO*t*-Bu (1.3)	80	18	**8**	66 (81)
5.	**2** (2.1 equiv)+**7**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (10)	NaO*t*-Bu (2.5)	80	42	**8**	18 (18)
							9	65 (65)
6.	**2** (2.05 equiv)+**16**	$Pd(OAc)_2$ (10)	P(*t*-Bu)$_3$ (15)	NaO*t*-Bu (2.3)	80	2	**17**	55 (57)
							18	24 (25)

[a] Yields in parentheses corrected for recovered starting material.

chromatography. Similarly, the coupling reaction between dibromocalix[4]arene **7** and threefold Boc-protected cyclen **2** was accomplished under identical conditions, using 2.1–2.5 equiv of protected cyclen **2**. Utilization of the already approved P(*t*-Bu)$_3$ led to the required bis[tris(Boc)cyclenyl]-calix[4]arene **9** in high yield, accompanied by a small amount of mono-conjugate **8** (presumably formed by a β-elimination during the coupling of the second cyclen unit). The reaction mixture was easily separated by column chromatography to yield the conjugates **9** and **8** in 65 and 18% yield, respectively, (see Table 1, run 5). The Boc protective groups were removed under acidic conditions (TFA–CH_2Cl_2, rt, overnight) to yield the corresponding *N*-protonated cyclenyl calix[4]arenes **10** and **11** in quantitative yields. These salts were then basified using strongly basic anion exchanger (Ion exchanger III; Merck®) to form quantitatively cyclenyl-calix[4]arene **12** and bis(cyclenyl)calix[4]arene **13**. The corresponding metallated derivatives **14** and **15** were then obtained in quantitative yields (see Scheme 1) by the reaction of free cyclen conjugates with 1 or 2 equiv of $Zn(ClO_4)_2\cdot 6H_2O$ (MeOH, rt, overnight). Structures of all the above mentioned compounds were unambiguously proven by ^{1}H, ^{13}C DEPT NMR, and ESIMS spectra.

To investigate the influence of the calix[4]arene conformation on the Pd-catalyzed N-arylation reaction, the dibromo derivative **16** in the *1,3-alternate* conformation was prepared (Scheme 2). The starting dibromo derivative **5** was alkylated using PrI in anhydrous THF and employing potassium trimethylsilyloxide as a base. Surprisingly, under these conditions the *1,3-alternate* conformer **16** was obtained in higher yield (75%), compared to the commonly used cesium carbonate. Furthermore, under these conditions, derivative **16** can be isolated by simple precipitation without column chromatography.

The Buchwald–Hartwig reaction between the dibromo derivative **16** and protected cyclen **2** gave the best results



Scheme 2. (a) PrI, $(CH_3)_3SiOK$, THF, rt (75%); (b) **2**, $Pd(OAc)_2$, P(*t*-Bu)$_3$, *t*-BuONa, toluene, 80 °C (55% for **17**, 24% for **18**).

in the presence of tris(*tert*-butyl)phosphine and the required bis[tris(Boc)cyclenyl]calix[4]arene (*1,3-alternate*) **17** was obtained in good yield (55%) together with mono-cyclen conjugate **18** (24%) (see Scheme 2). The presence of by-product **18** in the reaction mixture represents the evidence for the β-elimination mechanism as the competitive process accompanying this N-arylation coupling reaction. On the other hand, when we applied this coupling reaction to tetrabromocalix[4]arene in the *1,3-alternate* conformation **19**,[16] we never obtained the required calix[4]arene substituted with four cyclen units. Using either Ph_3P, DPPF or P(*t*-Bu)$_3$

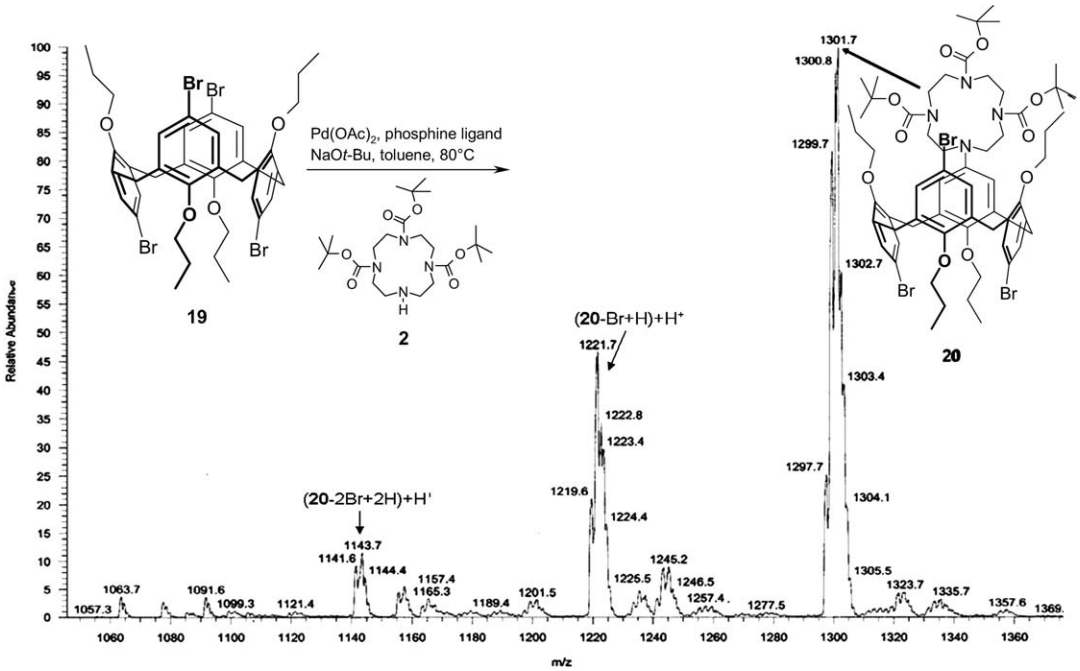


Figure 1. ESIMS (+) of the inseparable reaction mixture after the coupling reaction between tetrabromo-derivative **19** and cyclen **2**.

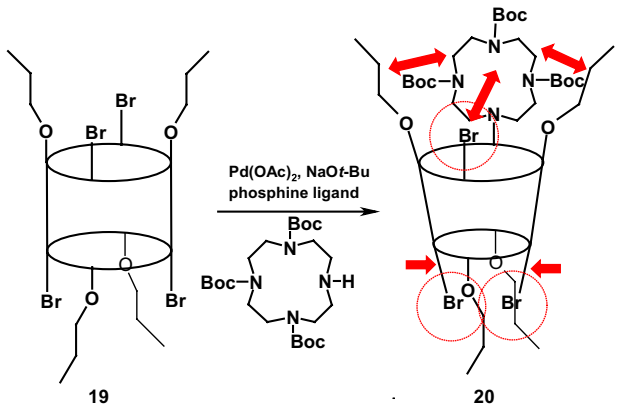


Figure 2. Proposed negative allosteric effect in a *1,3-alternate* derivative.

as phosphine ligands (otherwise under identical conditions as specified above) we have always obtained only very complicated (according to ^{1}H NMR) and inseparable reaction mixtures. As shown by ESIMS analysis of such a mixture, tribromo-tri(Boc)cyclenylcalix[4]arene **20** was obtained together with the β-elimination products (Fig. 1). Surprisingly, not more than one cyclen unit could be appended to the tetrabromocalix[4]arene **19** under the above mentioned conditions. The explanation could lie in the increased steric hindrance in the *1,3-alternate* system. The presence of one bulky tri(Boc)cyclen unit at one side of the calix[4]arene may cause the outstretching of the two proximal propoxy groups, which implies the slight change in the conformation (see Fig. 2). As a consequence, the two bromine atoms on the opposite side of the *1,3-alternate* conformer become closer to each other thus making their substitution impossible. This phenomenon resembles a complexation-induced negative allosteric effect observed in some *1,3-alternate* calixarenes.[17]

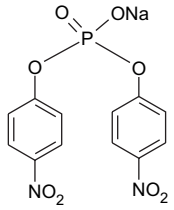
2.2. Complexation study

Having developed the synthetic route leading to the calix[4]-arene–cyclen conjugates in reasonable yields, we have carried out a preliminary study of the hydrolytic activities of the Zn(II) complexes towards the cleavage of phosphodiester bonds. These measurements were done in buffered 0.01 M solution of Tris-base, in a mixture of MeOH–H_2O 9:1 at pH=8 (I=0.1 M). As a model compound containing activated phosphodiester bonds we used sodium bis(*p*-nitrophenyl)phosphate (BNPP). The buffered solution in the UV-cell containing either ligand **14** or **15** ($c=4\times10^{-4}$ mol l^{-1}) and BNPP ($c=1.6\times10^{-5}$ mol l^{-1}) at 30 °C was scanned every 5 min for 9 h in the region between 380 and 420 nm in the UV spectrophotometer. However, the expected absorption signal at 400 nm indicating the presence of free *p*-nitrophenolate anion in the solution was not observed. Thus both Zn-complexes were found to be inactive to cleave the activated phosphodiester bond in BNPP under the conditions used. Neither increasing the pH value to 9, nor increasing the concentration of ligand led to a desired catalytic activity. These results are in agreement with the previous findings of Akkaya and Ozturz.[7] However, the steric hindrance seems to be even more effective here. This could be ascribed to a rigid connection between bulky Zn(II)cyclen and the calix[4]arene moieties. Thus, the entrance to the calixarene cavity seems to be blocked even in the case of the mono Zn(II)cyclenyl derivative **14**, which excludes the efficient binding of the BNPP substrate necessary for the catalytic activity.

Table 2. Complexation constants K_c of conjugate **14** toward selected anions[a] (^{1}H NMR, CD_3CN, 25 °C, 300 MHz)

Anion	Cl^-	AcO^-	BzO^-	$H_2PO_4^-$	HSO_4^-	NO_3^-
K_c [mol^{-1} l]	1120	205	950	[b]	[b]	[c]

[a] Corresponding TBA^+ salts used.
[b] Precipitate formed during the NMR titration.
[c] Small induced chemical shifts (<10 Hz) observed.



Nevertheless, the rigid connection between both subunits was found to be effective in the case of coordination of selected anions. We performed several measurements using ^{1}H NMR titration and Job's plot techniques (acetonitrile-d_3). As follows from Table 2, quite interesting affinity of ligand **14** towards spherical chloride anion and planar acetate/benzoate anions was observed.[18] All these anions formed a complex with ligand **14** with 1:1 stoichiometry (Fig. 3). On the other hand, the presence of the nitrate anion in the solution of **14** didn't cause any changes in the ^{1}H NMR spectrum. Meanwhile, the gradual addition of either $H_2PO_4^-$ or HSO_4^- anions into the CD_3CN solution of **14** led in both cases to the formation of white precipitates (probably the corresponding complexes), which were not further analyzed owing to their total insolubility. Ligand **15** bearing two Zn(II)cyclen units was also subjected to ^{1}H NMR titration experiments with TBA^+chloride$^-$ and TBA^+benzoate$^-$. The addition of these salts to the ligand **15** led in both cases to considerable shifts in ^{1}H NMR spectra, however, the titration curves indicated nontrivial stoichiometry different from 1:1.

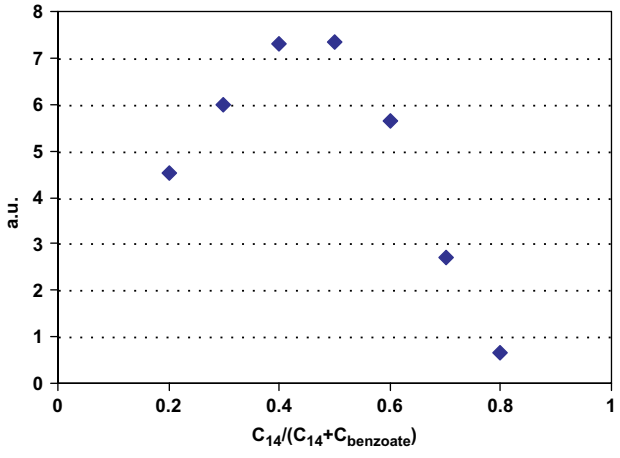


Figure 3. Job's plot for **14**/Bu_4N^+benzoate$^-$ system (300 MHz, CD_3CN, c_{total}=2 mmol l^{-1}).

3. Conclusions

In summary, we have reported the synthesis of calix[4]-arene–cyclen conjugates, with direct *N*-aryl bonds and constrained calixarene conformations. Optimized conditions for the palladium-catalyzed *N*-aryl bond formation to connect protected cyclen with bromocalix[4]arenes were developed. The cyclen ligands were deprotected and converted into the bis-zinc(II) complexes. Attempts to use the complexes to hydrolyze activated phosphodiester bonds were unsuccessful. However, NMR titration experiments revealed binding affinity of the bis complexes in acetonitrile for chloride, acetate, and benzoate anions with defined stoichiometry.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points are uncorrected and were determined using a Boetius Block apparatus (Carl Zeiss Jena, Germany). NMR spectra were recorded at 250 and 400 MHz (^{1}H) and at 63 and 100 MHz (^{13}C). The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2, and (C_{quat}) for quaternary carbons. ^{1}H NMR titrations were performed with tetrabutylammonium salts of corresponding anions that were dried and stored in evacuated desiccator over P_2O_5. Elemental analyses were measured on Elementar vario EL (Elementar, Germany) instruments. All samples were dried in the desiccator over P_2O_5 under vacuum (1 Torr) at 80 °C for 8 h. It is known that the elemental analyses of the calixarene derivatives are sometimes ambiguous.[19] Mass spectra were measured using ESI technique on Q-TOF (Micromass) spectrometer or MALDI-TOF technique on HP G2030A (Hewlett Packard) with delayed extraction option. The IR spectra were measured on an FTIR spectrometer, Nicolet 740 or Bruker IFS66 spectrometers equipped with a heatable Golden Gate Diamante ATR-Unit (SPECAC) in $CHCl_3$ and/or in KBr. UV–vis spectra were measured on a JASCO V-530 spectrophotometer. The purity of the substances and the courses of reactions were monitored by TLC using TLC alumina sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck) or Al_2O_3 type G (Fluka). The column chromatography was performed using Silica gel 60 (Merck).

Compounds **2**,[1d] **3**,[20] **4**,[21] **6**,[22] **7**,[23] and **19**[16] were prepared according to known procedures.

4.2. Synthesis of 5-[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) 8

The protected cyclen **2** (223 mg, 0.47 mmol), 5-bromo-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) **6** (300 mg, 0.447 mmol), and 56 mg of sodium *tert*-butoxide (0.58 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (13.6 mg, 0.067 mmol, 15 mol %) and palladium acetate (10.1 mg, 0.045 mmol, 10 mol %) were added. The solid materials were suspended in absolute toluene (4 ml). The tube was sealed, and the mixture was degassed by three freeze–pump–thaw cycles, then stirred at 80 °C for 18 h. The reaction mixture was cooled to rt, diluted with CH_2Cl_2 (30 ml), filtered through Celite, and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 10:1–2:1) to give 314 mg (66%) of **8**. Mp: 72 °C (ethyl acetate). R_f=0.66 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.04 (m, 12H, –CH_2–CH_3), 1.46 (s, 9H, –C–(CH_3)$_3$), 1.47 (s, 18H, –C–(CH_3)$_3$), 1.94 (m, 8H, –CH_2–CH_3), 3.08 (d, 2H, J=12.7 Hz, Ar–CH_2–Ar, eq.), 3.13 (d, 2H, J=12.7 Hz, Ar–CH_2–Ar, eq.), 3.25 (m, 16H, –N–CH_2–CH_2–N–), 3.76 (m, 8H, –O–CH_2–CH_2–), 4.43 (d, 2H, J=13.1 Hz, Ar–CH_2–Ar, ax.), 4.44 (d, 2H, J=13.2 Hz, Ar–CH_2–Ar, ax.), 6.36 (s, 2H, ArH), 6.39 (m, 6H, ArH), 6.70 (t, 1H, J=7.1 Hz, ArH), 6.88 (d, 2H, J=7.3 Hz, ArH). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.1 (+), 10.2 (+), 10.5 (+), 23.0 (−), 23.1 (−), 23.4 (−), 28.5 (+), 28.7 (+), 30.9 (−), 31.3 (−), 49.4 (−), 50.6 (−), 76.7 (−), 76.8 (−), 79.4 (C_{quat}), 79.7 (C_{quat}), 121.9 (+), 127.3 (+), 127.9 (+), 128.5 (+), 134.1 (C_{quat}), 134.5 (C_{quat}), 135.9 (C_{quat}), 136.3 (C_{quat}), 155.8 (C_{quat}), 157.1 (C_{quat}). EA calcd for $C_{63}H_{90}N_4O_{10}$: C, 71.16; H, 8.53; N, 5.27. Found: C, 71.09; H, 8.83; N, 5.18. MS (ESI, 70 eV): *m/z* (rel int.) 1064 $[MH]^+$ (100). IR (KBr) cm^{-1}: 2970, 2927, 1695, 1601, 1462, 1248, 1167 cm^{-1}.

4.3. Synthesis of 5,17-bis[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) 9

The protected cyclen **2** (397 mg, 0.84 mmol), 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*cone*) **7** (300 mg, 0.4 mmol), and sodium *tert*-butoxide (96 mg, 1 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (8 mg, 0.04 mmol, 10 mol %) and palladium acetate (9 mg, 0.04 mmol, 10 mol %) were added and the solid materials were suspended in dry toluene (4 ml). The tube was sealed, degassed by three freeze–pump–thaw cycles, and stirred at 80 °C for 42 h. The reaction mixture was then cooled to rt, diluted with CH_2Cl_2 (20 ml), filtered through Celite, and evaporated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 5:1–1:1) to give 77 mg (18%) of mono-conjugate **8** and 399 mg (65%) of compound **9** as white solid. Mp: 114 °C. R_f=0.21 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.88 (t, 6H, J=7.3 Hz, –CH_2–CH_3), 1.10 (t, 6H, J=7.3 Hz, –CH_2–CH_3), 1.47 (s, 18H, –C–(CH_3)$_3$), 1.49 (s, 36H, –C–(CH_3)$_3$), 1.80–2.10 (m, 8H, –CH_2–CH_3), 3.02 (d, 4H, J=13.3 Hz, Ar–CH_2–Ar, eq.), 3.45 (br s, 32H, –N–CH_2–CH_2–N–), 3.63 (t, 4H, J=7.7 Hz, –O–CH_2–CH_2–), 3.93 (t, 4H, J=7.1 Hz, –O–CH_2–CH_2–), 4.42 (d, 4H, J=13.1 Hz, Ar–CH_2–Ar, ax.), 6.11 (s, 6H, Ar*H*), 6.53 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 9.9 (+), 10.9 (+), 22.9 (−), 23.6 (−), 28.5 (+), 28.6 (+), 31.5 (−), 50.1 (−), 50.9 (−), 76.4 (−), 77.0 (−), 79.8 (C_{quat}), 117.8 (+), 121.8 (+), 127.0 (+), 133.2 (C_{quat}), 137.5 (C_{quat}), 155.1 (C_{quat}). EA calcd for $C_{86}H_{132}N_8O_{16}$: C, 67.34; H, 8.67; N, 7.30. Found: C, 67.27; H, 8.82; N, 7.19. MS (ESI, 70 eV): *m/z* (rel int.) 1535 $[MH]^+$ (100), 768 $[M+2H^+]^{2+}$ (60). IR (KBr) cm^{-1}: 2974, 2933, 1695, 1466, 1250, 1165 cm^{-1}.

4.4. Synthesis of 5-(1,4,7,10-tetrakis[4H$^+$]cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene tetrakis-(trifluoroacetate) (*cone*) 10

Compound **8** (202 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (10 ml) and trifluoroacetic acid (0.43 ml, 5.6 mmol) was added. The reaction mixture was stirred for 16 h (until no starting compound was indicated by TLC (SiO_2, EtOAc–MeOH 100:1), evaporated, and dried under vacuum to yield 225 mg of title compound **10** (100%) as a brown viscous solid. Mp: 116–117 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.95 (m, 12H, –CH_2–CH_3), 1.98 (m, 8H, –CH_2–CH_3), 2.71–3.20 (m, 16H, –NCH_2–CH_2–N–), 3.10 (d, 4H, Ar–CH_2–Ar, eq.), 3.70–3.88 (m, 4H, –O–CH_2–CH_2–), 3.93–3.99 (m, 4H, –O–CH_2–CH_2–), 4.43 (d, 4H, Ar–CH_2–Ar, ax.), 6.23–6.31 (m, 3H, Ar*H*), 6.47 (d, 2H, ^3J=7.3 Hz, Ar*H*), 6.74–6.93 (m, 6H, Ar*H*), 8.80–10.4 (br s, 4H, –NH(*H*$^+$)). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.0 (+), 10.5 (+), 10.6 (+), 23.0 (−), 23.3 (−), 23.4 (−), 30.9 (−), 43.3 (−), 44.9 (−), 45.5 (−), 51.9 (−), 76.7 (−), 77.3 (−), 77.4 (−), 116.4 (C_{quat}, q, $^1J_{(C,F)}$=287.7 Hz), 121.6 (+), 122.3 (+), 123.4 (+), 127.6 (+), 128.3 (+), 128.9 (+), 134.3 (C_{quat}), 135.7 (C_{quat}), 136.3 (C_{quat}), 140.2 (C_{quat}), 156.2 (C_{quat}), 157.0 (C_{quat}), 161.9 (C_{quat}, q, $^2J_{(C,F)}$=40.2 Hz). MS (ESI, 70 eV) *m*/*z* (rel int.) 763 [MH]$^+$ (50), 382 [M+2H]$^{2+}$ (100). IR (KBr) cm^{-1}: 3630–3310, 2965, 2875, 1685, 1461 cm^{-1}.

4.5. Synthesis of 5,17-bis(1,4,7,10-tetrakis[4H$^+$]-cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene octakis-(trifluoroacetate) (*cone*) 11

Compound **9** (530 mg, 0.345 mmol) was dissolved in CH_2Cl_2 (10 ml) and trifluoroacetic acid (1.6 ml, 20.7 mmol) was added. Reaction mixture was stirred for 16 h (until no starting compound was indicated by TLC (SiO_2, EtOAc–MeOH 100:1), evaporated, and dried under vacuum. Compound **11** was obtained in quantitative yield as brown viscous solid. Mp: 165–167 °C. ^{1}H NMR ($CDCl_3$–CD_3OD 1:1, 400 MHz) δ (ppm): 0.9 (t, 6H, *J*=7.5 Hz, –CH_2–CH_3), 1.3 (t, 6H, *J*=7.5 Hz, –CH_2–CH_3), 1.87–2.01 (m, 8H, –CH_2–CH_3), 3.05–3.42 (m, 36H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.66 (t, 4H, *J*=6.7 Hz, –O–CH_2–CH_2–), 4.03 (t, 4H, *J*=8.2 Hz, –O–CH_2–CH_2–), 4.45 (d, 4H, *J*=13.2 Hz, Ar–CH_2–Ar, ax.), 4.98 (br s, 8H, –NH(*H*$^+$)), 6.07 (d, 4H, *J*=7.6 Hz, Ar*H*), 6.18 (t, 2H, *J*=7.5 Hz, Ar*H*), 7.11 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$–CD_3OD 1:1, 100 MHz) δ (ppm): 10.0 (+), 11.1 (+), 23.5 (−), 24.0 (−), 31.4 (−), 43.1 (−), 44.3 (−), 46.0 (−), 51.4 (−), 77.1 (−), 77.6 (−), 117.0 (C_{quat}, q, $^1J_{(C,F)}$=291.0 Hz), 122.6 (+), 124.9 (+), 127.7 (+), 133.3 (C_{quat}), 139.0 (C_{quat}), 142.5 (C_{quat}), 155.8 (C_{quat}), 156.7 (C_{quat}), 162.1 (C_{quat}, q, $^2J_{(C,F)}$=35.7 Hz). MS (ESI, 70 eV) *m*/*z* (rel int.) 933 [MH]$^+$(15), 467 [M+2H]$^{2+}$ (100).

4.6. Synthesis of 5-(cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene (*cone*) 12

Derivative **10** (225 mg, 0.19 mmol) was dissolved in H_2O–MeOH 1:1 (v/v) mixture (10 ml) and poured onto the column of strongly basic anion exchanger (Ion exchanger III; Merck©). The column was washed with 100 ml of the above solvent mixture and the fractions with basic reaction on pH-paper were combined, evaporated, and dried under vacuum to give 133 mg (95%) of **12** as white solid. Mp: 90–92 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.00 (m, 12H, –CH_2–CH_3), 1.91 (m, 8H, –CH_2–CH_3), 2.63–3.17 (m, 20H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.83 (m, 8H, –O–CH_2–CH_2–), 4.43 (d, 2H, *J*=13.1 Hz), 4.45 (d, 2H, *J*=13.2 Hz), 6.16 (s, 2H, Ar*H*), 6.59 (m, 9H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.3 (+), 10.4 (+), 10.5 (+), 23.2 (−), 23.3 (−), 23.4 (−), 31.0 (−), 31.3 (−), 47.0 (−), 47.4 (−), 49.2 (−), 52.8 (−), 76.7 (−), 76.8 (−), 77.3 (−), 116.7 (+), 121.8 (+), 121.9 (+), 128.0 (+), 135.0 (C_{quat}), 144.0 (C_{quat}), 150.4 (C_{quat}), 156.6 (C_{quat}), 156.8 (C_{quat}). EA calcd for $C_{48}H_{66}N_4O_4$: C, 75.55; H, 8.72; N, 7.34. Found: C, 75.30; H, 8.61; N, 7.19. MS (ESI, 70 eV) *m*/*z* (rel int.) 763 [MH]$^+$ (100), 382 [M+2H$^+$]$^{2+}$ (100). IR (KBr) cm^{-1}: 2962, 2931, 2872, 2362, 1689, 1458, 1199 cm^{-1}.

4.7. Synthesis of 5,17-bis(cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene (*cone*) 13

Derivative **11** (536 mg, 0.29 mmol) was dissolved in H_2O–MeOH 1:1 (v/v) mixture (20 ml) and poured onto the column of strongly basic anion exchanger (Ion exchanger III; Merck©). The column was then washed with 100 ml of the same solvent mixture and the fractions with basic reaction on pH-paper were combined, evaporated, and dried under vacuum to give 270 mg (99%) of compound **13** as white solid. Mp: 198 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.86 (t, 6H, *J*=7.4 Hz, –CH_2–CH_3), 1.08 (t, 6H, *J*=7.4 Hz, –CH_2–CH_3), 1.80–2.01 (m, 8H, –CH_2–CH_3), 2.68 (s, 8H, –N–CH_2–CH_2–N–), 2.85 (s, 16H, –N–CH_2–CH_2–N–), 3.32 (s, 8H, –N–CH_2–CH_2–N–), 3.06 (d, 4H, *J*=13.3 Hz, Ar–CH_2–Ar, eq.), 3.63 (t, 4H, *J*=6.7 Hz, –O–CH_2–CH_2–), 3.93 (t, 4H, *J*=8.2 Hz, –O–CH_2–CH_2–), 4.38 (d, 4H, *J*=13.2 Hz, Ar–CH_2–Ar, ax.), 6.08 (d, 4H, *J*=7.4 Hz, Ar*H*), 6.21 (t, 2H, *J*=6.9 Hz, Ar*H*), 6.77 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 9.8 (+), 10.9 (+), 22.9 (−), 23.5 (−), 31.2 (−), 46.1 (−), 46.4 (−), 47.6 (−), 52.5 (−), 76.4 (−), 76.8 (−), 119.9 (+), 122.1 (+), 127.1 (+), 133.1 (C_{quat}), 137.1 (C_{quat}), 145.0 (C_{quat}), 152.3 (C_{quat}), 155.1 (C_{quat}). MS (ESI, 70 eV) *m*/*z* (rel int.) 933 [MH]$^+$(10), 476 [M+2H]$^{2+}$ (100). EA calcd for $C_{56}H_{84}N_8O_4$: C, 72.07; H, 9.07; N, 12.01. Found: C, 71.89; H, 9.21; N, 11.91. IR (KBr) cm^{-1}: 3375–3290, 2929, 2873, 1602, 1456, 1222 cm^{-1}.

4.8. Synthesis of 5-([Zn^{2+}]cyclen-1-yl)-25,26,27,28-tetra-propoxycalix[4]arene bis(perchlorate) (*cone*) 14

Conjugate **12** (325 mg, 0.426 mmol) was dissolved in MeOH (10 ml) and $Zn(ClO_4)_2\cdot 6H_2O$ (159 mg, 0.426 mmol) was added. The reaction mixture was stirred at rt for 20 h, and then heated to 50 °C for 1 h. The solvent was evaporated and the residue was dried under vacuum to give 439 mg (quantitative) of **14** as white crystalline solid. Mp: 198 °C (decomp.). ^{1}H NMR ($CDCl_3$–CD_3OD 1:1, 250 MHz) δ (ppm): 0.91–1.06 (m, 12H, –CH_2–CH_3), 1.84–1.97 (m, 8H, –CH_2–CH_3), 2.49–3.05 (m, 16H, –N–CH_2–CH_2–N–), 3.13 (d, 2H, *J*=13.1 Hz, Ar–CH_2–Ar, eq.), 3.15 (d, 2H, *J*=13.2 Hz, Ar–CH_2–Ar, eq.), 3.72 and 3.92 (2m, 8H, –O–

CH_2–CH_2–), 4.42 (d, 2H, J=12.9 Hz, Ar–CH_2–Ar, ax.), 4.43 (d, 2H, J=13.3 Hz, Ar–CH_2–Ar, ax.), 6.38–6.88 (m, 11H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$–CD_3OD 1:1, 63 MHz) δ (ppm): 11.2 (+), 11.6 (+), 11.7 (+), 24.4 (−), 24.6 (−), 24.7 (−), 32.2 (−), 32.3 (−), 44.7 (−), 45.3 (−), 46.8 (−), 55.3 (−), 78.0 (−), 78.6 (−), 78.7 (−), 123.2 (+), 123.8 (+), 124.0 (+), 129.2 (+), 129.8 (+), 130.3 (+), 135.6 (C_{quat}), 136.5 (C_{quat}), 137.3 (C_{quat}), 137.4 (C_{quat}), 142.7 (C_{quat}), 156.2 (C_{quat}), 157.4 (C_{quat}), 158.1 (C_{quat}). MS (ESI, 70 eV, 1% AcOH in MeOH) *m/z* (rel int.) 885 $[M+CH_3COO]^+$ (100), 422 $[M+H_2O]^{2+}$ (40). IR (KBr) cm^{-1}: 3516, 3302, 2960, 2927, 2875, 1460, 1088 cm^{-1}.

4.9. Synthesis of 5,17-bis([Zn^{2+}]cyclen-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene tetrakis(perchlorate) (*cone*) 15

Conjugate **13** (260 mg, 0.28 mmol) was dissolved in MeOH (10 ml) and $Zn(ClO_4)_2\cdot 6H_2O$ (208 mg, 0.56 mmol) was added. The reaction mixture was stirred at rt for 20 h, and then heated to 50 °C for 1 h. The solvent was evaporated and the residue was dried under vacuum to give 407 mg (100%) of **15** as white crystalline solid. Mp: 220 °C (decomp.). ^{1}H NMR (CD_3CN, 250 MHz) δ (ppm): 0.92 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.08 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.81–2.02 (m, 8H, –CH_2–CH_3), 2.77–3.40 (m, 36H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, eq.), 3.66 (t, 4H, J= 6.9 Hz, –O–CH_2–CH_2–), 3.82 (m, 4H, –N–CH_2–CH_2–N–), 4.05 (t, 4H, J=8.2 Hz, –O–CH_2–CH_2–), 4.45 (d, 4H, J=13.0 Hz, Ar–CH_2–Ar, ax.), 6.32 (s, 6H, Ar*H*), 7.17 (s, 4H, Ar*H*). ^{13}C NMR, DEPT (135) (CD_3CN, 63 MHz) δ (ppm): 10.2 (+), 11.2 (+), 24.0 (−), 24.3 (−), 31.5 (−), 44.2 (−), 44.5 (−), 45.9 (−), 54.7 (−), 77.5 (−), 78.2 (−), 123.6 (+), 124.5 (+), 128.7 (+), 133.9 (C_{quat}), 139.0 (C_{quat}), 142.2 (C_{quat}), 156.4 (C_{quat}), 156.9 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1361 $[M+3ClO_4]^+$ (10), 631 $(M+2ClO_4)^{2+}$ (80), 415 $[M+ClO_4+2CH_3CN]^{3+}$ (100), 307 $[M+4CH_3CN]^{4+}$ (60). IR (KBr) cm^{-1}: 3700–3300, 3290, 2962, 2875, 1635, 1479 cm^{-1}.

4.10. Synthesis of 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) 16

5,17-Dibromo-26,28-dipropoxycalix[4] arene (*cone*) **5** (3 g, 4.5 mmol) and Me_3SiOK (2.89 g, 22.5 mmol) were dissolved in 50 ml dry THF and cooled to −5 °C. Then PrI (2.2 ml, 22.5 mmol) was slowly added. Reaction mixture was then stirred at rt for 120 h. After this time the reaction mixture was quenched with 1 M solution of HCl (100 ml) and extracted three times with $CHCl_3$ (3×30 ml). Combined organic layers were dried over Na_2SO_4 and evaporated to give crude product. Crystallization from $CHCl_3$–MeOH yielded 1.63 g (50%) of pure **16**. Mp: 235–237 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.89 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.03 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.55–1.74 (m, 8H, –CH_2–CH_3), 3.74 (t, 4H, J=7.2 Hz, –O–CH_2–CH_2–), 3.60 (t, 4H, J=7.2 Hz, –O–CH_2–CH_2–), 3.60 (s, 8H, Ar–CH_2–Ar), 6.71 (t, 2H, J=7.5 Hz, Ar*H*), 6.98 (d, 4H, J=7.5 Hz, Ar*H*), 7.19 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.4 (+), 10.5 (+), 23.4 (−), 23.5 (−), 36.4 (−), 73.2 (−), 73.5 (−), 114.3 (C_{quat}), 121.7 (+), 130.0 (+), 132.4 (+), 133.1 (C_{quat}), 135.5 (C_{quat}), 155.6 (C_{quat}), 156.5 (C_{quat}). MS (EIMS) *m/z* (rel int.) 750 $[M]^+$ (100). EA calcd for $C_{40}H_{46}O_4Br_2$: C, 64.01; H, 6.18; Br, 21.29. Found: C, 64.05; H, 6.29; Br, 21.18.

4.11. Synthesis of 5,17-bis[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) 17

The protected azamacrocycle **2** (388 mg, 0.82 mmol), 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (*1,3-alternate*) **16** (300 mg, 0.4 mmol), and sodium *tert*-butoxide (88 mg, 0.92 mmol) were placed into a Schlenk tube. To this mixture P(*t*-Bu)$_3$ (14 mg, 0.07 mmol) and palladium acetate (10 mg, 0.044 mmol) were added and the solid materials were suspended in dry toluene (3 ml). The tube was sealed, and degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred at 80 °C for 2 h, cooled to rt, diluted with CH_2Cl_2 (20 ml), filtered through Celite, and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2, PE–EtOAc 10:1–1:1) to give 366 mg (55%) of the title product **17**. Mp: 158–160 °C. R_f=0.22 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.67 (t, 6H, J=7.4 Hz, –CH_2–CH_3), 1.09–1.26 (m, 6H, –CH_2–CH_3), 1.46 (s, 18H, –C–(CH_3)$_3$), 1.47 (s, 36H, –C–(CH_3)$_3$), 1.50–1.60 (br s, 8H, –CH_2–CH_3), 3.22–3.78 (m, 48H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, –O–CH_2–CH_2–), 6.43 (s, 4H, Ar*H*), 6.76 (t, 2H, J=7.4 Hz, Ar*H*), 6.99 (d, 4H, J=7.4 Hz, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 100 MHz) δ (ppm): 10.0 (+), 10.2 (+), 22.2 (−), 23.2 (−), 28.5 (+), 28.6 (+), 38.7 (−), 50.0 (−), 72.1 (−), 72.3 (−), 79.4 (C_{quat}), 79.6 (C_{quat}), 117.7 (+, br), 121.7 (+), 129.4 (+), 133.8 (C_{quat}), 134.4 (C_{quat}), 143.7 (C_{quat}, br), 150.3 (C_{quat}, br), 155.5 (C_{quat}, br), 156.5 (C_{quat}, br), 156.8 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1535 $[MH]^+$ (100), 768 $[M+2H]^{2+}$ (15). EA calcd for $C_{86}H_{132}N_8O_{16}$: C, 67.34; H, 8.67; N, 7.30. Found: C, 67.11; H, 8.79; N, 7.22.

The evaporation of first chromatographic fractions yielded 103 mg (24%) of *5-[4,7,10-tris(Boc)cyclen-1-yl]-25,26,27,28-tetrapropoxy-calix[4]arene (1,3-alternate)* ***18*** Mp: 76–78 °C. R_f=0.50 (SiO_2, PE–EtOAc 2:1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.82–1.00 (m, 12H, –CH_2–CH_3), 1.48 (s, 9H, –C–(CH_3)$_3$), 1.50 (s, 18H, –C–(CH_3)$_3$), 1.58–1.77 (m, 8H, –CH_2–CH_3), 3.33–3.67 (m, 32H, –N–CH_2–CH_2–N–, Ar–CH_2–Ar, –O–CH_2–CH_2–), 6.55 (s, 2H, Ar*H*), 6.65 (t, 2H, J=7.4 Hz, Ar*H*), 6.97−7.01 (m, 7H, Ar*H*). ^{13}C NMR, DEPT (135) ($CDCl_3$, 63 MHz) δ (ppm): 10.5 (+), 10.55 (+), 10.6 (+), 23.5 (−), 23.7 (−), 23.8 (−), 28.6 (+), 28.7 (+), 36.2 (−), 36.7 (−), 48.3–49.9 (−, br), 73.9 (−), 74.0 (−), 74.4 (−), 79.4 (C_{quat}), 79.6 (C_{quat}), 120.1 (+, br), 121.3 (+), 121.7 (+), 129.7 (+), 130.0 (+), 130.1 (+), 133.3 (C_{quat}), 133.4 (C_{quat}), 133.7 (C_{quat}), 133.9 (C_{quat}), 143.7 (C_{quat}), 151.0 (C_{quat}), 155.5 (C_{quat}), 156.4 (C_{quat}), 156.7 (C_{quat}), 171.1 (C_{quat}). MS (ESI, 70 eV) *m/z* (rel int.) 1063 $[M]^+$(100). EA calcd for $C_{63}H_{90}N_4O_{10}$: C, 71.16; H, 8.53; N, 5.27. Found: C, 71.07; H, 8.64; N, 5.28.

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Enantioselective synthesis of (−)-cytoxazone and (+)-*epi*-cytoxazone, novel cytokine modulators via Sharpless asymmetric epoxidation and L-proline catalyzed Mannich reaction

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Abstract—A short and efficient enantioselective synthesis of (−)-cytoxazone and its stereoisomer (+)-*epi*-cytoxazone, novel cytokine modulators, has been described with good yield and enantioselectivity. Ti-catalyzed Sharpless asymmetric epoxidation of allyl alcohol and L-proline catalyzed three-component Mannich reaction constitute the key steps in introducing stereogenicity into the molecule.

1. Introduction

Cytoxazone **1**, containing a novel 4,5-disubstituted-2-oxazolidinone moiety was isolated[1] from *Streptomyces* sp., and its absolute configuration was unambiguously established by asymmetric synthesis.[2] (−)-Cytoxazone [(−)-**1**] exhibits cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Since Th2 cells play a role in mediating the immune response to allergens, cytoxazone **1** could be a useful lead compound for the development of therapeutic agents for atopic dermatitis and asthma.

Due to its potential bioactivity and the simple structure, several methods of synthesizing (−)-cytoxazone (**1**) have been accomplished.[3] The stereoisomer of (−)-cytoxazone (**1**), (+)-*epi*-cytoxazone (**2**) has also been synthesized.[4] In this paper, we wish to report a short enantioselective synthesis of (−)-cytoxazone and its stereoisomer (+)-*epi*-cytoxazone in good yields by employing Ti-catalyzed Sharpless asymmetric epoxidation of allyl alcohol and L-proline catalyzed Mannich reaction, respectively, as the key steps in introducing stereogenic centers into the molecule.

2. Results and discussion

Retrosynthetic analysis of cytoxazone (**1**) reveals that amino alcohol **3** could be visualized as a key intermediate (Fig. 1).

The key intermediate (*Z*)-olefinic ether (**8**) was obtained in three steps: (i) Sonogashira coupling (cat. $Pd(PPh_3)_4$ (0.5 mol %), cat. CuI (10 mol %), Et_2NH, 25 °C, 96%) of 4-iodoanisole with propargyl alcohol to give aryl propargyl alcohol **6** in 96% yield; (ii) acetylenic alcohol **6** was protected with TBS chloride to give TBS ether **7**, which was

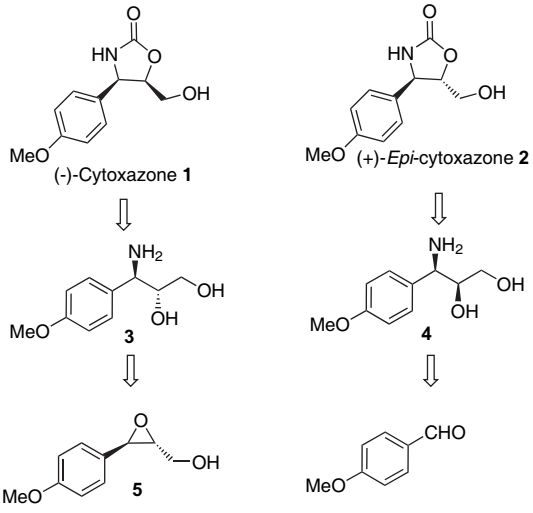

Figure 1. Retrosynthesis of (−)-cytoxazone (**1**) and (+)-*epi*-cytoxazone (**2**).

Keywords: Asymmetric synthesis; Aminohydroxylation; Epoxidation; Mannich reaction; Oxidation; Ozonolysis.
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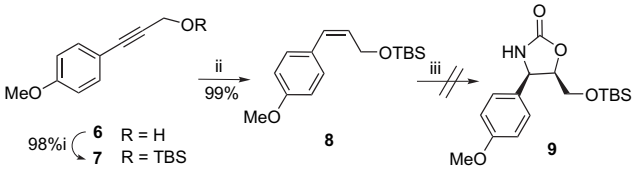
stereospecifically reduced with Lindlar catalyst to obtain (*Z*)-olefinic ether **8** in 99% yield. However, several attempts to functionalize (*Z*)-olefinic ether **8** with Os-catalyzed asymmetric aminohydroxylation (AA) failed despite employing various reaction conditions (Scheme 1).[5]



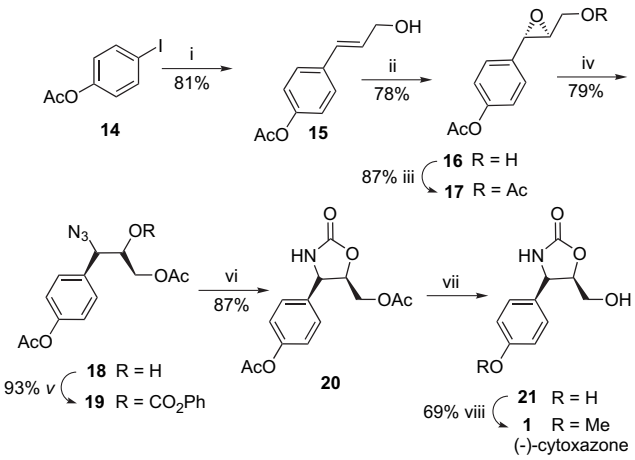
Scheme 1. Reagents and conditions: (i) TBSCl, Et_3N, CH_2Cl_2, 0–25 °C, 98%; (ii) Lindlar catalyst (5% Pd on $CaCO_3$ with Pb poisoned), dry hexane, H_2 (1 atm), 25 °C, 99 %; (iii) cat. K_2OsO_6, $(DHQD)_2PHAL$, Urethane, *tert*-BuOCl or 1,3-dichoro-5,5-dimethyl hydantoin, aq 10% NaOH, *n*-PrOH, 25 °C, 24 h.

After failing to functionalize aminohydroxylate (*Z*)-olefinic ether **8**, we then turned our attention to functionalize (*E*)-allyl alcohol **11**.

Accordingly, we subjected (*E*)-allyl alcohol **11** to Ti-catalyzed asymmetric epoxidation (AE) under standard reaction conditions;[6] here again, all our attempts to obtain chiral epoxide **12** failed. The reason may be due to the positive inductive effect of methoxy group present on an aromatic ring, which facilitates the opening of epoxide ring, thus deactivating the Ti-catalyst by forming metal chelate **13** (Scheme 2).

In order to eliminate this positive inductive effect due to OMe group, we changed our strategy by replacing electron-rich OMe group on the aromatic ring with electron-deficient OAc group. This protecting group can be further deprotected easily during the course of the synthesis (Scheme 3).

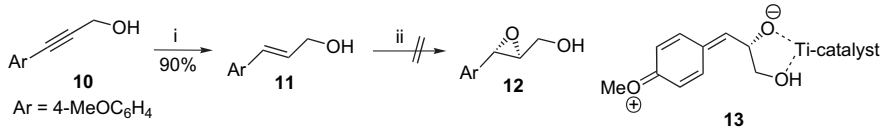
4-Iodophenol was protected as its acetyl derivative **14** (Et_3N, CH_2Cl_2, 25 °C). The Pd-catalyzed arylation of allyl alcohol with **14** gave the *trans*-allylic alcohol **15** in 81% yield.[7] The allylic alcohol **15** was subjected to Sharpless asymmetric epoxidation [(+)-DIPT, $Ti(O^iPr)_4$, anhyd TBHP, 25 °C] to give the chiral epoxide **16** in 78% yield and 92.5% ee (determined by chiral HPLC using Chiralcel OD-H® column). The alcohol **16** was acetylated (CH_3COCl, Et_3N, DMAP (cat.), CH_2Cl_2, 25 °C) to give epoxy acetate **17** in 86% yield. The nucleophilic opening of the epoxide at the benzylic position with N_3 was achieved (NaN_3, NH_4Cl (cat.), THF, 25 °C) to give azido alcohol **18** in 88% yield. We then followed reported procedure[8] for the conversion of azido alcohol **18** to the corresponding oxazolidinone **21** in two steps by alcohol protection followed by reductive cyclization with triphenylphosphine. Basic hydrolysis of both acetate groups in MeOH gave the phenol **21** which was directly subjected to



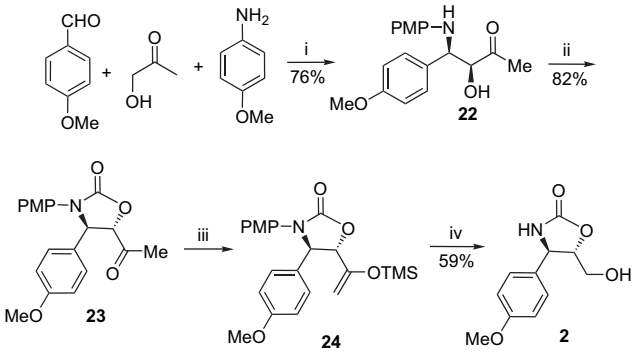
Scheme 3. Reagents and conditions: (i) allyl alcohol (3 equiv), AgOAc (1 equiv), cat. $Pd(OAc)_2$ (5 mol %), cat. PPh_3 (10 mol %), DMF, 70 °C, 16 h, 81%; (ii) anhyd 5.4 M TBHP in CH_2Cl_2, 4 Å Molecular sieves, cat. $Ti(O^iPr)_4$ (10 mol %), cat. (+)-DIPT (12 mol %), CH_2Cl_2, −20 °C, 20 h, 78%; (iii) AcCl, Et_3N, cat. DMAP (10 mol %), CH_2Cl_2, 25 °C, 87%; (iv) NaN_3, cat. NH_4Cl (30 mol %), THF/H_2O (2:1), 50 °C, 3 h, 79%; (v) PhOCOCl, pyridine, CH_2Cl_2, −5 to 25 °C, 1 h, 93%; (vi) PPh_3 (4 equiv), THF/H_2O (10:1), 50 °C, 2 h, 87%; (vii) aq $NaHCO_3$, MeOH, reflux, 1 h; (viii) NaH, MeI, THF, 0–25 °C, 3 h, 69%, 83% ee.

methylation with methyl iodide in the presence of NaH to afford (−)-cytoxazone (**1**) in 65% yield and 83% ee [determined by HPLC using Chirasphere® column and optical rotation].

Based on the retrosynthetic analysis of (+)-*epi*-cytoxazone **2** (Fig. 1), amino alcohol **4** is the key intermediate, which can be obtained from L-proline catalyzed asymmetric Mannich reaction (Scheme 4).[9] Thus, 4-methoxybenzaldehyde was condensed with hydroxyacetone and *p*-anisidine in the presence of 30 mol % L-proline, to obtain chiral amino alcohol **22** in 76% yield with *syn*/*anti* ratio 2:1. Efforts to improve the diastereomeric ratios were not successful despite replacing OMe group with electron withdrawing groups such as OAc or OMs on the aromatic nucleus. However, the required diastereomer was separated by simple column chromatographic purification. Amino alcohol **22** was then protected with triphosgene to give oxazolidinone **23** in 82% yield. Attempts to convert methyl ketone in **23** to the corresponding carboxylic acid via haloform reaction were not fruitful. Alternately, we tried to prepare kinetically controlled silyl enol ether **7** from oxazolidinone **23** so that enol ether **24** could be further easily converted to *epi*-cytoxazone (**2**) by ozonolysis with reductive work up. However, all attempts to isolate enol ether **24** in pure form resulted in the isolation of the starting ketone **23**. Then we subjected in situ generated silyl enol ether for ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN gave (+)-*epi*-cytoxazone **2** in 59% yield and 81% ee.



Scheme 2. Reagents and conditions: (i) LAH, THF, 0 °C, 3 h, 90%. (ii) $Ti(O^iPr)_4$ (10 mol %), (+)-DIPT (12 mol %), anhydrous TBHP, CH_2Cl_2, −20 °C, 24 h.



Scheme 4. Reagents and conditions: (i) *p*-anisidine (1.1 equiv), hydroxyacetone (10 equiv), cat. L-proline (20 mol %), DMSO, 25 °C, 24 h, 76%; (ii) triphosgene, Et_3N, CH_2Cl_2, −10 to 25 °C, 82%; (iii) Li-HMDS, TMSCl, THF, −78 °C; (iv) (a) O_3, PPh_3, CH_2Cl_2, −78 °C; (b) $NaBH_4$, MeOH, 25 °C; (c) CAN, CH_3CN, 5 h, (59% in three steps), 81% ee.

3. Conclusion

In conclusion, we have achieved a simple and efficient asymmetric synthesis of (−)-cytoxazone (**1**) using asymmetric epoxidation of allylic alcohol (AE) in the presence of $Ti(O^iPr)_4$ as a catalyst and (+)-DIPT as ligand with a overall yield of 23%, and optical purity of 83% ee (by HPLC) in nine steps starting from readily available 4-iodophenol. We have also achieved asymmetric synthesis of (+)-*epi*-cytoxazone (**1**) using L-proline catalyzed Mannich reaction with overall yield of 37%, and optical purity of 81% in six steps starting from readily available *p*-anisaldehyde.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points were uncorrected. HPLC analyses were performed on a chiral column (Chiralcel OD-H® and Chirasphere®). Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer. ^1H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020B-70 eV mass spectrometer. Elemental analysis was carried out on a Carlo Erba EA 110B CHNS-O analyzer.

4.2. Preparation of 3-(4-methoxyphenyl)prop-2-yn-1-ol (6)

A two-necked 100 ml RB flask was charged with *p*-iodoanisole (4.68 g, 20 mmol), propargyl alcohol (1.68 g, 30 mmol), CuI (0.40 g, 2 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), and diethylamine (50 ml). The resulting mixture was stirred at 25 °C for 6 h. Then the reaction was diluted with ethyl acetate (80 ml), washed with 10% HCl (10 ml), water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give black colored thick oil. This crude product was purified on column chromatography using 20% ethyl acetate in pet. ether as eluent to afford pure **6** (3.10 g, 96%) as pale yellow colored solid.

Yield: 96%; mp: 74–75 °C; IR ($CHCl_3$, cm^{-1}): 669, 757, 833, 1033, 1172, 1215, 1249, 1292, 1463, 1510, 1606, 2856, 2927, 3018, 3421; ^1H NMR (200 MHz, $CDCl_3$): δ 2.61 (br s, 1H), 3.78 (s, 3H), 4.48 (s, 2H), 6.79 (d, J=9.0 Hz, 2H), 7.34 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.42, 55.13, 85.38, 85.90, 113.83, 114.57, 133.06, 159.59; LRMS *m*/*z* (% rel intensity): 162 (M+, 100), 145 (33), 131 (40), 108 (30), 102 (33), 91 (57), 77 (30), 63 (43); Analysis: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.17; H, 6.14 %.

4.3. Preparation of (3-(4-methoxyphenyl)prop-2-ynyloxy)(*tert*-butyl)dimethylsilane (7)

To a stirred solution of alcohol **6** (2.46 g, 15.2 mmol) in dry CH_2Cl_2 (25 ml), Et_3N (2.29 g, 22.7 mmol) and *tert*-butyldimethylsilyl chloride (2.75 g, 18.2 mmol) were added portion wise at 0 °C. This mixture was then brought to room temperature and stirred for 12 h and then quenched with MeOH. It was poured into water and extracted with EtOAc. The organic phase was washed with aq $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$ and purified over column chromatography using pet. ether as eluent to afford pure **7** (4.11 g, 98%) as yellow colored oil.

Yield: 98%; IR ($CHCl_3$, cm^{-1}): 776, 845, 1125, 1230, 1522, 1605; ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.78 (s, 9H), 3.61 (s, 3H), 4.34 (s, 2H), 6.61 (d, J=8.9 Hz, 2H), 7.15 (d, J=8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.23, 18.03, 25.62, 51.94, 54.64, 84.62, 86.26, 113.62, 114.90, 132.70, 159.37; LRMS *m*/*z* (% rel intensity): 276 (M^+, 5), 261 (3), 231 (3), 219 (65), 205 (5), 189 (80), 174 (5), 159 (5), 145 (100), 130 (15), 115 (10), 102 (20), 94 (20), 75 (15), 57 (10), 41 (12); Analysis: $C_{16}H_{24}O_2Si$ requires C, 69.51; H, 8.75; found C, 69.47; H, 8.70%.

4.4. Preparation of (*Z*)-(4-methoxycinnamyloxy)(*tert*-butyl)dimethylsilane (8)

To a 50 ml two-necked RB flask equipped with a condenser and a balloon filled with H_2 at 1 atm was added Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with lead, 1.4 g), silyl ether **7** (2.76 g, 10 mmol), quinoline (2.6 g, 21 mmol), and 45 ml of dry *n*-hexane. The resulting mixture was stirred at room temperature under H_2 (1 atm) for 1 h. When starting material was consumed (monitored by TLC), the reaction mixture was filtered through sintered funnel. After distilling off hexane, we obtained 2.75 g (99%) of pure (*Z*)-olefin **8** as yellow colored oil.

Yield: 99%; IR ($CHCl_3$, cm^{-1}): 534, 617, 650, 668, 814, 837, 909, 938, 960, 983, 1006, 1035, 1085, 1175, 1216, 1253, 1302, 1361, 1405, 1442, 1464, 1471, 1511, 1575, 1607, 1681, 2401, 2857, 2897, 2931, 2956, 3019, 3443; ^1H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.84 (s, 9H), 3.76 (s, 3H), 4.37 (d, J=5.9 Hz, 2H), 5.61 (q, J=5.9 Hz, 1H), 6.34 (d, J=12.0 Hz, 1H), 6.79 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.18, 18.25, 25.87, 55.08, 60.36, 113.51, 129.04, 129.49, 130.00, 130.76, 158.55; LRMS *m*/*z* (% rel intensity): 278 (M^+, 5), 222 (15), 221 (50), 205 (5), 189 (5), 175 (10), 166 (5), 147 (100), 131 (45), 115 (75), 103 (65), 91 (90), 75

(90), 57 (80), 41 (90); Analysis: $C_{16}H_{26}O_2Si$ requires C, 69.01; H, 9.41; found C, 69.00; H, 9.35%.

4.5. Preparation of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (11)

LAH (0.29 g, 7.8 mmol) was taken in THF (23 ml) and the slurry was cooled to 0 °C in an ice bath under nitrogen atmosphere. To this mixture, alcohol **6** (1.60 g, 9.88 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. After completion of reaction (monitored by TLC), ice-cold water (20 ml) was added and extracted with ether (3×30 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution, and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish **11** as colorless solid (1.18 g).

Yield: 73%; IR ($CHCl_3$, cm^{-1}): 761, 890, 1098, 1375, 1452, 1504, 2989, 3010, 3409, 3610; ^1H NMR (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 3.81 (s, 3H), 4.28 (d, J=6.0 Hz, 2H), 6.17–6.30 (m, 1H), 6.52–6.60 (d, J=16.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.13, 63.58, 113.90, 126.29, 127.54, 129.42, 130.67, 159.15; Analysis: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.12; H, 7.80%.

4.6. Preparation of 4-((*E*)-3-hydroxyprop-1-enyl)phenyl acetate (15)

A mixture of 4-iodophenyl acetate (7.89 g, 30 mmol) and allyl alcohol (3.48 g, 60 mmol) was stirred for 16 h in the presence of the AgOAc (5.01 g, 30 mmol), PPh_3 (0.78 g, 3 mmol), and $Pd(OAc)_2$ (0.33 g, 1.5 mmol) at 70 °C in 50 ml DMF. The reaction mixture was filtered through sintered funnel and washed with aq HCl (15 ml), water (15 ml), aq $NaHCO_3$ (15 ml), and brine (15 ml) sequentially. The crude allyl alcohol was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish 4.65 g of **15** as colorless solid.

Yield: 81%; mp: 81–83 °C (crystallized from EtOH); IR ($CHCl_3$, cm^{-1}): 504, 524, 692, 755, 872, 970, 1016, 1087, 1151, 1196, 1332, 1414, 1503, 1600, 1677, 1714, 2869, 2939, 3029, 3366; ^1H NMR (200 MHz, $CDCl_3$): δ 1.67 (br s, 1H), 2.38 (s, 3H), 4.32 (d, J=4.9 Hz, 2H), 6.27–6.40 (m, 1H), 6.57 (d, J=15.9 Hz, 1H), 7.20 (d, J=8.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.74, 61.84, 121.52, 127.15, 128.01, 129.76, 135.84, 147.80, 169.28; LRMS m/z (% rel intensity): 192 (M^+, 5), 174 (3), 150 (50), 131 (10), 121 (10), 107 (100), 94 (60), 76 (30), 65 (15), 50 (20); Analysis: $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29; found C, 68.61; H, 6.18%.

4.7. Preparation of 4-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)phenyl acetate (16) using Sharpless asymmetric epoxidation

A 100 ml two-necked RB flask was charged with 4 Å molecular sieves (1 g), 20 ml CH_2Cl_2, and cooled at −25 °C. Then $Ti(O^iPr)_4$ (0.59 ml, 0.568 g, 2 mmol) and L-(+)-DIPT (0.53 ml, 0.585 g, 2.5 mmol) was added sequentially and the mixture was stirred for 10 min before the addition of allyl alcohol **15** (3.84 g, 20 mmol). Finally, a 5.4 M anhydrous TBHP solution in CH_2Cl_2 (7.6 ml, 41 mmol) was added and the resulting mixture was stirred at −20 °C for 20 h. After completion of reaction (monitored by TLC), 10% aq tartaric acid (20 ml) was added and the aqueous layer solidifies. After 1 h the reaction was brought to room temperature and stirring was continued until the aqueous layer becomes clear. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether/EtOAc (3:1) as eluent to furnish epoxide **16** as white solid (3.23 g).

Yield: 78%; mp: 96 °C (crystallized from EtOH); $[\alpha]_D^{25}$ +23.59 (*c* 1.3, $CHCl_3$); HPLC: 92.5% ee, Chiralcel OD-H®, λ=254 nm, 5% 2-propanol/hexane, 1 ml/min, retention time: (*R*,*R*) 10.81 min, (*S*,*S*) 15.716 min; IR ($CHCl_3$, cm^{-1}): 527, 605, 703, 736, 784, 872, 971, 1045, 1152, 1175, 1200, 1232, 1369, 1417, 1504, 1605, 1740, 2939, 3029, 3060, 3499; ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (br s, 1H), 2.39 (s, 3H), 3.78–4.08 (m, 4H), 7.25–7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.75, 54.67, 60.89, 62.63, 122.11, 127.22, 136.13, 148.81, 149.23, 170.11; Analysis: $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81; found C, 63.38; H, 5.78%.

4.8. Preparation of 4-((2*S*,3*S*)-3-(acetoxymethyl)oxiran-2-yl)phenyl acetate (17)

The mixture of epoxy alcohol **16** (2.08 g, 10 mmol), acetyl chloride (0.858 g, 11 mmol), Et_3N (1.52 g, 15 mmol), and DMAP (0.122 g, 10 mol %) in dry CH_2Cl_2 (10 ml) was stirred at room temperature. After the reaction was complete (TLC, 2 h), the solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (10 ml) and was extracted with ethyl acetate (2×25 ml). The organic layer was washed with saturated $NaHCO_3$ (2×15 ml) and brine (15 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to afford 2.17 g (87%) of epoxy ester **17** as colorless gum.

Yield: 87%; IR ($CHCl_3$, cm^{-1}): 526, 604, 702, 735, 783, 871, 970, 1016, 1044, 1109, 1152, 1175, 1200, 1232, 1369, 1418, 1504, 1605, 1740, 1913, 2939, 3029, 3062, 3499; ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.40 (s, 3H), 3.20–3.25 (m, 1H), 3.84 (d, J=2.0 Hz, 1H), 4.07–4.16 (m, 1H), 4.44–4.51 (m, 1H), 7.22 (d, J=9.1 Hz, 2H), 7.30 (d, J=7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.55, 20.76, 55.45, 59.29, 63.67, 122.09, 127.15, 129.71, 135.57, 148.93, 170.51; Analysis: $C_{13}H_{14}O_5$ requires C, 50.34; H, 4.93; found C, 50.28; H, 4.89%.

4.9. Preparation of (2*R*,3*R*)-3-azido-2-hydroxy-3-(4-acetoxyphenyl)propyl acetate (18)

To a solution of NaN_3 (0.29 g, 5.2 mmol) and NH_4Cl (0.054 g, 1 mmol) in water (5 ml), a solution of epoxy ester **17** (0.775 g, 3.1 mmol) in THF (10 ml) was added. The reaction mixture was stirred at 50 °C for 3 h. Cooled to room temperature and the solution was extracted with EtOAc and washed with water (50 ml), dried over anhydrous

Na_2SO_4. Upon evaporation of the solvent, the crude product was purified by column chromatography over silica gel (EtOAc/pet. ether, 2:8) yielding 0.717 g (79%) of azido alcohol **18** as yellow colored solid.

Yield: 79%; mp: 61 °C; $[\alpha]_D^{25}$ −9.16 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 527, 604, 668, 757, 873, 908, 970, 1018, 1044, 1108, 1151, 1176, 1217, 1332, 1371, 1417, 1503, 1603, 1735, 2108, 2401, 2939, 3022, 3472; ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.38 (s, 3H), 2.66 (br s, 1H), 3.98–4.09 (m, 1H), 4.15 (d, *J*=2.5 Hz, 1H), 4.17 (d, *J*=1.4 Hz, 1H), 4.63 (d, *J*=6.3 Hz, 1H), 7.31 (d, *J*=8.7 Hz, 2H), 7.43 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.62, 20.76, 64.79, 66.09, 72.03, 122.27, 129.40, 135.17, 148.96, 169.12, 171.21; Analysis: $C_{13}H_{15}N_3O_5$ requires C, 53.24; H, 5.16; N, 14.33; found C, 53.15; H, 5.10; N, 14.30%.

4.10. Preparation of (1*R*,2*R*)-3-acetoxy-1-azido-1-(4-acetoxyphenyl)propan-2-yl phenyl carbonate (19)

To a solution of azido alcohol **18** (0.469 g, 1.6 mmol) and pyridine (0.14 ml, 1.7 mmol) in CH_2Cl_2 (20 ml), a solution of phenylchloroformate (0.22 ml, 0.28 g, 1.7 mmol) in CH_2Cl_2 (1 ml) was added at −5 °C over10 min. After stirring at −5 °C for 1 h, the reaction mixture was poured into water. The organic layer was washed with 1% H_3PO_4, then with 3% $NaHCO_3$, and dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, 0.614 g of gummy azido ester **19** was obtained as brown colored gum.

Yield: 93%; IR (KBr, cm^{-1}): 602, 670, 761, 873, 1045, 1109, 1150, 1175, 1245, 1510, 1610, 1760, 2100, 2955; ^1H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.37 (s, 3H), 4.16–4.20 (m, 2H), 4.45–4.56 (m, 1H), 4.63 (d, *J*=6.3 Hz, 1H), 7.12–7.48 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.64, 20.75, 64.81, 66.11, 72.05, 122.32, 124.95, 129.44, 135.22, 148.98, 152.24, 159.73, 166.65, 171.37; Analysis: $C_{20}H_{19}N_3O_7$ requires C, 58.11; H, 4.63; N, 10.16; found C, 58.05; H, 4.60; N, 10.10%.

4.11. Preparation of ((4*R*,5*R*)-4-(4-acetoxyphenyl)-2-oxooxazolidin-5-yl)methyl acetate (20)

Azido ester **19** (0.454 g, 1.1 mmol) and PPh_3 (1.18 g, 4.5 mmol) were dissolved in THF (20 ml) and water (2 ml). The reaction mixture was heated at 50 °C for 2 h. Evolution of N_2 was observed during the first 1 h of the reaction. Solvent was evaporated; the solid residue was dissolved in EtOAc (20 ml), washed with brine (10 ml), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography and recrystallized from $CHCl_3$ to obtain 0.280 g (87%) of oxazolidinone **20** as gray colored solid.

Yield: 87%; mp: 103 °C (crystallized from $CHCl_3$); $[\alpha]_D^{25}$ −54.82 (*c* 0.8, $CHCl_3$); IR (KBr, cm^{-1}): 971, 1025, 1043, 1051, 1173, 1233, 1367, 1514, 1605, 1712, 1720, 1740, 2938, 3228, 3255, 3475; ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.34 (s, 3H), 3.14–3.16 (m, 2H), 4.66–4.78 (m, 1H), 4.92 (d, *J*=8.2 Hz, 1H), 7.13–7.25 (m, 4H), 8.11 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.64, 20.75, 56.86, 67.49, 80.55, 121.51, 128.59, 132.73, 148.66, 159.92, 170.10, 171.15; Analysis: $C_{14}H_{15}NO_6$ requires C, 57.34; H, 5.16; N, 4.78; found C, 57.28; H, 5.12; N, 4.69%.

4.12. Preparation of (4*R*, 5*R*)-5-hydroxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one: (−)-cytoxazone (1)

A mixture of oxazolidinone **20** (0.237 g, 0.81 mmol), and 10% aq $NaHCO_3$ (2 ml) in methanol (5 ml) was heated under reflux for 1 h. After the reaction was complete (TLC), solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (5 ml) and was extracted with ethyl acetate (2×5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product **21**, which without purification, was then added to THF (5 ml) containing NaH (60% suspension in paraffin) (0.034 g, 0.85 mmol) at 0 °C and stirred for 1 h. To this mixture was further added MeI (0.12 g, 0.85 mmol) at 0 °C and then stirred at room temperature for 3 h. After the reaction was complete, the reaction mixture was diluted with water (3 ml) and extracted with diethyl ether (2×5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was purified by column chromatography and recrystallized from MeOH to afford the required (−)-cytoxazone **1** in 69% (0.124 g) yield as colorless solid.

Yield: 69%; mp: 117–120 °C (crystallized from MeOH), (lit.[1] 118–121 °C); $[\alpha]_D^{25}$ −60.16 (*c* 0.3, MeOH), (lit.[1] $[\alpha]_D^{25}$ −71 (*c* 0.1, MeOH)); HPLC: 83% ee, Chirasphere®, λ=254 nm, 5% 2-propanol/hexane, 1 ml/min, retention time: (*S*,*S*) 16.776 min, (*R*,*R*) 21.001 min; IR (KBr, cm^{-1}): 450, 766, 965, 997, 1026, 1041, 1050, 1177, 1215, 1236, 1254, 1398, 1514, 1615, 1712, 1720, 2948, 3228, 3255, 3352, 3476; ^1H NMR (200 MHz, DMSO-d_6): δ 2.95–2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J*=5.0 Hz, 1H), 4.90 (d, *J*=4.9 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=8.8 Hz, 2H), 7.92 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.17, 56.82, 61.93, 80.48, 113.79, 128.17, 129.45, 158.81, 160.09; Analysis: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.17; H, 5.80; N, 6.19%.

4.13. Preparation of (3*S*,4*R*)-4-(4-methoxyphenylamino)-3-hydroxy-4-(4-methoxyphenyl)butan-2-one (22)

A mixture of L-proline (0.23 g, 2 mmol), *p*-anisidine (1.35 g, 11 mmol), *p*-anisaldehyde (1.36 g, 10 mmol), and hydroxyacetone (2 ml) in DMSO (10 ml), was stirred at 25 °C for 24 h. After completion of reaction, aq saturated NH_4Cl (10 ml) was added and the mixture was extracted with ethyl acetate. Upon evaporation of the solvent, crude product was purified by column chromatography on silica gel (EtOAc/pet. ether, 3:4) yielding required Mannich product (**22**) 2.39 g (76%) as yellow oil.

Yield: 76%; $[\alpha]_D^{25}$ −1.28 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1092, 1237, 1346, 1513, 1709, 2360, 2916, 3269; ^1H NMR (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 4.42 (d, *J*=2.20 Hz, 1H), 4.91 (d, *J*=2.0 Hz, 1H), 6.54–6.63 (m, 2H), 6.72–6.81 (m, 2H), 6.96–7.05 (m, 2H), 7.35–7.44 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.79, 55.62, 56.12, 60.14, 81.32, 114.15, 115.24, 115.76, 128.60, 131.58,

140.00, 152.77, 159.44, 207.98; Analysis: $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44; found C, 68.50; H, 6.80; N, 4.39%.

4.14. Preparation of (4*R*,5*S*)-5-acetyl-3,4-bis(4-methoxyphenyl)oxazolidin-2-one (23)

The Mannich product **22** (0.315 g, 1 mmol), in dry CH_2Cl_2 (20 ml) was cooled to −20 °C and to this Et_3N (506 mg, 5 mmol) and triphosgene (297 mg, 1 mmol) was added. The mixture was warmed to room temperature, stirred for 3 h, and quenched with aq NH_4Cl (10 ml). After extraction with CH_2Cl_2 (20 ml), the organic layer was dried over Na_2SO_4 and concentrated to furnish crude *trans*-oxazolidinone **23**, which was further purified by column chromatography (EtOAc/pet. ether, 5:3) yielding 0.28 g (82%) of white solid.

Yield: 82%; mp: 106–108 °C (crystallized from EtOH); $[\alpha]_D^{25}$ −18.14 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 740, 807, 927, 1035, 1099, 1179, 1248, 1367, 1452, 1513, 1612, 1726, 2860, 2934, 3228, 3300; ^1H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 4.58 (d, *J*=4.8 Hz, 1H), 5.41 (d, *J*=4.8 Hz, 1H), 6.55–6.59 (m, 2H), 6.71–6.82 (m, 2H), 6.95–7.06 (m, 2H), 7.37–7.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.72, 55.24, 55.97, 62.43, 83.12, 114.16, 115.24, 115.76, 128.87, 129.19, 129.34, 137.77, 157.00, 204.55; Analysis: $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.61; N, 4.10; found C, 66.77; H, 5.56; N, 4.04%.

4.15. Preparation of (4*R*,5*S*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one: (+)-*epi*-cytoxazone (2)

To a 1 M solution of lithium hexamethyldisilylamide (1.6 ml, 1.6 mmol) at −78 °C under an argon atmosphere was added chlorotrimethylsilane (0.64 ml, 4.88 mmol) dropwise. A cold (−78 °C) solution of oxazolidinone **23** (0.275 g, 0.8 mmol) in THF (2 ml) was then added dropwise. After being stirred for 25 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred for 30 min and then concentrated in vacuum. After drying ($MgSO_4$) and removal of the solvent in vacuum, the crude silyl enol ether **24** was used directly in the next step without further purification because it partly rearranged to ketone **23** during attempted purification. A solution of this crude silyl enol ether **24** in MeOH (15 ml) and CH_2Cl_2 (10 ml) was cooled to −78 °C, and ozone was bubbled through this solution for 45 min. Triphenylphosphine (0.223 g, 0.885 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated in vacuum, and the residue was dissolved in absolute EtOH (4 ml), $CaCl_2$ (0.15 g, 1.35 mmol) and $NaBH_4$ (0.16 g, 4 mmol) was added, and the reaction mixture was stirred for 20 min at 25 °C. The excess of reducing agent was destroyed by the addition of satd NH_4Cl (0.5 ml) and then EtOH was evaporated; the residue was then dissolved in CH_3CN (5 ml) at 0 °C which was then treated with cerium ammonium nitrate (2.2 g, 4 mmol) in water (3 ml). The mixture was stirred for 5 min, treated with 10 ml of satd aq $NaHCO_3$, warmed to 25 °C, and treated with solid Na_2SO_3 (0.126 g, 1 mmol). The reaction mixture was extracted with ethyl acetate (3×6 ml), dried, and concentrated to furnish after column chromatography pure (+)-*epi*-cytoxazone (**2**) as colorless solid in (0.105 g) 59% yield and 81% ee.

Yield: 59%; mp: 159–160 °C (crystallized from MeOH), (lit.[4b] 158–160 °C); $[\alpha]_D^{25}$ +22.89 (*c* 0.4, MeOH), (lit.[4b] $[\alpha]_D^{25}$ +28.6 (*c* 1, MeOH)); HPLC: 81% ee, Chiracel OD-H®, λ=280 nm, 15% 2-propanol/hexane, 0.8 ml/min, retention time: (*R*,*S*) 14.32 min, (*S*,*R*) 15.28 min; IR (KBr, cm^{-1}): 830, 1025, 1240, 1510, 1720, 2920, 3290; ^1H NMR (200 MHz, DMSO-d_6): δ 3.62–3.66 (m, 1H), 3.75 (s, 3H), 3.80–3.84 (m, 1H), 4.43–4.47 (m, 1H), 4.78 (d, *J*=5.9 Hz, 1H), 6.93 (d, *J*=8.7 Hz, 2H), 7.2 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.41, 57.12, 62.23, 85.58, 114.81, 128.73, 131.52, 159.77, 161.00; Analysis: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.14; H, 5.72; N, 6.22%.

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Synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of nucleobases

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Abstract—The synthesis of novel 3-pyrrolidinyl derivatives of nucleobases is described. Starting from malic acid, we improved the synthesis of both racemic and optically active *N*-benzyl-3-hydroxypyrrolidine-2,5-diones, which were transformed in four steps into *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines, the key synthons for the alkylation of purine and pyrimidine nucleobases. Alkylations of cesium salts of purines and sodium salts of pyrimidines with *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines proceeded smoothly, giving high yields of 9-substituted purine derivatives and moderate yields of 1-substituted pyrimidine derivatives. Using (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine as the same intermediate for the synthesis of both enantiomeric *N*-Boc-3-pyrrolidinyladenines, and considering the results obtained on chiral HPLC analysis of the products, we proved that nucleophilic displacement of the mesyloxy group proceeded with inversion and not with retention of the configuration. Prepared compounds were tested for cytostatic and antiviral properties, but no significant activity was found.

1. Introduction

Sugar-modified nucleoside analogues form an important group of potential antimetabolites, and compounds exhibiting remarkable antiviral and anticancer properties were found among them.[1] Replacement of the sugar moiety in nucleosides by a pyrrolidine ring seems to be one of the interesting modifications reported in the literature. The synthesis of the first L-nucleoside analogues **1** bearing D-prolinol residue was published by Kaspersen.[2,3] From L-prolinol, Ng and Orgel[4] synthesized D-thymidine analogue **2**, which inhibited the growth of breast carcinoma (MCF-7M), colon carcinoma (HT-29), and SK-MES-1 lung carcinoma cell lines. Kaspersen and Pandit[3,5] published the synthesis of a series of pyrrolidine nucleosides **1**, **3**, **5**, **8a**–**8d**, **9a**, **9b** corresponding to L-nucleosides. The L-uridine analogue **3** exhibited a weak inhibition of Baby hamster kidney cell (BHK) growth. Also purine D-nucleosides with a L-prolinol ring, **4a**–**4d**, **5** prepared by Peterson and Vince,[6] as well as a series of thymidine analogues,[4,6] exhibited a weak inhibition activity in vitro on P388 mouse leukemia cells and HIV-1 and HSV-1 at the concentrations of about 100 μM. Adenine-containing analogue **4a** was used for the preparation of *N*-phosphonomethyl derivative as the nucleoside 3′-phosphate analogue.[7] Harnden[8,9] published the synthesis of L-prolinol nucleosides **6a**–**6c** with a nucleobase connected to the nitrogen atom of a pyrrolidine ring, and a series of phosphonomethoxy derivatives **7a**–**7e** related to 2′,3′-dideoxynucleoside 5′-phosphates (Fig. 1). Westwood et al.[10] reported the synthesis of 5-ethyluracil and *E*-5-(2-bromovinyl)uracil derivatives **8a**–**8d**, **9a**, **9b**. These compounds were not capable of inhibiting the replication of HIV-1 and HIV-2, vesicular stomatitis at sub-toxic concentrations, or phosphorylation of thymidine by HSV-1 TK, but 5-ethyluracil derivative **8d** was found to inhibit (IC_{50} 40 μM) vaccinia virus. Pyrrolidine analogues of oxetanocin A **10a**, **10b** prepared by Oohashi et al. as potential antivirals against HSV-1, HSV-2, and HIV-1 were found completely inactive.[11] Temple et al. reported the synthesis of several 9-pyrrolidin-1-yl-9*H*-purine derivatives (**11**), which were inactive toward L1210 leukemic cells implanted in mice (Fig. 2).[12] No significant biological activity was found in case of 4′-aza nucleosides **12a**–**12n** and **13a**–**13d**,[13–18] as well as in case of oxazolidine **14**[19] and isooxazolidine **15**[20] ring-containing nucleoside analogues (Fig. 3). Richichi et al. reported the preparation of (*R*)-3-(pyrimidin-1-yl)pyrrolidine nucleoside analogues **16a**, **16b** and **17a**, **17b** by Mitsunobu reaction of unprotected pyrimidine bases with appropriate (*S*)-*N*-benzyl-3-hydroxypyrrolidine.[21] Miyabe et al. reported the total synthesis of uridine, thymidine, and adenosine analogues **18a**–**18c** including construction of heterocyclic base (Fig. 4).[22] A pyrrolidine ring, as a sugar mimic, was introduced into modified oligonucleotides,[23–33] and we can also find it as an important part in

Keywords: Malic acid; Pyrrolidine derivatives; Nucleoside analogues; N-,O-alkylation; Inversion of configuration.
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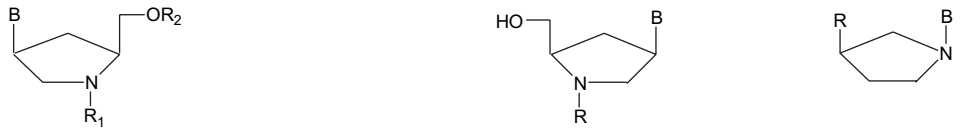
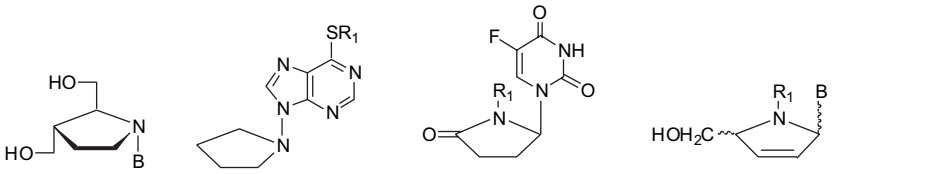


Comp.	B	R_1	R_2
1	2-Amino-6-chloropurin-9-yl	Ts	
3	Uracil-1-yl	H	
5	Guanin-9-yl	H	
8a	5-Ethyluracil-1-yl	Ts	*t*BDPS
8b	5-Ethyluracil-1-yl	Ts	Bz
8c	5-Ethyluracil-1-yl	H	H
8d	5-Ethyluracil-1-yl	Ts	Ac
9a	*E*-5-(2-bromovinyl)uracil-1-yl	Ts	Ac
9b	*E*-5-(2-bromovinyl)uracil-1-yl	Ts	H

Comp.	B	R
2	Thymin-1-yl	OH
4a	Adenin-9-yl	H
4b	Inosin-9-yl	H
4c	2,6-Diaminopurin-9-yl	H
4d	Guanin-9-yl	H

Comp.	B	R
6a	Cytosin-1-yl	CH_2OH
6b	Uracil-1-yl	CH_2OH
6c	Thymin-1-yl	CH_2OH
7a	Adenin-9-yl	$OCH_2P(O)(OH)_2$
7b	Hypoxanthin-9-yl	$OCH_2P(O)(OH)_2$
7c	Cytosin-1-yl	$OCH_2P(O)(OH)_2$
7d	Thymin-1-yl	$OCH_2P(O)(OH)_2$
7e	Uracil-1-yl	$OCH_2P(O)(OH)_2$

Figure 1.



10a B = Adenin-9-yl
10b B = Thymin-1-yl

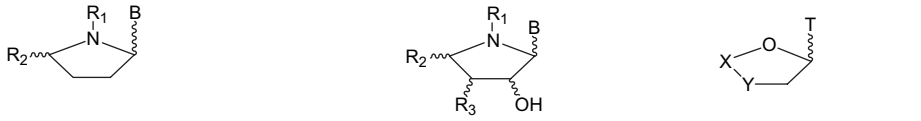
11 R_1 = H, CH_3, Ph_2CH

Comp.	R_1
12a	H
12b	C_4H_9
12c	$PhCH_2OCO$

Comp.	B	R_1
12d	Thymin-1-yl	Boc
12e	Uracil-1-yl	Boc
12f	Cytosin-1-yl	Boc
12g	Thymin-1-yl	Ac

Figure 2.

biologically active, non-nucleoside compounds.[34–44] In our previous paper,[45] we published the conditions for a reliable synthesis of pyrrolidine nucleosides **28d** and **28f** by nucleophilic displacement of the mesyloxy group in *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine by pyrimidine nucleobases, giving an excess of the desired 1-*N* regioisomer over the undesired 2-*O* isomer in a good overall yield. Herein, we report the synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of nucleobases **28a**–**28f** and **36**, **38**, respectively, as nucleoside analogues and also as the

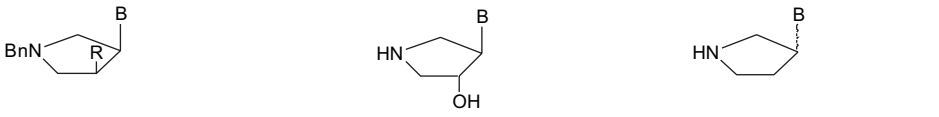


Comp.	B	R_1	R_2
12h	Thymin-1-yl	Boc	CH_2OH
12i	Uracil-1-yl	Boc	CH_2OH
12j	Cytosin-1-yl	Boc	CH_2OH
12k	Thymin-1-yl	Boc	CH_2OH
12l	Uracil-1-yl	Boc	H
12m	Thymin-1-yl	BnOCO	CH_2OH
12n	Thymin-1-yl	Ac	CH_2OH

Comp.	B	R_1	R_2	R_3
13a	Thymin-1-yl	Ac	CH_2OH	H
13b	Thymin-1-yl	Ac	CH_2OH	OH
13c	Thymin-1-yl	Ac	CH_3	OH
13d	Uracil-1-yl	Boc	CH_2OH	OH

14 X = CHOH, Y = NCOO-L-Menthyl
15 X = NH, Y = CH_2

Figure 3.



16a B = Thymin-1-yl; R = H
16b B = Uracil-1-yl; R = H
17a B = Thymin-1-yl; R = OH
17b B = Uracil-1-yl; R = OH

18a B = Thymin-1-yl
18b B = Uracil-1-yl
18c B = Adenin-9-yl

28a B = Adenin-9-yl
28b B = Guanin-9-yl
28c B = 2,6-Diaminopurin-9-yl
28d B = Thymin-1-yl
28e B = Uracil-1-yl
28f B = Cytosin-1-yl

Figure 4.

compounds for potential further derivatization. In addition, an improved preparation of starting (*RS*)- and (*S*)-*N*-protected-3-pyrrolidinol derivatives is described in detail.

2. Results and discussion

2.1. Improvement of the synthesis of 3-pyrrolidinols

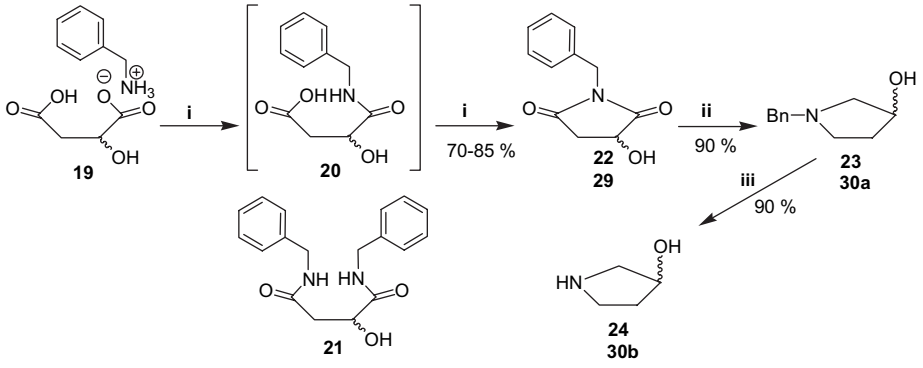
There are several approaches for the synthesis of *N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**) described in the literature (Schemes 1 and 3). Currently used procedures for the synthesis of *N*-benzyl-3-hydroxypyrrolidine-2,5-diones (**22**, **29**)[46–54] consist of azeotropic removal of water from the mixture of malic acid (**19**) and benzylamine in refluxing xylene[46,53] or in ethanol at 160 °C.[47–49,52,54] We repeated the 'xylene' procedure several times with varying yields of **22**. We observed that under experimental conditions, benzylamine distilled with xylene and the heterogeneous reaction mixture turned dark. The addition of benzylamine, to compensate for any loss during the azeotropic distillation, did not improve the yield of *N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**). An excess of benzylamine in the reaction mixture caused a drop in the yield of **22** due to the formation of dibenzylamide **21** as undesired product. Undoubtedly, the five-membered benzylimide ring of **22** was readily opened by benzylamine to form compound **21**. A similar ring-opening reaction of *N*-benzylsuccinimide, but with ammonia, has already been described by Werner.[55]

Concerning the mechanism of the benzylimide ring closure, a two-step reaction seems to be plausible. The first, rate-limiting step of the whole reaction involves thermal dehydration of the monobenzylammonium salt of malic acid **19**, resulting in formation of benzylamide **20**, which then undergoes a ring closure to yield benzylimide **22**. If the acid and benzylamine are mixed in xylene, a suspension is obtained, and monobenzylammonium salt **19** is formed very slowly. Concerning these observations, we elaborated a procedure giving consistently high yields of benzylimide **22**. Thus, first the monobenzylammonium salt of racemic or (*S*)-malic acid was prepared in aqueous methanol and then heated in refluxing xylene in the Dean–Stark apparatus. In contrast to the original procedure,[46,53] a clear homogeneous solution was obtained within several minutes of heating. Further heating (24 h) followed by crystallization of **22** (or **29**) from hot benzene afforded pure product in ~70% yield.

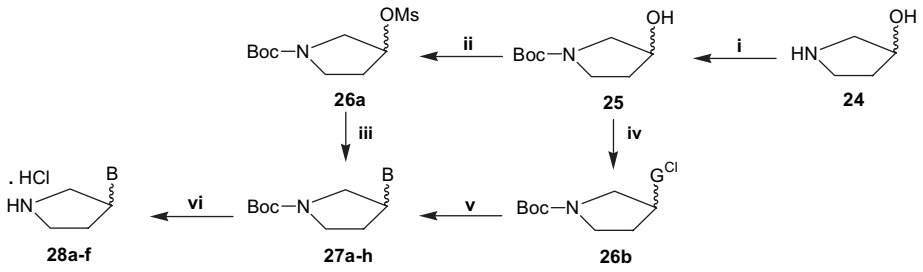
The reduction of benzylimide **22** and **29** to benzylamide **23** and **30a**, respectively, proceeded smoothly by treatment with diborane generated in situ from $NaBH_4$ and iodine in THF.[56] Desalting of *N*-benzyl-3-pyrrolidinol (**23**, **30a**) on Dowex 50W (H^+) followed by removal of *N*-benzyl group using catalytic hydrogenation afforded pure 3-pyrrolidinol (**24** and **30b**) (Schemes 1 and 3).

2.2. Synthesis of racemic 3-pyrrolidinyl derivatives of nucleobases

3-Pyrrolidinol **24** was first transformed into *N*-Boc derivative **25** and this compound was mesylated to derivative **26a**, which was used for the reaction with nucleobases (Scheme 2). For alkylation reactions of purine and pyrimidine nucleobases with **26a**, we selected DMSO as a solvent providing better yields of pyrrolidine derivatives of nucleobases than DMF. Thus, the alkylation of adenine and 2,6-diaminopurine with **26a** proceeded smoothly in the presence of Cs_2CO_3 as a base providing high yields of the desired 9-substituted compounds **27a** and **27c**. In contrast, the alkylation of sodium salts of pyrimidine nucleobases in DMSO led to a mixture of the desired 1-*N* substituted compounds **27e**–**27g** and the undesired 2-*O*-substituted derivatives as side products.[45] The Mitsunobu reaction of 2-amino-6-chloropurine with *N*-*tert*-butoxycarbonyl-3-pyrrolidinol (**25**) provided higher yield of **26b** than the alkylation of the same nucleobase with mesyl derivative **26a**. The obtained 2-amino-6-chloro-purine derivative **26b** was hydrolyzed in aqueous NaOH to afford guanine compound **27b**. The alkylation of sodium salt of cytosine by mesyl derivative **26a** in DMSO provided high overall yields of 1-*N*- and 2-*O*-substituted derivatives **27f** and **27g** (Scheme 2). The deprotection of *N*-*tert*-butoxycarbonyl derivatives **27a**–**27f** was accomplished by treatment with 20% TFA in dichlormethane and the crude products **28a**–**28f** were deionized on Dowex 50W. The obtained pyrrolidine nucleosides **28a**–**28f** were transformed into stable hydrochlorides.



Scheme 1. Synthesis of 3-pyrrolidinol.



In formulae **27** and **28**
a = Adenin-9-yl
b = Guanin-9-yl
c = 2,6-Diaminopurin-9-yl
d = Thymin-1-yl
e = Uracil-1-yl
f = Uracil-2,4-di-*O*-yl
g = Cytosin-1-yl
h = Cytosin-2-*O*-yl

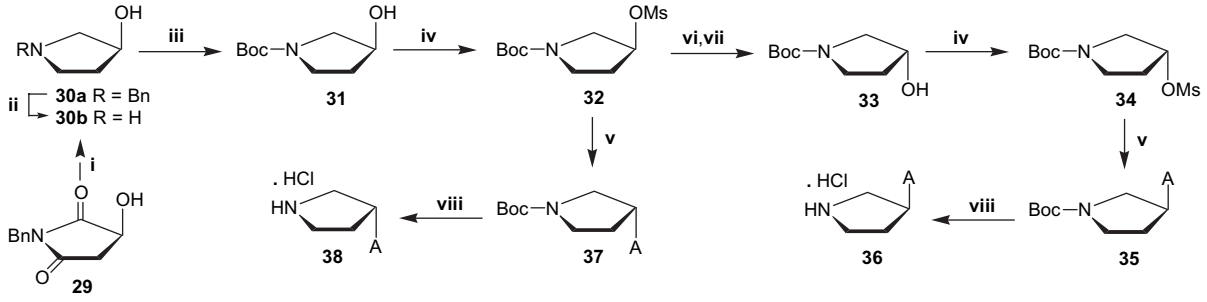
(**i**) Di(*tert*-butyl)dicarbonate, $NaHCO_3$ in *aq* dioxane;
(**ii**) MsCl, pyridine, DCM;
(**iii**) DMSO, NaH or Cs_2CO_3, base;
(**iv**) 2-amino-6-chloropurine, Ph_3P, DIAD, THF;
(**v**) 2-amino-6-chloro-purine derivative **26b**, 1M NaOH in *aq* dioxane;
(**vi**) a) 20% TFA in DCM, b) 1M HCl in diethylether

Scheme 2. Synthesis of racemic 3-pyrrolidinyl derivatives of nucleobases.

2.3. Synthesis of enantiomeric 3-pyrrolidinyl derivatives of adenine

Starting from (*S*)-malic acid (Fluka; information on enantiomeric purity is unavailable), we prepared (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**32**) via intermediates **30b** and **31** (Scheme 3). Inversion of the configuration on the C3-atom of **32**, bearing the mesyloxy group, was achieved by heating with sodium acetate in DMF. Treatment of the product with methanolic ammonia afforded 3-hydroxypyrrolidine derivative **33**, and its mesylation provided (*R*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**34**). Both mesyl derivatives **32** and **34** were subjected to the reaction with adenine in DMSO in the presence of Cs_2CO_3. The obtained (*S*)- and (*R*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) and (**37**), respectively, were deprotected to afford the derivatives **36** and **38**.

The enantiomeric purity of compounds **35** and **37** was checked on the cyclodextrin chiral HPLC column (ChiraDex, Merck). The results of analysis of the enantiomers **35** and **37** are shown in Figures 5 and 6, respectively, while Figure 7 shows the HPLC pattern of a mixture of the enantiomers **35** and **37**. Since the preparation of adenine compounds **35** and **37** started from the same chiral precursor **32**, and the reaction pathways to **35** and **37** included two nucleophilic displacements in the former case and one in the latter, we can conclude that the nucleophilic displacement of the mesyloxy group in compounds **32** and **34** must proceed with inversion, not retention of the configuration. In the latter case we would have obtained identical peaks on chiral HPLC. For the double inversion (**32**→**33** and **34**→**35**; Fig. 5) and for the single inversion (**32**→**37**; Fig. 6) of the configuration we found about 85% and 90% enantiomeric purities of the products **35** and **37**, respectively. Since there is 5% difference in the content of minor enantiomer, one can conclude that the increased amount of the minor enantiomer in compound **35** has to come from the displacement of the mesyloxy group for acetate moiety in the reaction **32**→**33** (Scheme 3). If this reaction is accompanied by a partial racemization then also the



(**i**) $NaBH_4$, I_2, THF;
(**ii**) Pd/C, Acetic acid, H_2 (*g*);
(**iii**) Di(*tert*-butyl)dicarbonate, $NaHCO_3$ in *aq* dioxane;
(**iv**) MsCl, pyridine, DCM;
(**v**) DMSO, Cs_2CO_3;
(**vi**) AcONa, DMF;
(**vii**) sat. NH_3 in MeOH;
(**viii**) a) 20% TFA in DCM, b) 1M HCl in diethylether

Scheme 3. Synthesis of enantiomeric 3-pyrrolidinyl derivatives of adenine.

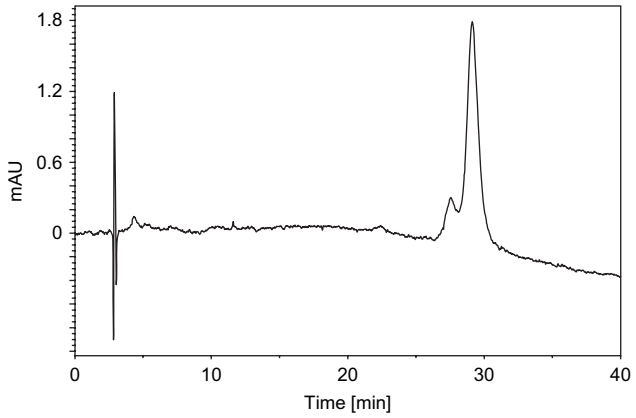


Figure 5. Chiral HPLC analysis: enantiomeric purity of (*S*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) (double inversion **32**→**33** and **34**→**35**).

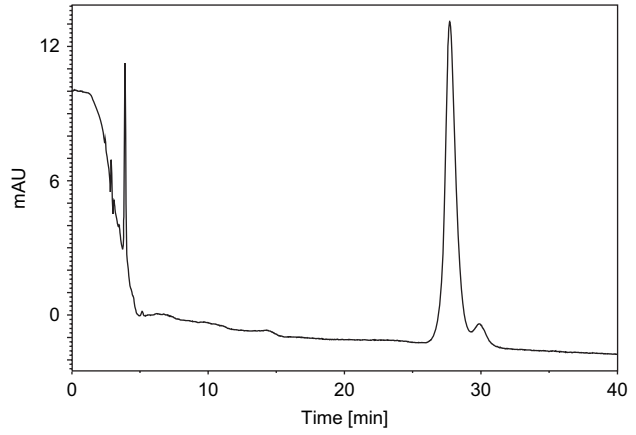


Figure 6. Chiral HPLC analysis: enantiomeric purity of (*R*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**37**) (single inversion **32**→**37**).

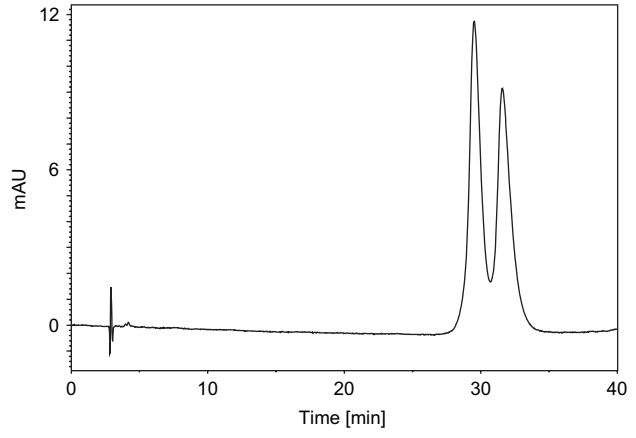


Figure 7. Chiral HPLC analysis: resolution of a mixture of **35** and **37** (the same pattern was obtained for racemic mixture **27**).

displacement of the mesyloxy group for adenine moiety in both reactions **32**→**37** and **34**→**35** should proceed with partial racemization but to the identical extent for both reactions. Nevertheless, potential presence of small amount of (*R*)-enantiomer in the starting (*S*)-malic acid (which cannot be excluded) and/or C3 racemization during thermal dehydration of benzylammonium salt of (*S*)-malic acid to dione **22** (Scheme 2) cannot influence, in any case, this 5% difference in the content of minor enantiomers (Figs. 5 and 6). This analysis suggests that mainly both nucleophilic displacements are responsible for found extent of racemization.

2.4. Biological activity

The cytostatic activity of analogues **28a–28f**, **32**, **34** was examined on L1210, L929, and HeLa S3 cell lines. The antiviral activity against DNA viruses was evaluated using infected E_6SM, HeLa, and Vero cell cultures. No significant activity was found.

3. Conclusion

In this paper, we report the synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of purine and pyrimidine nucleobases as novel nucleoside analogues **28a–28f**, **36**, and **38**. These can be used for further derivatization at the pyrrolidine nitrogen atom in an attempt to modulate their potential biological activity. We have improved the synthesis of racemic and enantiomeric *N*-benzyl-3-pyrrolidinols with respect to reproducibility and high yields of these compounds. The racemic, as well as both enantiomeric *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines **26a**, **32**, **34** as key synthons for alkylation of nucleobases have been prepared in high yields after five steps. We have elaborated conditions providing acceptable yields for both 1-substituted pyrimidine and 9-substituted purine compounds. Using the same chiral precursor **32** for the preparation of enantiomeric adenine compounds **35** and **37**, which provided two different peaks on chiral HPLC, we proved that the nucleophilic displacement of 3-mesyloxy group in *N*-Boc-3-mesyloxypyrrolidines proceeded with inversion, not retention of the configuration. Concerning the cytostatic and antiviral properties of novel 3-pyrrolidinyl derivatives of nucleobases **28a–28f**, **36**, **38**, no significant activities were found.

4. Experimental

4.1. General

Unless stated otherwise, all solvents were evaporated at 13 kPa. Products were dried over P_2O_5 at 13 Pa. All chemicals were obtained from commercial suppliers and all used solvents were anhydrous. Chiral HPLC analysis was performed on Alliance HPLC system (Waters) with DAD detector using ChiraDex® column (Merck, 254×4 mm, 5 μm), isocratically in 10% aqueous acetonitrile at flow rate 1 mL/min. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance 400 and Bruker Avance 500 spectrometers (^{1}H at 400 and 500 MHz, ^{13}C at 100.6 and 125.8 MHz, respectively) in DMSO-d_6 and were referenced to the residual solvent signal (δ_H=2.50 ppm, δ_C=39.7 ppm). Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV). Glycerol and thioglycerol were used as matrices.

4.1.1. (*RS*)-*N*-Benzyl-3-hydroxypyrrolidine-2,5-dione (22). Benzylamine (160.7 mL, 1.5 mol) was slowly added to a stirred suspension of racemic malic acid (201.1 g;

1.5 mol) in 50% aqueous methanol (300 mL), and the resulting mixture was stirred at 50 °C until clear solution was obtained. The viscous solution was concentrated in vacuo, xylene (4 L) was added, and the mixture was refluxed in Dean–Stark apparatus at 190 °C in an oil bath for 24 h. During this time, xylene was added in two portions (2×500 mL). The dark brown solution was concentrated in vacuo, the residue was co-evaporated with ethanol (2×500 mL) to remove remaining xylene, and dissolved in refluxing benzene (1000 mL). Then the solution was concentrated in vacuo until crystallization took place. The suspension was left to crystallize overnight in the refrigerator. White crystals were filtered off, washed with cold benzene (2×100 mL), and the filtrates were concentrated for the next crystallization. Yield, 224.6 g (74%, white crystals) of **22**. (*Note: Mother liquor can provide additional 10–15% of the pure product* **22**.) Mp 105–109 °C.

HRMS: for $C_{11}H_{12}NO_3$ $(M+H)^+$ calcd 206.0817, found 206.0815.

^{1}H NMR (400 MHz, DMSO-d_6): 2.48 (dd, 1H, J_{gem}=17.8, $J_{4'b,3'}$=4.4, H-4′b); 3.05 (dd, 1H, J_{gem}=17.8, $J_{4'a,3'}$=8.3, H-4′a); 4.55 (s, 2H, NCH_2); 4.57 (ddd, 1H, $J_{3',4'}$=8.3, 4.4, $J_{3',OH}$=6.7, H-3′); 6.15 (d, 1H, $J_{OH,3'}$=6.7, OH); 7.20–7.40 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, DMSO-d_6): 38.03 (CH_2-4′); 41.36 (NCH_2); 66.51 (CH-3′); 127.60, 127.71 and 128.66 (CH–Ph); 136.29 (*i*-C–Ph); 174.98 (C-5); 178.25 (C-2).

4.1.2. (*RS*)-*N*-Benzyl-3-pyrrolidinol (23). A solution of iodine (95.2 g, 375 mmol) in THF (450 mL) was added dropwise under argon to an ice-cooled, vigorously stirred suspension of $NaBH_4$ (28.4 g, 750 mmol) in a solution of (*RS*)-*N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**) (co-evaporated with THF) (30.8 g, 150 mmol) in THF (700 mL). After completion of iodine addition, the reaction mixture was stirred at rt for 5 d, then cooled to 0 °C, and the excess $NaBH_4$ was decomposed by slowly adding 3 M HCl (143 mL). (*Note: Vigorous gas evolution*.) The reaction mixture was concentrated to about 150 mL and carefully basified with aqueous 2 M NaOH to pH 10 at 0 °C. DCM (500 mL) was added, and the aqueous phase was saturated with solid K_2CO_3 under vigorous stirring. The organic layer was separated, and the aqueous phase extracted once again with DCM (300 mL). The combined organic layers were concentrated in vacuo, and the residue was deionized on Dowex 50W (500 mL) in H^+ form. (*Note: Column of Dowex was first washed with EtOH to remove color impurities*.) The elution with 3% aqueous ammonia afforded a TLC pure compound (detection with ninhydrin), which was co-evaporated with ethanol (2×100 mL) to give 24.7 g (93%) of product **23** as light brown oil.

HRMS: for $C_{11}H_{16}NO$ $(M+H)^+$ calcd 178.1232, found 178.1233.

^{1}H NMR (500 MHz, DMSO-d_6): 1.53 (dddd, 1H, J_{gem}=12.9, $J_{4'b,5'}$=7.8, 5.6, $J_{4'b,3'}$=3.4, H-4′b); 1.98 (ddt, 1H, J_{gem}=12.9, $J_{4'a,5'}$=7.8, 6.5, $J_{4'a,3'}$=7.8, H-4′a); 2.29 (dd, 1H, J_{gem}=9.6, $J_{2'b,3}$=3.8, H-2′b); 2.38 (ddd, 1H, J_{gem}=8.9, $J_{5'b,4'}$=7.8, 5.6, H-5′b); 2.54 (dt, 1H, J_{gem}=8.9, $J_{5'a,4'}$=7.8, 6.5, H-5′a); 2.65 (dd, 1H, J_{gem}=9.6, $J_{2'a,3'}$=6.2, H-2′a); 3.50 and 3.56 (2×d, 2×1H, J_{gem}=13.0, CH_2–Ph); 4.18 (ddt, 1H, $J_{3',4'}$=7.8, 3.4, $J_{3',2'}$=6.2, 3.8, H-3′); 4.54 (br s, 1H, OH); 7.20–7.35 (m, 5H, Ph). ^{13}C NMR (125.8 MHz, DMSO-d_6) for **23a**: 34.64 (CH_2-4′); 52.61 (CH_2-5′); 59.95 (CH_2–Ph); 62.80 (CH_2-2′); 69.59 (CH-3′); 126.91, 128.29 and 128.66 (CH–Ph); 139.44 (*i*-C–Ph).

4.1.3. (*RS*)-3-Pyrrolidinol (24). A solution of *N*-benzyl-3-hydroxypyrrolidine **23a** (26.6 g, 150 mmol) in concentrated acetic acid (900 mL) was treated at rt with hydrogen gas (10 psi) in the presence of 10% palladium on charcoal (2 g) under vigorous stirring for 5 d. The suspension was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was co-evaporated with ethanol (2× 100 mL) and dried in vacuo over P_2O_5 to afford 12.0 g (92%) of product **24** as yellow oil.

EI$^+$: for C_4H_9NO (M^+) calcd 87.0684, found 87.0685.

^{1}H NMR (500 MHz, DMSO-d_6): 1.58 (m, 1H, H-4′b); 1.75 (ddt, 1H, J_{gem}=13.1, $J_{4'a,5'}$=8.6, 8.3, $J_{4'a,3'}$=5.8, H-4′a); 2.67 (ddd, 1H, J_{gem}=11.5, $J_{2'b,3'}$=2.4, $J_{2'b,NH}$=1.0, H-2′b); 2.78 (ddd, 1H, J_{gem}=10.8, $J_{5'b,4'}$=8.6, 4.5, H-5′b); 2.81 (dd, 1H, J_{gem}=11.5, $J_{2'a,3'}$=4.8, H-2′a); 2.93 (dt, 1H, J_{gem}= 10.8, $J_{5'a,4'}$=8.3, 7.8, H-5′a); 4.19 (ddt, 1H, $J_{3',4'}$=5.8, $J_{3',2'}$=4.8, 2.4, H-3′); 4.49 (br s, 2H, NH+OH). ^{13}C NMR (125.8 MHz, DMSO-d_6): 35.11 (CH_2-4′); 44.61 (CH_2-5′); 54.83 (CH_2-2′); 70.60 (CH-3′).

4.1.4. (*RS*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (25). Boc anhydride (36.0 g, 165 mmol) was added to a vigorously stirred suspension of (*RS*)-3-pyrrolidinol (13.1 g, 150 mmol) (**24**) and sodium hydrogen carbonate (126.1 g, 1.5 mol) in 50% aqueous dioxane (750 mL) at rt. After the completion of reaction, the mixture was concentrated, the solids were filtered off, and the filtration cake was washed with ethanol. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (elution with a linear gradient of ethyl acetate in toluene). Yield, 26.4 g (94%, white solid) of **25**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 188.1280.

^{1}H NMR (500 MHz, DMSO-d_6, a mixture of amide isomers, 1:1): 1.39 (s, 9H, *t*-Bu); 1.72 (br m, 1H, H-4′b); 1.84 (br m, 1H, H-4′a); 3.10 (br d, 1H, J_{gem}=11.5, H-2′b); 3.22–3.32 (m, 3H, H-2′a and H-5′); 4.21 (br m, 1H, H-3′); 4.86 (d, 1H, $J_{OH,3'}$=6.5, OH-3′). ^{13}C NMR (125.8 MHz, DMSO-d_6): 28.33 (CH_3–*t*-Bu); 33.04 and 33.80 (CH_2-4′); 43.68 and 43.92 (CH_2-5′); 53.98 and 54.23 (CH_2-2′); 68.59 and 69.43 (CH-3); 78.15 (C–*t*-Bu); 153.82 (CO).

4.1.5. (*RS*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (26a). Mesylchloride (74.4 mL, 961.5 mmol) was added dropwise to a solution of (*RS*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**25**) (24 g, 128.2 mmol) and pyridine (77.4 mL, 961.5 mmol) in DCM (300 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h. The reaction was quenched by pouring onto an ice (100 g), and the organic layer was washed twice with 1 M HCl and saturated solution of sodium hydrogen carbonate. The organic phase was concentrated and the crude product was purified by flash chromatography on silica gel (elution with a linear gradient of

ethyl acetate in toluene). Yield, 29.2 g (85%, yellow foam) of **26a**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1066.

^{1}H NMR (400 MHz, 80 °C, DMSO-d_6, a mixture of amide isomers A:B, 3:2): 1.43 (s, 18H, *t*-Bu-A and *t*-Bu-B); 2.13 (m, 2H, H-4′bA and H-4′bB); 2.18 (dd, 1H, J_{gem}=8.9, $J_{4'a,3'}$=4.6, H-4′aA); 2.21 (dd, 1H, J_{gem}=9.2, $J_{4'a,3'}$=4.6, H-4′aB); 3.19 (s, 6H, CH_3–SO_2–); 3.31 (dd, 1H, J_{gem}=8.4, $J_{5'b,4'b}$=7.0, H-5′bB); 3.34 (dd, 1H, J_{gem}=11.7, $J_{5'b,4'b}$=7.3, H-5′bA); 3.41 (dd, 1H, J_{gem}=11.7, $J_{5'a,4'b}$=3.5, H-5′aA); 3.44 (dd, 1H, J_{gem}=8.4, $J_{5'a,4'b}$=3.6, H-5′aB); 3.49 (dd, 1H, J_{gem}=12.8, $J_{2'b,3'}$=1.8, H-2′bB); 3.50 (dd, 1H, J_{gem}=12.8, $J_{2'b,3'}$=1.8, H-2′bA); 3.55 (dd, 1H, J_{gem}=12.8, $J_{2'a,3'}$=4.3, H-2′aA and H-2′aB); 5.23 (tt, 2H, $J_{3',4'a}$=4.6, 2.4, $J_{3',2'a}$=4.3, 1.8, H-3′A and H-3′B). ^{13}C NMR (100.6 MHz, DMSO-d_6): 27.51 (CH_3–Boc); 31.11 and 31.94 (CH_2-4′); 37.82 (CH_3–SO_2–); 43.44 and 43.63 (CH_2-5′); 51.97 and 52.20 (CH_2-2′); 78.92 (C–Boc); 80.33 and 81.11 (CH-3′); 153.49 and 153.60 (CO).

4.2. General method for alkylation reactions

Prior to use, the nucleobases were dried in vacuo at 50–100 °C for 16 h. A suspension of the nucleobase and Cs_2CO_3 (1.5 equiv for purine nucleobases) or NaH (1.5 equiv for pyrimidine nucleobases) in DMSO (5 mL/mmol) was stirred under argon atmosphere at 100 °C for 20 min. Then, mesyl derivative **26a** (1 equiv) in DMSO (5 mL/mmol) was added and the mixture was stirred at 110 °C. After completion of reaction (~18 h) the mixture was concentrated under vacuum on an oil pump, adsorbed onto column of silica gel and purified by flash chromatography (elution with a linear gradient of ethanol in chloroform) to afford the compounds **27a**–**27f**.

4.2.1. (*RS*)-2-Amino-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-6-chloropurine (26b). *Method A*. A mixture of (*RS*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**25**) (4.3 g, 23 mmol), 2-amino-6-chloro-purine (4.48 g, 29 mmol), and triphenyl phosphine (10.9 g, 41.4 mmol) was co-evaporated twice with THF and suspended in THF (115 mL) under an argon atmosphere at 0 °C. Then, DIAD (10.3 mL, 53 mmol) was added under stirring. The suspension became clear within 5 min. The solution was concentrated, adsorbed onto a column of silica gel, and the compound was eluted with a linear gradient of ethanol in chloroform to afford crude product **26b** (ca. 70%, yellow solid), which was used directly for the preparation of guanine derivative **27b**.

Method B. The 2-amino-6-chloro-purine derivative **26b** was prepared from (*RS*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (0.8 g, 3 mmol) and 2-amino-6-chloropurine (0.8 g, 4.5 mmol) according to the general method for alkylation, but DMF was used instead of DMSO. Yield, 0.340 g (33%, yellow foam).

HRMS: for $C_{14}H_{20}ClN_6O_2$ $(M+H)^+$ calcd 339.1336, found 339.1327.

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C, a mixture of amide isomers, 1:1): 1.48 (s, 9H, *t*-Bu); 2.36–2.49 (m, 2H, H-4′); 3.45 and 3.58 (2×m, 2×1H, H-5′); 3.71 (dd, 1H, J_{gem}=12.0, $J_{2'b,3'}$=6.9, H-2′b); 3.89 (dd, 1H, J_{gem}=12.0, $J_{2'a,3'}$=6.5, H-2′a); 5.01 (p, 1H, $J_{3',2'}$=6.9, 6.5, $J_{3',4'}$=6.4, H-3′); 5.08 (br s, 2H, NH_2); 7.74 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, $CDCl_3$): 28.42 (CH_3–Boc); 30.54 and 31.48 (CH_2-4′); 43.95 (CH_2-5′); 50.01 and 50.62 (CH_2-2′); 53.22 and 53.85 (CH-3′); 80.30 (C–Boc); 125.47 (C-5); 139.84 (CH-8); 151.59 (C-4); 153.55 (CO); 154.22 (C-6); 158.91 (C-2).

4.2.2. (*RS*)-9-(*N*-*tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (27a). The title compound was prepared from (*RS*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (3.7 g, 14 mmol) and adenine (2.8 g, 20.7 mmol) according to the general method for alkylations provided above. Yield, 3 g (71%, yellow foam).

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1724.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (s, 9H, *t*-Bu); 2.35–2.53 (m, 2H, H-4′); 3.42 (dt, 1H, J_{gem}=10.9, $J_{5'b,4'}$=7.6, H-5′b); 3.56 (ddd, 1H, J_{gem}=10.9, $J_{5'a,4'}$=8.0, 5.5, H-5′a); 3.65 (dd, 1H, J_{gem}=11.1, $J_{2'b,3'}$=6.1, H-2′b); 3.81 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=7.0, H-2′a); 5.08 (p, 1H, $J_{3',2'}$=7.0, 6.1, $J_{3'4'}$=6.0, H-3′); 7.11 (br s, 2H, NH_2); 8.12 (s, 1H, H-8); 8.15 (s, 1H, H-2).

^{13}C NMR (100.6 MHz, DMSO-d_6, 50 °C): 28.16 (CH_3–Boc); 29.99 (CH_2-4′); 44.11 (CH_2-5′); 50.05 (CH_2-2′); 53.12 (CH-3′); 78.73 (C–Boc); 119.20 (C-5); 138.97 (CH-8); 149.53 (C-4); 152.38 (CH-2); 153.54 (CO); 156.09 (C-6).

4.2.3. (*RS*)-9-(*N*-*tert*-Butoxycarbonyl-3-pyrrolidinyl)-guanine (27b). The crude mixture of (*RS*)-2-amino-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-6-chloropurine (**26b**) (prepared by *Method A*) was treated with 600 mL of 1 M NaOH in 30% aqueous dioxane. After 5 d of stirring, the mixture was mixed with Dowex 50 (Et_3NH^+) (500 mL), the suspension was filtered, the resin was washed with ethanol, and the combined filtrates were concentrated. The residue was adsorbed onto silica gel (100 g) and the dried sorbent was transferred onto dry silica gel column, which was eluted with a linear gradient of ethanol in chloroform to give the title compound as a white foam. Yield, 2.6 g (35% calculated for compound **25** from *Method A*).

HRMS: for $C_{14}H_{21}N_6O_3$ $(M+H)^+$ calcd 321.1675, found 321.1678.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.38 and 1.41 (2×s, 9H, *t*-Bu); 2.26–2.42 (m, 2H, H-4′); 3.35 (m, 1H, H-5′b); 3.45–3.57 (m, 2H, H5′a and H-2′b); 3.72 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=6.8, H-2′a); 4.82 (m, 1H, H-3′); 6.49 (br s, 2H, NH_2); 7.70 (s, 1H, H-8); 10.25 (br s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.30 (CH_3–Boc); 29.50 and 30.43 (CH_2-4′); 44.08 and 44.28 (CH_2-5′); 50.15 and 50.40 (CH_2-2′); 52.38 and 53.04 (CH-3′); 78.95 (C–Boc); 117.10 (C-5); 135.33 and 135.44 (CH-8); 151.29 (C-4); 153.64 (CO and C-6); 156.09 (C-2).

4.2.4. (*RS*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)-2,6-diaminopurine (27c). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (1.3 g, 5 mmol) and 2,6-diaminopurine (1.1 g, 7.5 mmol) according to the general method for alkylation. Yield, 1.2 g (76%, white foam).

HRMS: for $C_{14}H_{22}N_7O_2$ $(M+H)^+$ calcd 320.1835, found 320.1845.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (s, 9H, *t*-Bu); 2.27–2.48 (m, 2H, H-4′); 3.40 (m, 1H, H-5′b); 3.51 (ddd, 1H, J_{gem}=11.0, $J_{5'a,4'}$=8.0, 5.5, H-5′a); 3.58 (dd, 1H, J_{gem}=11.0, $J_{2'b,3'}$=6.2, H-2′b); 3.74 (dd, 1H, J_{gem}=11.0, $J_{2'a,3'}$=7.0, H-2′a); 4.86 (br p, 1H, $J_{3',2'}$=7.0, 6.2, $J_{3',4'}$=6.0, H-3′); 5.69 and 6.57 (2×br s, 2×2H, NH_2); 7.69 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.33 (CH_3–Boc); 29.39 and 30.37 (CH_2-4′); 44.16 and 44.36 (CH_2-5′); 50.00 and 50.32 (CH_2-2′); 52.22 and 52.90 (CH-3′); 78.94 (C–Boc); 113.10 (C-5); 135.45 and 135.54 (CH-8); 151.88 (C-4); 153.71 (CO); 156.38 (C-6); 160.37 (C-2).

4.2.5. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)thymine (27d). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (6.0 g, 22.6 mmol) and thymine (4.3 g, 34 mmol) according to the general method for alkylation. Yield, 2.6 g (40%, yellow foam).

HRMS: for $C_{14}H_{22}N_3O_4$ $(M+H)^+$ calcd 296.1610, found 296.1612.

^{1}H NMR (500 MHz, DMSO-d_6, 30 °C, a mixture of amide isomers, 1:1): 1.40 (br s, 9H, *t*-Bu); 1.77 (d, 3H, *J*=1.2, CH_3-5); 2.13 (br m, 2H, H-4′); 3.22–3.31 (br m, 2H, H-5′b and H-2′b); 3.46 (dt, 1H, J_{gem}=10.8, $J_{5'a,4'}$=6.3, H-5′a); 3.58 (br m, 1H, H-2′a); 4.92 (br m, 1H, H-3′); 7.50 (br m, 1H, H-6); 11.23 (br s, 1H, NH).

^{13}C NMR (125.8 MHz, DMSO-d_6): 12.20 (CH_3-5); 28.25 and 28.33 (CH_3–Boc); 29.29 (CH_2-4′); 43.68 and 43.92 (CH_2-5′); 48.51 and 48.77 (CH_2-2′); 53.27 and 53.80 (CH-3′); 78.80 (C–Boc); 109.43 (C-5); 137.56 (CH-6); 151.08 (C-2); 153.55 (CO); 163.79 (C-4).

4.2.6. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)uracil (27e) and (*RS*)-2,4-bis-*O*-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)uracil (27f). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxy-pyrrolidine (**26a**) (7.4 g, 28 mmol) and uracil (4.7 g, 42 mmol) according to the general method for alkylation. Yield, 2.6 g (32%, yellow foam) of **27e** and 1.3 g (10%, yellow foam) of **27f**.

27e: HRMS: for $C_{13}H_{20}N_3O_4$ $(M+H)^+$ calcd 282.1454, found 282.1452.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (br s, 9H, *t*-Bu); 2.06–2.23 (br m, 2H, H-4′); 3.24–3.37 (br m, 2H, H-5′b and H-2′b); 3.44 (ddd, 1H, J_{gem}=13.4, $J_{5'a,4'}$=7.9, 5.1, H-5′a); 3.61 (dd, 1H, J_{gem}=11.3, $J_{2'a,3'}$=7.4, H-2′a); 4.90 (br p, 1H, $J_{3',2'}$=7.4, 7.0, $J_{3'4'}$=7.0, H-3′); 5.57 (d, 1H, $J_{5,6}$=8.0, H-5); 7.56 (d, 1H, $J_{6,5}$=8.0, H-6); 11.18 (br s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.31 (CH_3–Boc); 28.94 and 29.45 (CH_2-4′); 44.00 and 44.27 (CH_2-5′); 48.82 and 49.06 (CH_2-2′); 53.82 and 54.47 (CH-3′); 78.90 (C–Boc); 101.81 (CH-5); 142.15 (CH-6); 151.19 (C-2); 153.61 (CO); 163.32 (C-4).

27f: HRMS: for $C_{22}H_{35}N_4O_6$ $(M+H)^+$ calcd 451.2557, found 451.2556.

^{1}H NMR (400 MHz, DMSO-d_6): 1.38 and 1.39 (2×br s, 2×9H, *t*-Bu); 2.00–2.25 (br m, 4H, H-4′); 3.25–3.48 (br m, 6H, H-2′b and H-5′); 3.52–3.64 (br m, 2H, H-2′a); 5.42 and 5.52 (2×br m, 2×1H, H-3′), 6.57 (d, 1H, $J_{5,6}$=5.7, H-5); 8.30 (d, 1H, $J_{6,5}$=5.7, H-6).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.39 (CH_3–Boc); 30.30 and 31.08 (CH_2-4′); 43.87, 43.93, 44.08 and 44.17 (CH_2-5′); 51.55, 51.71, 51.75 and 51.90 (CH_2-2′); 75.27, 75.76, 76.07 and 76.62 (CH-3′); 78.85 and 78.90 (C–Boc); 102.79 (CH-5); 153.79 (CO); 159.73 (CH-6); 163.90 (C-2); 170.09 (C-4).

4.2.7. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)-cytosine (27g) and (*RS*)-2-*O*-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)cytosine (27h). The title compounds were prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxy-pyrrolidine (**26a**) (8.7 g, 33 mmol) and cytosine (5.5 g, 50 mmol) according to the general method for alkylation. Yield, 5.0 g (54%, yellow foam) of **27g** and 3.6 g (39%, yellow foam) of **27h**.

27g: HRMS: for $C_{13}H_{21}N_4O_3$ $(M+H)^+$ calcd 281.1614, found 281.1610.

^{1}H NMR (500 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (br s, 9H, *t*-Bu); 2.03–2.19 (br m, 2H, H-4′); 3.23 (dd, 1H, J_{gem}=11.2, $J_{2'b,3'}$=6.2, H-2′b); 3.32 (dt, 1H, J_{gem}=10.9, $J_{5'b,4'}$=7.5, H-5′b); 3.43 (ddd, 1H, J_{gem}=10.9, $J_{5'a,4'}$=8.2, 5.4, H-5′a); 3.60 (dd, 1H, J_{gem}=11.2, $J_{2'a,3'}$=7.4, H-2′a); 4.90 (p, 1H, $J_{3',4'}$=7.6, $J_{3',2'}$=7.4, 6.2, H-3′); 5.71 (d, 1H, $J_{5,6}$=7.4, H-5); 6.92 (br s, 2H, NH); 7.49 (d, 1H, $J_{6,5}$=7.4, H-6).

^{13}C NMR (125.8 MHz, DMSO-d_6, 50 °C): 28.14 (CH_3–Boc); 28.54 (CH_2-4′); 43.96 (CH_2-5′); 49.38 (CH_2-2′); 54.66 (CH-3′); 78.60 (C–Boc); 93.82 (CH-5); 142.17 (CH-6); 153.49 (CO); 155.58 (C-2); 165.40 (C-4).

27h: HRMS: for $C_{13}H_{21}N_4O_3$ $(M+H)^+$ calcd 281.1614, found 281.1623.

^{1}H NMR (500 MHz, DMSO-d_6, 50 °C): 1.40 (br s, 9H, *t*-Bu); 2.00 (br m, 2H, H-4′b); 2.11 (br m, 2H, H-4′a); 3.30–3.37 (br m, 2H, H-2′b and H-5′b); 3.41 (ddd, 1H, J_{gem}=10.5, $J_{5'a,4'}$=8.8, 3.2, H-5′a); 3.53 (br dd, 1H, J_{gem}=12.3, $J_{2'a,3'}$=4.6, H-2′a); 5.34 (br m, 1H, H-3′); 6.10 (d, 1H, $J_{5,6}$=5.7, H-5); 6.71 (br s, 2H, NH_2); 7.85 (d, 1H, $J_{6,5}$=5.7, H-6).

^{13}C NMR (125.8 MHz, DMSO-d_6, 50 °C): 28.16 (CH_3–Boc); 30.69 (CH_2-4′); 43.83 (CH_2-5′); 51.69 (CH_2-2′);

73.92 (CH-3′); 78.38 (C–Boc); 99.58 (CH-5); 153.61 (CO); 156.17 (CH-6); 164.17 (C-2); 165.46 (C-4).

4.2.8. (*RS*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (28a). (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**27a**) (3.0 g, 10 mmol) was treated with 20% (v/v) TFA in DCM (100 mL) for 1 d. Pyrrolidine derivative was deionized on Dowex 50 (H^+ form) as described previously, treated with 1 M HCl in MeOH (50 mL) for 30 min, and the solution was concentrated in vacuo. Obtained solid residue was co-evaporated several times with methanol and the compound was freeze-dried from aqueous solution to give dihydrochloride salt. Yield, 1.8 g (66%, white powder).

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1200.

ν_{max}(KBr) 3350 (m), 3301 (s), 3119 (s, br), 2746 (w), 1674 (vs), 1647 (s), 1600 (vs),1570 (s), 1535 (m), 1480 (s), 1421 (s), 1415 (s), 1373 (s), 1331 (s), 1307 (s), 1229 (m), 845 (m), 798 (m), 728 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 2.34 (dddd, 1H, J_{gem}=13.5, $J_{4'b,5'}$=8.1, 6.9, $J_{4'b,3'}$=5.6, H-4′b); 2.49 (dtd, 1H, J_{gem}=13.5, $J_{4'a,5'}$=8.2, 6.5, $J_{4'a,3'}$=7.9, H-4′a); 3.30 (ddd, 1H, J_{gem}=11.5, $J_{5'b,4'}$=8.2, 6.9, H-5′b); 3.51 (ddd, 1H, J_{gem}=11.5, $J_{5'a,4'}$=8.1, 6.5, H-5′a); 3.58 (dd, 1H, J_{gem}=12.3, $J_{2'b,3'}$=5.4, H-2′b); 3.64 (dd, 1H, J_{gem}=12.3, $J_{2'a,3'}$=7.4, H-2′a); 5.25 (tt, 1H, $J_{3',4'}$=7.9, 5.6, $J_{3',2'}$=7.4, 5.4, H-3′); 7.31 (br s, 2H, NH_2); 8.15 (s, 1H, H-2); 8.31 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, DMSO-d_6): 30.69 (CH_2-4′); 44.48 (CH_2-5′); 49.10 (CH_2-2′); 53.26 (CH-3′); 119.28 (C-5); 139.81 (CH-8); 149.25 (C-4); 152.53 (CH-2); 156.30 (C-6).

4.2.9. (*RS*)-9-(3-Pyrrolidinyl)guanine dihydrochloride (28b). The title compound was prepared from (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-guanine (**27b**) (1.5 g, 4.7 mmol) according to the procedure described for compound **28a**. Yield, 1.2 g (84%, white powder).

HRMS: for $C_9H_{13}N_6O$ $(M+H)^+$ calcd 221.1151, found 221.1154.

ν_{max}(KBr) 3299 (m), 3112 (s, br), 2756 (m, br), 1720 (s), 1656 (vs), 1606 (s), 1536 (w), 1377 (m), 1162 (w), 766 (m), 732 (w), 674 (w).

^{1}H NMR (500 MHz, DMSO-d_6): 2.31 (dddd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.2, 6.4, $J_{4'b,3'}$=4.1, H-4′b); 2.54 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=8.6, 6.8, H-4′a); 3.32 (ddd, 1H, J_{gem}=11.9, $J_{5'b,4'}$=8.6, 6.4, H-5′b); 3.54–3.73 (m, 3H, H-4′ and H-5′a); 5.22 (tt, 1H, $J_{3',4'}$=8.8, 4.1, $J_{3',2'}$=7.4, 3.9, H-3′); 7.23 (br s, 2H, NH_2); 8.82 (s, 1H, H-8); 9.25, 9.83 and 11.56 (3×br s, 3×1H, NH).

^{13}C NMR (125.8 MHz, DMSO-d_6): 31.63 (CH_2-4′); 44.74 (CH_2-5′); 49.19 (CH_2-2′); 54.83 (CH-3′); 111.00 (C-5); 136.92 (CH-8); 149.81 (C-4); 154.77 (C-6); 155.25 (C-2).

4.2.10. (*RS*)-2,6-Diamino-9-(3-pyrrolidinyl)purine trihydrochloride (28c). The title compound was prepared from (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-2,6-diaminopurine (**27c**) (2.3 g, 7.1 mmol) according to the procedure described for compound **28a**. Yield, 1.7 g (73%, white powder).

HRMS: for $C_9H_{14}N_7$ $(M+H)^+$ calcd 220.1311, found 220.1321.

ν_{max}(KBr) 3318 (s, br), 3099 (s, vbr), 2942 (s, vbr, sh), 2738 (m, br), 1705 (s), 1686 (s, sh), 1636 (vs), 1612 (s), 1593 (s, sh), 1570 (m, sh), 1532 (m, w), 1515 (w, sh), 1480 (m), 1414 (m), 1345 (m), 1205 (w), 790 (w), 658 (w).

^{1}H NMR (400 MHz, DMSO-d_6): 2.20 (dddd, 1H, J_{gem}=11.3, $J_{4'b,5'}$=8.2, 6.9, $J_{4'b,3'}$=4.4, H-4′b); 2.48 (dtd, 1H, J_{gem}=11.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=8.2, 6.6, H-4′a); 3.32 (br m, 1H, H-5′b); 3.55 (br m, 1H, H-5′a); 3.61 (br m, 2H, H-2′); 5.16 (tt, 1H, $J_{3',4'}$=8.8, 4.4, $J_{3',2'}$=6.8, 4.3, H-3′); 7.09 (br s, 2H, NH_2); 8.09 (s, 1H, H-8); 8.10 (br s, 2H, NH_2); 9.52 and 9.96 (2×br s, 2H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 31.03 (CH_2-4′); 44.43 (CH_2-5′); 49.06 (CH_2-2′); 53.20 (CH-3′); 112.20 (C-5); 138.89 (CH-8); 151.03 (C-4); 157.43 (C-6); 160.14 (C-2).

4.2.11. (*RS*)-1-(3-Pyrrolidinyl)thymine hydrochloride (28d). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)thymine (**27d**) (2.6 g, 8.8 mmol) according to the procedure described for compound **28a**. Yield, 1.2 g (73%, white powder).

HRMS: for $C_9H_{14}N_3O_2$ $(M+H)^+$ calcd 196.1086, found 196.1095.

ν_{max}(KBr) 3331 (m), 3064 (m), 1694 (vs), 1673 (vs), 1649 (vs), 1605 (m, sh), 1481 (s), 1438 (s, sh), 1398 (s), 1379 (m), 1275 (s), 760 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 1.78 (d, 3H, J=1.2, CH_3-5); 2.10 (dq, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.9, 7.4, $J_{4'b,3'}$=7.4, H-4′b); 2.31 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=7.8, 4.7, H-4′a); 3.17 (br m, 1H, H-5′b); 3.32 (br m, 1H, H-2′b); 3.40–3.53 (br m, 2H, H-2′a and H-5′a); 5.02 (tdd, 1H, $J_{3',2'}$=8.8, 6.3, $J_{3',4'}$=8.8, 7.4, H-3′); 7.77 (q, 1H, J=1.2, H-6); 7.48 (br s, 2H, +NH_2); 11.36 (s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 12.19 (CH_3-5); 28.99 (CH_2-4′); 44.54 (CH_2-5′); 47.12 (CH_2-2′); 54.81 (CH-3′); 109.61 (C-5); 139.09 (CH-6); 151.13 (C-2); 164.03 (C-4).

4.2.12. (*RS*)-1-(3-Pyrrolidinyl)uracil hydrochloride (28e). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)uracil (**27e**) (1.2 g, 4.3 mmol) according to the procedure described for compound **28a**. Yield, 0.763 g (93%, yellow powder).

HRMS: for $C_8H_{12}N_3O_2$ $(M+H)^+$ calcd 182.0930, found 182.0939.

ν_{max}(KBr) 3339 (s), 3089 (m), 3054 (m), 1766 (m), 1695 (vs, vbr), 1625 (s), 1531 (m), 1408 (s), 992 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 1.66 (dddd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.1, 6.8, $J_{4'b,3'}$=4.4, H-4′b); 2.11 (dtd, 1H, J_{gem}=13.3,

$J_{4'a,3'}$=8.9, $J_{4'a,5'}$=8.4, 5.5, H-4′a); 2.76 (ddd, 1H, J_{gem}=10.5, $J_{5'b,4'}$=8.4, 6.8, H-5′b); 2.77 (dd, 1H, J_{gem}=11.2, $J_{2'b,3'}$=3.8, H-2′b); 2.99 (ddd, 1H, J_{gem}=10.5, $J_{5'a,4'}$=8.1, 5.5, H-5′a); 3.00 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=7.4, H-2′a); 4.85 (ddt, 1H, $J_{3',4'}$=8.9, 4.4, $J_{3',2'}$=7.4, 3.8, H-3′); 5.56 (d, 1H, $J_{5,6}$=8.0, H-5); 7.70 (d, 1H, $J_{6,5}$=8.0, H-6).

^{13}C NMR (100.6 MHz, DMSO-d_6): 31.81 (CH_2-4′); 45.81 (CH_2-5′); 51.89 (CH_2-2′); 55.53 (CH-3′); 101.59 (CH-5); 142.81 (CH-6); 151.22 (C-2); 163.42 (C-4).

4.2.13. (*RS*)-1-(3-Pyrrolidinyl)cytosine dihydrochloride (28g). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)cytosine (**27g**) (5 g, 17.8 mmol) according to the procedure described for compound **28a**. Yield, 2.9 g (65%, white powder).

HRMS: for $C_8H_{13}N_4O$ $(M+H)^+$ calcd 181.1089, found 181.1087.

ν_{max}(KBr) 3350 (m, sh), 3294 (m), 3133 (m), 2753 (m), 1705 (s), 1671 (vs), 1645 (s, sh), 1628 (s, sh), 1526 (m), 1413 (m), 1300 (m), 1213 (w), 780 (w).

^{1}H NMR (400 MHz, DMSO-d_6): 2.15 (dtd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.4, $J_{4'b,3'}$=6.6, H-4′b); 2.33 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=7.7, 5.0, H-4′a); 3.17 (dt, 1H, J_{gem}=11.2, $J_{5'b,4'}$=8.4, 7.7, H-5′b); 3.36 (dd, 1H, J_{gem}=12.5, $J_{2'b,3'}$=5.4, H-2′b); 3.45 (ddd, 1H, J_{gem}=11.2, $J_{5'a,4'}$=8.3, 5.0, H-5′a); 3.46 (dd, 1H, J_{gem}=12.5, $J_{2'a,3'}$=8.5, H-2′a); 4.96 (tt, 1H, $J_{3',4'}$=8.8, 6.6, $J_{3',2'}$=8.5, 5.4, H-3′); 5.97 (d, 1H, $J_{5,6}$=7.6, H-5); 8.01 (d, 1H, $J_{6,5}$=7.6, H-6); 8.08, 8.74, 9.47 and 9.60 (4×br s, 4×1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.95 (CH_2-4′); 44.67 (CH_2-5′); 47.43 (CH_2-2′); 57.36 (CH-3′); 94.12 (CH-5); 146.68 (CH-6); 151.40 (C-2); 162.49 (C-4).

4.2.14. (*S*)-*N*-Benzyl-3-hydroxypyrrolidine-2,5-dione (29). The title compound was prepared from (*S*)-malic acid (201.1 g; 1.5 mol) according to the procedure described for compound **22**. Yield, 223 g (73%, white crystals) of **29**. Mp 94–97 °C.

HRMS: for $C_{11}H_{12}NO_3$ $(M+H)^+$ calcd 206.0817, found 206.0808.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **22**.

4.2.15. (*S*)-*N*-Benzyl-3-pyrrolidinol (30a). The title compound was prepared from (*S*)-*N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**29**) (30.8 g, 150 mmol) according to the procedure described for compound **23**. Yield, 24.4 g (92%, yellowish oil) of **30a**.

HRMS: for $C_{11}H_{16}NO$ $(M+H)^+$ calcd 178.1232, found 178.1236.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **23**.

4.2.16. (*S*)-3-Pyrrolidinol (30b). The title compound was prepared from (*S*)-*N*-benzyl-3-hydroxypyrrolidine (**30a**) (26.6 g, 150 mmol) according to the procedure described for compound **24**. Yield, 11.8 g (90%, yellowish oil) of **30b**.

EI$^+$: for C_4H_9NO M^+ calcd 87.0684, found 87.0684.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **24**.

4.2.17. (*S*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (31). The title compound was prepared from (*S*)-3-pyrrolidinol (**30b**) (13.1 g, 150 mmol) according to the procedure described for compound **25**. Yield, 26.0 g (92%, white solid) of **31**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 188.1287.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **25**.

4.2.18. (*S*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (32). The title compound was prepared from (*S*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**31**) (24 g, 128.2 mmol) according to the procedure described for compound **26a**. Yield, 29.2 g (85%, yellowish solid) of **32**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1068.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **26a**.

4.2.19. (*R*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (33). A mixture of (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**31**) (8 g, 30 mmol) and sodium acetate (24.6 g, 300 mmol) in DMF (300 mL) was heated at 110 °C for 3 d. Dark brown solution was concentrated in vacuo, and the crude (*R*)-*N*-*tert*-butyloxycarbonyl-3-acetyloxypyrrolidine was purified on silica gel column (elution with a linear gradient of ethyl acetate in toluene). The obtained product was treated with saturated methanolic ammonia (300 mL) at 0 °C overnight, the solution was evaporated to dryness, the residue was co-evaporated with ethanol (2×30 mL), and the compound **33** was purified by silica gel chromatography (elution with a linear gradient of ethyl acetate in toluene). Yield, 4.2 g (76%, white solid) of **33**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 189.1284.

^{1}H NMR and ^{13}C NMR spectra identical with those of compound **25**.

4.2.20. (*R*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (34). The title compound was prepared from (*R*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**33**) (4 g, 21.8 mmol) according to the procedure described for compound **26a**. Yield, 5.2 g (90%, yellowish solid) of **34**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1067.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **26a**.

4.2.21. (*S*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (35). The title compound was prepared from (*R*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**34**) (5.1 g, 19.3 mmol) according to the procedure described for compound **27a**. Yield, 4 g (68%, white solid) of **35**.

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1726.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **27a**.

4.2.22. (*S*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (36). The title compound was prepared from (*S*)-9-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) (4 g, 13 mmol) according to the procedure described for compound **28a**. Yield, 1.9 g (71%, white solid) of **36**.

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1196.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **28a**.

4.2.23. (*R*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (37). The title compound was prepared from (*S*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**32**) (7.0 g, 26.6 mmol) according to the procedure described for compound **27a**. Yield, 5.5 g (68%, white solid) of **37**.

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1725. ^1H NMR and ^{13}C NMR spectra were identical with those of compound **27a**.

4.2.24. (*R*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (38). The title compound was prepared from (*R*)-9-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**37**) (5.5 g, 18 mmol) according to the procedure described for compound **28a**. Yield, 2.4 g (65%, white solid) of **38**.

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1206.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **28a**.

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One-pot cyclization of dilithiated nitriles with isothiocyanates and epibromohydrin. Synthesis of 2-cyano-1-(hydroxymethyl)-cyclopropanes and 2-cyanomethylidene-4-(hydroxymethyl)-thiazolidines

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Abstract—The cyclization of dilithiated nitriles with epibromohydrin afforded 2-cyano-1-(hydroxymethyl)cyclopropanes. 2-Cyanomethylidene-(4-hydroxymethyl)thiazolidines were prepared by one-pot cyclization of dilithiated nitriles with isothiocyanates and epibromohydrin.

1. Introduction

One-pot cyclizations of dianions with dielectrophiles are of considerable synthetic utility.[1] In this context, epibromohydrin (EBH) has been used as a versatile synthetic building block. In recent years, we reported one-pot cyclizations of epibromohydrin with dilithiated 1,3-dicarbonyl compounds,[2] amides,[3] oximes and hydrazones.[4] The Lewis acid mediated cyclization of EBH with 1,3-bis-silyl enol ethers has been reported.[5] 2-Cyano-1-(hydroxymethyl)cyclopropanes are available by cyclization of epihalohydrins with nitriles in the presence of weak or strong bases.[6,7] Recently, we have shown that the sequential addition of isothiocyanates and EBH to dilithiated nitriles provides a convenient approach to 2-cyanomethylidene-(4-hydroxymethyl)thiazolidines.[8] With respect to our preliminary communications in this field,[6,8] we herein report full details of one-pot cyclizations of EBH with nitriles with[8] or without[6] addition of isothiocyanates.

2. Results and discussion

2.1. Synthesis of 2-cyano-1-(hydroxymethyl)cyclopropanes

The reaction of the dianion[9] of phenylacetonitrile (**1a**), generated by addition of *n*-BuLi (2.3 equiv), with epibromohydrin (**2**, EBH) afforded the 2-cyano-1-(hydroxymethyl)-cyclopropane **3a**.[10,11] Optimal yields (up to 79%) were obtained when (a) lithium perchlorate was added, (b) an excess of the dianion was used (2.5 equiv) and (c) the reaction mixture was stirred for 10 h at −35 °C and subsequently for 8 h at 20 °C (Scheme 1, Table 1). The use of 1-tosyloxy-2, 3-epoxypropane and epichlorohydrin proved to be unsuccessful. Cyclopropane **3a** was isolated as an inseparable diastereomeric mixture (*cis*/*trans*=8:1, the CN and the CH_2OH group are located cis to each other). The presence of Lewis acid proved to be important for the activation of the epoxide in the cyclization step. The tuning of the temperature proved to be important as the first attack of **1a** onto **2** occurred selectively at −35 °C. Upon warming to 20 °C and stirring at this temperature, the cyclization step occurred. Therefore, selectivity and yield decreased when the temperature of the reaction mixture was not maintained at −35 °C for 10 h. The use of an excess of the dianion was important to achieve a complete conversion of **2**.

The formation of **3a** can be explained by attack of the dianion onto the carbon attached to the bromine atom, cyclization and subsequent protonation upon aqueous work-up. Alternatively, attack of the dianion onto the sterically less encumbered carbon atom of the epoxide and subsequent S_Ni reaction is in principle possible. The diastereoselectivity can be explained by steric interaction of the phenyl and the hydroxymethyl group during the cyclization (Scheme 1).

The cyclization of arylacetonitriles **1a–g** with EBH afforded the 2-cyano-1-(hydroxymethyl)cyclopropanes **3a–g** in

Keywords: Cyclizations; Cyclopropanes; Epibromohydrin; Heterocycles; Isothiocyanates.
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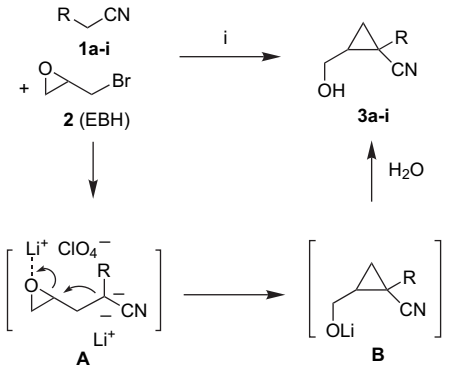


Scheme 1. Cyclization of dilithiated arylacetonitriles with epibromohydrin; *i*: (1) 2.3 *n*-BuLi, (2) **2**, $LiClO_4$, THF, (3) H_2O.

Table 1. Optimization of the reaction of dilithiated **1a** with functionalized epoxides

Entry		Lewis acid (equiv)	**1a** (equiv)	*t* [h][a]	(%)[b]
1	OTos	—	2.5	10+8	0
2	OTos	$LiClO_4$ (2.5)	2.5	10+8	0
3	Cl	$LiClO_4$ (2.5)	2.5	10+8	36
4	Br	—	1.0	10+8	22
5	Br	—	2.5	10+8	30
6	Br	LiCl (2.5)	2.5	10+8	35
7	Br	$LiClO_4$ (2.5)	2.5	10+8	79
8	Br	$LiClO_4$ (2.5)	1.0	10+8	48
9	Br	$LiClO_4$ (2.5)	2.5	1+12	24

[a] Reaction-time at −35 °C + reaction-time at 20 °C.
[b] Isolated yield of non-separable diastereomeric mixtures.

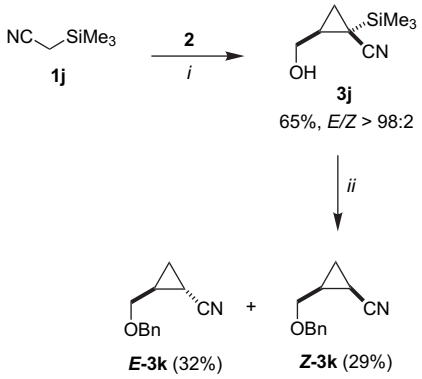
moderate to good yields and with good diastereoselectivity (Scheme 1, Table 2). The reaction of (*N*-methylpyrrol-2-yl)acetonitrile with EBH afforded the cyclopropane **3h**. The cyclopropyl-substituted thiophene **3i** was prepared from (thien-2-yl)acetonitrile; the trans-diastereomer could be isolated in pure form. The yields of **3a–i** were generally good (except for **3f** containing a substituent at the *ortho* position of the aryl group). For all products (except for **3h**, dr=3:1) good diastereoselectivities in favour of the cis configured products were observed (dr=5:1–8:1). The selectivity can be explained by steric interaction of the aryl group with the oxygen atom of the epoxide in intermediate **A** (Scheme 1). An electronic impact on the stereoselectivity cannot be excluded.

Table 2. Synthesis of 2-cyano-1-(hydroxymethyl)cyclopropanes **3a–i**

3	R	(%)[a]	*cis*/*trans*[b]
a	Ph	79	8:1
b	4-MeC_6H_4	56	7:1
c	4-(MeO)C_6H_4	52	7:1
d	3-MeC_6H_4	71	7:1
e	3-(MeO)C_6H_4	75	6:1
f	2-MeC_6H_4	34	5:1
g	2-Naphthyl	81	5:1
h	*N*-Methylpyrrol-2-yl	83[c]	3:1
i	Thien-2-yl	39[c]	<2:98[d]

[a] Isolated yields of non-separable diastereomeric mixtures.
[b] By ^1H NMR of the isolated product.
[c] LDA was used.
[d] Besides, a mixture of diastereomers (*cis*/*trans*=1:4) was isolated (43%).

The cyclization of dilithiated (trimethylsilyl)acetonitrile (**1j**) with EBH afforded the TMS-substituted cyclopropane **3j** with excellent diastereoselectivity (Scheme 2).[12,13] Notably, this transformation required the use of freshly prepared **1j**. Treatment of **3j** with TBAF afforded **3k**; however, the yield was low, due to decomposition and volatility of the product. The reaction of **3j** with NaH (2.4 equiv) and benzylic bromide (1.2 equiv) afforded the benzylated TMS-free cyclopropane **3k** as a separable mixture of diastereomers. The formation of **3k** can be explained by benzylation of the hydroxyl group, nucleophilic attack of NaH onto the TMS-group, extrusion of $HSiMe_3$ and formation of a cyclopropyl carbanion, which was protonated during the aqueous work-up. The use of 2 equiv (rather than only one) of NaH proved to be important. The configuration of cyclopropanes **3a**, **3j**, *cis*-**3k** and *trans*-**3k** was proved by NOESY experiments.



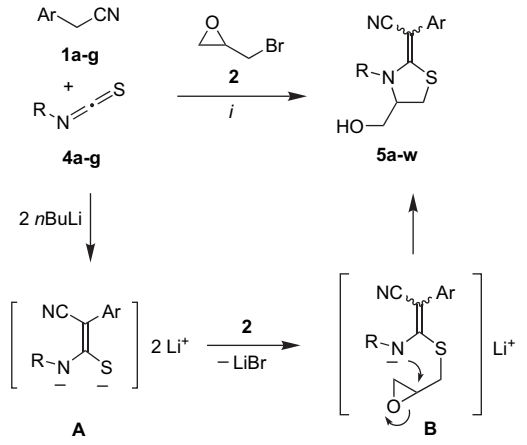
Scheme 2. Cyclization of dilithiated (trimethylsilyl)acetonitrile with epibromohydrin; *i*: (1) 2.3 LDA, (2) **2**, $LiClO_4$, THF, (3) H_2O; *ii*: BnBr (1.2 equiv), NaH (2.4 equiv), THF, 20 °C, 48 h.

2.2. Synthesis of 2-cyanomethylidene-(4-hydroxymethyl)thiazolidines

One-pot cyclizations often rely on the addition of a nucleophile onto a relais species (e.g., a nitrile or cumulene) and subsequent cyclization with a dielectrophile. Isothiocyanates represent interesting relais species in this type of transformation.[14] For example, one-pot cyclizations of arylmethylnitriles (dinucleophile) with isothiocyanates (relais species) and 1,2-dibromoethane, chloroacetic chloride[15] or ethyl 2-chloro-2-oxoacetate (dielectrophile) have been reported.[16] Recently, we have found that the reaction of the dianion of arylacetonitriles with isothiocyanates and epibromohydrin (EBH) afforded 2-alkylidene-(4-hydroxymethyl)thiazolidines.[8] Notably, (4-hydroxymethyl)thiazolidines and -oxazolidines are present in a variety of pharmacologically relevant compounds.[17] Related compounds have been employed as building blocks in the synthesis of penicillinic derivatives, D-biotin and allokainic acid.[18] Previous syntheses of (4-hydroxymethyl)thiazolidines and -oxazolidines rely on cyclization reactions with direct formation of the hydroxymethyl group. This includes, for example, cyclizations of aziridines with carbon disulfide,[19] hydrolysis of 4-thioxo-2-azetidinones[20] or cyclizations of ketenethioacetals with 1,3-propanedioles.[21] Other syntheses are based on the reduction of carboxylic derivatives and include, for example, condensations of aldehydes or ketones with L-cysteine,[22a,b] cyclizations of L-serinal derivatives,[23] cyclizations of potassium

malonate with isothiocyanatoacrylates[24] or hydrogenations of 2-vinylthiazetidines followed by rearrangement.[25]

The reaction of the dianion of phenylacetonitrile (**1a**) with *N*-phenylisothiocyanate (**4a**) and EBH afforded the 2-alkylidene-(4-hydroxymethyl)thiazolidine **5a** in up to 82% yield (Scheme 3).[8] During the optimization, the use of epibromohydrin proved to be mandatory; the employment of epichlorohydrin was unsuccessful. The following parameters also played an important role: (a) the sequential addition of the starting materials, (b) the temperature (0 °C rather than −78 °C) and (c) the generation of a dianion[9] by using a strong base (*n*-BuLi); employment of a weak base (NaH or K_2CO_3, THF, reflux) and a sequential deprotonation process proved to be unsuccessful. The formation of **5a** presumably proceeds by attack of the dianion onto the central carbon atom of **4a** to give intermediate **A**, attack of the sulfur atom onto **2** and subsequent cyclization. The reaction of **A** with **2** can proceed by initial attack of the sulfur atom of **A** onto the bromide group and subsequent cyclization via the epoxide or, alternatively, by attack onto the epoxide, Payne rearrangement and subsequent cyclization. The cyclization proceeded with very good regioselectivity and with good *E*-diastereoselectivity (*E*/*Z*=5:1), due to steric repulsion of the phenyl groups. The *S*-regioselectivity is a result of the higher nucleophilicity of sulfur compared to nitrogen.



Scheme 3. Synthesis of 2-alkylidenethiazolidines **5a**–**w**, *i*: (a) *n*-BuLi (2.2 equiv), 1 h, 0 °C, (b) **4a**–**g**, 1 h, 0 °C, (c) **2**, 16 h, 0→20 °C.

The reaction of arylmethylnitriles **1a**–**g** with **4a**–**g** and EBH afforded the thiazolidines **5a**–**w** (Scheme 3, Table 3). All products were formed in moderate to good to very good yields, with very good regioselectivity and with good *E*/*Z*-diastereoselectivity (except for **5f**). The *E*/*Z*-diastereoselectivity can be presumably explained by steric interaction between the aryl group and the substituent R; however, an electronic impact on the stereoselectivity cannot be excluded. The low yield of **5f** can be explained by competing metal/bromide exchange.

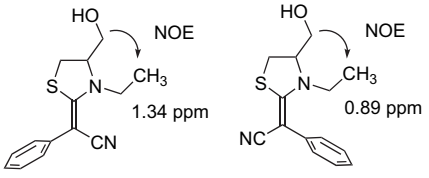
The structure of the products was established by spectroscopic methods (NOESY, COSY, DEPT). For example, a NOESY interaction was observed between the CH_3 and the CH_2OH group of **5l**, which indicates that the latter is located next to the *N*-ethyl group. The *Z*-configuration of the exocyclic double bond of the major isomer is supported

Table 3. Products and yields

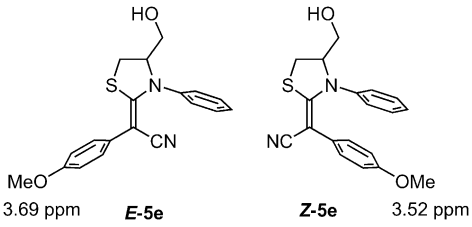
5	Ar	R	% (5)[a]	*Z*/*E*[b]
a	Ph	Ph	82	1:5
b	4-MeC_6H_4	Ph	86	1:3
c	4-(MeO)C_6H_4	Ph	94	1:2
d	2-MeC_6H_4	Ph	75	1:2
e	2-(MeO)C_6H_4	Ph	87	1:2
f	4-BrC_6H_4	Ph	23	1:2
g	Ph	Allyl	53	1:3
h	4-MeC_6H_4	Allyl	56	1:3
i	4-(MeO)C_6H_4	Allyl	83	1:3
j	2-MeC_6H_4	Allyl	54	1:5
k	2-(MeO)C_6H_4	Allyl	52	1:3
l	Ph	Me	41	1:3
m	Ph	Et	75	1:3
n	4-MeC_6H_4	Et	90	1:2
o	4-(MeO)C_6H_4	Et	89	1:3
p	2-MeC_6H_4	Et	72	1:3
q	2-(MeO)C_6H_4	Et	72	1:2
r	Ph	Pr	67	1:3
s	Ph	Bu	70	1:3
t	Ph	*i*-Bu	67	1:5
u	Thien-2-yl	Ph	70	5:1
v	Thien-2-yl	Allyl	67	5:1
w	Thien-2-yl	Et	64	5:1

[a] Yields of isolated products.
[b] By ^1H NMR.

by the fact that the resonance of the CH_3 group (0.89 ppm) is significantly shifted upfield compared to the CH_3 group of the *E*-configured minor isomer (1.34 ppm) (Scheme 4). This can be explained by the fact that the CH_3 group of the *Z*-isomer is located within the anisotropic cone of the phenyl group. Similar effects are observed also for other derivatives. For example, the resonance of the OCH_3 group of *Z*-**5e** (3.52 ppm) is shifted upfield with respect to *E*-**5e** (3.69 ppm) (Scheme 5). The structure of *E*-**5v** (the minor isomer) was independently confirmed by crystal structure analysis (Fig. 1).[26]



Scheme 4. Structure of **5l**.



Scheme 5. Structure of **5e**.

In conclusion, we have reported the synthesis of 2-cyano-1-(hydroxymethyl)cyclopropanes by cyclization of dilithiated nitriles with epibromohydrin. 2-Cyanomethylidene-(4-hydroxymethyl)thiazolidines were prepared by one-pot cyclization of dilithiated nitriles with isothiocyanates and epibromohydrin.

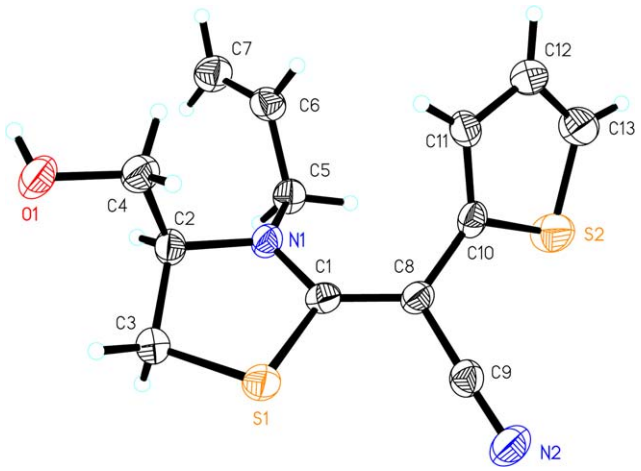


Figure 1. Crystal structure of *E*-**5v**.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O) or FT-ICR–MS. For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.2. Experimental procedures

3.2.1. Experimental procedure for the synthesis of cyclopropanes (3a–j). To a THF solution (20 mL) of phenylacetonitrile (0.58 g, 5.00 mmol) was added *n*-BuLi (10.48 mmol, 4.23 mL, solution in *n*-hexane) at 0 °C. The solution was stirred for 1 h and subsequently a THF solution (20 mL) of $LiClO_4$ (0.34 g) and epibromohydrin (0.33 g, 2.40 mmol) was added at −78 °C. The temperature was increased to −35 °C during 2 h and the solution was stirred at this temperature for 10 h. The solution was warmed to ambient during 1 h and stirred for 8 h. To the solution was added a saturated aqueous solution of NH_4Cl (40 mL) and ether (50 mL). The organic layer was separated and the aqueous layer was extracted with ether (2×50 mL) and dichloromethane (2×50 mL). The combined organic layers were extracted with a saturated aqueous solution of NaCl, dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ether=4:1→1:1) to give **3a** as a colourless oil (330 mg, 79%, *Z*/*E*=8:1).

3.2.2. 2-Cyano-1-(hydroxymethyl)-2-phenylcyclopropane (3a). Starting with phenylacetonitrile (0.58 g, 5.00 mmol), **3a** was isolated as yellow oil (0.33 g, 79%, *E*/*Z*=1:8). ^{1}H NMR ($CDCl_3$, 250 MHz, major diastereomer): δ=1.55 (m, 2H, CCH_2CH), 1.91 (m, 1H, CH), 3.34 (br, 1H, OH), 3.76 (dd, *J*=12 Hz, *J*=5 Hz, 1H, CH_2OH), 3.98 (dd, *J*=12 Hz, *J*=5 Hz, 1H, CH_2OH), 7.28 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz, major diastereomer): δ=16.1 (CN), 21.2 (CH_2), 31.3 (CH), 62.6 (CH_2OH), 120.6 (C), 125.8, 127.6, 128.7 (CH–Ph), 135.5 (C). MS (EI, 70 eV): 173 (M^+, 18), 143 (24), 129 (100), 115 (26), 103 (34). HRMS (EI, 70 eV): calcd: *m*/*z*=173.0841 for $C_{11}H_{11}NO$ (M^+); found: *m*/*z*=173.0841±2 ppm. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40. Found: C, 76.46; H, 6.28.

3.2.3. 2-Cyano-1-(hydroxymethyl)-2-(*p*-tolyl)cyclopropane (3b). Starting with *p*-tolylacetonitrile (0.65 g, 5.00 mmol), **3b** was isolated as a colourless oil (0.548 g, 56%, *E*/*Z*=1:7). IR (neat): $\tilde{\nu}$=3347 (br, m), 3088 (m), 3054 (m), 3035 (m), 3005 (m), 2948 (m), 2921 (m), 2873 (m), 2232 (w), 1764 (s), 1663 (s), 1592 (w), 1517 (s), 1448 (w), 1386 (m), 1367 (m), 1303 (w), 1248 (w), 1129 (w), 1111 (w), 1076 (m), 1039 (m), 1007 (m), 988 (w), 813 (w), 545 (w), 519 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.55 (m, 2H, CCH_2CH), 1.92 (m, 1H, CH), 2.33 (s, 3H, CH_3), 3.14 (dd, ^{2}J=12 Hz, ^{3}J=9 Hz, A of AB, 1H, 0.5×CH_2OH, trans-diastereomer), 3.46 (dd, ^{2}J=12 Hz, ^{3}J=5 Hz, B of AB, 1H, 0.5×CH_2OH, trans-diastereomer), 3.78 (dd, ^{2}J=12 Hz, ^{3}J=8 Hz, A of AB, 1H, 0.5×CH_2OH, cis-diastereomer), 4.04 (dd, ^{2}J=12 Hz, ^{3}J=6 Hz, B of AB, 1H, 0.5×CH_2OH, cis-diastereomer), 7.19 (m, 4H, 4×CH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, major diastereomer): δ_c=16.0 (C), 20.9 (CH_3), 21.1 (CCH_2CH), 31.2 (CH), 63.0 (CH_2OH), 120.9 (CN), 126.0, 129.5 (CH, Ar), 132.6, 137.6 (C, Ar). MS (EI, 70 eV): 187 (M^+, 12), 157 (32), 143 (100), 115 (16). HRMS (EI, 70 eV): calcd: *m*/*z*=187.0997 for $C_{12}H_{13}NO$ (M^+); found: *m*/*z*=187.0997±2 ppm.

3.2.4. 2-Cyano-1-(hydroxymethyl)-2-(*p*-methoxyphenyl)-cyclopropane (3c). Starting with *p*-methoxyphenylacetonitrile (0.73 g, 5.00 mmol), **3c** was isolated as a colourless oil (0.48 g, 52%, *E*/*Z*=1:7). IR (neat): $\tilde{\nu}$=3324 (br, m), 3079 (m), 3039 (m), 3004 (w), 2960 (m), 2907 (m), 2839 (m), 2231 (m), 1763 (m), 1667 (s), 1611 (s), 1581 (m), 1515 (s), 1462 (s), 1447 (s), 1397 (m), 1368 (m), 1298 (m), 1249 (s), 1181 (s), 1108 (m), 1072 (m), 1033 (s), 963 (m), 833 (s), 585 (w), 551 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.52 (m, 2H, CCH_2CH), 1.86 (m, 1H, CH), 2.37 (br, 1H, OH), 3.14 (dd, ^{2}J=12 Hz, ^{3}J=9 Hz, A of AB, 1H, 0.5×CH_2OH, trans-diastereomer), 3.45 (dd, ^{2}J=12 Hz, ^{3}J=5 Hz, B of AB, 1H, 0.5×CH_2OH, trans-diastereomer), 3.77 (dd, ^{2}J=12 Hz, ^{3}J=8 Hz, A of AB, 1H, 0.5×CH_2OH, cis-diastereomer), 3.78 (s, 3H, CH_3), 4.05 (dd, ^{2}J=12 Hz, ^{3}J=5 Hz, B of AB, 1H, 0.5×CH_2OH, cis-diastereomer), 6.84 (m, 2H, 2×CH, Ar), 7.23 (m, 2H, 2×CH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, major diastereomer): δ_c=16.2 (C), 20.7 (CCH_2CH), 30.8 (CH), 55.3 (CH_3), 63.0 (CH_2OH), 114.3 (CH, Ar), 121.1 (CN), 127.6 (C, Ar), 127.9 (CH, Ar), 159.2 (C, Ar). MS (EI, 70 eV): 203 (M^+, 32), 173 (57), 159 (100), 116 (11). HRMS (EI, 70 eV): calcd: *m*/*z*=203.0946 for $C_{12}H_{13}NO_2$ (M^+); found: *m*/*z*=203.0946±2 ppm.

3.2.5. 2-Cyano-1-(hydroxymethyl)-2-(*m*-tolyl)cyclopropane (3d). Starting with *m*-tolylacetonitrile (0.65 g, 5.00 mmol), **3d** was isolated as a yellow oil (0.32 g, 71%, *E*/*Z*=1:7). ^{1}H NMR ($CDCl_3$, 250 MHz, major diastereomer): δ=1.59 (m, 2H, CCH_2CH), 1.95 (m, 1H, CH), 2.34 (s, 3H, CH_3), 3.79 (dd, ^{2}J=12 Hz, ^{3}J=8 Hz, A of AB, 1H, 0.5×CH_2OH), 4.06 (dd, ^{2}J=12 Hz, ^{3}J=5 Hz, A of AB, 1H, 0.5×CH_2OH), 7.18 (m, 4H, 4×CH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, major diastereomer): δ_c=16.1 (C), 21.2

(C*C*H$_2$CH), 21.3 (CH$_3$), 31.3 (CH), 63.1 (CH$_2$OH), 120.8 (CN), 122.9, 126.9, 128.5, 128.8 (CH, Ar), 135.5, 138.7 (C, Ar). MS (EI, 70 eV): 187 (M$^+$, 25), 143 (100), 142 (13), 115 (17). HRMS (EI, 70 eV): calcd: *m*/*z*=187.0997 for $C_{12}H_{13}NO$ (M$^+$); found: *m*/*z*=187.0997±2 ppm.

3.2.6. 2-Cyano-1-(hydroxymethyl)-2-(*m*-methoxyphenyl)cyclopropane (3e). Starting with *m*-methoxyphenylacetonitrile (0.73 g, 5.00 mmol), **3e** was isolated as a yellow oil (0.36 g, 75%, *E*/*Z*=1:6). ^{1}H NMR (CDCl$_3$, 250 MHz, major diastereomer): δ=1.59 (m, 2H, CC*H*$_2$CH), 1.91 (m, 1H, CH), 2.33 (br, 1H, OH), 3.80 (s, 3H, CH$_3$), 3.81 (dd, ^2J=12 Hz, ^3J=8 Hz, A of AB, 1H, 0.5×C*H*$_2$OH), 4.05 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH), 6.85 (m, 3H, 3×CH, Ar), 7.25 (m, 1H, CH, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, major diastereomer): δ_c=16.1 (C), 21.4 (C*C*H$_2$CH), 31.6 (CH), 55.3 (CH$_3$), 63.1 (CH$_2$OH), 112.1, 113.1, 118.1 (CH, Ar), 120.6 (CN), 130.0 (CH, Ar), 137.2, 160.0 (CH, Ar). MS (EI, 70 eV): 203 (M$^+$, 18), 173 (12), 159 (100). HRMS (EI, 70 eV): calcd: *m*/*z*=203.0946 for $C_{12}H_{13}NO_2$ (M$^+$); found: *m*/*z*=203.0946±2 ppm.

3.2.7. 2-Cyano-1-(hydroxymethyl)-2-(*o*-tolyl)cyclopropane (3f). Starting with *o*-tolylacetonitrile (0.65 g, 5.00 mmol), **3f** was isolated as a colourless oil (0.15 g, 34%, *E*/*Z*=1:5). IR (neat): $\tilde{\nu}$=3343 (br, m), 3126 (m), 3105 (m), 3003 (w), 2947 (m), 2907 (w), 2229 (w), 1765 (m), 1673 (w), 1587 (w), 1489 (m), 1452 (w), 1412 (w), 1387 (m), 1362 (m), 1309 (m), 1256 (w), 1105 (m), 1077 (m), 1044 (s), 999 (m), 977 (m), 960 (m), 722 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$, 250 MHz, major diastereomer): δ=1.50 (m, 2H, CC*H*$_2$CH), 1.82 (m, 1H, CH), 2.54 (s, 3H, CH$_3$), 3.84 (dd, ^2J=12 Hz, ^3J=8 Hz, A of AB, 1H, 0.5×C*H*$_2$OH), 4.12 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH), 7.22 (m, 4H, 4×CH, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, major diastereomer): δ_c=17.0 (C), 19.3 (C*C*H$_2$CH), 19.4 (CH), 29.0 (CH$_3$), 63.0 (CH$_2$OH), 120.6 (CN), 126.3, 128.8, 129.5, 130.7 (CH, Ar), 133.5, 138.8 (C, Ar). MS (EI, 70 eV): 187 (M$^+$, 16), 157 (18), 143 (100), 115 (34). HRMS (EI, 70 eV): calcd: for *m*/*z*=187.0997 for $C_{12}H_{13}NO$ (M$^+$); found: *m*/*z*=187.0997±2 ppm.

3.2.8. 2-Cyano-1-(hydroxymethyl)-2-(naphth-1-yl)cyclopropane (3g). Starting with (naphth-1-yl)acetonitrile (0.83 g, 5.00 mmol), **3g** was isolated as a yellow oil (0.43 g, 81%, *E*/*Z*=1:5). IR (neat): $\tilde{\nu}$=3406 (br, m), 3056 (w), 2961 (w), 2932 (w), 2234 (m), 1261 (m), 1133 (w), 1100 (s), 1039 (s), 1023 (s), 860 (w), 817 (s), 748 (m), 478 (w) cm^{-1}. ^{1}H NMR (CDCl$_3$, 250 MHz): δ=1.69 (m, 2H, CC*H*$_2$CH, cis-diastereomer), 1.82 (m, 2H, CC*H*$_2$CH, trans-diastereomer), 2.06 (m, 1H, CH, cis-diastereomer), 2.22 (m, 1H, CH, trans-diastereomer), 2.47 (br, 1H, OH), 3.13 (dd, ^2J=12 Hz, ^3J=8 Hz, A of AB, 1H, 0.5×C*H*$_2$OH, trans-diastereomer), 3.49 (dd, ^2J=12 Hz, ^3J=6 Hz, B of AB, 1H, 0.5×C*H*$_2$OH, trans-diastereomer), 3.84 (dd, ^2J=12 Hz, ^3J=9 Hz, A of AB, 1H, 0.5×C*H*$_2$OH, cis-diastereomer), 4.12 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH, cis-diastereomer), 7.35 (m, 1H, CH, Ar), 7.51 (m, 2H, 2×CH, Ar), 7.82 (m, 4H, 4×CH, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, major diastereomer): δ_c=16.4 (C), 21.5 (C*C*H$_2$CH), 31.7 (CH), 63.3 (*C*H$_2$OH), 121.1 (CN), 123.7, 125.7, 126.7, 127.0, 127.9, 128.0, 129.2 (CH, Ar), 132.8, 133.1, 133.3 (C, Ar). MS (EI, 70 eV): 223 (M$^+$, 31), 193 (37), 179 (100), 165 (35). HRMS (EI, 70 eV): calcd: *m*/*z*=223.0997 for $C_{15}H_{13}NO$ (M$^+$); found: *m*/*z*=223.0997±2 ppm.

3.2.9. 2-Cyano-1-(hydroxymethyl)-2-(*N*-methylpyrrolyl)cyclopropane (3h). Starting with *N*-methylpyrrolylacetonitrile (0.60 g, 5.00 mmol), **3h** was isolated as a yellow oil (0.35 g, 83%, *E*/*Z*=1:3). LDA rather than *n*-BuLi was used. IR (neat): $\tilde{\nu}$=3343 (br, s), 3126 (m), 3105 (m), 3003 (w), 2947 (m), 2907 (m), 2229 (w), 1765 (m), 1673 (s), 1587 (w), 1489 (s), 1452 (m), 1412 (m), 1387 (m), 1362 (m), 1309 (s), 1256 (w), 1105 (m), 1077 (s), 1044 (s), 999 (w), 977 (w), 960 (w), 722 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$, 250 MHz, major diastereomer): δ=1.48 (m, 1H, 0.5×CC*H*$_2$CH), 1.59 (m, 1H, 0.5×CC*H*$_2$CH), 1.84 (m, 1H, CH), 3.71 (m, A of AB, 1H, 0.5×C*H*$_2$OH), 3.78 (s, 3H, CH$_3$), 4.16 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH), 6.03 (m, 2H, 2×CH, Ar), 6.61 (m, 1H, CH, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, major diastereomer): δ_c=11.5 (C), 19.4 (C*C*H$_2$CH), 29.7 (CH), 34.0 (CH$_3$), 62.8 (CH$_2$OH), 107.0, 109.2 (CH, Ar), 120.0 (CN), 123.5 (CH, Ar), 126.3 (C, Ar). MS (EI, 70 eV): 176 (M$^+$, 44), 145 (100), 132 (54), 118 (15). HRMS (EI, 70 eV): calcd: *m*/*z*=176.0950 for $C_{10}H_{12}N_2O$ (M$^+$); found: *m*/*z*=176.0950±2 ppm.

3.2.10. 2-Cyano-1-(hydroxymethyl)-2-(2-thienyl)cyclopropane (3i). Starting with 2-thienylacetonitrile (0.61 g, 5.00 mmol), **3i** was isolated in two fractions as yellow oils (fraction A: *E*-**3i**: 168 mg, 39%, *E*/*Z*<2:98; fraction B: 182 mg, 43%, *E*/*Z*=4:1; combined yield of fractions A+B: 350 mg, 82%, *E*/*Z*=9:1). LDA rather than *n*-BuLi was used. IR (neat): $\tilde{\nu}$=3453 (s), 3376 (br, s), 3105 (m), 2972 (m), 2908 (m), 1765 (s), 1525 (s), 1470 (w), 1439 (m), 1384 (s), 1366 (s), 1346 (m), 1292 (m), 1251 (m), 1227 (m), 1111 (s), 1078 (s), 1037 (s), 994 (s), 850 (m), 702 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$, 250 MHz): cis-diastereomer: δ=1.60 (d, ^3J=7 Hz, 2H, CC*H*$_2$CH), 1.98 (m, 1H, CH), 3.02 (br, 1H, OH), 3.74 (dd, ^2J=12 Hz, ^3J=8 Hz, A of AB, 1H, 0.5×C*H*$_2$OH), 4.00 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH), 6.91 (dd, ^3J=5 Hz, ^3J=4 Hz, 1H, CH, Ar), 7.04 (dd, ^3J=3 Hz, ^4J=1 Hz, 1H, CH, Ar), 7.15 (dd, ^3J=5 Hz, ^4J=1 Hz, 1H, CH, Ar); trans-diastereomer: δ=1.48 (m, 1H, A of AB, 0.5×CC*H*$_2$CH), 1.84 (m, 1H, B of AB, 0.5×CC*H*$_2$CH), 2.16 (m, 1H, CH), 2.74 (br, 1H, OH), 3.26 (dd, ^2J=12 Hz, ^3J=8 Hz, A of AB, 1H, 0.5×C*H*$_2$OH), 3.59 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×C*H*$_2$OH), 6.97 (dd, ^3J=5 Hz, ^3J=4 Hz, 1H, CH, Ar), 7.09 (dd, ^3J=4 Hz, ^4J=2 Hz, 1H, CH, Ar), 7.28 (dd, ^3J=5 Hz, ^4J=1 Hz, 1H, CH, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, cis-diastereomer): δ_c=15.0 (C), 22.7 (C*C*H$_2$CH), 32.5 (CH), 62.2 (*C*H$_2$OH), 119.9 (CN), 124.7, 125.9, 127.0 (CH, Ar), 139.6 (C, Ar). MS (EI, 70 eV): 179 (M$^+$, 18), 149 (27), 135 (100). HRMS (EI, 70 eV): calcd: *m*/*z*=179.0405 for C_9H_9SNO (M$^+$); found: *m*/*z*=179.0405±2 ppm.

3.2.11. 2-Cyano-1-(hydroxymethyl)-2-(trimethylsilyl)cyclopropane (3j). Starting with trimethylsilylacetonitrile (0.56 g, 5.00 mmol), **3j** was isolated as a colourless oil (0.26 g, 65%, *E*/*Z*>98:2). LDA rather than *n*-BuLi was used. IR (neat): $\tilde{\nu}$=3408 (br, s), 3050 (w), 3017 (w), 2925 (m), 2883 (m), 2239 (m), 1765 (m), 1750 (m), 1661 (m), 1450 (m), 1412 (w), 1380 (m), 1056 (m), 1034 (s), 994 (m), 974 (m) cm^{-1}. ^{1}H NMR (CDCl$_3$, 250 MHz): δ=0.13

(s, 9H, $SiMe_3$), 1.06 (dd, ^2J=8 Hz, ^3J=5 Hz, A of AB, 1H, 0.5×CCH_2CH), 1.15 (dd, ^2J=8 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×CCH_2CH), 1.46 (m, 1H, CH), 2.16 (br, 1H, OH), 3.68 (dd, ^2J=12 Hz, ^3J=7 Hz, A of AB, 1H, 0.5×CH_2OH), 3.93 (dd, ^2J=12 Hz, ^3J=6 Hz, B of AB, 1H, 0.5×CH_2OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c=−3.6 ($Si(CH_3)_3$), 1.0 (C), 15.6 (CCH_2CH), 24.4 (CH), 63.7 (CH_2OH), 122.4 (CN). MS (DCI, NH_3): 204 ((M+18+17)$^+$, 13), 187 ((M+18)$^+$, 100), 170 ((M+1)$^+$, 11). Anal. Calcd for $C_8H_{15}NOSi$: C, 56.75; H, 8.93. Found: C, 56.79; H, 8.98.

3.2.12. 2-Cyano-1-(benzyloxymethyl)cyclopropane (3k). To a THF suspension (15 mL) of NaH (99 mg, 4.2 mmol) was added **3j** (303 mg, 1.79 mmol) at 0 °C and the mixture was stirred for 30 min. Benzylic bromide (370 mg, 2.15 mmol) was added, the mixture was warmed to ambient and stirred for 2 d. An aqueous solution of Na_2CO_3 (50 mL, 10%) and ether was added; the organic and the aqueous layers were separated. The latter was extracted with ether (3×100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether=1:20→1:1) to give **3k** as a yellow oil (235 mg, 70%, *E*/*Z*=1:1). The diastereomers were separated by chromatography to give the pure trans-diastereomer *E*-**3k** (106 mg, 32%) and the cis-diastereomer *Z*-**3k** (97 mg, 29%). The isomers were assigned by NOESY experiments. IR (neat): $\tilde{\nu}$=3031 (w), 2863 (m), 2236 (w), 1452 (m), 1359 (m), 1093 (s), 1081 (s), 1029 (m), 741 (m), 700 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): trans-diastereomer: δ=1.07 (m, 1H, NCCH), 1.23 (m, 1H, A of AB, 0.5×CHCH_2CH), 1.36 (m, 1H, B of AB, 0.5×CHCH_2CH), 1.79 (m, 1H, CH), 3.19 (dd, ^2J=12 Hz, ^3J=6 Hz, A of AB, 1H, 0.5×CH_2OBn), 3.52 (dd, ^2J=12 Hz, ^3J=5 Hz, B of AB, 1H, 0.5×CH_2OBn), 4.54 (s, 2H, CH_2Ph), 7.33 (m, 5H, 5×CH, Ar); cis-diastereomer: δ=0.99 (m, 1H, A of AB, 0.5×CHCH_2CH), 1.27 (m, 1H, B of AB, 0.5×CHCH_2CH), 1.61 (m, 2×1H, 2×CH), 3.53 (dd, ^2J=12 Hz, ^3J=8 Hz, 1H, A of AB, 0.5×CH_2OBn), 3.75 (dd, ^2J=12 Hz, ^3J=5 Hz, 1H, B of AB, 0.5×CH_2OBz), 4.59 (s, 2H, CH_2Ph), 7.19 (m, 5H, 5×CH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, cis-diastereomer): δ_c=1.0 (CH), 11.3 (C), 20.5 (CH), 69.4, 72.9 (CH_2), 121.4 (CN), 127.6, 127.8, 128.4 (CH, Ar), 137.6 (C, Ar). MS (EI, 70 eV): 187 (M$^+$, 10), 91 (100), 79.1 (8). HRMS (EI, 70 eV): calcd: *m*/*z*=187.0997 for $C_{12}H_{13}NO$ (M$^+$); found: *m*/*z*=187.0997±2 ppm.

3.2.13. Typical procedure for the preparation of (4-hydroxymethyl)thiazolidines (5a–w). To a THF solution (10 mL) of 4-tolylmethylnitrile (0.262 g, 2.0 mmol) was added *n*-butyllithium (4.4 mmol, 1.6 M) at 0 °C. After stirring for 1 h, ethylisothiocyanate (0.174 g, 2.0 mmol) was added and the solution was stirred for 1 h at 0 °C. Subsequently, epibromohydrin (0.274 g, 2.0 mmol) was added. After warming to 20 °C during 16 h, an aqueous solution of hydrochloric acid (20 mL, 1 M) was added. The organic and the aqueous layers were separated and the latter was extracted with ethyl acetate (3×30 mL). The combined organic layers were extracted with brine (30 mL), dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc=3:2) to give **5n** as colourless oil (0.491 g, 90%, *E*/*Z*=5:1).

3.2.14. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-phenylthiazolidine (5a). Starting with phenylacetonitrile (0.234 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5a** was isolated as a colourless solid (0.507 g, 1.65 mmol, 82%, *E*/*Z*=2:1). Mp 143 °C. IR (KBr): $\tilde{\nu}$=3459 (s), 2184 (s), 1594 (w), 1544 (s), 1492 (m) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=239.85 (4.05), 254.93 (4.02), 276.16 (4.02), 331.10 (4.06) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.19 (dd, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *Z*), 3.22 (dd, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *E*), 3.32 (dd, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *E*), 3.33 (dd, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *Z*), 3.67 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *Z*), 3.74 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *E*), 3.85 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *Z*), 3.89 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *E*), 3.95 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *E*), 3.98 (dd, ^3J=11 Hz, ^3J=7 Hz, 1H, CH, *Z*), 4.25 (dddd, ^3J=11 Hz, ^3J=7 Hz, ^3J=7 Hz, ^3J=4 Hz, 1H, CH, *E*), 4.36 (dddd, ^3J=11 Hz, ^3J=7 Hz, ^3J=7 Hz, ^3J=4 Hz, 1H, CH, *Z*), 6.77–6.98 (m, 6H, CH, *E*, *Z*), 7.19–7.47 (m, 4H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.02 (*Z*), 30.75 (*E*), 61.11 (*E*), 61.55 (*Z*) (CH_2), 70.72 (*E*), 72.70 (*Z*) (CH), 80.20 (*E*), 81.82 (*Z*), 118.60 (*E*), 122.13 (*Z*) (C), 122.57 (*E*), 124.67 (*Z*), 125.87 (*E*), 127.08 (*Z*), 127.24 (*E*), 127.50 (*Z*), 128.36 (*Z*), 128.47 (*E*), 128.49 (*E*), 128.57 (*Z*), 128.58 (*Z*), 129.51 (*E*) (CH), 132.59 (*Z*), 135.79 (*E*), 141.60 (*Z*), 142.42 (*E*), 158.32 (*Z*), 162.36 (*E*) (C). MS (EI, 70 eV): *m*/*z*=308 (M$^+$, 7), 277 (10), 250 (1), 77 (8), 28 (100). Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 69.86; H, 5.26; N, 8.86.

3.2.15. 2-(1-Cyano-1-(4-tolyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5b). Starting with 4-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5b** was isolated as a colourless solid (0.553 g, 1.72 mmol, 86%, *E*/*Z*=3:1). Mp 85 °C. IR (KBr): $\tilde{\nu}$=3477 (s), 2188 (s), 1592 (w), 1570 (w), 1544 (s), 1510 (w), 1492 (m) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=240.34 (4.08), 256.84 (4.02), 276.90 (4.02), 332.23 (4.07) nm. ^{1}H NMR (acetone-d_6, 300 MHz): δ=2.32 (s, 3H, CH_3, *E*), 2.87 (s, 3H, CH_3, *Z*), 3.31 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *Z*), 3.34 (dd, ^3J=6 Hz, ^2J=11 Hz, 1H, CH_2, *E*), 3.48 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *Z*), 3.53 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *E*), 3.74 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *Z*), 3.83 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *E*), 4.08 (dd, ^3J=7 Hz, ^2J=11 Hz, 1H, CH_2, *E*), 4.31–4.37 (m, 1H, CH, *E*, *Z*), 6.77 (d, ^3J=8 Hz, 2H, CH, *E*), 6.83 (d, ^3J=8 Hz, 2H, CH, *Z*), 6.96 (d, ^3J=8 Hz, 2H, CH, E), 7.02 (d, ^3J=8 Hz, 2H, CH, *Z*), 7.08 (dd, ^3J=8 Hz, ^2J=2 Hz, 1H, CH, *E*), 7.09 (dd, ^3J=8 Hz, ^2J=2 Hz, 1H, CH, *Z*), 7.18 (dd, ^3J=8 Hz, ^2J=2 Hz, 2H, CH, *E*), 7.24 (dd, ^3J=8 Hz, ^2J=2 Hz, 2H, CH, *Z*), 7.35 (dd, ^3J=8 Hz, ^4J=2 Hz, 2H, CH, *E*), 7.42 (dd, ^3J=8 Hz, ^4J=2 Hz, 2H, CH, *Z*). ^{13}C NMR (acetone-d_6, 75 MHz): δ=21.35 (*E*), 21.49 (*Z*) (CH_3), 30.99 (*E*), 31.81 (*Z*), 62.13 (*Z*), 62.86 (*E*) (CH_2), 72.81 (*Z*), 74.70 (*E*) (CH), 81.98 (*Z*), 84.00 (*E*), 119.14 (*Z*), 122.48 (*E*) (C), 123.90 (*E*), 125.44 (*Z*), 126.97 (*E*), 128.35 (*Z*), 129.45 (*E*), 129.60 (*Z*), 129.79 (*E*), 129.81 (*Z*), 130.37 (*Z*), 130.49 (*E*) (CH), 131.93 (*E*), 135.21 (*Z*), 136.58 (*E*), 137.93 (*Z*), 144.04 (*E*), 144.97 (*Z*), 158.75 (*E*), 162.71 (*Z*). MS (EI, 70 eV)

m/*z*=322 (M^+, 100), 291 (99), 264 (10), 232 (5), 188 (7). HRMS (EI, 70 eV): calcd: *m*/*z* (%)=322.1140 for $C_{19}H_{18}N_2OS$ (M^+); found: *m*/*z* (%)=322.1140±2 ppm.

3.2.16. 2-(1-Cyano-1-(4-methoxyphenyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5c). Starting with 4-(methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5c** was isolated as a colourless solid (0.638 g, 1.89 mmol, 94%, *E*/*Z*=2:1). Mp 123 °C. IR (KBr): $\tilde{\nu}$=3420 (s), 2938 (w), 2910 (w), 2879 (w), 2836 (w), 2184 (s), 1601 (w), 1544 (s), 1510 (s), 1492 (m), 1461 (w), 1415 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=214.46 (4.25), 239.89 (4.13), 280.10 (4.06), 332.13 (4.04) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.99–3.29 (m, 2H, CH_2, *E*, *Z*), 3.52 (s, 3H, CH_3, *Z*), 3.69 (s, 3H, CH_3, *E*), 3.57–3.85 (m, 2H, CH_2, *E*, *Z*), 4.12–4.27 (m, 1H, CH, *E*, *Z*), 6.37 (dd, ^3J=7 Hz, ^4J=2 Hz, 1H, CH, *E*, *Z*), 6.71–6.89 (m, 4H, CH, *E*, *Z*), 7.15–7.33 (m, 4H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.95 (*Z*), 30.68 (*E*) (CH_2), 54.99 (*Z*), 55.14 (*E*) (CH_3), 60.97 (*E*), 61.42 (*Z*) (CH_2), 70.75 (*E*), 72.57 (*Z*) (CH), 79.06 (*E*), 81.40 (*Z*) (C), 112.96 (*Z*), 113.83 (*E*) (CH), 118.72 (*E*), 122.26 (*Z*) (C), 122.47 (*E*), 124.53 (*Z*) (CH), 125.02 (*Z*) (C), 125.81 (*E*), 126.89 (*Z*) (CH), 128.04 (*E*) (C), 128.24 (*Z*), 128.38 (*E*), 129.38 (*Z*), 130.01 (*E*) (CH), 141.44 (*Z*), 142.33 (*E*), 157.07 (*Z*), 157.51 (*E*), 158.58 (*E*), 161.95 (*Z*) (C). MS (EI, 70 eV) *m*/*z*=338 (M^+, 100), 307 (51), 280 (12), 248 (3), 233 (7). HRMS (EI, 70 eV): calcd: *m*/*z* (%)=338.1089 for $C_{19}H_{18}N_2O_2S$ (M^+); found: *m*/*z* (%)=338.1089±2 ppm. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.63; H, 5.74; N, 8.19.

3.2.17. 2-(1-Cyano-1-(2-tolyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5d). Starting with 2-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5d** was isolated as a colourless solid (0.438 g, 1.50 mmol, 75%, *E*/*Z*=2:1). Mp 146 °C. IR (KBr): $\tilde{\nu}$=3411 (s), 2181 (s), 1593 (w), 1547 (s), 1491 (s), 1454 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.13 (s, 3H, CH_3, *Z*), 2.33 (s, 3H, CH_3, *E*), 3.13–3.35 (m, 2H, CH_2, *E*, *Z*), 3.63–3.66 (m, 2H, CH_2, *E*, *Z*), 4.12–4.20 (m, 1H, CH, *E*, *Z*), 6.73–6.89 (m, 4H, CH, *E*, *Z*), 7.14–7.44 (m, 5H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.59 (*E*), 19.73 (*Z*) (CH_3), 30.23 (*E*), 30.35 (*Z*), 60.80 (*E*), 60.93 (*Z*) (CH_2), 71.49 (*E*), 72.59 (*Z*) (CH), 74.91 (*E*), 78.14 (*Z*), 117.74 (*E*), 121.98 (*Z*) (C), 124.27 (*E*), 125.21 (*Z*), 125.52 (*Z*), 126.07 (*E*), 126.93 (*E*), 127.12 (*Z*), 127.64 (*Z*), 128.10 (*E*), 128.52 (*Z*), 129.43 (*E*), 129.59 (*Z*), 130.29 (*E*), 130.41 (*Z*), 131.33 (*E*) (CH), 131.82 (*Z*), 134.86 (*E*), 136.13 (*Z*), 138.01 (*E*), 141.03 (*Z*), 141.37 (*E*), 160.34 (*Z*), 163.73 (*E*) (C). MS (EI, 70 eV) *m*/*z*=322 (M^+, 84), 291 (100), 264 (9), 231 (6), 188 (4). HRMS (EI, 70 eV): calcd: *m*/*z* (%)=322.1140 for $C_{19}H_{18}N_2OS$ (M^+); found: *m*/*z* (%)=322.1140±2 ppm.

3.2.18. 2-(1-Cyano-1-(2-methoxyphenyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5e). Starting with 2-(methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5e** was isolated as a colourless solid (0.590 g, 1.74 mmol, 87%, *E*/*Z*=2:1). Mp 145 °C. IR (KBr): $\tilde{\nu}$=3446 (s), 2950 (m), 2178 (s), 1594 (m), 1543 (s), 1491 (s), 1454 (m), 1433 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=296.72 (4.03), 323.21 (4.04) nm. ^1H NMR (acetone-d_6, 300 MHz): δ=3.25 (dd, ^3J=11 Hz, ^3J=7 Hz, 2H, CH_2, *Z*), 3.44 (dd, ^3J=11 Hz, ^3J=7 Hz, 2H, CH_2, *E*), 3.68 (s, 3H, CH_3, *Z*), 3.73 (s, 3H, CH_3, *E*), 3.90–4.17 (m, 2H, CH_2, *E*, *Z*), 4.33–4.42 (m, 1H, CH, *E*, *Z*), 6.44–6.52 (m, 1H, CH, *Z*), 6.56–6.64 (m, 1H, CH, *E*), 6.67–6.81 (m, 1H, CH, *E*, *Z*), 6.86–7.07 (m, 5H, CH, *E*, *Z*), 7.18–7.52 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, acetone-d_6): δ=31.04 (*E*), 31.54 (*Z*) (CH_2), 56.01 (*E*), 56.70 (*Z*) (CH_3), 59.06 (*Z*), 62.36 (*E*) (CH_2), 73.91 (*Z*), 74.23 (*E*) (CH), 77.54 (*Z*), 77.66 (*E*) (C), 111.71 (*E*), 113.03 (*Z*), 121.29 (*E*), 121.93 (*Z*) (CH), 123.05 (*E*), 124.07 (*Z*), 124.54 (*E*) (C), 124.67 (*E*) (CH), 124.93 (*Z*) (C), 125.79 (*Z*), 127.13 (*E*), 127.49 (*Z*), 129.13 (*E*), 129.81 (*Z*), 130.58 (*Z*), 131.31 (*E*), 131.53 (*E*), 131.91 (*Z*) (CH), 142.71 (*E*), 144.99 (*Z*), 157.05 (*E*), 159.25 (*Z*), 160.87 (*Z*), 164.19 (*E*) (C). MS (EI, 70 eV): *m*/*z*=338 (M^+, 100), 307 (39), 274 (3), 243 (3), 207 (5). Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.13; H, 5.77; N, 8.29.

3.2.19. 2-(1-Cyano-1-(4-bromophenyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5f). Starting with 4-(bromophenyl)acetonitrile (0.390 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenylisothiocyanate (0.270 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5f** was isolated as a colourless solid (0.182 g, 0.47 mmol, 23%, *E*/*Z*=2:1). Mp 140–143 °C. IR (KBr): $\tilde{\nu}$=3453 (s), 2186 (s), 1594 (w), 1537 (s), 1490 (s), 1443 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=240.09 (4.10), 277.52 (4.06), 336.59 (4.08) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.18–3.47 (m, 2H, CH_2, *E*, *Z*), 3.79–4.04 (m, 2H, CH_2, *E*, *Z*), 4.27–4.42 (m, 1H, CH, *Z*), 4.44–4.56 (m, 1H, CH, *E*), 6.83–7.05 (m, 4H, CH, *E*, *Z*), 7.24–7.43 (m, 5H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.27 (*Z*), 30.83 (*E*), 61.56 (*Z*), 62.07 (*E*) (CH_2), 70.84 (*E*), 72.86 (*Z*) (CH), 79.48 (*E*), 79.49 (*Z*), 119.61 (*E*), 120.98 (*Z*) (C), 122.72 (*Z*), 122.91 (*E*) (CH), 126.04 (*Z*), 126.31 (*E*) (C), 127.37 (*Z*), 127.67 (*E*), 128.70 (*Z*), 128.82 (*E*), 129.78 (*E*), 130.34 (*Z*), 130.67 (*Z*), 131.67 (*E*) (CH), 135.01 (*E*), 135.70 (*Z*), 141.76 (*E*), 142.17 (*Z*), 162.33 (*E*), 162.34 (*Z*) (C). MS (EI, 70 eV): *m*/*z*=388 (M^+, 16), 357 (12), 308 (47), 277 (65), 218 (4), 77 (100). HRMS (EI, 70 eV): calcd: *m*/*z*=386.0089 for $C_{18}H_{15}BrN_2OS$ [M^+]; found: *m*/*z*=386.0089±2 ppm.

3.2.20. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-allylthiazolidine (5g). Starting with phenylacetonitrile (0.234 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5g** was isolated as a colourless oil (0.286 g, 1.05 mmol, 53%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3412 (s), 2927 (w), 2178 (s), 1535 (s), 1492 (w), 1442 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=310.07 (4.12) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.00–3.23 (m, 2H, CH_2, *E*, *Z*), 3.44–3.54 (m, 2H, CH_2, *E*, *Z*), 3.57–3.69 (m, 2H, CH_2, *E*, *Z*), 3.99–4.06 (m, 1H, CH, *E*, *Z*), 4.16 (m, 1H, CH_2, *Z*), 4.63 (m, 1H, CH_2. *E*), 5.00 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH_2, *Z*), 5.28 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH_2, *E*), 5.46 (m, 1H, CH,

Z), 5.94 (m, 1H, CH, *E*), 7.12–7.32 (m, 4H, CH, *E*, *Z*), 7.38–7.43 (m, 1H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.50 (*Z*), 29.61 (*E*), 52.18 (*E*), 53.64 (*Z*), 60.56 (*E*), 61.16 (*Z*) (CH_2), 68.11 (*Z*), 68.33 (*E*) (CH), 72.99 (*E*), 75.17 (*Z*) (C), 118.24 (*E*), 119.10 (*Z*) (CH_2), 121.11 (*E*), 123.24 (*Z*) (C), 126.37 (*Z*), 126.84 (*E*), 128.17 (*Z*), 128.32 (*E*), 128.40 (*Z*), 129.16 (*E*), 131.69 (*Z*), 132.33 (*E*) (CH), 133.75 (*Z*), 136.43 (*E*), 162.27 (*E*), 163.35 (*Z*) (C). MS (EI, 70 eV) *m*/*z*=272 (M^+, 32), 241 (40), 232 (100), 200 (30), 173 (10). HRMS (EI, 70 eV): calcd: *m*/*z*=272.0983 for $C_{15}H_{16}N_2OS$ (M^+); found: *m*/*z*=272.0983±2 ppm. Anal. Calcd for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 65.92; H, 5.89; N, 10.27.

3.2.21. 2-(1-Cyano-1-(4-tolyl))methylidene-4-hydroxymethyl-3-allylthiazolidine (5h). Starting with 4-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5h** was isolated as a colourless oil (0.32 g, 1.11 mmol, 56%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3426 (s), 3083 (w), 3024 (m), 2975 (m), 2942 (s), 2872 (m), 2178 (s), 1687 (w), 1643 (m), 1612 (w), 1548 (s), 1443 (s), 1411 (m) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=306.97 (4.11) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.27 (s, 3H, CH_3, *Z*), 2.31 (s, 3H, CH_3, *E*), 3.00–3.23 (m, 2H, CH_2, *E*, *Z*), 3.43–3.67 (m, 4H, CH_2, *E*, *Z*), 3.97–4.06 (m, 1H, CH, *E*, *Z*), 4.14 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *Z*), 4.62 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *E*), 5.03 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH, *Z*), 5.29 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH, *E*), 5.43–5.54 (m, 1H, CH, *Z*), 5.87–6.00 (m, 1H, CH, *E*), 7.06–7.16 (m, 2H, CH, *E*, *Z*), 7.27–7.30 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.97 (*E*), 25.38 (*Z*) (CH_3), 29.54 (*Z*), 29.62 (*E*), 52.14 (*E*), 53.41 (*Z*), 60.59 (*E*), 61.14 (*Z*) (CH_2), 68.09 (*Z*), 68.36 (*E*) (CH), 72.87 (*E*), 75.28 (*Z*) (C), 118.14 (*E*), 118.94 (*Z*) (CH_2), 121.15 (*E*), 123.29 (*Z*) (C), 128.11 (*Z*), 129.03 (*E*), 129.08 (*E*), 129.09 (*Z*) (CH), 130.70 (*Z*) (C), 131.82 (*Z*), 132.42 (*E*) (CH), 133.47 (*E*), 136.18 (*Z*), 136.69 (*E*), 161.73 (*Z*), 163.06 (*E*) (C). MS (EI, 70 eV) *m*/*z*=286 (M^+, 42), 255 (33), 246 (100), 214 (28), 187 (17). HRMS (EI, 70 eV): calcd: *m*/*z*=286.1140 for $C_{16}H_{18}N_2OS$ (M^+); found: *m*/*z*=286.1140±2 ppm.

3.2.22. 2-(1-Cyano-1-(4-methoxyphenyl))methylidene-4-hydroxymethyl-3-allylthiazolidine (5i). Starting with 4-(methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5i** was isolated as a colourless oil (0.499 g, 1.65 mmol, 83%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3422 (s), 3076 (w), 3033 (w), 2939 (s), 2877 (m), 2836 (m), 2176 (s), 1692 (w), 1642 (m), 1605 (s), 1550 (s), 1510 (s), 1445 (s), 1415 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=232.44 (4.01), 301.58 (4.12) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.91–3.24 (m, 2H, CH_2, *E*, *Z*), 3.43–3.67 (m, 4H, CH_2, *E*, *Z*), 3.76 (s, 3H, CH_3, *Z*), 3.77 (s, 3H, CH_3, *E*), 3.98–4.04 (m, 1H, CH, *E*, *Z*), 4.16 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *Z*), 4.62 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *E*), 5.03 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH, *Z*), 5.29 (dd, ^2J=1 Hz, $^3J_{trans}$=17 Hz, 1H, CH, *E*), 5.42–5.53 (m, 1H, CH, *Z*), 5.89–5.98 (m, 1H, CH, *E*), 6.82–6.87 (m, 2H, CH, *E*, *Z*), 7.18 (d, ^3J=7 Hz, 2H, CH, *Z*), 7.19 (d, ^3J=7 Hz, 2H, CH, *E*), 7.30 (d, ^3J=7 Hz, 2H, CH, *Z*), 7.31 (d, ^3J=7 Hz, 2H, CH, *E*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.30 (*Z*), 29.51 (*E*), 51.84 (*E*), 52.99 (*Z*) (CH_2), 55.05 (*E*), 55.06 (*Z*) (CH_3), 60.62 (*E*), 61.03 (*Z*) (CH_2), 68.15 (*Z*), 68.43 (*E*) (CH), 71.92 (*E*), 74.67 (*Z*) (C), 113.67 (*E*), 113.79 (*Z*) (CH), 118.00 (*E*), 118.69 (*Z*) (CH_2), 121.18 (*E*), 123.31 (*Z*), 128.25 (*Z*), 128.71 (*E*) (C), 129.59 (*Z*), 130.63 (*E*), 131.76 (*Z*), 132.34 (*E*) (CH), 157.98 (*Z*), 158.40 (*E*), 161.21 (*Z*), 162.99 (*E*) (C). MS (EI, 70 eV) *m*/*z*=302 (M^+, 80), 271 (35), 262 (100), 230 (40), 203 (36). Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.72; H, 5.78; N, 8.46.

3.2.23. 2-(1-Cyano-1-(2-tolyl))methylidene-4-hydroxymethyl-3-allylthiazolidine (5j). Starting with 2-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5j** was isolated as a colourless oil (0.31 g, 1.08 mmol, 54%, *E*/*Z*=5:1). IR (KBr): $\tilde{\nu}$=3412 (s), 3075 (w), 3002 (w), 2938 (s), 2877 (m), 2837 (m), 2174 (s), 1675 (m), 1643 (m), 1593 (m), 1552 (s), 1536 (s), 1489 (s), 1455 (s), 1438 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=305.12 (4.00) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.26 (s, 3H, CH_3, *Z*), 2.32 (s, 3H, CH_3, *E*), 2.93 (dd, ^2J=11 Hz, ^3J=3 Hz, 1H, CH_2, *Z*), 2.97 (dd, ^2J=11 Hz, ^3J=3 Hz, 1H, CH_2, *E*), 3.08 (ddd, ^2J=11 Hz, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *E*), 3.12 (ddd, ^2J=11 Hz, ^3J=7 Hz, ^3J=4 Hz, 1H, CH_2, *Z*), 3.21–3.39 (m, 2H, CH_2, *E*, *Z*), 3.61–3.72 (m, 2H, CH_2, *E*, *Z*), 3.91–4.04 (m, 1H, CH, *E*, *Z*), 4.15 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *Z*), 4.73 (dd, ^2J=1 Hz, $^3J_{cis}$=10 Hz, 1H, CH, *E*), 4.82–5.04 (m, 1H, CH, *Z*), 5.27–5.33 (m, 1H, CH, *E*), 5.31–5.42 (m, 1H, CH, *Z*), 5.88–6.01 (m, 1H, CH, *E*), 7.12–7.24 (m, 4H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.56 (*Z*), 19.74 (*E*) (CH_3), 29.31 (*E*), 29.56 (*Z*), 50.93 (*E*), 50.94 (*Z*), 60.70 (*E*), 60.82 (*Z*) (CH_2), 68.87 (*Z*), 69.17 (*E*) (CH), 69.87 (*E*), 69.88 (*Z*) (C), 117.72 (*E*), 117.96 (*Z*) (CH_2), 120.38 (*E*), 120.39 (*Z*) (C), 125.99 (*Z*), 126.03 (*E*), 127.94 (*Z*), 128.43 (*E*), 130.23 (*E*), 130.73 (*Z*), 131.53 (*Z*), 131.73 (*E*), 132.19 (*E*), 132.42 (*Z*) (CH), 135.37 (*E*), 135.38 (*Z*), 137.69 (*Z*), 138.24 (*E*), 163.30 (*Z*), 163.31 (*E*). MS (EI, 70 eV) *m*/*z*=286 (M^+, 93), 255 (100), 246 (93), 214 (32), 128 (13). Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.89; H, 5.82; N, 8.49.

3.2.24. 2-(1-Cyano-1-(2-methoxyphenyl))-methylidene-4-hydroxymethyl-3-allylthiazolidine (5k). Starting with (2-methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5k** was isolated as a colourless solid (0.590 g, 1.74 mmol, 87%). IR (KBr): $\tilde{\nu}$=3415 (s), 2975 (w), 2936 (m), 2843 (w), 2177 (s), 1549 (s), 1490 (m), 1457 (m), 1441 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=309.61 (4.06) nm. ^{1}H NMR (acetone-d_6, 300 MHz): δ=2.62 (dd, ^2J=14 Hz, ^3J=5 Hz, 1H, CH, *Z*), 2.77 (dd, ^2J=14 Hz, ^3J=5 Hz, 1H, CH, *E*), 3.04 (dd, ^2J=11 Hz, ^3J=4 Hz, 1H, CH_2, *Z*), 3.17 (dd, ^2J=11 Hz, ^3J=4 Hz, 1H, CH_2, *E*), 3.18–3.38 (m, 2H, CH_2, *E*), 3.39–3.59 (m, 2H, CH_2, *Z*), 3.67–3.76 (m, 2H, *E*, *Z*), 3.81 (s, 3H, CH_3, *Z*), 3.82 (s, 3H, CH_3, *E*), 4.05–4.35 (m, 1H, CH, *E*, *Z*), 4.40–4.57 (m, 1H, CH_2, *E*), 4.73–4.83 (m, 1H, CH_2, *Z*), 4.98 (dd, ^2J=2 Hz, $^3J_{trans}$=16 Hz, $^3J_{cis}$=10 Hz, 1H, CH_2, *E*), 5.33 (dd, ^2J=2 Hz, $^3J_{trans}$=16 Hz, $^3J_{cis}$=10 Hz,

1H, CH_2, *Z*), 5.51 (ddt, $^3J_{trans}$=16 Hz, $^3J_{cis}$=10 Hz, ^3J=6 Hz, 1H, *E*), 6.03 (ddt, $^3J_{trans}$=16 Hz, $^3J_{cis}$=10 Hz, ^3J=6 Hz, 1H, *Z*), 6.88–7.01 (m, 2H, CH, *E*, *Z*), 7.19–7.33 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=36.30 (*Z*), 36.72 (*E*), 52.31 (*Z*), 52.71 (*E*) (CH_2), 56.16 (*Z*), 56.41 (*E*) (CH_3), 61.66 (*E*), 61.85 (*Z*) (CH_2), 68.60 (*Z*), 69.24 (*E*) (CH), 70.26 (*Z*), 70.87 (*E*) (C), 112.47 (*E*), 112.83 (*Z*) (CH), 118.26 (*Z*), 118.69 (*E*) (C), 119.65 (*E*), 119.84 (*Z*) (CH_2), 121.74 (*E*), 121.91 (*Z*) (CH), 124.59 (*E*), 124.86 (*Z*) (C), 130.04 (*Z*), 130.80 (*E*), 131.87 (*Z*), 132.30 (*E*), 134.13 (*Z*), 134.45 (*E*) (CH), 158.32 (*Z*), 159.22 (*E*), 163.79 (*E*), 164.22 (*Z*) (C). MS (EI, 70 eV): *m*/*z*=302 (M^+, 25), 262 (100), 146 (9), 83 (69), 68 (10). Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.24; H, 6.18; N, 9.07.

3.2.25. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-methylthiazolidine (5l). Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), methylisothiocyanate (0.262 g, 3.0 mmol) and epibromohydrin (0.493 g, 3.6 mmol) in 15 mL of THF, **5l** was isolated as a yellow oil (0.302 g, 1.2 mmol, 41%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3413 (br s), 3098 (w), 3079 (m), 3056 (m), 3027 (m), 2939 (s), 2876 (m), 2176 (s), 1692 (w), 1645 (m), 1593 (s), 1569 (s), 1561 (s), 1491 (s), 1423 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=310.76 (4.20) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.25 (br s, 1H, OH), 2.69 (s, 3H, CH_3, *Z*), 2.99–3.28 (m, 2H, CH_2, *E*, *Z*), 3.47 (s, 3H, CH_3, *E*), 3.80–3.99 (m, 3H, CH_2, CH, *E*, *Z*), 7.15–7.45 (m, 5H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.35 (*Z*), 28.58 (*E*) (CH_2), 37.36 (*E*), 39.76 (*Z*) (CH_3), 60.13 (*E*), 60.65 (*Z*) (CH_2), 70.25 (*E*) (C), 70.51 (*E*) (CH), 71.43 (*Z*) (C), 71.90 (*Z*) (CH), 121.45 (*E*), 123.65 (*Z*) (C), 125.47 (*Z*), 126.15 (*E*), 127.72 (*Z*), 127.92 (*E*), 128.13 (*Z*), 128.61 (*E*) (CH), 135.31 (*Z*), 126.33 (*E*), 161.45 (*Z*), 163.17 (*E*) (C). MS (EI, 70 eV): *m*/*z*=246 (M^+, 81), 215 (100), 200 (11), 174 (7), 159 (15). HRMS (FT-ICR): calcd for $C_{13}H_{15}N_2OS$ *m*/*z*=247.08996; found: *m*/*z*=247.09004±2 ppm.

3.2.26. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-ethylthiazolidine (5m). Starting with phenylacetonitrile (0.234 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5m** was isolated as a colourless oil (0.388 g, 1.49 mmol, 75%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3427 (s), 3024 (w), 2970 (m), 2934 (m), 2873 (m), 2177 (s), 1692 (m), 1643 (s), 1598 (m), 1546 (s), 1490 (w), 1462 (m), 1445 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=309.83 (4.05) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.89 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 1.34 (t, ^3J=7 Hz, 3H, CH_3, *E*), 2.91–3.22 (m, 4H, CH_2, *E*, *Z*), 3.59–3.72 (m, 2H, CH_2, *E*, *Z*), 4.00–4.12 (m, 1H, CH, *E*, *Z*), 7.21–7.34 (m, 3H, CH, *E*, *Z*), 7.40–7.43 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.98 (*Z*), 13.94 (*E*) (CH_3), 29.87 (*E*), 29.88 (*Z*), 44.80 (*E*), 45.95 (*Z*), 61.14 (*E*), 61.60 (*Z*) (CH_2), 68.66 (*E*), 68.81 (*Z*) (CH), 72.83 (*E*), 75.37 (*Z*), 121.30 (*E*), 123.50 (*Z*) (C), 126.48 (*Z*), 126.99 (*E*), 128.33 (*Z*), 128.34 (*E*), 128.49 (*Z*), 129.45 (*E*) (CH), 134.11 (*Z*), 136.86 (*E*), 162.12 (*Z*), 163.14 (*E*) (C). MS (EI, 70 eV): *m*/*z*=260 (M^+, 100), 229 (86), 201 (57), 174 (20), 159 (10). HRMS (EI, 70 eV): calcd: *m*/*z*=260.0983 for $C_{14}H_{16}N_2OS$ (M^+); found: *m*/*z*=260.0983±2 ppm.

3.2.27. 2-(1-Cyano-1-(4-tolyl))methylidene-4-hydroxymethyl-3-ethylthiazolidine (5n). Starting with 4-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5n** was isolated as a colourless oil (0.491 g, 1.79 mmol, 90%, *E*/*Z*=2:1). IR (KBr): $\tilde{\nu}$=3432 (s), 2975 (w), 2934 (m), 2873 (w), 2177 (s), 1645 (w), 1548 (s), 1464 (m), 1444 (m) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=307.35 (4.08) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ=^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 1.27 (t, ^3J=7 Hz, 3H, CH_3, *E*), 2.28 (s, 3H, CH_3, *Z*), 2.30 (s, 3H, CH_3, *E*), 2.94–3.22 (m, 2H, CH, CH_2, *E*, *Z*), 3.56–3.66 (m, 2H, CH_2, *E*, *Z*), 3.94–4.08 (m, 3H, CH_2, *E*, *Z*), 7.05–7.14 (m, 2H, CH, *E*, *Z*), 7.26–7.30 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.53 (*Z*), 13.43 (*E*), 20.74 (*E*), 21.89 (*Z*), (CH_3), 27.49 (*Z*), 29.39 (*E*), 43.93 (*E*), 45.15 (*Z*), 60.30 (*E*), 60.87 (*Z*), (CH_2), 68.48 (*Z*), 68.57 (*E*) (CH), 70.88 (*E*), 73.87 (*Z*), 121.24 (*E*), 123.47 (*Z*) (C), 127.87 (*E*), 128.75 (*Z*), 128.76 (*E*), 128.99 (*Z*) (CH), 130.62 (*Z*), 133.61 (*E*), 135.78 (*Z*), 136.29 (*E*), 161.23 (*Z*), 162.62 (*E*) (C). MS (EI, 70 eV): *m*/*z*=274 (M^+, 100), 243 (84), 215 (46), 188 (14), 119 (33). HRMS (EI, 70 eV): calcd: *m*/*z*=274.1140 for $C_{15}H_{18}N_2OS$ (M^+); found: *m*/*z*=274.1140±2 ppm.

3.2.28. 2-(1-Cyano-1-(4-methoxyphenyl)methylidene-4-hydroxymethyl-3-ethylthiazolidine (5o). Starting with (4-methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5o** was isolated as a colourless oil (0.514 g, 1.77 mmol, 89%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3428 (s), 2975 (s), 2935 (m), 2873 (m), 2840 (w), 2177 (s), 1640 (w), 1606 (m), 1549 (s), 1509 (s), 1463 (m), 1444 (m), 1415 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=232.31 (4.05), 303.00 (4.16) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.84 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 1.32 (t, ^3J=7 Hz, 3H, CH_3, *E*), 2.95–3.20 (m, 2H, CH_2, *E*, *Z*), 3.55–3.82 (m, 6H, CH, CH_2, CH_3, *E*, *Z*), 3.96–4.06 (m, 2H, CH_2, *E*, *Z*), 6.81–6.86 (m, 2H, CH, *E*, *Z*), 7.17 (dd, ^3J=8 Hz, ^4J=2 Hz, 2H, CH, *Z*), 7.29 (dd, ^3J=8 Hz, ^4J=2 Hz, 2H, CH, *E*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.52 (*Z*), 13.55 (*E*) (CH_3), 29.34 (*E*), 29.42 (*Z*), 43.80 (*E*), 44.87 (*Z*) (CH_2), 54.86 (*E*), 54.87 (*Z*) (CH_3), 60.35 (*E*), 60.86 (*Z*) (CH_2), 68.51 (*E*), 68.59 (*Z*) (CH), 70.23 (*E*), 73.48 (*Z*) (C), 113.49 (*E*), 113.54 (*Z*) (CH), 121.31 (*E*), 123.52 (*Z*), 125.73 (*Z*), 128.84 (*E*) (C), 129.41 (*Z*), 130.59 (*E*) (CH), 157.74 (*Z*), 158.17 (*E*), 160.83 (*Z*), 162.67 (*E*) (C). MS (EI, 70 eV): *m*/*z*=290 (M^+, 100), 275 (10), 259 (65), 231 (18), 216 (12). HRMS (EI, 70 eV): calcd: *m*/*z*=290.1089 for $C_{15}H_{18}N_2O_2S$ (M^+); found: *m*/*z*=290.1089±2 ppm.

3.2.29. 2-(1-Cyano-1-(2-tolyl))methylidene-4-hydroxymethyl-3-ethylthiazolidine (5p). Starting with 2-tolylacetonitrile (0.262 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5p** was isolated as a colourless oil (0.393 g, 1.4 mmol, 72%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3413 (s), 3093 (m), 3063

(m), 3016 (m), 2972 (s), 2934 (s), 2873 (s), 2174 (s), 1644 (s), 1551 (s), 1483 (m), 1461 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=294.94 (4.08) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.89 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 1.33 (t, ^3J=7 Hz, 3H, CH_3, *E*), 2.12 (s, 3H, CH_3, *Z*), 2.34 (s, 3H, CH_3, *E*), 2.89–3.22 (m, 2H, CH_2, *E*, *Z*), 3.56–3.69 (m, 2H, CH_2, *E*, *Z*), 3.88–4.11 (m, 3H, CH_2, CH, *E*, *Z*), 7.12–7.25 (m, 4H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.46 (*Z*), 13.40 (*E*), 19.30 (*Z*), 19.54 (*E*) (CH_3), 29.17 (*E*), 29.47 (*Z*), 42.97 (*E*), 42.98 (*Z*), 60.26 (*E*), 60.46 (*Z*) (CH_2), 67.84 (*Z*) (CH), 68.03 (*E*) (C), 69.07 (*E*) (CH), 71.12 (*Z*), 120.48 (*E*), 120.49 (*Z*) (C), 125.72 (*E*), 125.78 (*Z*), 127.69 (*Z*), 128.09 (*E*), 129.96 (*E*), 130.25 (*Z*), 131.59 (*E*), 132.40 (*Z*) (CH), 135.40 (*E*), 136.58 (*Z*), 137.75 (*Z*), 138.04 (*E*), 162.45 (*Z*), 162.93 (*E*) (C). MS (EI, 70 eV): *m*/*z*=274 (M^+, 93), 243 (100), 198 (7), 188 (9), 173 (13). HRMS (EI, 70 eV): calcd: *m*/*z*=274.1140 for $C_{15}H_{18}N_2OS$ (M^+); found: *m*/*z*=274.1140±2 ppm.

3.2.30. 2-(1-Cyano-1-(2-methoxyphenyl))methylidene-4-hydroxymethyl)-3-ethylthiazolidine (5q). Starting with (2-methoxyphenyl)acetonitrile (0.294 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5q** was isolated as a colourless oil (0.418 g, 0.14 mmol, 72%, *E*/*Z*=2:1). IR (KBr): $\tilde{\nu}$=3431 (s), 3074 (w), 2976 (m), 2933 (m), 2871 (m), 2175 (s), 1652 (m), 1596 (m), 1551 (s), 1489 (m), 1458 (s), 1440 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=286.42 (4.07), 302.59 (4.07) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.81 (t, ^3J=7 Hz, 3H, CH_3, *E*), 1.35 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 2.70 (q, ^3J=7 Hz, 2H, CH_2, *E*), 2.86 (q, ^3J=7 Hz, 2H, CH_2, *Z*), 3.09 (dd, ^3J=7 Hz, ^2J=18 Hz, 1H, CH_2, *E*), 3.10 (dd, ^3J=7 Hz, ^2J=18 Hz, 1H, CH_2, *Z*), 3.26 (dd, ^3J=11 Hz, ^2J=18 Hz, 1H, CH_2, *E*), 3.27 (dd, ^3J=11 Hz, ^2J=18 Hz, 1H, CH_2, Z), 3.45–3.78 (m, 2H, CH_2, *E*, *Z*), 3.80 (s, 3H, CH_3, *E*), 3.84 (s, 3H, CH_3, *Z*), 3.98–4.06 (m, 1H, CH, *E*, *Z*), 6.85–6.96 (m, 2H, CH, *E*, *Z*), 7.17–7.31 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.06 (*E*), 14.90 (*Z*) (CH_3), 30.04 (*E*), 30.22 (*Z*), 44.70 (*E*), 44.98 (*Z*) (CH_2), 56.21 (*E*), 56.79 (*Z*) (CH_3), 61.91 (*E*), 62.30 (*Z*) (CH_2), 69.36 (*E*), 69.73 (*Z*) (CH), 76.28 (*E*), 77.48 (*Z*) (C), 111.08 (*Z*), 111.45 (*E*), 120.92 (*E*), 121.25 (*Z*) (CH), 123.12 (*Z*), 123.30 (*E*), 124.87 (*Z*), 125.37 (*E*) (C), 129.27 (*Z*), 129.61 (*E*), 131.03 (*Z*), 131.39 (*E*) (CH), 156.83 (*Z*), 157.73 (*E*), 162.67 (*E*), 163.31 (*Z*). MS (EI, 70 eV): *m*/*z*=290 (M^+, 100), 259 (67), 231 (20), 216 (13), 135 (71). HRMS (EI, 70 eV): calcd: *m*/*z*=290.1089 for $C_{15}H_{18}N_2O_2S$ (M^+); found: *m*/*z*=290.1089±2 ppm.

3.2.31. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-propylthiazolidine (5r). Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), *n*-propylisothiocyanate (0.304 g, 3.0 mmol) and epibromohydrin (0.493 g, 3.6 mmol) in 15 mL of THF, **5r** was isolated as a yellow oil (0.549 g, 2.0 mmol, 67%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3424 (s), 3080 (w), 3058 (w), 2964 (m), 2935 (m), 2875 (w), 2172 (s), 1692 (w), 1644 (m), 1596 (w), 1544 (s), 1491 (m), 1463 (m), 1442 (m) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)= 309.07 (4.06) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.50 (t, ^3J=8 Hz, 3H, CH_3, *Z*), 0.96 (t, ^3J=8 Hz, 3H, CH_3, *E*), 1.28 (tq, ^3J=8 Hz, 2H, CH_2, *Z*), 1.77 (tq, ^3J=8 Hz, 2H, CH_2, *E*), 2.85–3.47 (m, 4H, CH_2, *E*, *Z*), 3.60–3.72 (m, 2H, CH_2, *E*, *Z*), 3.96–4.08 (m, 1H, CH, *E*, *Z*), 7.15–7.31 (m, 3H, CH, *E*, *Z*), 7.38–7.42 (m, 2H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.30 (*Z*), 10.39 (*E*) (CH_3), 20.52 (*Z*), 21.26 (*E*), 29.09 (*Z*), 29.24 (*E*), 50.59 (*E*), 51.92 (*Z*), 60.22 (*E*), 60.79 (*Z*) (CH_2), 69.03 (*E*), 69.35 (*Z*) (CH), 70.96 (*E*), 73.15 (*Z*), 121.22 (*E*), 123.65 (*Z*) (C), 126.15 (*Z*), 126.54 (*E*), 128.10 (*E*), 128.31 (*Z*), 129.15 (*Z*), 129.16 (*E*) (CH), 133.64 (*Z*), 136.69 (*E*), 161.33 (*Z*), 162.69 (*E*) (C). MS (EI, 70 eV): *m*/*z*=274 (M^+, 24), 200 (23), 143 (30), 129 (65), 101 (87), 86 (100). HRMS (EI, 70 eV): calcd: *m*/*z*=274.1140 for $C_{15}H_{18}N_2OS$ [M^+]; found: *m*/*z*= 274.1140±2 ppm.

3.2.32. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-butylthiazolidine (5s). Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), *n*-butylisothiocyanate (0.346 g, 3.0 mmol) and epibromohydrin (0.493 g, 3.6 mmol) in 15 mL of THF, **5s** was isolated as a yellow oil (0.607 g, 2.1 mmol, 70%, *E*/*Z*=3:1). IR (KBr): $\tilde{\nu}$=3421 (s), 3078 (w), 3056 (w), 3025 (w), 2959 (s), 2933 (s), 2871 (m), 2177 (s), 1691 (m), 1646 (w), 1596 (w), 1548 (s), 1492 (m), 1463 (s), 1443 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=310.68 (4.06) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.64 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 0.96 (t, ^3J=7 Hz, 3H, CH_3, *E*), 0.89 (quin, ^3J=7 Hz, 2H, CH_2, *E*), 1.26 (quin, ^3J=7 Hz, 2H, CH_2, *E*), 1.37 (quin, ^3J=7 Hz, 2H, CH_2, *E*), 1.72 (quin, ^3J=7 Hz, 2H, CH_2, *E*), 2.90–3.24 (m, 3H, CH_2, *E*, *Z*), 3.40–3.69 (m, 3H, CH_2, *E*, *Z*), 3.95–4.14 (m, 1H, CH, *E*, *Z*), 7.12–7.31 (m, 4H, CH, *E*, *Z*), 7.33–7.42 (m, 1H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.38 (*Z*), 13.89 (*E*) (CH_3), 19.36 (*Z*), 19.61 (*E*), 29.46 (*E*), 29.51 (*Z*), 29.56 (*E*), 30.26 (*Z*), 49.24 (*E*), 50.45 (*Z*), 60.56 (*E*), 61.11 (*Z*) (CH_2), 69.19 (*E*), 69.55 (*Z*) (CH), 71.45 (*E*), 73.55 (*Z*), 121.51 (*E*), 123.94 (*Z*) (C), 126.44 (*Z*), 126.83 (*E*), 128.41 (*E*), 128.62 (*Z*), 129.30 (*Z*), 129.45 (*E*) (CH), 134.01 (*Z*), 136.99 (*E*), 161.67 (*Z*), 163.01 (*E*) (C). MS (EI, 70 eV): *m*/*z*=288 (M^+, 100), 256 (19), 200 (85), 175 (24), 143 (17). HRMS (EI, 70 eV): calcd: *m*/*z*=288.1296 for $C_{16}H_{20}N_2OS$ [M^+]; found: *m*/*z*=288.1296±2 ppm.

3.2.33. 2-(1-Cyano-1-phenyl)methylidene-4-hydroxymethyl-3-isobutylthiazolidine (5t). Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), *iso*-butylisothiocyanate (0.346 g, 3.0 mmol) and epibromohydrin (0.493 g, 3.6 mmol) in 15 mL of THF, **5t** was isolated as a yellow oil (0.582 g, 2.0 mmol, 67%, *E*/*Z*=5:1). IR (KBr): $\tilde{\nu}$=3425 (s), 3078 (w), 3057 (m), 3023 (w), 2959 (s), 2872 (s), 2234 (m), 2175 (s), 1676 (w), 1645 (w), 1623 (w), 1596 (m), 1552 (s), 1532 (s), 1493 (s), 1463 (s), 1443 (s) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=309.70 (4.03) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.68 (d, ^3J=7 Hz, 6H, CH_3, *Z*), 0.98 (d, ^3J=7 Hz, 6H, CH_3, *E*), 1.46–1.73 (m, 1H, CH, *E*, *Z*), 1.86–1.95 (m, 2H, CH_2, Z), 2.22–2.31 (m, 2H, CH_2, *E*), 2.63–3.41 (m, 3H, CH_2, *E*, *Z*), 3.60–3.71 (m, 1H, CH_2, *E*, *Z*), 3.97–4.10 (m, 1H, CH, *E*, *Z*), 7.13–7.42 (m, 5H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.19 (*E*), 19.74 (*Z*) (CH_3), 26.75 (*Z*), 26.87 (*E*) (CH), 28.82 (*Z*), 29.05 (*E*) (CH_2), 55.93 (*E*), 57.69 (*Z*), 60.32 (*E*), 60.50 (*Z*) (CH_2), 70.10 (*E*), 70.87 (*Z*) (CH), 71.25 (*E*), 72.79 (*Z*), 120.75 (*Z*), 121.49 (*E*) (C), 126.42 (*E*), 126.84 (*Z*), 128.30 (*Z*),

128.41 (*E*), 129.40 (*Z*), 129.51 (*E*) (CH), 135.68 (*Z*), 137.02 (*E*), 160.31 (*Z*), 162.05 (*E*) (C). MS (EI, 70 eV): *m*/*z*=288 (M^+, 100), 233 (32), 201 (69), 175 (69), 143 (19). HRMS (FT-ICR): Calcd for $C_{16}H_{21}N_2OS$ *m*/*z*=289.13691; found: *m*/*z*=289.13720±2 ppm. Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.53; H, 6.94; N, 9.32.

3.2.34. 2-(1-Cyano-1-(2-thiophenyl))methylidene-4-hydroxymethyl-3-phenylthiazolidine (5u). Starting with 2-thiophenylacetonitrile (0.380 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), phenylisothiocyanate (0.405 g, 3.0 mmol) and epibromohydrin (0.420 g, 3.1 mmol) in 15 mL of THF, **5u** was isolated as a colourless solid (0.656 g, 2.1 mmol, 70%, *Z*/*E*=5:1). IR (KBr): $\tilde{\nu}$=3454 (s), 2184 (s), 1592 (w), 1549 (s), 1516 (s), 1494 (m), 1430 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=246.17 (4.00), 279.43 (4.04), 345.92 (4.05) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.27 (dd, ^2J=12 Hz, ^3J=5 Hz, 1H, CH_2, *E*), 3.37 (dd, ^2J=12 Hz, ^3J=7 Hz, 1H, CH_2, *Z*), 3.72 (d, ^3J=7 Hz, 1H, CH_2, *Z*), 3.74 (d, ^3J=5 Hz, 1H, CH_2, *E*), 4.27 (dddd, ^3J=5 Hz, ^3J=7 Hz, 1H, CH, *Z*), 4.45–4.51 (m, 1H, CH, *E*) 6.96 (d, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *E*), 6.98 (d, ^3J=5 Hz, ^4J=1 Hz, 1H, CH, *Z*), 7.06 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *Z*), 7.22 (dd, ^3J=5 Hz, ^4J=1 Hz, 1H, CH, *Z*), 7.29–7.34 (m, 3H, CH, *Z*, *E*), 7.41–7.43 (m, 2H, CH, *Z*+*E*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.47 (*E*), 30.30 (*Z*), 60.02 (*Z*), 60.51 (*E*) (CH_2), 70.38 (*Z*), 72.34 (*E*) (CH), 72.62 (*Z*), 72.63 (*E*), 116.90 (*Z*), 120.10 (*E*) (C), 121.63 (*Z*), 123.72 (*E*), 124.09 (*Z*), 124.27 (*E*), 125.33 (*E*), 125.50 (*Z*), 125.58 (*E*), 125.70 (*Z*), 126.18 (*Z*), 126.65 (*E*), 127.82 (*E*), 128.69 (*Z*) (CH), 133.77 (*E*), 137.49 (*Z*), 141.03 (*Z*), 141.04 (*E*), 158.24 (*E*), 162.17 (*Z*) (C). MS (EI, 70 eV): *m*/*z*=314 (M^+, 6), 283 (5), 84 (13), 77 (7), 28 (100). Anal. Calcd for $C_{16}H_{14}N_2O_2S_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 61.34; H, 4.17; N, 9.03.

3.2.35. 2-(1-Cyano-1-(2-thiophenyl))methylidene-4-hydroxymethyl-3-allylthiazolidine (5v). Starting with 2-thiophenylacetonitrile (0.246 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), allylisothiocyanate (0.198 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5v** was isolated as a colourless solid (0.373 g, 1.3 mmol, 67%, *Z*/*E*=5:1). Mp 99 °C. IR (KBr): $\tilde{\nu}$=3401 (s), 2943 (w), 2179 (s), 1546 (s), 1519 (s), 1436 (w) cm^{-1}. UV–VIS (MeCN): λ_{max} (log ε)=240.21 (4.00), 310.29 (4.02) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=2.99–3.24 (m, 3H, CH_2, *E*, *Z*), 3.67–3.71 (m, 2H, CH_2, *E*, *Z*), 4.04–4.12 (m, 1H, CH, *E*, *Z*), 4.19 (dd, ^3J=6 Hz, ^4J=2 Hz, 1H, CH, *E*), 4.63 (dd, ^3J=6 Hz, ^4J=2 Hz, 1H, CH, *Z*), 5.03–5.17 (m, 1H, CH, *Z*), 5.27–5.39 (m, 1H, CH, *Z*), 5.52–5.64 (m, 2H, CH, *E*), 5.87–6.00 (m, 2H, CH, *Z*), 6.89–6.97 (m, 1H, CH, *E*, *Z*), 7.02 (dd, ^3J=4 Hz, 1H, CH, *E*, *Z*), 7.21–7.24 (m, 1H, CH, *E*, *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.04 (*E*), 29.05 (*Z*), 51.43 (*Z*), 52.13 (*E*), 59.94 (*Z*), 60.17 (*E*) (CH_2), 66.11 (*Z*), 66.12 (*E*) (C), 67.63 (*E*), 68.01 (*Z*) (CH), 117.65 (*Z*), 117.99 (*E*) (CH_2), 119.28 (*Z*), 121.15 (*E*) (C), 124.28 (*Z*), 124.90 (*E*), 126.00 (*Z*), 126.10 (*E*), 126.39 (*Z*), 126.80 (*E*), 131.07 (*E*), 131.40 (*Z*) (CH), 134.38 (*E*), 137.88 (*Z*), 162.69 (*E*), 163.42 (*Z*) (C). MS (EI, 70 eV) *m*/*z*=278 (M^+, 40), 238 (60), 207 (68), 180 (17), 146 (38), 41 (100). HRMS (EI, 70 eV): calcd: *m*/*z*=278.0548 for $C_{13}H_{14}N_2OS_2$ [M^+]; found: *m*/*z*=278.0548±2 ppm.

3.2.36. 2-(1-Cyano-1-(2-thiophenyl))methylidene-4-hydroxymethyl-3-ethylthiazolidine (5w). Starting with 2-thiophenylacetonitrile (0.246 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), ethylisothiocyanate (0.174 g, 2.0 mmol) and epibromohydrin (0.274 g, 2.0 mmol) in 10 mL of THF, **5w** was isolated as a colourless solid (0.339 g, 1.2 mmol, 64%, *Z*/*E*=5:1). IR (KBr): $\tilde{\nu}$=3452 (s), 2923 (w), 2186 (s), 1594 (w), 1537 (s), 1490 (s), 1444 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.97 (t, ^3J=7 Hz, 3H, CH_3, *E*), 1.34 (t, ^3J=7 Hz, 3H, CH_3, *Z*), 2.89–2.91 (m, 1H, CH, *E*, *Z*), 3.04–3.22 (m, 2H, CH_2, *E*, *Z*), 3.58–3.73 (m, 2H, CH_2, *E*, *Z*), 4.03–4.11 (m, 2H, CH_2, *E*, *Z*), 6.86 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *E*), 6.90–6.92 (m, 1H, CH, *E*), 6.96 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *E*), 6.99 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *Z*), 7.20 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *Z*), 7.21 (dd, ^3J=4 Hz, ^4J=1 Hz, 1H, CH, *E*). ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.05 (*E*), 14.15 (*Z*), (CH_3), 30.13 (*E*), 30.22 (*Z*), 44.75 (*Z*), 45.29 (*E*), 61.16 (*Z*), 61.33 (*E*) (CH_2), 65.86 (*Z*), 65.87 (*E*) (C), 69.15 (*E*), 69.35 (*Z*) (CH), 120.53 (*Z*), 122.34 (*E*) (C), 125.37 (*Z*), 125.93 (*E*), 127.07 (*Z*), 127.12 (*E*), 127.57 (*Z*), 127.87 (*E*) (CH), 136.73 (*E*), 139.23 (*Z*), 162.62 (*E*), 164.34 (*Z*) (C). Anal. Calcd for $C_{12}H_{14}N_2OS_2$: C, 54.11; H, 5.30; N, 10.52. Found: C, 53.78; H, 4.97; N, 10.33.

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A new synthesis of the phytotoxin porritoxin

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Abstract—A convenient synthesis of the phytotoxin porritoxin is described. Central to the approach employed is the formation of the isoindolinone template obtained via a directed lithiation/Parham cyclization process enabling the concomitant connection of an acetal appendage. Further conversion into the requisite hydroxyalkyl chain, selective deprotection, and O-prenylation complete the synthesis of the title compound.

1. Introduction

Porritoxin, as well as some other isoindolinone centered alkaloids, e.g., fumaridine,[1] fumaramidine,[2] nuevamine,[3] and piperolactam B,[4] belongs to this unique class of compounds whose structural assignments have been a subject of discussion and controversy. Initially this phytotoxin produced by the fungus *Alternaria porri* (Ellis) Ciferri, the causal fungus of black spot disease in stone-leek and onion was ascribed structure **1** characterized by a benzoxazocine skeleton.[5] However, probably shaken by the suggestion of Ayer and Miao who isolated stachybotramide **2** having an isoindole moiety[6] and then pointed out that the structure of porritoxin might be incorrect, the isolating group decided to launch a detailed structural reinvestigation. Finally persuasive data based upon detailed 2D NMR analysis ^{1}H–^{13}C and ^{1}H–^{15}N HMBC experiments convinced the authors to reassign their structure from **1** to **3** (Fig. 1).[7] Recently this revised structure was unambiguously confirmed by Kelly and Cornella[8] who reported the first total synthesis of the natural product. The marked advantages of their elegant synthesis lie mainly in the small number of steps and efficiency of the process. In this synthetic approach the key reaction is the formylation of the aromatic ring system by making use of iron pentacarbonyl then allowing the formation of the lactam unit by reductive amination and subsequent trans-amidification.

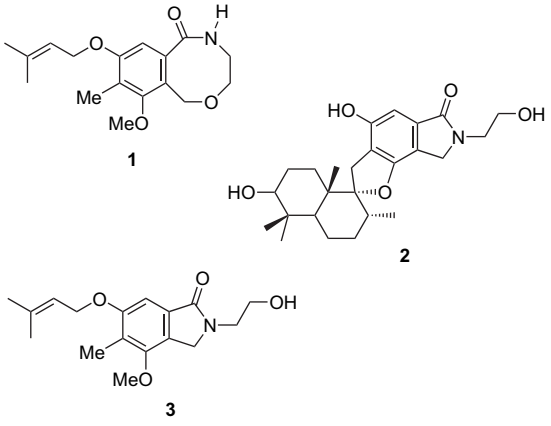

Figure 1.

2. Results and discussion

In this paper we wish to delineate an alternative synthesis of the title compound that relies upon our long standing experience in the field of isoindolinone chemistry.[9] Our synthetic tactic outlined in the retrosynthetic analysis shown in Scheme 1 hinges upon the Parham cyclization reaction of the aromatic carbamate **4** equipped with diverse and dense functionalities liable to secure the assembling of the rather congested isoindolinone template. Compound **4** could be in turn obtained by acylation of the secondary amine **6**. We also conjectured that the annulation process likely to give rise to **5** would allow the concomitant connection of an acetal appendage, which may serve as a handle for further conversion into the hydroxyalkyl chain present in the target

Keywords: Alkaloids; Parham procedure; Isoindolinones.
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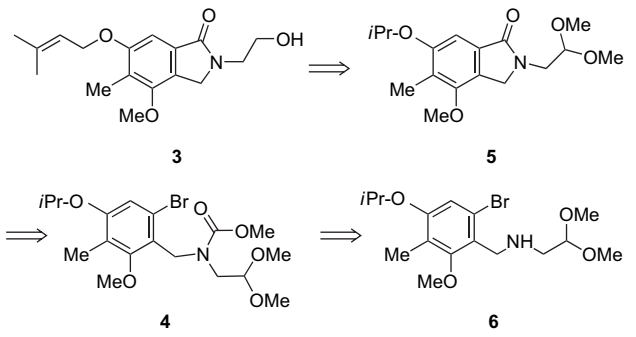
natural product. De-isopropylation followed by ultimate prenylation then should complete the total synthesis of the target compound.



Scheme 1.

The first facet of the synthesis was then the elaboration of the benzylamine derivative **6**. This compound was readily obtained as depicted in Scheme 2 by a reductive amination process involving the readily accessible benzaldehyde derivative **7** with aminoacetaldehyde dimethyl acetal. Acylation with methyl chloroformate proceeded uneventfully to deliver the carbamate **4**, a possible candidate for the planned Parham cyclization process. The Parham protocol hinges upon the trapping of an aromatic organometallic species with a suitable internal electrophile thereby providing the potential for direct access to an annulated compound.[10] Optimal conditions to ensure the requisite generation of the aryl metalled species derived from **4** by bromine–metal interconversion were then explored. For this purpose variations of the base, solvent, temperature profile, and incorporation of carbanion modifiers were all screened based upon literature precedents.[10] After various experimentation we found that upon adding a solution of carbamate **4** in THF to a solution of *n*-BuLi (3 equiv) and TMEDA (3 equiv) in THF at −78 °C for 30 min, the consumption of the parent compound was essentially complete and the desired annulated compound **5** was obtained with a very satisfactory yield (63%) upon immediate aqueous workup. Subsequent manipulation of the acetal residue by a two-step sequence provided the hydroxyalkylated isoindolinone **8** in fairly good yield. Regeneration of the 6-hydroxyphenolic function delivered the phenolic isoindolinone **9**, which can be regarded as an immediate precursor of the target alkaloid.[8] Indeed prenylation of **9** afforded **3** whose spectral data are in excellent agreement with those reported for natural porritoxin.[7]

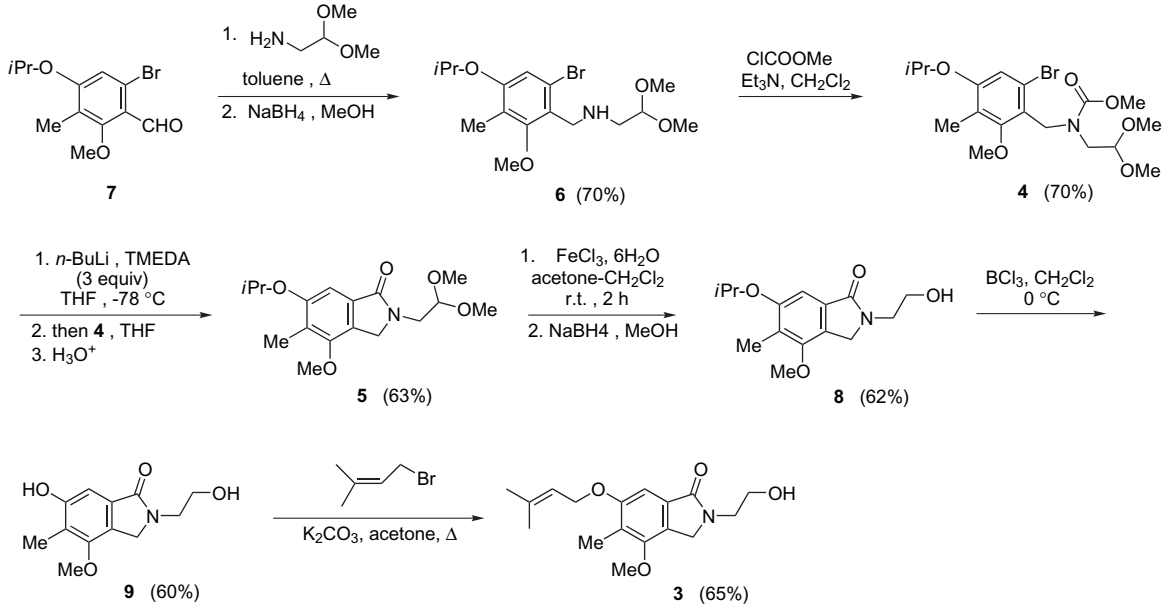
3. Conclusion

In conclusion we have defined a new synthetic route to natural product porritoxin. The key step of this approach made use of a directed lithiation/Parham cyclization process, which enabled the rapid construction of a highly functionalized isoindolinone. The concomitant incorporation of an acetal residue was used as a way to connect the requisite hydroxyethyl appendage. With this versatile synthetic route in hand, further studies will concentrate on exploring the potential of this approach for the elaboration of structurally modified biogenetic congeners.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm, 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert–Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300



Scheme 2.

(300 and 75 MHz, for ^1H and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

4.1.1. *N*-(6-Bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)-*N*-(2,2-dimethoxyethyl)amine (6). A solution of benzaldehyde derivative **7**[9e] (2.10 g, 7.3 mmol) and 2,2-dimethoxyethylamine (0.77 g, 7.3 mmol) in toluene (50 mL) was refluxed for 3 h in a Dean–Stark apparatus. After evaporation of the solvent the crude oily imine (2.60 g) was dissolved in MeOH (50 mL) and $NaBH_4$ (0.53 g, 13.9 mmol) was added portionwise and the mixture was stirred for 2 h at room temperature. After addition of solid NH_4Cl and stirring for 30 min, the solution was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent left the amine **6** as a yellow oil, which was purified by column chromatography using ethyl acetate–NEt_3 (90:10) as eluent. Yield 1.91 g (70%); ^1H NMR (δ_H) 1.30 (d, J=6.1 Hz, 6H, 2×CH_3), 2.05 (s, 3H, CH_3), 2.71 (d, J=5.6 Hz, 2H, NCH_2), 3.31 (s, 6H, 2×OCH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 2H, $ArCH_2N$), 4.41–4.50 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 6.81 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.5, 22.1, 47.7, 50.1, 53.6, 61.3, 70.8, 103.7, 113.4, 120.7, 121.7, 125.0, 156.6, 158.6 ppm. Anal. Calcd for $C_{16}H_{26}BrNO_4$ (376.3): C, 51.07; H, 6.96; N, 3.72%. Found: C, 50.98; H, 7.09; N, 3.93%.

4.1.2. Methyl *N*-(6-bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)-*N*-(2,2-dimethoxyethyl)carbamate (4). Methyl chloroformate (0.45 g, 4.8 mmol) was added dropwise to a stirred solution of amine **6** (1.40 g, 3.7 mmol) and NEt_3 (0.76 g, 7.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C. Stirring was maintained for 3 h at room temperature. The mixture was washed with water and brine, and dried (Na_2SO_4). After evaporation of the solvent the oily residue was purified by column chromatography using ethyl acetate–hexanes (50:50) as eluent to furnish **4** as a colorless oil. Yield 1.13 g (70%); ^1H NMR (δ_H) 1.32 (d, J=6.1 Hz, 6H, 2×CH_3), 2.06 (s, 3H, CH_3), 3.12–3.23 (m, 2H, NCH_2), 3.32 (s, 6H, 2×OCH_3), 3.66 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.43–4.56 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 4.67–4.72 (br s, 2H, $ArCH_2N$), 6.83 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.6, 22.1, 45.9, 47.0, 52.7, 54.3, 61.0, 70.7, 102.4, 113.4, 120.8, 121.4, 122.2, 157.1, 159.6 ppm. Anal. Calcd for $C_{18}H_{28}BrNO_6$ (434.3): C, 49.78; H, 6.50; N, 3.22%. Found: C, 49.85; H, 6.38; N, 3.01%.

4.1.3. 2-(2,2-Dimethoxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (5). A solution of *n*-BuLi (2 M in pentane, 3 mL, 6.0 mmol) and TMEDA (0.7 g, 6.0 mmol) in dry THF (5 mL) was carefully degassed by three freeze–thaw cycles and stirred at −78 °C under dry deoxygenated Ar. A solution of methyl carbamate derivative **4** (0.87 g, 2.0 mmol) in degassed THF (25 mL) was then added dropwise through a canula. The mixture was stirred for 30 min at −78 °C. After addition of aqueous satd NH_4Cl solution (5 mL) and Et_2O (25 mL), the aqueous layer was separated and extracted with Et_2O (25 mL). The organic layers were cumulated, dried (Na_2SO_4), and concentrated under vacuum. The crude oily residue was purified by column chromatography using ethyl acetate–hexanes–CH_2Cl_2 (40:40:20) as eluent to give **5** as a yellow oil. Yield 0.41 g (63%); ^1H NMR (δ_H) 1.30 (d, J=5.9 Hz, 6H, 2×CH_3), 2.12 (s, 3H, CH_3), 3.37 (s, 6H, 2×OCH_3), 3.66 (d, J=5.1 Hz, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.47 (s, 2H, $ArCH_2N$), 4.50–4.60 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 7.03 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.6, 22.1, 44.4, 49.7, 54.4, 59.6, 70.6, 102.5, 102.9, 123.7, 123.8, 131.4, 153.5, 157.5, 168.8 ppm. Anal. Calcd for $C_{17}H_{25}NO_5$ (323.4): C, 63.14; H, 7.79; N, 4.33%. Found: C, 62.99; H, 7.98; N, 4.39%.

4.1.4. 2-(2-Hydroxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (8). A solution of **5** (0.39 g, 1.2 mmol) and iron(III) chloride hexahydrate (0.92 g, 3.4 mmol) in a mixture of acetone–dichloromethane (1:4, 10 mL) was vigorously stirred over a period of 2 h at room temperature. The crude mixture was poured onto a aqueous satd NH_4Cl solution (5 mL), filtered on Celite, and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were washed successively with water, brine, and dried over Na_2SO_4. The solvents were removed in vacuo then the crude solid residue was dissolved in MeOH (15 mL) and treated under stirring by portionwise addition of $NaBH_4$ (95 mg, 2.5 mmol). Stirring was maintained at room temperature for an additional 1 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with aqueous satd NH_4Cl solution (10 mL). After drying (Na_2SO_4) the solvent was evaporated under vacuum to afford a solid residue, which was purified by flash column chromatography on silica using acetone–hexanes (80:20) as eluent. White crystals, yield 207 mg (62%); mp 113–114 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=6.0 Hz, 6H), 2.15 (s, 3H), 3.10–3.52 (br s, 1H), 3.73 (t, J=5.0 Hz, 2H), 3.84 (s, 3H), 3.90 (t, J=5.0 Hz, 2H), 4.52 (s, 2H), 4.58 (heptuplet, J=6.0 Hz, 1H), 7.04 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 22.4, 46.6, 50.3, 60.0, 62.0, 71.0, 102.7, 123.8, 124.3, 131.8, 153.8, 157.9, 170.1 ppm. Anal. Calcd for $C_{15}H_{21}NO_4$ (279.3): C, 64.50; H, 7.58; N, 5.01%. Found: C, 64.59; H, 7.76; N, 4.83%.

4.1.5. 6-Hydroxy-2-(2-hydroxyethyl)-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (9). A solution of BCl_3 (1 M in CH_2Cl_2, 0.8 mL, 0.8 mmol) was added dropwise by syringe to a degassed solution of isoindolinone **8** (112 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar. After stirring for 2 h at 0 °C, the reaction mixture was quenched with a few pieces of crushed ice. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and Et_2O (3×10 mL). The organic solvents were combined and dried (Na_2SO_4). The solvents were removed in vacuum and the crude solid residue was finally recrystallized from toluene–ethanol to afford **7**. White crystals, yield 57 mg (60%); mp 176–178 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.1 (s, 3H), 3.53–3.67 (m, 4H), 4.61 (s, 2H), 6.87 (s, 1H), 9.81 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.3, 45.6, 49.8, 59.1, 60.2, 61.8, 104.2, 120.0, 122.1, 132.8, 154.3, 157.5, 168.3 ppm. Anal. Calcd for $C_{12}H_{15}NO_4$ (237.3): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.54; H, 6.19; N, 6.09.

4.1.6. Porritoxin (3). By prenylation of **9** (40 mg) following a reported procedure.[8] White crystals from hexane–toluene, yield 34 mg (65%); mp 115–116 °C (lit.[7] 115–116 °C). Analytical and spectral data matched those reported for the natural product.[7,8]

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Exploration of conjugate addition routes to advanced tricyclic components of mangicol A

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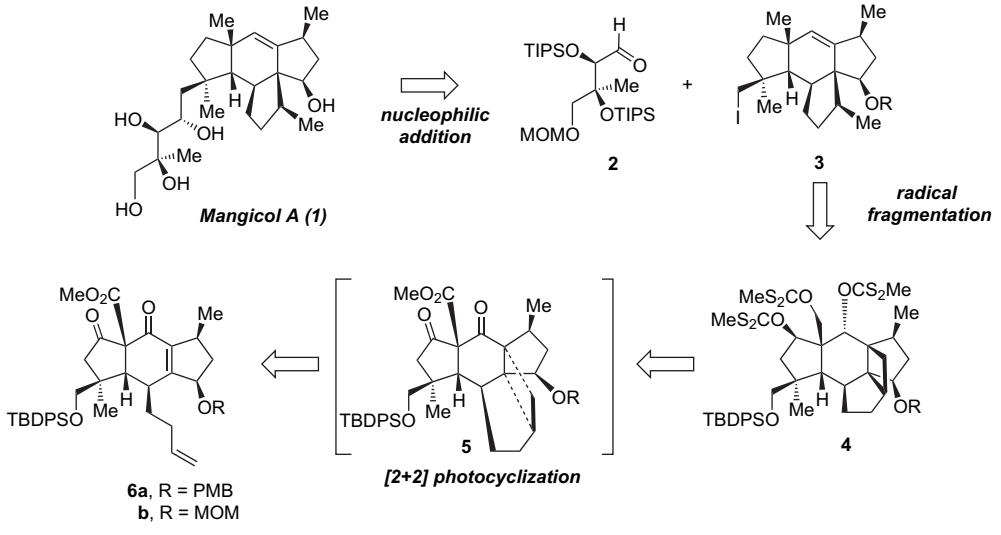
Abstract—Two synthetic approaches to the cytotoxic marine natural product known as mangicol A are described. The starting material common to both pathways is the cyclopentenonecarboxylate **11**. The first tactic involves the 1,4-addition to **11** of the cuprate derivable from iodide **10**, while the second proceeds via base-promoted conjugate addition of the regiospecifically generated enolate anion of **41**. The first strategy proceeds by a series of efficient steps to tricyclic aldol **21** and subsequently to β-diketone **7**. The latter proved to be totally unresponsive to schemes aimed at introduction of a butenyl group. The second approach involves earlier introduction of this substituent as realized in stereocontrolled fashion via transition state **42**. While further passage to **44** proved uneventful, this advanced intermediate and analogs thereof proved remarkably recalcitrant to cyclization in the precedented fashion. In no instance was generation of a suitable product realized. These studies serve to underscore the extent to which steric considerations can complicate matters and the extent to which they must be skirted. Finally, a direct enantioselective route to the side chain aldehyde **2** is detailed.

1. Introduction

In a preceding paper,[1] we reviewed background issues concerning the antiinflammatory agent mangicol A (**1**)[2] and reported on the possible application of intramolecular [4+2] cycloaddition strategies for assembly of its central core.[3] In the light of these early results, the decision was made to evaluate alternative routes to **1** that feature convergent Michael reactions as the mode of structural assembly. As outlined in Scheme 1, the retrosynthesis is keyed to the availability of enedione **6** whose role is ultimately to enter into intramolecular photochemical [2+2] cyclization and



Scheme 1.

Keywords: Mangicols; Conjugate additions; Aldol reactions; Functionalized diquinanes; Steric constraints.
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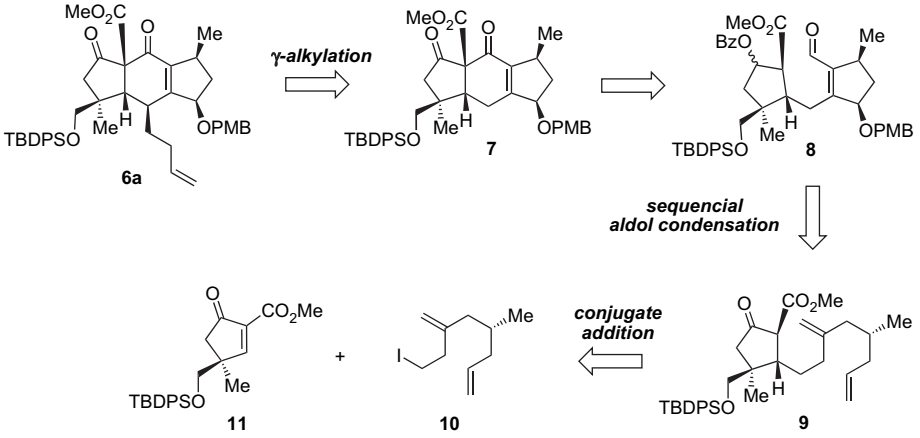
deliver **4**. Presently, the focus of our attention is the need to develop a workable route to **6**. Two subsequences aimed at exploiting conjugate addition pathways to this enedione form the subject of the present account. Also documented is a brief synthesis of the enantiomerically enriched aldehyde **2**.

2. Exploration of a cuprate-based approach

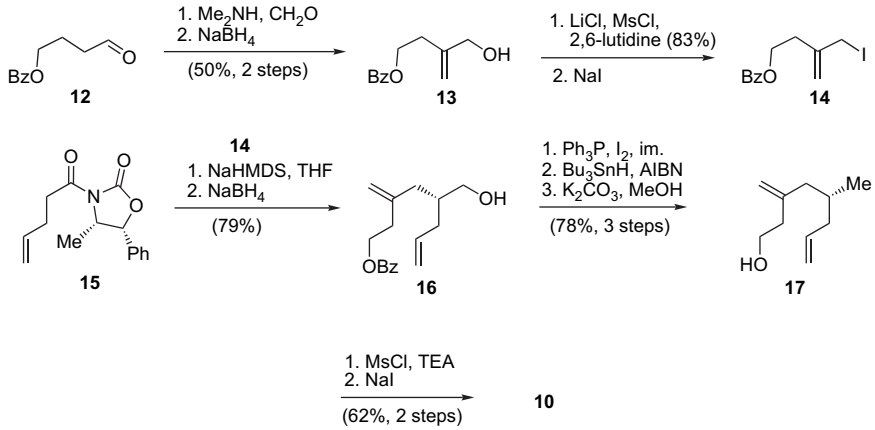
The first option to be explored for ultimately reaching **6a** was based on the suitability of engaging dienyl iodide **10** in 1,4-conjugate addition to the enantiopure cyclopentenonecarboxylate **11**.[1] This step was anticipated to proceed with the very dominant formation of **9** as a result of kinetically favored approach from that direction *syn* to the adjacent methyl substituent (Scheme 2). As matters worked out, the doubly activated nature of the Michael acceptor **11** facilitated capture of the organocopper species derived from **10**.[4] The conversion of **9** to **8**, or a variant of this system, was designed to allow assembly of a highly functionalized cyclopentene, whose cyclization under appropriate conditions would allow the generation of **7**. γ-Alkylation of this cyclohexenone with 4-iodo-1-butene[5] was to ensue, this step setting the stage for more advanced functional group manipulation within **6a**.

Aldehyde **12**, prepared in two steps from commercially available 1,4-butanediol, was methylenated in Mannich fashion[6] and reduced with sodium borohydride to furnish the allylic alcohol **13** (Scheme 3). Formation of iodide **14** was most efficiently accomplished by treatment with lithium chloride and methanesulfonyl chloride in DMF containing 2,6-lutidine, followed by the addition of sodium iodide.[7] The targeted oxazolidinone was generated through reaction of **14** with the sodium enolate of **15** with a de in excess of 95%.[8] Removal of the chiral auxiliary was smoothly achieved with $NaBH_4$. The carbinol **16** so formed was chemoselectively reduced in a two-step process involving initial production of the iodide followed by the action of tri-*n*-butyltin hydride.[9] Finally, the benzoate group was saponified and the resultant chiral alcohol was transformed without event into **10** by a closely related halogenation protocol.

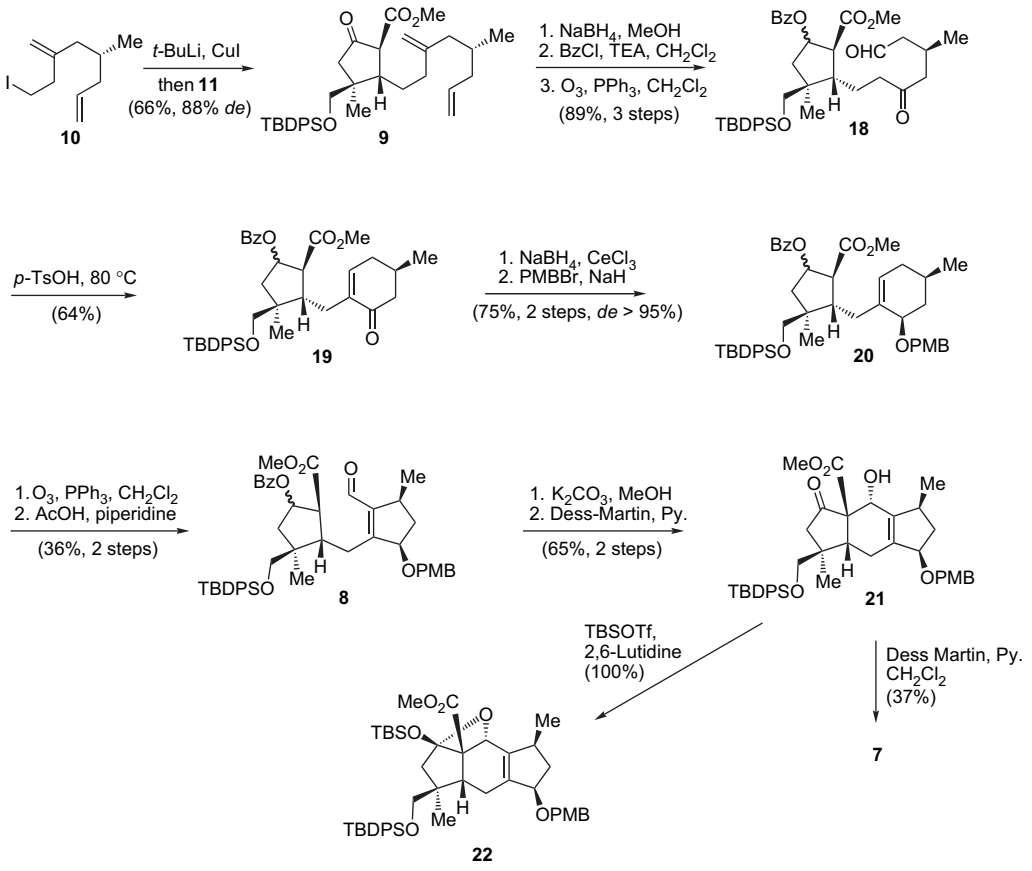
The coupling of iodide **10** to cyclopentenonecarboxylate **11** was most efficiently achieved using *tert*-butyllithium and CuI to form the cuprate. Under these conditions, **9** was isolated as a 16:1 mixture of diastereomers. With the benefit of COSY and NOESY experiments, the major isomer could be readily identified as the expected **9** (Scheme 4). Selective borohydride reduction of the ketone carbonyl in this intermediate gave rise to a 2:1 diastereomeric mixture of alcohols, which were protected as their benzoates. Subsequent reductive ozonolysis furnished the keto aldehyde **18**, which was directly cyclized to cyclohexenone **19** under acidic conditions. Recourse was next made to a Luche reduction



Scheme 2.



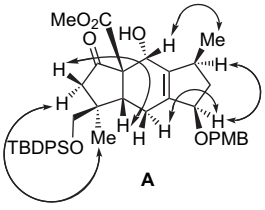
Scheme 3.



Scheme 4.

(de>95%) and subsequent formation of the *p*-methoxybenzyl ether. Ozonolytic of the trisubstituted double bond and ensuing cyclization of the resulting keto aldehyde with piperidine in acetic acid delivered **8** in 36% yield over the two steps.

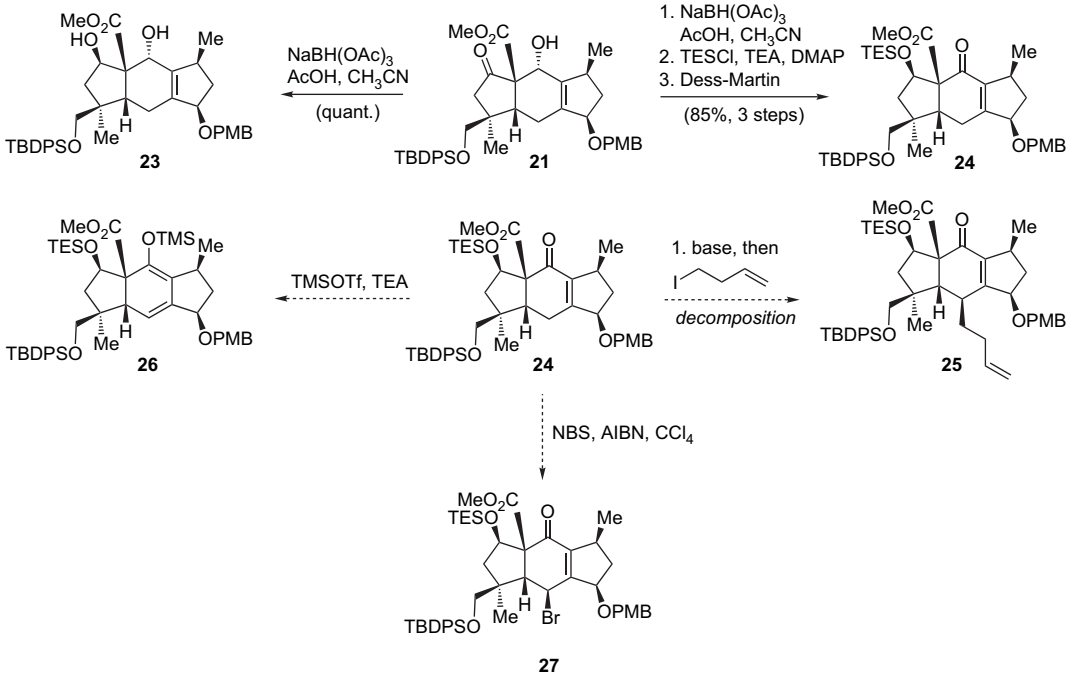
With aldehyde **8** in hand, the time had arrived for removal of the benzoate protecting group and regeneration of the β-keto ester functionality. Pleasingly, use of the Dess–Martin periodinane and pyridine in CH_2Cl_2 proceeded with in situ cyclization to generate the tricyclic aldol **21** as a 10:1 mixture of diastereomers at the allylic alcohol center. The first-stage oxidation is a very quick process (complete in less than 5 min) and cyclization ensues immediately. In contrast, the second-stage oxidation involving **21** is a rather slow process, which required 16 h to reach completion. The stereochemical assignments to **21** are soundly based on ^{1}H NMR, ^{13}C NMR, HMQC, and NOESY experiments (see **A**).



Transient protection of the secondary hydroxyl group in **21** came to be regarded as desirable. When initial attempts to accomplish this transformation with *tert*-butyldimethylsilyl or triethylsilyl chlorides were met with failure, presumably as a result of steric congestion, enhanced reactivity was sought in the form of *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine. These conditions resulted in formation of acetal **22** (100% yield).

Our arrival at the tricyclic intermediates **7** and **21** was met with the breakdown of many potentially useful transformations. For example, attempts to reduce the ester moiety in **21** with $LiAlH_4$ or DIBAL-H led to rather complex product mixtures. Similarly, while **21** could be chemoselectively reduced with sodium triacetoxyborohydride by way of intramolecular hydride transfer[10] with introduction of a β-hydroxyl subunit as in **23** (Scheme 5), controlled conversion to a monoxanthate was not possible as a prelude to tin hydride reduction.[11] Direct reduction of the ketone carbonyl in **21** via the formation of the tosylhydrazone[12] promoted wholesale degradation.

On a more positive note, treatment of **23** with triethylsilyl chloride served as a means for achieving efficient monoprotection. As a result, arrival at **24** proved not to be a challenge. Various options for the exploration of routes to the γ-alkylated product **25** could now begin. The most direct route involving generation of the extended anion of enone **24** and reaction with 4-iodo-1-butene was disadvantaged from the start due to a sensitivity of this intermediate to strong base. Upon admixture with a variety of bases, decomposition was seen to set in quickly in all cases. Experiments designed to generate the conjugated silyl enol ether **26**[13] and to



Scheme 5.

brominate the γ-position as in **27**[5a,14] were likewise met with failure. These and related problems prompted consideration of means for introduction of the butenyl group earlier in the synthesis.

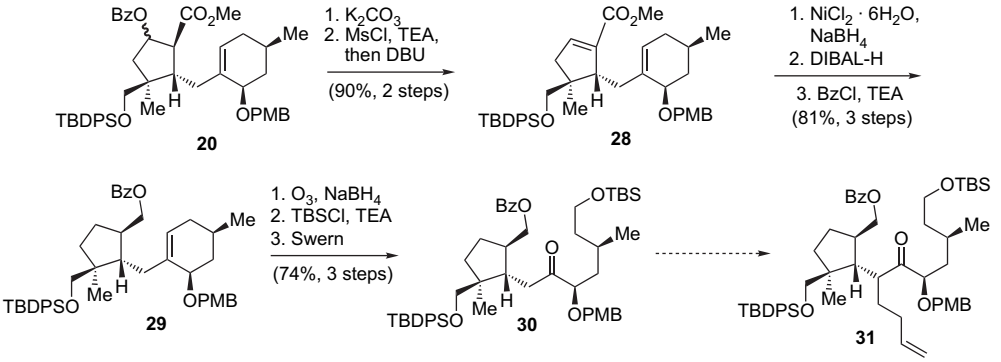
3. Consideration of earlier incorporation of the alkenyl chain

Ketone **30** was successfully prepared from **20** via the sequence outlined in Scheme 6.[15] The benzoate group was excised with potassium carbonate, and the secondary hydroxyl so uncovered was transformed into the mesylate. β-Elimination now became possible by treatment with DBU, and provided **28** in 90% overall yield. Next to be explored was selective reduction of the double bond conjugated with the carbomethoxy substituent. The utilization of $NaBH_4$ and $NiCl_2$ in tandem[16] proved quite amenable to this transformation. There followed the direct reduction to the primary carbinol with DIBAL-H and formation of the benzoate to furnish **29**. Continued success was realized with reductive ozonolysis of the remaining double bond in **29**. The diol so formed proved entirely accommodative of chemoselective O-silylation at the primary site with TBSCl. Finally, the targeted **30** was secured by the application of Swern oxidation conditions.

While the conversion of **20** to **30** proceeded quite satisfactorily, **30** resisted alkylation via its enolate at every turn. These attempts at functionalization included treatment with bases such as NaHMDS, KHMDS, LDA, NaH, and KH, as well as recourse to electrophiles exemplified by 4-bromo-1-butene, 4-iodo-1-butene, allyl bromide, methyl iodide, and gaseous formaldehyde. In the light of these developments, the decision was made to advance on these intermediates in an alternate fashion.

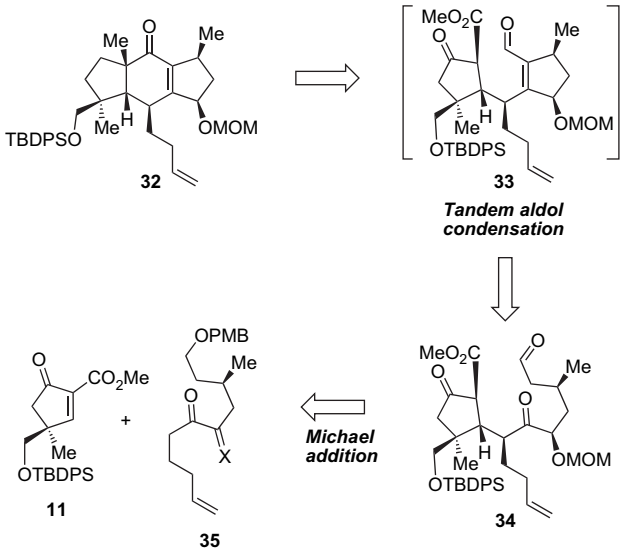
4. The quest for more direct assembly

The prominent complications witnessed so far for achieving proper alkylation of relevant advanced intermediates



Scheme 6.

emphasize the need for a strategic disconnection that makes provision for the earlier introduction of a suitable side chain. To this end, the involvement of **35** as a central building block was considered attractive (Scheme 7). The implementation of this plan called for site-specific deprotonation of **35** in advance of its Michael addition to **11**. The appeal offered by the framework where X was to be an appropriately configured protected carbinol center defined our original thrust in this direction. Further along the retrosynthetic pathway, **34** was to be cyclized to **33** in a manner paralleling the earlier conversion of **19** to **20**. The execution of a second-stage aldol ring closure followed by minor functional group adjustments was to lead to the tricyclic framework represented by **32**.

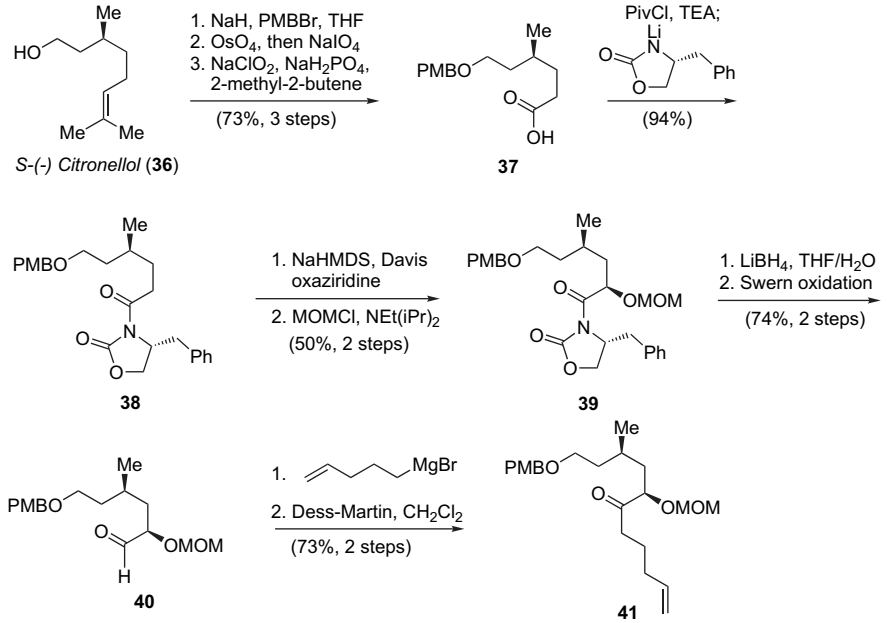


Scheme 7.

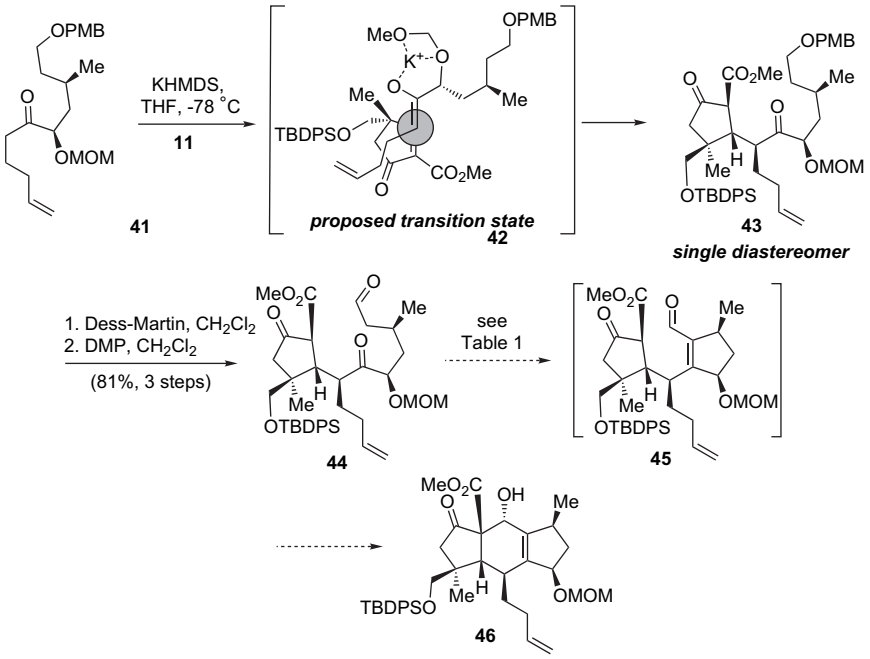
The conversion of *S*-citronellol (**36**) to carboxylic acid **37**, shown in Scheme 8, was conveniently accomplished in a three-step sequence consisting of PMB protection, double bond cleavage via the 1,2-diol, and oxidation with sodium chlorite.[17] The coupling of **37** to the Evans auxiliary (*R*)-4-benzyl-2-oxazolidinone[18] was mediated via the mixed anhydride generated with pivaloyl chloride. The availability of **38** allowed for the implementation of an enantioselective α-hydroxylation step involving the Davis oxaziridine.[19] Although a diastereomeric excess of 5:1 was realized, the enantiomeric purity could be readily enhanced to the 100% level by chromatographic separation of the pair of derived MOM ethers on silica gel. Since attempts to transform **39** into its Weinreb amide resulted in destruction of the material, an alternative pathway involving reduction to the alcohol and Swern oxidation provided aldehyde **40** in 74% overall yield. The route to **41** was then completed by 1,2-addition of 4-pentenylmagnesium bromide and exposure of the resulting carbinol to the Dess–Martin periodinane reagent.[20]

The deprotonation of **41** with KHMDS at −78 °C proceeded with high regioselectivity to generate the enolate anion depicted in **42** (Scheme 9). The intramolecular chelation involving the MOM substituent specifically defined in this transition state serves to enhance steric biases and allows for the specific formation of **43** as the only observed diastereomer. Chemoselective deprotection of the OPMB group was easily accomplished with DDQ in conventional fashion, thereby making possible ensuing periodinane oxidation to the highly functionalized diketo aldehyde **44** in 80% isolated yield.

When conditions previously developed by Hiranuma and Hudlicky[21] for intermolecular aldol condensations of the projected **44**→**45** type were examined (see Table 1, experiments 1 and 5), enamine formation was observed as in the other cases (^{1}H NMR analysis). However, this intermediate underwent no further chemical reaction and resisted cyclization on prolonged heating. Treatment of **44** in the manner devised in entries 2 and 3 of Table 1 resulted in clean amidation of the carbomethoxy group to give **47**, with this conversion



Scheme 8.



Scheme 9.

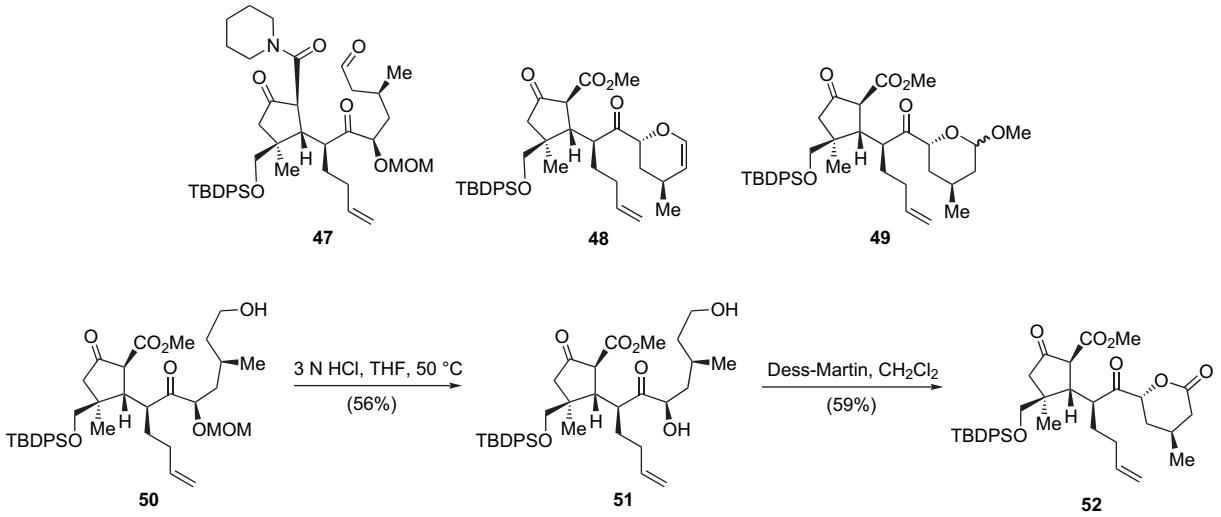
Table 1. Representative conditions applied to **44** for attempted cyclization

Expt.	Reagent	Solvent	Result
1	Piperidine, HOAc	Ether, reflux	Clean enamine formation
2	Piperidine, HOAc	Benzene, reflux	Slow conversion to **47**
3	Piperidine, HOAc	Toluene, reflux	Conversion to **47**
4	Martin sulfurane	CH_2Cl_2, rt	No reaction
5	Pyrrolidine, CSA	Ether, reflux	Clean enamine formation
6	CSA (Dean–Stark)	Benzene, reflux	Formation of **48** and **49**
7	$Et_2NH{\cdot}HCl$	$ClCH_2CH_2Cl$, 70 °C	MOM cleavage and lactol formation **48**

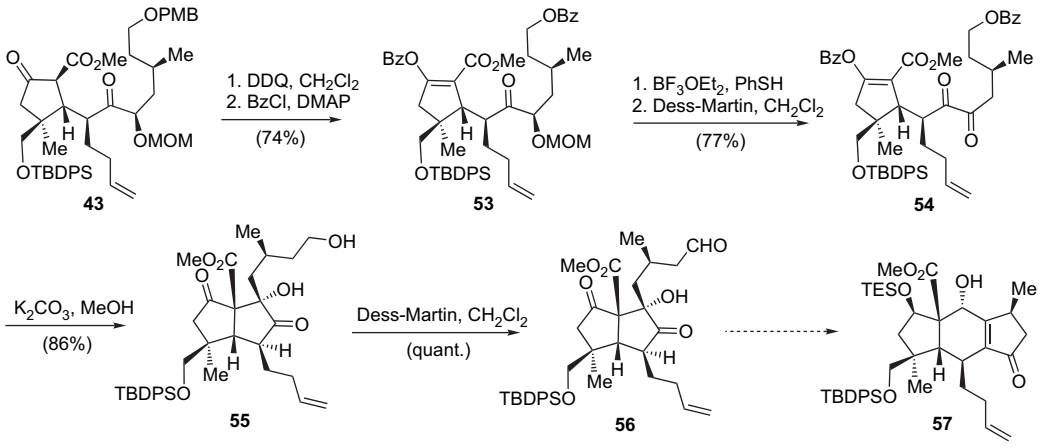
occurring faster in refluxing toluene solution as expected. Other notable transformations included MOM deprotection and subsequent cyclization with lactol formation when conditions such as those in experiment 7 were utilized. More advanced dehydrative elimination to generate the pyran **48** and lactol ether **49** was noted when **44** was heated with CSA in benzene under a Dean–Stark trap. A parallel direction was followed when **50**, the primary carbinol derived from **43** (Scheme 9), was further deprotected as in **51** and subjected to periodinane oxidation. When processed in this manner, lactone **52** was formed as the predominant product (Scheme 10).

5. Determining the suitability of aldol cyclizations for construction of the tricyclic core

We next investigated the possibility of forming a major portion of the mangicol A framework through an aldol ring-forming reaction. To enlist the proper regioselectivity, the strategy was designed to involve an α-diketone such as that resident in **54**. Although several reaction parameters

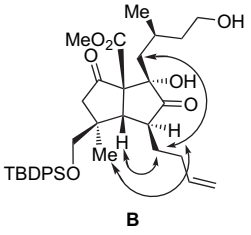


Scheme 10.



Scheme 11.

are thereby introduced, the added complexity was expected to shed light on which mode of cyclization would be kinetically favored. Another advantage would stem from the reversibility of aldol condensations, which could serve to clarify available thermodynamic options as well. Thus, **43** was transformed into enol benzoate **53**, thereby making possible removal of the MOM protection group[22] and mild oxidation to gain access to **54** (Scheme 11). The benzoate groups were then hydrolyzed with K_2CO_3 in methanol, a process during which spontaneous passage to diquinane **55** materialized. Although this eventuality was not the desired one, two positive consequences of this reaction pathway were made apparent. First, our provisional assignments to the configuration of several stereocenters could now be fully corroborated by NOE correlations (see **B**).



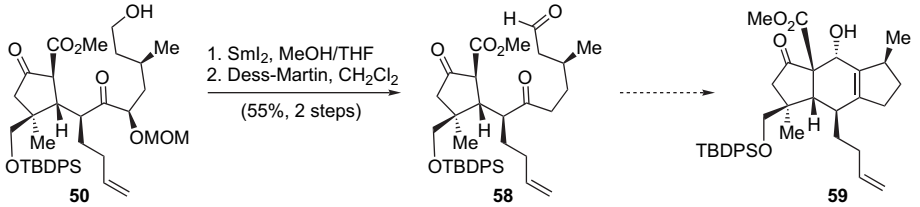
B

Secondly, the availability of **55** allowed for one-step conversion to aldehyde **56**. However, all attempts to bring about retroaldolization with **56** and alternative generation of **57** were to no avail, nor was any reaction observed when **58** was comparably exposed to a range of basic conditions. In fact, **56** and **58** are quite stable entities and can be stored on the shelf for prolonged periods of time.

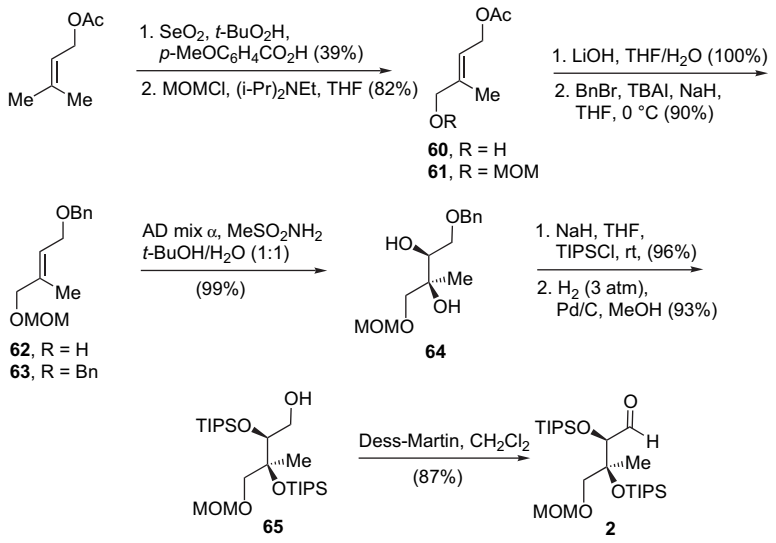
A final approach was envisioned to involve samarium diiodide reduction of carbinol **50** and subsequent Dess–Martin oxidation to obtain keto aldehyde **58**. We attempted the transformation of **58** to **59** by applying the same conditions as from **44** to **45**, with resultant in destruction of **58** (Scheme 12).

6. Synthesis of the side chain

The launching point for arrival at **2** was the allylic alcohol **60** previously shown by Mechelke and Wiemer[23] to be available in two steps from prenyl alcohol (Scheme 13). MOM protection of the hydroxyl group in **60** was followed by deacetylation and O-benzylation to deliver **63**. With this functionality in place, it proved straightforward to effect Sharpless asymmetric dihydroxylation[24] with AD-mix-α to afford **64** in 99% yield. This critical step was followed by reaction with triisopropylsilyl chloride in the presence of NaH, thus making possible chemoselective debenzylation[25] and generation of the primary alcohol **65**. This very efficient two-step process made possible the ultimate production of the targeted **2** via the Dess–Martin protocol.[20]



Scheme 12.



Scheme 13.

7. Overview

In this paper, we have detailed the ability of cyclopentenonecarboxylate **11** to serve as a Michael acceptor under two sets of circumstances. In the first instances, the employment of the cuprate derived from **10** as co-reagent proved to be beneficial since subsequent conversion to the tricyclic aldol **21** and diketone **7** was efficiently realized. Our inability to bring about the proper alkylation of these advanced intermediates prompted examination of a second approach, which involved the conjugate addition of the enolate of **41** to **11**. While the subsequent elaboration of **44** proceeded uneventfully, the intrinsic inability to bring about the appropriate cyclization at this stage highlighted the impact of a butenyl side chain on impeding ring formation. While these strategies ultimately prove unsuccessful, they are expected to facilitate further investigation of the synthetic chemistry of the mangicols. The availability of aldehyde **2** constitutes a positive step in that direction.

8. Experimental

8.1. Alkylation of oxazolidinone 15 with iodide 14. Reduction to the hydroxy benzoate

Oxazolidinone **15** (13.41 g, 51.7 mmol) was dissolved in dry THF (85 mL) and cooled to −78 °C at which point sodium hexamethyldisilazide (52 mL, 1.51 M) was introduced. The reaction mixture was stirred for 1 h when iodide **14** (12.3 g, 34.2 mmol) was added via cannula as a solution in dry THF (65 mL). After 3 h, reaction was judged to be completed and water was added. After warming to rt, the product was extracted into CH_2Cl_2 (3×100 mL) and the combined organic layers were dried and freed of solvent to leave an orange residue that was dissolved in MeOH (350 mL) at 0 °C. $NaBH_4$ (9.85 g, 0.26 mmol) was added in portions over a period of 30 min. The reaction mixture was stirred overnight, quenched with water, and extracted with ethyl acetate (3×350 mL). The combined organic layers were dried and the solvent was evaporated to leave an oil that solidified. Flash chromatography of the residue on silica gel (gradient–hexane–ethyl acetate=5:1 to 3:1) afforded 7.4 g (79%) of **16**; IR (neat, cm^{-1}) 3434, 1721, 1641; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2H), 7.63–7.29 (m, 3H), 5.92–5.72 (m, 1H), 5.13–4.87 (m, 2H), 4.45 (dt, J=1.6, 6.9 Hz, 2H), 5.58 (d, J=5.3 Hz, 2H), 2.51 (t, J=6.8 Hz, 2H), 2.23–2.00 (m, 4H), 1.92–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 143.5, 136.3, 132.6, 129.9, 129.2 (2C), 128.0 (2C), 127.0, 126.6, 116.2, 113.0, 64.4, 63.0, 38.0, 37.6, 34.1, 34.4; HRMS ES m/z $(M+Na)^+$ calcd 297.1461, obsd 297.1460.

8.2. Coupling of 10 with 11

A 250 mL round-bottomed flask was charged with **10** (4.06 g, 15.4 mmol) and ether (30 mL), and the solution was cooled to −78 °C while *t*-BuLi (18.2 mL, 1.7 M in pentane) was introduced. The mixture was stirred in the cold for 5 min, then transferred to a suspension of CuI (1.46 g, 7.67 mmol) in dry ether (20 mL) being stirred at −20 °C. The mixture was stirred for another 5 min, cooled to −30 °C, and treated with **11** (3.25 g, 9.64 mmol) as a solution in dry ether (25 mL). The reaction mixture developed a blue color while it was being stirred for another 50 min. After quenching with saturated NH_4Cl solution (200 mL), the product was extracted into CH_2Cl_2 (3×300 mL), the combined organic layers were dried, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=40:1 to 20:1) to give 2.86 g (66%) of **9** as a pale yellowish oil; IR (neat, cm^{-1}) 1757, 1730, 1640; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.60 (m, 4H), 7.60–7.32 (m, 6H), 5.87–5.65 (m, 1H), 5.07–4.92 (m, 2H), 4.72 (s, 2H), 3.75 (s, 3H), 3.60 (d, J=10.2 Hz, 1H), 3.49 (dd, J=10.2, 1.0 Hz, 1H), 3.10–2.77 (m, 3H), 2.13–1.20 (series of m, 9H), 1.10 (s, 9H), 0.88–0.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 170.4, 147.6, 137.1, 135.5 (4C), 133.1 (2C), 129.8 (2C), 127.7 (4C), 115.8, 110.7, 99.8, 67.3, 60.2, 52.4, 50.0, 43.9, 43.7, 42.7, 40.9, 34.4, 30.7, 28.1, 26.8 (3C), 19.3, 17.7; HRMS ES m/z $(M+Na)^+$ calcd 583.3214, obsd 583.3229; $[\alpha]_D^{20}$ 27.0 (c 1.07, C_6H_6).

8.3. Cyclohexenone 19

A solution of **9** (5.80 g, 10.3 mmol) in methanol (400 mL) was cooled to 0 °C, treated with $NaBH_4$ (783 mg, 20.6 mmol) over a period of 5 min, stirred for another 10 min, quenched with water (250 mL), and extracted with CH_2Cl_2 (3×400 mL). The combined organic layers were dried and evaporated to give 6.0 g (100%) of the β-hydroxy ester as a pale yellow foam which was not further purified; IR (neat, cm^{-1}) 3455, 1734, 1641; ^1H NMR (250 MHz, $CDCl_3$, mixture of diastereomers) δ 7.75–7.63 (m, 4H), 7.48–7.28 (m, 6H), 5.84–5.63 (m, 1H), 5.05–4.93 (m, 2H), 4.68 (d, J=5.0 Hz, 2H), 4.42–4.25 (m, 1H), 3.77–3.68 (m, 3H), 3.41 (s, 1H), 3.35 (d, J=1.1 Hz, 1H), 2.67–2.50 (m, 2H), 2.40–1.12 (series of m, 9H), 1.00–0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 175.7 and 173.9, 148.2 and 148.2, 137.3, 135.8 (4C), 133.5 (2C) and 132.9 (2C), 129.8 (2C), 127.6 (4C), 115.8, 110.4 and 110.3, 100.0, 75.9, 72.5, 71.3, 70.5, 59.4, 56.3, 53.8, 51.7, 47.2, 45.4, 45.2, 43.7, 43.5, 41.0, 34.6 and 34.3, 30.7, 29.9, 29.4, 28.7 and 28.6, 26.9 and 26.8, 20.5, 20.2, 19.3; HRMS ES m/z $(M+Na)^+$ calcd 585.3371, obsd 585.3351.

The alcohol above (117 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (5 mL), cooled to 0 °C, and treated sequentially with triethylamine (0.15 mL, 1.04 mmol), benzoyl chloride (75 μL, 0.62 mmol), and DMAP (25 mg, 0.21 mmol). The reaction mixture was stirred for 9 h, quenched with water (20 mL), and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried and evaporated to dryness. The residue was purified by chromatography on silica gel (gradient–hexane to hexane–ethyl acetate=10:1) to give 124 mg (89%) of the benzoate as a colorless oil; IR (neat, cm^{-1}) 1740, 1722; ^1H NMR (250 MHz, $CDCl_3$, mixture of diastereomers) δ 8.08–7.92 (m, 2H), 7.70–7.23 (series of m, 13H), 5.82–5.62 (m, 1.6H) and 5.53–5.42 (m, 0.4H), 5.05–4.97 (m, 1H), 4.95 (s, 1H), 4.73–4.64 (m, 2H), 3.74 (s, 1.1H) and 3.57 (s, 1.6H), 3.56–3.43 (m, 2H), 2.98 (dd, J=10.3, 8.0 Hz, 0.6H), 2.84 (dd, J=10.7, 5.3 Hz, 0.4H), 2.50–2.61 (m, 0.7H), 2.55 (dd, J=14.2, 8.0 Hz, 0.4H), 2.44–2.30 (m, 0.5H), 2.22 (dd, J=13.5, 4.9 Hz, 0.7H), 2.13–1.20 (series of m, 9H), 1.10 (s, 3H), 1.06 (s, 9H), 0.83 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 175.2 and 172.2, 165.7 and 165.5, 148.0 and 147.9, 135.6 (4C), 133.3 (2C), 130.1 and 129.6 (2C), 127.6 and 127.5 (4C), 115.7 and 115.7, 110.5 and 110.3, 74.3, 70.9 and 69.4, 57.4, 53.7, 53.3, 51.8 and 51.5, 46.8, 46.4, 45.1, 44.8, 43.6, 43.0, 42.6, 41.0, 34.4 and 34.1, 30.6, 28.6 and 28.4, 26.8 (3C), 19.3 and 19.0, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 689.3633, obsd 689.3616.

The benzoyl ester (7.2 g, 10.8 mmol) from above was dissolved in a 1:1 CH_2Cl_2–MeOH mixture (500 mL), cooled to −78 °C, and ozonolyzed until a blue color persisted. After purging with oxygen, triphenylphosphine (4.25 g, 16.2 mmol) was added and the solution was warmed to rt. The solvent was evaporated and the white solid was dissolved in dry benzene (150 mL). The benzene was evaporated again and the remaining solid was redissolved in dry benzene (600 mL). *p*-Toluenesulfonic acid (1.08 g, 5.6 mmol) was introduced and the mixture was heated at 75 °C overnight, cooled to rt, and freed of solvent. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=10:1 to 5:1) to give 4.48 g (64%) of pure **19**; IR (neat, cm^{-1}) 1721, 1677; ^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.06–8.00 (m, 0.7H), 7.97–7.90 (m, 1.3H), 7.74–7.62 (m, 5H), 7.62–7.28 (m, 8H), 6.69–6.60 (m, 1H), 5.66 (dd, J=14.4, 6.4 Hz, 0.8H), 5.47–5.37 (m, 0.2H), 3.66 (s, 1H), 3.56 (dd, J=13.7, 9.9 Hz, 1H), 3.49 (s, 3H), 3.03 (dd, J=10.9, 8.1 Hz, 0.7H), 2.83 (dd, J=10.7, 5.3 Hz, 0.3H), 2.75 (dt, J=10.8, 4.3 Hz, 0.7H), 2.60–1.77 (series of m, 9H), 1.73 (dd, J=14.2, 3.2 Hz, 0.3H), 1.10 (s, 2.1H) and 1.09 (s, 0.7H), 1.06 (s, 9H), 1.00 (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 198.8 and 198.5, 174.5 and 171.7, 165.6 and 165.3, 145.3 and 144.8, 137.9 and 137.2, 135.5 (4C), 133.4 (2C), 132.7, 129.8, 129.5 (2C), 129.4 (2C), 129.1 (2C), 127.5 (2C), 77.4, 70.3 and 69.9, 56.7, 53.2, 51.7 and 51.4, 46.3 and 46.2, 45.5, 45.4 and 45.3, 44.3, 43.3 and 42.9, 34.3 and 34.2, 30.3 and 30.2, 29.7 and 29.4, 26.7, 21.2, 19.3, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 675.3112, obsd 675.3129.

8.4. Unsaturated aldehyde 8

A solution of **20** (1.55 g, 2.00 mmol) in 1:1 MeOH–CH_2Cl_2 was cooled to −78 °C, ozonolyzed until a blue color persisted, and purged with oxygen for 15 min. Triphenylphosphine (784 mg, 3.00 mmol) was added, the reaction mixture was warmed to rt, the solvent was evaporated, and the residue was dissolved in dry ether (125 mL) and repeatedly evaporated to dryness. At this point, dry ether (100 mL) and piperidine (100 μL, 1.00 mmol) were added. After 5 min, AcOH (57 μL, 1.00) was introduced, and the mixture was heated to reflux for 4 days. Flash column chromatography of the residue after solvent evaporation (hexane–ethyl acetate=5:1) furnished 0.53 g (36%) of **8**; ^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 10.06 (s, 0.5H) and 10.05 (s, 0.5H), 8.09–7.88 (m, 2H), 7.72–7.20 (m, 13H), 7.12–7.00 (m, 0.4H), 6.85 (d, J=8.6 Hz, 1H), 6.75–6.66 (m, 0.4H), 5.72–5.60 (m, 0.4H), 5.56–5.47 (m, 0.4H), 4.57–4.27 (m, 3H), 3.82 (s, 0.4H), 3.78 (s, 2.6H), 3.76–3.70 (m, 0.4H), 3.60 (s, 1H), 3.49 (s, 1H), 3.46–3.30 (m, 1H), 3.28 (d, J=10.0 Hz, 0.4H), 3.10–1.90 (series of m, 10.6H), 1.70 (dd, J=14.5, 2.49 Hz, 0.4H), 1.40–1.20 (m, 1.3H), 1.17 (s, 1.5H), 1.11 (s, 4.5H), 1.08 (s, 1.5H), 1.05 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 189.0 and 188.9, 174.1 and 171.2, 165.9 and 165.6, 160.2 and 159.3, 143.3 and 143.0, 135.7 (4C), 133.1, 130.3, 130.2, 130.1, 129.9, 129.8, 129.7 (2C), 129.6 (2C), 129.5, 129.3, 129.2, 128.4, 127.8, 113.8, 99.7, 83.8, 77.2 and 73.6, 71.7 and 71.5, 70.1 and 69.7, 57.1, 55.2, 53.3, 52.0 and 51.8, 47.0 and 45.1, 45.9 and 44.2, 43.4 and 43.2, 37.1 and 37.0, 36.5 and 36.4, 26.9 (3C), 25.8 and 25.7, 20.5 and 20.4, 19.4 and 19.3, 19.1 and 18.7; HRMS ES m/z $(M+Na)^+$ calcd 811.3637, obsd 811.3635.

8.5. α-Oxygenation of 38 and MOM protection

To a solution of **38** (48.9 mg, 0.12 mmol) in dry THF (1.5 mL) was added sodium hexamethyldisilazide (141 μL, 0.141 mmol, 1 M in THF) at −78 °C. The mixture was stirred for 30 min, treated with the Davis reagent (39.9 mg, 0.15 mmol) dissolved in dry THF (1 mL) in a dropwise manner and quenched after 10 min with a solution of camphorsulfonic acid (137 mg, 0.59 mmol) in THF (0.9 mL). The

cooling bath was removed, the white slurry was stirred for 20 min, water (20 mL) and ether were added, and the product was extracted into CH_2Cl_2 (4×10 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 4:1) to give a colorless oil (37.7 mg, 74%) as a mixture of α-hydroxylated diastereomers (de 76%); IR (neat, cm^{-1}) 1783, 1697, 1247; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.13 (m, 7H), 6.87 (dt, J=8.6, 2.8 Hz, 2H), 5.07 (br d, J=7.2 Hz, 1H), 4.78–4.70 (m, 1H), 4.43 (dd, J=15.4, 11.5, 2H), 4.27–4.19 (m, 2H), 3.80 (s, 3H), 3.44–3.13 (m, 3H), 3.19 (dd, J=13.5, 3.2 Hz, 1H), 2.83 (dd, J=13.4, 9.3 Hz, 1H), 2.03–1.46 (series of m, 5H), 0.98 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.1, 153.2, 134.9, 130.8, 129.5 (2C), 129.3 (2C), 129.1 (2C), 127.5, 113.7 (2C), 72.5, 69.4, 68.3, 66.9, 55.5, 55.3, 41.3, 37.5, 35.3, 27.1, 20.6; HRMS ES m/z $(M+Na)^+$ calcd 464.2044, obsd 464.2062; $[\alpha]_D^{20}$ −29.2 (c 1.89, $CHCl_3$).

The above product (246 mg, 0.56 mmol) was dissolved in dry CH_2Cl_2 (6 mL) and diisopropylethylamine (573 μL, 3.35 mmol) was added. The reaction mixture was cooled to 0 °C and MOMCl (252 μL, 3.35 mmol) was introduced and stirring was maintained overnight. Half-saturated NH_4Cl solution (5 mL) was introduced, the aqueous layer was extracted with CH_2Cl_2 (4×4 mL), and the combined organic layers were filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 4:1) to provide 180 mg (67%) of **39** as a single diastereomer; IR (neat, cm^{-1}) 1780, 1708, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.13 (m, 7H), 6.86 (d, J=8.6 Hz, 2H), 5.36 (dd, J=7.4, 5.5 Hz, 1H), 4.77 (d, J=6.9 Hz, 1H), 4.57–4.20 (m, 4H), 4.42 (dd, J=17.4, 11.5 Hz, 2H), 4.16 (d, J=5.2 Hz, 2H), 3.79 (s, 3H), 3.54–3.44 (m, 2H), 3.38 (s, 3H), 3.32 (dd, J=13.1, 3.0 Hz, 1H), 2.79 (dd, J=13.4, 9.5 Hz, 1H), 2.00–1.78 (m, 2H), 1.72–1.57 (m, 3H), 1.46–1.30 (m, 1H), 0.96 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.0, 153.0, 135.2, 130.9, 129.5 (2C), 129.2 (2C), 129.0 (2C), 127.4, 113.7 (2C), 97.5, 74.5, 72.5, 68.0, 66.4, 56.3, 55.3 (2C), 40.4, 37.5, 35.3, 26.8, 20.5; HRMS ES m/z $(M+Na)^+$ calcd 508.2306, obsd 508.2320; $[\alpha]_D^{20}$ −27.2 (c 1.24, $CHCl_3$).

8.6. Ketone 41

5-Bromopentene (2.19 mL, 19.7 mmol) was added to a suspension of activated Mg turnings (478 mg, 19.7 mmol) in dry ether (27 mL) and a crystal of I_2. After 1 h, a solution of **40** in ether cooled to −78 °C was introduced via cannula. The reaction mixture was stirred for 30 min at −78 °C and for 20 min at 0 °C prior to quenching with saturated NH_4Cl solution and extraction with ether. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 5:1) to give the alcohol (1.37 g, 85%). The alcohol (1.37 g) was immediately oxidized to **41**. Dissolution in dry CH_2Cl_2 (42 mL) and pyridine (3.2 mL, 31.0 mmol) preceded addition of the Dess–Martin periodinane (3.43 mg, 9.0 mmol). The reaction mixture was stirred overnight and quenched with a 1:1 $Na_2S_2O_3$–$NaHCO_3$ solution (40 mL). The biphasic mixture was stirred for 3 h, and extracted with ether (3×30 mL). The combined organic layers were dried and evaporated to dryness under high vacuum to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=25:1 to 10:1) to give 1.17 g (86%) of **41**; IR (neat, cm^{-1}) 1716, 1613, 1514; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J=9.0 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 5.84–5.67 (m, 1H), 5.06–4.94 (m, 2H), 4.59 (dd, J=10.1, 6.9 Hz, 2H), 4.41 (dd, J=11.6, 10.1 Hz, 2H), 4.07 (dd, J=8.1, 5.4 Hz, 1H), 3.80 (s, 3H), 3.57–3.48 (m, 2H), 3.33 (s, 3H), 2.47 (t, J=7.2 Hz, 2H), 2.04 (q, J=4.4 Hz, 2H), 1.38–1.33 (m, 5H), 0.93 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 130.6, 129.2 (2C), 115.2, 113.7 (2C), 96.5, 81.0, 72.6, 67.9, 56.1, 55.3, 39.4, 37.2, 35.7, 33.1, 26.7, 22.3, 20.3; HRMS ES m/z $(M+Na)^+$ calcd 401.2298, obsd 401.2301; $[\alpha]_D^{20}$ −24.2 (c 1.54, $CHCl_3$).

8.7. Coupling of 41 to 11. Deprotection of 43

Ketone **41** (538 mg, 1.42 mmol) was dissolved in dry THF (6.7 mL) and potassium hexamethyldisilazide (2.84 mL, 1.42 mmol, 0.5 M in toluene) was added at −78 °C within 20 s. The mixture turned red after the addition of the first drops and finally changed to an orange solution after a few minutes. Stirring was maintained at −78 °C for 1 h. A solution of **11** (500 mg, 1.18 mmol) in dry THF (3.6 mL) precooled at −78 °C was transferred in and stirring was maintained for 5 min prior to quenching with saturated NH_4Cl solution (20 mL). After extraction with ether (3×20 mL), the combined organic layers were dried and evaporated to leave an oil that was purified by rapid filtration chromatography through silica gel to afford 716 mg of **43**.

Coupling product **43** (1.28 g, 1.60 mmol) was dissolved in 10:1 CH_2Cl_2–H_2O (47 mL) and DDQ (544 mg, 2.40 mmol) was introduced. The reaction mixture turned green-black within seconds and after some minutes became intense orange in color. The product was extracted into CH_2Cl_2 (3×20 mL), and the combined organic layers were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (gradient–hexane–ethyl acetate=8:1 to 3:1) to give a total of 826 mg (76%) of pure carbinol as a colorless oil, along with 119 mg of a mixed fraction which was further purified to give 878 mg (81%) of **50**; IR (neat, cm^{-1}) 3512, 1751, 1726; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.18 (m, 4H), 7.50–7.34 (m, 6H), 5.73–5.55 (m, 1H), 5.00–4.90 (m, 2H), 4.55 (dd, J=12.3, 6.8 Hz, 2H), 4.00 (t, J=4.0 Hz, 1H), 3.80–3.55 (m, 5H), 3.73 (s, 3H), 3.49–3.30 (m, 2H), 3.30 (s, 3H), 2.94 (dd, J=8.1, 5.7 Hz, 1H), 2.53 (dd, J=17.6, 1.3 Hz, 1H), 2.30 (d, J=17.6 Hz, 1H), 2.10–1.18 (m, 9H), 1.14 (s, 3H), 1.03 (s, 9H), 0.89 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 208.8, 170.5, 137.2, 135.8 (4C), 132.6, 132.4, 130.0 (4C), 127.8 (2C), 115.6, 96.3, 80.3, 68.3, 60.3, 60.2, 56.2, 52.6, 51.7, 48.0, 45.9, 43.0, 38.8, 37.9, 30.3, 29.7, 29.2, 26.7 (3C), 26.1, 24.2, 20.3, 19.1; HRMS ES m/z $(M+Na)^+$ calcd 703.3642, obsd 703.3637; $[\alpha]_D^{20}$ −18.4 (c 4.12, $CHCl_3$).

8.8. Diquinane 55

Diketone **54** (79.3 mg, 0.094 mmol) was dissolved in MeOH (4.8 mL), potassium carbonate (172.9 mg, 1.25 mmol) was added, and the suspension was stirred at rt for 4 h until the reaction mixture was quenched with saturated NH_4Cl

solution (5 mL), and extracted with ether (4×3 mL). The combined organic layers were dried and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=2:1 to 1:1) to yield **55** (48.1 mg, 80%); IR (neat, cm^{-1}) 3431, 1708, 1218; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 4H), 7.48–7.34 (m, 6H), 5.73–5.62 (m, 1H), 5.0–4.90 (m, 2H), 3.78–3.58 (m, 3H), 3.64 (s, 3H), 3.38–3.30 (m, 2H), 2.50 (t, J=6.5 Hz, 1H), 2.40 (d, J=15.5 Hz, 1H), 2.34 (dd, J=12.5, 7.0 Hz, 1H), 2.10–1.95 (m, 2H), 1.84 (dt, J=6.5, 6.5 Hz, 1H), 1.72–1.61 (m, 1H), 1.62–1.48 (m, 2H), 1.40–1.30 (m, 1H), 1.08 (s, 9H), 1.06 (s, 3H), 0.87 (d, J=5.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 175.4, 167.3, 157.7, 147.8, 137.5, 135.7 (2C), 132.9 (2C), 129.8, 127.7 (2C), 115.4, 69.5, 60.5, 52.0, 51.3, 47.7, 42.4, 38.9, 38.2, 32.8, 30.7, 30.0, 29.7, 29.6, 26.9 (3C), 20.6, 20.1, 19.3; HRMS ES m/z $(M+Na)^+$ calcd 657.3224, obsd 657.3206; $[\alpha]_D^{20}$ −31.12 (c 1.12, $CHCl_3$).

8.9. Aldehyde 58

Alcohol **50** (249.9 mg, 0.368 mmol) was dissolved in a 2:1 THF–MeOH mixture (13 mL) and SmI_2 was added until the deep blue color persisted (5.4 mL, 0.54 M suspension in THF). Stirring was continued for another 15 min, and the reaction mixture was quenched with a 1:1 THF–H_2O mixture (10 mL) when the color disappeared. Then HCl (2 mL, 2 N solution) followed by water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=4:1 to 3:1) to afford 189.4 (83%) of pure product; IR (neat, cm^{-1}) 3513, 1757, 1728, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.54 (m, 4H), 7.52–7.33 (m, 6H), 5.65–5.48 (m, 1H), 4.99–4.86 (m, 2H), 3.78–3.64 (m, 1H), 3.70 (s, 3H), 3.59 (d, J=10.4 Hz, 1H), 3.45–3.37 (m, 1H), 3.37 (d, J=10.4 Hz, 1H), 2.83–2.70 (m, 2H), 2.47 (d, J=18.0 Hz, 1H), 2.33 (d, J=18.0 Hz, 1H), 2.40–2.30 (m, 1H), 1.90–1.15 (series of m, 9H), 1.13 (s, 3H), 1.06 (s, 9H), 0.88 (d, J=5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 208.7, 170.4, 137.3, 136.2, 135.7, 132.9, 132.2, 130.2, 127.9, 127.7, 115.5, 69.0, 60.8, 60.5, 52.6, 52.3, 52.1, 49.6, 43.2, 39.6, 30.9, 29.4, 28.8, 26.9, 24.8, 19.4, 17.9; HRMS ES m/z $(M+Na)^+$ calcd 643.3451, obsd 643.3599; $[\alpha]_D^{20}$ −40.09 (c 1.39, $CHCl_3$).

The above alcohol (170.9 mg, 0.275 mmol) was dissolved in dry CH_2Cl_2 (34 mL), Dess–Martin periodinane (209.1 mg, 0.550 mmol) was added, the mixture was stirred for 1.5 h, quenched by the addition of saturated 1:1 $Na_2S_2O_3$–$NaHCO_3$ solution (10 mL), and extracted with ether (3×25 mL). The combined organic layers were dried and evaporated to give a residue that was purified by flash chromatography on silica gel (hexane–ethyl acetate=4:1) to give pure **58** (164.6, 91%); IR (neat, cm^{-1}) 1757, 1726, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J=2.0 Hz, 1H), 7.72–7.52 (m, 4H), 7.52–7.32 (m, 6H), 5.66–5.47 (m, 1H), 5.96–4.84 (m, 2H), 3.72–3.62 (m, 1H), 3.67 (s, 3H), 3.58 (d, J=10.5 Hz, 1H), 3.94–3.86 (m, 1H), 3.36 (d, J=10.5 Hz, 1H), 2.81–2.67 (m, 2H), 2.46 (d, J=18.0 Hz, 1H), 2.42–2.30 (m, 2H), 2.23 (dd, J=7.7, 5.4 Hz, 1H), 2.60–1.15 (series of m, 6H), 1.11 (s, 3H), 1.07 (s, 9H), 0.91 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 208.5, 202.2, 170.3, 137.2, 135.8 (4C), 132.4, 132.0, 130.2 (2C), 127.9 (4C), 115.6, 69.0, 60.8, 52.6, 52.2, 52.1, 50.9, 49.7, 42.7, 42.5, 31.0, 30.9, 29.7, 27.3, 27.0 (3H), 24.8, 19.6, 18.9; HRMS ES m/z $(M+Na)^+$ calcd 641.3274, obsd 641.3297; $[\alpha]_D^{20}$ −40.0 (c 1.03, $CHCl_3$).

8.10. Asymmetric dihydroxylation of 63

AD-mix-α [1.19 g containing 2.0 mg of $K_2OsO_4\cdot 2H_2O$, 6.5 mg of $(DHQ)_2$–PHAL, 0.35 g of K_2CO_3, and 0.83 g of $K_3Fe(CN)_6$] was added to 8.6 mL of a 1:1 H_2O–*tert*-butyl alcohol solvent system. The mixture was stirred vigorously at rt until dissolution was complete. Methanesufonamide (81 mg, 0.85 mmol) was introduced, the reaction mixture was cooled to 0 °C, and **63** (200 mg, 0.85 mmol) was added in one portion. After 20 h in the cold, the reaction mixture was quenched with solid Na_2SO_3 (1.30 g, 12.62 mmol), allowed to warm to rt for 1 h, and extracted with ethyl acetate (5×10 mL). The combined organic extracts were washed with 2 M KOH (5 mL), dried, and concentrated prior to flash chromatography on silica gel (hexane–ethyl acetate=2:3). There was isolated 230 mg (99%) of **64** as a colorless oil; IR (neat, cm^{-1}) 3460, 1454, 1110; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.63 (s, 2H), 4.57 (s, 2H), 3.83 (dt, J=6.3, 4.0 Hz, 1H), 3.73–3.61 (m, 2H), 3.59 (d, J=9.7 Hz, 1H), 3.49 (d, J=9.7 Hz, 2H), 3.36 (s, 3H), 3.03 (s, 1H), 2.96 (d, J=4.4 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.5 (2C), 127.8, 127.7 (2C), 99.7, 96.9, 73.6, 73.2, 73.0, 72.7, 71.1, 55.3, 21.0; HRMS ES m/z $(M+Na)^+$ calcd 293.1359, obsd 293.1356; $[\alpha]_D^{20}$ −10.1 (c 1.25, $CHCl_3$).

Acknowledgements

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Supplementary data

Experimental details for all compounds except for **8**, **9**, **16**, **19**, **39**, **41**, **43**, **50**, **55**, **58**, and **56**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.066.

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A facile method for the synthesis of 1,3-oxathiolan-2-ones by reaction of oxiranes, sulfur, and carbon monoxide

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Abstract—A new method for the synthesis of 1,3-oxathiolan-2-ones has been developed. When oxiranes were allowed to react with sulfur in the presence of a catalytic amount of sodium hydride under pressurized carbon monoxide, the three-component coupling of oxiranes, sulfur, and carbon monoxide smoothly proceeded to give the 1,3-oxathiolan-2-ones in moderate to good yields. The reaction proceeded with a high regioselectivity and stereospecificity. For the reaction of oxiranes possessing an aromatic ring, the yields of the 1,3-oxathiolan-2-ones were lower than that of the oxiranes possessing no aromatic ring due to the formation of alkenes and thiiranes as byproducts. However, the product yields were improved by the addition of a catalytic amount of selenium.

1. Introduction

The development of the process to replace the use of phosgene as a carbonylating reagent has received considerable attention in recent years due to environmental and industrial concerns. Carbon monoxide is one of the promising agents to replace phosgene; the development of new methods for the carbonylation of various organic compounds with carbon monoxide could have a significant impact on organic and industrial chemistries.[1]

Since 1,3-oxathiolan-2-one is an important synthetic intermediate in organic[2] and polymer sciences,[3] considerable attention has been devoted to the development of a convenient method for the synthesis of 1,3-oxathiolan-2-one. Although various synthetic methods of 1,3-oxathiolan-2-one, such as the carbonylation of β-hydroxy thiol with phosgene, the treatment of oxirane with carbonyl sulfide in the presence of triethylamine, the base-catalyzed cyclization of the imidazolide derivative prepared by the treatment of epoxy alcohol with thiocarbonyl diimidazole, the oxidation of 2-alkoxy-1,3-oxathiolane, and the acid-assisted cyclization of 2-hydroxyethyl thiocarbonate have been reported,[2–6] these methods have the following disadvantages: (i) the use of poisonous phosgene and carbonyl sulfide, (ii) the use of intolerable and odorous thiol, (iii) the harsh reaction conditions for the preparation of carbonyl sulfide, and (iv) limitation of starting materials. Furthermore, the decarboxylation of 1,3-oxathiolan-2-one sometimes occurred under these reaction conditions, and thiirane was formed as a byproduct.[7]

We have now developed a facile method for the synthesis of 1,3-oxathiolan-2-ones by the reaction of oxiranes with sulfur and carbon monoxide in the presence of a catalytic amount of sodium hydride under mild reaction conditions.[8,9] Furthermore, it was confirmed that the yields of the 1,3-oxathiolan-2-ones possessing an aromatic ring were improved by the addition of a selenium catalyst.

2. Results and discussion

In order to determine the optimized reaction conditions, 2-decyloxirane (**1a**) was allowed to react with sulfur and carbon monoxide under various reaction conditions and the results are shown in Table 1. When **1a** was treated with sulfur (5 equiv) in the presence of sodium hydride under pressurized carbon monoxide (10 kg cm^{-2}) in THF solvent at 60 °C for 3 h, 5-decyl-1,3-oxothiolan-2-one (**2a**) was obtained in 96% yield (entry 5). The yield of **2a** decreased when the reaction was carried out at lower reaction temperatures and carbon monoxide pressures (entries 5 and 13–16). The product yield was also affected by the amount of sulfur used (entries 1–5). Although **1a** was coupled with sulfur and carbon monoxide, even using 1,4-dioxane, DMSO, DMF, and acetonitrile instead of THF as the solvent, the best yield was observed in the THF solvent (entries 5 and 7–10). In the case of hydrocarbon solvents, such as toluene and hexane, the reaction did not proceed

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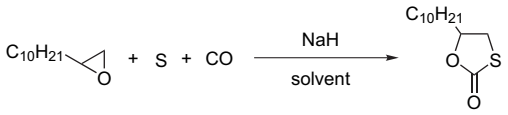
Table 1. The reaction of 2-decyloxirane with carbon monoxide and sulfur under various reaction conditions[a]



Entry	Sulfur (mmol)	Solvent	Temp (°C)	CO (kg cm^{-2})	Yield (%)[b]
1	2	THF	60	10	28
2	4	THF	60	10	67
3	6	THF	60	10	76
4	8	THF	60	10	85
5	10	THF	60	10	96 (92)
6[c]	10	THF	60	10	95
7	10	1,4-Dioxane	60	10	22
8	10	DMSO	60	10	56
9	10	DMF	60	10	82
10	10	Acetonitrile	60	10	60
11	10	Toluene	60	10	0
12	10	Hexane	60	10	0
13	10	THF	50	10	72
14	10	THF	40	10	29
15	10	THF	60	5	37
16	10	THF	60	1	0

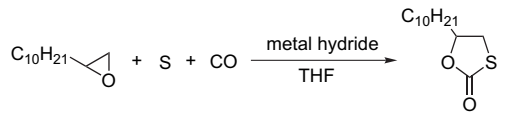
[a] Reaction conditions: 2-decyloxirane (2 mmol), NaH (2 mmol), and solvent (2 mL) for 3 h.
[b] GC yield. The number in parenthesis shows the isolated yield.
[c] NaH (0.5 mmol) was used.

and **1a** (92 and 95%, respectively) was recovered (entries 11 and 12). In this reaction, it is possible to still further reduce the amount of sodium hydride (25 mol %) and form **2a** in 95% yield (entry 6).

The reaction of **1a** with sulfur and carbon monoxide was next examined in the presence of various metal hydrides, and these results are shown in Table 2.[10] Although the other metal hydrides, lithium, potassium, and calcium hydrides and sodium borohydride also functioned as a base, the yields of **2a** were distinctly decreased (entries 2, 3, 5, and 6). For the reaction in the presence of potassium hydride, it is interesting to note that the yield of **2a** was dramatically increased by the addition of dibenzo-18-crown-6, which strongly binds with the potassium cation (entry 4).

To determine the scope and limitation of the synthesis of the 1,3-oxathiolan-2-ones, various oxiranes were reacted with

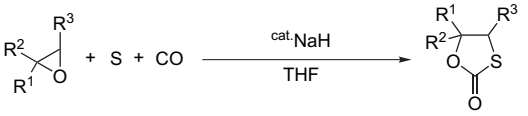
Table 2. The reaction of 2-decyloxirane with carbon monoxide and sulfur in the presence of metal hydride[a]



Entry	Metal hydride	Yield (%)[b]
1	LiH	0
2	NaH	95
3	KH	28
4[c]	KH	82
5	CaH_2	61
6	$NaBH_4$	7

[a] Reaction conditions: 2-decyloxirane (2 mmol), S (10 mmol), CO (10 kg cm^{-2}), metal hydride (0.5 mmol), and THF (2 mL) at 60 °C for 3 h.
[b] GC yield.
[c] Dibenzo-18-crown-6 (0.5 mmol) was added.

Table 3. The reaction of various oxiranes with carbon monoxide and sulfur[a]

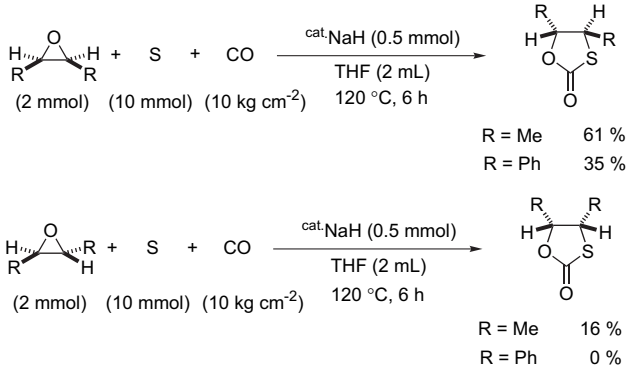


Entry	R^1	R^2	R^3	Yield (%)[b]
1	n-$C_{10}H_{21}$	H	H	95
2	C_2H_5	H	H	87
3	CH_3	CH_3	H	99
4	H	—(CH$_2$)$_4$—		61
5[c]	CH_3	CH_3	CH_3	4
6	Ph	H	H	39
7	4-Tol	H	H	32
8	4-BrC_6H_5	H	H	4
9	$PhCH_2$	H	H	53
10	$PhOCH_2$	H	H	24

[a] Reaction conditions: oxirane (2 mmol), S (10 mmol), CO (10 kg cm^{-2}), NaH (0.5 mmol), and THF (2 mL) at 60 °C for 3 h.
[b] GC yield.
[c] The reaction was carried out at 150 °C for 8 h.

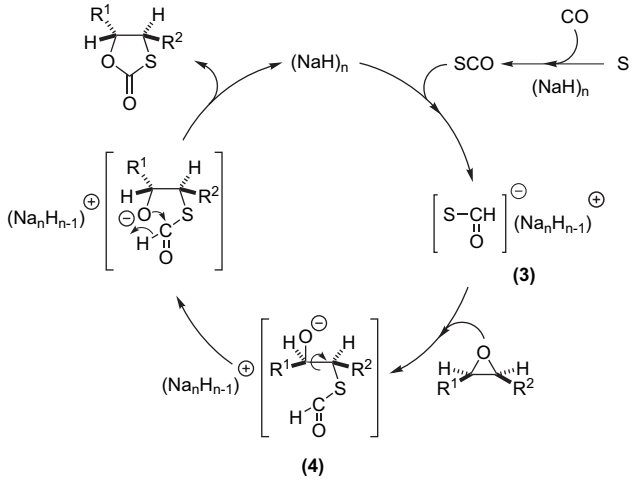
sulfur and carbon monoxide in the presence of a catalytic amount of sodium hydride, and these results are shown in Table 3. The yields of the products were influenced by the structure of the oxiranes. For the 2-alkyl and 2,2-dialkyl substituted oxiranes, 5-alkyl and 5,5-dialkyl substituted 1,3-oxathiolane-2-ones were obtained in 95, 87, and 99% yields, respectively, (entries 1–3). The treatment of 7-oxabicyclo[4.1.0]heptane with sulfur and carbon monoxide produced 4,5-tetramethylene-1,3-oxathiolan-2-one in a 61% yield (entry 4). For the sterically hindered oxirane, such as 2,2,3-trimethyloxirane, the product yield was low (entry 5). For the reaction of the oxiranes possessing an aromatic ring, such as 2-phenyl-, 2-(4-methylphenyl)-, 2-(4-bromophenyl)-, 2-benzyl-, and 2-phenoxymethyl oxirane, the yields of the 1,3-oxathiolan-2-ones were low compared to those of the oxiranes possessing no aromatic ring due to the formation of alkene, thiirane, and oligomers of oxirane as byproducts (entries 6–10).

The reaction of *cis*-2,3-disubstituted oxiranes, such as *cis*-2,3-dimethyl- and 2,3-diphenyloxiranes, stereospecifically proceeded and formed the *trans*-4,5-disubstituted 1,3-oxathiolan-2-ones in moderate yields (Scheme 1). Similarly, *trans*-2,3-dimethyloxirane produced the *cis*-4,5-dimethyl-1,3-oxothiolan-2-one, however, for *trans*-2,3-diphenyloxirane, *cis*-4,5-diphenyl-1,3-oxathiolan-2-one was not confirmed and the oxirane (86%) was recovered.



Scheme 1.

Although the reaction pathway for the formation of 1,3-oxathiolan-2-one has not been fully clarified, one of the plausible reaction pathways is shown in Scheme 2. It was suggested that the preparation of carbonyl sulfide by the reaction of sulfur and carbon monoxide was the first step in the reaction. The hydride anion attacked the carbonyl sulfide to give the corresponding thioformate anion (**3**).[11] The attack of **3** on the oxirane from the less hindered side then formed an intermediate (**4**). Rotation of the carbon–carbon bond followed by intramolecular cyclization gave the corresponding 1,3-oxathiolan-2-one and regenerated the hydride anion. For the reaction of the *trans*-2,3-dimethyl or *trans*-2,3-diphenyl substituted oxiranes, it was suggested that the rotation of the carbon–carbon bond of **4** was strongly suppressed by the steric effect and the oxygen anion attacked the β-carbon to regenerate the oxirane.

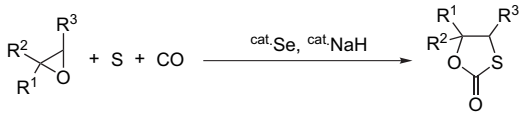


Scheme 2. A plausible reaction pathway.

We have recently reported that selenium acts as a catalyst for the reaction of sulfur and carbon monoxide producing carbonyl sulfide in the presence of an amine.[12] During the continuing study of the selenium-catalyzed reaction of sulfur and carbon monoxide, it was found that various organosulfur compounds having a thiolester (–C(=O)S–) group were synthesized in moderate to good yields using this catalytic reaction system under mild conditions.[13] Based on these results, we next investigated the application of the selenium-catalyzed reaction system on the preparation of 1,3-oxathiolan-2-ones. Various oxiranes were allowed to react with sulfur and carbon monoxide in the presence of a catalytic amount of sodium hydride and selenium, and these results are shown in Table 4. It is interesting to note that the yields of the 1,3-oxathiolan-2-ones having an aromatic ring were improved using the selenium-catalyzed reaction system.[14,15]

In summary, we found that the reaction of oxiranes with sulfur and carbon monoxide in the presence of a catalytic amount of sodium hydride produced the corresponding 1,3-oxathiolan-2-ones. In addition, for the reaction of oxiranes having an aromatic ring, the yields of the 1,3-oxathiolan-2-ones were improved by the addition of the selenium catalyst. From the viewpoint of a simple operation, mild reaction conditions, and good yields, the present reaction provides a useful method for the synthesis of the 1,3-oxathiolan-2-ones.

Table 4. Selenium-catalyzed synthesis of 1,3-oxathiolan-2-ones[a]



Entry	R^1	R^2	R^3	Yield (%)[b]
1[b]	Ph	H	H	79
2	*p*-Tol	H	H	50
3	*p*-BrC_6H_5	H	H	22
4	$PhCH_2$	H	H	97
5	$PhOCH_2$	H	H	66
6	H	—$(CH_2)_4$—		16
7[c]	H	CH_3	CH_3	31
8[c]	CH_3	H	CH_3	7
9[c,d]	H	Ph	Ph	10
10[e]	CH_3	CH_3	CH_3	4

[a] Reaction conditions: epoxide (2 mmol), S (10 mmol), CO (10 atm), Se (0.05 mmol), NaH (0.5 mmol), and THF (2 mL) at 60 °C for 3 h.
[b] GC yield.
[c] The reaction was carried out at 120 °C for 6 h.
[d] *cis*-Stillbene (24%) was formed as byproduct.
[e] The reaction was carried out at 150 °C for 8 h.

3. Experimental

3.1. General procedure

The ^1H and ^{13}C NMR spectra were recorded by 400 or 270 and 99.5 or 67.8 MHz spectrometers using $CDCl_3$ as a solvent with tetramethylsilane as an internal standard. IR spectra were obtained using a FT-IR spectrophotometer. The mass spectra were measured by GC–MS. Gas chromatography (GC) was carried out using a spectrometer with flame-ionizing detector and a capillary column. 2-(4-Methylphenyl) oxirane was synthesized by the oxidation of 4-methylstyrene with MCPBA. Powdered sulfur, sodium hydride, and elemental selenium were commercially available and used without purification. The solvents oxiranes and amines were distilled before use.

3.2. General procedure for the synthesis of 1,3-oxathiolan-2-ones

In a 50 mL stainless steel autoclave were placed powdered sulfur (10 mmol, 0.321 g), THF (2 mL), oxirane (2 mmol), and NaH (0.5 mmol, 0.024 g in mineral oil). The apparatus was flushed several times with carbon monoxide and then charged with carbon monoxide at 10 kg cm^{-2}. The mixture was heated with stirring at 60 °C for 3 h. After the reaction was complete, H_2O was added to the resulting solution and extracted with diisopropyl ether (15×3 mL). The combined organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure. Purification by column chromatography (hexane/AcOEt=3/1) on silica gel and HPLC ($CHCl_3$) gave the corresponding 1,3-oxathiolan-2-ones. The product was characterized by comparison of its spectral data with those of authentic samples (5-decyl-1,3-oxathiolan-2-one,[16] 5-ethyl-1,3-oxathiolan-2-one,[17,18] 4,5-tetramethylene-1,3-oxathiolan-2-one,[19] *trans*-4,5-dimethyl-1,3-oxathiolan-2-one,[20] and 2-phenylthiirane[21]).

3.3. General procedure for the selenium-catalyzed synthesis of 1,3-oxathiolan-2-ones

In a 50 mL stainless steel autoclave were placed powdered sulfur (10 mmol, 0.321 g), elemental selenium (0.05 mmol, 0.004 g), THF (2 mL), oxirane (2 mmol), and NaH (0.5 mmol, 0.024 g in mineral oil). The apparatus was flushed several times with carbon monoxide and charged with carbon monoxide at 10 kg cm^{-2}. The mixture was then heated with stirring at 60 °C for 3 h. After the reaction was complete, H_2O was added to the resulting solution and extracted with diisopropyl ether (15×3 mL). The combined organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure. Purification by column chromatography (hexane/AcOEt=3/1) on silica gel and HPLC ($CHCl_3$) gave the corresponding 1,3-oxathiolan-2-ones.

3.3.1. 5,5-Dimethyl-1,3-oxathiolan-2-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.377 (s, 2H), 1.584 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.663, 85.381, 42.426, 26.447; IR (neat) 2981, 2937, 1732 cm^{-1}; MS 132 (M^+); yellow oil. Anal. Calcd for $C_5H_8O_2S$: C, 45.43; H, 6.10; S, 24.26. Found: C, 45.27; H, 6.21; S, 24.35.

3.3.2. 4,5,5-Trimethyl-1,3-oxathiolan-2-one. ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.876 (q, J=6.8 Hz, 1H), 1.552–1.384 (m, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.280, 88.165, 51.963, 25.997, 21.102, 16.075; IR (neat) 2996, 1730 cm^{-1}; MS 146 (M^+); yellow oil. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.51; H, 6.72; S, 21.88.

3.3.3. 5-Phenyl-1,3-oxathiolan-2-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.313–7.360 (m, 5H), 5.560 (dd, J=6.8 and 9.4 Hz, 1H), 3.660 (dd, J=6.8 and 10.8 Hz, 1H), 3.463 (dd, J=9.4 and 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.001, 136.206, 128.889, 128.559, 125.367, 81.686, 38.318; IR (neat) 1740, 770, 697 cm^{-1}; MS 180 (M^+); yellow oil. Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 60.21; H, 4.32; S, 17.67.

3.3.4. 5-(4-Toly)-1,3-oxathiolan-2-one. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.244–7.139 (m, 4H), 5.516 (dd, J=6.5 and 9.5 Hz, 1H), 3.628 (dd, J=6.6 and 11.1 Hz, 1H) 3.450 (t, 1H), 2.307 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.864, 138.658, 133.046, 129.040, 125.321, 81.747, 38.174, 20.822; IR (neat) 3030, 2923, 1738 cm^{-1}; MS 194 (M^+); yellow oil. Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19; S, 16.51. Found: C, 61.71; H, 5.18; S, 16.28.

3.3.5. 5-(4-Bromophenyl)-1,3-oxathiolan-2-one. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.529–7.249 (m, 4H), 5.601 (dd, J=6.5 and 9.5 Hz, 1H), 3.761 (dd, J=6.5 and 11.2 Hz, 1H), 3.507 (dd, J=9.5 and 11.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.749, 135.276, 131.738, 127.123, 122.935, 80.925, 38.314; IR (KBr) 1719 cm^{-1}; MS 260 (M^+); colorless crystals. Anal. Calcd for $C_9H_7BrO_2S$: C, 41.72; H, 2.72; S, 12.37. Found: C, 41.85; H, 2.68; S, 12.35.

3.3.6. 5-Benzyl-1,3-oxathiolan-2-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.358–7.218 (m, 5H), 4.863 (quintet, J=6.9 Hz, 1H), 3.416–2.990 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.331, 134.771, 129.236, 128.765, 127.272, 81.257, 39.795, 35.687; IR (neat) 2923, 1716, 764, 703 cm^{-1}; MS 194 (M^+); yellow oil. Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19; S, 16.51. Found: C, 62.04; H, 5.02; S, 16.53.

3.3.7. 5-(Phenoxymethyl)-1,3-oxathiolan-2-one. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.334–6.892 (m, 5H), 5.052–4.961 (m, 1H), 4.197 (d, J=4.9 Hz, 2H), 3.641 (d, J=7.3 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 172.103, 157.548, 129.517, 121.643, 114.353, 77.749, 66.674, 33.130; IR (neat) 1736, 1244, 1077, 755 cm^{-1}; MS 210 (M^+); yellow oil. Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; S, 15.25. Found: C, 57.32; H, 4.76; S, 15.21.

Acknowledgements

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Synthesis and fluoride-induced chemiluminescent decomposition of bicyclic dioxetanes substituted with a 2-hydroxynaphthyl group

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Abstract—Five bicyclic dioxetanes bearing a 2-hydroxynaphthyl group, **1aA**–**1eA**, were synthesized and their chemiluminescent decomposition was examined by the use of tetrabutylammonium fluoride (TBAF) as a base in DMSO. It was found that these dioxetanes hold completely the '*odd*/*even*' relationship between the substitution pattern of hydroxy as a trigger on the naphthalene ring and their chemiluminescent efficiency, and that dioxetane **1aA** exhibited chemiluminescence with the highest efficiency among those for the oxynaphthyl-substituted dioxetanes hitherto known. The significant change in chemiluminescent efficiency depending on the substitution pattern was clarified to be attributed to the marked change in singlet-chemiexcitation efficiency for charge-transfer-induced chemiluminescence (CTICL) of **1aA**–**1eA**. In respect of the rate of CTICL-decomposition, '*odd*/*even*' relationship was observed for **1aA**–**1dA**.

1. Introduction

Dioxetanes substituted with an aromatic electron donor such as the phenoxide anion or naphthoxide anion undergo intramolecular charge-transfer-induced chemiluminescence (CTICL). The phenomenon has received much attention from the viewpoints of mechanistic interest related to bioluminescence and application to modern chemiluminescent biological analysis.[1–4] As a very recent development, it has been reported that the atropisomeric 2-hydroxy-1,1′-binaphthyl-5-yl moiety also acts as an electron donor after deprotonation, and dioxetanes bearing such substituent display CTICL, the spectrum of which varies depending on the microenvironment.[5] In the course of our further investigation to design such type of dioxetanes, we synthesized various dioxetanes substituted with the 2-hydroxynaphthyl moiety and examined their base-induced decomposition to know what kind of substitution pattern, namely, the position of a dioxetane ring relative to the 2-hydroxy group on the naphthalene ring, leads to effective chemiluminescence.

There are five types of dioxetane bearing a 2-hydroxynaphthyl moiety, **1a**–**1e** (Y=H) that relate to dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl group **2** except one with a sterically too congested 2-hydroxy-1,1′-binaphthyl-8-yl group (Fig. 1). Among them, three analogs having a 3,3-diisopropyl-4-methoxy-1,2-dioxetane skeleton (**1aB**, **1bB**, **1eB**; Y=*t*-BuMe_2Si) have already been reported to exhibit '*odd*/*even*' relationship between the chemiluminescent properties and substitution pattern of a trigger (YO group).[6–9] On the other hand, a bicyclic dioxetane skeleton, namely, 5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane, substituted with various aryl groups at the 1-position, has been known to exhibit marked thermal stability[10] and synthetic versatility of its precursor.[11] Thus, we synthesized bicyclic dioxetanes **1cA** and **1dA** with new substitution pattern and examined their chemiluminescent decomposition in tetrabutylammonium fluoride (TBAF)/DMSO system. Bicyclic dioxetanes **1aA**, **1bA**, and **1eA** were also synthesized and their chemiluminescent properties were compared with those of **1cA**, **1dA**, as well as with those for diisopropyldioxetanes **1aB**, **1bB**, and **1eB**, and their related dioxetanes.

Keywords: Dioxetane; Chemiluminescence; 'Odd/even' relationship.
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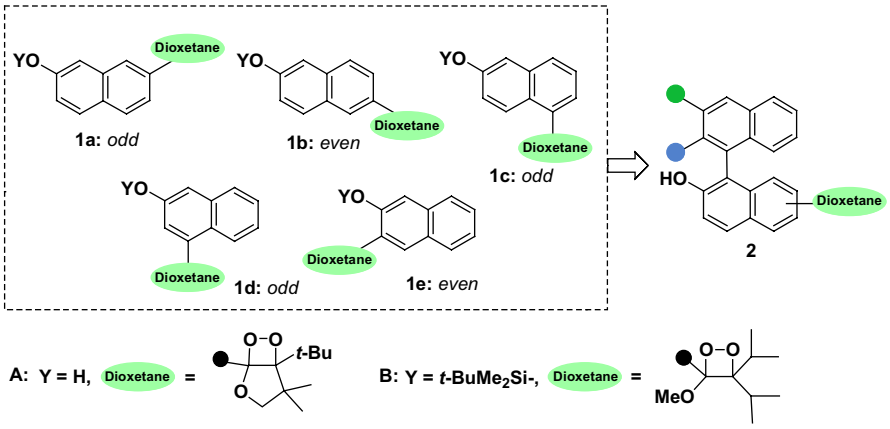
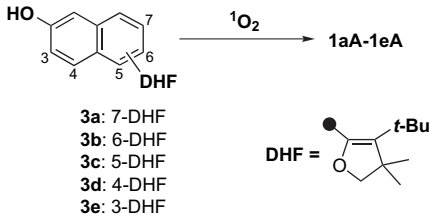


Figure 1.

2. Results and discussion

2.1. Synthesis of bicyclic dioxetanes substituted with a 2-hydroxynaphthyl group

Sensitized photooxygenation has been reported to be very effective to transform 5-aryl-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofurans into the corresponding bicyclic dioxetanes, namely, 1-aryl-5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo [3.2.0]heptanes.[3,4,10,11] The precursors leading to dioxetanes **1aA**–**1eA** were 4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofurans **3a**–**3e** bearing a 2-hydroxynaphthyl group at the 5-position (Scheme 1).

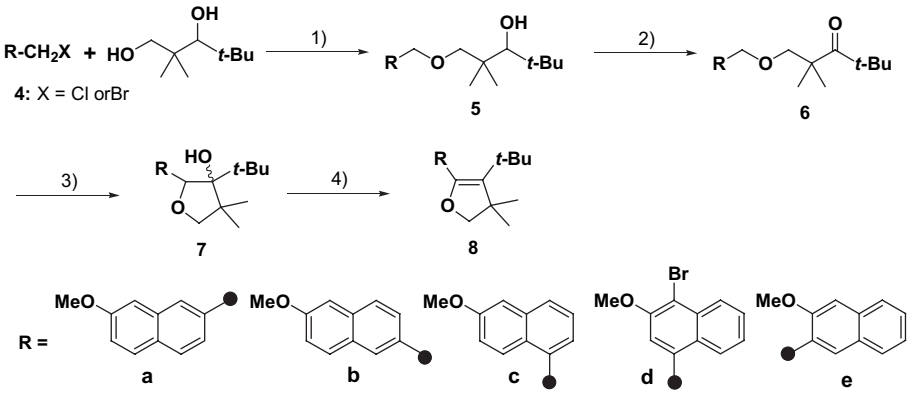


Scheme 1.

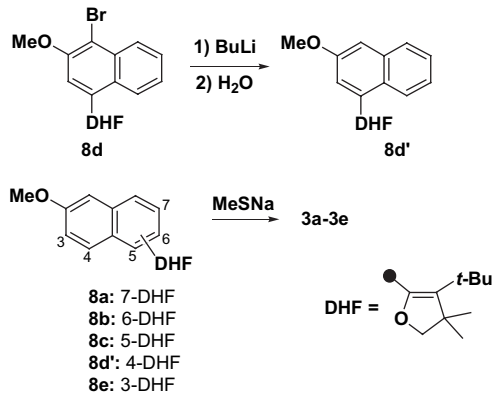
Synthesis of the precursors **3a**–**3e** started from the Williamson synthesis of 2-methoxynaphthylmethyl halides **4a**–**4e** with 2,2,4,4-tetramethylpentane-1,3-diol to afford the corresponding hydroxy ethers **5a**–**5e**. Successive oxidation of **5a**–**5e** with pyridinium chlorochromate (PCC) gave the corresponding ketones **6a**–**6e** in high yields. On treatment with a base such as lithium diisopropylamide (LDA) in tetrahydrofuran (THF) or *t*-BuOK in DMSO, the ketones **6a**–**6e** underwent intramolecular cyclization smoothly to yield 3-hydroxytetrahydrofurans **7a**–**7e**, respectively. Dehydration of **7a**–**7e** into the corresponding dihydrofurans **8a**–**8e** was effectively attained on heating with an acid catalyst or on treatment with $SOCl_2$/pyridine (Scheme 2).

Dihydrofuran **8d** was treated with butyllithium in THF to give debrominated product **8d′**. Demethylation of the methoxy group in (methoxynaphthyl)dihydrofurans **8a**–**8c**, **8d′**, and **8e** took place on heating with sodium methanethiolate in hot dimethylformamide (DMF) to give dihydrofurans **3a**–**3e**, respectively (Scheme 3).

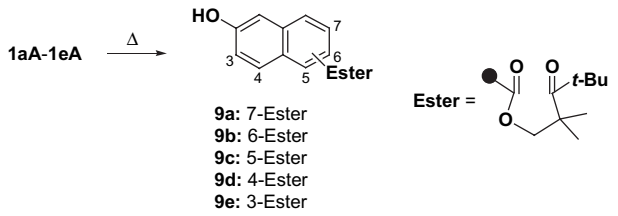
When dihydrofurans **3a**–**3e** were irradiated in the presence of tetraphenylporphin (TPP) (catalytic amount) in dichloromethane with Na lamp under an oxygen atmosphere at −78–0 °C for 0.5–1 h, the corresponding dioxetanes **1aA**–**1eA** were produced exclusively. The structures of these dioxetanes were determined by ^{1}H NMR, ^{13}C NMR, IR, Mass, and HR mass spectral analysis. All dioxetanes synthesized here were thermally stable enough to permit handling at room temperature, though they decomposed into the corresponding keto esters **9a**–**9e** on heating in xylene (Scheme 4).



Scheme 2. *Reagents*: (1) NaH/THF–DMF; (2) PCC/CH_2Cl_2; (3) LDA/THF or *t*-BuOK/DMSO; (4) TsOH/toluene or pyridine/$SOCl_2$/CH_2Cl_2.



Scheme 3.



Scheme 4.

2.2. Fluoride-induced chemiluminescent decomposition of bicyclic dioxetanes substituted with a 2-hydroxynaphthyl group

A dioxetane bearing a siloxyaryl or hydroxyaryl group is triggered with TBAF in an aprotic solvent such as DMSO and acetonitrile; its desilylation or deprotonation with fluoride affords an unstable oxidoaryl-substituted dioxetane, which decomposes rapidly by the intramolecular CTICL process. Such fluoride-triggered decomposition has been reported to proceed following the pseudo-first-order kinetics independent of the TBAF concentration, when a large excess of fluoride concentration is used.[12] Thus, we used a large excess of TBAF to examine the fluoride-induced decomposition of dioxetanes **1aA–1eA** for simplifying the system, so that we could estimate the rate of decomposition of intermediary oxidonaphthyldioxetanes **10a–10e** into keto esters **11a–11e** in the singlet-excited state (Scheme 5).

When a solution of **1aA** in DMSO (1.0×10^{-5} mol dm^{-3}, 1 mL) was added to a TBAF solution in DMSO (1.0×10^{-2} mol dm^{-3}, 2 mL) at 25 °C, **1aA** underwent the CTICL-decomposition accompanied with emission of light: maximum wavelength λ_{max}^{CTICL}=559 nm, chemiluminescent efficiency Φ^{CTICL}=0.11, the rate of CTICL-decomposition $k^{CTICL}=5.8\times10^{-3}$ s^{-1}, and half-life $t_{1/2}=\log_e 2/k^{CTICL}$= 120 s. On treatment with TBAF in DMSO similarly to the case of **1aA**, dioxetanes **1bA–1eA** displayed chemiluminescence, the spectra of which are illustrated in Figure 2. The chemiluminescent properties for **1aA–1eA** are summarized in Table 1, in which those for diisopropyldioxetanes **1aB**, **1bB**, **1eB**, and **1c′B**, **1d′B** (Scheme 5, vide infra) are also cited.[6]

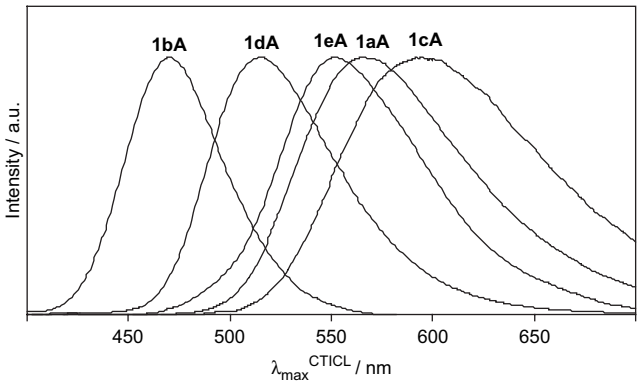
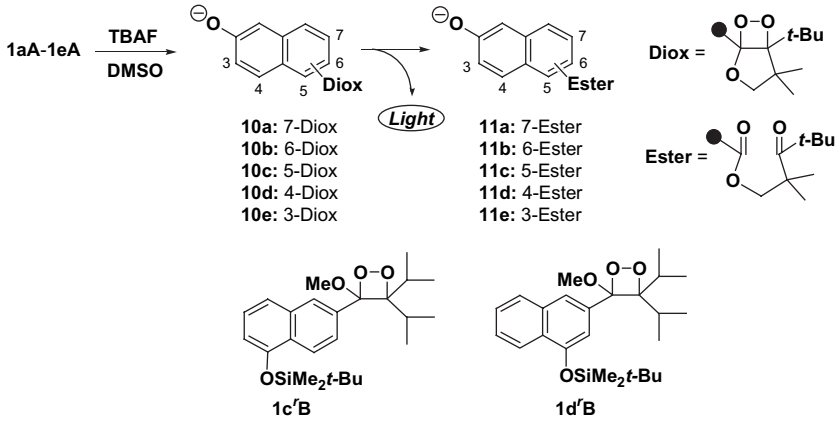


Figure 2. Chemiluminescent spectra of dioxetanes **1aA–1eA** in TBAF/DMSO system.

The results in Table 1 exhibit several characteristic features for the CTICL of dioxetanes **1aA–1eA**, as follows. First, dioxetane **1aA** gave light in very high yield: Φ^{CTICL} for **1aA** was twice higher than that for **1aB**, and was the highest among those for hitherto-known dioxetanes bearing a naphtholic group (Φ^{CTICL}<0.06).[6,8,9] Second, bicyclic dioxetanes (group **1A**) appeared to give higher Φ^{CTICL} than the corresponding diisopropyldioxetanes (group **1B**). Third, dioxetanes **1aA**, **1cA**, and **1dA** with '*odd*' substitution pattern afforded far higher Φ^{CTICL} than isomers **1bA** and **1eA** with '*even*' substitution pattern. Thus, bicyclic dioxetanes (group **A**) are completely in the category of the '*odd/even*'



Scheme 5.

Table 1. Chemiluminescent decomposition of dioxetanes substituted with 2-hydroxynaphthyl group in TBAF/DMSO system[a]

Dioxetane[b]	λ_{max}^{CTICL}/nm	Φ^{CTICL}[c]	$t_{1/2}$/s	k^{CTICL}/s^{-1}	Substitution pattern
1aA	559	0.11	120	5.8×10^{-3}	*Odd*
1aB	558	5.6×10^{-2}	250	2.8×10^{-3}	*Odd*
1bA	470	1.7×10^{-5}	0.04	18	*Even*
1bB	470	3.2×10^{-6}	0.15	4.6	*Even*
1cA	582	1.7×10^{-2}	19	3.7×10^{-2}	*Odd*
1c^{r}B	628	7.4×10^{-3}	4.8	0.14	*Odd*
1dA	516	6.8×10^{-2}	220	3.2×10^{-3}	*Odd*
1d^{r}B	496	5.2×10^{-2}	0.076	9.1	*Odd*
1eA	551	6.6×10^{-4}	170	4.2×10^{-3}	*Even*
1eB	548[d]	1.6×10^{-4}[d]	46[d]	1.5×10^{-2}[d]	*Even*

[a] A solution of dioxetane in DMSO (1.0×10^{-5} mol dm^{-3}, 1 mL) was added into a TBAF solution in DMSO (1.0×10^{-2} mol dm^{-3}, 2 mL) at 25 °C, for **1aA**, **1cA**, **1dA**, and **1eA**. Similarly, a solution of dioxetane (1.0×10^{-4} mol dm^{-3}) and a solution of TBAF (1.0×10^{-2} mol dm^{-3}) were used for **1bA**.

[b] Chemiluminescent properties for a class of dioxetanes **1B** summarized here are the values reported already (Ref. 6).

[c] Chemiluminescent efficiencies (Φ^{CTICL}) were based on the reported value for 3-(3-*tert*-butyldimethylsiloxyphenyl)-3-methoxy-4-(2′-spiroadamantane)-1,2-dioxetane (Φ^{CTICL}=0.29) (Ref. 12).

[d] Revised value after the reexamination.

Table 2. Fluorescence of 2-oxidonaphthoates **11a–11e** and singlet-chemiexcitation efficiency for CTICL of dioxetanes **1aA–1eA**

Naphthoate[a]	λ_{max}^{fl}/nm	Φ^{fl}	Dioxetane	Φ_S[b]	Substitution pattern
11a	558	0.23	**1aA**	0.49	*Odd*
11b	471	0.74	**1bA**	2.3×10^{-5}	*Even*
11c	586	0.078	**1cA**	0.22	*Odd*
11d	513	0.77	**1dA**	8.8×10^{-2}	*Odd*
11e	550	0.21	**1eA**	3.2×10^{-3}	*Even*

[a] Fluorescence of **11a–11e** generated from the corresponding keto esters **9a–9e** in TBAF/DMSO.

[b] Singlet-chemiexcitation efficiency: $\Phi_S=\Phi^{CTICL}/\Phi^{fl}$.

relationship in respect of Φ^{CTICL} as illustrated in Figure 3A. Although similar '*odd*/*even*' relationship has been observed also for diisopropyldioxetanes (group **1B**) as shown in Figure 3B, it has been little known whether this '*odd*/*even*' relationship is based on the difference in fluorescent efficiency of emitters and/or the difference in singlet-chemiexcitation efficiency of dioxetanes.

Authentic emitters **11a–11e** were prepared by dissolving the corresponding neutral keto esters **9a–9e** in TBAF/DMSO. They displayed fluorescence with maximum wavelength (λ_{max}^{fl}) and efficiency (Φ^{fl}) as summarized in Table 2, and their fluorescence spectra coincided substantially with the chemiluminescent spectra of the corresponding dioxetanes **1aA–1eA**, as shown in Figure 4. Since Φ^{CTICL} is described as the product of $\Phi^{fl}\times\Phi_S$ (singlet-chemiexcitation efficiency) for CTICL of the dioxetanes, Φ_S for **1aA–1eA** are estimated as summarized in Table 2. The results reveal that the significant change in Φ^{CTICL} among **1aA–1eA** is attributed predominantly to the difference in Φ_S but not to that in Φ^{fl} of emitters **11a–11e**, as illustrated in Figure 5.

The '*odd*/*even*' relationship in respect of k^{CTICL} has been reported to hold for diisopropyldioxetanes **1aB**, **1bB**, and **1c^{r}B**, but for neither **1d^{r}B** nor **1eB**, as shown in Figure 6B.[6] On the other hand, such relationship held even for dioxetane **1dA** as well for **1aA–1cA** as illustrated in Table 1 and Figure 6A. It should be noted here that dioxetane **1dA** has the '*odd*' substitution pattern (2-OH/4-dioxetane on naphthalene ring), whereas **1d^{r}B** has the reverse '*odd*' substitution pattern (4-OH/2-dioxetane) (Scheme 5). Considering that k^{CTICL} is smaller for bicyclic dioxetanes **1dA** and **1eA** than for the respective diisopropyldioxetanes **1d^{r}B** and **1eB**, significant difference in k^{CTICL} between **1dA** and **1d^{r}B** is presumably attributed to the difference in the ease of oxidation between the 2-oxidonaphthalene anion and 1-oxidonaphthalene anion, which act as an electron donor for the CTICL, but not to the structural difference in the dioxetane skeleton. In fact, 1-oxidonaphthalene anion has been reported to possess formal oxidation potential (E vs Ag/Ag$^+$ in DMSO=−498 mV) considerably lower than that of the 2-oxidonaphthalene anion (E=−369 mV).[6] Such tendency was observed also between dioxetanes with the reverse substitution pattern **1cA** (2-OH/5-dioxetane) and **1c^{r}B** (5-OH/2-dioxetane).

It has been suggested that the rate of CTICL-decomposition is affected also by the conformation of the aromatic electron donor relative to the dioxetane ring,[3] and that such steric

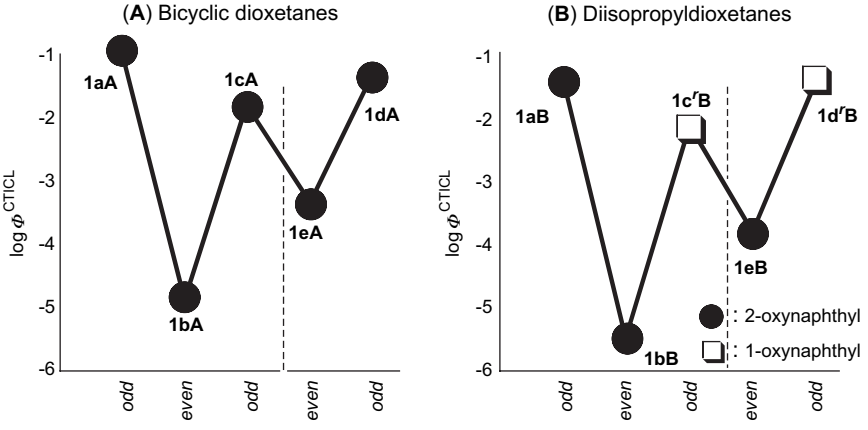


Figure 3. '*Odd*/*even*' relationship between substitution pattern and chemiluminescent efficiency Φ^{CTICL} for dioxetanes **1aA–1eA** (group A) and **1aB–1d^{r}B** (group B).

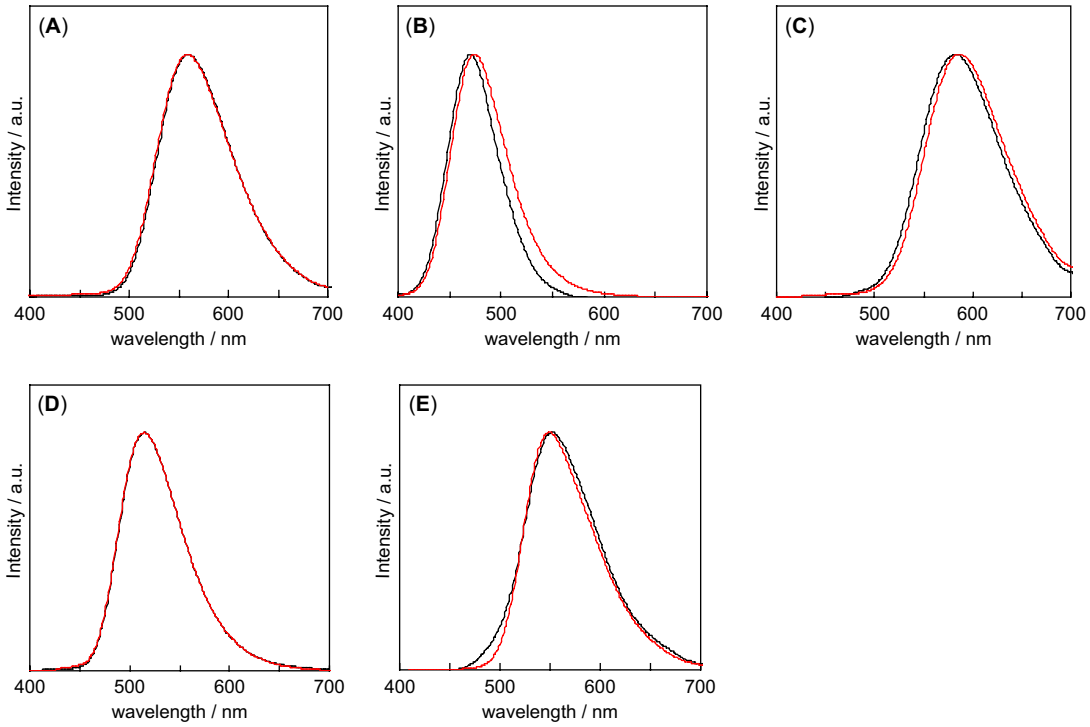


Figure 4. Chemiluminescent spectra of **1aA–1eA** and fluorescence spectra of 2-oxidonapthoates **11a–11e** prepared from keto esters **9a–9e** in TBAF/DMSO. Black line: chemiluminescence, red line: fluorescence spectra, (A) **1aA** versus **11a** (B) **1bA** versus **11b**, (C) **1cA** versus **11c**, (D) **1dA** versus **11d**, (E) **1eA** versus **11e**.

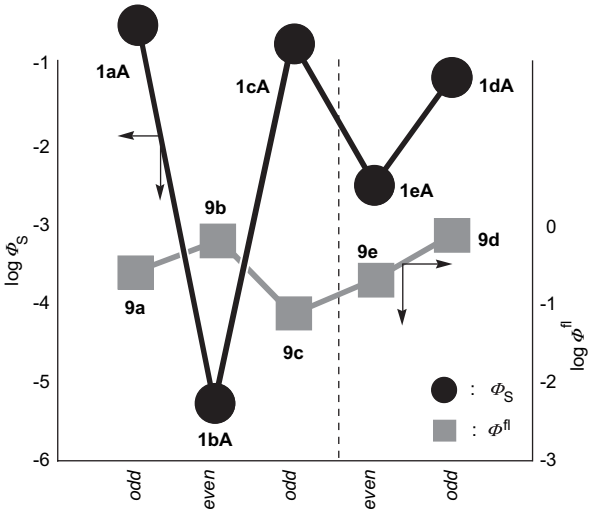


Figure 5. '*Odd/even*' relationship between substitution pattern and singlet-chemiexcitation efficiency Φ_S and fluorescent efficiency Φ^{fl} for chemiluminescence of dioxetanes **1aA–1eA**.

factor causes presumably the unusual thermal stability of 2-methoxyphenyl-substituted bicyclic dioxetane.[10] This suggestion should be also applied to account for the fact that dioxetane **1eA** as well as **1eB** decompose slowly, even though they have the '*even*' substitution pattern, in TBAF/DMSO.

3. Conclusion

It was found that bicyclic dioxetanes **1aA–1eA** bearing a 2-hydroxynaphthyl moiety hold completely the '*odd/even*' relationship between the substitution pattern on the naphthalene ring and their chemiluminescent efficiency in TBAF/DMSO system, and **1aA** exhibited chemiluminescence with the highest efficiency among those for the oxynaphthyl-substituted dioxetanes hitherto known. The significant change of Φ^{CTICL} among **1aA–1eA** was found to be attributed mainly to the difference in Φ_S but not to that in Φ^{fl} of emitters **11a–11e**. Difference in the oxidation potential between the 1-oxidonaphthyl and 2-oxidonaphthyl moieties, which act as an electron donor for the intramolecular CTICL of dioxetanes **1**, was suggested to cause significant difference in the rate of CTICL-decomposition between dioxetane **1dA** (2-OH/4-dioxetane) and **1d'B** with the reverse substitution pattern (4-OH/2-dioxetane).

4. Experimental

4.1. General

Melting points were measured with a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were taken on a JASCO FT/IR-300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX-400 and JEOL EPC-500 spectrometers. Mass spectra were obtained by using JEOL JMS-AX-505H and JEOL JMS-T-100LC mass spectrometers. Reagents were purchased from Aldrich, Tokyo Chemical Industries, Wako Pure Chemical Industries, and/or Kanto Chemical Industries. Column chromatography was carried out with silica gel, unless otherwise stated.

4.1.1. Preparation of (halomethyl)methoxynaphthalenes 4a–4e. 1-Bromo-4-bromomethyl-2-methoxynaphthalene (**4d**)

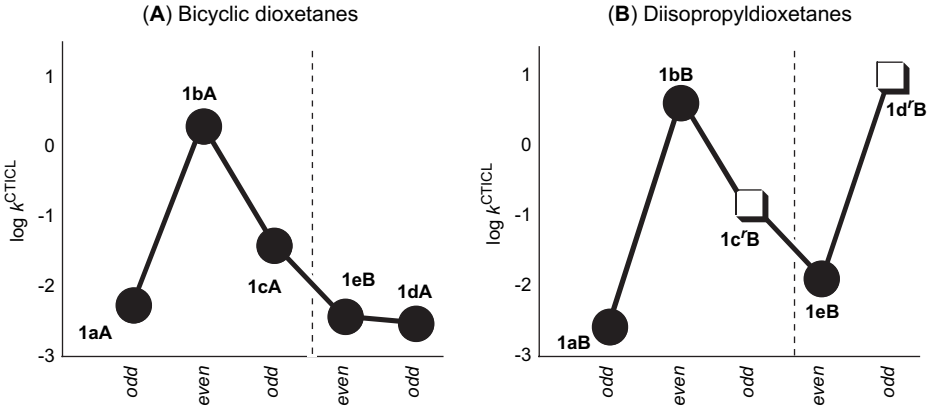


Figure 6. '*Odd*/*even*' relationship between substitution pattern and rate of CT-induced chemiluminescent decomposition (k^{CTICL}) for dioxetanes **1aA–1eA** (group A) and **1aB–1eB**.

was synthesized by bromination of 3-methoxy-1-methylnaphthalene with *N*-bromosuccinimide (NBS) in the presence of azobisisobutyronitrile (AIBN) in hot CCl_4: 79.8% yield.

4d: Pale yellow needles melted at 151.0–153.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.04 (s, 3H), 4.93 (s, 2H), 7.35 (s, 1H), 7.53 (dd with fine coupling, J=8.5 and 6.8 Hz, 1H), 7.60 (dd with fine coupling, J=8.5 and 6.8 Hz, 1H), 8.07 (d with fine coupling, J=8.5 Hz, 1H), 8.20 (d with fine coupling, J=8.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 30.9, 57.1, 110.3, 115.3, 123.9, 125.0, 127.1, 127.4, 128.1, 133.7, 134.4, 153.0 ppm. IR (KBr): 3037, 3019, 2965, 2936, 2844, 1597 cm^{-1}. Mass (*m*/*z*, %): 332 (M^++4, 20), 330 (M^++2, 41), 328 (M^+, 22), 266 (34), 264 (27), 252 (33), 251 (99), 250 (34), 249 (100), 208 (25), 206 (26), 140 (51), 139 (37), 127 (82), 126 (36). Anal. Calcd for $C_{12}H_{10}Br_2O$: C, 43.67; H, 3.05%. Found: C, 43.78; H, 2.68%.

2-Chloromethyl-7-methoxynaphthalene (**4a**),[13] 2-chloromethyl-6-methoxynaphthalene (**4b**),[14] 1-chloromethyl-6-methoxynaphthalene (**4c**),[15] and 2-chloromethyl-3-methoxynaphthalene (**4e**)[16] were synthesized by chlorination of the corresponding (hydroxymethyl)naphthalenes with CCl_4/$(C_6H_5)_3P$.

4.1.2. Synthesis of 1-(7-methoxynaphthalen-2-yl)-methoxy-2,2,4,4-tetramethylpentan-3-ol (5a); typical procedure. A solution of 2,2,4,4-tetramethyl-1,3-pentanediol (904 mg, 5.64 mmol) in dry THF (5.0 mL) was added dropwise over 5 min to a suspension of sodium hydride (60% in oil, 236 mg, 5.90 mmol) in dry DMF (30 mL) and dry THF (30 mL) at 0 °C under a nitrogen atmosphere and was stirred at 0 °C for 30 min. 2-Chloromethyl-7-methoxynaphthalene (**4a**) (1.06 g, 5.13 mmol) was added to the solution and was stirred for 3 h at room temperature. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed twice with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:9) to give 1-(7-methoxynaphthalen-2-yl)methoxy-2,2,4,4-tetramethylpentan-3-ol (**5a**) (1.53 g, 4.63 mmol, 90.3%) as a colorless solid.

5a: Colorless needles melted at 90.0–91.0 °C (from AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.05 (s, 3H), 1.08 (s, 3H), 3.25 (d, J=4.4 Hz, 1H), 3.30 (d, J=8.9 Hz, 1H), 3.44 (d, J=8.9 Hz, 1H), 3.51 (d, J=4.4 Hz, 1H), 3.92 (s, 3H), 4.64 (s, 2H), 7.12 (s, 1H), 7.12–7.14 (m, 1H), 7.29 (d, J=8.3 Hz, 1H), 7.65 (s, 1H), 7.72 (d, J=9.2 Hz, 1H), 7.74 (d, J=8.3 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.8, 25.8, 28.7, 37.3, 40.6, 55.3, 73.7, 82.2, 84.8, 105.9, 118.7, 123.3, 125.3, 128.0, 128.5, 129.2, 134.4, 135.8, 157.9 ppm. IR (KBr): 3487, 2959, 2870, 1632 cm^{-1}. Mass (*m*/*z*, %): 330 (M^+, 12), 188 (41), 172 (34), 171 (100), 128 (14). HRMS (ESI): 353.2099, calcd for $C_{21}H_{30}O_3Na$ (M+Na^+) 353.2093. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15%. Found: C, 76.48; H, 9.46%.

After following the above procedure using the corresponding (halomethyl)methoxynaphthalene **4b–4e**, 1-(methoxynaphthyl)methoxy-2,2,4,4-tetramethylpentan-3-ol **5b–5e** were obtained; **5b**: 91.9%, **5c**: 97.9%, **5d**: 94.8%, **5e**: 80.7%.

5b: Colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.04 (s, 3H), 1.07 (s, 3H), 3.24 (d, J=4.9 Hz, 1H), 3.28 (d, J=8.8 Hz, 1H), 3.42 (d, J=8.8 Hz, 1H), 3.50 (br d, J=4.9 Hz, 1H), 3.91 (s, 3H), 4.61 (s, 2H), 7.12 (d, J=2.4 Hz, 1H), 7.15 (dd, J=8.7 and 2.4 Hz, 1H), 7.41 (dd, J=8.5 and 1.7 Hz, 1H), 7.66 (br s, 1H), 7.70–7.73 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.9, 25.9, 28.7, 37.3, 40.6, 55.3, 73.7, 82.0, 84.8, 105.9, 118.9, 126.2, 126.4, 127.0, 128.5, 129.3, 132.8, 134.1, 157.6 ppm. IR (KBr): 3437, 2954, 2865, 1610 cm^{-1}. Mass (*m*/*z*, %): 330 (M^+, 28), 278 (11), 188 (89), 187 (27), 186 (33), 172 (55), 171 (100), 128 (19). HRMS (ESI): 353.2090, calcd for $C_{21}H_{30}O_3Na$ (M+Na^+) 353.2093. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15%. Found: C, 76.61; H, 8.96%.

5c: Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.99 (s, 12H), 1.04 (s, 3H), 3.20–3.22 (m, 1H), 3.26 (d, J=4.8 Hz, 1H), 3.28 (d, J=8.7 Hz, 1H), 3.45 (d, J=8.7 Hz, 1H), 3.93 (s, 3H), 4.90 (q_{AB}, J=12.0 Hz, 2H), 7.16 (d, J=2.5 Hz, 1H), 7.19 (dd, J=9.2 and 2.5 Hz, 1H), 7.30 (d with fine coupling, J=7.0 Hz, 1H), 7.38 (dd, J=8.2 and 7.0 Hz, 1H), 7.71 (d, J=8.2 Hz, 1H), 8.00 (d, J=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.7, 25.7, 28.6, 37.2, 40.6, 55.2,

72.1, 81.9, 84.4, 106.5, 118.7, 124.3, 125.5, 125.7, 127.1, 127.6, 133.2, 135.0, 157.4 ppm. IR (liquid film): 3500, 2954, 1626 cm^{-1}. Mass (*m/z*, %): 330 (M^+, 15), 188 (49), 172 (33), 171 (100), 128 (18). HRMS (ESI): 353.2076, calcd for $C_{21}H_{30}O_3Na$ (M+Na^+) 353.2093.

5d: Pale yellow granules melted at 71.0–71.5 °C (from hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.01 (s, 9H), 1.03 (s, 3H), 1.09 (s, 3H), 3.01 (d, *J*=5.1 Hz, 1H), 3.26 (d, *J*=5.1 Hz, 1H), 3.32 (d, *J*=8.5 Hz, 1H), 3.52 (d, *J*=8.5 Hz, 1H), 4.05 (s, 3H), 4.95 (q_{AB}, *J*=12.7 Hz, 2H), 7.34 (s, 1H), 7.44 (dd with fine coupling, *J*=8.5 and 6.8 Hz, 1H), 7.58 (dd with fine coupling, *J*=8.5 and 6.8 Hz, 1H), 7.96 (d, *J*=8.5 Hz, 1H), 8.28 (d, *J*=8.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.8, 25.7, 28.6, 37.2, 40.8, 57.0, 71.3, 82.0, 84.2, 108.6, 113.7, 123.7, 124.6, 126.8, 127.7, 133.3, 134.9, 134.9, 153.1 ppm. IR (KBr): 3474, 3071, 2955, 2870, 1619 cm^{-1}. Mass (*m/z*, %): 410 (M^++2, 16), 408 (M^+, 18), 268 (47), 266 (61), 252 (25), 251 (99), 250 (26), 249 (100), 127 (19), 57 (16). HRMS (ESI): 431.1213, calcd for $C_{21}H_{29}^{79}BrO_3Na$ (M+Na^+) 431.1198 and 433.1199, calcd for $C_{21}H_{29}^{81}BrO_3Na$ (M+Na^+) 433.1177. Anal. Calcd for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14%. Found: C, 61.61; H, 7.20%.

5e: Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.06 (s, 3H), 1.11 (s, 3H), 3.26 (s, 1H), 3.32 (d, *J*=8.8 Hz, 1H), 3.52 (d, *J*=8.8 Hz, 1H), 3.65 (br s, 1H), 3.94 (s, 3H), 4.65 (s, 2H), 7.11 (s, 1H), 7.31–7.36 (m, 1H), 7.40–7.45 (m, 1H), 7.72 (d, *J*=8.3 Hz, 1H), 7.75 (s, 1H), 7.77 (d, *J*=8.1 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.7, 26.0, 28.6, 37.2, 40.6, 55.2, 69.3, 82.4, 84.4, 105.0, 123.7, 126.2, 126.3, 127.6, 127.7, 127.9, 128.4, 134.1, 155.7 ppm. IR (liquid film): 3484, 2954, 2864, 1635, 1604 cm^{-1}. Mass (*m/z*, %): 330 (M^+, 19), 188 (66), 172 (35), 171 (100), 141 (31), 91 (7), 57 (8). HRMS (ESI): 353.2064, calcd for $C_{21}H_{30}O_3Na$ (M+Na^+) 353.2093.

4.1.3. Synthesis of 1-(7-methoxynaphthalen-2-yl)-methoxy-2,2,4,4-tetramethylpentan-3-one (6a); typical procedure. 1-(7-Methoxynaphthalen-2-yl)methoxy-2,2,4,4-tetramethylpentan-3-ol (**5a**) (1.53 g, 4.63 mmol) was added to a suspension of Celite (2.41 g) and PCC (1.20 g, 5.57 mmol) in CH_2Cl_2 (20 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred overnight. 2-Propanol (3.0 mL) was added to the reaction mixture and stirred for 30 min, then diethyl ether (ca. 200 mL) was added to the reaction mixture and was stirred for 30 min. The reaction mixture was filtered twice through Celite and was concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:6) to give 1-(7-methoxynaphthalene-2-yl)methoxy-2,2,4,4-tetramethylpentan-3-one (**6a**) (1.38 g, 4.20 mmol, 90.7%) as colorless solid.

6a: Colorless needles melted at 82.0–82.5 °C (from AcOEt). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.24 (s, 9H), 1.29 (s, 6H), 3.54 (s, 2H), 3.92 (s, 3H), 4.62 (s, 2H), 7.10–7.14 (m, 1H), 7.11 (s, 1H), 7.25–7.28 (m, 1H), 7.63 (br s, 1H), 7.71 (d, *J*=9.5 Hz, 1H), 7.72 (d, *J*=8.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.1, 28.2, 45.8, 50.2, 55.3, 73.4, 78.6, 105.8, 118.4, 123.3, 125.0, 127.6, 128.3, 129.1, 134.3, 136.5, 157.7, 217.2 ppm. IR (KBr): 3440, 2966, 2914, 2864, 1684, 1633 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 20), 272 (6), 188 (11), 172 (25), 171 (100), 157 (6), 128 (13), 57 (20). HRMS (ESI): 351.1940, calcd for $C_{21}H_{28}O_3Na$ (M+Na^+) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%. Found: C, 76.39; H, 8.31%.

After following the above procedure using the corresponding 1-(methoxynaphthyl)methoxy-2,2,4,4-tetramethylpentan-3-ol **5b–5e**, 1-(methoxynaphthyl)methoxy-2,2,4,4-tetramethylpentan-3-one **6b–6e** were obtained; **6b**: 91.3%, **6c**: 91.8%, **6d**: 94.1%, **6e**: 94.7%.

6b: Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.23 (s, 9H), 1.28 (s, 6H), 3.52 (s, 2H), 3.91 (s, 3H), 4.60 (s, 2H), 7.11–7.15 (m, 1H), 7.12 (s, 1H), 7.38 (dd, *J*=8.4 and 1.6 Hz, 1H), 7.65 (br s, 1H), 7.68–7.71 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.1, 28.1, 45.8, 50.2, 55.3, 73.4, 78.5, 105.7, 118.7, 126.1, 126.4, 126.7, 128.6, 129.2, 133.6, 133.9, 157.5, 217.2 ppm. IR (KBr): 2966, 1677, 1608 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 51), 272 (13), 188 (26), 187 (74), 172 (61), 171 (100), 128 (25), 57 (36). HRMS (ESI): 351.1940, calcd for $C_{21}H_{28}O_3Na$ (M+Na^+) 351.1936.

6c: Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.19 (s, 9H), 1.24 (s, 6H), 3.54 (s, 2H), 3.92 (s, 3H), 4.86 (s, 2H), 7.14 (d, *J*=2.4 Hz, 1H), 7.16 (dd, *J*=8.9 and 2.4 Hz, 1H), 7.29 (d, *J*=7.1 Hz, 1H), 7.37 (dd, *J*=8.1 and 7.1 Hz, 1H), 7.69 (d, *J*=8.1 Hz, 1H), 7.98 (d, *J*=8.9 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.0, 28.0, 45.7, 50.0, 55.2, 72.0, 78.6, 106.3, 118.5, 124.1, 125.7, 126.0, 127.1, 127.3, 133.9, 134.9, 157.3, 217.4 ppm. IR (liquid film): 2964, 1684, 1473 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 49), 272 (24), 188 (22), 172 (54), 171 (100), 128 (33), 57 (32). HRMS (ESI): 351.1924, calcd for $C_{21}H_{28}O_3Na$ (M+Na^+) 351.1936.

6d: Pale yellow granules melted at 77.0–77.5 °C (from AcOEt–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.22 (s, 9H), 1.30 (s, 6H), 3.62 (s, 2H), 4.04 (s, 3H), 4.92 (s, 2H), 7.35 (s, 1H), 7.41 (dd with fine coupling, *J*=8.5 and 6.8 Hz, 1H), 7.56 (dd with fine coupling, *J*=8.5 and 6.8 Hz, 1H), 7.90 (d, *J*=8.5 Hz, 1H), 8.26 (d, *J*=8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.0, 28.0, 45.8, 50.1, 57.0, 71.1, 79.3, 108.0, 113.2, 123.8, 124.4, 126.7, 127.5, 133.2, 135.6, 135.6, 153.2, 217.2 ppm. IR (KBr): 2977, 2852, 1682 cm^{-1}. Mass (*m/z*, %): 408 (M^++2, 30), 406 (M^+, 30), 352 (14), 350 (13), 268 (14), 266 (16), 252 (22), 251 (99), 250 (23), 249 (100), 127 (19), 85 (15), 57 (59). HRMS (ESI): 429.1059, calcd for $C_{21}H_{27}^{79}BrO_3Na$ (M+Na^+) 429.1041 and 431.1042, calcd for $C_{21}H_{27}^{81}BrO_3Na$ (M+Na^+) 431.1021. Anal. Calcd for $C_{21}H_{27}BrO_3$: C, 61.92; H, 6.68%. Found: C, 62.06; H, 6.68%.

6e: Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.25 (s, 9H), 1.32 (s, 6H), 3.64 (s, 2H), 3.90 (s, 3H), 4.64 (s, 2H), 7.07 (s, 1H), 7.30–7.33 (m, 1H), 7.38–7.41 (m, 1H), 7.70 (d, *J*=8.1 Hz, 1H), 7.74 (d, *J*=8.1 Hz, 1H), 7.76 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.1, 28.1, 45.8, 50.3, 55.2, 68.5, 79.0, 104.6, 123.6, 125.9, 126.3, 126.9, 127.6, 128.58, 128.64, 133.8, 155.4, 217.4 ppm. IR (liquid film): 2963, 2865, 1685, 1635 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 25), 272 (9), 188 (16), 187 (19), 172 (28), 171 (100),

141 (31), 128 (9), 57 (18). HRMS (ESI): 351.1930, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936.

4.1.4. Synthesis of 3-*tert*-butyl-*r*-3-hydroxy-*c*-2-(7-methoxynaphthalen-2-yl)-4,4-dimethyl-tetrahydrofuran (7a). A solution of 1-(7-methoxynaphthalen-2-yl)methoxy-tetramethylpentane-3-one (**6a**) (1.00 g, 3.04 mmol) in dry DMSO (5 mL) was added dropwise over 5 min to a suspension of *t*-BuOK (682 mg, 6.08 mmol) in DMSO (10 mL) at 0 °C under a nitrogen atmosphere and stirred for 2 h at room temperature. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed twice with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:5) to give 3-*tert*-butyl-*r*-3-hydroxy-*c*-2-(7-methoxynaphthalen-2-yl)-4,4-dimethyltetrahydrofuran (**7a**-*cis*) (879 mg, 2.68 mmol, 88.1%) as a colorless solid.

7a-*cis*: Colorless needles melted at 110.5–111.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.20 (s, 3H), 1.44 (s, 3H), 1.63 (s, 1H), 3.55 (d, *J*=7.3 Hz, 1H), 3.92 (s, 3H), 4.21 (d, *J*=7.3 Hz, 1H), 5.58 (s, 1H), 7.12–7.14 (m, 1H), 7.15 (s, 1H), 7.43 (dd, *J*=8.3 and 1.6 Hz, 1H), 7.71–7.73 (m, 1H), 7.75 (d, *J*=8.3 Hz, 1H), 7.82 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.2, 26.6, 28.1, 38.1, 48.3, 55.3, 82.0, 84.2, 85.0, 105.9, 118.9, 124.7, 127.0, 127.5, 128.6, 129.0, 134.3, 138.2, 157.7 ppm. IR (KBr): 3456, 2963, 2870, 1631, 1515 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 61), 272 (18), 188 (25), 187 (59), 172 (30), 171 (100), 159 (20), 85 (40), 57 (31). HRMS (ESI): 351.1939, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$+hexane (3.2 w/w %): C, 77.00; H, 8.94%. Found: C, 76.88; H, 9.34.

4.1.5. Synthesis of 3-*tert*-butyl-3-hydroxy-2-(6-methoxynaphthalen-2-yl)-4,4-dimethyltetrahydrofuran (7b); typical procedure. BuLi (1.62 M in hexane) (47.0 mL, 76.1 mmol) was added to a solution of diisopropylamine (11.2 mL, 7.99 mmol) in dry THF (70 mL) under a nitrogen atmosphere at room temperature and stirred for 0.5 h. To the solution, 1-(6-methoxynaphthalen-2-yl)methoxy-2,2,4,4-tetramethylpentan-3-one (**6b**) (12.5 g, 38.1 mmol) in dry THF (24 mL) was added dropwise under a nitrogen atmosphere at −78 °C and stirred and then stirred at 0 °C for 2.5 h. The solution was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:4) to give 3.35 g of **7b** as a mixture of 3-*tert*-butyl-*r*-3-hydroxy-*c*-2-(6-methoxynaphthalen-2-yl)-4,4-dimethyltetrahydrofuran (**7b**-*cis*) and 3-*tert*-butyl-*r*-3-hydroxy-*t*-2-(6-methoxynaphthalen-2-yl)-4,4-dimethyltetrahydrofuran (**7b**-*trans*) in 91.1%.

7b-*trans*: Colorless needles melted at 125.0–125.5 °C (from AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.87 (br s, 9H), 1.22 (s, 3H), 1.45 (s, 3H), 1.98 (s, 1H), 3.74 (d, *J*=8.3 Hz, 1H), 3.91 (s, 3H), 3.96 (d, *J*=8.3 Hz, 1H), 5.17 (s, 1H), 7.11–7.15 (m, 1H), 7.12 (s, 1H), 7.63 (dd, *J*=8.7 and 1.5 Hz, 1H), 7.68 (d, *J*=8.7 Hz, 1H), 7.71 (d, *J*=8.9 Hz, 1H), 7.88 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 22.5, 26.2, 28.3, 39.2, 47.9, 55.3, 80.9, 88.7, 94.7, 105.5, 118.7, 125.9, 127.5, 127.7, 128.3, 129.5, 134.0, 136.4, 157.6 ppm. IR (KBr): 3487, 2964, 2875, 1605 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 25), 310 (35), 296 (28), 295 (100), 239 (33), 188 (19), 187 (99), 186 (49), 185 (78), 172 (14), 171 (75), 157 (26), 57 (20). HRMS (ESI): 351.1937, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%. Found: C, 76.89; H, 9.10%.

7b-*cis*: Colorless plates melted at 126.0–126.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.97 (s, 9H), 1.19 (s, 3H), 1.43 (s, 3H), 1.61 (s, 1H), 3.54 (d, *J*=7.1 Hz, 1H), 3.90 (s, 3H), 4.20 (d, *J*=7.1 Hz, 1H), 5.57 (s, 1H), 7.11 (d, *J*=2.3 Hz, 1H), 7.14 (dd, *J*=9.0 and 2.3 Hz, 1H), 7.54 (d with fine coupling, *J*=8.2 Hz, 1H), 7.71–7.75 (m, 2H), 7.83 (br s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.2, 26.5, 28.0, 38.0, 48.2, 55.3, 81.9, 84.2, 84.9, 105.6, 119.0, 126.7, 127.6, 128.0, 128.6, 129.6, 134.4, 135.3, 157.9 ppm. IR (KBr): 3547, 2960, 1631, 1604 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 53), 272 (9), 188 (20), 187 (100), 172 (14), 171 (68), 85 (19), 57 (12). HRMS (ESI): 351.1934, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%. Found: C, 76.99; H, 8.81%.

After following the above procedure using the corresponding 1-(methoxynaphthyl)methoxy-2,2,4,4-tetramethylpentan-3-one **6c**, **6d**, and **6e**, 3-*tert*-butyl-3-hydroxy-2-(methoxynaphthyl)-4,4-dimethyltetrahydrofurans **7c**, **7d**, and **7e** were obtained as mixture of cis- and trans-isomers; **7c**: 90.1%, **7d**: 99.2%, **7e**: 98.1%.

7c-*trans*: Colorless needles melted at 100.5–101.0 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.78 (br s, 9H), 1.32 (s, 3H), 1.43 (s, 3H), 1.98 (s, 1H), 3.84 (q_{AB}, *J*=3.8 Hz, 2H), 3.91 (s, 3H), 5.80 (s, 1H), 7.12 (d, *J*=2.7 Hz, 1H), 7.16 (dd, *J*=9.3 and 2.7 Hz, 1H), 7.43 (dd, *J*=8.1 and 7.3 Hz, 1H), 7.67 (d, *J*=8.1 Hz, 1H), 7.86 (d, *J*=7.3 Hz, 1H), 8.23 (d, *J*=9.3 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.7, 25.9, 28.2, 39.6, 48.7, 55.1, 79.7, 88.0, 88.5, 106.3, 118.3, 124.2, 125.5, 126.5, 126.7, 127.6, 134.7, 136.9, 156.7 ppm. IR (KBr): 3571, 2964, 1473, 1251 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 58), 310 (36), 295 (89), 280 (28), 239 (24), 187 (37), 186 (20), 172 (31), 171 (100), 157 (26), 115 (29), 85 (25), 57 (41). HRMS (ESI): 351.1919, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$+hexane (4.2 w/w %): C, 77.08; H, 8.92%. Found: C, 76.96; H, 9.20%.

7c-*cis*: Colorless needles melted at 102.5–103.0 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.88 (s, 9H), 1.22 (s, 3H), 1.49 (s, 3H), 1.98 (s, 1H), 3.57 (d, *J*=7.1 Hz, 1H), 3.90 (s, 3H), 4.26 (d, *J*=7.1 Hz, 1H), 6.15 (s, 1H), 7.13 (d, *J*=2.7 Hz, 1H), 7.18 (d, *J*=9.2 Hz, 1H), 7.44 (dd, *J*=7.8 and 6.4 Hz, 1H), 7.60 (d, *J*=6.4 Hz, 1H), 7.70 (d, *J*=7.8 Hz, 1H), 8.22 (d, *J*=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.3, 27.0, 27.9, 38.2, 48.3, 55.2, 80.6, 81.9, 85.9, 106.7, 118.6, 125.8, 126.0, 126.0, 127.4, 127.7, 135.6, 136.3, 157.0 ppm. IR (KBr): 3560, 2964, 1473 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 90), 272 (29), 188 (26), 187 (62), 172 (40), 171 (100), 85 (40), 57 (34). HRMS (ESI): 351.1927, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$+hexane (4.2 w/w %): C, 77.08; H, 8.92%. Found: C, 77.00; H, 9.18%.

7d-*trans*: Colorless prisms melted at 151.5–153.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.79 (br s, 9H), 1.37 (s, 3H), 1.42 (s, 3H), 1.99 (s, 1H), 3.90 (s, 2H), 4.04 (s, 3H), 5.87 (s, 1H), 7.41 (dd with fine coupling, J=8.5 and 6.8 Hz, 1H), 7.54 (dd with fine coupling, J=8.5 and 6.8 Hz, 1H), 7.79 (s, 1H), 8.27 (d, J=8.5 Hz, 1H), 8.31 (d, J=8.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 25.6, 25.7, 27.9, 39.7, 48.7, 57.0, 79.7, 86.8, 88.5, 108.4, 114.2, 124.3, 125.1, 126.7, 127.2, 128.8, 132.9, 138.7, 153.1 ppm. IR (KBr): 3614, 2972, 2936, 2881, 1596 cm^{-1}. Mass (*m*/*z*, %): 408 (M^++2, 60), 406 (M^+, 60), 390 (11), 388 (11), 375 (27), 373 (27), 352 (28), 350 (28), 266 (44), 251 (100), 249 (99), 158 (29), 127 (22), 85 (66), 57 (72). HRMS (ESI): 461.1356, calcd for $C_{22}H_{31}^{79}BrO_4Na$ (M+Na$^+$+MeOH) 461.1303, 463.1332, calcd for $C_{22}H_{31}^{81}BrO_4Na$ (M+Na$^+$+MeOH) 463.1283. Anal. Calcd for $C_{21}H_{27}BrO_3$: C, 61.92; H, 6.68%. Found: C, 62.15; H, 7.15%.

7d-*cis*: Colorless granules melted at 126.5–128.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.89 (s, 9H), 1.24 (s, 3H), 1.52 (s, 3H), 1.65 (br s, 1H), 3.60 (d, J=7.3 Hz, 1H), 4.06 (s, 3H), 4.26 (d, J=7.3 Hz, 1H), 6.22 (s, 1H), 7.42–7.46 (m, 1H), 7.54–7.58 (m, 1H), 7.65 (s, 1H), 8.21 (d, J=8.7 Hz, 1H), 8.31 (d, J=8.7 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.5, 27.2, 28.0, 38.2, 48.4, 57.0, 79.0, 82.0, 86.2, 109.4, 116.0, 123.9, 124.4, 127.1, 127.3, 128.3, 133.3, 137.7, 152.9 ppm. IR (KBr): 3548, 3507, 2965, 2879, 1596 cm^{-1}. Mass (*m*/*z*, %): 408 (M^++2, 20), 406 (M^+, 20), 390 (11), 388 (11), 375 (27), 373 (27), 352 (28), 350 (28), 267 (27), 266 (41), 265 (38), 264 (36), 252 (24), 251 (100), 250 (25), 249 (99), 158 (29), 85 (75), 57 (87). HRMS (ESI): 429.1079, calcd for $C_{21}H_{27}^{79}BrO_3Na$ (M+Na$^+$) 429.1041. Anal. Calcd for $C_{21}H_{27}BrO_3$: C, 61.92; H, 6.68%. Found: C, 61.47; H, 6.89%.

7e-*trans*: Colorless needles melted at 102.0–103.0 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.96 (br s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 3.87 (br s, 1H), 3.88 (d, J=8.2 Hz, 1H), 4.00 (s, 3H), 4.01 (d, J=8.2 Hz, 1H), 5.54 (s, 1H), 7.10 (s, 1H), 7.33–7.37 (m, 1H), 7.41–7.40 (m, 1H), 7.71 (d, J=8.2 Hz, 1H), 7.79 (d, J=7.8 Hz, 1H), 8.09 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 25.4, 28.7, 29.0, 40.1, 48.8, 55.6, 80.1, 84.5, 86.4, 105.1, 124.1, 126.2, 126.3, 127.1, 128.0, 129.0, 131.4, 133.4, 155.0 ppm. IR (KBr): 3502, 2967, 2875, 1631, 1468 cm^{-1}. Mass (*m*/*z*, %): 328 (M^+, 40), 295 (28), 188 (26), 187 (100), 172 (28), 171 (80), 141 (18), 57 (29). HRMS (ESI): 351.1919, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%. Found: C, 76.81; H, 9.11%.

7e-*cis*: Colorless granules melted at 113.5–114.5 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.21 (s, 3H), 1.44 (s, 3H), 3.51 (d, J=7.1 Hz, 1H), 3.96 (s, 3H), 4.23 (d, J=7.1 Hz, 1H), 6.02 (s, 1H), 7.13 (s, 1H), 7.32–7.36 (m, 1H), 7.41–7.45 (m, 1H), 7.71 (d, J=8.3 Hz, 1H), 7.79 (d, J=8.1 Hz, 1H), 7.94 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.3, 26.8, 27.6, 38.2, 48.5, 55.1, 82.0, 82.0, 85.6, 105.6, 123.9, 126.2, 126.5, 128.0, 128.6, 130.4, 130.7, 134.1, 155.5 ppm. IR (KBr): 3455, 2963, 2874, 1631, 1470 cm^{-1}. Mass (*m*/*z*, %): 328 (M^+, 38), 272 (15), 188 (29), 187 (100), 172 (29), 171 (77), 141 (16), 85 (19), 57 (22). HRMS (ESI): 351.1918, calcd for $C_{21}H_{28}O_3Na$ (M+Na$^+$) 351.1936. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%. Found: C, 76.79; H, 9.17%.

4.1.6. Synthesis of 4-*tert*-butyl-5-(7-methoxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (8a). $SOCl_2$ (0.24 mL, 3.29 mmol) was added to a solution of 3-*tert*-butyl-*r*-3-hydroxy-*c*-2-(7-methoxynaphthalen-2-yl)-4,4-dimethyltetrahydrofuran (**8a**) (879 mg, 2.68 mmol) and pyridine (2.17 mL, 26.8 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under a nitrogen atmosphere and the solution was stirred for 30 min. The reaction mixture was allowed to warm from 0 °C to room temperature and was stirred at room temperature for 2 h. The reaction mixture was poured into satd aq NaCl and then extracted with AcOEt. The organic layer was washed with 1 N HCl, washed twice with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:5) to give 4-*tert*-butyl-5-(7-methoxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (**8a**) (749 mg, 2.41 mmol, 89.9%) as colorless viscous oil.

8a: Colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.07 (s, 9H), 1.37 (s, 6H), 3.91 (s, 3H), 3.92 (s, 2H), 7.12 (d, J=2.3 Hz, 1H), 7.14 (dd, J=8.9 and 2.3 Hz, 1H), 7.26 (dd, J=8.3 and 1.7 Hz, 1H), 7.68 (br s, 1H), 7.72 (d, J=8.9 Hz, 1H), 7.73 (d, J=8.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.5, 32.5, 32.7, 47.3, 55.2, 83.1, 105.9, 118.9, 125.4, 125.9, 127.1, 127.9, 128.3, 129.0, 133.9, 134.1, 150.1, 157.6 ppm. IR (KBr): 3330, 2961, 2871, 1628, 1516 cm^{-1}. Mass (*m*/*z*, %): 310 (M^+, 30), 296 (23), 295 (100), 239 (16), 185 (21), 171 (20), 157 (10), 57 (13). HRMS (ESI): 333.1829, calcd for $C_{21}H_{26}O_2Na$ (M+Na$^+$) 333.1831.

4.1.7. Synthesis of 4-*tert*-butyl-5-(6-methoxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (8b); typical procedure. $TsOH\cdot H_2O$ (457 mg, 2.40 mmol) was added to a solution of tetrahydrofuran **7b**-*trans* (7.98 g, 21.8 mmol) in toluene (80 mL) under a nitrogen atmosphere at room temperature and stirred for 1.5 h at refluxed temperature. The reaction mixture was poured into satd aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed twice with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:6) to afford 4-*tert*-butyl-5-(6-methoxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (**8b**) (6.46 g, 20.8 mmol, 85.7%) as a colorless solid.

8b: Colorless needles melted at 95.0–96.0 °C (from AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.06 (s, 9H), 1.36 (s, 6H), 3.90 (s, 3H), 3.91 (s, 2H), 7.11 (d, J=2.4 Hz, 1H), 7.13 (dd, J=8.8 and 2.4 Hz, 1H), 7.36 (dd, J=8.3 and 1.7 Hz, 1H), 7.67–7.72 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.5, 32.6, 32.7, 47.3, 55.3, 83.1, 105.6, 118.8, 125.9, 126.2, 128.2, 128.3, 128.7, 129.5, 131.3, 134.0, 150.1, 157.8 ppm. IR (KBr): 2958, 1861, 1627, 1599 cm^{-1}. Mass (*m*/*z*, %): 310 (M^+, 61), 296 (41), 295 (100), 253 (10), 239 (22), 185 (33), 157 (10), 57 (15). HRMS (ESI): 333.1830, calcd for $C_{21}H_{26}O_2Na$ (M+Na$^+$) 333.1831. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%. Found: C, 81.26; H, 8.95%.

After following the above procedure using the corresponding 3-*tert*-butyl-*r*-3-hydroxy, *tert*-2-methoxynaphthyl-4,4-dimethyltetrahydrofurans **7c**–**7e**, 4-*tert*-butyl-5-methoxynaphthyl-3,3-dimethyl-2,3-dihydrofurans **8c**–**8e** were obtained; **8c**: 98.9%, **8d**: 90.8%, **8e**: 85.3%

8c: Colorless plates melted at 83.5–84.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.99 (s, 9H), 1.40 (s, 3H), 1.46 (s, 3H), 3.89 (s, 3H), 3.97 (q_{AB}, J=7.8 Hz, 2H), 7.10 (d, J=2.7 Hz, 1H), 7.16 (dd, J=9.2 and 2.7 Hz, 1H), 7.28 (d with fine coupling, J=8.1 Hz, 1H), 7.38 (d, J=8.3 and 8.1 Hz, 1H), 7.70 (d, J=8.3 Hz, 1H), 7.85 (d, J=9.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 27.7, 32.0, 32.7, 47.3, 55.2, 83.3, 105.8, 118.9, 125.5, 125.8, 127.3, 127.4, 127.6, 127.7, 133.4, 134.5, 147.9, 157.4 ppm. IR (KBr): 2959, 1625, 1469 cm^{-1}. Mass (*m*/*z*, %): 310 (M^+, 35), 296 (23), 295 (100), 280 (33), 239 (25), 185 (11), 157 (13), 57 (11). HRMS (ESI): 333.1822, calcd for $C_{21}H_{26}O_2Na$ (M+Na^+) 333.1831. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%. Found: C, 81.41; H, 8.94%.

8d: Amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.01 (s, 9H), 1.43 (s, 3H), 1.48 (s, 3H), 4.00 (q_{AB}, J=7.8 Hz, 2H), 4.03 (s, 3H), 7.22 (s, 1H), 7.41 (dd with fine coupling, J=7.8 and 6.8 Hz, 1H), 7.54 (dd with fine coupling, J=8.5 and 6.8 Hz, 1H), 7.88 (d, J=7.8 Hz, 1H), 8.22 (d, J=8.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 27.6, 32.0, 32.7, 47.4, 57.2, 83.4, 109.3, 115.8, 124.7, 126.1, 126.3, 127.7, 128.6, 128.8, 133.0, 134.7, 146.8, 152.8 ppm. IR (KBr): 2958, 2931, 2862, 1590 cm^{-1}. Mass (*m*/*z*, %) 390 (M^++2, 43), 388 (M^+, 43), 376 (25), 375 (100), 374 (26), 373 (99), 360 (27), 358 (28), 238 (19), 128 (11), 57 (37). HRMS (ESI): 443.1234, calcd for $C_{22}H_{29}^{79}BrO_3Na$ (M+Na^++MeOH) 443.1198 and 445.1220, calcd for $C_{22}H_{29}^{81}BrO_3Na$ (M+Na^++MeOH). Anal. Calcd for $C_{21}H_{25}BrO_2$+hexane (3.6 w/w %): C, 65.46; H, 6.82%. Found: C, 65.52; H, 6.83%.

8e: Colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.37 (s, 6H), 3.92 (q_{AB}, J=7.6 Hz, 2H), 3.93 (s, 3H), 7.11 (s, 1H), 7.30–7.34 (m, 1H), 7.40–7.45 (m, 1H), 7.67 (s, 1H), 7.72 (d, J=7.8 Hz, 1H), 7.74 (d. J=7.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.2, 31.9, 32.5, 47.1, 55.6, 83.1, 105.3, 123.6, 126.4, 126.5, 126.9, 127.0, 127.8, 128.2, 131.3, 134.6, 145.9, 155.9 ppm. IR (KBr): 2955, 2866, 1654, 1466 cm^{-1}. Mass (*m*/*z*, %): 310 (M^+, 31), 296 (23), 295 (100), 239 (23), 185 (28). HRMS (ESI): 333.1812, calcd for $C_{21}H_{26}O_2Na$ (M+Na^+) 333.1831. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%. Found: C, 81.09; H, 8.94%.

4.1.8. Synthesis of 4-*tert*-butyl-5-(3-methoxynaphthalen-1-yl)-3,3-dimethyl-2,3-dihydrofuran (8d′). Butyllithium (1.61 mol L^{-1} in hexane, 4.0 mL, 6.44 mmol) was added to a solution of 5-(4-bromo-3-methoxynaphthalen-1-yl)-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**8d**) (2.11 g, 5.42 mmol) in THF (20 mL) under a nitrogen atmosphere at −78 °C. After stirring for 10 min, the reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1:10) to give 4-*tert*-butyl-5-(3-methoxynaphthalen-1-yl)-3,3-dimethyl-2,3-dihydrofuran (**8d′**) (1.67 g, 5.38 mmol, 99.3%) as a colorless solid.

8d′: Colorless granules melted at 83.0–84.0 °C (from hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.02 (s, 9H), 1.41 (s, 3H), 1.47 (s, 3H), 3.92 (s, 3H), 3.97 (q_{AB}, J=7.8 Hz, 2H), 7.12 (s, 2H), 7.35 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.42 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.71 (d, J=8.1 Hz, 1H), 7.85 (d, J=8.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.3, 27.7, 32.0, 32.7, 47.3, 55.3, 83.3, 106.4, 120.7, 123.9, 125.7, 126.3, 126.9, 127.8, 127.9, 134.6, 135.1, 147.2, 156.5 ppm. IR (KBr): 3062, 2955, 2863, 1598 cm^{-1}. Mass (*m*/*z*, %): 310 (M^+, 34), 296 (20), 295 (100), 280 (20), 265 (11), 239 (22). HRMS (ESI): 333.1856, calcd for $C_{21}H_{26}O_2Na$ (M+Na^+) 333.1831. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%. Found: C, 81.32; H, 8.87%.

4.1.9. Synthesis of 4-*tert*-butyl-5-(7-hydroxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (3a); typical procedure. CH_3SNa (338 mg, 4.82 mmol) was added to a solution of 4-*tert*-butyl-5-(7-methoxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (**8a**) (749 mg, 2.41 mmol) in dry DMF (10 mL) at room temperature under a nitrogen atmosphere and was refluxed for 2 h. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed twice with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:3) to give 4-*tert*-butyl-5-(7-hydroxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (**3a**) (664 mg, 2.24 mmol, 92.9%) as a colorless solid.

3a: Colorless granules melted at 196.0–197.0 °C (from CH_2Cl_2–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.06 (s, 9H), 1.38 (s, 6H), 3.93 (s, 2H), 5.15 (s, 1H), 7.03–7.07 (m, 1H), 7.06 (s, 1H), 7.24 (dd, J=8.3 and 1.6 Hz, 1H), 7.59 (br s, 1H), 7.69 (d, J=8.5 Hz, 1H), 7.70 (d, J=8.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.5, 32.6, 32.6, 47.3, 83.2, 109.7, 118.0, 125.5, 126.1, 127.2, 127.5, 128.3, 129.4, 133.9, 134.1, 149.9, 153.4 ppm. IR (KBr): 3330, 2961, 2871, 1628, 1518 cm^{-1}. Mass (*m*/*z*, %): 296 (M^+, 29), 282 (24), 281 (100), 225 (17), 171 (23), 143 (10), 115 (4), 57 (12). HRMS (ESI): 319.1672, calcd for $C_{20}H_{24}O_2Na$ (M+Na^+) 319.1674. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%. Found: C, 80.70; H, 8.63%.

After following the above procedure using the corresponding 4-*tert*-butyl-5-methoxynaphthyl-3,3-dimethyl-2,3-dihydrofurans **8b**–**8c**, **8d′**, and **8e**, 4-*tert*-butyl-5-hydroxynaphthyl-3,3-dimethyl-2,3-dihydrofurans **3b**–**3e** were obtained; **3b**: 88.1%, **3c**: 84.8%, **3d**: 95.1%, **3e**: 85.0%.

3b: Colorless plates melted at 202.5–203.0 °C (from AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.06 (s, 9H), 1.37 (s, 6H), 3.93 (s, 2H), 5.54 (s, 1H), 6.94 (d, J=2.4 Hz, 1H), 6.98 (dd, J=8.8 and 2.4 Hz, 1H), 7.31 (dd, J=8.5 and 1.6 Hz, 1H), 7.49 (d, J=8.5 Hz, 1H), 7.60 (d, J=8.8, 1H), 7.65 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.5, 32.6, 32.7, 47.3, 83.0, 109.4, 118.0, 125.9, 126.2, 128.1, 128.2, 128.9, 129.8, 130.9, 134.0, 149.9, 153.7 ppm. IR (KBr): 3385, 2956, 1856, 1655, 1628, 1478,

1600 cm^{-1}. Mass (*m/z*, %): 296 (M^+, 50), 282 (32), 281 (100), 225 (19), 171 (32). HRMS (ESI): 319.1693, calcd for $C_{20}H_{24}O_2Na$ (M+Na^+) 319.1674. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; O, 10.80. Found: C, 81.12; H, 8.63.

3c: Colorless needles melted at 197.5–198.0 °C (from AcOEt–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.99 (s, 9H), 1.41 (s, 3H), 1.46 (s, 3H), 4.00 (q_{AB}, *J*=8.0 Hz, 2H), 5.97 (s, 1H), 6.83 (d, *J*=2.4 Hz, 1H), 6.95 (d, *J*=9.0 and 2.4 Hz, 1H), 7.26 (d with fine coupling, *J*=7.0 Hz, 1H), 7.32 (d, *J*=8.2 and 2.4 Hz, 1H), 7.34 (d, *J*=8.2 Hz, 1H), 7.77 (d, *J*=9.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.3, 27.7, 32.0, 32.7, 47.3, 83.1, 109.6, 118.2, 125.4, 125.7, 127.1, 127.5, 127.5, 128.0, 133.1, 134.6, 147.6, 153.3 ppm. IR (KBr): 3330, 2959, 1633, 1433 cm^{-1}. Mass (*m/z*, %): 296 (M^+, 35), 282 (21), 281 (100), 266 (29), 225 (23), 171 (17), 143 (15), 57 (22). HRMS (ESI): 297.1877, calcd for $C_{20}H_{25}O_2$ (M+H^+) 297.1855 and 319.1671, calcd for $C_{20}H_{24}O_2Na$ (M+Na^+) 319.1674. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%. Found: C, 81.38; H, 8.63%.

3d: Pale yellow granules melted at 152.5–154.0 °C (from AcOEt–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.02 (s, 9H), 1.41 (s, 3H), 1.47 (s, 3H), 3.98 (q_{AB}, *J*=8.1 Hz, 2H), 5.05 (s, 1H), 7.07 (d, *J*=2.4 Hz, 1H), 7.10 (br d, *J*=2.4 Hz, 1H), 7.34 (dd with fine coupling, *J*=8.3 and 6.8 Hz, 1H), 7.41 (dd with fine coupling, *J*=8.1 and 6.8 Hz, 1H), 7.64 (d, *J*=8.1 Hz, 1H), 7.85 (d, *J*=8.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.3, 27.5, 31.9, 32.7, 47.3, 83.2, 110.3, 120.1, 123.9, 125.6, 126.3, 126.6, 127.8, 128.2, 134.6, 135.1, 146.8, 152.3 ppm. IR (KBr): 3344, 2958, 2870, 1600 cm^{-1}. Mass (*m/z*, %): 296 (M^+, 46), 282 (23), 281 (100), 266 (39), 251 (23), 225 (29), 171 (13), 115 (14). HRMS (ESI): 319.1718, calcd for $C_{20}H_{24}O_2Na$ (M+Na^+) 319.1674. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%. Found: C, 81.06; H, 8.76%.

3e: Colorless columns melted at 133.5–134.0 °C (from AcOEt–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.11 (s, 9H), 1.41 (s, 6H), 3.96 (s, 2H), 5.55 (s, 1H), 7.28 (s, 1H), 7.31 (dd with fine coupling, *J*=8.1 and 6.8 Hz, 1H), 7.42 (dd with fine coupling, *J*=7.8 and 6.8 Hz, 1H), 7.69 (d, *J*=7.8 Hz, 1H), 7.71 (s, 1H), 7.74 (d, *J*=8.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 32.0, 32.8, 47.5, 83.1, 110.0, 123.7, 124.4, 126.4, 126.8, 127.9, 128.1, 130.6, 131.3, 135.0, 144.4, 151.4 ppm. IR (KBr): 3372, 2962, 1659, 1452 cm^{-1}. Mass (*m/z*, %): 296 (M^+, 42), 282 (23), 281 (100), 225 (55), 171 (41), 115 (15), 57 (22). HRMS (ESI): 319.1665, calcd for $C_{20}H_{24}O_2Na$ (M+Na^+) 319.1674. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%. Found: C, 81.08; H, 8.60%.

4.1.10. Singlet oxygenation of 4-*tert*-butyl-5-(7-hydroxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (3a); typical procedure. A solution of a 4-*tert*-butyl-5-(7-hydroxynaphthalen-2-yl)-3,3-dimethyl-2,3-dihydrofuran (**3a**) (100 mg, 0.337 mmol) and tetraphenylporphin (TPP) (1.0 mg) in CH_2Cl_2 (10 mL) was irradiated externally with 940 W Na lamp under an oxygen atmosphere at 0 °C for 1 h. The photolysate was concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 to give a 5-*tert*-butyl-1-(7-hydroxynaphthalen-2-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**1aA**) (91.1 mg, 0.277 mmol, 82.2%) as a colorless solid.

1aA: Colorless needles melted at 122.0–123.0 °C (from CH_2Cl_2–hexane). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.99 (s, 9H), 1.19 (s, 3H), 1.43 (s, 3H), 3.87 (d, *J*=8.2 Hz, 1H), 4.63 (d, *J*=8.2 Hz, 1H), 4.95 (s, 1H), 7.16 (dd, *J*=8.7 and 2.5 Hz, 1H), 7.21 (d, *J*=2.5 Hz, 1H), 7.48 (d with fine coupling, *J*=8.7 Hz, 1H), 7.77 (d, *J*=8.7 Hz, 1H), 7.78 (d, *J*=8.7 Hz, 1H), 8.02 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.5, 25.1, 26.8, 36.8, 45.7, 80.4, 105.2, 110.4, 117.0, 119.1, 122.9, 126.9, 127.5, 129.0, 129.5, 133.6, 133.7, 153.9 ppm. IR (KBr): 3744, 3421, 2966, 1692, 1609 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 9), 296 (2), 272 (19), 188 (29), 172 (16), 171 (100), 143 (18), 115 (8), 57 (21). HRMS (ESI): 351.1558, calcd for $C_{20}H_{24}O_4Na$ (M+Na^+) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 72.83; H, 7.75%.

After following the above procedure using the corresponding 4-*tert*-butyl-5-hydroxynaphthyl-3,3-dimethyl-2,3-dihydrofurans **3b–3e**, 5-*tert*-butyl-1-(hydroxynaphthalen-2-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptanes **1bA–1eA** were obtained; **1bA**: 53.7%, **1cA**: 88.2%, **3d**: 80.5%, **3e**: 83.5%.

1bA: Colorless needles melted at 158.0–159.0 °C (CH_2Cl_2–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.99 (s, 9H), 1.18 (s, 3H), 1.43 (s, 3H), 3.86 (d, *J*=8.1 Hz, 1H), 4.62 (d with fine coupling, *J*=8.1 Hz, 1H), 5.07 (s, 1H), 7.12 (d, *J*=2.4 Hz, 1H), 7.14–7.16 (m, 1H), 7.59 (dd, *J*=8.6 and 1.7 Hz, 1H), 7.69 (d, *J*=8.6 Hz, 1H), 7.81 (d, *J*=8.8 Hz, 1H), 8.09 (d, *J*=1.7 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.5, 25.1, 26.8, 36.7, 45.6, 80.3, 104.9, 109.3, 117.0, 118.3, 125.9, 126.1, 127.9, 128.4, 130.7, 130.9, 134.9, 154.5 ppm. IR (KBr): 3368, 2972, 1631, 1482 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 11), 272 (17), 188 (24), 172 (13), 171 (100), 143 (14), 57 (14). HRMS (ESI): 351.1584, calcd for $C_{20}H_{24}O_4Na$ (M+Na^+) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$+CH_2Cl_2 (1.0 w/w %): C, 72.62; H, 7.32%. Found: C, 72.78; H, 6.80%.

1cA: Colorless needles melted at 162.5–163.0 °C (from CH_2Cl_2–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.89 (s, 9H), 1.29 (s, 3H), 1.61 (s, 3H), 4.06 (d, *J*=8.7 Hz, 1H), 4.79 (d, *J*=8.7 Hz, 1H), 5.12 (s, 1H), 7.10 (dd, *J*=9.4 and 2.6 Hz, 1H), 7.14 (d, *J*=2.6 Hz, 1H), 7.43–7.47 (m, 1H), 7.72 (d, *J*=8.2 Hz, 1H), 8.06 (br s, 1H), 8.50 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.0, 26.1, 26.7, 36.8, 45.6, 80.5, 106.0, 110.5, 117.7, 125.2, 126.6, 127.8, 128.3, 129.6, 131.3, 135.8, 152.8 ppm. IR (KBr): 3363, 2975, 1633, 1514 cm^{-1}. Mass (*m/z*, %): 328 (M^+, 20), 278 (12), 272 (20), 188 (34), 172 (13), 171 (100), 143 (18), 115 (8), 57 (26). HRMS (ESI): 351.1590, calcd for $C_{20}H_{24}O_4Na$ (M+Na^+) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$+CH_2Cl_2 (6.1 w/w %): C, 69.56; H, 7.06%. Found: C, 69.61; H, 7.18%.

1dA: Pale yellow granules melted at 157.5–158.0 °C (from CH_2Cl_2–hexane). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.91 (s, 9H), 1.30 (s, 3H), 1.63 (s, 3H), 4.07 (d, *J*=8.4 Hz, 1H), 4.68 (d, *J*=8.4 Hz, 1H), 4.97 (s, 1H), 7.24 (d, *J*=2.7 Hz,

1H), 7.34 (dd with fine coupling, J=8.3 and 6.8 Hz, 1H), 7.41 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.70 (d with fine coupling, J=8.1 Hz, 1H), 7.87 (br s, 1H), 8.47 (br d, J=8.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.0, 26.1, 26.8, 36.9, 45.6, 80.7, 106.5, 112.6, 117.2, 122.0, 123.7, 126.1, 126.1, 126.7, 127.6, 133.2, 135.8, 152.0 ppm. IR (KBr): 3461, 2970, 2907, 1512 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 24), 272 (18), 188 (44), 172 (14), 171 (100), 115 (17), 57 (37). HRMS (ESI): 351.1589, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.36; H, 7.21%.

1eA: Colorless needles melted at 159.5–160.0 °C (from CH_2Cl_2–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.00 (s, 9H), 1.22 (s, 3H), 1.46 (s, 3H), 3.97 (d, J=8.7 Hz, 1H), 4.68 (d, J=8.7 Hz, 1H), 7.29 (s, 1H), 7.35 (dd with fine coupling, J=8.2 and 6.9 Hz, 1H), 7.47 (dd with fine coupling, J=8.2 and 6.9 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.86 (br s, 1H), 8.22 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.7, 25.0, 26.4, 36.6, 45.7, 80.3, 105.8, 112.5, 117.2, 121.9, 124.0, 126.1, 127.7, 127.7, 128.6, 131.5, 135.7, 152.3 ppm. IR (KBr): 3398, 2970, 1636, 1458 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 48), 296 (3), 188 (38), 172 (13), 171 (100), 170 (97), 141 (61), 115 (34), 57 (66). HRMS (ESI): 351.1578, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.22; H, 7.34%.

4.1.11. Thermal decomposition of 5-*tert*-butyl-1-(7-hydroxynaphthalen-2-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1aA); typical procedure. A solution of 5-*tert*-butyl-1-(7-hydroxynaphthalen-2-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane **1aA** (53.8 mg, 0.164 mmol) in xylene (3 mL) was refluxed for 6.5 h. After cooling, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:10) to give 2,2,4,4-tetramethyl-3-oxopentyl 7-hydroxynaphthalene-2-carboxylate (**9a**) (46.7 mg, 0.142 mmol, 86.6%) as a colorless solid.

9a: Colorless columns melted at 157.0–158.0 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.31 (s, 9H), 1.43 (s, 6H), 4.48 (s, 2H), 6.10 (s, 1H), 7.22 (dd, J=8.7 and 2.3 Hz, 1H), 7.25 (d, J=2.3 Hz, 1H), 7.73 (d, J=8.7 Hz, 1H), 7.75 (d, J=8.7 Hz, 1H), 7.80 (dd, J=8.7 Hz, 1H), 8.36 (br s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.8, 28.2, 46.0, 49.3, 72.2, 110.7, 120.5, 122.7, 127.6, 128.0, 129.5, 129.6, 130.9, 133.7, 154.3, 166.8, 216.7 ppm. IR (KBr): 3415, 2973, 1695, 1605 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 16), 278 (18), 272 (23), 188 (28), 172 (16), 171 (100), 143 (17), 57 (24). HRMS (ESI): 351.1569, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.04; H, 7.78%.

9b: Colorless granules melted at 126.0–126.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.32 (s, 9H), 1.43 (s, 6H), 4.48 (s, 2H), 7.08 (br s, 1H), 7.15 (d with fine coupling, J=8.7 Hz, 1H), 7.16 (s, 1H), 7.54 (d, J=8.7 Hz, 1H), 7.71 (d, J=8.7 Hz, 1H), 7.84 (d with fine coupling, 1H), 8.38 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 28.2, 46.0, 49.4, 72.0, 109.5, 118.9, 124.5, 125.5, 126.5, 127.5, 131.0, 131.3, 137.2, 156.2, 167.0, 217.3 ppm. IR (KBr): 3402, 2976, 1697, 1623, 1484 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 16), 272 (23), 188 (26), 172 (14), 171 (100), 143 (13), 57 (12). HRMS (ESI): 351.1572, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 72.96; H, 7.67%.

9c: Colorless needles melted at 109.0–109.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.28 (s, 9H), 1.42 (s, 6H), 4.48 (s, 2H), 6.65 (s, 1H), 7.71 (d, J=2.7 Hz, 1H), 7.19 (dd, J=9.4 and 2.7 Hz, 1H), 7.34 (dd, J=8.2 and 7.3 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.89 (d with fine coupling, J=7.3 Hz, 1H), 8.72 (d, J=9.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 28.1, 46.0, 49.2, 72.3, 110.1, 119.7, 125.0, 126.4, 126.7, 127.6, 127.7, 131.9, 135.4, 153.9, 167.6, 217.0 ppm. IR (liquid film): 3331, 2973, 1707, 1669 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 23), 278 (3), 272 (22), 188 (36), 172 (14), 171 (100), 143 (18), 115 (7), 57 (17). HRMS (ESI): 351.1573, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.22; H, 7.44%.

9d: Colorless needles melted at 158.0–159.0 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.27 (s, 9H), 1.41 (s, 6H), 4.49 (s, 2H), 7.11 (br s, 1H), 7.36–7.42 (m, 3H), 7.61–7.64 (m, 1H), 7.73 (d, J=2.7 Hz, 1H), 8.71–8.73 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.6, 28.1, 46.0, 49.3, 72.3, 115.3, 121.9, 125.2, 125.6, 126.6, 126.7, 127.0, 128.3, 135.3, 152.3, 167.0, 217.5 ppm. IR (KBr): 3409, 2968, 1716, 1671, 1576 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 26), 278 (16), 272 (21), 188 (47), 172 (14), 171 (100), 115 (21), 57 (27). HRMS (ESI): 351.1572, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 72.96; H, 7.67%.

9e: Pale yellow needles melted at 89.0–90.0 °C (from MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.32 (s, 9H), 1.44 (s, 6H), 4.48 (s, 2H), 7.28–7.32 (m, 1H), 7.29 (s, 1H), 7.46–7.49 (m, 1H), 7.66 (d, J=8.2 Hz, 1H), 7.74 (d, J=8.2 Hz, 1H), 8.32 (s, 1H), 10.4 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.6, 28.0, 45.9, 49.1, 72.6, 111.7, 114.1, 123.9, 126.2, 126.9, 129.1, 129.1, 132.0, 137.8, 156.3, 169.4, 215.7 ppm. IR (liquid film): 3239, 2968, 1681, 1637, 1514 cm^{-1}. Mass (*m*/*z*, %): 328 (M$^+$, 44), 188 (38), 171 (97), 170 (100), 141 (68), 142 (26), 141 (61), 115 (28), 57 (53). HRMS (ESI): 351.1558, calcd for $C_{20}H_{24}O_4Na$ (M+Na$^+$) 351.1572. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.19; H, 7.56%.

4.1.12. Chemiluminescence measurement; general procedure. Chemiluminescence was measured using a Hitachi FP-750 spectrometer and/or Hamamatsu Photonics PMA-11 multi-channel detector.

Freshly prepared solution (2 mL) of TBAF (1.0×10^{-2} mol L^{-1}) in DMSO was transferred to a quartz cell ($10\times10\times50$ mm) and the latter placed in the spectrometer, which was thermostated with stirring at 25 °C. After 3–5 min, a solution of the dioxetane in DMSO (1.0×10^{-4} mol L^{-1}–1.0×10^{-6} mol L^{-1}, 1 mL) was added by means of a syringe with immediate starting of measurement. The intensity of the light emission time-course was recorded and processed according to first-order kinetics. The total light emission was estimated by comparing it with that of an

adamantylidene dioxetane, whose chemiluminescent efficiency Φ^{CTICL} has been reported to be 0.29 and was used here as a standard.[11]

4.1.13. Fluorescence measurement; general procedure. Freshly prepared solution of $2.05–2.10\times10^{-5}$ mol dm^{-3} of **9a–9e** and of 1.0×10^{-2} mol dm^{-3} of TBAF in DMSO was transferred to a quartz cell ($10\times10\times50$ mm) and the latter placed in the spectrometer, which was thermostated with stirring at 25 °C. Thus, the fluorescence spectra of **11a–11e** were measured and their fluorescence efficiencies (Φ^{fl}) were estimated using fluorescein as a standard.

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