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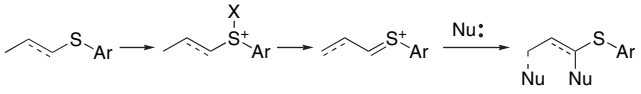
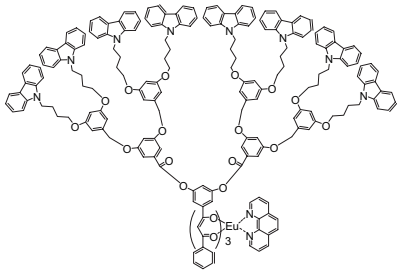
Contents

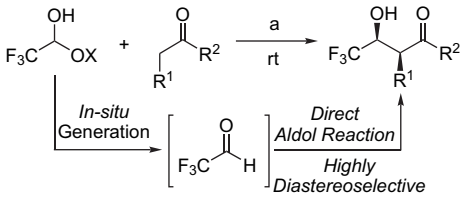
REPORT



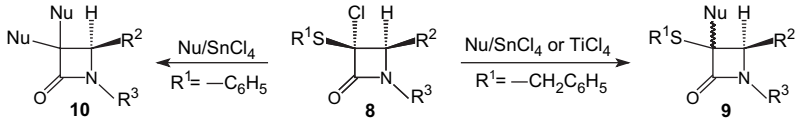
ARTICLES



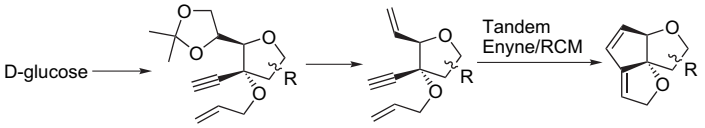
Antenna-functionalized europium dendrimers



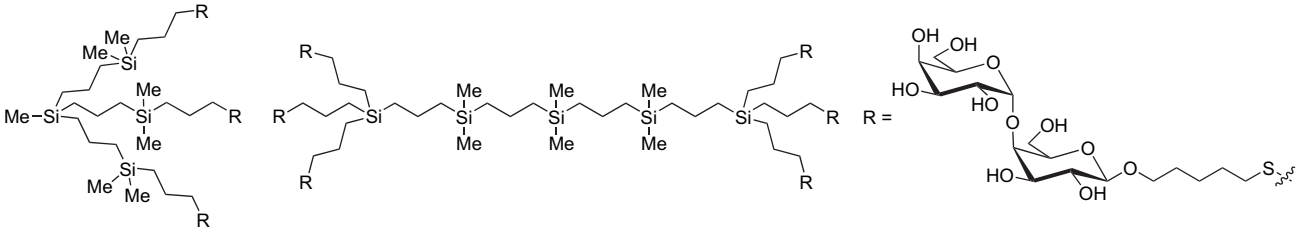
(a) 30-50 mol% amine / 30-50 mol% organic acid or 30-50 mol% amine / solid acid

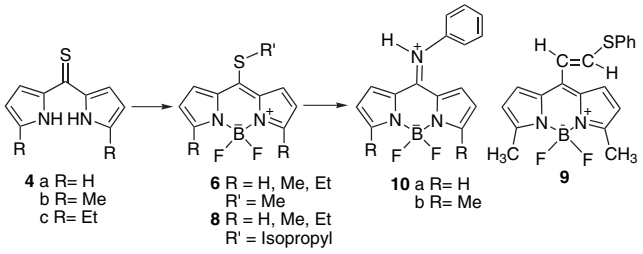


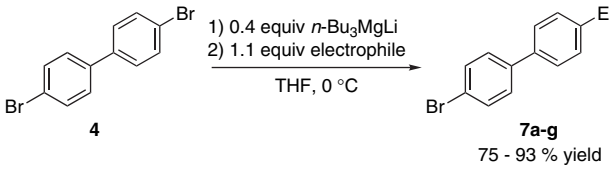
An efficient and operationally simple strategy for the synthesis of differently C-3 monosubstituted (**9**) and disubstituted (**10**) monocyclic β-lactams is described. This involves reaction of β-lactam carbocation equivalents (**8**) with an active aromatic, aliphatic and heterocyclic substrates in the presence of a Lewis acid.

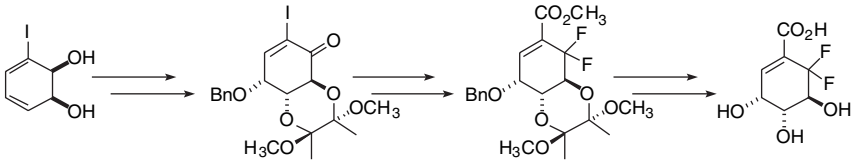


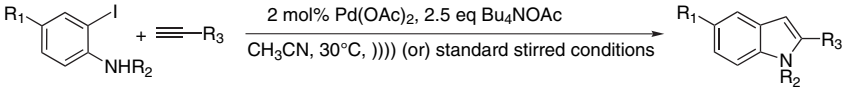
A novel class of angularly fused dioxa-triquinanes is synthesized by a tandem enyne/RCM of a dienyne derived from a sugar template. The effect of ethylene atmosphere and different protecting groups on the tandem enyne/RCM reaction is demonstrated here.

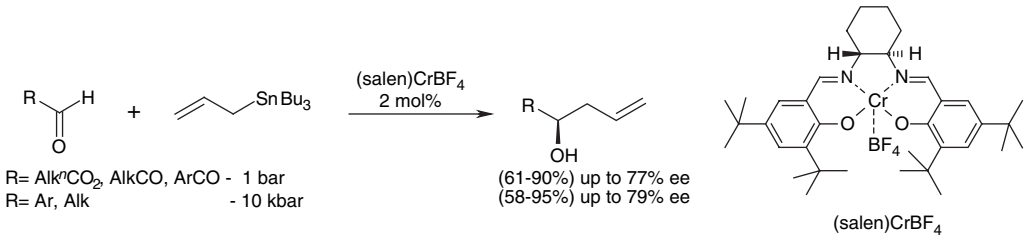


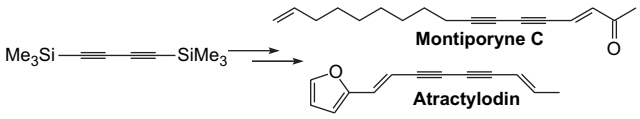




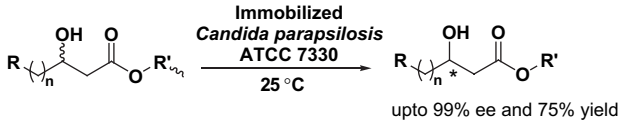




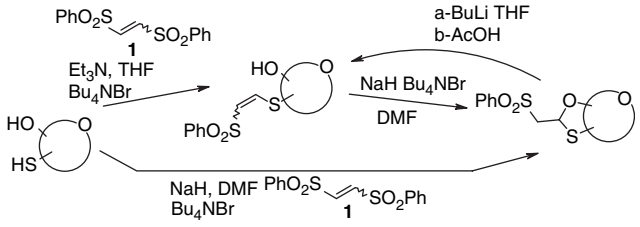


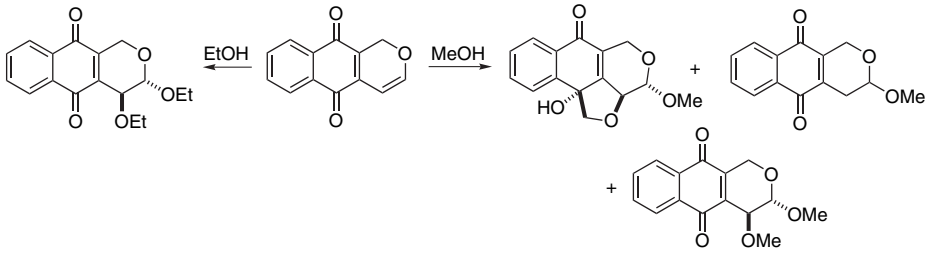


A series of naturally occurring acetylenes has been synthesized starting from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.



R=C_6H_5, *p*-MeC_6H_4, *o*-MeC_6H_4, *p*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, *p*-EtC_6H_4, *p*-ClC_6H_4, *m*-BrC_6H_4, *m*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4$, 1-Naphthyl, 9-Anthranyl and Me; *n*=0, 1 and 2; R′=Me, Et, *n*-Pr, *n*-Bu, $-CH_2C_6H_5$ and $-CH_2CH{=}CH-C_6H_5$.





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Modern Pummerer-type reactions

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Contents

1. Introduction

Who discovered the Pummerer reaction? A simple, if not rhetorical, question that belies a straightforward answer. Ultimately, provenance for this well-known transformation depends on a second question: what chemical process actually constitutes a Pummerer reaction? Perhaps the original candidate for this role was reported by Fromm and Achert in 1903,[1] who described the decomposition of dibenzylsulfoxide (**1**) upon attempted distillation to furnish the suite of products **2**–**5** (Scheme 1). This study did not include the deliberate treatment of the sulfoxide with an electrophile (i.e., H^+, Ac_2O), a precondition of the modern version of the Pummerer reaction, and so it is likely that adventitious

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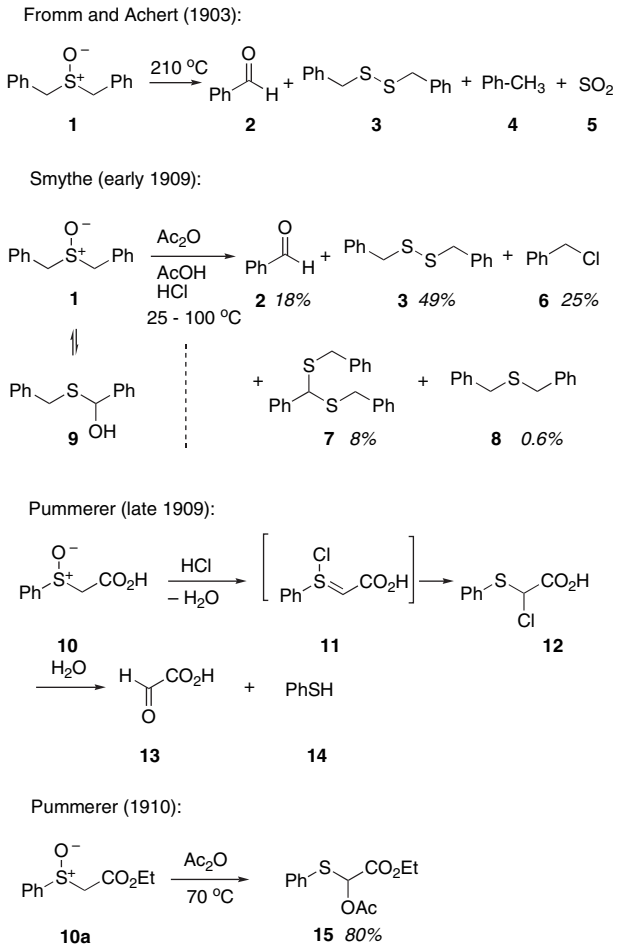


Scheme 1. Early examples of Pummerer (and related) reactions.

and unacknowledged acid autocatalyzed the decomposition. No mechanistic discussion attended this observation, and the surprising formal oxidative transposition that was observed caused the authors to doubt the structure of their starting material: "Der merkwürdige Zerfall des Benzylsulfoxyds bei 210°, insbesondere die Bildung von Benzaldehyd bei dieser Zersetzung, liess Zweifel darüber autkommen, ob die dem Sulfoxyd zugeschriebene Constitutions-formel: $(C_6H_5{\cdot}CH_2)_2S{:}O$, die richtige sei. Es musste in diesem Fall-eja eine Wanderung des Sauerstoffs vom Schwefel an den Kohlenstoff stattgefunden haben. Eine solche Wanderung konnte man ausschliessen, wenn man dem Benzylsulfoxyd die folgende Constitutions-formel, in welcher der Sauerstoff von vornherein an Kohlenstoff gebunden ist, zuschrieb: $C_6H_5{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$."[1] (The unusual decomposition of benzylsulfoxide at 210°, in particular the formation of benzaldehyde upon this decomposition, raises concerns about whether the constitutional formula assigned to the sulfoxide, $(C_6H_5{\cdot}CH_2)_2S{:}O$, is correct. If it is so, then migration of the oxygen from sulfur to carbon must have taken place. Such a migration can be excluded if one assigns the following constitutional formula, in which the oxygen is bound at carbon from the outset, to the benzylsulfoxide: $C_6H_5{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$.) Six years later in early 1909, Smythe picked up this train of research and described the products detected upon exposing **1** to the undeniable Pummerer activators HCl and Ac_2O.[2] Smythe observed formation of the characteristic Pummerer reaction product benzaldehyde (**2**) (and its derived thioacetal **7**), and his mechanistic speculation started out in a productive vein by suggesting that the hydroxysulfide **9** preceded the aldehyde. However, Smythe was apparently at a loss to rationalize the intermediacy of this alcohol, and he resorted to invoking what he termed 'dynamic isomerism' between **1** and **9**, by analogy with known keto-enol tautomerizations, to justify its presence. Later in that same year, in a paper that cites the work of Smythe, Rudolph Pummerer authored his now famous report on the consequences of treating the sulfinyl acetic acid **10** with HCl.[3a] Pummerer meticulously characterized the product distribution, which included the aldehyde **13** and thiophenol. Once again, a formal oxidation at carbon required explanation, and Pummerer rose to this challenge by invoking the intermediacy of the sulfurane **11** and then its formal 1,2-chloride shift product, the sulfide **12**. The similarity of Pummerer's sulfurane to the currently adopted thionium ion intermediate, Ph(+)S=CH–, should not be overlooked (simple chloride ionization from **11**), and this hypothesis provided for the first time a rational mechanistic framework for discussing sulfoxide decomposition chemistry. Pummerer evaluated and then rejected Smythe's dynamic isomerism explanation, noting that "Auf die ausführlichen Desmotropie-Betrachtungen des Verfassers kann ich nicht näher eingehen, sie stehen in beträchtlichem Gegensatz zur heutigen Kenntnis derartiger Probleme."[3a] (I don't want to elaborate further on the author's detailed discussion of 'desmotropy', as it stands in considerable contrast to modern understanding of such problems.) Thus, while Pummerer was perhaps not the first researcher to observe his eponymous reaction, he appears to be the first to understand what he was observing.

It is unclear whether Pummerer appreciated the significance of his (or Smythe's) discovery. He published only one follow-up report on the topic in 1910,[3b] which did, however, describe the reaction of a sulfoxide **10a** with acetic anhydride in the classical Pummerer sense, before embarking on a long and distinguished career in the general area of industrial organic chemistry. In fact, Pummerer's biographer, R.E. Oesper, wrote a 1951 encomium that noted Pummerer's many contributions to both industrial chemistry and organic mechanistic studies, but failed even to mention the sulfoxide chemistry that now bears his name![4] So, why is the Pummerer reaction called 'The Pummerer reaction'? Perhaps the genesis of this term can be traced to a 1960 supplement for a 1959 article by Horner and Kaiser from Universität Mainz,[5a] who christened the reaction thusly: "Die Analogie zur POLONOVSKI-Reaction liegt auf der Hand. Die Reaktion zwischen Sulfoxyden und Säureanhydriden wollen wir in Zukunft als 'Pummerer-Reaktion' bezeichnen."[5b] (The analogy to the POLONOVSKI reaction is obvious. In the future, we would like to designate the reaction between sulfoxides and acid anhydrides as the 'Pummerer reaction'.)

Research into the electrophile-promoted decomposition of sulfoxides proceeded only fitfully for the 50 years following Pummerer's initial observation, Figure 1. Sporadic reports of Pummerer-like chemistry appeared, but no systematic efforts to explore the process were documented until the 1959 Horner and Kaiser work. Perhaps the Mainz groups' attention to this obscure reaction, coupled with their elevation of the chemistry to 'named reaction' status, piqued the

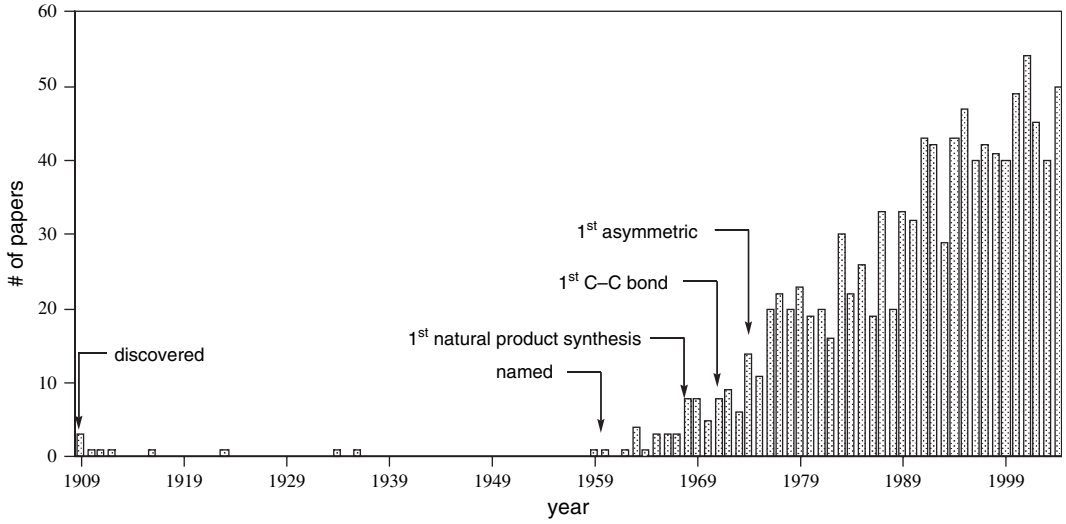
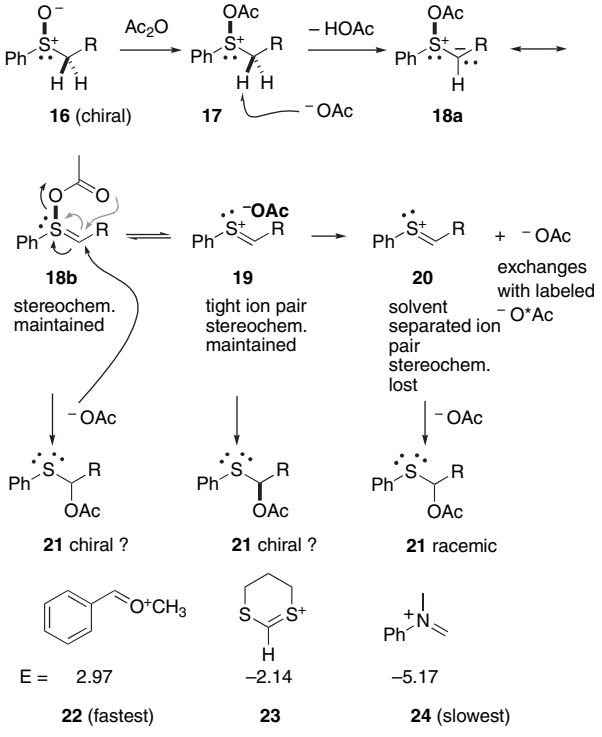


Figure 1. Timeline for Pummerer reaction research.

interest of other researchers, as the 1960s saw the beginning of an upsurge of research work that continues unabated to the present day. Early studies largely focused on mechanistic issues and attempted to explore the scope of the process, leading to elucidation of a detailed reaction mechanism. Other milestones include the first use in a natural product synthesis (illudin M by Matsumoto et al.[6]), the first example of C–C bond formation,[7] and the first claim for asymmetric synthesis from a chiral sulfoxide.[8]

The mechanistic course of the Pummerer rearrangement has been explored through judicious use of deuterium- and O^{18}-labeling experiments, kinetic analysis, and product identification studies.[9] The confluence of results from these studies provides a self-consistent mechanistic picture, Scheme 2.



Scheme 2. Current mechanistic thinking about the Pummerer reaction.

A chiral sulfoxide is invoked to illustrate some of the mechanistic subtleties uncovered by the labeling studies, as the observation of significant levels of asymmetric induction would otherwise be at odds with passage through the commonly cited achiral thionium ion intermediate **20**. Treatment of sulfoxide **16** with Ac_2O rapidly provides the chiral sulfonium salt **17**, which can racemize under certain circumstances (e.g., high acetate concentration) via the intermediacy of a sulfurane $PhS(OAc)_2CH_2R$. To limit this undesirable outcome, the effective acetate trap DCC has been introduced into the Pummerer mixture, albeit at some sacrifice in yield.[10] If acetate acts as a base with **17** instead, ylide **18a** will be formed, itself a resonance form of the sulfurane **18b**. This ylide preserves the chirality at sulfur under standard Pummerer conditions, and it is postulated to serve as a direct precursor to (chiral) α-acetoxysulfide **21** via either intramolecular S-to-C transposition of the acetate group,[11] or by intermolecular addition of exogenous acetate.[12] Ejection of acetate from **18** competes with product formation, and this process can lead first to a tight ion pair **19** and then to a solvent separated ion pair **20**. Both **19** and **20** can serve as precursors to α-acetoxysulfide **21**, although the stereochemical consequences for each path may differ.

The broader utility of the Pummerer reaction in organic synthesis stems, at least in large part, from the capability of the electrophilic intermediate **20** to combine productively with carbon π-nucleophiles and fashion new C–C bonds. The question then can be raised, 'How good of an electrophile is thionium ion **20**?' Many studies have shown that electron rich arenes and alkenes are effective partners for **20**. Some qualitative measure of sulfur-stabilized carbocation **20**'s electrophilicity can be gleaned from the seminal contributions of Mayr, who measured/calculated the electrophilicity parameter E for the species **22**–**24**.[13] By this scale, the doubly sulfur-stabilized carbocation ion **23** reacts with Mayr's reference π-type carbon nucleophiles a few orders of magnitude slower than the phenyl/oxygen stabilized carbocation **22**, but significantly faster than the iminium ion **24**.

The energetics that govern the various competitive pathways that extend from **18** seem to be finely balanced, as variations

of substrate structure/functionality, solvent, additives, etc. appear sufficient to steer the reaction down one channel or another. Oxygen-18 labeling studies provide evidence for the predominant or exclusive operation of each of these pathways under differing circumstances.[9b] From this perspective, it may not be fruitful to define one Pummerer 'mechanism', but rather a more valuable exercise might entail identifying relationships between reaction/substrate parameters and specific mechanistic consequences. Thus, Kita's search for conditions that favor reaction through **18b** or **19** has led to the discovery of a new set of Pummerer activators that proceed with high levels of asymmetric induction (vide infra).[14] The application and extension of these mechanistic considerations underlie all of the recent advances in Pummerer technology, and have led to the development of a broad suite of synthetic methods, which, taken together, establish this chemistry as a fundamental strategy-level reaction in organic synthesis.

From these episodic beginnings, the pace of Pummerer rearrangement-based research has ever quickened as the broad scope and high efficiency of this transform have become apparent. Over 1000 research papers have been published on this topic, with about 40% appearing over the past decade. The five most active groups in the Pummerer field include Oae, who was responsible for many of the fundamental advances in mechanistic understanding in the formative years of Pummerer reaction research, and Furukawa, Bravo, Padwa and Kita, all of whom have made, and continue to make, significant contributions that extend the scope of the reaction in directions that are particularly valuable for organic synthesis.

2. Scope of the review

Numerous reviews of Pummerer chemistry, both focused and exhaustive, have been written.[9,15] These earlier, authoritative accounts of the transformation serve to track its development and to fill in many of the mechanistic intricacies that attend its execution. As the volume of Pummerer research has expanded continually over the more recent decades, so has the emergence of new knowledge and applications that fall under the Pummerer umbrella. It is toward these more contemporary developments that this review is directed.

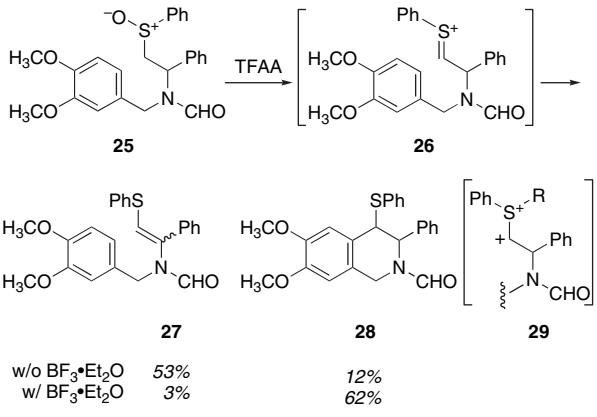
Specifically, discoveries in the area of Pummerer reaction initiation that feature chemistry distinct from the classical sulfoxide acylation trigger have broadened the scope of tolerated substrates, and prominent examples will be discussed. Likewise, recent extensions of the permissible classes of both sulfur-bearing substrates and, independently, the nucleophilic addends, probe the limits of functional group compatibilities and help to define the ultimate utility of the transform. Finally, the use of sulfoxide substrates bearing either adjacent or distal unsaturated moieties has led to novel reaction modes that further extend the scope of the reaction. Many of these newer developments help illuminate some of the mechanistic subtleties of the putative electrophilic Pummerer intermediates as well. This review is organized by reaction component, and will focus, in turn, on initiator, then nucleophile, and finally substrate chemistry. This latter category will include discussions of additive, vinylogous, and cascade-type Pummerer sequences.

3. Initiator chemistry

If the roster of serviceable Pummerer initiators had never expanded beyond the harsh, acidic reagents described in the seminal Fromm/Smythe/Pummerer studies, it is unlikely that this transform would have found much use in organic synthesis. However, much effort has been expended to address this original limitation, and a whole suite of mild and selective initiators have been developed. In particular, electrophilic silyl transfer reagents and hypervalent iodine compounds have extended the reach of Pummerer chemistry to include both thermally labile and acid-labile substrates. In addition, a range of Lewis acids have been brought to bear on the problem of selective initiation, sometimes unintentionally, and these reagents conceivably can introduce a certain level of 'tunability' to the task of chemoselective sulfoxide activation in polyfunctional substrates. A survey of these advances follows.

3.1. Acidic additives with acylative initiators

The classical Pummerer recipe for initiation, treatment of a sulfoxide with a potent acylating agent like trifluoroacetic anhydride (TFAA) in a non-participating solvent, is sufficient to generate the electrophilic thionium ion **20**, but the somewhat muted electrophilicity of this species (cf. **22**–**24**) can limit the range of acceptable carbon π-nucleophiles. This issue is illustrated by the problematic conversion of sulfoxide **25** into the desired tetrahydroisoquinoline product **28**, Scheme 3.[16a] Apparently, when the rate of nucleophile capture is rendered slow by structural (electronic) features, alternative processes, such as deprotonation or even dealkylation,[16,17] can intervene. Sano and co-workers have devised a solution to the problem of insufficient thionium ion electrophilicity by including highly acidic activators in the reaction medium.[15] Both $BF_3 \cdot Et_2O$ and CF_3SO_3H[15b] have shown promise in this regard. For example, treating sulfoxide **25** with TFAA and then with $BF_3 \cdot Et_2O$ leads to isolation of a much improved yield of the Pummerer cyclization product **28**.[15a] Control experiments discounted **27** as a precursor to **28** under the reaction conditions. Sano's group has gone on

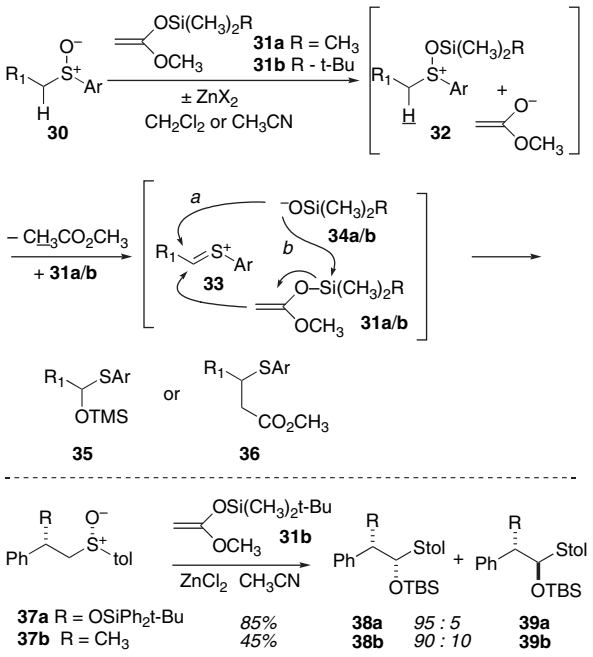


Scheme 3. Examples of Sano's acid promoted acylative Pummerer initiation conditions.

to exploit this enhanced Pummerer reactivity in the synthesis of numerous tetrahydroisoquinoline-containing natural products and related targets.[15c] In mechanistic discussions, Sano entertains the notion that a 'superelectrophilic' dicationic species **29** is the key intermediate, a proposition in alignment with the dicationic intermediate invoked to rationalize certain kinetic data from both Friedel–Crafts and Pictet–Spengler reactions.[18] However, alternative explanations, such as sequestration of the (weak) base/nucleophile CF_3COO^- by the added acid, a scenario in which the lifetime of a singly charged thionium ion might be extended sufficiently to react with the sluggish aryl nucleophile, cannot be dismissed at this point. The scope of this technique for promoting otherwise reluctant Pummerer reactions has yet to be determined, but it holds promise for extending the reaction in directions useful for complex molecule synthesis.

3.2. Silyl initiators

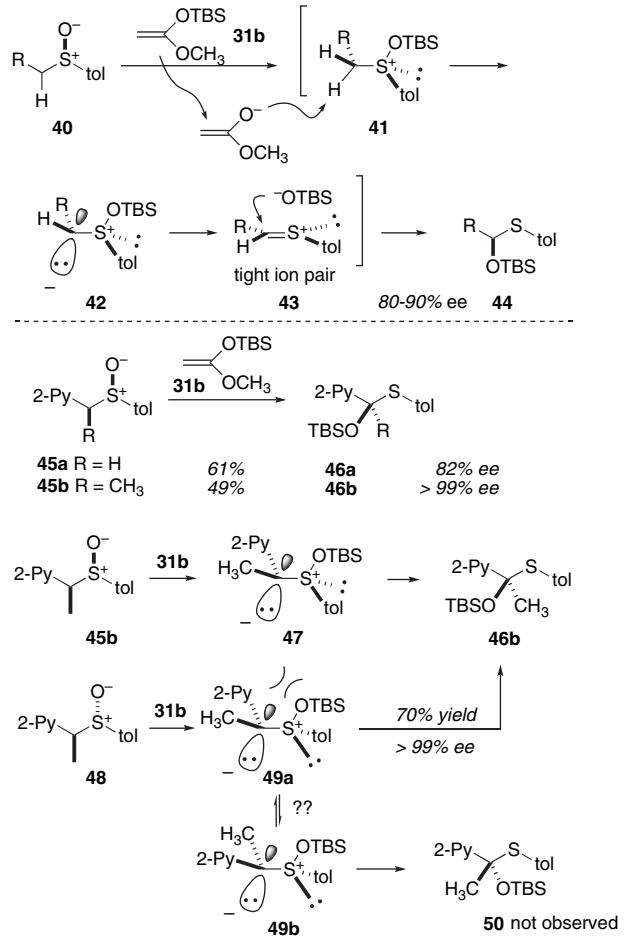
One of the first deviations from sulfoxide acylation orthodoxy can be traced to Kita, who in 1984 introduced the silyl ketene acetals **31a** and **31b** as effective Pummerer initiators, Scheme 4.[14] Related studies by other workers expanded the repertoire of useful silyl electrophiles to include TMSCl(I),[19] TMSOTf,[20] TBSOTf,[21] and $H_2C{=}CHCH_2{-}SiCl_3$,[22] although most of the chemistry that delineated the scope of silicon electrophile initiation was conducted with silyl ketene acetals of the type **31**.



Scheme 4. Kita's introduction of silyl ketene acetal Pummerer initiators.

These reactive silyl cation donors share the desirable characteristics of (1) rapid and chemoselective R_3Si addition to the sulfoxide oxygen under completely neutral conditions, and (2) no requirement for added acid or base, although catalytic ZnX_2 can be used to advantage on occasion. Despite their superficial similarities, the ketene acetals **31a** and **31b** actually proceed to give different products, **36** and **35**, respectively, through the common intermediate **32**. Thus, initial R_3Si transfer driven by the oxophilicity of silicon furnishes the activated sulfonium species **32** in proximity to the basic acetate enolate. Facile proton transfer should promote loss of silanoxide to generate the common thionium ion intermediate **33**, now in the presence of both the silanoxide nucleophile **34** and excess silyl ketene acetal **31**. At this point, the difference between **31a** and **31b**, in terms of the silyl appendages' steric bulk, becomes manifest. Arguably, the less sterically hindered TMS species **31a** (R=CH_3) is more susceptible to attack at silicon by the nucleophilic silanoxide **34a**, and this combination leads to activation of the silyl ketene acetal **31a** for further nucleophilic attack on **33**. The C–C bonded addition product **36** ensues. In contrast, the increased steric bulk around silicon in **31b** apparently suppresses the silanoxide addition of **34b**, and so this nucleophile takes the other option, direct addition to the carbon of thionium ion **33**, to afford the α-siloxysulfide product **35**. The reaction typically proceeds with good yield and with excellent diastereoselectivity if applicable, as exemplified by the conversion of **37a** into predominantly **38a**, and **37b** preferentially into **38b**.[23] The stereochemical outcome of the former reaction can be rationalized by invoking a Felkin–Ahn-type transition state for addition of silanoxide to thionium ion, whereas the bias toward **38b** from **37b** is a bit of a puzzle. The observed preference for diastereomer **38b** is inconsistent with the predictions of the Cram model for nucleophilic addition to α-stereogenic (but otherwise electronically unbiased) aldehydes. Thus, some other effect that overrides the Cram selectivity must be operational. This 'anomalous' result leaves open the possibility that the chirality at sulfur may play a role, a hypothesis not anticipated by the simple thionium intermediate **20** of Scheme 2. This argument is developed further below.

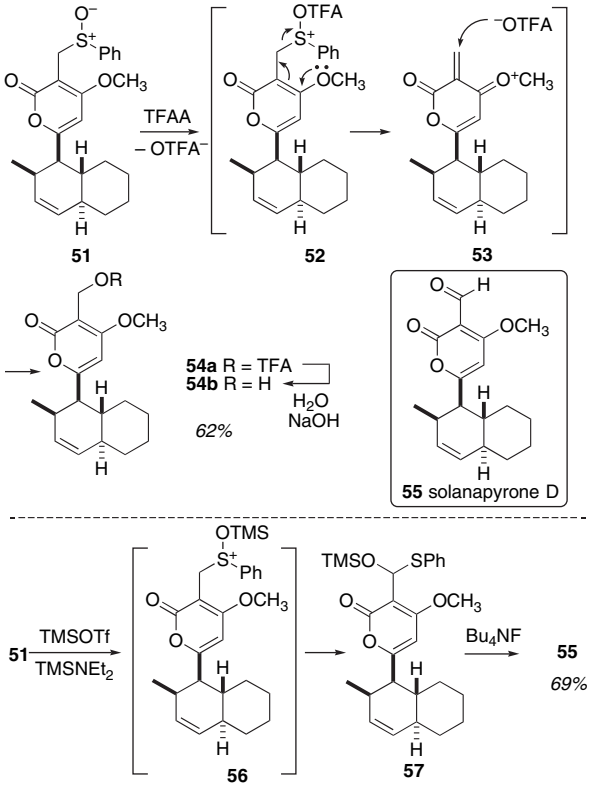
A major advantage of this silicon-based initiator, and a major advance in Pummerer chemistry, derives from its application to chiral sulfoxide substrates in asymmetric syntheses. Whereas the conversion of chiral sulfoxides into chiral α-acyloxysulfides in high ee appears to be beyond the scope of standard acylative activation of the Pummerer process (cf. the discussion with Scheme 2), it is well within the purview of the silyl ketene acetal initiation methodology, as illustrated in Scheme 5. Kita's interpretation of the formation of α-silyloxysulfides **44** in excellent ee from the chiral sulfoxides **40** cites formation of a sulfonium ylide **42** with a strictly antiperiplanar orientation of the anion and S–O bond. This geometrical arrangement presumably leads to facile E2-type elimination of silanoxide to deliver the expected thionium ion **43** as a tight ion pair with the ejected silanoxide. To the extent that this tight ion pair maintains its integrity, internal transfer of alkoxide from sulfur to carbon should lead to a single enantiomer of the α-silyloxysulfide product, as shown for the conversion of **43** into **44**. This argument acknowledges an explicit and central role for the tight ion pair **19** of Scheme 2, rather than the free thionium ion **20**. As an alternative to the E1CB-type mechanism shown for **41** to **43**, Kita also speculates that a formal Stevens-type process involving homolytic scission of the S–O bond, followed by electron reapportionment and radical recombination at carbon, might be operational as well.



Scheme 5. Asymmetric synthesis via chiral sulfoxides and silyl ketene acetal Pummerer initiators.

Successful examples of this self-immolative asymmetric induction process include the chiral sulfoxides **45a** and **45b**.[24] The α-unsubstituted species **45a** performs as indicated with an ee of 82%. Replacing one of the α-hydrogens with a methyl group provides a more challenging example in that a quaternary stereogenic center is now formed. Quite remarkably, this substrate combines with **31b** to provide the isomer **46b** with complete enantioselectivity. The greater selectivity in the more hindered case might be attributable to differences in the initial deprotonation step. For the conversion of **45b** into **46b**, there is only a single proton that can be removed, and so only one intermediate ylide with antiperiplanar alignment of anion and S–O bond is possible, **47**. This single ylide then leads inevitably to a single product, **46b**. However, in the case of the unsubstituted system **45a** (modeled by **40**, R=2-Py), either one of two diastereotopic protons can be removed. Deprotonation from conformer **41** (R=2-Py) leads to minimized *gauche* interactions between the remaining substituents on carbon and sulfur. However, it is possible that the erosion of stereoselectivity for the substrate **45a** may be tied to deprotonation of the alternative and diastereotopic proton through a higher energy conformation that experiences destabilizing steric interactions between the substituent R and the toluene moiety. This stereochemical analysis illuminates a subtlety of the mechanism when applied to the diastereomeric (to **45b**) chiral sulfoxide **48**. In this instance, the single, stereoelectronically aligned ylide that could be formed directly is shown as **49a**, and despite experiencing the unfavorable *gauche* interactions described above (and illustrated on the structure), the observed product **46b** must derive from this species. Therefore, either rotation/anion inversion about the C–S bond to form the presumably more stable ylide **49b** is slower than silanoxide elimination from **49a**, or, in fact, thionium ylide/ion pair **43** (R=2-Py) is formed directly from the sulfonium salt by a concerted E2-type elimination of silanoxide, and there is no intermediate ylide like **49a** on the reaction coordinate.

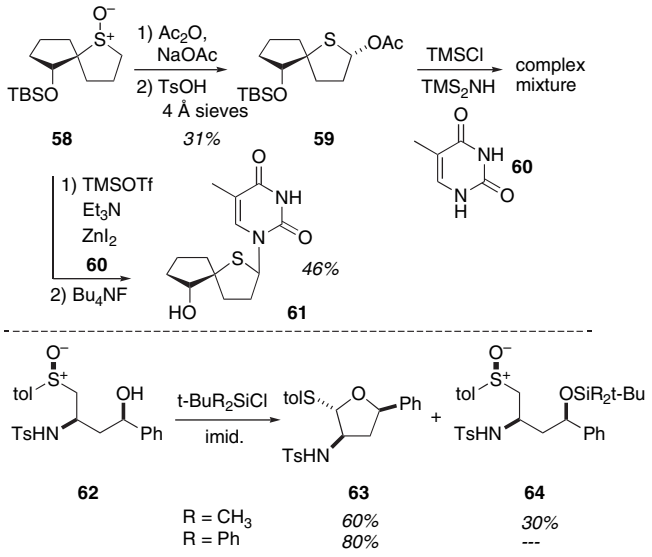
An exploitable difference in the course of the Pummerer process following either silyl electrophile initiation or acylative initiation can be found in Hagiwara's recent synthesis of the phytotoxic principle solanapyrone D (**55**), Scheme 6.[25] Treatment of pyrone sulfoxide **51** with TFAA was pursued with the expectation that Pummerer chemistry would deliver the aldehyde-containing natural product **55**. However, the alcohol **54b** was isolated instead. This deviation from Pummerer convention can be attributed to an oxygen lone pair-promoted elimination of the good leaving group PhSOTFA from **52**, followed by trifluoroacetate conjugate addition to the enone of **53** and eventual OTFA hydrolysis to deliver the alcohol product. In contrast, the use of the silyl initiator TMSOTf with the very same sulfoxide **51** led to the expected 'oxidation' product **55** via the α-trimethylsilyloxy sulfide **57**. Apparently, the diminished nucleofugacity of the silylated sulfonium salt within **56** accounts for its resistance to elimination, and the otherwise slower Pummerer rearrangement can compete effectively.



Scheme 6. An advantage of a silyl Pummerer initiator over the standard acylative initiator.

A second example of reaction rescue by silyl initiation can be found in Paquette's synthesis of the thiothymidine

analogue **61**, Scheme 7.[26] In this instance, the traditional Pummerer sequence with Ac_2O and sulfoxide **58** performed adequately to furnish the anticipated α-acetoxysulfide **59**. However, contrary to expectations, condensation of **59** with thymine under standard Vorbrüggen conditions[27] did not provide the desired thionucleoside **61**. It fell to silyl electrophile initiation to rectify this tactical failure. Treatment of sulfoxide **58** with TMSOTf, base, and a Lewis acid catalyst, all in the presence of thymine (**60**), delivered the thymidine analogue **61** in satisfactory yield.

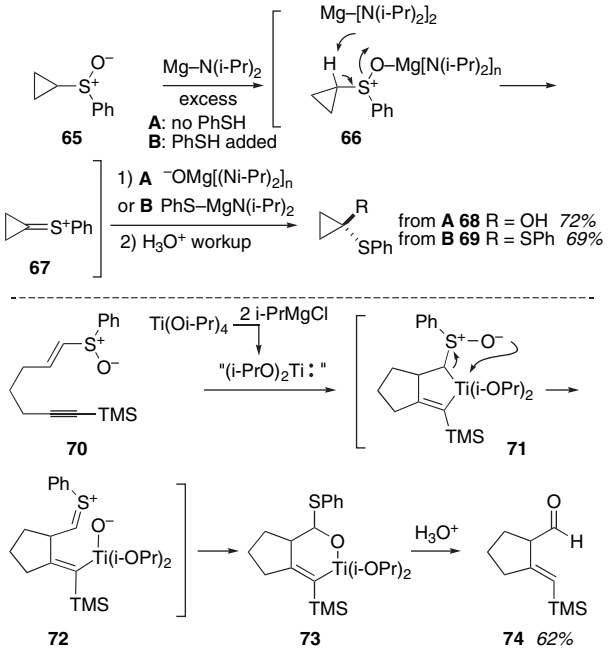


Scheme 7. Further examples of silyl electrophile initiation used to advantage in Pummerer chemistry.

A question of comparative reactivity was explored with substrate **62**.[28] Raghavan and co-workers intended nothing more elaborate than simple alcohol silylation when they treated hydroxy sulfoxide **62** with TBSCl. However, a Pummerer process intervened, leading to formation of the tetrahydrofuran derivative **63** via internal alcohol–thionium ion combination. Use of the sterically more demanding diphenyl analogue *t*-Bu*Ph*$_2$SiCl suppressed even the modest amount of alcohol silylation seen with *t*-Bu*Me*$_2$SiCl, and in this instance the Pummerer cyclization product **63** was the exclusive species observed. The preference for S(+)–O$^-$ silylation over –OH silylation is instructive, as it points to the feasibility of conducting Pummerer reactions on complex substrates without the need for alcohol protection.

3.3. Lewis acidic metal initiators

The discovery that certain Lewis acidic metals promote Pummerer rearrangement seemed to be an unintended benefit of exposing sulfoxide substrates to metal-based reagents with other goals in mind. This chemical serendipity is illustrated by treatment of sulfoxide **65** with the strong base magnesium bis(diisopropylamide), Scheme 8.[29] Kobayashi et al. were exploring sulfoxide deoxygenation protocols, and with *diaryl* sulfoxide substrates, sulfoxide→sulfide reduction was observed as expected.[29a] However, when sulfoxides bearing α-protons were examined, the reaction took a different course and Pummerer-type oxidative transposition products were formed instead. The Pummerer reaction itself was discovered by adding strong mineral acid to a sulfoxide, and potent electrophiles constitute the standard Pummerer triggers. However, in this example the magnesium counterion of the highly basic amide reagent appears sufficient to activate the sulfoxide's oxygen within **65** for departure. Whether deprotonation at the α-position precedes or follows this activation is unclear, and the putative intermediate **66** is shown just for convenience. Whatever the precise sequence of 'H$^+$' and '–OMgX' loss, the intermediate thionium ion **67** so formed is trapped readily by the highly nucleophilic magnesium alkoxides present (Condition A, no added PhSH) to furnish the α-hydroxysulfide **68** following aqueous acidic workup. One advantage of this nonacylative initiation procedure can be seen when substrate **65** is allowed to react with the amide base in the presence of various thiols, including PhSH (Condition B). The magnesium thiolate so generated out-competes the alkoxides for thionium ion **67**, and the dithioketal **69** is formed in good yield. In contrast, use of acylative Pummerer initiation to achieve the same transformation would have to confront the problem of competitive thiol acylation.[30]



Scheme 8. Pummerer initiation with Lewis acidic metals.

A second example of an 'accidental' Pummerer reaction evolved from exposure of the sulfoxide **70** to the formal titanium(II) reagent (*i*-PrO)$_2$Ti: formed by reduction of Ti(*i*-OPr)$_4$.[31] An intermediate titanocycle **71** was expected by analogy to the similar reaction of (*i*-PrO)$_2$Ti: with a sulfone substrate related to **70**. In fact, protonolysis of the intermediate derived from **70** led to formation of the aldehyde **74**. Apparently, the α-titanium sulfoxide intermediate **71** can access a transition state geometry for C-to-O transfer of titanium. The transient thionium ion within the derived **72** can be quenched rapidly by the proximal alkoxide, leading to the titanacycle-containing product **73**. Protonolysis upon acidic workup then delivers the sensitive aldehyde **74**. These adventitious examples of Lewis acidic metal mediated

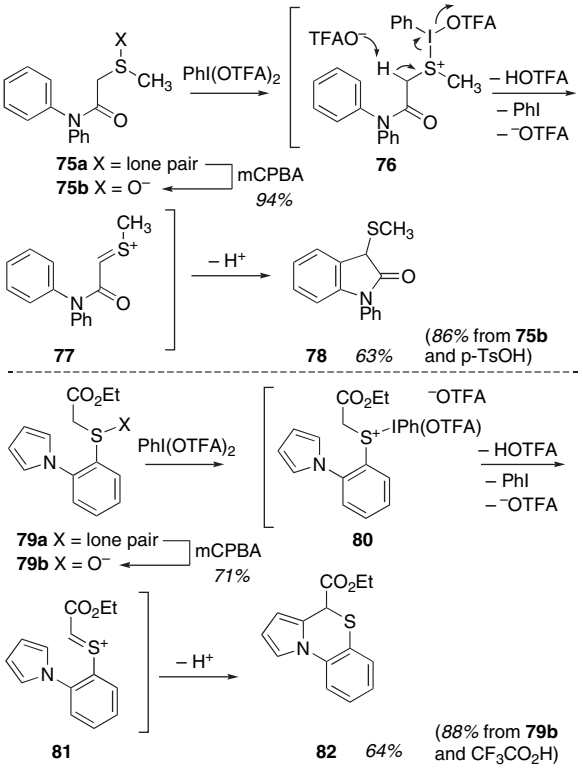
Pummerer initiation by no means define the scope of the chemistry, and it seems within reason to expect that deliberate surveys which test reactions of acidic/oxophilic metals with sulfoxides will uncover further cases of metal mediated Pummerer reactions. For example, Mukaiyama and coworkers have described the results of some preliminary scouting experiments on the utility of $Sn(OTf)_2$, $TiCl_4$, $SnCl_4$, $Cu(OTf)_2$, and $BF_3{\cdot}Et_2O$ for promoting the Pummerer reaction of β-carbonyl sulfoxides.[32] In this series, only $Sn(OTf)_2$ was an effective initiator.

3.4. Iodonium initiators

The introduction of hypervalent iodine-based Pummerer reaction initiators represents a real departure in strategy for this transform. For this family of initiators, a sulfide substrate and not a sulfoxide serves as the starting point, and so the sulfide oxidation and (derived) sulfonium salt rearrangement are no longer temporally separated events. This consolidation of steps leads to greater efficiency in synthesis, but at the cost of possible product oxidation. The sulfide product might, in principle, be susceptible to iodonium-mediated oxidation much as the starting sulfide is. The fact that this 'overoxidation' rarely is observed perhaps can be attributed to the difference in both steric and electronic environments about the starting and final sulfide moieties. The Pummerer sequence replaces a hydrogen α-positioned to the sulfide with a non-hydrogen group, thus increasing the steric shielding of the product sulfide over the less encumbered starting sulfide. Furthermore, to the extent that electronegative nucleophiles are used in the Pummerer reaction, the product sulfide should be protected from further oxidation by virtue of the electron withdrawing inductive influence of the newly attached α-nucleophile unit.

Three hypervalent iodine reagents have been explored as Pummerer initiators: $PhI(OTFA)_2$,[33] PhI(CN)OTf,[34] and tol-IF_2.[35] The former two reagents do not contribute a competitive nucleophile to the reaction medium, and so trapping the putative electrophilic thionium ion with added (or intramoleculary disposed) nucleophiles is feasible. The latter species is used primarily as a fluorinating reagent to form α-fluorosulfides, but a few cases of competitive intramolecular nucleophilic addition have been described, vide infra.

The seminal report of hypervalent iodine initiated Pummerer reaction falls to Tamura and colleagues, who showed that $PhI(OTFA)_2$ effectively promotes cyclization of sulfide **75a** into oxindole **78** in good yield, Scheme 9.[33] Presumably, the thiophilic character of the 'soft' iodonium reagent confines initial reaction to the sulfide function, and the authors propose the familiar sulfonium salt and thionium ion intermediates, **76** and **77**, respectively, en route from starting material to product. Whatever the precise mechanistic details, the overall result is competitive with the conventional two-step Pummerer procedure (oxidation of **75a** to give sulfoxide **75b**, and then treatment of this sulfoxide with an acidic initiator).[36] A limited series of sulfide substrates were studied, and in all cases, C–C bond-forming cyclizations proceeded to the exclusion of detectable $CF_3CO_2^-$ addition to the electrophilic intermediate.

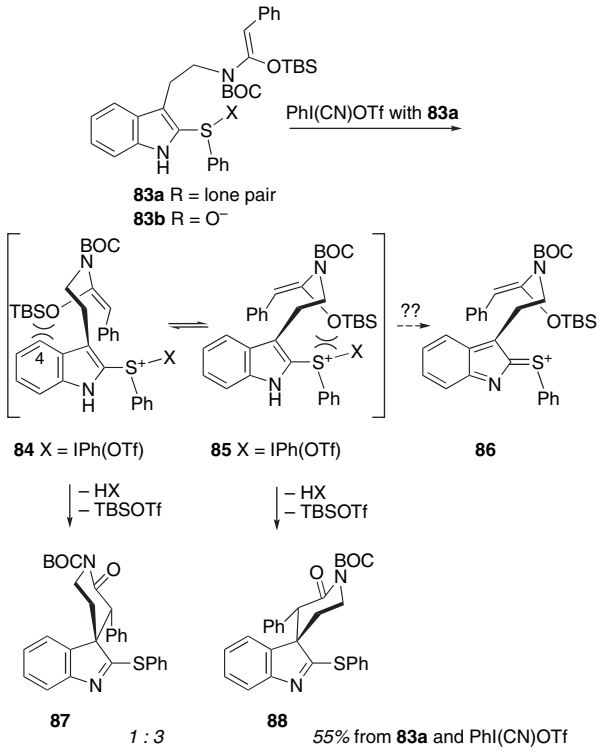


Scheme 9. Use of $PhI(OTFA)_2$ as a Pummerer initiator with sulfide substrates.

A conceptually related example is provided by Chen et al., who demonstrated that the one-step oxidative cyclization of **79a** into **82** compares favorably with the two-step alternative passing through sulfoxide **79b**.[37a] As with the Tamura chemistry, the acidifying β-carbonyl function appears to be an important structural feature. Attempted Pummerer rearrangements on sulfoxide substrates similar to **79b** but lacking the carbonyl moiety were not productive.[37b] This observation seems to have some generality for modestly reactive aryl and alkenyl nucleophiles, although the workaround discussed in Section 3.1 (strongly acidic additives) can be used to promote reaction with these types of reluctant Pummerer substrates.

The study of biomimetic indole oxidative cyclizations has had a long and varied history within the area of tryptophan-derived natural products total synthesis.[38] The use of Pummerer chemistry with a C(2) sulfinyl or sulfide-substituted indole as a trigger for oxidative cyclization was envisioned as a solution to both overoxidation and/or regiochemical problems encountered with standard oxidants (cf. Section 5.4.2 for further discussion) (Scheme 10).[38] For example, hypervalent iodine initiation with the sulfide **83a** was examined. $PhI(OTFA)_2$ did not perform satisfactorily in this regard, and starting material consumption without concomitant product formation was observed under all conditions examined. These failures led to examination of Stang's reagent, PhI(CN)OTf, as an alternative Pummerer initiator with sulfide substrates of the type **83a**.[38] The incorporation of a cyanide unit within PhI(CN)OTf may serve the dual roles of both diminishing the oxidative power and 'softening' the iodonium center even further when compared to $PhI(OTFA)_2$. Both of these characteristics converge favorably when using sensitive and functional rich substrates

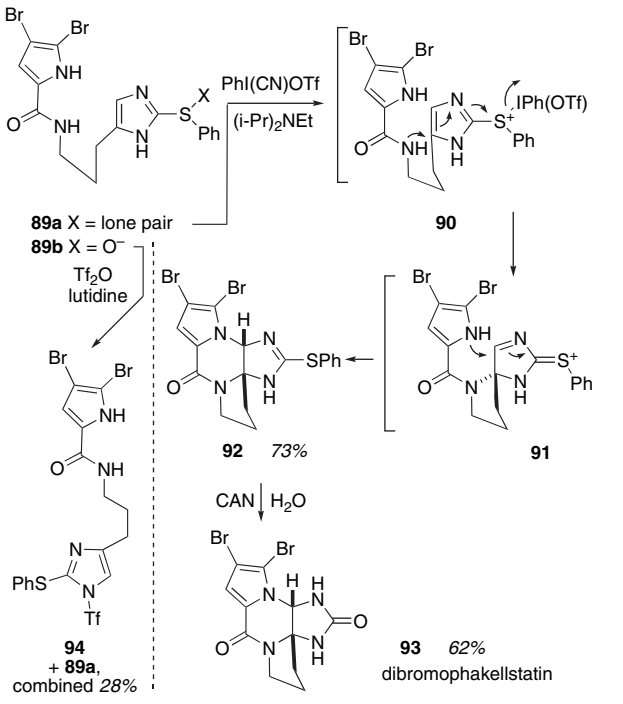
like **83a**, and lead to successful realization of this sulfide-based Pummerer oxidative cyclization.



Scheme 10. Use of PhI(CN)OTf as a Pummerer initiator with a sulfide substrate.

The observation that diastereomer **88** is favored over **87** plausibly can be traced to the differential steric interactions shown in **84** and **85**. Specifically, the key C–C bond formation might pass through either an S_N2'-like displacement within the sulfonium ion intermediates **84** and **85** or through the thionium ion **86**. (This S_N2'-like pathway has been termed an 'additive Pummerer' mechanism, whereas the alternative via **86** is called a 'vinylogous Pummerer' reaction. Both pathways will be discussed further in Section 5.4.1. For simplicity, only the additive pathway is cited in the following discussion, but the same arguments would apply to the vinylogous process as well.) Two salient steric interactions can be identified as shown in **84** and **85**, and the trade-off between these penalizing 1,3-diaxial collisions should, in large measure, determine the stereochemical outcome of cyclization. In general, it appears that the interaction between –OTBS and C(4)–H in **84** is more severe than the –OTBS//–S(X)Ph contact, as diastereomer **88**, evolving from **85**, is favored. Whatever the mechanistic subtleties, the overarching benefit of using PhI(CN)OTf in this sulfide-based Pummerer reaction lies in the facility of oxidative cyclization on the electron rich indole nucleus without interference from either product overoxidation or loss of desired C–C bond formation regioselectivity.

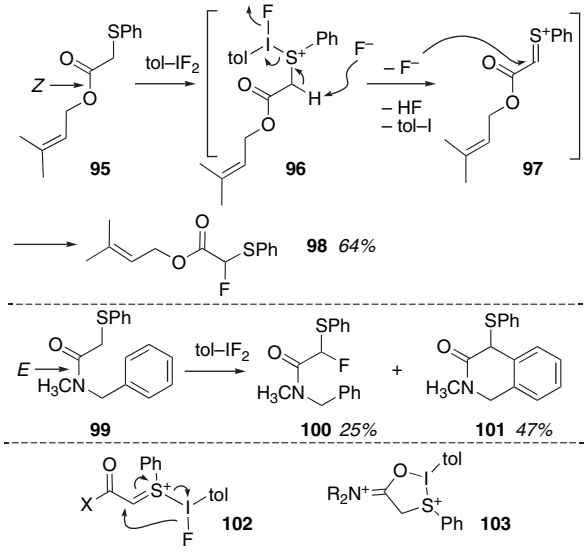
The value of iodonium salt initiation with the Pummerer sequence can be seen in an application to the biomimetic total synthesis of the sponge alkaloid dibromophakellstatin (**93**), Scheme 11.[39] This attempt to extend aromatic heterocycle oxidative cyclization methodology to the imidazole nucleus began with the sulfoxide **89b** and conventional Tf_2O-based Pummerer initiation. Surprisingly, only the deoxygenated sulfide **89a** admixed with its triflamide derivative **94** was isolated. The latter compound presumably arises from the former under the reaction conditions, but the origin of **89a** remains a mystery. Apparently, if a sulfonium salt was accessed from **89b** and Tf_2O, it must have suffered formal reduction rather than productive Pummerer-type rearrangement chemistry. This disappointing turn was reversed by resorting to sulfide/iodonium initiation chemistry. Portionwise treatment of **89a** with PhI(CN)OTf in the presence of base delivered the tetracyclic product **92** as a single diastereomer. Whether sulfide activation leads to a bona fide thionium ion (not shown) or the reaction transpires through the additive mechanistic course **90**→**91**→**92** is not settled at present. The additive mechanism shown below has the advantage of providing a quite electrophilic partner **91** for the sterically hindered and electronically deactivated pyrrole nucleophile. In contrast, a thionium ion-based mechanism would present this modest nucleophile with a neutral imine electrophile. The tetracyclic sulfide **92** is completely inert to further hypervalent iodine-mediated oxidation, but it is susceptible to the stronger oxidant ceric ammonium nitrate, a process that facilitates the hydrolysis of the thioimidate function and furnishes the intact natural product.



Scheme 11. Synthesis of the marine isolate dibromophakellstatin via a PhI(CN)OTf-mediated Pummerer cyclization on an imidazole sulfide substrate.

The Pummerer initiation chemistry of tol-IF_2 has been developed by Motherwell and co-workers as a direct means of introducing fluorine into organic molecules, Scheme 12.[35,40] Exemplifying this strategy is the conversion of alkenyl ester **95** into the α-fluorosulfide **98**.[35] The lack of participation by the alkene nucleophile is a hallmark of this chemistry. This unanticipated result prompted Motherwell to speculate that perhaps an alternative mechanistic path is operational. A formal reductive elimination of iodine,

as illustrated in **102**, was proposed as a rationale for the complete fluoride addition selectivity. Curiously, C–C bond formation in the tol-IF_2-promoted Pummerer reaction was seen for certain amide substrates, for example, **99**→**100**+**101**,[40a] although reaction of the dimethylalkene analogue of **99** (similar to **95**) led only to the fluoride capture product. An explanation for the disparate behavior of amide and ester may be tied to conformational preferences wherein the tertiary amide of **99** can adopt the requisite *E*-amide bond disposition with much less energetic penalty than the ester must pay to access the analogous *E*-O–C(=O) rotomer. As a final twist, observation of alkene-containing elimination products from more complex amide substrates encouraged the authors to speculate that a new intermediate, the cyclization product **103** emerging from internal participation of the nucleophilic amide carbonyl and the electrophilic iodonium center, may play a role in this Pummerer process.[40c] In any event, the tol-IF_2-mediated Pummerer fluorination sequence represents one of the mildest methods for introduction of fluorine into organic substrates, and its value in organofluorine chemistry just is beginning to be assessed.



Scheme 12. Use of tol-IF_2 as a Pummerer initiator with sulfide substrates.

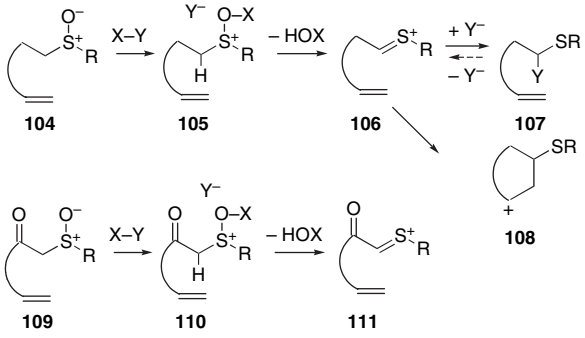
4. Nucleophiles

Successful Pummerer reaction requires that the nucleophilic addend and the electrophilic initiator do not combine destructively prior to initiation of the reaction sequence. Thus, advances in initiation chemistry, which broaden the available palette of useful electrophiles, provide an indirect benefit to the nucleophilic capture portion of the transform as well. Carbon–carbon bond formation holds a place of special prominence in the Pummerer portfolio, and the extension of simple alkene and arene thionium ion traps to include highly functionalized partners is a testament to the successful matching of initiator with nucleophile. Consequently, these effective Pummerer examples have a large and continuing impact on natural product synthesis, as described below. In a separate vein, the productive use of phosphorus nucleophiles in the Pummerer process portends new strategies for organophosphonate synthesis.

4.1. Arenes and alkenes

One of the great virtues of the Pummerer reaction lies in its capacity to form core carbon–carbon bonds within a variety of molecular contexts. The requirement for compatibility between the nucleophile and the initiating electrophile limits carbon nucleophiles to those species that are unreactive to acid and acylating reagents, a significant narrowing of options that rarely falls outside of moderately electron rich alkenes and arenes. Nevertheless, this transformation has been exploited innumerable times in complex molecule synthesis, particularly in the alkaloid arena. Both inter- and intramolecular C–C bond formation have been documented in a wide range of systems, although the latter process has seen the most intense development.

In principle, the generation of a thionium ion **106** from alkene(arene)-bearing sulfoxide **104** sets up a competition between addition of the desired C-nucleophile and the initiator counterion Y^- (Scheme 13). To the extent that Y^- is a competent nucleophile, the reaction may be diverted to the sulfide product **107**. Fortunately, the addition of Y^- is reversible with common initiators, and so if sulfide **107** is treated under sufficiently vigorous reaction conditions to regenerate **106**, productive C–C bond formation may still prevail. A sequestering agent is often employed to prevent Y^- from re-adding to thionium ion **106**. As a matter of practice, many of the C–C bond-forming Pummerer reactions initiated with Ac_2O or TFAA provide a counterion (AcO^- or $TFAO^-$, respectively) that wins the competition for **106** under typical reaction conditions. However, in all cases where the goal is C–C bond formation, conditions have been devised, typically involving higher temperatures and an acidic additive to trap RCO_2^-, to reform, and then redirect, **106** to the carbon nucleophile addition alternative **108**. However, when the initiator counterion is arguably non-nucleophilic (e.g., $Y{=}OTf^-$), direct and productive combination of the thionium ion with the alkene(arene) typically ensues.

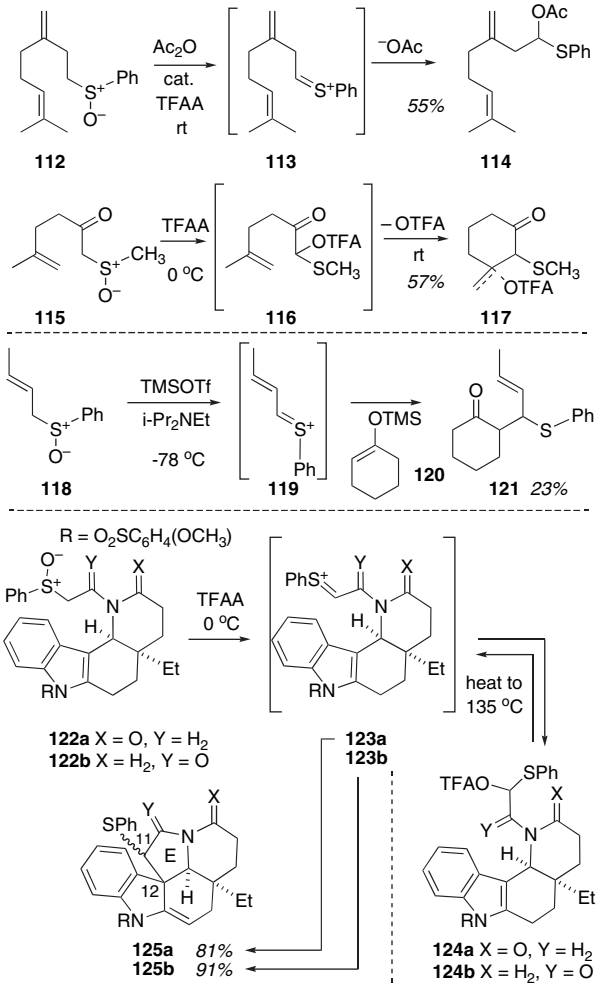


Scheme 13. Mechanistic paradigms for Pummerer reaction-mediated C–C bond formation.

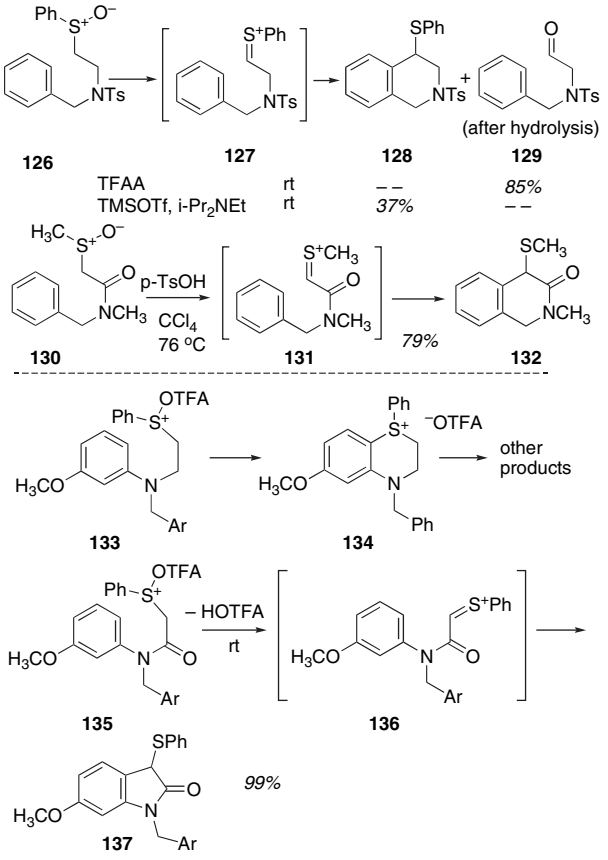
Carbon–carbon bond-forming Pummerer reaction sequences generally fall into one of two classes: with and without a carbonyl function β to the thionium ion intermediate (**109** vs **104**, Scheme 13). The acyl thionium ion **111** derived from **109** has been categorized as being more reactive than the non-acyl version **106**,[15g] but quantitative kinetic data on this question are lacking. Using chemical yield as a criterion for judging reactivity does not provide an unequivocal test of this hypothesis either (vide infra). However, there is much

experimental support for the contention that the enhanced acidity of the α-protons in **110** compared to **105** does have an influence on the reaction course, as it promotes facile loss of H–OX from **110** to the exclusion of other possible but undesired processes. These points are illustrated by examples as detailed in Schemes 14–16.

The trisubstituted and disubstituted alkenes in **112** and **115**, respectively, do not appear to be sufficiently nucleophilic to capture the intermediate thionium ions in preference to the initiator counterions AcO^- and $TFAO^-$, Scheme 14.[41] Apparently, even incorporation of the allegedly activating carbonyl of **115** does not increase the reactivity of this cationic intermediate toward alkene nucleophiles to the extent that C–C bond formation can compete with trifluoroacetate trapping. However, this example is typical of the cases where subsequent reaction of the first-formed trifluoroacetoxy sulfide **116** under more vigorous conditions does lead to productive C–C bond formation, **116**→**117**.[41b] The value of using an initiator bearing a non-nucleophilic counterion is illustrated in the counterpoint example **118**→**121**.[42] In this instance, there is no evidence that the intermediate thionium ion **119** is trapped by any nucleophile other than the silyl enol ether shown. Unfortunately, no systematic studies have been described wherein the initiator counterion and/

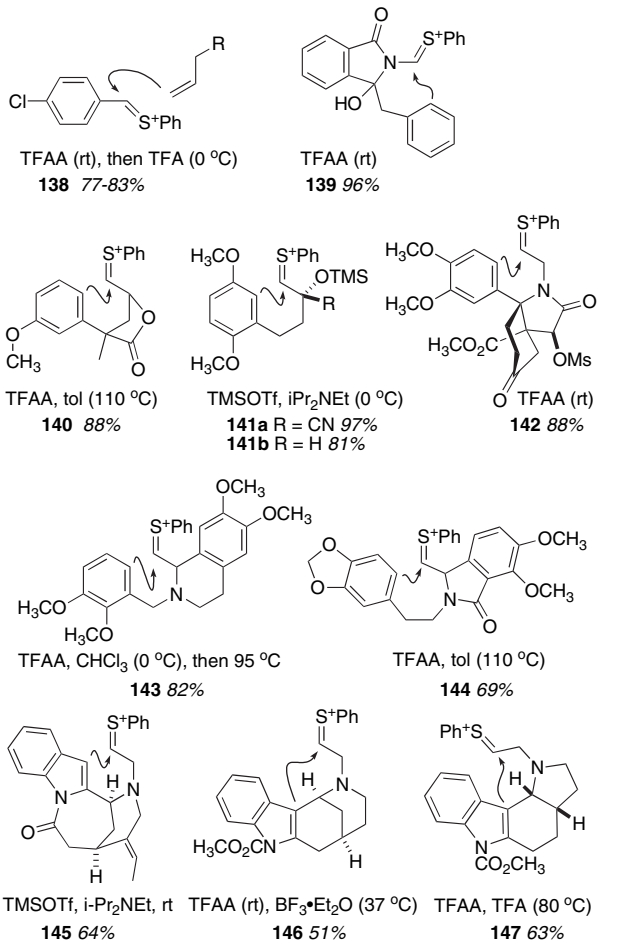


Scheme 14. Direct comparison of acyl- versus non-acyl Pummerer cyclizations for C–C bond formation.



Scheme 15. Further examples of the influence of an α-acyl group on thionium ion chemistry.

or the β-carbonyl presence have been varied within the same substrate, and so it is impossible to draw broad conclusions from these examples. Differences in alkene nucleophilicities (Mayr *N* values: 2-methyl-2-butene (0.65), 2-methylpent-1-ene (0.96), cyclohexanone trimethylsilylenol ether (5.21))[13a] may play a role in some instances as well. Two related examples particularly germane to the question of β-carbonyl activation of a thionium ion are provided by Magnus as part of his comprehensive program on indole alkaloid synthesis via Pummerer chemistry.[43] Work toward the aspidosperma alkaloids required the means to close the E-ring at a late stage of the synthesis, **122**→**125**, Scheme 14. Much prior art[44] had met with only limited success in identifying competent electrophiles for the indole C(12) nucleophile (aspidosperma numbering, see structure **125**), and so it is particularly gratifying to note that the Pummerer reaction stood alone in its capacity to close this demanding bond in excellent yield. Both the β-carbonyl version **122b** and its β- $-CH_2-$ analogue **122a** were explored, but with neither substrate was the indole nucleophilic enough (Mayr N=7.81 for N,2-dimethylindole)[45] to capture the first-formed thionium ions **123a/b** prior to $TFAO^-$ trapping. Thus, trifluoroacetoxy sulfides **124b** and **124a**, respectively, were formed first. Upon heating to 135 °C, however, both species presumably entered into an equilibrium with **123a/b**, and under these more forcing conditions, cyclization to fashion the sterically encumbered C(11)–C(12) bond proceeded smoothly. Interestingly, there did not appear to be any advantage attending the use of the β-carbonyl version



Scheme 16. Examples of non-acyl-containing Pummerer substrates for C–C bond formation.

of the substrate **122b**, as yields from both series were similarly high.

Some further examples reinforce the value of excluding nucleophilic initiator counterions, and in addition bring out the indisputable advantage of a β-carbonyl group in acidifying the α-proton, Scheme 15. Sulfoxides **126** and **130** differ principally by the incorporation of the β-carbonyl function in the latter species. In the presence of TsOH, the β-carbonyl-containing sulfoxide **130** at elevated temperature proceeded to cyclized product through the expected Pummerer process.[46] The carbonyl-less analogue **126** with the standard initiator TFAA delivered only the $TFAO^-$ trapping product, isolated after hydrolysis as the aldehyde **129**.[47] No C–C bond-forming cyclization product **128** was detected, an observation in line with the Pummerer transformations discussed in Scheme 14. An interesting feature of these similar examples was revealed when substrate **126** was treated with TMSOTf, an initiator that lacks a nucleophilic counterion. In this example, the thionium ion generated from **126** is both long-lived enough and reactive enough to trap the proximate nucleophilic aryl ring to form exclusively the cyclized product **128**.

The comparison between attempted Pummerer reactions of **133** and its β-carbonyl-containing analogue **135** highlights the importance of acidifying the α-proton.[48] Sulfonium intermediate **135**, with the acidifying carbonyl, performed as expected and favored C–C bond formation to form **137**. In this case, loss of trifluoroacetic acid from **135** generated putative thionium ion **136**, which apparently cyclized either directly or after diversion to an unobserved trifluoroacetoxy sulfide intermediate, in excellent yield. The similar substrate lacking this acidifying carbonyl never got to the thionium ion intermediate. The now only weakly basic α-proton was not susceptible to the usual TFAOH elimination. Rather, the sulfonium salt **133** persisted long enough for its intrinsic electrophilicity to be expressed through C–S cyclization onto the adjacent aryl ring in essentially a Friedel–Crafts thionation reaction. The nascent sulfonium salt **134** then proceeded to a suite of products. No experiments that described the results of incorporating a hindered base (e.g., *i*-Pr_2NEt, cf. **126**→**128**) to overcome the diminished acidity of the α-proton were reported.

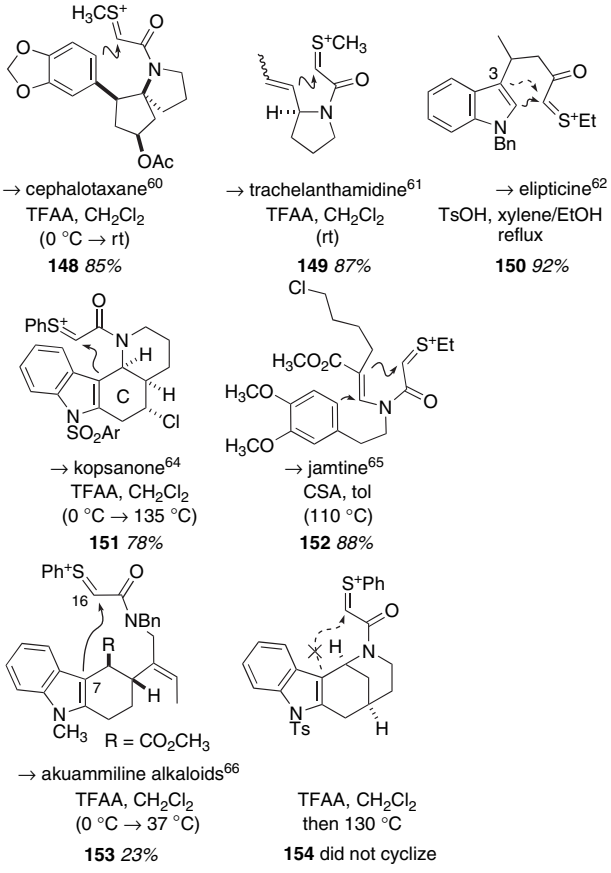
A survey of C–C bond-forming reactions with non-β-carbonyl-containing Pummerer substrates bearing mostly internal arene and alkene nucleophiles is shown in Scheme 16. Reaction of a *p*-chlorobenzyl, phenyl sulfoxide precursor to **138** proceeded through an α-trifluoroacetoxy sulfide intermediate. Treatment of this labile species with further strong acid (TFA) was required to reformulate a thionium intermediate **138** that was capable of being intercepted by external alkenes.[49] This two-step procedure, discussed in detail along with Scheme 14, is characteristic of most (**140**,[50] **143**,[51] **144**,[52] **146**,[53] and **147**[54]) but not all (**139**, **142**) TFAA-initiated Pummerer reactions. Substrate **142**, a key intermediate in Sano's erythrina alkaloid synthesis program,[55a] may enjoy a uniquely favorable convergence of both preorganization for cyclization and minimal strain in the product. The facile room temperature cyclization of thionium ion **139** is a bit anomalous, given the lack of defined conformational restrictions, but this species may benefit from an electronic advantage not shared by the other examples in Scheme 14.[56] In a resonance form, this electrophile can be viewed as an *N*-acyl iminium ion, a species that can be expected to display different (and perhaps greater) electrophilicity than the simple thionium moiety.

The extension of Magnus' seminal indole C(12) (aspidosperma numbering) functionalization chemistry beyond the aspidosperma alkaloids attests to its potential for impacting on many related problems, as exemplified by **145** (geissoschizine),[57] **146** (strychnos alkaloids),[53,58] and **147** (ibophyllidine alkaloids),[54] inter alia. Thus, C(3) of the indole nucleus appears to be a well-matched nucleophilic partner for thionium ion electrophiles, and even some rather strained and otherwise difficult ring closures (e.g., **145**, **146**) can be achieved. The Pummerer thionium ions formed from TMSOTf/*i*-Pr_2NEt initiation, **141a/b**,[59] and **145**,[57] all proceed to product under much milder experimental conditions than those typically necessary for the TFAA-initiated processes. Again, the value of using an initiator bearing a non-nucleophilic counterion is evident.

It should not escape notice that with **138** and **139** as exceptions, all of the thionium ions listed in Scheme 16 bear an inductively electron withdrawing atom (N or O) in a position adjacent to the electrophilic carbon. Even **138** and **139** arguably can fall under this classification by noting the inductive

effect of the chloride in **138** and the carbonyl in **139**. Is this feature critical for success in C–C bond-forming reactions, or is it largely just an artifact of the synthesis plans that utilize the Pummerer reaction? Many examples of Pummerer reactions proceeding through the thionium ion formed from DMSO, or thionium ions derived from other simple sulfoxides that do not contain a β-electron withdrawing group, have been documented.[15e] Therefore, this common structural/electronic feature of the systems in Scheme 16 does not appear crucial for success.

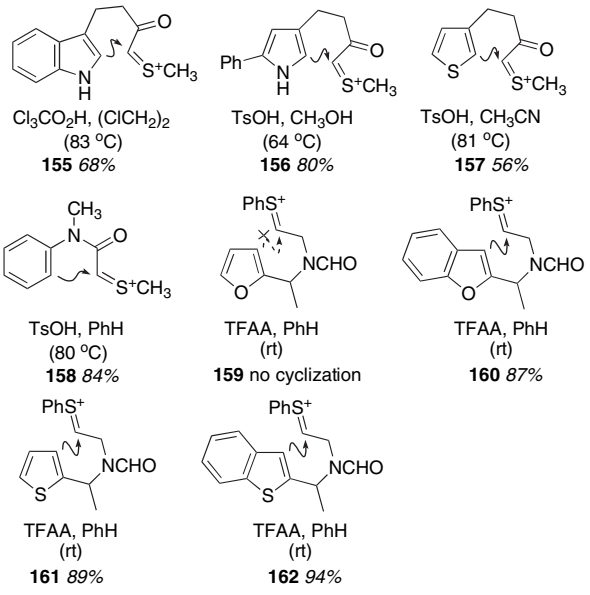
The number of successful C–C bond-forming Pummerer transformations that employ a β-carbonyl sulfoxide greatly exceeds the number reported without the carbonyl, as detailed by several earlier reviews.[15g,k] The use of β-carbonyl-containing thionium ions in carbocyclization reactions directed toward natural product targets is illustrated in Scheme 17. Ikeda's concise synthesis of cephalotaxine (cf. **148**) benefited enormously from the Pummerer reaction's ability to fashion seven-membered rings upon thionium ion initiated cyclization.[60] The extension of this methodology beyond the common five- and six-membered ring domain (cf. **144** also) distinguishes Pummerer chemistry from many other acyclic closure strategies. Ishibashi's trachelanthamidine synthesis (cf. **149**) is notable for the complete regiocontrol exhibited upon thionium ion cyclization to afford the desired five-membered ring product instead of the six-membered ring alternative.[61] The authors favor an explanation that cites greater strain in the six-membered ring transition state as a consequence of incorporating five sp^2 atoms within the forming ring. The five-membered ring alternative transition state would only contain four sp^2 atoms and perhaps pay a lesser energetic penalty to conform to the stereoelectronic requirements for C–C bond formation embodied in Baldwin's rules. This distinction is not general, as many successful Pummerer cyclizations that form the six-membered ring product have been documented.[15e] The elipticine cyclization substrate **150** presents an interesting mechanistic puzzle in light of the trachelanthamidine cyclization result.[62] In this case, the regiochemistry of cyclization favors the six-membered ring product, despite (1) the greater nucleophilicity of the C(3) position of *N*-alkyl indoles, and (2) the stereoelectronic preference for five-membered ring formation (cf. **149**). It is possible that initial kinetically favored cyclization occurs at C(3) to form a spirocyclic indolenine intermediate, but then under the vigorous reaction conditions, rearrangement proceeds via a 1,2-alkyl shift to afford the observed six-membered ring product. This mechanistic course finds precedence in Pictet–Spengler and Bischler–Napieralski cyclizations on tryptamine derivatives.[63] Magnus' syntheses of the kopsane alkaloids (cf. **151**) extend his earlier aspidosperma work to systems that have a higher oxidation level in the C ring.[64] The yield decreases slightly compared to the simpler case **125b** (Scheme 14). The jamtine synthesis by Padwa (cf. **152**), in contrast, breaks new ground by employing the Pummerer-generated thionium ion intermediate as an initiator of a polyene cascade cyclization.[65] This extension of Pummerer chemistry will be explored in more depth in Section 6.1. Bosch's approach to members of the akuammiline family of indole alkaloids exemplifies his many contributions that use Pummerer chemistry to forge C–C bonds to C(3) of the indole core within the context of complex alkaloid synthesis.[66] This substrate demonstrates that even eight-membered rings, usually a significant challenge for acyclic closure methodologies, can be accessed via Pummerer chemistry and thionium ion capture. As in previous indole C(3) additions, a first-formed α-trifluoroacetoxy sulfide intermediate is then heated to promote subsequent trifluoroacetate loss and cyclization. Whereas the yield suffers compared to other indole–thionium ion cyclizations, the formation of the highly sterically encumbered C(7)–C(16) bond (akuammiline numbering) sets this strategy apart from several other unrewarded attempts at this key segment of the target. The curious failure of thionium ion **154** to cyclize, in contrast to the successful closure of the related species **146**, is a reminder that intrinsic and energetically penalizing features of the substrate can trump even the usually favorable indole-Pummerer cyclization.[67] In this instance, the planarity of the amide linkage is postulated to misalign the nucleophile's approach to such an extent that a low energy path is no longer available. The amine analogue **146** does not suffer from this conformational rigidity and apparently can access a geometry conducive to nucleophile–electrophile union.



Scheme 17. Examples of acyl-containing Pummerer substrates for C–C bond formation.

The electrophilicity of both non-acyl thionium ion intermediates and the β-acyl analogues generated in Pummerer processes appears sufficient to combine with heteroaromatic nucleophiles, Scheme 18.[68–70] Note that in each successful case, relatively elevated temperatures are required to achieve acceptable yields of cyclization products in the acyl thionium ion series, whereas the non-acyl series realizes equivalently high yields at room temperature. These apparent rate

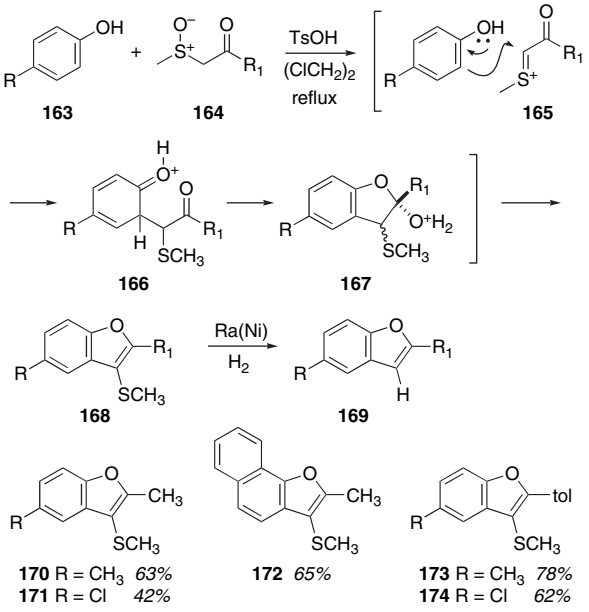
differences just might reflect the variation in initiation protocols. Comparing the reaction yields with Mayr nucleophilicities within each series, or between series (N=5.80 for indole; 4.63 for pyrrole; 1.26 for 2-methylthiophene; 5.5 for *N*,*N*-dimethylaniline)[13a,45] does not reveal any trend between the heteroaryl rings' intrinsic nucleophilicity and the reaction yield, an observation that does not conflict with the hypothesis of slow (S_N1-like) thionium ion formation followed by rapid electrophile quenching by any proximal and competent nucleophile. The authors present no data that bear on the question of whether the six-membered ring forms by direct cyclization, or, alternatively, by spirocyclization followed by 1,2-shift. The failure of the furan-containing system **159** to furnish cyclized product was attributed to the sensitivity of the furan nucleus to the generated TFA.[70]



Scheme 18. Examples of acyl and non-acyl thionium ion cyclizations with aromatic and heteroaromatic partners.

4.2. Phenols

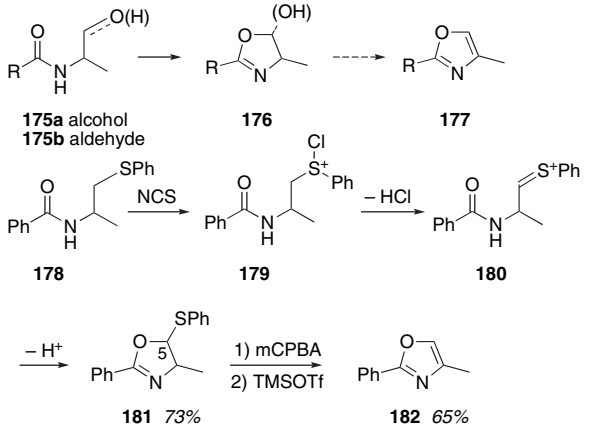
An application of Pummerer reactions with arene nucleophiles can be seen in an expedient preparation of benzofurans, Scheme 19.[71] In these instances, the doubly nucleophilic character of the phenol species **163** enables a formal [3-atom+2-atom] cyclocondensation with the doubly electrophilic Pummerer intermediate **165**. This first-formed thionium ion appears to favor initial addition to the phenol's carbon center rather than the hydroxyl, a result in accord with the expectations of hard–soft acid/base theory.[72] The *para*-positioned substituent directs addition to the *ortho* site of the phenol. From the addition product **166**, thermodynamically driven proton transfers and dehydration then deliver the intact benzofuran nucleus in **168**. Sulfur removal can be accomplished by simple Raney nickel-mediated hydrogenolysis to furnish the parent benzofuran **169**. The scope of the reaction includes both electron rich and electron deficient phenolic substrates, cf. **170** and **171**, respectively. The yields tend to be higher with the more electron rich phenols, **170** versus **171** and **173** versus **174**, but the fact that the reaction works at all with the electron deficient species **171** and **174** is a notable observation. Both alkyl (**170/171**) and aryl (**173/174**) ketones perform satisfactorily in the transform. The only major limitations encountered thus far involve the need to block the *para* position of the phenolic substrate from reaction, and the requirement for product refunctionalization to generate a sulfur-free compound.



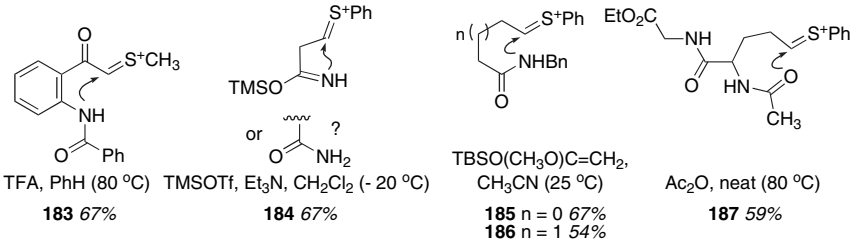
Scheme 19. Benzofuran formation from Pummerer reactions with phenol substrates.

4.3. Amides

The observation of amide participation in Pummerer-derived thionium ion trapping reactions dates back at least to the early work of Connor (Scheme 21),[73] and Magnus recently has developed a concise synthesis of oxazoles that exploits this process,[74] Scheme 20. This chemistry grew out of frustrated attempts to convert either the alcohol **175a** or the aldehyde **175b** into the oxazole product. A Pummerer-based strategy accomplishes the difficult oxidation (equivalent of **176** (no hydroxyl)→**177**) in advance of cyclization by transposing the relatively easy S→S(X) oxidative charge to the more challenging C(H)→C(X) goal. Thus, exposure



Scheme 20. Oxazole synthesis via Pummerer reaction on an amide substrate.

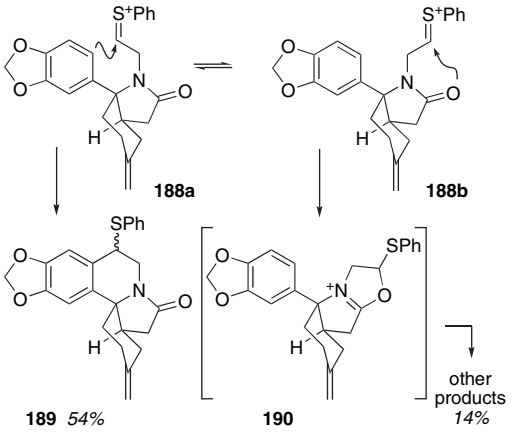


Scheme 21. N- versus O-cyclization in Pummerer reactions with amide nucleophiles.

of sulfide **178** to a Cl^+ source led to a presumed thionium ion intermediate **180**, which is sufficiently electrophilic to trap the proximal amide function on oxygen. The product retains the oxidation level increase at C(5), and through somewhat unorthodox TMSOTF assisted sulfoxide elimination, the oxazole product **182** is formed in good yield.

The 'amide-endo' nature of the cyclization substrate **180** guaranteed that only O–C and not N–C bond formation could occur. However, this preference is not general, and, in fact, C–N bond formation appears to be favored when that option is accessible geometrically, Scheme 21. Connor's seminal effort **183** demonstrated that C–N bond formation was feasible, but the 5-enol(*exo*)-*exo*-trig cyclization shown should enjoy sufficient stereoelectronic benefits over the alternative 7-enol (*endo*)-*exo*-trig O→C closure to diminish the importance of the latter process under any circumstance. The trade-offs become less clear-cut with the four-, five-, and six-membered ring closures **184**–**186**, respectively.[75,76] In each of these cases, the cyclization of either N or O of the amide function forms the same-sized ring, and so the aforementioned stereoelectronic differences are not applicable. In each case, only N→C bond formation is observed. Curiously, this preference switches again with the acetamide substrate **187**.[77] In this case, the 7-enol(*endo*)-*exo*-trig cyclization appears to be preferred. The fact that the O→C cyclization product is kinetically favored can be deduced from the results of a control experiment wherein the alternative N→C cyclization product, prepared by an independent route, remains unchanged when exposed to reaction conditions.

Numerous β-amido thionium ions were generated as substrates in C–C bond-forming reactions via chemistry discussed in Section 4.1. For example, either **123a** or **142** could have cyclized as per **180**→**181**, but rather they exclusively followed the C–C bond-forming alternative instead. The underlying structural and electronic features that steer a thionium ion intermediate toward either arene or amide nucleophiles are difficult to disentangle with these substrates, and so a simple set of predictive tools is not yet in hand. This point is emphasized by the observations of Desmaële in his approach to the erythrina alkaloids,[78] Scheme 22. Thionium ion **188**, generated by treatment of a precursor sulfoxide with TMSOTf/*i*-Pr_2NEt, is quite similar to the related species **142** invoked by Sano et al. in their erythrina alkaloid work, but the subsequent cyclization chemistry is quite different. Sano's thionium ion **142** proceeded uneventfully and in high yield to a C–C bonded product via an internal Friedel–Crafts alkylation process. In contrast, the thionium ion **188** apparently partitions between the two proximal nucleophiles present, and a mixture of products derived from both C–C and C–O bond formation ensues.

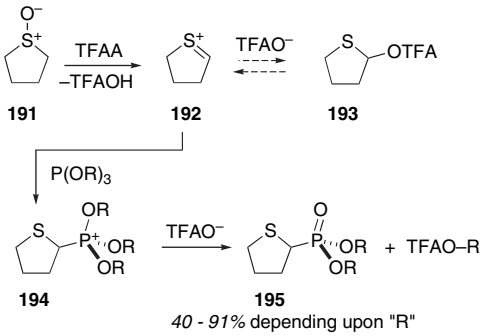


Scheme 22. Carbon–carbon versus O–C bond formation upon Pummerer-mediated cyclization in the erythrina alkaloid series.

The basis for this divergent reactivity may be related to the presence of the mesylate in **142**. The electron-withdrawing character of this moiety could suppress the nucleophilicity of the amide carbonyl in **142** sufficiently to steer the reaction to the alternative Friedel–Crafts process. Perhaps thionium ion **188**, lacking this governor on the amide's reactivity, can engage both nearby nucleophiles in productive cyclocondensations. Whatever the reason, the observation of competition between an arene and an amide is a reminder of the subtle effects that, collectively, contribute to the reactivity profile of Pummerer-derived thionium ions.

4.4. Phosphites

It was not until 2001 that phosphorus was explored as a nucleophile in Pummerer reactions,[79] Scheme 23. In this study, Masson et al. demonstrated that a concatenation of Pummerer and Arbuzov reactions leads to the formation of α-thiophosphonates from sulfoxide **191** and trialkyl



Scheme 23. Phosphite as a nucleophile in the Pummerer transform.

phosphites. The yield of phosphonate product **195** is responsive to the steric and electronic character of the phosphite's 'R' group. The highest yield attended use of the triisopropyl phosphite substrate. The authors speculate that the trialkylphosphite itself serves as a base in this sequence by promoting the loss of the elements of triflic acid from the sulfonium salt derived from **191**. The scope of this Pummerer transform with respect to the sulfoxide component may be rather restricted, as pentamethylene sulfoxide, dimethyl sulfoxide, and phenyl methyl sulfoxide all failed to deliver phosphonate product under similar treatment.

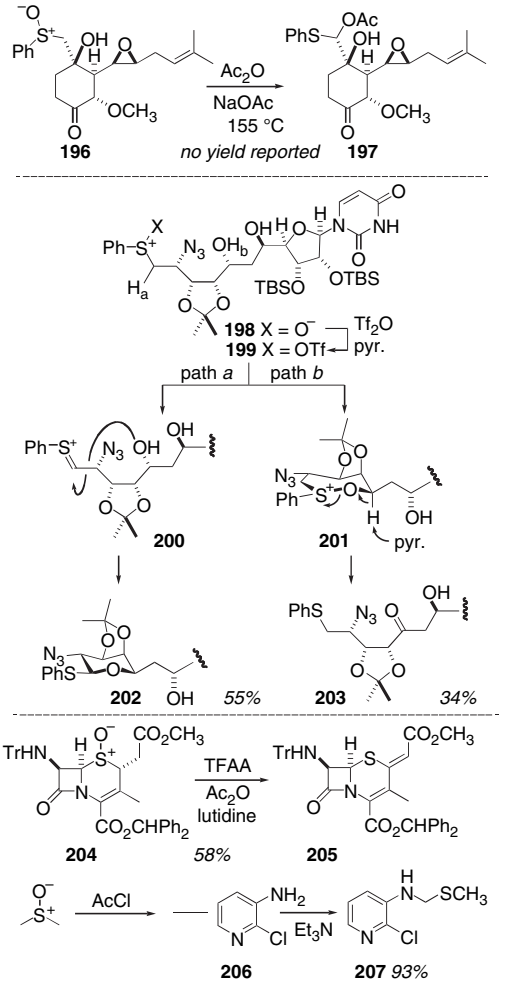
5. Substrates

The expansion of Pummerer chemistry into the natural products synthesis arena inevitably has led to the examination of substrates of ever increasing complexity in transformations that test the limits of functional group compatibility and tolerance. In addition, exploration of regioselectivity control elements in unsymmetrical dialkyl sulfoxides has added mechanistic nuance to an overall understanding of the process. Finally, extensions of Pummerer chemistry to sulfoxide analogues (e.g., sulfilimines), and in separate studies, to the solid state, add to the burgeoning versatility of this reaction. Each of these topics will be addressed in turn, and illustrated with examples from the recent literature.

5.1. Functional group compatibilities

The presence of nucleophiles in the Pummerer reaction solution is inevitable, given the second-step quenching of the electrophilic thionium ion, but just what nucleophiles can be tolerated? The competition between the sulfoxide oxygen and the resident nucleophile(s)for the acylating (or silylating) initiator is the key, and it is no surprise that the carbon nucleophiles discussed earlier (alkenes, arenes) fail to offer any challenge to the sulfoxide. On the other hand, nucleophiles that do react with acylating/silylating agents readily, such as alcohols and amines, raise the possibility that the reaction may be diverted down undesired pathways.

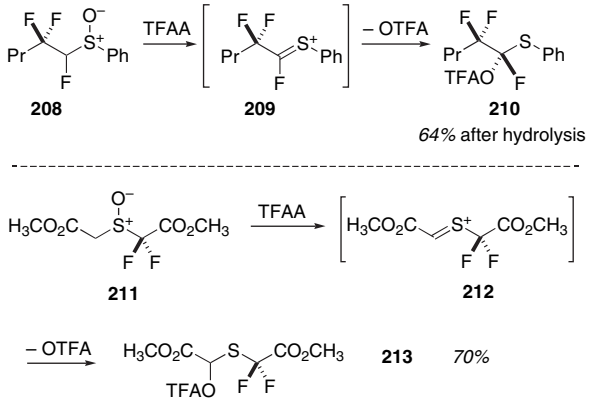
Several examples of hydroxyl-containing Pummerer substrates that do undergo uneventful reaction at the sulfoxide, followed by standard thionium ion trapping suggest that, in general, initiation conditions can be identified that favor reaction at sulfoxide rather than hydroxyl.[15e] One illustration of this phenomenon can be seen with the fumagolone precursor **196**,[80] Scheme 24. In this instance, reaction of the acylating agent, even under rather forcing conditions, is localized at the sulfoxide oxygen, despite the presence of the tertiary alcohol and the sensitive (to the NaOAc present) epoxide. A more revealing example can be found in Matsuda's tunicaminyluracil synthesis work, **198**→**202/203**.[81] Treatment of **198** with Tf_2O leads only to acylation at the sulfoxide function, despite the presence of the nucleophilic secondary alcohols and the imide residue. In contrast, use of TFAA led to competitive alcohol trifluoroacetylation, an observation perhaps consistent with the dogma that the 'harder' sulfoxide alkoxide prefers reaction with the 'harder' acylating agent, and vice versa. The sulfonium salt **199** unexpectedly partitions between the conventional Pummerer reaction (path a, **199**→**200**→**202**) and a formal Swern-type oxidation (path b, **199**→**201**→**203**) promoted, presumably, by the proximity of alcohol and sulfonium salt within **199**. It is possible that the divergence in reaction pathways from **199** is tied to the relative acidities of H_a and H_b, but the authors did not report the results of experiments that might test this premise.



Scheme 24. Examples of alcohol and amine compatibility with Pummerer reaction conditions.

There does not appear to be any systematic studies that probe the compatibility of amines with Pummerer conditions. Sporadic application of the Pummerer reaction to amine-containing substrates reveals that, at the very least, amines are not incompatible with the desired reaction path. Tertiary amine-containing substrates (e.g., **143**, Scheme 16) and the N–H indole and pyrrole species **155** and **156**, respectively, (Scheme 18) are perhaps the best-represented classes of amine-bearing compounds that survive the Pummerer process unchanged. Extension of this immunity to secondary or primary amines is suggested by the specific cases **204** and **206**, but cannot be claimed as general without substantiation through more examples. The secondary amine of **204** is not acylated under the Pummerer conditions, but that lack of reactivity can be attributed to steric hindrance as much as any inherent reactivity difference between N: and O^-.[82] Similarly, the lack of acylation with the primary amine of **206** is intriguing, but may be due to no more than the sequence of mixing.[83]

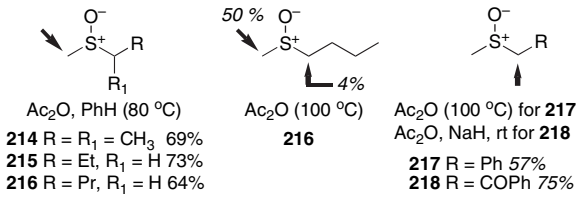
One of the more remarkable attributes of the Pummerer reaction is its ability to access exceedingly electron deficient carbocations derived from fluorinated substrates, Scheme 25. Nucleophile substitution chemistry on highly fluorinated compounds is often plagued by slow rates due to the inductive electron-withdrawing character of the fluorine atoms. Therefore, the observation that these types of compounds function in the Pummerer process is not without its merits, as it opens up a host of nucleophilic substitution possibilities for the preparation of highly functionalized fluorinated compounds. Fluorinated thionium ions that feature fluorine on either side of the carbocationic site are accessible, and the nucleophile trapping products **210** and **213**, respectively, are formed in good yield.[84,85]



Scheme 25. Highly electrophilic thionium ions generated from fluorinated Pummerer substrates.

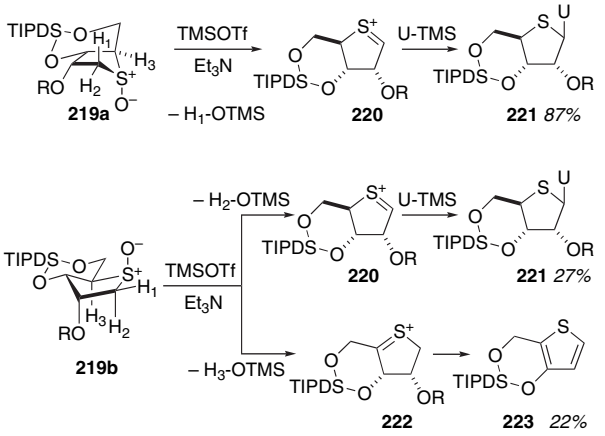
5.2. Regioselectivity

Pummerer reactions on unsymmetrical dialkyl sulfoxides bearing α and α′ protons can lead, in principle, to two different sulfide products, depending on the direction of proton loss. Numerous studies during the formative stages of Pummerer investigations provide guidance on the question of which proton loss is preferred, as illustrated by the canonical examples in Scheme 26. In all cases, elimination of the elements of HOAc occurred exclusively or greatly favoring loss of the more acidic proton, an observation consistent with either an E2- or E1CB-type mechanistic course. In sulfoxides without an acidifying β-group (**214–216**),[86] elimination occurs at the less substituted side (= most stable anion = most acidic proton). With sulfoxides where there is an identifiable β-acidifying group, (e.g., **217** and **218**),[86b,87] elimination favors that position. Subsequent deuterium labeling studies on rigid cyclic sulfoxides revealed that there is a strong preference for *anti* elimination of HOAc from a conformation where antiperiplanar alignment of H and OAc can be achieved (cf. Scheme 5).[88]



Scheme 26. Historical basis for the observation that Pummerer reaction regioselectivity is responsive to proton acidity.

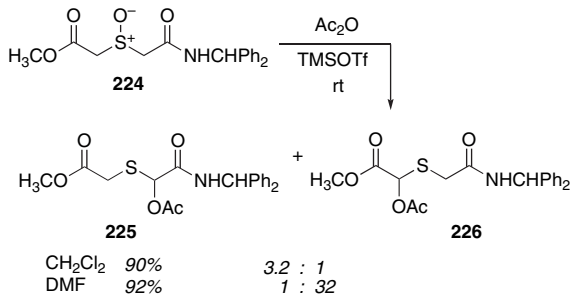
The influence of this stereoelectronic preference for elimination on Pummerer reaction regioselectivity can be seen in a more recent example in the thionucleoside field, Scheme 27.[89] Matsuda et al. demonstrated that the sulfoxides **219a** and **219b**, which differ only at the sulfur configuration, undergo Pummerer reaction to form protected thiouracil derivatives (Vorbrüggen reaction) with markedly different results. The α-sulfoxide **219a** can achieve the necessary stereoelectronic overlap between S-OTMS (derived from **219a** and TMSOTf) and H_1, leading to thionium ion formation away from the ring juncture, **220**. An excellent yield for uracil attachment ensued. In contrast, the diastereomer (at sulfur) **219b** has two protons, H_2 and H_3, which can meet the strict stereoelectronic criterion for alignment, and two products in roughly equal amounts were formed. The desired product **221** derives from elimination of H_2-OTMS, but the equally accessible H_3 elimination diverts sulfoxide to the undesired thionium **222**, and thence to the aromatized thiophene elimination product **223**. Thus, careful consideration of the stereoelectronic requirements for HX elimination from an activated sulfonium salt can provide insight into both the regiochemical outcome, and the facility, of a Pummerer process.



Scheme 27. Pummerer reaction regioselectivity dictated by stereoelectronic effects.

An interesting addendum to the settled theory of Pummerer regioselectivity can be found in the examples reported by Nagao,[90] Scheme 28. In this instance, the sulfoxide **224** has two flanking acidifying groups, and conventional wisdom would dictate that the ester, being more acidic than the amide (pK_a's in DMSO: ethyl acetate=30.5; dimethyl acetamide=34.5)[91], would direct proton loss with a preference for forming sulfide **226**. However, in CH_2Cl_2 solvent, the opposite result is observed! The reaction regioselectivity returns to 'normal' (**226** favored) when DMF is used as a solvent. This profound solvent effect can be traced to the competition between the various carbonyls for the added activator TMSOTf. In the non-participating solvent CH_2Cl_2, both the ester and amide carbonyls will bind TMS+ to slightly differing extents. The more basic amide should be preferred, and that differential carbonyl activation favoring the amide will translate to the differential acidities that are expressed in the **225/226** ratio. In DMF, however, the solvent's carbonyl appears to swamp out substrate carbonyl binding to TMS+, and the natural preference for deprotonation toward the ester function dominates. This example illustrates one method

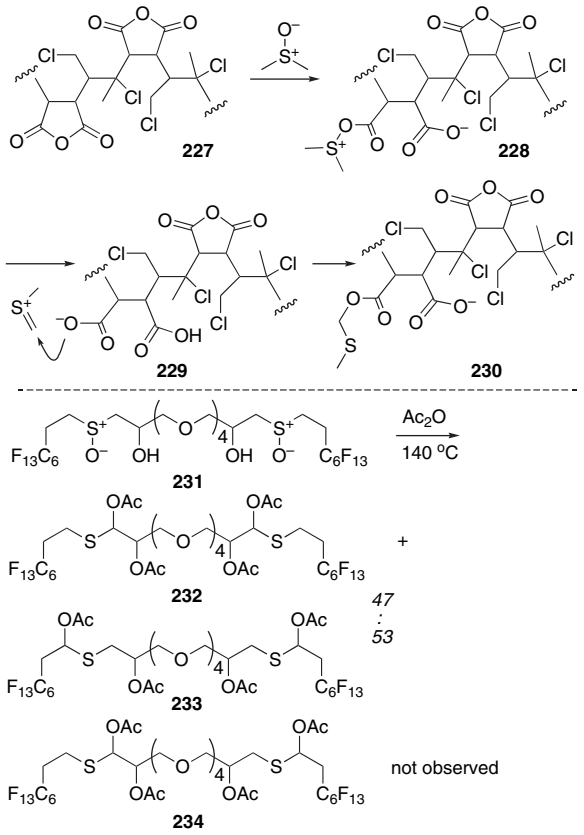
wherein the regioselectivity of a Pummerer reaction can be manipulated in a predictable manner by experimental design.



Scheme 28. Pummerer reaction regioselectivity is responsive to Lewis acid additives.

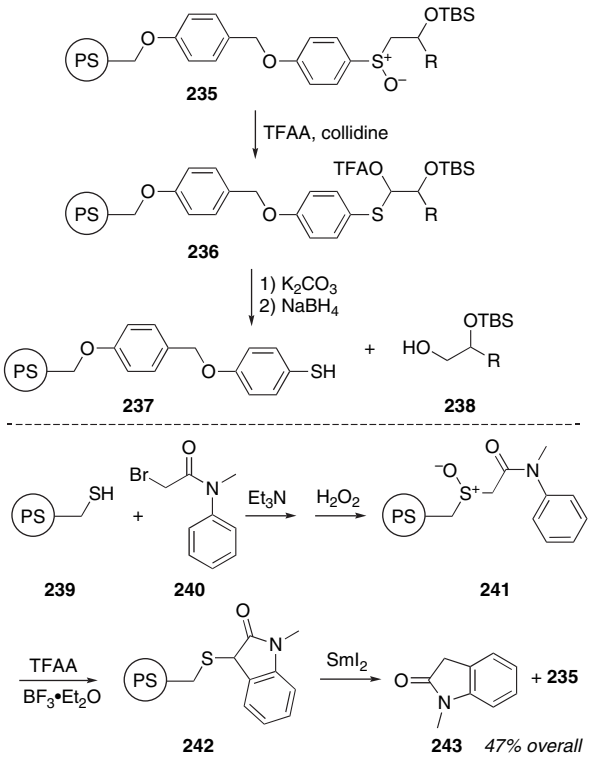
5.3. Polymer and solid-state chemistry

The Pummerer reaction has not yet had a significant impact in the area of macromolecular chemistry, although there does not appear to be any fundamental reason why this chemistry can't translate into the realm of polymer reactions, Scheme 29. Markarian et al. have observed, quite by accident, that dissolving a maleic anhydride/1,3-dichlorobutadiene copolymer **227** in DMSO leads to a modification of the polymer's functionality.[92] This structural change was characterized as resulting from the intervention of essentially a Pummerer reaction on DMSO using the polymeric anhydride as an initiator, **227**→**230**. The complimentary process, a Pummerer reaction on a polymeric (oligomeric) sulfoxide substrate, was investigated by Hedhli and colleagues.[93] They observed that treatment of a series of oligoethyleneglycol bis sulfoxides, including the tetrameric species **231**, with the initiator Ac_2O led to the isolation of two products in roughly equal amounts, as exemplified by the two regioisomeric bis sulfides **232** and **233**. The almost equal partitioning between the fluorinated and non-fluorinated sides of the sulfoxide is a bit surprising, but perhaps is just a reflection of the trade-off between the acidifying effects of the inductively electron withdrawing groups on either side of the sulfoxide. By far, the bigger surprise is a complete absence of any of the unsymmetrical regioisomer **234**. The basis of this remarkable claim by the authors remains obscure, given the almost equal facility with which either side of the sulfoxide group apparently participates in the Pummerer reaction to form **232** or **233**. In short, this result must reflect the operation of a completely dominant electronic effect that is exerted over 16 non-conjugated atoms, a phenomenon likely to have little precedence in all of organic chemistry.



Scheme 29. Pummerer reactions with polymeric and oligomeric components.

The push to identify chemical transformations that work with functionality tethered to a solid support has led to testing of the Pummerer process in this environment, Scheme 30. In the initial foray, Solladié and co-workers demonstrated that the resin-bound sulfoxide **235** participates in a conventional Pummerer reaction upon treatment with TFAA to furnish an initial sulfide product **236** and then the desired resin-free alcohol **238** upon hydrolysis/reduction.[94] This sequence has the net effect of cleaving the molecule of interest from the resin, and so it falls under the category of 'traceless linker' technology. No yields were reported, and so the overall efficiency of the strategy cannot be judged.



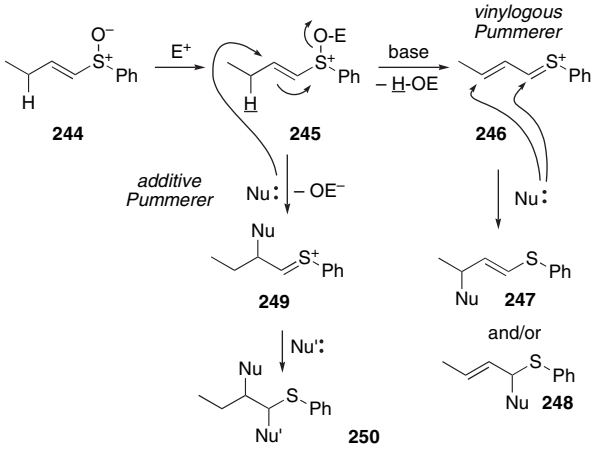
Scheme 30. Pummerer chemistry on beads.

The use of Pummerer chemistry to effect a desired cyclization within a resin-bound substrate was probed by Proctor et al., **241**→**242**.[95] The Glasgow group employed chemistry very similar to that described by Sano (Scheme 15, **135**→**137**) to effect closure of the oxindole nucleus. In a second independent step, the heterocycle was cleaved from the resin under reductive conditions. This example illustrates how the Pummerer reaction can be an asset to library synthesis by virtue of its productive use in 'on-bead' chemistry.

5.4. α,β-Unsaturated sulfoxides

The introduction of alkenyl and aryl sulfoxides as substrates in Pummerer chemistry has expanded the basic repertoire of useful processes for oxidative transposition in significant and fundamental ways, particularly in the area of heterocycle synthesis. The alkene adjacent to the sulfoxide function efficiently extends the thionium ion's electrophilicity down the molecular framework and introduces many new options for single and double nucleophile capture. With this multiplexed reactivity, of course, comes issues of both regioselectivity and stereoselectivity of bond formation. These questions are often cast in terms of the grand mechanistic dichotomy that defines this area of Pummerer chemistry, vinylogous versus additive pathways for nucleophile–electrophile pairing. A survey of historical precedents, and the current trends that have evolved from them, follows.

5.4.1. Vinylogous and additive mechanisms. Captured in Scheme 31 is the essence of the underlying mechanistic picture for Pummerer reaction with unsaturated sulfoxides. Whereas an alkenyl substrate **244** is shown for convenience, these pathways extend to the aromatic versions as well. Initiation of the Pummerer sequence by activation of the sulfoxide in **244** leads to the branch point in this mechanistic proposal, sulfonium ion **245**. If this sulfonium salt bears a γ-proton whose C–H bond can maintain overlap with the π-system of the alkene, then simple E2-like elimination of the elements of H–OE follows from direct analogy with the alkyl Pummerer substrates. The product of this elimination is the electrophilic unsaturated thionium ion **246**, which is capable of trapping nucleophiles at either the α- or γ-positions to deliver **248** or **247**, respectively. This pathway has been termed the 'vinylogous Pummerer reaction'.[96] The factors



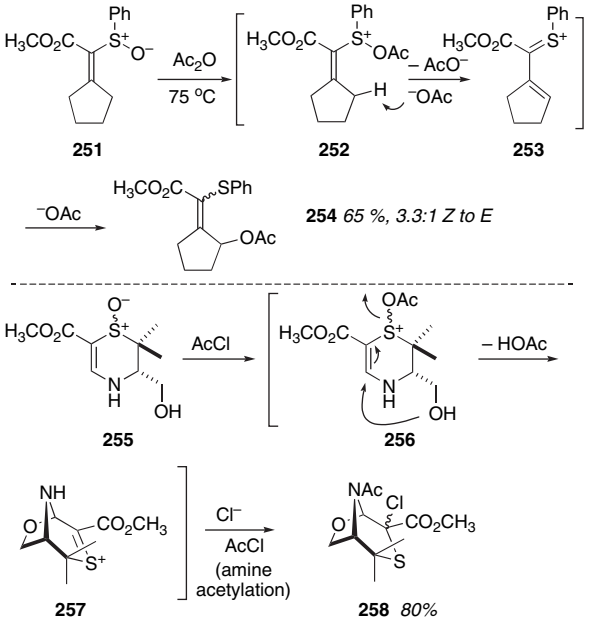
Scheme 31. Vinylogous and additive mechanistic pathways for the unsaturated sulfoxide Pummerer reaction.

that govern the choice of α or γ nucleophile attack are not well understood, and examples exist that favor either outcome. Built in biases have been used to steer the nucleophile to one site or the other, as illustrated by example below. Despite the fact that the elimination of H–OE is most likely to be bimolecular with respect to base, the overall vinylogous Pummerer sequence bears a strong resemblance to S_N1-type chemistry in that the leaving group departs to form a high-energy electrophilic intermediate prior to nucleophile addition.

The sulfonium salt **245** can engage the nucleophile directly in a process competitive with the vinylogous channel to afford the thionium ion **249**. The nascent thionium ion in **249**, like any Pummerer-generated thionium ion, will react rapidly with available nucleophiles to furnish the double adduct **250**. Depending on the particulars, the two nucleophiles can be the same or different, and clever substrate design has been used to serve up a specific sequence of nucleophiles for controlled introduction of the two addends. This mechanistic pathway had been labeled the 'additive Pummerer reaction'.[97] In contrast to the vinylogous alternative, this reaction scheme most closely aligns with an S_N2'-type process in that the introduction of the first nucleophile occurs in concert with departure of the leaving group OE. In some of the examples described below, the mechanistic path is unambiguous. However, other Pummerer transforms on unsaturated sulfoxides could proceed by either mechanism, and in none of the ambiguous cases has any evidence been presented that allows for a definitive conclusion about which might be operational.

The inaugural example of a vinylogous Pummerer reaction on an unsaturated substrate can be ascribed to Uda and coworkers (1975),[96] who demonstrated that the alkenyl sulfoxide **251**, upon reaction with acetic anhydride, leads to the vinylogous acetate addition product **254**, Scheme 32. The fact that no acetate addition occurred at the ring juncture excludes an additive mechanism from further consideration. The additive mechanism was known at the time, although not yet christened as such, through Stoodley's study of the Pummerer reaction of the unsaturated sulfoxide **255** (1972).[98] This example features the double nucleophilic addition characteristic of the additive mechanism, with first hydroxyl and then chloride quenching electrophilic sites on the substrate. These rather humble Pummerer 'curiosities' have spawned a great deal of the modern Pummerer literature, as many research groups have actively pursued the development and exploitation of the myriad reactions that stem from treatment of unsaturated sulfoxides with activators, as detailed in the following sections.

5.4.2. Aromatic Pummerer substrates. The sub-field of aromatic sulfoxide Pummerer rearrangement chemistry has seen more development than the aliphatic counterpart, presumably because of the ready availability of the starting aryl sulfoxides, and the role that such transformations might play in total synthesis endeavors. The seminal report by King demonstrated no more than the fact that aryl ring oxidation was possible (**259**→**262**) via the agency of a Pummerer reaction on a phenolic substrate,[99] Scheme 33. No arguments were advanced that supported one mechanistic path over another, but the acidity of the phenolic hydroxyl in **260** would tend to lend weight to a vinylogous Pummerer

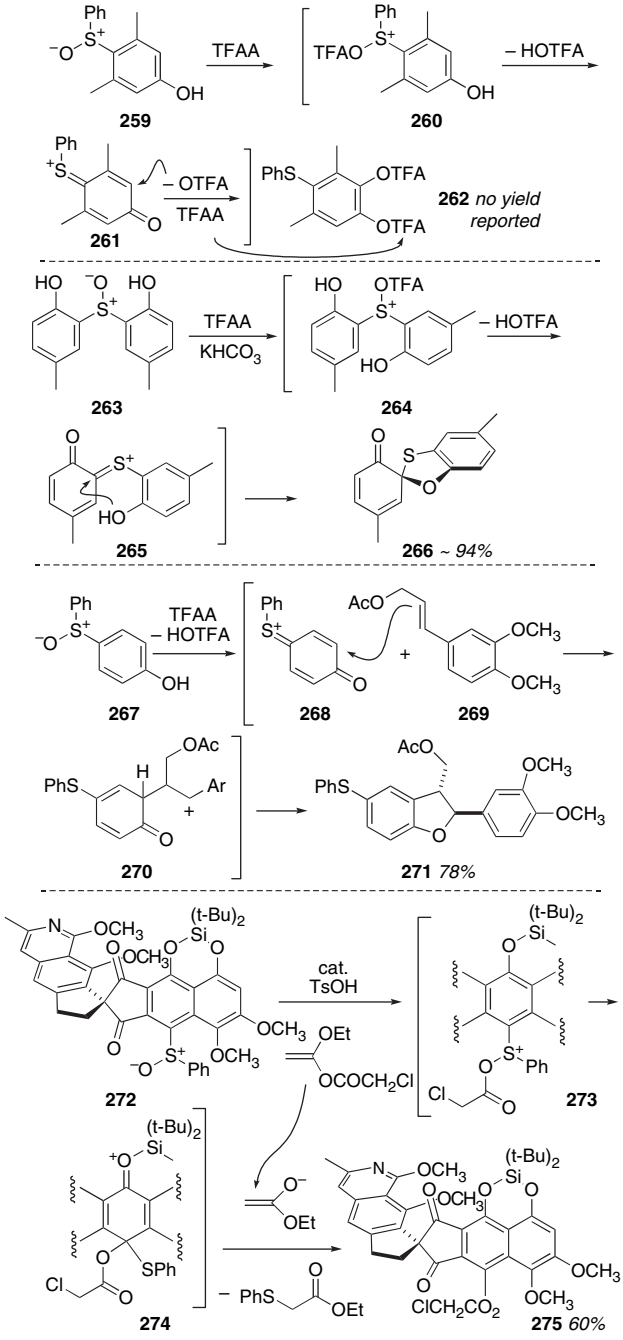


Scheme 32. Early examples of the unsaturated sulfoxide Pummerer reaction.

mechanistic sequence over the additive alternative. Kita, and independently, Jung, picked up on this line of inquiry and fleshed out much of the scope of the process within the context of phenol oxidative addition chemistry.

Jung, for example, showed that the bis phenolic sulfoxide **263**, upon subjection to TFAA-mediated Pummerer initiation, furnished the spirocyclic cyclohexadienone product **266** in excellent yield,[100] Scheme 33. A vinylogous Pummerer process was proposed to rationalize this result. The facile loss of the elements of trifluoroacetic acid from **264** presumably leads to the electrophilic orthoquinone analogue **265** that plays a central role in this transformation. The product **266** can be reductively desulfurized to provide a bis phenolic ether, a common structural element of many phenol (e.g., tyrosine)-derived natural products. As with the work of King, these phenol sulfoxide substrates combined with the TFAA electrophile preferentially on the sulfoxide oxygen and not the phenol hydroxyl.

Kita et al. extended the phenolic sulfoxide Pummerer chemistry through systematic investigations that probed the role of activator, nucleophile, and solvent on the facility and the scope of the process.[101] His group identified conditions that supported the addition of a carbon (alkene) nucleophile to the intermediate (thionio)quinone electrophile, as exemplified by the combination of sulfoxide **267** with styrene derivative **269** to provide good yields of the formal [3-atom+2-atom] addition product dihydrobenzofuran **271**,[102] Scheme 33. This reaction provides facile access to neolignan-type structures with excellent stereochemical control. The value and selectivity of this aryl Pummerer rearrangement chemistry can be seem in Kita's efforts directed toward the antitumor antibiotic fredericamycin via an Ar–S(O)Ph → Ar–OCOR transformation (**272** → **275**, Scheme 33).[103] This sequence was executed in good yield and without interference from undesired degradative pathways, despite the presence of a nucleophile sensitive

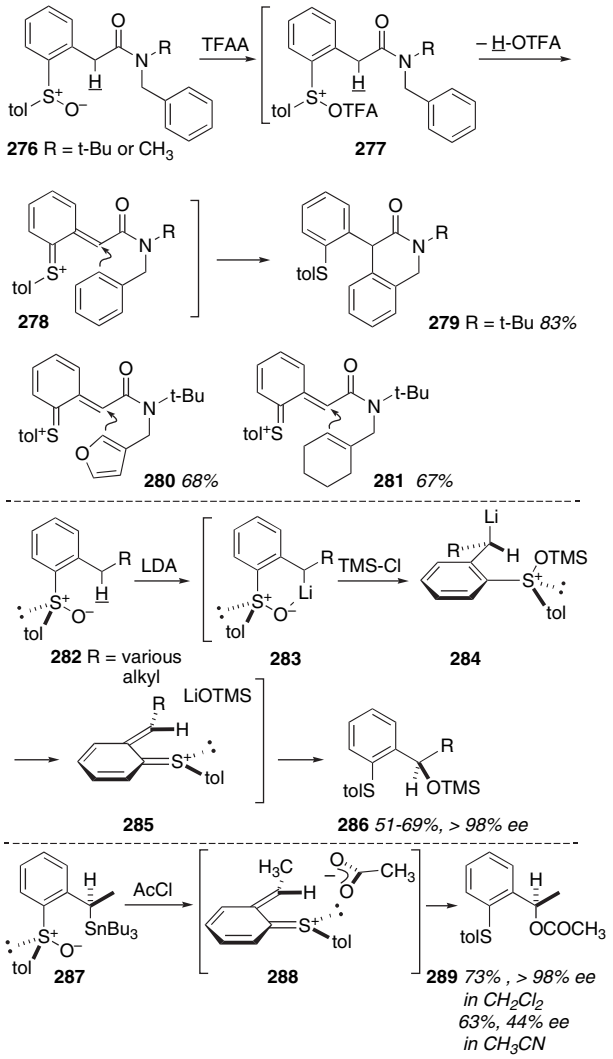


Scheme 33. Examples of phenolic sulfoxide Pummerer reactions.

quaternary β-dicarbonyl and oxidation sensitive masked hydroquinones.

Contemporaneous studies by Padwa and co-workers on a non-phenolic variant of the aryl Pummerer reaction led to the development of a benzylic C–H activation strategy to trigger the Pummerer sequence,[104] Scheme 34. In a representative example, the aryl sulfoxide **276** bearing a pendant aryl nucleophile was exposed to standard Pummerer initiation conditions to deliver the cyclized material **279**.[104a] In this instance, loss of H–OTFA through a vinylogous mechanistic pathway is required to activate the benzylic position for C–C bond formation. The highly electrophilic *ortho*-(thionio)quinone methide intermediate **278** is reactive

enough to trap even the unactivated aryl ring in good yield. The fate of this transformation rests on the identity of the amide's 'R' substituent. When R=*t*-Bu (large), an amide rotomer favoring juxtaposition of the two aryl rings is preferred. When R=CH_3 (small), the alternative rotomer is preferred, and aryl trapping of the electrophilic species is not seen. In this instance, the *ortho*(thionio)quinone methide is quenched by simple $TFAO^-$ addition. Extension of this chemistry to more nucleophilic (furan, **280**) and less nucleophilic (alkene, **281**) traps speaks to the promise of generality for the transform.

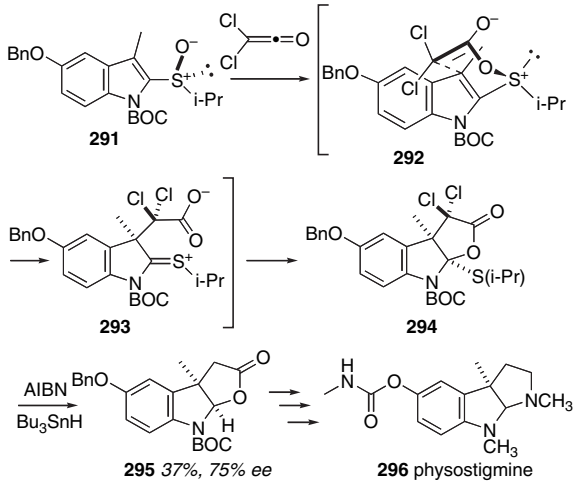


Scheme 34. Padwa's exploration of benzylic activation through aromatic Pummerer reactions.

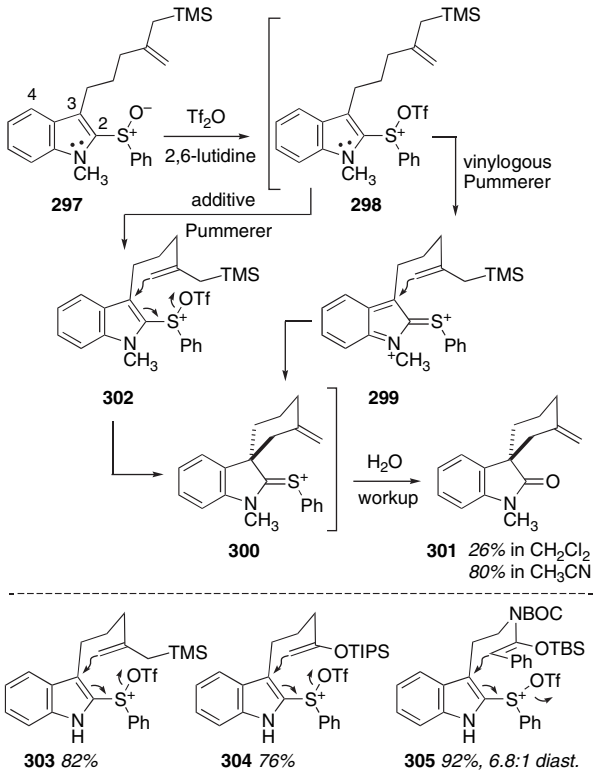
An intriguing variant on the benzylic activation theme recently has emerged from the Padwa lab, **282**→**286**, and the related **287**→**289**,[105] Scheme 34. In these examples, sulfoxide activation of the benzylic position is aided by chelation rather than by the carbonyl-induced acidification within **277**, but the net result, formation of a *ortho*(thionio)-quinone methide intermediate, is the same. In the key advance of this work, a high level of chirality transfer from stereogenic sulfoxide to the benzylic position was detected. This observation was explained by invoking a tight ion pair (**285** in the case of **282** and **288** from **287**) that preserved the original stereochemical information despite having only sp^2 centers. The tight ion pair has sufficient integrity to sustain the apparent planar chirality of **285/288** and enable this transfer. This speculation is supported by the solvent effects seen with **287**, wherein use of a more polar solvent, which presumably would better promote ion separation, provides product with lower ee. Given the planar nature of the typical thionium ion electrophile, Pummerer reactions on chiral sulfoxides that proceed with high levels of asymmetric induction are rare (cf. Kita's work, Scheme 5), and so these examples may presage the opening of new vistas in the field.

The expansion of aryl sulfoxide Pummerer chemistry into heteroaromatic systems was led by Marino and colleagues, who explored the use of indole sulfoxide substrates with ketene initiators,[106] Scheme 35. The goal of the synthesis involved preparation of 3,3-disubstituted indoline products en route to members of the physostigmine family of medicinally active alkaloids. Toward this end, treatment of the chiral sulfoxide **291** with dichloroketene led to a transient sulfonium intermediate that is poised to reorganize via [3,3] sigmatropy to furnish the C(3) disubstituted lactone **294** following cyclization within **293** of the carboxylate nucleophile into the thionium ion electrophile. Further functional group transformations led ultimately to physostigmine itself. The modest yield of Pummerer rearrangement was offset somewhat by the favorable level of asymmetric induction in the key C–C bond formation. The authors cite a transition state resembling **292** as the vehicle for establishing absolute stereochemistry at C(3), and they note that the sterically bulky isopropyl group serves as a conformational anchor for this assembly. Smaller sulfoxide substituents (e.g., CH_3) proceeded with much lower ee's. It is not clear whether the minor enantiomer emerges from a similar chair-like transition state construct with an axial isopropyl group, or from a boat-like alternative with an equatorial isopropyl. The sequential addition of two nucleophiles to the sulfonium/thionium ion intermediates is characteristic of the additive Pummerer mechanistic pathway.

The synthesis of 3,3-dialkyl indolone derivatives from indole-2-sulfoxides also can be realized when the nucleophilic



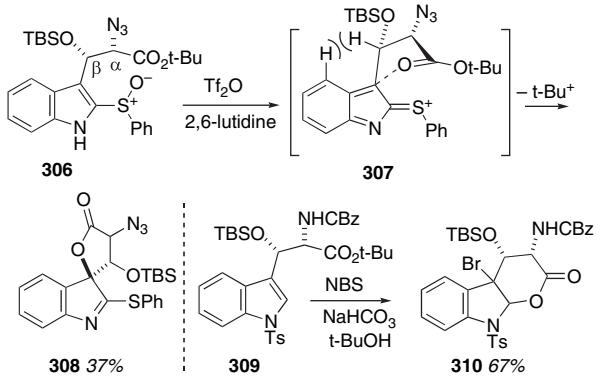
Scheme 35. Marino's Pummerer rearrangement on the indole platform, directed toward physostigmine synthesis.



Scheme 36. Oxidative carbocyclizations extending from indole-2-sulfoxides.

entity is tethered to the indole framework,[38] Scheme 36. The allylsilane of substrate **297** is a relatively poor nucleophile (Mayr N=1.8)[13a] yet the transformation proceeds in high yield, again a reminder of the functionally useful levels of electrophilicity that can be achieved under mild conditions via Pummerer chemistry. The vinylogous versus additive mechanistic dichotomy is brought into sharp relief with the *N*-methyl substrate shown. A putative vinylogous path would proceed inescapably through the dicationic intermediate **299**, whereas the additive alternative would avoid this presumably high-energy species by favoring an S_N2'-type displacement (**302**→**300**) without any involvement of the nitrogen's lone pair. In both scenarios, the same thionium-bearing species **300** would result, and hydrolysis upon workup then affords the oxindole product in excellent yield (in CH_3CN). No independent evidence exists that allows discrimination between these two mechanistic hypotheses at this juncture. Only the vague unease at invoking a doubly cationic intermediate, despite Sano's reliance on same (cf. Scheme 3 and accompanying discussion), tends to shade mechanistic thinking toward the additive pathway. This transformation formally represents an oxidative cyclization onto a heteroaromatic nucleus with complete control of (1) oxidant delivery and (2) regiochemistry of nucleophilic attack. Many prior studies on oxidation-initiated aromatic heterocycle functionalizations have been attempted, and the not infrequent observations of product (over)oxidation, and/or lack of regiochemical control upon nucleophile addition have compromised the value of these transforms in the past.[107] With **297** and related substrates, the site of oxidation is completely controlled by the starting sulfide's (precursor to **297**) unmatched susceptibility to oxidants. The regiochemistry of nucleophile addition is governed by the intermediate's energy gain by rearomatization, as alternative addition sites, such as C(2) or C(4), would not lead to aromatic products. Only the C(3) addition shown, either by additive or vinylogous mechanistic paths, preserves (or returns) the benzene ring to full aromaticity. Successful cyclizations with alternative nucleophiles have been documented as well. The silyl enol ether of **304** and the silyl ketene iminal function in **305** both participate satisfactorily in this Pummerer reaction. Since each of these species has a proton on the indole nitrogen, the first-formed and isolated products are 2-thiophenyl indolenines. The thioimidate function of these compounds can be readily hydrolyzed to the carbonyl (indolone) product in a second step. In this way, a range of functionalized 3,3-spirocyclic indolones are available from simple indole precursors. A detailed mechanistic picture of the cyclization of **305**, with the sulfur activated by hypervalent iodine rather than sulfoxide sulfonylation, has been presented in Scheme 10.

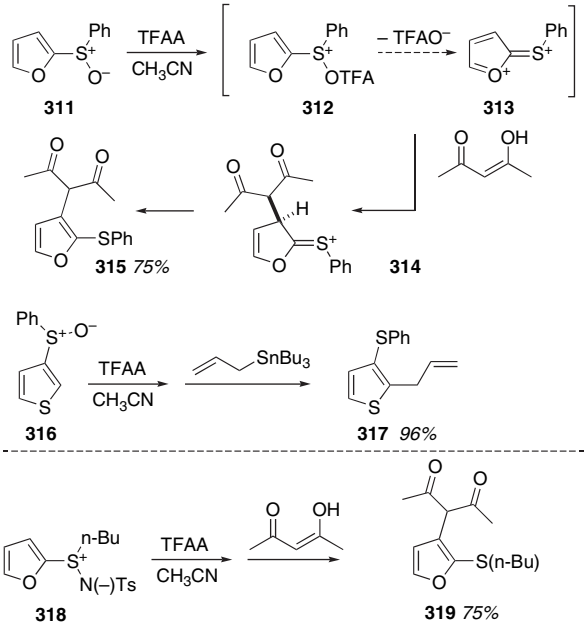
An example of an errant regiochemical result can be found in the tryptophan cyclization literature, where the β-*O*-silyl tryptophan diastereomer **309** leads to C(2) bond formation upon treatment with a bromonium ion source, **309**→**310**,[38] Scheme 37. The C(3) spirocyclic butyrolactone product was desired for a synthesis project, and was expected based upon much precedent.[108] In contrast, the β-*O*-silyl diastereomer of **309** (not shown) does provide the butyrolactone product (C(3) bond formation) under the same conditions, although that diastereomer was not useful for the synthesis objective. This undesired regiochemical outcome with **309** can be corrected by turning to Pummerer chemistry, which forces C(3) bond formation in a tryptophan-derived substrate that bears the same erythro stereochemical relationship between C(α) and C(β). Exposure of sulfoxide **306** to Tf_2O leads to a single diastereomeric product, **308**, in modest yield. The stereochemical outcome can be rationalized by focusing on the steric interaction between the C(β) substituents and the *peri* positioned aryl hydrogen as indicated in **307**. The alternative transition state model would place the TBSO– group in steric conflict with the *peri* hydrogen, and presumably the energetic penalty associated with that $A^{1,3}$ interaction disfavors that option. The generally poorer yield of carboxylate C(3) cyclization[38] as compared to the C–C bond-forming cyclizations of Scheme 36 might be attributable to a mismatch between the soft



Scheme 37. Oxidative cyclizations of tryptophan derivatives: Pummerer chemistry versus bromonium ion initiation.

electrophile and the harder nucleophile oxygen compared with the alkene nucleophiles of Scheme 36.

Exploration of the scope of Pummerer-based oxidative activation of heteroaromatic species for C–C bond formation is just beginning. Along with the indole-based examples described above and the imidazole-based system featured in Scheme 11, furan and thiophene rings apparently participate in this chemistry with great ease,[109] Scheme 38. Kita's furan sulfoxide system **311** can be activated with trifluoroacetic anhydride to provide an electrophilic intermediate that is susceptible to nucleophilic capture by carbon nucleophiles like the β-dicarbonyl shown, or allyl tributylstannane.[109a] The Osaka group portrays this chemistry as proceeding through the vinylogous pathway, although there is no reason, a priori, to exclude the additive route at this time.

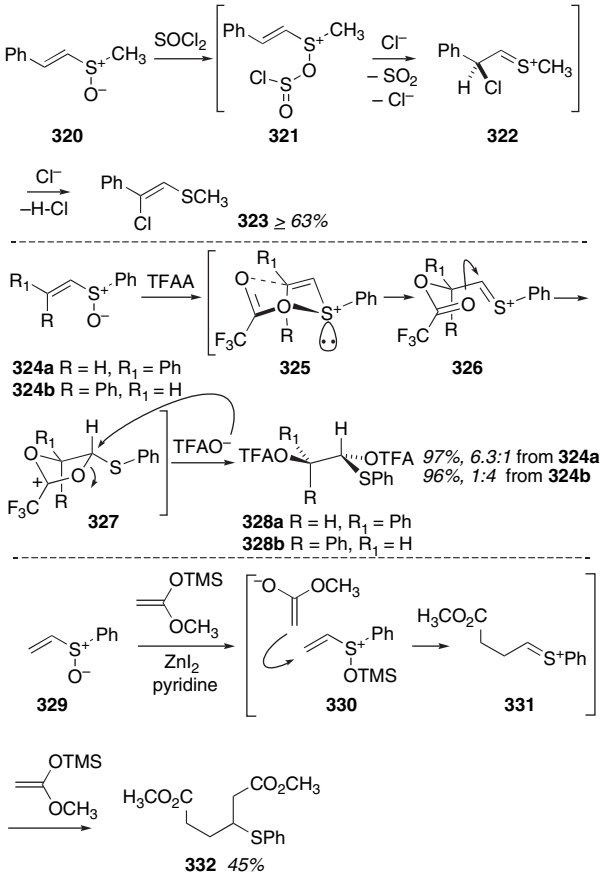


Scheme 38. Pummerer chemistry for functionalization of furan and thiophene rings.

A similar study by Padwa et al. exploited the nitrogen analogue of a sulfoxide, an *N*-tosyl sulfilimine, in a related transform.[109b] Furan, benzofuran and thiophene cores were examined with the Kita nucleophiles, and in all cases the reaction proceeded smoothly with clean C–C bond formation, as exemplified by the conversion of **318** into **319**. Since the nitrogen (or oxygen function) is lost upon Pummerer reaction and the overall yields are similar, the advantages of the sulfilimine system over the archetypal sulfoxide case remain to be established.

5.4.3. Alkenyl Pummerer substrates. Much of the alkenyl sulfoxide Pummerer chemistry that has been developed within the context of synthesis programs was designed to proceed through an additive pathway, as this process yields the largest increase in molecular complexity upon rearrangement/double nucleophile addition. The two nucleophiles that add to the α- and β-alkenyl sulfoxide positions, respectively, can be the same or different, and intramolecular variants add another level of control to the double addition sequencing. The discovery of the unsaturated sulfoxide/dichloroketene [3-atom+2-atom] butyrolactone annelation (cf. Scheme 35) by Marino served as the launch point for much of this chemistry, and several variations have seen use in natural products synthesis, vide infra.

The initial observation of alkenyl sulfoxide Pummerer chemistry germane to the additive process might be found in Russell's 1966 report on the consequences of treating vinyl sulfoxide **320** with thionyl chloride,[110] Scheme 39. The β-chlorovinyl sulfide product **323** plausibly arises from the beginning of the additive sequence **321**→**322**, but the process is interrupted by proton loss to form the alkene product **323**. This cryptic example of additive Pummerer chemistry was not appreciated as such at that time, but it did reveal that the alkene function of vinyl sulfoxides can be engaged in productive bond formation upon sulfoxide activation.



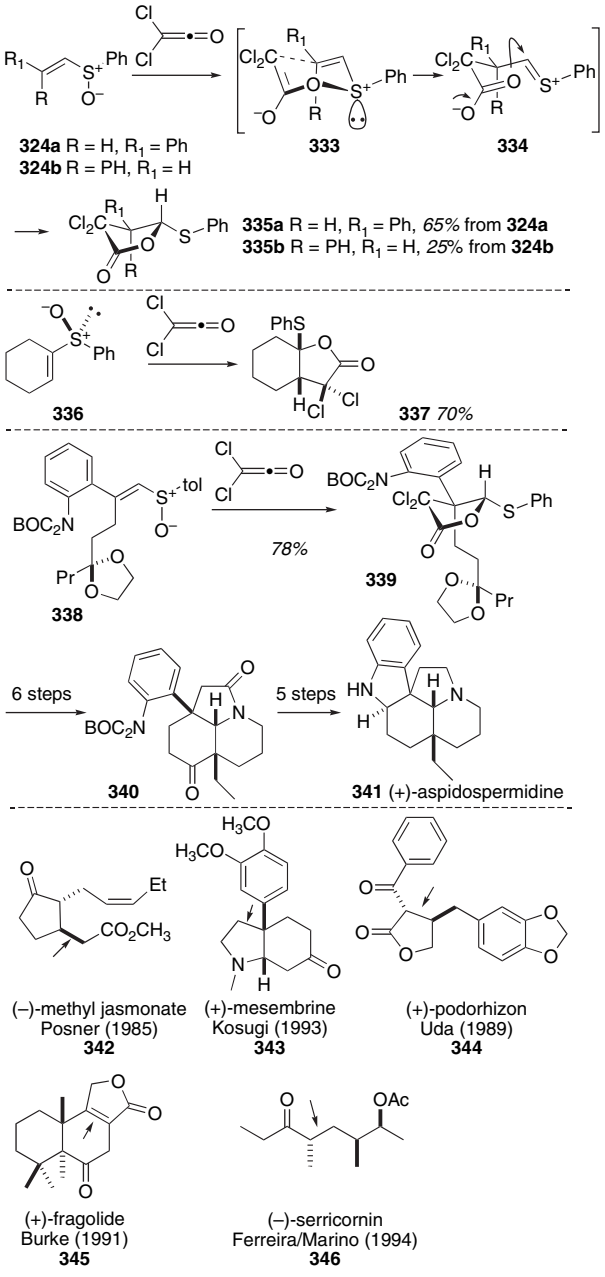
Scheme 39. Some early examples of additive Pummerer rearrangements on alkenyl sulfoxide substrates.

An example of double trifluoroacetate addition was described by Craig and Daniels,[111] **324**→**328**. Of particular interest is the observation that the different geometrical isomers of the starting alkene **324a/324b** furnish distinct and stereochemically opposite major and minor bis trifluoroacetate adducts **328a/328b**, respectively. Unfortunately, the relative stereochemistry of these adducts was not assigned, precluding any definitive mechanistic conclusions. Speculation can fill this gap, and it is possible to rationalize this conservation of stereochemical information by citing first a concerted [3,3]-sigmatropic shift within the intermediate sulfonium salt **325**, anchored by an equatorial phenyl substituent, to deliver the transient thionium ion **326**. In what

will become a common theme in the discussion of alkenyl sulfoxide Pummerer chemistry to follow, a mechanistic course for nucleophile addition that preserves the alkene's geometrical information now is required. Perhaps facile intramolecular cyclization of the pendant trifluoroacetate within **326** can fill this requirement. This transition state geometry modeled by **326** includes a Felkin–Ahn-type alignment of the σ^*_{C-O} and $\pi^*_{C=S(+)}$ orbitals, but also includes an unfavorable steric clash between the 'R' substituent and =S(+)Ph. When R=H (from the *E*-alkene precursor **324a**), no further convolutions are necessary to justify formation of a single stereoisomer. However, when R=Ph (from the *Z*-alkene precursor **324b**), there must be a reason why C–C bond rotation to exchange the positions of R and R_1 does not compete with direct nucleophilic addition, or the same stereoisomer that was formed from the *E*-alkene precursor would be formed here as well. The reason may be supplied by the relatively long C=S bond length, which could mitigate the severity of the Ph/=S(+)Ph steric interaction. This moderation of an otherwise significant steric clash could promote facile nucleophilic addition at a rate faster than bond rotation.

Kita et al. have documented that carbon-based nucleophiles can serve as effective components of the alkenyl sulfoxide additive Pummerer reaction,[112] **329→332**. The great benefit of using silyl ketene acetals as group transfer initiators is illustrated by this chemistry, as these species, almost uniquely, maintain compatibility with the requirements of sulfoxide electrophilic activation without themselves consuming the carbon-based nucleophile. The net result is formation of two new C–C bonds to adjacent carbons under exceedingly mild experimental conditions, a sequence of great potential value in synthesis.

An arguably transforming event in this area of Pummerer chemistry was supplied in a 1981 report by Marino and colleagues that details their alkenyl sulfoxide/dichloroketene cyclocondensation sequence, **324a/b→335a/b**,[113] Scheme 40. Similar to the Craig work, different geometric isomers of the alkenyl sulfoxide substrate lead predictably to distinct and mutually exclusive stereoisomers of product butyrolactone. The mechanistic picture of this transformation emerged over the course of several subsequent studies, and it features the [3,3]-sigmatropic shift/facile intramolecular cyclization sequence (**333→334→335**) discussed in detail earlier. In general, the yield improves when the dichloroketene is prepared by zinc-mediated reduction of trichloroacetyl chloride as compared to triethylamine-promoted dehydrohalogenation of $Cl_2CHCOCl$. Marino attributes this difference to the formation of the Bronsted acidic byproduct $Et_3N\cdot HCl$ in the latter case, which might consume intermediate anions **333/334** by protonation.[113] In addition, a beneficial role for the $ZnCl_2$ produced in the former process might be anticipated from the Kita work (ZnI_2-catalysis). The overall butyrolactone-forming reaction displays sufficient versatility and substrate scope to qualify as one of the more valuable [3-atom+2-atom] annelation procedures currently available. Extensions to chiral sulfoxide substrates might be expected to provide butyrolactone products with high levels of asymmetric induction, given the exquisitely organized transition states involved, and indeed this expectation is borne out experimentally, as illustrated by the conversion of **336→337** with complete control of absolute stereochemistry.[114]

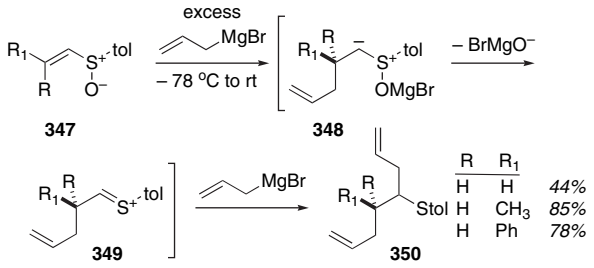


Scheme 40. Marino's butyrolactone annelation via an additive Pummerer rearrangement on alkenyl sulfoxide substrates.

The value of this reaction can be gauged by its impact in total synthesis endeavors. Marino's aspidospermidine synthesis **338→341** speaks to this point, as the readily available chiral sulfoxide **338** is converted to the chiral lactone **339** in good yield and with complete and predictable stereochemical fidelity.[115] This pivotal intermediate led to aspidospermidine in 11 further manipulations. The Marino chemistry was quickly adopted by several other researchers, who capitalized on the reliable chirality transfer of the Pummerer reaction to fix absolute stereochemistry in the lactone product as part of the syntheses of (−)-methyl jasmonate (**342**),[116] (+)-mesembrine (**343**),[117] (+)-podorhizon (**344**),[118] (+)-fragolide (**345**),[119] and (−)-serricornin (**346**).[120] The key C–C

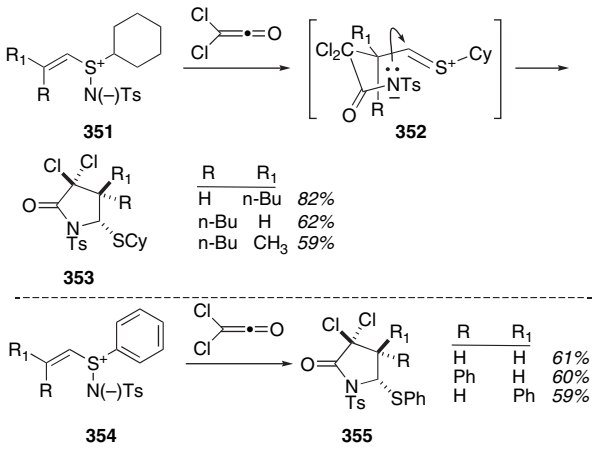
bond formed by the additive Pummerer reaction is indicated by an arrow in each structure. These total syntheses from the 1980s to 1990s cemented the value of this Pummerer-based transform in natural product synthesis by providing the first legitimate bridge between the original developmental/exploratory studies of additive Pummerer chemistry and the later applications phase of the field.

In 1991, Iwata described the observation of additive Pummerer chemistry when attempting to develop the 1,4-conjugate addition reaction of Grignard reagents and alkenyl sulfoxides,[121] Scheme 41. This chemistry emphasizes the doubly electrophilic character of the alkenyl sulfoxide synthon, and illustrates how the two very different electrophiles involved (vinyl sulfonium salt derived from **347** and thionium ion **349**) both are satisfactory partners for a Grignard reagent. No proton transfer/deprotonation products were reported with the acyclic substrates, but cyclohexenyl sulfoxides did provide substantial alkenyl sulfide byproducts. The sulfoxide activation by a magnesium Lewis acid in **348** is reminiscent of the later $Mg(N(i\text{-}Pr_2))_2$ Pummerer activation chemistry of Kobayashi (Scheme 8).



Scheme 41. Iwata's additive Pummerer rearrangement using the Lewis acid '$MgBr^{+}$' as an activator.

Recent extrapolations from the Marino butyrolactone synthesis have involved sulfilimine substrates applied to the analogous lactam construction, Scheme 42. Marino observed that a competition existed within the thionium ion intermediate **352** between N–C bond formation to provide the desired lactam **353**, and O–C bond formation to deliver a lactone imine byproduct.[122] An exploration of the effects of sulfur and nitrogen substituents on this partitioning led to the conclusions that (1) the electron donating or electron-withdrawing character of the nitrogen substituent does not affect the lactam/lactone imine ratio much, but (2) the product ratio was responsive to the electronic contributions of the sulfur moiety. The optimum substituent pairing appeared to be a tosyl unit on the nitrogen and a cyclohexyl group on the sulfur, and with this combination, ratios as high as 20:1 favoring the lactam were observed with no compromise in overall product yield. As with all of the other Marino-type [3-atom+2-atom] annelations, the geometric information in the starting alkene is accurately and predictably translated to product stereochemistry. At the same time, Padwa and colleagues pursued similar studies,[123] and the Emory group found that the *phenyl* substituted sulfilimines **354** performed comparably with the (saturated) *cyclohexyl* analogues of Marino, **354**→**355**. No discussion on the lactam/lactone imine dichotomy was presented in this work.



Scheme 42. Extension of Marino's dichloroketene–alkenyl sulfoxide Pummerer transform to sulfilimine analogues.

The more than two-dozen examples of unsaturated sulfoxide Pummerer chemistry presented in Section 5 are not comprehensive but are arguably representative of the scope of this area of chemistry. Taken collectively, they help to define the structural and experimental parameters that steer the transform down either the vinylogous or the additive path, but also reveal unresolved mechanistic aspects of this topic. Many systems fall into unambiguous territory where either (1) a lack of γ-protons or severe steric hindrance at the β-position excludes the vinylogous route, or (2) intramolecular delivery of the nucleophile from a sulfoxide oxygen attachment point guarantees that only the additive process can be accessed (e.g., Marino, Iwata, and Craig chemistry). The weight of evidence with arene sulfoxide derivatives points to a vinylogous pathway, perhaps reflecting the reluctance of a phenyl ring to suffer direct nucleophilic attack with the attendant loss of aromaticity (e.g., Kita and Padwa chemistry). The mechanistically unassigned cases mostly evolve from treating *heteroaryl* sulfoxides with activators/nucleophiles. In these cases, the loss of aromatic resonance energy via an additive process might not be so debilitating, while at the same time offering the prospect of proceeding through presumably lower energy singly cationic intermediates (cf. **302** vs **299**, and **312** vs **313**). This question has more than pedagogical interest, as opportunities for achieving asymmetric C–C bond formation from readily available unsaturated chiral sulfoxides may depend on the precise mechanistic course of the transformation.

6. Pummerer-initiated cascade cyclizations

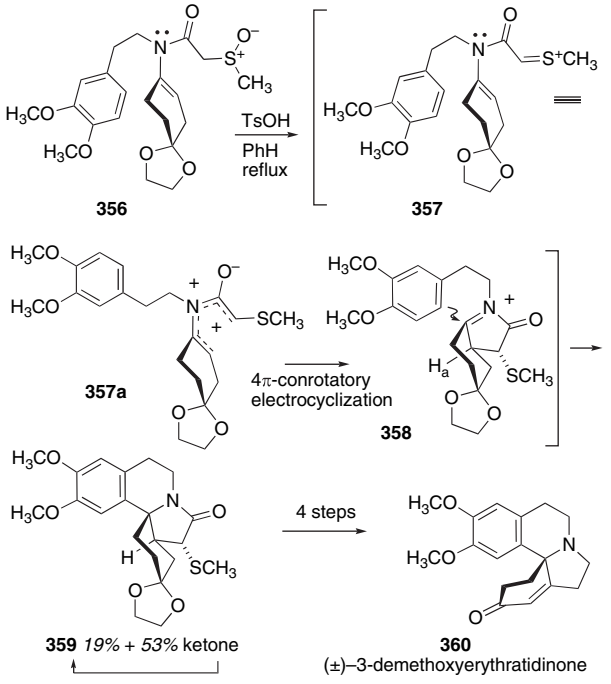
The development of Pummerer chemistry as an enabling technology for multi-part cascade sequences has ensured that this field will have a continuing impact on strategy-level synthesis design. Most of the recent thrusts in this burgeoning area have originated from Padwa and co-workers, and the promise implicit in their preliminary studies seems likely to fuel much additional research on this topic. At present, the Emory group has identified two different and distinct mechanistic venues to reduce this concept to practice: (1) using the Pummerer-generated thionium ion to initiate a cationic polyolefin cyclization, and (2) using the Pummerer-generated thionium ion to fashion a transient 4π electron component for [4π+2π] cycloaddition. Both approaches to cascade

chemistry require compatibility between the acidic/electrophilic Pummerer initiator and the remainder of the functionality that is incorporated to complete the multi-part sequence, and the remarkably high yields obtained (vide infra) attest to the clever substrate design and careful optimization that undergirds these efforts.

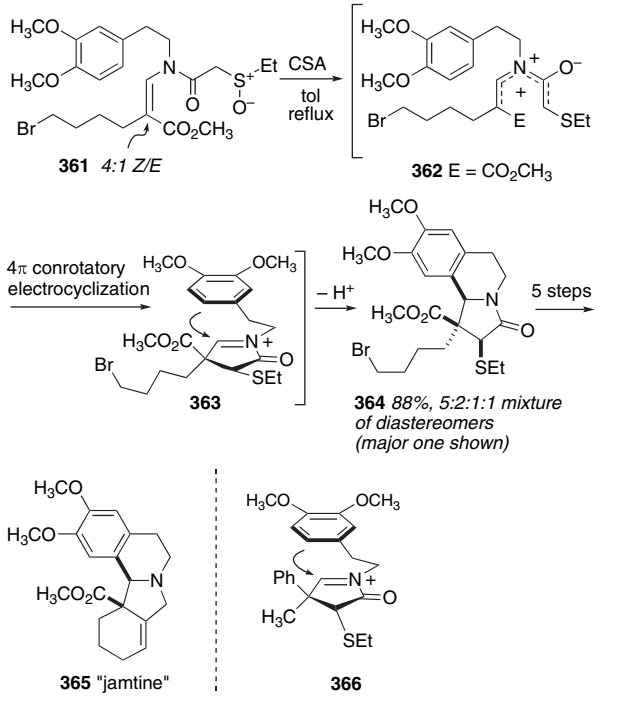
6.1. Cationic polyene-type cyclizations

The development of biomimetic cationic polyene cyclizations for terpenoid assembly, and later, the related iminium ion analogues for alkaloid preparation, have unarguably advanced the whole field of organic synthesis. The fact that Pummerer-derived thionium ions can contribute to this area preceded Padwa's work and was first recognized by Tamura and Ishibashi in the early 1980s,[124] Scheme 43. They developed this chemistry in the area of erythrina alkaloid synthesis, and eventually recorded a concise preparation of the representative member (±)-demethoxyerythratidinone (**360**).[124d] Initiation of the Pummerer sequence with β-carbonyl sulfoxide **356** and tosic acid led to the putative thionium ion **357**, which is faced with a choice: combine with the cyclohexenyl alkene (likely distorted from enamide resonance in the transition state for addition), or with the electron rich aryl appendage. Not surprisingly, five-membered ring closure is favored over seven-membered ring formation, although in preliminary model studies,[124a] a 7.5:1 ratio of the alkene-to-arene cyclization products was observed. The closure of **357** to **358** proceeded with exquisite control for strictly the *cis* cyclopentenone-iminium ion (H_a and SCH_3 *cis* in **358**), a level of stereoselectivity that might not have been anticipated on strictly steric/stereoelectronic grounds. However, Padwa has provided a retrospective explanation for this observation that cites the intervention of a 4π-conrotatory electrocyclization within **357a** to rationalize the result.[125a] The electrophilic iminium ion so derived is poised perfectly to capture the juxtaposed electron rich aryl ring and form the key quaternary C–C bond of the erythrina framework. Some of the ketal function was lost upon reaction, but its reinstallation and then further functional group manipulations led efficiently to the target. It is noteworthy that nothing was 'wasted' in this synthesis design, as the obligatory thioether residue resulting from the Pummerer process played a productive role as well: it served as an oxidation placeholder for the cyclohexene moiety of the final product.

Padwa and co-workers have executed a version of the Pummerer-initiated cationic cyclization cascade that bears some resemblance to the Tamura conceptualization, but in this case leads to a synthesis of the structure assigned to the polycyclic alkaloid jamtine (**365**),[125b,c] Scheme 44. Thus, an enamide **361** bearing the β-sulfoxide trigger was exposed to a Bronsted acid, leading to the 4π-electron pentadiene moiety within **362**. As with the Tamura/Ishibashi precedent, conrotatory cyclization within this unit provided the acyliminium electrophile of **363** with a cis stereochemical disposition between ester and thioether. Friedel–Crafts alkylation of the pendant electron rich arene completes the cascade to afford the tricyclic framework of jamtine, **364**, in excellent yield, as a mixture of diastereomers. The major isomer (shown) resulted from arene ring addition *syn* to the ester function, a preference that the Emory group attributed to steric effects. Available *A*-value data support this sterically based interpretation of stereoselectivity (ethyl=1.75, CO_2CH_3=1.27).[126] Curiously, a similar cyclization within the model substrate **366** led to a single product stereoisomer wherein the new Ar–C bond and the resident phenyl ring are *syn* disposed. Again, a reaction trajectory that minimizes steric hindrance was proposed to explain this observation,[125a] but in this instance the *A*-values (Ph=3.0, Et=1.75) do not appear to be consistent with this interpretation. Perhaps



Scheme 43. Ishibashi's synthesis of (±)-3-demethoxyerythratidinone by use of the Pummerer reaction to initiate a polyene cyclization.



Scheme 44. Padwa's synthesis of the structure assigned to the alkaloid jamtine by use of the Pummerer reaction to initiate a polyene cyclization.

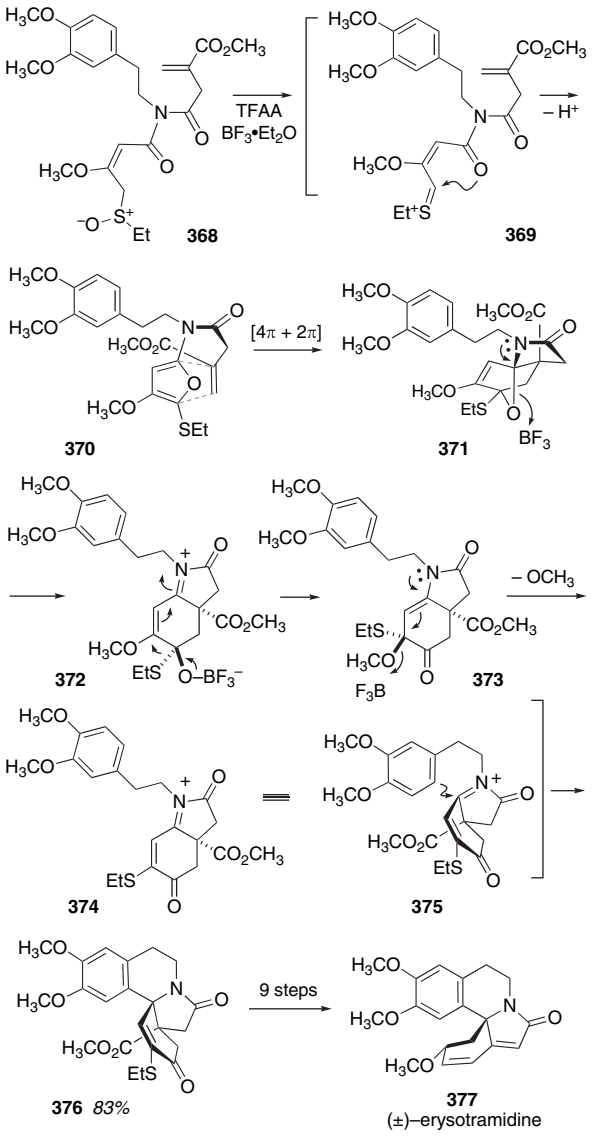
this dilemma can be resolved by noting that these *A*-values can be no more than imperfect measures of what is essentially a torsional (i.e., 1,2)-type interaction.

With tricycle **364** in hand, five additional steps were required to access compound **365**, the putative structure of jamtine. Unfortunately, a lack of congruence between the spectral data of the amine oxide derived from **365** and the natural product jamtine *N*-oxide raises doubts about the legitimacy of the original structural assignment.[125c] Nevertheless, Padwa's work and the earlier Ishibashi's chemistry begins to bring into focus the possibilities that Pummerer-initiated polyene cyclization has to offer natural products synthesis. Compatibility issues can be minimized with prudent substrate design, and the apparent participation of several stereochemical control elements raises the prospects for obtaining cyclization products with high levels of relative asymmetric induction.

6.2. Cationic cyclization–cycloaddition–fragmentation sequences

The redirection of Pummerer-initiated polyene cyclizations to a cycloaddition-mediated cascade could be accomplished by the expedient of replacing the central linchpin alkene with a carbonyl unit,[127] Scheme 45. In this scenario, the nascent thionium ion is captured by the carbonyl oxygen, leading to a five-membered oxygen-containing heterocycle bearing 4π electrons (e.g., furan or carbonyl ylide). This reactive unit then engages an appropriately situated 2π addend in intramolecular [4π+2π] cycloaddition. The cycloadducts so formed are designed to be labile and they readily convert to other structures of interest.

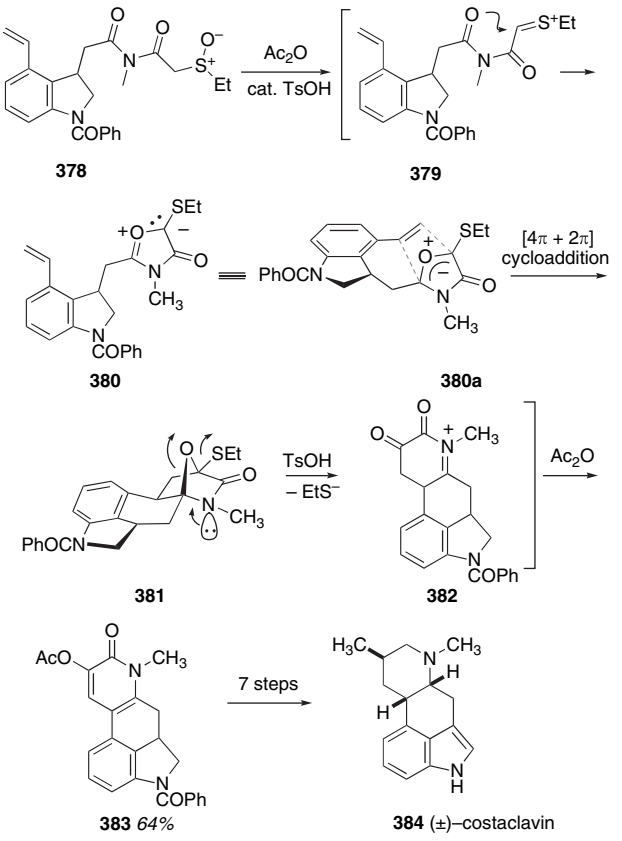
Padwa's construction of the erythrina alkaloid (±)-erysotramidine (**377**) exemplifies the application of this complex multi-step process to target directed synthesis.[127] In this reduction to practice, treatment of the imidosulfoxide **368** with the standard Pummerer initiator trifluoroacetic anhydride and the Lewis acid $BF_3\cdot Et_2O$ leads to the expected thionium ion-containing species **369**, which is poised to cyclize into the adjacent imide carbonyl. This cyclization delivers an intermediate electron rich furan ring following loss of a proton. The proximity of an activated alkene dienophile encourages facile Diels–Alder-type [4π+2π] cycloaddition to forge a short-lived oxonorbornane product **371**. At this point in the mechanistic speculation, the Lewis acid's role becomes prominent. The electrophilic boron presumably triggers rupture of the strained bicyclic system with an assist from the amide's stereoelectronically aligned lone pair, and an intermediate iminium ion **372** is generated. A pinacol-type shift within this species fashions a transient mixed ketal **373**, which suffers loss of methoxide to regenerate the iminium ion. The loss of the oxygen bearing nucleofuge rather than the sulfur-containing alternative might be traced to the oxophilicity of the BF_3 available to assist in this process. Finally, an iminium ion electrophile that lacks a facile decomposition pathway is accessed, and this species can now trap the tethered arene ring in a transformation that is reminiscent of Ishibashi's final erythrina alkaloid closure to deliver the tetracyclic product **376** in an astonishing 83% yield for a seven-step sequence that features the formation of three new C–C bonds. Support for this mechanistic hypothesis



Scheme 45. Padwa's synthesis of an erythrina alkaloid via a Pummerer-initiated cyclization/cycloaddition/cyclization cascade sequence.

can be found in the isolation of a water-trapped adduct of iminium ion **374**, and its further conversion into **376** under $BF_3\cdot Et_2O$ treatment.

A variation of this theme[128] was developed for the synthesis of the ergot alkaloid (±)-costaclavin (**384**),[128c] Scheme 46. In this study, the Pummerer sequence begins by treatment of the imidosulfoxide **378** with acetic anhydride to provide the anticipated thionium ion in **379**. As with the erysotramidine work, cyclization into the adjacent imide carbonyl quenches the sulfur-stabilized carbocation and furnishes a five-membered ring oxoheterocycle bearing 4π electrons. In this manifestation of the cycloaddition partner, however, the 4π-system is expressed as an isomünchnone dipole **380**. Deployment of the requisite 2π electron addend at C(4) of the indoline framework ensures that facile cycloaddition can be achieved, and the pentacyclic product **381** is formed as a transient intermediate. The stereochemical course of this cycloaddition has not been elucidated, and the formulation of **381** as an *endo* adduct is based strictly on mechanistic grounds and limited precedent,[128b] and is



Scheme 46. A Pummerer-initiated cyclization–cycloaddition–fragmentation sequence developed by Padwa for the synthesis of (±)-costaclavin.

offered only as a convenience. As with the erythrina alkaloid synthesis, the bicylo[2.2.1]heptane's inherent strain and favorable stereoelectronic overlap between the oxo bridge and the nitrogen's lone pair converge to promote facile C–O bond scission, possibly assisted by the strong Bronsted acid TsOH present. Acylation of the derived enol formed from tautomerization within **382** then delivers the observed product tetracycle **383** in excellent yield for the putative six-step sequence. This intermediate can be processed on to the target (±)-costaclavin (**384**) in seven additional steps. These seminal examples of cation-initiated cyclization–cycloaddition–fragmentation cascade sequences for rapid assembly of polycyclic materials from simple precursors demonstrate some of the power of Pummerer chemistry to impact on complex molecule synthesis. The merging of strong electrophile chemistry with the essentially orthogonal reactivity found in cycloadditions raises all types of compatibility issues, but the unique aspect of the Pummerer reaction, the generation of a reactive carbon electrophile under exceedingly mild conditions, provides the means to overcome or avoid many potential pitfalls that could be envisioned. Furthermore, these types of cascade sequences, with their obvious benefits for efficiency in synthesis, are likely to come into even greater prominence as more opportunities to link Pummerer chemistry with other types of downstream reactions are identified and then implemented.

7. Conclusion and perspectives

The arc of the Pummerer story is far from complete. While this chemistry lay dormant for nearly a half-century, the explosion of recent activity has more than compensated for the slow start. It is difficult to identify one transforming incident that catapulted this reaction to the fore, but rather the field seemed to benefit from the convergence of three historical events in the late 1950s–1960s: (1) the official 'naming' of the reaction by Horner and Kaiser, (2) the illuminating mechanistic studies by Oae, Russell, and others, and (3) the emergence of the new field of 'natural products synthesis', with its requirements for effective transforms on complex, highly functionalized substrates. The recognition that the Pummerer reaction can provide useful carbocationic intermediates under mild and essentially neutral or even slightly basic conditions opened up whole new opportunities for designing synthesis strategies that formed C–X bonds between carbon electrophiles and a wide range of nucleophiles with a high degree of chemoselectivity. Further developments in the areas of initiator chemistry, substrate scope and compatibilities, and linked, multi-part reaction sequences have continued to add to the value of the transformation. The future looks very bright, as advances in each of these areas might be merged in unforeseen ways to expand the scope, and hence, the impact, of the Pummerer reaction.

It is interesting to speculate what Pummerer might have thought about the vibrant and influential field of organic chemistry that has evolved from his (and his contemporary's) modest initial reports on sulfoxide decomposition. Over the course of his academic lifespan, this chemistry gained little traction. Almost no follow-up work appeared in the literature, perhaps (falsely!) corroborating a sense that the transform was little more than a curiosity of limited interest. Would he have been amazed, or perhaps would he feel a sense of vindication, a time-lapsed "I told you so?"

Acknowledgment

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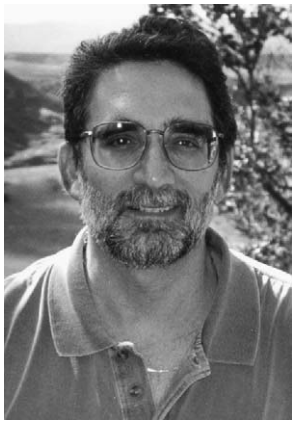
Biographical sketch



Ken Feldman was born and raised in Miami Beach, Florida. In 1978, he obtained his B.S. degree in chemistry while exploring the *ipso* nitration reaction of substituted aromatics in Philip Myhre's lab at Harvey Mudd College. His Ph.D. work at Stanford University with E.E. van Tamelen focused on biomimetic syntheses of marine and terrestrial natural products. After a yearlong stint as a postdoctoral fellow at Dupont, he joined the faculty of the Chemistry Department at Penn State as an Assistant Professor in 1984, where he currently holds the rank of Professor. His research interests include the total synthesis of natural products via Pummerer chemistry, the development of azatrimethylenemethane diyl reactions for alkaloid synthesis, and biological mechanism-of-action studies for the kinamycin family of diazo-containing antibacterial and anticancer terrestrial and marine metabolites.

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Antenna-functionalized dendritic β-diketonates and europium complexes: synthetic approaches to generation growth

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Abstract—Six dendritic β-diketonates and their corresponding europium complexes were synthesized. These dendritic β-diketonate ligands consist of dibenzoylmethane cores, Fréchet-type poly(aryl ether) dendrons, and the carbazole-grafted peripheral functional groups. The designs of dendrimers are on the basis of high light-harvesting capability and dendron functionalization in virtue of the high extinction coefficient and carrier-injection adjustment of carbazole units. Different approaches to generation growth were utilized: the first generation europium complexes through etheral connectivity were developed via convergent synthetic approach; the second and third generation dendrons through esteral connectivity were developed by a hyperbranch core approach containing the advantages of convergent and divergent approaches. Their chemical structures were well characterized. Preliminary results show that the dendron-functionalized carbazole units not only tune the carrier-transporting capability, but also exhibit strong light-harvesting potential, resulting in a strong intense emission from the central Eu(III) ion via sensitization.

1. Introduction

Due to the extreme narrow-width emission band, europium complexes have attracted considerable interest for the design of laser materials,[1] organic light-emitting diodes,[2–5] and fluorescent probes.[6–9] However, the luminescence efficiency is suffered from the low extinction coefficient and non-radiative deactivation of Eu(III) ion.[10–13] Up to now, little work was concerned about modifying the light harvesting of β-diketonate ligand except the pursuit of novel second ligands.[3,14–17]

Dendrimers have attracted much interest because of their unique structures and properties.[18–22] The globular shape of dendrimers provides a large surface area that can be decorated with chromophores,[23–25] resulting in a large absorption cross section and efficient capture of photons. Another interesting properties of dendritic molecules are the site-isolation effect of dendrons to create a micro-environment to prevent the intermolecular interaction and avoid self-quenching effect.[11]

On the basis of our earlier work,[26,27] here we report a series of novel carbazole-terminated dendritic β-diketonates and their corresponding Eu(III) complexes developed through diverse approaches (see Scheme 1). The dendritic β-diketonates consist of dibenzoylmethane cores, Fréchet-type poly (aryl ether) dendrons, and carbazole (CZ) peripheral functional groups. Once they were chelated with Eu(III) ions, such dendritic ligands were expected to create encapsulating cages, thus reducing the self-quenching process and environmental influence. In virtue of high extinction coefficient of the terminated carbazole units, more photons could be efficiently harvested and then transferred to the focal ion.

Due to the acceptable yield of Claisen condensation, convergent synthetic approach was utilized to achieve the first generation europium complexes. The second and third generation dendrons were synthesized via hypercore synthetic approach[28] to circumvent the weak reactivity of senior generation esters. These complexes ranging from the first generation to the third generation are denoted by $[x\text{Caz-G}_y]_3$-Eu, where [*x*Caz] refers to the number of carbazole units incorporated into dendron and [G_y] denotes the generation number (y=1, 2, 3).

2. Results and discussion

2.1. β-Diketonate as core

In order to obtain different generations of dendritic β-diketonates, it is necessary to synthesize the branched

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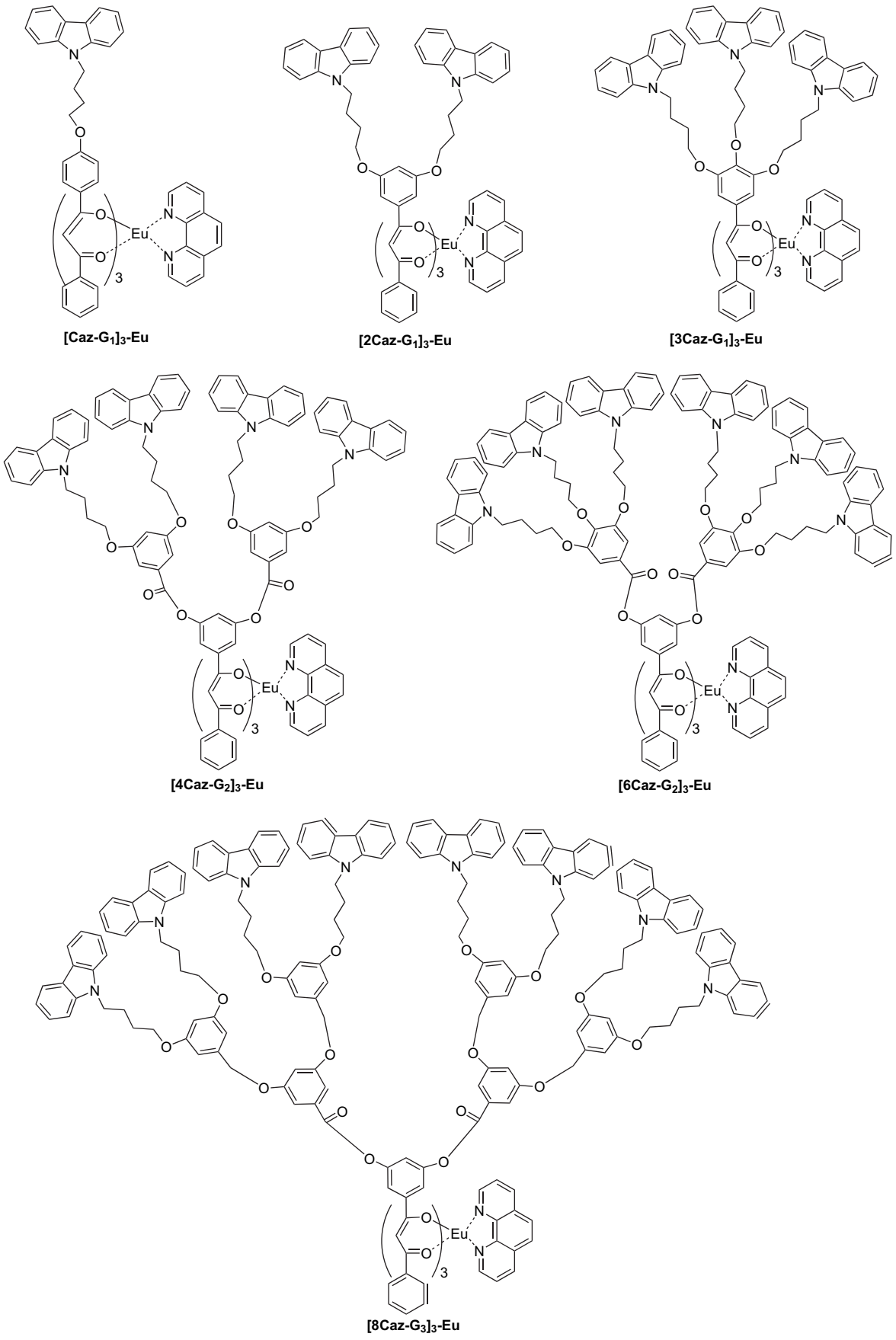
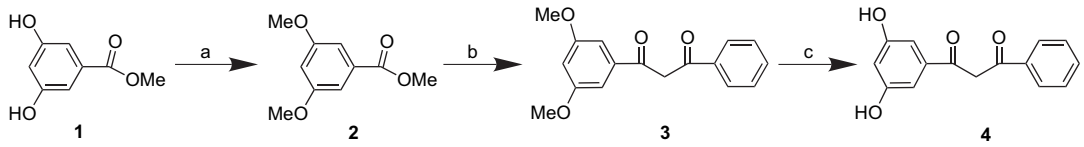


Scheme 1. Chemical structures of six target dendritic europium complexes.



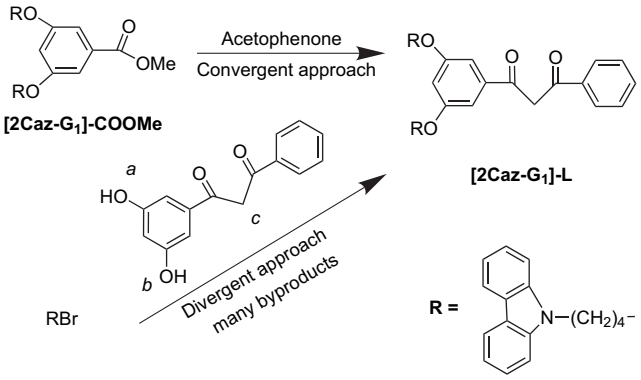
Scheme 2. Divergent synthesis of focal β-diketonate **4**. Reagents and conditions: (a) CH_3I, acetone, K_2CO_3, reflux, 48 h, 92%; (b) NaH, acetophenone, THF, 60 °C, 72 h, 22%; (c) BBr_3, CH_2Cl_2, −78 °C for 0.5 h, then rt, overnight, 84%.

dibenzoylmethane derivatives. Phenolate **4** (Scheme 2) is an ideal intermediate with two phenolic hydroxyl groups on which convergent carboxylate dendrons can be incorporated to form a higher generation derivatives. As shown in Scheme 2, phenolate **4** was synthesized via three steps with good overall yield, that was, O-alkylation of methyl 3,5-dihydroxybenzoate (**1**) with methyl iodide, Claisen condensation between methyl 3,5-dimethoxybenzoate (**2**) and acetophenone, and finally the methyl deprotection by BBr_3.

2.2. The first generation dendron via convergent approach

There are two basic approaches to construct dendrimers: the divergent approach and convergent approach.[29] The synthesis of first generation (**8**) was very straightforward without any group protection and deprotection via convergent approach with acceptable yield. In Scheme 3, the alkylation of phenol group of ethyl 4-hydroxybenzoate (**5**) with 9-(4-bromobutyl)-9*H*-carbazole underwent smoothly in the presence of anhydrous potassium carbonate and 18-crown-6 in acetone under reflux. Then, the resulting intermediate **6** reacted with acetophenone via Claisen condensation in the presence of sodium hydride to give **7**, followed by chelating with europium ion.

In the synthesis of first generation dendrons (**11a** and **11b**), Claisen condensation became the crucial step and was accompanied with many side reactions, such as aldol condensation and hydrolysis. Once the steric hindrance of the ester (**10a** and **10b**) was increased, the resulting yield of Claisen condensation dropped dramatically. Therefore, we attempted to synthesize the first generation derivatives in two paths to optimize the reaction procedures. Taking the synthesis of [2Caz-G_1]-L as an example shown in Scheme 4, the first approach was convergent one in which [2Caz-G_1]-COOMe was coupled with acetophenone in an acceptable yield. In contrast, treatment of 9-(4-bromobutyl)-9*H*-carbazole with phenolate **4** via the divergent way yielded several byproducts owning to three active sites (a, b, and c indicated in Scheme 4), which was a time-consuming work to determine and purify the target ligands.

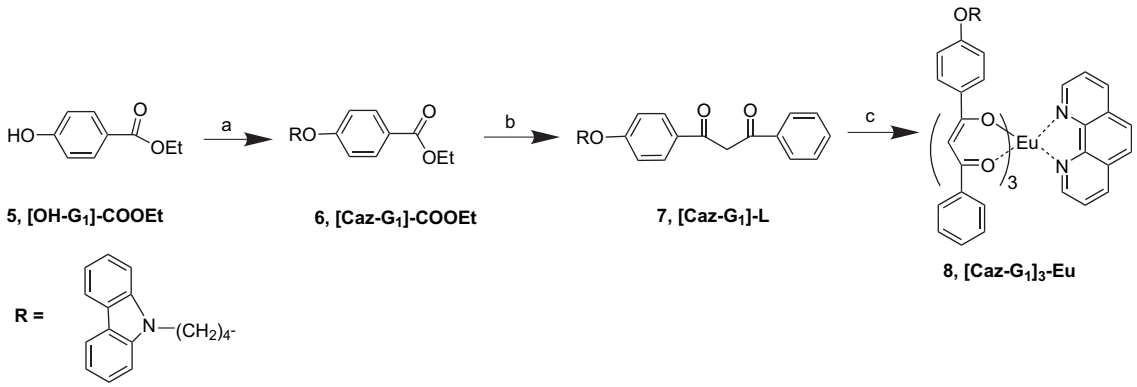


Scheme 4. Procedure for designing the first generation dendritic ligand [2Caz-G_1]-L.

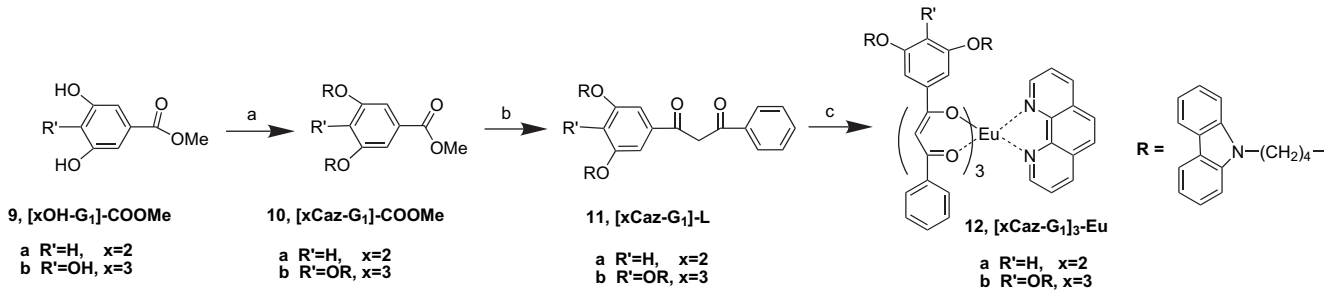
Dendritic europium complexes with the first generation dendron of AB_2 and AB_3 type were synthesized in convergent approach, which were identical to that of AB type **7** (Scheme 5). Furthermore, since β-diketonates **11a** and **11b** have green-yellowish fluorescence, the reaction can be monitored easily by TLC, and the target β-diketonates were separated smoothly by column chromatography.

2.3. The second and third generation dendrons via hypercore approach

Although the convergent approach seemed to be very helpful during the syntheses of the first generation dendrons, many unexpected problems took place during the preparation of



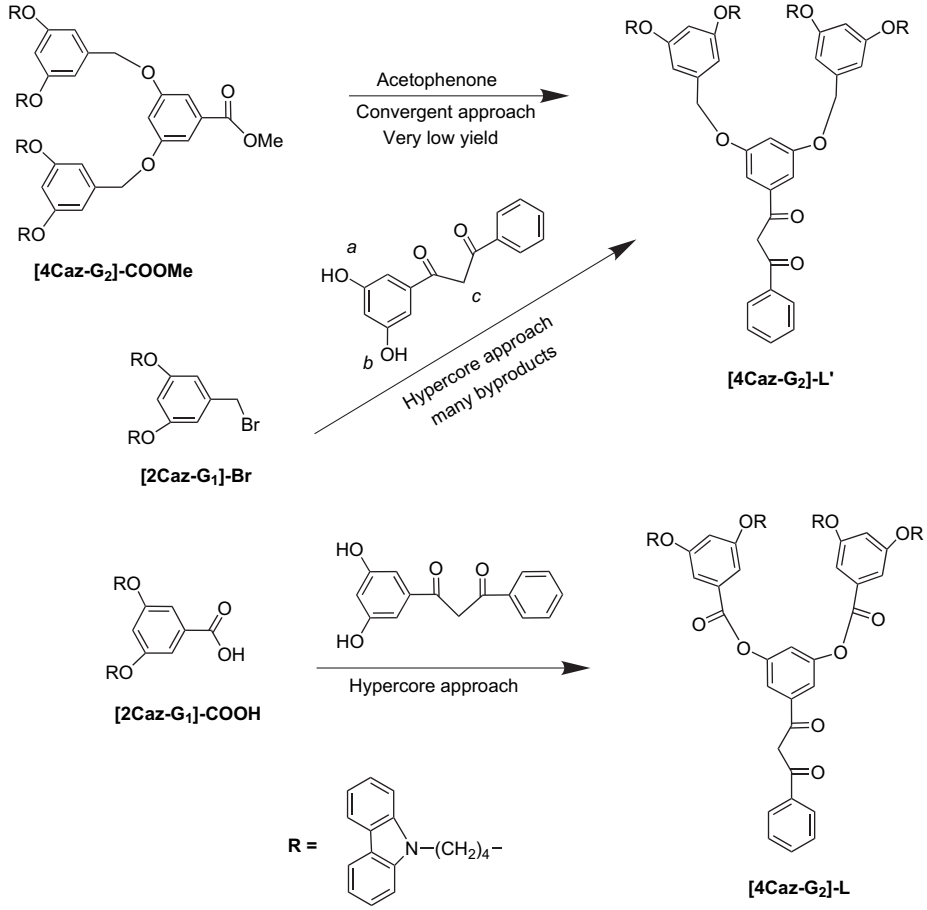
Scheme 3. Convergent synthesis of the first generation complex [Caz-G_1]$_3$-Eu. Reagents and conditions: (a) 9-(4-bromobutyl)-9*H*-carbazole, acetone, K_2CO_3, reflux, 56 h, 66%; (b) NaH, acetophenone, THF, 60 °C, 90 h, 16%; (c) $EuCl_3 \cdot 6H_2O$, phenanthroline·H_2O, NaOH, THF, ethanol, 60 °C, 4 h, 76%.



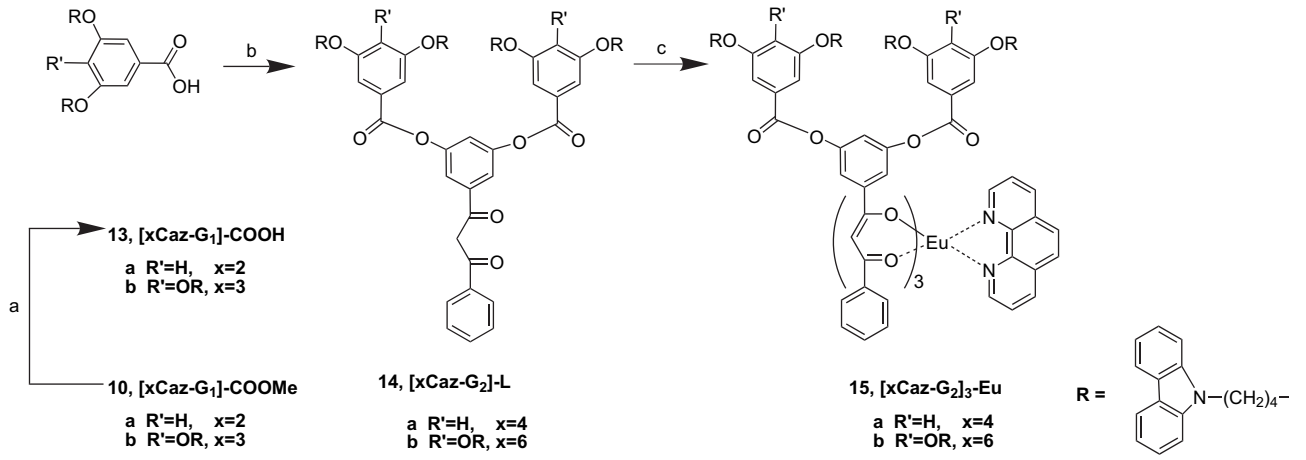
Scheme 5. Convergent synthesis of the first generation dendrimer. Reagents and conditions: (a) 9-(4-bromobutyl)-9*H*-carbazole, acetone, K_2CO_3, reflux, 56 h, 70–90%; (b) NaH, acetophenone, THF, 60 °C, 90 h, 19–30%; (c) $EuCl_3 \cdot 6H_2O$, phenanthroline·H_2O, NaOH, THF, ethanol, 60 °C, 4 h, 45–75%.

the second generation dendrons. When the generation of corresponding methyl benzoxylate [4Caz-G_2]-COOMe was increased, Claisen condensation between the ester and acetophenone became very difficult, and little corresponding ligand [4Caz-G_2]-L′ was obtained (Scheme 6).

To solve the problem, a hypercore (hyperbranch core) synthetic approach[28] containing the advantages of convergent and divergent approaches was introduced. It involved the pre-assembly of oligomeric species, which could then be linked together to give dendrimers in a short route and high yields. In our design, phenolate **4** containing two reactive phenolic hydroxyl groups at its extremity was utilized for divergent growth by attaching other preformed dendritic wedges through their single focal point reactive group. As shown in Scheme 6, we firstly attempted to use ether bond as the dendritic wedge bridge between [2Caz-G_1]-Br with **4**, but the yields were unacceptable with many byproducts, which were similar to the aforementioned O-alkylation in Scheme 4. Fortunately, the esterification could be preceded smoothly with the assistance of dicyclohexylcarbodiimide (DCC) at room temperature with a fairly good yield when esteral connectivity was chosen as the dendritic wedge. As a case shown in Scheme 7, the dendron propagation was started with the saponification of **10**. Then the dendritic wedge **13** containing focal carboxylic group was esterified with **4** to give the corresponding dendritic β-diketonate **14** with around 55% yield. Treatment of compound **13** with **4** could achieve the second generation dendron **14**, which was a rapid generation-growth approach with respect to



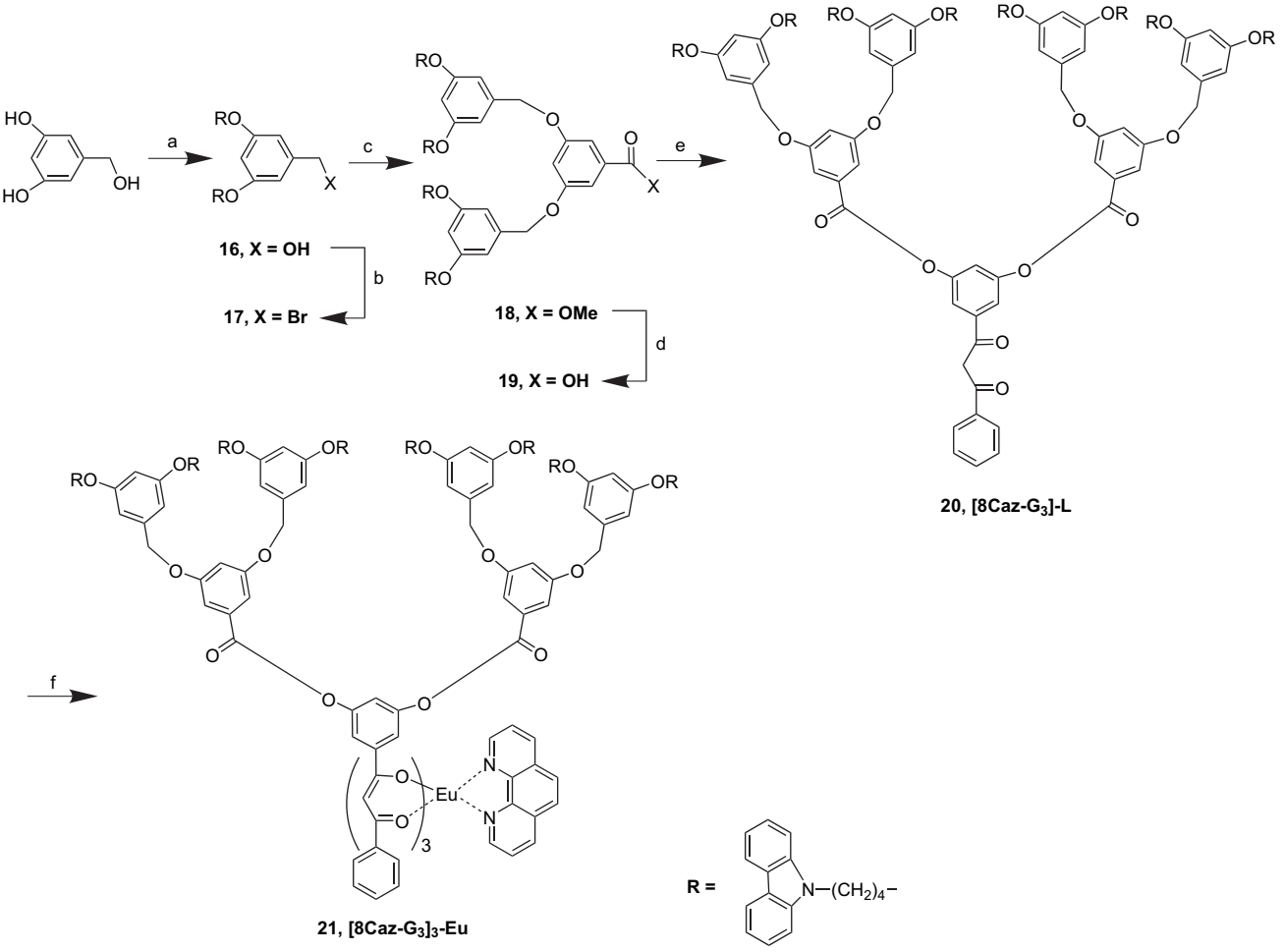
Scheme 6. Procedure for designing the second dendritic ligands.



Scheme 7. Hypercore synthesis of the second dendritic complexes. Reagents and conditions: (a) NaOH, THF, H_2O, reflux, 8 h, ~93%; (b) **4**, DCC, DPTS, CH_2Cl_2, rt, 24 h, ~55%; (c) $EuCl_3 \cdot 6H_2O$, phenanthroline·H_2O, triethylamine, THF, ethanol, 60 °C, 4 h, ~80%.

the convergent synthesis from the reaction of [4Caz-G_2]-COOMe and acetophenone.

The third generation dendrimer was also obtained via hypercore approach with multiple steps consisting O-alkylation, bromo-substitution, hydrolysis, and esterification. Two simple synthetic transformations were used for synthesizing dendrons: (1) selective alkylation of phenolic hydroxyl groups, and (2) conversion of a benzylic alcohol to a benzylic bromide to generate a reactive focal moiety (Scheme 8). Herein, O-alkylation was the repetitive steps for the synthesis of higher generation of Fréchet-type poly(aryl ether)



Scheme 8. Hypercore synthesis of the third dendritic complexes. Reagents and conditions: (a) 9-(4-bromobutyl)-9*H*-carbazole, acetone, K_2CO_3, reflux, 56 h, 83%; (b) PPh_3, CBr_4, CH_2Cl_2, rt, 5 h, 92%; (c) methyl 3,5-dihydroxyl benzoate, 18-crown-6, acetone, K_2CO_3, reflux, 56 h, 81%; (d) NaOH, THF, H_2O, reflux, 5 h, 93%; (e) **4**, DCC, DPTS, CH_2Cl_2, rt, 24 h, 17%; (f) $EuCl_3 \cdot 6H_2O$, phenanthroline·H_2O, triethylamine, THF, ethanol, 60 °C, 4 h, 87%.

dendrons. The O-alkylation of 9-(4-bromobutyl)-9*H*-carbazole and 3,5-dihydroxyl benzyl alcohol afforded the first generation of benzyl alcohol **16**, which was facile to be purified via recrystallization. Then the corresponding dendritic benzyl bromide **17** was prepared by the combinatorial bromination reagents of PPh_3 and CBr_4, followed by phenolic alkylation of methyl 3,5-dihydroxyl benzoate to yield the second generation of methyl benzoate **18**. Treatment of product **19** with **4** in the presence of DCC/DPTS gave the third generation of desirable dendritic ligand **20**. The third generation dendrimer of Eu(III) complex **21** was finally obtained by the treatment of the corresponding ligand with $EuCl_3 \cdot 6H_2O$ in the mixing solvents of ethanol and THF kept in oil bath at 60 °C. The coordination was easily observed by instantaneous color change of the reaction mixture upon addition of Eu(III) salt.

2.4. Structure characterization

All dendrimers were recrystallized from acetone for several times. Further purification of the obtained Eu(III) coordinated dendrimers by silica gel column chromatography failed, only yielding the corresponding starting dendrons. This might be the result of ligand exchange reaction between the coordinated dendrimers and surface silanol groups (Si–OH) of silica gel, resulting in the adsorption of Eu(III) onto the silica gel.[11] Dendritic β-diketonates and their europium complexes were well characterized. In order to assign functional groups in detail, the IR spectra of [2Caz-G_1]-L and [2Caz-G_1]$_3$-Eu are illustrated in Figure 1. The ligand [2Caz-G_1]-L (Fig. 1a) has a broad vibration band at 3300–3600 cm^{-1} assigned to hydroxyl group of enol form of β-diketonates, which almost disappeared after the coordination with Eu(III) (complex [2Caz-G_1]$_3$-Eu, Fig. 1b). A single peak at 3051 cm^{-1} and a doublet at about 2855 and 2930 cm^{-1} are corresponding to the C–H stretching vibration of aryl ring and alkyl chain. The C=O and C=C stretching vibrations of ligand in the complex [2Caz-G_1]$_3$-Eu (Fig. 1b) appear at about 1551 and 1592 cm^{-1}, respectively, whereas these vibrations in ligand [2Caz-G_1]-L (Fig. 1a) are at 1600 cm^{-1}. The ring vibration of the second ligand, 1,10-phenanthroline, usually observed at 1610 cm^{-1}, is difficult to be distinguished due to the overlapping with the vibration peak of double bond. Another peak at 1340 cm^{-1} is attributed to the stretching vibration of C–N bond.[5,30] Two spectra both contain two sharp and strong absorption peaks at 726 and 747 cm^{-1}, associated with the characteristic absorption of the carbazole moieties. All demonstrate a successful coordination between [2Caz-G_1]-L and Eu(III) ion.

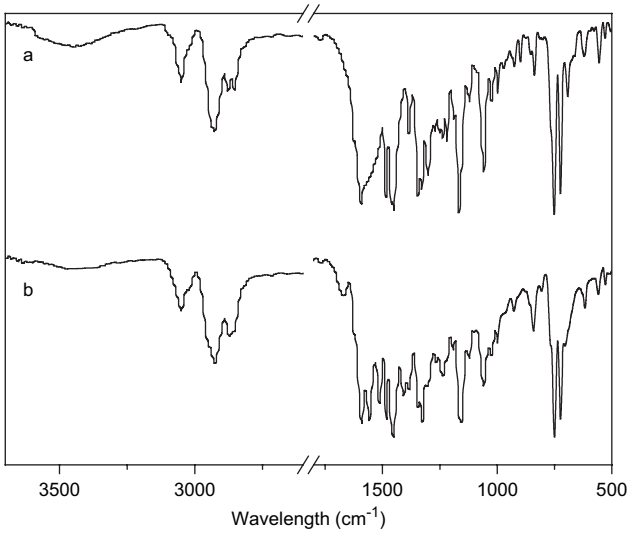


Figure 1. IR spectra of [2Caz-G_1]-L (a) and [2Caz-G_1]$_3$-Eu (b).

To date, most europium complexes haven't been characterized by ^{1}H NMR spectrum due to the Eu(III) paramagnetism.[3,17,31,32] Although NMR signals for the second- and third-generation Eu(III) dendrimers are too complicated and broad, ^{1}H NMR spectra of dendritic ligands and their first generation europium complexes provide useful information and solid evidences for Eu(III) coordination. As a result of the ring current effect between phenanthroline and β-diketonate, the proton chemical shifts of ligands in the complexes have a dramatic change with respect to that of corresponding free ligands. For Eu(III) complexes, protons of phenanthroline are deshielded while protons linking to β-diketonates are shielded. As a typical example, the ^{1}H NMR spectra of [2Caz-G_1]-L and [2Caz-G_1]$_3$-Eu are shown in Figure 2. Owing to the ligand of [2Caz-G_1]-L existing in enol form,[13,33] each of the protons (H_h, H_i, and H_j) in [2Caz-G_1]-L is characteristic of single peak. Comparing with the assignment of the proton signals of [2Caz-G_1]-COOMe, the chemical shift of H_g in [2Caz-G_1]-L is shifted downfield to 7.97 ppm due to the adjacent electron-withdrawing effect of carbonyl group, indicating that the form of enol-1 is more favorable as shown in Scheme 9. Thermodynamically, the conjugation state of enol-1 is more stable than that of enol-2. Upon coordination with Eu(III) ion, ^{1}H NMR spectrum of [2Caz-G_1]$_3$-Eu becomes complicated. Due to [2Caz-G_1]-L existing in anionic form, the protons of the focal β-diketonate in the complex are shielded so that dramatic changes are observed for the chemical shifts of H_e, H_f, H_g, H_h, H_i, and H_j, which are shifted from 7.55, 7.49, 7.97, 6.75, 7.04, and 6.53 ppm to approximately 7.53, 7.26, 7.40, 6.00, 6.61, and 5.67 ppm, respectively. In contrast, due to the deshield effect, H_a, H_b, H_c, and H_d signals of phenanthroline ligand appear at the downfield of 10.71, 7.97, 10.42, and 8.53 ppm.

With the dendron-generation growth, ^{1}H NMR signals become more complicated and difficult to discern structures. To assess more clearly the identity of chemical structures, further characterization has been performed by MALDI-TOF mass spectroscopy. This technique provides macromolecular mass determinations for intact molecular ions of nonvolatile species, and is particularly useful for structural characterization of high molecular weight dendrimers. MALDI-TOF results of the ligand dendrons and their corresponding europium complex dendrimers are shown in Section 4. Some signals observed are either potassium or sodium adducts of the molecular ions, depending on the matrix used. The MALDI-TOF spectra of the second- and third-generation β-diketonate ligands are shown in Figure 3. The MALDI-TOF spectra of the europium dendrimers for the first- and second-generation derivatives are presented in Figure 4. These peaks occurred at *m*/*z* values consistently within 0.2% of the theoretical values. Thus, the MALDI-TOF data provided additional support for the identity of these dendrimers.

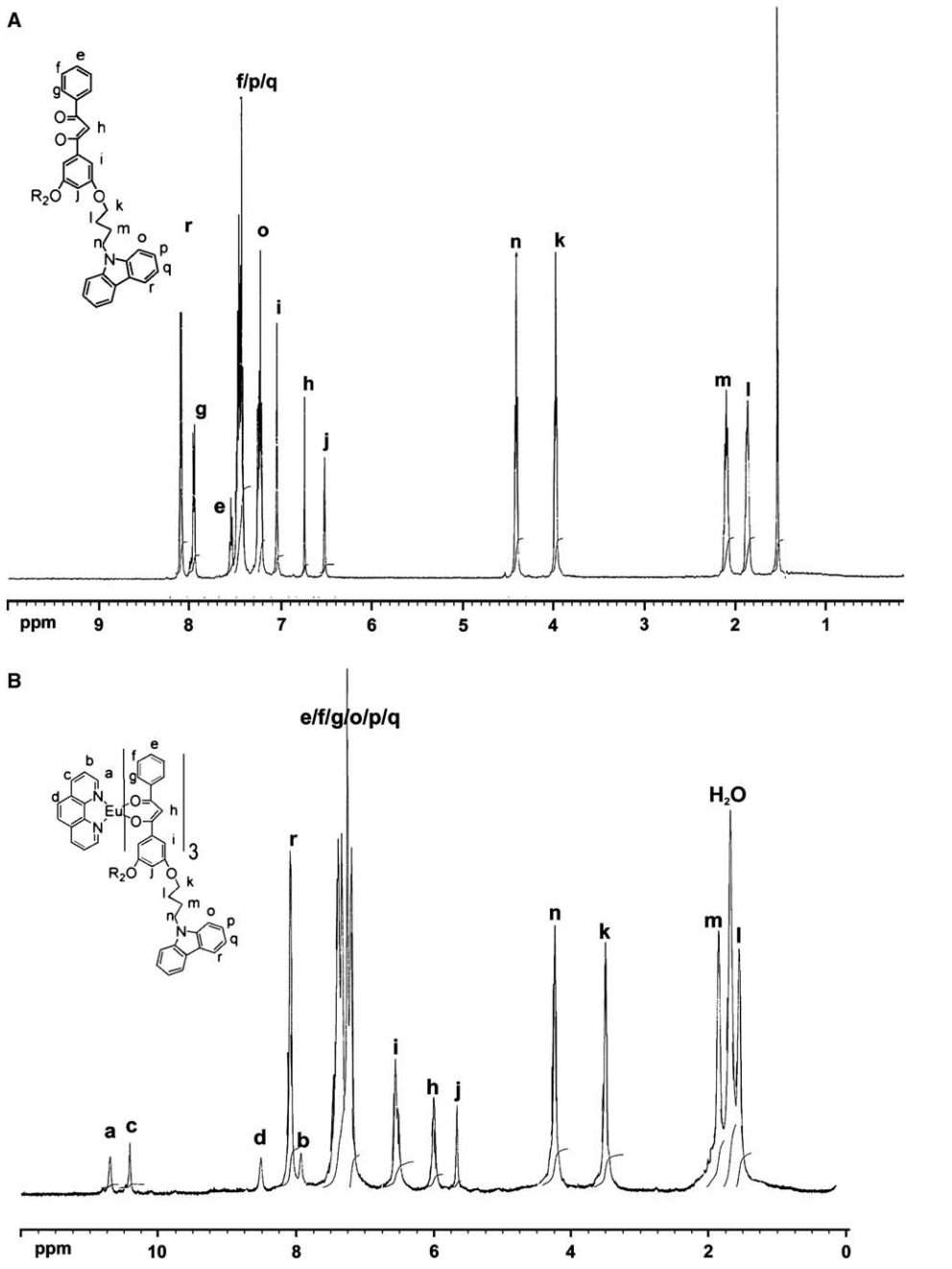
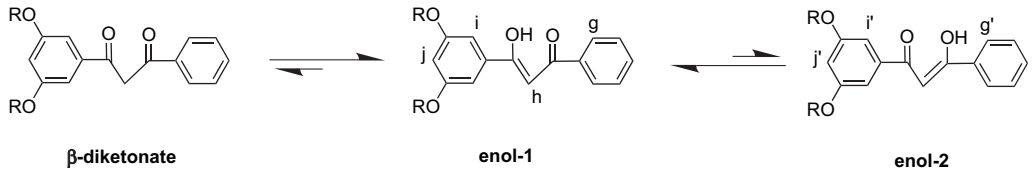


Figure 2. ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of (A) [2Caz-G_1]$_3$-L and (B) [2Caz-G_1]$_3$-Eu.



Scheme 9. Tautomers of [2Caz-G_1]-L. Note: NMR spectra suggest that the form of enol-1 is more favorable.

2.5. Light-harvesting effect of the peripheral carbazole units in europium complexes

Generally, because the central Eu(III) ion shows little or no absorption in the visible light region, the luminescence of lanthanide complexes is critically dependent on the energy transfer from 'light-harvesting antenna' ligand (donor) to central lanthanide ion. Excitation mechanism of the central metal ion also differs widely from that of organic fluorescent compounds. For Eu(III) complexes with π-conjugated ligands such as β-diketonate, Eu(III) ions are excited via intramolecular energy transfer from the triplet excited states of

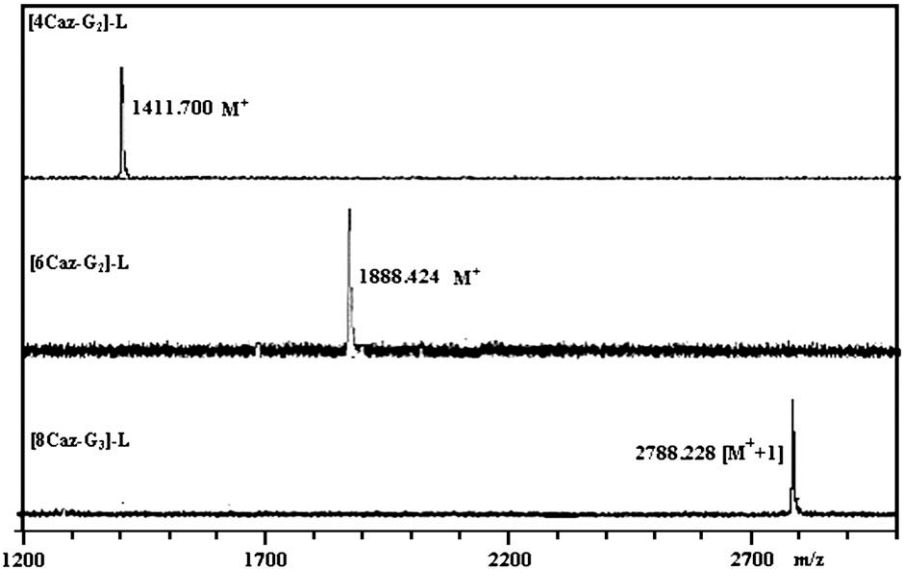


Figure 3. MALDI-TOF mass spectra of [4Caz-G_2]-L, [6Caz-G_2]-L, and [8Caz-G_3]-L.

the ligands.[2] To improve the energy transfer to Eu(III) ions, the triplet states of ligands must be closely matched to or slightly above the emitting resonance levels of center Eu(III) ions.

When excited at the absorption wavelength of the grafted carbazole units, all dendritic europium complexes in CH_2Cl_2 or solid film emit a characteristic sharp luminescence peak at 615 nm with four shoulders ascribed to

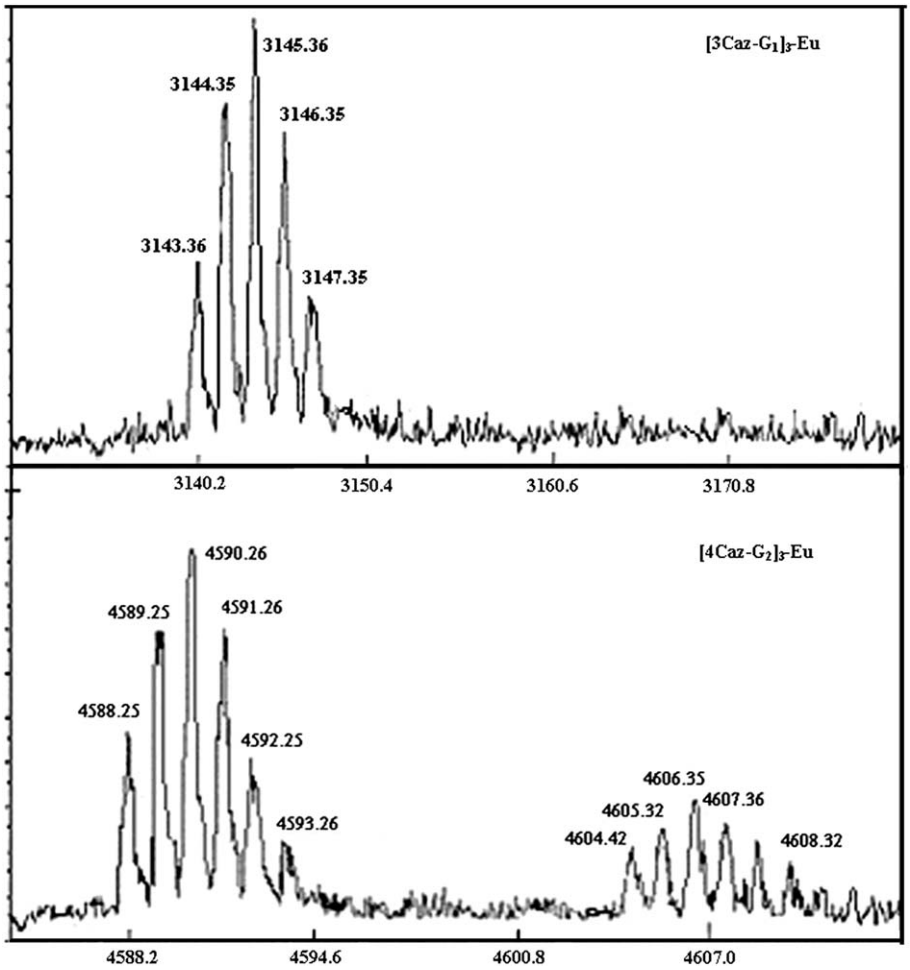


Figure 4. MALDI-TOF mass spectra of [3Caz-G_1]$_3$-Eu ([M^+]), top) and [4Caz-G_2]$_3$-Eu ([M^++Na], [M^++K], bottom).

transitions between 4f states of Eu(III) ion. All five peaks at 586, 591, 615, 651, and 702 nm are corresponding to Eu(III) characteristic transitions ($^5D_0 \rightarrow {}^7F_j$, j=0–4).

Notably, with respect to carbazole, the emission of peripheral donor carbazole unit in the system of the synthesized europium dendrimers is almost completely quenched under the direct excitation of 331 nm (curve c, Fig. 5). As can be seen in Figure 5 (curves a and b), the luminescence of carbazole units is overlapped with the absorption of [3Caz-G_1]$_3$-Eu to a certain extent, thus an efficient Förster-resonance energy transfer in the complex system can take place from the singlet excited state of the grafted carbazole to the singlet excited state of β-diketonate ligand, and followed by the intersystem crossing to the excited triplet state of β-diketonate, where it is finally transferred to the central Eu(III) ion. The efficient energy transfer is further confirmed by the excitation spectrum of [3Caz-G_1]$_3$-Eu (Fig. 6), indicating that the peripheral carbazole units in such complexes can exhibit efficient light-harvesting potential. Thus, it is possible to obtain a strong intense emission from the central Eu(III) when excited via sensitization from a large light-harvesting antenna. Moreover, the site isolation of dendrons can also be favorable to enhance luminance. For comparing the relative luminescence quantum yields, we normalized the spectra of the absorption peak at β-diketonate region (360 nm), and compared the relative intensity of luminescence. As a result of the carbazole light harvesting and the site isolation of dendrons, in comparison with the luminescence intensity of reference complex Eu(BPPD)$_3$Phen[26] in solid film excited at 331 nm (carbazole absorption maximum), the relative luminescence quantum yields of [Caz-G_1]$_3$-Eu, [2Caz-G_1]$_3$-Eu, and [3Caz-G_1]$_3$-Eu are 3.3, 7.9, and 4.5 folds, respectively. It should be noted that the luminescence of [3Caz-G_1]$_3$-Eu containing three carbazole units is unexpectedly weaker than that of [2Caz-G_1]$_3$-Eu containing two carbazole units, which might be attributed to the spatial hindrance of three neighboring carbazole units incorporated into one side of ligand and leading to a less effective energy transfer between carbazole and β-diketonate. The detailed studies of energy transfer, luminescence dynamics, and photo-physical properties with these dendrimers are now undergoing, and will be reported elsewhere. Notably,

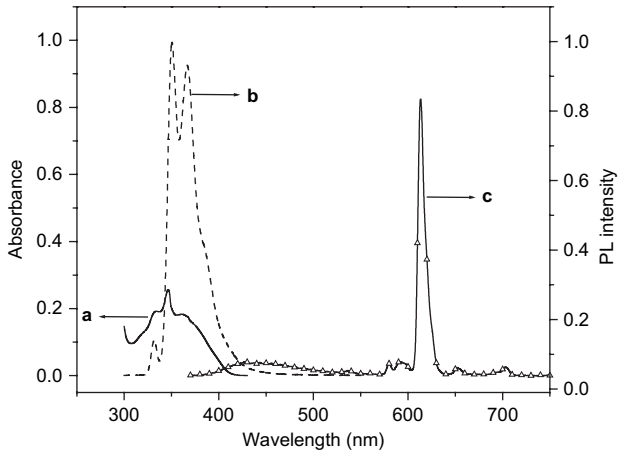


Figure 5. Absorption spectrum of [3Caz-G_1]$_3$-Eu in CH_2Cl_2 (2.0×10^{-5} mol L^{-1}, curve a), and PL spectra excited at 331 nm in CH_2Cl_2 (2.0×10^{-5} mol L^{-1}) of carbazole (curve b) and [3Caz-G_1]$_3$-Eu (curve c).

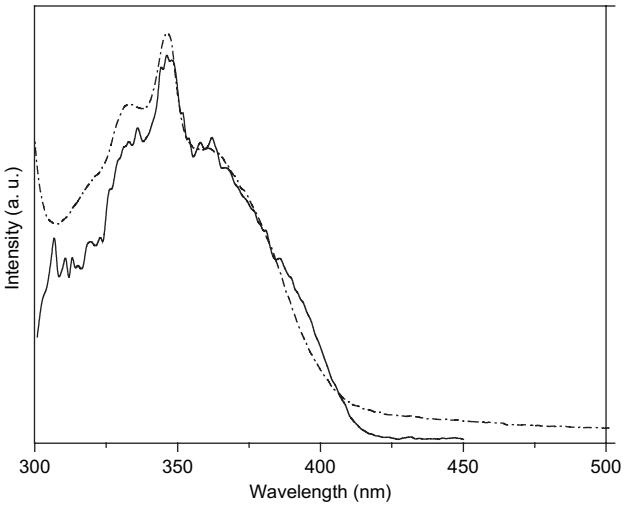


Figure 6. Absorption spectrum (solid line) and excitation spectrum (dash dot line) of [3Caz-G_1]$_3$-Eu monitored at 615 nm. The excitation spectrum is normalized at the absorption peak at β-diketonate region (360 nm). All measurements are in CH_2Cl_2 (1.2×10^{-6} mol L^{-1}).

preliminary results show that white light electroluminescence (CIE: 0.333, 0.348) using a complex [3Caz-G_1]$_3$-Eu can be achieved,[27] indicating that modifying ligands can not only tune the carrier-transporting properties of complexes, but also provide a useful clue to use electroplex or exciplex to realize a broad or even white electroluminescence.

3. Conclusions

Several dendritic β-diketonates and corresponding europium complexes were designed and synthesized based on the following consideration: (1) high light-harvesting capability and efficient energy transfer to the focal ion in virtue of high extinction coefficient of the terminated carbazole units, (2) dendron functionalization to incorporate carbazole units to realize the carrier-injection adjustment, and (3) avoiding core luminescence quenching by the means of the dendron to enhance core luminescence. Their dendritic β-diketonate ligands consist dibenzoylmethane cores, Fréchet-type poly (aryl ether) dendrons, and the grafted carbazole (CZ) peripheral functional groups. Due to the acceptable yield of Claisen condensation, convergent synthetic approach through etheral connectivity was utilized to achieve the first generation europium complexes. For the second and third generation dendrons, a hyperbranch core synthetic approach containing the advantages of convergent and divergent approaches was introduced. Preliminary results showed that the peripheral carbazole units in such complexes can not only tune the carrier-transporting capability, but also exhibit strong light-harvesting potential, thus resulting in a strong intense emission from the central Eu(III) via the sensitization.

4. Experimental

4.1. General

THF was dried from metal sodium. Sodium hydride was purchased from *J&K*, kept in a vacuum drier at room

temperature. $EuCl_3 \cdot 6H_2O$ (99.9%) and carbazole were obtained from Aldrich. Acetophenone from Aldrich was dried with $MgSO_4$ and redistilled prior to usage. All other starting materials and reagents were of analytic purity without treatment. Melting points were measured on X4 Micro-melting point apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker AM-500 spectrometer. TMS was used as internal reference for all the compounds. MS were recorded on FAB or MALDI-TOF mass spectroscopy. IR spectra of thin films on KBr plates were recorded on a Nexus 470 FTIR spectrometer. Elemental analyses were obtained on a Perkin–Elmer 240C elemental analyzer.

4.1.1. Synthesis of methyl 3,5-dimethoxybenzoate ([2Me-G_1]-COOMe, 2). To a 100 mL flask were added methyl iodide (9.0 g, 63.4 mmol), methyl 3,5-dihydroxybenzoate (5.0 g, 29.5 mmol), potassium carbonate (8.6 g, 62.3 mmol), and anhydrous acetone (60 mL). The mixture was heated at reflux and stirred vigorously under argon for 48 h. Then it was allowed to cool and evaporate to dryness under reduced pressure. The residue was washed with water. After filtration and recrystallization, pink crystals were obtained (5.3 g), yield 92%. Mp: 55–57 °C. ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 3.82 (s, 6H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 6.54 (s, 1H, Ph–H), 7.14 (s, 2H, Ph–H). MS (FAB): *m/z* 197.1 [M^++1], 196.1 [M^+] (100%).

4.1.2. 1-(3,5-Dimethoxyphenyl)-3-phenylpropane-1,3-dione ([2Me-G_1]-L, 3). To a dry flask containing a solution of acetophenone (1.2 g, 10.2 mmol) and **2** (2.0 g, 10.2 mmol) in THF (60 mL) was added quickly 60% sodium hydride (0.4 g, 10.0 mmol). The reaction mixture was heated under argon at 60 °C for 72 h. The solution was then acidified with dilute HCl and extracted with CH_2Cl_2. After removal of solvent, the pure product was obtained (0.63 g) as a yellow solid over a silica gel column (CH_2Cl_2/CCl_4, 1:5/v:v), yield 21.7%. Mp: 62–63 °C. ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 3.83 (s, 6H, $-OCH_3$), 6.65 (t, 1H, *J*=2.0 Hz, Ph–H), 6.80 (s, 1H, =CH), 7.12 (d, 2H, *J*=2.0 Hz, Ph–H), 7.48 (t, 2H, *J*=7.4, 7.3 Hz, Ph–H), 7.55 (t, 1H, *J*=7.3 Hz, Ph–H), 7.97 (d, 2H, *J*=7.4 Hz, Ph–H); MS (FAB): *m/z* 286.1 [M^++2], 285.1 [M^++1], 284.1 [M^+] (100%).

4.1.3. 1-(3,5-Dihydroxyphenyl)-3-phenylpropane-1,3-dione ([2OH-G_1]-L, 4). To a solution of **2** (1.6 g, 5.63 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C was slowly syringed BBr_3 (1.6 mL), and after stirring at −78 °C for 0.5 h, the solution was allowed to warm to room temperature and left overnight. A dilute solution of NaOH (1 mol L^{-1}, 5 mL) was then added at 0 °C. The mixture was extracted with ethyl acetate to remove the unreacted reagent and the remaining aqueous solution was neutralized with hydrochloric acid (2 mol L^{-1}). Large amount of yellow solid was precipitated and filtered. The crude product was purified by chromatography on silica gel (CH_2Cl_2/acetone, 10:1/v:v). The total yield was 84% (1.3 g). ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 6.60 (s, 1H, Ph–H), 6.78 (s, 1H, =CH), 7.10 (s, 2H, Ph–H), 7.48 (t, 2H, *J*=7.4, 7.8 Hz, Ph–H), 7.55 (t, 1H, *J*=7.3 Hz, Ph–H), 7.97 (d, 2H, *J*=7.1 Hz, Ph–H). MS (FAB): *m/z* 257 [M^++1], 256 [M^+] (100%), 255 [M^+-1], 239 [M^+-OH].

4.1.4. Ethyl 4-[4-(9*H*-carbazol-9-yl)butoxy]benzoate ([Caz-G_1]-COOEt, 6). A mixture of 9-(4-bromobutyl)-9*H*-carbazole (2.00 g, 6.62 mmol), **5** (1.43 g, 8.61 mmol), potassium carbonate (1.30 g, 9.42 mmol), and 18-crown-6 (0.13 g, 4.72 mmol) in anhydrous acetone (60 mL) was heated at reflux and stirred vigorously under nitrogen for 56 h. The mixture was allowed to cool and evaporated to dryness under reduced pressure. The residue was washed with water and a large amount of precipitate appeared followed by filtration. After recrystallization, a white needle-like crystal was obtained (1.71 g), yield 66%. Mp: 80–82 °C. ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 1.37 (t, 3H, *J*=6.2 Hz, $-CH_3$), 1.87–1.91 (m, 2H, $-CH_2$), 2.10–2.14 (m, 2H, $-CH_2$), 3.98 (t, 2H, *J*=6.2 Hz, $-OCH_2$), 4.32 (t, 2H, *J*=6.0 Hz, $-OCH_2$), 4.40 (t, 2H, *J*=7.0 Hz, $-NCH_2$), 6.84 (d, 2H, *J*=8.8 Hz, Ph–H), 7.23 (t, 2H, *J*=7.0, 8.2 Hz, Ph–H), 7.43 (d, 2H, *J*=8.1 Hz, Ph–H), 7.47 (t, 2H, *J*=7.2, 8.3 Hz, Ph–H), 7.96 (d, 2H, *J*=8.8 Hz, Ph–H), 8.10 (d, 2H, *J*=7.6 Hz, Ph–H). MS (FAB): *m/z* 389.2 [M^++2], 388.2 [M^++1], 387.2 [M^+] (100%). Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.28; H, 6.32; N, 3.75.

4.1.5. 1-[4-[4-(9*H*-Carbazol-9-yl)butoxy]phenyl]-3-phenylpropane-1,3-dione ([Caz-G_1]-L, 7). To a dry flask containing a solution of acetophenone (0.37 g, 3.08 mmol) and **6** (1.20 g, 3.09 mmol) in THF (60 mL) was added quickly 60% sodium hydride (0.30 g, 7.5 mmol). The reaction mixture was heated under argon at 60 °C for 90 h. The solution was then acidified with dilute HCl and extracted with CH_2Cl_2. After solvent removal, the solid residue was separated over a silica gel column (CH_2Cl_2/CCl_4, 1:2/v:v) and a light yellow solid was obtained (0.23 g), yield 16.2%. Mp: 159–162 °C. ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 1.89–1.92 (m, 2H, CH_2), 2.11–2.15 (m, 2H, CH_2), 4.01 (t, 2H, *J*=6.1 Hz, $-OCH_2$), 4.43 (t, 2H, *J*=7.0 Hz, $-NCH_2$), 6.79 (s, 1H, =CH), 6.91 (d, 2H, *J*=5.2 Hz, Ph–H), 7.25 (d, 2H, *J*=6.5 Hz, Ph–H), 7.42 (d, 2H, *J*=8.1 Hz, Ph–H), 7.44–7.50 (m, 4H, Ph–H), 7.53 (t, 1H, *J*=1.4, 1.2 Hz, Ph–H), 7.93–7.97 (m, 4H, Ph–H), 8.11 (d, 2H, *J*=7.6 Hz, Ph–H). MS (FAB): *m/z* 463 [M^++2], 462 [M^++1], 461 [M^+]. Anal. Calcd for $C_{31}H_{27}NO_3$: C, 80.67; H, 5.90; N, 3.03. Found: C, 80.38; H, 5.69; N, 3.13.

4.1.6. Tris[1-[4-[4-(9*H*-carbazol-9-yl)butoxy]phenyl]-3-phenylpropane-1,3-dione](1,10-phenanthroline) europium (III) ([Caz-G_1]$_3$-Eu, 8). To a solution of **7** (120 mg, 0.26 mmol) and 1,10-phenanthroline monohydrate (18 mg, 90.9 μmol) in THF (10 mL), aqueous NaOH (1 mol L^{-1}, 0.2 mL) was syringed dropwise, followed by aqueous $EuCl_3$ hexahydrate (31.7 mg, 87.4 μmol). Under the protection of argon, the mixture was stirred at 60 °C for 4 h and then cooled. The product was collected by filtration and washed with deionized water twice before crystallization with acetone and vacuum drying (112 mg), yield 75.5%. Mp: 110–113 °C. ^1H NMR (500 MHz, $CDCl_3$): δ ppm, 1.72 (br, 6H, CH_2), 2.17 (br, 6H, CH_2), 3.77 (br, 6H, $-OCH_2$), 4.35 (br, 6H, $-NCH_2$), 5.59 (br, 6H, =CH, Ph–H), 5.95 (br, 6H, Ph–H), 6.20 (br, 6H, Ph–H), 6.61–6.78 (m, 12H, Ph–H), 7.26–7.46 (m, 15H, Ph–H), 8.11 (br, 9H, Ph–H), 8.97 (br, 2H, phenanthroline–H), 9.90 (br, 2H, phenanthroline–H), 10.64 (br, 2H, phenanthroline–H), 11.01 (br, 2H, phenanthroline–H). MS (FAB): *m/z* 1752.6 [M^++K], 1736.7 [M^++Na], 1714 [M^+] (100%). Anal. Calcd for

$C_{105}H_{86}EuN_5O_9$: C, 73.59; H, 5.06; N, 4.09. Found: C, 73.21; H, 4.69; N, 4.38.

4.1.7. Methyl 3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]benzoate ([2Caz-G$_1$]-COOMe, 10a). A mixture of 9-(4-bromobutyl)-9*H*-carbazole (3.00 g, 9.93 mmol), **9a** (0.78 g, 4.64 mmol), potassium carbonate (1.82 g, 13.1 mmol), and 18-crown-6 (0.13 g, 4.7 mmol) in anhydrous acetone (100 mL) was heated at reflux and stirred vigorously under nitrogen for 56 h. The mixture was allowed to cool and evaporated to dryness under reduced pressure. The residue was washed with water and a large amount of precipitate appeared followed by filtration. After recrystallization with ethanol, a white powder was obtained (2.5 g), yield 88.3%. Mp: 124–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.82–1.87 (m, 4H, CH_2), 2.05–2.11 (m, 4H, CH_2), 3.88 (s, 3H, –OCH_3), 3.94 (t, 4H, J=6.1 Hz, –OCH_2), 4.39 (t, 4H, J=7.0 Hz, –NCH_2), 6.54 (s, 1H, Ph–H), 7.14 (s, 2H, Ph–H), 7.23 (t, 4H, J=7.2, 7.4 Hz, Ph–H), 7.42 (d, 4H, J=8.1 Hz, Ph–H), 7.46 (t, 4H, J=7.4 Hz, 7.8 Hz, Ph–H), 8.10 (d, 4H, J=7.8 Hz, Ph–H). MALDI-TOF MS (FAB): *m/z* 612.5 [M$^+$+2], 611.5 [M$^+$+1], 610.5 [M$^+$] (100%). Anal. Calcd for $C_{40}H_{38}N_2O_4$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.40; H, 6.00; N, 4.82.

4.1.8. 1-[3,5-Bis[4-(9*H*-carbazol-9-yl)butoxy]phenyl]-3-phenylpropane-1,3-dione ([2Caz-G$_1$]-L, 11a). To a dry flask containing a solution of acetophenone (0.39 g, 3.3 mmol) and **10a** (2.00 g, 3.28 mmol) in THF (80 mL) was added quickly 60% sodium hydride (0.20 g, 5.0 mmol). The reaction mixture was heated under argon at 60 °C for 90 h. The solution was then acidified with dilute HCl and extracted with CH_2Cl_2. After solvent removal, the solid residue was separated over a silica gel column (CH_2Cl_2/CCl_4, 1:5/v:v) and a light yellow solid was obtained (0.43 g), yield 19.0%. Mp: 57–59 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.88–1.91 (m, 4H, CH_2), 2.06–2.10 (m, 4H, CH_2), 3.98 (t, 4H, J=6.1 Hz, –OCH_2), 4.41 (t, 4H, J=7.0 Hz, –NCH_2), 6.53 (s, 1H, Ph–H), 6.75 (s, 1H, =CH), 7.04 (s, 2H, Ph–H), 7.25 (t, 4H, J=7.2 Hz, Ph–H), 7.42–7.51 (m, 10H, Ph–H), 7.55 (t, 1H, J=7.2, 7.0 Hz, Ph–H), 7.97 (d, 2H, J=7.6 Hz, Ph–H), 8.11 (d, 4H, J=7.7 Hz, Ph–H). ^{13}C NMR ($CDCl_3$): δ ppm, 26.5, 27.6, 43.4, 68.5, 94.0, 106.0, 106.4, 109.3, 119.6, 121.1, 123.6, 126.4, 127.8, 129.3, 133.1, 136.0, 138.4, 141.1, 160.9, 185.9, 186.6. MS (FAB): *m/z* 700 [M$^+$+2], 699 [M$^+$+1], 698 [M$^+$]. Anal. Calcd for $C_{47}H_{42}N_2O_4$: C, 80.78; H, 6.06; N, 4.01. Found: C, 80.50; H, 5.85; N, 4.23.

4.1.9. Tris[1-[3,5-bis[4-(9*H*-carbazol-9-yl)butyloxy]-phenyl]-3-phenylpropane-1,3-dione](1,10-phenanthroline) europium (III) ([2Caz-G$_1$]$_3$-Eu, 12a). To a solution of **11a** (0.10 g, 0.14 mmol) and 1,10-phenanthroline monohydrate (11.3 mg, 57.2 μmol) in THF (10 mL), aqueous NaOH (1 mol L^{-1}, 0.20 mL) was syringed dropwise followed by aqueous $EuCl_3$ hexahydrate (17.5 mg, 48.2 μmol). Under the protection of argon, the mixture was stirred at 60 °C for 4 h and then cooled. The product was collected by filtration and washed with deionized water twice before crystallization with acetone and vacuum drying (57 mg), yield 49%. Mp: 89–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.56 (br, 12H, CH_2), 1.86 (br, 12H, CH_2), 3.51 (br, 12H, CH_2), 4.24 (br, 12H, CH_2), 5.67 (br, 3H, =CH), 6.00 (br, 6H, Ph–H), 6.61–6.78 (m, 9H, Ph–H), 7.26–7.45 (m, 12H, Ph–H), 7.40–7.76 (m, 30H, Ph–H), 7.97 (br, 2H, phenanthroline–H), 8.10 (br, 15H, Ph–H), 8.53 (br, 2H, phenanthroline–H), 10.42 (br, 2H, phenanthroline–H), 10.71 (br, 2H, phenanthroline–H); MALDI-TOF MS *m/z*: 2425 [M$^+$]. Anal. Calcd for $C_{153}H_{131}EuN_8O_{12}$: C, 75.76; H, 5.44; N, 4.62. Found: C, 75.28; H, 5.07; N, 4.85.

4.1.10. Methyl 3,4,5-tris[4-(9*H*-carbazol-9-yl)butoxy]-benzoate ([3Caz-G$_1$]-COOMe, 10b). A mixture of 9-(4-bromobutyl)-9*H*-carbazole (3.00 g, 9.93 mmol), methyl 3,4,5-trihydroxy benzoate (0.60 g, 3.31 mmol), potassium carbonate (1.51 g, 10.9 mmol), and 18-crown-6 (0.13 g, 4.7 mmol) in anhydrous acetone (60 mL) was stirred vigorously, and refluxed for 56 h under the protection of nitrogen. After cooling, solvents under reduced pressure were removed, the resulting solid was filtrated, and recrystallized from ethanol to give a white needle-like crystal (2.13 g), yield 75%. Mp: 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.55–1.60 (m, 2H, –CH_2), 1.72–1.75 (m, 4H, –CH_2), 1.92–1.98 (m, 6H, –CH_2), 3.84–3.88 (m, 5H, –OCH_3, –CH_2), 3.91 (t, 4H, J=6.1 Hz, –CH_2), 4.10 (t, 2H, J=7.1 Hz, –CH_2), 4.21 (t, 4H, J=7.0 Hz, –CH_2), 7.17 (s, 2H, Ph–H), 7.19–7.21 (m, 6H, Ph–H), 7.24 (t, 2H, J=1.3, 7.2 Hz, Ph–H), 7.29 (d, 4H, J=8.2 Hz, Ph–H), 7.36–7.42 (m, 6H, Ph–H), 8.05 (d, 2H, J=7.7 Hz, Ph–H), 8.06 (d, 4H, J=5.0 Hz, Ph–H). MALDI-TOF MS (FAB): *m/z* 847.9 [M$^+$+1], 846.9 [M$^+$]. Anal. Calcd for $C_{56}H_{53}N_3O_5$: C, 79.31; H, 6.30; N, 4.95. Found: C, 79.08; H, 6.11; N, 5.20.

4.1.11. 1-[3,4,5-Tris[4-(9*H*-carbazol-9-yl)butoxy]phenyl]-3-phenylpropane-1,3-dione ([3Caz-G$_1$]-L, 11b). To a dry flask containing a solution of acetophenone (0.21 g, 1.76 mmol) and **10b** (1.50 g, 1.76 mmol) in THF (60 mL) was added quickly 60% sodium hydride (0.10 g, 2.5 mmol). The reaction mixture was heated at 60 °C for 90 h under argon. The solution was then acidified with dilute HCl, and extracted with CH_2Cl_2. After solvent removal, the solid residue was purified via a silica gel column (CH_2Cl_2/CCl_4, 1:2/v:v), a light yellow oil was obtained (0.49 g), yield 29.7%. Mp: 71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.60–1.65 (m, 2H, –CH_2), 1.74–1.78 (m, 4H, –CH_2), 1.94–2.03 (m, 6H, –CH_2), 3.88 (t, 2H, J=6.1 Hz, –CH_2), 3.94 (t, 4H, J=7.2 Hz, –CH_2), 4.12 (t, 2H, J=6.1 Hz, –CH_2), 4.22 (t, 4H, J=7.1 Hz, –CH_2), 6.65 (s, 1H, =CH), 7.08 (s, 2H, Ph–H), 7.17–7.21 (m, 6H, Ph–H), 7.25–7.28 (m, 2H, Ph–H), 7.30 (d, 4H, J=8.2 Hz, Ph–H), 7.37–7.41 (m, 6H, Ph–H), 7.47 (t, 2H, J=7.8, 7.5 Hz, Ph–H), 7.54 (t, 1H, J=7.8, 7.7 Hz), 7.92 (d, 2H, J=7.2 Hz), 8.07 (t, 6H, J=7.6, 6.8 Hz, Ph–H). MS (FAB): *m/z* 974.4 [M$^+$+K], 958.4 [M$^+$+Na]. Anal. Calcd for $C_{63}H_{57}N_3O_5$: C, 80.83; H, 6.14; N, 4.49. Found: C, 80.58; H, 5.87; N, 4.70.

4.1.12. Tris[1-[3,4,5-tris[4-(9*H*-carbazol-9-yl)butoxy]-phenyl]-3-phenyl-propane-1,3-dione](1,10-phenanthroline) europium (III) ([3Caz-G$_1$]$_3$-Eu, 12b). To a solution of **11b** (226 mg, 240 μmol) and 1,10-phenanthroline monohydrate (16 mg, 81 μmol) in THF (10 mL), aqueous NaOH (mol L^{-1}, 0.38 mL) was syringed dropwise, followed by aqueous $EuCl_3 \cdot 6H_2O$ (29.4 mg, 80 mmol). The mixture was stirred at 60 °C for 4 h under the protection of nitrogen. After cooling, the product was filtrated, washed with deionized water, and recrystallized from acetone to give light

yellow powder (180 mg), yield 71.6%. Mp: 84–87 °C. MALDI-TOF MS *m/z*: 3143.6 [M^+]. Anal. Calcd for $C_{201}H_{176}EuN_{11}O_{15}$: C, 76.94; H, 5.65; N, 4.91. Found: C, 76.58; H, 5.28; N, 5.16.

4.1.13. 3,5-Bis[4-(9*H*-carbazol-9-yl)butoxy]benzoic acid ([2Caz-G$_1$]-COOH, 13a). To a solution of **12a** (3.0 g, 4.92 mmol) in THF (60 mL) was added NaOH (0.4 g, 10 mmol) aqueous solution (20 mL) and the solution was heated to reflux with stirring for 8 h. When the solution was cooled to room temperature, it was poured into dilute HCl solution. The precipitate was filtrated and dried to get a white solid (2.7 g) in 93% yield. Mp: 179–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.72–1.76 (m, 4H, CH_2), 2.10–2.15 (m, 4H, CH_2), 3.90 (t, 4H, J=6.0 Hz, –OCH_2), 4.40 (t, 4H, J=7.0 Hz, –NCH_2), 6.54 (s, 1H, Ph–H), 7.17 (s, 2H, Ph–H), 7.22 (t, 4H, J=6.9 Hz, Ph–H), 7.38–7.50 (m, 8H, Ph–H), 8.10 (d, 4H, J=7.4 Hz, Ph–H). MALDI-TOF MS (FAB): *m/z* 597.2 [M^++1], 596.2 [M^+] (100%), 595.2 [M^+−1]. Anal. Calcd for $C_{39}H_{36}N_2O_4$: C, 78.50; H, 6.08; N, 4.69. Found: C, 78.23; H, 5.80; N, 4.83.

4.1.14. 1-[3,5-Bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy] benzoyloxy]phenyl]-3-phenylpropane-1,3-dione ([4Caz-G2]-L, 14a). To a solution of **13a** (0.28 g, 0.47 mmol), **4** (55 mg, 0.21 mmol) in dry CH_2Cl_2 (50 mL) was added 4-(dimethylamino)-pyridinium *p*-toluenesulphonate (DPTS) (25 mg, 0.08 mmol). The mixture was stirred at 25 °C for 15 min under nitrogen atmosphere. Dicyclohexylcarbodiimide (DCC) (0.10 g, 0.48 mmol) was then added and stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. Pure product was obtained (0.16 g) via column chromatograph eluting with initially CH_2Cl_2 and then a mixture of CH_2Cl_2/acetone (4:1). The yield was 55%. Mp: 62–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.89 (m, 8H, CH_2), 2.11–2.15 (m, 8H, CH_2), 3.99 (t, 8H, J=6.1 Hz, –OCH_2), 4.41 (t, 8H, J=7.1 Hz, –NCH_2), 6.61 (s, 2H, Ph–H), 6.84 (s, 1H, =CH), 7.21 (t, 8H, J=7.4, 7.2 Hz, Ph–H), 7.26 (d, 4H, J=5.7 Hz, Ph–H), 7.34 (s, 1H, Ph–H), 7.41 (t, 8H, J=8.0, 7.8 Hz, Ph–H), 7.44 (d, 8H, J=7.5 Hz), 7.46 (t, 2H, J=8.0, 8.2 Hz, Ph–H), 7.56 (t, 1H, J=7.4, 7.9 Hz, Ph–H), 7.74 (d, 2H, J=2.0 Hz, Ph–H), 7.98 (d, 2H, J=7.8 Hz, Ph–H), 8.10 (d, 8H, J=7.7 Hz, Ph–H). MALDI-TOF MS *m/z*: 1412.7 [M^+], 1411.7 [M^+−1]. Anal. Calcd for $C_{93}H_{80}N_4O_{10}$: C, 79.01; H, 5.70; N, 3.96. Found: C, 78.75; H, 5.56; N, 4.23.

4.1.15. Tris[1-[3,5-bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]-benzoyloxy]phenyl]-3-phenylpropane-1,3-dione](1,10-phenanthroline) europium (III) ([4Caz-G$_2$]$_3$-Eu, 15a). To a solution of **14a** (0.15 g, 106 μmol) and 1,10-phenanthroline monohydrate (7.1 mg, 35.8 μmol) in THF (10 mL), triethylamine (0.10 mL) was syringed dropwise, followed by a solution of $EuCl_3$ hexahydrate (12.9 mg, 35.3 μmol) in ethanol (4 mL). After injection of argon repeatedly, the mixture was stirred at 60 °C for 4 h and then cooled. The product was collected by filtration and washed with deionized water twice before crystallization with acetone and vacuum drying (0.12 g), yield 74.4%. Mp: 60–62 °C. MALDI-TOF MS *m/z*: 4590.3 [M^++Na], 4606.4 [M^++K]. Anal. Calcd for $C_{291}H_{245}EuN_{14}O_{30}$: C, 76.48; H, 5.40; N, 4.29. Found: C, 76.09; H, 5.13; N, 4.50.

4.1.16. 3,4,5-Tris[4-(9*H*-carbazol-9-yl)butoxy]benzoic acid ([3Caz-G$_1$]-COOH, 13b). Similar to **13a** to get white solid in 95% yield. Mp: 85–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.58–1.62 (m, 2H, CH_2), 1.76–1.81 (m, 4H, CH_2), 1.97–2.02 (m, 6H, CH_2), 3.88 (t, 2H, J=6.0 Hz, –OCH_2), 3.92 (t, 4H, J=6.0 Hz, –OCH_2), 4.13 (t, 2H, J=7.2 Hz, –NCH_2), 4.22 (t, 4H, J=7.0, 7.0 Hz, –NCH_2), 7.20–7.22 (m, 8H, Ph–H), 7.23–7.25 (m, 2H, Ph–H), 7.29 (d, 4H, J=8.1 Hz, Ph–H), 7.39–7.44 (m, 6H, Ph–H), 8.08–8.12 (m, 6H, Ph–H). MALDI-TOF MS (FAB): *m/z* 835.4 [M^++1], 834.4 [M^+], 833.4 [M^+−1]. Anal. Calcd for $C_{55}H_{51}N_3O_5$: C, 79.21; H, 6.16; N, 5.04. Found: C, 79.04; H, 6.01; N, 5.20.

4.1.17. 1-[3,5-Bis[3,4,5-tri[4-(9*H*-carbazol-9-yl)butoxy]-benzoyloxy]phenyl]-3-phenylpropane-1,3-dione ([6Caz-G$_2$]-L, 14b). Similar to **14a** to get light yellow solid in 60% yield. Mp: 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.55–1.61 (m, 4H, CH_2), 1.69–1.74 (m, 8H, CH_2), 1.89–1.98 (m, 12H, CH_2), 3.88 (t, 4H, J=6.1, 6.2 Hz, CH_2), 3.91 (t, 8H, J=6.1 Hz, CH_2), 4.10 (t, 4H, J=7.0 Hz, CH_2), 4.21 (t, 8H, J=7.1 Hz, CH_2), 6.80 (s, 1H, =CH), 7.16–7.21 (m, 13H, Ph–H), 7.25–7.31 (m, 10H, Ph–H), 7.30 (d, 8H, J=6.6 Hz, Ph–H), 7.37 (t, 12H, J=7.1, 7.4 Hz, Ph–H), 7.46 (t, 2H, J=7.5, 8.1 Hz, Ph–H), 7.62 (t, 1H, J=7.4, 7.7 Hz, Ph–H), 7.85 (d, 2H, J=7.7 Hz, Ph–H), 8.04 (d, 8H, J=5.3 Hz, Ph–H), 8.07 (d, 4H, J=7.8 Hz, Ph–H). ^{13}C NMR ($CDCl_3$): δ ppm, 25.6, 25.7, 27.0, 27.8, 42.5, 68.8, 72.9, 93.4, 108.6, 118.0, 118.8, 119.7, 120.4, 122.8, 123.4, 125.6, 127.3, 128.7, 132.8, 135.1, 137.9, 140.3, 142.8, 151.6, 152.6, 164.2, 183.4, 186.2. MALDI-TOF MS *m/z*: 1890.4 [M^++2], 1889.4 [M^++1], 1888.4 [M^+], 1887.4 [M^+−1]. Anal. Calcd for $C_{125}H_{110}N_6O_{12}$: C, 79.51; H, 5.87; N, 4.45. Found: C, 79.33; H, 5.68; N, 4.68.

4.1.18. Tris[1-[3,5-bis[3,4,5-tri[4-(9*H*-carbazol-9-yl)butoxy]-benzoyloxy]phenyl]-3-phenylpropane-1,3-dione](1,10-phenanthroline) europium (III) ([6Caz-G$_2$]$_3$-Eu, 15b). Similar to **15a** to get light yellow solid in 85% yield. Mp: 83–85 °C. MALDI-TOF MS *m/z*: 5989.2 [M^+−4]. Anal. Calcd for $C_{387}H_{335}EuN_{20}O_{36}$: C, 77.55; H, 5.63; N, 4.67. Found: C, 77.16; H, 5.36; N, 4.96.

4.1.19. 3,5-Bis[4-(9*H*-carbazol-9-yl)butoxy]benzyl alcohol ([2Caz-G$_1$]-OH, 16). A mixture of 9-(4-bromobutyl)-9*H*-carbazole (4.40 g, 14.5 mmol), 3,5-dihydroxybenzyl alcohol (1.00 g, 7.1 mmol), potassium carbonate (3.40 g, 60 mmol), and 18-crown-6 (0.38 g, 1.42 mmol) in anhydrous acetone (50 mL) was heated at reflux and stirred vigorously under nitrogen for 56 h. The mixture was allowed to cool and evaporated to dryness under reduced pressure. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 (40 mL×3). The combined extracts were dried with anhydrous $MgSO_4$ and evaporated. The product was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give **16** as pale yellow crystalline solid (3.5 g, yield 83%). Mp: 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.83–1.88 (m, 4H, CH_2), 2.14–2.19 (m, 4H, CH_2), 3.85 (t, 4H, J=6.1 Hz, –OCH_2), 4.37 (t, 4H, J=7.1 Hz, –NCH_2), 4.71 (s, 2H, –CH_2OH), 6.25 (s, 1H, Ph–H), 6.54 (s, 2H, Ph–H), 7.21 (t, 4H, J=6.8, 1.0 Hz, Ph–H), 7.42 (d, 4H, J=8.0 Hz, Ph–H), 7.48 (t, 4H, J=7.9, 1.0 Hz, Ph–H), 8.23 (d, 4H,

J=7.8 Hz, Ph–H). MS (FAB): m/z 597.7 [M^++1], 596.6 [M^+] (100%).

4.1.20. 3,5-Bis[4-(9*H*-carbazol-9-yl)butoxy]benzyl bromide ([2Caz-G$_1$]-Br, 17). A mixture of compound **16** (1.00 g, 1.68 mmol), CBr_4 (0.57 g, 1.72 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C. Triphenylphosphine (0.48 g, 1.72 mmol) was then slowly added and stirred for 5 h. After removal of CH_2Cl_2, the product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give pale yellow powder (1.02 g), yield 92.1%. Mp: 163–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.83–1.87 (m, 4H, CH_2), 2.15–2.19 (m, 4H, CH_2), 3.85 (t, 4H, J=6.1 Hz, –OCH_2), 4.22 (s, 2H, –CH_2Br), 4.37 (t, 4H, J=7.1 Hz, –NCH_2), 6.30 (s, 1H, Ph–H), 6.45 (s, 2H, Ph–H), 7.22 (t, 4H, J=7.3 Hz, Ph–H), 7.4 (d, 4H, J=8.0 Hz, Ph–H), 7.48 (t, 4H, J=7.8 Hz, 1.0 Hz, Ph–H), 8.21 (d, 4H, J=7.8 Hz, Ph–H). MS (FAB): m/z 659.6 [M+2]$^+$, 657.6 [M^+] (100%), 579.8 [M^+−Br]. Anal. Calcd for $C_{39}H_{37}BrN_2O_2$: C, 72.55; H, 5.78; N, 4.34. Found: C, 72.32; H, 5.62; N, 4.53.

4.1.21. Methyl 3,5-bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]benzyloxy]benzoate ([4Caz-G$_2$]-COOMe, 18). A mixture of **17** (3.00 g, 4.64 mmol), methyl 3,5-dihydroxybenzoate (0.40 g, 2.38 mmol), potassium carbonate (1.00 g, 7.25 mmol), and 18-crown-6 (0.13 g, 4.7 mmol) in anhydrous acetone (100 mL) was heated at reflux and stirred vigorously under nitrogen for 56 h. The mixture was allowed to cool and evaporated to dryness under reduced pressure. The residue was washed with water and a large amount of precipitate appeared followed by filtration. After column chromatography on silica gel using CH_2Cl_2 as eluent, a white powder was obtained (2.5 g), yield 81%. Mp: 75–77 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.89–1.93 (m, 8H, CH_2), 2.05–2.09 (m, 8H, CH_2), 3.88 (s, 3H, –OCH_3), 3.99 (t, 8H, J=6.0 Hz, –OCH_2), 4.37 (t, 8H, J=7.1 Hz, –NCH_2), 4.92 (s, 4H, –OCH_2Br), 6.25 (s, 2H, Ph–H), 6.40 (s, 5H, Ph–H), 6.51 (s, 2H, Ph–H), 7.23 (t, 8H, J=7.8, 1.0 Hz, Ph–H), 7.42 (d, 8H, J=8.1 Hz, Ph–H), 7.46 (t, 8H, J=7.9, 1.0 Hz, Ph–H), 8.20 (d, 8H, J=7.8 Hz, Ph–H). Anal. Calcd for $C_{86}H_{80}N_4O_8$: C, 79.60; H, 6.21; N, 4.32. Found: C, 79.42; H, 6.02; N, 4.25.

4.1.22. 3,5-Bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]benzyloxy]benzoic acid ([4Caz-G$_2$]-COOH, 19). To a solution of **18** (1.27 g, 0.985 mmol) in THF (30 mL) was once added sodium hydroxide aqueous solution (0.20 g, 10 mL). The solution was heated to reflux for 5 h prior to concentration. The residue was washed with water and filtered. The crude product was column chromatographed eluting with initially dichloromethane and then with chloroform/ethanol (25:1) to give **19**, and it was further purified by recrystallization from ethanol as a white solid (1.10 g) in 93% yield. Mp: 94–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.80–1.84 (m, 8H, CH_2), 2.06–2.11 (m, 8H, CH_2), 3.90 (t, 8H, J=6.0 Hz, –OCH_2), 4.40 (t, 8H, J=7.0 Hz, –NCH_2), 4.92 (s, 4H, –OCH_2), 6.32 (s, 2H, Ph–H), 6.50 (s, 4H, Ph–H), 6.75 (s, 1H, Ph–H), 7.20 (t, 8H, J=7.1 Hz, Ph–H), 7.25 (s, 2H, Ph–H), 7.30–7.50 (m, 16H, Ph–H), 8.12 (d, 8H, J=7.6 Hz, Ph–H). MALDI-TOF MS m/z: 1282.8 [M^+]. Anal. Calcd for $C_{85}H_{78}N_4O_8$: C, 79.54; H, 6.13; N, 4.36. Found: C, 79.30; H, 5.95; N, 4.53.

4.1.23. 1-[3,5-Bis[3,5-bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]benzyloxy]benzoyloxy]phenyl]-3-phenyl propane-1,3-dione ([8Caz-G$_3$]-L, 20). To a solution of **19** (0.60 g, 0.47 mmol), **4** (55 mg, 0.22 mmol) in dry dichloromethane (50 mL) was added 4-(dimethylamino)-pyridinium p-toluenesulphonate (DPTS) (50 mg, 0.17 mmol). The contents were stirred at 25 °C for 15 min under nitrogen atmosphere. Dicyclohexylcarbodiimide (DCC) (0.20 g, 0.97 mmol) was then added and stirring continued at room temperature for 24 h, during this time a precipitate of dicyclohexyl urea appeared. The reaction mixture filtered and the filtrate evaporated to dryness under reduced pressure, pure product (0.15 g) was obtained via column chromatograph eluting with initially CH_2Cl_2 and then a mixture of CH_2Cl_2/acetone (4:1), yield 17%. Mp: 68–70 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm, 1.89–1.95 (m, 16H, CH_2), 2.05–2.13 (m, 16H, CH_2), 3.99 (t, 16H, J=6.2 Hz, –OCH_2), 4.37 (t, 16H, J=7.2 Hz, –NCH_2), 4.98 (s, 8H, –OCH_2), 5.30 (s, 1H, Ph–H), 6.32 (s, 4H, Ph–H), 6.51 (s, 8H, Ph–H), 6.73 (s, 1H, Ph–H), 6.78 (s, 1H, Ph–H), 6.83 (s, 1H, ═CH), 7.19 (t, 16H, J=7.3 Hz, Ph–H), 7.38–7.48 (m, 40H, Ph–H), 7.54 (t×d, 1H, J=7.8 Hz, 1.2 Hz, Ph–H), 7.95 (d, 2H, J=7.6 Hz, Ph–H), 8.07 (d, 16H, J=7.8 Hz, Ph–H). MALDI-TOF MS m/z: 2788.2 [M^++1]. Anal. Calcd for $C_{185}H_{164}N_8O_{18}$: C, 79.72; H, 5.93; N, 4.02. Found: C, 79.32; H, 5.75; N, 4.35.

4.1.24. Tris[1-[3,5-bis[3,5-bis[3,5-bis[4-(9*H*-carbazol-9-yl)butoxy]benzyloxy]benzoyloxy]phenyl]-3-phenylpropane-1,3-dione](1,10-phenanthroline) europium (III) ([8Caz-G$_3$]$_3$-Eu, 21). Similar to **15** in yield 87.4%. Mp: 81–82 °C. MALDI-TOF MS m/z: 8722.2 [M^++Na]. Anal. Calcd for $C_{567}H_{497}EuN_{26}O_{54}$: C, 78.36; H, 5.76; N, 4.19. Found: C, 77.95; H, 5.44; N, 4.31.

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Direct aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with ketones by use of the combination of amines and acids

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Abstract—Trifluoroacetaldehyde ethyl hemiacetal reacts with unmodified ketones in the presence of 30–50 each mol % of amines and acids at ambient temperature, affording the corresponding β-hydroxy-β-trifluoromethylated ketones in good yields with good to excellent diastereoselectivities.

1. Introduction

Despite significant progress in the area of efficient synthesis of trifluoromethylated molecules using trifluoroacetaldehyde (CF_3CHO), the method for the generation of CF_3CHO from its hemiacetal or hydrate is still dependent on the early protocol, which includes a serious indispensable condition such as use of an excess amount of concentrated sulfuric acid under high reaction temperature.[1] Therefore, an environmentally-friendly, practical, and efficient method for the in situ generation of CF_3CHO attended by its simultaneous stereoselective carbon–carbon bond formation reaction is really required. Recently, we have found that a stoichiometric amount of enamines or imines react well with CF_3CHO ethyl hemiacetal via the regio- and/or stereoselective carbon–carbon bond formation reaction under mild conditions without any additives, producing β-hydroxy-β-trifluoromethylated ketones in good to excellent yields.[3] This reaction can serve as a new expedient method for the general, practical, and regio- and/or stereoselective synthesis of β-hydroxy-β-trifluoromethylated ketones. However, in this method a couple of steps for the preparation of enamines and imines as well as for the hydrolysis of the intermediates producing β-hydroxy-β-trifluoromethylated ketones are absolutely necessary. For the further development of a new atom-economical method for the synthesis of β-trifluoromethylated aldol adducts, we describe herein the direct aldol reaction of CF_3CHO ethyl hemiacetal with unmodified ketones by the use of the combination of a small amount (30–50 mol %) of amine and acid,[3–6] affording the good yields of β-hydroxy-β-trifluoromethyl ketones with good to excellent *syn*-diastereoselectivities. Importantly, this method could achieve a reduction of the steps for in situ generation of CF_3CHO and successive carbon–carbon bond formation reactions. That is, a single manipulation may include multi steps in the reaction, such as (1) the formation of enamine or imine, (2) the enamine- or imine-assisted in situ generation of CF_3CHO, (3) the successive carbon–carbon bond formation reaction of CF_3CHO, and (4) the hydrolysis of the intermediates, producing β-hydroxy-β-trifluoromethylated ketones as well as reproduction of amine and acid.

2. Results and discussion

CF_3CHO ethyl hemiacetal **1a** reacted smoothly with acetone **2a** in the presence of 50 each mol % of piperidine and acetic acid at room temperature for 24 h to produce the β-hydroxy-β-trifluoromethylated ketone **3a** in 60% yield, together with a trace amount of 1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-heptanone **4** (Table 1, entry 3). The direct aldol reactions of CF_3CHO ethyl hemiacetal **1a** with acetone **2a** under the various reaction conditions are summarized in Table 1.

The use of only piperidine gave no product **3a** with a trace amount of bis-adduct **4** at various temperatures (entries 1 and 2). Other organic acids, such as trifluoroacetic acid and *p*-toluenesulfonic acid were not effective to give a trace amount of or no product (entries 4 and 5). Among the solid acids examined, such as silica gel (Wakogel C200),[5] Montmorillonite K10, $H_4SiW_{12}O_{40}$, and Nafion R-50 (entries 6–9), Wakogel C200 was most effective for the direct aldol reaction with acetone to provide the aldol product **3a** in 58% yield, along with a 10% yield of **4** (entry 6). Out of a variety of amines screened in both cases of acetic acid and Wakogel C200, cyclic secondary amines, such as morpholine and

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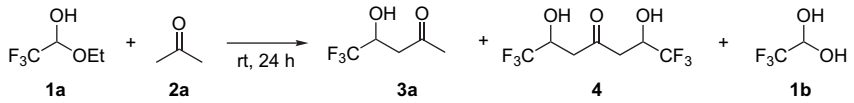
Table 1. In situ generation of trifluoroacetaldehyde from its hemiacetal **1a** and successive direct aldol reaction with acetone using the combination of amines and acids under the various conditions[a]



1a **2a** **3a** **4** **1b**

Entry	Amine	Acid	Solvent	Yield (%)[b]
1	Piperidine (50 mol %)	None	Acetone	**3a** (0), **4** (10), **1b** (22), **1a** (16)
2[c]	Piperidine (50 mol %)	None	Acetone	**3a** (0), **4** (6), **1b** (17), **1a** (13)
3	Piperidine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (60), **4** (5), **1b** (0), **1a** (0)
4	Piperidine (50 mol %)	CF_3CO_2H (50 mol %)	Acetone	**3a** (1), **4** (0), **1b** (32), **1a** (14)
5	Piperidine (50 mol %)	*p*-TsOH·H_2O (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (45), **1a** (11)
6	Piperidine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (58), **4** (10), **1b** (0), **1a** (0)
7	Piperidine (50 mol %)	Montmorillonite K 10 (120 mg)	Acetone	**3a** (32), **4** (22), **1b** (0), **1a** (0)
8	Piperidine (50 mol %)	$H_4SiW_{12}O_{40}$ (120 mg)	Acetone	**3a** (9), **4** (18), **1b** (18), **1a** (9)
9	Piperidine (50 mol %)	Nafion R-50 (120 mg)	Acetone	**3a** (0), **4** (8), **1b** (16), **1a** (19)
10	*n*-$PrNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (65), **4** (3), **1b** (0), **1a** (0)
11	*c*-$HexNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (65), **4** (1), **1b** (0), **1a** (0)
12	*t*-$BuNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (17), **4** (11), **1b** (19), **1a** (22)
13	Morpholine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (61), **4** (1), **1b** (0), **1a** (2)
14	1-Methylpiperazine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (53), **4** (7), **1b** (0), **1a** (0)
15[d]	Et_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (30), **4** (18), **1b** (0), **1a** (0)
16	*i*-Pr_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (1), **4** (1), **1b** (49), **1a** (22)
17	Ph_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (21), **1a** (57)
18	Et_3N (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (56), **1a** (24)
19	*n*-$PrNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (53), **4** (3), **1b** (0), **1a** (0)
20	*c*-$HexNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (50), **4** (14), **1b** (0), **1a** (0)
21	*t*-$BuNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (3), **4** (13), **1b** (23), **1a** (5)
22	Morpholine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (52), **4** (0), **1b** (0), **1a** (0)
23	1-Methylpiperazine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (67), **4** (0), **1b** (0), **1a** (0)
24	Et_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (28), **4** (27), **1b** (0), **1a** (0)
25	*i*-Pr_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (28), **1a** (24)
26	Ph_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (39), **1a** (8)
27	Et_3N (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (26), **1a** (9)
28	Piperidine (30 mol %)	CH_3CO_2H (30 mol %)	Acetone	**3a** (53), **4** (21), **1b** (0), **1a** (0)
29	*n*-$PrNH_2$ (30 mol %)	CH_3CO_2H (30 mol %)	Acetone	**3a** (62), **4** (3), **1b** (0), **1a** (0)
30	Piperidine (30 mol %)	Silica gel (72 mg)	Acetone	**3a** (38), **4** (21), **1b** (0), **1a** (0)
31	*n*-$PrNH_2$ (30 mol %)	Silica gel (72 mg)	Acetone	**3a** (16), **4** (14), **1b** (6), **1a** (17)
32	Piperidine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone–DMSO	**3a** (23), **4** (34), **1b** (0), **1a** (0)
33	*n*-$PrNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone–DMSO	**3a** (18), **4** (23), **1b** (0), **1a** (0)
34	Piperidine (50 mol %)	Silica gel (120 mg)	Acetone–DMSO	**3a** (0), **4** (2), **1b** (19), **1a** (8)
35	*n*-$PrNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone–DMSO	**3a** (14), **4** (23), **1b** (4), **1a** (2)

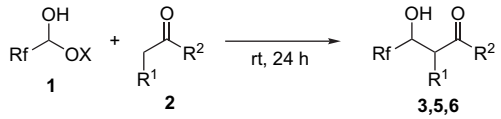
[a] All the reaction was carried out with trifluoroacetaldehyde ethyl hemiacetal **1a** (1 mmol) with amine **2** and organic acid or solid acid in dry acetone (10 ml) or in the mixed solvent of DMSO (8 ml) and dry acetone (2 ml).
[b] Yields were measured by ^{19}F NMR.
[c] Carried out at reflux.
[d] Many unidentified by-products were formed.

1-methylpiperazine (entries 13, 14, 22, and 23) as well as primary amines bearing *n*-propyl or *c*-hexyl group were suitable for the reaction to give acceptable yields of the aldol product **3a** (entries 10, 11, 19, and 20). The use of diethylamine as an acyclic secondary amine resulted in the increase of the formation of bis-adduct **4**, together with **3a** in 28–30% yields (entries 15 and 24).

The reaction with *tert*-butylamine (entries 12 and 21) or diisopropylamine (entries 16 and 25) having the bulky group produced only trace amount of the aldol product. Diphenylamine also was not effective for the reaction to afford no product, probably due to its low nucleophilicity (entries 17 and 26). The use of triethylamine also gave no product (entries 18 and 27). These results may suggest that (1) the reaction proceeds via enamine or imine, which is produced from the corresponding ketone in the presence of the acid and the corresponding secondary or primary amine, and (2) the resulting enamine or imine reacts with CF_3CHO ethyl hemiacetal **1a** via not only in situ generation of CF_3CHO but also carbon–carbon bond formation reaction to give the corresponding β-hydroxy-β-trifluoromethyl ketones.[2] The reaction of hemiacetal **1a** with acetone **2a** in the presence of 30 each mol % of piperidine or *n*-propylamine and acetic acid afforded the corresponding aldol product **3a** in acceptable yields (53–62%) (entries 28 and 29). Reducing the amount of amines to 30 mol % and the amount of silica gel to 60% of the former amount gave rise to lowering the yield of **2a**, together with the formation of bis-adduct **4** (entries 30 and 31). Irrespective of the amines as well as the acids, the use of DMSO as a polar co-solvent resulted in decreasing the yield of **3a**, along with the increase of bis-adduct **4**. In all cases, mass balances in the yield are not good, probably due to these high volatility and self-polymerization of CF_3CHO.

The results of cyclic ketones as well as other polyfluoroalkylaldehyde hemiacetal or hydrate are summarized in Table 2.

Table 2. In situ generation of polyfluoroalkylaldehyde from its hemiacetal or hydrate and successive direct aldol reaction with ketones using the combination of amines and acids[a]



Entry	1	R_f	X	2	R^1, R^2	Method[b]	3,5,6	Yield (%)[c]	*syn*:*anti*[d]
1	**1a**	CF_3	Et	**2a**	H, Me	A	**3a**	60	—
2	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	A	**3b**	82 (41)	93:7
3	**1a**	CF_3	Et	**2c**	$-(CH_2)_4-$	A	**3c**	45	40:60
4	**1b**	CF_3	H	**2b**	$-(CH_2)_3-$	A	**3b**	88	92:8
5	**1c**	CHF_2	Et	**2b**	$-(CH_2)_3-$	A	**5**	47 (46)	78:22
6	**1d**	CF_3CF_2	H	**2b**	$-(CH_2)_3-$	A	**6**	77 (50)	94:6
7	**1a**	CF_3	Et	**2a**	H, Me	B	**3a**	58	—
8	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	B	**3b**	86 (42)	90:10
9	**1a**	CF_3	Et	**2c**	$-(CH_2)_4-$	B	**3c**	33	54:46
10	**1b**	CF_3	H	**2b**	$-(CH_2)_3-$	B	**3b**	77 (40)	89:11
11	**1c**	CHF_2	Et	**2b**	$-(CH_2)_3-$	B	**5**	74 (71)	74:26
12	**1d**	CF_3CF_2	H	**2b**	$-(CH_2)_3-$	B	**6**	70 (61)	93:7
13	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	C	**3b**	85	79:26

[a] All the reaction was carried out with polyfluoroalkylaldehyde ethyl hemiacetal (1 mmol) or hydrate (1 mmol) in the corresponding ketone (10 ml).
[b] Method A; piperidine (50 mol %) and acetic acid (50 mol %). Method B; piperidine (50 mol %) and Wakogel C200. Method C; *n*-$PrNH_2$ (50 mol %) and acetic acid (50 mol %).
[c] Measured by ^{19}F NMR using benzotrifluoride. Values in parentheses stand for the yields of isolated products.
[d] Determined by ^{19}F NMR.

Cyclopentanone **2b** could also participate well in the direct aldol reaction of CF_3CHO ethyl hemiacetal **1a** to produce the corresponding β-hydroxy-β-trifluoromethyl ketone **5** in good yields with high *syn*-diastereoselectivities by the use of acetic acid (Method A) or Wakogel C200 (Method B) (entries 2 and 8). Major diastereomer of **3b** could be assigned *syn*-isomer by comparison with the chemical shift of β-methine proton of aldol product attached to the hydroxyl group ($CF_3CH(OH)$–) in ^1H NMR according to the reported values.[4] This result could also be supported by the literature by Denmark.[7] The literature describes that in the aldol products, derived from cyclopentanone or cyclohexanone, the methine proton at β-carbon of *syn*-products appears in the lower field than those of *anti*-products in ^1H NMR. The reaction of CF_3CHO ethyl hemiacetal **1a** with cyclohexanone **2c** gave a 45% yield of the aldol product **3c** with low diastereoselectivity, because many unidentified by-products were produced (entries 3 and 9).

syn-Selective direct aldol reaction of CF_3CHO ethyl hemiacetal **1a** with cyclopentanone **2b** by using *n*-propylamine in place of piperidine also occurred to produce the aldol product **3b** in 85% yield with slight reduction of diastereoselectivity (entry 13). CF_3CHO hydrate **1b** also reacted well with cyclopentanone **2b** to produce the aldol product **3b** in the similar yields with similar diastereoselectivities (entries 4 and 10). The direct aldol reaction of difluoroacetaldehyde ethyl hemiacetal **1c** as well as pentafluoropropionaldehyde hydrate **1d** with cyclopentanone **2b**, also successfully occurred to produce the corresponding β-difluoromethyl or pentafluoroethyl aldol adduct **5** or **6** in good yields with good to excellent *syn*-diastereoselectivities in both cases of acetic acid and silica gel with piperidine (entries 5, 6, 11, and 12). The yields of isolated trifluoromethylated aldol product, derived from cyclopentanone, are lower than those of difluoromethylated or pentafluoroethylated aldol ones, because it is troublesome to isolate the trifluoromethylated aldol product from the reaction mixtures by column chromatography. Degree of *syn*-diastereoselectivities of the products **3b**, **5**, and **6**, derived from cyclopentanone, may depend on the bulkiness of the fluoroalkyl groups[8] in the following orders under the same conditions: the pentafluoroethyl (*syn*:*anti*=94:6, 88% de)>trifluoromethyl (*syn*:*anti*=93:7, 86% de)>difluoromethyl (*syn*:*anti*=78:22, 56% de) group (entries 2, 5, and 6), though the reason for this *syn*-selective outcome is not clear at this present.

3. Conclusions

In summary, we have achieved the direct aldol reaction of CF_3CHO ethyl hemiacetal, with unmodified ketones by the use of small amount of acids and amines without any strong acid and high reaction temperature, producing β-hydroxy-β-trifluoromethylated ketones in good yields. Studies addressing catalytic process for the asymmetric direct aldol reaction of CF_3CHO ethyl hemiacetal will be reported in due course.

4. Experimental

4.1. General

^1H NMR spectra were measured with a JEOL α-400 (400 MHz) FT-NMR spectrometer, a JNM-AL400 (400 MHz) FT-NMR spectrometer, or a JNM-ECA500 (500 MHz) FT-NMR spectrometer in deuteriochloroform ($CDCl_3$) solutions with tetramethylsilane (Me_4Si) as the internal standard. ^{13}C NMR spectra were measured with a JEOL α-400 (100 MHz) FT-NMR spectrometer, a JNM-AL400 (100 MHz) FT-NMR spectrometer, or a JNM-ECA500 (126 MHz) FT-NMR spectrometer in $CDCl_3$ solutions with tetramethylsilane (Me_4Si) as the internal standard. ^{19}F NMR spectra were recorded on a JEOL α-400 (376 MHz) FT-NMR spectrometer, a JNM-AL400

(372 MHz) FT-NMR spectrometer, or a JNM-ECA500 (471 MHz) FT-NMR spectrometer in $CDCl_3$ solutions using trifluoroacetic acid as the external standard.

4.2. A typical procedure

To a solution of a catalytic amount of silica gel (Wakogel C200) (0.120 g) and piperidine (0.043 g, 0.5 mmol) in dry acetone **2a** (10 ml) was added trifluoroacetaldehyde ethyl hemiacetal **1a** (0.144 g, 1 mmol) at room temperature under an inert atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was quenched with NH_4Cl aq solution (40 ml), followed by extraction with Et_2O (30 ml×3). The organic layer was dried over Na_2SO_4 and the solvents were removed by distillation under reduced pressure with cold ice bath. After the measurement of the residue by ^{19}F NMR using benzotrifluoride (58% of **3a** and 10% of **4**), purification by flash chromatography on silica gel (hexane–Et_2O=3:1) gave **3a** (44%, 0.068 g) and trace amount of **4**.

4.2.1. 5,5,5-Trifluoro-4-hydroxy-2-pentanone (3a).[9] IR (KBr) 1716.9 (C=O), 3411.2 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.78 (1H, dd, J=17.83, 3.01 Hz), 2.84 (1H, dd, J=17.83, 8.88 Hz), 3.41 (1H, br s), 4.44–4.51 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6 (s), 42.8 (s), 66.3 (q, J=32.2 Hz), 124.6 (q, J=280.6 Hz), 206.4 (s); ^{19}F NMR (471 MHz, $CDCl_3$) δ −1.8 (3F, d, J=6.9 Hz); HRMS (CI) Found: m/z 157.0476. Calcd for $C_5H_8F_3O_2$: M+H, 157.0479.

4.2.2. 1,1,1,7,7,7-Hexafluoro-2,6-dihydroxy-4-heptanone (4). Mp 70–71 °C; IR (KBr) 3392.9 (OH), 1732.3 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (1H×2, ddd, J=7.08, 2.69 Hz), 2.94 (1H×2, dd, J=17.57, 9.27 Hz), 3.06 (1H×2, br s), 4.50–4.60 (1H×2, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0 (s), 66.4 (q, J=32.8 Hz), 66.4 (q, J=32.5 Hz), 124.3 (q, J=279.5 Hz), 204.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −1.99 (3F, d, J=6.8 Hz), −2.02 (3F, d, J=6.8 Hz); HRMS (EI) Found: m/z 254.0374. Calcd for $C_7H_8O_3F_6$: M, 254.0377.

4.2.3. 2-(2,2,2-Trifluoro-1-hydroxyethyl)cyclopentanone (3b).[4] *syn Isomer*: IR (KBr) 1713.0 (C=O), 3458.8 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72–1.89 (1H, m), 2.06–2.23 (4H, m), 2.34–2.51 (1H, m), 3.17–3.27 (1H, m), 4.58 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.3 (s), 38.0 (s), 49.2 (s), 67.7 (q, J=31.7 Hz), 125.0 (q, J=282.0 Hz), 218.6 (s); ^{19}F NMR (471 MHz, $CDCl_3$) δ −0.3 (3F, d, J=7.5 Hz); HRMS (EI) Found: m/z 182.0555. Calcd for $C_7H_9F_3O_2$: M, 182.0555.

4.2.4. 2-(2,2,2-Trifluoro-1-hydroxyethyl)cyclohexanone (3c).[10] *anti Isomer*: IR (KBr) 1792.1 (C=O), 3447.2 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64–1.81 (3H, m), 1.93–1.98 (1H, m), 2.14–2.24 (2H, m), 2.37–2.49 (2H, m), 2.74–2.80 (1H, m) 4.00–4.09 (1H, m), 4.38 (1H, d, J=5.85 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (s), 28.1 (s), 31.6 (s), 43.0 (s), 50.3 (s), 71.8 (q, J=31.4 Hz), 124.7 (q, J=282.9 Hz), 213.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ 2.0 (3F, d, J=7.6 Hz); HRMS (EI) Found: m/z 196.0711. Calcd for $C_8H_{11}F_3O_2$: M, 196.0711.

4.2.5. 2-(2,2-Difluoro-1-hydroxyethyl)cyclopentanone (5). IR (KBr) 3439.1 (OH), 1736.1 (C=O) cm^{-1}; *syn Isomer*: ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.88 (4H, m), 2.32–2.41 (2H, m), 3.74 (1H, br s), 4.26 (1H, br s), 5.76 (1H, dt, J=55.78, 4.59 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.7 (s), 38.1 (s), 49.3 (t, J=2.5 Hz), 68.5 (t, J=24.6 Hz), 115.7 (t, J=244.1 Hz), 220.0 (d, J=6.6 Hz); ^{19}F NMR (372 MHz, $CDCl_3$) δ −52.9 (2F, ddd, J=55.8, 22.1, 11.5 Hz); *anti Isomer*: ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.88 (2H, m), 2.10–2.31 (3H, m), 2.38–2.46 (2H, m), 3.87–3.95 (1H, m), 4.05 (1H, br s), 5.92 (1H, dt, J=55.78, 3.86 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (s), 27.0 (d, J=2.5 Hz), 39.1 (s), 48.8 (t, J=2.9 Hz), 72.4 (t, J=25.0 Hz), 116.0 (dd, J=245.0, 241.7 Hz), 222.4 (s); ^{19}F NMR (372 MHz, $CDCl_3$) δ −51.4 (1F, ddd, J=289.2, 55.8, 10.3 Hz), −55.6 (1F, ddd, J=289.2, 55.8, 11.4 Hz); HRMS (EI) Found: m/z 164.0656. Calcd for $C_7H_{10}O_2F_2$: M, 164.0649.

4.2.6. 2-(2,2,3,3,3-Pentafluoro-1-hydroxypropyl)cyclopentanone (6). *syn Isomer*: mp 58–58.5 °C; IR (KBr) 3457.0 (OH), 1736.1 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.88 (1H, m), 2.05–2.27 (4H, m), 2.35–2.50 (2H, m), 3.50 (1H, d, J=6.28 Hz), 4.70 (1H, dt, J=20.77, 6.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.6 (d, J=2.5 Hz), 37.8 (s), 49.3 (s), 66.5 (dd, J=27.4, 21.7 Hz), 114.0 (ddq, J=260.5, 255.6, 36.1 Hz), 118.7 (qt, J=286.7, 36.1 Hz), 218.8 (s); ^{19}F NMR (372 MHz, $CDCl_3$) δ −6.1 (3F, s), −45.9 (1F, dd, J=275.4, 20.6 Hz), −52.4 (1F, ddd, J=275.4, 20.6, 2.3 Hz); HRMS (EI) Found: m/z 232.0528. Calcd for $C_8H_9O_2F_5$: M, 232.0523.

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C-3 β-lactam carbocation equivalents: versatile synthons for C-3 substituted β-lactams

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Abstract—An efficient and operationally simple strategy for the synthesis of differently C-3 monosubstituted (**9**) and disubstituted (**10**) monocyclic β-lactams is described. This involves reaction of β-lactam carbocation equivalents (**8**) with an active aromatic, aliphatic and heterocyclic substrates in the presence of a Lewis acid.

1. Introduction

The unique structural features and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the synthetic organic chemists as they present a variety of synthetic challenges. β-Lactams are well-acknowledged structural elements of the widely used penicillins, cephalosporins, thienamycin and other monocyclic β-lactam antibiotics[1] such as monobactams. In recent years, various natural and unnatural monocyclic β-lactams have been shown to exhibit high biological activity, suggesting that a suitably substituted monocyclic 2-azetidinone ring is the minimum requirement for biological activity. The discoveries of new monocyclic biologically active β-lactams such as **1** and **2** as cholesterol acyl transferase inhibitors,[2,3] thrombin inhibitor[4] and human cytomegalovirus protease inhibitor,[5] have renewed the interest in the synthesis of these differently substituted 3-alkyl/aryl azetidin-2-ones (Fig. 1).

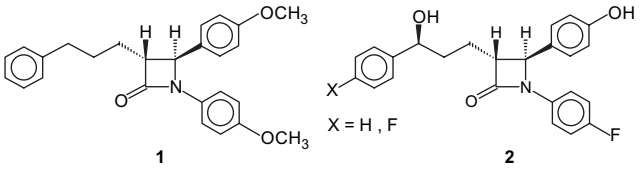

Figure 1. Cholesterol absorption inhibitors.

Cholesterol acyl transferase[6] is considered mainly responsible for atherosclerotic coronary heart disease and recently, C-3 aryl substituted monocyclic β-lactams has been shown to be potential inhibitors of this enzyme. Therefore, the development of convenient approaches for the synthesis of monocyclic azetidin-2-ones, bearing a varied array of appendages at C-3 and C-4, continues to be an area of active research. Thus, new and practical synthetic routes to α-aryl/substituted aryl-β-lactams are of particular importance. These β-lactams are not so easily accessible via the classical Staudinger reaction, the ketene–imine cycloaddition. However, synthesis of these C-3 substituted β-lactams is brought about via transformation at C-3 involving either cationic or anionic β-lactams **3** and **4**, respectively (Fig. 2). The potential of anionic β-lactam **4** has been explored by many groups[7] for the preparation of different β-lactam synthons. However, the chemistry involving cationic β-lactam **3** has not been fully explored.

In continuation to our earlier studies published in a preliminary communication,[8] we wish to report here the details of a general and operationally simple strategy for the preparation of a variety of C-3 substituted β-lactams. It has been observed that *trans*-3-chloro-3-phenylthio-β-lactams provide an easy access to 3,3-disubstituted azetidin-2-ones. Whereas, *trans*-3-chloro-3-benzylthio-β-lactams provide mainly C-3 monosubstituted β-lactams. The strategy involves the reaction of β-lactam carbocation equivalents of type **8** with active

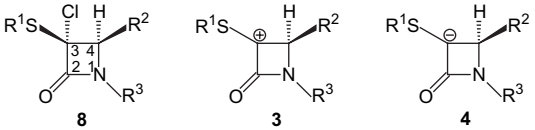

Figure 2. Cationic and anionic β-lactam equivalents.

Keywords: β-Lactam; Lewis acid; Nucleophiles; Disubstituted β-lactams; Monosubstituted β-lactams.
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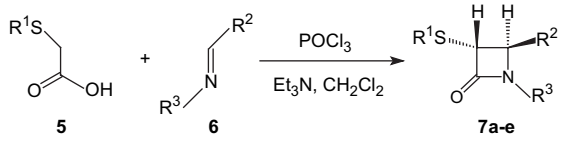
an aromatic, aliphatic and heterocyclic nucleophiles in the presence of a Lewis acid such as $TiCl_4$ or $SnCl_4$ to afford various C-3 monosubstituted and disubstituted β-lactams in excellent yields.

2. Results and discussion

We have successfully employed *trans*-3-chloro-3-phenyl/benzylthio-β-lactams (**8a–e**) as the most appropriate β-lactam carbocation equivalents for the synthesis of C-3 monosubstituted as well as disubstituted β-lactams, which may be prepared by reacting an acid chloride or an acid derivative with an imine in the presence of a base,[9] followed by stereospecific chlorination at C-3. These β-lactams **8a–e** are capable of functioning as a C-3 β-lactam carbocation in the presence of a Lewis acid[10] and have been observed to react with variety of active aromatic, aliphatic and heterocyclic substrates (nucleophiles).

The starting substrates, **7a–e** required for this study, were prepared from appropriate Schiff's bases **6** and 2-phenyl/benzylthioethanoic acid (**5**) in presence of triethylamine as the base and phosphorus oxychloride ($POCl_3$) as the condensing reagent according to reported procedure,[11] in good yields (Scheme 1, Table 1). The structures of these azetidin-2-ones **7a–e** were established on the basis of their spectral data such as IR, ^1H and ^{13}C NMR. All these cycloaddition reactions were found to be stereoselective and only *trans*-β-lactam (J=2.1–2.3 Hz, C3-H and C4-H) formation was observed.



Scheme 1. Synthesis of azetidin-2-ones **7a–e**.

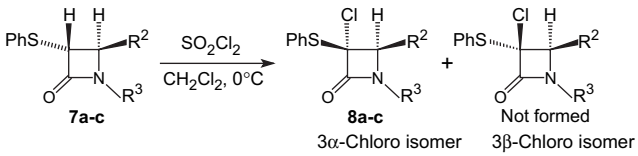
Table 1. Azetidin-2-ones **7a–e**

Entry	7	R^1	R^2	R^3	Yield[a] (%)
1	**a**	C_6H_5	C_6H_5	C_6H_4(OMe)(4)	55
2	**b**	C_6H_5	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	53
3	**c**	C_6H_5	C_6H_5	$CH_2C_6H_5$	52
4	**d**	$CH_2C_6H_5$	C_6H_5	C_6H_4(OMe)(4)	43
5	**e**	$CH_2C_6H_5$	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	44

[a] Isolated yield.

The β-lactam carbocation equivalents **8a–c**, were prepared from their corresponding azetidin-2-ones **7a–c** by α-chlorination with sulfuryl chloride (SO_2Cl_2)[12] in dichloromethane. In this reaction, although the formation of two stereoisomers (α- and β-chloro) is possible, only α-chloro isomer, i.e., *trans*-3-chloro-3-phenylthioazetidin-2-one (**8a–c**) was obtained in quantitative yields, which was evident from the ^1H NMR spectral analysis. In addition, the stereochemistry of **8a** at C-3 was established from single crystal X-ray crystallographic studies (Scheme 2).[13]

Chlorination using sulfuryl chloride (SO_2Cl_2) did not afford clean product. However, **7d–e** were transformed to corresponding **8d–e** in nearly quantitative yields using *N*-chlorosuccinimide (NCS) with catalytic amount of AIBN in carbon tetrachloride. No chlorination at the benzylic carbon was observed by ^1H NMR spectroscopy. However, the stereochemistry in this case was tentatively assigned to it keeping in view the stereochemistry of **8a** (Scheme 3, Table 2).



Scheme 2. Synthesis of *trans*-3-chloroazetidin-2-ones **8a–c**.

Scheme 3. Synthesis of *trans*-3-chloroazetidin-2-ones **8d–e**.

Table 2. *trans*-3-Chloroazetidin-2-ones **8a–e**

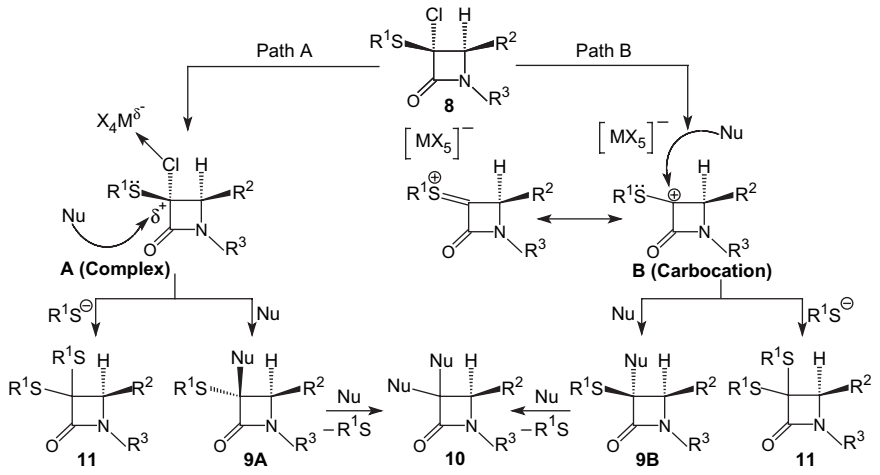
Entry	8	R^1	R^2	R^3	Yield[a] (%)
1	**a**	C_6H_5	C_6H_5	C_6H_4(OMe)(4)	95
2	**b**	C_6H_5	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	94
3	**c**	C_6H_5	C_6H_5	$CH_2C_6H_5$	94
4	**d**	$CH_2C_6H_5$	C_6H_5	C_6H_4(OMe)(4)	63
5	**e**	$CH_2C_6H_5$	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	44

[a] Isolated yield.

The juxtaposition of chlorine and sulfur atoms attached to the same carbon produce functionality with several attractive features in chemical synthesis. The potential of these α-chlorosulfides as reactive intermediates has been explored recently. These are useful and reactive electrophiles for many of sulfur-mediated alkylation reactions of aromatic substrates,[14] alkenes[15] and trimethylsilylenol ethers[16] etc.

Initial studies were carried out by reacting **8a** with anisole as the aromatic substrate in the presence of $SnCl_4$ at −78 °C. Instead of leading to the formation of the expected monosubstituted product of type **9** (Scheme 4), a mixture of two compounds was formed. These products, after chromatographic purification, were identified as **10a** and **11a** on the basis of their spectroscopic data and X-ray crystallographic analysis.[17,18] (Fig. 3). The reaction proceeds well with one equivalent of $SnCl_4$ in CH_2Cl_2 at −78 °C. However, $TiCl_4$ was not the Lewis acid of choice for this reaction since it produced invariably a mixture of nonseparable products.

The reaction was found to be general for several active aromatic substrates and the results are summarized in Table 3. Most of the activated aromatic substrates on reaction with **8a–c** produced mainly 3,3-disubstituted azetidin-2-ones of type **10**, along with the varying amount of 3,3-bis(alkylthio)azetidin-2-ones of the type **11**. However, in case of β-lactams **8a** and **8c** (Table 3, entries 3, 8 and 9) monosubstituted products of the type **9** were also formed along with disubstituted products (Scheme 4). Benzene and toluene failed to give the anticipated products.



Scheme 4. Synthesis of C-3 substituted β-lactams.

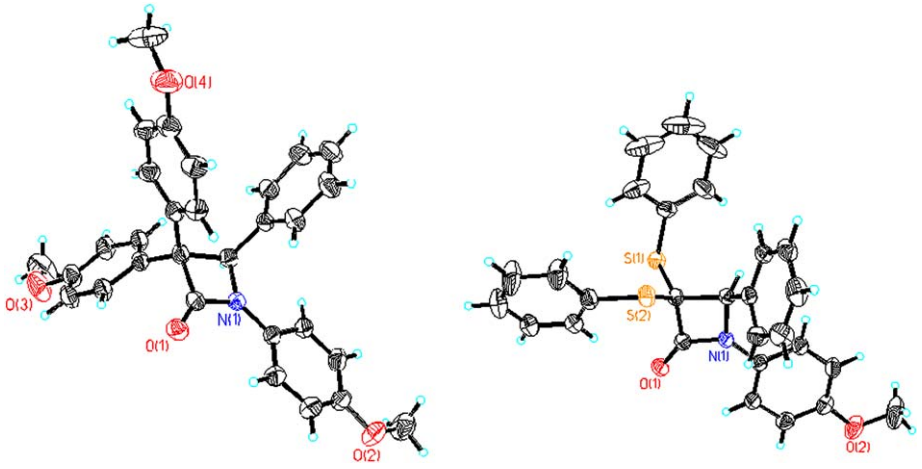
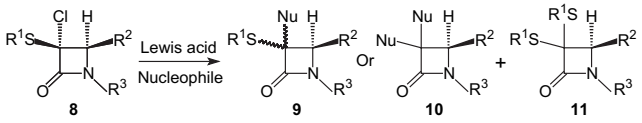


Figure 3. ORTEP diagrams for compounds **10a** and **11a**.

Table 3. Reaction of **8a–c** with various active aromatic substrates using $SnCl_4$ as the Lewis acid



Entry	8	Substrates (Nu)	Products[a] of type (% yield)[b]		
			9	10	11
1	**8a**	C_6H_5OMe	—	**10a** (47)	**11a** (42)
2	**8b**	C_6H_5OMe	—	**10b** (42)	**11b** (39)
3	**8c**	C_6H_5OMe	**9c** (45)	**10c** (35)	**11c** (16)
4	**8a**	1,3-$C_6H_4(OMe)_2$	—	**10f** (43)	**11a** (35)
5	**8b**	1,3-$C_6H_4(OMe)_2$	—	**10g** (39)	**11b** (32)
6	**8a**	1,4-$C_6H_4(OMe)_2$	—	**10h** (38)	**11a** (43)
7	**8b**	C_6H_5OH	—	**10i** (36)	**11b** (26)
8	**8a**	$C_{10}H_7(OMe)(2)$	**9j** (48)	—	**11a** (29)
9	**8c**	$C_{10}H_7(OMe)(2)$	**9k** (42)	—	**11c** (20)

[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H NMR, ^{13}C NMR and MS.

2.1. C-3 monosubstituted β-lactams

Since C-3 monosubstituted azetidin-2-ones are also very important synthons from the biological point of view, this methodology has also been successfully employed for the synthesis of C-3 monosubstituted azetidin-2-ones. It was envisaged that replacement of good leaving and resonance stabilized PhS-group by a poor leaving and less stable group such as benzylthio ($PhCH_2S$–) would allow monosubstitution. Thus, studies were carried out by treating **8d** with aromatic substrates such as 1,4-dimethoxybenzene in the presence of one equivalent of $SnCl_4$ at 0 °C. This reaction surprisingly resulted in the formation of only monosubstituted product, **9d**, in excellent yield. No formation of 3,3-disubstituted product was observed by ^1H NMR spectroscopy. $TiCl_4$ also promoted the formation of only monosubstituted product.

Various reactions were carried out successfully with different active substrates and the results are summarized in Table 4. Interestingly, all the active substrates react to give C-3 monosubstituted products. However, in some cases varying amounts of 3,3-bis(arylthio)azetidin-2-ones were also formed along with 3,3-disubstituted azetidin-2-ones (Table 4, entries 2 and 4). Here, again, benzene was found to be unreactive under given set of conditions. However, toluene did afford a C-3 monosubstituted product.

In continuation to our studies with cationic β-lactam equivalents, reactions were carried out, by treating **8a–b**,**d** with

Table 4. Reaction of **8d** with various active aromatic substrates using $SnCl_4$ or $TiCl_4$ as Lewis acid

Entry	Substrates (Nu)	Products[a] of type (% yield)[b]		
		9	**10**	**11**
1	1,4-$C_6H_4(OMe)_2$	**9d** (67)	—	—
2	C_6H_5OMe	**9l** (60)	**10a** (21)	**11d** (17)
3	$C_{10}H_7(OMe)(2)$	**9m** (61)	—	**11d** (21)
4	1,3-$C_6H_4(OMe)_2$	**9n** (51)	**10f** (23)	**11d** (33)
5	C_6H_5Me	**9o** (58)	—	—
6	C_6H_5OH	**9p** (26)	—	**11d** (42)

[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H and ^{13}C NMR.

various active aliphatic and heterocyclic substrates and the results are summarized in Table 5. Initially, allyltrimethylsilane and 1-cyclohexenyltrimethylsilyl ether, as the alkyl reactive substrates, were treated with **8a**,**d** and **8b**, respectively, in the presence of one equivalent of $SnCl_4$ or $TiCl_4$ at 0 °C and this resulted in the formation of only monosubstituted product of type **9** (Table 5, entries 1, 2 and 3). To extend these studies further, the reaction of cationic equivalents **8a**,**d** with heterocyclic substrates was examined. The heterocyclic substrates such as furan, pyrrole and indole react with **8a**,**d** under these conditions and the results are summarized in Table 5. Quite interestingly pyrrole reacts with cationic β-lactam equivalents, **8a**,**d**, to give only 3,3-disubstituted products along with varying amount of 3,3-bis(arylthio)azetidin-2-ones of the type **11**.

The spatial relationship of the C-4 hydrogen and new substituent at C-3 in **9j** was assigned the trans configuration on the basis of its transformation to the *cis*-β-lactam (J=6.2 Hz, C3-H and C4-H) on stereospecific[19] Raney-nickel desulfurization was further confirmed by X-ray crystallographic analysis[20] of **9j** (Fig. 4). It is interesting to note that approach of the nucleophile to more hindered face of the β-lactams forms the monosubstituted products. A possible explanation is that the Lewis acid first forms a complex (A) with β-lactam (Scheme 4), which being bulkier in size thus prevents the approach of the incoming nucleophiles from its side. Thus the reaction probably follows *Path A* and proceeds via an S_N2 mechanism.

Table 5. Reaction of **8a–b**,**d** with various active aliphatic and heterocyclic substrates using $SnCl_4$ or $TiCl_4$ as Lewis acid

Entry	**8**	Substrates (Nu)	Products[a] of type (% yield)[b]		
			9	**10**	**11**
1	**8d**	$CH_2{=}CHCH_2Si(Me)_3$	**9q** (90)	—	—
2	**8a**	$CH_2{=}CHCH_2Si(Me)_3$	**9r** (86)	—	—
3	**8b**	$C_6H_9OSi(Me)_3$	**9s** (44)	—	—
4	**8d**	C_4H_4O	**9t** (78)	—	—
5	**8d**	C_8H_6NH	**9u** (17)	—	**11d** (58)
6	**8a**	C_8H_6NH	—	**10v** (36)	**11a** (42)
7	**8d**	C_4H_4NH	—	**10w** (57)	**11d** (22)
8	**8a**	C_4H_4NH	—	**10w** (46)	**11a** (31)

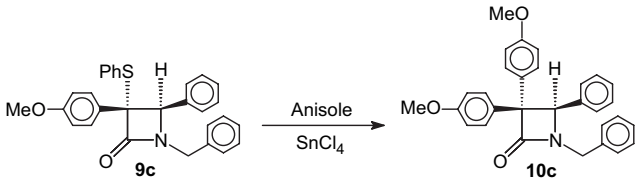
[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H NMR, ^{13}C NMR and MS.

However, the spatial juxtaposition of the C-4 hydrogen and new substituent at C-3 in case of **9r**[21] and **9s** was assigned cis on the basis of single crystal X-ray crystallography[22] (Fig. 4). Here, the reaction most likely follows *Path B* involving the intermediate formation of carbocation at C-3 (Scheme 4). The silylenol ether approaches the carbocation from the side of hydrogen atom at C-4, which is less hindered.

The possible role of **9** as an intermediate in the formation of disubstituted products **10** was supported by transformation of monosubstituted β-lactam **9c** into the disubstituted β-lactam **10c** on treatment with anisole, in the presence of $SnCl_4$ (Scheme 5). The formation of **11** was totally unexpected. The ambiphilic behaviour of –SPh and $–SCH_2Ph$ as the leaving group (leading to **10**) and at the same time acting as nucleophiles (leading to **11**) is remarkable.

Raney-nickel desulfurization of **9c** and **9k** led to the formation of *cis*-β-lactam **12** and *cis*-β-lactam **13** (J=5.6 Hz, C3-H and C4-H), respectively (Scheme 6).

The trans stereochemistry of monosubstituted β-lactams **9d** and **9t** was also established on the basis of their stereospecific desulfurization with Raney-nickel leading to the formation of *cis*-β-lactams **14** and **15** (J=6 Hz, C3-H and C4-H), respectively (Scheme 7).



Scheme 5. Transformation of monosubstituted β-lactam **9c** into disubstituted β-lactam **10c**.

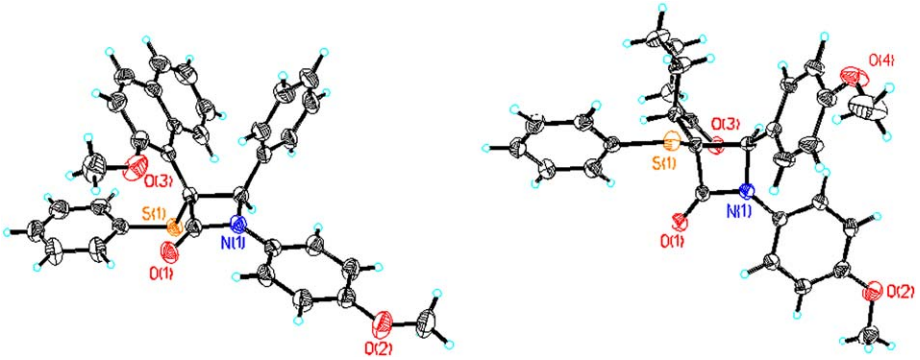
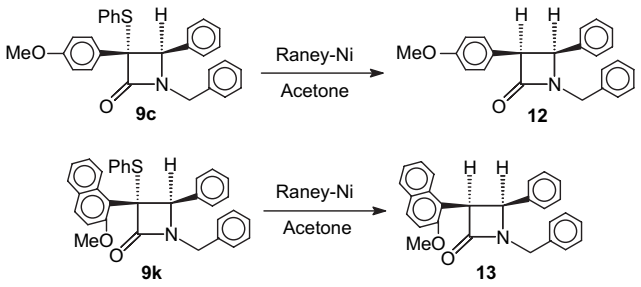
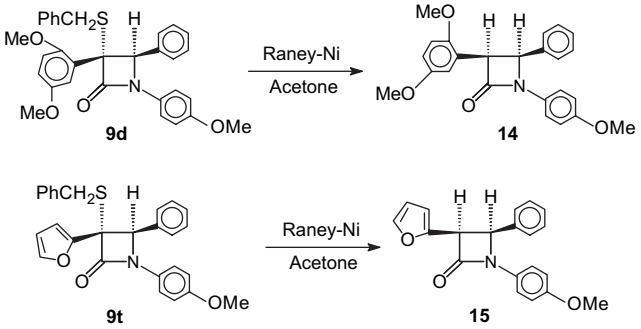


Figure 4. ORTEP diagrams for compounds **9j** and **9s**.



Scheme 6. Raney-nickel desulfurization of 3-phenylthio-β-lactams (**9c**, **9k**).



Scheme 7. Raney-nickel desulfurization of 3-benzylthio-β-lactams (**9d**, **9t**).

3. Conclusion

In conclusion, we have shown that the reactions of *trans*-3-chloro-3-benzylthio-β-lactams with an active aromatic, aliphatic and heterocyclic substrates provide an easy access to novel C-3 monosubstituted β-lactams and *trans*-3-chloro-3-phenylthio-β-lactams allows the formation of bis(arylthio)-β-lactams and 3,3-disubstituted β-lactams fairly efficiently.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solution using BRUKER or JEOL 300 MHz NMR spectrometers. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard (δ=0 ppm) for ^{1}H NMR and $CDCl_3$ (δ=77.0 ppm) for ^{13}C NMR spectra. IR spectra were taken on a FTIR spectrophotometer and are reported in cm^{-1}. Mass spectra were recorded at 70 eV using VG ANALYTICAL 11-250-J 70S spectrometer. The elemental analysis (C, H, N) was carried out using a PERKIN–ELMER 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (100–200 mesh). Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapours. Melting points are uncorrected. All commercially available compounds/reagents were used without further purification. Dichloromethane and carbon tetrachloride distilled over P_2O_5 were redistilled over CaH_2 before use. Crystallographic data (excluding structure factors) of compounds **9j**,[20] **9s**,[22] **10a**[17] and **11a**[18] in CIF format have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internet.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk]. All other relevant information regarding the data and supplementary publication CCDC number is presented in respective references.

4.2. General procedure for synthesis of *trans*-3-phenyl/benzylthio-β-lactams (7a–e)

Compounds **7a**–**c**[11] were prepared by the procedure described in the cited reference. The spectroscopic data of compound **7a**[11] were reported in the cited reference.

4.2.1. *trans*-1-(4′-Methoxyphenyl)-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (7b). Yellow crystalline solid; yield 53%; mp 94–96 °C; [Found: C, 73.27; H, 5.22; N, 3.41. $C_{23}H_{21}NO_3S$ requires C, 73.57; H, 5.40; N, 3.58%]; IR (cm^{-1}, $CHCl_3$): 1747 (C=O); δ_H (300 MHz, $CDCl_3$) 7.60–6.70 (13H, m, Ph), 4.70 (1H, d, *J* 2.2 Hz, C4-*H*), 4.20 (1H, d, *J* 2.2 Hz, C3-*H*), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.3, 160.0, 156.2, 132.5, 131.9, 130.7, 129.1, 128.1, 127.8, 127.4, 118.7, 114.6, 114.3, 63.0, 61.4, 55.4, 55.3.

4.2.2. *trans*-1-Benzyl-3-phenylthio-4-phenylazetidin-2-one (7c). Colourless crystalline solid; yield 52%; mp 124–126 °C; [Found: C, 76.34; H, 5.43; N, 4.01. $C_{22}H_{19}NOS$ requires C, 76.49; H, 5.54; N, 4.05%]; IR (cm^{-1}, KBr): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.52–6.73 (15H, m, Ph), 4.70 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 4.20 (1H, d, *J* 2.2 Hz, C4-*H*), 4.14 (1H, d, *J* 2.2 Hz, C3-*H*), 3.60 (1H, d, *J* 15.1 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 165.8, 135.9, 134.5, 133.6, 133.2, 131.2, 129.2, 129.1, 128.9, 128.6, 128.3, 127.5, 61.9, 61.6, 44.5.

4.2.3. *trans*-1-(4′-Methoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (7d). This compound was prepared by using the same method as for **7a**–**c**, starting from 2-benzylthioethanoic acid. Colourless crystalline solid; yield 43%; mp 95–97 °C; [Found: C, 73.46; H, 5.52; N, 3.64. $C_{23}H_{21}NO_2S$ requires C, 73.58; H, 5.63; N, 3.70%]; IR (cm^{-1}, KBr): 1739 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.71 (14H, m, Ph), 4.80 (1H, d, *J* 2.2 Hz, C4-*H*), 3.97 (2H, d, *J* 4.8 Hz, CH_2S), 3.88 (1H, d, *J* 2.4 Hz, C3-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.3, 156.2, 137.7, 137.0, 131.1, 129.2, 128.7, 128.6, 127.3, 125.9, 118.5, 114.3, 63.2, 59.1, 55.2, 35.3.

4.2.4. *trans*-1-(4′-Methoxyphenyl)-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (7e). This compound was prepared by using the same method as for **7a**–**c**, starting from 2-benzylthioethanoic acid. White solid; yield 44%; mp 108–111 °C; [Found: C, 71.01; H, 5.62; N, 3.37. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.71; N, 3.45%]; IR (cm^{-1}, KBr): 1731 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.70 (13H, m, Ph), 4.51 (1H, d, *J* 2.2 Hz, C4-*H*), 3.95 (2H, d, *J* 4.8 Hz, CH_2S), 3.85 (1H, d, *J* 2.2 Hz, C3-*H*), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.4, 156.9, 156.1, 137.7, 131.1, 129.2, 128.7, 128.5, 127.3, 127.2, 118.5, 114.5, 114.2, 62.8, 59.0, 55.1, 55.0, 35.2.

4.3. General procedure for synthesis of *trans*-3-chloro-3-phenylthio-β-lactams (8a–c)

Compounds **8a–c**[11] were prepared by the procedure as described in the cited reference. The spectroscopic data of compound **8a**[11] were reported in the cited reference.

4.3.1. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (8b). Colourless crystalline solid; yield 94%; mp 75–76 °C; [Found: C, 64.56; H, 4.61; N, 3.14. $C_{23}H_{20}NO_3ClS$ requires C, 64.24; H, 4.73; N, 3.28%]; IR (cm^{-1}, KBr): 1764 (C=O); δ_H (300 MHz, $CDCl_3$) 7.50–6.81 (13H, m, Ph), 5.39 (1H, s, C4-*H*), 3.80 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.6, 160.2, 156.7, 135.3, 129.8, 129.6, 129.3, 128.7, 128.4, 123.4, 119.2, 114.4, 114.0, 80.3, 71.5, 55.4, 55.3.

4.3.2. *trans*-1-Benzyl-3-chloro-3-phenylthio-4-phenylazetidin-2-one (8c). Colourless crystalline solid; yield 94%; mp 90–92 °C; [Found: C, 69.47; H, 4.71; N, 3.63. $C_{22}H_{18}NOClS$ requires C, 69.55; H, 4.78; N, 3.68%]; IR (cm^{-1}, KBr): 1776 (C=O); δ_H (300 MHz, $CDCl_3$) 7.45–7.15 (15H, m, Ph), 5.05 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.82 (1H, s, C4-*H*), 3.90 (1H, d, *J* 15.1 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 163.9, 135.1, 134.1, 131.8, 129.7, 129.1, 129.0, 128.6, 128.5, 128.3, 128.2, 80.9, 71.1, 44.6.

4.4. General procedure for synthesis of *trans*-3-chloro-3-benzylthio-β-lactams (8d–e)

To a solution of **7d/7e** (1 mmol) in 80 mL dry carbon tetrachloride were added *N*-chlorosuccinimide (NCS) (1.2 mmol) and catalytic amount of AIBN. The reaction mixture was refluxed and progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was filtered and the filtrate was evaporated in vacuo. This crude product was purified by silica gel column chromatography (10% EtOAc/hexane).

4.4.1. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-benzylthio-4-phenylazetidin-2-one (8d). Colourless crystalline solid; yield 63%; mp 135–137 °C; [Found: C, 67.29; H, 4.84; N, 3.36. $C_{23}H_{20}NO_2ClS$ requires C, 67.39; H, 4.91; N, 3.42%]; IR (cm^{-1}, KBr): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.38–6.75 (14H, m, Ph), 5.38 (1H, s, C4-*H*), 4.28 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.98 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S), 3.74 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 159.9, 156.7, 135.4, 135.3, 131.4, 131.5, 129.7, 129.6, 129.4, 128.6, 128.5, 127.9, 127.4, 119.1, 114.4, 80.7, 71.5, 55.3, 34.7, 25.1.

4.4.2. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (8e). Yellow oil; yield 44%; [Found: C, 65.47; H, 4.97; N, 3.11. $C_{23}H_{20}NO_3ClS$ requires C, 65.52; H, 5.04; N, 3.18%]; IR (cm^{-1}, $CHCl_3$): 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 7.32–6.71 (14H, m, Ph), 5.30 (1H, s, C4-*H*), 4.29 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 4.00 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S), 3.77 (3H, s, OC$H_3$), 3.76 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 160.5, 159.7, 156.6, 135.7, 130.1, 129.5, 129.3, 128.7, 128.5, 127.4, 123.3, 119.0, 114.4, 114.0, 81.1, 71.2, 55.1, 55.0, 34.8, 25.2, 23.6.

4.5. General procedure for synthesis of C-3 substituted azetidin-2-ones

To a well stirred solution of **8a–e** (1 mmol) in 10 mL dry methylene chloride was added substrates (nucleophile) (1.1 mmol) followed by stannic chloride (1.2 mmol) via a syringe, under inert atmosphere, at −78 °C for **8a–c** and at 0 °C for **8d–e**. The reaction mixture was stirred for 1 h at the same temperature. The progress of the reaction was checked by TLC, which showed the appearance of spots different from the starting compound. The reaction mixture was quenched with water, extracted with methylene chloride (4×10 mL), washed with 5% $NaHCO_3$ solution and then dried (anhydrous Na_2SO_4). The residue after solvent evaporation in vacuo, was purified by silica gel column chromatography (10% EtOAc/hexane).

4.5.1. *cis*-1-Benzyl-3-(4′-methoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (9c). Colourless oil; yield 45%; [Found: C, 77.28; H, 5.52; N, 3.04. $C_{29}H_{25}NO_2S$ requires C, 77.34; H, 5.58; N, 3.10%]; R_f (10% EtOAc/hexane) 0.42; IR (cm^{-1}, $CHCl_3$): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.65–6.53 (19H, m, Ph), 4.75 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.59 (1H, s, C4-*H*), 3.70 (1H, d, *J* 14.9 Hz, CH$_a$$H_b$Ph), 3.63 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 167.9, 158.8, 136.5, 134.3, 134.0, 130.6, 130.0, 129.4, 129.0, 128.5, 128.3, 128.1, 127.4, 125.9, 113.2, 72.2, 66.8, 55.1, 44.0.

4.5.2. *cis*-1-(4′-Methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9d). White semisolid; yield 67%; [Found: C, 72.75; H, 5.63; N, 2.69. $C_{31}H_{29}NO_4S$ requires C, 72.78; H, 5.71; N, 2.74%]; IR (cm^{-1}, $CHCl_3$): 1741 (C=O); δ_H (300 MHz, $CDCl_3$) 7.44–6.40 (17H, m, Ph), 5.19 (1H, s, C4-*H*), 3.96 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.73 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.38 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 165.0, 156.0, 153.6, 151.2, 137.2, 133.8, 131.2, 129.2, 128.6, 128.1, 127.8, 127.6, 126.7, 118.7, 114.7, 114.4, 114.2, 113.2, 66.9, 65.2, 56.0, 55.5, 55.1, 34.5; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 129.3 (+), 129.2 (+), 128.6 (+), 128.1 (+), 127.8 (+), 126.7 (+), 118.7 (+), 114.7 (+), 114.4 (+), 114.2 (+), 113.2 (+), 66.9 (+), 56.0 (+), 55.5 (+), 55.2 (+), 34.5 (−).

4.5.3. *cis*-1-(4′-Methoxyphenyl)-3-(2′-methoxynaphthyl)-3-phenylthio-4-phenylazetidin-2-one (9j). Colourless crystalline solid; yield 45%; mp 190–192 °C; [Found: C, 76.48; H, 5.22; N, 2.64. $C_{33}H_{27}NO_3S$ requires C, 76.57; H, 5.27; N, 2.70%]; R_f (10% EtOAc/hexane) 0.40; IR (cm^{-1}, KBr): 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 8.50–6.60 (20H, m, Ph), 5.24 (1H, s, C4-*H*), 3.68 (3H, s, OCH_3), 3.56 (3H, s, OCH_3) (for one isomer) and 9.40–6.60 (20H, m, Ph), 5.32 (1H, s, C4-*H*), 3.82 (3H, s, OCH_3), 3.71 (3H, s, OCH_3) (for other isomer); *m/z*: 306 (M^+); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.4. *cis*-1-Benzyl-3-(2′-methoxynaphthyl)-3-phenylthio-4-phenylazetidin-2-one (9k). Yellow oil; yield 42%; [Found: C, 78.96; H, 5.38; N, 2.73. $C_{33}H_{27}NO_2S$ requires C, 79.02; H, 5.42; N, 2.79%]; R_f (10% EtOAc/hexane)

0.35; IR (cm^{-1}, $CHCl_3$): 1725 (C=O); δ_H (300 MHz, $CDCl_3$) 9.35–6.65 (21H, m, Ph), 4.74 (1H, s, C4-*H*), 4.56 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 3.70 (1H, d, *J* 15.0 Hz, CH$_a$$H_b$Ph), 3.32 (3H, s, OC$H_3$) (for one isomer) and 8.20–6.63 (21H, m, Ph), 4.78 (1H, s, C4-*H*), 4.75 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 3.79 (3H, s, OCH_3), 3.75 (1H, d, *J* 14.9 Hz, CH$_a$$H_b$Ph), (for other isomer); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.5. *cis*-1-(4′-Methoxyphenyl)-3-(4′-methoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9l). Colourless oil; yield 60%; [Found: C, 74.73; H, 5.56; N, 2.87. $C_{30}H_{27}NO_3S$ requires C, 74.82; H, 5.65; N, 2.91%]; R_f (10% EtOAc/hexane) 0.31; IR (cm^{-1}, $CHCl_3$): 1751 (C=O); δ_H (300 MHz, $CDCl_3$) 7.59–6.66 (18H, m, Ph), 5.10 (1H, s, C4-*H*), 3.85 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.76 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.22 (1H, d, *J* 11.1 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 165.3, 159.4, 156.2, 136.8, 135.7, 133.1, 130.8, 130.5, 130.3, 129.2, 129.6, 128.3, 128.1, 128.1, 128.0, 126.9, 126.8, 118.8, 118.7, 114.3, 114.2, 102.4, 67.9, 67.5, 56.0, 55.2, 54.5, 34.4.

4.5.6. *cis*-1-(4′-Methoxyphenyl)-3-(2′-methoxynaphthyl)-3-benzylthio-4-phenylazetidin-2-one (9m). Yellow oil; yield 61%; [Found: C, 76.73; H, 5.44; N, 2.58. $C_{34}H_{29}NO_3S$ requires C, 76.81; H, 5.49; N, 2.63%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1745 (C=O); δ_H (300 MHz, $CDCl_3$) 8.00–6.68 (20H, m, Ph), 5.21 (1H, s, C4-*H*), 4.14 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.70 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.22 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S) (for one isomer) and 8.20–6.72 (20H, m, Ph), 5.26 (1H, s, C4-*H*), 4.29 (1H, d, *J* 12.3 Hz, CH_aH$_b$S), 3.93 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.58 (1H, d, *J* 12.3 Hz, CH$_a$$H_b$S) (for other isomer); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.7. *cis*-1-(4′-Methoxyphenyl)-3-(2′,4′-dimethoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9n). Brown oil; yield 51%; [Found: C, 72.73; H, 5.65; N, 2.67. $C_{31}H_{29}NO_4S$ requires C, 72.78; H, 5.71; N, 2.74%]; R_f (10% EtOAc/hexane) 0.30; IR (cm^{-1}, $CHCl_3$): 1745 (C=O); δ_H (300 MHz, $CDCl_3$) 7.79–6.37 (17H, m, Ph), 5.18 (1H, s, C4-*H*), 3.95 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.35 (1H, d, *J* 12.0 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 161.0, 158.1, 156.0, 137.3, 133.8, 131.1, 129.7, 129.2, 129.1, 128.6, 128.1, 127.8, 126.6, 118.7, 114.2, 103.6, 99.9, 68.1, 67.0, 65.8, 65.0, 55.3, 55.2, 34.5.

4.5.8. *cis*-1-(4′-Methoxyphenyl)-3-(4′-methylphenyl)-3-benzylthio-4-phenylazetidin-2-one (9o). White semisolid; yield 58%; [Found: C, 77.32; H, 5.80; N, 2.94. $C_{30}H_{27}NO_2S$ requires C, 77.39; H, 5.84; N, 3.01%]; IR (cm^{-1}, $CHCl_3$): 1751 (C=O); δ_H (300 MHz, $CDCl_3$) 7.59–6.67 (18H, m, Ph), 5.10 (1H, s, C4-*H*), 3.92 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.70 (3H, s, OCH_3), 3.25 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S), 2.30 (3H, s, C$H_3$); δ_C (75 MHz, $CDCl_3$) 156.2, 137.5, 136.9, 136.3, 134.4, 130.9, 129.5, 129.4, 128.9, 128.6, 128.3, 128.2, 127.7, 127.3, 126.8, 118.8, 118.6, 114.3, 114.2, 68.9, 68.1, 55.1, 34.4, 21.2.

4.5.9. *cis*-1-(4′-Methoxyphenyl)-3-(4′-hydroxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9p). Brownish-yellow oil; yield 26%; [Found: C, 74.56; H, 5.31; N, 2.96. $C_{29}H_{25}NO_4$ requires C, 74.50; H, 5.38; N, 2.99%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1729 (C=O), 3374 (OH); δ_H (300 MHz, $CDCl_3$) 7.46–6.39 (18H, m, Ph), 5.20 (1H, s, C4-*H*), 3.77 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.66 (3H, s, OCH_3), 3.19 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S).

4.5.10. *trans*-1-(4′-Methoxyphenyl)-3-allyl-3-phenylthio-4-phenylazetidin-2-one (9q). Colourless crystalline solid; yield 86%; mp 130–132 °C; [Found: C, 74.64; H, 5.66; N, 3.39. $C_{25}H_{23}NO_2S$ requires C, 74.78; H, 5.77; N, 3.48%]; IR (cm^{-1}, KBr): 1745 (C=O), 1510 (C=C); δ_H (300 MHz, $CDCl_3$) 7.62–6.83 (14H, m, Ph), 6.01 (1H, m, C*H*=CH$_2$), 5.30 (1H, br s, CH=CH_aH$_b$), 5.26 (1H, m, CH=CH$_a$$H_b$), 5.15 (1H, s, C4-*H*), 3.78 (3H, s, OCH_3), 2.68 (2H, d, *J* 7.3 Hz, CH_2CH=); δ_C (75 MHz, $CDCl_3$) 165.7, 156.2, 135.2, 133.6, 132.8, 130.9, 130.7, 128.6, 128.2, 128.0, 126.3, 119.4, 118.5, 114.3, 65.9, 63.5, 55.1, 38.0; *m/z*: 401 (M^+).

4.5.11. *trans*-1-(4′-Methoxyphenyl)-3-allyl-3-benzylthio-4-phenylazetidin-2-one (9r). Colourless crystalline solid; yield 90%; mp 143–144 °C; [Found: C, 77.11; H, 6.02; N, 3.34. $C_{26}H_{25}NO_2S$ requires C, 77.16; H, 6.06; N, 3.37%]; IR (cm^{-1}, KBr): 1750 (C=O), 1515 (C=C); δ_H (300 MHz, $CDCl_3$) 7.22–6.63 (14H, m, Ph), 5.88 (1H, m, C*H*=CH$_2$), 5.26 (1H, br s, CH=CH_aH$_b$), 5.22 (1H, m, CH=CH$_a$$H_b$), 4.88 (1H, s, C4-*H*), 3.63 (2H, d, *J* 11.4 Hz, CH_2S), 3.61 (3H, s, OCH_3), 2.73 (2H, d, *J* 7.3 Hz, CH_2CH=); δ_C (75 MHz, $CDCl_3$) 165.1, 156.1, 137.1, 133.8, 132.8, 131.0, 129.2, 128.7, 128.4, 128.3, 128.1, 127.8, 127.2, 127.0, 119.4, 118.4, 114.3, 114.2, 65.3, 64.4, 55.1, 39.1, 33.6; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 132.8 (+), 129.2 (+), 128.4 (+), 128.3 (+), 128.1 (+), 127.8 (+), 127.0 (+), 119.4 (−), 118.4 (+), 114.3 (+), 114.2 (+), 64.4 (+), 55.1 (+), 39.1 (−), 33.6 (−).

4.5.12. *trans*-1-(4′-Methoxyphenyl)-3-(2′-oxocyclohexanyl)-3-phenylthio-4-phenylazetidin-2-one (9s). Colourless crystalline solid; yield 44%; mp 179–181 °C; [Found: C, 71.49; H, 5.96; N, 2.83. $C_{29}H_{29}NO_4S$ requires C, 71.43; H, 6.01; N, 2.87%]; IR (cm^{-1}, KBr): 1755 (lactam C=O), 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 7.68–6.79 (13H, m, Ph), 5.21 (1H, s, C4-*H*), 3.61 (3H, s, OCH_3), 2.76 (2H, m, $C_5H_7H_{h-i}$C=O), 2.37 (1H, m, $C_5H_8H_a$C=O), 2.27 (1H, m, $C_5H_8H_f$C=O), 2.08 (2H, m, $C_5H_7H_{b-c}$C=O), 1.82 (2H, m, $C_5H_7H_{d,g}$C=O), 1.49 (1H, m, $C_5H_8H_e$C=O); δ_C (75 MHz, $CDCl_3$) 210.2, 167.5, 159.9, 156.1, 135.6, 131.8, 130.3, 129.6, 128.9, 125.7, 118.8, 114.4, 113.7, 66.6, 62.3, 55.5, 55.3, 50.0, 42.5, 29.9, 27.9, 25.3.

4.5.13. *cis*-1-(4′-Methoxyphenyl)-3-(2′-furanyl)-3-benzylthio-4-phenylazetidin-2-one 9t. White solid; yield 78%; mp 148–150 °C; [Found: C, 73.46; H, 5.21; N, 3.11. $C_{27}H_{23}NO_3S$ requires C, 73.45; H, 5.25; N, 3.17%]; IR (cm^{-1}, KBr): 1744 (C=O); δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 7.39–6.75 (14H, m, Ph), 6.61 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 6.38 (1H, dd, *J* 1.8, 1.8 Hz, $C_4H_aH_bH_c$O), 5.33 (1H, s, C4-*H*), 3.94 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.74 (3H, s, OCH_3), 3.47 (1H,

d, *J* 11.4 Hz, CH_aH_bS); δ_C (75 MHz, $CDCl_3$) 156.4, 149.6, 143.3, 136.7, 132.8, 131.0, 129.3, 128.9, 128.4, 128.3, 128.1, 127.0, 118.8, 114.4, 110.7, 109.6, 65.3, 63.1, 55.2, 34.6; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 143.3 (+), 129.3 (+), 128.9 (+), 128.3 (+), 128.1 (+), 127.0 (+), 118.8 (+), 114.4 (+), 110.7 (+), 109.6 (+), 65.3 (+), 55.2 (+), 34.6 (−).

4.5.14. *cis*-1-(4′-Methoxyphenyl)-3-(3′-indolyl)-3-benzylthio-4-phenylazetidin-2-one (9u). Reddish-brown oil; yield 17%; [Found: C, 75.84; H, 5.31; N, 5.67. $C_{31}H_{26}N_2O_2S$ requires C, 75.89; H, 5.34; N, 5.71%]; R_f (10% EtOAc/hexane) 0.43; IR (cm^{-1}, $CHCl_3$): 1764 (C═O); δ_H (300 MHz, $CDCl_3$) 8.12 (1H, br s, N*H*, D_2O exchangeable), 7.82–6.67 (19H, m, Ph), 5.10 (1H, s, C4-*H*), 3.87 (1H, d, *J* 11.4 Hz, CH_aH_bS), 3.66 (3H, s, OCH_3), 3.24 (1H, d, *J* 11.4 Hz, CH_aH_bS).

4.5.15. 1-(4′-Methoxyphenyl)-3,3-bis(4′-methoxyphenyl)-4-phenylazetidin-2-one (10a). Colourless crystalline solid; yield 47%; mp 135–137 °C; [Found: C, 77.47; H, 5.81; N, 2.96. $C_{30}H_{27}NO_4$ requires C, 77.39; H, 5.86; N, 3.01%]; R_f (10% EtOAc/hexane) 0.39; IR (cm^{-1}, KBr): 1735 (C═O); δ_H (300 MHz, $CDCl_3$) 7.54–6.53 (17H, m, Ph), 5.67 (1H, s, C4-*H*), 3.79 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.65 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.0, 158.8, 158.1, 156.1, 135.1, 133.3, 131.1, 129.7, 129.5, 128.4, 128.3, 128.1, 127.6, 118.7, 114.2, 114.1, 113.2, 71.2, 67.5, 55.3, 55.3, 55.0; *m*/*z*: 465 (M^+).

4.5.16. 1-(4′-Methoxyphenyl)-3,3-bis(4′-methoxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10b). Yellow oil; yield 42%; [Found: C, 75.21; H, 5.81; N, 2.76. $C_{31}H_{29}NO_5$ requires C, 75.14; H, 5.89; N, 2.83%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1739 (C═O); δ_H (300 MHz, $CDCl_3$) 7.48–6.53 (16H, m, Ph), 5.58 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.67 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.2, 159.4, 158.7, 158.1, 156.1, 133.6, 131.2, 129.8, 129.6, 128.9, 128.4, 127.1, 118.8, 114.3, 114.1, 113.8, 113.3, 71.1, 67.5, 55.4, 55.2.

4.5.17. 1-Benzyl-3,3-bis(4′-methoxyphenyl)-4-phenylazetidin-2-one (10c). Colourless crystalline solid; yield 35%; mp 145–147 °C; [Found: C, 80.21; H, 6.01; N, 3.07. $C_{30}H_{27}NO_3$ requires C, 80.15; H, 6.07; N, 3.11%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, KBr): 1741 (C═O); δ_H (300 MHz, $CDCl_3$) 7.33–6.53 (18H, m, Ph), 5.06 (1H, s, C4-*H*), 4.95 (1H, d, *J* 15.2 Hz, CH_aH_bPh), 3.90 (1H, d, *J* 14.9 Hz, CH_aH_bPh), 3.76 (3H, s, OCH_3), 3.66 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 170.2, 158.6, 158.1, 135.4, 135.1, 133.5, 129.6, 128.8, 128.6, 128.3, 128.1, 127.8, 114.0, 113.2, 72.0, 67.1, 55.3, 55.1, 44.3.

4.5.18. 1-(4′-Methoxyphenyl)-3,3-bis(2′,4′-dimethoxyphenyl)-4-phenylazetidin-2-one (10f). Colourless crystalline solid; yield 43%; mp 175–177 °C; [Found: C, 73.19; H, 5.90; N, 2.63. $C_{32}H_{31}NO_6$ requires C, 73.12; H, 5.96; N, 2.66%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, KBr): 1740 (C═O); δ_H (300 MHz, $CDCl_3$) 7.71–5.95 (15H, m, Ph), 5.75 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.01 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.2, 160.4, 159.9, 158.5, 155.9, 155.7, 136.8, 132.7, 132.3, 132.1, 130.2, 129.1, 128.7, 128.6, 127.6, 127.3, 127.0, 126.3, 119.6, 119.4, 118.8, 118.7, 117.3, 114.5, 114.1, 104.3, 103.6, 99.1, 98.4, 68.7, 66.5, 59.5, 55.4, 55.3, 54.0.

4.5.19. 1-(4′-Methoxyphenyl)-3,3-bis(2′,4′-dimethoxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10g). Brownish-yellow oil; yield 39%; [Found: C, 71.17; H, 5.90; N, 2.47. $C_{32}H_{31}NO_7$ requires C, 71.13; H, 5.98; N, 2.52%]; R_f (10% EtOAc/hexane) 0.30; IR (cm^{-1}, $CHCl_3$): 1736 (C═O); δ_H (300 MHz, $CDCl_3$) 7.69–6.01 (14H, m, Ph), 5.70 (1H, s, C4-*H*), 3.76 (3H, s, 2×OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.07 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.9, 160.7, 160.2, 158.8, 155.7, 132.3, 132.1, 130.1, 129.7, 128.9, 118.9, 118.7, 117.5, 114.1, 112.5, 104.2, 103.6, 99.1, 98.5, 68.7, 66.1, 55.9, 55.4, 55.3, 55.2, 54.2.

4.5.20. 1-(4′-Methoxyphenyl)-3,3-bis(2′,5′-dimethoxyphenyl)-4-phenylazetidin-2-one (10h). Colourless crystalline solid; yield 38%; mp 268–270 °C; [Found: C, 73.02; H, 5.92; N, 2.61. $C_{32}H_{31}NO_6$ requires C, 73.12; H, 5.96; N, 2.66%]; R_f (10% EtOAc/hexane) 0.42; IR (cm^{-1}, KBr): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.42–6.27 (15H, m, Ph), 5.84 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.01 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 155.8, 153.4, 152.3, 150.8, 136.5, 132.1, 128.6, 127.1, 127.0, 125.1, 118.7, 118.0, 115.8, 114.1, 113.9, 113.1, 112.5, 110.7, 69.5, 66.3, 56.5, 55.8, 55.6, 55.4, 54.3.

4.5.21. 1-(4′-Methoxyphenyl)-3,3-bis(4′-hydroxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10i). Yellow oil; yield 36%; [Found: C, 74.57; H, 5.35; N, 2.97. $C_{29}H_{25}NO_5$ requires C, 74.51; H, 5.39; N, 3.00%]; R_f (10% EtOAc/hexane) 0.29; IR (cm^{-1}, $CHCl_3$): 1725 (C═O), 3369 (OH), 3383 (OH); δ_H (300 MHz, $CDCl_3$) 7.32–6.43 (16H, m, Ph), 5.61 (1H, s, C4-*H*), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 159.3, 156.3, 155.2, 154.5, 132.7, 130.8, 129.8, 129.2, 128.9, 128.6, 126.9, 119.0, 115.8, 114.9, 114.3, 113.8, 71.0, 67.7, 55.5, 55.2.

4.5.22. 1-(4′-Methoxyphenyl)-3,3-bis(3′-indolyl)-4-phenylazetidin-2-one (10v). Reddish-brown oil; yield 36%; [Found: C, 79.59; H, 5.16; N, 8.65. $C_{32}H_{25}N_3O$ requires C, 79.64; H, 5.20; N, 8.69%]; R_f (10% EtOAc/hexane) 0.40; IR (cm^{-1}, $CHCl_3$): 1762 (C═O); δ_H (300 MHz, $CDCl_3$) 7.35 (1H, br s, N*H*, D_2O exchangeable), 7.10 (1H, br s, N*H*, D_2O exchangeable), 7.32–6.43 (19H, m, Ph), 5.63 (1H, s, C4-*H*), 3.76 (3H, s, OCH_3).

4.5.23. 1-(4′-Methoxyphenyl)-3,3-bis(3′-pyrrolyl)-4-phenylazetidin-2-one (10w). Black oil; yield 46%; [Found: C, 75.14; H, 5.48; N, 10.91. $C_{24}H_{21}N_3O_2$ requires C, 75.18; H, 5.52; N, 10.96%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1743 (C═O); δ_H (300 MHz, $CDCl_3$) 8.51 (1H, br s, N*H*, D_2O exchangeable), 7.83 (1H, br s, N*H*, D_2O exchangeable), 7.51–5.89 (15H, m, Ph), 5.58 (1H, s, C4-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.1, 156.4, 134.3, 131.0, 128.7, 128.4, 127.4, 127.0, 124.8, 119.8, 118.9, 118.7, 118.4, 114.4, 108.8, 108.7, 108.3, 105.8, 67.6, 63.1, 55.5.

4.5.24. 1-(4′-Methoxyphenyl)-3,3-bis(phenylthio)-4-phenylazetidin-2-one (11a). Colourless crystalline solid;

yield 29%; mp 118–120 °C; [Found: C, 71.54; H, 4.90; N, 2.94. $C_{28}H_{23}NO_2S_2$ requires C, 71.61; H, 4.95; N, 2.98%]; R_f (10% EtOAc/hexane) 0.55; IR (cm^{-1}, KBr): 1741(C═O); δ_H (300 MHz, $CDCl_3$) 7.68–6.73 (19H, m, Ph), 5.15 (1H, s, C4-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.7, 156.3, 139.6, 139.1, 135.7, 134.9, 132.5, 130.5, 130.1, 128.5, 18.3, 128.1, 118.9, 114.2, 72.5, 67.0, 55.4; *m/z*: 469 (M^+).

4.5.25. 1-(4′-Methoxyphenyl)-3,3-bis(phenylthio)-4-(4′-methoxyphenyl)azetidin-2-one (11b). Yellow oil; yield 38%; [Found: C, 69.76; H, 4.98; N, 2.74. $C_{29}H_{25}NO_3S_2$ requires C, 69.72; H, 5.04; N, 2.80%]; R_f (10% EtOAc/hexane) 0.50; IR (cm^{-1}, $CHCl_3$): 1748 (C═O); δ_H (300 MHz, $CDCl_3$) 7.78–6.71 (18H, m, Ph), 5.12 (1H, s, C4-*H*), 3.75 (3H, s, OCH_3), 3.72 (3H, s, OCH_3).

4.5.26. 1-Benzyl-3,3-bis(phenylthio)-4-phenylazetidin-2-one (11c). Colourless crystalline solid; yield 16%; mp 134–136 °C; [Found: C, 74.09; H, 5.06; N, 3.04. $C_{28}H_{23}NOS_2$ requires C, 74.14; H, 5.11; N, 3.09%]; R_f (10% EtOAc/hexane) 0.55; IR (cm^{-1}, KBr): 1763 (C═O); δ_H (300 MHz, $CDCl_3$) 7.57–6.78 (20H, m, Ph), 4.80 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 4.62 (1H, s, C4-*H*), 3.90 (1H, d, *J* 15.0 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 166.1, 136.1, 134.8, 134.2, 132.7, 130.5, 130.1, 129.5,129.2, 128.7, 128.5, 128.3, 127.7, 73.0, 66.5, 44.6.

4.5.27. 1-(4′-Methoxyphenyl)-3,3-bis(benzylthio)-4-phenylazetidin-2-one (11d). White crystalline solid; yield 17%; mp 103–104 °C; [Found: C, 74.77; H, 5.62; N, 2.88. $C_{30}H_{27}NOS_2$ requires C, 74.81; H, 5.65; N, 2.91%]; R_f (10% EtOAc/hexane) 0.50; IR (cm^{-1}, KBr): 1755 (C═O); δ_H (300 MHz, $CDCl_3$) 7.29–6.65 (19H, m, Ph), 4.84 (1H, s, C4-*H*), 4.14 (2H, m, CH_2S), 3.84 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.67 (3H, s, OCH_3), 3.55 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 162.1, 156.4, 137.2, 136.3, 132.8, 130.6, 129.4, 129.4, 129.0, 128.7, 128.4, 128.3, 128.2, 127.3, 127.2, 118.8, 114.3, 71.3, 68.9, 55.2, 35.6, 34.7.

4.6. General procedure for Raney-nickel desulfurization

To a suspension of Raney-nickel (10 mmol, 100% activated) in dry acetone (10 mL) were added **9c/9d/9k/9t** (1 mmol). The suspension was refluxed for 1 h. The progress of reaction was checked by TLC. After disappearance of spot for starting β-lactam and appearance of new spot, suspension was filtered and acetone was evaporated in vacuo, extracted with methylene chloride (3×20 mL) and then dried (anhydrous Na_2SO_4). The residue so obtained was purified by silica gel column chromatography (10% EtOAc/hexane).

4.6.1. *cis*-1-Benzyl-3-(4′-methoxyphenyl)-4-phenylazetidin-2-one (12). Yellow oil; yield 53%; [Found: C, 80.50; H, 6.13; N, 4.04. $C_{23}H_{21}NO_2$ requires C, 80.46; H, 6.16; N, 4.09%]; IR (cm^{-1}, $CHCl_3$): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.30–6.60 (14H, m, Ph), 5.02 (1H, d, *J* 14.9 Hz, CH_aH$_b$Ph), 4.81 (1H, d, *J* 5.5 Hz, C3-*H*), 4.76 (1H, d, *J* 5.6 Hz, C4-*H*), 3.92 (1H, d, *J* 14.8 Hz, CH$_a$$H_b$Ph), 3.66 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 168.5, 158.4, 135.5, 134.9, 129.8, 129.1, 128.8, 127.5, 126.5, 124.8, 113.5, 60.4, 59.9, 55.1, 44.7.

4.6.2. *cis*-1-Benzyl-3-(2′-methoxynaphthyl)-4-phenylazetidin-2-one (13). Yellow oil; yield 56%; [Found: C, 82.54; H, 5.26; N, 3.67. $C_{26}H_{20}NO_2$ requires C, 82.52; H, 5.32; N, 3.70%]; IR (cm^{-1}, $CHCl_3$): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.84–6.92 (16H, m, Ph), 5.26 (1H, d, *J* 5.5 Hz, C3-*H*), 5.05 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.97 (1H, d, *J* 5.7 Hz, C4-*H*), 4.16 (1H, d, *J* 14.8 Hz, CH$_a$$H_b$Ph), 3.86 (3H, s, OC$H_3$).

4.6.3. *cis*-1-(4′-Methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-4-phenylazetidin-2-one (14). White solid; yield 78%; mp 122–123 °C; [Found: C, 74.05; H, 5.89; N, 3.56. $C_{24}H_{23}NO_4$ requires C, 74.02; H, 5.95; N, 3.60%]; IR (cm^{-1}, $CHCl_3$): 1735 (C═O); δ_H (300 MHz, $CDCl_3$) 7.23–6.25 (12H, m, Ph), 5.27 (1H, d, *J* 6.0 Hz, C3-*H*), 5.00 (1H, d, *J* 5.7 Hz, C4-*H*), 3.65 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.44 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.2, 155.9, 153.0, 150.7, 134.7, 131.4, 128.8, 127.5, 127.2, 126.2, 122.0, 118.4, 115.2, 114.2, 113.3, 110.0, 96.1, 61.7, 60.2, 55.9, 55.3, 55.0.

4.6.4. *cis*-1-(4′-Methoxyphenyl)-3-(2′-furanyl)-4-phenylazetidin-2-one (15). White semisolid; yield 90%; [Found: C, 75.18; H, 5.27; N, 4.36. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.36; N, 4.39%]; IR (cm^{-1}, $CHCl_3$): 1759 (C═O); δ_H (300 MHz, $CDCl_3$) 7.25–6.67 (9H, m, Ph), 6.97 (1H, dd, *J* 11.4, 11.4 Hz, $C_4H_aH_bH_c$O), 6.07 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 6.00 (1H, dd, *J* 1.8, 1.8 Hz, $C_4H_aH_bH_c$O), 5.25 (1H, d, *J* 5.7 Hz, C3-*H*), 4.88 (1H, d, *J* 5.7 Hz, C4-*H*), 3.68 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 156.2, 146.2, 142.5, 131.2, 128.3, 128.2, 126.9, 118.4, 114.4, 110.1, 109.8, 96.2, 59.7, 55.3, 54.7, 29.8.

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17. Crystal data for **10a**: monoclinic, $P2_1/n$, a=11.361(1), b=11.083(1), c=19.635(1) Å, β=92.33(1)°, V=2470.2(3) Å^3, Z=4, ρ_{calcd}=1.252 mg/m^3, μ(Mo Kα)=0.083 mm^{-1}, full matrix least-square on F^2, R_1=0.0493, wR_2=0.1102 for 2339 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **10a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292646.
18. Crystal data for **11a**: monoclinic, $C2/c$, a=16.546(1), b=12.185(1), c=24.07(2) Å, β=93.24(1)°, V=4845.1(3) Å^3, Z=8, ρ_{calcd}=1.288 mg/m^3, μ(Mo Kα)=1.288 mm^{-1}, full matrix least-square on F^2, R_1=0.0384, wR_2=0.1011 for 3147 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **11a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292647.
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20. Crystal data for **9j**: monoclinic, $P2_1/c$, a=10.546(1), b=21.341(2), c=12.501(1) Å, β=108.60(1)°, V=2666.5(4) Å^3, Z=4, ρ_{calcd}=1.289 mg/m^3, μ(Mo Kα)=0.157 mm^{-1}, full matrix least-square on F^2, R_1=0.0407, wR_2=0.1115 for 3655 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **9j** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292645.
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22. Crystal data for **9s**: triclinic, $P1^-$, a=9.784(1), b=11.675(1), c=11.905(1) Å, β=72.69(1)°, V=1262.7(2) Å^3, Z=2, ρ_{calcd}=1.282 mg/m^3, μ(Mo Kα)=0.164 mm^{-1}, full matrix least-square on F^2, R_1=0.0344, wR_2=0.0915 for 3511 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **9s** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292648.

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A tandem enyne/ring closing metathesis approach to the synthesis of novel angularly fused dioxa-triquinanes

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Abstract—Triquinanes and their oxygenated congeners, oxa- and dioxa-triquinanes, exhibit versatile biological activities in conjunction with synthetically challenging molecular architecture. Owing to these properties, several new strategies have been developed to accomplish the synthesis of these sesquiterpenes. Among the new strategies, cascade radical cyclization strategy has been broadly explored and well studied. Herein, we report our efforts in detail for the synthesis of dioxa-triquinanes using a domino enyne/RCM strategy as the key step. Carbohydrate based synthesis not only allows the use of inexpensive and optically pure starting materials, but also the furanose derivatives, which already possess one of the requisite dihydro-furan moieties in the desired dioxa-triquinane. The other two five-membered rings were constructed simultaneously by the cascade enyne/RCM reaction using the Grubbs' second-generation catalyst. During the course of our synthesis it was observed that the acetonide protection hinders the RCM reaction, after the initial enyne metathesis reaction. The reaction underwent smoothly under argon atmosphere, whilst use of ethylene atmosphere was found to hinder the formation of the tandem enyne/RCM product. The effect of substitution on the key reaction is described here.

1. Introduction

Sesquiterpenoids can be considered as important biochemical intermediates and natural products. This has driven the development of several new methodologies and strategies developed over the last four decades. Polyquinanes,[1] an important class of natural products belonging to the sesquiterpenoid family, consist of three or more fused five-membered ring systems. Amongst the polyquinanes, the triquinane framework natural products are most versatile and abundant in nature. The triquinane natural products consist of three five-membered rings fused together and depending on the fusion pattern they can be broadly classified into three types: propellanes, linear, and angular triquinanes.[1g] They are usually isolated either from plants or marine sources and occasionally show microbial origin (Fig. 1).

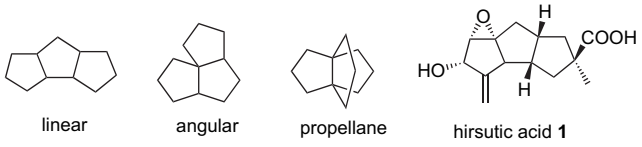

Figure 1.

Hirsuitic acid-C_1 **1** was the first polyquinane natural product isolated[2] from Basidomycetes *Stereum hirsutum* and since then synthetic chemists have been engaged in the synthesis of this novel family of sesquiterpenes. The promising biological activities have led efforts to prepare triquinane framework, which can be considered an emerging area of natural product synthesis. As a consequence, several strategies,[3] especially cascade radical methods,[4] transannulation reactions,[5] alkene–arene photocycloaddition reactions,[6] have been employed to meet the challenges posed by this family of compounds. Despite the wealth of literature available for the isolation of carbocyclic triquinanes, there are only scattered reports on the isolation[7,8] or syntheses[9] of these structurally novel siblings oxa- and dioxa-triquinanes (Fig. 2).

The oxa- and dioxa-triquinanes bear one and two dihydrofuran moieties, respectively, either in linear or angular fashion. In 1989, Kouno reported the first isolation of anislactone A (**2**) and B (**3**) from *Illicium anisatum*.[10] These anislactone-type sesquiterpenes consist of two consecutive

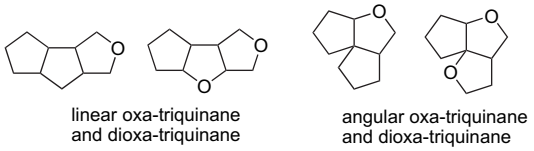

Figure 2.

Keywords: Triquinanes; Dioxa-triquinanes; Grubbs' catalyst; Tandem enyne/RCM; Carbohydrates.
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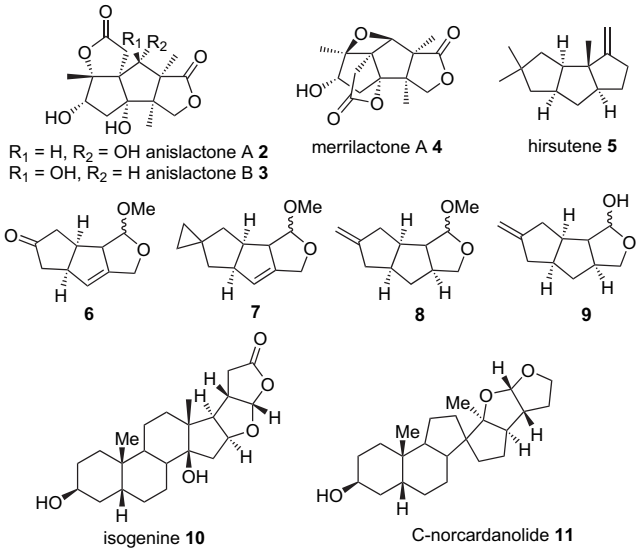


Figure 3.

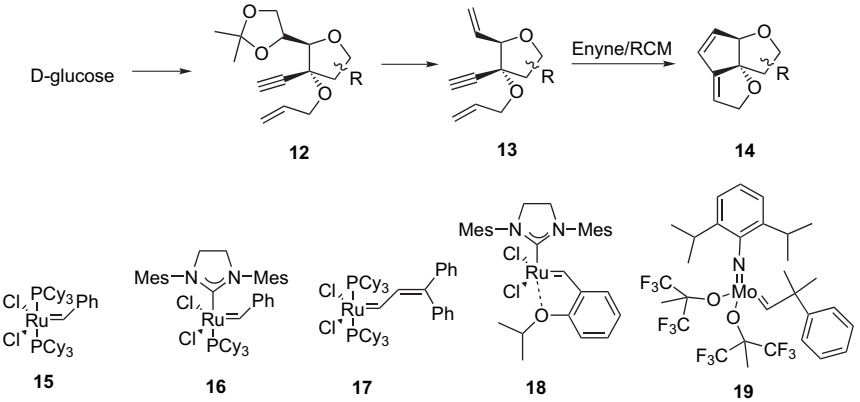
five-membered ring frameworks fused with two γ-lactones. Merrilactone A (**4**), another interesting sesquiterpene lactone, was recently isolated from *Illicium merrillianum*.[11] It was shown that merrilactone A (**4**) significantly promotes neurite growth in primary cultures of fetal rat cortical neurons at very low concentration (0.1–10 μmol). These promising biological activities can be attributed to the oxygenated pentacyclic architecture making them attractive synthetic targets.[12] Furthermore, there are a couple of steroid based hybrid natural products isogenine **10**[7] and C-norcardanolide **11**[8] possessing dioxa-triquinane subunits (Fig. 3). Moreover, interestingly some of the reported syntheses of carbocyclic triquinanes proceed via oxa-triquinanes. For example, Fukumoto's synthesis of hirsutene **5** involved oxa-triquinanes **6**, **7**, **8**, and **9** as key intermediates and fortuitously when these intermediates were subjected to biological activity testing, all these exhibited potent in vitro cytotoxic activity against murine leukemia cells and KB human epidermoid carcinoma cells.[13] From these examples, one may speculate that the oxygen in these natural and unnatural products could be important for biological activity. Thus the design and synthesis of natural and unnatural oxa- and dioxa-triquinanes become a promising area for organic synthesis. Most of the approaches employed for the construction of triquinane framework elegantly explored cascade radical cyclization methods.[4] Herein, we report our alternate approach involving a domino enyne/RCM strategy to dioxa-triquinanes.

2. Results and discussion

As a part of our Chiron approach program,[14] we developed interest in the preparation of oxa- and dioxa-triquinanes. This paper details a carbohydrate based enantiospecific route to angularly fused dioxa-triquinanes using a tandem enyne/RCM reaction.[15]

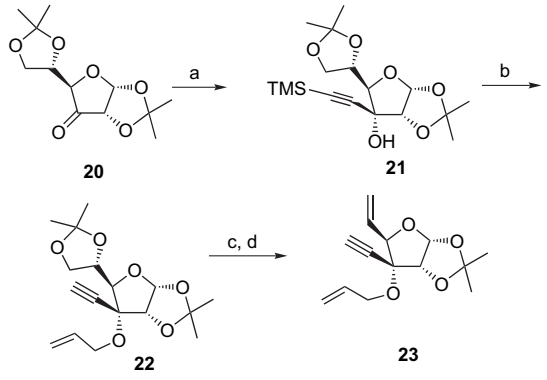
In view of developing a strategy for the synthesis of dioxa-triquinanes, it was necessary to consider some of the following points: sugar templates have been useful starting materials and they have been elegantly transformed[16] into triquinanes, oxa-triquinanes, and dioxa-triquinanes. Also cascade reactions[17] provide easy and rapid access to the polycyclic systems. The structural complexity associated with the promising biological activity has necessitated the development of new approaches for the synthesis of dioxa-triquinanes. But to date, most of the synthetic strategies elegantly utilized cascade radical cyclization methods.[4] However, to the best of our knowledge until our initial report, a tandem metathetic strategy had not been employed to construct these triquinanes. With the advent of air stable ruthenium catalysts and Schrock's molybdenum catalysts,[18] the last decade has witnessed a huge exploitation of enyne[19] and ring closing metathesis[20] (RCM) in organic synthesis and we describe here our results in detail about our successful cascade metathetic strategy[21,22] to synthesize dioxa-triquinanes.[15]

From a synthetic perspective, we envisaged that the enyne **12** could be easily prepared from a sugar template and in a couple of steps it could be transformed into the dienyne **13**, a precursor for the key tandem enyne/ring closing metathesis reaction leading to the desired dioxa-triquinane **14** using Grubbs' first generation catalyst **15** and second-generation catalyst **16** (Scheme 1). We envisaged that this new tandem metathetic strategy, if successful, would allow rapid access to a range of such dioxa-triquinanes from different sugar templates.



Scheme 1. Retrosynthesis for desired dioxa-triquinanes.

Our route to the synthesis of dioxa-triquinane commenced from the readily available ketone **20**[23] (Scheme 2), which possesses one oxaquinane unit. Treatment of the ketone **20**, with lithium trimethylsilylacetylide, generated in situ from trimethylsilylacetylene and ^{n}BuLi, afforded the alcohol **21** in high yield. The stereochemical outcome of this Grignard addition reaction is well established in the literature, which takes place from the β-face[24] to give a tertiary alcohol **21** with the required stereochemistry at C-3. This stereochemistry is important from the point of view of the key tandem metathetic reaction. Subsequent protection of the tertiary alcohol **21** as allyl ether on treatment with sodium hydride and allyl bromide in THF resulted in only 30% yield. Use of ^{n}BuLi in THF/HMPA worked well on a small scale (0.1 g). However, while on scaling up (1.0 g), this reaction failed to give **22** in consistent yield and so an alternate method was sought. Sodium hydride and allyl bromide in DMF not only achieved the protection of the tertiary alcohol **21**, but also simultaneously removed the trimethylsilyl group to generate the enyne **22** in good yield. At this stage, our next task was to install the other alkene moiety required for the tandem reaction. This was successfully achieved through selectively deprotecting the more labile acetonide group of enyne **22** under mild acidic conditions. The resultant vicinal diol, without purification, was then converted into the desired dienyne **23** in a single step following Garregg's protocol.[25]



Scheme 2. Reagents and conditions: (a) TMS–acetylene, ^{n}BuLi, THF, 0 °C, rt, 80%; (b) NaH, allyl bromide, DMF, 2 h, 78%; (c) 60% AcOH, rt, 18 h; (d) PPh_3, I_2, imidazole, toluene, reflux, 5 h, 85% (for two steps).

With the dienyne **23** in hand, we were set for the key tandem enyne/RCM reaction using the Grubbs' catalysts. However, as shown in Table 1, all efforts to obtain **25** did not succeed at this stage. The use of catalyst **15** in refluxing CH_2Cl_2 afforded only the enyne metathesis product **24** (entry 1). The use of more reactive catalyst **16** improved the yield of enyne product **24** but still could not provide the required tandem enyne/RCM product **25**. Unfortunately, alteration of solvent from refluxing CH_2Cl_2 to toluene at 80 °C also did not alter the outcome. Substituting ethylene[26] for argon atmosphere gave the intermediate enyne product, although the yield was slightly improved (see Table 1). Speculating that the activity of the catalyst would have reduced due to longer reaction time, we subjected the isolated triene **24** to RCM reaction conditions independently with catalysts **15** and **16** and unfortunately, all attempts to access the diene **25** were thwarted.

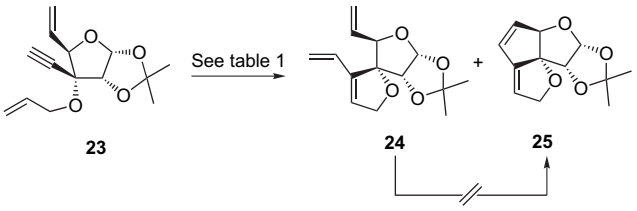


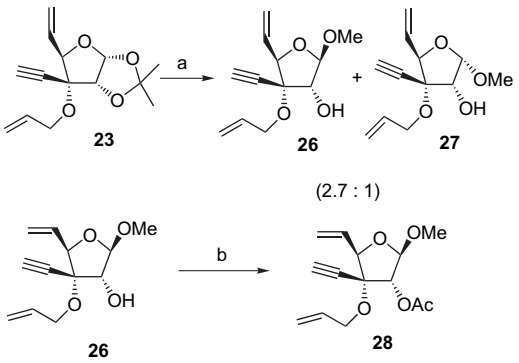
Table 1. Effect of solvent and catalyst on tandem enyne/RCM

	Catalyst	Conditions	Yield of **24**[a] (%)
1	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (argon)	65
2	**16** (5 mol %)	CH_2Cl_2, reflux, 12 h (argon)	73
3	**16** (5 mol %)	Toluene, 80 °C, 12 h (argon)	75
4	**16** (5 mol %)	CH_2Cl_2, reflux, 12 h (ethylene)	78

[a] Product **25** didn't form under these reaction conditions.

At this stage, the failure of the RCM reaction after initial enyne metathesis reaction led us to study the acetonide protection. We envisaged that the acetonide protection in the enyne product **24** would not force the two double bonds to come closer for the RCM reacton.[15,27] So we decided to remove the acetonide group of **23**, anticipating a relief in the ring strain, which in turn could probably bring the two double bonds closer after the initial enyne metathesis reaction.

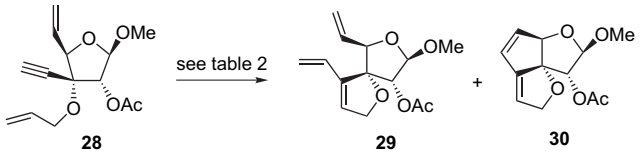
To probe the feasibility of this hypothesis, the dienyne **23** was first treated with concd HCl in methanol at room temperature to afford a readily separable anomeric mixture of hydroxy dienynes **26** and **27** in the ratio 2.7:1 with a global yield of 89% (Scheme 3). To avoid any complicated interference of OH group during the tandem metathetic process, the major anomer **26**, under standard conditions, was converted to its acetate **28** in excellent yield. It was found that the stereochemistry reported at the anomeric center for the acetate in our preliminary communication[15] was actually the opposite diastereomer, which was supported by X-ray crystallography.



Scheme 3. Reagents and conditions: (a) concd HCl, MeOH, rt, 36 h, 89% (3:11); (b) Ac_2O, Py, DMAP, rt, 8 h, 90%.

With the precursor **28** in hand, the next important task was to check the feasibility of the key tandem enyne/RCM reaction (see Table 2). To begin with, we first attempted the reaction in refluxing CH_2Cl_2 using catalyst **15** under argon atmosphere. To our surprise, the normally facile enyne metathesis

did not work under these conditions (entry 1). When this reaction was carried out under ethylene atmosphere, only a trace of the enyne product **29** was obtained, with the remainder being the starting material. When the more reactive catalyst **16** was employed in CH_2Cl_2 under argon atmosphere at room temperature, though the enyne product **29** was the major product (54%), for the first time the tandem metathesis product **30** (36%) was produced. Encouraged by this result, we attempted this reaction under reflux conditions keeping the other parameters identical. The dienyne acetate **28** underwent a smooth tandem enyne metathesis/RCM to afford a mixture of **29** and **30** in approximately a 1:2 ratio with a combined yield of more than 95% (entry 4). The yield of the tandem enyne/RCM product **30** was found to be almost unaffected when the solvent was changed from refluxing CH_2Cl_2 to toluene at 80 °C (entry 5). This shows that the solvent do not make much difference in the overall distribution of the products. When the tandem enyne/RCM metathesis of dienyne acetate **28** was carried out under ethylene atmosphere using catalyst **16** in either solvent, the major product obtained was the enyne metathesis **29** with only traces of product **30** formed (entries 6 and 7).



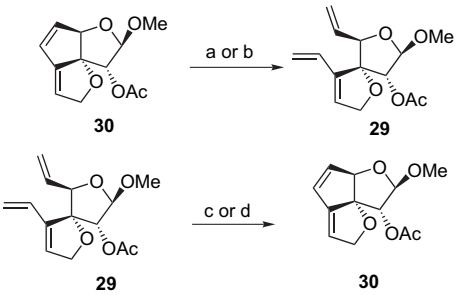
28 **29** **30**

Table 2. Effect of solvent and catalyst on tandem enyne/RCM

	Catalyst	Conditions	Products ratio (%) [**29**:**30**]	
1	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (argon)	No reaction	
2	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (ethylene)	08	00
3	**16** (5 mol %)	CH_2Cl_2, rt, 48 h (argon)	54	36
4	**16** (5 mol %)	CH_2Cl_2, reflux, 36 h (argon)	*36*	*60*
5	**16** (5 mol %)	Toluene, 80 °C, 36 h (argon)	*35*	*59*
6	**16** (5 mol %)	CH_2Cl_2, reflux, 36 h (ethylene)	61	13
7	**16** (5 mol %)	Toluene, 80 °C, 36 h (ethylene)	73	05

As shown in Table 2, ethylene atmosphere did not assist in driving the equilibrium in favor of the tandem metathesis product. Presumably, it could be due to the reversibility of the reaction or ring-opening metathetic (ROM) reaction. To support this assumption, the tandem metathesis product **30** was treated with catalyst **16** under ethylene atmosphere in refluxing CH_2Cl_2 and we observed that the reaction reverts back to give the product **29** in 40% (74% based on recovery of starting material) yield. The same reaction was found to be sluggish when the first generation catalyst **15** was used (Scheme 4).

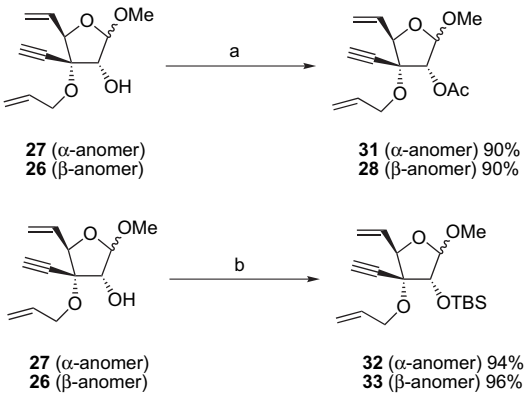
We also reasoned that during the tandem metathetic reaction, the catalyst appeared to become deactivated over time and so, we decided to isolate the enyne metathesis product **29** and subjected it to the RCM reaction conditions. As anticipated, the reaction proceeded well with catalyst **16**, though the starting material was not completely consumed. The reaction was too slow when catalyst **15** was employed.



30 **29** **29** **30**

Scheme 4. Reagents and conditions: (a) **16** (5 mol %), ethylene, CH_2Cl_2, reflux, 24 h, 40% (74% BRSM); (b) **15** (10 mol %), ethylene, CH_2Cl_2, reflux, 24 h, 19% (68% BRSM); (c) **16** (5 mol %), argon, CH_2Cl_2, reflux, 24 h, 38%; (d) **15** (10 mol %), argon, CH_2Cl_2, reflux, 24 h, 9%.

From Table 2, it is clear that use of catalyst **16** (5 mol %) in refluxing CH_2Cl_2 under argon atmosphere gives a good yield from the tandem enyne/RCM reaction. Thus we decided to study the effect of substitution at *C*-2 on the key cascade enyne/RCM reaction by employing the above standard parameters. Both the anomeric alcohols **26** (major/β-anomer) and **27** (minor/α-anomer) were protected as their acetates and TBS ethers, following the standard protocols in excellent yields (Scheme 5).



27 (α-anomer)
26 (β-anomer)

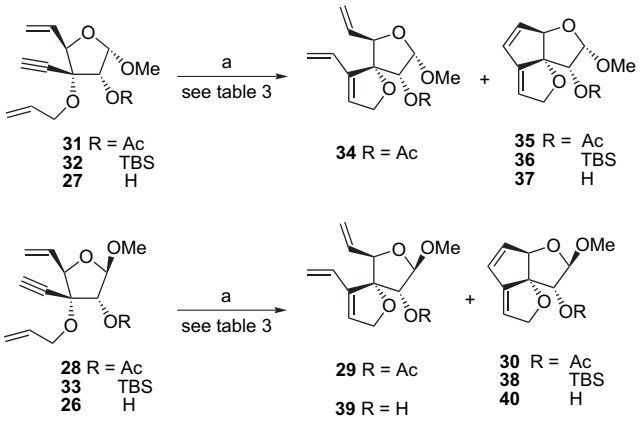
31 (α-anomer) 90%
28 (β-anomer) 90%

27 (α-anomer)
26 (β-anomer)

32 (α-anomer) 94%
33 (β-anomer) 96%

Scheme 5. Reagents and conditions: (a) Ac_2O, Py, DMAP, rt, 8 h; (b) TBSCl, imidazole, DMAP (cat.), 50 °C, 24 h.

With the anomeric substrates in hand, we evaluated the feasibility of the tandem reaction (Scheme 6 and Table 3). The tandem enyne/RCM reaction of the acetate **31** with the standard reaction conditions gave the diene **35** as the major product (56%) along the enyne product **34** (40%). The combined yield was excellent (96%) and the ratio of the tandem enyne/RCM **35** product to the interrupted product **34** was almost 3:2, which was comparable to that of the other anomeric acetate **30** (entries 1 and 2). In the case of the TBS ether **32** (α-anomer) only the tandem enyne/RCM product **36** was isolated in 76% yield (entry 3). As expected, similar results were found for TBS ether **33** (β-anomer) giving **38** in 68% yield (entry 4). After these interesting results, we employed the same reaction parameters on the dienyne alcohols **27** and **26**. The dienyne alcohol **27** (α-anomer) gave diene **37** in 58% yield after refluxing for 48 h (entry 5). In this case there was no interrupted product observed. For the major



Scheme 6. Reagents and conditions: (a) **16** (5 mol %), argon, CH_2Cl_2, reflux.

Table 3. Effect of substitution on tandem enyne/RCM

Entry	Substrate	Product ratio (%)	
		Enyne product	Tandem product
1	**31**	40	58
2	**28**	36	60
3	**32**	Not isolated	76
4	**33**	Not isolated	68
5	**27**	Not isolated	56
6	**26**	63	18

anomeric alcohol **26**, the enyne product **39** was found to be the major isolated product (63%) with a small amount of the required tandem enyne product **40** formed (entry 6). Thus the two-anomeric alcohols were found to exhibit a noticeable difference in reactivity in the key tandem enyne/RCM reaction.

The dioxa-triquinanes **36** and **37** derived from the α-anomer (minor anomer) were found to be colorless crystalline solids. The structures were confirmed by single X-ray crystallography. The ORTEP drawings for compounds **36** and **37** are shown in Figure 4.

3. Conclusion

In summary, we have developed a simple and efficient enantiospecific route to angularly fused dioxa-triquinanes utilizing a tandem enyne/ring closing metathesis reaction as the key step. We also observed and indirectly proved that the presence of an acetonide group in the system hindered the ring closing metathesis after the initial enyne metathesis reaction. We also successfully demonstrated that ethylene atmosphere hinders the progress of the final ring closing metathesis process and instead, facilitates the ring opening of the triquinanes. The generality of this synthetic scheme has been demonstrated on substrates with different alcohol protecting groups. Using this pathway, it should be possible to make several such oxa-, dioxa-triquinanes and other naturally occurring triquinanes. Efforts are underway to prepare linearly fused oxa-, dioxa-triquinanes, and linear and angular triquinanes.

4. Experimental

4.1. General

Unless and otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Solvents used: tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and hexanes were freshly distilled from calcium hydride. DMF was distilled over calcium hydride and stored over molecular sieves 4 Å. Solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried in an oven at 100 °C for 12 h before use. Air and moisture sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100–200 mesh, Acme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation was recorded on Jasco DIP-370 digital polarimeter. IR spectra were recorded from Thermo Nicolet Avater 320 FTIR and Nicolete Impact 400 machine. Mass spectra were obtained

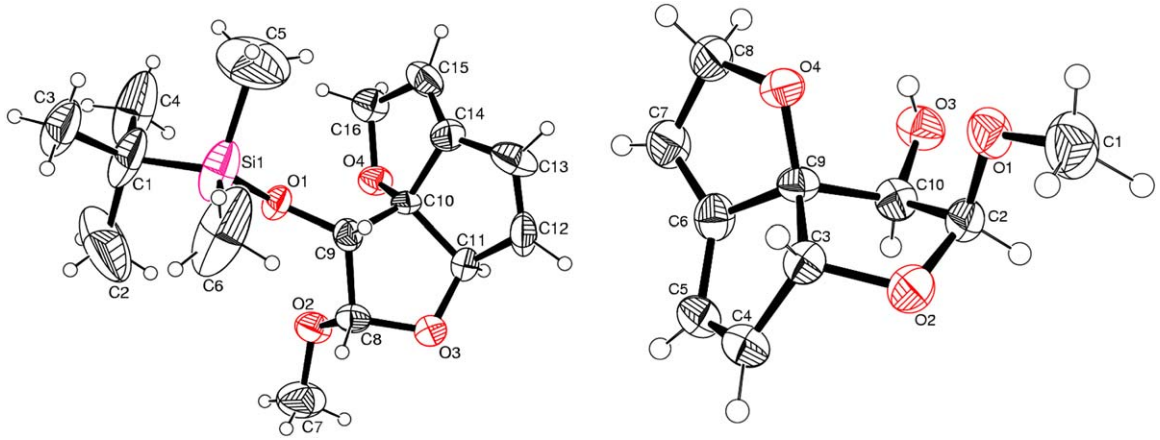


Figure 4. ORTEP diagrams for dioxa-triquinanes **36** and **37** elipsoid at 50% probability.

with Waters Micromass-Q-Tof micro™ (YA105) spectrometer. Elemental analysis was recorded on Thermo Finnigan Flash EA 1112. ^{1}H and ^{13}C NMR spectra were recorded either on Varian AS 400, Varian AS 500 or Varian ASM 300 instruments in $CDCl_3$ solutions. ^{1}H NMR data were reported in the order of chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constant J in Hertz (Hz).

4.1.1. 3-*C*-Trimethylsilylethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (21). To a solution of TMS–acetylene (1.3 ml, 9.68 mmol) in THF (15 ml) under argon atmosphere at 0 °C was added 1.6 M ^{n}BuLi in hexane (6.05 ml, 9.68 mmol). The reaction mixture was stirred at room temperature for 1 h and then a THF (20 ml) solution of the ketone **20**[23] (2.0 g, 7.75 mmol) was added dropwise at 0 °C. After 2 h at 0 °C, a saturated ammonium chloride solution (20 ml) was added and the reaction mixture was extracted with hexanes. The combined organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under vacuo and the residue was purified by flash column chromatography using 9:1 hexane/ethyl acetate to afford alcohol **21** (2.2 g) in 80% yield. R_f=0.59 (1:1 hexanes/ethyl acetate); mp 116–117 °C; $[\alpha]_D^{25}$ +12.66 (*c* 1.0, $CHCl_3$); IR (KBr) 3490, 2172, 1459, 1387, 1255, 1209, 1036, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 9H), 1.38 (s, 6H), 1.46 (s, 3H), 1.59 (s, 3H), 3.02 (br s, 1H), 3.89 (d, 1H, J=7.0 Hz), 4.03 (dd, 1H, J=8.8, 5.5 Hz), 4.14 (dd, 1H, J=8.8, 6.6 Hz), 4.38–4.40 (m, 1H), 4.58 (d, 1H, J=3.7 Hz), 5.82 (d, 1H, J=3.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.2, 25.1, 26.7, 26.8, 26.8, 66.9, 74.8, 76.0, 81.5, 84.0, 94.4, 101.7, 104.3, 109.5, 113.8; Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92. Found C, 57.15; H, 7.77. LRMS (EI) [M+Na]$^+$ 379.2010.

4.1.2. 3-*O*-Allyl-3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (22). Sodium hydride (0.18 g, 4.5 mmol) was washed with 3×10 ml of dry hexane to remove the mineral oil coatings and DMF (21 ml) was added to this fine powder under argon atmosphere followed by a DMF (7 ml) solution of alcohol **21** (1.06 g, 3 mmol) dropwise at 0 °C over a period of 15 min. Then the resultant suspension was stirred at room temperature for 2 h before quenching with allyl bromide (0.57 ml, 6.6 mmol). After 2 h, the reaction was quenched with ammonium chloride solution (20 ml) and extracted with ethyl acetate. The combined organic phase was washed with excess water, brine, and dried over anhydrous sodium sulfate. The residue thus obtained after evaporation under reduced pressure was purified by silica gel column chromatography (95:5 hexanes/ethyl acetate) to afford **22** (0.8 g, 78%). R_f=0.53 (5:1 hexanes/ethyl acetate); mp 63–65 °C; $[\alpha]_D^{25}$ +44.99 (*c* 1.0, $CHCl_3$); IR (KBr) 3246, 3094, 2991, 2951, 2900, 2116, 1652, 1398, 1158, 1057, 879, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.57 (s, 3H), 2.70 (s, 1H), 4.09–4.20 (m, 4H), 4.33–4.43 (m, 2H), 4.60 (d, 1H, J=3.7 Hz), 5.16 (ddd, 1H, J=10.8, 3.3, 1.5 Hz), 5.34 (ddd, 1H, J=17.1, 3.6, 1.8 Hz), 5.81 (d, 1H, J=3.7 Hz), 5.90–6.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.4, 26.7, 26.9, 27.0, 66.1, 67.5, 74.6, 79.3, 79.4, 80.9, 81.3, 83.3, 104.3, 109.6, 113.7, 116.6, 134.4; LRMS (EI) [M+Na]$^+$ 347.1474; Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found C, 62.39; H, 7.46. HRMS (EI) calcd for $C_{17}H_{24}O_6Na$ *m/z* 347.1471, found *m/z* 347.1474.

4.1.3. 5,6-Deoxy-1,2-*O*-isopropylidene-3-*O*-allyl-3-*C*-ethynyl-α-D-*ribo*-hex-5-enofuranose (23). AcOH (10 ml, 60%) in water was added to the enyne **22** (0.6 g, 1.85 mmol) and the mixture was stirred for 18 h. Then toluene (3×20 ml) was successively added and evaporated under vacuo to remove traces of water and acetic acid. The crude diol was used in the next step without further purification.

To a refluxing solution of the crude diol (0.58 g), imidazole (0.55 g, 8.16 mmol), and triphenylphosphine (2.14 g, 8.16 mmol) in dry toluene, iodine (1.55 g, 6.13 mmol) was added portion wise through the condenser. The reaction mixture was further refluxed for 5 h and cooled to room temperature. The organic layer was washed with saturated sodium thiosulfate solution (3×10 ml), water, brine, and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification by column chromatography (49:1 hexanes/ethyl acetate) yielded **23** (0.39 g) in 85% yield (for two steps). R_f=0.57 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +31.30 (*c* 1.15, $CHCl_3$); IR (film) 3290, 3083, 2109, 1642, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.59 (s, 3H), 2.66 (s, 1H), 4.16 (ddt, 1H, J=7.3, 3.0, 1.5 Hz), 4.31 (ddt, 1H, J=7.0, 3.0, 1.5 Hz), 4.49 (d, J=6.6 Hz), 4.64 (d, 1H, J=3.7 Hz), 5.18 (ddd, 1H, J=10.3, 3.0, 1.5 Hz), 5.28–5.39 (m, 2H), 5.49 (ddd, 1H, J=14.3, 2.6, 1.3 Hz), 5.86 (d, 1H, J=3.7 Hz), 5.83–6.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 26.8, 67.8, 78.6, 79.2, 81.7, 82.2, 82.6, 104.2, 113.6, 117.3, 120.3, 132.4, 134.4; LRMS (EI) [M+Na]$^+$ 273.1250; HRMS (EI) calcd for $C_{14}H_{18}O_4Na$ *m/z* 273.1103, found *m/z* 273.1100.

4.1.4. Methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-D-*ribo*-hex-5-enofuranosides (26 and 27). To a solution of dienyne diacetonide **23** (0.7 g, 2.8 mmol) in dry methanol (30 ml) was slowly added concd HCl (4 ml) and stirred at room temperature for 36 h. Then solid sodium bicarbonate was added to neutralize the acid and filtered. The residual solid was washed with ethyl acetate. The organic solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using 93:7 hexanes/ethyl acetate to afford a mixture of anomeric alcohols **27** (0.15 g, 24%) and **26** (0.41 g, 65%).

β-Anomer **26**: R_f=0.3 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −20.59 (*c* 1.02, $CHCl_3$); IR (film) 3467, 3296, 3092, 2993, 2118, 1645, 1124, 1045, 928 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 1H), 3.47 (s, 3H), 4.14 (d, 1H, J=2.6 Hz), 4.23 (d, 2H, J=5.5 Hz), 4.52 (d, 1H, J=6.9 Hz), 4.89 (d, 1H, J=2.6 Hz), 5.23 (dd, 1H, J=10.2, 1.5 Hz), 5.31–5.37 (m, 2H), 5.44 (dd, 1H, J=17.1, 1.5 Hz), 5.91–6.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.3, 67.2, 78.2, 79.2, 80.4, 80.6, 84.3, 109.0, 117.9, 118.9, 133.8, 134.9; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ *m/z* 247.0946, found *m/z* 247.0935.

α-Anomer **27**: R_f=0.24 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +147.27 (*c* 1.10, $CHCl_3$); IR (film) 3353, 3296, 3092, 2105, 1650, 1144, 1030, 933 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (s, 1H), 3.50 (s, 3H), 4.24–4.29 (m, 3H),

4.47 (d, 1H, J=7.3 Hz), 5.04 (d, 1H, J=4.8 Hz), 5.15–5.20 (m, 1H), 5.30–5.45 (m, 3H), 5.89–6.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.9, 67.4, 77.6, 78.0, 79.9, 80.3, 83.6, 101.9, 116.9, 119.1, 134.1, 134.4; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ m/z 247.0946, found m/z 247.0943.

4.2. General procedure for methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-D-*ribo*-hex-5-enofuranosides (28 and 31)

Acetic anhydride (3 ml) and a catalytic amount of DMAP were added to alcohol **26** or **27** (0.24 g, 1.07 mmol) in pyridine (3 ml) at room temperature. After 8 h at room temperature, toluene (10 ml×3) was successively added and removed under reduced pressure. The crude residue was chromatographically purified using 95:5 hexanes/ethyl acetate as eluent. The acetate **28** or **31** was obtained as colorless oil.

Compound **28**: R_f=0.59 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −23.58 (c 1.06, $CHCl_3$); IR (film) 3310, 2258, 1743, 1641, 1231, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.74 (s, 1H), 3.45 (s, 3H), 3.98 (ddt, 1H, J=7.2, 3.0, 1.5 Hz), 4.25 (ddt, 1H, J=6.6, 3.0, 1.5 Hz), 4.46 (d, 1H, J=6.9 Hz), 4.93 (d, 1H, J=1.5 Hz), 5.14 (ddd, 1H, J=10.8, 3.0, 1.5 Hz), 5.27 (ddd, 1H, J=17.7, 3.6, 1.8 Hz), 5.32 (d, 1H, J=1.5 Hz), 5.36 (ddd, 1H, J=10.2, 2.4, 1.5 Hz), 5.46 (ddd, 1H, J=17.1, 2.4, 1.5 Hz), 5.80–5.91 (m, 1H), 6.00–6.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 56.0, 67.9, 78.0, 78.7, 79.4, 79.7, 85.1, 107.3, 116.8, 119.5, 134.2, 169.4; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1053 .

Compound **31**: R_f=0.53 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +139.86 (c 1.43, $CHCl_3$); IR (film) 3272, 2109, 1753, 1653, 1239, 1050, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 2.70 (s, 1H), 3.47 (s, 3H), 4.01 (ddt, 1H, J=7.0, 2.9, 1.5 Hz), 4.26 (ddt, 1H, J=7.0, 2.9, 1.5 Hz), 4.53 (d, 1H, J=6.9 Hz), 5.15 (ddd, 1H, J=10.2, 2.9, 1.5 Hz), 5.23–5.31 (m, 2H), 5.34 (d, 1H, J=4.4 Hz), 5.39 (ddd, 1H, J=10.2, 1.5, 0.7 Hz), 5.47 (dt, 1H, J=17.5, 1.8 Hz), 5.82–6.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 56.6, 67.9, 75.2, 78.8, 79.1, 80.0, 83.1, 102.1, 116.9, 120.1, 133.2, 134.1, 169.9; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1055.

4.3. General procedure for methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-2-*O*-tertiary butyl dimethyl silyl-D-*ribo*-hex-5-enofuranosides (32 and 33)

To a solution of alcohols **26** or **27** (0.2 g, 0.89 mmol) in DMF (1.3 ml) was added imidazole (0.182 g, 2.67 mmol), DMAP (cat.) and TBSCl (0.161 g, 1.07 mmol) and the reaction mixture was stirred for 24 h at 40–50 °C. The solution was then diluted with diethyl ether and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column chromatography using 97:3 hexanes/ethyl acetate as eluent to afford the TBS ethers **33** or **32** in excellent yields.

Compound **32**: Yield=94%; R_f=0.53 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +134.71 (c 1.03, $CHCl_3$); IR (film) 3297, 3240, 2245, 1649, 1254, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 2.66 (s, 1H), 3.46 (s, 3H), 4.22–4.27 (m, 3H), 4.54 (d, 1H, J=6.9 Hz), 4.96 (d, 1H, J=3.9 Hz), 5.11 (ddd, 1H, J=10.6, 3.3, 1.5 Hz), 5.23–5.34 (m, 2H), 5.42 (dt, 1H, J=17.2, 1.8 Hz), 5.86–6.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7, −4.5, 18.5, 25.9, 56.0, 67.6, 77.7, 78.9, 80.5, 81.1, 83.9, 103.5, 116.2, 118.9, 134.6, 135.1; HRMS (EI) calcd for $C_{18}H_{30}O_4Na$ m/z 361.1811, found m/z 361.1829.

Compound **33**: Yield=96%; R_f=0.47 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +27.94 (c 1.02, $CHCl_3$); IR (film) 3290, 3240, 2240, 1652, 1263, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 2.65 (s, 1H), 3.48 (s, 3H), 4.12 (d, 1H, J=3.7 Hz), 4.29 (ddd, 2H, J=6.9, 2.9, 1.5 Hz), 4.51 (dt, 1H, J=6.2, 1.2 Hz), 4.84 (d, 1H, J=3.7 Hz), 5.14 (ddd, 1H, J=10.2, 2.7, 1.2 Hz), 5.26–5.33 (m, 2H), 5.46 (dt, 1H, J=17.2, 1.8 Hz), 5.87–6.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7, 18.1, 25.8, 56.7, 67.7, 78.1, 79.5, 80.6, 82.0, 85.3, 109.0, 116.2, 118.0, 135.1, 135.4; HRMS (EI) calcd for $C_{18}H_{30}O_4Na$ m/z 361.1811, found m/z 361.1821.

4.4. General procedure for tandem enyne/RCM reaction

A 1 mmol portion of dienyne was dissolved in 325 ml of dry dichloromethane under argon/ethylene atmosphere and the solution was degassed. To this was added a dichloromethane solution of Grubbs' catalyst (10 mol % of **15** or 5 mol % of **16**). The reaction mixture was refluxed for 12–48 h as mentioned Tables 1–3. The reaction mixture was cooled to room temperature and DMSO (50 equiv to catalyst) was added and stirred for 6 h. Evaporation of the solvent and purification by column chromatography yielded the corresponding product(s).

4.4.1. Enyne products. *Compound* **24**: Yield=78%; R_f=0.23 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −27.18 (c 1.03, $CHCl_3$); IR (film) 3085, 2987, 2934, 2854, 1643, 1382, 1374, 1088, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.65 (s, 3H), 4.34 (d, 1H, J=3.7 Hz), 4.64–4.7 (m, 3H), 5.22 (d, 2H, J=10.6 Hz,), 5.42 (d, 1H, J=17.2 Hz), 5.58 (dd, 1H, J=17.4, 0.9 Hz), 5.69–5.78 (m, 1H), 5.81 (d, 1H, J=3.7 Hz), 6.08–6.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 26.8, 75.0, 81.5, 82.4, 96.3, 103.8, 112.8, 118.7, 119.0, 124.9, 127.7, 132.2, 138.4; HRMS (EI) calcd for $C_{14}H_{18}O_4Na$ m/z 273.1103, found m/z 273.1100.

Compound **29**: Yield=36%; R_f=0.48 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −60.82 (c 1.15, $CHCl_3$); IR (film) 3085, 2926, 2851, 1745, 1234, 1071, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 3.55 (s, 3H), 4.32 (d, 1H, J=6.9 Hz), 4.45 (ddd, 1H, J=13.8, 1.8, 0.9 Hz), 4.58 (ddd, 1H, J=13.8, 1.8, 1.2 Hz), 4.97 (d, 1H, J=3.9 Hz), 5.02 (d, 1H, J=3.9 Hz), 5.19–5.24 (m, 2H), 5.37 (ddd, 1H, J=17.1, 3.0, 1.5 Hz), 5.62 (dd, 1H, J=18.0, 0.6 Hz), 5.83 (ddd, 1H, J=17.4, 10.5, 6.9 Hz), 6.01 (br s, 1H), 6.35 (ddd, 1H, J=18.0, 11.4, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 57.0, 74.8, 79.0, 85.1, 93.2, 107.1, 117.7, 118.7, 125.1, 128.3, 133.1, 138.7, 169.9; LRMS (EI) [M+Na]$^+$ 289.1233; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1064.

Compound **34**: Yield=40%; R_f=0.39 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +87.42 (c 1.15, $CHCl_3$); IR (film) 3087,

2926, 2851, 1748, 1234, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 3.47 (s, 3H), 4.62–4.69 (m, 3H), 5.04 (d, 1H, J=4.8 Hz), 5.19–5.26 (m, 3H), 5.35 (dt, 1H, J=17.2, 1.6 Hz), 5.44 (d, 1H, J=18.0 Hz), 5.85–5.94 (m, 1H), 6.03 (br s, 1H), 6.35 (dd, 1H, J=18.0, 11.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 55.4, 74.6, 74.7, 84.4, 93.1, 100.8, 117.9, 118.2, 126.9, 128.4, 133.1, 138.8, 170.5; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ *m/z* 289.1052, found *m/z* 289.1061.

Compound **39**: Yield=63%; R_f=0.43 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −14.99 (*c* 3.00, $CHCl_3$); IR (film) 3434, 2925, 2855, 1454, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.98 (d, 1H, J=7.2 Hz), 3.56 (s, 3H), 3.97 (dd, 1H, J=6.0, 4.39 Hz) 4.39 (d, 1H, J=8 Hz), 4.70 (s, 2H), 4.79 (d, 1H, J=4.4 Hz), 5.216 (t, 2H, J=10.6 Hz), 5.37 (d, 1H, J=17.6 Hz), 5.58 (d, 1H, J=18.0 Hz), 5.81–5.89 (m, 1H), 6.04 (br s, 1H), 6.26 (dd, 1H, J=17.6, 11.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.1, 74.5, 85.2, 94.8, 110.1, 118.1, 124.9, 128.1, 133.9, 138.5; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ *m/z* 247.0946, found *m/z* 247.0949.

4.4.2. Tandem enyne/RCM products. *Compound* **30**: Yield=60%; R_f=0.32 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −109.31 (*c* 1.15, $CHCl_3$); IR (film) 3079, 2933, 1742, 1377, 1242, 1110, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 3.37 (s, 3H), 4.80 (dd, 1H, J=13.5, 2.6 Hz), 4.90 (dd, 1H, J=13.5, 0.7 Hz), 5.03 (br s, 1H), 5.11–5.15 (m, 2H), 5.62 (dd, J=2.1, 1.8 Hz), 6.11 (dd, 1H, J=6.6, 1.5 Hz), 6.31 (dd, 1H, J=6.6, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 55.2, 81.2, 83.0, 87.4, 102.8, 109.8, 115.4, 126.4, 141.4, 146.3, 170.2; LRMS (EI) $[M+Na]^+$ 261.2724; HRMS (EI) calcd for $C_{12}H_{14}O_5Na$ *m/z* 261.0739, found *m/z* 261.0734.

Compound **35**: Yield=58%; R_f=0.13 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +55.22 (*c* 2.30, $CHCl_3$); IR (film) 3079, 2933, 1742, 1377, 1242, 1110, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 3.45 (s, 3H), 4.84 (d, 1H, J=2.4 Hz), 4.88 (d, 1H, J=4.0 Hz), 5.03 (br s, 1H), 5.10 (d, 1H, J=4.4 Hz), 5.21 (d, 1H, J=13.5 Hz), 5.71 (dd, 1H, J=2.2, 1.8 Hz), 6.16 (d, 1H, J=5.9 Hz), 6.27 (d, 1H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 55.5, 77.4, 82.8, 85.1, 100.5, 103.0, 116.6, 125.9, 140.7, 145.6, 170.7; HRMS (EI) calcd for $C_{12}H_{14}O_5Na$ *m/z* 261.0739, found *m/z* 261.0745.

Compound **36**: Yield=76%; R_f=0.39 (2:1 hexanes/ethyl acetate); mp 96–98 °C; $[\alpha]_D^{25}$ −4.90 (*c* 1.02, $CHCl_3$); IR (in $CHCl_3$) 2951, 2926, 1653, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 3.46 (s, 3H), 4.02 (d, 1H, J=4.4 Hz), 4.74 (d, 1H, J=4.4 Hz),4.80 (d, 1H, J=4.4 Hz), 4.97 (s, 1H), 5.24 (d, 1H, J=13.2 Hz), 5.71 (t, 1H, J=1.8 Hz), 6.14 (d, 1H, J=5.9 Hz), 6.25 (d, 1H, J=5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9, −4.8, 18.3, 25.8, 55.3, 77.1, 82.6, 85.0, 100.9, 105.1, 116.3, 125.7, 140.9, 146.3; HRMS (EI) calcd for *m/z* $C_{16}H_{26}O_4Na$ 333.1498, found *m/z* 333.1484.

Compound **38**: Yield=68%; R_f=0.29 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −131.02 (*c* 1.02, $CHCl_3$); IR (in $CHCl_3$) 2953, 2926, 1653, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 3.48 (s, 3H), 4.03 (d, 1H, J=6.0 Hz), 4.86 (dd, 1H, J=13.4, 2.4 Hz), 4.90 (s, 1H), 4.95 (d, 1H, J=6.0 Hz), 5.18 (d, 1H, J=13.4 Hz), 5.62 (br s, 1H), 6.22 (AB q, 2H, J=11.6, 6.0 Hz), 6.25 (d, 1H, J=5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, 18.2, 25.8, 57.1, 80.4, 82.8, 85.6, 102.7, 111.4, 115.0, 125.6, 142.7, 146.5; HRMS (EI) calcd for $C_{16}H_{26}O_4Na$ *m/z* 333.1498, found *m/z* 333.1507.

Compound **37**: Yield=56%; R_f=0.30 (1:1 hexanes/ethyl acetate); mp 112–114 °C; $[\alpha]_D^{25}$ +62.14 (*c* 1.03, $CHCl_3$); IR (in $CHCl_3$) 3447, 3019, 1657, 1217, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (d, 1H, J=12.3 Hz), 3.49 (s, 3H), 4.07 (dd, 1H, J=12.3, 4.5 Hz), 4.82–4.91 (m, 2H), 5.00 (s, 1H), 5.24 (d, 1H, J=13.2 Hz), 5.68 (dd, 1H, J=2.1, 1.8 Hz), 6.12 (d, 1H, J=5.7 Hz), 6.27 (d, 1H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 76.7, 83.3, 85.3, 101.1, 104.5, 115.8, 125.9, 140.6, 145.6; HRMS (EI) calcd for $C_{10}H_{12}O_4Na$ *m/z* 219.0633, found *m/z* 219.0639.

Compound **40**: Yield=18%; R_f=0.33 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −207.69 (*c* 1.04, $CHCl_3$); IR (in $CHCl_3$) 3443, 3033, 1656, 1115, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.38 (s, 3H), 4.04 (dd, 1H, J=6.8, 2.2 Hz), 4.90 (dd, 2H, J=13.2, 2.4 Hz), 4.94 (d, 1H, J=2.2 Hz), 5.02 (s, 1H), 5.12 (d, 1H, J=13.6 Hz), 5.58 (s, 1H), 6.15 (d, 1H, J=5.8 Hz), 6.26 (d, 1H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 80.8, 82.7, 86.4, 102.9, 112.4, 113.7, 125.7, 142.8, 147.1; HRMS (EI) calcd for $C_{10}H_{12}O_4Na$ *m/z* 219.0633, found *m/z* 219.0638.

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Syntheses and Vero toxin-binding activities of carbosilane dendrimers periphery-functionalized with galabiose

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Abstract—Carbosilane dendrimers bearing galabiose (Galα1–4Gal) with three, four, and six galabiose units at the periphery of the dendrimers were synthesized for use as artificial inhibitors against Shiga toxins (Stxs) produced by *Escherichia coli* O157:H7. The galabiose unit, prepared from penta-*O*-acetyl-β-D-galactopyranose, was linked with carbosilane dendrimers of three shapes to afford acetyl-protected glycodendrimers in good yields. De-O-acetylation of the clusters was carried out in the presence of NaOMe and then aq NaOH to give the desired three shapes of galabiose-coated carbosilane dendrimers. Their biological activities toward Stxs were evaluated by kinetic analysis, binding assays, and cytotoxic assays.

1. Introduction

Protein–carbohydrate interactions play important roles in many biological phenomena such as processes of cell adhesion with proteins of pathogens.[1] Although the interactions between single carbohydrate ligands and protein receptors are usually weak, it is known that clustering of carbohydrate ligands induces enhancement of the interaction due to the glycoside cluster effect.[2] Artificial clustering carbohydrate models,[2,3] i.e., glycopolymers and glycodendrimers, have been utilized extensively for the enrichment of protein–carbohydrate interaction. Recently, a large number of neoglycoconjugates carrying a globotriaose cluster have been synthesized by several groups,[4] and their activities have been evaluated.[5]

Shiga toxins (Stxs: Stx1 and Stx2) produced by *Escherichia coli* O157:H7, known as Vero toxins, cause diarrhea and hemolytic uremic syndrome (HUS). Stxs are multimeric toxins consisting a single catalytically active A subunit and a pentamer of B subunits.[6] The B subunit is responsible for binding to globotriaose (Galα1–4Galβ1–4Glc).[7] Successful preparation of carbosilane dendrimers periphery-functionalized with globotriaose for the purpose of neutralizing Stxs has been reported.[4a] It was found that the dendrimers carrying globotriaose, named Dumbbell(1)6 and Dumbbell(2)18 (Fig. 1), completely inhibited Stxs in vivo.[5a]

On the other hand, galabiose (Galα1–4Gal), the constitutive part of globotriaose, is also known to have the ability to bind to Stxs.[7] Enhancement of the binding ability by clustering of galabiose would be advantageous compared to clustering of globotriaose from the viewpoint of practical use for a Stxs neutralizer, because preparation of the former disaccharide cluster is easier than that of the latter trisaccharide one.

Magnusson[8a] and Pieters[8b] independently reported the preparation of galabiose clusters using dendrimers and the results of evaluation of their potency for inhibiting *Streptococcus suis*. We describe herein the syntheses and Stxs binding activities of dendritic galabiose clusters using a carbosilane dendrimer as a glycocluster backbone.

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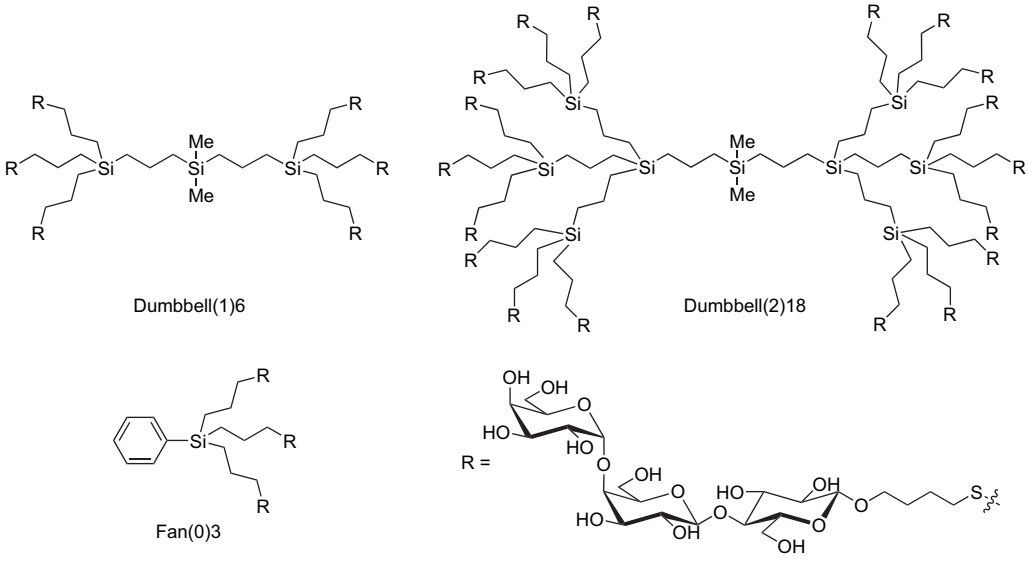


Figure 1. Structure of globotriaose cluster compounds.

2. Results and discussion

2.1. Syntheses of glycoclusters

In the course of our studies on the synthesis of an Stxs inhibitor,[4a] the preparation and characterization of new carbosilane dendrimers of three shapes having galabiose were carried out. One essential point for the molecular design of a carbosilane dendrimer bearing peripheral galabiose is adjustment of the molecular size to that of Stxs adhesion-point distance, ca. 46 Å (The information is obtained from crystallographic analysis.), because the size of galabiose is smaller than that of the already reported Dumbbell(1)6 for globotriaose (Fig. 1). Thus, a carbosilane dendrimer larger than that of Dumbbell(1)6 was designed. Another essential point is that the carbosilane dendrimer derivative must have sufficient water solubility. The water solubility of the glycocluster is influenced by the balance between hydrophobicity of the carbosilane dendrimer and hydrophilicity of the saccharide used. Either an increase of hydrophobicity by using a longer-armed carbosilane dendrimer or a decrease of hydrophilicity by using a disaccharide results in low water solubility of the galabiose clusters.

At first, new carbosilane dendrimers shown in Figure 2 were designed. The carbosilane dendrimers were prepared in a manner similar to that described in the literature (Scheme 1).[9] The hydrosilylation reaction of commercially available triallylmethylsilane (**1**) with chlorodimethylsilane catalyzed by H_2PtCl_6 followed by alkylation with allyl grignard reagent gave tri-branched dendrimer **2** in 31% yield. In the reaction mixture, a small amount of probably olefin-rearranged by-products was detected by ^{1}H NMR spectra, 5.93–6.08 (m), 5.58–5.63 (m), 1.82 (d, J=1.6, 6.2 Hz) ppm. The by-products were carefully removed by distillation. Both tetra-branched dendrimer (**4**) and hexa-branched dendrimer (**5**) were also synthesized from bis(allyldimethylsilylpropyl)dimethylsilane (**3**)[10] using the corresponding chlorosilanes. The ω-brominated carbosilane dendrimers **6–8** were prepared by: (i) hydroxylation of terminal olefin, (ii) mesylation, and then (iii) bromination using excess sodium bromide. The carbosilane dendrimers **6**, **7**, and **8** were obtained in 18%, 41%, and 15% yields, respectively. The structures of these bromide dendrimers were confirmed by ^{1}H, ^{13}C NMR, and FABMS spectra.

On the other hand, galabiose derivatives were synthesized by a procedure closely analogous to that used for the synthesis of a globotriaose derivative (Scheme 2).[4a] Reductive opening of the 4,6-*O*-benzylidene ring of 4-pentenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopylanoside (**9**)[11] gave 4-pentenyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**10**) in 90% yield. Stereoselective glycosylation of **10** and 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride[12] was carried out in the presence of AgOTf as a promoter in ether at −20 °C to afford galabioside (**11**) in 71% yield. The α-galactose linkage was confirmed by the ^{1}H NMR signal at δ 5.02 ppm ($J_{1',2'}$=1.2 Hz, H-1′) and the ^{13}C NMR

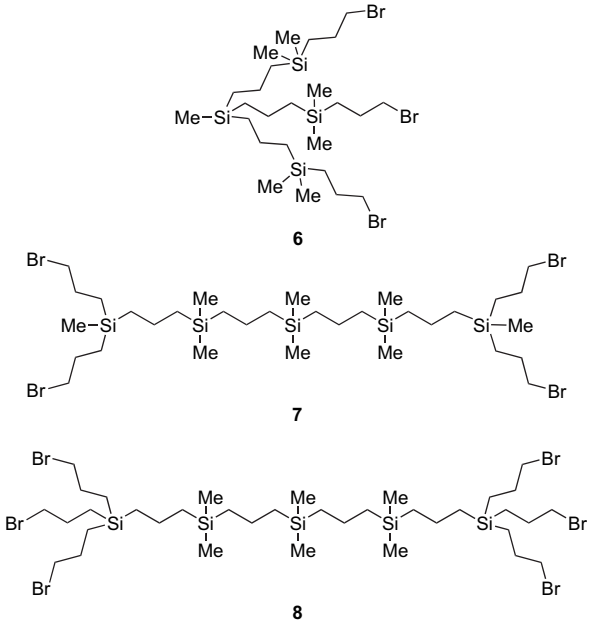
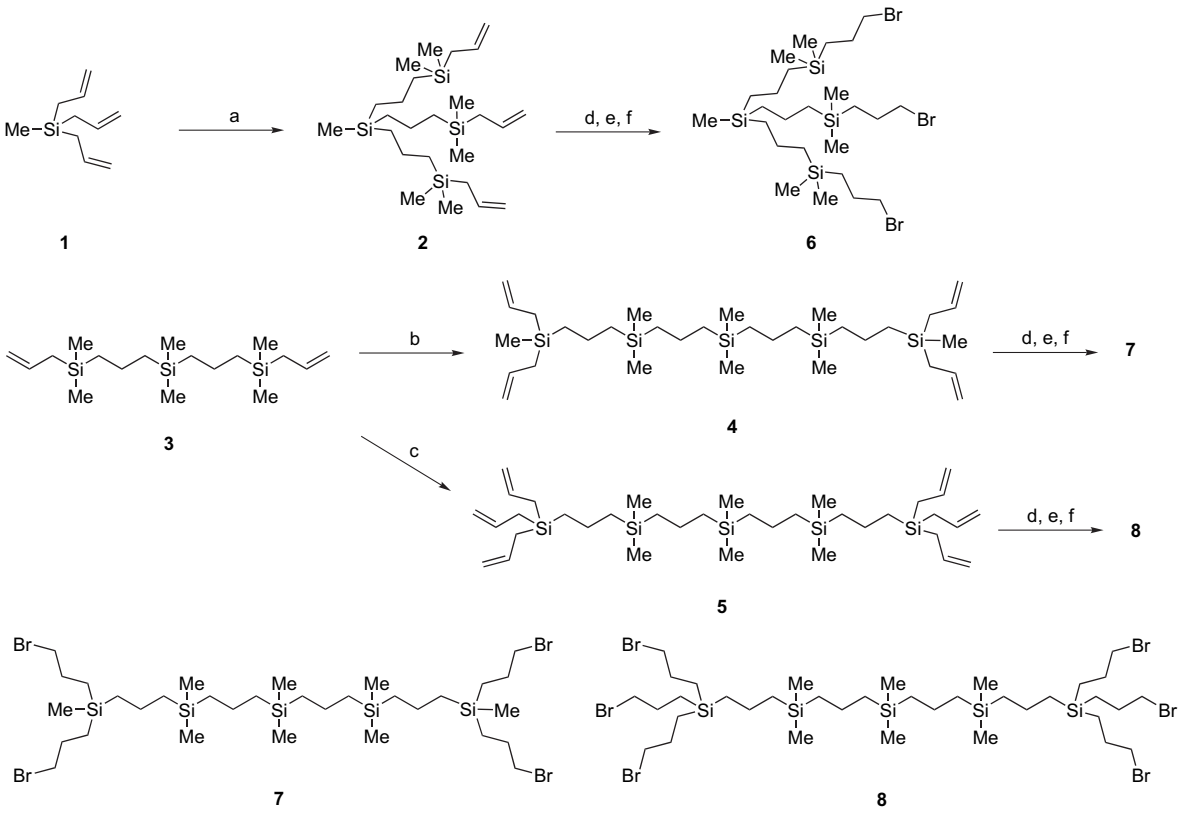


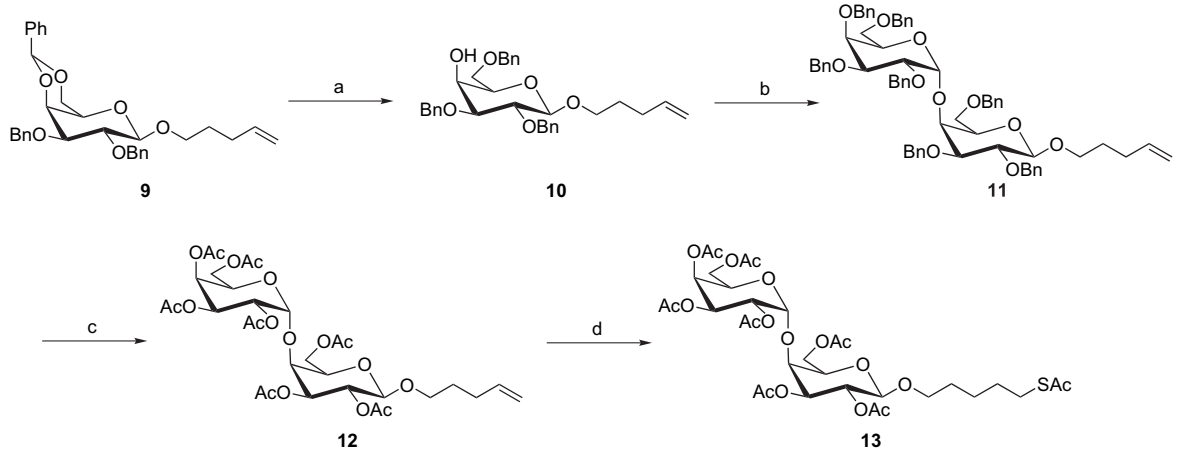
Figure 2. Structure of new carbosilane dendrimers.



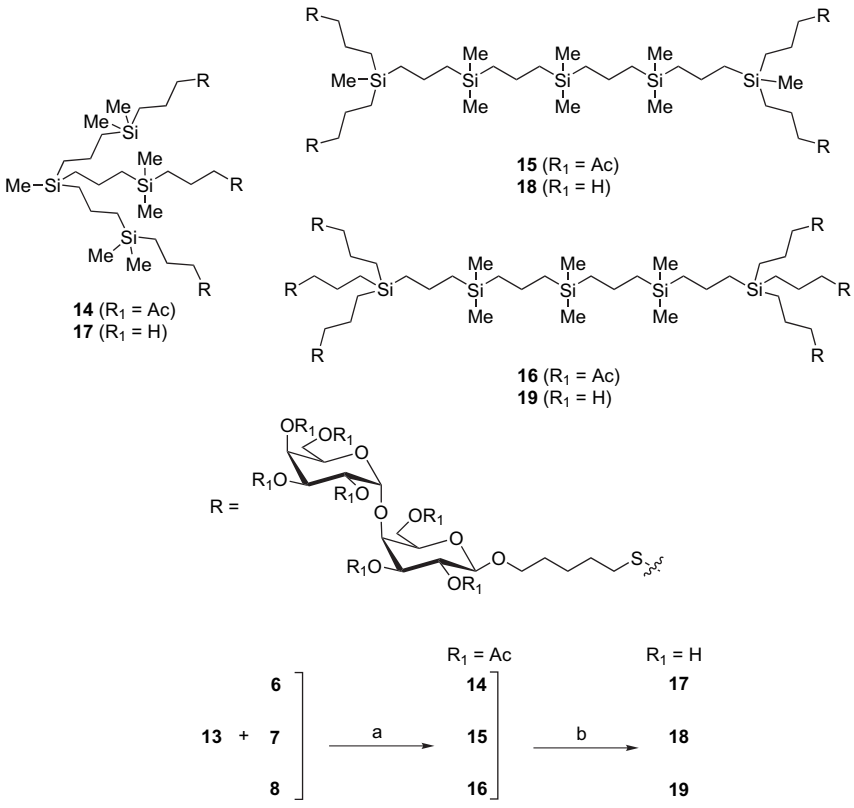
Scheme 1. Reagents and conditions: (a) $HSiMe_2Cl$, Speier cat., THF, 50 °C, then allyl grignard, reflux (31%); (b) $HSiMeCl_2$, Speier cat., THF, 40 °C, then allyl grignard, reflux (81%); (c) $HSiCl_3$, Speier cat., THF, rt-reflux, then allyl grignard, reflux (37%); (d) cyclohexylborane, THF, then 3 M NaOH aq, 30% H_2O_2 aq, 60 °C; (e) MsCl, Py, −20 °C; (f) NaBr, DMF, 80 °C.

signals at δ 103.87 and 100.37 ppm (C-1 and C-1′, respectively). Elemental analysis and FABMS spectrum ($[M-H]^+$ 1039.0) also support the disaccharide structure. Debenzylation of **11** without affecting the terminal double bond of the aglycon was conducted through Birch reduction. Removal of the benzyl groups from **11** followed by acetylation afforded acetyl-protected galabioside (**12**) in 38% yield (Scheme 2), and about 60% of the starting compound **11** was recovered. Acetylthio function was introduced into **12** carrying an olefin terminal by treatment with AcSH and AIBN to give **13** in 93% yield after purification by silica gel column chromatography. The structure of **13** was confirmed by ^1H and ^{13}C NMR spectra, FABMS spectrum, and elemental analysis. The signals at 2.86 (t, 2H, J=7.2 Hz, CH_2SAc) and 2.32 (s, 3H, CH_2SAc) ppm in the ^1H NMR spectrum of **13** prove the formation of acetylthio function.

Finally, acetylated glycocluster Fan(1)3-Ga2OAc (**14**) was synthesized by coupling of the dendrimer **6** with the acetylthio-terminated galabiose **13** (2.1 equiv for each terminal branch) in the presence of NaOMe (1.1 equiv for sugar



Scheme 2. Reagents and conditions: (a) $AlCl_3$, Me_3N–BH_3, MS4A, THF, rt (90%); (b) 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl chloride, AgOTf, MS4A, Et_2O, −20 °C (71%); (c) Na, liq. NH_3, dimethoxyethane, −72 °C, then Ac_2O, Py, rt (38%); (d) AcSH, AIBN, 1,4-dioxane, 80 °C (93%).



Scheme 3. (a) NaOMe, DMF, MeOH, rt, then Ac_2O, Py, rt (86% for **14**, 72% for **15**, and 75% for **16**); (b) NaOMe, MeOH, rt, then dil NaOH aq, rt (91% for **17**, 99% for **18**, 98% for **19**).

Table 1. HRMS (ESI) of galabiose clusters

Compounds	Formula	*m/z* (Calculated)	*m/z* (Found)
Fan(1)3-Ga2OAc (**14**)	$C_{118}H_{192}O_{54}S_3Si_4+Na^+$	2704.04148	2704.04324
Dumbbell(2)4-Ga2OAc (**15**)	$C_{156}H_{252}O_{72}S_4Si_5+2Na^+$	1795.67912	1795.68283
Dumbbell(2)6-Ga2OAc (**16**)	$C_{222}H_{348}O_{108}S_6Si_5+2Na^+$	2559.93525	2559.92997
Fan(1)3-Ga2 (**17**)	$C_{76}H_{150}O_{33}S_3Si_4+Na^+$	1821.81962	1821.81874
Dumbbell(2)4-Ga2 (**18**)	$C_{100}H_{196}O_{44}S_4Si_5+Na^+$	2392.07263	2392.07023
Dumbbell(2)6-Ga2 (**19**)	$C_{138}H_{264}O_{66}S_6Si_5+2Na^+$	1677.71339	1677.71763

moiety) (Scheme 3).[13] Purification by recycling preparative HPLC afforded pure **14** in 86% yield. Dumbbell(2)4-Ga2OAc (**15**) and Dumbbell(2)6-Ga2OAc (**16**) were prepared from the corresponding dendrimers in a manner similar to that described above in 72% and 75% yields, respectively. De-O-acetylation by NaOMe in MeOH and successive saponification of **14**, **15**, and **16** gave target compounds Fan(1)3-Ga2 (**17**), Dumbbell(2)4-Ga2 (**18**), and Dumbbell(2)6-Ga2 (**19**) in 91%, 99%, and 98% yields, respectively. The galabiose clusters **18** and **19** were soluble in an aqueous solution. Fortunately, the level of water solubility was adequate for biological assay systems, although that of **17** was low. All the synthesized acetyl- and de-acetylated clusters were fully characterized by high-resolution mass spectrometry (Table 1). The results showed good agreement with the calculated values for the expected structures.

2.2. Inhibition studies of the glycoclusters

The synthesized galabiose cluster compounds were assessed by using a BIAcore instrument. The dissociation constants (K_D) of these clusters to the Stx1 and Stx2 B subunits were determined by Scatchard plot analysis. Compound **19** showed K_D values of 1.3 and 1.6 μM for Stx1 and Stx2, respectively (Table 2). Previously reported K_D values of hexavalent globotriaose cluster Dumbbell(1)6 were 0.11 and 0.21 μM for Stx1 B subunit and Stx2 B subunit, respectively.[5a,14] Therefore, the potency of **19** is one-tenth of that of Dumbbell(1)6. However, the K_D values of **17** are similar to those of trivalent globotriaose cluster Fan(0)3 (structure of Fan(0)3 is shown in Fig. 1). The potency of the clusters **17**,

Table 2. Kinetic analysis of dendrimers having oligosaccharide toward Stxs

Dendrimers	Stx1 B subunit	Stx2 B subunit
	K_D, μM	K_D, μM
Fan(1)3-Ga2 (**17**)	61.1	53.9
Dumbbell(2)4-Ga2 (**18**)	10.5	10.1
Dumbbell(2)6-Ga2 (**19**)	1.3	1.6
Fan(0)3[a]	64.8	124
Dumbbell(1)6[a]	0.11	0.21

[a] See Refs. 5a and 14.

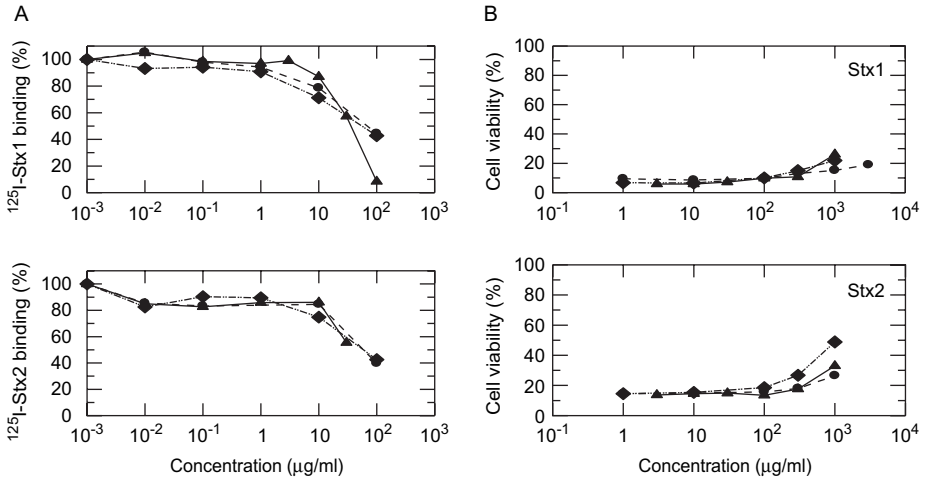


Figure 3. Inhibitory effects of carbosilane dendrimers having galabiose on the biological activities of Stxs in Vero cells. (A) Results of ^{125}I-Stxs binding assay. (B) Results of cytotoxicity assay using Vero cells. The symbols ▲, ●, and ◆ indicate Fan(1)3-Ga2 (**17**), Dumbbell(2)4-Ga2 (**18**), and Dumbbell(2)6-Ga2 (**19**), respectively.

18, and **19** was further evaluated by ^{125}I-labeled Stxs (^{125}I-Stxs) binding assay and cytotoxic assay. It was found that the clusters **17**, **18**, and **19** inhibited the binding of ^{125}I-Stx1 and ^{125}I-Stx2 to Vero cells (Fig. 3A). The IC_{50} values in the ^{125}I-Stxs binding assay are shown in Table 3. The minimum IC_{50} value was 13.6 μM, which is larger than that of Dumbbell(1)6.[5a] On the other hand, **17**, **18**, and **19** showed very weak inhibitory effects (Fig. 3B) in the cytotoxic assay. Only the IC_{50} value of **19** for Stx2 was determined (362 μM). Interestingly, the inhibitory potency in these analyses of **19** is lower than that of Dumbbell(1)6, although the potency of **17** is similar to that of Fan(0)3. The intra-sugar distances between each branches of **17**, about 29 Å, are similar to those of globotriaose clusters, about 27 Å. In contrast, the intra-sugar distances of **19**, about 15 Å, are shorter than those of globotriaose clusters. These results suggest that a long intra-sugar distance in dendritic galabiose is preferable for high binding activity of Stxs.

Table 3. Determination of the IC_{50} values in ^{125}I-Stxs binding assay

Dendrimers	Stx1 B subunit	Stx2 B subunit
	IC_{50}, μM	IC_{50}, μM
Fan(1)3-Ga2 (**17**)	18.9	17.8
Dumbbell(2)4-Ga2 (**18**)	23.6	23.6
Dumbbell(2)6-Ga2 (**19**)	14.2	13.6
Fan(0)3[a]	21.4	>50
Dumbbell(1)6[a]	0.08	0.50

[a] See Ref. 5a.

3. Conclusion

A series of new carbosilane dendrimers periphery-functionalized with galabiose was synthesized. The synthesized dendrimers having galabiose were evaluated by biological potency of Stx1 and Stx2 using kinetic analysis, binding assays, and cytotoxic assays. The results show that about 29 Å intra-sugar distance between each branches is required for increasing binding activity toward Stxs.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 and DRX 400, at 400 and 400 MHz for proton and at 100 and 100 MHz for carbons, respectively. Proton chemical shifts are given in parts per million with the use of tetramethylsilane (0 ppm) or residual solvent peaks as internal standard. NMR signals were assigned by ^{1}H, ^{13}C, HH, and HC COSY measurements. FAB and ESI mass spectra were obtained with a JEOL JMS-HX110A spectrometer and a JEOL JMS-T100LC spectrometer, respectively. Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter at ambient temperature, using a 10-cm micro cell. Recycling preparative HPLC was performed with a LC-908 or LC-918W (Japan Analytical Industry Co., Ltd) connected to an RI detector RI-5. The computer generated low energy conformations were calculated using the CaChe software (Fujitsu Inc.).

4.1.1. Tris[3-(allyldimethylsilyl)propyl]methylsilane (2). A solution of chlorodimethylsilane (16.8 g, 177.6 mmol) in THF (3 mL) was added dropwise to a mixture of **1** (1.97 g, 11.8 mmol) and Speier catalyst (six drops) in THF (3 mL) under Ar, and the reaction mixture was stirred at 50 °C for 24 h. Chlorodimethylsilane and THF were eliminated by heating the mixture. The residue was dissolved in THF (25 mL) and a solution of allyl grignard reagent (88.8 mmol) in diethyl ether (45 mL) was added to the reaction solution at 0 °C. The mixture was refluxed overnight and then 1 M HCl aq was added dropwise to the resulting mixture. The mixture was extracted with diethyl ether and washed with water and brine. The organic layer was dried (Na_2SO_4) and the filtrate concentrated. Distillation of the residue gave compound **2** (1.73 g, 31%). Bp 220 °C/4 torr. ^{1}H NMR ($CDCl_3$) δ 5.75–5.81 (m, 3H, –C*H*=CH_2), 4.80–4.86 (m, 6H, –CH=CH_2), 1.52 (d, 6H, J=16.8 Hz, SiCH_2CH=CH_2), 1.32–1.34 (m, 6H, $SiCH_2CH_2CH_2Si$), 0.53–0.61 (m, 12H, $SiCH_2$), 0.01 (s, 21H, Si–CH_3); ^{13}C NMR ($CDCl_3$) δ 135.28 (–*C*H=CH_2), 112.54 (–CH=*C*H_2), 23.53, 19.72, 19.01, 18.38, −3.88, −4.97.

4.1.2. Bis(diallylmethylsilylpropyldimethylsilylpropyl)-dimethylsilane (4). A solution of dichloromethylsilane (3.38 g, 29.3 mmol) in THF (10 mL) was added dropwise to a mixture of **3** (2.00 g, 5.87 mmol) and Speier catalyst (five drops) in THF (10 mL) under Ar, and the reaction mixture was stirred at 40 °C for 39 h. The reaction mixture was then processed in the same way described for compound **2**. The residue was chromatographed on silica gel with hexane as eluent to give **4** (2.82 g, 81%). ^{1}H NMR ($CDCl_3$) δ 5.73–5.84 (m, 4H, –C*H*=CH_2), 4.81–4.90 (m, 8H, –CH=C*H*$_2$), 1.55 (d, 8H, J=8.2 Hz, SiC*H*$_2$CH=CH_2), 1.26–1.41 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.49–0.64 (m, 16H, $SiCH_2$), −0.01 (s, 6H, $SiCH_3$), −0.05 (s, 18H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 134.86 (–*C*H=CH_2), 112.99 (–CH=*C*H$_2$), 21.48, 20.13, 20.09, 18.43, 18.19, 17.80, −3.21, −5.74.

4.1.3. Bis(triallylsilylpropyldimethylsilylpropyl)dimethylsilane (5). A solution of trichlorosilane (2.38 g, 17.6 mmol) in THF (3 mL) was added dropwise to a mixture of **3** (2.00 g, 5.87 mmol) and Speier catalyst (six drops) in THF (4 mL) under Ar, and the reaction mixture was stirred at room temperature overnight and then refluxed for 2 h. The reaction mixture was then processed in the same way described for compound **4** to give **5** (1.40 g, 37%). ^{1}H NMR ($CDCl_3$) δ 5.73–5.82 (m, 6H, –C*H*=CH_2), 4.85–4.91 (m, 12H, –CH=C*H*$_2$), 1.58 (d, 12H, J=8.1 Hz, SiC*H*$_2$CH=CH_2), 1.25–1.40 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.63–0.67 (m, 4H, $CH_2CH_2SiCH_2CH$=CH_2), 0.52–0.57 (m, 12H, $SiCH_2$), −0.05 (s, 18H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 134.50 (–*C*H=CH_2), 113.44 (–CH=*C*H$_2$), 20.23, 20.14, 20.07, 19.72, 18.42, 18.10, 16.28, −3.20, −3.23.

4.1.4. Tris(3-bromopropyldimethylsilylpropyl)methylsilane (6).

4.1.4.1. Synthesis of tris(3-hydroxypropyldimethylsilylpropyl)methylsilane. A solution of **2** (0.98 g, 2.1 mmol) in THF (4 mL) was added to a solution of cyclohexylborane, which was prepared from borane/THF complex (4.7 mL of 1 M solution) and cyclohexene (0.39 g, 4.7 mmol) in THF at 0 °C under Ar. After stirring at room temperature for 2 h, MeOH (3 mL) was added to the reaction mixture. Aqueous NaOH (5 mL of 3 M solution) and H_2O_2 (2 mL of 30% solution) were added to the resulting solution at 0 °C, subsequently. The reaction mixture was stirred at 60 °C for 1 h. The resulting mixture was extracted with THF; the solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by reprecipitation from cold hexane (−30 °C) to yield the title compound (0.79 g, 73%). ^{1}H NMR ($CDCl_3$) δ 3.58 (t, 6H, J=6.8 Hz, C*H*$_2$OH), 1.64 (br s, 3H, OH), 1.50–1.58 (m, 6H, C*H*$_2$CH$_2$OH), 1.27–1.35 (m, 6H, $SiCH_2CH_2CH_2Si$), 0.52–0.60 (m, 12H, SiC*H*$_2$CH$_2$C*H*$_2$Si), 0.45–0.50 (m, 6H, SiC*H*$_2$CH$_2$CH$_2$Br), −0.04 (s, 18H, $CH_2Si(CH_3)_2CH_2$), −0.09 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 65.83, 27.17, 19.99, 18.78, 18.43, 10.89, −3.37, −4.93.

4.1.4.2. Synthesis of tris(3-methylsulfonyloxypropyldimethylsilylpropyl)methylsilane. Methanesulfonyl chloride (1.8 mL, 32.2 mmol) was added dropwise to a solution of the above hydroxylated compound (1.29 g, 1.94 mmol) in pyridine (7 mL) at −20 °C under Ar, and the reaction mixture was stirred at same temperature for 3 h. The solution was diluted with $CHCl_3$ (10 mL), and water (10 mL) was added dropwise to the solution. The mixture was extracted with $CHCl_3$, and washed with 5% H_2SO_4 aq (v/v), 5% $NaHCO_3$ aq (w/w) and brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (1:100 MeOH/$CHCl_3$) to yield the title compound (1.86 g, 98%). ^{1}H NMR ($CDCl_3$) δ 4.15 (t, 6H, J=6.9 Hz, CH_2O), 2.98 (s, 9H, SO_2CH_3), 1.67–1.75 (m, 6H, C*H*$_2$CH$_2$O), 1.27–1.31 (m, 6H, $SiCH_2CH_2CH_2Si$), 0.48–0.56 (m, 18H, $SiCH_2$), −0.04 (s, 18H, $CH_2Si(CH_3)_2CH_2$), −0.09 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 72.54, 37.28, 23.89, 19.73, 18.66, 18.21, 10.62, −3.54, −5.05.

4.1.4.3. Synthesis of 6. NaBr (4.89 g, 45.5 mmol) was added to a solution of above mesylated compound (2.39 g, 3.17 mmol) in DMF (17 mL) under Ar. The mixture was heated at 80 °C for 3 h. The resulting mixture was diluted with water and toluene. The solution was extracted with toluene, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (1:99 EtOAc/hexane) to yield compound **6** (1.78 g, 79%). ^{1}H NMR ($CDCl_3$) δ 3.38 (t, 6H, J=7.1 Hz, CH_2Br), 1.81–1.85 (m, 6H, C*H*$_2$CH$_2$Br), 1.29–1.31 (m, 6H, $SiCH_2CH_2CH_2Si$), 0.52–0.62 (m, 18H, SiC*H*$_2$), −0.02 (s, 18H, $CH_2Si(CH_3)_2CH_2$), −0.08 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 37.18 (CH_2Br), 28.01 (*C*H$_2$CH$_2$Br), 19.90, 18.97, 13.39, 14.64, −3.37, −4.96. FABMS (negative): $[M+Br]^-$ 786.8.

4.1.5. Bis(bis(3-bromopropyl)methylsilylpropyldimethylsilylpropyl)dimethylsilane (7).

4.1.5.1. Synthesis of bis(bis(3-hydroxypropyl)methylsilylpropyldimethylsilylpropyl)dimethylsilane. Reaction conditions and workup were as described in Section 4.1.4.1, with compound **4** (2.00 g, 3.37 mmol). The residue was purified by reprecipitation from hexane then a mixture of 1:5 EtOAc/hexane again to yield title compound (1.34 g, 60%). ^{1}H NMR (DMSO-d_6) δ 4.40 (t, 4H, J=5.2 Hz, –OH), 3.28–3.33 (m, 8H, C*H*$_2$OH), 1.26–1.41 (m, 16H, $SiCH_2CH_2$), 0.47–0.53 (m, 16H, $SiCH_2$), 0.39–0.43 (m, 8H, $SiCH_2$), −0.09 and −0.10 (each s, 24H, $SiCH_3$); ^{13}C NMR (DMSO-d_6) δ 64.13, 27.19, 19.82, 19.70, 19.68, 18.27, 18.209.53, −2.91, −4.90.

4.1.5.2. Synthesis of bis(bis(3-methylsulfonyloxypropyl)methylsilylpropyldimethylsilylpropyl)dimethylsilane. Reaction conditions and workup were as described in Section 4.1.4.2, with above hydoxylated compound (1.29 g, 1.94 mmol). Title compound (1.86 g, 98%) was obtained. ^{1}H NMR δ 4.15 (t, 8H, J=6.8 Hz, CH_2O), 2.99 (s, 12H, SO_2CH_3), 1.69–1.73 (m, 8H, $SiCH_2CH_2CH_2O$), 1.27–1.31 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.50–0.61 (m, 24H, $SiCH_2$), −0.02 and −0.07 (each s, 24H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 72.29, 37.31, 23.81, 20.14, 20.03, 19.99, 18.32, 18.21, 18.01, 9.10, −3.27, −5.52.

4.1.5.3. Synthesis of 7. Reaction conditions and workup were as described in Section 4.1.4.3, with above mesylated compound (1.81 g, 1.85 mmol). The compound **7** (1.40 g, 83%) was obtained. ^{1}H NMR δ 3.38 (t, 8H, J=7.0 Hz, CH_2Br), 1.79–1.86 (m, 8H, C*H*$_2$CH$_2$Br), 1.29–1.33 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.52–0.65 (m, 24H, $SiCH_2$), −0.02 and −0.05 (each s, 24H, $SiCH_3$); ^{13}C NMR ($CDCl_3$)

δ 37.05, 27.83, 20.18, 20.11, 20.06, 18.40, 18.28, 18.23, 12.99, −3.19, −5.26. FABMS (negative): $[M+Br]^-$ 995.0.

4.1.6. Bis(tris(3-bromopropyl)silylpropyldimethylsilylpropyl)dimethylsilane (8).

4.1.6.1. Synthesis of bis(tris(3-hydroxypropyl)silylpropyldimethylsilylpropyl)dimethylsilane. Reaction conditions and workup were as described in Section 4.1.4.1, with compound **5** (1.38 g, 2.14 mmol). The residue was purified by reprecipitation from a mixture of 1:5 EtOAc/hexane to yield the title compound (1.35 g, 84%). ^{1}H NMR (DMSO-d_6) δ 4.40 (t, 6H, J=5.2 Hz, –OH), 3.28–3.37 (q, 12H, J=6.6 Hz, CH_2OH), 1.26–1.60 (m, 20H, SiCH$_2$CH_2CH$_2$), 0.50–0.56 (m, 16H, CH_2SiCH_2CH$_2$CH$_2$OH), 0.40–0.44 (m, 12H, SiCH$_2$), −0.08 (s, 18H, SiCH$_3$); ^{13}C NMR (DMSO-d_6) δ 64.20, 27.21, 19.94, 19.69, 19.65, 18.24, 18.21, 17.00, 8.15, −2.89.

4.1.6.2. Synthesis of bis(tris(3-methylsulfonyloxypropyl)silylpropyldimethylsilylpropyl)dimethylsilane. Reaction conditions and workup were as described in Section 4.1.4.2, with the above hydoxylated compound (1.03 g, 1.37 mmol). Purification by chromatography on silica gel (1:50 MeOH/$CHCl_3$) yielded the title compound (1.62 g, 96%). ^{1}H NMR δ 4.17 (t, 12H, J=6.4 Hz, CH$_2$O), 3.02 (s, 18H, SO$_2$CH$_3$), 1.70–1.76 (m, 12H, CH_2CH$_2$O), 1.28–1.31 (m, 8H, SiCH$_2$CH_2CH$_2$Si), 0.52–0.67 (m, 28H, SiCH$_2$), −0.05 (s, 18H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 72.11, 37.34, 23.75, 20.31, 20.02, 19.98, 18.31, 18.23, 16.56, 7.57, −3.26, −3.29.

4.1.6.3. Synthesis of 8. Reaction conditions and workup were as described in Section 4.1.4.3, with above mesylated compound (2.08 g, 1.70 mmol). Purification was effected by column chromatography on silica gel (5:95 EtOAc/hexane) to yield compound **8** (0.98 g, 51%). ^{1}H NMR ($CDCl_3$) δ 3.39 (t, 12H, J=6.8 Hz, CH$_2$Br), 1.79–1.85 (m, 12H, CH_2CH$_2$Br), 1.30–1.32 (m, 8H, SiCH$_2$CH_2CH$_2$Si), 0.52–0.69 (m, 28H, SiCH_2), −0.05 (s, 18H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 30.99, 27.67, 20.32, 20.12, 20.05, 18.40, 18.28, 16.79, 11.44, −3.19. FABMS (negative): $[M+Br]^-$ 1208.8.

4.1.7. 4-Pentenyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (10) one half hydrate. A mixture of compound **9** (5.03 g, 9.75 mmol) and molecular sieves (4 Å powder, 5.0 g) in THF (80 mL) was stirred at room temperature for 2 h under Ar, trimethylamine boron complex (4.98 g, 68.2 mmol) was added. Aluminum chloride (9.10 g, 68.2 mmol) was added to the reaction mixture in some portion at 0 °C. After stirring at room temperature for 4 h, the resulting mixture was filtered through Celite and filtrate was diluted with $CHCl_3$. The solution was poured into ice-water and extracted with $CHCl_3$. The organic solution was washed with water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (1:4 EtOAc/hexane) to give compound **10** in hydrated form (4.54 g, 90%). $[\alpha]_D^{31}$ +7.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.28–7.37 (m, 15H, aromatics), 5.76–5.87 (m, 1H, –CH=CH$_2$), 4.94–5.03 (m, 2H, –CH=CH_2), 4.91 (d, 1H, J=11.2 Hz, CH_2Ph), 4.73 (d, 1H, J=11.6 Hz, CH_2Ph), 4.72 (s, 2H, CH_2Ph), 4.59 (s, 2H, CH_2Ph), 4.35 (d, 1H, $J_{1,2}$=7.7 Hz, H-1), 4.02 (d, 1H, $J_{3,4}$=3.2 Hz, H-4), 3.93–3.98 (m, 1H, one of OCH_2CH$_2$CH$_2$CH=CH$_2$), 3.80 (dd, 1H, J=6.0 Hz, J=9.9 Hz, H-6a), 3.72 (dd, 1H, J=6.0 Hz, J=9.9 Hz, H-6b), 3.64 (dd, 1H, $J_{1,2}$=7.8 Hz, $J_{2,3}$=9.2 Hz, H-2), 3.53–3.57 (m, 2H, H-5 and one of OCH_2CH$_2$CH$_2$CH=CH$_2$), 3.49 (dd, 1H, $J_{2,3}$=9.4 Hz, $J_{3,4}$=3.4 Hz, H-3), 2.13–2.19 (m, 2H, OCH$_2$CH$_2$CH_2CH=CH$_2$), 1.69–1.80 (m, 2H, OCH$_2$CH_2CH$_2$CH=CH$_2$), 1.60 (br s, 2H, –OH and H_2O); ^{13}C NMR ($CDCl_3$) δ 138.55, 138.05, 137.96, 137.85, 128.39, 128.37, 128.25, 128.05, 127.81, 127.77, 127.72, 127.69, 127.56, 114.80 (–C=CH_2), 103.63 (C-1), 80.55, 78.91, 75.14, 73.65, 73.10, 72.34, 69.17, 66.83 (C-4), 30.17, 28.91; Anal. Calcd for $C_{32}H_{38}O_6$+0.5H_2O: C, 72.84; H, 7.45. Found: C, 73.08; H, 7.35. FABMS (positive): $[M+Na]^+$ 541.3.

4.1.8. 4-Pentenyl (2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (11). A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (17.4 g, 31.0 mmol), compound **10** (7.58 g, 14.6 mmol), and molecular sieves (4 Å powder, 7.6 g) in diethyl ether (300 mL) was stirred at room temperature for 1 h under Ar. Silver triflate (12.0 g, 47.0 mmol) was added to the mixture at −20 °C under darkness and reaction mixture was stirred at same temperature for 2 h. The insoluble solids were separated by filtration through a Cerite bed, the filtrate was diluted with $CHCl_3$ and washed with ice-water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (3:97 then 5:95 EtOAc/toluene) to yield compound **11** (10.8 g, 71%). $[\alpha]_D^{31}$ +41.0 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.16–7.38 (m, 35H, aromatics), 5.76–5.86 (m, 1H, –CH=CH$_2$), 5.02 (d, 1H, $J_{1',2'}$=1.3 Hz, H-1′), 4.87–4.99 (m, 5H, –CH=CH2, CH_2Ph), 4.77–4.80 (m, 4H, CH_2Ph), 4.68 (d, 1H, J=11.9 Hz, CH_2Ph), 4.55 (d, 1H, J=3.1 Hz, CH_2Ph), 4.52 (d, 1H, J=4.6 Hz, CH_2Ph), 4.12–4.45 (m, 1H, H-5′), 4.31 (d, 1H, $J_{1,2}$=7.6 Hz, H-1), 4.26 (d, 1H, J=11.8 Hz, CH_2Ph), 4.21 (d, 1H, J=11.8 Hz, CH_2Ph), 4.10–4.17 (m, 5H, H-2′, H-3′, H-4′ and CH_2Ph), 4.02 (d, 1H, $J_{3,4}$=2.4 Hz, H-4), 3.91–3.98 (m, 2H, H-6a and one of OCH_2CH$_2$CH$_2$CH=CH$_2$), 3.67 (dd, 1H, $J_{1,2}$=7.6 Hz, $J_{2,3}$=9.9 Hz, H-2), 3.51–3.57 (m, 4H, H-5, H-6b, H-6′a and one of OCH_2CH$_2$CH$_2$CH=CH$_2$), 3.38 (dd, 1H, $J_{2,3}$=9.9 Hz, $J_{3,4}$=2.8 Hz, H-3), 3.24 (dd, 1H, J=4.7 Hz, J=8.3 Hz, H-6′b), 2.15–2.19 (m, 2H, OCH$_2$CH$_2$CH_2CH=CH$_2$), 1.76–1.78 (m, 2H, OCH$_2$CH_2CH$_2$CH=CH$_2$); ^{13}C NMR ($CDCl_3$) δ 138.90, 138.74, 138.67, 138.60, 138.06, 137.99, 128.25, 128.19, 128.16, 128.14, 128.10, 128.02, 127.96, 127.86, 127.72, 127.50, 127.47, 127.35, 127.24, 114.79, 103.87 (C-1), 100.37 (C-1′), 80.86, 78.91, 78.86, 76.51, 75.02, 74.80, 74.76, 74.64, 73.58, 73.51, 73.07, 72.95, 72.27, 72.17, 69.57, 69.26, 69.19, 67.97, 67.87, 30.12, 28.89; Anal. Calcd for $C_{66}H_{72}O_{11}$: C, 76.13; H, 6.97. Found: C, 75.99; H, 7.01. FABMS (positive): $[M-H]^+$ 1039.0. $[M+Na]^+$ 1062.9.

4.1.9. 4-Pentenyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-galactopyranoside (12). A solution of compound **11** (5.16 g, 4.92 mmol) in dimethoxyethane (30 mL) was added dropwise to sodium (4.56 g, 198 mmol) in liq. NH_3 (150 mL) at −72 °C. After stirring at same temperature for 45 min, NH_4Cl (10.6 g, 198 mmol) in limited amounts was added to the reaction

mixture. The mixture was allowed to warm at room temperature and stirred overnight, and then evaporated to dryness. The residue was treated with pyridine (33.5 mL, 420 mmol) and Ac_2O (19.7 mL, 210 mmol) at room temperature for 19 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The solution was washed with 1 M HCl aq, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (1:1 EtOAc/hexane) to give compound **12** (1.32 g, 38%) and 3.26 g of the starting compound. $[\alpha]_D^{29}$ +73.5 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.75–5.85 (m, 1H, –C*H*=CH_2), 5.57 (d, 1H, $J_{3',4'}$=3.1 Hz, H-4′), 5.39 (dd, 1H, $J_{2',3'}$=10.9 Hz, $J_{3',4'}$=3.1 Hz, H-3′), 5.16–5.21 (m, 2H, H-2 and H-2′), 4.96–5.04 (m, 3H, H-1′, –CH=C*H*$_2$), 4.82 (dd, 1H, $J_{2,3}$=10.7 Hz, $J_{3,4}$=2.4 Hz, H-3), 4.54 (t, 1H, *J*=6.9 Hz, H-5′), 4.44–4.48 (m, 2H, H-1 and H-6b), 4.06–4.25 (m, 4H, H-4, H-6a and H-6′ab), 3.87–3.93 (m, 1H, one of OC*H*$_2$CH$_2$CH$_2$CH=CH$_2$), 3.78 (t, 1H, *J*=6.6 Hz, H-5), 3.47–3.53 (m, 1H, one of OC*H*$_2$CH$_2$CH$_2$CH=CH$_2$), 1.99–2.13 (m, 23H, –OAc, OCH$_2$CH$_2$C*H*$_2$CH=CH$_2$), 1.64–1.76 (m, 2H, OCH$_2$C*H*$_2$CH$_2$CH=CH$_2$); ^{13}C NMR ($CDCl_3$) δ 170.70, 170.55, 170.45, 170.41, 170.10, 169.72, 169.06, 137.90 (–*C*H=CH$_2$), 114.95 (–CH=*C*H$_2$), 101.17 (C-1), 99.30 (C-1′), 72.75 (C-3), 71.79 (C-5), 69.12, 68.76, 68.56, 67.81 (C-4′), 67.35 (C-3′), 66.99 (C-5′), 61.94 (C-6), 60.46, 29.84, 28.55, 20.92, 20.73, 20.66, 20.64, 20.59; Anal. Calcd for $C_{31}H_{44}O_{18}$: C, 52.84; H, 6.29. Found: C, 52.66; H, 6.23. FABMS (positive): $[M+Na]^+$ 726.9.

4.1.10. 5-Acetylthiopentyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-galactopyranoside (13). A solution of compound **12** (1.41 g, 2.00 mmol) in 1,4-dioxane (1 mL) was treated with thioacetic acid (3.0 ml, 42.6 mmol) and AIBN (0.679 g, 4.26 mmol) at 80 °C for 2 h under Ar. Cyclohexene (432 μL, 4.26 mmol) was added with stirring for 10 min. The resulting solution was purified by column chromatography on silica gel (1:1 EtOAc/hexane) to yield compound **13** (1.46 g, 93%). $[\alpha]_D^{32}$ +66.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57 (d, 1H, $J_{3',4'}$= 2.6 Hz, H-4′), 5.39 (dd, 1H, $J_{2',3'}$=11.0 Hz, $J_{3',4'}$=3.3 Hz, H-3′), 5.15–5.21 (m, 2H, H-2 and H-2′), 5.00 (d, 1H, $J_{1',2'}$= 3.6 Hz, H-1′), 4.81 (dd, 1H, $J_{2,3}$=10.8 Hz, $J_{3,4}$=2.7 Hz, H-3), 4.53 (t, 1H, *J*=6.6 Hz, H-5′), 4.43–4.47 (m, 2H, H-1 and H-6b), 4.06–4.19 (m, 4H, H-4, H-6a and H-6′ab), 3.85–3.91 (m, 1H, one of OC*H*$_2$CH$_2$), 3.78 (t, 1H, *J*= 6.6 Hz, H-5), 3.45–3.51 (m, 1H, one of OC*H*$_2$CH$_2$–), 2.86 (t, 2H, *J*=7.2 Hz, C*H*$_2$SAc), 2.32 (s, 3H, SAc), 2.13 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.55–1.66 (m, 4H, OCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$S), 1.39–1.48 (m, 2H, OCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$S); ^{13}C NMR ($CDCl_3$) δ 195.83 (SC=O), 170.68, 170.53, 170.43, 170.39, 170.08, 169.71, 169.05, 101.09 (C-1), 99.31 (C-1′), 72.72 (C-3), 71.80 (C-5), 69.51 (O*C*H$_2$CH$_2$), 68.69, 68.54, 67.80, 67.33, 66.98, 61.93, 60.44, 30.57, 29.16, 28.89, 28.83, 25.03, 20.90, 20.72, 20.63, 20.58. Anal. Calcd for $C_{33}H_{48}O_{19}S$: C, 50.76; H, 6.20. Found: C, 50.47; H, 6.10. FABMS (positive): $[M+H]^+$ 781.2. $[M+Na]^+$ 803.2.

4.1.11. Fan(1)3-Ga2OAc (14). A mixture of **6** (22.1 mg, 31.0 μmol) and **13** (152.6 mg, 195.0 μmol) was dissolved in a mixture of DMF (0.25 mL) and MeOH (0.25 mL), the solution was treated with NaOMe (11.6 mg, 215 μmol) at room temperature for 21 h. Acetic acid (0.25 mL) was then added to the mixture, the resulting solution was evaporated under reduced pressure. The residue was suspended in a mixture of pyridine (6 mL) and acetic acid (3 mL). The suspension was stirred for 5 h at room temperature, after resulting solution was poured into ice-water and extracted with EtOAc. The organic solution was washed with 1 M HCl aq, saturated $NaHCO_3$ aq, and brine. Organic phase was dried ($MgSO_4$) and concentrated. Purification by recycling preparative HPLC (column, JAIGEL-1H and 2H; solvent, chloroform) afforded Fan(1)3-Ga2OAc **14** (75.6 mg, 86%). $[\alpha]_D^{33}$ +59.0 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57 (d, 3H, $J_{3',4'}$=2.8 Hz, H-4′), 5.39 (dd, 3H, $J_{2',3'}$=11.0 Hz, $J_{3',4'}$=3.3 Hz, H-3′), 5.15–5.21 (m, 6H, H-2 and H-2′), 5.00 (d, 3H, $J_{1',2'}$=3.6 Hz, H-1′), 4.81 (dd, 3H, $J_{2,3}$=10.8 Hz, $J_{3,4}$=2.7 Hz, H-3), 4.53 (t, 3H, *J*=6.7 Hz, H-5′), 4.43–4.48 (m, 6H, H-1 and H-6b), 4.06–4.20 (m, 12H, H-4, H-6a and H-6′ab), 3.88–3.90 (m, 3H, one of OC*H*$_2$CH$_2$), 3.77 (t, 3H, *J*=6.6 Hz, H-5), 3.46–3.48 (m, 3H, one of OC*H*$_2$CH$_2$–), 2.50 (t, 12H, *J*=7.5 Hz, CH$_2$S), 1.99–2.13 (m, 63H, OAc), 1.53–1.61 (m, 18H, OCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$SCH$_2$C*H*$_2$CH$_2$Si), 1.43–1.47 (m, 6H, OCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$S), 1.26–1.32 (m, 6H, SiCH$_2$C*H*$_2$CH$_2$Si), 0.51–0.60 (m, 18H, SiCH$_2$), −0.04 (s, 18H, SiCH$_3$), −0.09 (s, 3H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 170.68, 170.53, 170.43, 170.39, 170.08, 169.71, 169.06, 101.13 (C-1), 99.31 (C-1′), 72.71, 71.79, 69.71, 68.71, 68.54, 67.80, 67.33, 66.98, 61.92, 60.45, 35.94, 31.98, 29.41, 29.03, 25.16, 24.38, 20.90, 20.72, 20.66, 20.62, 20.58, 19.98, 18.74, 18.37, 15.13, −3.39, −5.01; HRMS (ESI) Anal. Calcd for $C_{118}H_{192}O_{54}S_3Si_4$ $[M+Na]^+$: 2704.04148. Found: 2704.04324.

4.1.12. Dumbbell(2)4-Ga2OAc (15). A coupling reaction between **7** (60.8 mg, 66.3 μmol) and **13** (312.5 mg, 400.0 μmol) was carried out in the same manner as described in synthesis of **14** to give Dumbbell(2)4-Ga2OAc **15** (169.6 mg, 72%) after purification by recycling preparative HPLC (column, JAIGEL-2H and 2.5H; solvent, chloroform). $[\alpha]_D^{34}$ +61.1 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57 (d, 4H, $J_{3',4'}$=2.4 Hz, H-4′), 5.39 (dd, 4H, $J_{2',3'}$=11.0 Hz, $J_{3',4'}$=3.2 Hz, H-3′), 5.15–5.21 (m, 8H, H-2 and H-2′), 5.00 (d, 4H, $J_{1',2'}$=3.6 Hz, H-1′), 4.81 (dd, 4H, $J_{2,3}$= 10.8 Hz, $J_{3,4}$=2.7 Hz, H-3), 4.52 (t, 4H, *J*=7.3 Hz, H-5′), 4.43–4.48 (m, 8H, H-1 and H-6b), 4.06–4.20 (m, 16H, H-4, H-6a and H-6′ab), 3.88–3.90 (m, 4H, one of OC*H*$_2$CH$_2$), 3.78 (t, 4H, *J*=6.6 Hz, H-5), 3.46–3.48 (m, 4H, one of OC*H*$_2$CH$_2$–), 2.50 (t, 16H, *J*=6.4 Hz, CH$_2$S), 1.98–2.22 (m, 84H, OAc), 1.53–1.61 (m, 24H, OCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$ SCH$_2$C*H*$_2$CH$_2$Si), 1.43–1.46 (m, 8H, OCH$_2$CH$_2$C*H*$_2$CH$_2$ CH$_2$S), 1.27–1.33 (m, 8H, SiCH$_2$C*H*$_2$CH$_2$Si), 0.52–0.61 (m, 28H, SiCH$_2$), −0.05 and −0.06 (s, 24H, SiCH$_3$); ^{13}C NMR ($CDCl_3$) δ 170.70, 170.54, 170.44, 170.40, 170.10, 169.72, 169.06, 101.15 (C-1), 99.34 (C-1′), 72.73, 71.80, 69.72, 68.72, 68.55, 67.80, 67.34, 66.99, 61.92, 60.46, 36.00, 32.04, 29.41, 29.05, 25.17, 24.33, 20.93, 20.75, 20.68, 20.65, 20.60, 20.21, 20.10, 18.36, 13.58, −3.22, −5.28; HRMS (ESI) Anal. Calcd for $C_{156}H_{252}O_{72}S_4Si_5$ $[M+2Na]^{2+}/2$: 1795.67912. Found: 1795.68283.

4.1.13. Dumbbell(2)6-Ga2OAc (16). A coupling reaction between **8** (49.3 mg, 43.6 μmol) and **13** (316.5 mg, 405.0 μmol) was carried out in the same manner as

described in synthesis of **14** to give Dumbbell(2)6-Ga2OAc **16** (166.2 mg, 75%) after purification by recycling preparative HPLC (column, JAIGEL-2.5H and 3H; solvent, chloroform). $[\alpha]_D^{35}$ +61.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57 (d, 6H, $J_{3',4'}$=2.4 Hz, H-4′), 5.38 (dd, 6H, $J_{2',3'}$=11.0 Hz, $J_{3',4'}$=3.3 Hz, H-3′), 5.15–5.21 (m, 12H, H-2 and H-2′), 5.00 (d, 6H, $J_{1',2'}$=3.6 Hz, H-1′), 4.81 (dd, 6H, $J_{2,3}$= 10.7 Hz, $J_{3,4}$=2.6 Hz, H-3), 4.53 (t, 6H, *J*=6.7 Hz, H-5′), 4.43–4.48 (m, 12H, H-1 and H-6b), 4.07–4.20 (m, 24H, H-4, H-6a and H-6′ab), 3.88–3.91 (m, 6H, one of OCH_2CH_2), 3.78 (t, 6H, *J*=6.6 Hz, H-5), 3.46–3.50 (m, 6H, one of OCH_2CH_2–), 2.50 (t, 24H, *J*=6.8 Hz, CH_2S), 1.99–2.23 (m, 126H, OAc), 1.58–1.62 (m, 36H, $OCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2Si$), 1.42–1.46 (m, 12H, $OCH_2CH_2CH_2CH_2CH_2S$), 1.25–1.31 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.54–0.61 (m, 28H, $SiCH_2$), −0.05 (s, 18H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 170.60, 170.46, 170.35, 170.30, 170.02, 169.64, 168.99, 101.05 (C-1), 99.24 (C-1′), 72.62, 71.70, 69.64, 68.63, 68.45, 67.71, 67.25, 66.89, 61.83, 60.38, 35.97, 34.04, 32.00, 29.96, 29.30, 29.10, 28.96, 27.75, 25.24, 25.06, 24.18, 23.13, 20.84, 20.66, 20.59, 20.56, 20.51, 20.27, 20.02, 18.39, 18.25, 16.96, 12.01, 11.40, −3.32; HRMS (ESI) Anal. Calcd for $C_{222}H_{348}O_{108}S_6Si_5$ $[M+2Na]^{2+}/2$: 2559.93525. Found: 2559.92997.

4.1.14. Fan(1)3-Ga2 (17). A solution of Fan(1)3-Ga2OAc **14** (103.6 mg, 29.2 μmol) in MeOH (1 mL) was treated with 28% NaOMe methanolic solution (20 μL) at room temperature for 1 h, DMF (7 mL) and 0.1 M NaOH aq (6 mL) were then added to the reaction mixture. After overnight, the solution was neutralized by Amberlite IR120B (H^+) resin. The resin was filtered off and filtrate was concentrated to dryness. Purification of the crude product was carried out by gel permeation chromatography (Sephadex G50, 5% HOAc aq eluent) to give Fan(1)3-Ga2 **17** (47.8 mg, 91%) as white powder after lyophilization. $[\alpha]_D^{31}$ +52.8 (*c* 1.1, DMSO); ^1H NMR (CD_3OD) δ 4.97 (s, 3H), 4.27–4.32 (m, 6H), 44.06–4.12 (m, 3H), 4.00 (d, 3H, *J*=2.5 Hz), 3.78–3.92 (m), 3.68–3.76 (m), 3.47–3.63 (m), 2.51 (t, 12H, *J*=7.2 Hz, CH_2S), 1.49–1.67 (m, 18H, $OCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2Si$), 1.43–1.47 (m, 6H, $OCH_2CH_2CH_2CH_2CH_2S$), 1.37–1.40 (m, 6H, $SiCH_2CH_2CH_2Si$), 0.57–0.65 (m, 18H, $SiCH_2$), −0.03 (s, 18H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (CD_3OD) δ 105.16, 102.51, 78.96, 76.08, 74.70, 72.82, 72.60, 71.38, 71.16, 71.05, 70.80, 62.63, 60.89, 36.80, 32.85, 30.76, 30.49, 26.38, 25.58, 21.04, 19.83, 19.79, 15.86, 14.46, −2.97, −4.67; HRMS (ESI) Anal. Calcd for $C_{76}H_{150}O_{33}S_3Si_4$ $[M+Na]^+$: 1821.81962. Found: 1821.81874.

4.1.15. Dumbbell(2)4-Ga2 (18). A mixture of Dumbbell(2)4-Ga2OAc **15** (50.1 mg, 14.0 μmol) and 1 M NaOMe methanolic solution (1 mL) was stirred at room temperature for 4 h, 0.25 M NaOH aq (3 mL) was then added to the reaction mixture. The solution was stirred for 14 h at room temperature. Workup and purification were as described in synthesis of Fan(1)3-Ga2 **17**. Dumbbell(2)4-Ga2 **18** (31.6 mg, 99%) was obtained as white powder after lyophilization. $[\alpha]_D^{28}$ +47.6 (*c* 1.1, H_2O); ^1H NMR (D_2O) δ 5.02 (br s, 4H), 4.36 (br s, 4H), 4.04 (br s), 3.55–3.90 (m), 2.55 (br s, 16H, CH_2S), 1.26–1.62 (m, 40H), 0.60 (br s, 24H, $SiCH_2$), −0.01 (br s, 24H, $SiCH_3$); ^{13}C NMR (D_2O) δ 103.47, 110.49, 76.97, 74.82, 72.80, 71.04, 70.32, 69.47, 69.21, 69.00, 60.82, 59.70, 35.93, 32.00, 29.61, 29.22, 25.25, 24.44, 20.36, 18.64, 13.51, −2.55, −4.55; HRMS (ESI) Anal. Calcd for $C_{100}H_{196}O_{44}S_4Si_5$ $[M+Na]^+$: 2392.07263. Found: 2392.07023.

4.1.16. Dumbbell(2)6-Ga2 (19). A mixture of Dumbbell(2)6-Ga2OAc **16** (35.2 mg, 7.0 μmol) and 1 M NaOMe methanolic solution (1 mL) was stirred at room temperature for 3 h, 0.25 M NaOH aq (3 mL) was then added to the reaction mixture. The solution was stirred overnight at room temperature. Workup and purification were as described in synthesis of Fan(1)3-Ga2 **17**. Dumbbell(2)6-Ga2 **19** (22.4 mg, 98%) was obtained as white powder after lyophilization. $[\alpha]_D^{31}$ +56.7 (*c* 1.0, H_2O); ^1H NMR (D_2O) δ 4.97 (s, 12H), 4.32 (br s, 12H), 4.00 (br s, 12H), 3.51–3.86 (m), 2.53 (br s, 24H, CH_2S), 1.19–1.61 (m, 98H), 0.57 (br s, 28H, $SiCH_2$), −0.03 (br s, 18H, $SiCH_3$); ^{13}C NMR (D_2O) δ 103.29, 100.34, 76.84, 74.70, 72.64, 70.92, 70.25, 69.31, 69.06, 68.81, 60.67, 59.61, 35.81, 31.88, 29.49, 29.09, 25.11, 24.30, 20.30, 20.13, 18.59, 11.90, −2.60; HRMS (ESI) Anal. Calcd for $C_{138}H_{264}O_{66}S_6Si_5$ $[M+2Na]^{2+}/2$: 1677.71339. Found: 1677.71763.

4.2. Kinetic analysis of dendrimers carrying galabiose binding to immobilized B subunits

The dendrimer binding to immobilized recombinant histidine-tagged Stx1 B (1B-His) and Stx2 subunits (2B-His) was quantified using a BIAcore instrument (BIAcore, Uppsala, Sweden) as described previously.[5b] Ni^{2+} was fixed on a nitrilotriacetic acid sensor chip (BIAcore), and recombinant 1B-His or 2B-His (10 μg/mL) was injected into the system, where it was immobilized on the chip. Various concentrations of the dendrimers were injected (time 0) over the immobilized 1B-His or 2B-His at flow rate of 20 μL/min to reach plateau at 25 °C. The binding kinetics were analyzed by Scatchard plot using the software BIAEVALUATION 3.0 (BIAcore).

4.3. ^{125}I-Stx binding assay

^{125}I-Stx binding assay was performed as described previously.[5a] Vero cells were treated with ^{125}I-Stx1 or ^{125}I-Stx2 (1 μg/mL) in the absence or presence of the desired amount of a given compound for 30 min at 4 °C. After extensive washing, the cells were dissolved in lysis solution (0.1 M NaOH, 0.5% SDS). Recovered radioactivity was measured by a γ-counter (Packard).

4.4. Cytotoxicity assay

Subconfluent Vero cells in a 96-well plate were treated with Stx1 or Stx2 (10 pg/mL) in the absence or presence of the desired amount of a given compound for 72 h. The relative number of living cells was determined by using a WST-1 Cell Counting Kit (Wako Pure Industries).

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Synthesis of 8-heteroatom-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-*s*-indacene dyes (BODIPY)

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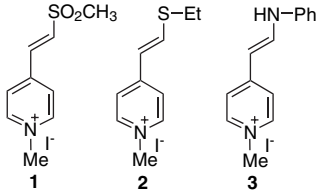
Abstract—Thioketones, bis-(5-R-1*H*-pyrrol-2-yl)-methanethiones (R=H, Me, Et), **4** react with methyl iodide or isopropyl triflate to give the pyrrolium salts, which are treated with tertiary amine and boron trifluoride to produce the 8-(thiomethyl/thioisopropyl) 4,4-difluoro-3,5-di-R-4-bora-3a,4a-diaza-*s*-indacenes **6a**–**6c** and **8a**–**8c**. The reaction of the methyl thioether group of **6a** and **6b** with aniline gives the substitution products whose structure corresponds to formula **10**. The structures of the thioethers **6a**–**6c** and compound **10a** were determined by X-ray diffraction. The thiomethyl groups in **6a**–**6c** are close to be coplanar to the flat ring system, the strain due to the interaction of methyl with the hydrogen at C1 is released by shifting of the sulfur atom away from carbon C1 and opening of the angle C8–*S*-methyl. This coplanarity of the thiomethyl group with ring system agrees with the preference of the *syn* conformation of methyl vinyl thioether. In the structures of the aniline compound **10a** the length of the nitrogen to C8 is close to that of N=C double bond. Thioethers **6a**–**6c** show high wavelength absorption at 523–530 nm and fluorescence with a Stokes shift of 12–24 nm and with a quantum yield of 0.15–0.37. In contrast the aniline substituted compounds **10a** and **10b** showed absorption at 410 and 430 nm, respectively, with no fluorescence. According to their spectral properties they are better described by structure **10** than **7**.

1. Introduction

In recent years, the search for selective and sensitive fluorescent probes for metal ions has tremendously gained an importance. The development of functional group molecules capable of performing chemically and/or physically controlled actions and reporting on or transducing these through luminescence signal has attracted considerable attention. Examples of functional supramolecular systems communicating through the luminescence include molecular scale sensors,[1] switches,[2] motors and machines,[3] wires or arrays,[4] cascades and cassettes that operate through energy or electron transfer process. Herein, we report the synthesis of sulfur containing BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) compounds under mild reaction conditions in good to reasonable yield. The high wavelength absorption at 523–530 nm and the fluorescence with a Stokes shift of 12–24 nm compounds are well described. BODIPY dyes are used for their physical properties in biotechnological applications.[5]

Earlier we described a thiol reagent sulfone **1**. The reaction of this sulfone **1** with thiol gave thioether **2** whose long wavelength absorption appears on the reaction.[6] But this vinylic thioether **2** is not fluorescent. So we planned synthesis of thioether with the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) group. BODIPY dyes are prepared by reaction of pyrroles with acid chlorides (or aldehydes) to the dipyrrolomethenes (or dipyrrolomethanes oxidized to former). The dipyrrolomethenes are then condensed to 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene by action of a tertiary base and boron trifluoride. A limited range of functional groups are compatible with these reaction conditions. In order to avoid further condensation, the pyrroles have to be substituted at C-2. In view of the interest of the spectral properties of this system, there is a need of preparation methods under milder reaction conditions compatible with most functional groups. We report herein such a reaction for the synthesis of sulfur containing BODIPY.



1 **2** **3**

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The reaction of thiophosgene with pyrrole and substituted pyrroles is fast and provides thioketones **4** in rather mild conditions. Even pyrrole itself gives the thioketone **4a** in a good yield.[7] The reaction is specially interesting because no further condensation products have been detected. This may be due to the reduced reactivity of the intermediate and of the thioketone **4**. We prepared the thioketones **4a**–**4c** by the reaction of thiophosgene with pyrrole, 2-methyl- and 2-ethyl-pyrrole in yields close to the published ones.[7]

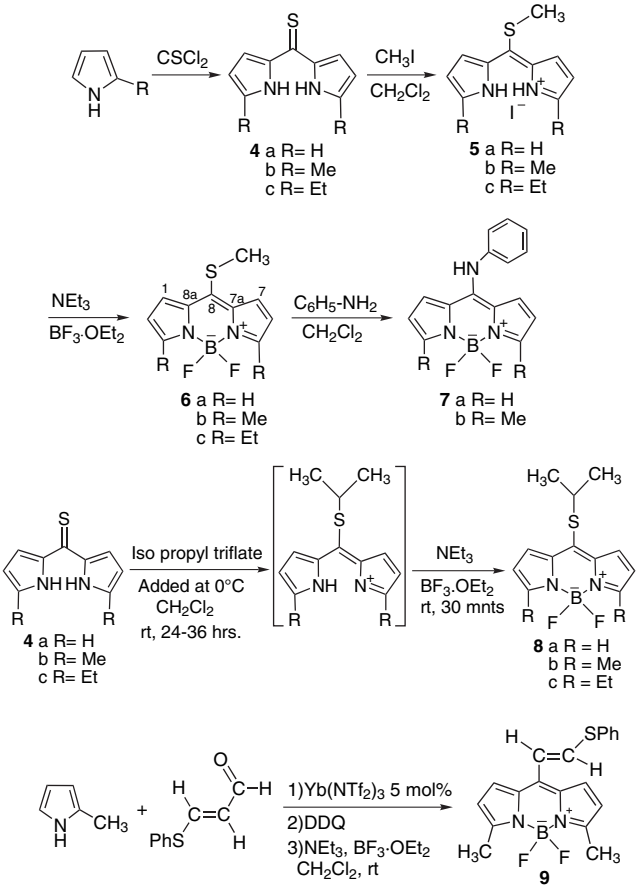
2. Results and discussion

The reaction of thioketones with electrophilic reagents tends to occur at the sulfur. With thiopyridone, for instance, one obtains the pyridinyl thioether.[8] So, we explored the reaction of the thioketones **4a**–**4c** with methyl iodide and isopropyl triflate. The reaction of thioketones **4a**–**4c** with methyl iodide gives the dipyrrolomethene probably as hydroiodides **5a**–**5c** as brown gummy solids. These compounds are not too stable and were characterized as crude products. Their purity seems to be high and they showed a high absorption in the range of 458–480 nm. Their NMR spectra indicate that they are present as single isomer or that the interconvertion of the (*E*) and (*Z*) isomers is rapid. The chemical shifts of the ring protons of pyrrolomethenes **5a**–**5c** are shifted to lower fields when compared to the pyrrolomethenes taken as base in CS_2.[9] So, we favor the presence of the pyrrolomethenes **5a**–**5c** as hydroiodides.

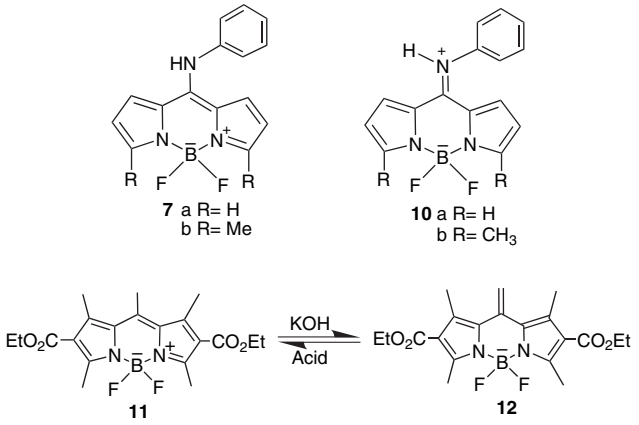
Reaction of pyrrolomethenes **5a**–**5c** with boron trifluoride etherate in presence of triethylamine gave the red colored 8-(thiomethyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes **6a**–**6c**. The thiomethyl group of **6a** and **6b** is displaced by aniline to give 8-(anilino) compounds, which initially we presented as **7a** and **7b**. But their spectral properties are in better agreement with structures **10a** and **10b**. In future discussion we use the structures **10a** and **10b**. The substitution reaction is similar to the one observed with *N*-methyl 4-thiomethylvinylic pyridinium salt.[10] The reaction of indacene **6c** with aniline was very slow and was not studied.

The same reaction sequence of thioketones **4a**–**4c** first with isopropyl triflate and later with boron trifluoride gave the isopropyl thioethers **8a**–**8c**. These compounds **8a**–**8c** were obtained as amorphous material and failed to crystallize in our hands.

In order to compare the spectral properties of vinylic thioether, we prepared 8-(2-thiophenylethene) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-*s*-indacene **9** (Scheme 1). The condensation of 2-methylpyrrole with 3-(phenylthio)-propenal in presence of ytterbium (III) trifluoromethane sulfonamide in catalytic amount gave the nonisolated dipyrrolomethane, which was oxidized by DDQ to the pyrrolomethene. By reaction of boron trifluoride etherate in presence of triethylamine, the indacene **9** was obtained in low yield. But the spectral properties of the vinylic thioether **9** were not what we had expected so that we did only limited attempts in preparing compound **9** and the related ones.



Scheme 1.



3. Structure

Structures of the three indacenes **6a**–**6c** were determined by X-ray diffraction study. As the indacene **6a** (Fig. 1) crystallized with two different molecules in the asymmetric unit, we have four structures. The general features of these four structures will be presented here. The indacene atoms except the fluorine atoms are close to be in one plane. The methyl group of the thiomethyl group is close to the plane of the indacene system (torsion angle CH_3–S–C8–C7a of 0.00°; 2.21°; 2.39°; 4.48°, respectively) and in close contact with the hydrogen at C7 (C of methyl group–H (at C7) 2.50–2.53 Å) whereas the van der Waals distance for hydrogen

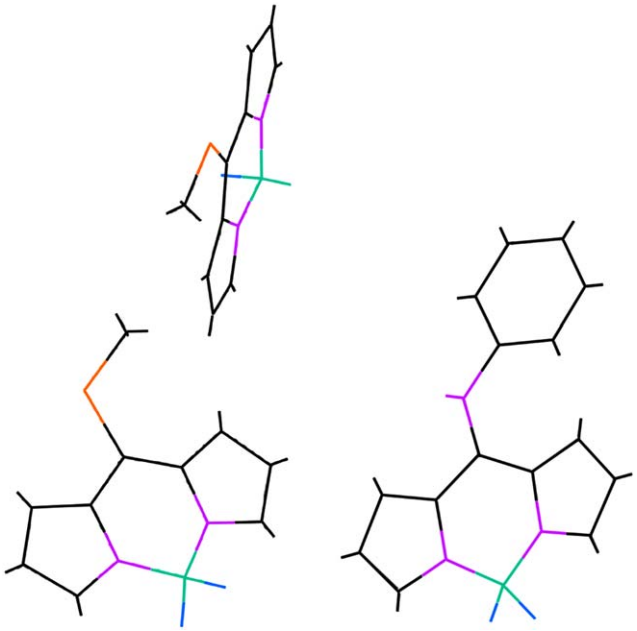


Figure 1. X-ray crystal structures of compounds **6a** (left) and **10a** (right). The carbon and hydrogen atoms are in black, the boron atoms in green, the nitrogen is magenta, and sulfur in yellow. The two molecules of compound **6a** present in the asymmetric unit are presented.

to carbon is 2.9–3.0 Å.[10] The sulfur is displaced toward carbon C1 so that the angles at C8 are in the range of 127.2–127.8° for S–C8–C7a and of 111.8–112.2° for S–C8–C8a. The distance of the sulfur to the hydrogens at C7 and C1 are in the range of 2.77–2.83 Å and 3.31–3.33 Å so that the sulfur atom is shifted by 0.25 Å. The van der Waals distance for sulfur to H is 2.91 Å.[11] The bond angles CH_3–S–C8 in **4a**–**4c** are in the range 109.89–110.22° to be compared with 104° found in thioethers. So the strain was in part released by increasing the angles C7a–C8–S and CH_3–S–C8. The length of the S–CH_3 bond is 1.77–1.78 Å compared to 1.789 Å (σ=0.008) for such bond whereas the length of the C8–S bond is 1.77 Å in the range for such bond 1.773 Å (σ=0.009).[12] In solution no hindrance of the rotation could be detected by NMR spectroscopy and this is not unexpected, since the barrier calculated for the methyl vinyl thioether is low.[13] The systems in the crystals are devoid of symmetry so that the bond distances are different. The solid state NMR of products **6a** and **6b** showed that all the carbon atoms were different in the solid.

The strain induced by the interaction of the methyl group with the hydrogen at C7 must reflect a preference of the methyl group to be coplanar with the indacene system. Indeed the experimental evidence and calculations show a preference for the *syn* conformation of methyl vinyl thioether over the next *gauche* preferred conformation by about 6.92 kJ mol^{-1}.[13] The effect of a donor–acceptor substituent on the equilibrium *gauche*–*syn* of vinylic thioethers as present in **6a**–**6c** does not seem to have been evaluated. The structure of vinylic thioethers seems to have been scarcely determined. We had prepared the vinylic thioether **2**, had determined its structure by X-ray diffraction, and found the cis conformation in the crystalline state with the torsion angle Et–S–C–C of 2.23° and the distance of the sulfur to the *syn* hydrogen of 2.62 Å.[6] The number of aromatic methyl thioether structures Ar–S–CH_3 collected in the data bank at the date of writing is about 150, if the *ortho*-disubstituted are excluded. On closer examination one finds that 47% have a torsional angle in the range of 0–5°, 67% in 0–10°, 80% in 0–15°, and 85% in 0–20°. Such abundance could reflect a preference for the *syn* conformation in solution of such thioethers.

In order to have more information about the systems studied here, we prepared the isopropyl thioethers **8a**–**8c** with the idea that the isopropyl group would be out of the indacene plane. But in our hands these thioethers failed to crystallize.

In view of the unexpected spectral data of the aniline compounds, we determine the structure of the two allotropic forms of **10a**. One contains two molecules in a different arrangement in the lattice, so we have the data for three molecules. The ring system is close to be planar except the two fluorine atoms and the phenyl group. The phenyl group makes an angle of 83°, 88°, and 56° with the plane of the ring system (Fig. 1). The noticeable feature is the short nitrogen–C8 (1.23 Å, 1.33 Å, and 1.34 Å). This bond length is close to the one found for Car-C=N–C (1.28 Å).[12]

4. Spectral properties

The absorption maximum of the thioethers **6a**, **6b** (Fig. 2), and **6c** is shifted to higher wavelength 523–530 nm (MeOH) (Table 1). Indeed related systems such as 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-propanol show an absorption maximum at 505 nm in ethanol.[14] So the introduction of a thioether group at C8 induces a shift of 18–25 nm to be compared to the shift 22–40 nm on going from *N*-methyl pyridinium salt to *N*-methyl 4-thiomethyl pyridinium salt.[15] The absorption maximum of 1-methyl-4-ethenylpyridinium iodide is at 265 nm (15,000)[16] and that of 1-methyl-4-[2-ethylsulfanyl-1-ethenyl]pyridinium salt **2** at 362 nm. So a shift of about 100 nm is observed by introduction of a thioether group in this system. In the crystal structure the thiovinylic group forms a torsion angle of 6.7° with the pyridinium plane so that conjugation may be

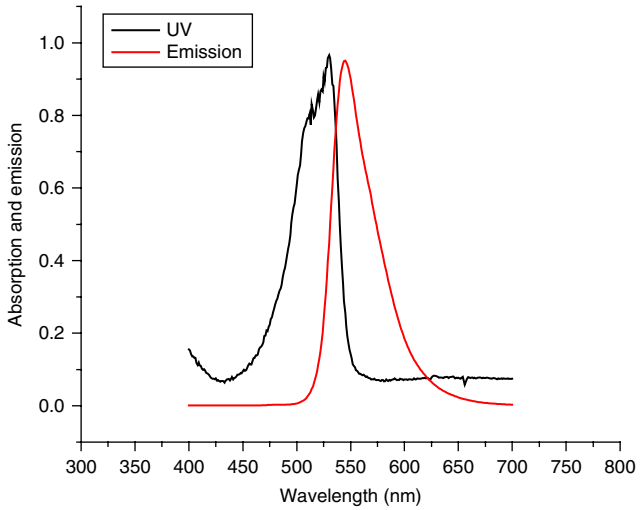


Figure 2. Absorption and fluorescence spectrum (excitation at 530 nm) of compound **6b** in methanol.

Table 1. Spectroscopic data for compounds **6a–c**, **8a–c**, **9** and **10a–b**

Compound	Absorption λ_{max} (nm)	ε (M^{-1} cm^{-1})	Emission λ_{max} (nm)	Stokes shift	Quantum yield
6a	527	40,000	539	12	0.15
6b	530	45,000	554	24	0.37
6c	523	35,000	544	21	0.27
8a	513	30,000	534		
8b	526	40,000	544		
8c	528	35,000	542		
9	528	20,000	580		
10a[a]	410	40,000			
10b[a]	430	20,000			

[a] Taken in MeOH except in CH_2Cl_2.

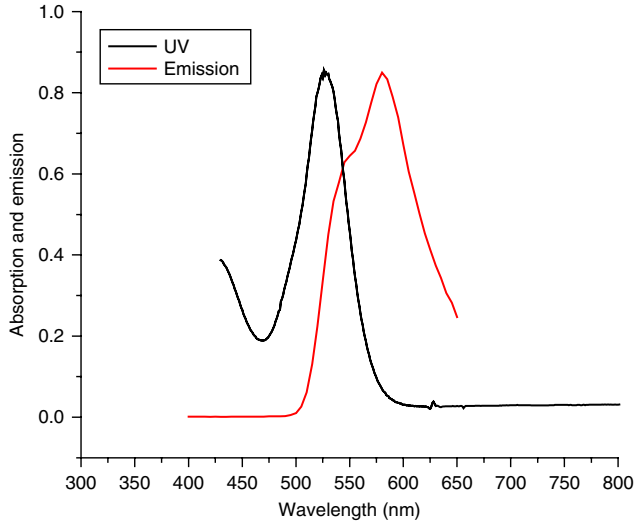


Figure 3. Absorption and fluorescence spectrum (excitation at 528 nm) of compound **9** in methanol.

achieved.[1] However, the introduction of the double bond as in **9** (Fig. 3) induces no shift, the absorption maximum is located at 528 nm in **9** compared to 523–530 nm for **6a–6c**. This can be attributed to the fact that the thiovinylic group of **9** is not coplanar with indacene plane due to the presence of the hydrogens at carbon C1 and C7. The torsion angle of the phenyl group at C8 in related indacene system (with hydrogens at C1 and C7) with the dipyrrolomethane is in the range of 51.5–87.8°.[17] So, for 8-phenyl substituted indacenes and product **9**, the conjugation between the aryl group and the thiovinylic group with the indacene system is low.[18]

In contrast the anilino substituted compounds **10a** and **10b** (Fig. 4) do not show any long wavelength absorption and any fluorescence. The analogous compound **3** shows absorption at 424 nm (ε 40,000).[10] This difference is unexpected. In the crystalline state of compound **10a**, the C8–N bond length (1.23–1.34 Å) is definitely shorter than a nitrogen bond to carbon of an aromatic ring (1.42 Å) and close to nitrogen–carbon double bond, so we propose that the structure of aniline substituted compounds is better described by structure **10** instead of structure **7**. In the NMR spectrum of these compounds one notices the upfield shift of about 1 ppm of the signals of indacene ring protons in agreement with the aromatic character of the structure **10**. The properties expected for structure **10** are close to the ones described by *Treibs* and *Kreuzer* about the compound **12** obtained by

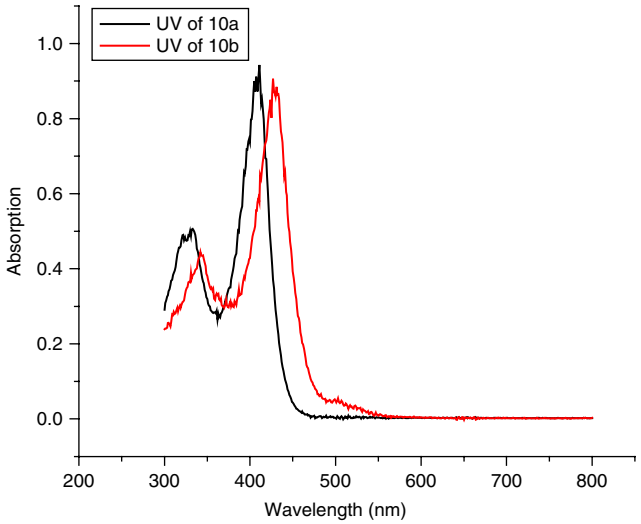


Figure 4. Absorption spectrum of compounds **10a** and **10b** in dichloromethane.

base treatment of 1,3,5,7,8-pentamethyl-2,6-carboethoxy derivative **11**. As found for the compounds **10a** and **10b**, compound **12** does not show any long wavelength absorption and fluorescence.[19] The related 3-phenyl imonomethyl indole hydrochloride has been described with an absorption maximum at 390 nm close to the maximum found for the compounds **10a** and **10b**.[20]

Compounds **6a**, **6b**, **6c**, **8a**, **8b**, **8c**, and **9** show fluorescence when excited at the wavelength of the absorption maximum. The emission spectrum of compound **9** shows an inflexion point at 550 nm.

5. Conclusion

The reaction of the electrophilic reagents occurs at the sulfur atom under mild conditions. This should allow the introduction of more functionalized groups. The vinylic thiother **9** does not show the spectral properties for a reporting group, so the preparation of the corresponding activated vinylic group was not undertaken. Also the thioethers directly attached to the ring as in **6** show some interesting properties, but we did not succeed in preparing any activated derivative, which would give rise to the thioethers **6** by substitution reaction.

6. Experimental

6.1. General procedure

All the reactions were carried out under an atmosphere of nitrogen. Melting points (mp) were taken on capillary tube apparatus and are uncorrected. UV and the fluorescent spectra were recorded in MeOH solution unless otherwise stated. The quantum yield was determined as in Ref. 21. FTIR spectra were recorded in CH_2Cl_2 solution. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, chemical shifts were reported using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. Purification by column chromatography was carried out with neutral silica gel 60

(70–230). MS spectra were determined on VG 70-250S spectrometer. HRMS spectra were collected on Autospec orthogonal acceleration-time of flight mass spectrometer with a resolution of 6000 (5%).

Caution: handling thiophosgene requires a fume hood and container has to be kept tightly closed for storage. Thiophosgene is highly toxic.

6.1.1. Bis-(5-methyl-1*H*-pyrrol-2-yl)-methanethione (4b). A solution of 2-methylpyrrole (0.81 g)[22] in dry ether (15 ml) was added dropwise to a vigorously stirred solution of thiophosgene (0.55 g) in dry toluene (13 ml) at 0 °C. After 10 min, aqueous methanol (10%) (12 ml) was added and the mixture stirred for further 30 min at room temperature (rt). The solvents were removed in vacuo and the residue, dissolved in toluene/chloroform (9:1), was chromatographed on neutral alumina. The pure compound fraction was collected, which, after removal of the solvents in vacuo, yielded the thioketone **4b** as a crystalline orange red solid (0.64 g; 65%), mp 106–108 °C. λ_{max}: 419 nm (ε 50,000), 293 (ε 3200). IR (CH_2Cl_2): 3405, 3360, 1280. ^{1}H NMR ($CDCl_3$): δ 2.78 (s, 6H), 6.10 (2H, d, J=6.0 Hz), 6.90 (2H, d, J=6.0 Hz), 9.58 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 111.7 (CH), 115.8 (CH), 137.4 (C), 139.5 (C), 187.2 (C). Mass spectrum (EI): m/z 204 (M^+); Anal. Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.62; H, 5.88; N, 13.67.

6.1.2. Bis-(5-ethyl-1*H*-pyrrol-2-yl)-methanethione (4c). A solution of 2-ethylpyrrole (0.81 g)[22] in dry ether (15 ml) was added dropwise to a vigorously stirred solution of thiophosgene (0.486 g) in dry toluene (10 ml) at 0 °C. After 10 min, aqueous methanol (10%) (12 ml) was added and the mixture stirred for further 30 min at rt. The solvents were removed in vacuo and the residue, dissolved in toluene/chloroform (9:1), was chromatographed on neutral alumina. The pure compound fraction was collected, which, after removal of the solvents in vacuo, yielded the thioketone **4c** as a crystalline orange red solid (0.62 g; 63%), mp 110–111 °C. λ_{max}: 416 nm (ε 50,000), 295 (ε 3100). IR (CH_2Cl_2): 3400, 3362, 1280. ^{1}H NMR ($CDCl_3$): δ 1.29 (6H, t, J=7.2 Hz), 2.66 (4H, q, J=7.2 Hz), 6.12–6.14 (m, 2H), 6.91–6.93 (m, 2H), 9.59 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 12.8 (CH_3), 21.1 (CH_2), 110.1 (CH), 115.7 (CH), 137.0 (C), 145.4 (C), 188.4 (C). Mass spectrum (EI): m/z 232 (M^+); Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.15; H, 6.90; N, 12.02.

6.1.3. 2-[Methyl sulfanyl-(1*H*-pyrrol-2-yl)-methylene]-2*H*-pyrrolium iodide (5a). To a solution of compound bis-(1*H*-pyrrol-2-yl)-methanethione **4a** (0.30 g) (**1b**) in anhydrous dichloromethane (5 ml) was added methyl iodide (0.48 ml) at rt. The reaction mixture was stirred for 24 h for completion (TLC monitoring). Solvent was removed under reduced pressure to obtain brown colored gummy solid. The compound **5a** was used without further purification for the next reaction. ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 3H), 6.63–6.64 (m, 2H), 7.23–7.24 (m, 2H), 7.87–7.88 (m, 2H), 12.0 (br s). ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3), 116.7 (CH), 128.6 (CH), 129.3 (CH), 138.4 (C), 162.2 (C). Mass spectrum (EI): m/z 190 (M^+); HRMS calcd for $C_{10}H_{11}N_2S$ 191.0637, found 191.0640.

6.1.4. 5-Methyl-2-[(5-methyl-1*H*-pyrrol-2-yl)-methylsulfanyl-methylene]-2*H*-pyrrolium iodide (5b). To a solution of compound bis-(5-methyl-1*H*-pyrrol-2-yl)-methanethione **4b** (0.30 g) in anhydrous dichloromethane (5 ml) was added methyl iodide (0.41 ml) at rt. The reaction mixture was stirred for 24 h for completion (TLC monitoring). Solvent was removed under reduced pressure to obtain brown colored gummy solid. The obtained compound **5b** is directly used for the next reaction. ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 6H), 2.76 (s, 3H), 6.35 (2H, d, J=8.0 Hz), 7.02 (2H, d, J=8.0 Hz), 11.6 (br s). ^{13}C NMR ($CDCl_3$): δ 14.8 (CH_3), 21.9 (CH_3), 118.1 (CH), 129.4 (CH), 129.8 (C), 152.6 (C), 156.3 (C). Mass spectrum (EI): m/z 218 (M^+); HRMS calcd for $C_{12}H_{15}N_2S$ 219.0951, found 219.0956.

6.1.5. 5-Ethyl-2-[(5-ethyl-1*H*-pyrrol-2-yl)-methylsulfanyl-methylene]-2*H*-pyrrolium iodide (5c). To a solution of compound **4c** (0.30 g) in anhydrous dichloromethane (5 ml) was added methyl iodide (0.36 ml) at rt. The reaction mixture was stirred for 24 h for completion (TLC monitoring). Solvent was removed under reduced pressure to obtain brown colored gummy solid. The obtained compound **5c** is directly used for the next reaction. ^{1}H NMR ($CDCl_3$): δ 1.21(6H, t, J=7.0 Hz), 2.72 (4H, q, J=7.0 Hz), 2.93 (s, 3H), 6.34–6.35 (m), 6.93–6.94 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 12.8 (CH_3), 21.6 (CH_3), 116.0 (CH), 129.2 (CH), 129.7 (C), 156.7 (C), 158.1 (C). Mass spectrum (EI): m/z 247 (M^+); HRMS calcd for $C_{14}H_{19}N_2S$ 247.1268, found 247.1262.

6.1.6. 8-(Thiomethyl)4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (6a). To a solution of compound **5a** (0.30 g) in anhydrous dichloromethane (7 ml) under nitrogen atmosphere at rt was added triethylamine (0.22 ml). After stirring for 30 min $BF_3\cdot OEt_2$ (0.18 ml) was added. The mixture was stirred for 30 min at rt. After the evaporation of solvents under vacuum, the crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **6a** as a dark red solid (0.21 g; 60%), mp 88–90 °C. λ_{max}: 527 nm (ε 40,000). IR (CH_2Cl_2): 1489, 1264 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.88 (s, 3H), 6.50–6.51 (m, 2H), 7.39–7.40 (m, 2H), 7.77–7.78 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 20.0 (CH_3), 117.6 (CH), 127.3 (CH), 133.4 (C), 140.8 (C), 154.0 (C). ^{19}F (CCl_3F in $CDCl_3$): δ −145.6, −145.7, −145.8, −145.9. Mass spectrum (EI): m/z 238 (M^+); Anal. Calcd for $C_{10}H_9BF_2N_2S$: C, 50.45; H, 3.81; N, 11.77. Found: C, 50.38; H, 3.78; N, 11.67.

6.1.7. 8-(Thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (6b). To a solution of compound **5b** (0.30 g) in anhydrous dichloromethane (7 ml) under nitrogen atmosphere at rt was added triethylamine (0.19 ml). After stirring for 30 min $BF_3\cdot OEt_2$ (0.16 ml) was added. The mixture was stirred for 30 min at rt. After the evaporation of solvents under vacuum, the crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **6b** as a dark red solid (0.23 g; 63%), mp 96–97 °C. λ_{max}: 515 (inflexion), 530 nm (ε 45,000). IR (CH_2Cl_2): 1558, 1264 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 6H), 2.68 (s, 3H), 6.24 (2H, d, J=5.2 Hz), 7.26 (2H, d, J=5.2 Hz). ^{13}C NMR ($CDCl_3$): δ 14.8 (CH_3), 21.5 (CH_3), 119.1 (CH), 128.2 (CH), 135.3 (C), 144.2 (C), 156.8 (C). Mass spectrum (EI): m/z 266 (M^+); Anal. Calcd for

$C_{12}H_{13}BF_2N_2S$: C, 54.16; H, 4.92; N, 10.53. Found: C, 54.10; H, 4.87; N, 10.50.

6.1.8. 8-(Thiomethyl) 4,4-difluoro-3,5-diethyl-4-bora-3a,4a-diaza-*s*-indacene (6c). To a solution of compound **5c** (0.30 g) in anhydrous dichloromethane (7 ml) under nitrogen atmosphere at rt was added triethylamine (0.17 ml). After stirring for 30 min $BF_3 \cdot OEt_2$ (0.14 ml) was added. The mixture was stirred for 30 min at rt. After the evaporation of solvents under vacuum, the crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **6c** as a dark red solid (0.21 g; 58%), mp 96–98 °C. λ_{max} (CH_2Cl_2): 523 nm (ε 35,000), 378 (ε 17,000). IR (CH_2Cl_2): 1546, 1262 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.31 (6H, t, J=6.2 Hz), 2.66 (s, 3H), 3.02 (4H, q, J=6.2 Hz), 6.32 (2H, d, J=3.2 Hz), 7.30 (2H, d, J=3.2 Hz). ^{13}C NMR ($CDCl_3$): δ 12.6 (CH_3), 21.5 (CH_3), 21.9 (CH_2), 117.0 (CH), 128.2 (CH), 135.0 (C), 144.5 (C), 162.7 (C). Mass spectrum (EI): m/z 294.16 (M^+); Anal. Calcd for $C_{14}H_{17}BF_2N_2S$: C, 57.16; H, 5.82; N, 9.52. Found: C, 57.10; H, 5.78; N, 9.47.

6.1.9. 8-(Thioisopropyl) 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (8a). To a dried 50 ml round-bottom flask was added compound **4a** (0.250 g) in anhydrous dichloromethane (10 ml) under nitrogen atmosphere at 0 °C and then isopropyl triflate (0.545 ml)[23] was added and the reaction mixture was stirred for 12–16 h at rt. To the reaction mixture triethylamine (0.161 ml, 1.14 mmol) was added. After stirring for 30 min $BF_3 \cdot OEt_2$ (0.13 ml) was added and the reaction mixture was stirred for another 30 min at rt. Solvents were evaporated in vacuo, the above crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **8a** (0.10 g: 34%) as a dark red gum. λ_{max}: 513 nm (ε 30,000), 388 (ε 3000). IR (CH_2Cl_2): 2932, 1552, 1264 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (6H, d, J=6.8 Hz), 3.80–3.82 (sept, 1H), 6.49–6.50 (m, 2H), 7.44–7.45 (m, 2H), 7.81 (2H, d, J=2.0 Hz). ^{13}C NMR ($CDCl_3$): δ 23.7 (CH_3), 44.1 (CH), 118.2 (CH), 129.5 (CH), 137.0 (C), 143.3 (CH), 148.4 (C). Mass spectrum (EI): m/z 266 (M^+); HRMS calcd for $C_{12}H_{13}BF_2N_2S$ 266.0861, found 266.0864.

6.1.10. 8-(Thioisopropyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (8b). To a dried 50 ml round-bottom flask was added compound **4b** (0.20 g) in anhydrous dichloromethane (10 ml) under nitrogen atmosphere at 0 °C and then isopropyl triflate (0.38 ml) was added and the reaction mixture was stirred for 12–16 h at rt. To the reaction mixture triethylamine (0.114 ml) was added. After stirring for 30 min $BF_3 \cdot OEt_2$ (0.95 ml) was added and the reaction mixture was stirred for another 30 min at rt. Solvents were evaporated in vacuo, the above crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **8b** (0.09 g: 38%) as a dark red gummy liquid. λ_{max}: 526 nm (ε 40,000). IR (CH_2Cl_2): 2937, 1550, 1270 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (6H, d, J=6.8 Hz), 2.58 (s, 6H), 3.53–3.55 (sept, 1H), 6.24 (2H, d, J=4.0 Hz), 7.30 (2H, d, J=4.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.9 (CH_3), 23.7 (CH_3), 44.1 (CH), 119.4 (CH), 129.5 (CH), 137.9 (C), 151.0 (C), 158.0 (C). Mass spectrum (EI): m/z 294 (M^+); Anal. Calcd for $C_{14}H_{17}BF_2N_2S$: C, 57.16; H, 5.82; N, 9.52. Found: C, 57.10; H, 5.78; N, 9.47.

6.1.11. 8-(Thioisopropyl) 4,4-difluoro-3,5-diethyl-4-bora-3a,4a-diaza-*s*-indacene (8c). To a dried 50 ml round-bottom flask was added compound **4c** (0.20 g) in anhydrous dichloromethane (10 ml) under nitrogen atmosphere at 0 °C and then isopropyl triflate (0.33 ml) was added and the reaction mixture was stirred for 12–16 h at rt. To the reaction mixture triethylamine (0.102 ml) was added, after stirring for 30 min $BF_3 \cdot OEt_2$ (0.086 ml) was added and the reaction mixture was stirred for another 30 min at rt. Solvents were evaporated in vacuo, the above crude product was chromatographed on silica gel (70–230 mesh, using 15% EtOAc in hexane), yielded compound **8c** (0.085 g: 36%) as a dark red gummy liquid. λ_{max} 528 nm (ε 35,000). IR (CH_2Cl_2): 2937, 1548, 1266 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (6H, d, J=6.8 Hz), 1.30 (6H, t, J=6.0 Hz), 3.01 (4H, q, J=6.0 Hz), 3.53–3.55 (sept, 1H), 6.32 (2H, d, J=4.4 Hz), 7.33 (2H, d, J=4.4 Hz). ^{13}C NMR ($CDCl_3$): δ 12.6 (CH_3), 22.0 (CH_2), 23.7 (CH_3), 44.2 (CH), 117.2 (CH), 129.6 (CH), 137.6 (C), 140.1 (C), 164.0 (C). Mass spectrum (EI): m/z 322 (M^+); HRMS calcd for $C_{16}H_{21}BF_2N_2S$ 322.1487, found 322.1489.

6.1.12. 8-(2-Thiophenylethene) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (9). To a solution of 2-methylpyrrole (162 mg) and 3-(phenylthio) propenal (164 mg)[24] in N_2-flushed dichloromethane (20 ml) was added ytterbium (III) trifluoromethane sulfonimide (50 mg) at once at rt. After 20 min TLC (silica–hexane/ethylacetate 9:1) showed that the propenal had been consumed. Then DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (0.25 g) was added at once and the reaction mixture was stirred at rt under nitrogen atmosphere. After stirring for 10 min, triethylamine (1 ml) and $BF_3 \cdot OEt_2$ (1.6 ml) were added and the mixture was stirred at rt for further 30 min. After evaporation of the solvent, the crude product was chromatographed on silica gel (70–230 mesh, 10% EtOAc in hexane) to give compound **9** (7 mg) as red gummy solid. λ_{max}: 528 nm (ε 20,000). ^1H NMR ($CDCl_3$): δ 2.58 (s, 6H), 6.22 (2H, d, J=4 Hz), 6.64 (1H, d, J=15 Hz), 6.98 (2H, d, J=4 Hz), 7.35–7.49 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 14.9 (CH_3), 118.7 (CH), 120.0 (CH), 127.0 (CH), 128.9 (CH), 129.8 (CH), 131.0 (C), 132.0 (CH), 132.9 (C), 137.6 (C), 142.1 (CH), 156.3 (C); ^{19}F (CCl_3F in $CDCl_3$): δ −147.9, −148.0, −148.1, −148.2. FABMS (*m*-NBA) m/z 354.0 $(M)^+$; HRMS calcd for $C_{19}H_{17}BF_2N_2S$ 354.1174, found 354.1179.

6.1.13. Compound 10a. To a dried 50 ml round-bottom flask was added compound **6a** (0.20 g) in anhydrous dichloromethane (5 ml) under nitrogen atmosphere at rt and then aniline (0.078 ml) was added. The reaction mixture was stirred for 12 h at rt. Solvent was evaporated in vacuo, the crude product was chromatographed on silica gel (70–230 mesh, using 20% EtOAc in hexane), yielded compound **10a** as a light red crystals from hexane/chloroform (0.130 g; 55%). Two allotropic forms were obtained: the first from hexane/chloroform and the second from chloroform: mp 191–193 °C; 199–201 °C. λ_{max} (CH_2Cl_2): 410 nm (ε 40,000), 332 (ε 21,000). IR (CH_2Cl_2): 3300, 1699, 1272 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.25 (2H, t, J=2.0, 1.6 Hz), 6.31 (2H, d, J=1.6 Hz), 7.27 (2H, d, J=2.0 Hz), 7.46–7.47 (m, 5H), 8.33 (br s). ^{13}C NMR ($CDCl_3$): δ 114.3 (CH), 120.5 (C), 123.9 (C), 126.4 (CH), 129.0 (CH), 130.0 (CH), 134.2 (CH), 137.4 (C), 147.7 (C). ^{19}F (CCl_3F in

$CDCl_3$): δ −144.8, −144.9, −145.0, −145.1. Mass spectrum (EI): *m/z* 283 (M^+); Anal. Calcd for $C_{15}H_{12}BF_2N_3$: C, 63.64; H, 4.27; N, 14.84. Found: C, 63.60; H, 4.20; N, 14.80.

6.1.14. Compound 10b. To a dried 50 ml round-bottom flask was added compound **6b** (0.20 g) in anhydrous dichloromethane (5 ml) under nitrogen atmosphere at rt and then aniline (0.07 ml) was added. The reaction mixture was stirred for further 12 h at rt. Solvent was evaporated in vacuo, the crude product was chromatographed on silica gel (70–230 mesh, using 20% EtOAc in hexane), yielded compound **10b** as a light yellow solid (0.04 g: 20%), mp 198–200 °C. λ_{max}(CH_2Cl_2): 430 nm (ε 20,000), 343 (ε 13,000). IR (CH_2Cl_2): 3310, 1692, 1270 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.54 (s, 6H), 6.03 (2H, d, *J*=4.0 Hz), 6.40 (2H, d, *J*=4.0 Hz), 7.24 (s, 1H), 7.36 (2H, d, *J*=6.0 Hz), 7.45 (2H, d, *J*=6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 115.4 (CH), 120.3 (CH), 123.8 (C), 126.8 (CH), 128.7 (CH), 130.2 (CH), 138.5 (C), 149.0 (C). Mass spectrum (EI): *m/z* 311 (M^+); HRMS calcd for $C_{17}H_{16}BF_2N_3$ 311.1400, found 311.1388.

7. Crystal structure determination

Diffraction measurements were made on an Enraf-Nonius CAD-4 diffractometer by use of graphite-monochromatized Mo Kα radiation (λ=0.7107 Å). Unit cell parameters were obtained by least-squares fit to the automatically centered settings for 25 reflections. Intensity data were collected by use of ω–2θ scan mode. All intensity data were collected for Lorentz polarization and absorption (empirical ψ corrections).

7.1. Crystal data

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 289285–289289.

7.1.1. 8-(Thiomethyl) 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 6a (CCDC 289286). $C_{10}H_9BF_2N_2S$, *M*=238.06 triclinic space group *P*-1, *a*=8.0683(14), *b*=9.0846(14), *c*=14.517(5) Å, α=98.89(2)°, β=92.70(2)°, γ=95.868(13)°, *V*=1043.6(4) $Å^3$, *T*=298(2) K, *Z*=4, μ (Mo Kα)=0.307 mm^{-1}, 3676 reflections measured (*R*(int)=0.0214), which were used in all calculations. The final $wR(F^2)$ was 1.010.

7.1.2. 8-(Thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-*s*-indacene 6b (CCDC 289285). $C_{12}H_{13}BF_2N_2S$, *M*=266.11 orthorhombic space group *Pnma*, *a*=15.994(3), *b*=7.053(4), *c*=10.856(3) Å, *V*=1224.6(9) $Å^3$, *T*=298(2) K, *Z*=4, μ(Mo Kα)=0.270 mm^{-1}, 1168 reflections measured (*R*(int)=0.0000), which were used in all calculations. The final $wR(F^2)$ was 1.041.

7.1.3. 8-(Thiomethyl) 4,4-difluoro-3,5-diethyl-4-bora-3a,4a-diaza-*s*-indacene 6c (CCDC 289287). $C_{14}H_{17}BF_2N_2S$, *M*=294.17 monoclinic space group *P*2(1)/*c*, *a*=7.4558(3), *b*=18.5780(5), *c*=10.6193(3) Å, α=90°, β=108.188(2)°, γ=90°, *V*=1397.43(8) $Å^3$, *T*=293(2) K, *Z*=4, μ (Mo Kα)=0.244 mm^{-1}, 2455 reflections measured (*R*(int)=0.0305), which were used in all calculations. The final $wR(F^2)$ was 1.048.

7.1.4. Compound 10a (CCDC 289288–289289). $C_{15}H_{12}BF_2N_3$, *M*=283.09

- Triclinic space group *P*-1, *a*=9.7381(2), *b*=11.7125(2), *c*=12.1698(3) Å, α=97.0980(10)°, β=105.3670(10)°, γ=96.0900(10)°, *V*=1314.12 $Å^3$, *T*=100(1) K, *Z*=4, μ (Mo Kα)=0.106 mm^{-1}, 4634 reflections measured (*R*(int)=0.0176), which were used in all calculations. The final $wR(F^2)$ was 1.051.
- Triclinic space group *P*-1, *a*=7.3696(3), *b*=9.6925(3), *c*=9.9641(4) Å, α=109.2870(10)°, β=101.8620(10)°, γ=100.4640°, *V*=633.00(4) $Å^3$, *T*=100(1) K, *Z*=2, μ (Mo Kα)=0.110 mm^{-1}, 2222 reflections measured (*R*(int)=0.0194), which were used in all calculations. The final $wR(F^2)$ was 1.040.

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Selective metal-halogen exchange of 4,4′-dibromobiphenyl mediated by lithium tributylmagnesiate

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Abstract—A selective metal–halogen exchange/electrophilic quench protocol on 4,4′-dibromobiphenyl **4** that proceeds under non-cryogenic conditions is reported. This method provides an economic alternative to traditional transition-metal catalyzed cross-coupling chemistry to prepare various biaryls **7a**–**g**. This novel route to functionalized biaryls was used as the basis for the kg-scale preparation of a biphenyl ketone **1**, a key intermediate in the synthesis of a potent cathepsin K inhibitor.

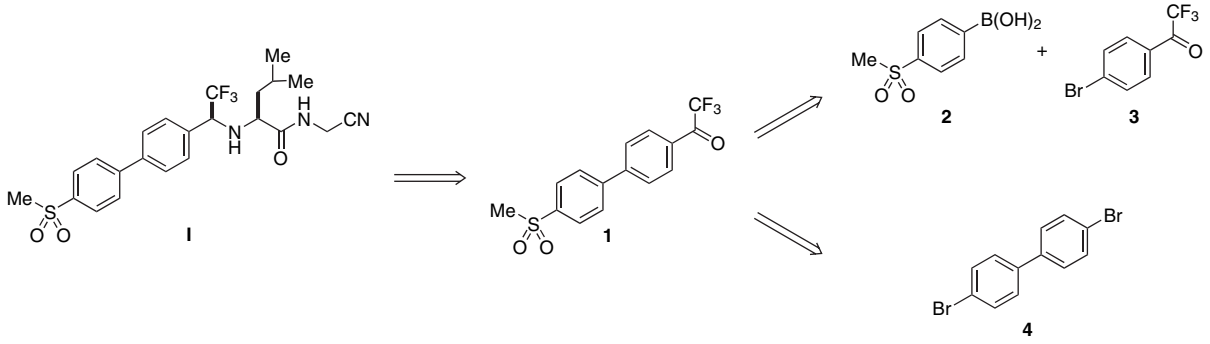
1. Introduction

Transition-metal catalyzed reactions represent some of the most widely used and powerful tools in synthetic organic chemistry.[1] Currently, these techniques are readily applied to various C–C bond constructions, including aryl–aryl bond formation.[2] In particular, the Suzuki–Miyaura[3] reaction has gained widespread use throughout preparative and medicinal chemistry due to the low toxicity and bench stability of organoboron species. Recent examples of pharmaceutically relevant molecules prepared utilizing this chemistry include VLA-4 antagonists,[4] angiotensin II antagonists,[5] and cathepsin K inhibitors.[6]

During the course of our investigations on cathepsin K inhibitors, we sought to develop a cost-efficient and practical synthesis of biphenyl ketone **1**, a precursor to potent cathepsin K inhibitor **I** (Scheme 1).[7] One obvious disconnection of biphenyl ketone **1** would be the aryl–aryl bond, which could be generated via a Suzuki–Miyaura[3] cross-coupling between boronic acid **2** and aryl bromide **3**. While these materials are commercially available, we felt that the price of the coupling partners was not justified for a simple molecule such as ketone **1**. The cost of these materials compelled us to develop an alternative strategy to ketone **1** that would avoid the use of metal-catalyzed cross-coupling.

2. Results and discussion

From the outset we aimed to use low-cost, commercial materials to avoid the use of cryogenic temperatures throughout



Scheme 1. Retrosynthetic analysis of cathepsin K inhibitor **I**.

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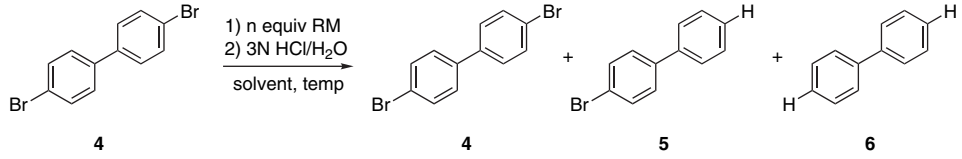
this process. We selected 4,4′-dibromobiphenyl (**4**) as starting material since it is a readily available, inexpensive commodity chemical. We sought to develop a protocol for stepwise functionalization of **4** via controlled, selective mono-metal–halogen exchange followed by electrophilic quench.

We investigated the selectivity of a variety of metal–halogen exchange reagents by examination of the ratio of di-, mono-, and non-brominated biphenyls (**4**, **5**, and **6**, respectively) resulting from direct quench with 3 N aqueous HCl (Table 1). Metal–halogen exchange using *n*-BuLi gave unsatisfactory ratios of mono- to di-metallation in THF at −46 °C, toluene at 22 °C, and toluene/THF (2:1) at −25 °C (Table 1, entries 1–3). Modest selectivity was observed with *n*-BuLi in MTBE, however a significant quantity of starting material remained (Table 1, entry 4). Grignard reagents have been used as an effective metal–halogen exchange reagents.[8] However, *i*-PrMgCl was completely ineffective in both THF and toluene, even after 16 h at 55 °C; the additive lithium chloride only marginally improved reactivity (Table 1, entries 5–7). The more reactive dibutylmagnesium[9] was also ineffective for metal–halogen exchange (Table 1, entry 8). While the Grignard reagent could be prepared by heating dibromide **4** with magnesium metal,[10] acceptable selectivity was not observed (Table 1, entry 10).

Lithium trialkylmagnesiates[11] have been used as metal–halogen exchange reagents for aryl and vinyl halides; the resultant magnesiates were successfully used as nucleophiles.[12] In fact, Oshima and co-workers have shown that addition of 1.0 equiv of *n*-Bu_3MgLi to dibromide **4**, followed by D_2O addition resulted in metal–halogen exchange and incorporation of deuterium at both the 4- and 4′-positions. Work within our own laboratories on 2,6-dibromopyridine has shown that all three alkyl groups on trialkylmagnesiates are active toward metal–halogen exchange and that direct addition of the dihalide to magnesiate, at −10 °C, afforded good mono- versus di-exchange selectivity.[13] We therefore examined the addition of dibromide **4** to 0.33 equiv *n*-Bu_3MgLi, but were disappointed to observe poor selectivity (Table 2, entry 1, **4**:**5**:**6**=47:36:17). Gratifyingly, by adding *n*-Bu_3MgLi to a solution of **4**, a substantial improvement in selectivity was observed (Table 2, entry 2, **4**:**5**:**6**= 24:73:3). In order to drive the reaction to completion, we tested the use of greater equivalents of reagent (Table 2, entries 3–4). As much as 0.43 equiv of *n*-Bu_3MgLi was needed in order to consume >98% dibromide **4**, however, at this point selectivity was significantly diminished (**4**:**5**:**6**= 1:89:10). We therefore settled upon the use of 0.40 equiv of magnesiate as the optimal stoichiometry, for which high conversion (94%) was obtained, and selectivity maintained

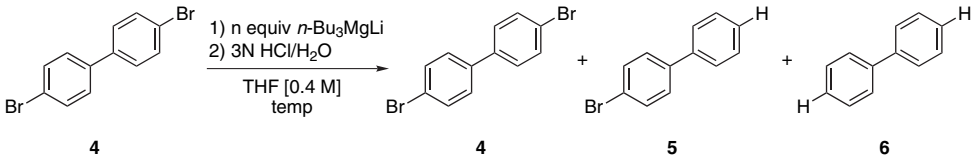
Table 1. Selectivity of various metal–halogen exchange reagents toward dibromobiphenyl **4**



4 **4** **5** **6**

Entry	Reagent	Solvent	*n* (equiv)	Temperature (°C)	Time (h)	HPLC area (%)		
						4	**5**	**6**
1	*n*-BuLi	THF	1.0	−46	0.1	32	41	27
2	*n*-BuLi	Toluene	1.0	22	0.1	10	43	47
3	*n*-BuLi	Toluene/THF	1.0	−25	0.1	23	50	27
4	*n*-BuLi	MTBE	1.0	−25	0.1	28	62	10
5	*i*-PrMgCl	THF	2.0	55	16	99	<1	0
6	*i*-PrMgCl	Toluene	2.0	55	16	99	<1	0
7	*i*-PrMgCl-LiCl	THF	1.1	22	24	83	16	1
8	*n*-Bu_2Mg	Toluene	1.0	22	1	99	<1	0
9	Mg	Toluene	1.5	80	24	99	<1	0
10	Mg	THF	1.5	55	24	64	16	18

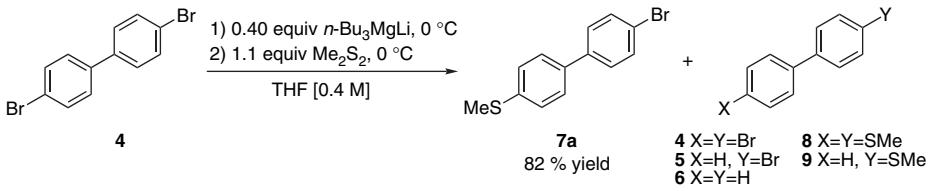
Table 2. Selectivity of *n*-Bu_3MgLi toward metal–halogen exchange of dibromobiphenyl[a]



4 **4** **5** **6**

Entry	Mode of addition	Addition time (min)	*n* (equiv)	Temperature (°C)	Time (h)	HPLC area (%)		
						4	**5**	**6**
1	Direct	60	0.33	22	0.1	47	36	17
2	Inverse	60	0.33	22	0.1	24	73	3
3	Inverse	90	0.40	22	0.1	6	88	6
4	Inverse	120	0.43	22	0.1	1	89	10
5	Inverse	90	0.40	0	1.0	6	90	4

[a] Reaction conditions: for direct addition, a THF solution (0.4 M) of dibromide **4** was added to a slurry of *n*-Bu_3MgLi in THF. For inverse addition, *n*-Bu_3MgLi was added to a THF solution (0.4 M) of dibromide **4**.

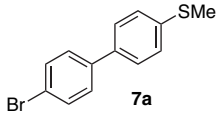
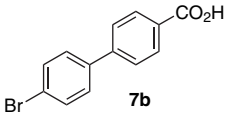
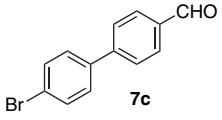
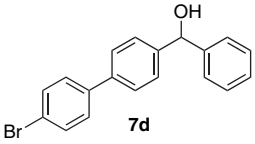
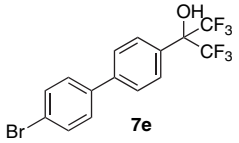
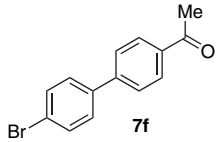
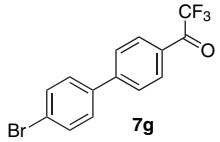


Scheme 2. Trialkylmagnesiate mediated mono-metal–halogen exchange followed by Me_2S_2 quench.

(**4**:**5**:**6**=6:88:6). Finally, we found that addition of magnesiate at 0 °C, followed by aging 1 h, provided optimal selectivity (Table 2, entry 5, **4**:**5**:**6**=6:90:4).

When addition of lithium tributylmagnesiate to dibromobiphenyl **4** was followed by addition of 1.1 equiv of methyl disulfide, biaryl **7a** was obtained in 82% yield (Scheme 2).[14] The crude organic stream was contaminated with several biphenyl impurities (**4**–**6**, **8**, and **9**), as indicated by HPLC analysis, however, these contaminants could be carried through the process sequence without detrimental effect.

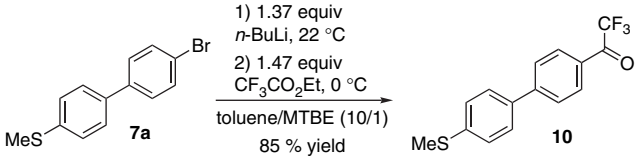
Table 3. Preparation of 4,4′-disubstituted biphenyls via magnesiate-mediated metal–halogen exchange and electrophilic quench[a]

Entry	Electrophile	Product	Yield[b] (%)
1	Me_2S_2	 **7a**	82 (73)[c]
2	CO_2	 **7b**	91 (73)[c]
3	DMF	 **7c**	83 (60)[c]
4	PhCHO	 **7d**	83 (55)[c]
5	$(CF_3)_2CO$	 **7e**	93 (59)[c]
6[d]	Ac_2O[d]	 **7f**	75 (63)[c]
7[d]	$(CF_3CO)_2O$[d]	 **7g**	79 (61)[c]

[a] Reaction conditions: 0.4 equiv *n*-Bu_3MgLi added over 90 min to a THF solution (0.4 M) of dibromide **4** at 0 °C. The reaction mixture was stirred 1 h, then 1.1 equiv of requisite electrophile was added.
[b] Assay yield determined by HPLC versus authentic standard.
[c] Isolated yield after column chromatography.
[d] Inverse addition was used: 0.4 equiv *n*-Bu_3MgLi added over 90 min to a THF solution (0.4 M) of dibromide **4** at 0 °C; then the crude reaction mixture was added over 60 min to a solution of the requisite electrophile in THF at −20 °C.

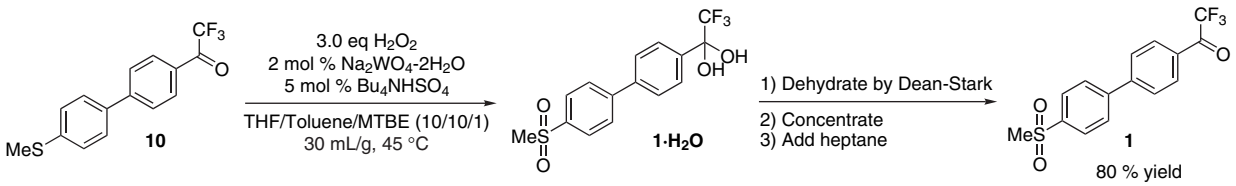
With a successful method for mono-metal–halogen exchange/electrophilic quench in hand, we briefly investigated the scope of addition to various electrophiles. We found that direct addition of carbon dioxide and DMF afforded high assay yields of the carboxylic acid and aldehyde derivatives, respectively (Table 3, entries 2 and 3). Non-enolizable ketones and aldehydes afforded both secondary and tertiary alcohols in good yield (Table 3, entries 4 and 5). Addition to acetic and trifluoroacetic anhydride necessitated the use of inverse addition to the electrophile at −20 °C to obtain good yields of the corresponding ketones (Table 3, entries 6 and 7).

In order to complete the synthesis of ketone **1**, we next investigated the introduction of the trifluoroacetyl moiety via aryllithium addition to ethyl trifluoroacetate, Scheme 3.[15] Metal–halogen exchange could be performed with *n*-BuLi at room temperature in a toluene/MTBE (10:1) solvent mixture. In the absence of MTBE as a co-solvent, exchange was sluggish (<15% conversion in 1 h at room temperature). The yield of thioketone **10** was found to be highly dependent upon the mode of electrophile addition. Direct addition of ethyl trifluoroacetate was not scalable; if the addition was completed in <5 s, thioketone **10** was obtained in ~80% yield on gram-scale. However upon scale-up to multigram, longer periods were needed for addition; greater amounts of unidentified impurities and variable yields were obtained. In contrast, slow addition of the aryllithium slurry to a solution of ethyl trifluoroacetate at 0 °C (inverse addition), consistently afforded material of higher purity and reproducibly in 85% yield on up to 50 g scale.



Scheme 3. Introduction of the trifluoroacetyl moiety.

The crude organic stream containing thioketone **10** was used directly for the tungstate-catalyzed oxidation[16] to sulfone **1**·$\mathbf{H_2O}$. Addition of 3.0 equiv H_2O_2 over 1.5–2 h to the reaction mixture at 45 °C, in the presence of 2 mol % $Na_2WO_4 \cdot 2H_2O$ and 5 mol % Bu_4NHSO_4, gave sulfone hydrate **1**·$\mathbf{H_2O}$ in 85% assay yield within 6 h (Scheme 4).[17] Azeotropic removal of water/toluene was used to drive the material to >99% ketone **1**, as determined by ^{19}F NMR



Scheme 4. Oxidation to sulfone and isolation.

spectroscopy. The material was then crystallized from toluene/heptane to afford desired ketone **1** in 80% yield from thioketone **10**.

In summary, we have developed a 3-step through process for the preparation of ketone **1** that proceeds in ~56% overall yield from inexpensive dibromobiphenyl **4**, without the use of cryogenic methods. The process features a selective mono-metal–halogen exchange of dibromobiphenyl **4**, mediated by lithium tributylmagnesiate. The metal–halogen exchange/electrophilic quench protocol provides access to a variety of functionalized biphenyls (**7a**–**g**) under non-cryogenic conditions and avoids the use of expensive transition-metal catalyzed cross-coupling chemistry.

3. Experimental

3.1. General

Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. ^{1}H NMR spectrum was recorded on a Bruker 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (acetone-d_6: δ 2.06, DMSO-d_6: δ 2.49, THF-d_8: δ 3.65). Data are reported as follow: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectrum was recorded on a Bruker 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent as the internal reference (acetone-d_6: δ 206.0, DMSO-d_6: δ 39.5, THF-d_8: δ 66.5). ^{19}F NMR spectrum was recorded on Bruker 400 (375 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million with α,α,α-trifluorotoluene added as an internal reference (δ −67.2). All compounds except **1**, **7g**, and **10** were characterized using the same HPLC conditions: Zorbax RX-C8 (4.6 mm×25.0 cm) column, gradient elution: (0.1% H_3PO_4/CH_3CN 50:10 to 10:90 over 7.5 min, hold 2.5 min), flow rate=2.0 mL/min, T=35 °C, UV detection at 220 nm. Compounds **1**, **7g**, and **10** were analyzed by GC: HP-1 (30 m, 0.32 mm, 0.25 μm film) column, gradient elution (100 °C–250 °C at 15 °C/min), flow rate=2.5 mL/min He, FID detection=300 °C. A 10 μL sample was injected at 250 °C.

3.2. Procedures

3.2.1. Preparation of lithium tri-*n*-butylmagnesiate. A 15-L round-bottom flask equipped with a dropping-funnel, thermocouple, mechanical stirrer, nitrogen inlet and outlet, was charged with anhydrous THF (3.21 L). *n*-BuMgCl (1.31 L, 2.0 M in THF, 2.63 mol, 100 mol %) was charged into the dropping-funnel, and added over 90 min at room temperature. The reactor's internal temperature rose from 20 °C to 31 °C during *n*-BuMgCl addition. Next *n*-BuLi (2.05 L, 2.5 M in hexane, 5.13 mol, 195 mol %) was charged to the dropping-funnel, and added to the reactor over 90 min. During the initial stages of *n*-BuLi addition the internal temperature rose from 30 °C to 34 °C, however, no external cooling bath was used. Upon complete addition of *n*-BuLi, a thin gray slurry formed, from which gray solids would settle if stirring was ceased. The slurry was stirred for 5 min, and then used to perform metal–halogen exchange. ^{1}H NMR (400 MHz, THF with an internal THF-d_8 standard) δ 1.49 (m, 2H), 1.22 (m, 2H), 0.81 (t, J=7.2, 3H), −0.79 (t, J=8.0, 2H). For comparison, the spectrum of *n*-BuMgCl is as follows: ^{1}H NMR (400 MHz, THF with an internal THF-d_8 standard) δ 1.34 (m, 2H), 1.67 (m, 2H), 0.68 (t, J=7.2, 3H), −0.80 (t, J=8.0, 2H).

3.2.2. Conversion of dibromobiphenyl 4 to 4-Bromo-4′-methylsulfanyl-biphenyl (7a). 4,4′-Dibromobiphenyl (2.00 kg, 6.41 mol, 100 mol %) was charged to a clean 50-L round-bottom flask equipped with a dropping-funnel, mechanical stirrer, thermocouple, nitrogen inlet and outlet. Anhydrous THF (16.0 L) was added with stirring, and the flask cooled to 0 °C in an ice/acetone bath. The dropping-funnel was charged with the *n*-Bu_3MgLi slurry (6.57 L, 2.63 mol, 40 mol %), which was added to the reaction flask over 2.25 h. The internal temperature rose from 0 °C to 4.4 °C during the addition of *n*-Bu_3MgLi (initial 4.0 L). The pale gray solution took on an amber color as *n*-Bu_3MgLi was added. Upon complete *n*-Bu_3MgLi addition, the internal temperature was 3.0 °C. The resultant yellow solution was aged for 60 min, while re-cooling to 0 °C. HPLC analysis of a crude aliquot (quenched into aqueous 3 N HCl/MTBE) showed a mixture of biphenyl, **6**, 4′-bromobiphenyl, **5**, and dibromobiphenyl, **4**. (**4**:**5**:**6**=6:84:3). A clean addition funnel was replaced for the used addition funnel, and charged with methyl disulfide (635 mL, 7.05 mol, 110 mol %), which was then added over 1.75 h. Addition of methyl disulfide caused an exotherm from 1.1 °C to 7.4 °C. The solution became a yellow-white slurry after 500 mL of methyl disulfide had been added. The slurry was aged for 15 h, then cooled with an external ice/acetone bath to −2.0 °C. Aqueous periodic acid (10 wt %, 4.04 L, 1.77 mol, 28 mol %) was added dropwise over 1 h into the reaction flask, and the resultant biphasic mixture stirred vigorously for 20 min. An exotherm was observed upon addition to aqueous periodic acid (internal temperature rose from −2.0 °C to 7.4 °C) and the mixture became deep-red. Aqueous 3 N HCl (4.04 L, 12.1 mol, 190 mol %) was then added dropwise over 1 h into the reaction flask, and the mixture stirred for 1 h, which raised the internal temperature

from 3.6 °C to 11.1 °C. Agitation was stopped and the mixture was transferred to a 50 L extractor; the flask was washed with 1.0 L THF, which was added to the extractor. The mixture was vigorously stirred, then allowed to settle for 5 min. The bottom (aqueous) layer was removed. Aqueous sodium thiosulfate (10 wt %, 8.1 L) was added to the extractor, causing the internal temperature to rise from 10 °C to 23 °C, the mixture was vigorously stirred for 5 min, which became pale-yellow. After agitation was stopped, the aqueous layer was cut. Aqueous sodium thiosulfate (10 wt %, 4.0 L) and toluene (5.0 L) were added to the extractor, and after vigorous stirring for 5 min, the aqueous layer was separated. The organic layer was then washed with water (2×4.0 L) and collected. HPLC analysis showed **7a** (15.95 kg at 9.16 wt % for a total of 1.46 kg, 5.24 mol, 82% assay yield). The crude solution was concentrated in vacuo, flushed with toluene (20 L), and re-concentrated to a thick beige slurry of 3.537 kg. Approximately 155 g of this slurry was dissolved in toluene and used for the subsequent transformation. An analytically pure sample was prepared by chromatography on silica gel, eluting with 5% MTBE in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.62 (m, 6H), 7.38 (d, J=8.0, 2H), 2.54 (s, 3H); mp=144.0–146.4 °C (lit.[18] 148–150 °C). HPLC retention time: 6.79 min. Anal. Calcd for $C_{13}H_{11}BrS$: C, 55.92; H, 3.97. Found: C, 55.65; H, 3.73.

3.2.3. 2,2,2-Trifluoro-1-(4′-methylsulfanyl-biphenyl-4-yl)-ethanone (10). A 2-L round-bottom flask equipped with a magnetic stirrer, thermocouple, nitrogen inlet and outlet, was charged with crude bromosulfide **7a** (8.76 wt % in toluene, 731 g, 230 mmol, 100 mol %) and MTBE (80 mL). *n*-BuLi (130 mL, [2.5 M] 322 mmol, 140 mol %) was via syringe pump over 0.5 h. The initial internal temperature was observed as 20.7 °C and increased to 37.7 °C during *n*-BuLi addition. Upon completion, a dark orange slurry formed, from which white solids would settle very slowly if stirring was ceased. HPLC analysis of a crude aliquot after *n*-BuLi was added (quenched into aqueous 3 N HCl/MTBE) showed >97% conversion to the aryllithium species. The slurry was stirred for 2 h, and then transferred to the apparatus described as follows. A second 2-L round-bottom flask, equipped with a magnetic stirrer, thermocouple, addition funnel, nitrogen inlet and outlet, was charged with ethyl trifluoroacetate (41 mL, 345 mmol, 150 mol %) and toluene (40 mL), and cooled in an ice/acetone bath. The prepared slurry of aryllithium was charged to the addition funnel, and added to the reaction flask over 1.0 h. An exotherm (internal temperature started at 4.4 °C and rose to 19.9 °C) was observed during aryllithium addition. Upon completion, a bright yellow-orange solution formed. GC analysis of an aliquot immediately after addition was complete indicated ~81% conversion to the thioketone (59.3 A% thioketone **10**, 10.4 A% sulfide **9** by GC). The slurry was aged for 30 min, then aqueous 3 N HCl (350 mL) and THF (350 mL) were added into the reaction flask. The resultant biphasic mixture stirred vigorously for 15 min, then allowed to settle. The bottom (aqueous) layer was removed and the bright yellow organic phase washed with aqueous 3 N HCl (200 mL) and collected. GC analysis showed thioketone **10** (1.2 kg at 4.84 wt % for a total of 58.11 g, 85.9% assay yield). The crude organic solution was concentrated in vacuo to 327 g of a yellow solution. An analytically pure sample was prepared by chromatography on silica gel, eluting with 25% MTBE in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.18 (d, J=7.6, 2H), 7.98 (d, J=7.6, 2H), 7.77 (d, J=8.4, 2H), 7.43 (d, J=8.4, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 180.3 (q, $^2J_{CF}$=34), 148.2, 141.5, 135.7, 131.4, 129.1, 128.4, 128.0, 127.2, 117.7 (q, $^1J_{CF}$=289), 14.9; ^{19}F NMR (375 MHz, acetone-d_6) δ−76.2; mp=114.6–116.2 °C. GC retention time: 13.24 min. Anal. Calcd for $C_{15}H_{11}F_3OS$: C, 60.80; H, 3.74; F, 19.24. Found: C, 60.56; H, 3.44; F, 19.19.

3.2.4. 2,2,2-Trifluoro-1-(4′-methylsulfonyl-biphenyl-4-yl)-ethanone (1). The crude thioketone **10** (18.0 wt % in toluene, 327 g, 198 mmol, 100 mol %) was charged into a visually clean, 2-L round-bottom flask equipped with a magnetic stirrer, reflux condenser, internal temperature probe, nitrogen inlet and outlet. Toluene (300 mL), THF (600 mL), $Na_2WO_4\cdot 2H_2O$ (22.8 g, 0.07 mol, 2 mol %), and Bu_4NHSO_4 (58.2 g, 0.17 mol, 5 mol %) were added to the reactor and the resultant mixture heated to 45 °C in an oil bath while stirring vigorously. Hydrogen peroxide (67 mL, 30% aqueous, 594 mmol, 300 mol %) was then added via syringe pump over 1.5 h, the resultant mixture was stirred with heating for an additional 2 h and then cooled to room temperature. (The internal temperature remained below 59 °C during peroxide addition.) Aqueous $Na_2S_2O_3\cdot 5H_2O$ (10 wt %, 300 mL) was added to the flask over 60 min (temperature remained <25 °C) and the mixture stirred for 5 min. At this point, starch-paper test indicated <10 mg/L of peroxide remained. Methyl ethyl ketone (750 mL) was added, and after 5 min stirring was stopped. The mixture was transferred to a separatory funnel, the cloudy bottom (aqueous) layer removed, and the organic solution collected. GC analysis indicated ketone-hydrate **1·H$_2$O** (3.66 wt % of 1.68 kg, 61.5 g, 95.2% assay yield). The solution was concentrated and solvent-switched to toluene. Analysis by ^{19}F NMR spectroscopy indicated a 10:1 mixture of **1·H$_2$O** (−88.7 ppm) & **1** (−76.3 ppm). The material was diluted to ~1.0 L toluene, then dehydrated by water/toluene azeotrope in a Dean–Stark apparatus. After 1 h only the ketone **1** remained (^{19}F NMR analysis). The toluene solution was concentrated in vacuo to ~643 g, whereupon white solids began to form in the orange solution. The material was transferred to a 3-neck round-bottom flask equipped with mechanical stirrer and addition funnel, then diluted with toluene (12 mL). Heptane (675 mL) was added dropwise over 1 h to the vigorously stirred slurry. After stirring for an additional 45 min, the material was filtered to afford sulfone **1** (68.8 g at 75 wt % for 51.6 g, 80% assay yield, 91.9 A% by GC). An analytically pure sample was prepared by chromatography on silica gel, eluting with 15% ethyl acetate in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.23 (d, J=7.4, 2H), 8.11 (d, J=8.2, 2H), 8.05 (m, 4H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 180.3 (q, $^2J_{CF}$=34), 146.6, 144.3, 142.2, 131.3, 130.0, 128.9, 128.7, 117.4 (q, $^1J_{CF}$=289), 116.7, 44.0; ^{19}F NMR (375 MHz, acetone-d_6) δ−76.3; mp=157.9–158.8 °C. GC retention time: 15.91 min. Anal. Calcd for $C_{15}H_{11}F_3O_3S$: C, 54.88; H, 3.38; F, 17.36. Found: C, 53.37; H, 3.60; F, 15.00.

3.2.5. 4′-Bromo-biphenyl-4-carboxylic acid (7b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.01 (d, J=8.0, 2H), 7.79 (d, J=8.0, 2H), 7.68 (m, 4H); mp=300.3–302.2 °C

(lit.[19] 301.5–302.5 °C). HPLC retention time: 3.96 min. Anal. Calcd for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.46; H, 3.34.

3.2.6. 4′-Bromo-biphenyl-4-carboxaldehyde (7c). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.12 (s, 1H), 8.05 (d, J=8.0, 2H), 7.92 (d, J=7.6, 2H), 7.73 (m, 4H); mp=159.1–161.4 °C (lit.[20] 158 °C). HPLC retention time: 5.27 min. Anal. Calcd for $C_{13}H_9BrO$: C, 59.80; H, 3.47. Found: C, 45.33; H, 2.65.

3.2.7. (4′-Bromo-biphenyl-4-yl)-phenyl-methanol (7d). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58 (m, 6H), 7.53 (d, J=8.0, 2H), 7.48 (d, J=7.2, 2H), 7.33 (t, J=7.6, 2H), 7.24 (t, J=7.4, 1H), 5.90 (d, J=3.8, 1H), 4.97 (d, J=3.8, 1H); mp=136.0–138.6 °C (lit.[21] 115–116 °C). HPLC retention time: 5.76 min. Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 67.22; H, 4.17.

3.2.8. 2-(4′-Bromo-biphenyl-4-yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol (7e). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.91 (d, J=8.4, 2H), 7.84 (d, J=8.4, 2H), 7.69 (m, 4H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 142.0, 139.3, 132.5, 130.7, 129.4, 128.0, 127.4, 123.7 (q, $^1J_{CF}$=286), 122.4, 77.9 (q, $^2J_{CF}$=30); ^{19}F NMR (375 MHz, acetone-d_6) δ−79.5; mp=44.8–45.5 °C. HPLC retention time: 6.40 min. Anal. Calcd for $C_{15}H_9F_6BrO$: C, 45.14; H, 2.27; F, 28.56. Found: C, 44.53; H, 2.10; F, 27.24.

3.2.9. 1-(4′-Bromo-biphenyl-4-yl)-ethanone (7f). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.09 (d, J=8.4, 2H), 7.82 (d, J=8.4, 2H), 7.70 (m, 4H), 2.63 (s, 3H); mp=124.9–127.5 °C (lit.[22] 121–122.5 °C). HPLC retention time: 5.38 min. Anal. Calcd for $C_{14}H_{11}BrO$: C, 61.11; H, 4.03. Found: C, 61.29; H, 3.82.

3.2.10. 1-(4′-Bromo-biphenyl-4-yl)-2,2,2-trifluoroethanone (7g). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.22 (d, J=8.4, 2H), 8.02 (d, J=8.4, 2H), 7.79 (d, J=8.4, 2H), 7.75 (d, J=8.4, 2H); ^{19}F NMR (375 MHz, acetone-d_6) δ−76.2; mp=72.5–74.8 °C (lit.[23] 75–77 °C). GC retention time: 11.47 min. Anal. Calcd for $C_{14}H_8F_3BrO$: C, 51.09; H, 2.45; F, 17.32. Found: C, 50.72; H, 2.38; F, 16.94.

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14. Reaction between n-Bu$_3$MgLi, dibromide **4** and Me$_2$S$_2$ leads to the formation of a stoichiometric amount of methanethiol. In order to control emissions and odor during work-up, we investigated the use of various adsorbents. We found that DARCO (KB and G60), Ecosorb (905, 908, 941, 962, 971, and 981),

silica and alumina powders were ineffective at odor removal, even at 1 g/g loadings. Treatment of the crude solution with aqueous copper salts ($CuSO_4$, $CuCl_2$, and $CuCO_3$) or KOH was also unsuccessful. Odor was effectively removed by treatment with either 10% aqueous HIO_3 or 1% aqueous NaOCl, however oxidation of **7a** to the corresponding sulfoxide (5–10%) was observed. Treatment with 10% aqueous H_5IO_6 removed virtually all odor, with <2% oxidation to sulfoxide. Therefore, the crude reaction was quenched by the direct addition of aqueous periodic acid.

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17. Initial studies showed that a strong, delayed exotherm occurred when this oxidation was performed at room temperature, even with slow addition (1 h) of peroxide. We attributed this to a slow initiation step, which is difficult to control due to the biphasic nature of the reaction mixture. Furthermore, the exotherm was not always observed (particularly on smaller scale) resulting in extended reaction times and incomplete conversion to the sulfone. By performing the oxidation at 45 °C, the reaction was complete within 6 h, and the internal temperature was maintained below 62 °C.
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Arene *cis*-dihydrodiols—useful precursors for the preparation of antimetabolites of the shikimic acid pathway: application to the synthesis of 6,6-difluoroshikimic acid and (6*S*)-6-fluoroshikimic acid

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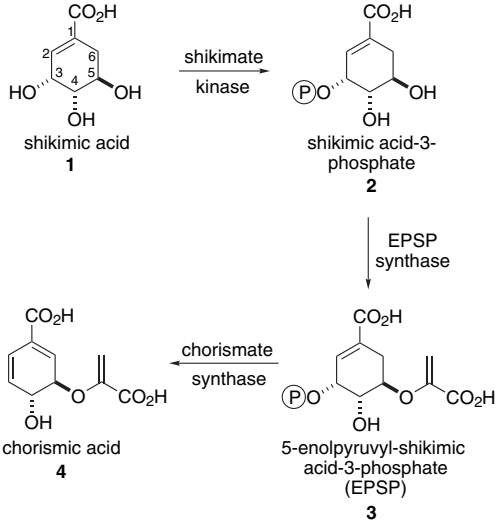
Abstract—The synthesis of 6,6-difluoroshikimic acid (**11**) has been achieved in ten steps from the enantiopure diol **16**, which is derived from enzymatic cis-dihydroxylation of iodobenzene. The versatility of the synthetic strategy has been demonstrated by the preparation of the known antimicrobial agent, (6*S*)-6-fluoroshikimic acid (**5**).

1. Introduction

Over recent years, there has been extensive interest in the efficient preparation of analogues of (−)-shikimic acid (**1**), which have been targeted as likely inhibitors of enzymes on the shikimic acid pathway and which are of relevance as potential antifungal, antibacterial and antiparasitic agents. A principal goal of our present research is the synthesis of analogues of (**1**), which may either inhibit shikimate kinase, or alternatively undergo intracellular phosphorylation by the kinase and thereby act as prodrugs for inhibitors of enzymes further downstream on the pathway (e.g., EPSP synthase or chorismate synthase (Scheme 1)).[1]

The feasibility of this approach is supported by the findings of extensive studies of the fluorinated analogues **5** and **6** of (−)-shikimic acid (**1**) (Scheme 2).[2] Both of these compounds display in vitro antibacterial activity against a range of *Escherichia coli* strains with (6*S*)-6-fluoroshikimic acid (**5**) being the more potent agent (MIC against *E. coli* K-12 of 0.1 μg/mL compared with 64 μg/mL for (6*R*)-6-fluoroshikimic acid (**6**)).[3] The fluorinated analogues are substrates for the shikimate transport system of *E. coli*[4] and importantly, the (6*S*)-isomer **5** has been shown to be protective against a range of bacterial intraperitoneal challenges in mice.[3] Both compounds are substrates for shikimate kinase from *E. coli* and are transformed to the corresponding 6-fluoro-



Scheme 1.

shikimate-3-phosphates **7** and **8** at rates comparable to (−)-shikimic acid itself. In turn, compounds **7** and **8** are transformed by EPSP synthase from *E. coli* to the corresponding 6-fluoro-EPSP analogues **9** and **10** at rates approximately one order of magnitude slower than the natural substrate.[5] Further studies have indicated that the antimicrobial activity of **6** is due, at least in part, to ultimate inhibition of chorismate synthase whereas **5** is proposed to act via ultimate inhibition of 4-amino-4-deoxychorismate synthase (ADCS), an enzyme on the post-chorismate branch of the pathway leading to *para*-aminobenzoic acid (PABA).[6]

Keywords: Shikimic acid; Fluorination; Antibacterial agents.
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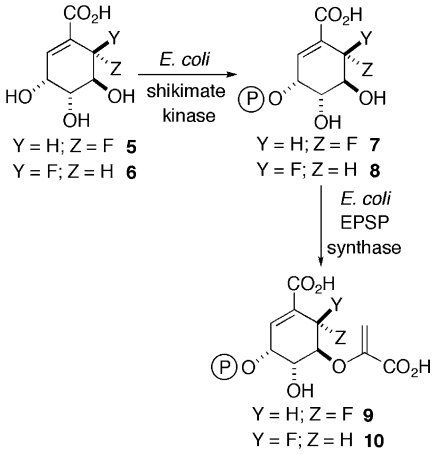
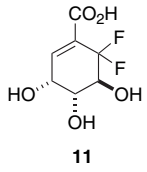


Scheme 2.

It has been disclosed quite recently that both **5** and **6** inhibit the growth of the parasite *Plasmodium falciparum*, the principal causative agent of malaria in humans.[7] In contrast to the situation with *E. coli*, the (6*R*)-compound **6** was significantly more potent than isomer **5** in this assay. This intriguing discovery has stimulated renewed interest in the design and synthesis of novel inhibitors of enzymes on the shikimate pathway. In this paper, we provide details of the synthesis of compound **11**, the final member of the series of 6-fluoroshikimic acids (Fig. 1). We also describe our investigations into modifications of the synthetic approach for the preparation of other 6-substituted analogues of (−)-shikimic acid.

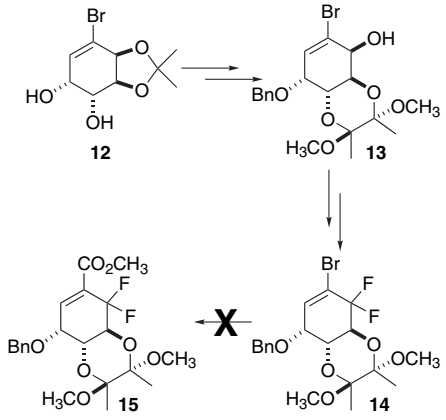


11

Figure 1.

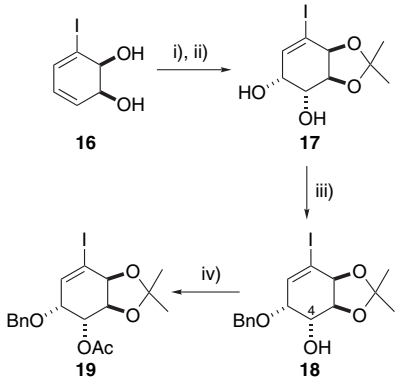
2. Results and discussion

Quite recently, we reported details of the synthesis of vinyl bromide **13** in four steps from commercially available diol **12** (Scheme 3).[1a] Oxidation of the allylic hydroxyl in **13** gave the expected α,β-unsaturated ketone which, on treatment with the nucleophilic fluorinating agent [bis-(2-methoxyethyl)]-aminosulfurtrifluoride (DeoxoFluor®)[8] was converted to the *gem*-difluoride **14**. Unfortunately, all attempts to introduce a carboxyl substituent at C1 of **14** using Pd(0) chemistry, as well as using other trans-metallation protocols, were unsuccessful.



Scheme 3.

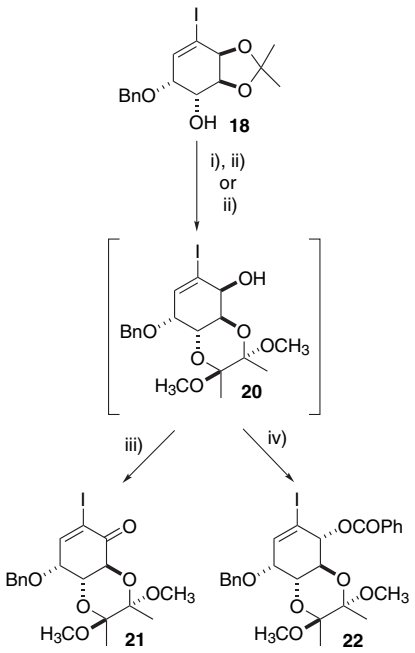
It is well documented that aryl and vinyl bromides exhibit diminished reactivity in Pd(0) catalysed C–C bond forming reactions when compared with the corresponding vinyl iodides. We decided, therefore, to turn our attention to the preparation of the analogue of **14**, which bears an iodine atom at C1. Our starting material for this synthesis was the enantiomerically pure diol **16**, which is obtained from the toluene-dioxygenase catalysed cis-dihydroxylation of iodobenzene (Scheme 4).[9,10]



Scheme 4. Reagents: (i) $(CH_3O)_2C(CH_3)_2$, *p*-TSA, CH_2Cl_2; (ii) OsO_4 (cat.), NMO, ^tBuOH, H_2O, 81% over two steps; (iii) Bu_2SnO, $C_6H_5CH_3$, CH_3OH, Δ, then BnBr, Bu_4NI, $C_6H_5CH_3$, 130 °C, 91%; (iv) Ac_2O, DMAP, py, CH_2Cl_2, quant.

Following the general procedure of Hudlicky,[11] the vicinal diol in **16** was protected as an acetonide and subsequent face-selective cis-dihydroxylation of the less substituted 3,4-double bond gave diol **17** in good yield. Using the excellent protocol reported recently by Simas and co-workers,[12] a high-yielding and regioselective mono-benzylation of the vicinal diol in **17** was accomplished via an intermediate stannylene acetal, to give the benzyl ether **18**.[13] The regioselectivity of this reaction was confirmed by acetylation of the remaining free hydroxyl of **18** to give **19**: comparison of the ^1H NMR spectra of the two compounds confirmed a significant downfield shift of the resonance assigned to C(4)*H* in compound **19** [δ_H (300 MHz; $CDCl_3$): ~4.41 for **18**, 5.53 for **19**].

Over recent years, the protection of substrates bearing vicinal di-equatorial hydroxyl groups as their butane-diacetal (BDA) derivatives, has received a great deal of attention.[14] The enhanced stability of compounds protected in this way permits the use of a wide variety of reagents and conditions and furthermore, their conformational rigidity often has a beneficial influence on the stereoselectivity of subsequent transformations. Prompted by these observations, we initiated investigations into the conversion of **18** into the BDA protected compound **20**, which we believed would be a robust and versatile intermediate, not only for the synthesis of our target compound **11** but also for other analogues of (−)-shikimic acid (Scheme 5).

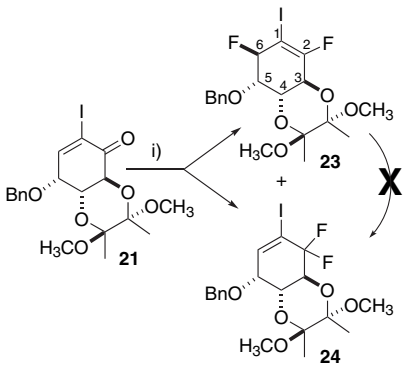


Scheme 5. Reagents: (i) TFA/H_2O (1:1), rt; (ii) butan-2,3-dione, $(CH_3O)_3CH$, CSA, CH_3OH, Δ; (iii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 15% over two steps; 36% over three steps; (iv) Ph_3P, DIAD, $C_6H_5CO_2H$, THF, 49% over three steps.

Direct trans-ketalisation of **18** with butan-2,3-dione gave an inseparable mixture of diacetals consisting predominantly of the desired isomer **20**. This mixture was then oxidised using Swern conditions[15] to give **21** in a disappointing 15% yield over two steps. A lengthier three-step procedure was thus developed, involving acid-catalysed hydrolysis of **18** to give the corresponding triol, followed by ketalisation to give an inseparable mixture of diacetals, which mostly comprised the desired isomer **20**. Oxidation of this mixture followed by chromatographic purification provided the enone **21** in an acceptable yield of 36% over three steps. Derivatisation of the inseparable mixture of diacetals with acetic anhydride and pyridine did not facilitate the purification of compound **20** (as the (6*S*)-acetate), however, exposure of the mixture of diacetals to Mitsunobu conditions[16] allowed isolation of the (6*R*)-benzoate **22** in 49% yield over three steps from **18**.

With the pivotal enone **21** in hand, we were able to investigate the key fluorodeoxygenation step necessary for the introduction of geminal fluorines at C6. Treatment of **21** with DeoxoFluor® in the absence of additional solvent for 72 h resulted in the formation of two isomeric difluorides. After chromatographic purification, the desired *gem*-difluoride **24** was isolated in 36% yield and the isomeric allylic fluoride **23** was isolated in 30% yield (Scheme 6).

The configuration at C6 of **23** was confirmed by comparison of its spectroscopic data with those of the corresponding vinyl bromide **25** (Fig. 2), the structure of which was previously assigned by the use of 2D heteronuclear Overhauser effect spectroscopy (HOESY).[1a] The formation of **23** is presumed to occur via allylic rearrangement during the difluorination reaction and the observed regiochemical outcome is likely to be a consequence of either a S_N2' or a S_N1' reaction of an activated intermediate of type **26** with ambient fluoride ion.



Scheme 6. Reagents: (i) DeoxoFluor®, rt, 72 h, 30% of **23**, 36% of **24**.

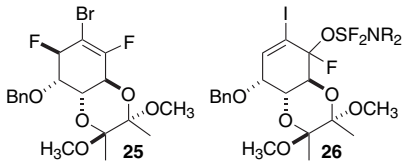
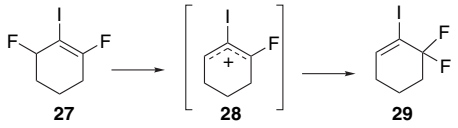


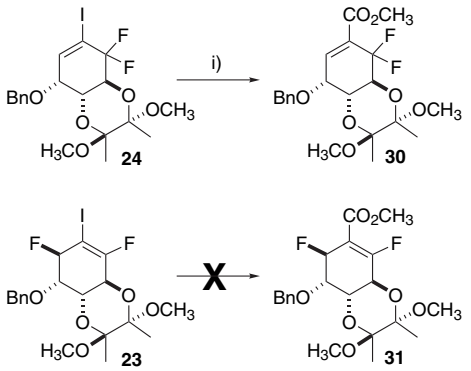
Figure 2.

Previous research efforts in our group have culminated in the development of mild reaction conditions for the isomerisation of the allylic fluoride **27** to the *gem*-difluoride **29** (Scheme 7).[17] In this model system, it transpired that simply stirring a solution of **27** in CH_2Cl_2 in the presence of 4 Å molecular sieves resulted in quantitative conversion of **27** to **29**. We have not carried out detailed investigations into the mechanism of this intriguing transformation, however, the reaction is presumed to proceed via the intermediacy of a transient allylic carbenium ion **28**. Unfortunately, despite extensive investigations, it proved impossible to discover conditions under which allylic fluoride **23** could be isomerised to *gem*-difluoride **24**. The contrasting reactivity of **23** and **27** is presumed to reflect the instability of the highly oxygenated carbenium ion, which is considered to be a necessary intermediate in the isomerisation of **23**.

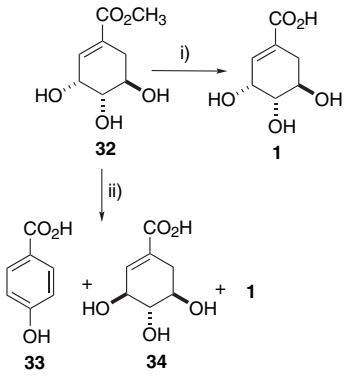


Scheme 7. Reagents: (i) 4 Å mol. sieves, CH_2Cl_2, rt, 8 h, quant.

Having successfully prepared the *gem*-difluoride **24**, we were in a position to investigate the key carbonylation reaction: the transformation that had thwarted progress in the corresponding vinyl bromide series.[1a] Previous model studies indicated that the vinyl iodide **29** was an excellent substrate in a variety of Pd(0)-mediated transformations. In particular, carbonylation using conditions modified from those described by Ortar[18] (tri-2-furyl phosphine and Hünigs base replacing triphenylphosphine and triethylamine, respectively) gave the corresponding unsaturated ester in 55% yield. Pleasingly, application of these reaction conditions to **24** yielded the desired ester **30** in comparable yield (56%) (Scheme 8).



Scheme 8. Reagents: (i) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, CH_3OH, CO, DMF, rt, 24 h, 56%.

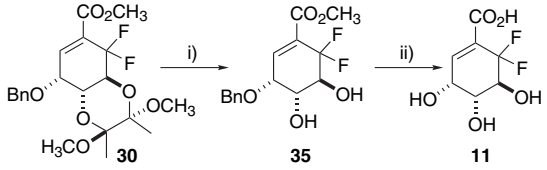


Scheme 9. Reagents: (i) concd HCl/H_2O (1:1), 60–70 °C, 12 h, 86%; (ii) concd HCl/H_2O (1:1), 100 °C, 30 h.

Exposure of the allylic rearrangement product **23** to the same carbonylation conditions failed to provide any of the expected unsaturated ester **31** and, indeed, starting material remained unchanged. This finding was particularly disappointing as we had envisaged that in the presence of fluoride ion, compound **31** might undergo relatively facile rearrangement to the *gem*-difluoride **30** via a conjugate addition–elimination sequence.

The successful preparation of unsaturated ester **30** meant that all that remained to be accomplished was complete deprotection to give the target material **11**. Several plausible sequences were considered with the main requirement being for conditions that would allow efficient removal of the benzyl protecting group without recourse to hydrogenolysis procedures. The possibility of effecting ester hydrolysis and concomitant debenzylation under acidic conditions was particularly attractive, however, we were cognizant of the pioneering work of J. F. Eykmann.[19] During his classic structural and reactivity studies of (−)-shikimic acid, Eykmann observed that the natural material underwent facile dehydrative aromatisation when heated in hydrochloric acid to give *para*-hydroxy benzoic acid. With a view to discovering reaction conditions under which aromatisation could be minimised, we carried out a brief investigation into the fate of methyl shikimate (**32**) when heated at different temperatures in ~6 M HCl. In accord with Eykmann's observations, heating **32** at 100 °C in ~6 M HCl for 30 h resulted in partial conversion to *para*-hydroxy benzoic acid **33**. A substantial quantity of 3-*epi*-shikimic acid (**34**) and a lesser quantity of **1** itself were also formed in the reaction (crude ratio **33**:**34**:**1** was 2:2:1). When the reaction time was shortened to 12 h, the product mixture was more complicated and analysis by ^1H NMR indicated the presence of other 'shikimate-like' materials as well as **33**, **34** and **1** (crude ratio **33**:**34**:**1** was 2:6:9). In contrast, when the temperature was decreased to ~60 °C and the reaction time maintained at 12 h, analysis of the crude reaction mixture indicated that no aromatisation or epimerisation had taken place and the only isolable product was (−)-shikimic acid (**1**) (Scheme 9).

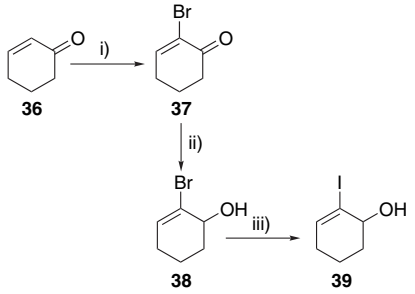
Encouraged by these observations, as well as the literature precedent for the cleavage of benzyl ethers under acidic conditions,[20] we embarked on the final deprotection sequence to give **11**. Ultimately, this was achieved in two straightforward steps (Scheme 10). Firstly, the BDA group was removed in quantitative fashion by stirring **30** in a mixture of TFA and water (6:1) at room temperature. Secondly, in accord with our model studies, removal of the benzyl protecting group and concomitant ester hydrolysis was accomplished by heating a solution of the diol **35** in ~6 M HCl at 60–70 °C for 12 h. Analysis of the crude product from this sequence by ^1H NMR spectroscopy indicated that no aromatisation had occurred and the target compound **11** was generated in essentially pure form.



Scheme 10. Reagents: (i) TFA/H_2O (6:1), rt, 3 h; (ii) concd. HCl/H_2O (1:1), 60–70 °C, 12 h then HPLC, 68% over two steps.

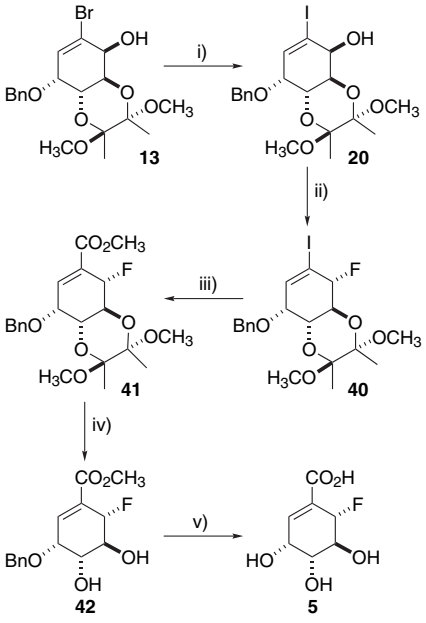
The shikimic acid pathway is a wonderful and elegant example of a divergent biosynthetic sequence: a plethora of aromatic end products is derived from a single, pre-branch-point intermediate of the pathway, chorismic acid (**4**).[21,22] Taking our lead from this impressive biosynthetic example, a major goal of our recent endeavours has been the development of a *divergent synthetic* strategy which will allow the efficient preparation of a range of analogues of shikimic acid. In this context, we envisaged vinyl iodide **20** (or an alternatively protected variant of **20**) to be a pivotal intermediate, however, high-yielding preparation of a sample of this compound had not been possible from the acetonide **18** (vide supra). During the course of our investigations, however, we became aware of the 'aromatic Finkelstein reaction' developed by Buchwald and co-workers.[23] This incredibly useful reaction effects the conversion of aryl bromides to the corresponding aryl iodides by the action of a catalytic quantity of CuI, KI and a 1,2-diamine additive. In the original publication, a single example of a halogen exchange of a vinyl bromide was reported and this prompted us to carry out a brief investigation into the halogen exchange of vinyl bromide **38**. This simple compound was readily prepared in two steps from 2-cyclohexenone (**36**)[24,25] and was selected as an appropriate model for the highly oxygenated vinyl bromide **13** (Scheme 11).

Reaction of **38** under the conditions described by Buchwald resulted in generation of crude product mixtures consisting



Scheme 11. Reagents: (i) Br_2, Et_3N, CH_2Cl_2, 0 °C to rt, 65%; (ii) $NaBH_4$, $CeCl_3$, CH_3OH, rt, 90%; (iii) KI, CuI, *N*,*N*′-dimethylethylenediamine, ^{n}BuOH, 130 °C, 24 h.

predominantly of vinyl iodide **39** (ratios assessed by ^{1}H NMR analysis). In our hands, the reaction was a little capricious and ratios of **39**:**38** generally varied unpredictably between 4:1 and 14:1. Interestingly, when the 1,2-diamine additive, *N*,*N*′-dimethylethylenediamine, was replaced with *trans*-1,2-diaminocyclohexane, the outcome was much inferior and ratios of **39**:**38** ranging from 1:3 to 1:7 were commonly obtained. The relative success of the conversion of **38** to **39** using *N*,*N*′-dimethylethylenediamine, encouraged us to attempt the halogen exchange of vinyl bromide **13**. Pleasingly, application of the conditions used in the model study resulted in good conversion to the vinyl iodide **20** (<10% contamination by **13**) (Scheme 12).



Scheme 12. Reagents: (i) CuI, KI, *N*,*N*′-dimethylethylenediamine, ^{n}BuOH, 130 °C; (ii) Et_2NSF_3, CH_2Cl_2, −78 °C to rt, 38% over two steps from **13**; (iii) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, CH_3OH, CO, DMF, rt, 24 h, 58%; (iv) TFA/H_2O (6:1), rt, 3 h, 72%; (v) concd HCl/H_2O (1:1), 60–70 °C, 10 h then HPLC, 61%.

Subsequent fluorodeoxygenation of **20** using the nucleophilic fluorinating agent DAST (Et_2NSF_3)[26] proceeded with inversion of configuration to give the allylic fluoride **40**, which could be obtained free of the corresponding vinyl bromide after chromatographic purification. Pd(0) mediated carbonylation of **40** occurred in comparable yield to the difluorinated analogue **24**, to give the α,β-unsaturated ester **41** and finally, two-stage removal of the protecting groups furnished (6*S*)-6-fluoroshikimic acid (**5**), which was identical in all respects to an authentic sample kindly provided by AstraZeneca.

3. Conclusions

In summary, we have prepared the novel compound, 6,6-difluoroshikimic acid (**11**), in ten steps from the enantiopure diol **16**. A key step in the synthesis, fluorodeoxygenation of enone **21**, was accomplished using the nucleophilic fluorinating agent DeoxoFluor®: although the total yield of difluorinated products from this reaction was reasonable, competing mechanistic processes resulted in the generation of only moderate quantities of the required *gem*-difluorinated product **24** together with equivalent amounts of an undesired vinyl fluoride **23**, arising from allylic rearrangement. In contrast to previous model studies, it proved impossible to isomerise the latter compound to *gem*-difluoride **24**, thus making the fluorine incorporation step the least efficient of the sequence.

Allylic alcohol **20**, an intermediate in the synthesis of 6,6-difluoroshikimic acid, was selected as an ideal candidate for a diversification point for the synthesis of other analogues of (−)-shikimic acid. Although not directly accessible in pure form from enantiopure diol **16**, compound **20** has been synthesised from the analogous vinyl bromide **13** via application of Buchwald's 'aromatic Finkelstein reaction'. The potential synthetic utility of **20** has been demonstrated by the preparation of the known antibacterial agent (6*S*)-6-fluoroshikimic acid (**5**).

4. Experimental

4.1. General

Solvents were dried and distilled before use. Chromatography was performed over Merck silica gel 60 (40–63 μm). IR spectra were recorded on a Perkin–Elmer 881 spectrometer or an AT1-Mattson Genesis Series FTIR spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Inova 400 MHz spectrometer or a Varian Inova 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak. Mass spectra were recorded on Fisons VG Trio 2000 quadrupole (EI/CI, low resolution), Kratos Concept 1*S* (EI/CI, high resolution) and Micromass Platform (electrospray) spectrometers.

4.1.1. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (17). To a stirred solution of (5*S*,6*S*)-1-iodo-5,6-dihydroxycyclohexa-1,3-diene (**16**) (1.109 g, 4.66 mmol) in CH_2Cl_2 (36 mL) was added 2,2-dimethoxypropane (0.63 mL, 5.13 mmol) and a catalytic quantity of *p*-TSA. The reaction mixture was stirred at room temperature for 1 h after which time it was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (40 mL). The organic phase was collected and combined with three further CH_2Cl_2 extracts (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide the crude acetonide as a pale yellow oil (1.203 g). This material was dissolved in ^{t}BuOH (15 mL) and *N*-methylmorpholine-*N*-oxide (0.56 g, 4.76 mmol) was

added followed by a solution of OsO_4 in ^tBuOH (1.8 mL of a 2.5% solution) and water (a few drops). The reaction mixture was stirred at room temperature for 36 h under an atmosphere of nitrogen when it was quenched by the addition of solid sodium metabisulphite (1.97 g) and filtered through a pad of silica, eluting with EtOAc. Concentration of the filtrate in vacuo gave the crude product as a dark-coloured solid, which was purified by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 7:13) to give the title compound as colourless crystals (1.175 g, 81%). R_f 0.41 (EtOAc/petroleum ether (40–60), 2:5); mp 146–148 °C; $[\alpha]_D^{27}$ +23.6 (*c* 0.78, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3502s and 3376s (O–H), 2923w and 2882w (C–H), 1631w (C=C); δ_H (300 MHz; $CDCl_3$) 1.38 and 1.41 (2×3H, 2×s, 2×acetonide CH_3), 2.5 (2H, br, O*H*), 4.21 (1H, ~t, *J* 4.4, C(4)*H*), 4.28–4.33 (1H, m, C(3)*H*), 4.38 (1H, t, *J* 5.2, C(5)*H*), 4.63 (1H, br d, *J* 5.2, C(6)*H*), 6.41 (1H, d, *J* 3.0, C(2)*H*); δ_C (75 MHz; $CDCl_3$) 26.5 and 27.9 (2×acetonide *C*H_3), 67.9 (*C*(3)H), 69.5 (*C*(4)H), 76.4 (*C*(5)H), 78.6 (*C*(6)H), 100.8 (*C*(1)), 110.2 (acetonide *C*), 139.2 (*C*(2)H); *m/z* (EI) 312 (M^+, 3%), 297 (12), 254 (12), 127 (15), 109 (68), 101 (100) (Found 311.9853, $C_9H_{13}IO_4$ (M^+) requires 311.9860).

4.1.2. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (18). A solution of the diol **17** (0.245 g, 0.79 mmol) and Bu_2SnO (0.236 g, 0.95 mmol) in a 1:1 mixture of methanol and toluene (4 mL) was heated at 130 °C for 3 h. After this time, the solvent was evaporated under reduced pressure. Dry toluene (4 mL) was added and then evaporated under reduced pressure. The resulting crude stannylene acetal was redissolved in toluene (4 mL) and Bu_4NBr (0.058 g, 0.16 mmol) and BnBr (0.19 mL, 1.58 mmol) were added. The mixture was then heated at 130 °C under an atmosphere of nitrogen for 6 h whereafter the solvent was removed in vacuo to give the crude product as a yellow oil. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 3:17), using a pad of KF at the top of the column to remove tin residues gave the title compound as colourless crystals (0.290 g, 91%). R_f 0.32 (EtOAc/petroleum ether (40–60), 3:17); mp 73–74 °C; $[\alpha]_D^{22}$ −28.5 (*c* 1.20, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3464br (O–H), 2985m and 2890m (C–H), 1630w (C=C); δ_H (300 MHz; $CDCl_3$) 1.42 and 1.43 (2×3H, 2×s, 2×acetonide CH_3), 2.51 (1H, d, *J* 2.3, O*H*), 4.13 (1H, dd, *J* 4.1, 3.6, C(3)*H*), 4.40–4.43 (1H, m, C(4)*H*), 4.45 (1H, t, *J* 4.8, C(5)*H*), 4.64–4.73 (3H, m, C(6)*H* and benzyl CH_2), 6.46 (1H, d, *J* 3.6, C(2)*H*), 7.34–7.45 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 26.5 and 27.8 (2×acetonide *C*H_3), 67.5 (*C*(4)H), 71.9 (benzyl *C*H_2), 75.0 (*C*(3)H), 76.1 (*C*(5)H), 78.5 (*C*(6)H), 101.5 (*C*(1)), 110.1 (acetonide *C*), 128.1, 128.5 and 128.9 (aromatic *C*H), 136.8 (*C*(2)H), 137.5 (aromatic *ipso-C*); *m/z* (CI/NH_3) 420 (MNH_4^+, 40%), 403 (MH^+, 35), 294 (60), 277 (25), 106 (45), 58 (100) (Found 420.0674, $C_{16}H_{23}INO_4$ (MNH_4^+) requires 420.0672).

4.1.3. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-4-*O*-acetyl-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (19). To a stirred solution of the benzyl ether **18** (0.04 g, 0.1 mmol) and DMAP (a few crystals) in CH_2Cl_2 (1 mL), under an atmosphere of nitrogen, was added acetic anhydride (0.5 mL, 5.3 mmol) followed by pyridine (0.5 mL, 6.2 mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL). Organic material was extracted into CH_2Cl_2 (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the product **19** as a viscous oil, which was of sufficient purity for spectroscopic analysis. ν_{max} (film)/cm^{-1} 2986w, 2932w and 2870w (C–H), 1747s (C=O); δ_H (300 MHz; $CDCl_3$) 1.37 and 1.40 (2×3H, 2×s, 2×acetonide CH_3), 2.09 (3H, s, OC(=O)CH_3), 4.14 (1H, td, *J* 3.5, 1.5, C(3)*H*), 4.39 (1H, t, *J* 5.5, C(5)*H*), 4.51 (1H, d, *J* 11.7, OC$H_a$$H_b$Ph), 4.62 (1H, d, *J* 11.7, OC$H_a$$H_b$Ph), 4.64 (1H, d, *J* 5.5, C(6)*H*), 5.53 (1H, dd, *J* 5.5, 3.5, C(4)*H*), 6.48 (1H, br d, *J* 3.5, C(2)*H*), 7.26–7.34 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 21.3 (OC(=O)*C*H_3), 26.4 and 27.8 (2×acetonide *C*H_3), 69.2 (*C*(4)H), 72.1 (benzyl *C*H_2), 73.3 (*C*(3)H), 74.2 (*C*(5)H), 79.0 (*C*(6)H), 100.1 (*C*(1)), 110.4 (acetonide *C*), 128.1, 128.3 and 128.8 (aromatic *C*H), 137.8 (aromatic *ipso-C*), 138.6 (*C*(2)H), 170.6 (*C*=O); *m/z* (CI/NH_3) 462 (MNH_4^+, 60%), 445 (MH^+, 25), 336 (100) (Found 462.0779, $C_{18}H_{25}INO_5$ (MNH_4^+) requires 462.0778).

4.1.4. (2′*S*,3′*S*,4*R*,5*R*,6*S*)-2-Iodo-4-*O*-benzyl-5-*O*,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-2-ene-1-one-4,5,6-triol (21). A solution of alcohol **18** (0.290 g, 0.72 mmol) in a 1:1 mixture of water and TFA (12 mL) was stirred at room temperature for 3 h and the residual solvents were then removed directly in vacuo to give the intermediate triol in quantitative yield. This material was dissolved in dry methanol (7 mL) under an atmosphere of nitrogen and to the stirred solution were added CSA (a few crystals), trimethylorthoformate (1.6 mL, 14.4 mmol) and 2,3-butandione (0.14 mL, 1.56 mmol). The reaction mixture was then heated at reflux for 24 h, during which time it developed a deep red colouration. It was then allowed to cool to room temperature and Et_3N (0.2 mL, 1.4 mmol) was added. Residual solvents were then removed in vacuo and the crude product was partially purified by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:9), to give a mixture of compounds consisting predominantly of the desired isomer **20** (0.256 g).

A solution of DMSO (0.05 mL, 0.70 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise, under an atmosphere of nitrogen, to a solution of oxalyl chloride (0.06 mL, 0.69 mmol) in CH_2Cl_2 (2.5 mL), maintaining the reaction temperature below −60 °C. The reaction mixture was stirred for 30 min at <−60 °C, before a pre-cooled solution of the crude bisacetal **20** (0.256 g) in CH_2Cl_2 (3.5 mL) was added dropwise. The reaction mixture was stirred below −60 °C for a further 65 min before Et_3N (0.34 mL, 2.43 mmol) was added dropwise and the resulting yellow solution was allowed to warm gradually to room temperature. After stirring for a further 4 h at room temperature, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (150 mL). The organic phase was collected and combined with three further CH_2Cl_2 extracts (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:12) gave the title compound as a viscous oil (0.125 g, 36% from **18**). R_f 0.16 (EtOAc/petroleum ether (40–60), 1:19); $[\alpha]_D^{27}$ −7.70 (*c* 1.03, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2924m (C–H), 1711s (C=O); δ_H (300 MHz; $CDCl_3$)

1.43 and 1.46 (2×3H, 2×s, 2×butyl CH_3), 3.31 and 3.38 (2×3H, 2×s, 2×acetal OCH_3), 4.11 (1H, dd, *J* 10.8, 3.5, C(5)*H*), 4.24 (1H, dd, *J* 6.4, 3.5, C(4)*H*), 4.72 (1H, d, *J* 11.3, OCH_aH$_b$Ph), 5.02 (1H, d, *J* 10.8, C(6)*H*), 5.12 (1H, d, *J* 11.3, OCH$_a$$H_b$Ph), 7.35–7.52 (5H, m, aromatic C*H*), 7.59 (1H, d, *J* 6.4, C(3)*H*); δ_C (75.4 MHz; $CDCl_3$) 17.88 and 17.90 (2×butyl *C*H$_3$), 48.4 and 48.7 (2×acetal O*C*H$_3$), 69.2 (*C*(6)H), 69.7 (*C*(5)H), 73.7 (*C*(4)H), 74.4 (benzyl *C*H$_2$), 99.7 and 100.4 (2×acetal *C*), 107.3 (*C*(2)), 128.4, 128.6 and 128.8 (aromatic *C*H), 138.3 (aromatic *ipso-C*), 151.3 (*C*(3)H), 186.4 (*C*=O); *m/z* (CI/NH$_3$) 492 (MNH_4^+, 32%), 391 (57), 136 (52), 124 (56), 106 (100), 100 (90), 88 (80) (Found 492.0885, $C_{19}H_{27}INO_6$ (MNH_4^+) requires 492.0883).

4.1.5. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*R*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-*O*-benzoyl-cyclohex-1-ene-3,4,5,6-tetraol (22). To a solution of the mixture of bis-acetals containing **20** prepared as described above (0.42 g, 0.88 mmol) in THF (8 mL) was added a solution of triphenylphosphine (0.92 g, 3.52 mmol) in THF (10 mL) followed by a solution of benzoic acid (0.22 g, 1.76 mmol) in THF (5 mL) and finally diisopropylazodicarboxylate (0.35 mL, 1.76 mmol). The reaction mixture was stirred for 18 h when the solvent was removed in vacuo to give the crude product as a yellow oil. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as colourless crystals (0.440 g, 49% from **18**). R_f 0.15 (EtOAc/petroleum ether (40–60), 1:9); mp 52.9–55.1 °C; $[\alpha]_D^{23}$ +63.71 (*c* 1.78, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2991w, 2945m and 2832w (C–H), 1730s (C=O); δ_H (300 MHz; $CDCl_3$) 1.28 and 1.39 (2×3H, 2×s, 2×butyl CH_3), 3.22 and 3.33 (2×3H, 2×s, 2×acetal OCH_3), 3.95 (1H, dd, *J* 11.0, 3.7, C(4)*H*), 4.03 (1H, dd, *J* 6.0, 3.7, C(3)*H*), 4.54 (1H, dd, *J* 11.0, 8.2, C(5)*H*), 4.70 (1H, d, *J* 11.3, OCH_aH$_b$Ph), 5.08 (1H, d, *J* 11.3, OCH$_a$$H_b$Ph), 5.94 (1H, d, *J* 8.2, C(6)*H*), 6.65 (1H, d, *J* 6.0, C(2)*H*), 7.30–7.76 (8H, m, aromatic C*H*), 8.16 (2H, d, *J* 8.5, benzoyl *o*-C*H*); δ_C (75.4 MHz; $CDCl_3$) 18.0 (2×butyl *C*H$_3$, coincident), 48.0 and 48.3 (2×acetal O*C*H$_3$), 67.5 (*C*(5)H), 69.1 (*C*(4)H), 73.8 (*C*(3)H), 74.0 (benzyl *C*H$_2$), 75.4 (*C*(6)H), 99.3 and 99.6 (2×acetal *C*), 102.7 (*C*(1)), 128.1, 128.6, 128.66, 128.70, 130.3 and 133.5 (aromatic *C*H), 130.1 & 138.8 (aromatic *ipso-C*), 138.7 (*C*(2)H), 165.6 (*C*=O); *m/z* (+ve ion electrospray) 603 ([M+Na]$^+$, 100%) (Found 603.0855, $C_{26}H_{29}O_7INa$ ([M+Na]$^+$) requires 603.0850).

4.1.6. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6,6-difluoro-cyclohex-1-ene-3,4,5-triol (24). A sample of the enone **21** (0.160 g, 0.34 mmol) was cooled to 0 °C under an atmosphere of nitrogen and [bis-(2-methoxyethyl)]-aminosulfurtrifluoride (DeoxoFluor®) (0.94 mL, 5.1 mmol) was carefully added. The reaction mixture was allowed to warm to room temperature and was stirred for 72 h before being diluted with CH_2Cl_2 (100 mL) and quenched by the careful addition of a saturated aqueous solution of sodium bicarbonate (100 mL). The organic phase was collected and combined with three subsequent CH_2Cl_2 extracts (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a brown oil. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as an oil (0.060 g, 36%) and the allylically rearranged isomer **23** also as an oil (0.050 g, 30%). Data for **24**: R_f 0.67 (EtOAc/petroleum ether (40–60), 1:4); $[\alpha]_D^{19}$ +26.1 (*c* 1.36, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2994m, 2957m, 2925m and 2836m (C–H); δ_H (300 MHz; $CDCl_3$) 1.42 and 1.46 (2×3H, 2×s, 2×butyl CH_3), 3.33 and 3.40 (2×3H, 2×s, 2×acetal OCH_3), 4.01 (1H, dd, *J* 11.0, 3.7, C(4)*H*), 4.06 (1H, ddd, *J* 5.5, 3.7, 1.9, C(3)*H*), 4.62 (1H, ddd, *J* 14.7, 11.0, 8.6, C(5)*H*), 4.67 (1H, d, *J* 11.1, OCH_aH$_b$Ph), 5.06 (1H, d, *J* 11.1, OCH$_a$$H_b$Ph), 6.75 (1H, dd, *J* 5.5, 2.4, C(2)*H*), 7.35–7.50 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 17.87 and 17.95 (2×butyl *C*H$_3$), 48.47 and 48.48 (2×acetal O*C*H$_3$), 65.9 (dd, *J* 23.0, 17.6, *C*(5)H), 67.3 (d, *J* 8.3, *C*(4)H), 73.4 (*C*(3)H), 74.4 (benzyl *C*H$_2$), 97.8 (dd, *J* 33.3, 27.9, *C*(1)), 99.6 and 99.9 (2×acetal *C*), 115.2 (dd, *J* 246.0, 243.3, *C*(6)F$_2$), 128.2, 128.5 and 128.7 (aromatic *C*H), 138.4 (aromatic *ipso-C*), 142.3 (t, *J* 7.2, *C*(2)H); δ_F (376.3 MHz; $CDCl_3$) −104.6 (1F, dd, *J* 265.3, 14.7, one of C(6)F_2), −91.6 (1F, ddd, *J* 265.3, 8.6, 2.4, one of C(6)F_2); *m/z* (CI/NH$_3$) 514 (MNH_4^+, 4%), 482 (3), 388 (3), 356 (6), 307 (6), 85 (100) (Found 514.0905, $C_{19}H_{27}F_2INO_5$ (MNH_4^+) requires 514.0896). Data for **23**: R_f 0.80 (EtOAc/petroleum ether (40–60), 1:4); $[\alpha]_D^{19}$ +84.8 (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2993m, 2949m, 2924m and 2834m (C–H), 1667m (C=C); δ_H (300 MHz; $CDCl_3$) 1.41 and 1.42 (2×3H, 2×s, 2×butyl CH_3), 3.31 and 3.36 (2×3H, 2×s, 2×acetal OCH_3), 4.04 (1H, dt, *J* 8.5, 2.3, C(5)*H*), 4.16 (1H, dt, *J* 9.0, 2.1, C(4)*H*), 4.72 (1H, d, *J* 11.6, OCH_aH$_b$Ph), 4.88 (1H, ddd, *J* 11.3, 9.0, 3.7, C(3)*H*), 5.00 (1H, d, *J* 11.6, OCH$_a$$H_b$Ph), 5.04 (1H, ddd, 46.7, 6.8, 2.3, C(6)*H*F), 7.35–7.43 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 17.90 and 17.94 (2×butyl *C*H$_3$), 48.4 and 48.5 (2×acetal O*C*H$_3$), 64.1 (dd, *J* 21.6, 2.9, *C*(3)H), 68.2 (d, *J* 4.1, *C*(4)H), 70.8 (dd, *J* 22.4, 21.9, *C*(1)), 74.0 (benzyl *C*H$_2$), 76.3 (dd, *J* 27.3, 1.7, *C*(5)H), 93.0 (dd, *J* 182, 7.5, *C*(6)HF), 100.7 (2×acetal *C*), 128.3 and 128.8 (aromatic *C*H), 137.9 (aromatic *ipso-C*), 161.4 (dd, *J* 279.3, 11.2, *C*(2)F); δ_F (376.3 MHz; *C*D*C*l$_3$) −163.7 (1F, ddddd, *J* 46.7, 11.3, 8.5, 6.8, 2.0, C(6)H*F*), −85.7 (1F, td, *J* 6.8, 3.7, C(2)*F*); *m/z* (CI/NH$_3$) 514 (MNH_4^+, 1%), 482 (2), 356 (1), 307 (1), 85 (100) (Found 514.0902, $C_{19}H_{27}F_2INO_5$ (MNH_4^+) requires 514.0896).

4.1.7. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Methoxycarbonyl-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6,6-difluoro-cyclohex-1-ene-3,4,5,-triol (30). Palladium acetate (0.5 mg, 0.002 mmol), tri-2-furylphosphine (1.2 mg, 0.005 mmol) and CH_3OH (0.17 mL) were placed in a three-necked, pear-shaped flask fitted with two Suba Seals® and a balloon filled with CO. Diisopropylethylamine (0.016 mL, 0.094 mmol) and a solution of the vinyl iodide **24** (0.044 g, 0.09 mmol) in DMF (1 mL) were added to the flask. CO was bubbled through the solution for 5 min and the whole system was then flushed several times with CO. The reaction mixture was stirred under a balloon atmosphere of CO at room temperature for 24 h. Diethyl ether (10 mL) and water (5 mL) were then added to the flask. The organic phase was collected and washed with water (3×5 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as colourless crystals (0.021 g, 56%). R_f 0.37 (EtOAc/petroleum ether (40–60), 1:4); mp 133 °C; $[\alpha]_D^{19}$ +2.9 (*c* 1.36, CH_2Cl_2); ν_{max}

(film)/cm^{-1} 1733s (C═O); δ_H (400 MHz; $CDCl_3$) 1.39 and 1.43 (2×3H, 2×s, 2×butyl CH_3), 3.30 and 3.36 (2×3H, 2×s, 2×acetal OCH_3), 3.82 (3H, s, CO_2CH_3), 3.96 (1H, dd, *J* 10.8, 3.8, C(4)*H*), 4.25 (1H, dd, *J* 5.8, 3.8, C(3)*H*), 4.50 (1H, dt, *J* 13.6, 10.8, C(5)*H*), 4.68 (1H, d, *J* 11.2, OCH_aH$_b$Ph), 5.05 (1H, d, *J* 11.2, OCH$_a$$H_b$Ph), 7.08 (1H, dd, *J* 5.8, 2.4, C(2)*H*), 7.29–7.40 (3H, m, aromatic *m*- and *p*-C*H*), 7.45 (2H, d, *J* 7.6, aromatic *o*-C*H*); δ_C (75.4 MHz; $CDCl_3$) 17.90 and 17.96 (2×butyl *C*H$_3$), 48.4 and 48.5 (2×acetal O*C*H$_3$), 52.8 (CO_2CH_3), 66.9 (dd, *J* 21.3, 18.4, *C*(5)H), 67.1 (dd, *J* 6.0, 1.2, *C*(4)H), 70.1 (*C*(3)H), 74.8 (benzyl *C*H$_2$), 99.6 and 99.8 (2×acetal *C*), 115.9 (t, *J* 245.1, *C*(6)F$_2$), 128.3, 128.6 and 128.7 (aromatic *C*H), 129.1 (dd, *J* 26.5, 22.9, *C*(1)), 138.4 (aromatic *ipso*-*C*), 141.3 (t, *J* 6.6, *C*(2)H), 163.2 (t, *J* 1.4, *C*═O); δ_F (376.3 MHz; $CDCl_3$) −106.5 (1F, ddd, *J* 278.3, 10.8, 2.4, one of C(6)F_2), −107.4 (1F, dd, *J* 278.3, 13.6, one of C(6)F_2); *m*/*z* (CI/NH_3) 446 (MNH_4^+, 100%), 414 (25), 340 (52), 188 (25), 102 (67) (Found 446.1987, $C_{21}H_{30}F_2NO_7$ (MNH_4^+) requires 446.1990).

4.1.8. (−)-Shikimic acid (1). Methyl shikimate (**32**) (0.024 g, 0.13 mmol) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 12 h. After this time, the solvent was removed directly in vacuo to give (−)-shikimic acid in essentially pure form as a yellow oil. Analytical material was obtained by purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: H_2O/formic acid, 99.9:0.1; UV detection at 255 nm] to give the title compound as colourless crystals (0.019 g, 86%). Mp 182–184 °C (Lit.[27] mp 184–186 °C); $[\alpha]_D^{23}$ −186.1 (*c* 1.07, H_2O) (Lit.[27] $[\alpha]_D^{25}$ −170.0 (*c* 0.86, H_2O)); δ_H (300 MHz; D_2O) 2.16 (1H, ddt, *J* 18.2, 6.3, 1.8, one of C(6)H_2), 2.67 (1H, ddt, *J* 18.2, 5.3, 1.8, one of C(6)H_2), 3.71 (1H, dd, *J* 8.2, 4.1, C(4)*H*), 3.97 (1H, ddd, *J* 8.2, 6.3, 5.3, C(5)*H*), 4.38 (1H, ~t, *J* 4.1, C(3)*H*), 6.80 (1H, ~dt, *J* 4.1, 1.8, C(2)*H*); δ_C (75.4 MHz; D_2O) 30.5 (*C*(6)H$_2$), 66.0 (*C*(3)H), 66.8 (*C*(5)H), 71.3 (*C*(4)H), 129.9 (*C*(1)), 137.6 (*C*(2)H), 170.3 (*C*═O); *m*/*z* (−ve ion electrospray) 347 ([M$_2$−H]$^-$, 60%), 173 ([M−H]$^-$, 100).

4.1.9. 3-*epi*-Shikimic acid (34). Methyl shikimate (**32**) (0.011 g, 0.06 mmol) was stirred at 100 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 30 h. After this time, the solvent was removed directly in vacuo to give the crude product mixture as a yellow solid. Purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: H_2O/formic acid, 99.9:0.1; UV detection at 255 nm] gave the title compound as a colourless solid (0.0021 g, 21%) as well as *para*-hydroxy benzoic acid (0.0016 g, 21%) and (−)-shikimic acid (0.0008 g, 8%). Data for **34**: mp 164–166 °C (Lit.[28] mp 164–165 °C); $[\alpha]_D^{21}$ −28.0 (*c* 0.1, H_2O) (Lit.[28] $[\alpha]_D$ −31.0 (*c* 0.1, H_2O)); δ_H (300 MHz; D_2O) 2.11 (1H, dddd, *J* 17.2, 10.0, 3.8, 2.9 one of C(6)H_2), 2.68 (1H, ddd, *J* 17.2, 5.9, 1.6, one of C(6)H_2), 3.38 (1H, dd, *J* 10.0, 8.1, C(4)*H*), 3.68 (1H, td, *J* 10.0, 5.9, C(5)*H*), 4.17 (1H, dddd, *J* 8.1, 3.8, 2.2, 1.6, C(3)*H*), 6.57 (1H, ~t, *J* 2.5, C(2)*H*); *m*/*z* (−ve ion electrospray) 347 ([M$_2$−H]$^-$, 43%), 173 ([M−H]$^-$, 100).

4.1.10. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Methoxycarbonyl-3-*O*-benzyl-6,6-difluoro-cyclohex-1-ene-3,4,5-triol (35). The methyl ester **30** (0.021 g, 0.050 mmol) was stirred at room temperature in a mixture of water and TFA (1:6, 1 mL) for 3 h and the solvent was then removed directly in vacuo. After storage under high vacuum for several hours, the title compound was obtained in a sufficiently pure state (assessed by ^{1}H NMR analysis) to be carried on directly to the final step (0.016 g, ~quant.). δ_H (300 MHz; $CDCl_3$) 3.89 (3H, s, CO_2CH_3), 4.09–4.14 (1H, m, C(4)*H*), 4.29 (1H, ~q, *J* 9.0, C(5)*H*), 4.37–4.43 (1H, m, C(3)*H*), 4.79 (2H, s, benzyl CH_2), 7.20 (1H, br s, C(2)*H*), 7.37–7.48 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 52.8 (CO_2CH_3), 69.1 (d, *J* 5.7, *C*(4)H), 71.5 (dd, *J* 26.2, 20.7, *C*(5)H), 71.9 (*C*(3)H), 73.1 (benzyl *C*H$_2$), 115.9 (dd, *J* 245.4, 241.3, *C*(6)F$_2$), 127.7 (t, *J* 25.6, C(1)), 128.3, 128.76 and 129.0 (aromatic *C*H), 137.1 (aromatic *ipso*-*C*), 142.9 (t, *J* 7.2, *C*(2)H), 163.30 (*C*═O).

4.1.11. 6,6-Difluoroshikimic acid (11). The diol **35** (0.016 g) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 12 h. After this time, the solvent was removed directly in vacuo to give the title compound in quantitative yield as a viscous, yellow oil. Analytical material could be obtained by further purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: H_2O/TFA, 99.9:0.1; UV detection at 254 nm] to give the title compound as a colourless foam (0.010 g, 68% from **30**). $[\alpha]_D^{25}$ −128.0 (*c* 0.10, H_2O); δ_H (400 MHz; D_2O) 3.78 (1H, ddd, *J* 9.6, 4.0, 1.6, C(4)*H*), 3.99 (1H, ~dt, *J* 12.0, 9.6, C(5)*H*), 4.38 (1H, br t, *J* 4.0, C(3)*H*), 6.91 (1H, dd, *J* 4.4, 2.0, C(2)*H*); δ_C (100 MHz; D_2O) 67.4 (*C*(3)H), 71.1 (d, *J* 6.8, *C*(4)H), 72.5 (dd, *J* 24.3, 19.9, *C*(5)H), 119.9 (t, *J* 241.2, *C*(6)F$_2$), 145.3 (t, *J* 7.2, *C*(2)H), 159.6 (*C*═O), (*C*(1) not detected); δ_F (376.3 MHz; D_2O) −104.8 (1F, br d, *J* 278.1, one of C(6)F_2), −109.3 (1F, dd, *J* 278.1, 12.0, one of C(6)F_2); *m*/*z* (−ve ion electrospray) 209 ([M−H]$^-$, 60%), 189 (100) (Found 209.0270, $C_7H_7F_2O_5$ ([M−H]$^-$) requires 209.0267).

4.1.12. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (20). The vinyl bromide **13** (0.150 g, 0.35 mmol), copper (I) iodide (4 mg, 0.02 mmol) and potassium iodide (0.087 g, 0.52 mmol) were placed in a flask, which was evacuated and backfilled with nitrogen five times. ^{n}Butanol (3 mL) and *N*,*N*′-dimethylethylenediamine (3.1 μL, 10 mol %) were added and the flask was evacuated and backfilled with nitrogen a further five times. The stirred mixture was then heated at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and washed with dilute aqueous ammonia solution (20 mL) followed by water (3×10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a viscous, dark yellow oil. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:9) yielded the title compound, contaminated with <10% of **13**, as a pale yellow oil (0.121 g). R_f 0.10 (EtOAc/petroleum ether (40–60), 1:9); ν_{max} (film)/cm^{-1} 3468br, m (O–H), 3027m, 2991m, 2948m, 2926m and 2832m (C–H), 1626w (C═C); δ_H (300 MHz; $CDCl_3$) 1.36 (6H, s, 2×butyl CH_3), 2.78 (1H, br s, 6-O*H*), 3.28 and 3.32 (2×3H, 2×s, 2×acetal OCH_3), 3.98 (1H, dd, *J* 6.0, 3.8, C(3)*H*), 4.10 (1H, dd, *J* 10.4, 3.8, C(4)*H*), 4.34–4.40 (2H, m, C(5)*H* and C(6)*H*), 4.60 (1H, d, *J* 11.1, OCH_aH$_b$Ph), 5.01 (1H, d, *J* 11.1, OCH$_a$$H_b$Ph), 6.51 (1H, d, *J* 6.0, C(2)*H*),

7.30–7.47 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 18.0 and 18.1 (2×butyl *C*H_3), 48.3 and 48.4 (2×acetal O*C*H_3), 65.7 (*C*(4)H), 65.9 (*C*(5)H), 74.1 (benzyl *C*H_2), 74.5 (*C*(3)H), 75.4 (*C*(6)H), 99.6 and 100.0 (2×acetal *C*), 101.8 (*C*(1)), 128.0, 128.5 and 128.6 (aromatic *C*H), 138.9 (*C*(2)H), 149.7 (aromatic *ipso-C*); *m/z* (CI/NH_3) 494 (MNH_4^+, 5%) (Found 494.1053, $C_{19}H_{29}O_6IN$ (MNH_4^+) requires 494.1040).

4.1.13. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*R*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-fluoro-cyclohex-1-ene-3,4,5-triol (40). DAST (0.06 mL, 0.49 mmol) was added under an atmosphere of nitrogen to a stirred solution of the allylic alcohol **20** (0.107 g, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C. The stirred reaction mixture was allowed to warm to room temperature, and stirring was continued for a further 2.5 h. The reaction mixture was then cooled to −20 °C and CH_3OH (10 mL) was gradually added followed by calcium carbonate and the mixture was then filtered. Concentration of the filtrate in vacuo gave a dark yellow viscous oil, which was purified by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:9) to give the title compound as a colourless oil (0.057 g, 38% from **13**). R_f 0.38 (EtOAc/petroleum ether (40–60), 1:9); $[\alpha]_D^{26}$ +52.0 (*c* 1.5, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2992–2883m (C–H), 1624w (C═C); δ_H (300 MHz; $CDCl_3$) 1.39 and 1.41 (2×3H, 2×s, 2×butyl C*H*$_3$), 3.32 and 3.39 (2×3H, 2×s, 2×acetal OC*H*$_3$), 3.79 (1H, ddd, *J* 11.0, 3.7, 0.7, C(4)*H*), 3.96 (1H, dd, *J* 6.0, 3.7, C(3)*H*), 4.54 (1H, ddd, *J* 18.3, 11.0, 7.3, C(5)*H*), 4.66 (1H, d, *J* 11.4, OC*H*$_a$H$_b$Ph), 4.88 (1H, ddd, *J* 50.1, 7.3, 1.2, C(6)*H*F), 5.02 (1H, d, *J* 11.4, OCH$_a$*H*$_b$Ph), 6.62 (1H, dd, *J* 6.0, 1.2, C(2)*H*), 7.33–7.49 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 17.9 (2×butyl *C*H_3, coincident), 48.3 and 48.4 (2×acetal O*C*H_3), 67.6 (d, *J* 13.1, *C*(5)H), 68.2 (d, *J* 8.7, *C*(4)H), 73.6 (*C*(3)H), 73.8 (benzyl *C*H_2), 93.1 (d, *J* 182.0, *C*(6)H), 99.2 and 99.6 (2×acetal *C*), 100.6 (d, *J* 22.5, *C*(1)), 128.0, 128.5 and 128.6 (aromatic *C*H), 138.7 (aromatic *ipso-C*), 139.2 (d, *J* 4.6, *C*(2)H); δ_F (376.3 MHz; $CDCl_3$) 172.2 (dd, *J* 50.1, 18.3, *C*(6)HF); *m/z* (+ve ion electrospray) 501 ([M+Na]$^+$, 70%) (Found 501.0549, $C_{19}H_{24}FIO_5Na$ ([M+Na]$^+$) requires 501.0545).

4.1.14. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Methoxycarbonyl-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxy-butane-2′,3′-diyl)-6-fluoro-cyclohex-1-ene-3,4,5,-triol (41). An identical procedure to that used in Section 4.1.7 was used to transform the vinyl iodide **40** (0.070 g, 0.17 mmol). Purification by flash column chromatography (SiO_2; Et_2O/petroleum ether (40–60), 1:1) gave the title compound as a colourless solid (0.035 g, 58%). R_f 0.28 (Et_2O/petroleum ether (40–60), 1:1); mp 113–115 °C; $[\alpha]_D^{19}$ +34.5 (*c* 1.08, $CHCl_3$); ν_{max} (film)/cm^{-1} 1730s (C═O); δ_H (300 MHz; $CDCl_3$) 1.47 and 1.49 (2×3H, 2×s, 2×butyl C*H*$_3$), 3.38 and 3.47 (2×3H, 2×s, 2×acetal OC*H*$_3$), 3.69 (1H, dd, *J* 11.4, 3.4, C(4)*H*), 3.89 (3H, s, CO_2CH_3), 4.20 (1H, dd, *J* 6.0, 3.4, C(3)*H*), 4.57 (1H, ddd, *J* 21.3, 11.4, 7.1, C(5)*H*), 4.73 (1H, d, *J* 11.4, OC*H*$_a$H$_b$Ph), 5.05 (1H, d, *J* 11.4, OCH$_a$*H*$_b$Ph), 5.38 (1H, dd, *J* 49.2, 7.1, C(6)*H*F), 6.91 (1H, d, *J* 6.0, C(2)*H*), 7.34–7.51 (5H, m, aromatic C*H*); δ_C (75.4 MHz; $CDCl_3$) 17.9 and 18.0 (2×butyl *C*H_3), 48.3 and 48.4 (2×acetal O*C*H_3), 52.5 (CO_2CH_3), 68.1 (d, *J* 4.6, *C*(4)H), 68.3 (d, *J* 8.1, *C*(5)H) 70.6 (*C*(3)H), 74.1 (benzyl *C*H_2), 88.6 (d, *J* 175.7, *C*(6)HF), 99.2 and 99.7 (2×acetal *C*), 128.1, 128.5 and 128.6 (aromatic *C*H), 131.9 (d, *J* 19.2, *C*(1)), 137.3 (d, *J* 5.4, *C*(2)H), 138.7 (aromatic *ipso-C*), 165.3 (*C*═O); δ_F (376.3 MHz; *C*DCl_3) −183.9 (dd, *J* 49.2, 21.3, C(6)H*F*); *m/z* (+ve ion electrospray) 433 (100%, [M+Na]$^+$) (Found 433.1631, $C_{21}H_{27}FO_7Na$ ([M+Na]$^+$) requires 433.1633).

4.1.15. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Methoxycarbonyl-3-*O*-benzyl-6-fluoro-cyclohex-1-ene-3,4,5-triol (42). The methyl ester **41** (0.035 g, 0.09 mmol) was stirred vigorously at room temperature in a mixture of water and TFA (1:9, 2 mL) for 2 h and the solvent was then removed in vacuo. Purification by flash column chromatography (SiO_2; EtOAc/petroleum ether (40–60), 1:2) gave the title compound as an oily half-solid (0.018 g, 72%). R_f 0.17 (EtOAc/petroleum ether (40–60), 1:2); $[\alpha]_D^{24}$ −128.6 (*c* 0.87, $CHCl_3$); ν_{max} (film)/cm^{-1} 3432br (O–H), 2925m (C–H), 1726s (C═O); δ_H (300 MHz; $CDCl_3$) 2.46 (2H, br s, 4-O*H* and 5 O–*H*), 3.67 (1H, dd, *J* 9.4, 4.1, C(4)*H*), 3.86 (3H, s, CO_2CH_3), 4.17–4.31 (2H, m, C(3)*H* and C(5)*H*), 4.72 (1H, d, *J* 11.6, OC*H*$_a$H$_b$Ph), 4.82 (1H, d, *J* 11.6, OCH$_a$*H*$_b$Ph), 5.26 (1H, dd, *J* 48.5, 6.2, C(6)*H*F), 6.99 (1H, d, *J* 5.0, C(2)*H*) 7.34–7.42 (5H, m, aromatic C*H*); *m/z* (+ve ion electrospray) 319 (100%, [M+Na]$^+$) (Found 319.0950, $C_{15}H_{17}FO_5Na$ ([M+Na]$^+$) requires 319.0952).

4.1.16. (6*S*)-6-Fluoroshikimic acid (5). The diol **42** (0.018 g, 0.06 mmol) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1.5 mL) for 10 h. After this time, the solvent was removed directly in vacuo to give the title compound as a viscous oil. Purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: H_2O/formic acid, 99.98:0.02; UV detection at 254 nm] followed by lyophilisation gave the title compound as a colourless solid (0.071 g, 61%). $[\alpha]_D^{24}$ −28.7 (*c* 0.71, H_2O); δ_H (300 MHz; D_2O) 3.64 (1H, dd, *J* 9.6, 3.9, C(4)*H*), 4.01 (1H, ddd, *J* 18.0, 9.6, 5.8, C(5)*H*), 4.39 (1H, ~td, *J* 4.5, 1.5, C(3)*H*), 5.10 (1H, dd, *J* 48.6, 5.8, C(6)*H*F), 6.83 (1H, d, *J* 4.8, C(2)*H*); δ_C (100 MHz; D_2O) 64.9 (d, *J* 2.3, *C*(3)H), 68.2 (d, *J* 7.6, *C*(4)H), 69.6 (d, *J* 20.6, *C*(5)H), 89.6 (d, *J* 169.4, *C*(6)HF), 139.1 (d, *J* 6.0, *C*(2)H), 168.4 (*C*═O), (*C*(1) not detected); δ_F (376.3 MHz; D_2O) −176.5 (dd, *J* 48.6, 18.0, C(6)H*F*); *m/z* (−ve ion electrospray) 191 ([M−H]$^-$, 100%), 171 (82) (Found 191.0357, $C_7H_8FO_5$ ([M−H]$^-$) requires 191.0361).

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Ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization

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Abstract—Results of the optimized conditions for the one-pot synthesis of 2-substituted indoles via palladium acetate catalyzed tandem Sonogashira coupling 5-*endo-dig* cyclization at room temperature under ultrasonic irradiation and standard stirred conditions are described. Electron-donating and electron-withdrawing groups present in both coupling partners were well tolerated under these mild conditions. A copper-, ligand- and amine-free condition is an important feature of this protocol. Significant enhancement of reaction rates was observed for the reactions employing ultrasonic irradiation.

1. Introduction

Indole derivatives occur widely in natural products and possess unique biological activity.[1] Various 2-substituted indoles exhibit interesting pharmacological properties such as antithrombatic,[2] anti-cancer,[3] histamine H_3 receptor antagonism,[4] etc. Many synthetic methods for the construction of indole ring have been reported.[5] Among these palladium catalyzed annulation of *o*-halo anilines and alkynes has been employed widely due to the versatile nature of these protocols, increased functional group tolerance, and improved yields.[6]

The synthesis of indoles via Sonogashira reaction is generally carried out in two steps viz. the palladium–copper catalyzed Sonogashira cross coupling between 2-aminoaryl halide and alkyne followed by cyclization of the resulting 2-alkynylanilines. The various catalysts and promoters reported for the cyclization of 2-alkynylanilines include copper(I),[7] metal alkoxide,[8] fluorides,[9] Lewis acids,[10] gold(III),[11] and iodine.[12] Very recently Sakamoto et al. reported cyclization of 2-ethynylaniline derivatives to indoles catalyzed by copper(II) salts in aqueous medium.[13a] Konakahara et al. reported cyclization of 2-alkynylanilines catalyzed by Indium bromide.[13b] Also, several methods are reported for one-pot synthesis of indole via tandem Sonogashira coupling 5-*endo-dig* cyclization.[14] Most of these reported methods suffer from some drawbacks such as harsh reaction conditions, prolonged reaction period, and cumbersome isolation procedure. Many of these methods employ moisture sensitive phosphine ligands and phosphine based palladium catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ and also make use of copper iodide as co-catalyst. With the presence of copper(I) co-catalyst the Glaser type oxidative dimerization of alkynes[15] is encountered thus lowering chemoselectivity. In addition, the starting amines have a characteristic foul smell and industrial wastes containing them would require treatment for environmental purposes.

As a part of our continuing interest in palladium catalyzed carbon–carbon cross coupling reactions,[16] we recently reported the ultrasound promoted ligand- and copper-free Sonogashira reaction at ambient temperature.[16c] Our interest in exploring the potential of this reaction prompted us to extend studies to the palladium catalyzed one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization. To the best of our knowledge, a copper-, ligand-, and amine-free one-pot synthesis of indole derivatives via Sonogashira coupling 5-*endo-dig* cyclization has not been reported. Herein, we wish to report an efficient one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization under ligand-, copper-, and amine-free conditions at room temperature using ultrasound irradiation and standard stirred conditions, respectively. The methodology developed makes use of 2 mol % of $Pd(OAc)_2$ in the presence of Bu_4NOAc as a base. Considerable rate enhancement and in most cases marginally improved yields were observed for the sonochemical reactions.

Keywords: Indole; Synthesis; 5-*endo-dig* Cyclization; Ultrasound.
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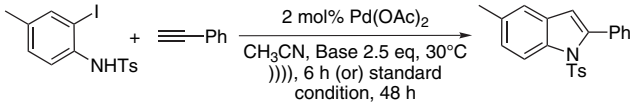
2. Results and discussion

Palladium catalyzed reactions are strongly dependent on a number of factors such as base, solvent, stabilizing ligand, temperature, and the combined effect of these. Based on our ongoing work on copper- and ligand-free palladium catalyzed C–C coupling reactions,[16c] our initial aim was to optimize the reactions conditions for this protocol under both ultrasound irradiation and standard stirred conditions at room temperature. For this purpose, we systematically evaluated the role of base and solvent for this synthetic protocol by subjecting 2-iodo-4-methyl-*N*-tosylbenzenamine to the tandem coupling–cyclization process. The results are summarized in Tables 1 and 2, respectively.

Bu_4NOAc was found to be the most effective base (entry 14, Table 1). Other bases (entries 1–7, Table 1) were substantially less effective. Potassium-*tert*-butoxide failed to promote the reaction. Tetrabutylammonium salts are known to facilitate the reduction of $Pd(OAc)_2$ to catalytically active Pd(0) species.[17] Recently Verkade and Urgaonkar reported the Bu_4NOAc promoted Sonogashira reaction.[18] We investigated the effect of counter anions (entries 10–14, Table 1) of the tetrabutylammonium salts. It was found that acetate and fluoride (entry 13 and 14, Table 1) promote this coupling–cyclization reaction whereas, bromide and hydroxide (entry 10 and 11, Table 1) did not promote the reaction. Even though Bu_4NF (in THF 1 M solution) gave an appreciable yield nearly comparable to that with Bu_4NOAc under standard stirred conditions, surprisingly, the yield was low under ultrasound irradiation.

Next, the above benchmark reaction using Bu_4NOAc as the base was examined in various solvents. As is evident, from Table 2 acetonitrile was found to be the most suitable solvent. These tests showed that the optimal reaction conditions for synthesizing 2-substituted indoles required 2 mol % of $Pd(OAc)_2$, 2.5 equiv of Bu_4NOAc and acetonitrile as the solvent.

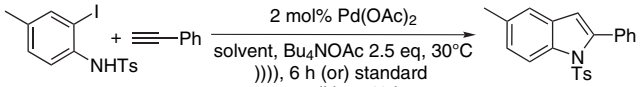
Table 1. Effect of base on Sonogashira coupling 5-*endo-dig*-cyclization reaction



Entry	Base	Yield (%)[a]	
		Ultrasonic irradiation	Standard stirred conditions
1	Diisopropyl amine	7	6
2	DABCO	44	25
3	Et_3N	23	26
4	NaOAc	4	5
5	Cs_2CO_3	10	9
6	K_2CO_3	13	12
7	K_3PO_4	11	9
8	Piperidine	0	0
9	KO^{t}Bu	0	0
10	Bu_4NBr	0	0
11	Bu_4NOH (in methanol 0.1 N)	0	0
12	Bu_4NF (in water 75% solution)	23	15
13	Bu_4NF (in THF 1 M solution)	39	68
14	Bu_4NOAc	74	71

[a] Isolated yields.

Table 2. Effect of solvent on Sonogashira coupling 5-*endo-dig*-cyclization reaction



Entry	Solvent	Yield (%)[a]	
		Ultrasonic irradiation	Standard stirred conditions
1	DMF	50	32
2	NMP	0	0
3	DMA	5	14
4	THF	44	26
5	CH_3CN	74	71
6	CH_3CN	74[b]	71[c]
7	Acetone	50	49

[a] Isolated yields.
[b] Yield after 5 h.
[c] Yield after 30 h.

The reaction time was optimized for the benchmark reaction under both ultrasonic irradiation and standard stirred conditions. The isolated yields at various time intervals are given in Table 3. It can be observed for the reaction employing ultrasonic irradiation, the yield was found to increase up to 5 h after which there was no further conversion. Similarly, for the standard stirred conditions the isolated yield was optimized at 30 h.

Table 3. Optimization of reaction time for the benchmark reaction

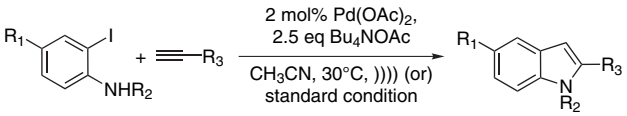
Standard stirred conditions	Time (h)	5	12	18	24	30	36
	Yield (%)[a]	39	48	58	64	71	71
Ultrasonic irradiation	Time (h)	3	4	5	6		
	Yield (%)[a]	58	65	74	74		

[a] Isolated yields.

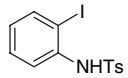
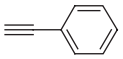
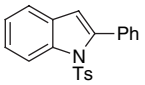
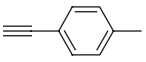
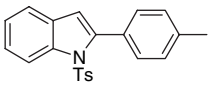
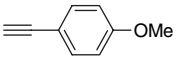
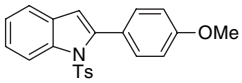
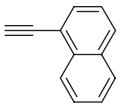
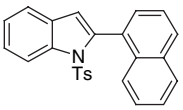
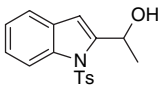
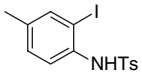
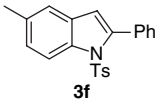
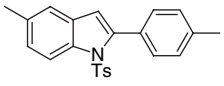
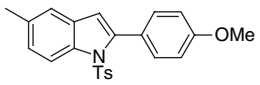
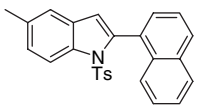
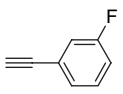
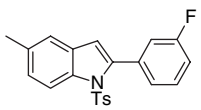
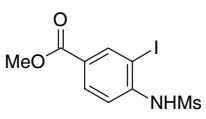
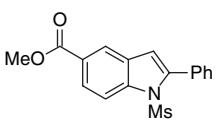
For the identical time (5 h) yield for the reaction employing ultrasonic irradiation was 74% in comparison to that for the standard stirred condition, which gave only 39% yield. This clearly shows significant enhancement in the reaction rate for the reaction employing ultrasonic irradiation.

To survey the generality of this protocol the optimized reaction conditions were applied to the synthesis of various 2-substituted indole derivatives. The results are summarized in Table 4. In all the cases, the reaction time was optimized as for the benchmark reaction. The time of reaction indicated in Table 4 is the optimized time after which no further conversion and improvement in the isolated yield were observed. We studied the effect of different substituents on *o*-iodoanilides and 1-alkynes. Both the unsubstituted *o*-iodoanilides and the substituted *o*-iodoanilides having an electron-donating group on the aromatic ring moiety gave indoles in good yields. It is noteworthy that even if R_1 (Table 4) is an electron-withdrawing group (–COMe, $–CO_2Me$, entries 11–18, Table 4) the reaction proceeded smoothly to afford the 2-substituted indoles in moderate yields. Another

Table 4. Synthesis of indole derivatives under silent conditions and ultrasound irradiation[a]

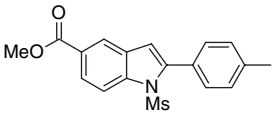
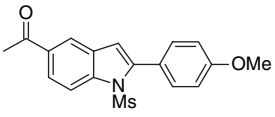
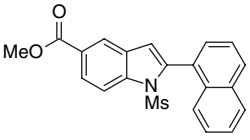
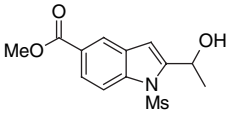
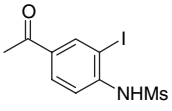
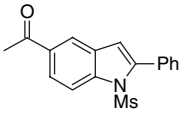
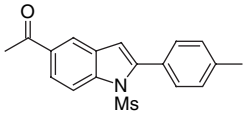
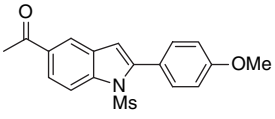


R_1 = H, CH_3, CO_2Me, COMe
R_2 = Ts, Ms
R_3 = Ph, p-tolyl, 4-methoxy phenyl, 3-fluoro phenyl, naphthyl, 1-hydroxy ethyl

Entry	*o*-Iodoanilide **1**	1-Alkyne **2**	Product **3**	Ultrasonic irradiation		Standard stirred conditions	
				Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	4	82	24	80
2	**1a**	 **2b**	 **3b**	5	71	30	69
3	**1a**	 **2c**	 **3c**	6	72	30	76
4	**1a**	 **2d**	 **3d**	6	63	24	67
5	**1a**	 **2e**	 **3e**	6	44	24	41
6	 **1b**	**2a**	 **3f**	5	74	30	71
7	**1b**	**2b**	 **3g**	5	90	36	87
8	**1b**	**2c**	 **3h**	5	90	36	74
9	**1b**	**2d**	 **3i**	6	42	30	46
10	**1b**	 **2f**	 **3j**	6	65	36	56
11	 **1c**	**2a**	 **3k**	6	51	12	43

(*continued*)

Table 4. (*continued*)

Entry	*o*-Iodoanilide **1**	1-Alkyne **2**	Product **3**	Ultrasonic irradiation		Standard stirred conditions	
				Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
12	**1c**	**2b**	 **3l**	6	54	12	58
13	**1c**	**2c**	 **3m**	6	60	12	54
14	**1c**	**2d**	 **3n**	6	61	12	60
15	**1c**	**2e**	 **3o**	6	58	12	56
16	 **1d**	**2a**	 **3p**	6	52	12	45
17	**1d**	**2b**	 **3q**	6	65	12	71
18	**1d**	**2c**	 **3r**	6	66	12	67

[a] Reaction conditions: 1.0 mmol 2-iodoanilide, 1.1 mmol alkyne, 0.02 mmol $Pd(OAc)_2$, and 2.5 mmol Bu_4NOAc with 5 mL of acetonitrile.
[b] Isolated yields.

remarkable feature of this protocol is that the base sensitive ester group was not affected by our mild reaction conditions. Moreover, various substituted terminal alkynes reacted smoothly giving moderate to good yields.

Ultrasound as a non-thermal energy transfer source is well known to enhance reaction rates/yields/selectivity in organic synthesis and has found widespread application in synthetic organic chemistry.[19] Significant enhancement in rate of reaction (5–10 folds) and improved yields for the sonochemical reactions relative to the standard stirred reactions were observed (Table 4).

During the course of the reaction under standard conditions as well as ultrasound conditions we did not observe any uncyclized product. However, the formation of the homo-coupled product arising out of the terminal acetylene was observed to an extent of 2–8%. It should also be noted that we did not observe any reaction when 2-bromo-*N*-tosyl-benzenamine and phenyl acetylene was subjected to this coupling–cyclization protocol under the optimized reaction conditions. Moreover, the reaction of *o*-iodoaniline with the free amino group and phenyl acetylene using the standard reaction conditions yielded only Sonogashira coupled product in 92 and 82% yield by employing the ultrasonic irradiation and standard stirred conditions, respectively. It is worth noting that the *p*-toluene sulfonyl/methane sulfonyl groups were found to be stable under the mild reaction conditions of this protocol. The corresponding *N*-*p*-toluene sulfonyl/methane sulfonyl indoles **3a**–**r** were isolated in

moderate to good yields. These *N*-protected indole derivatives allow us the flexibility to further functionalize the indole nucleus.

3. Conclusion

In conclusion, we have developed a mild, efficient, and general one-pot synthesis of 2-substituted indoles at room temperature under ultrasound irradiation and standard stirred conditions in the absence of any ligand, copper, and amine by using $Pd(OAc)_2$ as the catalyst, Bu_4NOAc as the base, in acetonitrile. Both electron-donating and electron-withdrawing substituents on the aryl ring of *o*-iodoanilides were tolerated.

4. Experimental

4.1. General

Melting points were recorded in open capillary using Buchi melting point B540 apparatus. Column chromatography was performed using silica gel (60–120 mesh size), and TLC was carried out using aluminum sheets precoated with silica gel 60F254. All solvents and chemicals used were reagent grade procured commercially and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 200 spectrometer. Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. Elemental analysis was performed on Flash EA 1112 Thermo Finnigan instrument. The reactions were carried out in a thermostated (30±1 °C) ultrasonic cleaning bath at 50 kHz. The ultrasonic cleaner had an output power of 120 W and a power supply of 450 W. The tank dimensions were 290×240×150 mm with a liquid holding capacity of 9.5 L. The reactions were carried out in a RB flask of 10 mL capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid. *o*-Iodoanilines were prepared according to the procedure described in the literature.[20]

4.2. General procedure for preparation of 2-substituted indoles

To the mixture of *o*-iodoanilide **1** (1 mmol), $Pd(OAc)_2$ (2 mmol %), and Bu_4NOAc (2.5 mmol) in dry acetonitrile under argon atmosphere was added phenyl acetylene **2** (1.1 mmol). The reaction mixture was then stirred at room temperature or sonicated for the time as shown in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue thus obtained was purified by column chromatography using ethyl acetate/petroleum benzine as eluent to afford the desired product **3**. To the best of our knowledge, *N*-tosyl derivative of indoles **3** have not been previously reported and hence the complete characterization data is given as follows.

4.2.1. 2-Phenyl-1-tosyl-1*H*-indole 3a. Light brown solid; mp 145–147 °C; IR (film, cm^{-1}) 3019, 2400, 1450, 1374, 1215, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H), 6.47 (s, 1H), 6.96 (d, J=8.13 Hz, 2H), 7.15–7.29 (m, 4H), 7.32–7.46 (m, 6H), 8.24 (d, J=7.58 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1, 130.1, 130.6, 134.5, 138.1, 138.5, 142.2, 144.4. Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.79; H, 5.15; N, 4.27.

4.2.2. 2-*p*-Tolyl-1-tosyl-1*H*-indole 3b. Light brown solid; mp 108–110 °C; IR (film, cm^{-1}) 3027, 2922, 1597, 1504, 1449, 1188, 812, 752, 571; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.36 (s, 3H), 6.43 (s, 1H), 6.96 (d, J=8.08 Hz, 2H), 7.14–7.37 (m, 9H), 8.22 (d, J=8.58 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1, 130.1, 130.6, 131.3, 134.6, 138.1, 138.5, 142.2, 144.4. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.96; H, 5.28; N, 4.26.

4.2.3. 2-(4-Methoxyphenyl)-1-tosyl-1*H*-indole 3c. Light brown solid; mp 126–128 °C; IR (film, cm^{-1}) 3019, 2400, 1505, 1215, 668, 572; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.88 (s, 3H), 6.48 (s, 1H), 6.93–7.05 (m, 4H), 7.24–7.34 (m, 4H), 7.40–7.44 (m, 3H), 8.30 (d, J=8.28 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 55.2, 112.7, 112.9, 116.5, 120.4, 122.3, 124.1, 126.6, 127.4, 129.1, 129.5, 131.6, 134.9, 135.9, 137.5, 139.1, 144.1, 144.4, 160.0. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.54; H, 4.72; N, 3.81.

4.2.4. 2-(Naphthalen-1-yl)-1-tosyl-1*H*-indole 3d. Light brown solid; mp 132–134 °C; IR (film, cm^{-1}) 3019, 2400, 1598, 1449, 1373, 667, 569; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 6.65 (s, 1H), 6.94 (d, J=8.06 Hz, 2H), 7.24–7.34 (m, 5H), 7.39–7.54 (m, 4H), 7.64 (d, J=8.79 Hz, 1H), 7.91 (dd, J=13.19, 8.06 Hz, 2H), 8.39 (d, J=8.79 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 113.6, 115.7, 120.7, 123.9, 124.4, 124.7, 125.7, 126.0, 126.2, 126.8, 127.9, 129.1, 129.4, 129.9, 132.9, 133.3, 135.2, 137.5, 138.7, 144.5. Anal. Calcd for $C_{25}H_{19}NO_2S$: C, 75.54; H, 4.82; N, 3.52. Found: C, 75.64; H, 4.52; N, 3.20.

4.2.5. 1-(1-Tosyl-1*H*-indol-2-yl) ethanol 3e. Light brown solid; mp 136–137 °C; IR (film, cm^{-1}) 3551, 3018, 2985, 2401, 1597, 1451, 1215, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.67 (d, J=6.57 Hz, 3H), 2.33 (s, 3H), 3.48 (br s, 1H), 5.35 (q, J=6.57 Hz, 1H), 6.68 (s, 1H), 7.16–7.33 (m, 4H), 7.45–7.50 (m, 1H), 7.66 (td, J=8.33, 1.76 Hz, 2H), 8.09 (d, J=8.08 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.5, 62.6, 108.8, 114.7, 121.1, 123.8, 124.9, 126.3, 127.4, 129.1, 129.9, 135.6, 137.2, 144.8, 145.0. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.62; H, 5.32; N, 4.34.

4.2.6. 5-Methyl-2-phenyl-1-tosyl-1*H*-indole 3f. Light brown solid; mp 113–114 °C; IR (film, cm^{-1}) 3019, 2400, 1598, 1372, 1215, 668, 588; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.33 (s, 3H), 6.39 (s, 1H), 6.94 (d, J=8.31 Hz, 2H), 7.06–7.21 (m, 4H), 7.32–7.45 (m, 5H), 8.09 (d, J=8.52 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.5, 113.5, 116.4, 120.6, 126.1, 126.7, 127.4, 129.1, 130.2, 131.4, 133.9, 134.6, 136.5, 142.2, 144.4.

Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.97; H, 5.21; N, 4.27.

4.2.7. 5-Methyl-2-*p*-tolyl-1-tosyl-1*H*-indole 3g. Light brown solid; mp 145–147 °C; IR (film, cm^{-1}) 3025, 2921, 1597, 1371, 1174, 811, 573; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 6.36 (s, 1H), 6.96 (d, J=8.00 Hz, 1H), 7.05–7.23 (m, 7H), 7.33 (td, J=8.21, 1.91 Hz, 2H), 8.08 (d, J=8.45 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.4, 21.5, 113.2, 116.4, 120.5, 125.9, 126.8, 128.2, 129.1, 129.6, 130.1, 130.9, 133.8, 134.6, 138.5, 144.3. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.85; H, 5.75; N, 3.92.

4.2.8. 2-(4-Methoxyphenyl)-5-methyl-1-tosyl-1*H*-indole 3h. Light brown solid; mp 138–139 °C; IR (film, cm^{-1}) 3028, 2924, 1611, 1506, 1371, 1175, 575; ^1H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.40 (s, 3H), 3.88 (s, 3H), 6.41 (s, 1H), 6.92–7.05 (m, 4H), 7.12–7.27 (m, 4H), 7.42 (td, J=8.83, 2.14 Hz, 2H), 8.16 (d, J=8.44 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.4, 55.2, 112.7, 112.9, 116.3, 120.4, 122.8, 124.8, 125.8, 126.7, 129.1, 131.5, 133.8, 134.6, 136.3, 139.2, 142.1, 144.3, 159.9. Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.26; H, 5.35; N, 3.81.

4.2.9. 5-Methyl-2-(naphthalen-1-yl)-1-tosyl-1*H*-indole 3i. Light brown solid; mp 159–161 °C; IR (film, cm^{-1}) 3020, 2924, 1597, 1365, 1172, 592; ^1H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.46 (s, 3H), 6.58 (s, 1H), 6.95 (d, J=7.95 Hz, 2H), 7.21–7.36 (m, 5H), 7.41–7.55 (m, 3H), 7.66 (d, J=8.34 Hz, 1H), 7.85–7.96 (m, 2H), 8.26 (d, J=8.46 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.3, 113.6, 115.5, 120.6, 124.4, 125.6, 126.1, 126.8, 127.4, 127.9, 129.1, 129.2, 129.4, 129.5, 129.9, 130.2, 130.3, 133.0, 133.3, 133.5, 135.2, 135.7, 138.8, 144.4. Anal. Calcd for $C_{26}H_{21}NO_2S$: C, 75.89; H, 5.14; N, 3.40. Found: C, 75.59; H, 5.03; N, 3.39.

4.2.10. 2-(3-Fluorophenyl)-5-methyl-1-tosyl-1*H*-indole 3j. Yellow Oil; IR (film, cm^{-1}) 2925, 2856, 1615, 1373, 757, 588; ^1H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.33 (s, 3H), 6.42 (s, 1H), 6.95–7.33 (m, 10H), 8.09 (d, J=8.33 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 21.4, 114.2, 116.3, 116.7, 120.8, 126.1, 126.5, 126.7, 129.1, 130.6, 134.1, 136.6, 140.7, 144.6, 159.4, 164.3. Anal. Calcd for $C_{22}H_{18}FNO_2S$: C, 69.64; H, 4.78; F, 5.01; N, 3.69. Found: C, 69.54; H, 4.72; F, 4.98; N, 3.81.

4.2.11. 1-Methanesulfonyl-2-phenyl-1*H*-indole-5-carboxylic acid methyl ester 3k. Colorless solid; mp 131–132 °C; IR (film, cm^{-1}) 3019, 2400, 1717, 1375, 1216, 669; ^1H NMR (200 MHz, $CDCl_3$) δ 2.82 (s, 3H), 3.96 (s, 3H), 6.76 (s, 1H), 7.43–7.46 (m, 2H), 7.54–7.59 (m, 2H), 8.03–8.20 (m, 2H), 8.32 (d, J=1.75 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.4, 52.2, 112.6, 115.3, 123.1, 126.1, 127.8, 130.3, 131.4, 140.3, 142.9, 167.1. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.31; H, 4.65; N, 4.47.

4.2.12. 1-Methanesulfonyl-2-*p*-tolyl-1*H*-indole-5-carboxylic acid methyl ester 3l. Colorless solid; mp 146–147 °C; IR (film, cm^{-1}) 3011, 2400, 1716, 1215, 669; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.86 (s, 3H), 4.01 (s, 3H), 6.77 (s, 1H), 7.30 (d, J=7.92 Hz, 2H), 7.50 (d, J=8.08 Hz, 2H), 8.10 (dd, J=7.27, 1.61 Hz, 1H), 8.22 (d, J=8.88 Hz, 1H), 8.36 (d, J=1.29 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 40.4, 52.1, 112.4, 115.3, 122.9, 125.9, 128.5, 130.2, 139.3, 143.1, 167.1. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.64; H, 4.88; N, 4.36.

4.2.13. 1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indole-5-carboxylic acid methyl ester 3m. Colorless solid; mp 144–146 °C; IR (film, cm^{-1}) 3019, 2400, 1716, 1290, 669; ^1H NMR (200 MHz, $CDCl_3$) δ 2.74 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.64 (s, 1H), 6.91 (d, J=8.73 Hz, 2H), 7.43 (d, J=8.83 Hz, 2H), 7.98 (dd, J=7.19, 1.64 Hz, 1H), 8.11 (d, J=8.73 Hz, 1H), 8.24 (d, J=1.19 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.4, 52.1, 55.3, 112.1, 113.3, 115.3, 118.9, 122.8, 123.4, 125.8, 129.8, 131.6, 140.2, 142.8, 160.3, 167.1. Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.15; H, 4.77; N, 3.90. Found: C, 59.70; H, 4.59; N, 4.30.

4.2.14. 1-Methanesulfonyl-2-(naphthalen-1-yl)-1*H*-indole-5-carboxylic acid methyl ester 3n. Colorless solid; mp 144–146 °C; IR (film, cm^{-1}) 3020, 2400, 1715, 1375, 1215, 668; ^1H NMR (200 MHz, $CDCl_3$) δ 2.91 (s, 3H), 3.98 (s, 3H), 6.86 (s, 1H), 7.45–7.61 (m, 4H), 7.71 (d, J=8.97 Hz, 1H), 7.90–7.99 (m, 2H), 8.09–8.22 (m, 2H), 8.39 (d, J=1.65 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.1, 52.2, 112.9, 114.5, 123.2, 124.7, 125.5, 126.1, 126.2, 126.7, 128.4, 128.8, 129.2, 129.5, 129.9, 133.1, 133.3, 139.5, 139.9, 167.1. Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.87; H, 4.71; N, 3.94.

4.2.15. 1-Methanesulfonyl-2-(1-hydroxyethyl)-1*H*-indole-5-carboxylic acid methyl ester 3o. Colorless solid; mp 132–133 °C; IR (film, cm^{-1}) 3326, 3019, 2930, 2400, 1716, 1215, 668; ^1H NMR (200 MHz, $CDCl_3$) δ 1.72 (d, J=6.57, 3H), 3.24 (s, 3H), 3.95 (s, 3H), 5.39 (q, J=6.44 Hz, 1H), 6.78 (s, 1H), 8.03–8.05 (m, 2H), 8.28 (d, J=1.39 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 41.3, 52.1, 62.1, 108.1, 113.7, 123.4, 126.2, 128.5, 131.1, 139.5, 145.4, 167.0. Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.56; H, 4.64; N, 4.44.

4.2.16. 1-(1-Methanesulfonyl-2-phenyl-1*H*-indol-5-yl)-ethanone 3p. Colorless solid; mp 170–171 °C; IR (film, cm^{-1}) 3019, 2919, 2400, 1681, 1374, 1215, 668; ^1H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 2.83 (s, 3H), 6.77 (s, 1H), 7.44–7.47 (m, 3H), 7.56 (dd, J=7.57, 2.24 Hz, 2H), 8.00 (dd, J=7.41, 1.40 Hz, 1H), 8.19 (d, J=8.87 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.7, 40.6, 112.7, 115.4, 121.8, 125.1, 127.8, 129.2, 130.3, 133.8, 140.3, 143.1, 197.5. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.15; H, 4.42; N, 4.52.

4.2.17. 1-(1-Methanesulfonyl-2-*p*-tolyl-1*H*-indol-5-yl)-ethanone 3q. Colorless solid; mp 138–139 °C; IR (film, cm^{-1}) 3019, 2400, 1678, 1375, 1216, 668; ^1H NMR (200 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.61 (s, 3H), 2.75 (s, 3H), 6.67 (s, 1H), 7.18 (d, J=7.75 Hz, 2H), 7.38 (d, J=8.17 Hz, 2H), 7.91 (dd, J=7.02, 1.70 Hz, 1H), 8.12 (d, J=9.56 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 26.6, 40.4, 112.4, 115.3, 121.7, 124.8, 128.2, 128.4, 130.1,

133.5, 139.2, 140.2, 143.1, 197.6. Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.89; H, 4.93; N, 4.52.

4.2.18. 1-(1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indol-5-yl)-ethanone 3r. Colorless solid; mp 187–189 °C; IR (film, cm^{-1}) 3019, 2400, 1677, 1216, 758, 669; ^1H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 2.81 (s, 3H), 3.87 (s, 3H), 6.72 (s, 1H), 6.97 (td, J=8.87, 2.19 Hz, 2H), 7.49 (d, J=8.87, 2.19 Hz, 2H), 7.98 (dd, J=6.97, 1.74 Hz, 1H), 8.18 (d, J=8.71 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.7, 40.4, 55.2, 112.2, 113.3, 115.5, 121.6, 123.4, 124.8, 129.9, 131.6, 140.3, 143.1, 160.4, 197.6. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.91; H, 4.91; N, 4.48.

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Catalytic asymmetric allylation of aldehydes using the chiral (salen)chromium(III) complexes

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Abstract—The enantioselective addition of allylstannanes to glyoxylates and glyoxals, as well as simple aromatic and aliphatic aldehydes, catalyzed by chiral (salen)Cr(III) complexes, has been studied. The reaction proceeded smoothly for the reactive 2-oxoaldehydes and allyltributyltin in the presence of small amounts (1–2 mol %) of (salen)Cr(III)BF_4 (**1b**) under mild, undemanding conditions. However, in the case of other simple aldehydes, the use of high-pressure conditions is required to obtain good yields. Classic chromium catalyst **1b**, easily prepared from the commercially available chloride complex **1a**, affords homoallylic alcohols usually in good yield and with enantiomeric purity of 50–79% ee. The stereochemical results are rationalized on the basis of the proposed model.

1. Introduction

The readily available chiral metallosalen complexes are potentially very attractive catalysts, e.g., for reactions catalyzed by Lewis acids. They have already been effectively applied in a variety of reactions,[1] e.g., epoxidation[2] and cyclopropanation[3] of alkenes, epoxide ring opening,[4] Diels–Alder,[5] and Strecker[6] reactions, as well as Michael-type additions,[7] alkylations of tin enolates,[8] and hydrocyanation of aldehydes.[9] One of the most promising and powerful salen-type Lewis acids is chromium(III) complex, well known as efficient enantioselective catalyst for several reactions.[5,8,10] Salen–chromium complexes have also been employed in the allylation of aldehydes in the catalytic Nozaki–Hiyama–Kishi reaction with allylic halides,[11] which is a redox process and requires anhydrous and oxygen-free conditions.

Until now, many efficient methods of enantioselective allylation have been developed which, however, were almost exclusively applied to simple aromatic and aliphatic aldehydes.[12] No efficient catalytic method for the enantioselective allylation of glyoxylates is currently known. This subject was investigated by Mikami et al.[13] with the use of a BINOL–titanium complex (10 mol %) as a catalyst. However, the results obtained were unsatisfactory in terms of both the yield and enantiomeric excess. In the case of reactions of glyoxylates with allyltrimethylsilane or allyltributyltin, the enantiomeric excess values were 30 and 10%, respectively, and the yield did not exceed 40%. Better results were obtained for crotyltin reagents. Of interest was the fact that the same catalytic system, independently used by Keck[14] and Umani-Ronchi[15] for the reaction of simple aliphatic and aromatic aldehydes with allyltributyltin, gave excellent results (the enantiomeric excess value was often above 90%).

The allylation of glyoxylates leads to the corresponding 2-hydroxypent-4-enoates, compounds of significant synthetic interest.[16] Recently, in order to synthesize these compounds and their derivatives in an enantiomerically pure form, diastereoselective methods, widely explored in our group,[17] using chiral auxiliaries attached to the glyoxylate moiety[18] or to the allylating reagents,[19] have been applied. These facts prompted us to search for a catalytic system useful for the enantioselective allylation of glyoxylates using metallosalen complexes. For some allylation reactions carried out under normal conditions, metallosalen complexes cannot be useful due to their relatively low Lewis acidity. In such cases, the problem can be solved by the application of a high-pressure technique.[20]

Recently, we have published two communications concerning catalytic asymmetric allylation of glyoxylates[21] and high-pressure methodology for the reaction with nonactivated aldehydes in the presence of a chromium–salen catalyst (Scheme 1).[22] In this paper, we present in detail the studies on enantioselective addition of allylstannanes to various aldehydes, catalyzed by chiral (salen)Cr(III) complexes

Keywords: Allylation; Asymmetric catalysis; Glyoxylates; High-pressure technique; Homoallylic alcohols; (Salen)chromiun complexes.
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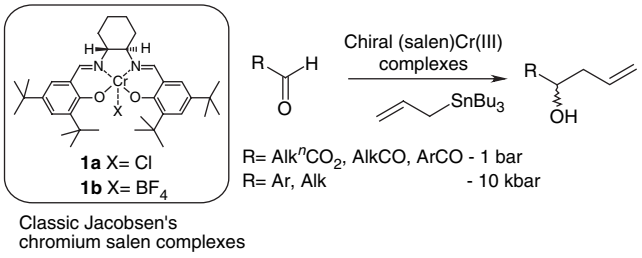
e.g., **1** (Scheme 1). Moreover, we decided to extend the investigation to other active aldehydes such as glyoxals, as well as to other allyltin reagents such as crotylstannanes.



Scheme 1.

2. Results and discussion

2.1. Allylation of activated aldehydes

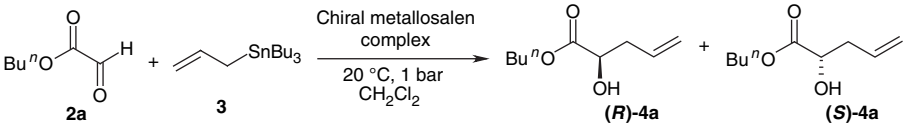
The metallosalen complexes were chosen as candidate chiral Lewis acids. In many cases, they are easily prepared and handled, and stable in the presence of moisture and oxygen. The model reaction was the allylation of *n*-butyl glyoxylate (**2a**) with allyltributyltin (**3**) leading to *n*-butyl 2-hydroxy-pent-4-enoate (**4a**) (Scheme 2). Subsequent to the preliminary screening of the chiral salen complexes of type **1** (Fig. 1) of the following metals: Ti(IV), VO(IV), Cr(III), Mn(III), Fe(III), Co(II) and (III), Ni(II) and (III), Cu(II) and Al(III), it transpired that the only enantioselectively efficient catalysts were the (salen)chromium(III) complexes **1a–c** (Table 1, entries 1–3). Although the remaining complexes **1d–m** (entries 4–13) did catalyze the allylation, the enantiomeric excess was 10% at best. The commercially available (salen)CrCl complex **1a** (2 mol %) provides the reaction at moderate enantioselectivity (54% ee) and in good yield. However, higher activity and slightly better enantioselectivity (over 60% ee) were observed for the chromium complexes with less coordinating counterions such as BF_4^- (**1b**) and ClO_4^- (**1c**) (entries 2 and 3, respectively) both easily prepared from **1a**.[6]

Table 1. Screening of the metallosalen complexes of type **1** with a classic salen ligand in the reaction of **2a** with **3**[a]

Entry	Catalyst	M	Yield (%)[b]	ee (%)[c]
1	**1a**	CrCl	73	54
2	**1b**	$CrBF_4$	82	61
3	**1c**	$CrClO_4$	90	65
4	**1d**	$TiCl_2$	82	<5
5	**1e**	VO	85	0
6	**1f**	MnCl	80	<5
7	**1g**	FeCl	83	<5
8	**1h**	Co	80	6
9	**1i**	CoCl	79	10
10	**1j**	Ni	66	<5
11	**1k**	$NiBF_4$	79	<5
12	**1l**	Cu	70	<5
13	**1m**	AlCl	78	<5

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate (**2a**), 2 mol % of complex **1**, and 1.1–1.2 mmol of allyltributyltin, in 1 ml of CH_2Cl_2, at 20 °C for 3–4 h.
[b] The yield was determined by GC.
[c] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.

We also tested the applicability of other chromium complexes with modified salen ligands. We studied the effect of the ligand structure with respect to the substituted



Scheme 2. The model reaction.

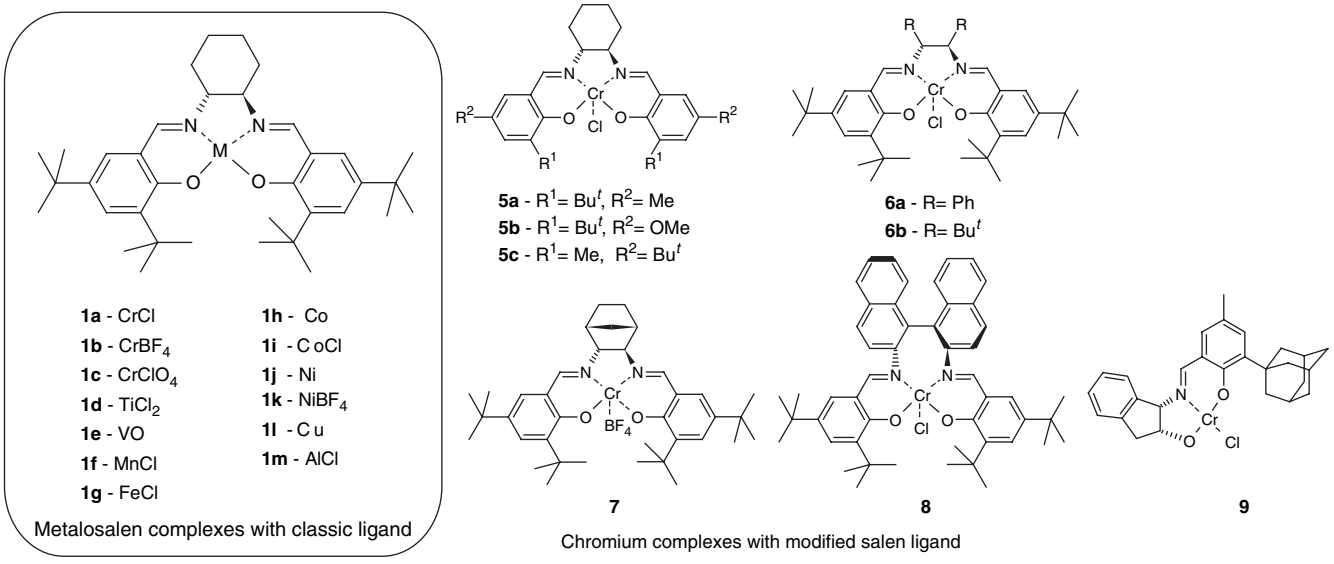


Figure 1. The metallosalen complexes used in this work.

Table 2. The reaction of **2a** with **3** catalyzed by chromium(III) complexes with modified salen ligands[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1a**	73	54
2	**5a**	82	55
3	**5b**	85	49
4	**5c**	75	29
5	**6a**	70	44
6	**6b**	52	21[d]
7	**7**	70	<5
8	**8**	65	<5
9	**9**	49	7

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate (**2a**), 2 mol % of chromium complex, and 1.1–1.2 mmol of allyltributyltin, in 1 ml of CH_2Cl_2, at 20 °C for 3–4 h.
[b] The yield was determined by GC.
[c] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.
[d] Opposite sense of asymmetric induction.

salicylidene and diamine (Table 2). When the R^1 substituent being *tert*-butyl was conserved, and the R^2 substituent was replaced by smaller groups such as methyl and methoxyl, the asymmetric induction remained similar (entries 1–3). A more significant decrease in induction was observed for replacing *tert*-butyl with methyl as an R^1 substituent (entry 4).

We investigated the chromium complexes with diamines other than 1,2-diaminocyclohexane, but the enantioselectivities obtained were lower (entries 5–9). Only the complex derived from 1,2-diphenylethylenediamine **6a** produced results similar to **1a** (entry 5). For the complex **6b**, reversed and lower enantioselectivity was observed (entry 6). This is a consequence of the altered conformation of the complex, since two *tert*-butyl groups of the amine, for steric reasons, cannot occupy both the pseudodiequatorial positions. The complex with 1,1′-binaphthyl-2,2′-diamine (**8**) gave practically no induction (entry 8); it likely adopts the cis-β configuration,[23] departing structurally from the complexes of type **1**, which typically adopt the trans conformation. In the context of the works of Jacobsen concerning the tridentate chromium(III) complex **9**,[24] we tested its performance in the model reaction. The results however, were unsatisfactory, and the enantiomeric excess of product **4a** was not greater than 10% (entry 9).

As already mentioned, (salen)chromium complexes have been applied to the enantioselective allylation reactions of simple aldehydes using allyl halides, via the Nozaki–Hiyama–Kishi reaction.[11] We examined this procedure for the allylation of glyoxylates, but in our hands the results were at best unsatisfactory.

We studied the influence of the enantiomeric purity of the catalyst **1b** on the enantioselectivity of the model reaction (Fig. 2, Scheme 2).[25] Linear correlation between enantiomeric purity of the catalyst and the enantioselectivity of the allylation reaction was found.

Next we tested different simple allylating reagents in the reaction of glyoxylate **2a**, e.g., allyltrimethylsilane. The chromium complex **1b** turned out to be too weak a Lewis acid to efficiently catalyze the reaction with allyltrimethylsilane, even under high-pressure conditions (10 kbar). We isolated

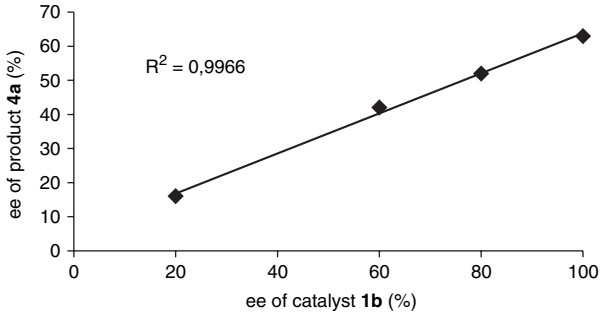


Figure 2. Absence of nonlinear effects in the reaction of **2a** with **3** catalyzed by **1b**.

the product **4a** in low yield (<40%), and enantioselectivity was within the range of 30–40% ee. The use of other tin allylating reagents did not improve the enantiomeric excess. Allyltrimethyltin gives practically the same results as allyltributyltin, being much more toxic owing to its volatility. When allyltriphenyltin was used, the enantioselectivity decreased to 46% ee. The reaction proceeded most rapidly for tetraallyltin, but the enantiomeric excesses obtained did not exceed 13%. Therefore, further studies were performed with commercially available allyltributyltin.

The natural consequence of the above studies was to optimize the reaction conditions. We investigated several factors such as concentration of reagents, solvent, temperature, and additives (Table 3).

Neither the presence of 4 Å molecular sieves (cf. entries 1 and 2 in Table 2) nor glyoxylate concentration (cf. entries 1 and 3) had considerable influence on the results of the model reaction in CH_2Cl_2. Moreover, the rate of addition of the allylating agent, based on a 1 mmol scale, and the amount of catalyst (2 mol % and more), seemed to have no influence on enantiomeric excess (cf. entries 1 and 4).

The reaction proceeded best at room temperature. Enhancing temperature to the boiling point of CH_2Cl_2 increased the reaction rate with an insignificant sacrifice in enantioselectivity (cf. entries 4 and 5). Surprisingly, lowering the temperature resulted in a drop in enantioselectivity to 36% ee (entries 6 and 7).

Out of the investigated solvents, $MeNO_2$ appeared to be the most efficient in terms of the enantiomeric excess (70% ee, entry 8). The allylation reactions are efficiently catalyzed even by minor amounts of the catalyst **1b** (0.2 mol %) yet accompanied by a decrease in enantioselectivity to 62% ee (entry 9). Of interest is the fact that the reaction proceeded well without any solvent (entry 10), which is a definite advantage of this procedure.

A slight improvement in enantioselectivity was observed for reactions conducted in the presence of amines or PPh_3 in CH_2Cl_2 (from 61 to 68% ee in the case of lutidine, cf. entries 1 and 11). This can be explained by additional coordination of the catalyst–aldehyde complex by the molecule of amine, which probably slightly deforms its structure. Beneficial effect of coordination of additional ligands on the reaction enantioselectivity is well known in the literature.[26] What is

Table 3. Results of the enantioselective reaction of *n*-butyl glyoxylate (**2a**) with allyltributyltin catalyzed by the complex **1b** under various reaction conditions[a]

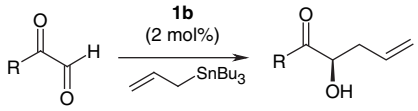
Entry	Mol % of the catalyst **1b**	Additives	Solvent	Concn of **2a** (mol/l)	*T* (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	2		CH_2Cl_2	1	20	3	82	61
2	2	4 Å MS	CH_2Cl_2	1	20	1	82	62
3	2		CH_2Cl_2	0.1	20	5	81	61
4	5		CH_2Cl_2	1	20	1	80	61
5	5		CH_2Cl_2	1	40	0.25	77	58
6	5		CH_2Cl_2	1	5	24	78	51
7	5		CH_2Cl_2	1	−78→−20	24	76	36
8	2		$MeNO_2$	1	20	3	79	70
9	0.2		$MeNO_2$	2	20	24	61	62
10	2		No solvent		5→20	5	90	65
11	2	2,6-Lutidine (2.5 mol %)	CH_2Cl_2	1	20	4	80	68
12	2	2,6-Lutidine (2.5 mol %)	$MeNO_2$	1	20	3	80	70

[a] The reactions were carried out using 1 mmol of *n*-butyl glyoxylate (**2a**) and 1.2 mmol of allyltributyltin.
[b] The yield was determined by GC.
[c] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.

more, Katsuki gave an example of the use of achiral salen complex coordinated by a chiral amine, as a catalyst in enantioselective epoxidation of olefins.[27] In contrast, the addition of lutidine to the reaction performed in $MeNO_2$ caused no change (entry 12).

We also performed allylations using the glyoxylates (R=OPr^i, OBu^t, and OBn) other than **2a**. This methodology was extended to other active 2-oxoaldehydes such as glyoxals (**2e–i**, R=Bu^n, Pr^i, Bu^t, Ph, and furyl) (Table 4). With respect to enantioselectivity, the results for alkyl glyoxylates (**2b–d**) and alkyl glyoxals (**2e–g**) were quite similar to those obtained for *n*-butyl glyoxylate and ranged from 61 to 77% ee. Of the alkyl glyoxylates, the highest enantiomeric excess was obtained for **2c** having the bulky *tert*-butyl group (entry 5). In contrast, for alkyl glyoxals **2e–g**, the best results were obtained for **2e**, which contained an *n*-alkyl substituent. However, a drop in enantioselectivity was observed for arylglyoxals **2h–i**. As regards the solvent, the change of CH_2Cl_2 for $MeNO_2$ had virtually no influence for alkyl glyoxals, but it was crucial in the case of arylglyoxals **2h–i**. Much better enantioselectivity was observed when the reaction was conducted in $MeNO_2$ (cf. entries 14–17).

Table 4. Enantioselective allylation of 2-oxoaldehydes catalyzed by **1b**[a]



2a-i **4a-i**

Entry	Aldehyde	R	Solvent	Yield (%)[b]	ee (%)[c]
1	**2a**	OBu^n	CH_2Cl_2	80	61
2	**2a**	OBu^n	$MeNO_2$	78	70
3	**2b**	OPr^i	CH_2Cl_2	78	66
4	**2b**	OPr^i	$MeNO_2$	74	73
5	**2c**	OBu^t	CH_2Cl_2	76	76
6	**2c**	OBu^t	$MeNO_2$	65	73
7	**2d**	OBn	CH_2Cl_2	84	61
8	**2e**	Bu^n	CH_2Cl_2	81	75
9	**2e**	Bu^n	$MeNO_2$	70	77
10	**2f**	Pr^i	CH_2Cl_2	71	67
11	**2f**	Pr^i	$MeNO_2$	65	67
12	**2g**	Bu^t	CH_2Cl_2	82	65
13	**2g**	Bu^t	$MeNO_2$	80	66
14	**2h**	Ph	CH_2Cl_2	78	14
15	**2h**	Ph	$MeNO_2$	74	36
16	**2i**	Furyl	CH_2Cl_2	75	15
17	**2i**	Furyl	$MeNO_2$	70	40

[a] The reactions were carried out using 1 mmol of 2-oxoaldehyde, 2 mol % of **1b**, and 1.1–1.2 mmol of allyltributyltin, in 1 ml of solvent, at 20 °C for 3–4 h.
[b] Isolated yield.
[c] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.

Complex **1b** catalyzed also the addition of allyltributyltin to active ketones, e.g., methyl pyruvate, in good yield but, unfortunately, with practically no enantioselectivity.

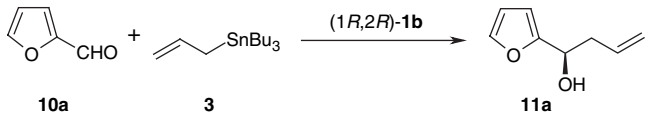
The absolute configuration of products **4a–d** derived from glyoxylates was determined by correlation with 1,2-pentanediol[17a] obtained via hydrogenation followed by $LiAlH_4$ reduction. In all cases where the chromium complexes (1*R*,2*R*)-**1b**, **5a–c**, and (1*R*,2*R*)-**6a** were used (with the exception of (1*R*,2*R*)-**6b**), the allylation product had the (*R*)-configuration.

2.2. Allylation of nonactivated aldehydes

The next stage of our study was an attempt to use salen–chromium complexes for allylation of simple aromatic and aliphatic aldehydes. As a model allylation, we chose the reaction of furfural (**10a**) with allyltributyltin in dichloromethane. Under the conditions similar to the ones used for glyoxylates and in the presence of **1b**, the reaction was very slow (Table 5, entry 1), leading, after three days, to the expected product with 56% ee, in a yield of ca. 10%. Unfortunately, the (salen)Cr(III) complexes are rather weak Lewis acids compared to the typical catalysts used for these reactions.[12] We tried to optimize the reaction conditions, e.g., by increasing temperature to 60 °C, but this change did not improve the yield satisfactorily, even when the reaction was carried out without any solvent. Addition of molecular sieves raised the yield to 46%, but the results were still unsatisfactory (entry 2). We concluded therefore that in the case of simple aldehydes and allyltributyltin, in the presence of **1b**, this reaction was apparently ineffective under ambient conditions.

We finally succeeded when high-pressure conditions (ca. 10 kbar) were applied.[20] More than 20 years ago, Yamamoto et al.[28] had found that allylic stannanes reacted with

Table 5. Results of the model reaction of furfural (**10a**) with allyltributyltin[a]



10a **3** **11a**

Entry	Catalyst	Mol % of catalyst	Concentration of **2a** (mol/L)	Pressure (bar)	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1b**	2	1.4	1	CH_2Cl_2	72	10	56
2	**1b**	2+4 Å MS	1.4	1	CH_2Cl_2	72	46	58
3	**1b**	2	0.5	7000	CH_2Cl_2	24	71	62
4	**1b**	2	0.5	10,000	CH_2Cl_2	24	91	67
5	**1b**	2+4 Å MS	0.5	10,000	CH_2Cl_2	24	95	52
6	no cat.	—	0.5	10,000	CH_2Cl_2	24	17	0
7	**1b**	5	0.5	10,000	CH_2Cl_2	24	94	68
8	**1b**	1	0.5	10,000	CH_2Cl_2	24	82	64
9	**1b**	0.5	0.5	10,000	CH_2Cl_2	24	69	61
10	**1b**	2	1.0	10,000	CH_2Cl_2	24	94	68
11	**1b**	1	1.5	10,000	CH_2Cl_2	24	89	67
12	**1b**	2	0.5	10,000	$CHCl_3$	24	91	66
13	**1b**	2	0.5	10,000	$(CH_2Cl)_2$	24	84	67
14	**1b**	2	0.5	10,000	$^{i}PrNO_2$	24	56	71
15	**1a**	2	0.5	10,000	CH_2Cl_2	24	67	66
16	**6a**	2	0.5	10,000	CH_2Cl_2	24	81	20
17[d]	**1b**	2	0.5	10,000	CH_2Cl_2	24	92	60

[a] High-pressure reactions were carried out in 2 ml Teflon ampoule using 1.1 equiv of allyltributyltin at 20 °C.
[b] The yield was determined by GC.
[c] The enantiomeric excess was determined by GC on capillary chiral β-dex 120 column.
[d] Instead of allyltributyltin, 1.1 equiv of allyltrimethyltin was used.

aldehydes at room temperature under high-pressure (10 kbar) without any catalyst. This procedure is a mild method for the allylation of aldehydes, which may be useful for preparation of the labile, thermally unstable, and acid-sensitive compounds. To the best of our knowledge, this high-pressure methodology has not been used for enantioselective allylation. Nonetheless, there are in the literature[29] some examples of diastereoselective allylation of chiral aldehydes, e.g., α-amino aldehydes.

Not only did high-pressure accelerate the reaction rate, but also increased the enantioselectivity from 56 to 67% ee (Table 5, entries 1, 3, and 4); the best results were achieved under a pressure of 10 kbar. Unfortunately, addition of molecular sieves to the reaction mixture under high-pressure conditions reduced the enantiomeric excess (entry 5). Unlike in numerous other enantioselective procedures, a catalyst concentration of 2 mol % proved to be sufficient in this method for effective allylation of furfural to afford the expected homoallylic alcohols in high yield of ca. 90% (e.g., entry 4). To compare, an analogous reaction, performed without any catalyst, proceeded with considerably lower yield (entry 6). This means that the (salen)$CrBF_4$ complexes, although rather weak Lewis acids, have a strong influence on the rate of the investigated reaction conducted under high-pressure conditions.

We continued our research with an attempt to optimize the reaction conditions at 10 kbar. We investigated several factors such as the amount of the catalyst, solvents, additives, and concentration of the aldehyde. The amount of the catalyst in the range of 0.5–5 mol % slightly influenced enantioselectivity (cf. entries 4 and 7–9). What is very promising in this method is that even 0.5 mol % of **1b** gave quite good results (entry 9). Allylation proceeded, without lowering enantiomeric excess, at a higher concentration of the aldehyde (entry 10), even when the 2 ml Teflon ampoule (cf. Section 4) was filled with 3 mmol of **10a**, 1 mol % of **1b**, 1 ml of allyltributyltin, and filled up with CH_2Cl_2 (entry 11). The possibility of using concentrated reaction mixtures is a great advantage in view of the limitation of the volume of high-pressure chambers (the average volume is 50 ml). Unfortunately, the reaction did not work well without solvent for furfural and other aldehydes insoluble in allyltributyltin.

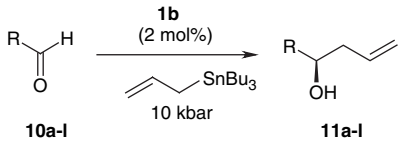
Of the solvents examined besides CH_2Cl_2, also $CHCl_3$, 1,2-dichloroethane, CH_2Cl_2/hexane (1:1), and $^{i}PrNO_2$ proved useful (e.g., entries 12–14). The latter gave the highest enantiomeric excess, but the yield was lower.

We also tested the applicability of two other chromium complexes for this reaction. The commercially available complex **1a**, bearing the chloride counterion, catalyzed the reaction practically with the same enantioselectivity (cf. entries 4 and 15), but in lower yield. We also investigated the chromium chloride complex **6a** having another widely used chiral 1,2-diamine, i.e., 1,2-diphenylethylenediamine, though the enantioselectivity decreased markedly (entry 16). The more reactive allyltrimethyltin in a non-catalyzed reaction[28] could also be used instead of allyltributyltin, although the enantiomeric excess was slightly lower (entry 17).

The next step was an endeavor to show the usefulness of the high-pressure method in reactions using other aldehydes. Table 6 summarizes the results achieved for the reactions of a wide variety of aromatic and aliphatic aldehydes with 1.1 equiv of allyltributyltin, in the presence of 2 mol % of catalyst **1b**.

The enantiomeric excesses obtained for aromatic aldehydes **10a–f** ranged from 55 to 68% ee and the yields exceeded

Table 6. High-pressure enantioselective allylation of aryl and alkyl aldehydes catalyzed by (1*R*,2*R*)-**1b**[a]



10a-l **11a-l**

Entry	Aldehyde	R	Yield (%)[b]	ee (%)[c]
1	**10a**	Furyl	89	67 (*R*)
2	**10b**	5-Methylfuryl	79	61
3	**10c**	Ph	82	55 (*R*)
4	**10d**	4-ClC_6H_4	81	60
5	**10e**	2-ClC_6H_4	85	68
6	**10f**	4-$O_2NC_6H_4$	83	68
7	**10g**	*n*-C_4H_9	52	75 (*S*)
8	**10h**	Pr^i	86	68
9	**10i**	*c*-C_6H_{11}	82	79 (*R*)
10	**10j**	Bu^t	70	35
11	**10k**	PhCH=CH	84	65 (*R*)
12	**10l**	Ph_3COCH_2	86	53 (*R*)

[a] Conditions: 1 mmol of the aldehyde, 2 mol % of (1*R*,2*R*)-(salen)$CrBF_4$ (**1b**), 1.1 mmol of allyltributyltin in CH_2Cl_2 in 2 ml Teflon ampoule; 10 kbar at 20 °C for 24 h.
[b] Isolated yield.
[c] The enantiomeric excess was determined by GC on a capillary chiral β-dex 120 column.

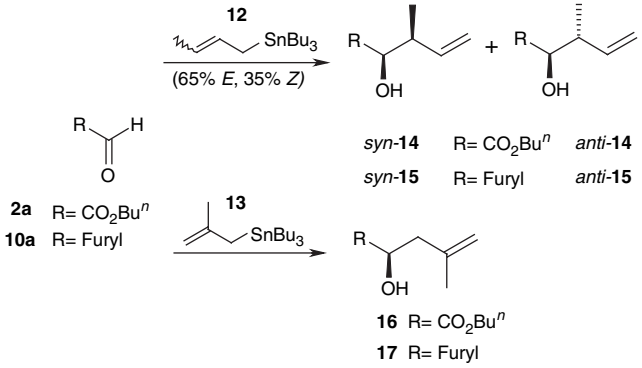
79%. This methodology also worked well for aliphatic aldehydes (e.g., **10g–i**), although the yields were sometimes less satisfactory. The lowest enantiomeric excess was obtained for the bulky pivalaldehyde **10j** (entry 10); it seems that the catalyst **1b** does not perform well for sterically demanding aldehydes such as pivalaldehyde. Allylation of α,β-unsaturated cinnamaldehyde **10k** (entry 11) and the glycolaldehyde derivative **10l** (entry 12) also proceeded in good yield and at moderate enantiomeric excess (65 and 53%, respectively).

2.3. Methyl-substituted allylating reagents

In our investigations, we also used other substituted allylating reagents such as crotyltributyltin **12** (as an *E*/*Z* mixture, 65:35) and methallyltributyltin **13**. In the case of **12** in the reaction with *n*-butyl glyoxylate, *syn*-**14** was formed as a main product with enantioselectivity of up to 75% ee (Table 7, entries 1–3). The results concerning the enantioselectivity for the *syn*-adduct were very similar to those obtained for simple allylations (Table 3). The minor *anti* product (23–29%) was isolated with a low enantioselectivity of up to 40% ee. Our results for crotylation were similar to those obtained by Mikami.[13]

When the allylating reagent was used in excess (2 equiv), a slight increase in diastereoselectivity was observed. The unreacted tin compound was investigated in the post-reaction mixture. It appeared that the contents of the *Z* isomer rose from 35 to 55%. This means that the *E*-isomer is more reactive. When less than the stoichiometric amount of the allylating reagent was used (**2a**:**12**=2:1), the diastereoselectivity slightly decreased to 66:34. Regardless of the amount of the allylating reagent (*E*/*Z*=65:35), the enantiomeric excesses for the *syn*-**14** product were similar. In the case of high-pressure crotylation of furfural (entry 4), the selectivities were similar to those obtained for *n*-butyl glyoxalate.

Table 7. Allylation of **2a** or **10a** with **12** and **13** catalyzed by **1b**[a]



Entry	Aldehyde	Allyl reagent	Solvent	Pressure (bar)	Yield (%)[b]	*syn* (ee (%))/ *anti* (ee (%))[c]
1	**2a**	**12**	CH_2Cl_2	1	69	71 (70)/29 (24)
2	**2a**	**12**	$MeNO_2$	1	62	72 (71)/28 (25)
3	**2a**	**12**	No solvent	1	70	77 (75)/23 (40)
4	**10a**	**12**	CH_2Cl_2	10,000	75	70 (68)/30 (43)
5	**2a**	**13**	CH_2Cl_2	1	80	(37)
6	**2a**	**13**	$MeNO_2$	1	79	(38)
7	**10a**	**13**	CH_2Cl_2	10,000	82	(23)

[a] The reactions were carried out using 1 mmol of aldehyde, 2 mol % of **1b**, and 1.5 mmol of **12** or **13**, in 1 ml of solvent, at 20 °C for 3–4 h under 1 bar and 24 h under 10 kbar.
[b] Isolated yield.
[c] The enantiomeric excesses were determined by GC on a capillary chiral β-dex 120 column.

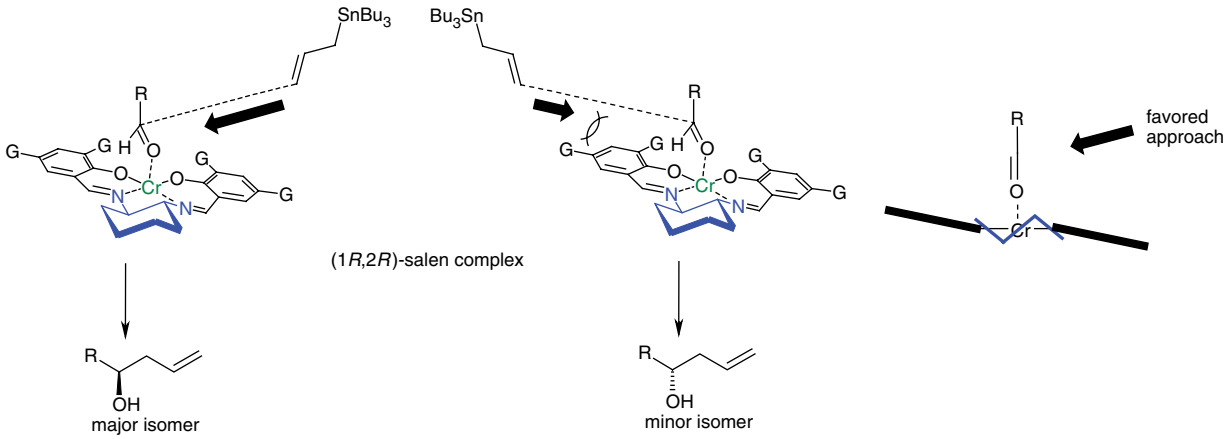
In spite of good yield, the enantioselectivity was much lower for methallyltributyltin (**13**) (up to 38%, entries 5–7). It seems that the allylating reagents containing any substituents (e.g., Me) at the β-position are poor in the studied reactions.

2.4. The stereochemical model

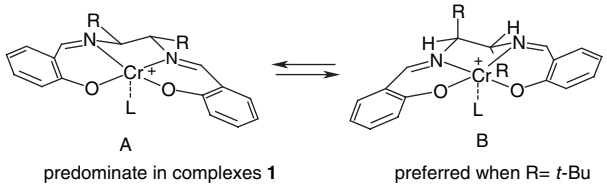
Rationalization of our results obtained in this work can be based on the stereochemical model shown in Scheme 3.

Our model originates from two sources: (i) from the conformational analysis of metallosalen complexes and their influence on the asymmetric induction of catalytic epoxidation of olefins presented by Katsuki et al.[27,30] and (ii) from the X-ray analysis of classic (salen)Co(III)SbF_6 complex modified by two molecules of benzaldehyde in the axial positions, published recently by Rawal et al.[31]

The crucial conclusion given by Katsuki et al. concerns the nonplanar, usually stepped conformation of the complex. To prove this assumption they presented some experiments in which it was shown that achiral complex modified by a chiral axial ligand (e.g., chiral amine or *N*-oxide) is able to catalyze epoxidation of an olefin in an enantioselective manner.[27] The chiral additive shifts the equilibrium to one of the enantiomeric conformers of the achiral complex (Scheme 4, in this case R=H, L=chiral ligand). They also synthesized a chiral complex bearing a 1,2-diamine moiety with a carboxylate group, which coordinates to the metal center, reversing the conformation of the catalyst, as well as the sense of asymmetric induction.[30] These experiments as well as some crystal structures of metallosalen complexes confirm the origin of asymmetric induction.



Scheme 3. The stereochemical model.



Scheme 4. Equilibrium of conformational isomers of *trans*-(salen)Cr(III) complexes.

In turn, the Rawal proposal based on the crystal structure[31] pointed out that the aldehyde molecules are not oriented perpendicularly to the complex plane, which is slightly deformed, and the aldehyde hydrogen is located close to the oxygen atoms in the complex, as shown in Scheme 3. Therefore, the approach of the allylating reagent to the complexed aldehyde should occur from the outer side. The direction of asymmetric induction we observed is in a good agreement with the proposed stereochemical model. When the salen–chromium complexes based on 1,2-diaminocyclohexane (**1a**, **1b**) and 1,2-diphenylethylenediamine (**6a**) of (*R*,*R*)-configuration were used, the same direction of the asymmetric induction was obtained, and the major product formed was most usually the homoallylic alcohol having the (*R*)-configuration.

A reversion of the product configuration and a decrease in enantioselection (Table 2, entry 6) were observed when using the complex **6b** based on (1*R*,2*R*)-1,2-di-*tert*-butyletylenediamine, the ligand having the same sense of chirality as the ones discussed above. This is caused by the change in the conformation of the complex (Scheme 4). The reason is that the *tert*-butyl groups at the 1,2-positions cannot adopt the pseudoequatorial orientation because of steric reasons, and the predominating conformer B promotes formation of the second enantiomer. Both our observations and the X-ray structure of this complex[32] support the proposed stereochemical model.

3. Conclusion

Summing up, we have developed a novel method for the enantioselective allylation of aldehydes with tin allylating reagents, catalyzed by chromium–salen complexes. The reaction is highly reproducible and not very sensitive to external factors such as oxygen or moisture and requires only 1–2 mol % of the catalyst. The yields are good, although the enantioselectivites at this stage of our studies are moderate (usually 50–79% ee). For active aldehydes such as glyoxylates and glyoxals, the allylation works well under ambient conditions even with no solvents and on large scale. Allylation of simple aromatic and aliphatic aldehydes requires application of a high-pressure technique.

4. Experimental

4.1. General remarks

All reported NMR spectra were recorded in $CDCl_3$ using a Varian Gemini spectrometer at 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR). Chemical shifts of ^{1}H NMR are reported as δ values relative to TMS peak defined at δ=0.00. Chemical shifts of ^{13}C NMR are reported as δ values relative to $CDCl_3$ peak defined at δ=77.0. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; dt, doublet of triplets; m, multiplet. High resolution mass spectra (HRMS) were recorded on a AMD 604 or Mariner PE Biosystems unit using the EI or ESI technique, respectively. Optical rotations were measured using a JASCO DIP-360 polarimeter. Analytical TLC was carried out on commercial plates coated with 0.25 mm of Merck Kieselgel 60. Preparative flash silica chromatography was performed using Merck Kieselgel 60 (230–400 mesh). Enantiomeric excesses of the products were determined using GC and HPLC techniques. GC analyses were carried out on Trace 2000 GC (Thermo Finnigan) apparatus equipped with a flame ionization detector (FID) and a chiral capillary β-dex 120 column (permethyl-β-cyclodextrin, 30 m×0.25 mm I.D. Supelco, Bellefonte, USA) employing nitrogen as a carrier gas. Data were collected under the following conditions: pressure of nitrogen—100 kPa, injector temperature—200 °C, detector temperature—250 °C. The oven temperature varied according to types of products (vide infra). HPLC analyses were performed on chromatograph fitted with the diode array detector (DAD) and Chiracel OD-H column eluted with 4% *iso*-propanol in hexane.

4.2. Materials

All commercially available chemicals were used as received unless otherwise noted. Reagent-grade solvents were dried and distilled prior to use. (*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminochromium(III) chloride (**1a**) was purchased from Aldrich and used for the preparation of catalysts **1b** and **1c**.[5a] Remaining chromium(III) complexes (**5**–**8**) and salen complexes of other metals (**1d**–**m**) were prepared according to the known procedures, starting from appropriate salen ligand and metal salt.[4a,33] The salen ligands were synthesized according to the method described by Jacobsen et al.[34]

n-Butyl (**2a**) and *iso*-propyl (**2b**) glyoxylates were prepared by oxidative cleavage of the appropriate tartrate esters using $NaIO_4$ in water,[35] and *tert*-butyl glyoxylate (**2c**) was prepared by ozonolysis of di-*tert*-butyl fumarate.[36] The glyoxylates **2a**–**c** were distilled in the presence of P_2O_5 prior to use. Benzyl glyoxylate (**2d**) was prepared using $Pb(OAc)_4$ in CH_2Cl_2. Distillation of **2d** in the presence of P_2O_5 leads to decomposition. The alkyl glyoxals were prepared from hexanal, isovaleraldehyde, and pinacolone by oxidation with SeO_2/H_2O in boiling MeOH[37] and arylglyoxylates from acetophenone and acetylfuran in boiling dioxane.[38] The allyltributyltin reagents were prepared from bis(tributyltin)oxide and the appropriate allyl Grignard reagent according to the known procedure.[39] Allyltributyltin (**3**) can be purchased from Aldrich.

4.3. General procedure for the allylation of activated aldehydes

To a solution of metallosalen complex (usually 2 mol %) in appropriate solvent (usually 1 ml), 2-oxoaldehyde (**2**) (1 mmol) was added. After 10 min, allyltributyltin (**3**) (365 mg, 1.1 mmol) was dropped into the solution, and stirred at room temperature. After 3–4 h the reaction mixture was diluted with wet Et_2O, dried and after concentration subjected to chromatography using hexane/AcOEt 9:1→8:2 as an eluent.

4.4. General procedure for the high-pressure allylation

The 2-ml Teflon ampoule was charged with (salen)$CrBF_4$ **1b** (usually 13.7 mg, 2 mol %), ca. 1 ml of the solvent (usually CH_2Cl_2), followed by the aldehyde (usually 1 mmol) and allyltributyltin (1.1 equiv). Finally, the ampoule was filled up with solvent, closed, and placed in a high-pressure chamber, and the pressure was slowly increased to 10 kbar at 20 °C. After stabilization of the pressure, the reaction mixture was kept under these conditions for 24 h. After decompression, the reaction mixture was diluted with wet Et_2O, and dried over $MgSO_4$. After evaporation of solvents, the residue was chromatographed on a silica gel column using hexane/AcOEt as an eluent.

4.4.1. *n*-Butyl 2-hydroxypent-4-enoate (4a). $[\alpha]_D^{25}$ +2.0 (*c* 5.01, $CHCl_3$, 61% ee, major (*R*)-**4a**); bp 64–65 °C/2 mmHg; ^{1}H NMR ($CDCl_3$) δ=0.94 (t, *J*=7.3 Hz, 3H), 1.30–1.48 (m, 2H), 1.58–1.72 (m, 2H), 2.36–2.66 (m, 2H), 2.84 (d, *J*=5.9 Hz, 1H), 4.13–4.31 (m, 3H), 5.11–5.21 (m, 2H), 5.71–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=13.6 (CH_3), 19.0 (CH_2), 30.5 (CH_2), 38.7 (CH_2), 65.6 (CH_2), 69.9 (CH), 118.7 (CH_2), 132.5 (CH), 174.5 (C); IR (film) 3475, 2962, 1737, 1642, 1466, 1210, 1086, 918 cm^{-1}; HRMS calcd for $C_9H_{16}O_3$: 172.1099, found: 172.1104; GC: *T*=120 °C, $t_{R(R)\text{-}\mathbf{4a}}$=13.6 min, $t_{R(S)\text{-}\mathbf{4a}}$=14.1 min, or analyzed as a trifluoroacetate, *T*=100 °C, $t_{R(R)\text{-}\mathbf{4c}}$=14.3 min, $t_{R(S)\text{-}\mathbf{4c}}$=14.6 min.

4.4.2. *iso*-Propyl 2-hydroxypent-4-enoate (4b). Bp 78–80 °C/14 mmHg; ^{1}H NMR ($CDCl_3$) δ=1.27 (d, *J*=6.2 Hz, 3H), 1.28 (d, *J*=6.2 Hz, 3H), 2.35–2.65 (m, 2H), 2.86 (d, *J*=5.9 Hz, 1H), 4.17–4.26 (m, 1H), 5.10 (sept, *J*=6.2 Hz, 1H), 5.10–5.20 (m, 2H), 5.70–5.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=21.7 (CH_3), 21.8 (CH_3), 38.7 (CH_2), 69.6 (CH), 69.9 (CH), 118.6 (CH_2), 132.5 (CH), 174.0 (C); IR (film) 3474, 2982, 1732, 1642, 1467, 1219, 1107, 916 cm^{-1}; HRMS calcd for $C_8H_{14}O_3Na$: 181.0835, found: 181.0821; GC: *T*=110 °C, $t_{R(R)\text{-}\mathbf{4b}}$=9.6 min, $t_{R(S)\text{-}\mathbf{4b}}$=9.8 min, or analyzed as a trifluoroacetate, *T*=90 °C, $t_{R(R)\text{-}\mathbf{4c}}$=8.2 min, $t_{R(S)\text{-}\mathbf{4c}}$=8.4 min.

4.4.3. *tert*-Butyl 2-hydroxypent-4-enoate (4c). ^{1}H NMR ($CDCl_3$) δ=1.49 (s, 9H), 2.33–2.62 (m, 2H), 2.88 (d, *J*=5.9 Hz, 1H), 4.14 (dt, *J*=5.9, 4.8 Hz, 1H), 5.09–5.21 (m, 2H), 5.71–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=28.0 (3×CH_3), 38.8 (CH_2), 69.9 (CH), 82.5 (C), 118.4 (CH_2), 132.6 (CH), 173.7 (C); IR (film) 3477, 2960, 2932, 1739, 1642, 1464, 1370, 1289, 1159, 1108, 843 cm^{-1}; HRMS calcd for $C_9H_{16}O_3Na$: 195.0997, found: 195.1016; GC: *T*=120 °C, $t_{R(S)\text{-}\mathbf{4c}}$=8.2 min, $t_{R(R)\text{-}\mathbf{4c}}$=8.5 min, or analyzed as a trifluoroacetate, *T*=80 °C, $t_{R(R)\text{-}\mathbf{4c}}$=14.5 min, $t_{R(S)\text{-}\mathbf{4c}}$=15.0 min.

4.4.4. Benzyl 2-hydroxypent-4-enoate (4d). ^{1}H NMR ($CDCl_3$) δ=2.38–2.50 (m, 1H), 2.52–2.67 (m, 1H), 2.84 (d, *J*=6.0 Hz, 1H), 4.28–4.37 (m, 1H), 5.06–5.18 (m, 2H), 5.22 (s, 2H), 5.69–5.89 (m, 1H), 7.35–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=38.6 (CH_2), 67.4 (CH_2), 70.0 (CH), 118.8 (CH_2), 128.4 (2×CH), 128.6 (CH), 128.7 (2×CH), 132.3 (CH), 135.1 (C), 174.2 (C); IR (film) 3464, 3068, 2951, 1738, 1642, 1456, 1214, 1199, 1134, 1083, 919, 698 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_3Na$: 229.0841, found: 229.0813; GC: analyzed as a isopropylidene derivative of pent-4-ene-1,2-diol; hydroxyester **4d** was reduced by $LiAlH_4$ followed by protection with acetone in the presence of TsOH, *T*=90 °C, $t_{R(R)}$=7.3 min, $t_{R(S)}$=7.5 min.

4.4.5. Chemical correlation of 4a–d with (*R*)-1,2-pentanediol. A mixture of *n*-butyl 2-hydroxypent-4-enoate (**4a**) (350 mg, 2 mmol) (obtained in the reaction catalyzed by (1*R*,2*R*)-**1b**), Pd/C (50 mg) in MeOH (20 ml) was stirred under H_2 for 12 h. After that time the catalyst was filtered off through a short pad of Celite and the filtrate concentrated to yield 354 mg (quant.) of *n*-butyl 2-hydroxy-pentanoate. The crude product was dissolved in THF (2 ml) and added to the stirred suspension of $LiAlH_4$ (90 mg, 2.4 mmol) in THF (5 ml). Then the mixture was refluxed for 2 h, cooled to rt, and the excess of $LiAlH_4$ was decomposed with 10% water in THF and aqueous NaOH. The resulting mixture was extracted with Et_2O (3×15 ml), washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography to give 133 mg (1.3 mmol, 64%) of the colorless oil. $[\alpha]_D^{22}$ +11.4

(*c* 2.8, EtOH, 61% ee), lit.[17a]: $[\alpha]_D^{20}$ −15.5 (*c* 0.81, EtOH) for (*S*)-isomer.

4.4.6. 4-Hydroxynon-1-en-5-one (4e). ^{1}H NMR ($CDCl_3$) δ=0.92 (t, *J*=7.2 Hz, 3H), 1.24–1.42 (m, 2H), 1.54–1.68 (m, 2H), 2.30–2.42 (m, 1H), 2.43–2.52 (m, 2H), 2.56–2.70 (m, 1H), 3.52 (d, *J*=5.1 Hz, 1H), 4.21–4.29 (m, 1H), 5.09–5.20 (m, 2H), 5.68–5.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=13.8 (CH_2), 22.3 (CH_2), 25.5 (CH_2), 37.9 (CH_2), 38.2 (CH_2), 75.8 (CH), 118.4 (CH_2), 132.5 (CH), 211.5 (C); IR (film) 3425, 2960, 1714, 1404, 1181, 920 cm^{-1}; HRMS calcd for $C_9H_{16}O_2$: 156.1150, found: 156.1141; GC: *T*=130 °C, t_{R1}=9.4 min, t_{R2}=9.8 min.

4.4.7. 4-Hydroxy-2-methylhept-6-en-3-one (4f). ^{1}H NMR ($CDCl_3$) δ=1.13 (dd, *J*=6.8, 6.8 Hz, 6H), 2.29–2.45 (m, 1H), 2.56–2.70 (m, 1H), 2.84 (sept, *J*=6.8 Hz, 1H), 3.51 (d, *J*=5.4 Hz, 1H), 4.42 (ddd, *J*=6.4, 5.4, 4.7 Hz, 1H), 5.09–5.20 (m, 2H), 5.68–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=16.9 (CH_3), 19.1 (CH_3), 35.8 (CH), 37.9 (CH_2), 73.9 (CH), 118.0 (CH_2), 132.3 (CH), 214.9 (C); IR (film) 3464, 2971, 1710, 1627, 1468, 1385, 1024, 920 cm^{-1}; HRMS calcd for $C_8H_{14}O_2$: 142.0994, found: 142.0995; *T*=120 °C, t_{R1}=9.1 min, t_{R2}=9.4 min.

4.4.8. 4-Hydroxy-2,2-dimethylhept-6-en-3-one (4g). ^{1}H NMR ($CDCl_3$) δ=1.22 (s, 9H), 2.18–2.34 (m, 1H), 2.50–2.64 (m, 1H), 3.22 (d, *J*=8.1 Hz, 1H), 4.59 (ddd, *J*=8.1, 7.1, 3.8 Hz, 1H), 5.08–5.19 (m, 2H), 5.69–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=26.7 (3×CH_3), 39.2 (CH_2), 42.8 (C), 71.8 (CH), 118.3 (CH_2), 132.8 (CH), 216.9 (C); IR (film) 3462, 2969, 1704, 1480, 1053, 971, 917 cm^{-1}; HRMS calcd for $C_9H_{16}O_2$: 156.1150, found: 156.1143; GC: *T*=120 °C, t_{R1}=8.3 min, t_{R2}=8.6 min.

4.4.9. 2-Hydroxy-1-phenylpent-4-en-1-one (4h). ^{1}H NMR ($CDCl_3$) δ=2.28–2.43 (m, 1H), 2.61–2.75 (m, 1H), 3.74 (d, *J*=6.6 Hz, 1H), 4.96–5.12 (m, 2H), 5.17 (dt, *J*=6.6, 4.1 Hz, 1H), 5.70–5.91 (m, 1H), 7.46–7.68 (m, 3H), 7.88–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=40.0 (CH_2), 72.6 (CH), 118.4 (CH_2), 128.5 (2×CH), 128.9 (2×CH), 132.4 (CH), 133.7 (C), 134.0 (CH), 201.2 (C); IR (film) 3458, 2921, 1682, 1598, 1450, 1263, 1073, 963, 691 cm^{-1}; HRMS calcd for $C_{11}H_{12}O_2$: 176.0837, found: 176.0841; enantiomeric excess determined by HPLC (Chiracel OD-H column, hexane/*i*-PrOH, 96:4, flow rate 1.0 ml/min, λ=240 nm) t_{R1}=7.7 min, t_{R2}=9.2 min.

4.4.10. 1-(Furan-2-yl)-2-hydroxypent-4-en-1-one (4i). ^{1}H NMR ($CDCl_3$) δ=2.40–2.56 (m, 1H), 2.65–2.79 (m, 1H), 3.50 (d, *J*=6.8 Hz, 1H), 4.92 (dt, *J*=6.8, 4.1 Hz, 1H), 5.03–5.14 (m, 2H), 5.72–5.93 (m, 1H), 6.61 (dd, *J*=3.6, 1.7 Hz, 1H), 7.34 (dd, *J*=3.6, 0.6 Hz, 1H), 7.66 (dd, *J*=1.7, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=39.7 (CH_2), 72.9 (CH), 112.6 (CH), 118.5 (CH_2), 119.0 (CH), 132.5 (CH), 147.1 (CH), 150.2 (C), 189.6 (C); IR (film) 3448, 2953, 1726, 1660, 1437, 1279, 1171, 986 cm^{-1}; HRMS calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0622; GC: *T*=130 °C, t_{R1}=16.5 min, t_{R2}=17.3 min.

4.4.11. *n*-Butyl 2-hydroxy-4-methylpent-4-enoate (16). ^{1}H NMR ($CDCl_3$) δ=0.95 (t, *J*=7.2 Hz, 3H), 1.30–1.49 (m, 2H), 1.58–1.73 (m, 2H), 1.80 (br s, 3H), 2.30–2.43 (m, 1H), 2.48–2.59 (m, 1H), 2.77 (d, *J*=5.8 Hz, 1H), 4.19 (t, *J*=6.6 Hz, 2H), 4.28–4.38 (m, 1H), 4.80–491 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=13.6 (CH_3), 19.0 (CH_2), 22.5 (CH_3), 30.6 (CH_2), 42.7 (CH_2), 65.5 (CH_2), 69.1 (CH), 113.9 (CH_2), 140.9 (C), 174.8 (C); IR (film) 3483, 2961, 1735, 1649, 1458, 1202, 1102, 893 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_3$: 186.1256, found: 186.1261; GC: analyzed as a trifluoroacetate, *T*=100 °C, t_{R1}=20.0 min, t_{R2}=20.6 min.

Homoallylic alcohols **11a–l**, **14**, **15**, and **17** are known and their NMR data are in agreement with those described in literature. In some cases the absolute configuration of the obtained homoallylic alcohols (**11a**, **11c**, **11i**, **11k**, and **11l**) was confirmed via measurement of optical rotation and comparison with literature data.

The enantiomeric excesses of the investigated homoallyl alcohols **11a–l** were determined by GC employing a capillary chiral β-dex 120 column, either directly or after derivatization. Alcohol **11k** was analyzed directly, **11a**, **11b**, **11d**, **11e**, **11f**, **11g**, **11h**, and **11j** as their *O*-trimethylsilyl derivatives, **11c** as an acetate, **11i** as a trifluoroacetate and **11l** as an isopropylidene derivative of pent-4-ene-1,2-diol.

Chromatographic parameters of enantioseparation of homoallylic alcohols or their derivatives are given in Table 8.

Table 8. Chromatographic parameters of enantioseparation of homoallylic alcohols **11a–l**

Compound	R	OPG	*T* (°C)	t_{R1} (min)	t_{R2} (min)
11a	Furyl	OTMS	85	18.6 (*R*)	19.1 (*S*)
11b	5-Methylfuryl	OTMS	90	24.6	25.2
11c	Ph	OAc	110	36.7 (*S*)	37.2 (*R*)
11d	4-ClC_6H_4	OTMS	125	25.6	26.3
11e	2-ClC_6H_4	OTMS	110	26.8	27.5
11f	4-$O_2NC_6H_4$	OTMS	150	40.7	41.7
11g	*n*-C_4H_9	OTMS	75	12.4	12.7
11h	Pr^i	OTMS	75	6.9	7.2
11i	*c*-C_6H_{11}	O_2CCF_3	85	27.7 (*S*)	28.3 (*R*)
11j	Bu^t	OTMS	80	9.2	9.8
11k	PhCH=CH	OH	155	27.5 (*R*)	28.2 (*S*)
11l	Ph_3COCH_2	[a]	90	7.3 (*R*)	7.5 (*S*)

[a] Analyzed as a isopropylidene derivative of pent-4-ene-1,2-diol.

Chromatographic parameters of enantioseparation of methyl-substituted homoallylic alcohols:

14[13]—analyzed as a isopropylidene derivative of 3-methylpent-4-ene-1,2-diol: *T*=80 °C, $t_{R1(syn)}$=17.9 min, $t_{R2(syn)}$=18.3 min, $t_{R1(anti)}$=19.2 min, $t_{R2(anti)}$=20.0 min.
15—analyzed as a *O*-allylated alcohol: *T*=80 °C, $t_{R1(syn)}$=41.3 min, $t_{R2(syn)}$=41.9 min, $t_{R1(anti)}$=44.9 min, $t_{R2(anti)}$=45.9 min.
17—analyzed as an OTMS protected alcohol: *T*=90 °C, t_{R1}=22.4 min, t_{R2}=23.1 min.

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Synthesis of naturally occurring polyacetylenes via a bis-silylated diyne

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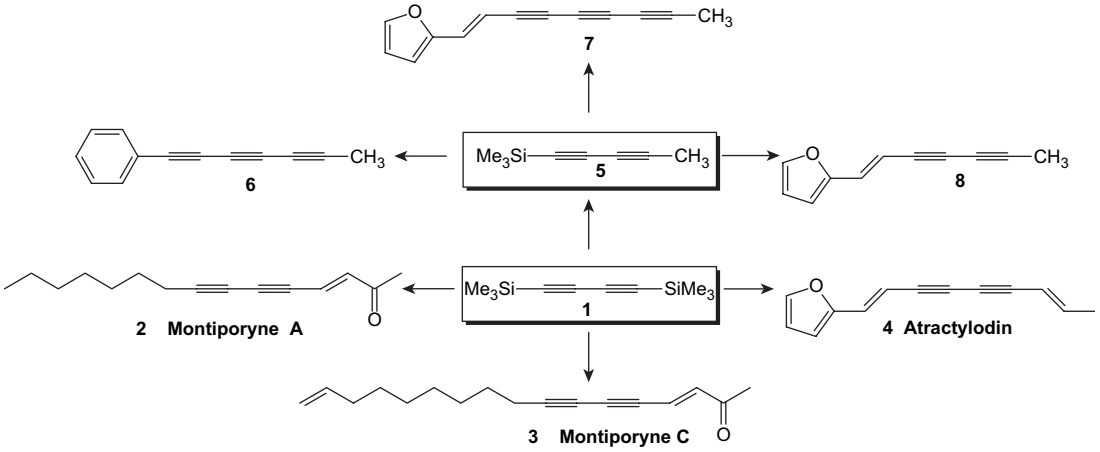
Abstract—A straightforward synthesis of a series of naturally occurring polyacetylenes has been developed, including the montiporynes A and C, possessing cytotoxic activity against several human solid tumor cells, the atractylodin, with antibiotic activity against *Escherichia coli*, and triynes, which display insecticidal activities, starting from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.

1. Introduction

Polyynes and acetylenic arrays are readily found in a series of natural products and exhibit a broad distribution in plant species[1] and stony corals[2] and display a wide range of biological activity for their antibacterial,[3] antifungal,[3,4] and pesticidal properties.[5] In particular the montiporynes,[6] possessing cytotoxic activity against human solid tumor cells, have been isolated from stony corals *Montipora* sp., whereas atractylodin, isolated from the roots of *Atractylis cancellata*,[7] is phototoxic and antibiotic against *Escherichia coli*.[8] Moreover, other acetylenic products, with a conjugated triyne structure,[1,8] isolated from various plant species, revealed to be extremely phototoxic toward mosquito larvae. Consequently, the search for improved synthetic methodologies for well-defined polyynes continues to expand.

We have recently reported successfully the applications of our methodology,[9] which led to the synthesis of a variety of unsymmetrically substituted conjugated diynes, to the preparation of a series of natural diacetylenic compounds, such as xerulins,[10] which are potent inhibitors of the biosynthesis of cholesterol, montiporic acids,[11] possessing antibacterial and cytotoxic properties, and virol C and 1-dehydroxyvirol A,[12] congeners of cicutoxin and isolated from *Cicuta virosa*. In connection with our ongoing work, we now wish to report the total synthesis of a series of naturally occurring polyacetylenes.

As reported in Scheme 1, we have devised a common strategy for the preparation of all these naturally occurring acetylenes. In particular the synthesis of the montiporynes A, C (**2**, **3**)[6] and the atractylodin **4**[8] can be realized starting



Scheme 1.

Keywords: Silicon and compounds; Polyacetylenes; Coupling reactions; Bioactive products.
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directly from the same bis-silylated diyne **1**, whereas the precursor for the synthesis of compounds **6**–**8**[8] can be achieved from the mono-silylated pentadiyne **5**.

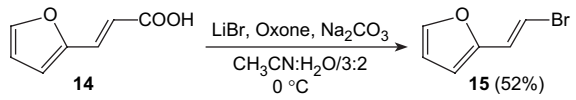
2. Results and discussion

The synthetic approach leading to the montiporynes **2**, **3** and to atractylodin **4** was based upon the selective and sequential substitution of the two silyl groups of the diyne **1**. Indeed, the montiporynes A **2** and C **3** differ in the aliphatic chain linked to the diyne moiety, a *n*-heptyl group for montiporyne A and a 8-nonenyl group for montiporyne C, and, therefore, the same strategy has been devised for the synthesis of both the montiporynes.

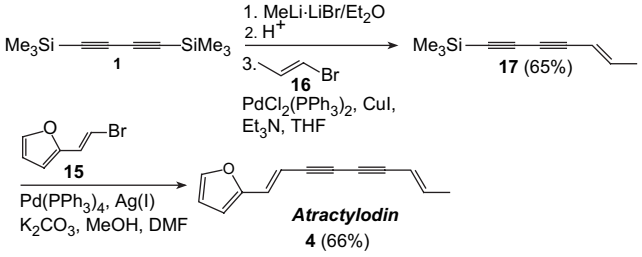
As depicted in Scheme 2, we started with a coupling reaction between the readily available iodides **9** or **10** and the lithium salt of the mono-silylated terminal diyne, obtained by selective desilylation of the diyne **1** with MeLi–Libr complex.[13] The coupling products were desilylated with K_2CO_3 in MeOH leading to the diyne **11** in 69% yield or to the enediyne **12** in 57% yield. Finally, a Sonogashira[14] cross-coupling reaction of the diyne **11** with the bromovinyl ketone **13**[15] of *E*-configuration led to the montiporyne A in 77% yield, whereas the reaction of the enediyne **12** with the same halide **13** led to the montiporyne C in 71% yield.

Following the same synthetic approach, in order to prepare atractylodin **4**, it was necessary to form the appropriate halovinyl intermediate possessing a furyl moiety. Thus, (Scheme 3), the bromoderivative **15** was synthesized, through modification of literature procedures,[16–18] in 52% yield (*E*:*Z*≥85:15) by halodecarboxylation of commercially available (2*E*)-3-(2-furyl)acrylic acid **14**.

Therefore, (Scheme 4), we began from diyne **1**, which was selectively desilylated with the MeLi–LiBr complex. The mono-silylated diyne was isolated and reacted with (*E*)-1-bromopropene **16** in the presence of a Pd(II) catalyst, leading to compound **17** in an overall 65% yield.[10] A further and



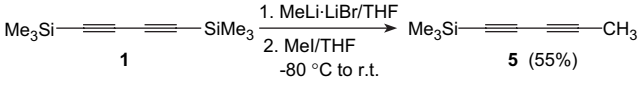
Scheme 3.



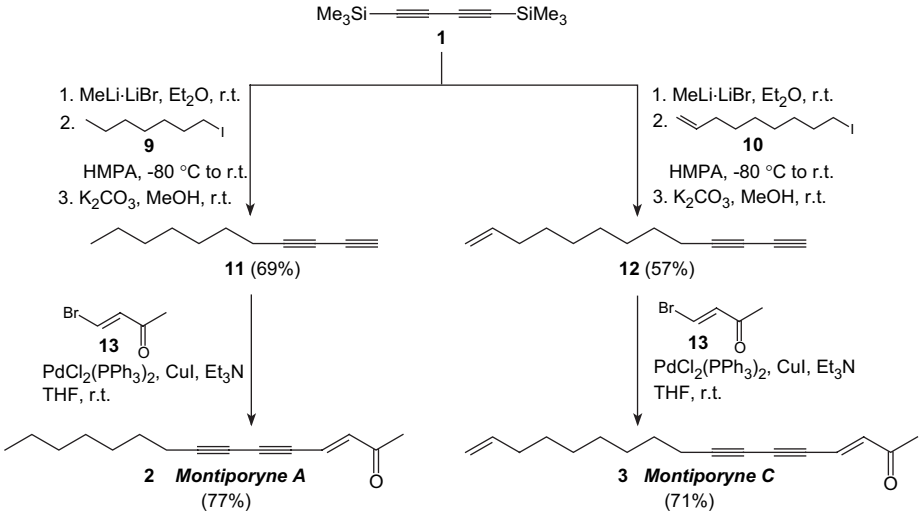
Scheme 4.

direct cross-coupling reaction[9,12,19] of the silylated enediyne **17** with the bromoderivative **15** in the presence of a Pd(0) catalyst led to atractylodin **4** in 66% yield. It is noteworthy that, notwithstanding the ≥85:15 mixture of compound **15**, essentially all *E* product **4** was isolated by chromatography.

As reported in Scheme 1, the key intermediate for the synthesis of triynes **6**, **7**, and enediyne **8**, a potential mosquito larvicidal agent, is mono-silylated pentadiyne **5**. This intermediate was readily prepared[20,21] in 55% yield (Scheme 5) by a coupling reaction between the lithium salt of the diyne **1** and methyl iodide.



Scheme 5.



Scheme 2.

The strategy employed for the synthesis of the triynes **6** and **7** was based upon the conversion of this mono-silylated diyne **5** into the 1-bromo-1,3-pentadiyne, which was subjected to a coupling reaction with the appropriate acetylenic intermediates, the phenylacetylene for the synthesis of compound **6** and the 2-[(1*E*)-but-1-en-3-ynyl]furan for the synthesis of compound **7**. The furyl intermediate was prepared according to Scheme 6, through a coupling reaction of bromovinylfuran **15** with trimethylsilylacetylene, in the presence of a Pd(II) catalyst, which led to the mono-silylated enyne **18**, and subsequently, after a desilylation reaction with K_2CO_3 in MeOH, to the desired enyne **19**.

Therefore, the synthesis of all acetylenic products **6**–**8** is outlined in Scheme 7.

Both triynes **6** and **7** were obtained following the same reaction sequence. In particular the diyne **5** was converted by NBS, in the presence of AgF in acetonitrile,[22] to the corresponding bromoderivative, which, without isolation, was directly coupled with phenylacetylene **20**, in the presence of a Pd(0) catalyst, to afford the triyne **6** in an overall 60% yield, or with the enyne **19** to lead to triyne **7** in an overall 72% yield. Finally, the enediyne **8** was obtained in 65% yield by a direct coupling reaction between the silylated diyne **5** and the bromovinyl derivative **15** in the presence of a Pd(0) catalyst.

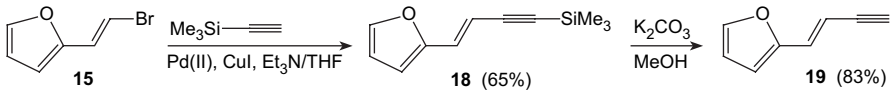
In summary, our synthetic approach to naturally occurring acetylenes compares favorably with other procedures. A special advantage of our strategy is represented by the possibility of preparing different acetylenes starting from the same compound and following the same reaction sequence. Moreover, the simplicity of the operations involved and the ready availability of the starting materials are additional features making the procedure useful.

3. Experimental

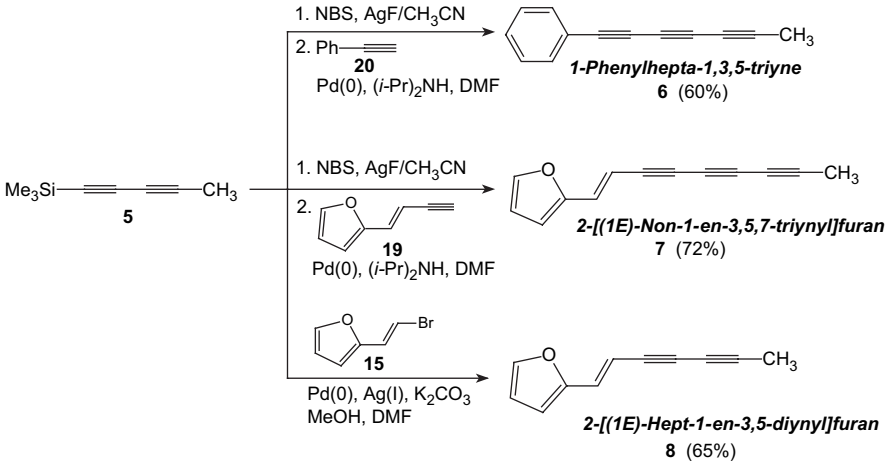
Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a J & W capillary column (DB-1301, 30 m×0.25 mm i.d.). GC/mass spectrometry analysis was performed on a Shimadzu GCMS-QP5000 gas chromatograph–mass spectrometer equipped with a Zebron capillary column (methyl polysiloxane, 30 m×0.25 mm i.d.). ^{1}H NMR spectra were recorded in deuterochloroform or CD_3OD on a Bruker AM 500 spectrometer at 500 MHz. ^{13}C NMR spectra were recorded in deuterochloroform or CD_3OD on a Bruker AM 500 spectrometer at 125.7 MHz. IR spectra were recorded on a Perkin–Elmer FTIR—Spectrum One and on a Shimadzu IR Prestige 21 spectrometers. Solvents were dried before use as follows: tetrahydrofuran was distilled from sodium, *N*,*N*-dimethylformamide and acetonitrile were distilled over molecular sieves. Melting points (uncorrected) were determined on a Reichert Microscope. The halide 9-iodonon-1-ene **10** was synthesized from commercial 1,9-nonandiol using literature procedures.[23,24]

3.1. General procedure for the synthesis of montiporynes A 2 and C 3

MeLi–LiBr complex (1.5 M) in ether (1.1 equiv) was added, under nitrogen, to a THF (0.5 M) solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.0 equiv) at room temperature. After complete monodesilylation (3–5 h), the reaction mixture was cooled to −80 °C. A solution of 1-iodoheptane **9** or 9-iodonon-1-ene **10** (1.1 equiv) in THF (1.1 M) and HMPA (2.0 equiv) were slowly dropped at the same temperature, then the mixture was slowly brought to room



Scheme 6.



Scheme 7.

temperature. After reaction completion (18 h), MeOH (10 mL) and K_2CO_3 (1.2 equiv) were added, then the reaction mixture was stirred for 1 h at room temperature. A saturated aqueous solution of NH_4Cl (100 mL) was added and then the reaction mixture extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (3×50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography leading to the compounds **11** or **12**. A solution of diyne **11** or **12** (1.0 equiv) in THF (0.2 M) was added at room temperature, under nitrogen, to a stirred mixture of **13** (1.0 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.04 equiv), and Et_3N (1.5 equiv) in THF (0.2 M). After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography leading to title compounds **2** and **3**.

3.1.1. Undeca-1,3-diyne (11).[25] Compound **11** was prepared from 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.00 g, 5.16 mmol) and 1-iodoheptane **9** (1.28 g, 5.67 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) gave compound **11** (0.527 g, 69% yield) as a pale yellow oil. ν_{max} (neat) 3310, 2955, 2930, 2857, 2297, 2224, 1458, 1425, 1375, 1244, 613; δ_H (500 MHz, $CDCl_3$) 2.22 (td, J=7.0, 1.1 Hz, 2H), 1.92 (t, J=1.1 Hz, 1H), 1.51 (quintet, J=7.0 Hz, 2H), 1.39–1.32 (m, 2H), 1.31–1.20 (m, 6H), 0.86 (t, J=6.9 Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 78.5, 68.5, 64.6, 64.4, 31.6, 28.7, 28.7, 28.0, 22.6, 19.0, 14.0; MS *m/z* 133 (1), 119 (5), 105 (29), 91 (68), 79 (30), 78 (31), 77 (18), 67 (14), 65 (16), 63 (31), 55 (48), 51 (24), 43 (62), 41 (100%).

3.1.2. Tridec-12-en-1,3-diyne (12). Compound **12** was prepared from 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.00 g, 5.16 mmol) and 9-iodonon-1-ene **10** (1.429 g, 5.67 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) gave compound **12** (0.512 g, 57% yield) as a pale yellow oil. [Found: C, 89.50; H, 10.43. $C_{13}H_{18}$ requires C, 89.59; H, 10.41%]; ν_{max} (neat) 3308, 3076, 2974, 2928, 2855, 2297, 2224, 1640, 1458, 1425, 1246, 995, 910, 617; δ_H (500 MHz, $CDCl_3$) 5.78 (ddt, J=17.1, 10.2, 6.7 Hz, 1H), 4.97 (ddt, J=17.1, 2.2, 1.6 Hz, 1H), 4.91 (ddt, J=10.2, 2.2, 1.2 Hz, 1H), 2.23 (td, J=7.1, 1.1 Hz, 2H), 2.05–1.99 (m, 2H), 1.93 (t, J=1.1 Hz, 1H), 1.51 (quintet, J=7.1 Hz, 2H), 1.41–1.32 (m, 4H), 1.31–1.25 (m, 4H); δ_C (125.7 MHz, $CDCl_3$) 139.0, 114.2, 78.4, 68.5, 64.7, 64.4, 33.7, 28.9, 28.8, 28.8, 28.7, 27.9, 18.9; MS *m/z* 145 (3), 131 (11), 117 (19), 105 (15), 91 (51), 79 (24), 78 (15), 77 (16), 67 (22), 65 (14), 63 (23), 55 (35), 51 (20), 41 (100%).

3.1.3. (3*E*)-Pentadec-3-en-5,7-diyn-2-one (2) (Montiporyne A).[6] Compound **2** was prepared from undeca-1,3-diyne **11** (0.423 g, 2.86 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 5% ethyl acetate/petroleum ether) gave compound **2** (0.476 g, 77% yield) as a yellow oil. ν_{max} (neat) 2955, 2928, 2857, 2228, 2139, 1694, 1676, 1589, 1466, 1424, 1360, 1248, 1171, 957; δ_H (500 MHz, CD_3OD) 6.76 (dt, J=16.1, 1.0 Hz, 1H), 6.61 (d, J=16.1 Hz, 1H), 2.44 (td, J=7.0, 1.0 Hz, 2H), 2.31 (s, 3H), 1.61 (quintet, J=7.0 Hz, 2H), 1.50–1.42 (m, 2H), 1.41–1.31 (m, 6H), 0. 96 (t, J=6.9 Hz, 3H); δ_C (125.7 MHz, CD_3OD) 199.3, 141.6, 124.5, 90.8, 85.3, 73.0, 65.9, 33.2, 30.2, 30.2, 29.5, 27.8, 24.0, 20.5, 14.7; MS *m/z* 216 (M^+, <1), 187 (1), 173 (2), 159 (2), 145 (4), 131 (6), 117 (4), 115 (4), 105 (3), 103 (3), 91 (7), 77 (5), 63 (4), 62 (3), 55 (7), 43 (100), 41 (17%).

3.1.4. (3*E*)-Heptadeca-3,16-dien-5,7-diyn-2-one (3) (Montiporyne C).[6] Compound **3** was prepared from tridec-12-en-1,3-diyne **12** (0.341 g, 1.96 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 5% ethyl acetate/petroleum ether) gave compound **3** (0.337 g, 71% yield) as a yellow oil. ν_{max} (neat) 3075, 2928, 2855, 2228, 2139, 1694, 1676, 1638, 1589, 1458, 1424, 1360, 1248, 1234, 1171, 957, 910; δ_H (500 MHz, CD_3OD) 6.76 (dt, J=16.1, 1.1 Hz, 1H), 6.61 (d, J=16.1 Hz, 1H), 5.85 (ddt, J=17.1, 10.2, 6.7 Hz, 1H), 5.03 (ddt, J=17.1, 2.2, 1.5 Hz, 1H), 4.96 (ddt, J=10.2, 2.2, 1.2 Hz, 1H), 2.44 (td, J=7.1, 1.1 Hz, 2H), 2.31 (s, 3H), 2.13–2.07 (m, 2H), 1.61 (quintet, J=7.1 Hz, 2H), 1.50–1.41 (m, 4H), 1.41–1.35 (m, 4H); δ_C (125.7 MHz, CD_3OD) 199.3, 141.5, 140.3, 124.5, 115.1, 90.8, 85.3, 73.0, 65.9, 35.1, 30.3, 30.3, 30.3, 30.2, 29.5, 27.8, 20.5; MS *m/z* 199 (2), 185 (1), 159 (2), 145 (4), 143 (3), 131 (5), 129 (5), 117 (5), 115 (4), 105 (3), 103 (3), 95 (3), 91 (8), 79 (5), 77 (6), 67 (6), 55 (10), 43 (100), 41 (29%).

3.2. Synthesis of the intermediates 15, 18, 19

3.2.1. 2-[(*E*)-2-Bromovinyl]furan (15).[16–18] Lithium bromide (3.74 g, 43.48 mmol) and sodium carbonate (1.54 g, 14.49 mmol) were added to a stirred solution of carboxylic acid **14** (2 g, 14.49 mmol) in 50 mL of CH_3CN–H_2O (3:2 v/v) at 0 °C, and then followed by the addition in one portion of a solution of Oxone (4.45 g, 7.25 mmol) in 24 mL of H_2O. After reaction completion (5 min), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaOH (10%, 3×50 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by percolation on a florisil column (petroleum ether) affording 0.65 g (52% yield) of compound **15** as a yellow oil. ν_{max} (neat) 3078, 1629, 1477, 1014, 926, 788, 771, 737, 689; δ_H (500 MHz, $CDCl_3$) (*E*+*Z* isomer): (*E* isomer) 7.37 (d, J=1.8 Hz, 1H), 6.89 (d, J=13.9 Hz, 1H), 6.72 (d, J=13.9 Hz, 1H), 6.38 (dd, J=3.3, 1.8 Hz, 1H), 6.26 (d, J=3.3 Hz, 1H), (*Z* isomer)[26] 7.44 (d, J=1.8 Hz, 1H), 7.10 (d, J=3.3 Hz, 1H), 7.06 (d, J=8.3 Hz, 1H), 6.50–6.47 (m, 1H), 6.31 (d, J=8.3 Hz, 1H); δ_C (125.7 MHz, $CDCl_3$) 151.1, 142.6, 125.4, 111.3, 108.6, 105.3; MS *m/z* 174 (M^{+2}, 55), 172 (M^+, 58), 145 (10), 143 (10), 119 (3), 117 (3), 93 (12), 87 (7), 86 (7), 65 (100), 64 (15), 63 (34), 62 (15), 61 (8), 50 (8%).

3.2.2. 2-[(1*E*)-4-Trimethylsilylbut-1-en-3-ynyl]furan (18). A solution of trimethylsilylacetylene (0.445 g, 4.528 mmol) in THF (5 mL) was added at room temperature, under nitrogen, to a stirred mixture of bromovinylfuran **15** (0.649 g, 3.773 mmol), $PdCl_2(PPh_3)_2$ (0.053 g,

0.075 mmol), CuI (0.0287 g, 0.151 mmol), and Et_3N (0.573 g, 5.660 mmol) in THF (7 mL). After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with H_2O (3×20 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.47 g of compound **18** (65% yield) as a pale yellow oil. [Found: C, 69.50; H, 7.36. $C_{11}H_{14}OSi$ requires C, 69.42; H, 7.41%]; ν_{max} (neat) 2959, 2897, 2115, 1481, 1251, 1086, 1065, 1015, 944, 844, 760, 738; δ_H (500 MHz, $CDCl_3$) 7.35 (d, J=1.8 Hz, 1H), 6.72 (d, J=16.0 Hz, 1H), 6.37 (dd, J=3.4, 1.8 Hz, 1H), 6.30 (d, J=3.4 Hz, 1H), 6.05 (d, J=16.0 Hz, 1H), 0.2 (s, 9H); δ_C (125.7 MHz, $CDCl_3$) 152.0, 143.1, 129.3, 111.8, 110.3, 106.1, 104.3, 97.7, –0.1; MS m/z 190 (M^+, 78), 175 (100), 160 (12), 147 (45), 145 (48), 131 (16), 116 (26), 115 (82), 105 (16), 91 (21), 88 (51), 75 (25), 73 (24), 67 (16), 59 (20), 53 (45), 45 (81), 43 (78%).

3.2.3. 2-[(1*E*)-But-1-en-3-ynyl]furan (19). K_2CO_3 (0.358 g, 2.589 mmol) was added to a MeOH solution (4 mL) of silylated compound **18** (0.41 g, 2.158 mmol). The reaction mixture was stirred for 1 h at room temperature, then quenched with H_2O (30 mL), and extracted with ethyl acetate (30 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum leading to compound **19** as a pale yellow oil; 0.212 g, yield 83%. [Found: C, 81.38; H, 5.10. C_8H_6O requires C, 81.34; H, 5.12%]; ν_{max} (neat) 3294, 2095, 1624, 1479, 1373, 1246, 1045, 1016, 947, 741; δ_H (500 MHz, $CDCl_3$) 7.36 (d, J=1.8 Hz, 1H), 6.75 (d, J=16.0 Hz, 1H), 6.49 (dd, J=3.4, 1.8 Hz, 1H), 6.33 (d, J=3.4 Hz, 1H), 6.01 (dd, J=16.0, 2.5 Hz, 1H), 3.07 (dd, J=2.5, 0.6 Hz, 1H); δ_C (125.7 MHz, $CDCl_3$) 151.7, 143.2, 130.1, 111.8, 110.4, 105.0, 82.8, 80.0; MS m/z 118 (M^+, 75), 90 (67), 89 (100), 64 (19), 63 (64), 62 (23), 59 (12), 51 (27), 50 (25), 45 (24), 40 (11%).

3.3. Synthesis of the atractylodin 4

3.3.1. (5*E*)-1-Trimethylsilyl-hept-5-en-1,3-diyne (17).[10] MeLi–LiBr complex (1.5 M) in ether (20.6 mL, 30.93 mmol) was added to an ether solution (40 mL) of 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (4 g, 20.57 mmol) at room temperature. After reaction completion (4 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl ether (3×20 mL). The organic extracts were washed with water (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The mono-silylated diyne 1-trimethylsilyl-1,3-butadiyne **1a** was purified by distillation (2.0 g, 79% yield). A THF solution (20 mL) of diyne **1a** (1.21 g, 9.92 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*E*)-1-bromopropene **18** (1.0 g, 8.26 mmol), Et_3N (1.25 g, 12.40 mmol), CuI (0.063 g, 0.33 mmol), and $Pd(PPh_3)_2Cl_2$ (0.116 g, 0.165 mmol) in THF (12 mL). After reaction completion (12 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with water (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography (petroleum ether) led to the title compound **17** as a yellow oil (1.1 g, 82% yield).

3.3.2. 2-[(1*E*,7*E*)-Nona-1,7-dien-3,5-diynyl]furan (4) (Atractylodin).[8] To a solution of bromovinylfuran **15** (0.238 g, 1.389 mmol) in anhydrous DMF (3.5 mL) at room temperature, under nitrogen, were successively added $Pd(PPh_3)_4$ (0.08 g, 0.0694 mmol), AgCl (0.0398 g, 0.278 mmol), and K_2CO_3 (1.533 g, 11.11 mmol). The resulting mixture was stirred for 5 min, then MeOH (0.355 g, 11.11 mmol) was added followed by a solution of mono-silylated enediyne **17** (0.225 g, 1.39 mmol) in anhydrous DMF (3.5 mL). The reaction mixture was warmed to 40 °C and stirred at same temperature. After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.17 g of compound **4** (66% yield) as a yellow solid (mp 49–51 °C). ν_{max} (KBr) 3133, 2964, 2929, 2852, 2194, 2126, 1616, 1475, 1440, 1261, 1096, 1016, 943, 802, 742; δ_H (500 MHz, $CDCl_3$) 7.37–7.35 (m, 1H), 6.77 (d, J=16.0 Hz, 1H), 6.40 (dd, J=3.4, 1.8 Hz, 1H), 6.35 (dd, J=3.4, 0.5 Hz, 1H), 6.31 (dq, J=15.8, 6.9 Hz, 1H), 6.09 (d, J=16.0 Hz, 1H), 5.61–5.50 (m, 1H), 1.81 (dd, J=6.9, 1.8 Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.9, 143.6, 143.5, 130.7, 112.1, 111.1, 109.9, 104.8, 81.9, 80.2, 77.2, 72.5, 18.9; MS m/z 182 (M^+, 100), 181 (14), 153 (46), 152 (89), 151 (21), 139 (15), 127 (13), 126 (13), 115 (12), 113 (8), 102 (9), 98 (8), 91 (7), 89 (8), 87 (14), 86 (10), 77 (21), 76 (55), 75 (23), 74 (22), 64 (26), 63 (36), 62 (14), 52 (11), 51 (32), 50 (18%).

3.4. Synthesis of compounds 5–8

3.4.1. 1-Trimethylsilyl-1,3-pentadiyne (5).[20,21] MeLi–LiBr complex (1.5 M) in ether (18.9 mL, 28.350 mmol) was slowly dropped, under nitrogen, to a THF solution (50 mL) of 1,4-bis(trimetilsilyl)-1,3-butadiyne **1** (5 g, 25.773 mmol) at room temperature. After complete monodesilylation (5 h), the reaction mixture was cooled to a −80 °C and a solution of methyl iodide (4 g, 28.350 mmol) in THF (40 mL) was slowly dropped at the same temperature, then the mixture was slowly brought to room temperature. After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl ether (3×30 mL). The organic extracts were washed with water (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 1.93 g of compound **5** (55% yield) as a pale yellow oil. ν_{max} (neat) 2961, 2232, 2113, 1251, 1196, 870, 844, 760; δ_H (500 MHz, $CDCl_3$) 1.92 (s, 3H), 0.17 (s, 9H); δ_C (125.7 MHz, $CDCl_3$) 88.5, 82.2, 75.5, 64.7, 4.0, −0.5; MS m/z 136 (M^+, 14), 121 (100), 107 (3), 105 (3), 93 (9), 91 (7), 79 (7), 77 (15), 53 (20), 43 (22%).

3.4.2. 1-Phenylhepta-1,3,5-triyne (6).[8,27] To a solution of the mono-silylated diyne **5** (0.345 g, 2.537 mmol) in anhydrous CH_3CN (4 mL) were added NBS (0.542 g, 3.044 mmol) and AgF (0.383 g, 3.044 mmol) in the dark. The resulting mixture was stirred for 1 h at room temperature; after reaction completion (1 h), the mixture was directly percolated on a florisil column with DMF (30 mL)

as eluent. To this mixture of bromodiyne in DMF, were added at room temperature, under nitrogen, $Pd(PPh_3)_4$ (0.147 g, 0.127 mmol) and *i*-Pr_2NH (0.51 g, 5.073 mmol) followed by a solution of phenylacetylene **20** (0.26 g, 2.537 mmol) in anhydrous DMF (3 mL). After reaction completion (70 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3×30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×30 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.25 g of compound **6** (overall 60% yield) as a white solid (mp 56–58 °C). ν_{max} (KBr) 2957, 2924, 2853, 2219, 1490, 1440, 1425, 1024, 756, 689, 525; δ_H (500 MHz, $CDCl_3$) 7.51–7.47 (m, 2H), 7.39–7.34 (m, 1H), 7.33–7.28 (m, 2H), 1.99 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 132.9, 129.5, 128.4, 121.1, 78.3, 75.2, 74.6, 67.4, 64.9, 58.9, 4.6; MS *m/z* 164 (M^+, 100), 163 (63), 138 (48), 137 (15), 110 (8), 98 (7), 88 (7), 87 (11), 86 (13), 82 (50), 74 (6), 69 (16), 67 (8), 63 (11), 55 (9), 51 (6), 50 (6%).

3.4.3. 2-[(1*E*)-Non-1-en-3,5,7-triynyl]furan (7).[8] To a solution of the mono-silylated diyne **5** (0.244 g, 1.797 mmol) in anhydrous CH_3CN (3 mL) were added NBS (0.384 g, 2.156 mmol) and AgF (0.272 g, 2.156 mmol) in the dark. The resulting mixture was stirred for 1 h at room temperature; after reaction completion (1 h), the mixture was directly percolated on a florisil column with DMF (21 mL) as eluent. To this mixture of bromodiyne in DMF, were added at room temperature, under nitrogen, $Pd(PPh_3)_4$ (0.104 g, 0.090 mmol) and *i*-Pr_2NH (0.363 g, 3.593 mmol) followed by a solution of the 2-[(1E)-but-1-en-3-ynyl]furan **19** (0.212 g, 1.797 mmol) in anhydrous DMF (2 mL). After reaction completion (70 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3×30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.233 g of compound **7** (overall 72% yield) as a pale yellow solid (mp 59–62 °C). ν_{max} (KBr) 2955, 2913, 2852, 2219, 2203, 2166, 1613, 1479, 1282, 1261, 1051, 938, 927, 804, 740; δ_H (500 MHz, $CDCl_3$) 7.37 (d, *J*=1.6 Hz, 1H), 6.83 (d, *J*=15.9 Hz, 1H), 6.41 (dd, *J*=3.4, 1.6 Hz, 1H), 6.39 (dd, *J*=3.4, 0.5 Hz, 1H), 6.03 (dd, *J*=15.9, 0.5 Hz, 1H), 1.98 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.6, 143.8, 132.3, 112.2, 111.7, 103.8, 79.0, 77.6, 75.1, 68.6, 65.0, 59.2, 4.6; MS *m/z* 180 (M^+, 100), 179 (6), 152 (38), 151(67), 150 (35), 126 (33), 102 (8), 100 (8), 99 (16), 98 (20), 90 (19), 87 (14), 86 (14), 77 (13), 76 (31), 75 (30), 74 (38), 63 (56), 62 (22), 51 (25), 50 (24%).

3.4.4. 2-[(1*E*)-Hept-1-en-3,5-diynyl]furan (8).[8] To a solution of bromovinylfuran **15** (0.214 g, 1.244 mmol) in anhydrous DMF (3 mL) at room temperature, under nitrogen, were successively added $Pd(PPh_3)_4$ (0.072 g, 0.0622 mmol), AgCl (0.0357 g, 0.2488 mmol), and K_2CO_3 (1.373 g, 9.953 mmol). The resulting mixture was stirred for 5 min, then MeOH (0.318 g, 9.953 mmol) was added followed by a solution of mono-silylated diyne **5** (0.169 g, 1.244 mmol) in anhydrous DMF (3 mL). The reaction mixture was warmed to 40 °C and stirred at same temperature. After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.126 g of compound **8** (65% yield) as a yellow oil. ν_{max} (neat) 3146, 3119, 3046, 2911, 2841, 2230, 2137, 1618, 1481, 1385, 1262, 1016, 941, 926, 883, 741; δ_H (500 MHz, $CDCl_3$) 7.36 (d, *J*=1.8 Hz, 1H), 6.76 (d, *J*=16.0 Hz, 1H), 6.39 (dd, *J*=3.4, 1.8 Hz, 1H), 6.33 (d, *J*=3.4 Hz, 1H), 6.03 (d, *J*=16.0 Hz, 1H), 1.99 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.9, 143.3, 130.7, 112.0, 110.8, 104.9, 81.4, 77.4, 73.8, 64.6, 4.7; MS *m/z* 156 (M^+, 100), 155 (19), 128 (32), 127 (51), 126 (18), 102 (40), 101 (12), 87 (8), 78 (27), 77 (25), 76 (17), 75 (25), 74 (20), 64 (21), 63 (39), 62 (17), 51 (82), 50 (57%).

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Deracemisation of β-hydroxy esters using immobilised whole cells of *Candida parapsilosis* ATCC 7330: substrate specificity and mechanistic investigation

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Abstract—Deracemisation of aryl substituted β-hydroxy esters by immobilised whole cells of *Candida parapsilosis* ATCC 7330 gave >99% ee and up to 75% yield of their corresponding (*S*)-enantiomers. Mechanistic investigation of the deracemisation reaction carried out using a deuterated substrate, ethyl 3-deutero-3-hydroxy-3-phenyl propanoate revealed that while the (*S*)-enantiomer remains unreacted the (*R*)-enantiomer undergoes enantioselective oxidation to its corresponding ketoester, which on complementary enantiospecific reduction gives the (*S*)-enantiomer in high yield and % ee.

1. Introduction

Optically pure β-hydroxy esters are important chiral synthons for the synthesis of numerous pharmaceuticals such as fluoxetine,[1] β-lactam antibiotics,[2] Tuckolide—an HMGCoA reductase-inhibitor[3] and dihydrokawain (a narcotic).[4] The amino derivative of a (*S*)-β-hydroxy ester is present in the side chain of Taxol®.[5] Ethyl 4-chloro-3-hydroxy butanoate is used in the preparation of L-carnitine, a nutraceutical.[6] Chiral β-hydroxy esters are also used as starting materials in the preparation of enantiomerically pure β-blockers, i.e., propranolol, alprenolol and 1-(isopropylamino)-3-*p*-methoxy-phenoxy-2-propanol.[7] The application of (*R*)-(−)-sodium β-hydroxy butanoate as a cerebral function improving agent on cerebral hypoxia, anoxia and ischeamia in mice and rats has been reported.[8] Both the enantiomers of ethyl 3-hydroxy butanoate and ethyl 3-hydroxy pentanoate are extremely useful in the synthesis of pheromones.[9] Optically pure β-hydroxy esters also play an important role in many biological reactions inside the human body.[10] With the varied applications of these molecules, there is much interest in their asymmetric synthesis. Asymmetric reduction and kinetic resolution are the two main biocatalytic approaches for the synthesis of these compounds. Asymmetric reduction of β-ketoesters by different microbial whole cells[11] and plant cells is known.[12] Engineered whole cells of baker's yeast are reported to carry out a highly stereoselective synthesis of α-unsubstituted and α-alkyl-β-hydroxy esters.[13] Kinetic resolution is widely used for the synthesis of optically pure β-hydroxy esters from racemic β-hydroxy esters.[14] The limited yield of each enantiomer (maximum 50%) and the formation of the 'unwanted' isomer are the major drawbacks in the resolution of a racemate. Deracemisation[15] is an attractive alternative approach to synthesise chiral β-hydroxy esters from their racemates in high ee and quantitative yield. Use of two-enzyme systems[16] and whole cells is known to deracemise secondary alcohols.[17] Azerad et al. used aged cultures of a local strain of *Geotrichum candidum* to deracemise ethyl 3-hydroxy butanoate into the (*R*)-enantiomer in 96% ee and 80% yield.[18] Nakamura et al. reported the stereoinversion of aliphatic β-hydroxy esters (methyl-3-hydroxy butanoate and methyl-3-hydroxy pentanoate) using *G. candidum* IFO 5767 to produce the (*R*)-enantiomers in 97–99% ee and 26–48% isolated yield.[15e] Deracemisation of β-hydroxy esters is restricted to the above examples, both of which use *G. candidum* for aliphatic β-hydroxy esters and the deracemised product is the (*R*)-antipode. Whole cells of *Candida parapsilosis* are a rich source of oxidoreductases[19] and different strains of this species are known to deracemise 1,2-diols[20] and 1,3-diols.[21] More recently, deracemisation of aryl and aryl substituted α-hydroxy esters by *C. parapsilosis* ATCC 7330 to the (*S*)-enantiomer [17] and asymmetric reduction of ethyl 4-chloro-3-oxo butanoate using genetically modified *C. parapsilosis* (IFO 1396) to the (*R*)-hydroxy ester in 99% ee and 95% yield[11c] were reported. We have previously reported the deracemisation of some racemic

Keywords: Deracemisation; β-Hydroxy esters; *Candida parapsilosis*; Mechanism.
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β-hydroxy esters using free and immobilised whole cells of *C. parapsilosis* ATCC 7330.[22] Here we report the deracemisation by immobilised *C. parapsilosis* ATCC 7330 (ICp) of 19 aryl and substituted aryl substrates with different electronic and steric effects. The substrate specificity of the biocatalyst and the investigated mechanism of deracemisation are discussed.

2. Results and discussion

2.1. Mechanistic investigation of deracemisation

The different mechanisms by which deracemisation can be carried out are (i) re-racemisation and repeated resolution, (ii) dynamic kinetic resolution and (iii) stereoinversion.[15a] Kato et al. reported the deracemisation of α-alkyl carboxylic esters, which involves enantioselective esterification, epimerization and then hydrolysis.[15b] All these deracemisation mechanisms share a common stereochemical phenomenon, i.e., one enantiomer of the substrate retains its configuration throughout the deracemisation process and the other enantiomer crosses the plane of symmetry (or inversion of configuration) to become product.[15a] Literature reports on the use of different strains of *C. parapsilosis* in the deracemisation of secondary alcohols reveal that oxidoreductases actively participate in the deracemisation by stereoinversion.[15c–e,20] Deracemisation of α-hydroxy esters by whole cells of *C. parapsilosis* ATCC 7330 also occurs via stereoinversion.[17] Mechanistic investigation of the deracemisation of β-hydroxy esters was done using ethyl 3-hydroxy-3-phenyl propanoate (**1**, Table 1). The deracemised product of racemic ethyl 3-hydroxy-3-phenyl propanoate (**1**) on HPLC analysis (reverse phase) showed the presence of ethyl 3-oxo-3-phenyl propanoate, along with acetophenone and 1-phenyl ethanol, which led us to propose and investigate the stereoinversion mechanism for deracemisation of β-hydroxy esters. In order to prove the proposed mechanism of this deracemisation reaction, the following substrates were incubated with immobilised cells of *C. parapsilosis* ATCC 7330 and are discussed in detail.

2.1.1. Substrate (*R*)-ethyl 3-hydroxy-3-phenyl propanoate [(*R*)-1]. Optically pure (*R*)-ethyl 3-hydroxy-3-phenyl propanoate [(*R*)-**1**] was incubated with ICp for 6 h and the product was analysed at the end of every hour for the formation of (i) the (*S*)-enantiomer [(*S*)-**1**] using chiral HPLC and (ii) ethyl 3-oxo-3-phenyl propanoate (**2**) using reverse-phase HPLC. Chiral HPLC confirmed the presence of (*S*)-hydroxy ester (68%) at the end of 6 h. The ketoester (**2**) intermediate could be detected from 4 h onwards and was confirmed by comparison with a standard (Scheme 1).

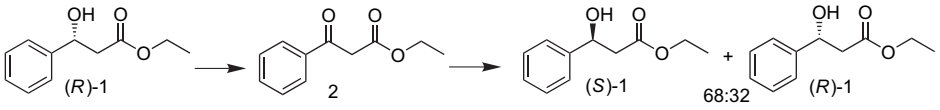
Oxidation of (*R*)-ethyl 3-hydroxy-3-phenyl propanoate [(*R*)-**1**] to the ketoester intermediate (**2**) followed by its reduction to [(*S*)-**1**] involves the loss of a methine proton. To prove the role of the methine proton in the stereoinversion, two experiments were carried out using ethyl 3-deutero-3-hydroxy-3-phenyl propanoate (**3**) and ethyl 3-hydroxy-3-phenyl butanoate (**4**) as the substrates.

2.1.2. Substrate ethyl 3-deutero-3-hydroxy-3-phenyl propanoate (3). Ethyl 3-deutero-3-hydroxy-3-phenyl propanoate (**3**) was incubated with ICp for 6 h and the resulting reaction mixture was analysed by ^{1}H NMR spectroscopy after work up. The ^{1}H NMR spectrum of the reaction mixture confirmed the presence of the starting reactant (deuterated, **3**) as well as its undeuterated counterpart (**1**) (dd at

Table 1. Deracemisation of β-hydroxy esters using immobilised whole cells of *Candida parapsilosis* ATCC 7330

Sub. no.	R	R′	*n*	ee%	Yield %	Abs. config.	$[\alpha]_D^{25}$ (This study)	$[\alpha]_D^{25}$ (Lit. reported)
1	Ph	Et	0	99	57	*S*	−50.1 (*c* 1.5, $CHCl_3$)	+43.7 (*c* 1.4, $CHCl_3$)[28]
7	*o*-MeC_6H_4	Et	0	09	68	Nd	Nd	
8	*p*-MeC_6H_4	Et	0	98	51	*S*	−44.6 (*c* 1.2, $CHCl_3$)	+44.7 (*c* 1.2, $CHCl_3$)[33a]
9	*p*-EtC_6H_4	Et	0	>99	42	*S*	−43.4 (*c* 1.2, $CHCl_3$)	Nr
10	*o*-$OMeC_6H_4$	Et	0	>99	75	*S*	−57.7 (*c* 1.8, $CHCl_3$)	−42.0 (*c* 2.30, $CHCl_3$)[33b]
11	*p*-$OMeC_6H_4$	Et	0	99	48	*S*	−43.7 (*c* 0.52, $CHCl_3$)	+39.4 (*c* 0.52, $CHCl_3$)[33a]
12	*p*-ClC_6H_4	Et	0	99	42	*S*	−43.7 (*c* 1.38, $CHCl_3$)	+44.2 (*c* 1.38, $CHCl_3$)[33a]
13	*m*-BrC_6H_4	Et	0	72	62	*S*	−21.4 (*c* 1.46, $CHCl_3$)	Nr
14	*p*-$NO_2C_6H_4$	Et	0	99	41	*S*	−59.5 (*c* 1.5, $CHCl_3$)	+23.1 (*c*, 1.0, $CHCl_3$)[28]
15	*m*-$NO_2C_6H_4$	Et	0	26	66	Nd	Nd	
16	1-Naphthyl	Et	0	00	63	—	—	
17	9-Anthranyl	Et	0	00	62	—	—	
18	Ph	Et	1	13	59	Nd	Nd	
19	Ph	Et	2	87	10	*S*	−2.35 (*c* 2.71, CH_2Cl_2)	+1.3 (*c* 1.0, $CHCl_3$)[33e]
20	Ph	Me	0	>99	48	*S*	−49.9 (*c* 1.0, $CHCl_3$)	−52.0 (*c* 1.0, $CHCl_3$)[33c]
21	Ph	*n*-Propyl	0	93	47	*S*	−51.6 (*c* 2.61, $CHCl_3$)	Nr
22	Ph	*n*-Butyl	0	67	71	*S*	−31.2 (*c* 3.78, $CHCl_3$)	+35.2 (*c* 3.78, $CHCl_3$)[33d]
23	Me	CH_2Ph	0	00	38	—	—	
24	Me	$CH_2CH{=}CHPh$	0	79	23	Nd	Nd	

Nd: not determined; Nr: not reported.



Scheme 1.

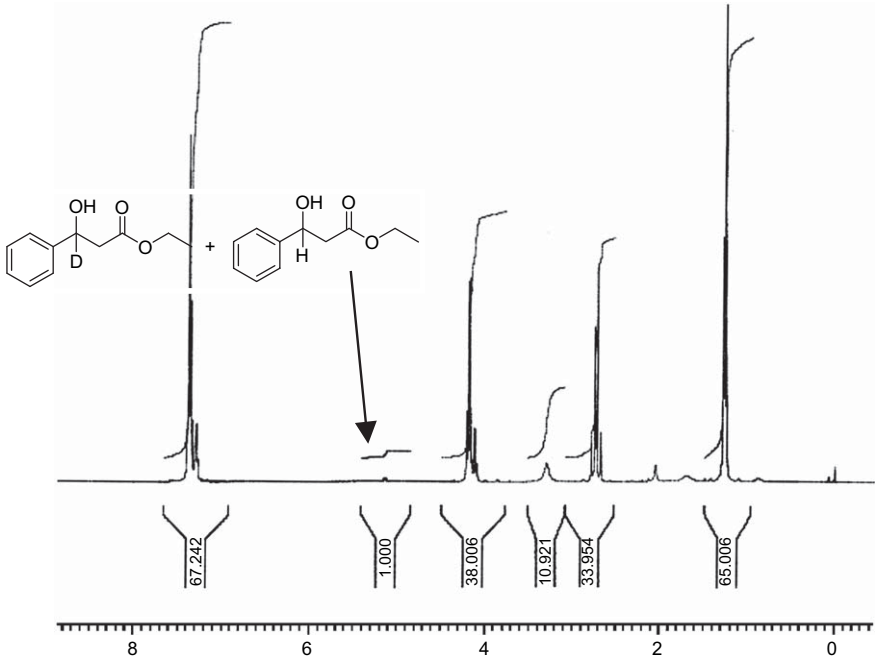
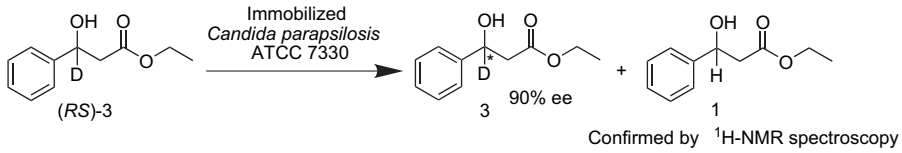


Figure 1. ^{1}H NMR of the deracemised product of ethyl 3-deutero-3-hydroxy-3-phenyl propanoate.



Scheme 2.

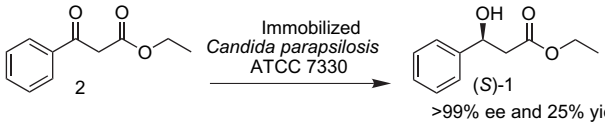
5.13 ppm, Fig. 1) as the products in the ratio of 94:6, respectively (Scheme 2).

The formation of the undeuterated product (**1**) is possible only by the reduction of the corresponding ketoester—ethyl 3-oxo-3-phenyl propanoate (**2**) detected earlier. The presence of the (*S*)-enantiomer in the product mixture (**3** and **1** in 94:6) in 90% ee indicates that the deuterated (*S*)-**3** is due to the retention of configuration of (*S*)-**3** from the racemic substrate while (*R*)-**3** is converted to (*S*)-**1** via the ketoester-**2**, which was detected earlier.

2.1.3. Substrate ethyl 3-hydroxy-3-phenyl butanoate (4). Ethyl 3-hydroxy-3-phenyl butanoate (**4**) when incubated with ICp for 6 h resulted in complete recovery of the starting racemate thus proving that the presence of a methine proton is mandatory for this deracemisation.

The experimental results described in Sections 2.1.2 and 2.1.3 unequivocally prove that ICp mediated deracemisation of β-hydroxy esters proceeds by a stereoinversion mechanism.

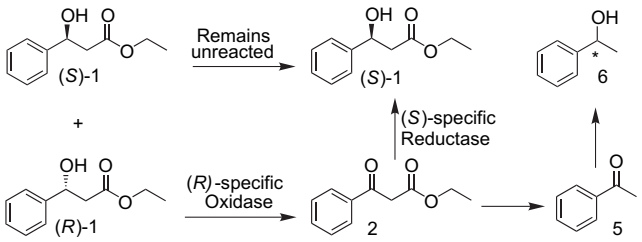
2.1.4. Reduction of ethyl 3-oxo-3-phenyl propanoate (2) using immobilised whole cells of *C. parapsilosis* ATCC 7330. Incubation of ethyl 3-oxo-3-phenyl propanoate with ICp resulted in the production of (*S*)-ethyl 3-hydroxy-3-phenyl propanoate [(*S*)-**1**] in >99% ee and 25% yield (Scheme 3) indicating the presence of a (*S*)-specific reductase in *C. parapsilosis* ATCC 7330.



Scheme 3.

In order to account for the low yield from ICp mediated reduction of **2**, the product mixture was analysed using reverse-phase HPLC, which confirmed the presence of ethyl 3-hydroxy-3-phenyl propanoate (**1**), acetophenone (**5**) and 1-phenyl ethanol (**6**). Formation of acetophenone could be due to decarboxylation of the hydrolysed[23] product of the ketoester intermediate (**2**) while 1-phenyl ethanol could be the reduced product of acetophenone accounting for ~15–20%, of the yield.[22b] Loss of another 10–15% of product can be attributed to the work up of the aqueous product mixture.[22c]

The scheme of reactions during deracemisation as proved from the above experiments can thus be represented as given in Scheme 4.



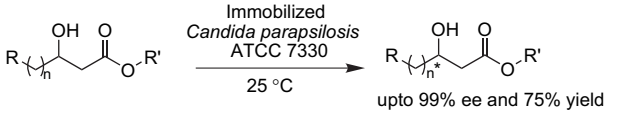
Scheme 4.

It is clear from Scheme 4 that, while the oxidation reaction is enantioselective and chemospecific, the reduction reaction is enantiospecific. The enantiospecificity of the reduction reaction is important as it is responsible for the high optical yield of the deracemised product. Notably, all earlier reported deracemisation reactions using different strains of *C. parapsilosis* were limited to substrates without multiple functional groups except in the case of α-hydroxy esters.[17] Thus, the appearance of the side products during deracemisation of β-hydroxy esters is not a surprise.

2.2. Deracemisation using immobilised whole cells of *C. parapsilosis* ATCC 7330

The number of biocatalytic methods for the preparation of chiral β-hydroxy esters is limited as compared to synthetic methods. Biocatalytic reduction of ketoesters of substrates **1**,[24] **18**,[25] **19**[26] and **20**[27] (Table 1) to their (*S*)-enantiomers has been reported in 87–97% ee and 42–87% yield. Lipase catalysed kinetic resolution of substrates **8**,[28] **11**,[28] **14**,[28] **18**,[25] **20**[25] and **22**[25] (Table 1) has also been reported in 86–94.5% ee and 42–48% yield. No suitable biocatalytic methods are reported for the preparation of substrates **7**, **9**, **10**, **12**, **13**, **15**, **16** and **21** (Table 1). Substrate **17** (Table 1) is a new compound and is used here for the first time for deracemisation.

Deracemisation of racemic ethyl 3-hydroxy-3-phenyl propanoate (**1**, Table 1) with ICp under optimised conditions[22b] gave its (*S*)-enantiomer in 99% ee and 57% isolated yield. In addition, a group of optically pure aryl and substituted aryl β-hydroxy esters was prepared using the ICp mediated deracemisation (Scheme 5) in order to study the substrate specificity of the biocatalyst. Deracemisation of substrates with electron donating (**8**, **9**, **11** and **12**, Table 1) and electron withdrawing (**14**, Table 1) substituents at the *para* position of the standard substrate resulted in the formation of their (*S*)-enantiomers in 98–99% ee and 41–51% yield. This indicates that the electronic nature of the substituents at the *para* position of the standard substrate does not affect the deracemisation. At the *ortho* position however, these substituents can obstruct the process of deracemisation due to their proximity to the reaction centre. Among the *meta* substituted substrates ethyl 3-hydroxy-3-(3-nitrophenyl) propanoate (**15**, Table 1) on deracemisation gave 26% ee and 66% isolated yield while ethyl 3-(3-bromophenyl)-3-hydroxy propanoate (**13**, Table 1) on deracemisation with ICp gave 72% ee and 62% isolated yield. The nitro group in the *meta* position lowers electron density in the aromatic ring, which could affect the removal of a hydride ion from the reaction centre, which we believe, is the initial step in this deracemisation reaction. The better optical yield in the case of *meta* bromo substituent than the *meta* nitro (**15**, Table 1) is because the bromo group does not have strong negative inductive effect as compared to the nitro group. Also the mesomeric effect is not active in the *meta* position for **15** (Table 1). Ethyl 3-hydroxy-3-naphthalen-1-yl-propanoate and ethyl 3-anthracen-9-yl-3-hydroxy-propanoate (**16**, **17**, Table 1) on ICp mediated deracemisation, were recovered in racemic form. The reaction centre in these molecules is sterically hindered due to the large size of the aromatic ring. Substrate **17** (Table 1), ethyl 3-anthracen-9-yl-3-hydroxy-propanoate in its racemic form is a new compound reported here for the first time and was used for deracemisation. β-Hydroxy esters with a spacer between the chiral centre and the phenyl ring, i.e., ethyl 3-hydroxy-4-phenyl butanoate and ethyl 3-hydroxy-5-phenylpentanoate (**18**, **19**, Table 1) on deracemisation gave 13% ee and 59% yield and 87% ee and 10% yield of the products, respectively. A similar study on the baker's yeast reduction[25] of the corresponding ketoesters of **1**, **18** and **19** (Table 1), indicates that with increasing number of carbon atoms between the keto group and the phenyl ring, the reduction proceeds at a faster rate. In this study substrate **1** without spacer and substrate **19** (Table 1) with two carbons as the spacer, undergoes deracemisation with high ee. The low yield of the product (**19**, Table 1) is due to hydrolysis of the ester group as a side reaction. The reasons for the poor ee of **18** (Table 1) are not clear at present. ICp mediated deracemisation of racemic β-hydroxy esters having ester moieties with increasing chain length (**1**, **20**–**22**, Table 1) resulted in a gradual decrease in the ee of the (*S*)-enantiomer product. High ee (>99%) of the product was obtained for methyl-3-hydroxy-3-phenyl propanoate (**20**, Table 1) with 48% yield. Phenylmethyl-3-hydroxy butanoate did not undergo deracemisation with ICp (**23**, Table 1). This molecule, with its aromatic ring on the opposite side of the reaction centre, is quite different from all the above substrates used for deracemisation. 3-Hydroxy-butyric acid 3-phenyl-allyl ester **24** (Table 1) on deracemisation resulted in 79% ee but a low isolated yield of 23%.



Scheme 5.

As evidenced from Table 1, the high ee (>99%) and high yield (up to 75%) of the products during the ICp mediated deracemisation of varied racemic β-hydroxy esters prove the broad substrate specificity of the biocatalyst.

Ethanol was used as the auxiliary solvent in the ICp mediated deracemisation to avoid the formation of side products due to transesterification except for substrates **20**, **21** and **22** (Table 1), where methanol, *n*-propanol and *n*-butanol were used, respectively.

3. Conclusion

The mechanism of ICp catalysed deracemisation of racemic β-hydroxy esters was proved to be via stereoinversion.

Experiments proving the mechanism showed that the (*S*)-enantiomer of ethyl 3-hydroxy-3-phenyl propanoate retained its absolute configuration and the (*R*)-enantiomer underwent an inversion of configuration via a ketoester intermediate, when incubated with ICp. Deracemisation of aryl and aryl substituted β-hydroxy esters by ICp gave >99% ee and up to 75% yield. High ee (98–99%) of the deracemised products was observed irrespective of the electronic nature of the substituents at the *para* position of the aromatic ring. A nitro group at the *meta* position of the aromatic ring decreases the ee of the deracemised product (26%). A methyl group at the *ortho* position of the aromatic ring decreases the ee of the deracemised product while a methoxy group does not. Substrates with polyaromatic rings did not undergo deracemisation. Increasing chain length of the ester moiety decreases the ee of the product.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million values using TMS as an internal standard. HPLC analysis was carried out on a Jasco PU-1580 liquid chromatograph with a PDA detector using Chiralcel-ODH and Chiralcel OJ-H chiral columns (Daicel, 4.6×250 mm). Optical rotations were recorded on a Jasco Dip 370 digital polarimeter. TLC was done on Kieselger $60F_{254}$ aluminium sheets (Merck 1.05554). The mobile phase was hexane/isopropanol, the proportion of solvents and the flow rate vary for different compounds.

4.2. Materials and methods

Racemic β-hydroxyl esters **1**, **7**–**11**, **14**, **15**, **18**, **23** and **24** were synthesised by sodium borohydride reduction of their corresponding ketoesters. The ketoesters of **1**, **11**, **14** and **15** were purchased from Fluka, Buchs SG, Switzerland; however, for substrates **7**, **8**, **9**, **10** and **18** the ketoesters were prepared by a literature known method.[29] The ketoesters of **23** and **24** were synthesised by a reported microwave irradiation method.[30] Substrates **12**, **13**, **16**, **17** and **19** were synthesised by Reformatsky reaction.[31] Substrates **20**, **21** and **22** were synthesised by our reported procedure,[32] i.e., sodium borohydride mediated reduction cum transesterification of the ethyl 3-oxo-3-phenyl propanoate. (*S*)-Ethyl 3-hydroxy-3-phenyl propanoate was prepared by baker's yeast reduction of the corresponding ketoester.[24] The (*R*)-ethyl 3-hydroxy-3-phenyl propanoate and the ketoester were purchased from Fluka, Buchs SG, Switzerland and used as such. Sodium borodeuteride was purchased from Sigma–Aldrich Chemical Co., Milwaukee, U.S.A. The deuterated hydroxy ester was prepared by the reduction of the corresponding ketoester with sodium borodeuteride. Acetophenone used as a standard was purchased from a local chemical company. 1-Phenyl ethanol was prepared by reducing acetophenone using sodium borohydride. Ethanol used in the biotransformation was of spectroscopic grade. *C. parapsilosis* ATCC 7330 was procured from American Type Culture Collection (ATCC 7330).

4.3. Culture medium

The composition of the media used for culturing *C. parapsilosis* ATCC 7330 was: YMB (yeast malt broth) [yeast extract (3 g L^{-1}), malt extract (3 g L^{-1}), peptone (5 g L^{-1}) and dextrose (10 g L^{-1}) at pH 6.5]. The yeast malt broth was sterilised in an autoclave at 121 °C and 15 lb kg^{-1} pressure for 20 min.

4.4. Cultivation of microorganism

The strain *C. parapsilosis* ATCC 7330 was routinely maintained in agar plates as well as slants (2.1% agar with the above mentioned culture media). Sub-culturing was performed every 12 weeks. The plates and slants were preserved at 4 °C.

4.5. Culture conditions

The pure culture of *C. parapsilosis* ATCC 7330 was inoculated with a loop, into the YMB media. A working volume of 50 mL (YMB media, after inoculation) in the 250 mL Erlenmeyer flasks was cultivated in an orbital shaker at 25 °C, 200 rpm. The cells were harvested by centrifuging the 44 h culture broth at 3750*g* followed by washing with sterile water. The process was repeated thrice and finally the wet biomass was used for biotransformation.

4.6. Immobilization

Immobilization was done following an earlier reported procedure.[22b]

4.7. Mechanistic investigation of deracemisation

In order to prove that the deracemisation follows a stereoinversion mechanism, different substrates were used with ICp. The details of these experiments are discussed below.

4.7.1. Substrate (*R*)-ethyl 3-hydroxy-3-phenyl propanoate [(*R*)-1]. To a suspension of 100 mL of immobilised *C. parapsilosis* ATCC 7330 in 50 mL of sterile distilled water taken in a 500 mL Erlenmeyer flask, 40 μL (210 μmol) of (*R*)-ethyl 3-hydroxy-3-phenyl propanoate (>99% ee) predissolved in 1 mL of absolute ethanol was added. The reaction mixture was incubated in a water-bath shaker for 6 h at 25 °C and 150 rpm. Aliquots were taken at different intervals of time (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0 and 6.0 h), extracted and analysed using both chiral HPLC (Chiralcel-ODH, hexane/isopropanol::95:05) and reverse-phase HPLC (Kromasil C-18 column, HPLC grade acetonitrile/water 40:60).

4.7.2. Substrate ethyl 3-deutero-3-hydroxy-3-phenyl propanoate (3). A suspension of 60 mL of immobilised beads of *C. parapsilosis* ATCC 7330 in 30 mL of sterile distilled water was prepared in a 500 mL Erlenmeyer flask. Ethyl 3-deutero-3-hydroxy-3-phenyl propanoate (15 μL, ~78 μmol) pre-dissolved in 375 μL of absolute ethanol was added to the above suspension. The reaction mixture was incubated in a water-bath shaker at 25 °C for 6 h at 150 rpm. Three similar experiments were carried out simultaneously to estimate the yield of the product. The reaction

mixture after the necessary work up was characterised using ^{1}H NMR. The reaction mixture was also analysed using chiral HPLC to determine the optical purity of the product.

4.7.3. Substrate ethyl 3-hydroxy-3-phenyl butanoate (4). To a suspension of 10 mL of immobilised *C. parapsilosis* ATCC 7330 in 5 mL of sterile distilled water taken in a 100 mL Erlenmeyer flask, 4 μL (21 μmol) of racemic ethyl 3-hydroxy-3-phenyl butanoate pre-dissolved in 100 μL of absolute ethanol was added. The reaction mixture was incubated in a water-bath shaker for 6 h at 25 °C and 150 rpm. After the incubation time, the reaction mixture was filtered to recover the immobilised beads and the filtrate was extracted with ethyl acetate (3×30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. This concentrated product was dissolved in 2 mL of hexane/isopropanol, 99:01 (HPLC grade), filtered through a 0.2-μm filter and analysed using chiral HPLC (Chiralcel-ODH, hexane/isopropanol::99:01). The chiral HPLC analysis (Chiralcel-ODH, hexane/isopropanol::99:01) indicated the presence of only the racemic substrate.

4.7.4. Reduction of ethyl 3-oxo-3-phenyl propanoate (2) using immobilised whole cells of *C. parapsilosis* ATCC 7330. The reaction was carried out as given in Section 4.7.3 using ethyl 3-oxo-3-phenyl propanoate as the substrate. The reaction mixture analysed by a reverse-phase HPLC (Kromasil C-18 column, HPLC grade acetonitrile/water 40:60) illustrated the presence of side products as shown in Scheme 4.

4.8. Typical procedure for the deracemisation using immobilised whole cells of *C. parapsilosis* ATCC 7330 (ICp)

Racemic β-hydroxy esters (504 μmol, 96 μL) dissolved in an appropriate amount of solvent (0.06% v/v, ethanol/methanol/*n*-propanol/*n*-butanol) were added to a suspension of 250 mL of ICp in 125 mL of distilled water, equally distributed in four 250 mL Erlenmeyer flasks. The biotransformation was carried out for 6 h at 25 °C and 150 rpm in a water-bath orbital shaker. The beads were filtered and the filtrate was extracted using ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The crude product after column purification (30:70::ethyl acetate/hexane, for substrate **1**) was analysed by chiral HPLC to determine the optical purity of the deracemised product. The standard substrate **1** under identical conditions gave 99% ee and 57% yield. Appropriate control experiments with the reaction mixture containing all the components except (i) racemic β-hydroxy ester and (ii) the immobilised whole cells of *C. parapsilosis* ATCC 7330, established the optical purity of the product and the chemical yield. Deracemisation of other aromatic β-hydroxy esters (**7**–**24**, Table 1) was carried out following the same procedure.

4.9. Spectroscopic characterisation of the deracemised products

4.9.1. (*S*)-Ethyl 3-hydroxy-3-phenyl propanoate (1). Colourless oil; spectroscopic data identical to that reported in literature,[22a] $[\alpha]_D^{25}$ −50.1 (*c* 1.5, $CHCl_3$). HRMS (ESI): found 217.0837, $C_{11}H_{14}O_3Na$ $[M+Na]^+$ requires 217.0837.

4.9.2. Ethyl 3-hydroxy-3-(2-methylphenyl) propanoate (7). Colourless oil; spectroscopic data identical to that reported in literature.[22a]

4.9.3. (*S*)-Ethyl 3-hydroxy-3-(4-methylphenyl) propanoate (8). Colourless oil; spectroscopic data identical to that reported in literature,[22a] $[\alpha]_D^{25}$ −44.6 (*c* 1.2, $CHCl_3$). HRMS (ESI): found 231.1004, $C_{12}H_{16}O_3Na$ $[M+Na]^+$ requires 231.0997.

4.9.4. (*S*)-Ethyl 3-(4-ethylphenyl)-3-hydroxy propanoate (9). Colourless oil; $[\alpha]_D^{25}$ −43.4 (*c* 1.2, $CHCl_3$). IR ν_{max} (neat): 3455, 3059, 2966, 1733, 1514, 1372, 1269, 1116, 1037, 965, 890, 871, 833, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, *J*=7.6 Hz, 3H), 1.24 (t, *J*=7.1 Hz, 3H), 2.63 (q, *J*=7.5 Hz, 2H), 2.7 (ddd, *J*=16.2, 9.1, 3.8 Hz, 2H), 3.3 (s, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 5.09 (dd, *J*=9.1, 3.8 Hz, 1H), 7.17 (d, *J*=8.0 Hz, 2H), 7.27 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 15.5, 28.5, 43.4, 60.7, 70.2, 125.7, 127.9, 139.9, 143.81, 172.3. HRMS (ESI): found 245.1161, $C_{13}H_{18}O_3Na$ $[M+Na]^+$ requires 245.1154.

4.9.5. (*S*)-Ethyl 3-hydroxy-3-(2-methoxyphenyl) propanoate (10). Colourless oil; spectroscopic data identical to that reported in literature,[34a] $[\alpha]_D^{25}$ −57.7 (*c* 1.8, $CHCl_3$).

4.9.6. (*S*)-Ethyl 3-hydroxy-3-(4-methoxyphenyl) propanoate (11). Colourless oil; spectroscopic data identical to that reported in literature,[22a] $[\alpha]_D^{25}$ −43.7 (*c* 0.52, $CHCl_3$).

4.9.7. (*S*)-Ethyl 3-(4-chlorophenyl)-3-hydroxy propanoate (12). Colourless oil; spectroscopic data identical to that reported in literature,[34a] $[\alpha]_D^{25}$ −43.7 (*c* 1.38, $CHCl_3$). HRMS (ESI): found 251.0457, $C_{11}H_{13}O_3ClNa$ $[M+Na]^+$ requires 251.0451.

4.9.8. (*S*)-Ethyl 3-(3-bromophenyl)-3-hydroxy propanoate (13). Pale yellow liquid; spectroscopic data identical to that reported in literature,[34b] $[\alpha]_D^{25}$ −21.4 (*c* 1.46, $CHCl_3$). HRMS (ESI): found 294.9946, $C_{11}H_{13}O_3BrNa$ $[M+Na]^+$ requires 294.9942.

4.9.9. (*S*)-Ethyl 3-hydroxy-3-(4-nitrophenyl) propanoate (14). Pale yellow liquid; spectroscopic data identical to that reported in literature,[22a] $[\alpha]_D^{25}$ −59.5 (*c* 1.5, $CHCl_3$).

4.9.10. Ethyl 3-hydroxy-3-(3-nitrophenyl) propanoate (15). Pale yellow liquid; IR ν_{max} (neat): 3451, 3073, 2986, 2972, 2938, 1990, 1713, 1538, 1463, 1380, 1346, 1304, 1277, 1226, 1203, 1182, 1073, 1043, 1007, 939, 914, 859, 816, 734, 692, 622, 566 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, *J*=7.1 Hz, 3H), 2.75 (m, 2H), 3.77 (s, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 5.25 (m, *J*=5.2 Hz, 1H), 7.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 43.0, 61.1, 69.2, 120.7, 122.6, 129.4, 131.7, 144.7, 148.4, 171.8. HRMS (ESI): found 262.0692, $C_{11}H_{13}NO_5Na$ $[M+Na]^+$ requires 262.0691.

4.9.11. Ethyl 3-hydroxy-3-napthalen-1-yl propanoate (16). Colourless oil; spectroscopic data identical to that reported in literature,[34a] HRMS (ESI): found 267.0999, $C_{15}H_{16}O_3Na$ $[M+Na]^+$ requires 267.0997.

4.9.12. Ethyl 3-anthracen-9-yl-3-hydroxy propanoate (17). Pale yellow liquid; IR ν_{max} (neat): 3486, 3049, 2983, 1707, 1621, 1447, 1332, 1282, 1174, 1077, 1105, 1024, 963, 892, 736, 422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, J=7.2 Hz, 3H), 3.18 (ddd, J=16.8, 10.5, 3.0 Hz, 2H), 3.38 (s, 1H), 4.22 (q, J=7.1 Hz, 2H), 6.74 (dd, J=10.4, 2.4 Hz, 1H), 7.47 (m, 4H), 7.98 (d, J=8.2 Hz, 2H), 8.4 (s, 1H), 8.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 41.7, 61.0, 67.2, 124.6, 124.8, 125.8, 128.5, 129.1, 129.3, 131.6, 132.34, 172.6; HRMS (ESI): found 317.1170, $C_{19}H_{18}O_3Na$ $[M+Na]^+$ requires 317.1154.

4.9.13. Ethyl 3-hydroxy-4-phenyl butanoate (18). Colourless oil; spectroscopic data identical to that reported in literature.[34b]

4.9.14. (*S*)-Ethyl 3-hydroxy-5-phenyl pentanoate (19). Colourless oil; spectroscopic data identical to that reported in literature,[34b] $[\alpha]_D^{25}$ −2.35 (*c* 2.71, CH_2Cl_2).

4.9.15. (*S*)-Methyl-3-hydroxy-3-phenyl propanoate (20). Colourless oil; spectroscopic data identical to that reported in literature,[22a] $[\alpha]_D^{25}$ −49.9 (*c* 1, $CHCl_3$).

4.9.16. (*S*)-*n*-Propyl 3-hydroxy-3-phenyl propanoate (21). Colourless oil; $[\alpha]_D^{25}$ −51.6 (*c* 2.61, $CHCl_3$). IR ν_{max} (neat): 3453, 3064, 3032, 2969, 2880, 1732, 1494, 1455, 1394, 1356, 1269, 1195, 1058, 915, 761, 700, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J=7.4 Hz, 3H), 1.62 (sextet, J=7 Hz, 2H), 2.69 (ddd, J=16.1, 8.9, 3.8 Hz, 2H), 3.56 (s, 1H), 4.03 (t, J=6.6 Hz, 2H), 5.14 (dd, J=7.7 Hz, 1H), 7.28 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) 10.3, 21.8, 43.4, 66.3, 70.2, 125.6, 127.6, 128.4, 142.7, 172.3. HRMS (ESI): found 231.0997, $C_{12}H_{16}O_3Na$ $[M+Na]^+$ requires 231.0997.

4.9.17. (*S*)-*n*-Butyl 3-hydroxy-3-phenyl propanoate (22). Colourless oil; spectroscopic data identical to that reported in literature,[28] $[\alpha]_D^{25}$ −31.2 (*c*, 3.78 $CHCl_3$).

4.9.18. Methyl phenyl 3-hydroxy butanoate (23). Colourless oil; spectroscopic data identical to that reported in literature.[34c]

4.9.19. 3′-Phenyl-prop-2′-enyl 3-hydroxy butanoate (24). Pale yellow liquid; IR ν_{max} (neat): 3445, 3069, 3023, 2979, 2937, 1731, 1578, 1494, 1449, 1372, 1275, 1224, 1147, 1039, 965, 886, 750, 693, 634, 607, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, J=6.3 Hz, 3H), 2.49 (ddd, J=16.5, 8.2, 4.1 Hz, 2H), 3.17 (s, br, 1H), 4.21 (m, 1H), 4.75 (d, J=6.4 Hz, 2H), 6.26 (dt, J=15.9, 6.4 Hz, 1H), 6.64 (d, J=15.9 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 42.8, 64.2, 65.2, 122.7, 126.6, 128.3, 128.5, 134.5, 136.0, 172.6. HRMS (ESI): found 243.0997, $C_{13}H_{16}O_3Na$ $[M+Na]^+$ requires 243.0998.

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Vinyl bis-sulfone methodology in thiosugars: selective access to chiral thiovinyl sulfones and PSE oxathianes

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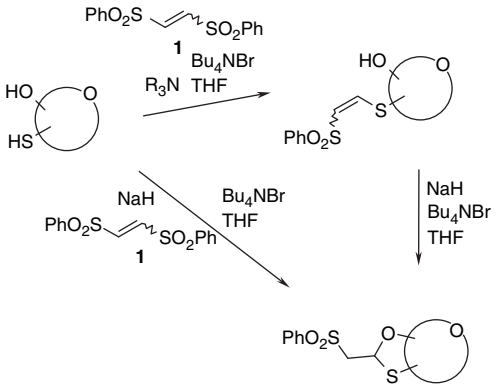
Abstract—Based on the vinyl bis-sulfone methodology previously developed to synthesize PSE acetals, an original approach to homochiral carbohydrate-derived PSE 1,3-oxathianes is described. The ready formation of intermediate phenylsulfonylvinyl sulfides, which have a synthetic potential of their own, emphasizes the versatility of the method.

1. Introduction

1,3-Oxathiane derivatives have found many applications in organic synthesis[1] but since the pioneering studies of Eliel and colleagues,[2] enantiopure 1,3-oxathianes have been mainly developed by several groups as efficient chiral auxiliaries in asymmetric syntheses.[3] Most of those auxiliaries were designed and prepared from terpenoid compounds—camphor, pulegone, myrtenal—with the notable exception of a tetralone-derived 1,3-oxathiane devised by Solladié-Cavallo and colleagues.[4] Carbohydrate-derived oxathianes were scarcely mentioned in the literature[5] and only recently, the use of a xylofuranose-based phosphinooxathiane was reported in asymmetric allylation.[6]

We have introduced in the carbohydrate field phenylsulfonylethylidene (PSE) acetals,[7] which display striking properties.[8] PSE acetals can readily be prepared through Michael type reaction of the corresponding diols with 1,2-bis(phenylsulfonyl)ethylene (BPSE, **1**). These atypical acetals often show properties opposite to those of classical acetals and in addition display uncommon synthetic features. An extension to PSE thioacetals has recently been outlined by us.[9] Developing synthetic pathways to sugar-based 2-(phenylsulfonylmethyl)-1,3-oxathianes (Scheme 1) appears profitable in several respects: (i) comparison of PSE thioacetals to PSE acetals with regard to unusual properties—reluctance to acid-catalyzed ring-opening, for example; (ii) introduction of a prochiral sulfur atom, ready to undergo tricoordination; and (iii) introduction of a stereogenic centre (the newly formed thioacetalic carbon) potentially exploitable in terms of chiral induction.



Scheme 1. Reactions of sugar-based mercaptans with BPSE.

2. Results and discussion

2.1. PSE oxathiane formation

1,3-Oxathiane derivatives are usually prepared according to a limited register of methods, mainly involving as follows: (i) acid-catalyzed thioacetalation of carbonyl functions; (ii) transthioacetalation of 1,3-dioxanes; and (iii) intramolecular Pummerer rearrangement of γ,δ-unsaturated sulfoxides.[1]

De Lucchi et al. have reported an efficient synthesis of isobornane-derived chiral 1,3-oxathianes through reaction of terpenoid hydroxythiols on electron poor acetylenes.[10] With

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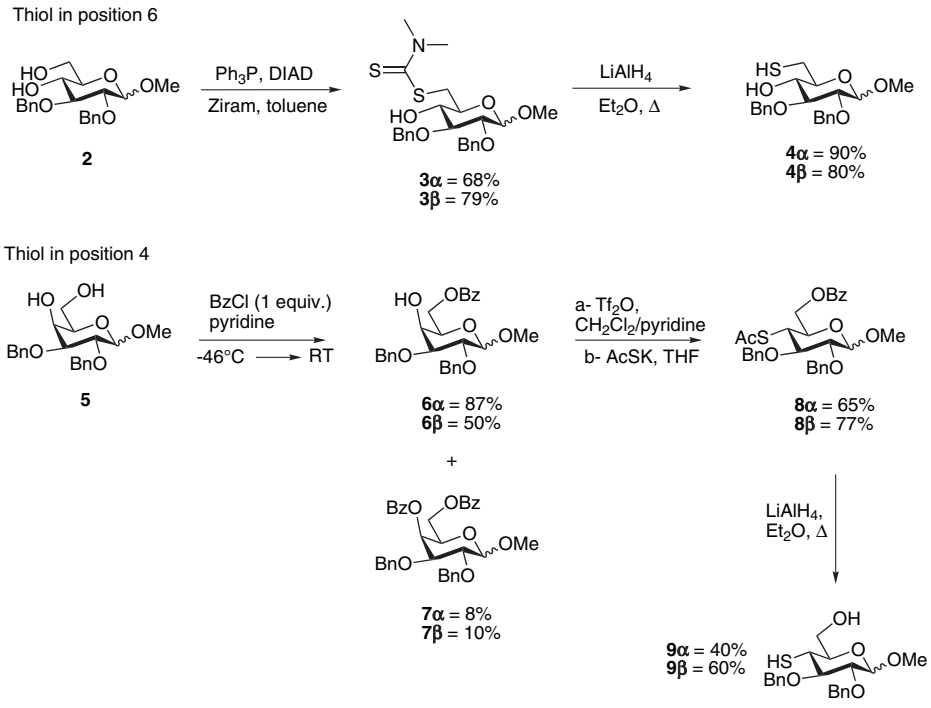


Scheme 2. Synthesis of the carbohydrate-derived hydroxythiols.

a view to applying a similar Michael addition approach to carbohydrate-derived hydroxythiols, we have prepared thiols derived from standard α- and β-D-glucopyranoside models.

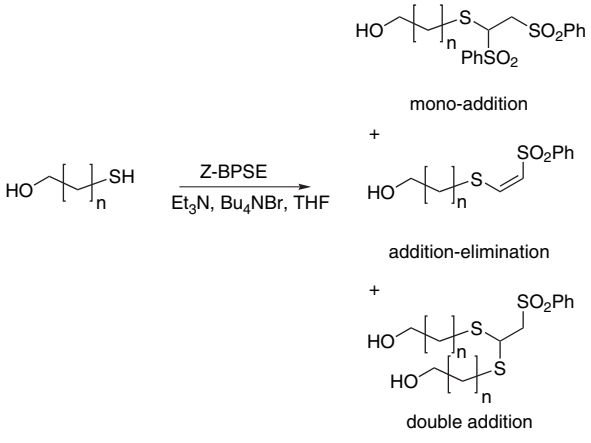
Our objective was to prepare both regioisomeric oxathianes, bearing the sulfur atom in either 6- or 4-position, and two different pathways were thus devised (Scheme 2). A direct approach involved methyl 2,3-di-*O*-benzyl-α- or β-D-glucopyranosides **2**, the primary position of which could be regioselectively thiofunctionalized through a Mitsunobu reaction with Ziram® under previously established conditions.[11] Reductive cleavage of the *N*,*N*-dimethyldithiocarbamates **3** was effected using lithium aluminohydride to deliver the thiols **4α** and **4β** in 61% and 63% yield, respectively, over the two-step sequence.

The Mitsunobu methodology having proven to be much less efficient on a secondary position, the introduction of sulfur at C-4 required stereoselective epimerization in the D-galactopyrano series. The primary position of methyl 2,3-di-*O*-benzyl-α- and β-D-galactopyranosides **5** was selectively *O*-benzoylated using 1 equiv of benzoyl chloride at low temperature, to give **6α** in 87% yield and **6β** in 50% yield only. 4,6-Dibenzoates **7α** and **7β** were also isolated in 8% and 10% yield, respectively. Sulfur introduction was effected through triflate activation followed by stereoselective nucleophilic displacement by potassium thioacetate to afford D-*gluco* configurated **8α** and **8β** in 65% and 77% yield, respectively. Final LAH reduction of both thioesters furnished both hydroxythiols **9α** and **9β** in 23% overall yield from **5**.

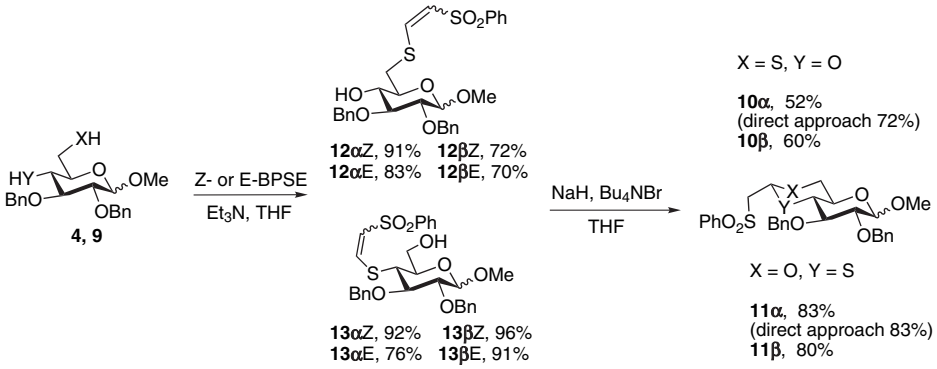
To prepare the corresponding PSE thioacetals, the four hydroxythiols **4α**,**β** and **9α**,**β** were then reacted with *Z*- or *E*-BPSE **1** under the conditions previously settled for 1,3-diols,[7] which proved equally efficient for synthesizing 1,3-oxathianes: for example, **10α** and **11α** (Scheme 4) were obtained in yields—72% and 83% yield, respectively—which compare with our preliminary results on 3-mercaptopropanol.[9]

Relying on the nucleophilicity ratio in favour of the thiol function as compared with the alcohol function, we have explored the possibility of a sequential pathway to the thioacetal: tertiary amine-catalyzed Michael addition–elimination should selectively lead to the formation of a thiovinyl sulfone intermediate, whereas stronger bases—NaH or LiHMDS—would directly afford the oxathiane.

However, earlier studies performed with aliphatic simple models—2-mercaptoethanol, 3-mercaptopropanol and 4-mercaptobutanol—have shown that side-reactions such as simple or double thiol conjugate additions (Scheme 3) can severely hamper the formation of the thiovinyl sulfone and lead to moderate yields.[9]



Scheme 3. Thiol conjugate additions on BPSE.



Scheme 4. Sequential synthesis of PSE oxathianes on glucopyranosides.

We were pleased to observe that applying the same conditions to the carbohydrate-derived thiols **4** and **9** led to the corresponding thiovinyl sulfones **12** and **13** with more rewarding 70–96% yields (Scheme 4). In addition, whatever the *Z*- or *E*-BPSE used, the reactions proceeded on α- or β-pyranosides with complete retention of the configuration of the double bond.[12] As compared with simple hydroxythiols, this improved selectivity towards thiovinyl sulfone formation might be attributed to the presence of the bulky glucopyranoside moiety.

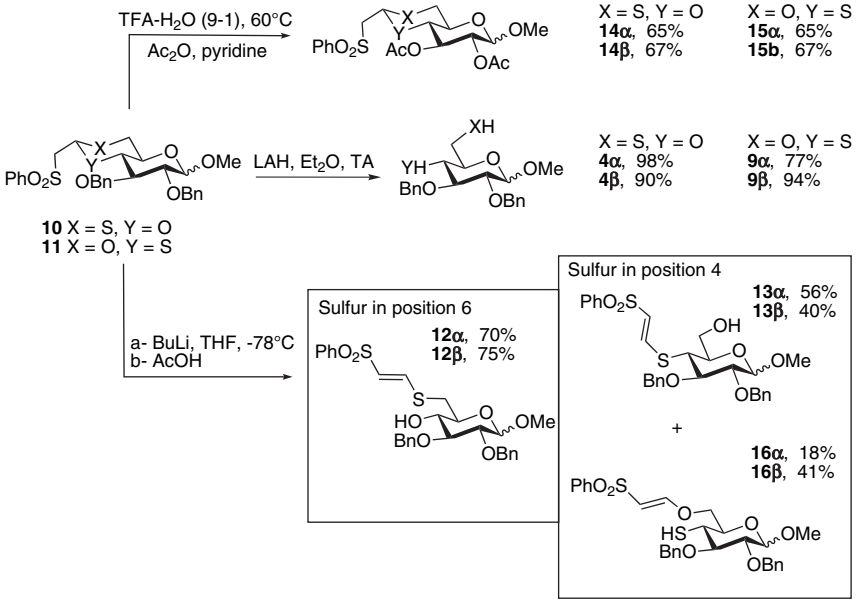
The thiovinyl sulfones could be converted into oxathianes through strong base-catalyzed cyclization, to give moderate to good yields of **10α** and **10β**—52% and 60%, respectively—as well as **11α** and **11β**—83% and 80%, respectively. The one-step procedure from hydroxythiols thus appears more efficient for the preparation of oxathianes.

2.2. Chemical behaviour of PSE oxathianes

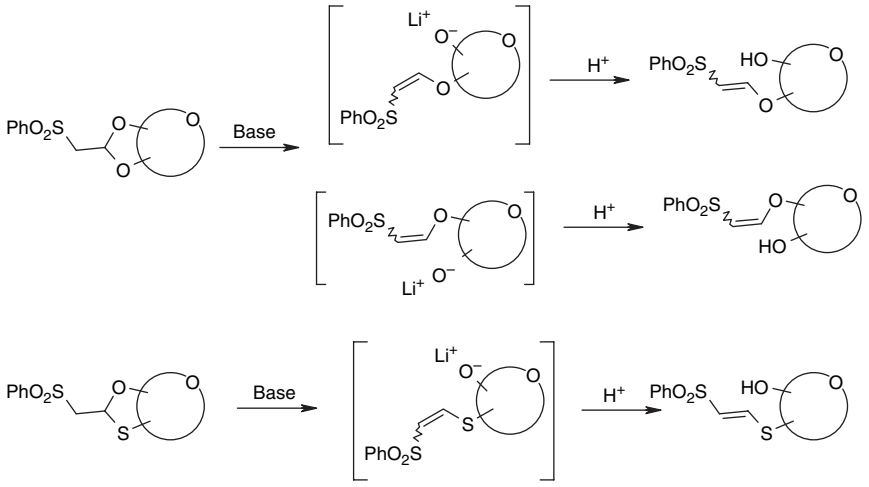
Our previous studies have disclosed that PSE acetals currently show inverse properties as compared to standard acetal protective groups.[8] We were, therefore, interested in estimating the influence of the sulfur atom on the reactivity of a PSE thioacetal. Under standard deprotection conditions in acidic media—80% aqueous acetic acid at 80 °C or 90% trifluoroacetic acid at room temperature—PSE oxathianes were not affected. Applying more severe conditions—90% trifluoroacetic acid at 60 °C for 24 h—to **10** or **11** afforded de-*O*-benzylated compounds **14** and **15** in reasonable yields. The above results clearly demonstrate that the introduction of a sulfur atom does not interfere with the acid-stability of PSE acetals.

In connection with anterior study of the behaviour of PSE acetals under reductive conditions,[7] oxathianes **10** and **11** were treated by lithium aluminium hydride to produce as expected full deprotection of the thioacetal moiety to restore the starting γ-hydroxythiols **4** and **9** in high yields (Scheme 5).

We then turned our attention to the possible selective opening of PSE oxathianes induced by strong bases: under such conditions, hydrogen-extrusion in alpha to the sulfone can take place and induce a retro-Michael reaction leading to the decyclized structures.



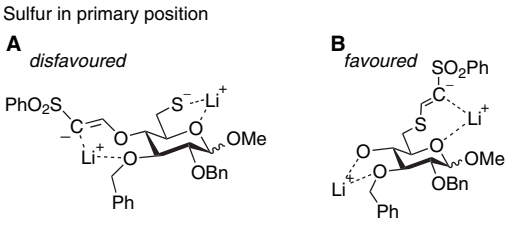
Scheme 5. Chemical behaviour of PSE oxathianes.



Scheme 6. Decyclization of PSE acetals and thioacetals.

When applied to PSE acetals, strongly basic conditions afforded equimolar mixtures of regioisomeric alkoxyvinyl sulfones, resulting from the lack of selectivity between intermediate lithium salts (Scheme 6).[13] In contrast, a better selectivity should be expected with PSE oxathianes considering the HSAB theory and preferred association of lithium with alcoholate rather than thiolate. Indeed, the results obtained with a couple of α,β-anomers have shown a good selectivity in favour of the formation of alkylthiovinylsulfones (Scheme 5). In the case of oxathianes **10α** and **10β** (sulfur in primary position), a good selective opening took place to afford **12α** and **12β** in 70% and 75% yield, respectively. In the case of oxathianes **11α** and **11β** (sulfur in secondary position), a more complex reaction occurred to produce alcohols **13** and thiols **16**: starting from **11α**, a 3:1 ratio in favour of the thiovinyl sulfone **13α** was attained, whereas no selectivity was observed with **11β**, which produced comparable amounts of alcohol **13β** and thiol **16β**. This latter case is indicative of a clear influence—due to implication of Li^+ complexation in transient structures—of the anomeric site on the formation of the vinyl sulfones.

Each anomer of either **10** or **11** might generate two possible fragmented intermediates complexed with lithium ions. The selectivity observed in the formation of **12α** and **12β** is consistent with the HSAB theory, predicting that complex **B** should be favoured over complex **A** (Scheme 7).

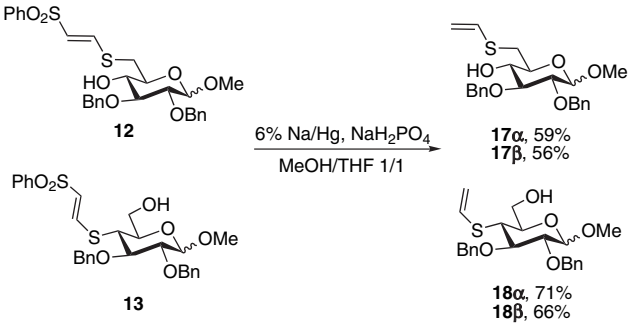


Scheme 7. Possible transient lithium salt complexes. Excess BuLi (3 equiv) being used, two deprotonation sites might be expected in the intermediates.

Thiovinyl sulfones **12** and **13** were finally subjected to monoelectronic reductive desulfonylation.

In previous works, we have shown that reductive desulfonylation is a powerful tool to generate highly reactive *O*- and *N*-vinyl derivatives.[14] In combination with chiral templates such as carbohydrates, these vinyl derivatives are much of interest in asymmetric reactions such as [3+2] cycloadditions or [4+2] reverse Diels–Alder reactions.[15] Extending the process to the formation of vinyl sulfides would open a number of new accesses to various derivatives—including useful vinyl sulfoxides and vinyl sulfones.

Standard amalgam methodology in phosphate-buffered protic solution[14] was therefore applied to thiovinyl sulfones **12** and **13**. The corresponding 4-*S*- and 6-*S*-vinyl sulfides **17** and **18** were isolated in reasonable (56–71%) yields, comparable to those obtained from parent nitrogen- and oxygen-derivatives (Scheme 8).



Scheme 8. Formation of sugar-derived vinyl sulfides.

3. Conclusion

We have investigated the first PSE oxathianes anchored on carbohydrate templates. Those chemical species, which can be prepared from the γ-hydroxythiols either in a single step or in a stepwise manner show a similar behaviour as compared to the parent PSE acetals: high reluctance to acid hydrolysis and removability under strongly basic conditions. PSE oxathianes can regioselectively be cleaved to afford thiovinyl sulfones, which can readily undergo monoelectronic reduction to promising *S*-vinyl sulfides. Further reactivity features of carbohydrate-based PSE oxathianes and *S*-vinyl sulfides are currently explored and will be published in due course.

4. Experimental

4.1. General methods

Solvents were dried and distilled by standard methods before use. All reagents were of commercial quality (Acros, Aldrich or Lancaster) and used without purification. Reactions were carried out under argon atmosphere and monitored by TLC analysis with silica gel plates (Kieselgel $60F_{254}$, Merck). Compounds were visualized with UV light and charring after a 10% H_2SO_4 ethanolic solution spray. Column chromatography was performed on silica gel 60 M (0.036–0.063 mm, Merck). ^{1}H NMR (250 MHz) and ^{13}C NMR (62.6 MHz) spectra ($CDCl_3$, internal TMS) were recorded on a Bruker AVANCE DPX 250 spectrometer. Chemical shifts (δ) are reported in parts per million downfield from TMS, coupling constants (J) are reported in Hertz and refer to apparent peak multiplicity. Assignments are based on H,H- and C,H-COSY experiments. Mass spectra were obtained using Ion Spray® (IS) method with an API 300 Perkin Elmer SCIEX spectrometer. HR-ESI-TOF-MS was performed on a Micromass LC TOF spectrometer. Optical rotations were measured at 20 °C with a Perkin Elmer 410 polarimeter.

4.2. Thiofunctionalization at the C-6 position: Mitsunobu dithiocarbamoylation[11]

To an ice-cold solution of the 4,6-diol **2α** [17791-36-5][16] or **2β** [31873-34-4][17] (1 g, 2.67 mmol) in toluene (10 mL) were successively added triphenylphosphine (1.05 g, 1.5 equiv), diethyl azodicarboxylate (0.63 mL, 1.5 equiv) and Ziram® (1.22 g, 1.5 equiv). The mixture was stirred overnight at room temperature. After filtration and concentration of the solution in vacuo, the residue was purified by column chromatography.

4.2.1. Methyl 2,3-di-*O*-benzyl-6-*S*-(*N*,*N*-dimethyldithiocarbamoyl)-6-thio-α-D-glucopyranoside (3α). Obtained from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **2α**; silica gel column chromatography (toluene/AcOEt 95:5, then 9:1) afforded **3α** with 68% yield as a colourless gum, $[\alpha]_D$ −23 (*c* 2.2, $CHCl_3$). ^{1}H NMR δ 3.39 (s, 3H, OMe), 3.40 (s, 3H, NMe), 3.45 (dd, 1H, H-2), 3.49–3.54 (m, 1H, H-4), 3.57 (s, 3H, NMe), 3.64 (dd, 1H, J_{5-6b}=3.2, H-6b), 3.85 (t, 1H, J_{2-3}=J_{3-4}=9.5, H-3), 3.87–3.93 (m, 1H, H-5), 4.13 (dd, 1H, J_{5-6a}=4.1, J_{6a-6b}=14.7, H-6a), 4.59 (d, 1H, J_{1-2}=3.6, H-1), 4.67 and 4.80 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.89 (s, 2H, PhCH_2O), 7.28–7.42 (m, 10H, H–Ar). ^{13}C NMR δ 40.2 (C-6), 42.2 and 46.7 (2*NMe), 55.7 (OMe), 70.4 (C-5), 72.1 (C-4), 73.7 and 76.2 (2*PhCH_2O), 79.5 (C-2), 81.1 (C-3), 98.8 (C-1), 126.3–128.8 (10*CH–Ar), 138.3 and 138.8 (2*C_{IV}–Ar), 197.6 (C═S). IR (film): 3478 cm^{-1} (OH), 1515 and 1555 cm^{-1} (C═S). MS IS *m*/*z*=446.5 [M−OMe]$^+$, 478.5 [M+H]$^+$, 495.5 [M+NH_4]$^+$, 500.5 [M+Na]$^+$. HRMS: $C_{24}H_{31}NO_5S_2$: calcd 477.1643; found 477.1628.

4.2.2. Methyl 2,3-di-*O*-benzyl-6-*S*-(*N*,*N*-dimethyldithiocarbamoyl)-6-thio-β-D-glucopyranoside (3β). Obtained from methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside **2β**; silica gel column chromatography (toluene/AcOEt 95:5, then 9:1) afforded **3β** with 79% yield as a colourless gum, $[\alpha]_D$ −57 (*c* 3.5, $CHCl_3$). ^{1}H NMR δ 2.34 (s, OH), 3.33 (t, 1H, J_{2-3}=J_{1-2}=7.7, H-2), 3.39 (s, 3H, NMe), 3.51–3.59 (m, 9H, H-3, H-4, H-5, NMe, OMe), 3.75 (d, 1H, J_{5-6b}< 0.5, H-6b), 4.13 (dd, 1H, J_{5-6a}=2.8, J_{6a-6b}=14.7, H-6a), 4.32 (d, 1H, J_{1-2}=7.7, H-1), 4.71 and 4.87 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 4.85 (s, 2H, PhCH_2O), 7.17–7.36 (m, 10H, H–Ar). ^{13}C NMR δ 40.1 (C-6), 42.3 and 46.7 (2*NMe), 57.6 (OMe), 72.0 (C-5), 74.7 (C-4), 75.2 and 76.0 (2*PhCH_2O), 81.9 (C-2), 83.7 (C-3), 105.0 (C-1), 125.7–129.5 (10*CH–Ar), 138.9 and 139.1 (2*C_{IV}–Ar), 198.3 (C═S). MS IS *m*/*z*=446.5 [M−OMe]$^+$, 478.5 [M+H]$^+$, 500.5 [M+Na]$^+$, 516.5 [M+K]$^+$. HRMS: $C_{24}H_{31}NO_5S_2$: calcd 477.1643; found 477.1634.

4.3. Thiofunctionalization at the C-6 position: dithiocarbamate reduction[11b]

To an ice-cold solution of the dithiocarbamate in dry ether (1 mmol/10 mL), LAH (2.5 equiv) was added and the reaction mixture was stirred for 4 h under reflux. AcOEt (10 mL) and then 10% aqueous HCl was carefully added to the cooled suspension; the organic phase was decanted and the aqueous phase washed with AcOEt (2×10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography.

4.3.1. Methyl 2,3-di-*O*-benzyl-6-thio-α-D-glucopyranoside (4α). Obtained from **3α**; silica gel column chromatography (petroleum ether/AcOEt 85:15, then 8:2) afforded thiol **4α** with 90% yield as a colourless gum, $[\alpha]_D$ +27 (*c* 2, $CHCl_3$). ^{1}H NMR δ 1.59 (dd, 1H, J_{SH-6a}=9.4, J_{SH-6b}=7.2, SH), 2.23 (br s, OH), 2.65 (ddd, 1H, J_{5-6b}=7.3, H-6b), 2.90 (ddd, 1H, J_{5-6a}=2.8, J_{6a-6b}=14.1, H-6a), 3.37–3.45 (m, 1H, H-4), 3.42 (s, 3H, OMe), 3.52 (dd, 1H, J_{2-3}=9.6, H-2), 3.64 (ddd, 1H, H-5), 3.77 (t, 1H, J_{3-4}=9.6, H-3), 4.62 (d, 1H, J_{1-2}=3.4, H-1), 4.67 and 4.77 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.69 and 5.04 (2d, AB system, 2H, J_{gem}=11.5, PhCH_2O), 7.30–7.41 (m, 10H, H–Ar). ^{13}C NMR δ 26.3 (C-6), 55.2 (OMe), 71.2 (C-5), 71.9 (C-4), 72.9 and 75.3 (2*PhCH_2O), 79.8 (C-2), 81.1 (C-3), 97.6 (C-1), 125.8–128.6 (10*CH–Ar), 137.8 and 138.4 (2*C_{IV}–Ar). MS IS *m*/*z*=359.5 [M−OMe]$^+$, 408.5 [M+NH_4]$^+$, 413.5 [M+Na]$^+$. HRMS: $C_{21}H_{26}O_5S$: calcd 390.1501; found 390.1492.

4.3.2. Methyl 2,3-di-*O*-benzyl-6-thio-β-D-glucopyranoside (4β). Obtained from **3β**; silica gel column chromatography (petroleum ether/AcOEt 85:15, then 8:2) afforded thiol **4β** with 80% yield as a colourless gum, $[\alpha]_D$ −16 (*c* 1, $CHCl_3$). ^{1}H NMR δ 1.70 (dd, 1H, J_{SH-6a}=9.8, J_{SH-6b}=7.9, SH), 2.29 (br s, OH), 2.69 (ddd, 1H, J_{5-6b}=7.9, H-6b), 2.92 (ddd, 1H, J_{5-6a}=2.8, J_{6a-6b}=14.5, H-6a), 3.30 (ddd, 1H, J_{4-5}=7.9, H-5), 3.38–3.46 (m, 3H, H-2, H-3, H-4), 3.58 (s, 3H, OMe), 4.34 (d, 1H, J_{1-2}=7.2, H-1), 4.64 and 4.96 (2d, AB system, 2H, J_{gem}=11.5, PhCH_2O), 4.69 and 4.93 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 7.23–7.37 (m, 10H, H–Ar). ^{13}C NMR δ 26.6 (C-6), 57.3 (OMe), 72.1 (C-4), 74.7 and 75.3 (2*PhCH_2O), 75.7 (C-5), 82.1 (C-2), 83.8 (C-3), 104.8 (C-1), 127.8–128.8 (10*CH–Ar), 138.4 and 138.5 (2*C_{IV}–Ar). MS IS *m*/*z*=408.5 [M+NH_4]$^+$, 413.5 [M+Na]$^+$, 429.5 [M+K]$^+$. HRMS: $C_{21}H_{26}O_5S$: calcd 390.1501; found 390.1500.

4.4. Thiofunctionalization at the C-4 position: regioselective benzoylation at O-6[18]

A pyridine solution of the 4,6-diol **5α** [29388-46-3][19] or **5β** [6988-40-5][20] (4 g, 10.7 mmol/20 mL) was cooled to −46 °C, then benzoyl chloride (1.24 mL, 1 equiv) was added dropwise under argon atmosphere and the mixture was stirred overnight while slowly reaching room temperature. The mixture was diluted with CH_2Cl_2 and then poured on ice; the organic layer was decanted and washed successively with saturated aqueous $NaHCO_3$ and brine. After drying the combined organic extracts over $MgSO_4$ and concentration in vacuo, the residue was purified by column chromatography.

4.4.1. Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-galactopyranoside (6α) [125884-36-8].[21] Obtained from methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside;[19] silica gel column chromatography (petroleum ether/AcOEt 7:3) afforded the 6-*O*-benzoate **6α** with 87% yield as a white amorphous solid, $[\alpha]_D$ +80 (*c* 1, $CHCl_3$); [lit.[21] $[\alpha]_D$ +83 ($CHCl_3$)]; ^{1}H NMR δ 2.78 (br s, OH), 3.35 (s, 3H, OMe), 3.89 (br s, 2H, H-2, H-3), 3.99–4.10 (m, 2H, H-4, H-5), 4.51–4.56 (m, 2H, H-6a and H-6b), 4.66 and 4,81 (2d, AB system, 2H, J_{gem}=11.9, Ph*CH*$_2$O), 4.67 (d, 1H, J_{1-2}=3.6, H-1), 4.68 and 4.81 (2d, AB system, 2H, J_{gem}=11.9, Ph*CH*$_2$O), 7.22–7.43 (m, 12H, H–Ar), 7.53 (t, 1H, J_{vic}=7.5, *para*-H–Bz), 8.02 (d, 2H, J_{vic}=7.5, *ortho*-H–Bz). ^{13}C NMR δ 55.2 (OMe), 64.1 (C-6), 67.6, 67.8 (C-4, C-5), 73.0 and 73.5 (2*Ph*CH*$_2$O), 75.6, 76.6 (C-2, C-3), 98.4 (C-1), 126.3–128.9 (CH–Ar), 129.5 (CH–*ortho*-Bz), 129.7 (C_{IV}–Bz), 133.0 (CH–*para*-Bz), 138.0 and 138.2 (2*C_{IV}–Ar), 166.2 (C═O). MS IS *m*/*z*=447.5 [M−OMe]$^+$, 479.5 [M+H]$^+$, 496.5 [M+NH_4]$^+$, 501.5 [M+Na]$^+$. HRMS: $C_{28}H_{30}O_7$: calcd 478.1991; found 478.1987.

4.4.2. Methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (6β) [20786-72-5].[22] Obtained from methyl 2,3-di-*O*-benzyl-β-D-galactopyranoside;[19] silica gel column chromatography (petroleum ether/AcOEt 7:3) afforded the 6-*O*-benzoate **6β** with 50% yield as a white amorphous solid, $[\alpha]_D$ +3 (*c* 1.4, $CHCl_3$); [lit.[22] $[\alpha]_D$ −1.63 (*c* 0.45, $CHCl_3$)]. ^{1}H NMR δ 2.84 (br s, OH), 3.51 (dd, 1H, J_{3-4}= 3.2, H-3), 3.53 (s, 3H, OMe), 3.59–3.73 (m, 2H, H-2, H-5), 3.96 (br s, 1H, H-4), 4.28 (d, 1H, J_{1-2}=7.7, H-1), 4.54–4.64 (m, 2H, H-6a, H-6b), 4.69 (s, 2H, Ph*CH*$_2$O), 4.71 and 4.89 (2d, AB system, 2H, J_{gem}=11.3, Ph*CH*$_2$O), 7.17–7.42 (m, 12H, H–Ar), 7.51 (t, 1H, J_{vic}=7.7, *para*-H–Bz), 8.03 (d, 2H, J_{vic}=7.5, *ortho*-H–Bz). ^{13}C NMR δ 56.8 (OMe), 63.5 (C-6), 66.6 (C-4), 71.9 (C-5), 72.8 and 74.9 (2*Ph*CH*$_2$O), 78.8 (C-2), 80.4 (C-3), 104.6 (C-1), 127.8–128.3 (CH–Ar), 129.8 (C_{IV}–Bz), 129.6 (CH–*ortho*-Bz), 133.0 (CH–*para*-Bz), 138.0 and 138.6 (2*C_{IV}–Ar), 166.2 (C═O). MS IS *m*/*z*=447.5 [M−OMe]$^+$, 479.5 [M+H]$^+$, 496.5 [M+NH_4]$^+$, 501.5 [M+Na]$^+$, 517.5 [M+K]$^+$. HRMS: $C_{28}H_{30}O_7$: calcd 478.1991; found 478.1979.

Di-*O*-benzoylated α- and β-galactopyranosides were also isolated in minor amounts.

4.4.2.1. Methyl 4,6-di-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-galactopyranoside (7α). Silica gel column chromatography (petroleum ether/AcOEt 8:2) afforded **7α** with 8% yield as a colourless gum, $[\alpha]_D$ +47 (*c* 4.2, $CHCl_3$). ^{1}H NMR δ 3.41 (s, 3H, OMe), 3.97 (dd, 1H, H-2), 4.13 (dd, 1H, J_{2-3}=10.0, H-3), 4.28–4.37 (m, 2H, H-5, H-6b), 4.49 (dd, 1H, J_{5-6a}= 3.8, J_{6a-6b}=8.8, H-6a), 4.62 and 4,84 (2d, AB system, 2H, J_{gem}=11.7, Ph*CH*$_2$O), 4.68 and 4.84 (2d, AB system, 2H, J_{gem}=11.7, Ph*CH*$_2$O), 4.80 (d, 1H, J_{1-2}=3.6, H-1), 5.89 (d, 1H, H-4), 7.20–7.54 (m, 16H, H–Ar), 8.03 (2d, 4H, *J*=7.5, *ortho*-H–Bz). ^{13}C NMR δ 55.4 (OMe), 63.1 (C-6), 66.9 (C-5), 68.7 (C-4), 72.0 and 73.7 (2*Ph*CH*$_2$O), 74.9 (C-2), 76.2 (C-3), 99.0 (C-1), 127.5–128.4 (CH–Ar), 129.6 and 129.9 (CH–*ortho*-Bz), 129.7 (2*C_{IV}–Bz), 133.1 and 133.2 (2*CH–*para*-Bz), 138.0 and 138.2 (2*C_{IV}–Ar), 165.7 and 166.0 (2*C═O). MS IS *m*/*z*=551.5 [M−OMe]$^+$, 583.5 [M+H]$^+$, 600.5 [M+NH_4]$^+$, 605.5 [M+Na]$^+$. HRMS: $C_{35}H_{34}O_8$: calcd 582.2253; found 582.2248.

4.4.2.2. Methyl 4,6-di-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (7β) [79698-16-1].[22] Silica gel column chromatography (petroleum ether/AcOEt 8:2) afforded **7β** with 10% yield as a white amorphous solid, $[\alpha]_D$ +13 (*c* 1.8, $CHCl_3$); [lit.[23] $[\alpha]_D$ +20.12 (*c* 0.83, $CHCl_3$)]. ^{1}H NMR δ 3.69 (s, 3H, OMe), 3.73–3.85 (m, 2H, H-2, H-3), 4.07 (br t, 1H, H-5), 4.46 (dd, 1H, J_{5-6b}=6.4, J_{6a-6b}=11.3, H-6b), 4.48 (d, 1H, J_{1-2}=7.6, H-1), 4.66 (dd, 1H, J_{5-6a}= 6.6, H-6a), 4.66 and 4,92 (2d, AB system, 2H, J_{gem}=11.5, Ph*CH*$_2$O), 4.82 and 4.96 (2d, AB system, 2H, J_{gem}=11.1, Ph*CH*$_2$O), 5.94 (br s, 1H, H-4), 7.26–7.52 (m, 14H, H–Ar), 7.55–7.65 (m, 2H, *para*-H–Bz), 8.12 and 8.21 (2d, 4H, *J*=7.2, *ortho*-H–Bz). ^{13}C NMR δ 57.4 (OMe), 62.6 (C-6), 66.7 (C-4), 70.7 (C-5), 72.6 and 75.3 (2*Ph*CH*$_2$O), 79.0 and 79.2 (C-2, C-3), 104.9 (C-1), 127.6–128.5 (CH–Ar), 129.6 and 129.7 (CH–*ortho*-Bz), 129.6 (2*C_{IV}–Bz), 133.2 and 133.3 (2*CH–*para*-Bz), 137.8 and 138.6 (2*C_{IV}–Ar), 165.8 and 166.1 (2*C═O). MS IS *m*/*z*=551.5 [M−OMe]$^+$, 583.5 [M+H]$^+$, 600.5 [M+NH_4]$^+$, 605.5 [M+Na]$^+$, 621.5 [M+K]$^+$. HRMS: $C_{35}H_{34}O_8$: calcd 582.2253; found 582.2241.

4.5. Thiofunctionalization at the C-4 position: nucleophilic inversion[23]

To an ice-cold solution of the monobenzoates **6** (2 g, 4.18 mmol/30 mL) in CH_2Cl_2/pyridine (14:1 v/v) trifluoromethanesulfonic anhydride (3 equiv) was added dropwise. The mixture was stirred for 30 min at 0 °C, then for 1 h at room temperature. The orange solution was poured into an ice-cold 10% $KHSO_4$ solution; the organic phase was decanted and washed successively with ice-cold aqueous saturated $NaHCO_3$ and iced water. After drying the combined organic extracts over $MgSO_4$ and concentration in vacuo, the residue was engaged in the next step without further purification. To a solution of the crude triflate in freshly distilled THF (1 g, ca. 1.6 mmol/20 mL), solid potassium thioacetate (3 equiv) was added and the resulting brown solution was stirred for 12 h at room temperature. The mixture was diluted with 10 mL AcOEt and then poured into iced water; the organic layer was washed with water and the aqueous phases re-extracted with AcOEt (10 mL). After drying the combined organic extracts over $MgSO_4$ and concentration in vacuo, the residue was purified by column chromatography.

4.5.1. Methyl 4-*S*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-4-thio-α-D-glucopyranoside (8α). Obtained from monobenzoate **6α**; silica gel column chromatography (petroleum

ether/AcOEt 9:1, then 8:2) afforded the *S*-acetylated compound **8α** with 65% yield as a beige gum, $[\alpha]_D$ +67 (*c* 2, $CHCl_3$). ^1H NMR δ 2.28 (s, 3H, SAc), 3.37 (s, 3H, OMe), 3.63 (dd, 1H, J_{1-2}=3.5, H-2), 3.78 (t, 1H, $J_{3-4}=J_{4-5}$=10.4, H-4), 3.86 (t, 1H, H-3), 4.04 (ddd, 1H, H-5), 4.40 (dd, 1H, J_{5-6b}=5.5, H-6b), 4.57 (dd, 1H, J_{5-6a}=2.3, J_{6a-6b}=11.9, H-6a), 4.65 and 4.79 (2d, AB system, 2H, J_{gem}=11.9, PhCH_2O), 4.67 (d, 1H, H-1), 4.72 and 4.93 (2d, AB system, 2H, J_{gem}=11.0, PhCH_2O), 7.24–7.38 (m, 10H, H–Ar), 7.42 (t, 2H, J_{vic}=7.6, *meta*-H–Bz), 7.54 (t, 1H, J_{vic}=7.3, *para*-H–Bz), 8.06 (d, 2H, J_{vic}=7.4, *ortho*-H–Bz). ^{13}C NMR δ 30.7 (SAc), 45.7 (C-4), 55.5 (OMe), 64.2 (C-6), 68.8 (C-5), 73.2 and 76.2 (2*PhCH_2O), 78.3 (C-3), 81.1 (C-2), 98.4 (C-1), 127.6–128.5 (CH–Ar), 129.8 (CH–*ortho*-Bz), 129.9 (C_{IV}–Bz), 133.1 (CH–*para*-Bz), 138.4 and 138.5 (2*C_{IV}–Ar), 166.2 (C=O Bz), 193.1 (C=O SAc). MS IS *m*/*z*=505.5 $[M-OMe]^+$, 537.5 $[M+H]^+$, 554.5 $[M+NH_4]^+$, 575.5 $[M+K]^+$. HRMS: $C_{30}H_{32}O_7S$: calcd 536.1869; found 536.1861.

4.5.2. Methyl 4-*S*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-4-thio-β-D-glucopyranoside (8β). Obtained from monobenzoate **6β**; silica gel column chromatography (petroleum ether/AcOEt 9:1, then 8:2) afforded the *S*-acetylated compound **8β** with 77% yield as a beige gum, $[\alpha]_D$ +35 (*c* 1.5, $CHCl_3$). ^1H NMR δ 2.27 (s, 3H, SAc), 3.50 (m, 1H, H-2), 3.55 (s, 3H, OMe), 3.65 (m, 1H, H-3), 3.69 (t, 1H, H-4, $J_{3-4}=J_{4-5}$=10.4), 3.88 (ddd, 1H, H-5), 4.35 (d, 1H, J_{1-2}=7.9, H-1), 4.43 (dd, 1H, J_{5-6b}=5.7, H-6b), 4.65 (dd, 1H, J_{5-6a}=3.0, J_{6a-6b}=12.1, H-6a), 4.68 and 4.88 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 4.71 and 4.93 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 7.22–7.38 (m, 10H, H–Ar), 7.43 (t, 2H, J_{vic}=7.6, *meta*-H–Bz), 7.55 (t, 1H, J_{vic}=7.3, *para*-H–Bz), 8.07 (d, 2H, J_{vic}=7.5, *ortho*-H–Bz). ^{13}C NMR δ 30.9 (SAc), 46.2 (C-4), 57.2 (OMe), 64.4 (C-6), 72.7 (C-5), 75.0 and 76.1 (2*PhCH_2O), 80.8 (C-3), 83.4 (C-2), 104.7 (C-1), 127.7–128.5 (CH–Ar), 129.9 (CH–*ortho*-Bz), 130.0 (C_{IV}–Bz), 133.2 (CH–*para*-Bz), 138.3 and 138.5 (2*C_{IV}–Ar), 166.4 (C=O Bz), 193.5 (C=O SAc). MS IS *m*/*z*=505.5 $[M-OMe]^+$, 537.5 $[M+H]^+$, 554.5 $[M+NH_4]^+$, 559.5 $[M+Na]^+$. HRMS: $C_{30}H_{32}O_7S$: calcd 536.1869; found 536.1854.

4.6. Thiofunctionalization at the C-4 position: reductive cleavage[24]

To an ice-cold solution of **8** in dry ether (1 mmol/10 mL), LAH (4 equiv) was added and the reaction mixture was stirred for 4 h under reflux. AcOEt (10 mL) and then 10% aqueous HCl was carefully added to the cooled suspension; the organic phase was decanted and the aqueous phase washed with AcOEt (2×10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography.

4.6.1. Methyl 2,3-di-*O*-benzyl-4-thio-α-D-glucopyranoside (9α). Obtained from thioacetate **8α**; silica gel column chromatography (petroleum ether/AcOEt 7:3, 65:35, then 6:4) afforded the thiol **9α** with 40% yield as a beige gum, $[\alpha]_D$ +11 (*c* 1, $CHCl_3$). ^1H NMR δ 1.71 (d, 1H, J_{vic}=7.2, SH), 1.90 (br s, 1H, OH), 2.90 (dt, 1H, J_{4-5}=10.4, H-4), 3.39 (s, 3H, OMe), 3.47 (dd, 1H, J_{1-2}=3.4, H-2), 3.65 (ddd, 1H, H-5), 3.71 (t, 1H, $J_{2-3}=J_{3-4}$=10.4, H-3), 3.79 (dd, 1H, J_{5-6b}=4.7, H-6b), 3.88 (dd, 1H, J_{5-6a}=2.6, J_{6a-6b}=11.9, H-6a), 4.64 (d, 1H, H-1), 4.65 and 4.79 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.84 and 4.97 (2d, AB system, 2H, J_{gem}=10.4, PhCH_2O), 7.25–7.43 (m, 10H, H–Ar). ^{13}C NMR δ 42.0 (C-4), 55.5 (OMe), 63.0 (C-6), 72.9 (C-5), 73.4 and 76.5 (PhCH_2O), 80.9 (C-2), 81.9 (C-3), 98.6 (C-1), 127.9–128.6 (CH–Ar), 138.1 and 138.5 (2*C_{IV}–Ar). MS IS *m*/*z*=359.5 $[M-OMe]^+$, 408.5 $[M+NH_4]^+$, 413.5 $[M+Na]^+$. HRMS: $C_{21}H_{26}O_5S$: calcd 390.1501; found 390.1488.

4.6.2. Methyl 2,3-di-*O*-benzyl-4-thio-β-D-glucopyranoside (9β). Obtained from thioacetate **8β**; silica gel column chromatography (petroleum ether/AcOEt 7:3, 65:35, then 6:4) afforded the thiol **9β** with 60% yield as a beige gum, $[\alpha]_D$ −28 (*c* 2.3, $CHCl_3$). ^1H NMR δ 1.73 (d, 1H, J_{vic}=6.6, SH), 2.10 (br s, 1H, OH), 2.86–2.99 (m, 1H, H-4), 3.31–3.42 (m, 3H, H-2, H-3, H-5), 3.58 (s, 3H, OMe), 3.80 (dd, 1H, J_{5-6b}=5.3, H-6b), 3.98 (dd, 1H, J_{5-6a}=2.8, J_{6a-6b}=12.0, H-6a), 4.36 (br d, 1H, J_{1-2}=7.4, H-1), 4.70 and 4.91 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 4.79 and 4.93 (2d, AB system, 2H, J=10.6, PhCH_2O), 7.28–7.45 (m, 10H, H–Ar). ^{13}C NMR δ 41.7 (C-4), 57.4 (OMe), 63.1 (C-6), 74.9 and 76.2 (PhCH_2O), 77.7 (C-5), 83.2 (C-2), 85.0 (C-3), 105.0 (C-1), 127.9–128.5 (CH–Ar), 138.2 and 138.4 (2*C_{IV}–Ar). MS IS *m*/*z*=359.5 $[M-OMe]^+$, 408.5 $[M+NH_4]^+$, 413.5 $[M+Na]^+$. HRMS: $C_{21}H_{26}O_5S$: calcd 390.1501; found 390.1483.

4.7. Chemoselective thiol addition: synthesis of phenylsulfonylvinyl sulfides

To an ice-cold solution of the thiols **4**, **9** (390 mg, 1 mmol/15 mL) in dry THF were successively added Et_3N (1 equiv), *Z*- or *E*-BPSE (1 equiv) and a few crystals of Bu_4NBr. The mixture was stirred for 12 h at room temperature, then diluted with AcOEt and poured into iced water; the aqueous phases were extracted with AcOEt (10 mL) and the combined organic extracts dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography.

4.7.1. Methyl 2,3-di-*O*-benzyl-6-*S*-[(*E*)-2′-(phenylsulfonyl)-vinyl]-6-thio-α-D-glucopyranoside (12α*E*). Obtained from **4α** and *E*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded compound **12α*E*** with 83% yield as a colourless gum, $[\alpha]_D$ +36 (*c* 3.7, $CHCl_3$). ^1H NMR δ 2.88 (dd, 1H, J_{5-6b}=8.1, J_{6a-6b}=13.8, H-6b), 3.21 (dd, 1H, J_{5-6a}=2.4, H-6a), 3.30 (s, 3H, OMe), 3.35 (m, 1H, H-4), 3.49 (dd, 1H, J_{1-2}=3.6, J_{2-3}=9.6, H-2), 3.68–3.76 (m, 2H, H-3, H-5), 4.56 (d, 1H, H-1), 4.65 and 4.75 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.66 and 5.03 (2d, AB system, 2H, J_{gem}=11.5, PhCH_2O), 6.28 (d, 1H, J_{vic}=14.7, H-2′), 7.32–7.39 (m, H–Ar), 7.46–7.61 (m, 3H, *Ph*SO_2), 7.78 (d, 1H, H-1′), 7.82–7.86 (m, 2H, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 34.4 (C-6), 55.4 (OMe), 70.2 (C-5), 72.5 (C-4), 73.2 and 75.5 (PhCH_2O), 79.8 (C-2), 81.0 (C-3), 98.1 (C-1), 122.1 (C-2′), 126.0–129.3 (CH–Ar), 133.1 (CH–*para*-*Ph*SO_2), 137.9 and 138.6 (2*C_{IV}–Ar), 141.4 (C_{IV}–*Ph*SO_2), 146.4 (C-1′). MS IS *m*/*z*=574.5 $[M+NH_4]^+$, 579.5 $[M+Na]^+$, 595.5 $[M+K]^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1578.

4.7.2. Methyl 2,3-di-*O*-benzyl-6-*S*-[(*Z*)-2′-(phenylsulfonyl)-vinyl]-6-thio-α-D-glucopyranoside (12α*Z*). Obtained from **4α** and *Z*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, 65:35, then 6:4) afforded compound **12α*Z*** with 91% yield as a colourless gum, $[\alpha]_D$ +26 (*c* 2.0, $CHCl_3$). ^{1}H NMR δ 2.77 (dd, 1H, J_{5-6b}=8.3, J_{6a-6b}=14.7, H-6b), 2.91 (br s, 1H, OH), 3.12 (br d, 1H, J_{5-6a}<0.5, H-6a), 3.14 (s, 3H, OMe), 3.26–3.37 (m, 1H, H-4), 3.43 (dd, 1H, J_{2-3}=9.6, H-2), 3.64 (br t, 1H, J_{4-5}=9.6, H-5), 3.72 (t, 1H, J_{3-4}=9.6, H-3), 4.53 (d, 1H, J_{1-2}=3.6, H-1), 4.60 and 4.69 (2d, AB system, 2H, J_{gem}=12.1, Ph*CH*$_2$O), 4.71 and 4.96 (2d, AB system, 2H, J_{gem}=11.5, Ph*CH*$_2$O), 6.16 (d, 1H, J_{vic}=10.2, H-2′), 7.21 (d, 1H, H-1′), 7.28–7.35 (m, H–Ar), 7.48 (m, 2H, *meta*-H–*Ph*SO$_2$), 7.86 (m, 1H, *para*-H–*Ph*SO$_2$), 7.95 (d, 2H, J_{vic}=7.7, *ortho*-H–*Ph*SO$_2$). ^{13}C NMR δ 37.2 (C-6), 56.5 (OMe), 72.4 (C-5), 73.5 (C-4), 74.0 and 76.3 (Ph*CH*$_2$O), 80.5 (C-2), 82.1 (C-3), 98.8 (C-1), 122.8 (C-2′), 128.1–130.8 (CH–Ar), 139.0 and 139.8 (2*C$_{IV}$–Ar), 142.4 (C$_{IV}$–*Ph*SO$_2$), 149.9 (C-1′). MS IS *m*/*z*=579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1583.

4.7.3. Methyl 2,3-di-*O*-benzyl-6-*S*-[(*E*)-2′-(phenylsulfonyl)-vinyl]-6-thio-β-D-glucopyranoside (12β*E*). Obtained from **4β** and *E*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded compound **12β*E*** with 70% yield as a colourless gum, $[\alpha]_D$ −13 (*c* 4.1, $CHCl_3$). ^{1}H NMR δ 2.66 (br s, 1H, OH), 2.91 (dd, 1H, J_{5-6b}=6.8, J_{6a-6b}=14.1, H-6b), 3.23 (br d, 1H, J_{5-6a}<0.5, H-6a), 3.34–3.40 (m, 4H, H-2, H-3, H-4, H-5), 3.48 (s, 3H, OMe), 4.28 (br d, 1H, J_{1-2}=6.8, H-1), 4.64 and 4.91 (2d, AB system, 2H, J_{gem}=11.1, Ph*CH*$_2$O), 4.67 and 4.93 (2d, AB system, 2H, J_{gem}=11.3, Ph*CH*$_2$O), 6.29 (d, 1H, H-2′, J_{vic}=14.7), 7.23–7.36 (m, H–Ar), 7.47 (t, 2H, *meta*-H–Ar *Ph*SO$_2$), 7.56 (t, 1H, *para*-H–*Ph*SO$_2$), 7.80 (d, 1H, H-1′), 7.84 (d, 2H, *ortho*-H–*Ph*SO$_2$, J_{vic}=7.5). ^{13}C NMR δ 34.4 (C-6), 57.1 (OMe), 72.6 (C-4), 74.6 and 75.2 (Ph*CH*$_2$O), 74.7 (C-5), 82.2 (C-2), 83.8 (C-3), 104.7 (C-1), 121.8 (C-2′), 127.3–129.2 (CH–Ar), 133.1 (CH–*para*-*Ph*SO$_2$), 138.3 (2*C$_{IV}$–Ar), 141.2 (C$_{IV}$–*Ph*SO$_2$), 146.5 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 574.5 [M+NH$_4$]$^+$, 579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1580.

4.7.4. Methyl 2,3-di-*O*-benzyl-6-*S*-[(*Z*)-2′-(phenylsulfonyl)-vinyl]-6-thio-β-D-glucopyranoside (12β*Z*). Obtained from **4β** and *Z*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, 6:4, then 1:1) afforded compound **12β*Z*** with 72% yield as a colourless gum, $[\alpha]_D$ +43 (*c* 3.6, $CHCl_3$). ^{1}H NMR δ 2.63 (br s, 1H, OH), 2.80 (dd, 1H, J_{5-6b}=7.7, J_{6a-6b}=14.7, H-6b), 3.21 (br d, 1H, J_{5-6a}< 0.5, H-6a), 3.29–3.53 (m, 4H, H-2, H-3, H-4, H-5), 3.56 (s, 3H, OMe), 4.22 (d, 1H, J_{1-2}=7.2, H-1), 4.63 and 4.88 (2d, AB system, 2H, J_{gem}=11.5, Ph*CH*$_2$O), 4.69 and 4.93 (2d, AB system, 2H, J_{gem}=11.7, Ph*CH*$_2$O), 6.16 (d, 1H, J_{vic} *J*= 10.4, H-2′), 7.23–7.36 (m, H–Ar, H-1′), 7.48 (m, 2H, *meta*-H–Ar *Ph*SO$_2$), 7.88 (m, 1H, *para*-H–*Ph*SO$_2$), 7.96 (d, 2H, J_{vic}=7.7, *ortho*-H–*Ph*SO$_2$). ^{13}C NMR δ 37.4 (C-6), 57.3 (OMe), 72.3 (C-4), 75.1 and 75.2 (Ph*CH*$_2$O), 75.8 (C-5), 81.7 (C-2), 83.4 (C-3), 104.7 (C-1), 121.7 (C-2′), 127.1–129.5 (CH–Ar), 133.4 (CH–*para*-*Ph*SO$_2$), 138.3 (2*C$_{IV}$–Ar), 141.4 (C$_{IV}$–*Ph*SO$_2$), 149.0 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 574.5 [M+NH$_4$]$^+$, 579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1594.

4.7.5. Methyl 2,3-di-*O*-benzyl-4-*S*-[(*E*)-2′-(phenylsulfonyl)-vinyl]-4-thio-α-D-glucopyranoside (13α*E*). Obtained from **9α** and *E*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, 65:35, then 6:4) afforded **13α*E*** with 76% yield as a colourless gum, $[\alpha]_D$ +38 (*c* 1.5, $CHCl_3$). ^{1}H NMR δ 2.45 (br s, 1H, OH), 3.25 (t, 1H, J_{3-4}= J_{4-5}=10.8, H-4), 3.36 (s, 3H, OMe), 3.52 (dd, 1H, J_{1-2}= 3.4, J_{2-3}=9.2, H-2), 3.64–3.79 (m, 3H, H-5, H-6a, H-6b), 3.84 (t, 1H, H-3), 4.60 and 4.74 (2d, AB system, 2H, J_{gem}=12.2, Ph*CH*$_2$O), 4.63 (d, 1H, H-1), 4.71 and 4.87 (2d, AB system, 2H, J_{gem}=10.9, Ph*CH*$_2$O), 6.45 (d, 1H, J_{vic}=14.7, H-2′), 7.25–7.34 (m, H–Ar), 7.45 (br t, 2H, *meta*-H–*Ph*SO$_2$), 7.55 (br t, 1H, J_{vic}=7.3, *para*-H–*Ph*SO$_2$), 7.80 (d, 2H, J_{vic}=7.3, *ortho*-H–*Ph*SO$_2$), 7.83 (d, 1H, H-1′). ^{13}C NMR δ 50.1 (C-4), 56.1 (OMe), 62.2 (C-6), 71.2 (C-5), 73.8 and 76.6 (Ph*CH*$_2$O), 79.1 (C-3), 81.2 (C-2), 98.8 (C-1), 123.9 (C-2′), 127.8–129.7 (CH–Ar), 133.6 (CH–*para*-*Ph*SO$_2$), 138.3 and 138.5 (2*C$_{IV}$–Ar), 141.5 (C$_{IV}$–*Ph*SO$_2$), 145.5 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$, 574.5 [M+NH$_4$]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1591.

4.7.6. Methyl 2,3-di-*O*-benzyl-4-*S*-[(*Z*)-2′-(phenylsulfonyl)-vinyl]-4-thio-α-D-glucopyranoside (13α*Z*). Obtained from **9α** and *Z*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 6:4, 55:45, then 1:1) afforded **13α*Z*** with 92% yield as a colourless gum, $[\alpha]_D$ +9 (*c* 1.9, $CHCl_3$). ^{1}H NMR δ 1.95 (br s, 1H, OH), 3.08 (t, 1H, J_{3-4}=J_{4-5}= 10.7, H-4), 3.38 (s, 3H, OMe), 3.48 (dd, 1H, J_{1-2}=3.4, J_{2-3}=9.4, H-2), 3.72 (dt, 1H, J_{5-6a}=J_{5-6b}=2.3, H-5), 3.79–3.85 (m, 2H, H-6a, H-6b), 3.87 (br t, 1H, H-3), 4.56 and 4.84 (2d, AB system, 2H, J_{gem}=10.2, Ph*CH*$_2$O), 4.62 (d, 1H, H-1), 4.63 and 4.77 (2d, AB system, 2H, J_{gem}=12.0, Ph*CH*$_2$O), 6.14 (d, 1H, J_{vic}=10.2, H-2′), 7.13–7.37 (m, H-1′, H–Ar), 7.45 (br t, 2H, *meta*-H–*Ph*SO$_2$), 7.57 (br t, 1H, J_{vic}=7.4, *para*-H–*Ph*SO$_2$), 7.95 (d, 2H, J_{vic}=7.6, *ortho*-H–*Ph*SO$_2$). ^{13}C NMR δ 52.3 (C-4), 55.7 (OMe), 61.9 (C-6), 70.6 (C-5), 73.4 and 76.4 (Ph*CH*$_2$O), 79.3 (C-3), 80.7 (C-2), 98.5 (C-1), 122.7 (C-2′), 127.2–129.2 (CH–Ar), 133.6 (CH–*para*-*Ph*SO$_2$), 137.9 (2*C$_{IV}$–Ar), 141.4 (C$_{IV}$–*Ph*SO$_2$), 145.8 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$, 574.5 [M+NH$_4$]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1575.

4.7.7. Methyl 2,3-di-*O*-benzyl-4-*S*-[(*E*)-2′-(phenylsulfonyl)-vinyl]-4-thio-β-D-glucopyranoside (13β*E*). Obtained from **9β** and *E*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, 65:35, then 6:4) afforded **13β*E*** with 96% yield as a colourless gum, $[\alpha]_D$ +62 (*c* 1, $CHCl_3$). ^{1}H NMR δ 2.55 (br s, 1H, OH), 3.28 (t, 1H, J_{3-4}=J_{4-5}= 10.4, H-4), 3.35–3.55 (m, 3H, H-2, H-3, H-5), 3.54 (s, 3H, OMe), 3.74 (d, 1H, J_{5-6b}<0.5, H-6b), 3.91 (br d, 1H, J_{5-6a}< 0.5, J_{6a-6b}=12.0, H-6a), 4.33 (d, 1H, J_{1-2}=7.7, H-1), 4.66 and 4.89 (2d, AB system, 2H, J_{gem}=11.1, Ph*CH*$_2$O), 4.69 and 4.83 (2d, AB system, 2H, J_{gem}=10.9, Ph*CH*$_2$O), 6.43 (d, 1H, J_{vic}=14.7, H-2′), 7.19–7.32 (m, H–Ar), 7.41 (br t, 2H, *meta*-H–*Ph*SO$_2$), 7.52 (br t, 1H, J_{vic}=7.2, *para*-H–*Ph*SO$_2$), 7.78 (d, 2H, J_{vic}=7.1, *ortho*-H–*Ph*SO$_2$), 7.82 (d, 1H, H-1′). ^{13}C NMR δ 49.5 (C-4), 57.3 (OMe), 61.8 (C-6), 74.8 and 75.9 (Ph*CH*$_2$O), 75.1 (C-5), 81.7 (C-3), 83.0 (C-2), 104.5 (C-1), 123.7 (C-2′), 127.3–129.5 (CH–Ar), 133.1 (CH–*para*-*Ph*SO$_2$), 137.7 and 138.1 (2*C$_{IV}$–Ar), 140.9 (C$_{IV}$–*Ph*SO$_2$), 144.8 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$,

574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1573.

4.7.8. Methyl 2,3-di-*O*-benzyl-4-*S*-[(*Z*)-2′-(phenylsulfonyl)-vinyl]-4-thio-β-D-glucopyranoside (13β*Z*). Obtained from **9β** and *Z*-BPSE; silica gel column chromatography (petroleum ether/AcOEt 7:3, 55:45, then 1:1) afforded **13β*Z*** with 91% yield as a colourless gum, $[\alpha]_D$ −23 (*c* 3.5, $CHCl_3$). ^{1}H NMR δ 2.10 (br s, 1H, OH), 3.12 (t, 1H, J_{3-4}=J_{4-5}=10.8, H-4), 3.37 (t, 1H, H-3), 3.40–3.55 (m, H-2, H-5), 3.56 (s, 3H, OMe), 3.81 (dd, 1H, J_{5-6b}=3.4, H-6b), 3.94 (dd, 1H, J_{5-6a}=2.0, J_{6a-6b}=12.3, H-6a), 4.34 (d, 1H, J_{1-2}=7.9, H-1), 4.58 and 4.83 (2d, AB system, 2H, J_{gem}=10.2, Ph*CH*$_2$O), 4.69 and 4.90 (2d, AB system, 2H, J_{gem}=11.1, Ph*CH*$_2$O), 6.14 (d, 1H, J_{vic}=10.2, H-2′), 7.10–7.35 (m, H-1′, H–Ar), 7.45 (br t, 2H, *meta*-H–*Ph*SO_2), 7.56 (br t, 1H, J_{vic}=7.3, *para*-H–*Ph*SO_2), 7.94 (d, 2H, J_{vic}=7.1, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 50.0 (C-4), 57.4 (OMe), 61.9 (C-6), 75.0 and 76.5 (Ph*CH*$_2$O), 75.1 (C-5), 82.5 (C-3), 83.0 (C-2), 104.7 (C-1), 122.7 (C-2′), 127.7–129.4 (CH–Ar), 133.6 (CH–*para*-*Ph*SO_2), 137.7 and 138.2 (2*C_{IV}–Ar), 141.3 (C_{IV}–*Ph*SO_2), 145.8 (C-1′). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$, 574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1596.

4.8. Oxathiane synthesis: base-catalyzed cyclization

To an ice-cold solution of the phenylsulfonylvinyl sulfides **12**, **13** (556 mg, 1 mmol/10 mL) in dry THF were successively added NaH (1 equiv) and a few crystals of Bu_4NBr. The mixture was stirred for 12 h at room temperature, then diluted with AcOEt and poured into iced water; the aqueous phases were extracted with AcOEt (10 mL) and the combined organic extracts dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography.

4.8.1. Methyl 2,3-di-*O*-benzyl-4-*O*, 6-*S*-[(1*S*)-2-(phenylsulfonyl)-ethylidene]-6-thio-α-D-glucopyranoside (10α). Obtained from either **12α*E*** or **12α*Z***; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **10α** with 52% yield as a white amorphous solid, $[\alpha]_D$ +70 (*c* 2.5, $CHCl_3$). ^{1}H NMR δ 2.75 (dd, 1H, J_{5-6b}=4.3, J_{6a-6b}=12.7, H-6b), 2.88 (d, 1H, J_{5-6a}=10.6, H-6a), 3.26 (t, 1H, J_{3-4}=J_{4-5}=9.3, H-4), 3.34 (dd, 1H, J_{7-8b}=4.1, H-8b), 3.38 (s, 3H, OMe), 3.46 (dd, 1H, J_{2-3}=9.3, H-2), 3.62 (dd, 1H, J_{7-8a}=7.2, J_{8a-8b}=14.5, H-8a), 3.74 (dt, 1H, H-5), 3.88 (t, 1H, J_{3-4}=9.3, H-3), 4.50 (d, 1H, J_{1-2}=3.7, H-1), 4.64 and 4.83 (2d, AB system, 2H, J_{gem}=12.1, Ph*CH*$_2$O), 4.73 and 4.98 (2d, AB system, 2H, J_{gem}=10.8, Ph*CH*$_2$O), 5.17 (dd, 1H, H-7), 7.20–7.55 (m, H–Ar), 7.64 (br t, 1H, J_{vic}=7.3, *para*-H–*Ph*SO_2), 7.95 (br d, 2H, J_{vic}=7.2, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 31.6 (C-6), 55.6 (OMe), 60.3 (C-8), 64.2 (C-5), 73.9 and 75.7 (Ph*CH*$_2$O), 76.1 (C-7), 78.7 and 78.9 (C-2, C-3), 84.3 (C-4), 98.9 (C-1), 127.6–129.4 (CH–Ar), 134.2 (CH–*para*-*Ph*SO_2), 138.2, 138.9, 139.3 (3*C_{IV}–Ar). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$, 574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1587.

4.8.2. Methyl 2,3-di-*O*-benzyl-4-*O*, 6-S-[(1*S*)-2-(phenylsulfonyl)-ethylidene]-6-thio-β-D-glucopyranoside (10β). Obtained from either **12β*E*** or **12β*Z***; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **10β** with 60% yield as a white amorphous solid, $[\alpha]_D$ +64 (*c* 1.7, $CHCl_3$). ^{1}H NMR δ 2.87 (dd, 1H, J_{5-6b}=4.7, J_{6a-6b}=13.8, H-6b), 2.95 (d, 1H, J_{5-6a}=9.1, H-6a), 3.27–3.40 (m, 4H, H-2, H-4, H-5, H-8b), 3.55 (s, 3H, OMe), 3.58 (t, 1H, J_{2-3}=J_{3-4}=9.1, H-3), 3.61 (dd, 1H, J_{7-8a}=7.4, J_{8a-8b}=14.5, H-8a), 4.32 (d, 1H, J_{1-2}=7.8, H-1), 4.70 and 4.84 (2d, AB system, 2H, J_{gem}=10.9, Ph*CH*$_2$O), 4.72 and 4.98 (2d, AB system, 2H, J_{gem}=10.8, Ph*CH*$_2$O), 5.14 (dd, 1H, J_{7-8b}=4.0, H-7), 7.24–7.42 (m, H–Ar), 7.52 (br t, 2H, *meta*-H–*Ph*SO_2), 7.63 (br t, 1H, *para*-H–*Ph*SO_2), 7.94 (d, 2H, J_{vic}=7.7, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 31.4 (C-6), 57.5 (OMe), 60.3 (C-8), 68.1 (C-5), 75.3 and 75.5 (Ph*CH*$_2$O), 76.2 (C-7), 81.2 (C-3), 82.0 (C-4), 83.7 (C-2), 104.7 (C-1), 127.7–129.5 (CH–Ar), 134.2 (CH–*para*-*Ph*SO_2), 138.4, 138.7, 139.2 (3*C_{IV}–Ar). MS IS *m*/*z*=525.5 [M−OMe]$^+$, 557.5 [M+H]$^+$, 574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1579.

4.8.3. Methyl 2,3-di-*O*-benzyl-6-*O*, 4-*S*-[(1*R*)-2-(phenylsulfonyl)-ethylidene]-4-thio-α-D-glucopyranoside (11α). Obtained from either **13α*E*** or **13α*Z***; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **11α** with 83% yield as a white amorphous solid, $[\alpha]_D$ −2 (*c* 1.5, $CHCl_3$). ^{1}H NMR δ 3.03 (t, 1H, J_{3-4}=J_{4-5}=10.2, H-4), 3.21 (t, 1H, J_{5-6b}=J_{6a-6b}=10.7, H-6b), 3.32 (s, 3H, OMe), 3.35 (dd, 1H, J_{7-8b}=2.5, H-8b), 3.55 (dd, 1H, J_{2-3}=9.2, H-2), 3.60 (dd, 1H, J_{8a-8b}=14.3, H-8a), 3.69 (dt, 1H, H-5), 3.85 (dd, 1H, J_{5-6a}=4.2, H-6a), 4.58 and 4.84 (2d, AB system, 2H, J_{gem}=10.6, Ph*CH*$_2$O), 4.59 (d, 1H, J_{1-2}=3.4, H-1), 4.63 and 4.77 (2d, AB system, 2H, J_{gem}=11.9, Ph*CH*$_2$O), 5.20 (dd, 1H, J_{7-8a}=9.2, H-7) 7.25–7.38 (m, 10H, H–Ar), 7.49–7.66 (m, 3H, *Ph*SO_2), 7.88 (d, 2H, J_{vic}=7.4, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 50.1 (C-4), 55.8 (OMe), 60.5 (C-8), 64.8 (C-5), 71.1 (C-6), 73.7 and 76.2 (Ph*CH*$_2$O), 77.7 (C-3), 78.3 (C-7), 81.4 (C-2), 99.2 (C-1), 126.6–129.8 (CH–Ar), 134.6 (CH–*para*-*Ph*SO_2, 138.5 and 138.6 (2*C_{IV}–Ar), 140.6 (C_{IV}–*Ph*SO_2). MS IS *m*/*z*=557.5 [M+H]$^+$, 574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1582.

4.8.4. Methyl 2,3-di-*O*-benzyl-6-*O*, 4-*S*-[(1*R*)-2-(phenylsulfonyl)-ethylidene]-4-thio-β-D-glucopyranoside (11α). Obtained from either **13α*E*** or **13α*Z***; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) (petroleum ether/AcOEt 7:3 and 6:4) afforded **11α** with 80% yield as a white amorphous solid, $[\alpha]_D$ +17 (*c* 3.5, $CHCl_3$). ^{1}H NMR δ 3.07 (t, 1H, J_{3-4}=J_{4-5}=9.4, H-4), 3.21–3.35 (m, 2H, H-5, H-6b), 3.37–3.46 (m, 3H, H-2, H-3, H-8b), 3.51 (s, 3H, OMe), 3.60 (dd, 1H, J_{7-8a}=9.2, J_{8a-8b}=14.7, H-8a), 3.91–4.01 (m, 1H, H-6a), 4.31 (d, 1H, J_{1-2}=7.0, H-1), 4.56 and 4.78 (2d, AB system, 2H, J_{gem}=10.8, Ph*CH*$_2$O), 4.69 and 4.88 (2d, AB system, 2H, J_{gem}=11.1, Ph*CH*$_2$O), 5.19 (dd, 1H, J_{7-8b}=2.8, H-7), 7.23–7.36 (m, 10H, H–Ar), 7.49–7.65 (m, 3H, *Ph*SO_2), 7.88 (d, 2H, J_{vic}=7.4, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 49.3 (C-4), 57.7 (OMe), 60.5 (C-8), 68.6 (C-5), 70.8 (C-6), 75.4 and 75.9 (Ph*CH*$_2$O), 78.2 (C-7), 80.9 (C-3), 83.9 (C-2), 105.5 (C-1), 127.3–129.5 (14*CH–Ar), 134.3 (CH–*para*-*Ph*SO_2), 138.1 and 138.6 (2*C_{IV}–Ar), 140.2 (C_{IV}–*Ph*SO_2). MS IS *m*/*z*=557.5 [M+H]$^+$, 574.5 [M+NH_4]$^+$, 579.5 [M+Na]$^+$, 595.5 [M+K]$^+$. HRMS: $C_{29}H_{32}O_7S_2$: calcd 556.1589; found 556.1586.

4.9. Oxathianes behaviour under acidic conditions: benzyl deprotection

The oxathiane was dissolved in 9:1 TFA/H_2O (100 mg/5 mL) and the mixture was stirred at 60 °C until complete consumption of the starting material. After evaporation and coevaporation with toluene, the raw product was acetylated (4 equiv of Ac_2O in 5 mL pyridine, 12 h at rt). The solution was evaporated, coevaporated with toluene and the residue was purified by column chromatography.

4.9.1. Methyl 2,3-di-*O*-acetyl-4-*O*, 6-*S*-[(1*S*)-2-(phenylsulfonyl)-ethylidene]-6-thio-α-D-glucopyranoside (14α). Obtained from **10α**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **14α** with 65% yield as a white amorphous solid, $[\alpha]_D$ +128 (*c* 0.9, $CHCl_3$). ^{1}H NMR δ 2.04, 2.07 (2s, 6H, 2*O*Ac*), 2.80 (dd, 1H, J_{5-6b}=4.2, H-6b), 2.97 (dd, 1H, J_{5-6a}=10.6, J_{6a-6b}=13.0, H-6a), 3.21 (dd, 1H, J_{7-8b}=3.2, H-8b), 3.34 (t, 1H, J_{3-4}=J_{4-5}=9.8, H-4), 3.35 (s, 3H, OMe), 3.55 (dd, 1H, J_{7-8a}=8.5, J_{8a-8b}=14.3, H-8a), 3.81 (dt, 1H, H-5), 4.86 (d, 1H, J_{1-2}=3.6, H-1), 4.80 (dd, 1H, J_{2-3}=9.8, H-2), 5.27 (dd, 1H, H-7), 5.46 (t, 1H, H-3), 7.51–7.67 (m, 3H, *Ph*SO_2), 7.87 (d, 2H, J_{vic}=7.4, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 21.1 and 21.2 (OAc), 31.9 (C-6), 55.9 (OMe), 60.1 (C-8), 64.4 (C-5), 68.7 (C-3), 71.5 (C-2), 76.4 (C-7), 81.6 (C-4), 97.6 (C-1), 128.5 and 129.8 (4*CH *ortho* and *meta*-*Ph*SO_2), 134.4 (CH–*para*-*Ph*SO_2), 140.1 (C_{IV}–*Ph*SO_2), 170.6 and 170.7 (2*CO). MS IS *m*/*z*=401.5 [M−AcOH]$^+$, 429.5 [M−OMe]$^+$, 461.5 [M+H]$^+$, 478.5 [M+NH_4]$^+$, 483.5 [M+Na]$^+$. HRMS: $C_{19}H_{24}O_9S_2$: calcd 460.0862; found 460.0852.

4.9.2. Methyl 2,3-di-*O*-acetyl-4-*O*, 6-*S*-[(1*S*)-(2-phenylsulfonyl)-ethylidene]-6-thio-β-D-glucopyranoside (14β). Obtained from **10β**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **14β** with 65% yield as a white amorphous solid, $[\alpha]_D$ +13 (*c* 2.1, $CHCl_3$). ^{1}H NMR δ 2.06, 2.10 (2s, 6H, 2*O*Ac*), 2.94 (dd, 1H, J_{5-6b}=4.2, H-6b), 3.04 (dd, 1H, J_{5-6a}=9.6, J_{6a-6b}=12.8, H-6a), 3.27 (dd, 1H, J_{7-8b}=3.2, H-8b), 3.41 (t, 1H, J_{3-4}=J_{4-5}=9.6, H-4), 3.49 (s, 3H, OMe), 3.47–3.53 (m, 1H, H-5), 3.59 (dd, 1H, J_{7-8a}=8.6, J_{8a-8b}=14.3, H-8a), 4.43 (d, 1H, J_{1-2}=7.9, H-1), 4.95 (dd, 1H, J_{2-3}=9.6, H-2), 5.24 (t, 1H, H-3), 5.25 (dd, 1H, H-7), 7.58 (t, 2H, *meta*-H–*Ph*SO_2), 7.69 (t, 1H, *para*-H–*Ph*SO_2), 7.91 (d, 2H, J_{vic}=7.4, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 21.1 and 21.2 (OAc), 31.7 (C-6), 57.6 (OMe), 60.0 (C-8), 68.5 (C-5), 71.7 (C-3), 72.0 (C-2), 76.5 (C-7), 80.6 (C-4), 102.1 (C-1), 127.7 (2*CH *ortho*-*Ph*SO_2), 129.3 (2*CH *meta*-*Ph*SO_2), 133.9 (CH–*para*-*Ph*SO_2), 139.4 (C_{IV}–*Ph*SO_2), 169.4 and 170.7 (2*CO). MS IS *m*/*z*=401.5 [M−AcOH]$^+$, 429.5 [M−OMe]$^+$, 461.5 [M+H]$^+$, 478.5 [M+NH_4]$^+$, 483.5 [M+Na]$^+$. HRMS: $C_{19}H_{24}O_9S_2$: calcd 460.0862; found 460.0849.

4.9.3. Methyl 2,3-di-*O*-acetyl-6-*O*, 4-*S*-[(1*R*)-2-(phenylsulfonyl)-ethylidene]-4-thio-α-D-glucopyranoside (15α). Obtained from **11α**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **15α** with 67% yield as a white amorphous solid, $[\alpha]_D$ +155 (*c* 2.0, $CHCl_3$). ^{1}H NMR δ 2.05, 2.09 (2s, 6H, 2*O*Ac*), 3.15 (t, 1H, J_{3-4}=J_{4-5}=9.4, H-4), 3.27–3.35 (m, 2H, H-6b, H-8b), 3.34 (s, 3H, OMe), 3.60 (dd, 1H, J_{7-8a}=9.1, J_{8a-8b}=14.7, H-8a), 3.81 (dt, 1H, H-5), 3.91 (dd, 1H, J_{5-6a}=4.5 J_{6a-6b}=10.8, H-6a), 4.90 (dd, 1H, J_{7-8b}=3.4, H-7), 4.92 (d, 1H, J_{1-2}=3.4, H-1), 5.24 (dd, 1H, J_{2-3}=9.4, H-2), 5.26 (t, 1H, J_{2-3}=9.4, J_{3-4}=9.4, H-3), 7.56 (t, 2H, *meta*-H–*Ph*SO_2), 7.67 (t, 1H, *para*-H–*Ph*SO_2), 7.89 (d, 2H, J_{vic}=7.7, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 20.9 and 21.2 (OAc), 48.9 (C-4), 55.8 (OMe), 60.3 (C-8), 64.4 (C-5), 68.5 (C-3), 71.1 (C-6), 72.3 (C-7), 78.5 (C-2), 97.8 (C-1), 128.9 (2*CH *ortho*-*Ph*SO_2), 129.5 (2*CH *meta*-*Ph*SO_2), 134.4 (CH–*para*-*Ph*SO_2), 140.2 (C_{IV}–*Ph*SO_2), 170.5 and 170.6 (2*CO). MS IS *m*/*z*=429.5 [M−OMe]$^+$, 461.5 [M+H]$^+$, 478.5 [M+NH_4]$^+$, 483.5 [M+Na]$^+$. HRMS: $C_{19}H_{24}O_9S_2$: calcd 460.0862; found 460.0857.

4.9.4. Methyl 2,3-di-*O*-acetyl-6-*O*, 4-*S*-[(1*R*)-2-(phenylsulfonyl)-ethylidene]-4-thio-β-D-glucopyranoside (15β). Obtained from **11β**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **15β** with 65% yield as a white amorphous solid, $[\alpha]_D$ −23 (*c* 3.2, $CHCl_3$). ^{1}H NMR δ 2.03, 2.09 (2s, 6H, 2*O*Ac*), 3.15 (t, 1H, J_{3-4}=J_{4-5}=9.4, H-4), 3.32 (dd, 1H, H-8b), 3.34–3.44 (m, 2H, H-5, H-6b), 3.46 (s, 3H, OMe), 3.60 (dd, 1H, J_{7-8a}=8.9, J_{8a-8b}=14.7, H-8a), 4.00 (dd, 1H, J_{5-6a}=3.8, J_{6a-6b}=10.8, H-6a), 4.39 (d, 1H, J_{1-2}=7.7, H-1), 4.90–4.97 (m, 1H, H-2), 4.99 (t, 1H, J_{2-3}=9.4, J_{3-4}=9.4, H-3), 5.22 (dd, 1H, J_{7-8b}=2.6, H-7), 7.56 (t, 2H, *meta*-H–*Ph*SO_2), 7.67 (t, 1H, *para*-H–*Ph*SO_2), 7.89 (d, 2H, J_{vic}=7.4, *ortho*-H–*Ph*SO_2). ^{13}C NMR δ 20.8 and 21.1 (OAc), 48.1 (C-4), 57.5 (OMe), 60.3 (C-8), 68.6 (C-5), 70.7 (C-6), 71.9 (C-3), 72.9 (C-2), 78.3 (C-7), 102.3 (C-1), 128.7 (2*CH *ortho*-*Ph*SO_2), 129.5 (2*CH *meta*-*Ph*SO_2), 134.4 (CH–*para*-*Ph*SO_2), 140.1 (C_{IV}–*Ph*SO_2), 169.9 and 170.6 (2*CO). MS IS *m*/*z*=429.5 [M−OMe]$^+$, 461.5 [M+H]$^+$, 478.5 [M+NH_4]$^+$, 483.5 [M+Na]$^+$, 499.5 [M+K]$^+$. HRMS: $C_{19}H_{24}O_9S_2$: calcd 460.0862; found 460.0851.

4.10. Vinyl ether synthesis: reductive desulfonylation

Six percent of NaHg (6.5 g) and NaH_2PO_4 (4 g) were added to a solution of the phenylsulfonylvinyl sulfide (150 mg) in MeOH (5 mL) and freshly distilled THF (1 mL). The mixture was stirred at room temperature until complete consumption of the starting material, and then filtered over Celite; after concentration of the filtrate, the residue was purified by column chromatography.

4.10.1. Methyl 2,3-di-*O*-benzyl-6-*S*-vinyl-6-thio-α-D-glucopyranoside (17α). Obtained from **12α**; silica gel column chromatography (petroleum ether/AcOEt 9:1, then 85:15) afforded **17α** with 59% yield as a colourless gum, $[\alpha]_D$ +38 (*c* 1.6, $CHCl_3$). ^{1}H NMR δ 2.93 (dd, 1H, J_{5-6b}=2.1, J_{6a-6b}=13.8, H-6b), 3.17 (d, 1H, J_{5-6a}<0.5, H-6a), 3.34–3.42 (m, 1H, H-4), 3.39 (s, 3H, OMe), 3.53 (dd, 1H, H-2), 3.75 (m, 1H, J_{4-5}=8.3, H-5), 3.77 (t, 1H, J_{2-3}=9.6, H-3), 4.62 (d, 1H, J_{1-2}=3.4, H-1), 4.66 and 4.77 (2d, AB system, 2H, J_{gem}=11.9, Ph*CH*$_2$O), 4.69 and 5.04 (2d, AB system, 2H, J_{gem}=11.5, Ph*CH*$_2$O), 5.16 (d, 1H, H-2′*Z*), 5.17 (d, 1H, $J_{2'Z-2'E}$<0.5, H-2′*E*), 6.40 (dd, 1H, $J_{1'-2'E}$=16.6, $J_{1'-2'Z}$=10.1, H-1′ vinyl), 7.30–7.38 (m, 10H, H–Ar). ^{13}C NMR δ 33.6 (C-6), 55.6 (OMe), 70.4 (C-5), 73.1 (C-4), 73.5 and 75.8 (Ph*CH*$_2$O), 80.3 (C-2), 81.6 (C-3), 98.3 (C-1), 111.5 (C-2′), 128.4–129.1 (CH–Ar), 135.2 (C-1′), 140.4 and 141.1 (2*C_{IV}–Ar). MS IS *m*/*z*=439.5 [M+Na]$^+$, 455.5 [M+K]$^+$. HRMS: $C_{23}H_{28}O_5S$: calcd 416.1657; found 416.1641.

4.10.2. Methyl 2,3-di-*O*-benzyl-6-*S*-vinyl-6-thio-β-D-glucopyranoside (17β). Obtained from **12β**; silica gel column chromatography (petroleum ether/AcOEt 9:1, then 85:15) afforded **17β** with 56% yield as a white amorphous solid, $[\alpha]_D$ +4 (*c* 1.7, $CHCl_3$). ^{1}H NMR δ 2.77 (dd, 1H, J_{5-6b}=8.3, J_{6a-6b}=13.8, H-6b), 3.17 (dd, 1H, J_{5-6a}=2.5, H-6a), 3.40–3.50 (m, 4H, H-2, H-3, H-4, H-5,), 3.58 (s, 3H, OMe), 4.34 (d, 1H, J_{1-2}=6.8, H-1), 4.66 and 4.98 (2d, AB system, 2H, J_{gem}=11.5, PhCH_2O), 4.71 and 4.94 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 5.16 (d, 1H, H-2′*Z*), 5.21 (d, 1H, $J_{2'Z-2'E}$<0.5, H-2′*E*), 6.45 (dd, 1H, $J_{1'-2'E}$=16.8, $J_{1'-2'Z}$=10.0, H-1′), 7.26–7.39 (m, 10H, H–Ar). ^{13}C NMR δ 34.0 (C-6), 57.5 (OMe), 73.3 (C-4), 74.9 and 75.6 (PhCH_2O), 75.5 (C-5), 82.4 (C-2), 84.1 (C-3), 105.2 (C-1), 111.3 (C-2′), 128.1–129.1 (CH–Ar), 133.6 (C-1′), 138.7 and 138.8 (2*C_{IV}–Ar). MS IS *m*/*z*=385.5 $[M-OMe]^+$, 417.5 $[M+H]^+$, 434.5 $[M+NH_4]^+$. HRMS: $C_{23}H_{28}O_5S$: calcd 416.1657; found 416.1648.

4.10.3. Methyl 2,3-di-*O*-benzyl-4-*S*-vinyl-4-thio-α-D-glucopyranoside (18α). Obtained from **13α**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **18α** with 71% yield as an amorphous white solid, $[\alpha]_D$ +40 (*c* 1.8, $CHCl_3$). ^{1}H NMR δ 2.93 (t, 1H, J_{3-4}=9.2, H-4), 3.39 (s, 3H, OMe), 3.50 (dd, 1H, J_{2-3}=9.2, H-2), 3.71 (ddd, J_{5-6a}=3.0, J_{5-6b}=10.2, H-5), 3.82–3.93 (m, 3H, H-3, H-6a, H-6b), 4.63 (d, 1H, J_{1-2}=3.4, H-1), 4.65 and 4.82 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.88 (s, 2H, PhCH_2O), 5.26 (d, 1H, H-2′*Z*), 5.38 (d, 1H, $J_{2'Z-2'E}$< 0.5, H-2′*E*), 6.45 (dd, 1H, $J_{1'-2'E}$=16.6, $J_{1'-2'Z}$=9.8, H-1′), 7.26–7.43 (m, 10H, H–Ar). ^{13}C NMR δ 49.2 (C-4), 55.7 (OMe), 62.9 (C-6), 71.6 (C-5), 73.7 and 76.8 (PhCH_2O), 79.2 (C-3), 81.2 (C-2), 98.9 (C-1), 115.1 (C-2′), 126.3–128.9 (CH–Ar), 131.3 (C-1′), 139.1 and 139.4 (2*C_{IV}–Ar). MS IS *m*/*z*=385.5 $[M-OMe]^+$, 417.5 $[M+H]^+$, 434.5 $[M+NH_4]^+$, 439.5 $[M+Na]^+$. HRMS: $C_{23}H_{28}O_5S$: calcd 416.1657; found 416.1639.

4.10.4. Methyl 2,3-di-*O*-benzyl-4-*S*-vinyl-4-thio-β-D-glucopyranoside (18β). Obtained from **13β**; silica gel column chromatography (petroleum ether/AcOEt 7:3, then 6:4) afforded **18β** with 66% yield as an amorphous white solid, $[\alpha]_D$ +39 (*c* 2.5, $CHCl_3$). ^{1}H NMR δ 2.98 (t, 1H, $J_{3,4}$=J_{4-5}= 10.0, H-4), 3.31–3.52 (m, 3H, H-2, H-3, H-5), 3.59 (s, 3H, OMe), 3.82–4.07 (m, 2H, H-6a, H-6b), 4.35 (d, 1H, J_{1-2}= 7.9, H-1), 4.72 and 4.92 (2d, AB system, 2H, J_{gem}=11.1, PhCH_2O), 4.86 (s, 2H, PhCH_2O), 5.27 (d, 1H, H-2′*Z*), 5.39 (d, 1H, $J_{2'Z-2'E}$<0.5, H-2′*E*), 6.43 (dd, 1H, $J_{1'-2'E}$=16.6, $J_{1'-2'Z}$=9.8, H-1′), 7.28–7.35 (m, 10H, H–Ar). ^{13}C NMR δ 48.7 (C-4), 57.6 (OMe), 63.4 (C-6), 75.3 and 76.9 (PhCH_2O), 76.2 (C-5), 82.5 (C-2), 83.8 (C-3), 105.1 (C-1), 116.1 (C-2′), 126.8–129.3 (CH–Ar), 131.8 (C-1′), 139.3 and 139.4 (2*C_{IV}–Ar). MS IS *m*/*z*=385.5 $[M-OMe]^+$, 417.5 $[M+H]^+$, 434.5 $[M+NH_4]^+$. HRMS: $C_{23}H_{28}O_5S$: calcd 416.1657; found 416.1650.

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The behaviour of the natural pyranonaphthoquinone pentalongin in alcoholic solvents

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Abstract—Pentalongin, the major constituent of the roots of the East African medicinal plant *Pentas longiflora* Oliv., undergoes degradation reactions when dissolved in alcoholic solvents. Although these reactions were thought initially to be of a photochemical nature, it is proven that degradation occurs also in the dark. These degradation reactions result in four new derivatives of pentalongin, which were elucidated as 3,4-dihydro-3-methoxypentalongin **4**, 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5**, 10b-hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]naphtho-[2,3-*c*]pyran-6-one **6** and 3,4-dihydro-*trans*-3,4-diethoxypentalongin **7**.

1. Introduction

Pentas longiflora Oliv. (Rubiaceae), a woody herb from oriental intertropical Africa (Rwanda, Kenia), locally known as Isagara or Nekilango is used in the African traditional medicine to treat scabies and the skin mycosis pityriasis versicolor.[1] The two major constituents of the root bark of *P. longiflora*, pentalongin **1** and mollugin **2** were previously isolated[1,2] and a bioassay-guided fractionation revealed that pentalongin was the antifungal principle.[3] Pentalongin is a member of the family of naturally occurring pyranonaphthoquinone antibiotics, which are the subject of many synthetic studies.[4] Mollugin is an important benzisochromene antibiotic isolated the first time from *Gallium mollugo*.[5] Recently, a new type of tetracyclic naphthoquinone was isolated from the hexane extract of the root bark of *P. longiflora*, which was named isagarin **3** (Fig. 1).[6,7]

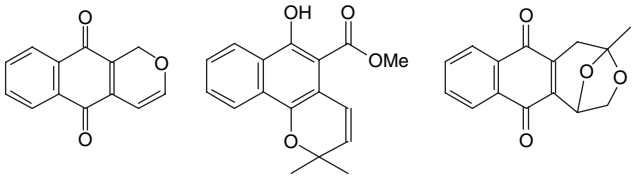

Figure 1. Isolated compounds from *P. longiflora*.

In continuation of the study of the chemical constituents of this plant, several new pyranonaphthoquinones **4**, **5** and **6**, originating from the intrinsic instability of pentalongin **1** towards the eluting solvent, are described. These results are important in view of the fact that pentalongin **1** is the active principle of the medicinal plant *P. longiflora* and that its instability in alcoholic solvents compromises its isolation.

2. Results and discussion

Previously, pentalongin **1** was synthesised in our group via several synthetic methods.[7a,b] It was observed that pentalongin **1** is not a very stable compound when dissolved in methanol. A change in colour appeared by which the intense red colour of pentalongin changes to yellow due to degradation upon standing. In contrast, crystalline pentalongin is not harmed by irradiation, even after a prolonged irradiation of 5 days. Due to the fact that pentalongin was discovered as the active principle of *P. longiflora*, the stability of this lead compound is important.

Indeed, during the fractionation of the hexane extract of the roots of *P. longiflora* on silica gel by MPLC and by elution with methanol, pentalongin **1** and other methoxylated derivatives **4**–**6** were obtained in small quantities. Similarly, when ethanol was used for elution over silica gel, a diethoxylated derivative **7** was isolated. These compounds are so-called artefacts from the isolation procedure of pentalongin and are a consequence of the instability of pentalongin towards the eluting solvent (Fig. 2).

Keywords: Pentalongin; Pyranonaphthoquinone; Natural products; *Pentas*.
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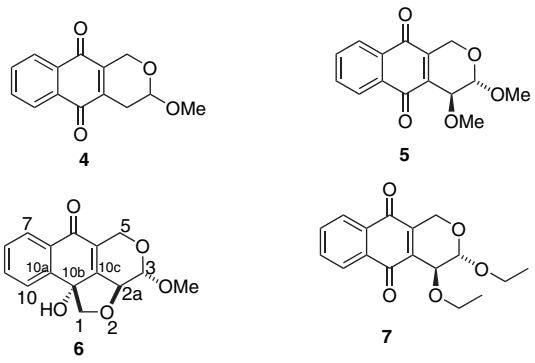


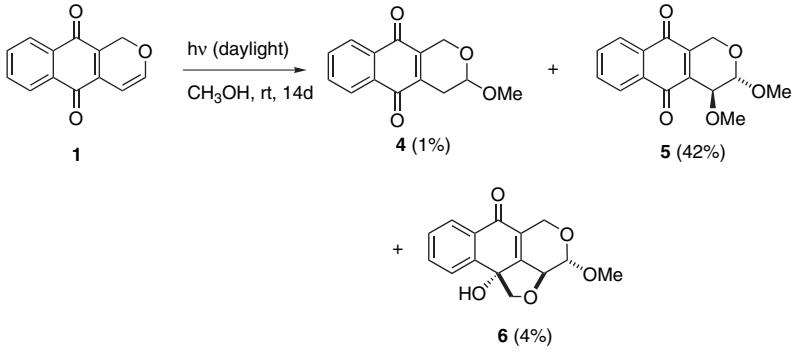
Figure 2. Artefacts in the isolation of pentalongin.

At first, the instability of pentalongin was thought to be of a photochemical nature. Based on the proposal that compounds **4**, **5** and **6** could be obtained by light irradiation of pentalongin, the photochemical reaction of pentalongin in methanol under daylight irradiation was carried out (Scheme 1).

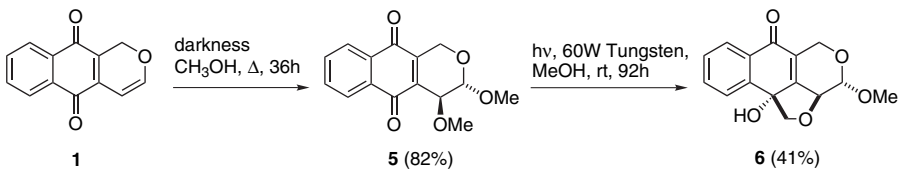
A solution of pentalongin in methanol was left in daylight at room temperature for 14 days in a glass vial. Chromatographic separation of the reaction mixture led to compounds **4**, **5** and **6** in 1%, 42% and 4% yield, respectively. This result does not exclude the possibility that pentalongin reacts with the solvent, i.e., methanol, in the absence of daylight. Therefore, a solution of pentalongin in methanol was heated under reflux in complete darkness (Scheme 2). The reaction was monitored on TLC and revealed the complete disappearance of pentalongin after 36 h. Spectroscopic analysis made clear that 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** was formed in 82% yield. No trace of compound **4** or compound **6** was found. In order to exclude the influence of radicals, the reaction was repeated in a degassed solution under a nitrogen atmosphere and with the addition of 20 mol % hydroquinone as a radical scavenger. Again, using these reaction conditions and after 64 h of reflux in methanol in the dark, all pentalongin was consumed and compound **5** was formed (isolated yield 76%).

In an attempt to explain the formation of the tetracyclic compound **6** in the daylight, the dimethoxy compound **5** was exposed to radiation. A solution of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** in methanol in a glass vial was irradiated by means of a 60 W tungsten lamp while being cooled in an ice-bath. The reaction was monitored by UV-analysis (Fig. 3). Compound **5** showed a typical absorption at 260 nm and 446 nm. After 36 h the absorption pattern was significantly different. After 96 h, no further change appeared and the reaction was stopped. Spectroscopic analysis revealed the absence of compound **5** and the presence of tetracylic compound **6** in 41% yield together with some unidentified material. In order to exclude the influence of the solvent, the reaction was repeated in hexane and this resulted in the same compound **6** in a similar yield of 37% together with unidentified material.

These findings make it possible to propose the following reaction mechanism (Scheme 3). The fact that the formation of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** is possible in complete absence of light, in a nitrogen atmosphere and in the presence radical scavengers strongly suggests a non-radicalar mechanism. A Michael addition is feasible at the C-3 carbon, which results in the adduct **8**. Bearing in mind the anomeric effect, it leaves the methoxy moiety to end up in a pseudoaxial manner.[8] In the next step, there are two possibilities. Keto–enol tautomerisation results in the formation of compound **4**, which can be found back in minor quantities (1%). More likely, a second Michael addition occurs across enone **8** to afford intermediate **9**, which results in the dimethoxy compound **5** after spontaneous oxidation by air. This compound **5** is isolated as the major fraction in an 82% yield. By reason of steric hindrance the methoxy group attacks from the *anti*-side. The reasoning behind the relative



Scheme 1.



Scheme 2.

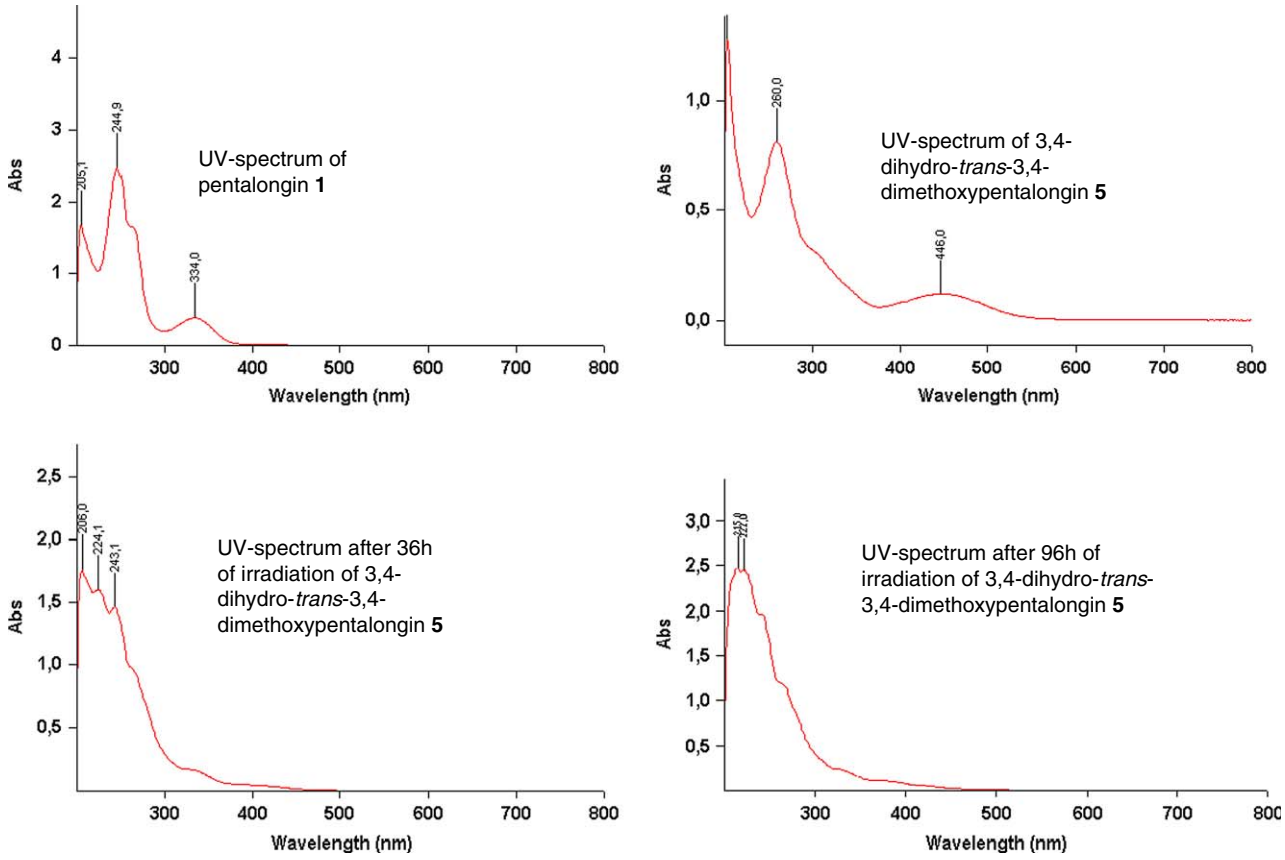
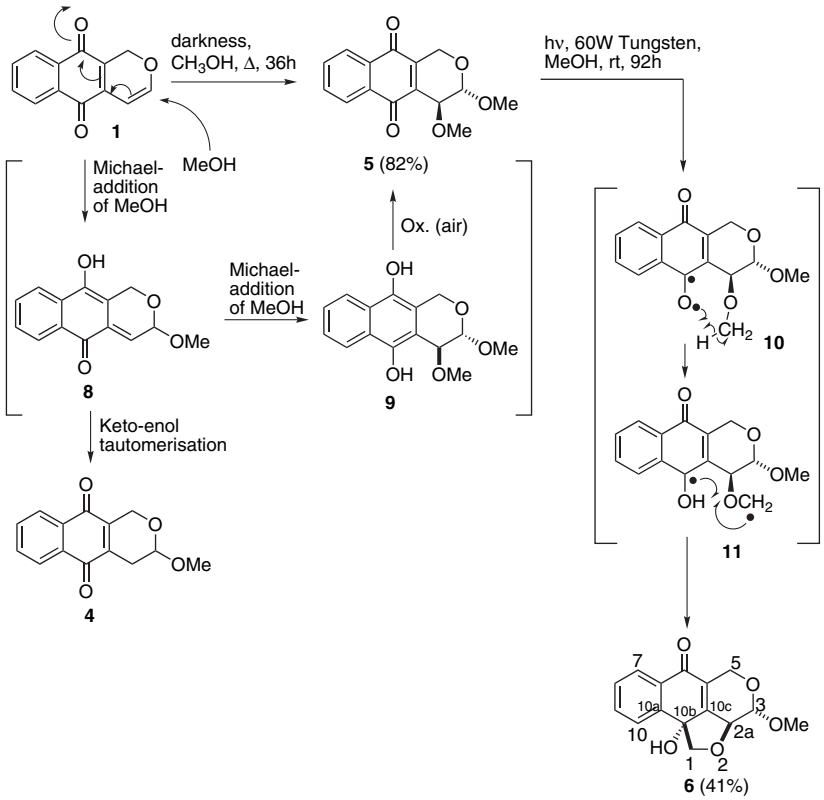


Figure 3. UV-spectra of the reaction mixture of the reaction of pentalongin **1** in methanol in the dark.



Scheme 3.

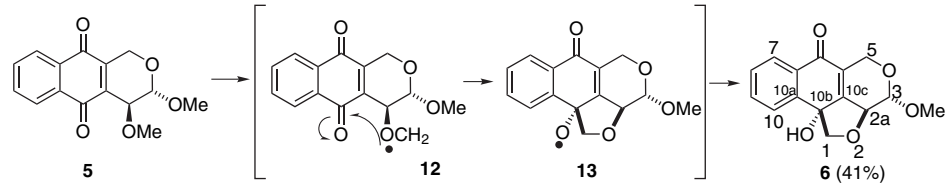
stereochemistry of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** was experimentally confirmed by ^{1}H NMR. The very small value of 0.9 Hz for the coupling constant ($J_{3,4}$=0.9 Hz) in the ^{1}H NMR spectrum of compound **5** indicates a pseudoequatorial–equatorial position for H-4 and H-3 in the half-chair conformation. In addition, the confirmation of the pseudoequatorial orientation of H-4 is based on the axial orientation of methoxy group at C-3, favoured by the anomeric effect.[8] Furthermore, the pseudoequatorial orientation of H-4 could be confirmed by long-range coupling between H-1 and H-4 with $J_{1,4}$=1.3 Hz ($Ja'a'>Ja'e'=Je'a'>Je'e'<0.5$ Hz).[9]

The formation of the tetracyclic compound **6** in the irradiation reaction can be explained by a Norrish type II photocyclisation. This type II photocyclisation has been observed before in the unusual photocyclisation of 2-alkoxy-1,4-naphthoquinones.[10] An intramolecular H-abstraction of the methoxy group at C-4 by the oxygen radical of the carbonyl results in radical **11**. This biradical undergoes a cyclisation reaction resulting in the final product **6**.[11] An alternative cyclisation mechanism is depicted in Scheme 4. Intermolecular H-abstraction of a proton at the methoxy group at C-4 results in compound **12**. This will result in a ring closure at the carbon of the carbonyl to form the intermediate radical **13**, which will result in the final compound **6** after intermolecular H-abstraction.

In addition, the trans-configuration of the two protons H-2a and H-3 of the tetracyclic compound **6** was determined by NOE-experiments. The coupling constant ($J_{2a,3}$=6.3 Hz) in the ^{1}H NMR spectrum is an insufficient indication for the stereochemistry of the compound. Therefore, NOE-experiments were performed (Fig. 4). Irradiation of the methoxy group at 3.59 ppm ($CDCl_3$) resulted in a NOE (4.6%) for the signal of H-2a at 4.20 ppm and a NOE (3.4%) for the signal of H-5 at 4.52 ppm. Irradiation of the signal at 4.20 ppm gave a substantial NOE (5.8%) for the methoxy peak at 3.59 ppm. These findings can only be explained if the compound adopts a structure in which H-2a and H-3 have a trans-configuration.

In order to check the influence of the alcoholic solvent on the isolation of natural products from *P. longiflora*, chromatographic separation of a pentalongin-rich fraction with silica gel was performed with ethanol. *trans*-3,4-Diethoxy-3,4-dihydropentalongin **7** was isolated by MPLC on silica gel by elution with EtOH to give a light yellow oil (3.1% yield). The mass spectrum (EIMS) displayed a molecular ion (M^+; 3%) at *m*/*z* 302, which is consistent with the molecular formula $C_{17}H_{18}O_5$. The isolated compound showed a close resemblance to *trans*-3,4-dihydro-3,4-dimethoxypentalongin **5** as demonstrated by the same pattern of IR, ^{1}H NMR and ^{13}C NMR spectral data. Only the two methoxy signals in **5** were replaced by two ethoxy signals. Accordingly, the structure of the isolated compound was deduced as *trans*-3,4-diethoxy-3,4-dihydropentalongin **7**. The trans-configuration for H-3 and H-4 was determined by ^{1}H NMR. The very small coupling constant ($J_{3,4}$=1.0 Hz) in the ^{1}H NMR spectrum ($CDCl_3$) of compound **7** indicates a pseudoequatorial–equatorial relationship of H-4 and H-3. In addition, the pseudoequatorial configuration was confirmed by long-range coupling of H-4 and H-1 ($J_{4a'1a'}$=1.8 Hz), which indicated the trans-configuration for H-3 and H-4. All signals of the IR spectrum, DEPT spectrum, 2D-COSY spectrum and the HETCOR spectrum were in accordance with the assigned structure **7**.

To verify the conversion of pentalongin to *trans*-3,4-diethoxy-3,4-dihydropentalongin **7**, pentalongin **1** was dissolved in absolute ethanol and left in daylight at room temperature for 14 days (Scheme 5). This reaction was much more complex as compared to the same reaction in methanol from which these compounds were isolated in a total yield of 47%. However, the reaction of pentalongin **1** in EtOH led to the formation of *trans*-3,4-diethoxy-3,4-dihydropentalongin



Scheme 4.

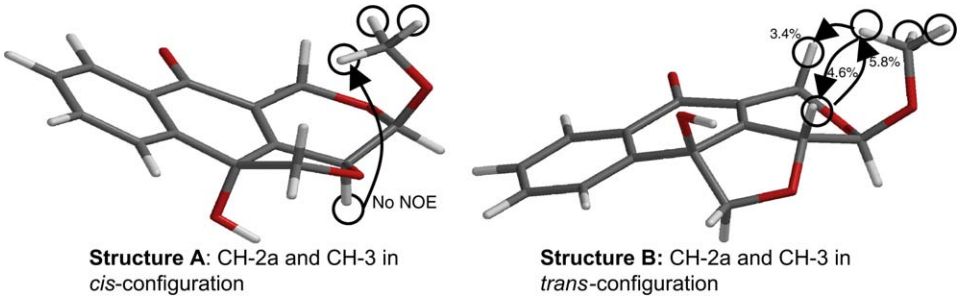
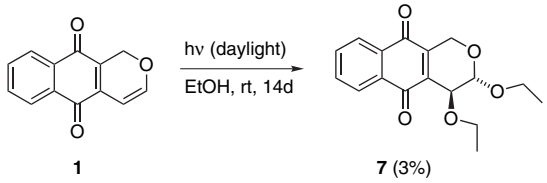


Figure 4. NOE analysis of the tetracyclic compound **6** ($CDCl_3$).

7 in only 3% yield. A range of unidentified compounds were noted by TLC analysis and by NMR spectroscopy. Apparently, several unidentified, not specific reactions took place and it was decided not to examine further this complex reaction.



Scheme 5.

3. Conclusion

Crystalline pentalongin **1** is not harmed by irradiation. Pentalongin **1** in methanol is easily transformed into compounds **4**, **5** and **6**. Pentalongin **1** can also be converted into the diethoxy analogue **7** in a low yield by treating it with ethanol. These compounds are new derivatives of the naturally occurring pentalongin **1**. Irradiation of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** results in the tetracyclic compound **6**, which is a novel compound with a novel heterocyclic skeleton.

4. Experimental

4.1. General

Melting points were determined on a Buchi 535 apparatus. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Jeol JNM-EX 300 NMR spectrometer. IR spectra were measured with a Perkin Elmer Model 983 spectrophotometer. Mass spectra were recorded with a Varian MAT 112 mass spectrometer (70 eV).

4.2. Plant material

The roots of *P. longiflora* were collected in the Menengai Crater (Nakuru District, Kenya) at an altitude of 2400 m on July 24, 1996. G. M. Mungai and D. O. Nyakundi (National Museum of Nairobi, Kenya) identified the plant and voucher herbarium species were deposited in the East African Herbarium at the National Museum in Nairobi (Kenya) (Mungai and Nyakundi no. 464). The roots were dried in a ventilated oven at 45 °C during 3 days and powdered mechanically (Retsch GmbH, type SK1, 1100 W, 2840 rpm, ∅ 2 mm).

4.3. Extraction

The powdered roots of *P. longiflora* (4.1 kg) were successively extracted in a percolator until exhaustion with *n*-hexane (C_6H_{12}), dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and methanol (MeOH). The extracts were filtered over a filter paper (Schleicher and Schuell, 5951/2 folded filters, ∅ 240 mm) and concentrated under reduced pressure at 40 °C yielding a dark red residue (44.0 g, yield 1.07%).

4.4. Isolation of pentalongin derivatives

The hexane extract (44 g) was absorbed on silica gel (440 g) and submitted to medium pressure liquid chromatography MPLC (glass column 460×100 mm ∅) on silica gel. Sample application was executed with a Prep Elute dry application column from Büchi (230×23 mm ∅). Solvent delivery was performed with a chromatography pump. Flow rate: ≅110 ml/min, corresponding to ≅25 bar backpressure. The elution was performed using an *n*-hexane/EtOAc gradient: Hex/EtOAc 5% (180 min), Hex/EtOAc 10% (60 min), Hex/EtOAc 25% (30 min), Hex/EtOAc 50% (30 min), EtOAc 100% (30 min), and finally washed with MeOH 100% (60 min). After monitoring by TLC, 26 fractions were obtained. Fraction 9 (Hex/EtOAc 5%) afforded a pure compound (5.870 g, 0.143% yield) that was identified as pentalongin **1**, based on its spectral data and its physical properties. Spectral data of pentalongin have been described previously.[1,2]

4.5. Reaction of pentalongin 1 in alcoholic solvents in daylight

Pure pentalongin **1** (700 mg) was dissolved in 35 ml of absolute methanol, and this solution was subjected to daylight (sunlight) during a period of two weeks. The solvent was removed in vacuo to give the crude product, which was chromatographed on silica gel by MPLC at pressure from 20 to 30 bar. Flow rate: ≅90 ml/min corresponding to ≅25 bar backpressure to give compounds **4** (1%), **5** (42%) and **6** (4%).

4.5.1. 3-Methoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (3-methoxy-3,4-dihydropentalongin) 4. Yellow crystals, mp 125.6–126.3 °C (from $CHCl_3$). IR (KBr) ν_{max}: 1655 (C=O), 1650 (C=O), 1590 (C=C), 1330, 1290, 1220, 1130, 1050, 1005, 860, 790 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.74–2.78 (2H, m, CH_2-4), 3.48 (3H, s, OMe), 4.56 (1H, d×t, J_d=18.5 Hz, J_t=3.3 Hz, C*H*H-1), 4.70 (1H, d×t, J_d=18.5 Hz, J_t=2.0 Hz, CH*H*-1) 5.02 (1H, t, J=3.0 Hz, CH-3), 7.70–7.74 (2H, m, =CH-7 and =CH-8), 8.05–8.10 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.42 (CH_2-4), 55.39 (OMe), 56.51 (CH_2-1), 96.63 (O–*C*H–OMe), 126.39 and 126.64 (=CH-6 and =CH-9), 131.76 and 131.98 (2×=C_q), 133.69 and 133.76 (=CH-7 and =CH-8), 139.22 and 141.14 (2×=C_q), 183.33 and 183.46 (2×C=O). EIMS *m*/*z* (rel int.): 244 (M^+; 9), 213 (8), 184 (100), 156 (27), 128 (38), 104 (12), 76 (17), 50 (8). Anal. Calcd $C_{14}H_{12}O_4$: C 68.85, H 4.95; found C 68.98, H 5.12.

4.5.2. *trans*-3,4-Dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (*trans*-3,4-dimethoxy-3,4-dihydropentalongin) 5. Yellow sticky compound, mp 90.4–91.1 °C (from MeOH). IR (KBr) ν_{max}: 1665 (C=O), 1650 (C=O), 1595 (C=C), 1330, 1290, 1252, 1190, 1180, 1150, 1110, 900, 700 cm^{-1}. ^{1}H NMR (270 MHz $CDCl_3$): δ 3.48 (3H, s, OMe), 3.59 (3H, s, OMe), 4.23 (1H, d×d, J=1.3, J=0.9 Hz, CH-4), 4.49 (1H, d×d, J_d=19.5 Hz, J_d=1.3 Hz, C*H*H-1), 4.75 (1H, d, J=19.5 Hz, CH*H*-1), 5.02 (1H, d, J=0.9 Hz, CH-3), 7.72–7.76 (2H, m, =CH-7 and =CH-8), 8.05–8.14 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 55.97 (OMe), 56.38 (CH_2-1), 59.08 (OMe), 68.60 (CH-4), 97.78 (CH-3), 126.16 and 126.55

(=CH-6 and =CH-9), 131.69 and 131.92 (2×=C_q), 133.79 and 134.10 (=CH-7 and =CH-8), 136.99 and 142.96 (2×=C_q), 182.94 and 183.66 (2×C=O). EIMS *m/z* (rel int.): 274 (M^+; 3), 242 (16), 227 (12), 214 (35), 197 (27), 183 (13), 163 (9), 155 (8), 141 (11), 127 (16), 115 (21), 97 (21), 85 (38), 71 (58), 57 (100). Anal. Calcd $C_{15}H_{14}O_5$: C 65.69, H 5.15; found C 65.87, H 5.27.

4.5.3. 10b-Hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]naphtho[2,3-*c*]pyran-6-one 6. Light yellow solid compound, mp 194.4–195.3 °C. IR (KBr) ν_{max}: 3400 (OH), 1650 (C=O), 1600 (C=C), 1450, 1400, 1390, 1300, 1120, 1230, 1175, 1150, 1105, 1075, 1045, 1015, 990, 935, 870, 810, 775, 710 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 3.58 (3H, s, OCH_3), 3.72 (1H, d, *J*=9.4 Hz, C*H*H-1), 4.19 (1H, d×t, *J*=6.3 Hz, *J*=2.3 Hz, CH-2a), 4.48 (1H, d×d, *J*=17.2 Hz, *J*=2.6 Hz, C*H*H-5), 4.51 (1H, d, *J*=9.4 Hz, CH*H*-1), 4.75 (1H, d, *J*=6.3 Hz, CH-3), 4.84 (1H, d×d, *J*=17.2, *J*=2.1 Hz, CH*H*-5), 7.50–7.70 (2H, m, =CH-8 and =CH-9), 8.09–8.75 (2H, m, =CH-7 and =CH-10). ^{13}C NMR (68 MHz, $CDCl_3$): δ 181.88 (C=O), 151.80 (=C_q-10c), 140.6 (=C_q-10a), 133.72 (=CH-7), 130.15 (=C_q-6a), 129.36 (=CH-9), 128.83 (=C_q-5a), 127.85 (=CH-10), 127.14 (=CH-8), 102.76 (OCO), 77.33 (CH_2-1), 73.92 (CH-2a), 72.18 (C_q-10b), 63.70 (CH_2-5), 56.69 (OCH_3). EIMS *m/z* (rel int.): no M^+, 258 (M^+-16; 1), 214 (47), 197 (100), 169 (10), 141 (15), 128 (13), 115 (14), 101 (4), 85 (7), 77 (11). Anal. Calcd $C_{15}H_{14}O_5$: C 65.69, H 5.15; found C 65.41, H 5.06.

4.5.4. *trans*-3,4-Diethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (*trans*-3,4-diethoxy-3,4-dihydropentalongin) 7. Pure pentalongin **1** (100 mg) was dissolved in 35 ml of absolute ethanol and this solution was subjected to daylight (sunlight) during a period of two weeks. The solvent was removed in vacuo to give the crude product, which was chromatographed on silica gel by MPLC at a pressure from 20 to 30 bar. Flow rate: ≅90 ml/min corresponding to ≅25 bar backpressure to afford compound **7** as a light yellow oil (3.1% yield). IR (KBr) ν_{max}: 1665 (C=O), 1650 (C=O), 1590 (C=C), 1480, 1450, 1430, 1410, 1330, 1290, 1250, 1180, 1150, 1110, 1100, 1070, 900, 880, 850, 790 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.21 (3H, t, *J*=7.3 Hz, CH_3), 1.25 (3H, t, *J*=7.3 Hz, CH_3), 3.48–3.73 (2H, m, OCH_2), 3.78–3.97 (2H, m, OCH_2), 4.30 (1H, dd, *J*=1.8 Hz, *J*=1.0 Hz, =CH-3), 4.47 (1H, d×d, *J*=19.4 Hz, *J*=1.8 Hz, C*H*H-1), 4.75 (1H, d, *J*=19.4 Hz, CH*H*-1), 5.09 (1H, d, *J*=1.0 Hz, CH-4), 7.73–7.76 (2H, m, =CH-7 and =CH-8), 8.06–8.14 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.98 (CH_3), 15.61 (CH_3), 56.33 (CH_2-1), 64.06 (OCH_2), 67.25 (OCH_2), 67.54 (CH-4), 97.03 (CH-3), 126.12 and 126.52 (CH-6 and CH-9), 131.7 and 132.09 (2×=C_q), 133.7 and 134.05 (=CH-7 and =CH-8), 137.4 and 142.9 (2×=C_q), 182.9 and 183.8 (2×C=O). EIMS *m/z*: 302 (M^+; 3), 257 (7), 228 (100), 221 (8), 212 (10), 200 (31), 194 (64), 187 (10), 186 (15), 173 (13), 172 (90), 144 (23). Anal. Calcd $C_{17}H_{18}O_5$: C 67.54, H 6.00; found C 67.69, H 5.88.

4.6. Reaction of pentalongin 1 in the absence of daylight

Absolute methanol (20 ml) was degassed by nitrogen and 20 mg hydrochinon was added. The solution was stirred for 30 min under a nitrogen atmosphere. Then 100 mg of pentalongin **1** was added in complete darkness. After 64 h of refluxing, the solution was cooled and the solvent was evaporated taking care to avoid daylight irradiation. Flash chromatography using Hex/EtOAc 85/15 as eluents resulted in 105 mg (82%) of *trans*-3,4-dimethoxy-3,4-dihydropentalongin) **5** as a yellow sticky compound (R_f-value: 0.2). Spectral data are as previously described, vide supra.

4.7. Reaction of *trans*-3,4-dimethoxy-3,4-dihydropentalongin 5 under irradiating conditions

A solution of 40 mg of *trans*-3,4-dimethoxy-3,4-dihydropentalongin **5** in 5 ml of absolute methanol in a glass vial was put in a reflexion chamber and a tungsten lamp of 60 W was used to irradiate the sample. The glass vial was put at a sufficient distance of the tungsten lamp taking care-not to heat the reaction. When the temperature reached 35 °C the glass vial was cooled down in an ice-bath. The reaction was monitored by UV and after 96 h the solvent was evaporated. Thin layer chromatography was applied to purify the mixture using Hex/EtOAc 9/1 as eluent, which resulted in 16 mg (41%) of a yellow solid compound, i.e., 10b-hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]-naphtho[2,3-*c*]pyran-6-one **6** (R_f-value: 0.48). Spectral data are as previously described, vide supra.

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