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Tetrahedron

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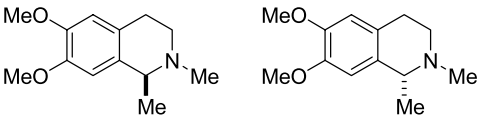
Andrea B. J. Bracca and Teodoro S. Kaufman*



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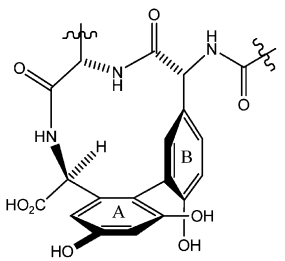

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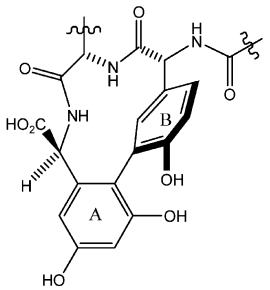

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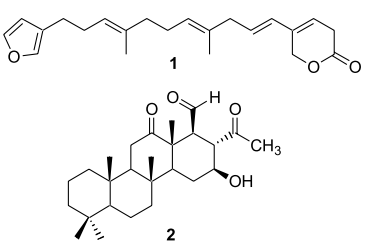

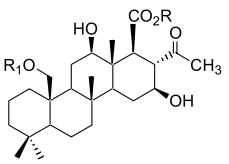

6 R=Me, R_1=H
7 R=H, R_1=H
8 R=Me, R_1=Ac

A new furanoterpene (**1**), and nine scalarane sesterterpenes, of which four (**2**, **6**–**8**) are new, were isolated from Madagascan *Lendenfeldia* sponges. Compound **1** was found to be a potent inhibitor of HIV-1 RT. Compounds **2**, **6**, **9** and **10** exhibited cytotoxicity against several tumor cells.

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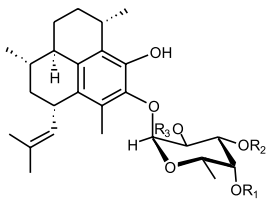

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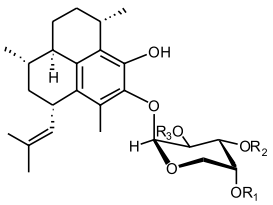
2: R_1 = Ac, R_2, R_3 = H
3: R_2 = Ac, R_1, R_3 = H
4: R_3 = Ac, R_1, R_2 = H



5: R_1, R_2, R_3 = H
6: R_1 = Ac, R_2, R_3 = H
7: R_2 = Ac, R_1, R_3 = H

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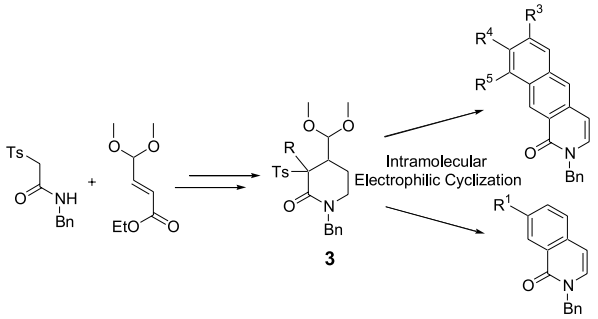

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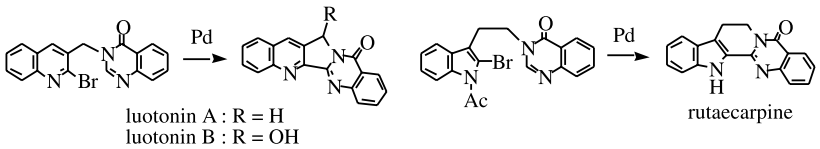

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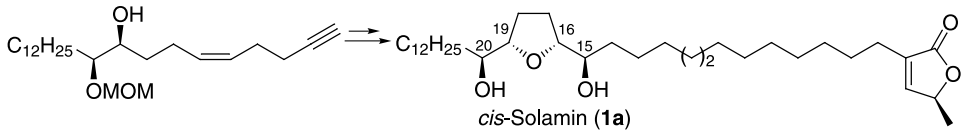
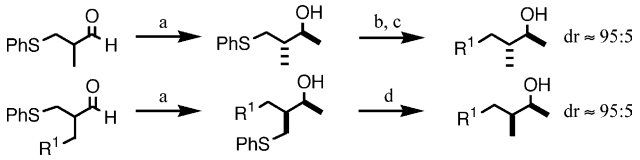


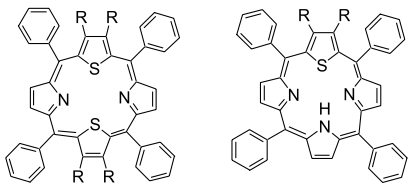
cis-Solamin (**1a**)

Diastereoselective addition of organozinc reagents to 2-alkyl-3-(arylsulfanyl)propanals **pp 10659–10669**
Michael Larsson, Elodie Galandrin and Hans-Erik Högberg*



(a) Lewis acid catalysed dimethylzinc addition; (b) 1. Prot. and oxidation to sulfone, 2. Alkylation; (c) Deprot. and desulfonation; (d) Desulfurisation.

Synthesis and crystal structures of 2,3,12,13-tetraalkoxy-21,23-dithiaporphyrins and 2,3-dialkoxy-21-monothiaporphyrins **pp 10671–10680**
Neeraj Agarwal, C.-H. Hung and Mangalampalli Ravikanth*



R = OCH_3, OC_4H_9, OC_8H_{17}, $OC_{12}H_{25}$

A series of 21,23-dithia and 21-monothiaporphyrins having methoxy, butoxy, octyloxy and dodecyloxy substituents at β-thiophene carbons were synthesized and characterized.

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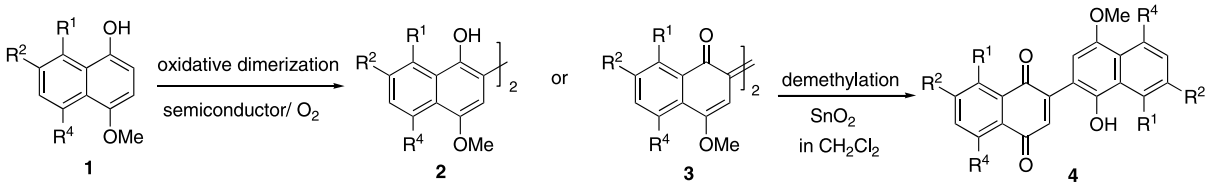

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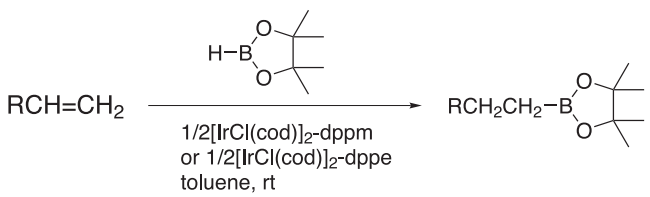

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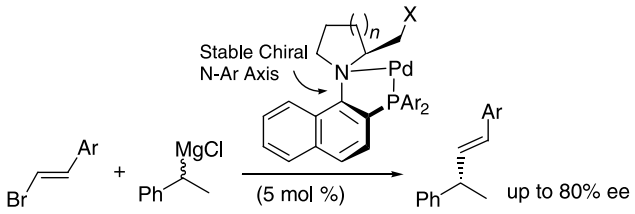
Hideo Horibe, Yoshimasa Fukuda, Kazuhiro Kondo,* Hiroaki Okuno, Yasuoki Murakami and Toyohiko Aoyama*



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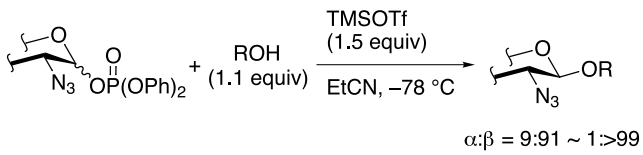

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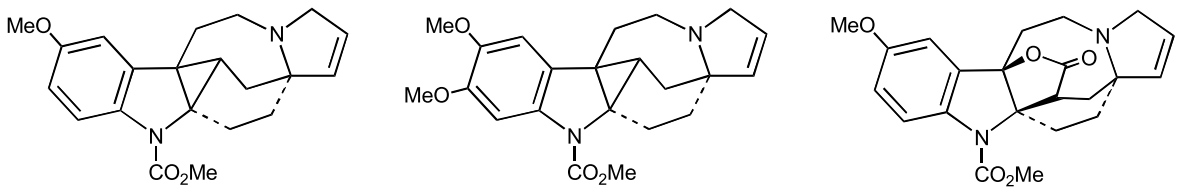
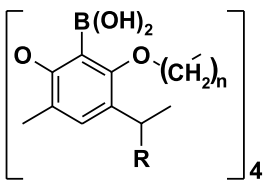
Toh-Seok Kam,* Kuan-Hon Lim, K. Yoganathan, Masahiko Hayashi and Kanki Komiyama



Lundurine B Lundurine D Tenuisine A

Synthesis of novel, boron-containing cavitands derived from calix[4]resorcinarenes and their molecular recognition of biologically important polyols in Langmuir films **pp 10747–10752**
Marek Pietraszkiewicz,* Piotr Prus and Oksana Pietraszkiewicz



Lipophilic tetra-boronic acid cavitands were synthesised from tetrabromocavitands via lithiation with butyllithium and reaction with triethylborate. Two lipophilic cavitands bearing four boronic acid residues were demonstrated to form stable Langmuir monolayers at the water/air interface. Langmuir techniques demonstrated molecular recognition of sugars.

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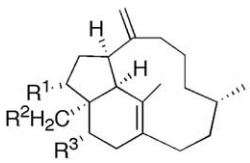
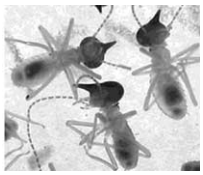
Chunjiu Zhao, Rodney W. Rickards and Stephen C. Trowell*



2: R^1, R^2, R^3 = OH
3: R^1, R^3 = OH ; R^2 = H
4: R^1 = OAc; R^2, R^3 = OH
5: R^1 = OH; R^2, R^3 = OAc
6: R^1, R^2, R^3 = OAc



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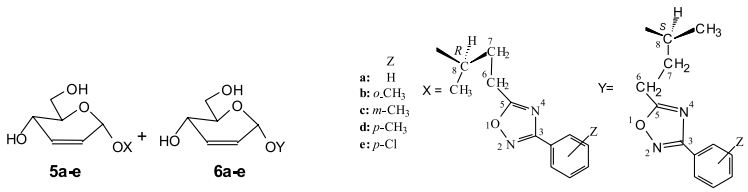

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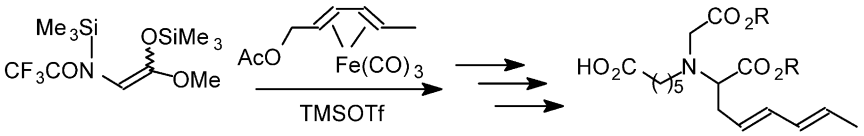

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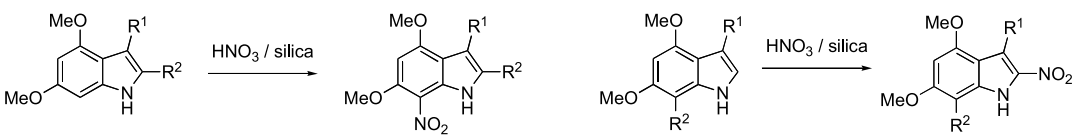

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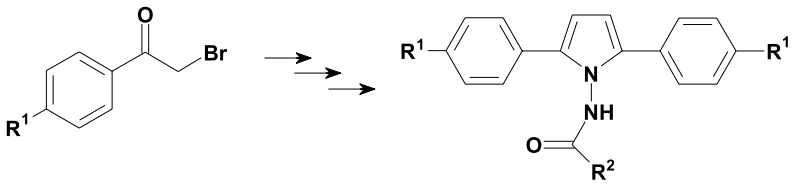

-diaryl-1,4-butanedione
-N-acylamino-2,5-diarylpyrroles.

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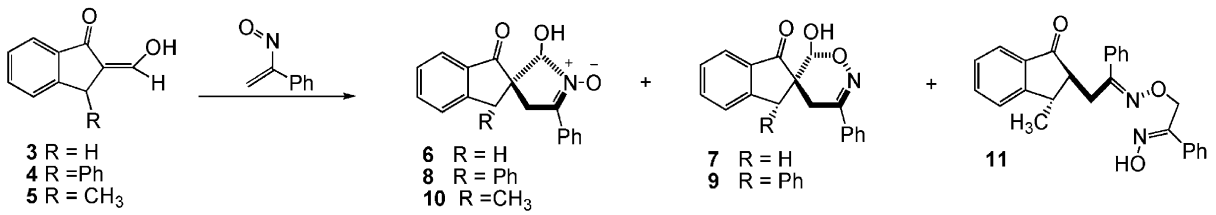

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Synthetic approaches to carnegine, a simple tetrahydroisoquinoline alkaloid

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Abstract—The different approaches towards the total synthesis of carnegine, a simple tetrahydroisoquinoline alkaloid isolated from several Cactaceae and Chenopodiaceae as well as other plants, are presented. Emphasis is placed on the various enantioselective strategies leading to the natural product in chiral form.

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1. Introduction

The development of organic chemistry has been closely associated to the chemistry of natural products, and natural products synthesis has clearly played a dominant role in driving the course of synthetic organic chemistry. Many extraction, separation, structural elucidation and chemical synthetic procedures have been developed and originally applied with the purpose of achieving a better understanding of the natural products, since the latter have proven to be an excellent source of novel chemical entities and extraordinary challenges to the organic chemistry community.

The toxicity of plants, which contributes to their ability to protect themselves against predation, is partially related to

Keywords: Carnegine; Simple tetrahydroisoquinolines; Plant alkaloids; Synthesis; Cyclization; Enantioselective synthesis.
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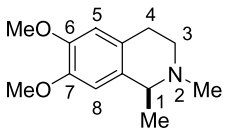
the diversity of small molecules that they synthesize. Alkaloids, which display a large variety of pharmaceutical activities and which importance in medicine has been highly publicized, compose one of the major classes of small molecules and accumulate in about 20% of all plant species.

The isoquinolines are the most numerous group among the alkaloids; they also display the widest range of structural diversity. Many of them are intensely bioactive and the biological activity attached to the isoquinoline nucleus coupled to the diversity characterizing these compounds, which is essential to the discovery of new drugs, have provided a great deal of interest in their synthesis.[1a–d] Furthermore, many natural, semisynthetic and synthetic isoquinolines with useful pharmacological properties, are currently part of mankind's therapeutic arsenal.[1e,f]

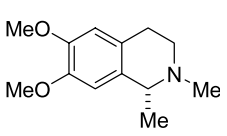
Structural diversity and biological activity of isoquinolines have long attracted the attention of synthetic chemists. The construction of the 1,2,3,4-tetrahydroisoquinoline ring system, specially in racemic form, has been a popular area of research in natural products chemistry since the early years of the past century. Activity in this field is almost as old as the discovery of the isoquinoline system itself; however, it is only in the past 20–25 years that the asymmetric synthesis of tetrahydroisoquinolines has been undertaken.

In a short compilation, Bentley listed 34 simple tetrahydroisoquinolines (methoxy, hydroxy and/or alkyl groups as substituents), 6 of their congener dihydro-isoquinolines and 6 related isoquinolines,[2] while Shamma et al. listed 99 structures belonging to natural and synthetic simple isoquinolines.[3] However, a more exhaustive listing of the most important plant isoquinolines and their natural sources has been recently collected by Shulgin and Perry, comprising approximately 45 isoquinolines, over 20 dihydroisoquinoline derivatives and more than 150 tetrahydroisoquinolines, including among the latter around 70 1-benzyl tetrahydroisoquinolines and tetrahydroisoquinolinium salts.[4] Numerous other natural products containing the isoquinoline moiety or derived from isoquinolines are known.

Carnegine (**1**, 1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, CAS 490-53-9) is a simple tetrahydroisoquinoline isolated from different plants around the world. Besides its simplicity, this natural product has one chiral carbon attached to nitrogen, an *N*-methyl moiety and a 6,7-dimethoxy substitution pattern on its aromatic ring as prominent structural features (Fig. 1), the establishment of all of which by synthetic means has been the subject of numerous research endeavors.



S-(-)-Carnegine, (-)-1



R-(+)-Carnegine, (+)-1

Figure 1. The enantiomers of carnegine.

Carnegine has been repeatedly employed during the last three decades as a model compound, serving as a superb test field where advantages of novel synthetic strategies, reactions and reagents were challenged and their disadvantages and limitations put in evidence; moreover, a phosphorus isostere of carnegine was proposed as test molecule during the study of the performance of a computer program designed for the analysis of synthetic routes towards organophosphorus compounds.[5]

According to Kametani,[6a] the synthetic approaches towards isoquinoline alkaloids and derivatives can be divided systematically into 15 different types, taking into account the mode of formation of the heterocyclic (1–8 and 15) and the homocyclic (9–14) rings.

Types 6–8 and 14 involve cycloaddition reactions, while type 15 entails a rearrangement. The 15 types are schematically represented in Figure 2. A previous and simplified classification presented earlier by Manske, useful for sorting carnegine syntheses, contained only the first five types.[6b,c]

Type 1 synthesis involves closure between the benzene ring and the carbon atom that forms *C*1 of the resulting isoquinoline ring. Pictet–Spengler and Bischler–Napieralski classical isoquinoline syntheses belong to this type. On the other hand, type 2 describes a synthesis in which the ring closure is made between the nitrogen atom and *C*1, while a type 3 synthesis entails *C–N* bond formation with *C*3. Analogously, types 4 and 5 are reserved for those syntheses in which the closing *C–C* bond is formed between *C*3 and *C*4, and *C*4 and the aromatic ring, respectively.

The most common syntheses of tetrahydroisoquinolines involve strategies of types 1, 2 and 5 and the literature does not record examples of the synthesis of carnegine employing types 3, 4 and 6–15. Noteworthy, however, this natural product was elaborated several times starting from an isoquinoline derivative, built according to one of the Kametani types described above.

Many of the most interesting isoquinolines are 1-substituted tetrahydroisoquinoline derivatives which, like carnegine, have been isolated or synthesized either as racemates or as pure enantiomers.

The absolute configuration of several 1-substituted tetrahydroisoquinolines, including that of carnegine, has been deduced by chemical correlations, thanks to the seminal work of Battersby and Edwards, which allowed unequivocal establishment of the absolute configuration of *S*-salsolidine (**8**).[7] As shown in Scheme 1, this was based on the oxidation of (−)-*N*-formyl salsolidine (**2**) with ozone to give the triformyl intermediate **3**, which was cleaved with hydrogen peroxide in formic acid to diacid **4** and hydrolyzed under acidic conditions to furnish *N*-carboxyethyl-L-alanine (**5**). This was compared with an identical material produced by Michael addition of L-alanine (**7**) onto acrylonitrile, followed by acid hydrolysis of the nitrile (**6**).

For correlation purposes, carnegine was accessed by Eschweiler Clarke *N*-methylation of natural *S*-salsolidine

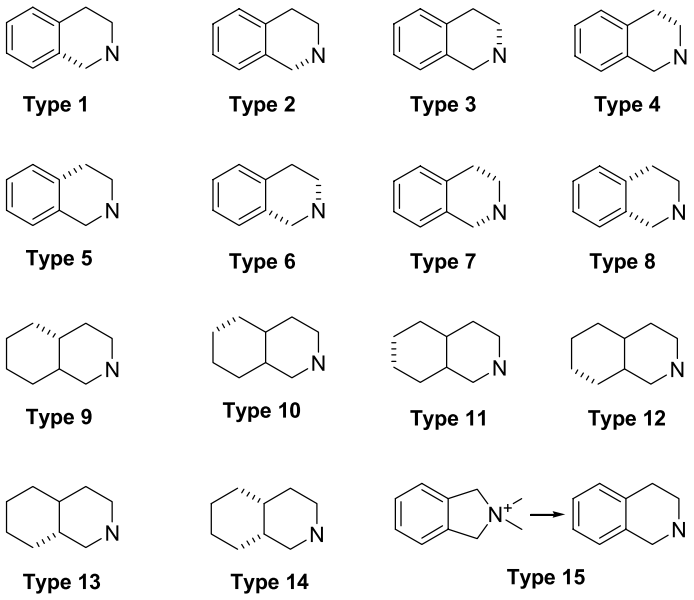
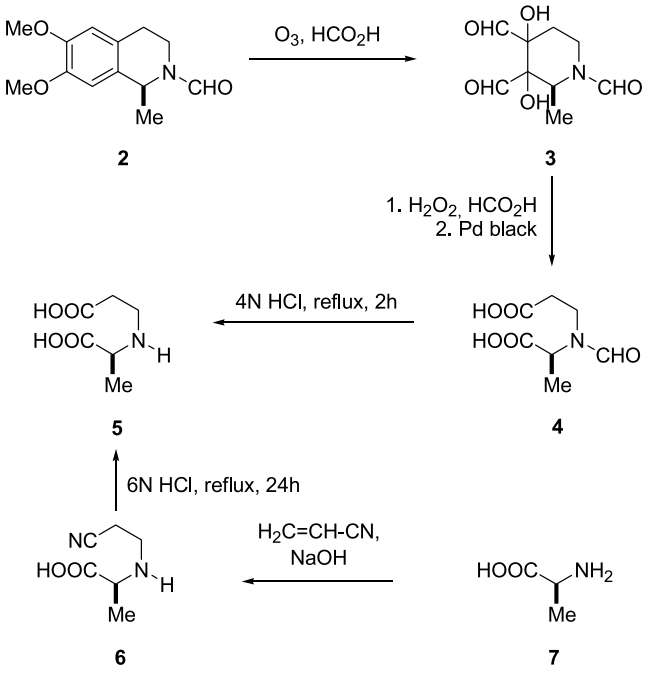


Figure 2. Synthetic strategies for the elaboration of the isoquinoline ring system, according to Kametani.

(**8**) with formaldehyde and formic acid,[8] in a procedure similar to that previously used by Orekhov.[9] Employing this correlation, Battersby and Edwards were able to demonstrate that natural carnegine possesses the 1-*S* configuration,[8b] observing that *S*-**1** is dextrorotatory in 1N HCl and levorotatory in benzene and EtOH. Correlating gigantine (**9**) to carnegine, Brown et al. established that the former also possesses the 1-*S* configuration.[10a] Similarly, Bobbitt deduced the absolute configuration of both enantiomers of **13b** by correlating them to carnegine[10b] and Brossi et al. correlated *N*-methyl salsolinol **13c** to the natural product.[10c] In both cases, smooth *O*-methylation with diazomethane brought about the required derivatized product.

As early as in 1987, Huber and Seebach[11] pointed out that



Scheme 1.

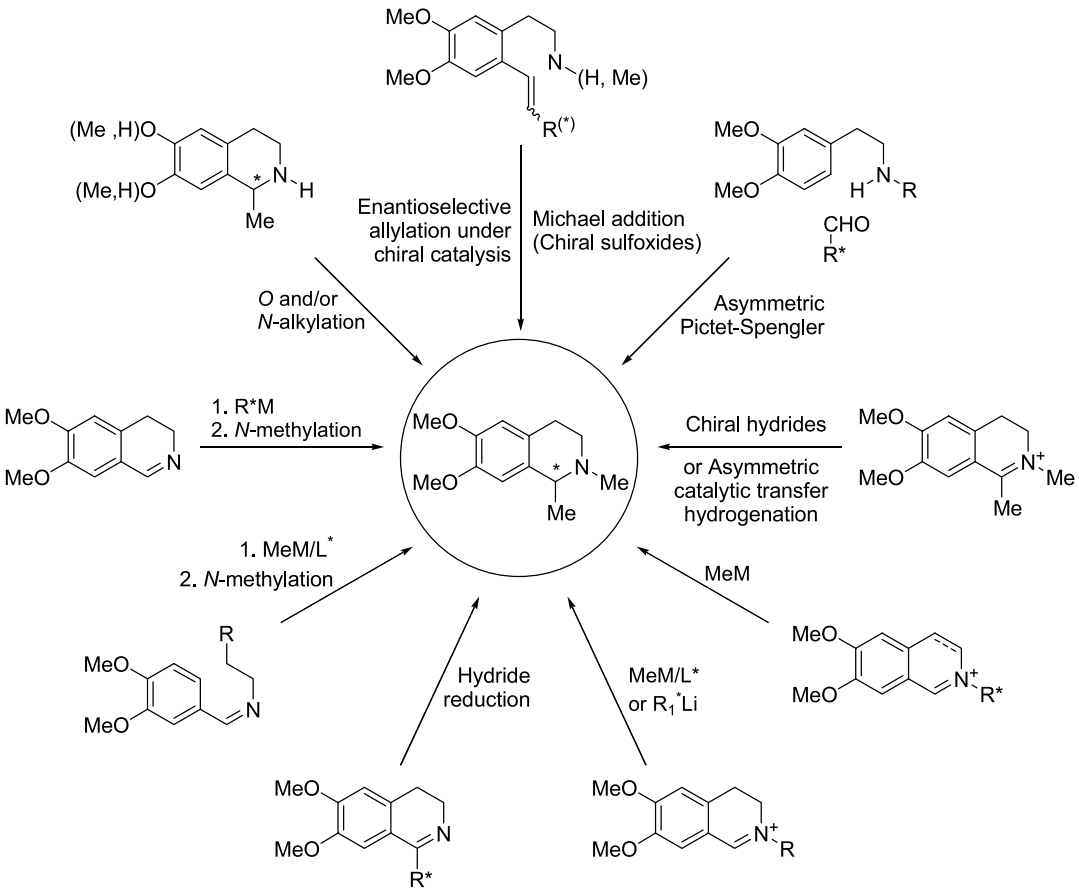
all possible methods of synthesizing enantiomerically pure compounds have been applied to the elaboration of chiral 1-substituted tetrahydroisoquinolines. These included resolution, catalytic and stoichiometric enantioselective reactions as well as the incorporation of components from the pool of chiral building blocks. Although this holds true for the elaboration of salsolidine (**8**),[7] a direct precursor of some syntheses of carnegine, many alternatives for the enantioselective elaboration of the latter still remain unexplored.

Carnegine has been prepared in chiral form by diastereoselective reduction of chiral iminium ions, enantioselective alkylation of imines with chiral organometallic reagents or with organometallics in the presence of chiral auxiliaries and by asymmetric modifications of the Pictet–Spengler condensation, as depicted in Scheme 2, among other routes. The body of current strategies for the enantioselective elaboration of 1-substituted tetrahydroisoquinolines have been recently compiled by Rozwadowska.[12]

The aim of this review is to highlight and discuss the most relevant strategies employed during the last 30 years for the total synthesis of carnegine and some of its precursors. Special emphasis was placed in those strategies leading to the natural product in optically active form, which started to appear in the literature less than 20 years ago. Brief details on the natural sources and probable biosynthesis of this alkaloid, as well as some details of its biological activity and interaction with biological systems, are also given.

2. Natural sources, isolation and structure elucidation

Carnegine was isolated from several Cactaceae, Chenopodiaceae and, more recently, from Boraginaceae. Among the first, sources of the natural product include *Carnegiea gigantea* (Engelm.) Br. & R., *Pachycereus pecten-aboriginum*, *P. pringlei*[13] and *Pachycereus weberi*. The first studies on carnegine were performed by Heyl in 1901,[14a] when the alkaloid, isolated from *P. pecten-aboriginum* was



Scheme 2.

termed pectenine; the same scientist isolated carnegine in 1928,[14b] while studying the alkaloids of *C. gigantea*, known as giant cactus or saguaro or the monarch of the Sonoran Desert.

This rare and endangered cactus which can reach 12 m high is native of the northern part of the Sonoran desert, where it is the predominant feature of its landscape; the fragrant, waxy white Saguaro Blossom was adopted as the floral emblem of the Arizona Territory of the United States, and officially confirmed as the state flower in 1931. Heyl prepared the hydrochloride, hydrobromide, chloroaurate and chloroplatinate salts of carnegine and also demonstrated that the natural product increases reflex excitability in frogs[14a] and is toxic to frogs and warm-blooded animals.

The structure of carnegine, the second most abundant alkaloid of *C. gigantea* after salsolidine, which accounts for approximately 50% of the total alkaloids, was shortly elucidated by Späth. This scientist first synthesized this natural product in 1929,[15a,b] by the Bischler Napieralski cyclization of *N*-acetyl homoveratrylamine with P_2O_5 in refluxing toluene, followed by MeI-mediated methylation and Sn/HCl reduction of the resulting methiodide. Späth also reported its presence in *P. pecten-aboriginum* and demonstrated its identity with pectenine through melting point determinations of the methiodide, hydrochloride, picrate and trinitro-*m*-cresolate derivatives[15c,d] and suggested to retain the name carnegine for the alkaloid as a consequence of the fact that pectenine was not as extensively studied as carnegine.

The alkaloid was also reported in *C. gigantea* by Bruhn and Lundström and by the McLaughlin group;[16] in the former case, carnegine was isolated as the inactive hydrochloride together with other three simple tetrahydroisoquinoline alkaloids shown in Figure 3: salsolidine (**8**), gigantine (**9**) and arizonine (**10**),[16a] while in the latter, the presence of 20 alkaloids including isosalsolidine (**11**), isonortehuanine (**12a**), isonorweberine (**12b**), isopachycereine (**12c**) and 13 new natural products were detected in *P. weberi* and additional confirmation of their structure was gained by mass-analyzed ion kinetic energy spectrometry (MIKES) analysis.[16d] These observations were confirmed by chromatography and, in many cases, by simple synthetic interconversions from known alkaloids. Particularly significant was the discovery of several alkaloids having the same molecular formula. Isomer distinctions such as these, which are difficult to make on pure compounds by mass spectrometry, were made by utilizing daughter spectra recorded successively during the evaporation of the material from the probe and/or from spectra recorded on different types of plant extracts.

Hodgkins et al.[17] also informed the isolation of carnegine in a reinvestigation of the alkaloids of *C. gigantea*, while Mata and McLaughlin isolated the natural product from the non-phenolic and phenolic extracts of the giant Mexican cereoid

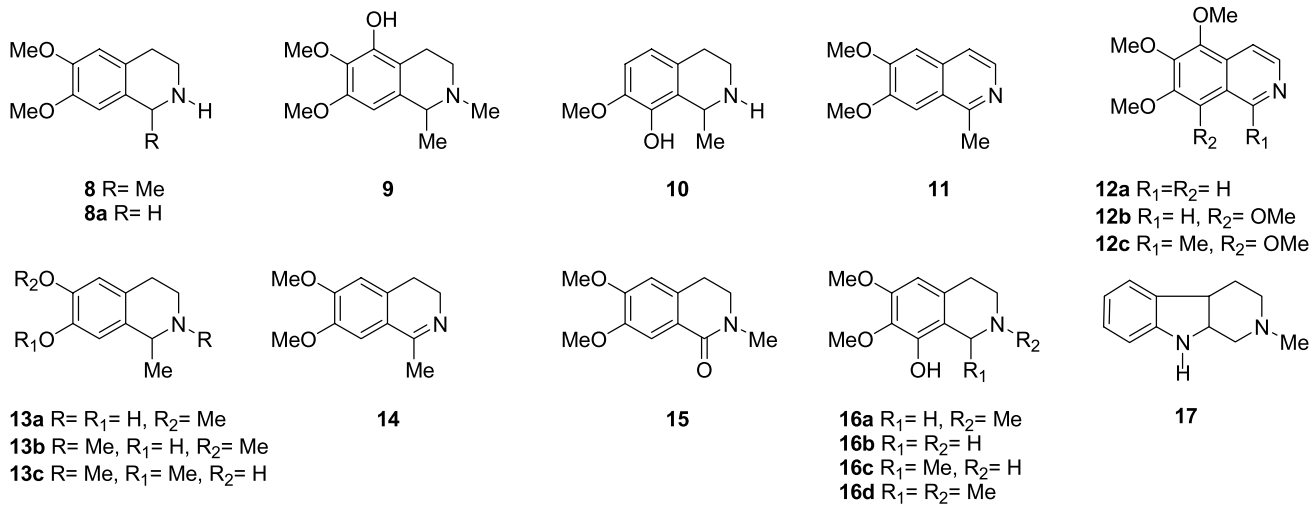


Figure 3.

cactus *P. weberi* (Coult.) Br. & R, together with seven other tetrahydroisoquinolines.[18]

Sources of carnegine among the Chenopodiaceae are *Hamada articulata* ssp. Scoparia,[19a] where it was found in its aerial parts together with isosalsoline (**13a**), **8**, dehydrosalsolidine (**14**), **11** and *N*-methylcorydaldine (**15**) and *Hamada scoparia* (pomel) Iljin,[19b] from where it was isolated together with isosalsoline (**13a**), *N*-methyl-isosalsoline (**13b**), *N*-methylcorydaldine (**15**), tryptamine, *N*-methyltryptamine, *N*-methyl-1,2,3,4-tetrahydro-β-carboline (**17**) and leptocladine. Other Chenopodeaceae sources are *Arthrocnemum glaucum*,[20] the aerial parts of which contain the natural product together with (−)-1-methyl-corypalline (**13b**, *N*-methylisosalsoline), *Haloxylon articulatum*[21] grown in Egypt, and *H. salicornicum*,[21] where it was found by El-Shazly et al. together with **8**, **13b** and tetrahydro-β-carboline **17**. In addition, the same group isolated (−)-carnegine from *Echium humile*, together with a series of pyrrolizidine alkaloids and also from *Arnebia decumbens*, being these the first records of the presence of carnegine among the Boraginaceae.[22] The recent discovery of carnegine in *Arnebia nobilis* further confirms that Boraginaceae are indeed a source of carnegine.[23]

By the use of GC-MS techniques, carnegine was also detected very recently in *Neobuxbaumia multiareolata*, *N. scoparia* and *N. tetetzo* (Cactaceae), together with anhalidine (**16a**) and salsolidine (**8**). The co-occurrence of these alkaloids in the three species of *Neobuxbaumia* studied has high chemotaxonomic value. It suggests that these species are closely related and since *Carnegiea* has all the alkaloids identified in the *Neobuxbaumia* species, plus others derived from the tetrahydroisoquinoline biosynthetic pathway, it can be speculated that *Carnegiea* is different from *Neobuxbaumia* and probably derived from it.[24]

Interestingly, in spite that some authors have isolated carnegine in optically active form from different Cactaceae, others found only racemic carnegine. Späth and Kesztler called the attention that many tetrahydro-isoquinolines isolated from cacti were obtained in racemic form and noted that some of them, particularly carnegine and those with free OH groups in certain positions readily racemized, especially in aqueous acidic solutions.[25]

In saguaro, gigantine (**9**) and carnegine are present in a 1:2 relationship, representing 1–2% of the dry weight of the cactus;[10] saguaro fruit has long been used by the Papago and Pima indians, who harvest the fruits and make syrup and a wine, used in their rain ceremonies. The group of Fogleman recently studied the successful utilization of necrotic cactus tissue by fly species (drosophilids) that are endemic to the Sonoran Desert. This plant–insect model represents an excellent context in which to investigate the chemical and molecular bases of interactions between insects and toxin-containing host plants. The scientists found that the cytochrome P450 monooxygenase system was implicated in plant utilization by *Drosophila nigrospiracula*, *D. mettleri*, and *D. Mojavensis* and that these insects adapt their metabolic pathways to better detoxify and tolerate the presence of cactus allelochemicals, which have been shown to be highly toxic to non-resident species. Total P450 levels, both basal and induced, were approximately 20 fold higher in adults than in larvae.[26] It was also evidenced that tolerance to carnegine can be induced and that there are very few—possibly only one—carnegine-metabolizing enzymes in *D. melanogaster*, a non-desert fly.

From the analytical chemistry point of view, the ^{13}C NMR spectrum of carnegine and other simple tetrahydroisoquinolines was analyzed and assigned[27] and the chiroptical properties of the natural product have been evaluated as part of the development of a semiempirical quadrant rule based on one-electron theory for the assignment of the absolute configuration of 1-methyl tetrahydroisoquinolines, independent of the substitution pattern of the benzene ring.[28] Physical data for the natural product have been compiled by Shamma et al.[3] and by others.[8,15d]In another publication, naturally occurring carnegine was proposed as a catalyst for the kinetic resolution of alkylphenyl carbinols with α-phenylethyl isocyanate.[29]

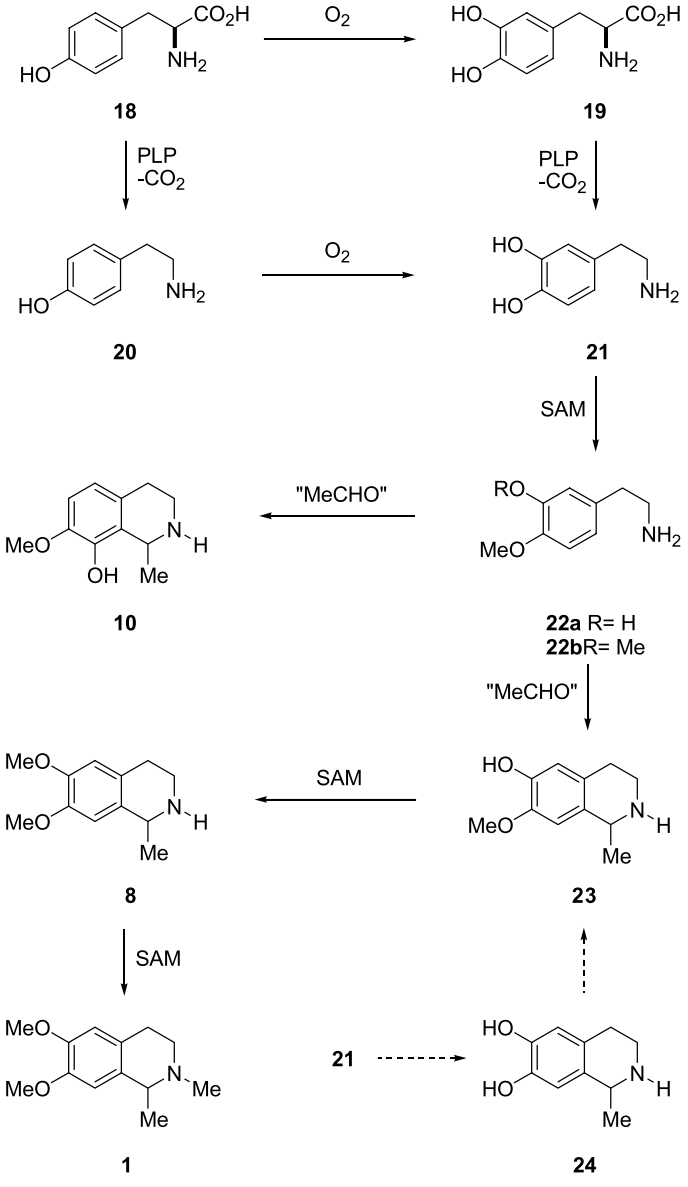
In addition, the fluorescence-inducing compound fluorescamine was introduced as visualization reagent for alkaloids in

TLC separations of carnegine and related substances,[30] while HPLC with UV detection was used to completely separate isomeric pairs of tetrahydro-isoquinolines and phenethylamines of Cactaceae, including carnegine.[31] Two interconnected stainless-steel columns (each 30 cm × 4.5 mm i.d.) were used, one packed with LiChrosorb Si 60 (10 μm) and the other with μPorasil (8 μm). Analyses were performed at a flow rate of 2 mL/min and a pressure of 1100 psi for one solvent system (acetonitrile–NH_3, 96:4) and flow rate of 1 mL/min at 900 psi for an alternative solvent mixture ($CHCl_3$–1% NH_3 in MeOH, 9:1). The isomeric pairs were separated by both solvent systems, and it was observed that the addition of alkali to the neutral solvent systems produced better separations with reduced tailing and faster elution.

In an analogous study, the gas–liquid chromatographic separation of 18 anhalonium alkaloids and related bases, including carnegine has been examined employing 1% methylsiloxane polymer containing about 5% phenyl substitution, as the liquid phase. It was observed that among the analytes *N*-monomethylation of primary and secondary amines, as well as *O*-methylation or *C*-monomethylation of the bases decrease the retention time, while introduction of hydroxyl, methoxyl, methylenedioxy group or an unsaturation, produced an increase in retentivity. These changes in retention time were attributed to the changes in polarity of amino and/or phenolic hydroxyl groups brought about by substitution in or adjacent to these groups.[32]

3. Biosynthesis of carnegine and its interaction with biological systems

Much of our current knowledge about the biosynthesis of cactus alkaloids is a result from thorough studies carried out on the Mexican peyote cactus *Lophophora williamsii*. The intense interest in the principal alkaloids of this plant anhalamine (**16b**), anhalonidine (**16c**) and pellotine (**16d**) is



Scheme 3.

a consequence of their pharmacological properties as hallucinogenic drugs.[33a] The biosynthetic path to carnegine was proposed by Agurell[16b] and also by Bruhn and Lundstrom.[16a] It follows the classical ideas set forth by Winterstein and Trier in 1910 for 1-benzyl-isoquinolines;[16f] however, some of its aspects are merely speculative or still remain unclear.

Being a simple tetrahydroisoquinoline alkaloid, carnegine is derived from tyrosine (**18**). Biosynthetic studies with ^{14}C-labeled amino acids and related compounds, including α-^{14}C-(±)-tyrosine (**18**), (±)-dopa (**19**), 3,4-dimethoxy-phenethylamine (**22b**), and methyl-^{14}C-labeled L-methionine, showed that in the cactus alternative routes operate from **18** via tyramine (**20**) or from **19** to dopamine (**21**),[33b,c] which is present in large amounts in the giant cactus.[34]

The labeled compounds were incorporated by *C. gigantea* plants into carnegine and the related alkaloid salsolidine (**8**), being the biosynthetic scheme similar to that of the peyote alkaloid pathway. Most probably, tetrahydroisoquinolines and phenolic phenethylamines are biosynthesized from 3-hydroxy-4-methoxy phenethylamine (**22a**), as shown in Scheme 3.

Precursor **22a** can be condensed with an acetaldehyde unit to furnish salsoline (**23**), a reaction that was demonstrated to occur in vivo, in *Echinocereus merkeri*,[35] as well as in vitro,[36] furnishing a 95:5 mixture of **23** and its isomer arizonine (**10**),[37] also found in cacti. Acetaldehyde is a chemical known to be present in *C. gigantea*;[38] however, the true cyclizing agent could be pyruvic acid, in which case a decarboxylation step would be necessary in order to get the 1-methyl tetrahydroisoquinolines.[39] Alternatively, acetaldehyde or its equivalent can condense with dopamine (**21**) to give salsolinol (**24**), which after *O*- and *N*-methylation would furnish **1**.

The presence of minor amounts of arizonine (**10**) in the *C. gigantea* extracts was regarded as an additional proof of the involvement of dopamine (**21**) or 3-hydroxy-4-methoxy-phenethylamine (**22a**) in the biosynthesis of carnegine and salsolidine.[40] Scheme 3 shows the proposed biosynthesis of some compounds found in *C. gigantea*, including carnegine.[41] *S*-adenosyl methionine (SAM) is involved in methylations, while pyridoxal phosphate (PLP) participates as a cofactor in decarboxylations.[33b]

On the other hand, Bahnmaier demonstrated the in vitro stereospecific *N*-methylation of salsolidine by amine-*N*-transferase A isolated from bovine liver. In this experiment, *S*-salsolidine was *N*-methylated by the enzyme, while the *R*-enantiomer remained essentially unchanged.[42] Interestingly, however, when (±)-salsolinol (**24**) was administered to Papaveraceae plants (*Corydalis pallida* var. Tenuis Yatabe and *C. incisa* Pers.) and their tissue-cultured cells the *O*- and *N*-mono and dimethylated derivatives were detected; the plants were incapable of producing carnegine, the *O*,*N*-trimethyl derivative of **24**.[43]

Interestingly enough, Stammel et al.[44] recently prepared highly specific and sensitive antibodies to salsolidine, which were able to distinguish a double bond between *C*1 and *N* and with less success, to recognize the absence of methyl groups on *C*1. However, in cross-reactivity tests, these antibodies were not capable of discriminating carnegine from salsolidine. The high cross-reactivity observed (99.1%) was explained as being a result of the strategy employed for the preparation of the immunogen consisting in coupling salsolidine to a carrier protein via the heteroatom of the natural product; besides carnegine, only heliamine (6,7-dimethoxy tetrahydroisoquinoline, **8a**) possessed appreciable cross reactivity (14.6%).

The pharmacological properties of carnegine have been investigated by the group of Furlanut. These Italian pharmacologists studied its acute toxicity as well as its effects on smooth muscle, isolated myocardial preparations and dog blood pressure and respiration.[45a] They observed that LD_{50} by intraperitoneal route in the mouse is approximately 15 mg/Kg, with its main toxic effects involving the central nervous system, as evidenced by strychnine-like tono-clonic convulsions. On isolated frog heart and guinea pig atria, the natural product produces a remarkable synusal bradycardia and on the latter model, the negative chronotropic effect is associated to a marked increase of the amplitude of the contractions; at lower concentration, however, carnegine can counteract the chronotropic effects of adrenaline and noradrenaline without affecting their inotropic properties.

In addition, in experiments with dogs, 0.5–2 mg/Kg carnegine demonstrated to possess hypotensive effect, with stimulation of the rate and amplitude of the respiration when 1–2 mg/Kg were given intravenously, while on smooth muscle preparations, the alkaloid elicited slight spasmolytic and vasodilator activities. It has also been demonstrated that, unlike other isoquinoline derivatives, carnegine has no effect on brain phosphodiesterase activity.[45b]

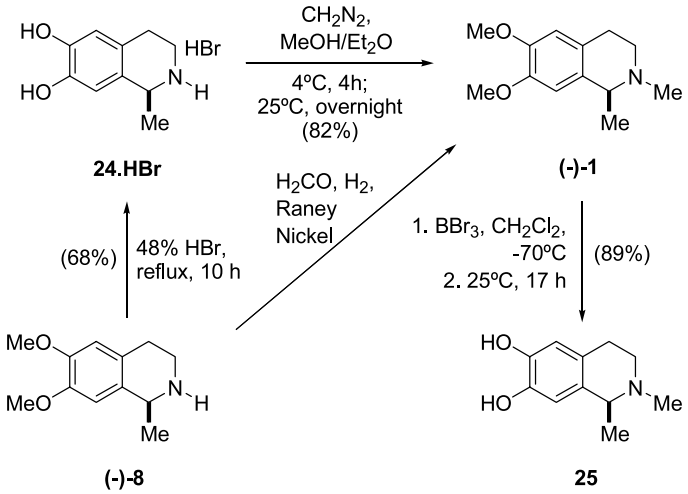
Finally, the effect of carnegine and other alkaloids on cellular metabolism employing the mouse ascites tumor cells model was examined by Schmitz. The natural product exhibited a threshold respiration inhibiting concentration of 80 μg/mL.[46] with the potency of carnegine being of the same order of magnitude as that of Cinchona alkaloids, physostigmine and strychnine.

4. Chemical synthesis of carnegine

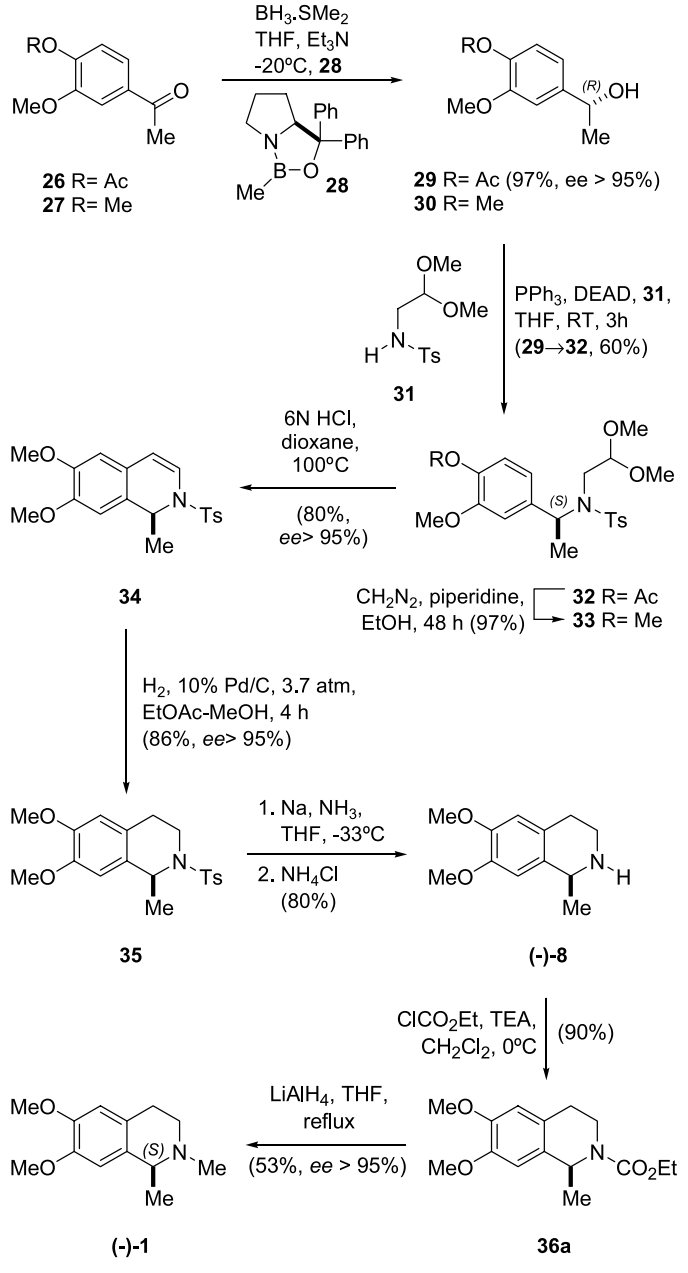
4.1. Alkylation reactions

4.1.1. *O*- and *N*-Alkylation of simple tetrahydroisoquinolines. This strategy constitutes the easiest access to the natural product, as it entails simple heteroatom alkylation procedures. Carnegine was elaborated by *N*-methylation of salsolidine (**8**),[7] *N*-methylation of dehydrosalsolidine with reduction of the resultant dihydroisoquinolinium derivative, as well as by *O*- and *N*-methylation of salsolinol (**24**). Synthesis of carnegine in optically active form following this alternative was carried out employing optically active tetrahydroisoquinoline precursors.

A simple synthesis of racemic carnegine was reported by



Scheme 4.



Scheme 5.

Japanese scientists, employing dehydrosalsolidine (**12**) as intermediate. This 1,2-dihydroisoquinoline was prepared by Bischler–Napieralski cyclization of *N*-acetyl homoveratrylamine or by cyclization of veratrylacetoxime, following the method of Sugasawa and Yoshikawa. For the elaboration of **1**, the methyl methosulfate derivative of **12** was prepared and catalytically reduced.[47] The reductive *N*-methylation of salsolidine to carnegine with the HCHO–HCO_2H system served to Orekhov et al. for correlation purposes.

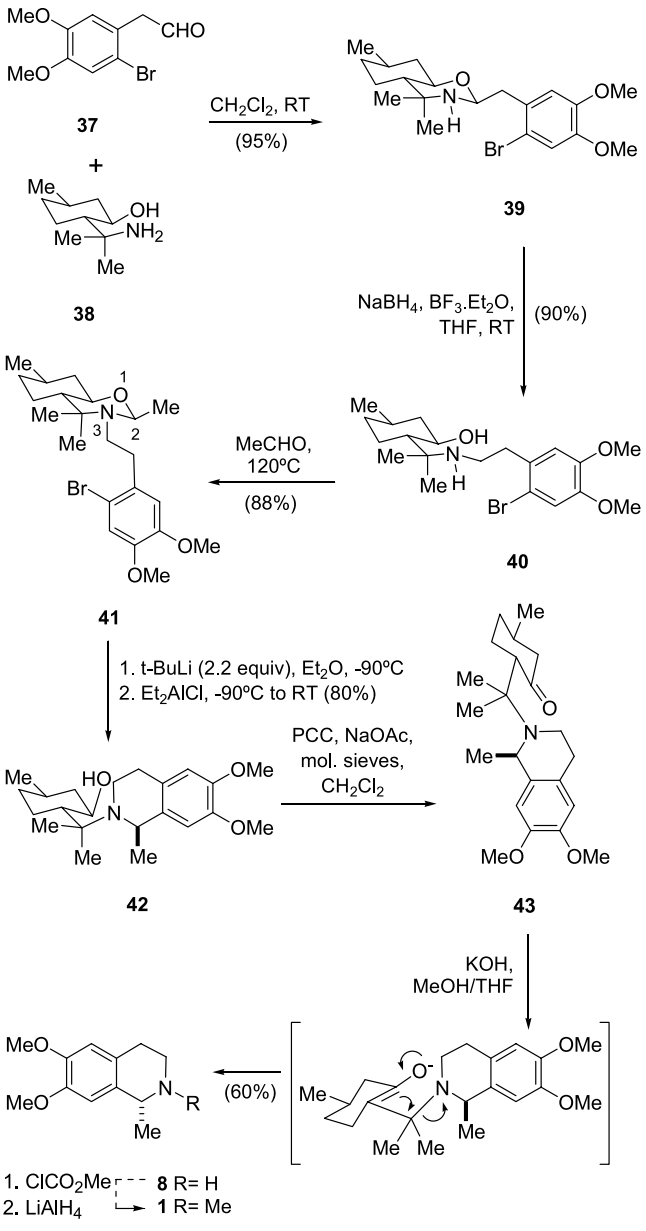
These authors characterized carnegine as its hydrochloride and picrate salts.[3b] The group of Brossi, while studying the concept of 'alkaloid formation in man', provided simple ways to access carnegine. In one example, the natural product was obtained from *S*-salsolinol hydrobromide (**24**·**HBr**), by *O*-and *N*-methylation of the latter in MeOH with excess ethereal diazomethane, as depicted in Scheme 4.[48] The research was part of their effort to ascertain that the configuration and optical purity of salsolinol, when prepared by demethylation of salsolidine, remains unchanged. These authors also prepared *S*-*N*-methylsalsolinol (**25**) in 89% yield, by selective *O*-demethylation of the thus obtained *S*-carnegine with boron tribromide.

The same procedure, when applied to *R*-carnegine hydrobromide, furnished the *R*-enantiomer of *N*-methylsalsolinol. In an alternative strategy, this group also prepared both enantiomers of **1** from the corresponding enantiomers of **8** by reductive *N*-methylation with formaldehyde and hydrogen under Raney nickel catalysis.[48] These compounds were tested as inhibitors of the monoaminooxidases (MAO) A and B, demonstrating stereoselective inhibition of the enzymes. The *R*-enantiomer was strikingly more potent than its enantiomer against MAO A (K_i=2 μM vs K_i=102 μM for *S*-**1**) and *R*-carnegine did not inhibit MAO B, while its enantiomer displayed only weak inhibition with K_i=1600 μM.[49]

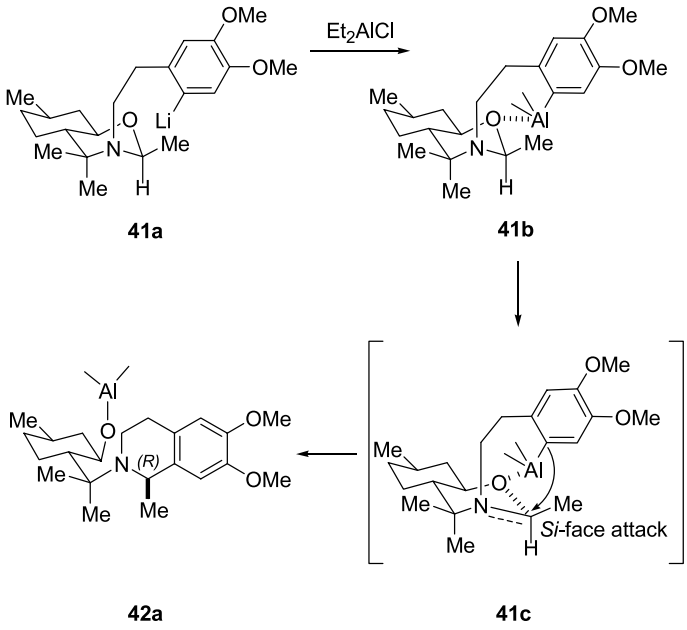
Ponzo and Kaufman[50] (Scheme 5) prepared *S*-carnegine from *S*-salsolidine in 48% overall yield by lithium aluminum hydride reduction of salsolidine-*N*-ethylcarbamate (**36a**). For the elaboration of salsolidine, these researchers coupled chiral alcohol **29** to sulfonamidoacetal **31** through a Mitsunobu sulfonamidation process, which proceeded with complete configurational inversion of the benzylic center. Acetate **26** derived from acetovanillone was used as starting material instead of acetophenone **27** a more straightforward precursor, because the Mitsunobu sulfonamidation of the more electron rich alcohol **30** yielded partially racemized sulfonamide **33**. The enantioselective elaboration of **29** and **30** was accomplished through CBS reductions with chiral oxazaborolidine **28**, a modern and highly improved version of the pioneering Itsuno's catalyst, developed by Corey's group.[51]

An extra step for the transformation of **32** into **33** consisting in an acetate to methyl ether transformation, was introduced.[52] Sulfonamidoacetal **33** was cyclized following Jackson's protocol, in a refluxing dioxane-6N HCl mixture and the resulting 1,2-dihydroisoquinoline **34** was submitted to catalytic hydrogenation providing *S*-**35**; subsequent removal of the sulfonyl moiety by means of a reductive desulfonylation with sodium in liquid ammonia furnished (−)-**8** in >95% ee, as determined by ^{1}H NMR spectrometry with chiral shift reagents. Reaction of salsolidine with ethyl chloroformate gave 90% the corresponding carbamate **36a**, which was finally reduced to (−)-**1** in 53% overall yield with lithium aluminum hydride in refluxing THF.

A total synthesis of salsolidine, leading to the *R*-enantiomer as shown in Scheme 6, was recently reported by a Spanish team, which also elaborated other 1-substituted tetrahydroisoquinolines.[53a] Their strategy consisted in the intramolecular attack of an appropriately substituted arylaluminum species to a chiral 1,3-perhydrobenzoxazine derived from (−)-8-aminomenthol (**38**) for the elaboration of the isoquinoline system. Subsequent *N*-methylation of the nitrogen after oxidative removal of the chiral auxiliary, completed the synthesis, serving compound **38** as chiral inductor and source of the nitrogen atom.



Scheme 6.



Scheme 7.

In this synthetic strategy, the aryl group was attached to the nitrogen of the *N*,*O*-acetal moiety of the 1,3-perhydrobenzoxazine through an ethylene tether. The elaboration of this synthetic intermediate was straightforward, by condensation of polysubstituted phenylacetaldehyde **37** with the chiral auxiliary, followed by reduction of the intermediate *N*,*O*-acetal **39** to amine **40**, which was transformed into 1,3-perhydrobenzoxazine **41** upon heating with acetaldehyde at 120 °C in a sealed tube.

Low temperature lithium–halogen exchange and transmetallation with diethylaluminum chloride provided an arylmetal (Scheme 7) which performed an intramolecular nucleophilic attack on *C*-2 of the *N*,*O*-heterocycle, forming the heterocyclic ring of the tetrahydroisoquinoline **42**.

A two-step efficient removal of the chiral auxiliary, leading to (+)-**8** culminated the synthesis; this was performed by PCC-mediated oxidation of chiral alcohol **42** to the corresponding ketone **43** followed by a retro-Michael process. These authors effected a final *N*-methylation of some of the synthesized chiral 1-substituted tetrahydroisoquinolines by reaction with methyl chloroformate, followed by lithium aluminum hydride reduction of the resulting carbamates.

In this sequence, the stereochemistry of the final product was determined beforehand by the stereochemical outcome of the reaction leading to the key perhydrobenzoxazine **41**, in which the methyl substituent is equatorially oriented.[53a]

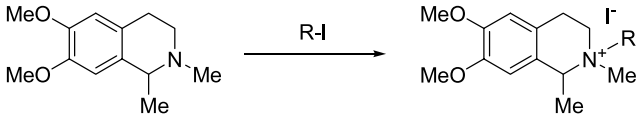
The key role of diethylaluminum chloride in the process leading to **42** was explained as shown in Scheme 7. The lithiated intermediate **41a** formed by lithium–halogen exchange of **41** with *tert*-butyl lithium is converted into the organoaluminum intermediate **41b** by transmetallation with Et_2AlCl; next, intramolecular transfer of the aryl group to the *si*-face of the incipient iminium ion from the aluminum atom, furnishes the aluminum species **42a**, which leads to **42** upon aqueous workup.

The stereochemical outcome of the intramolecular ring opening of the 1,3-perhydrobenzoxazine is similar to previous findings in related systems,[53b] while the stereodiscrimination is better for organoaluminum derivatives than for related organometallic species because of their comparative greater nucleophilic character.[54] The high selectivity observed is probably a consequence of the fact that transfer of the aryl group to the intermediate iminium moiety proceeds by synchronous intramolecular arylation in the early transition state **41c**, while the aluminum is still complexed to the oxygen atom of the chiral auxiliary. Employing the less nucleophilic and less reactive organomagnesium species, formation of minor amounts of the diastereomeric species resulting from attack to the *re*-face was observed.

It is worth mentioning that Battersby and Edwards also prepared carnegine methiodide, by *N*-methylation of the natural product with methyl iodide. A few years later, a Hungarian group studied the quaternarization of 1,2-disubstituted tetrahydroisoquinolines, finding that the transformation proceeds with moderate degrees of stereoselectivity, as shown in Table 1.[55a] Furthermore, the selectivity of the alkylation increased with the increase in the bulk of the new substituent; from NMR data it was concluded that all the major diastereomers of the mixtures (**44a**) have the same configuration and in these isomers, as expected the bulkier substituent on nitrogen and the *C*1-methyl group are *trans*-oriented.

In a related investigation, another group examined the quaternarization of *N*-methyl-6,7-dialkoxytetrahydroisoquinolines and the demethylation of the resulting quaternary salts, concluding that during both processes, methylation of the tetrahydroisoquinolines and demethylation of the

Table 1. Diastereoselective quaternarization of carnegine with different alkyl iodides



Entry No.	R	**44a** (%)	**44b** (%)	^{1}H NMR (δ-*N*–Me, **44a**)	^{1}H NMR (δ-*N*–Me, **44b**)
1	Me	100		3.53	
2	Et	70	30	3.38	3.28
3	*i*-Pr	75	25	3.42	3.33
4	*i*-Bu	75	25	3.42	3.33
5	Bn	100	0	3.29	3.12

tetrahydroisoquinolinium derivatives, the *C*1 substituent and the entering or leaving group are located preferentially *trans* in the respective transition states.[55b]

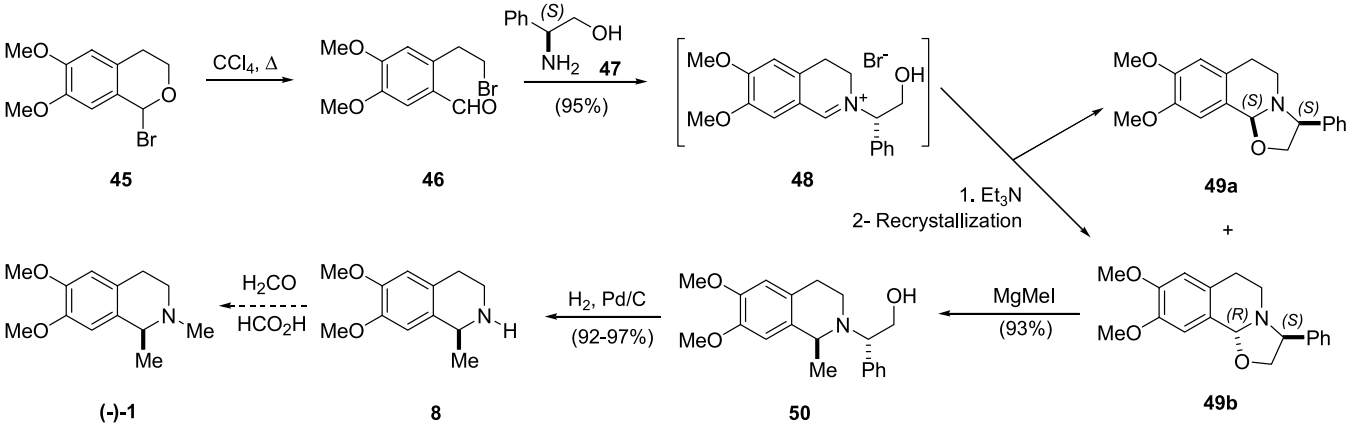
In a separate communication, it was also disclosed that experiments with the enantiomers of the *N*,*N*-dimethyl derivative (entry 1) demonstrated that it possesses ability to competitively inhibit acetylcholinesterase, being the potency of the *S*-enantiomer twice that of the *R*-enantiomer.[56a] These results reflect the stereochemical preferences of the neuromuscular junction towards nondepolarizing blocking agents. Other isoquinolines and isoquinolinium derivatives are known to behave similarly and the relationship between structure and curariform activity has been reviewed.[56b]

4.1.2. Alkylation of isoquinolinium derivatives. Addition of Grignard or organolithium reagents to isoquinolines or 3,4-dihydroisoquinolines is sluggish and sometimes there is no reaction unless external activation or strenuous conditions are employed; however, the transformation proceeds readily with synthetically useful yields if the heterocycles are activated as isoquinolinium or 3,4-dihydroisoquinolinium species, respectively. This key observation has been employed for the development of several syntheses of 1-substituted tetrahydro-isoquinolines, including salsolidine.[7] *N*-methylation of the latter by reductive alkylation or reduction of salsolidine carbamates constitute a direct access to carnegine. The use of chiral organometallic reagents, optically active ligands or chiral auxiliaries bound to the nitrogen offer the possibility of accessing the natural product in its optically active forms.

A Japanese team headed by Yamato[57] prepared optically active salsolidine and related 1-substituted tetrahydroisoquinolines as well as some *N*-methyl tetrahydroisoquinolines by *N*-methylation of chiral 1-substituted heterocycles. The tetrahydroisoquinolines were elaborated by diastereoselective methylation of a dihydroisoquinolinium-derived oxazolotetrahydroisoquinoline. This can be considered as an *N*,*O*-acetal, and was found to undergo facile nucleophilic substitution by organolithium and Grignard reagents.

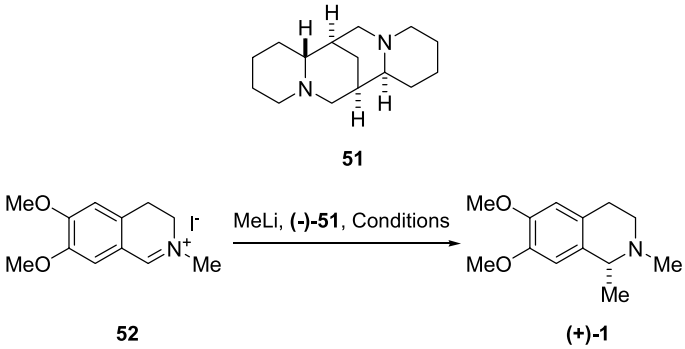
This group synthesized diastereomeric chiral oxazolo[2,3-a]-tetrahydroisoquinolines **49a** and **49b** (*de*=90%) in a highly selectively manner. This was done by base-assisted intramolecular cyclization of the 3,4-dihydroisoquinolinium salt **48** derived from *S*-phenylglycinol (*S*-**47**) and 1-bromoisochromane **45**, through the condensation of the chiral auxiliary with **46**, the open form of the isochromane.

Upon purification of the major diastereomer (**49a**) from the 19:1 mixture of tricyclic intermediates by crystallization, and subsequent ring opening of the oxazolidine ring by asymmetric methylation with MeMgI, compound **50** was



Scheme 8.

Table 2. Enantioselective addition of MeLi to methiodide **52** in the presence of 1 equiv of (−)-sparteine



Entry No.	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	Et_2O	−76 to 10	24	67
2	Et_2O	−76	2.5	59
3	PhMe	−76 to 10	24	76
4	PhMe	−76	24	76

obtained in 93% yield (Scheme 8). Removal of the *N*-benzyl moiety was appropriately and efficiently carried out with Pd/C in acidic EtOH, furnishing (−)-**8**.

Both enantiomers of the chiral alcohol **47** were submitted to the same sequence of transformations, leading to both enantiomers of salsolidine. In this process, *S*-**47** afforded the 1*S* enantiomer of salsolidine (**8**), a precursor of carnegine. The same sequence was employed for the elaboration of other tetrahydroisoquinolines, which were reductively methylated with the formaldehyde-formic acid reagent (Eschweiler Clarke) to give the corresponding *N*-methyl derivatives.

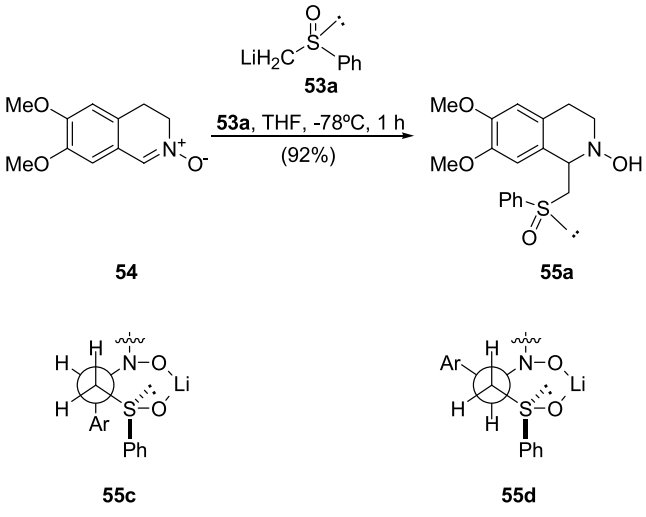
In more recent work, Chrzanowska and Sokolowska[58] provided an example of an interesting concept, the enantioselective alkylation of a dihydroisoquinolinium derivative in the presence of natural lupine alkaloid (−)-sparteine (**51**) as external ligand. In this case, no covalent bonds mediate between the ligand and the isoquinoline ring, thus shortening the synthetic sequence by avoiding the need of chemically removing the chiral inductor.

This inexpensive diamine is a natural product, which forms amine–organolithium complexes and acts as a bidentate ligand; it has also found use in asymmetric deprotonation and enantioselective addition of organolithium and Grignard reagents to carbonyl compounds.[59] The enantioselective addition of organometallic reagents to prochiral imines in the presence of a chiral ligands/catalysts has been recently reviewed.[60]

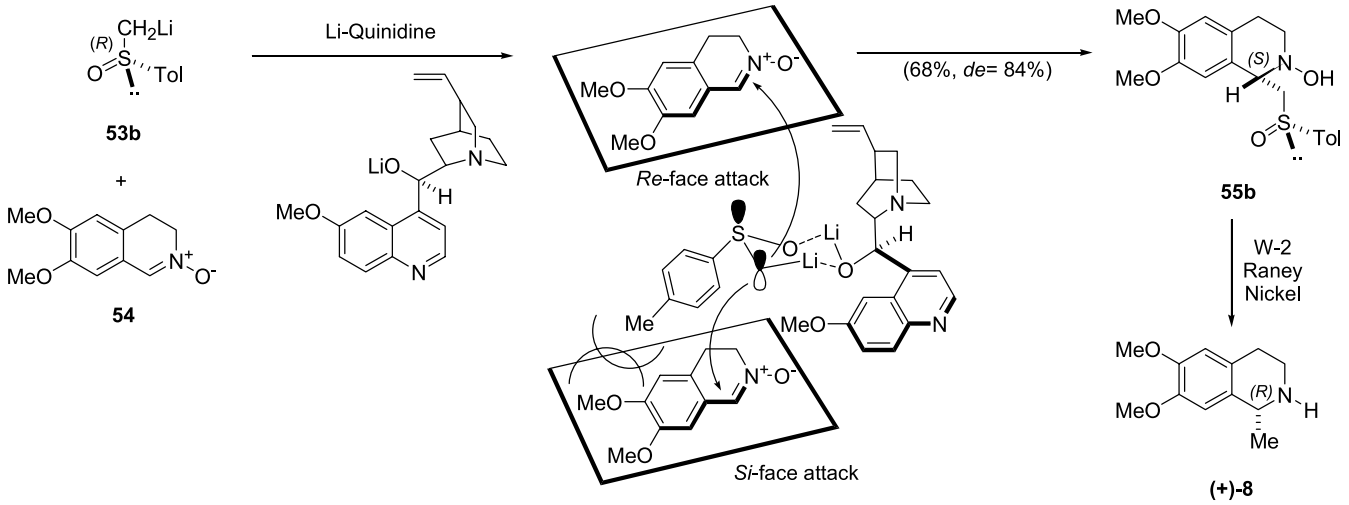
However, in spite that chemical yields of carnegine were reasonable (Table 2), optical yields were disappointingly low, being recorded values of 7%, at best and addition of the bulkier phenyllithium to **52** efficiently furnished the corresponding 1-phenyltetrahydroisoquinoline derivative, albeit in even lower ee. Interestingly enough, in mass spectrometry loss of the C-1 methyl with the formation of iminium derivatives such as **52** occurs readily and chemical ionization techniques have to be used in order to generate the molecular ion and deduce an accurate molecular weight. The recorded results indicated that in this system, enantioselection by organolithium addition to isoquinolinium salts is the opposite to that observed for the analogous reaction, carried out on the less reactive 3,4-dihydroisoquinolines; in addition, its performance is lower.

The electroreductive alkylation of dihydroisoquinolinium species such as **52** in DMF at −1.8 V vs the standard calomel electrode employing a lead cathode was demonstrated to furnish 1-substituted *N*-methyl tetrahydroisoquinolines; among them, racemic carnegine was produced in 35% yield by electroreductive methylation with methyl iodide.[61]

The ability of sulfur to stabilize negative charges on adjacent carbon atoms has been especially important in the development of new methods to form carbon–carbon bonds. The addition of methyl phenyl sulfoxide anion to nitrones, has been studied by Pyne and Hajipour.[62] This group added racemic organolithium derivative **53** to nitrone **54**,



Scheme 9.



Scheme 10.

observing the formation of a 86:14 mixture of diastereomeric hydroxylamines **55** in 92% yield, as shown in Scheme 9.

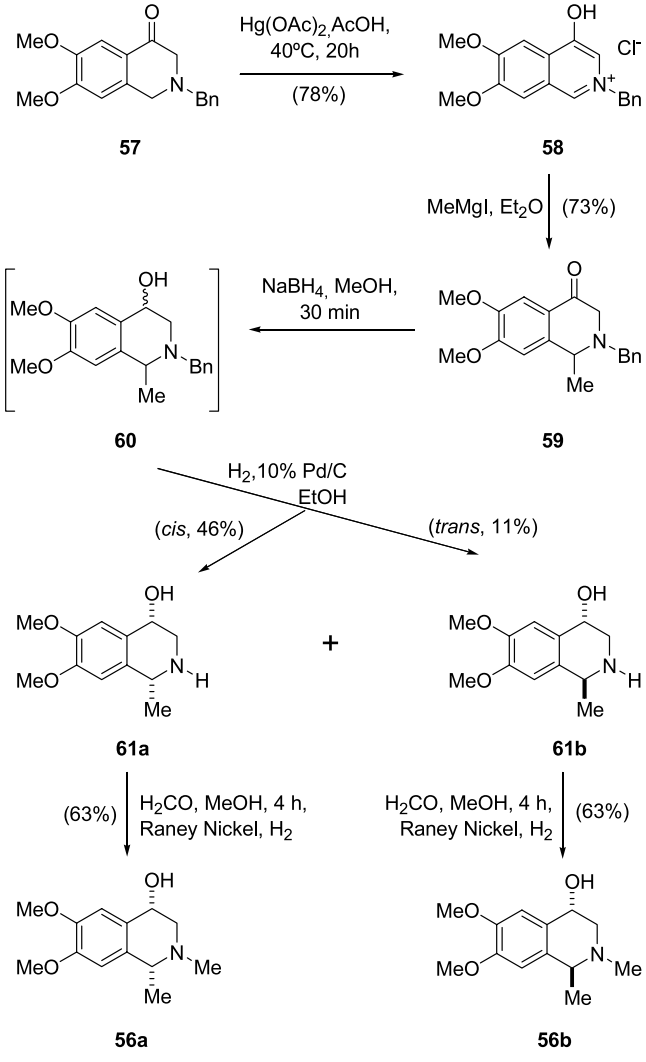
The election of the substrate is advantageous since nitrones offer enhanced reactivity over imines towards 1,2-addition of organometallic reagents.[63] By analogy with similar additions, a chelated chair-like transition state (**55c** vs **55d**) was proposed as the origin of the diastereoselection The diastereoselection observed with cyclic nitrone **54** was better than that observed in the cases of acyclic congeners, displaying less steric demand of the group bound to the nitrogen of the nitrone.

In a related synthesis, Murahashi et al.[64a] reacted nitrone **54** with *R*-(+)-methyl p-tolyl sulfoxide (**53b**) anion in the presence of lithium quinidine, accessing β-sulfinyl hydroxylamine **55b** in 68% yield and 84% *de*. Comparing with the results of Pyne, it is evident that the addition of quinidine was essential for attaining good diastereomeric excess of product. The reaction mechanism and the rationalization of the reaction course are shown in Scheme 10. Although the protocol was exploited for the elaboration of (+)-salsolidine (**8**), this transformation could in principle, be employed for accessing a variety of *N*-substituted tetrahydroisoquinoline derivatives,[63d] since several procedures for reduction of the hydroxylamine moiety are available.[64]

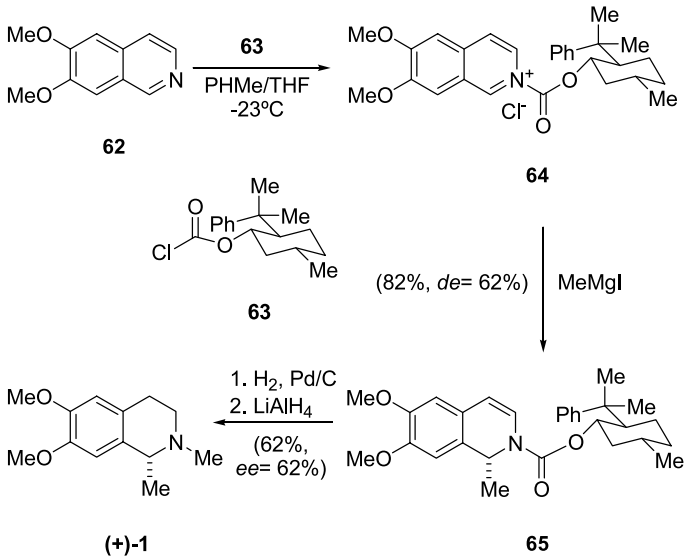
An interesting synthesis of the diastereomers of 4-hydroxycarnegine in racemic form was presented by Brossi et al. during their attempts to solve the problem of the identity of gigantine (**9**), proposed as **56**.[65]

To that end, isoquinolin-4-one **57** was oxidized with mercury(II) acetate to the isoquinolinium salt **58**, which was submitted to Grignard addition employing MeMgI. This furnished the corresponding isoquinolin-4-one **59**, which was reduced to a mixture of alcohols **60** with sodium borohydride and then subjected to Pd/C debenzylation, giving access to the separable diastereomeric tetrahydroisoquinolin-4-ols **61a** and **61b**.

Finally these were individually *N*-methylated with formaldehyde and hydrogen under Raney nickel catalysis, furnishing **56a** and **56b**, respectively, which proved to be different from the natural product (Scheme 11).



Scheme 11.



Scheme 12.

Another example of alkylation of an isoquinolinium derivative en route to carnegine was provided by Comins and Badawi.[66] These authors observed that, analogously to the pyridine series, isoquinolines react with chloroformates to form *N*-acyl isoquinolinium salts. In turn, these activated intermediates can be attacked by nucleophiles such as Grignard reagents to give 1,2-dihydroisoquinoline derivatives. Subsequent reduction of the double bond and the carbamate group generate 1,2-substituted tetrahydroisoquinolines in which the nitrogen atom supports a methyl group. In order to impart diastereofacial differentiation during the nucleophilic addition step, a homochiral chloroformate is required in this protocol. Thus, reaction of 6,7-dimethoxyisoquinoline **62**, easily accessible employing Jackson's isoquinoline synthesis[67a–c] and related procedures,[67d] with (−)-8-phenylmenthyl chloroformate **63**[68] in THF/toluene at −23 °C readily produced the corresponding *N*-acyl intermediate **64** (Scheme 12). Without isolation, this intermediate was reacted with methylmagnesium iodide to give 82% of a 78:22 mixture of diastereomers, in which **65** was predominant.

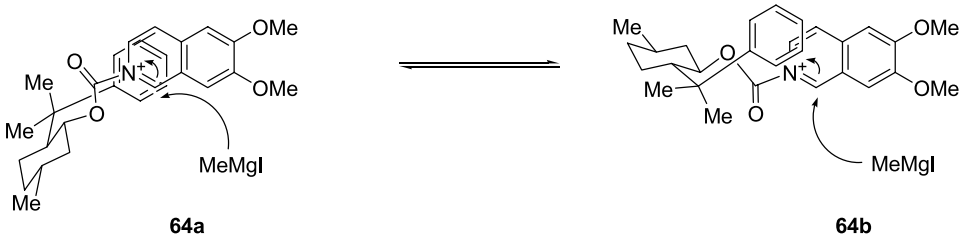
Temperature effects on the diastereomeric excess of product were observed, since a 83:17 mixture was obtained when the reaction was carried out at −78 °C; in this case, however, the yield dropped to 26%. Experiments with model isoquinolines demonstrated that under given solvent and temperature conditions, MeMgI was superior to MeMgCl, $MeTi(OiPr)_3$ and methylmagnesium 2,6-dimethylphenoxide, a bulky modified Grignard reagent, in terms of product yield and diastereomeric ratio.

When submitted to catalytic hydrogenation, a 81:19 mixture of **65** and its diastereomer afforded the corresponding tetrahydroisoquinolines in 95% yield. In turn, these were reduced with $LiAlH_4$ in refluxing THF, affording *R*-carnegine with an optical purity of 62%. Concomitantly, 71% of the valuable chiral alcohol (−)-8-phenylmenthol was also recovered.

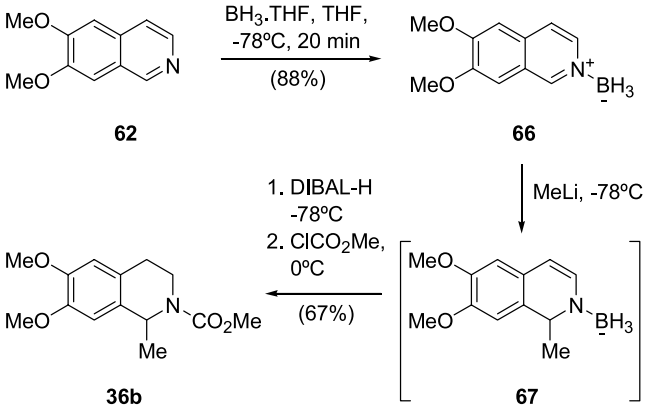
Since the energy difference between the two low energy reactive conformations **64a** and **64b** is very small, the observed diastereoselectivity of the reaction was explained as being a result of the π–π interaction between the phenyl ring of the chiral auxiliary and the electron deficient azomethine *C*=*N* bond, as shown in **64a**, which would stabilize the transition state (Scheme 13).[69]

Being 8-phenylmenthol readily accessible only as the (−)-enantiomer,[70] this process is highly suitable only for the synthesis of *R*-carnegine.

Finally, Minter[71] disclosed the elaboration of *N*-carboxymethyl salsolidine (**36a**),[50b] from isoquinoline **62** (backebergine) employing a very similar strategy, in which the nitrogen heterocycle was activated by formation of the zwitterionic complex with borane (**66**). The method is a one-pot procedure in which substituents are added sequentially as nucleophiles and electrophiles, accompanying the reduction of the heterocyclic ring. Alkylation of such complex with methyllithyium, followed by reduction with DIBAL-H of the 1,2-dihydroisoquinolineborane intermediate **67** and in situ acylation of the product with methyl



Scheme 13.

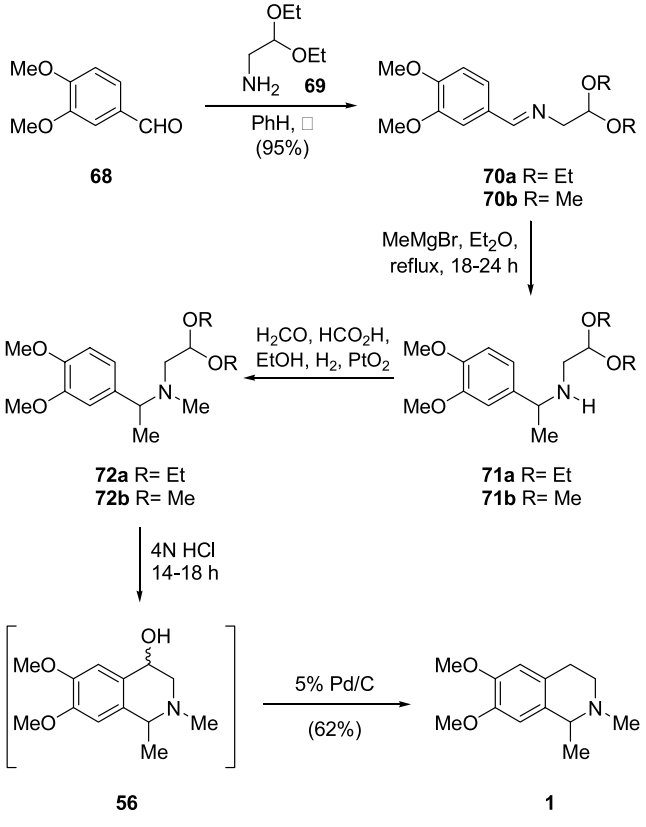


Scheme 14.

chloroformate gave the final product, as shown in Scheme 14. Tetrahydroisoquinoline **36b** is a precursor of carnegine (Scheme 5).

4.1.3. Alkylation of imines with organometallic reagents. Imines react with Grignard and organolithium reagents leading to the formation of new carbon–carbon bonds. Although the transformation is analogous to that involving organometallic addition to carbonyl compounds leading to alcohols, it has found less use than the latter because of the comparatively poorer reactivity of the nitrogen derivatives.

Nevertheless, the addition of organomagnesium and organolithium reagents to azomethines has been successfully employed as an entry to carnegine; both, 3,4-dihydroisoquinolines and Schiff base-type isoquinoline precursors served as suitable substrates. Enantioenriched carnegine emerged from protocols employing chiral auxiliaries or an optically active organometallic reagent.



Scheme 15.

In their modification of the classical Pomeranz–Fritsch isoquinoline synthesis leading to tetrahydroisoquinolines, the group of Bobbitt disclosed a synthesis of carnegine in racemic form, which resulted more practical and less laborious when compared with previous syntheses of carnegine.[72]

To that end, veratraldehyde **68** was condensed with aminoacetaldehyde diethylacetal (**69**) in 95% yield and the resulting Schiff base **70a**[73] was alkylated with methyl Grignard reagent, furnishing amine **71a**, as depicted in Scheme 15; in order to complete the transformation,[74a] the reaction mixture had to be heated to reflux in ether for 18–24 h, since Grignard reagents add sluggishly to Schiff bases like **70a**.[74b]

In turn, this was reacted with formaldehyde and acetic acid in ethanol, and the resulting intermediate was hydrogenated under platinum catalysis to furnish the *N*-methyl acetal **72a**. Final cyclization of **72a** in 4N HCl followed by catalytic hydrogenation with 5% Pd/C as catalyst provided carnegine in 62% yield, probably through the intermediacy of tetrahydroisoquinolin-4-ols **56**, like those elaborated by Brossi et al. (see Scheme 11).[73,74a]

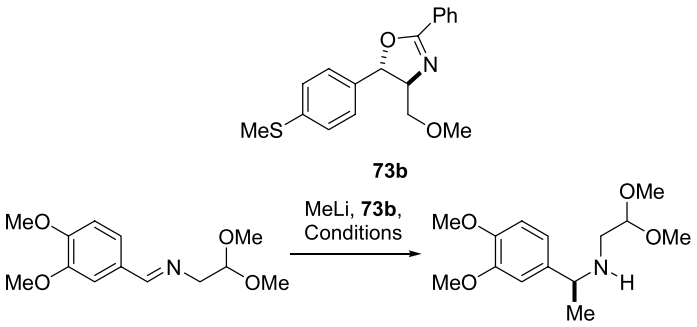
The oxidation of carnegine was studied;[75] the natural product withstood treatment with chromium trioxide-sulfuric acid during 1 h at 20 °C;[75b] however, when the oxidation was carried out at 60 °C in an acetic acid–acetic anhydride mixture, the 1,3,4-trioxo derivative was obtained, in a reaction entailing loss of the *C*1 methyl group.

A modern and chiral version of Bobbitt's group synthesis of carnegine was very recently provided by Gluszynska and Rozwadowska.[76] Table 3 summarizes the results of the optimization efforts towards the enantioselective addition of MeLi to imine **70b**, elaborated by condensation of **68** with aminoacetaldehyde dimethyl acetal.

These Polish scientists reported the enantioselective synthesis of this natural product and related alkaloids by enantioselective addition of methyllithium to imine **70a** in the presence of oxazolidine-type ligands **73a–d** (Fig. 4), which control the steric course of the reaction. The required ligands were obtained from (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols, inexpensive and widely available industrial waste products.[77] Noteworthy, the enantioselective addition of carbon nucleophiles to imines, not as intensively studied and not as widely used as the analogous reaction involving prochiral carbonyl compounds, has been recently reviewed.[78]

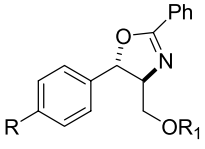
Incubation of a mixture of imine and ligand prior to MeLi addition produced some variation in yield and ee of the resulting product which was considered convenient; 2.5 equiv of MeLi and 2.5–3.5 h reaction time were judged as optimal for conducting the reaction and a non-coordinating medium such as toluene was found to be superior to the commonly used ethereal solvents.

Table 3. Addition of MeLi to imine **70b** in the presence of ligand **73b**



Entry	Reaction conditions			Product	
	Ligand (equiv)	Solvent	Temp (°C)	Yield (%)[a,b]	ee (%)[b,c]
1	0.1	PhMe	−65	43	7
2	0.5	PhMe	−65	55 (44)	23 (22)
3	1.0	PhMe	−65	78	28
4	2.0	PhMe	−65	85 (78)	37 (34)
5	2.6	PhMe	−65	85 (92)	38 (49)
6	2.6	PhMe	−42	85	33
7	2.6	PhMe	−42→20	81	15
8	2.6	PhMe	−90	(14)	(45)
9	3.0	PhMe	−65	(78)	(42)
10	2.6	THF	−65	NR	
11	2.6	Et_2O	−60	40 (40)	(14)
12	2.6	PhMe	0	56	8
13	2.6	PhMe	rt	(47)	(8)

[a] Chemical yields were established by NMR of crude reaction products.
[b] Numbers in parenthesis are chemical and optical yields of the addition product when 1 h of preliminary interaction of imine **70a** with ligand **73b** was produced.
[c] Enantiomeric excesses were determined in the presence of TADDOL.[79]



Compound	R_1	R_2
73a	SMe	H
73b	SMe	Me
73c	H	H
73d	H	Me

Figure 4.

It was also observed that the imine was essentially unreactive towards the organolithium reagent at low temperatures and in the absence of added ligand, and that enantioselectivity progressively increased from room temperature to −90 °C. Sub-stoichiometric amounts of ligand gave worse results than employing 1–2 equiv of oxazoline, while the best performance (ee=49%) was achieved in the presence of 2.6 equiv of ligand.

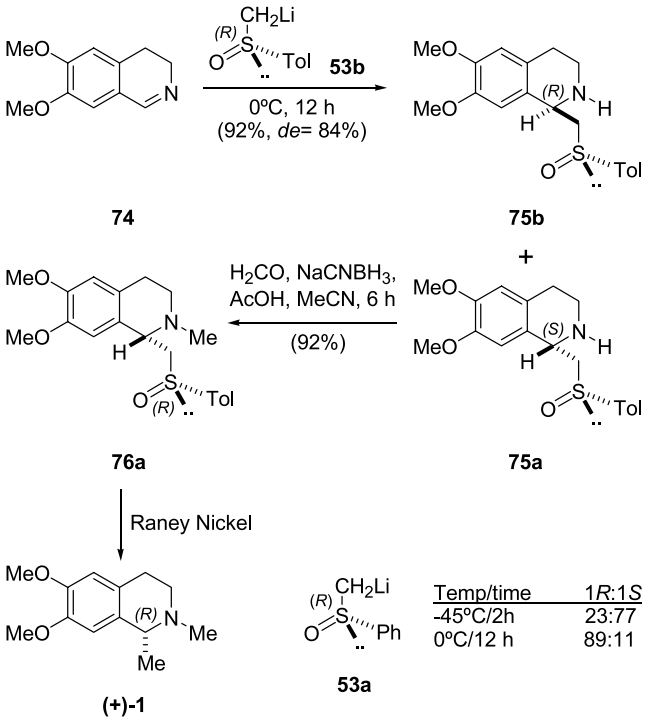
When the optimized conditions were applied to other ligands, lower asymmetric induction was observed; enantiomeric excesses were rather poor with **73a** and **73c** (1–9%), while **73d** allowed access to the addition product in 40% ee.

For the elaboration of carnegine, a protocol analogous to that of Bobbitt was followed (Scheme 14) and the resulting amine **71b** (ee=38%) was *N*-methylated with the H_2CO/AcOH–$NaBH_4$ system to furnish 86% of the corresponding *N*-methyl derivative. In turn, this was cyclized in 6N HCl during 2 days, after which Pd/C-catalyzed hydrogenolysis was carried out to furnish the natural product in 79% yield and 36% ee, that is, essentially without loss of optical purity. Interestingly, a related transformation, involving addition of methyllithium to *N*-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide in the presence of sparteine proceeds with poor performance,[77] as discussed above.

Due to the acidic character of the a-protons of sulfoxides and sulfoximines, deprotonation is readily achieved with strong bases such as n-butyllithium, furnishing the corresponding α-metallated species. An attractive synthesis of (+)-**1** entailing the nucleophilic addition of a chiral α-sulfinyl carbanion compound[80] to an imine was reported by the group of Pyne.[80a] These Australian scientists added the versatile lithium carbanion of *R*-(+)-*p*-tolyl sulfoxide (**53b**) to 3,4-dihydroisoquinoline **74**, obtaining a mixture of diastereomeric sulfoxides **75a** and **75b**, which were characterized after chromatographic separation.

N-Methylation of **75a** by reductive alkylation of formaldehyde with sodium cyanoborohydride[81] to **76a** followed by reductive desulfurization with Raney nickel furnished the final product, as shown in Scheme 16. Chronologically speaking, this can be regarded as the first diastereoselective total synthesis of carnegine.[80a]

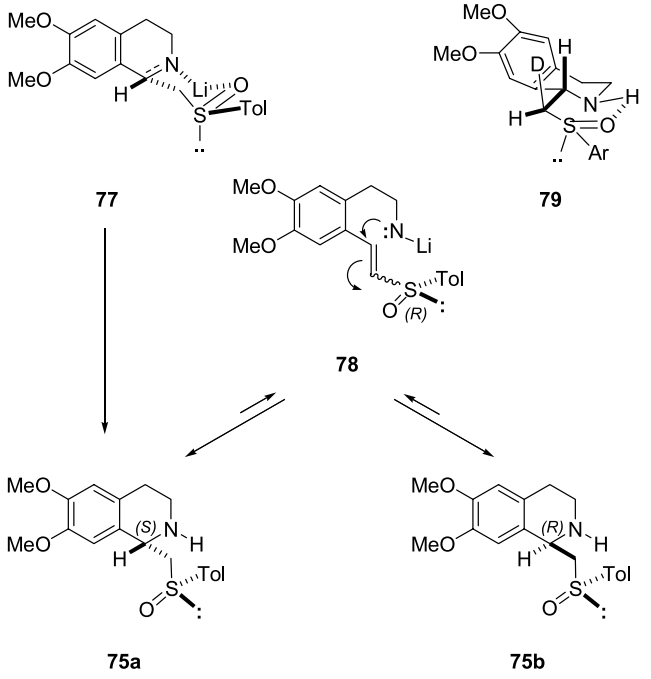
Appropriate temperature and reaction time were crucial to attain good chemical and optical yields. Experiments involving addition of phenylmethyl sulfoxide anion (**53a**)



Scheme 16.

to **74** demonstrated that better performance was achieved at room temperature than at −45 °C and that selectivity at the lower temperature was different than that observed at 0 °C.

Diastereoselectivity of the kinetically controlled addition of methyl-*p*-tolyl sulfoxide anion (**53b**) to imine **74** was rationalized by assuming a chair-like transition state **77**, as shown in Scheme 17, while diastereomer interconversion, leading to diminished diastereomeric excesses upon long reaction times, was proposed to occur through a retro Michael–Michael addition process involving vinylsulfoxides **78**.



Scheme 17.

Interestingly enough, quenching the addition reaction with D_2O lead to mono-deuterated species, which for the most abundant diastereomer **75a** probably exists in the intramolecular hydrogen-bonded form **79**, depicted in Scheme 17. A similar strategy consisting in a Mannich type reaction and based on the addition of the lithium anion of sulfoximines to complexes between 3,4-dihydroisoquinolines like **74** and $BF_3.Et_2O$ allowed the synthesis of more complex 1-susbtituted tetrahydro-isoquinolines;[80d] diastereoselectivities up to 95% were recorded for this approach.

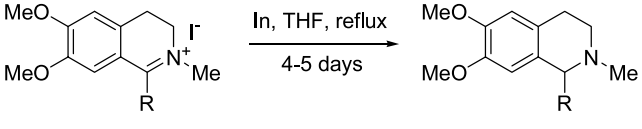
4.2. Reduction reactions

4.2.1. Reduction of dehydrosalsolidine methiodide. Reduction of 3,4-dihydroisoquinolinium derivatives has long been known to yield tetrahydroisoquinolines. For the purpose of accessing carnegine through this route, chemists have resorted to conventional reducing agents such as borohydrides, as well as novel reagents like indium metal. In addition, enantioselective transfer hydrogenation and chiral reducing agents have been employed for the preparation of optically active *N*-alkyl 1-substituted tetrahydroisoquinolines. To date, however, the use of this strategy for the elaboration of enantioenriched carnegine has met with rather poor success, being the best enantiomeric excesses recorded not more than 65%.

As part of their studies of the properties of indium metal as a reducing agent for use in organic synthesis, Moody et al. disclosed the efficient reduction of dehydrosalsolidine methiodide (**80**) with indium powder (1 g/mmol) in refluxing THF during 4–5 days, to provide 83% of carnegine. Notably, the reducing agent is stable towards water and air. The dehydrosalsolidine precursor **12** of the methiodide is easily available from 3,4-dimethoxyphenethylamine through the Bischler–Napieralski procedure.[82]

The full scope of the reaction, however, is still unclear because the related 1-pentenyl methiodide (**81**) was recovered unchanged after being submitted to the same treatment, and no tetrahydroisoquinoline **81a** could be isolated, as shown in Scheme 18.[83] The first ionization potential of indium (5.8 eV) is lower than that of reducing metals such as zinc (9.4 eV) and tin (7.3 eV) and close to that of alkali metals like sodium (5.1 eV), suggesting that the metal ought to participate in single electron transfer processes.

Interestingly enough, no radical intermediates could be intercepted during the reduction and no evidence of cyclized product derived from the pentenyl compound was observed.



80 R= Me
81 R= $(CH_2)_3CH=CH_2$

1 R= Me (83%)
81a R= $(CH_2)_3CH=CH_2$ (0%)

Scheme 18.

Moreover, dimeric products, which could have been formed by coupling of two heterocyclic rings, were not detected. This is in contrast with the facts that such coupling reactions are known to occur on treatment of isoquinolines and related heterocycles with zinc,[84] and that the effectiveness of indium in the aza-pinacol-type reductive coupling of imines to give 1,2-diamines has been demonstrated.[85]

Analogous syntheses of carnegine following similar protocols were previously disclosed by others. For studies on chemistry of 1-thienyl tetrahydroisoquinolines, Baker et al. also elaborated carnegine from **12**,[86] by methyl iodide methylation and reduction of **80** with sodium borohydride in aqueous ethanol. In an early synthesis of the natural product, Rozwadowska reported the use of 6,7-dimethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinaldo nitrile, a Reissert compound produced by reaction of isoquinoline **62** with ethyl chloroformate and potassium cyanide, as an intermediate.[87a,c]

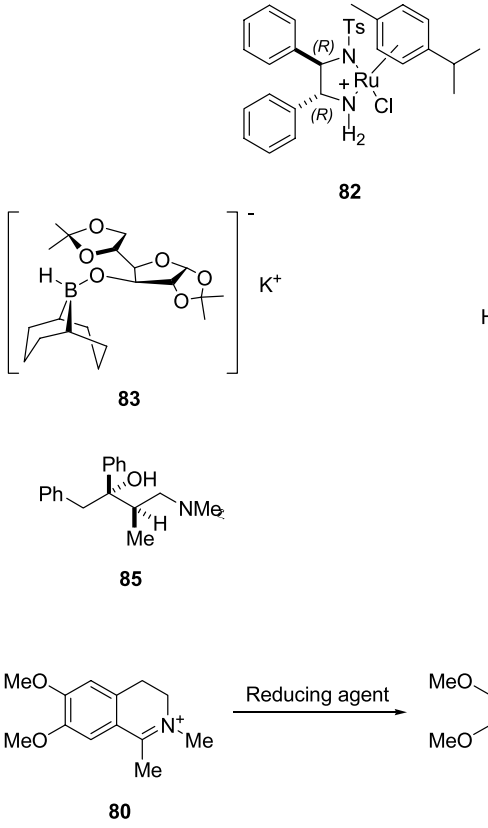
In the final step, 6,7-dimethoxy-1,2-dimethyl isoquinolinium iodide was reduced with sodium borohydride in MeOH, furnishing 60% of racemic carnegine.[87d] In addition, Späth's preparation of carnegine involved alkylation of **12** with methyl iodide, followed by Sn/HCl reduction of the resulting quaternary salt **80**.[10c]

On the other hand, and based on ruthenium neutral hydrocarbyl complex catalysts developed and popularized by the group of Noyori,[88] Blacker and Campbell recently disclosed a transfer hydrogenation process leading to carnegine;[89] employing the catalyst derived from bidentate ligand (*R*,*R*)-*N*-tosyl-1,2-diamino-1,2-diphenylethane. Carnegine was accessed in 63% ee and 72% yield when sodium isopropoxide-isopropanol was employed as hydrogen donor, while chemical yields of the natural product in excess of 98% were realized with little loss of optical purity when the advantageous triethylamine-formic acid azeotropic mixture in acetonitrile served as the hydrogen donor (Table 4, entries 1 and 2). These acceptable results were recorded with substrate/catalyst ratios of 400. Interestingly enough, Noyori previously demonstrated that these ruthenium catalysts perform better with the related imines; thus, salsolidine **8** was prepared from **12** in 99% yield and >95% ee.[88]

The use of chiral catalysts is one of the most attractive methods for performing asymmetric reactions, because compared to the stoichiometric use of chiral auxiliaries, a smaller amount of not always readily available chiral material is required. Therefore, large quantities of the resulting chiral materials are directly obtained, often with no need for further manipulation and little worry on recovery of the chiral auxiliary.

In addition, Cho and Han experienced the use of various chiral hydride reagents, such as K-glucoride (**83**),[90b] Itsuno's borane reagent (**84**)[90c] and Mosher's reagent,[90d] a complex prepared from aminoalcohol **85** (Darvon alcohol) and $LiAlH_4$ with the aim of enantioselectively reducing dihydrosalsolidine methiodide to carnegine.[90] Their results, consigned in Table 4 (entries 3–5), were slightly

Table 4. Synthesis of enantioenriched carnegine by enantioselective reduction of dehydrosalsolidine methiodide



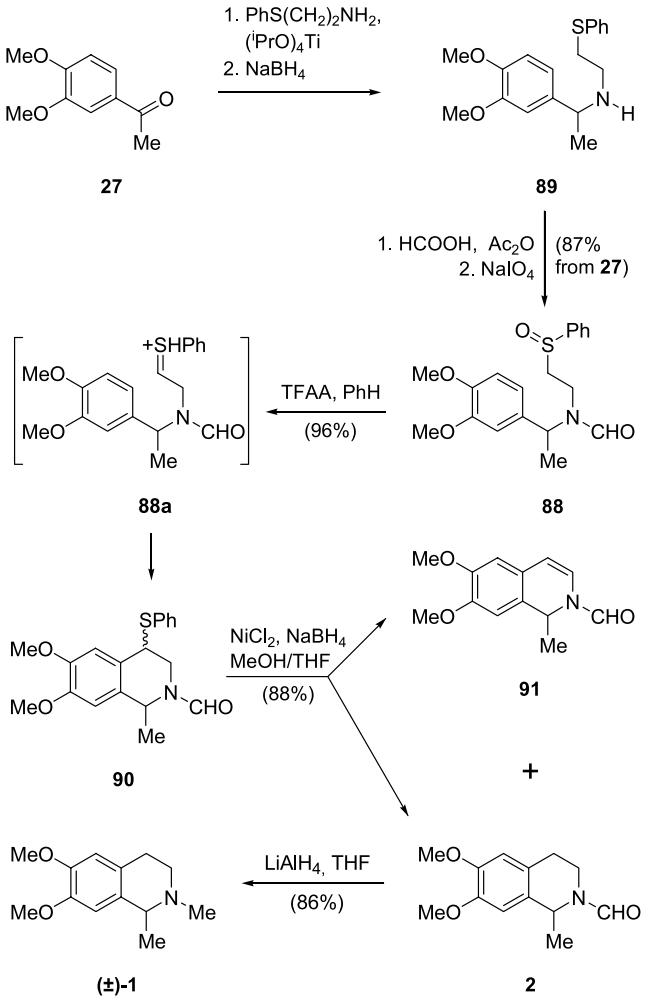
Entry No.	Reducing agent	ee, % (configuration)
1	Me_2CHOH, **82**	63
2	Et_3N, HCO_2H (2:5), **82**	≈ 60
3	K-Glucoride (**83**)	52.3 (*R*)
4	Itsuno's reagent (**84**)	17.8 (*R*)
5	Mosher' reagent (**85**)	66.4 (*S*)
6	Triacyloxyborohydride	11.9 (*R*)
7	Baker's yeast	No reaction

disappointing in terms of enantiomeric excess; since at best a 3:1 mixture of enantiomeric products was obtained.

Finally, Indian researchers informed that reduction of **80** with the chiral triacyloxy borohydride prepared from *S*-*N*-benzyloxycarbonyl proline (**86**) and sodium borohydride (3:1)[91a] provided 83% of carnegine slightly enriched in the dextrorotatory enantiomer (ee=11.9%).[91b] The same authors disclosed that submission of methiodide **80** to fermenting baker's yeast did not result in carnegine, being the substrate destroyed in the reaction medium, presumably by hydrolysis. Methods for the enantioselective reduction of the *C*=*N* function have been recently reviewed.[91c]

4.2.2. Reduction of imines, enamines and enamides. The reduction of imines and enamines serves as a convenient strategy for the installation of an 1-alkyl group in tetrahydroisoquinoline derivatives. This resource has been scarcely exploited in connection with the synthesis of carnegine.

The reductive amination of conveniently substituted



Scheme 19.

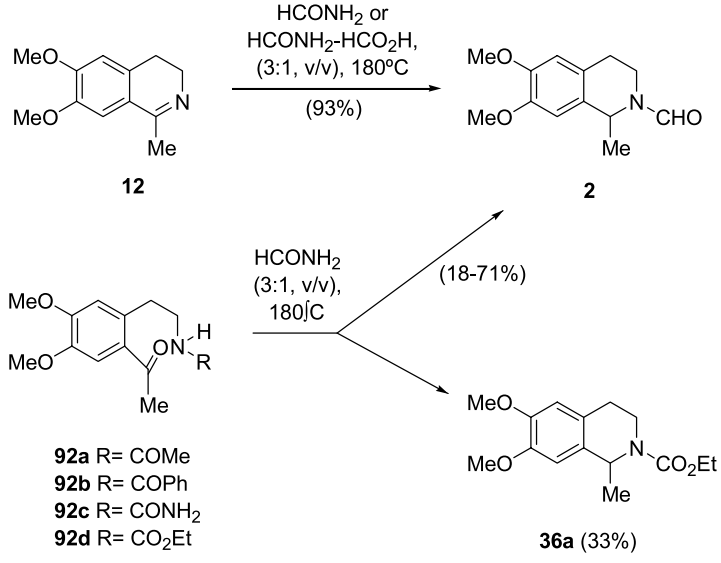
acetophenones is an acceptable alternative for the elaboration of 1-substituted tetrahydroisoquinolines.[92] In combination with the Pummerer sulfoxide rearrangement and an electrophilic aromatic cyclization reaction, this sequence proposed by Japanese scientists as a new modification of the Pomeranz–Fritsch isoquinoline synthesis constitute the key steps of another example of a Kametani type 5 synthetic strategy towards tetrahydroisoquinolines (Scheme 19).

This protocol has been developed only recently, as a special case of the Bobbitt sequence and it has been explored not as extensively as other classical cyclizations leading to tetrahydroisoquinoline derivatives. Initial work was done by the groups of Takano and Sano,[93] inspired in other sulfoxide-mediated electrophilic reactions[94] and has already resulted in the elaboration of several tetrahydroisoquinoline natural products, other polycyclic alkaloids, as well as biologically interesting tetrahydroisoquinolines.

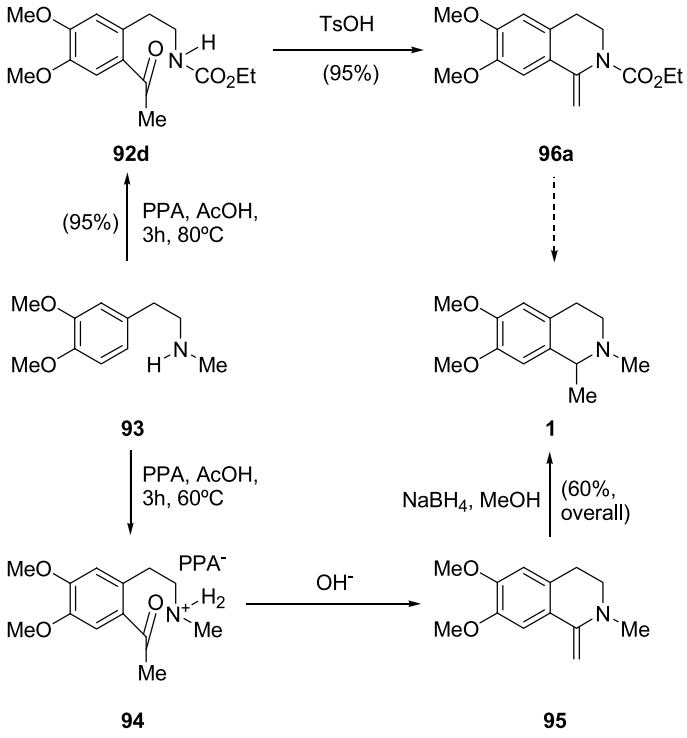
For the synthesis of (±)-carnegine, the required *N*-acyl-sulfoxide **88** was prepared in 87% overall yield from 3,4-dimethoxy acetophenone (**27**). Thus, reductive amination of the latter with 2-phenylthioethylamine under titanium isopropoxide promotion[95] in an EtOH–AcOH medium furnished **89**, which was acylated with mixed formyl-acetyl anhydride and then oxidized to the diastereomeric mixture of sulfoxides **88** with $NaIO_4$ in aqueous MeOH. Treatment of **88** with TFAA in benzene at room temperature for 18 h gave 96% of the cyclized product **90**,[94f] which was reductively desulfurized in 88% yield with the sodium borohydride–nickel chloride reagent, yielding a mixture of dihydroisoquinoline **91** and formyl tetrahydroisoquinoline **2**, which was subsequently reduced to the natural product in 86% yield by lithium aluminum hydride in THF.[96]

In a systematic study,[97] it was demonstrated that this type of cyclization is sensitive to the solvent and the nature of the *N*-acyl substituent. In CH_2Cl_2, a complex mixture of products is obtained and apparently, the formyl moiety as *N*-protecting group plays an important role in facilitating the intramolecular cyclization to take place.

Despite that to date only the elaboration of racemic carnegine has been reported following this route, the strategy has been adapted to large scale preparation of both enantiomers of



Scheme 20.



Scheme 21.

1-methyl tetrahydroisoquinoline[98] as well as of the four stereoisomers of 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline, which suggests its potential applicability to an enantioselective synthesis of carnegine. This route seems to be very attractive for preparing substrates for use in biological studies since isotope labeling at the $C-4$ position is possible by reductive elimination of the phenylthio group.

An alternative synthesis of racemic carnegine resorting to the reduction of the $C{=}N$ bond was provided by the group of Venkov. These Bulgarian scientists made use of the old finding that formamide can be used in the Leuckart-Wallach[99] reaction for the reductive amination of carbonyl compounds and for the reductive formylation of heterocycles, including methylisoquinolines.[100]

After heating of a mixture of **12** and formamide to 180 °C for 1–2 h, the *N*-formyl derivative **2** was obtained in 67% yield, as shown in Scheme 20.[101] Other *N*-formyl tetrahydroisoquinolines were accessed under similar conditions in yields ranging from 38 to 93%. Yields of **2** increased to 93% when 98% formic acid was added to formamide to form a 3:1 v/v mixture and the reaction was refluxed for 2 h. From analysis of the products it was proposed that the reaction probably proceeds with an initial reduction of the $C{=}N$ bond, followed by the *N*-formylation of the resulting tetrahydroisoquinoline.

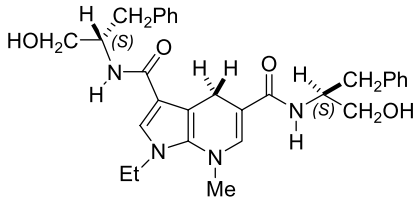
In a slight variation of their strategy, this group disclosed that heating to reflux during 3 h acetophenone derivatives[102a] **92a–d** in a 3:1 mixture of formamide and formic acid lead predominantly to *N*-formyltetrahydroisoquinoline **2**. However, in the case of **92d**, not possessing a good leaving group on nitrogen, the transamidation could not be made to reach completion leading to a mixture of **2** (18%) and carbamate **36** (33%).

In still another modification of their strategy, depicted in Scheme 21, the same group reported a two-step synthesis of carnegine. This involved the acid-catalyzed acylation of the conveniently substituted homoveratrylamine **93** with acetic acid to furnish acetophenone derivative **94**, which was not isolated, being instead submitted in situ to cyclization under basic conditions, to give enamine **95**.

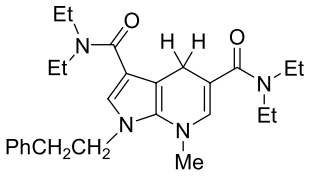
Conventional reduction of the enamine with sodium borohydride in methanol furnished 60% of the product.[103] These authors observed that the preferred acylation pattern of the aromatic ring of the homoveratrylamine precursor is general and takes place in good yields with many different carboxylic acids under polyphosphoric acid promotion. Following a somehow analogous strategy, the same group elaborated in good yield *N*-carboxyethyl enamine **96a**. This precursor of carnegine was prepared from the same starting material, the homoveratrylamine derivative **93** through acetophenone derivative **92d**.[104]

Bourguignon et al.[105] studied the biomimetic reduction of enamides with NADH models as hydride donors employing the chiral NADH mimic **97** (Fig. 5) derived from *S*-phenylalaninol, which reduces $C{=}O$ and $C{=}N$ bonds in the presence of $Mg(ClO_4)_2$. The biomimetic enantioselective reduction of the carnegine precursors **96b** and **96c** with NADH analog **97** was achieved, furnishing up to 95% yield of *N*-acetylsalsolidine (**36b**) in 87% optical yield. Addition of excess $Mg(ClO_4)_2$ to the reaction medium was critical, since the use of 1 equiv of the salt provided the product in only 32% ee.

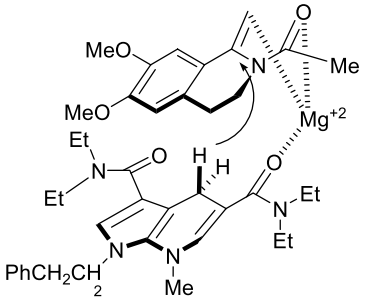
However, the related methyl carbamate **96a** was reduced to furnish 95% of (+)-**36b**, but in only 26% ee. Table 5 summarizes the variation of the enantiomeric excess of **36b** and **36c** with the concentration of $Mg(ClO_4)_2$ in the reaction



97



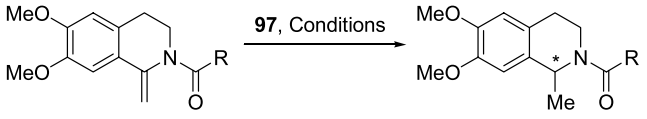
98



98a

Figure 5.

Table 5. Asymmetric reduction of enamides **96** and **96a** with NADH model **97**



96b R= OMe
96c R= Me

36b R= OMe
36c R= Me

$MgClO_4$ (equiv)	0.25	0.5	0.75	1	2	4	8
36c, ee(config)	13(*R*)	20(*R*)	25(*R*)	32(*R*)	51(*R*)	80(*R*)	87(*R*)
36b, ee %	—	—	0	+7	+13	+18	+26

medium. Curiously, inversion of selectivity depending upon the amount of $Mg(ClO_4)_2$ employed occurred during the reduction of methyl benzoyl formate to methyl mandelate. However, no such inversion was observed when reduction of 3,4-dihydroisoquinoline enamides was carried out.

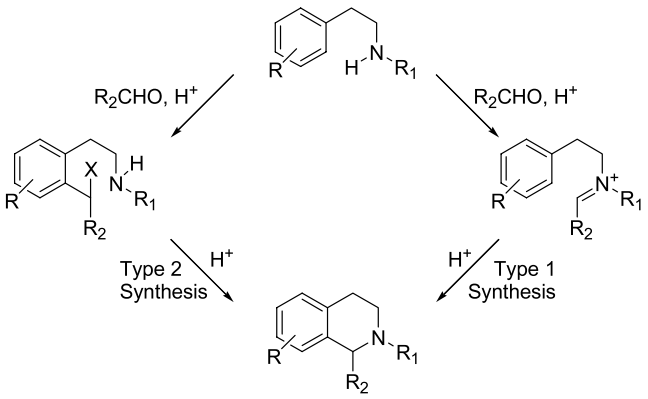
Use of non-chiral NADH models such as **98** to provide racemic **36c** have also been described by this group in earlier publications. A ternary complex model (**98a**) between the substrate, the NADH mimic **98** and Mg^{++} was assumed to be responsible for the hydride transfer; in the case of chiral NADH mimic **97**, the model correctly explains the preferential *si*-face hydrogen transfer to **96c**, leading to enantioenriched *R*-**36c**.

4.3. Cyclization reactions

4.3.1. Cyclizations employing the Pictet–Spengler reaction. The Pictet–Spengler reaction of β-phenethylamines with aldehydes is a well-known and widely used procedure for the synthesis of tetrahydroisoquinolines.[106d] The reaction is limited to phenethylamines without electron-withdrawing groups in their benzene rings. A variation of the Pictet–Spengler reaction, termed 'activated Pictet–Spengler'[106a–d] is carried out employing phenethylamines in which electron withdrawing groups, in the form of amides, carbamates and sulfonamides, are bound to the nitrogen. The *N*-acyliminium or *N*-sulfonyliminium intermediates formed enhance electrophilic reactivity often leading to more efficient cyclizations.[107b]

Although the Pictet–Spengler cyclization is usually regarded as a type 1 tetrahydroisoquinoline synthesis, two alternative mechanisms have been suggested as operative, especially in the case of the 'activated Pictet–Spengler' cyclization (Scheme 22).[107] One of them involves reaction of the aldehyde with the aromatic ring prior to cyclization by attack of the 'activated' nitrogen atom (type 2 synthesis), while the other comprises the formation of an iminium species between the aldehyde and the nitrogen moiety followed by nucleophilic attack by the aromatic ring to the iminium intermediate (type 1 synthesis).

Asymmetric versions of the Pictet–Spengler reaction



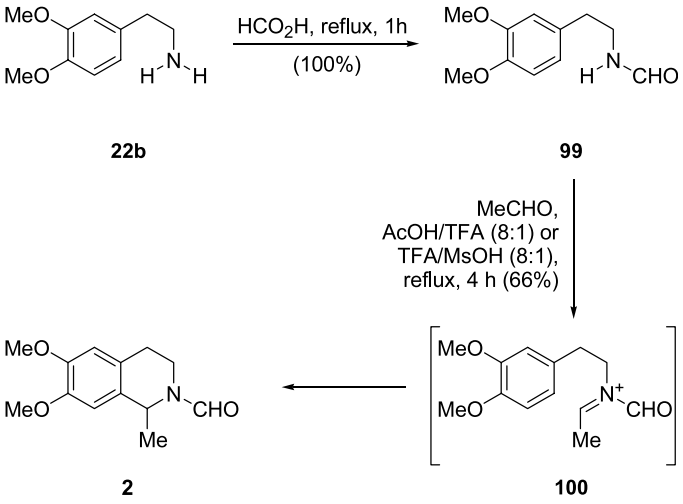
Scheme 22.

involve the presence of chirality either in the amine component or the aldehyde substrate.[106e] Thus, the use of chiral aldehydes may be exploited for the elaboration of enantioenriched tetrahydroisoquinolines.

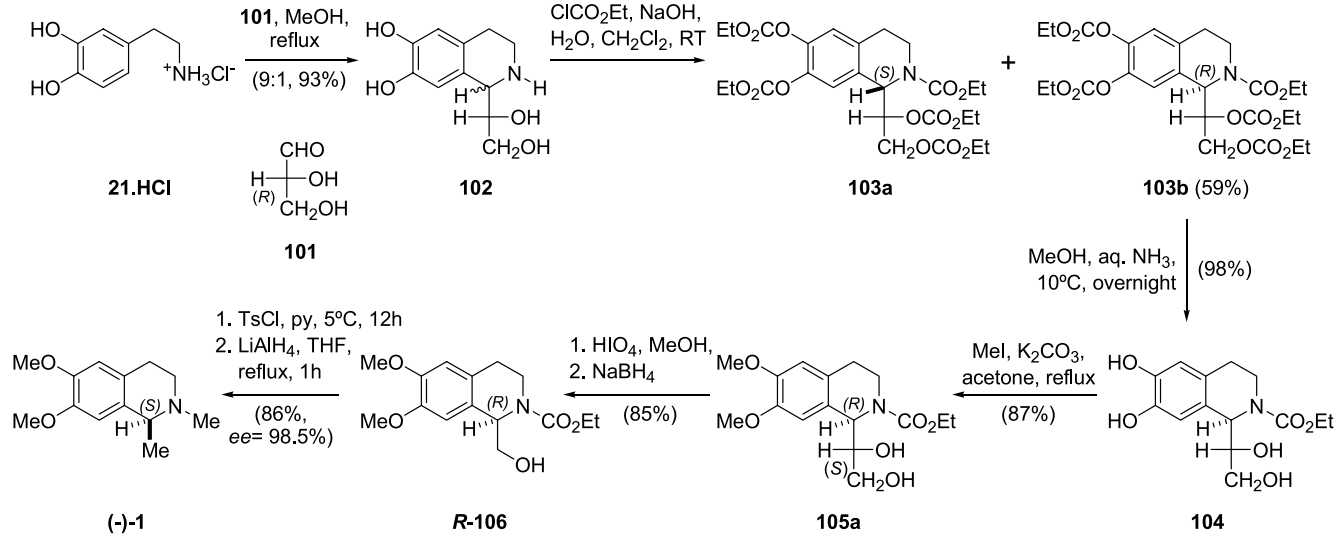
Venkov et al. developed an activated Pictet–Spengler protocol capable of providing 1-substituted *N*-formyl tetrahydroisoquinolines via *N*-formyliminium ions **100**.[108]

The synthetic strategy shown for carnegine in Scheme 23, consists in reacting an appropriately substituted *N*-formyl phenethylamine (**99**) with the required aldehyde (for carnegine, acetaldehyde) in the presence of an acid promoter (AcOH/TFA 8:1 or TFA/MsOH 8:1). The required *N*-formyl phenethylamine can be quantitatively prepared in situ by refluxing the phenethylamine **22b** with an excess of formic acid.

The use of optically active phenethylamine carbamates of less reactive nature was exploited by the group of Comins for the elaboration of substituted 1-benzyl tetrahydroisoquinolines. However, this chiral auxiliary mediated Pictet–Spengler reaction required more strenuous conditions and an enolether was employed as aldehyde surrogate.[109]



Scheme 23.

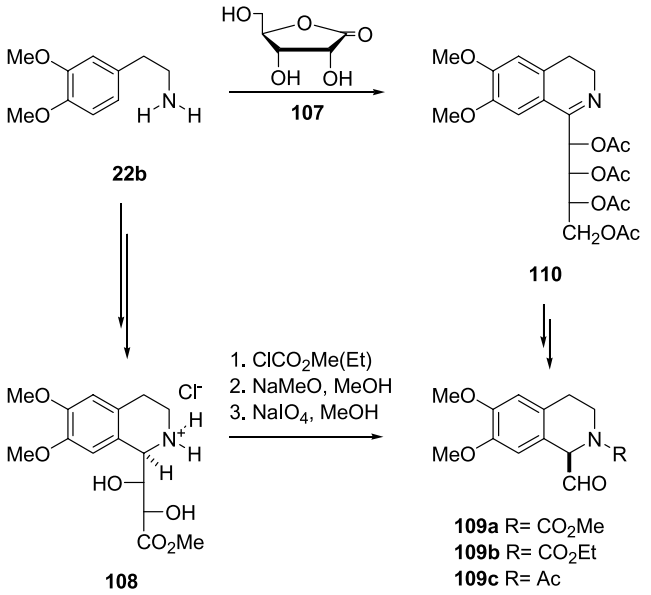


Scheme 24.

A Polish–Canadian group found that sugars and their derivatives could be used as the aldehyde part of the Pictet–Spengler condensation. The importance of this finding stems from the facts that carbohydrates are readily available in enantiomerically pure form and that sugar chirality is transferred to the newly generated asymmetric center. The suitability of this observation for the elaboration of optically active natural products was successfully tested in several occasions. Along these lines, Czarnocki et al. disclosed a total synthesis of (−)-carnegine which employs *R*-(+)-glyceraldehyde (**101**) and dopamine (**21**) as starting materials.[110]

Their synthesis, depicted in Scheme 24, commenced with the Pictet–Spengler condensation of dopamine hydrochloride and (+)-glyceraldehyde to furnish a 9:1 mixture of cyclized diols **102** in 93% yield; the mixture was treated with ethyl chloroformate and the resulting tetracarbonates **103** were chromatographically separated, affording 59% of the most abundant compound **103b**. Mild ammonolysis of **103b** lead to catechol **104** in 98% yield, which was submitted to a conventional Williamson etherification to give 87% of *R*,*S*-diol **105a**.

Next, periodic-acid mediated oxidative fission of the glycol moiety, followed by a reductive work-up provided 85% of carboxyethyl calycotomine (**106**). In turn, this product was reduced in 86% to carnegine via the tosylate of the primary alcohol, employing lithium aluminum hydride in refluxing THF. Analogously, compound **108**, prepared by cyclization of the corresponding phenethylamine **22b** with tartaric acid, has been employed for the elaboration of the versatile aldehydes **109a** and **109b** (Scheme 25). The use of ribonolactone (**107**) for the synthesis of **109c** via the highly unstable tetraacetate **110**, has also been disclosed.



Scheme 25.

The cyclization strategy in both cases was a Bischler–Napieralski reaction,[111w] followed by reduction of the cyclized product to a tetrahydroisoquinoline intermediate. Reduction was carried out directly on the 3,4-dihydroisoquinoline for the elaboration of **108**; however, due to the instability of **110**, the corresponding nitrone was prepared and then reduced. In addition, this group informed the elaboration of **109b** by Bischler–Napieralski reaction of **22b** with diethyl oxalate, followed by functional group transformations and chemical resolution, yielding **106**, which furnished the aldehyde after Swern oxidation.[110c]

Intramolecular radical cyclization reactions have emerged as powerful synthetic tools for the construction of carbocyclic and heterocyclic rings. With the aid of a properly placed chiral auxiliary, these can yield diastereoselective ring closures. An intramolecular aryl radical cyclization to an aldimine leading to **105b**, a diastereomer of glycol **105a** and somehow reminiscent of the outcome of a Pictet–Spengler condensation, was reported by Tomaszewski and Warkentin.[112a]

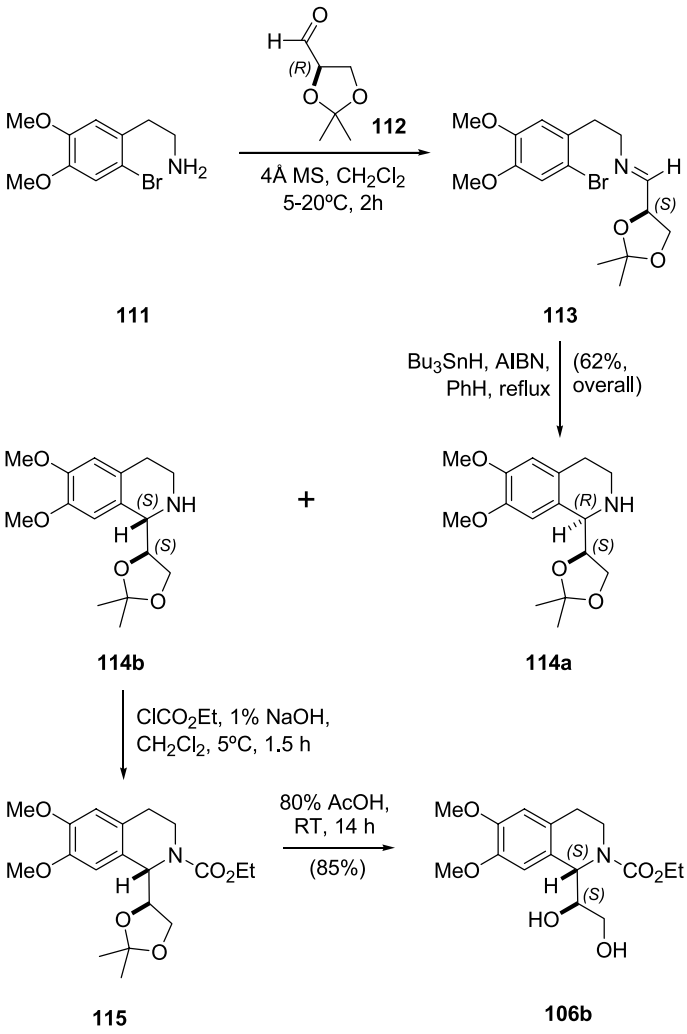
In this sequence depicted in Scheme 26, bromodopamine **111** was condensed with the acetonide of glyceraldehyde (**112**), furnishing imine **113**, which was cyclized with Bu_3SnH and AIBN furnishing 62% of a diastereomeric mixture of acetonides **114a** and **114b** (*de*=53%). This cyclization proceeded exclusively in a *6-endo* fashion and no products derived from the *5-exo* alternative pathway were observed.[112b] Protection of the amino group of the major diastereomer as the ethyl carbamate (**115**) and unmasking of the glycol, provided compound **105b**.

4.3.2. Cyclization of vinyl sulfoxides and sulfoximines. Nowadays, the sulfinyl group is widely used as an important tool in asymmetric synthesis. The sulfoxide moiety is very effective in diastereoselective auxiliary-induced reactions, being its effectiveness due to the steric as well as the stereoelectronic differences existing between the four different substituents of the sulfur atom, which are able to differentiate the diastereotopic faces of the proximal reaction center. Other influential factors contributing to the wide use of sulfoxides are their high configurational stability, the availability of an important array of efficient synthetic methods to obtain homochiral sulfoxides, as well as their synthetic versatility.[113]

The cyclization of vinyl sulfinyl derivatives leading to tetrahydroisoquinoline derivatives reported to date can be regarded as cases somehow reminiscing the Pictet–Spengler reaction in which either the nitrogen moiety or the aromatic part conclude the heterocyclic ring closure. An important difference with regards to the classical Pictet–Spengler condensation is that cyclization of vinyl sulfinyl entail a diastereoselective Michael addition.

This strategy employs the sulfinyl group as a removable stereocontrolling agent, as well as an activating moiety. The use of the stereogenic sulfur center of chiral sulfoxides to achieve enantioselective control in asymmetric synthesis and the participation of chiral sulfoxides in Michael addition reactions has many precedents.[113,114]

With regards to carnegine, Pyne et al. were the first in using organosulfur chemistry. However, this group reported two different procedures for the diastereoselective elaboration of carnegine derivatives based on the same general strategy.



Scheme 26.

This strategy relied on sulfur chirality for diastereoselection and on the Michael acceptor properties of the vinyl sulfur derivatives including their capability of adding amines, for tetrahydroisoquinoline ring formation.[115]

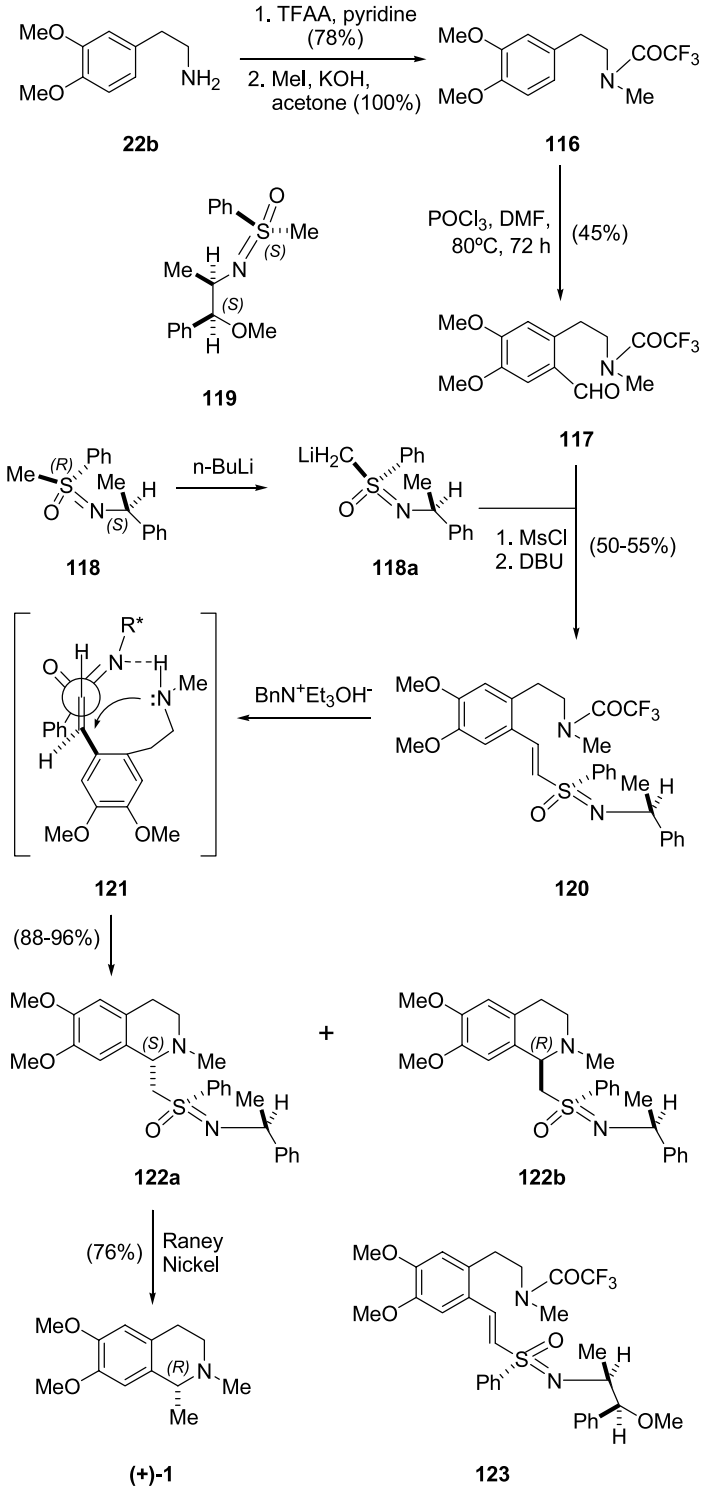
In the first approach, Pyne carried out one of the first successful intramolecular Michael addition to vinyl sulfoximines, employing chiral vinyl sulfoximines derived from compounds **118** and **119**, bearing opposite configurations on the heteoatom. To this end, these researchers appropriately acylated and *N*-alkylated 3,4-dimethoxyphenethylamine (**22b**), by successive treatment with trifluoroacetic anhydride and methyl iodide, accessing **116**, which was submitted to a Vilsmeier formylation providing 45% of aldehyde **117**,[116] as shown in Scheme 27.

Hydroxyalkylation of aldehyde **117** by addition of **118a**, the readily formed lithium anion of (R_S)-sulfoximine **118**,[115d] was followed by conventional mesylation of the resulting alcohol, and DBU-mediated mild elimination of the intermediate mesylate, furnishing the *E*-vinyl sulfoxymine **120** in good overall yield.

Next, uncovering of the nucleophilic nitrogen by basic hydrolysis of **120** triggered the expected Michael addition, giving a mixture of chromatographically separable cyclized products **122** in high yield, presumably through chelated intermediate **121**. Final reductive removal of the chiral auxiliary with Raney nickel furnished 76% of (+)-**1**. A similar sequence of reactions was carried out with **119**, leading to sulfoximine **123**.

In spite that cyclization yields were high, the diastereoselectivity obtained was only moderate, as shown in Table 6, being this the major drawback of the synthesis. Analysis of the reaction products derived from **120** and **123** indicated that the stereochemical course of this kinetically controlled cyclization seems to be governed by the chirality at the sulfur atom rather than by the chiral auxiliary ligand.

Solvent effects were also put in evidence; changing from CH_2Cl_2 to MeOH, a dramatic reduction in diastereoselectivity (from 48 to 16%) was observed. Interestingly, however, temperature had little effect on diastereoselectivity. Lithium anions of sulfoximines have also been employed for the elaboration of chiral 1-substituted tetrahydroisoquinoline derivatives by addition to Lewis

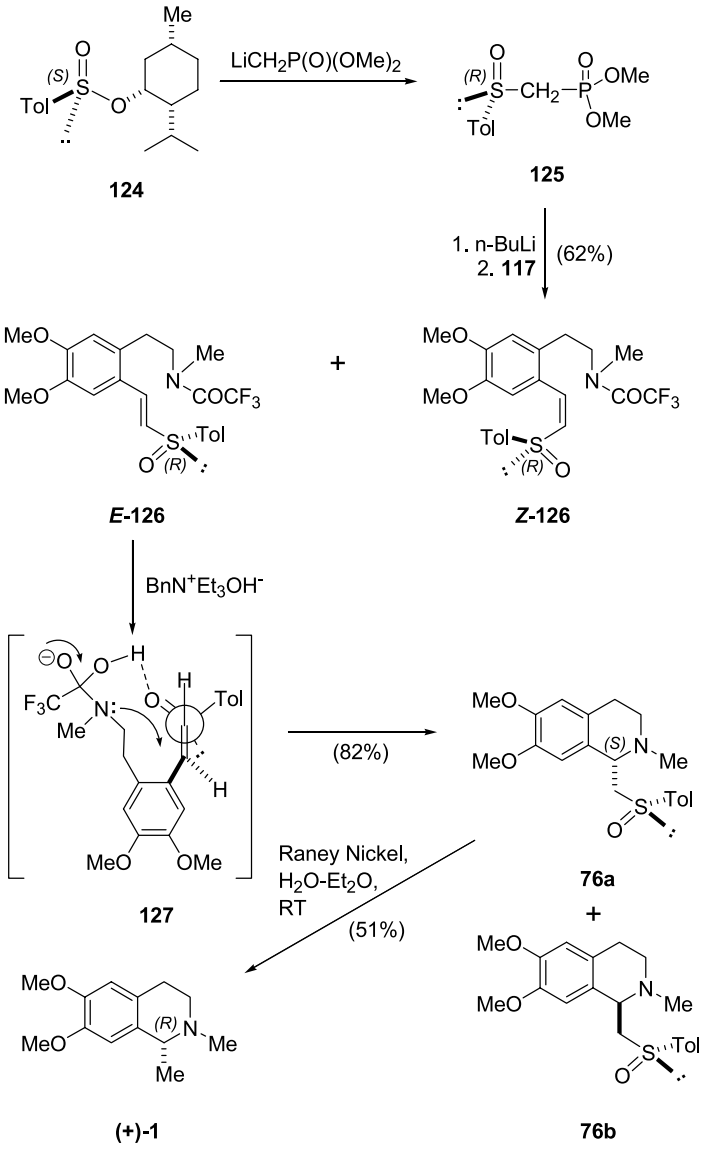


Scheme 27.

Table 6. Cyclization of sulfoximides **120** and **123**

Entry No.	Sulfoximine	Base	Solvent	Temperature (°C)	Diastereo-selection[a]
1	**120**	$BTEA^+OH^-$	CH_2Cl_2	0	26:74
2	**120**	$BTEA^+OH^-$	CH_2Cl_2	−40	28:72
3	**120**	$BTEA^+OH^-$	MeOH	0	58:42
4	**120**	LiOH	MeOH, H_2O	0	65:35
5	**123**	$BTEA^+OH^-$	CH_2Cl_2	0	71:29
6	**123**	$BTEA^+OH^-$	CH_2Cl_2	−40	68:32
7	**123**	$BTEA^+OH^-$	MeOH	0	54:46
8	**123**	LiOH	MeOH, H_2O	0	65:35

[a] Diastereomeric ratio between 1*S*- and 1*R*-tetrahydroisoquinoline derivatives.



Scheme 28.

acids activated 3,4-dihydroisoquinolines, such as **74**, resembling the strategy depicted in Scheme 16.

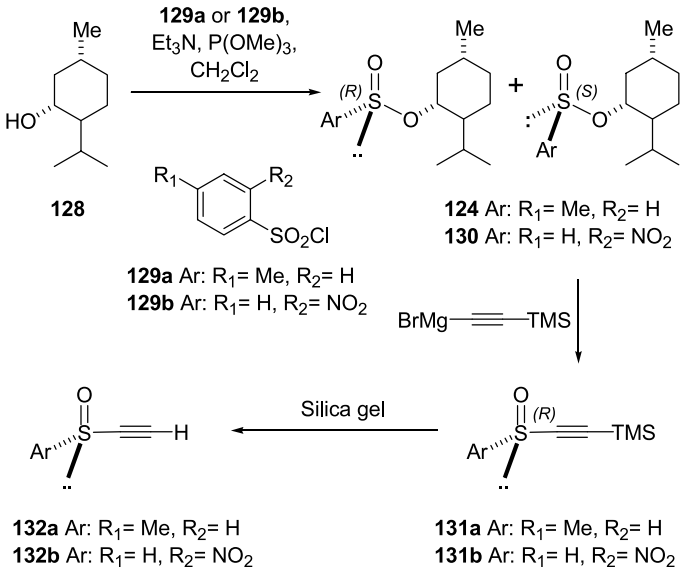
The second strategy devised by Pyne was based on properties of vinyl sulfoxides analogous to those of the vinylsulfoximides and relied on results of Stirling[115e] on the intermolecular addition of amines to chiral *Z*-vinyl sulfoxides, furnishing β-aminosulfoxides in 70% *de*. In order to synthesize the required sulfoxides, these researchers prepared **117** in 41% yield by submission of **116** to a Duff-type formylation with hexamethylene-tetraamine and trifluoroacetic acid.[115c]

In turn, this was submitted to a Wittig Horner olefination with the lithium salt of *R*-(dimethoxyphosphoryl)methyl aryl sulfoxide (**125**), yielding a mixture of separable *E*- and *Z*-vinyl sulfoxides **126** in 62% combined yield, as shown in Scheme 28. Compound **125** was prepared by *n*-BuLi treatment of the product arising from reaction of dimethoxyphosphoryl methyl lithium and Andersen's reagent (**124**).

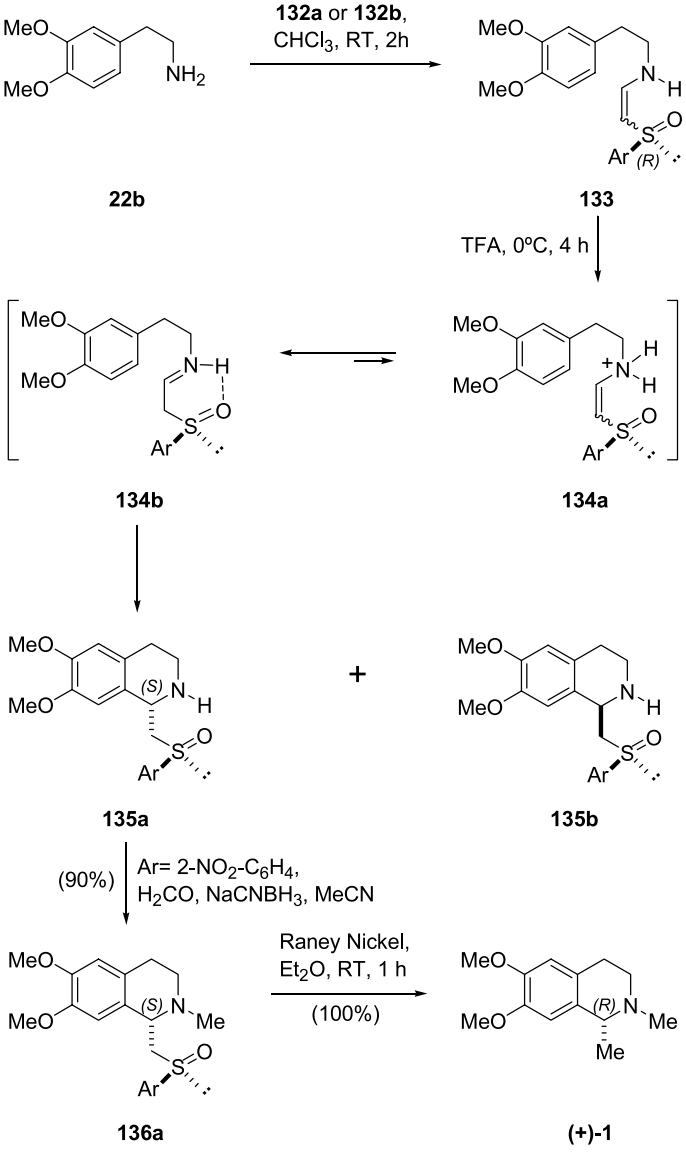
Cyclization of the vinyl sulfoxides was performed under basic conditions, leading to tetrahydroisoquinolines **76**. Interestingly, it was observed that the isomeric compounds **126** underwent cyclization in the opposite stereochemical

Table 7. Intramolecular diastereoselective Michael addition of vinyl sulfoxides **126**, leading to tetrahydroisoquinolines **76**

Entry No.	Sulfoxide	Base	Solvent	Temperature (°C)	Diastereo-selection
1	*E*-**126**	$BTEA^+OH^-$	CH_2Cl_2	−40	42:58
2	*E*-**126**	$BTEA^+OH^-$	MeOH	−40	38:62
3	*E*-**126**	LiOH	MeOH, H_2O	0	37:63
4	*Z*-**126**	$BTEA^+OH^-$	CH_2Cl_2	−40	83:17
5	*Z*-**126**	$BTEA^+OH^-$	MeOH	−40	84:16



Scheme 29.



Scheme 30.

Table 8. Diastereoselectivity of the cyclization of vinyl sulfoxides **135** to tetrahydroisoquinolines **135** in $CHCl_3$

Entry No.	Ar	Acid	Temperature (°C)	**135a/135b**	Yield (%)
1	2-NO_2–C_6H_4	TFA	−20	—	—
2	2-NO_2–C_6H_4	TFA	0	100:0	65
3	2-NO_2–C_6H_4	TFA	rt	100:0	35
4	2-NO_2–C_6H_4	$BF_3.Et_2O$	0	100:0	20
5	4-Me–C_6H_4	TFA	0	67:33	45

sense in this kinetically controlled process, as shown in Table 7. The most abundant of the diastereomeric tetrahydroisoquinolines was further elaborated into (+)-**1** by Raney nickel desulfurization.

This strategy was elaborated further by Pyne to enantioselectively provide *R*-(+)-canadine, a tetrahydroprotoberberine alkaloid.[117] By analogy with similar cyclizations, a chelated transition state **127** involving the cyclizing promoter and the starting vinyl sulfoxide can be proposed to rationalize the reaction outcome.

The group of Lee[118] prepared chiral acetylenic sulfoxides **132a** and **132b** by reaction of trimethylsilyl magnesium bromide with chiral menthyl sulfinates **124** and **130**, through the intermediacy of **131a** and **131b**. Anderson synthesis was employed for the elaboration of (−)-menthyl-*p*-toluenesulfinate (**124**) and the Sharpless' procedure[119] was used for the preparation of (−)-menthyl *o*-nitrobenzene sulfinate, both from natural menthol (**128**) and sulfonyl chlorides **129a** and **129b**, as depicted in Scheme 29.

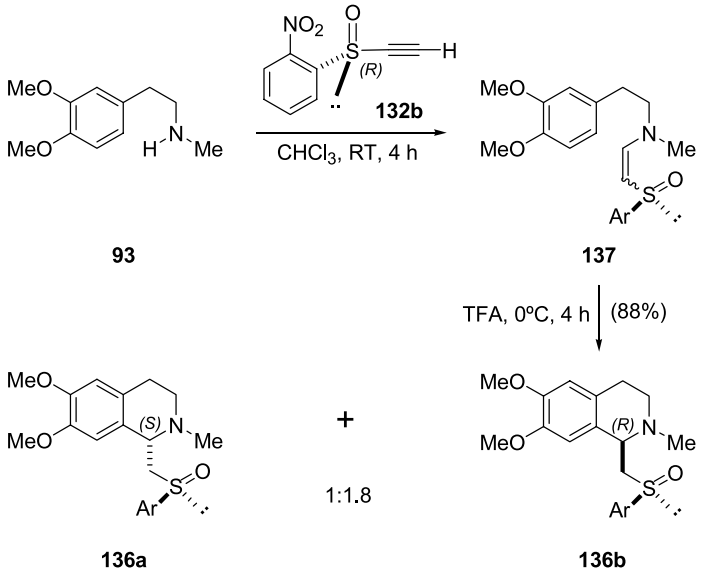
The acetylenic sulfoxides were submitted to a Michael addition with 3,4-dimethoxyphenethylamine (**22b**), furnishing vinyl sulfoxides **133**, which were cyclized in chloroform under TFA catalysis (Scheme 30). Several factors affecting the yield and diastereomeric ratio were detected. The type of acid and the temperature were found to be important, with the transformation having its best performance in the presence of TFA at 0 °C.

On the other hand, the substituent on the benzene ring of the starting aryl sulfoxide influenced the optical course of the cyclization; when *para*-toluenesulfinate was employed, a 4:1 mixture of diastereomers **135a** and **135b** (Ar=4-Me–C_6H_4) was realized; however, when the nitroderivative was used, exclusive formation of **135a** (Ar=2-NO_2–C_6H_4) was observed, as consigned in Table 8. This substituent effect on diastereoselectivity was rationalized assuming that under the influence of the acid, the protonated amine **134a** and the enamine **134b** are in equilibrium, with the latter as the predominant species. A hydrogen bond could be formed under these conditions, leading to a six-membered ring intermediate, which locks the conformation of the molecule.

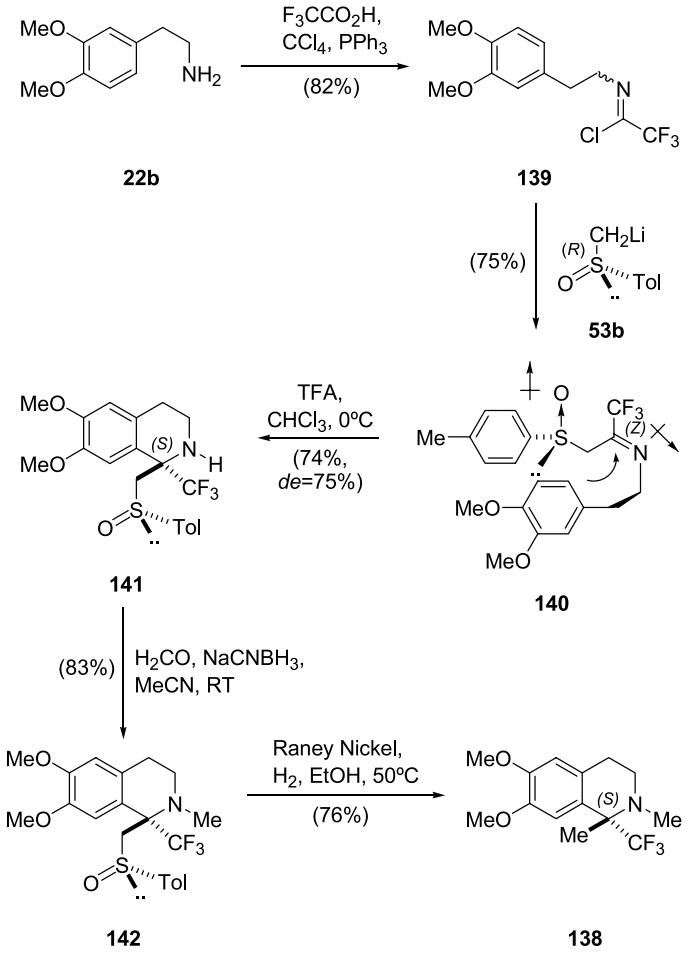
The higher diastereoselectivity observed with the nitro derivative was assigned to the differential stability of the transition states, involving hydrogen bond stabilization of the cyclizing intermediate by the presence of the electron withdrawing substituent in close proximity to the sulfoxide.

To complete the synthesis, sulfoxide **135a** was reductively *N*-methylated under conventional conditions and then desulfurized with Raney nickel in water-saturated ether. Interestingly enough, the resulting **136a** is analogous to **76a**, previously accessed by a slightly different route by Pyne et al.[115a,b]

An interesting feature of this sequence disclosed by the same group (Scheme 31),[120] is that employing *N*-methyl-3,4-dimethoxy phenethylamine (**93**) as starting amine and nitroderivative **132b** as chiral sulfoxide. Cyclization of intermediate vinylsulfoxide **137** proceeds with reverse diastereoselectivity, furnishing a 1.8:1 mixture of



Scheme 31.



Scheme 32.

diastereomers in favor of **136b**, less polar than its congener **136a**. Raney nickel desulfurization of the chiral auxiliary in the major diastereomer, as above, provides *S*-carnegine, being this a complementary and more convergent way of accessing the natural product.

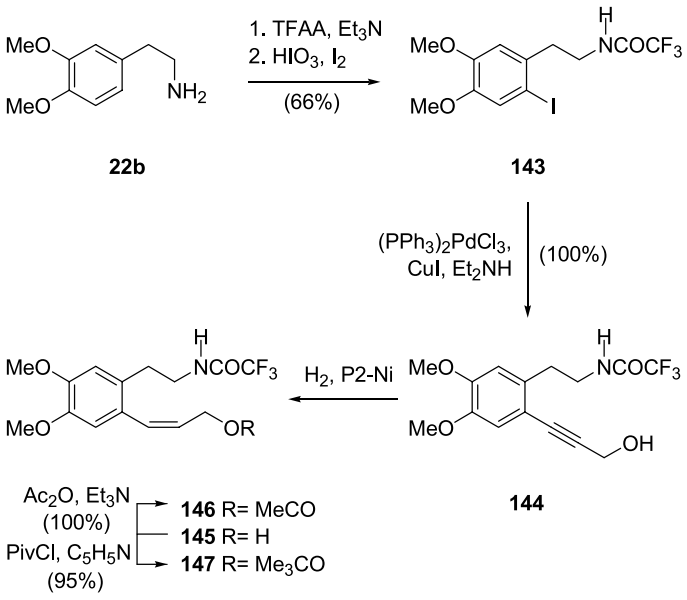
Notably enough, an extension of this cyclization reaction involving a stabilized sulfinylimine intermediate was recently employed for the elaboration of 1-trifluoromethyl carnegine (**138**).[121] The synthetic sequence, shown in Scheme 32, involved initial formation of trifluoroacetimidoyl chloride **139** by condensation of dimethoxy phenethylamine **22b** with trifluoroacetic acid in the presence of carbon tetrachloride and triphenylphosphine. Subsequent addition of *para*-toluenesulfonyl methyl anion **53b** to **139** furnished the required β-aminovinylsulfoxide **140**, which was submitted to trifluoroacetic acid in chloroform in order to assemble the crucial *C*–*C* bond by Pictet–Spengler cyclization of the electron reach aromatic moiety to the β-carbon of the chiral sulfoxide. This proceeded in 74% yield, furnishing a 6:1 mixture of diastereomers, in favor of the one possessing 1*S* configuration (**141**).

Opposite to similar processes discussed above, this cyclization is irreversible and no changes in diastereomeric ratio are observed by increasing the reaction time. *N*-methylation under reducing conditions of the major diastereomer to give **142**, followed by Raney-nickel desulfurization, furnished the final product **138**.

The good diastereoselectivity of this intramolecular Pictet–Spengler reaction was explained considering that, due to the *cis* geometry of the *C*=*N* bond of the substrate **140**, the electron-rich 3,4-dimethoxyphenyl group and the stereogenic *p*-tolylsulfinyl group should be spatially close to each other.

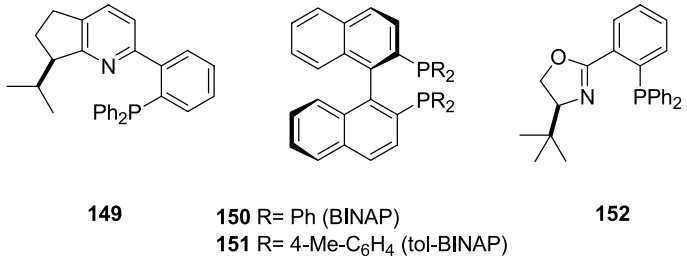
Thus, the sulfinyl auxiliary can exert a strong stereodirecting effect on the ring closure through a reactive conformation which minimizes the dipole–dipole interactions between the *S*=*O* and *C*=*N* bonds.[122] Then, attack of the 3,4-dimethoxyphenyl group is induced to occur from the less hindered *re* face of the stabilized carbocation on *C*1 formed via protonation of the imine nitrogen of **140** by TFA. Finally, it is worth mentioning that the use of chiral *N*-sulfinyl intermediates in a Pictet–Spengler reaction leading to the carnegine precursor (+)-salsolidine in > 98% ee was recently reported by Koomen et al.[123] This sequence involves a chiral sulfinyl-directed Pictet–Spengler condensation as the key step.

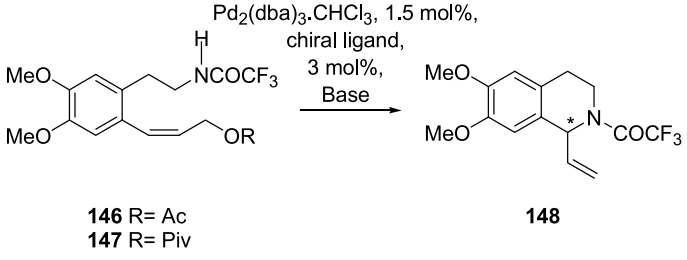
4.3.3. Catalytic asymmetric intramolecular allylic amination. Catalytic enantioselective synthesis of natural products is one of the most recent and elegant approaches



Scheme 33.

Table 9. Catalytic asymmetric intramolecular amination of olefins **146** and **147**





Entry No.	Olefin/ligand	Base	Solvent	Temperature (°C)	Time	Yield/ee (config.)
1	**146/149**	Cs_2CO_3	CH_2Cl_2	rt	4 h	90/39 (*R*)
2	**146/149**	Cs_2CO_3	DMF	rt	—	—
3	**146/149**	—	DMF	60	18 d	52/67 (*R*)
4	**146/150**	Cs_2CO_3	CH_2Cl_2	rt	4 d	83/53 (*S*)
5	**146/150**	—	DMF	60	18 h	82/23 (*R*)
6	**146/151**	Cs_2CO_3	CH_2Cl_2	rt	4 d	76/24 (*R*)
7	**146/151**	Cs_2CO_3	DMF	60	24 d	51/32 (*R*)
8	**146/152**	Cs_2CO_3	CH_2Cl_2	rt	3 d	58/12 (*R*)
9	**146/152**	—	DMF	60	13 d	42/23 (*R*)
10	**147/149**	Cs_2CO_3	CH_2Cl_2	rt	21 h	92/75 (*R*)
11	**147/149**	Cs_2CO_3	CH_2Cl_2	0	5 d	89/40 (*R*)
12	**147/149**	K_2CO_3	CH_2Cl_2	rt	12 d	89/88 (*R*)
13	**147/149**	Na_2CO_3	CH_2Cl_2	rt	23 d	49/88 (*R*)
14	**147/149**	Li_2CO_3	CH_2Cl_2	rt	—	—
15	**147/149**	—	DMF	60	23 d	58/82 (*R*)
16	**147/149**	—	DMF	60	3 h	76/79 (*R*)
17	**147/149**	—	DMF	100	3 h	78/77 (*R*)
18	**147/151**	Cs_2CO_3	CH_2Cl_2	rt	36 d	63/33 (*S*)

to the acquisition of natural products in chiral form and one of the most important innovations in organic synthesis. Almost all of the enantioselective syntheses of carnegine described above relied on diastereoselective reactions for the introduction of chirality at *C*1 and this implied the use of stoichiometric amounts of the chiral source. Furthermore, the asymmetric reduction of 1-alkylidene tetrahydroisoquinolines or the alkylation of imines, among them the 3,4-dihydroisoquinolines arising from Bischler–Napieralski cyclization demonstrated not to be efficient approaches for the elaboration of carnegine, since only moderate optical yields of the natural product were realized.

The use of transition metal complexes as catalysts for organic transformations is currently a subject of intense activity. Among the reasons to explain this interest are the possibility, offered by organometalic complexes, to carry out transformations which are difficult or not possible through the methods of 'classical' organic chemistry and the ability to control the selectivities associated with the transformation, that is, the distribution of products, through the use of appropriate ligands.

Very recently, however, Katsuki et al. disclosed a new palladium-catalyzed asymmetric intramolecular allylic amination, potentially very useful for the elaboration of various 1-substituted tetrahydroisoquinolines. Their strategy was explained in the form of a new total synthesis of carnegine.

The enantioselective synthesis of *R*-carnegine was employed in order to better evaluate the scope and limitations of the synthetic strategy. To that end, the known phenethylamine **22b** was protected as its trifluoroacetamide derivative under conventional conditions and then nuclearly iodinated furnishing **143** in 66% overall yield, with the iodic acid-iodine reagent.

Next, quantitative propargylation of **143** under palladium catalysis provided acetylene derivative **144**, which was partially and quantitatively reduced to *Z*-olefin **145** with the assistance of a nickel catalyst. Acetylation and pivaloylation of **145** afforded good yields of the corresponding esters **146** and **147**, as shown in Scheme 33.[124]

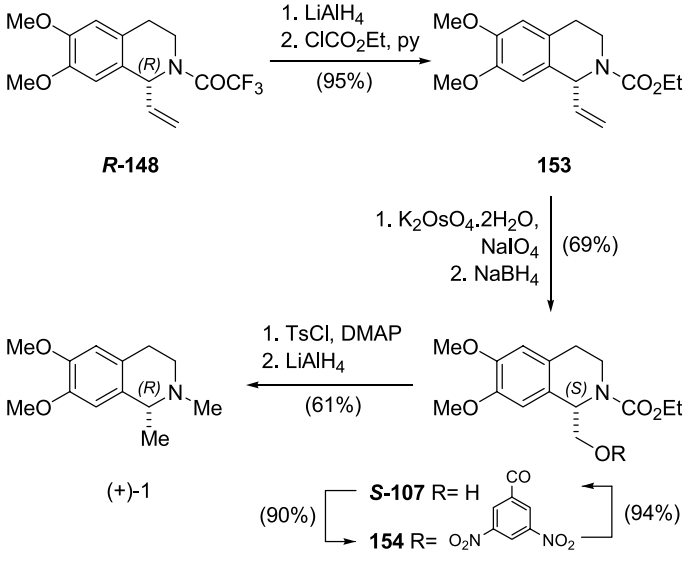
As depicted in Table 9, optimization experiments carried out towards the elaboration of tetrahydroisoquinoline **148** were run in different solvents with both esters, in the absence of base or employing alkaline carbonates with the aid of 1.5 mol% of $Pd_2(dba)_3.CHCl_3$ as palladium source and 3 mol% of ligands **149–152**.

It was observed that the bulkier ester **147** gave better enantiomeric excesses of product than its congener **146**, the most convenient conditions (89% yield, ee=88%) being achieved when potassium carbonate was employed as base, in the presence of pyridine derivative **149** as chiral ligand. On the other hand, chiral oxazoline **152** offered unexpectedly poor chemical and optical yields of product and BINAP derivatives **150** and **151** performed as poor ligands and exhibited inversion of the sense of asymmetric induction, depending on the reaction conditions (entries 4–7 and 18).

Culmination of the synthesis was carried out as depicted in Scheme 34, by changing the trifluoracetamide group of **148** into an ethyl carbamate (**153**) and producing the loss of the extra carbon atom by oxidative fision of the vinyl group employing the potassium osmate-sodium periodate reagent system, followed by a reductive step to calycotomine derivative *S*-**107**. Transformation of the *S*-**107** into the 3,5-dinitrobenzoate, followed by fractional crystallization increased the ee of the product to 98%, yielding back *S*-**107** upon basic alcoholysis (EtOH, K_2CO_3). Finally, conversion of the latter into the corresponding *para*-toluenesulfonate followed by lithium aluminum hydride reduction gave (+)-carnegine.[110b]

5. Conclusions

The various syntheses of carnegine published during the last thirty years are the result of investigations carried out by



Scheme 34.

different synthetic organic chemists around the world, and their steady efforts to devise novel and ingenious alternative solutions to this simple but important synthetic target.

The observed results in the synthesis of carnegine have accompanied the remarkable progress experienced by synthetic organic chemistry during the last 25 years, showing the evolution of reactions, reagents and synthetic strategies, from furnishing the product in low yields or in racemic form into elegant transformations which provide carnegine or related compounds in good chemical and optical yields.

While diastereoselective cyclization of vinyl sulfoxides and asymmetric Pictet–Spengler reactions appeared to be very promising strategies in the beginnings of the enantioselective synthesis of 1-substituted tetrahydroisoquinolines, moderate diastereoselectivities and the need of chromatographic separation of diastereomers remain as practical limitations associated with these type of strategies. On the other hand, the comparatively new catalytic enantioselective routes to the natural product rank among the major achievements in the synthesis of carnegine, being these results a consequence of the outstanding developments in catalysis which took place during the last couple of decades.

A significant group of the rosary of efficient synthetic procedures which have been explored and devised to accomplish some of the many syntheses of carnegine have already found important applications in the conquering of other interesting targets, including complex natural products, and providing a better understanding of our world. Not less important, they also constitute a fundamental part of a developing body of new and more sophisticated synthetic strategies or new synthetic tools, useful for accessing more demanding synthetic targets.

The continuous research and discovery of more practical and powerful catalysts, ligands, and other reagents, displaying more synthetic power and versatility are still formidable challenges for the synthetic organic chemists' community and therefore these are currently highly active areas of research. Consequently, it is expected that new, concise and more efficient diastereo- and enantioselective syntheses of carnegine will be conceived and carried out in the near future.

Acknowledgements

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Formation, isolation and characterization of an AB-biaryl atropisomer of oritavancin

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Abstract—Oritavancin is a semi-synthetic glycopeptide antibiotic which is structurally related to vancomycin. When oritavancin bisphosphate is dried in vacuo with heat, a new compound forms. This new compound is stable only in the solid state and reverts to oritavancin in solution. Highly enriched samples of this compound were obtained by preparative HPLC and the structure of this compound was elucidated by using one and two-dimensional (^{1}H and ^{13}C) NMR spectroscopy in conjunction with computer-assisted molecular modeling. It has been determined that oritavancin adopts a conformation similar to that of vancomycin in solution, while the new compound is the unnatural *R*-AB-biaryl atropisomer of oritavancin. This is the first observation and isolation of an AB-biaryl atropisomer in an intact member of the vancomycin family of glycopeptide antibiotics.

1. Introduction

Vancomycin (**1**) is a fermentation-derived glycopeptide antibiotic that was first introduced to the clinic in 1958 for the treatment of serious gram-positive bacterial infections.[1,2] It has been described as the antibiotic of last resort, having retained significant activity after nearly five decades of clinical use. Vancomycin and related analogs act by inhibiting the biosynthesis of bacterial cell wall peptidoglycan by binding with the C-terminal acyl-D-alanyl-D-alanine (acyl-D-Ala-D-Ala) dipeptide residues of bacterial cell-wall precursors.[2] Since 1986, when the first clinical isolates of vancomycin-resistant *Enterococcus* (VRE) were detected, the incidence of bacterial resistance to this important antibiotic has been on the rise. The resulting threat to global health has inspired a continuing effort toward the discovery and development of new therapeutic agents to treat VRE and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[3,4] Significant progress has been made in recent years in developing new active vancomycin analogs, which differ primarily in the number and type of functionalized sugar substituents.[5–8]

Oritavancin (**2**, formerly known as LY333328) is a semi-synthetic glycopeptide antibiotic that presently is in Phase III clinical development for the treatment of complicated skin and skin structure infections caused by gram-positive bacteria.[9–11] It is an analog of vancomycin that contains the same cyclic heptapeptide core and five aromatic rings (A–E, see Fig. 1). Carbohydrate-modified vancomycin derivatives such as oritavancin also inhibit peptidoglycan biosynthesis, although through a modified mechanism of action.[14–16] Reductive alkylation of chloroeremomycin (**3**) with 4-chloro-4′-biphenylcarboxaldehyde in the presence of $NaCNBH_3$ and Cu(II) salts affords oritavancin,[7] which is isolated as the copper complex. Subsequent decomplexation, chromatography and crystallization, affords the purified bisphosphate salt of oritavancin.[12,13]

The structural characterization of vancomycin required a significant effort due to the complexity of its multi-ringed system. While early work relied heavily on chemical degradation analysis, within recent years the structure of

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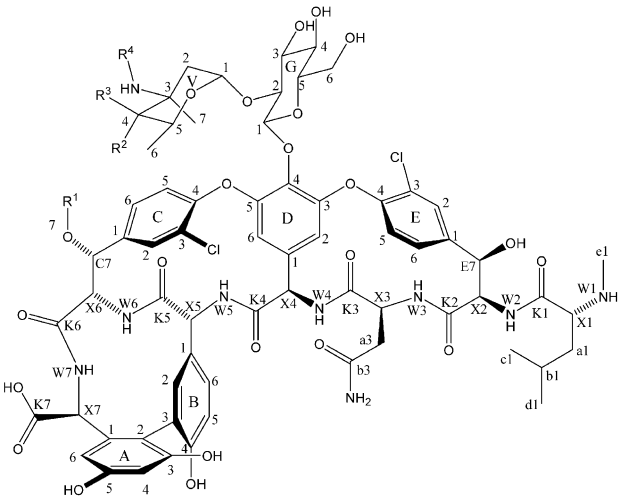


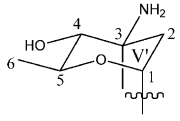
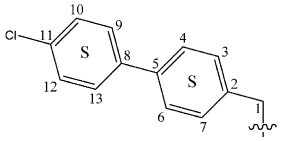
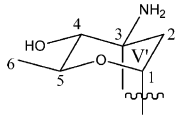
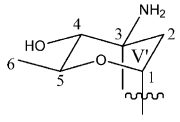
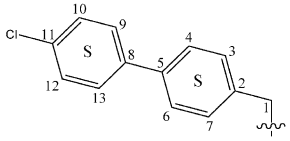
Compound	R^1	R^2	R^3	R^4
Vancomycin (**1**)	H	H	OH	H
Oritavancin (**2**)		OH	H	
Chloremomycin (**3**)		OH	H	H
4		OH	H	

Figure 1. Structures and atomic labels for vancomycin, oritavancin and chloremomycin. Note: the carbohydrate rings are arbitrarily labeled. The glucose ring is labeled as G, the vancosamine ring is labeled as V, the epivancosamine is labeled as V′, and S represents the biphenyl ring.

intact vancomycin has been extensively investigated by using NMR[17–19] spectroscopy and X-ray crystallography.[20] The results of these studies show that all of the amide bonds in vancomycin adopt the *trans* conformation, except for the amide between amino acids 5 and 6, and the AB-biaryl, D–O–E and C–O–D biaryl ethers are found in the *S* configuration (see Fig. 1).[21] To date, all of the naturally occurring glycopeptide antibiotic possess the same configuration as vancomycin. CDP-I, a rearrangement product of vancomycin with an added methylene unit in the N-terminal cyclophane ring, exists as two atropisomers of the D–O–E ring in equilibrum.[22] There are no reports of an AB-biaryl *R*-atropisomer in an intact glycopeptide, although in total synthesis studies of vancomycin, atropisomers of the AB-biaryl were observed in synthetic intermediates. In these examples, the unnatural *R*-atropisomer is the kinetically favored product, while the natural *S*-atropisomer is thermodynamically more stable.[23–25] Atropisomers of the C–O–D– and D–O–E-biaryl ethers have been synthesized as well. The D–O–E framework exhibits a higher degree of flexibility than the C–O–D system and no thermal isomerization has been observed in the C–O–D system.[26,27] The synthetic approaches to vancomycin describing these observations of atropisomerism have been well reviewed.[1]

In the final step of the production of oritavancin, the crystalline bisphosphate salt is isolated by filtration and washed with mixtures of ethanol and water. An unknown compound (**4**) was observed to form in the isolated product when it was dried with heating under vacuum. HPLC studies showed that **4** had a similar retention time to that of oritavancin under a variety of experimental conditions. Mass spectral analysis also revealed that **4** possessed an identical molecular weight and a similar fragmentation pattern to that of oritavancin. Subsequent isolation and characterization studies showed **4** to be unnatural *R*-AB-biaryl atropisomer of oritavancin. The results of these studies are presented below.

2. Results and discussion

2.1. Formation and stability of 4

Typically, low levels of **4** (less than 2%) were detected in

the isolated oritavancin product. However, samples of oritavancin bisphosphate subjected to high temperature (100 °C) drying in vacuo, generated elevated levels of **4** (3–5%, as determined by HPLC peak area). Once formed, **4** that is present in solid oritavancin was found to be stable indefinitely at room temperature or below, showing no change over a period of months. However, **4** converts back to oritavancin in solution and the conversion rate depends on pH and temperature. Aqueous solutions of materials enriched in **4** were prepared and the decomposition half-lives ($T_{1/2}$) were measured under various conditions. At ambient temperature, in pH 4.5 aqueous solution, the estimated $T_{1/2}$ for **4** is greater than 48 h; at pH 7.4, the $T_{1/2}$ was estimated to be 9 h. While at pH 7.4 and 37 °C, the $T_{1/2}$ was estimated to be 3 h. Therefore, the conversion of **4** to oritavancin in solution dramatically increases at high pH and elevated temperature. As a result, special precautions were taken to maintain solution acidity and temperature during all phases of the isolation process (preparative HPLC chromatography, desalting, and lyophilization).

Circular dichroism (CD) spectroscopy was used to monitor the conversion of **4** to **2** in aqueous solution as shown in Figure 2. The broad and unstructured UV absorption spectra of **4** and **2** are essentially identical and consist of multiple overlapping electronic transitions below 300 nm, leading to several positive and negative Cotton effects. The CD spectra of both **4** and **2** have prominent positive and negative bands centered at ca. 228 and 210 nm, respectively, but with significant differences in intensity and small shifts of position. These differences diminish gradually during the conversion of **4** to **2** (Fig. 2). The differential ellipticity at longer wavelengths (250–300 nm) is much smaller in magnitude, but exhibits a dramatic spectral change during the conversion: the positive Cotton effect observed for **4** undergoes sign inversion to the negative band characterizing **2** (inset, Fig. 2). Within approximately 48 h the CD spectra of **4** and **2** over the entire 200–300 nm region have become nearly identical. Although these spectra are difficult to interpret in detail due to the multiple chiral centers and spectrally overlapping chromophores, the results strongly support the notion that transformation of **4** to **2** is a slow chiral process involving spatial re-orientation of chromophores.

2.2. Structural elucidation studies by NMR

Vancomycin gives relatively sharp NMR signals when it is run in DMSO-d_6 and the complete ^{1}H and ^{13}C assignments for vancomycin have been previously reported.[17] NMR studies of vancomycin in solution have shown that the backbone conformation of the cyclic peptide correlates well with structural data obtained from the X-ray diffraction studies.[20] However, from these studies, the first amino acid residue and the glucose-vancosamine rings were observed to have considerable conformational flexibility in solution.[18,19] With the addition of the *p*-chlorophenylbenzyl side chain on sugar V and the 4-epivancosamine at the sixth amino acid residue (see Fig. 1), significant line broadening was observed in the NMR spectra of oritavancin. To address this problem, we collected proton spectra of the bisphosphate and bisformate salts of oritavancin in different solvents, including DMSO-d_6, D_2O, DMF-d_7, D_2O/CD_3CN, and CD_3OD, to determine which solvent produced the best spectra, in terms of lineshape and signal dispersion. The best NMR spectra were obtained with the bisformate salt of oritavancin in DMSO-d_6 (see Fig. 3(d)).

Since **4** reverts to oritavancin in solution, particularly at high pH and elevated temperature, the NMR spectra of **4** were collected at 25 °C in DMSO-d_6 with addition of 2% formic acid-d_2 to increase sample stability. However, even under these conditions, **4** slowly converts to oritavancin over time, as can be seen in Figure 3(a)–(c). The ^{1}H and ^{13}C

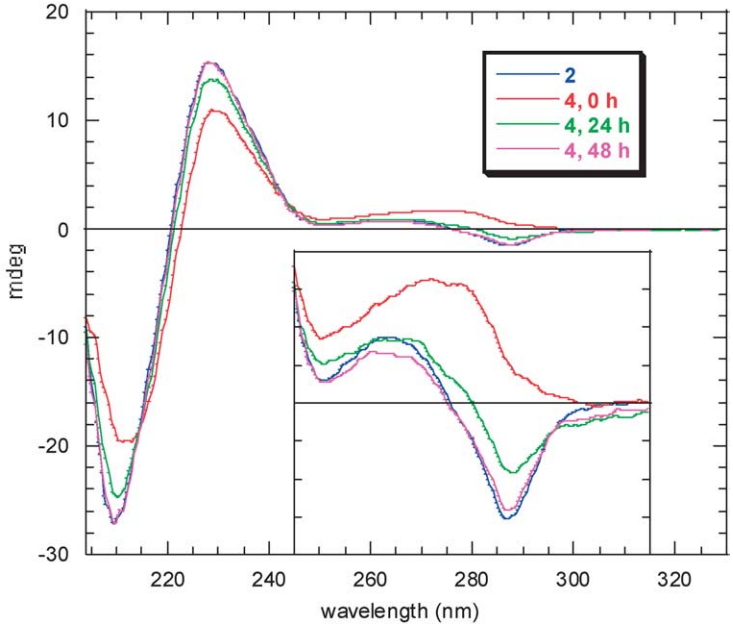


Figure 2. CD spectra of **2** (blue line) and **4** (red line) at 1 mg/mL in water. Compound **4** is converting into **2** with time as indicated by the green line at 24 h and the purple line at 48 h. The inset shows an enlarged view of the 245–315 nm region. The CD spectrum of **2** over the same time period is stable and undergoes no changes.

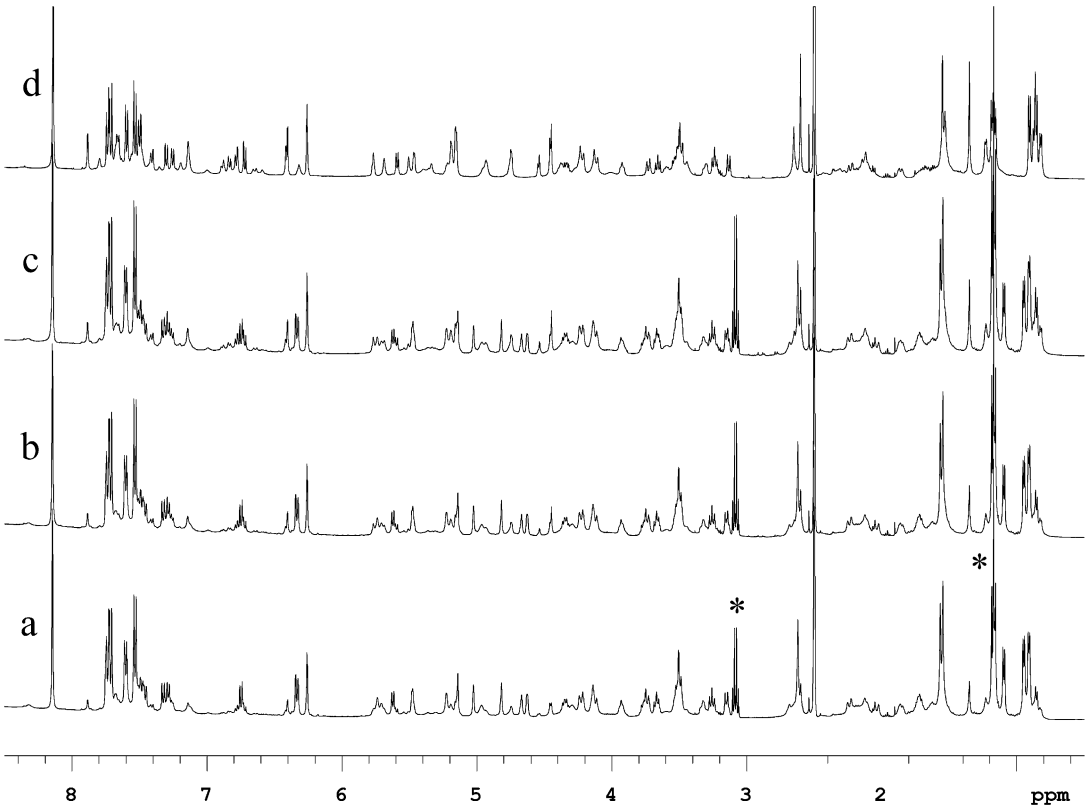


Figure 3. ^{1}H spectra of: (a) **4**- freshly dissolved in DMSO-d_6; (b) 60 h; (c) 134 h after dissolution; (d) oritavancin (**2**) in DMSO-d_6. Both samples were dissolved in DMSO-d_6 with 2% formic acid-d_2 and recorded at 25 °C. * Noted impurity peak is triethylamine.

chemical shifts for oritavancin and **4** were assigned with the aid of standard g-DQCOSY, TOCSY, NOESY, g-HSQC, and g-HMBC experiments. Most of proton and carbon chemical shifts for the two major components in solution could be assigned from these studies, as shown in the labeled g-HSQC spectrum (see Fig. 4). There were a few NMR signals from minor impurities present in the samples of oritavancin and **4** that were not identified in these studies. Some of the cross peaks in the g-HSQC spectra of both oritavancin and **4** were very weak, as in the case of the methylene group in amino acid 3 (position a3, see Fig. 1). While these signals only were seen at low contour levels in the g-HSQC spectra, the a3 protons were easily identified in the g-DQCOSY and TOCSY spectra. In some regions of the 2-D spectra there were closely spaced or overlapping signals, as with the E2 resonances, where both the proton and carbon signals were very close to those from S10, S12 and E6 (at ~7.5 ppm for proton and ~128.8 ppm for carbon). In this case, it was difficult to make definitive assignments for these nuclei. In addition, a number of the carbonyl carbons could not be assigned since they showed no cross peaks in the g-HMBC spectra.

The ^{1}H and ^{13}C chemical shift assignments for those resonances displaying the largest shift-differences, when comparing oritavancin to **4**, are presented in Table 1. An overlay of the g-HSQC spectra for both compounds is shown in Figure 4. The arrows in Figure 4 are used to display the largest changes in the position of the ^{1}H and ^{13}C chemical shifts, in going from oritavancin (blue) to **4** (red). It is of interest to note that the largest changes are found at positions B2 and B6, and as shown with the arrows in Figure 4, the changes in the ^{1}H and ^{13}C signals at these positions are in opposite directions. Generally, the atoms with largest chemical shift differences observed between oritavancin and **4** are located in AB-biaryl ring, the backbone of residues 5, 6, and 7, and in the V′ 4-epivancosamine region.

The proton–proton distances for oritavancin and **4** were estimated from a series of 2D-NOESY experiments. NOESY spectra were acquired with four mixing times of 50, 100, 150, and 200 ms and the resulting NOE buildup curves were used to calculate the proton–proton distances for both compounds. The NOE build-up curves were found to be linear with mixing times in the 50–150 ms range and as a result the 100 ms data sets were used to calculate the proton–proton distances. Since there was no clearly resolved geminal-pair of protons that could be used as an internal distance standard, the NOE intensity of the E5–E6 proton pair in oritavancin and the B5–B6 pair in **4** were used as an internal reference, with a calculated distance of 2.45 Å. The largest differences in observed NOE intensities between oritavancin and **4** were found in the region of the AB biaryl ring system and the calculated proton–proton distances in this region are listed in Table 2.

The NOE intensities between the proton pairs C2–C7, C2–X6, E2–E7, and E2–X2 were observed to be similar in both oritavancin and **4**. These observations suggest that C–O–D and D–O–E biaryl ethers have adopted the same atropisomer as found in vancomycin.[17–19,28] A large NOE is observed between protons X5 and X6 in both oritavancin and **4** and this is consistent with the presences of a *cis*-amide

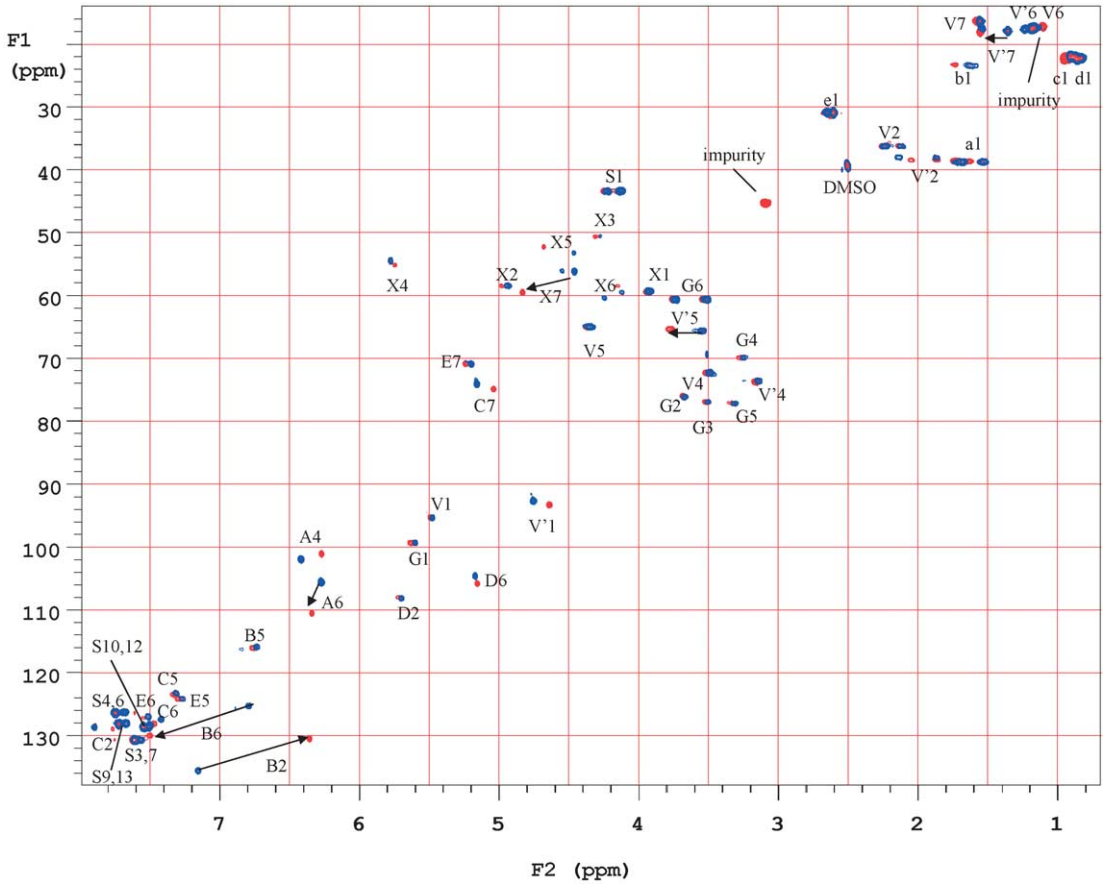


Figure 4. Overlay of the g-HSQC spectra of **2** (blue) and **4** (red), showing the chemical shift assignments. The signal from a3 is not visible at this contour level and some signal overlap is seen as E2 very close to S10, S12 and E6. The arrows from blue to red represent the largest differences of chemical shifts in going from oritavancin (**2**) to **4**.

bond between amino acid residues 5 and 6, a conformation that is also common in a variety of vancomycin analogs. The observed NOE intensities between proton B2 and those at positions X5, X6, and W7 were strong in oritavancin and medium to weak in **4** (see Fig. 5). Conversely, the NOE intensity between protons A6 and X7 was very strong in **4** and weak in oritavancin. These changes in NOE intensities suggest that the AB-biaryl rings in **4** adopts the unnatural *R*-atropisomer configuration, unlike oritavancin, which is found in the *S*-configuration. The large anti-parallel arrows for B2 and B6 in the g-HSQC spectra also indicate that the environments of B2 and B6 have switched, such that the

Table 1. ^{1}H and ^{13}C NMR chemical shifts for those signals which differ by more than 0.1 ppm for ^{1}H or 1.0 ppm for ^{13}C in oritavancin and **4**

Position	^{1}H Chemical shifts (ppm)[a]			^{13}C Chemical shifts (ppm)[b]		
	Oritavancin	**4**	Δ	Oritavancin	**4**	Δ
B2	7.16	6.35	−0.81	135.7	130.5	−5.2
A6	6.28	6.35	0.07	105.5	110.5	5.0
B6	6.78	7.49	0.71	125.3	130.0	4.7
X7	4.46	4.83	0.37	56.2	59.5	3.3
X6	4.25	4.15	−0.10	60.5	58.6	−1.9
D6	5.17	5.15	−0.02	104.6	105.9	1.3
X5	4.48	4.68	0.20	53.3	52.2	−1.1
A4	6.42	6.27	−0.15	102.1	101.2	−0.9
C7	5.16	5.03	−0.13	74.1	75.0	0.9
V′1	4.77	4.64	−0.13	92.8	93.3	0.5
V′5	3.55	3.77	0.22	65.7	65.3	−0.4
V′7	1.37	1.55	0.18	17.9	18.1	0.2
W7	8.59	7.69	−0.90	—	—	—
W6	6.65	7.27	0.62	—	—	—
W5	8.72	8.32	−0.40	—	—	—
A2	—	—	—	117.6	115.3	−2.3
K7	—	—	—	171.9	169.8	−2.1
A1	—	—	—	135.7	136.7	1.0

[a] Relative to residual signal of DMSO-d_6 assigned to 2.50 ppm.
[b] Relative to DMSO-d_6 assigned to 39.5 ppm.

Table 2. Proton–proton distances (Å) calculated from 2D-NOESY spectra and from computer modeling for oritavancin and **4**

Atoms	Distance from NOE data (Å)		Distance from computer modeling (Å)	
	Oritavancin	**4**	Oritavancin	**4**
A6–X7	4.1	2.1	3.7	2.3
B2–X5	2.4	3.6	2.3	3.5
B2–X6	2.3	3.4	2.4	3.3
B2–W6[a]	[b]	2.9	4.8	3.0
B2–W7[a]	2.5	3.4	2.6	3.3
B6–X5	[b]	2.7	3.8	2.8
X4–W5[a]	2.7	2.9	2.2	2.2
X5–X6	2.1	2.1	2.0	2.0
X5–W5[a]	[b]	[b]	2.8	2.8
X6–W7[a]	2.6	2.7	2.3	2.3
X6–C7	2.5	2.6	2.3	2.3
C7–W7[a]	3.1	3.4	2.6	3.4

[a] Amide proton was partially exchanged with deuterium due to the presence of 2% formic acid-d_2. NOESY experiment was also performed for oritavancin in DMSO-d_6 with 2% formic acid. The deviation of distances derived from both experiments are within $\pm 10\%$.
[b] NOE cross peak was not observed in NOESY spectra.

B-ring is now flipped to the opposite orientation in **4**, relative to that in oritavancin.

2.3. Computer modeling

Computer modeling was used to assist our structural assignments for oritavancin and **4**, and the X-ray crystallographic structure of vancomycin was used as a template. Sugar modifications and the *p*-chlorophenylbenzyl extension were modeled using the Insight® molecular modeling software. Due to the acidic condition in NMR experiments, the carboxylate (K7) was modeled in the neutral form and the amines (W1, and NH or NH_2 in 4-epivancosamine) were protonated. The atropisomer was built manually by breaking two bonds within the AB-12-membered ring and reconnecting with the desired *R*-configuration. After energy minimization, the unnatural *R*-configuration atropisomer (here assigned to **4**) was calculated to be 2.3 kcal/mol higher in energy than the natural *S*-configuration atropisomer in oritavancin. This result is consistent with the previous studies of AB-biaryl atropisomer fragments[23–25] which found that the natural *S*-configuration is thermally more stable than the *R*-configuration. The magnitude of the calculated energy difference between the atropisomers suggests that a ring system possessing an unnatural *R*-isomer of oritavancin might be energetically accessible under the conditions employed in this study. The energy minimized structures are shown in Figure 6.

The proton–proton distances measured from the models of oritavancin and **4** are also listed in Table 2. The distances derived from the NMR experiments and computer modeling studies are in good agreement. The K7 carboxyl group appears in the equatorial orientation in the natural *S*-configuration and the distance between A6–X7 is large. In contrast, in the unnatural *R*-configuration, the K7 carboxyl group is in the axial orientation, and this brings X6 very closed to A6 as shown in Figure 6. This conformational change of the carboxyl group from equatorial to axial potentially provides a hydrogen bond network that stabilizes the unnatural *R*-configuration and provides a rationale for the observation of decreased solution stability of **4** at higher pH.

3. Conclusions

Compound **4**, a minor component formed in the synthetic process used for preparing oritavancin, has been identified as the unnatural *R*-configuration AB-biaryl atropisomer, which differs from the natural *S*-configuration found in oritavancin. Both chemical shifts and NOE-derived distances were used in deriving this conclusion. Distances and energies from energy minimized molecular models were consistent with this structural assignment. This unnatural *R*-configuration atropisomer appears to form only in solid state when dry oritavancin bisphosphate (or the Cu(II) complex) is heated in vacuo. The *R*-atropisomer is stable in solid state and reverts back to oritavancin in solution and this conversion is accelerated on exposure to base. This is the first example of an unnatural *R*-AB-biaryl atropisomer configuration in an intact member of the vancomycin family of glycopeptide antibiotics.

4. Experimental

Solid oritavancin (**2**), obtained from chloroeremomycin as described previously[7,12,13] was heated at 100 °C in vacuo until levels of **4** exceeded 5% (typically 3–5 days). Once the initial enhancement was achieved, preparative chromatography was employed to obtain purified **4**. The reversed phase preparatory liquid chromatographic system consisted

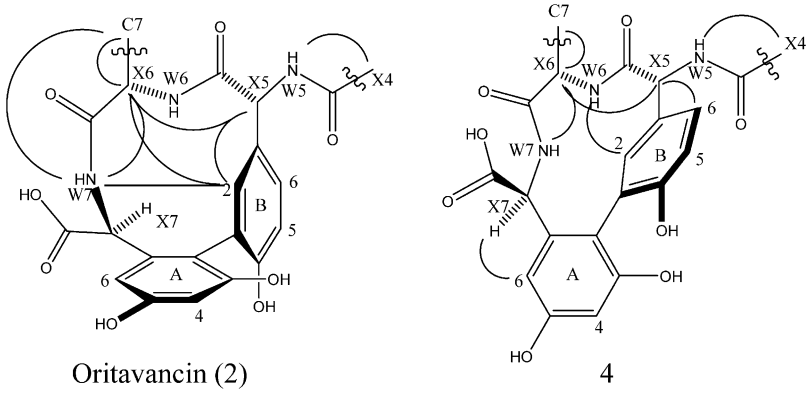


Figure 5. NOE diagrams of AB-biaryl macrocyclic region for oritavancin (**2**) and **4**, strong NOE's are indicated by curved lines.

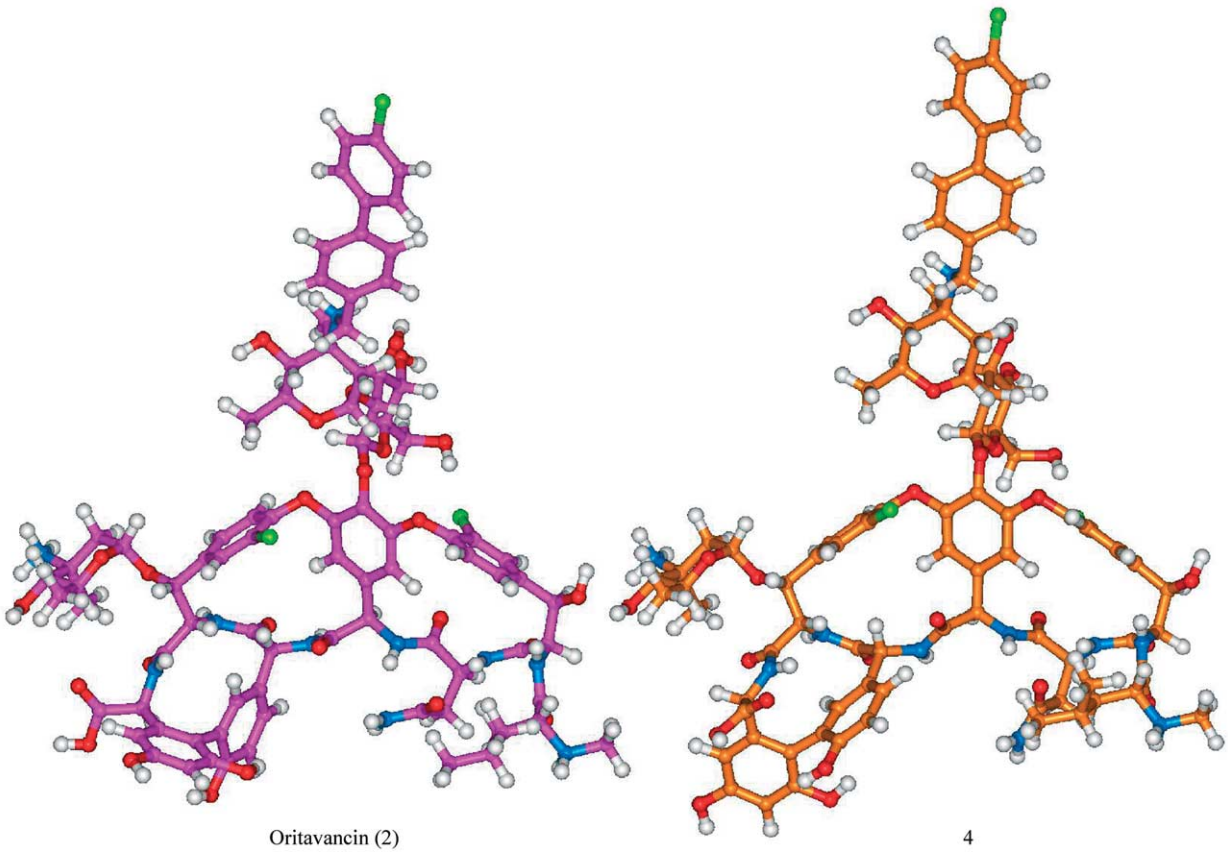


Figure 6. Energy minimized structures of oritavancin (**2**) and **4**.

of a Phenomenex 5μ Luna CN column (21.2×250 mm) heated to 50 °C, with less than 40 mg of sample per injection, a mobile phase containing 35% acetonitrile, 20 mM H_3PO_4, 40 mM KH_2PO_4, and 40 mM TEA (pH 6.5), a flow rate of 20 mL/min and UV detection at 230 nm. To minimize the conversion of **4** to **2**, sufficient formic acid was added to the collection vials to keep the fraction pH below 4. Fractions enriched in **4** were combined and the acetonitrile was distilled off. The enriched fractions were then desalted using an OASIS HLB solid phase extraction cartridge. The extraction cartridge was conditioned with methanol and water prior the application of the enriched fractions. The cartridge was subsequently washed with 0.1% formic acid solution to remove inorganic salts and eluted with 60% acetonitrile containing 0.1% formic acid. The eluent was distilled and then lyophilized to remove acetonitrile, water and the excess formic acid. After two complete passes, approximately 80 mg of material that was usually 80% **4** and 20% **2** was obtained from 5 g oritavancin. Higher purity material was obtained by repetition of this procedure on a smaller scale.

Circular dichroism spectroscopy was performed on a Jasco J-810 spectropolarimeter at 23 °C with cells of path length ranging from 0.05 to 0.5 mm, as appropriate for any particular combination of compound concentration and wavelength range being studied. The phosphoric acid salts of oritavancin and **4** were dissolved in water at concentrations between 1 and 10 mg/mL.

The NMR spectra were recorded on a Varian Unity Plus 500 MHz spectrometer equipped with a 5 mm inverse broadband-gradient probe. Both oritavancin and **4** were dissolved in DMSO-d_6 (at a concentration of ~10 mg/0.7 mL) in the presence of 2% formic acid-d_2. All data were recorded at 25 °C and the proton chemical shifts were referenced relative to the residual ^{1}H signal of DMSO-d_6 at 2.50 ppm and carbon chemical shifts were reference relative to the DMSO-d_6 solvent signal at 39.5 ppm. ^{1}H spectra were obtained with a spectral width of 10 kHz using a 45° pulse, a 3.2 s acquisition time, and 1.0 s relaxation delay. The standard 2-D pulse sequences were used and all 2-D data sets were zero filled to 2048×2048 and processed with Gaussian or sine-bell weighting functions. g-DQCOSY experiments were performed using 2048 data points, 16 scans/512 increments for oritavancin and 32 scans/256 increments for **4**, and a relaxation delay of 1.0 s. TOCSY experiments were collected with a mixing time of 80 ms using 2048 data points, 16 scans/2×512 increments, and 1.0 s relaxation delay. NOESY experiments were performed with 2048 data points, 8 scans/2×256 increments, 1.0 s relaxation delay, with four mixing times of 50, 100, 150, and 200 ms. g-HSQC spectra were collected using 2048 data points, 128 scans/2×256 increments, using the ^{13}C-WURST decoupling sequence. g-HMBC spectra were collected with 2048 data points, 384 scans/256 increments using a delay optimized for a coupling constant of 8 Hz.

The Insight® molecular modeling software (Accelerys, Inc. San Diego, CA USA) was used to build oritavancin and **4** models. The starting point for oritavancin modeling work was the vancomycin structure obtained from the Cambridge

Crystallographic Database (entry TUCMEJ01). The *p*-chlorophenylbenzyl side chain and sugar 4-epivancosamine of oritavancin were added. For **4**, the unnatural *R*-atropisomer was built manually by breaking two bonds within the AB 12-membered ring and reconnecting with the desired configuration. The DISCOVER® module with the CFF91 force field was used to carry out energy minimizations. Typically 500–2000 iterations were required to reach a final energy minimized structure.

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New sesterterpenes from Madagascan *Lendenfeldia* sponges

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Abstract—A new furanoterpene designated dehydrofurodendin and nine scalarane sesterterpenes of which four are new, were isolated from two different species of Madagascan sponges of the genus *Lendenfeldia*, both of which seem to be yet undescribed. The structure of the compounds was elucidated by interpretation of 1D and 2D NMR data. Dehydrofurodendin was found to be a potent inhibitor of HIV-1 RT. Several of the isolated scalaranes exhibited cyctotoxicity against several human tumor cells.

1. Introduction

Sponges have been shown to be a rich source of both linear sesterterpenes and polycyclic sesterterpenes.[1] Whereas linear furanosesterterpenes as well as C_{21} degraded furanosesterterpenes are common,[1] C_{22} furanoterpenes are very rare and there is only one prior example of a C_{22} furanoterpene, furodendin.[2] Conversely, tetra- and pentacyclic sesterterpenes are well known in sponges.[3] The latter are of interest because they often exhibit a wide spectrum of biological activities including significant anti inflamatory,[4] cytotoxic,[5] antimicrobial,[6] ichthiotoxic,[7] and anti-HIV[8] activities.

2. Results and discussion

The present report describes the isolation and structure elucidation of a new C_{22} furanoterpenoid designated dehydrofurodendin (**1**) as well as nine scalarane sesterterpenes (**2**–**10**) of which four (**2**, **6**–**8**) are novel. The compounds were isolated from two different species of the sponge *Lendenfeldia* sp. collected at Madagascar (referred to below as spp. 1 and 2) which both seem to be yet undescribed. Both sponges were collected in the region of Barren Islands, Madagascar, by SCUBA at a depth of 10–20 m. The chloroform–methanol (2:1) extracts of each dried sponge were subjected to partition by the method of Kupchan et al.[9] The carbon tetrachloride and the chloroform fractions of each extract were repeatedly chromatographed over Sephadex LH-20 columns followed by vacuum–liquid chromatography over silica gel and ODS HPLC ($MeCN/H_2O$) separations. *Lendenfeldia* sp. 1 yielded compounds **1**–**4** (Fig. 1) and *Lendenfeldia* sp. 2 yielded compounds **5**–**10**.

The EI mass spectrum of dehydrofurodendin (**1**) exhibited a molecular ion $[M]^+$ at *m/z* 340. The molecular formula, $C_{22}H_{28}O_3$, was determined by HREIMS and ^{13}C NMR data. Both the ^1H NMR and the ^{13}C NMR spectrum were well resolved (Table 1) thus, the determination of the structure of part **a** of **1** (Fig. 2) was quite straight forward by interpretation of COSY (that exhibited many correlations resulting from ^2J, ^3J as well as long range ^4J, ^5J and ^6J couplings, for example, $^5J_{6,9}$) and HMBC data (Figs. 2 and 3). Concerning part **b** of **1**, in the COSY spectrum, inter alia, correlations were observed between the two proton broad singlet at δ 4.98 ppm (H_2-19) and the olefinic protons H-17 (δ 6.07 ppm) and H-20 (δ 5.78 ppm). Other correlations were observed between H-17 and H-20, H-17 and H-16 and between H-16 and the two methylene protons H_2-21 (δ 3.07 ppm, $^6J_{16,21}$). The HMBC experiment showed correlations between both methylenes H_2-19, H_2-21 and all three ring carbon atoms C-18, C-20 and C-22 thus establishing the presence of the β,γ-unsaturated-δ-lactone in part **b** (Figs. 2 and 3). The appearance of both vinyl methyl carbons upfield at δ_C 15.2 ppm in the ^{13}C NMR spectrum established the stereochemistry about both double bonds at C-7–C-8 and C-12–C-13 as *E* (in the case of *Z* geometry the vinyl methyl carbon should resonate around δ_C 22 ppm because of the absence of γ effects). The signal

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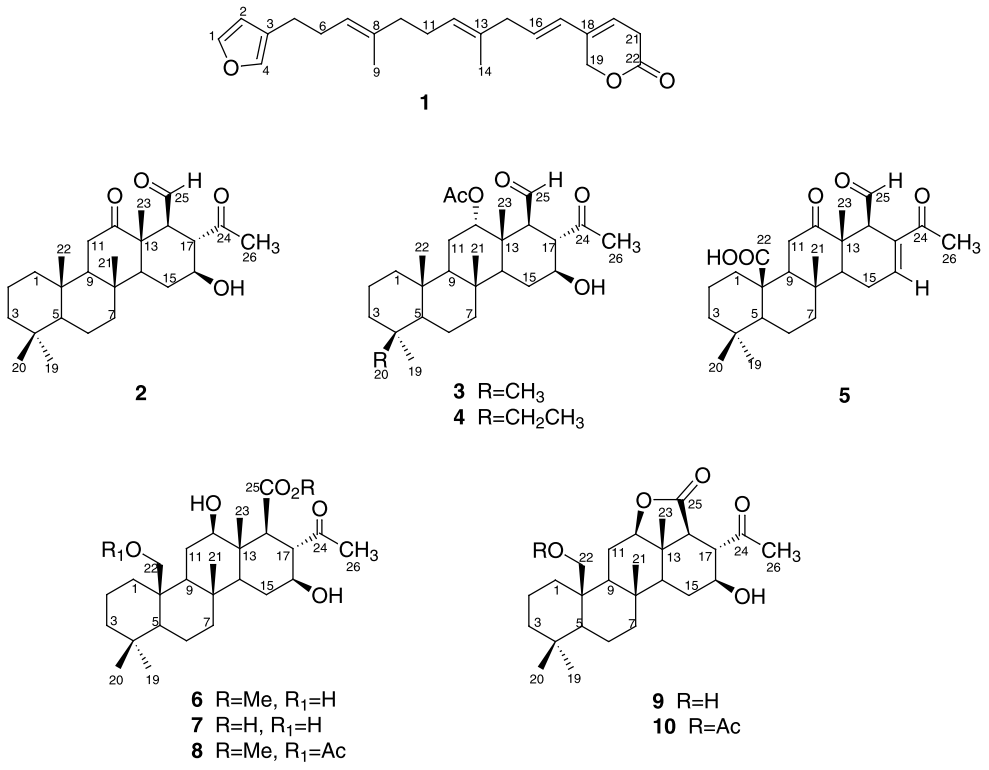

Figure 1. Compounds **1**–**10** isolated from the two sponges.

of H-17 is a doublet showing a 16.1 Hz coupling due to coupling to H-16, and therefore both protons are *trans* related. It should be noted that compound **1** closely resembles furodendin which was isolated from *Phyllospongia dendyi*.[2] Whereas in furodendin there are five double bonds, in **1** there is an additional double bond at C-16–C-17 probably resulting from an oxidation occurring at a later stage. The β,γ-unsaturated-δ-lactone terminus in **1** is very rare among marine metabolites and in fact exists only in compound **1**, in furodendin[2] and in another C_{21} terpenoid.[10]

The EI mass spectrum of **2** exhibited a molecular ion $[M]^+$ at *m/z* 416. The ^{13}C, ^1H NMR and HMBC spectra (Table 2) revealed the presence of: (a) six methyl singlets; (b) seven

Table 1. NMR data for dehydrofurodendin (**1**) in CD_3COCD_3

Position	δ_C, ppm[a,b]	δ_H, ppm, (m)[c,d,e]	COSY (^1H–^1H)	HMBC (H to C)[f]
1	143.0 CH	7.38 (t, 1.5)	2	2, 3, 4
2	111.4 CH	6.31 (s)	1, 4	1, 3, 4
3	125.0 C			
4	139.3 CH	7.27 (s)	2, 5	1, 2, 3
5	25.1 CH_2	2.40 (t, 7.0)	4, 6	3, 4, 6
6	28.6 CH_2	2.20 (q, 7.0)	5, 7, 9, 10	5, 8
7	124.4 CH	5.14 (dq, 6.5, 1.5)	6, 9, 10	9, 10
8	135.0 C			
9	15.2 CH_3	1.55 (s)	6, 7	7, 8, 10
10	39.7 CH_2	1.96 (q, 8.0)	6, 7, 12	7, 8, 9, 11
11	26.7 CH_2	2.05 (q, 8.0)	10, 12, 14, 15	10, 12, 13
12	125.7 CH	5.13 (m)	11, 14, 15	15
13	133.0 C			
14	15.2 CH_3	1.55 (s)	11, 12	12, 13, 15
15	43.1 CH_2	2.72 (d, 7.0)	11, 12, 16, 17	12, 13, 14, 15, 17
16	128.6 CH	5.60 (dt, 16.1, 7.0)	15, 17, 21	15, 18
17	128.3 CH	6.07 (d, 16.1)	15, 16, 19, 20	15, 18, 19, 20
18	132.0 C			
19	68.0 CH_2	4.98 (bs)	17, 20	18, 20, 22
20	120.3 CH	5.78 (t, 4.0)	17, 19, 21	
21	30.4 CH_2	3.07 (m)	16, 20	18, 20, 22
22	168.0 C			

[a] CD_3COCD_3, Bruker Avance-400 instrument, chemical shifts refer to CD_3COCD_3 (δ_C=29.8, 205.7 ppm).
[b] Multiplicities were determined by DEPT and HMQC experiments.
[c] CD_3COCD_3, Bruker ARX-500 instrument, chemical shifts refer to TMS (δ_H=0).
[d] The CH correlations were assigned by a HMQC experiment.
[e] Multiplicity and coupling constants are indicated in parentheses.
[f] HMBC experiment with a delay of 55 ms optimized for 8 Hz coupling.

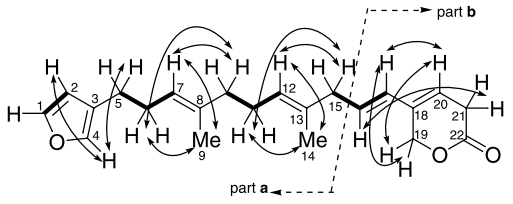

Figure 2. COSY correlations in **1**: ^{2}J–^{3}J (▬) and ^{4}J–^{6}J (⌒).

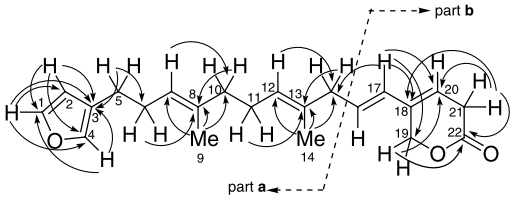

Figure 3. Key HMBC correlations in **1**.

methylenes; (c) one oxygenated methine (δ_C 73.6 ppm, δ_H 3.35, respectively); (d) five non-oxygenated methines (δ_C 56.1, 60.6, 56.6, 53.7, 57.9 ppm, δ_H 0.51, 0.71, 0.71, 2.82, 3.33 ppm, respectively); (e) four quaternary sp^3 carbons [δ_C 33.4, 37.7 (two carbons), 53.0 ppm]; (f) two ketones (δ_C 214.0, 210.0 ppm) and (g) an aldehyde (δ_C 203.9 CHO ppm). On the basis of this analysis the molecular formula was determined to be $C_{26}H_{40}O_4$. In the structure elucidation process, first the strong HMBC correlations of the methyl protons with their neighboring C-atoms were analyzed and then the resulting units were extended by COSY correlations (Fig. 4).

The relative stereochemistry of the substituents on ring D was determined based on the coupling constants of H-16, H-17 and H-18. The latter protons all reveal 10.5 Hz coupling constants indicating their axial position. Thus, the relative stereochemistry of the asymmetric centers in ring D of **2** was elucidated to be 16*S**, 17*S**, 18*S** and the structure of **2** was determined to be 16β-hydroxy-24-methyl-12,24-dioxoscalaran-25-al (Fig. 1). It should be noted that compound **2** is closely related to 16β-acetoxy-24-methyl-12,24-dioxoscalaran-25-al[11,12] which was isolated from *Carteriospongia flabellifera* and the relative stereochemistries of the asymmetric centers 16, 17 and 18 are identical in the latter compound and in **2**. Full assignment of ^{1}H NMR data was not available for the 16β-acetoxy congener[11,12] and is reported here for the first time.

The structure of compound **3** was shown to be identical to 12α-acetoxy-16β-hydroxy-24-methyl-24-oxoscalarane-25-al, a homoscalarane previously reported from

Table 2. NMR data for **2** in C_6D_6

Position	δ_C, ppm[a,b]	δ_H, ppm (m)[c,d,e]	COSY (^{1}H–^{1}H)[f]	HMBC (H to C)[g]
1	39.4 CH_2	1.35 (m)	2A	
		0.64 (m)		
2	18.3 CH_2	1.50 (m)	1A, 1B, 3A	
		1.33 (m)		
3	42.2 CH_2	1.46 (m)	2A	
		1.11 (m)	2A	
4	33.4 C			
5	56.1 CH_2	0.51 (m)	6B	
6	18.8 CH_2	1.36 (m)		5
		1.11 (m)	7B	
7	41.2 CH_2	1.33 (m)		5
		0.35 (m)	6B	
8	37.7 C			
9	60.6 CH	0.71 (m)	11A, 11B	
10	37.7 C			
11	35.1 CH_2	2.14 (s)	9	8, 9, 10, 12
		2.12 (m)	9	8, 9, 10, 12
12	214.0 C			
13	53.0 C			
14	56.6 CH	0.71 (m)	15B	
15	30.0 CH_2	1.30 (m)	16	
		0.99 (q, 13.0)	16,14	
16	73.6 CH	3.35 (dt, 10.5, 4.0)	15A, 15B, 17	
17	53.7 CH	2.82 (t, 10.5)	16, 18	18
18	57.9 CH	3.33 (d 10.5)	16, 23	16
19	33.5 CH_3	0.85 (s)		3, 4, 5, 19
20	21.4 CH_3	0.76 (s)		3, 4, 5, 20
21	17.0 CH_3	0.57 (s)		7, 8, 9, 14
22	15.5 CH_3	0.57 (s)		1, 5, 9, 10
23	16.8 CH_3	0.75 (s)		12, 13, 14, 18
24	210.0 C			
25	203.9 CH	10.29 (s)		
26	33.8 CH_3	2.47 (s)		17, 24

[a] C_6D_6, Bruker Avance-400 instrument, chemical shifts refer to C_6D_6 (δ_C=128.0).
[b] Multiplicities were determined by DEPT and HMQC experiments.
[c] C_6D_6, Bruker ARX-500 instrument, chemical shifts refer to TMS (δ_H=0).
[d] The CH correlations were assigned by a HMQC experiment.
[e] Multiplicity and coupling constants are indicated in parentheses.
[f] A and B denote downfield and upfield resonances, respectively, of a geminal pair.
[g] HMBC experiment with a delay of 55 ms optimized for 8 Hz coupling.

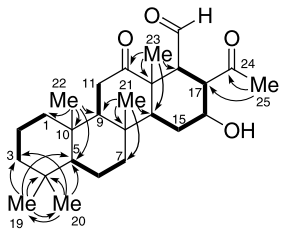

Figure 4. COSY (▬) and HMBC (⌒) correlations in **2**.

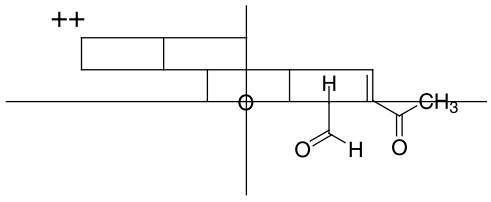

Figure 5. Projection through the carbonyl C-12 of compound **5**.

Phyllospongia sp.[13] The structure of compound **4** was identified as 12α-acetoxy-16β-hydroxy-20,24-dimethyl-24-oxoscalarane-25-al which was previously isolated from *Carteriospongia foliascens*.[8] The structure of compound **5** was identified as 24-methyl-12,24,25-trioxoscalar-16-en-22-oic acid which was previously reported from *Lendenfeldia* sp. collected in Western Australia.[14]

The absolute configuration of compounds **2** and **5** was determined by CD measurements. A positive Cotton effect was measured for compounds **2** and **5** ($\Delta\varepsilon = +0.62, +1.91$, respectively) consistent with the reported absolute configuration of scalaranes.[11,12] According to the octant rule the C-12 carbonyl group in **2** as well as in **5** is expected to give a strong positive Cotton effect. The contribution of the aldehyde group, if at all, is expected to be minimal. According to reported X-ray analysis of the 16β-acetoxy congener of **2**[11,12] and NMR data of the CHO proton (δ_H 10.29 and 10.15 s in **2** and in **5**, respectively), the angle between the CHO proton and H-18 is ca. 90°. In both possible conformers the tetracyclic ring system will be approximately in the nodal plane resulting in a minimal perturbation of the $n \rightarrow \pi^*$ transition of the CO group. Thus,

Table 3. NMR data for compounds **6–8** in $CDCl_3$

Position	**6**		**7**		**8**
	δ_C, ppm[a,b]	δ_H, ppm[c,d,e]	δ_C, ppm[a,b]	δ_H, ppm[c,d,e]	δ_C, ppm[a,b]
1	34.2 CH_2	2.14 (d, 12.5) 0.63 (dt, 3.0, 12.5)	34.1 CH_2	2.20 (m) 0.64 (dt, 3.0, 12.2)	34.8 CH_2
2	18.3 CH_2	1.52 (m) 1.40 (m)	18.2 CH_2	1.58 (m) 1.38 (m)	18.4 CH_2
3	41.6 CH_2	1.36 (m) 1.11 (dt, 3.8, 12.6)	41.6 CH_2	1.40 (m) 1.12 (m)	41.5 CH_2
4	32.9 C		33.5 C		33.5 C
5	56.8 CH	0.82 (m)	56.7 CH	0.88 (m)	56.9 CH
6	17.9 CH_2	1.45 (m) 1.29 (dd, 2.9, 13.3)	17.8 CH_2	1.45 (m) 1.31 (m)	18.1 CH_2
7	41.9 CH_2	1.74 (m) 0.84 (m)	41.8 CH_2	1.77 (m) 0.90 (m)	41.9 CH_2
8	37.5 C		37.4 C		37.6 C
9	58.6 CH	0.84 (m)	58.5 CH	0.87 (m)	58.4 CH
10	42.1 C		42.0 C		41.9 C
11	29.9 CH_2	1.81 (m) 1.76 (m)	29.7 CH_2	1.82 (m) 1.80 (m)	32.9 CH_2
12	79.3 CH	3.25 (dd, 4.9, 10.5)	79.1 CH	3.26 (dd, 6.0, 9.9)	79.2 CH
13	43.9 C		43.8 C		44.1 C
14	55.8 CH	0.85 (m)	55.7 CH	0.89 (m)	55.2 CH
15	30.0 CH_2	1.84 (m) 1.48 (m)	29.7 CH_2	1.85 (m) 1.50 (m)	29.7 CH_2
16	72.9 CH	3.50 (m)	72.7 CH	3.52 (m)	73.4 CH
17	55.7 CH	3.02 (t, 11.5)	55.4 CH	3.05 (t, 11.4)	55.7 CH
18	55.4 CH	2.27 (d, 11.5)	55.6 CH	2.29 (d, 11.4)	55.7 CH
19	21.7 CH_3	0.71 (s)	21.6 CH_3	0.74 (s)	21.8 CH_3
20	33.7 CH_3	0.80 (s)	33.6 CH_3	0.82 (s)	33.7 CH_3
21	16.3 CH_3	0.95 (s)	16.1 CH_3	0.98 (s)	16.5 CH_3
22	62.1 CH_2	3.92 (d, 11.8) 3.76 (d, 11.8)	61.7 CH_2	3.96 (m) 3.78 (m)	64.5 CH_2
23	9.9 CH_3	1.01 (s)	9.7 CH_3	1.03 (s)	10.2 CH_3
24	215.3 C		215.1 C		212.0 C
25	174.7 C		174.8 C		174.0 C
26	33.3 CH_3	2.19 (s)	33.5 CH_3	2.22 (s)	33.5 CH_3
27	51.8 CH_3	3.51 (s)			51.9 CH_3
28					171.0 C
29					21.2 CH_3

[a] $CDCl_3$, Bruker Avance-400 instrument, chemical shifts refer to $CDCl_3$ ($\delta_C = 77.0$).
[b] Multiplicities were determined by DEPT and HMQC experiments.
[c] $CDCl_3$, Bruker ARX-500 instrument, chemical shifts refer to TMS ($\delta_H = 0$).
[d] The CH correlations were assigned by a HMQC experiment.
[e] Multiplicity and coupling constants are indicated in parentheses.

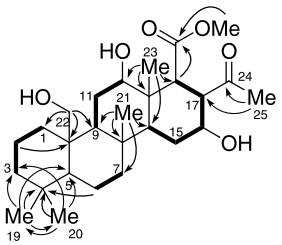

Figure 6. COSY (▬) and HMBC (⌒) correlations in **6**.

the absolute configuration of compound **2** was established to be 16*S*, 17*S* and 18*S* (Fig. 5).

The electrospray mass spectrum of **6** exhibited a molecular ion $[M+Na]^+$ at *m/z* 487. The ^{13}C, ^1H NMR and HMBC spectra (Table 3) revealed the presence of: (a) one methyl ester moiety (δ_C 174.7, 51.8 ppm, δ_H 3.51 ppm); (b) five additional methyl singlets; (c) seven methylenes; (d) one oxygenated methylene (δ_C 62.1 ppm, δ_H 3.92, 3.76 ppm); (e) two oxygenated methines (δ_C 79.3, 72.9 ppm, δ_H 3.25, 3.50 ppm, respectively); (f) five non-oxygenated methines (δ_C 56.8, 58.6, 55.8, 55.7, 55.4 ppm, δ_H 0.82, 0.84, 0.85, 3.02, 2.27 ppm, respectively); (g) four quaternary sp^3 carbons (δ_C 32.9, 37.5, 42.1, 43.9 ppm) and (h) one ketone (δ_C 215.3 ppm). On the basis of this analysis the molecular formula was determined to be $C_{27}H_{44}O_6$. First, the strong HMBC correlations of the methyl protons with the neighboring C-atoms were analyzed and then the resulting units were extended by COSY correlations (Fig. 6). Other observed HMBC correlations between H-22A (in the following discussions A and B denote downfield and upfield resonances, respectively, of a geminal pair) and C-1, C-9 and C-10 as well as between H-2B and C-10 enabled the establishment of the connections between C-1 and C-10, between C-9 and C-10 and between C-10 and C-22. HMBC correlations between H-6B and C-4 determined the connection between C-5 and C-6 (Fig. 6). Since H-5, H-7B, H-9 and H-14 exhibit overlapping resonances, correlations corroborating the connection between C-5 and C-10 were not observed. However, the multiplicity of C-5 and C-10, the molecular mass of 464 and the fact that the NMR data of compound **6** is in close agreement with these of related compounds,[15] undoubtedly proved that the latter carbons are in fact connected, thus completing the planar structure of **6**.

The relative stereochemistry of the substituents on rings C and D was determined based on the coupling constants of H-12, H-16, H-17 and H-18. H-12 is a double doublet presenting coupling constants of 10.5, 4.9 Hz indicating that H-12 is axial. H-17 is a triplet with a coupling constant of 11.5 Hz due to couplings to both H-16 and H-18 indicating that H-16, H-17 and H-18 are all axial. Thus, the relative stereochemistry of the asymmetric centers in rings C and D of **6** was elucidated to be 12*R**, 16*S**, 17*S**, 18*S** (Fig. 1). This conclusion was further corroborated by NOE correlations between H-18 and both H-12 and H-16 as well as between H-17 and H-23. Thus, the structure of **6** was determined to be 12β,16β,22-trihydroxy-24-methyl-24-oxoscalaran-25-oxo methyl ester. It should be noted that compound **6** is closely related to 12β-hydroxy-16β,22-diacetoxy-24-methyl-24-oxoscalaran-25-oxo methyl ester which was isolated from *Lendenfeldia frondosa*[15] and the relative stereochemistry of the asymmetric centers 12, 16, 17, 18 is identical in the latter compound and in **6**. The absolute stereochemistry of the 16β,22-diacetoxy congener was established to be 12*R*, 16*S*, 17*S* and 18*S*[15] and thus it is suggested that the absolute stereochemistry of the respective asymmetric centers in compound **6** is identical.

The ^{13}C and ^1H NMR spectra of compounds **7** and **8** (Table 3) were very similar to those of **6**. In the case of compound **7**, the spectra revealed the absence of the OMe signal of **6** at δ_C 51.8 ppm, δ_H 3.51 ppm, indicating the presence of a free carboxylic acid instead of the methyl ester at C-25. This conclusion was further corroborated by the CI mass spectrum of **7** which exhibited a molecular ion $[M+H]^+$ at *m/z* 451. In the case of compound **8**, the spectra revealed the presence of an additional acetate group (δ_C 171.0, 21.2 ppm, δ_H 2.05 ppm) compared to **6**. The signals corresponding to C-22, H-22A and H-22B were shifted downfield (δ_C 64.5 ppm, δ_H 4.56, 4.11 ppm) compared to those of **6**. The CI mass spectrum of **8** exhibited a molecular ion $[M+H]^+$ at *m/z* 507 and thus, it was concluded that **8** differs from **6** by the presence of an acetate group attached at C-22. The relative stereochemistry of the asymmetric centers in **7** and **8** was elucidated, based on coupling constants analysis, to be identical to that of **6** namely, 12*R**, 16*S**, 17*S**, 18*S**. Thus, the structures of **7** and **8** were determined to be 12β,16β,22-trihydroxy-24-methyl-24-oxoscalaran-25-oic acid and

Table 4. Inhibition of cancer cell line growth (GI_{50}) by scalaranes **2–4**

Cancer cell line	**2**		**3**		**4**	
	M	μg/mL	M	μg/mL	M	μg/mL
Prostate DU-145	6.65×10^{-6}	2.77	3.54×10^{-6}	1.63	2.91×10^{-6}	1.38
Prostate LN-caP	5.78×10^{-6}	2.41	4.54×10^{-6}	2.09	3.62×10^{-6}	1.72
Ovary IGROV	5.93×10^{-6}	2.47	4.88×10^{-6}	2.25	2.95×10^{-6}	1.40
Ovary IGROV-ET	7.47×10^{-6}	3.11	5.30×10^{-6}	2.44	4.21×10^{-6}	1.99
Breast SK-BR3	9.27×10^{-6}	3.86	3.63×10^{-6}	1.67	3.86×10^{-6}	1.75
Melanoma SK-MEL-28	4.99×10^{-6}	2.08	3.15×10^{-6}	1.45	2.72×10^{-6}	1.29
Lung NSCL A-549	6.48×10^{-6}	2.70	4.04×10^{-6}	1.86	3.10×10^{-6}	1.47
Leukemia K-562	4.37×10^{-6}	1.82	6.12×10^{-6}	2.82	3.14×10^{-6}	1.49
Pancreas PANC1	5.11×10^{-6}	2.13	3.32×10^{-6}	1.53	2.38×10^{-6}	1.13
Colon HT-29	8.02×10^{-6}	3.34	4.30×10^{-6}	1.98	4.21×10^{-6}	1.99
Colon LOVO	5.74×10^{-6}	2.39	4.10×10^{-6}	1.89	2.74×10^{-6}	1.30
Colon LOVO-DOX	5.33×10^{-6}	2.22	3.86×10^{-6}	1.78	2.93×10^{-6}	1.39
Cervix HELA	5.40×10^{-6}	2.25	4.10×10^{-6}	1.88	3.37×10^{-6}	1.60
Cervix HELA-APL	5.88×10^{-6}	2.45	3.23×10^{-6}	1.50	3.14×10^{-6}	1.49

12β,16β-dihydroxy-22-acetoxy-24-methyl-24-oxoscalaran-25-oxo methyl ester, respectively (Fig. 1).

The structure of compound **9** was shown to be 16β,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone and the structure of compound **10** was identified as 21-acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25,12β-olactone which were both previously isolated from *Lendenfeldia* sp.[14] Biogenetically, compound **7** is the precursor of **9** and **10**, that is the 12-hydroxy and 25-carboxylic acid groups of **7** close to a lactone.

3. Biological evaluation

Dehydrofurodendin (**1**) has been found to be a potent inhibitor of the HIV-1 RT-associated DNA polymerase activities. The IC_{50} values calculated from dose–response curves were 3.2 and 5.6 μM for the RNA- and DNA-directed DNA polymerase functions, respectively. In addition, this compound displayed a capacity to inhibit the RNase H activity of HIV-1 RT, albeit to a lesser extent, with an IC_{50} value of 29.5 μM.

Compounds **2**–**4** have been screened against several cultured human tumor cell lines and were shown to be cytotoxic with GI_{50} values in the micromolar range (Table 4). The methyl ester derivative of compound **5** exhibited cytotoxic activity against breast MDA-MB-231 carcinoma, lung NSCL A-549 carcinoma and HT-29 colon carcinoma with GI_{50} values of 4.54×10^{-6} M (2.0 μg/mL), 2.42×10^{-7} M (0.1 μg/mL) and 2.26×10^{-6} M (1.0 μg/mL) respectively. Compounds **6**, **9** and **10** were cytotoxic against lung NSCL A-549 carcinoma with GI_{50} values of 8.07×10^{-6} M (3.7 μg/mL), 1.27×10^{-6} M (0.5 μg/mL) and 2.13×10^{-6} M (1.0 μg/mL) respectively.

In this context it should be mentioned that compound **3** was previously reported to exhibit weak cytotoxicity[13] and compound **4** was reported to exhibit mild cytotoxicity against P-388 (lymphoid neoplasm from DAB/2 mouse), A-549 (human lung carcinoma), HT-29 (human colon carcinoma) and CV-1 (monkey kidney fivroblast) cells in culture with IC_{50} values of ca. 0.1 μg/mL.[6] Other biological roles of the compounds isolated in this study were also examined previously. Compounds **9** and **10** were previously reported to be potent inhibitors of platlet aggregation and anti-microbial compounds.[14,16] Induction of differentiation of K562 (myelogenous leukemia cell line) to hemoglobin producing erythroblast cells by compounds **5** and **10** was also reported.[17] Nevertheless, the cytotoxicity exhibited by the novel compounds **2** and **6**, reported here, as well as the cytotoxicity exhibited by the known compounds **5**, **9**, **10** are new results.

4. Experimental

4.1. General

Optical rotations were obtained with a Jasco P-1010 polarimeter. IR spectra were obtained with a Bruker FTIR Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX-500 and Avance-400 spectrometers. ^{1}H, ^{13}C, COSY, HMQC and HMBC were recorded using standard Bruker pulse sequences. EIMS and CIMS and HRMS measurements were recorded on a Fisons, Autospec Q instrument.

4.2. Biological material

Lendenfeldia sp. 1 was collected in Madagascar, at the south of Barren Islands, between Nosy Drano and Nosy Manghily (18°, 34′, 643″ south; 43°, 53′, 533″ east) in May 2001 by SCUBA at a depth of 15–19 m. A voucher specimen is deposited at Station Marine d'Endoume, Marseille (voucher number AMT-839).

Lendenfeldia sp. 2 was collected at Barren Island, South of Nosy Lava (18°, 36′, 250″ south; 43°, 56′, 421″ east), in the North–West of Madagascar in May 2001 by SCUBA at a depth of 10–12 m. A voucher specimen is deposited at Station Marine d'Endoume, Marseille (voucher number AMT-815).

Lendenfeldia sp. 1 [order Dictoyoceratida, family Thoretidae (AMT-839)] is a red sponge. Ten species are known from the Indo Pacific area but none of them is red. *Lendenfeldia* sp. 2 (AMT-815) is blue under water and chestnut in the air. The sponge is covered with massive acropores of fine thickness. There are digitations in the shape of thimbles on the surface of the sponge. The two sponges belong to different species which are undoubtedly new.

4.3. Extraction and isolation

Freeze-dried *Lendenfeldia* sp. 1 (AMT-839—17 g) was homogenized and extracted with $CHCl_3$–MeOH (2:1) to give after evaporation a brown gum (0.92 g). The gum was subjected to partition by the method of Kupchan et al.[9] The carbon tetrachloride fraction (320 mg) was repeatedly chromatographed on a Sephadex LH-20 column, eluting with acetone. Then it was subjected to vacuum–liquid chromatography (VLC) over silica gel, using heptane with increasing proportions of acetone as eluent. Dehydrofurodendin (**1**, 4.5 mg, 0.026% dry weight) was afforded by elution with 5% acetone in heptane. The fraction eluted with 15% acetone in heptane was subjected to HPLC reversed-phase separation (Merck purospher STAR RP-18e column, 5 μm, 250×10 mm) using a mixture of 90% acetonitrile–10% H_2O as the eluent to afford **2** (2.1 mg, 0.012% dry weight), **3** (5.1 mg, 0.03% dry weight), and **4** (4.3 mg, 0.025% dry weight).

Freeze-dried *Lendenfeldia* sp. 2 (AMT-815—20 g) was homogenized and extracted with $CHCl_3$–MeOH (2:1) to give after evaporation a brown gum (1.2 g). The gum was subjected to partition by the method of Kupchan et al.[9] For better separation, the carbon tetrachloride fraction (280 mg) was methylated with freshly destilled diazomethane and chromatographed on a Sephadex LH-20 column, eluting with a mixture of heptane–$CHCl_3$–MeOH (2:1:1) to obtain compound **10** (9.5 mg 0.047%). A fraction of the latter column was subjected to VLC over silica gel, using heptane with increasing proportions of ethyl acetate as eluent.

Compound **5**, (4.5 mg, 0.022% dry weight) was afforded by elution with 30% ethyl acetate in heptane as the methyl ester derivative. The chloroform fraction (530 mg) was chromatographed on a Sephadex LH-20 column, eluting with a mixture of heptane–$CHCl_3$–MeOH (2:1:1) to obtain 12 fractions. Compound **9** (6.5 mg 0.032% dry weight) was afforded in fraction 8. Fractions 9–10 were subjected to a second Sephadex LH-20 column, eluting with a mixture of $CHCl_3$–MeOH (1:1) to obtain compound **7** (3.0 mg, 0.015% dry weight). Fractions from the latter column were subjected to VLC over silica gel, using heptane with increasing proportions of ethyl acetate as eluent. Compound **8**, (3.5 mg, 0.027% dry weight) was afforded by elution with 40% ethyl acetate in heptane and compound **6** (2.5 mg 0.012% dry weight) was afforded by elution with 50% ethyl acetate in heptane.

4.3.1. Dehydrofurodendin (1). Colorless oil; IR (neat) ν_{max} 1743, 1725 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; EIMS *m/z* (%) 340 [M^+] (15), 325 (7), 191 (30), 149 (25), 135 (25), 81 (characteristic of β-substituted furans) (100); HREIMS *m/z* 340.2041 (Calcd. for $C_{22}H_{28}O_3$, 340.2038).

4.3.2. Compound 2. Colorless oil; $[\alpha]_D^{25}=+43$ (*c* 0.08, $CHCl_3$); IR (neat) ν_{max} 3500, 2935, 1715, 1226 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 2; EIMS *m/z* (%) 416 [M^+] (30), 401 (30), 370 (65), 327 (35), 288 (30), 191 (characteristic of tetramethylated decalins of terpenoids) (100); HREIMS *m/z* 416.2908 (Calcd. for $C_{26}H_{40}O_4$, 416.2916).

4.3.3. Compound 3. Colorless crystals (crystallized from acetone); $[\alpha]_D^{25}=+113$ (*c* 0.38, $CHCl_3$) (lit. $[\alpha]_D^{25}=+138$)[13]; IR (neat) ν_{max} 3500, 2935, 1737, 1716, 1371, 1234, 1025 cm^{-1}; EIMS *m/z* (%) 460 [M^+] (5), 400 (25), 372 (22), 354 (100), 311 (42), 205 (75), 191 (characteristic of tetramethylated decalins of terpenoids) (70) 43 (78); identical in all respects to 12α-acetoxy-16β-hydroxy-24-methyl-24-oxoscalarane-25-al.[13]

4.3.4. Compound 4. Colorless oil; $[\alpha]_D^{25}=+87$ (*c* 0.35, $CHCl_3$) (lit. $[\alpha]_D^{25}=+87$); IR (neat) ν_{max} 3448, 2935, 1715, 1238 cm^{-1}; EIMS *m/z* (%) 474 [M^+] (10), 457 (12), 439 (15), 415 (40), 397 (45), 369 (15), 85 (67), 73 (100). Identical in all respects to 12α-acetoxy-16β-hydroxy-20,24-dimethyl-24-oxoscalarane-25-al.[6]

4.3.5. Compound 5. Was isolated as the methyl ester. Colorless oil; IR (neat) ν_{max} 3400–2500 br, 1714, 1225 cm^{-1}; ESMS *m/z* (%) 443 $[M+H]^+$ (100), 414 (10), 383 (5); identical to 24-methyl-12,24,25-trioxoscalar-16-en-22-oic acid.[14]

4.3.6. Compound 6. Colorless oil; $[\alpha]_D^{25}=+41$ (*c* 0.11, $CHCl_3$); IR (neat) ν_{max} 3500, 1730, 1715, 1226 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 3; ESMS *m/z* (%) 487 $[M+Na]^+$ (100), 397 (30); HRESMS *m/z* 487.3033 (Calcd for $C_{27}H_{44}O_6Na$, 487.3037).

4.3.7. Compound 7. Colorless oil;[18] IR (neat) ν_{max} 3400–2500 br, 1715, 1226 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 3; CIMS *m/z* (%) 451 $[M+H]^+$ (15), 433 (55), 415 (50), 397 (35), 117 (45), 74 (100); HRCIMS *m/z* 451.3065 (Calcd for $C_{26}H_{43}O_6$, 451.3061).

4.3.8. Compound 8. Colorless oil;[18] IR (neat) ν_{max} 3500, 1748, 1730, 1715, 1220 cm^{-1}; for ^{13}C NMR data, see Table 3; ^1H NMR ($CDCl_3$) d 4.55 (1H, d, $J=12.1$ Hz), 4.11 (1H, d, $J=12.1$ Hz), 3.65 (1H, dt, $J=5.4$, 11.0 Hz), 3.59 (3H, s), 3.42 (1H, dd, $J=4.9$, 11.3 Hz), 3.10 (1H, t, $J=11.0$ Hz), 2.38 (1H, d, $J=11.0$ Hz), 2.27 (3H, s), 2.05 (3H, s), 1.07 (3H, s), 0.90 (3H, s), 0.87 (3H, s), 0.82 (3H, s); CIMS *m/z* (%) 507 $[M+H]^+$ (5), 489 (12), 475 (15), 435 (5), 284 (10), 146 (20), 74 (100); HRCIMS *m/z* 507.3319 (Calcd for $C_{29}H_{47}O_7$, 507.3323).

4.3.9. Compound 9. Colorless oil; IR (neat) ν_{max} 3450, 1750, 1724, 1224 cm^{-1}; CIMS *m/z* (%) 433 $[M+H]^+$ (60), 415 (70), 397 (100), 379 (35), 353 (25); identical in all respects to 16β,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone.[14]

4.3.10. Compound 10. Colorless oil; IR (neat) ν_{max} 3450, 1748, 1723, 1227 cm^{-1}; EIMS *m/z* (%) 474 $[M]^+$ (25), 446 (20), 428 (25); identical in all respects to 21-acetoxy-16β-hydroxy-24-methyl-24-oxoscalaran-25,12β-olactone.[14]

4.4. HIV-1 RT inhibition assay

4.4.1. Enzymes. The HIV-1 reverse transcriptase (RT) used in this study was a recombinant heterodimeric p66/p51 enzyme expressed in *E. coli* with six-histidine tags and purified as previously described in detail.[19] The plasmid designated as pHIV-1 RT induce the expression of the wild-type HIV-1 RT of the BH-10 isolate of HIV-1.[20]

4.4.2. Enzymatic assays. The HIV-1 RT associated RDDP, DDDP and RNase H activities were assayed as described in detail previously.[21–23] In short the RDDP activity was assayed by monitoring the poly(rA)$_n$·oligo(dT)$_{12-18}$-directed incorporation of [^{3}H]dTTP into trichloroacetic acid-insoluble DNA product. The DDDP activity was assayed with an activated DNA as primer-template and with all four deoxynucleotides present (of which only one, dTTP, was radioactively labeled). The RNase H activity was assayed by measuring the release of trichloroacetic acid-soluble material from the synthetic substrate [^{3}H]poly(rA)$_n$poly(dT)$_n$.

4.5. Cytotoxicity assays

A colorimetric type of assay, using the sulforhodamine B (SRB) reaction[24–26] has been employed for the cytotoxicity assays against 13 human tumor cell lines: leukemia, K-562 (ATCC-CCL-243); lung carcinoma A-549 (ATCC-CCL-185); melanoma, SK-MEL-28 (ATCC HTB-72); colon carcinoma, HT-29 (ATCC-HTB-38), LoVo (ATCC-CCL-229) & LoVo-Dox, MDR cell line; prostate carcinoma, DU-145 (ATCC-HTB-81) & LNCaP (ATCC-CRL-1740); breast carcinoma SK-BR3 (ATCC-HTB-30); ovary carcinoma SK-OV-3 (ATCC-HTB-77) JGROV & IGROV-ET resistant to ET-743 (both provided by Mario Negri Institute of Milan) and pancreas carcinoma, PANC1 (ATCC-CRL-1469).

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Pseudopterosins P–V, new compounds from the gorgonian octocoral *Pseudopterogorgia elisabethae* from Providencia island, Colombian Caribbean

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Abstract—Seven new diterpene glycosides, pseudopterosins P (**1**), Q (**2**), R (**3**), S (**4**), T (**5**), U (**6**) and V (**7**) along with two known compounds PsG and PsK have been isolated from the methanol/dichloromethane extract of the gorgonian octocoral *Pseudopterogorgia elisabethae* collected off Providencia Island, Colombian Caribbean. The structures of the new metabolites, including their relative and absolute configuration, were established by MS and NMR spectroscopic studies as well as their conversion to known compounds.

1. Introduction

Pseudopterosins are an interesting group of diterpene glycosides first discovered by Fenical and collaborators[1] about 15 years ago from specimens of the gorgonian coral *Pseudopterogorgia elisabethae*. So far, 15 pseudopterosins (PsA–PsO) isolated from specimens collected in the Bahamas,[1] Bermuda,[2] and the Florida Keys[3] have been reported. The structurally related secopseudopterosins A–D have also been identified in *Pseudopterogorgia kallos* collected near the Marquesas Keys in Florida.[4] These pseudopterosins and secopseudopterosins exhibit more potent antiinflammatory and analgesic activities than the common market drug indomethacin.[5,6] It is suggested that the mechanism of action of the pseudopterosins may involve membrane stabilization, different from inhibition of eicosanoid release from inflammatory cells mediated by traditional non-steroidal drugs.[6] Due to their excellent antiinflammatory and analgesic activity, partially purified extracts containing pseudopterosins are currently incorporated into skin care preparations.[7] The availability of pseudopterosins however, is limited by the actual supply of organic extracts of *Pseudopterogorgia elisabethae* which currently only comes from the Bahamas islands. The complex and expensive chemical synthesis of these compounds makes these animals an attractive study target in other areas of the Caribbean.

As part of our continuous search for biologically active compounds from Colombian marine invertebrates,[8,9] we have recently examined *Pseudopterogorgia elisabethae* specimens from San Andrés and Providencia islands from the Colombian Caribbean, finding distinct chemotypes regarding to the pseudopterosin content, in each island.[10] Samples from Providencia island afforded seven new pseudopterosins, together with the known pseudopterosins G and K. In this paper, we report the isolation and structure elucidation of the seven new pseudopterosins.

2. Results and discussion

Pseudopterogorgia elisabethae specimens were collected at Providencia island, Colombian Caribbean, and air-dried. Animal tissue was extracted with a $MeOH/CH_2Cl_2$ (1:1) mixture and the extract was separated on silica gel CC and reversed phase HPLC to yield seven new compounds which we named pseudopterosins P–V (**1**–**7**), along with the known compounds pseudopterosins G[2] and K.[2]

Pseudopterosin-P (**1**) showed a molecular ion at *m/z* 446 and intense fragment ions at *m/z* 300 and 244. The former fragment ion corresponds to the pseudopterosin aglycone, suggesting the loss of a deoxyhexose (146 mass unit) and

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Table 1. ^{1}H NMR (500 MHz, $CDCl_3$) data for compounds **1–7**

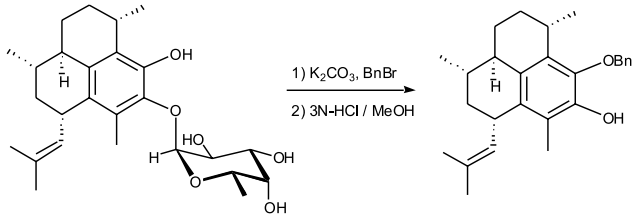
H No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	3.66 q-like (8.5)	3.66 q-like (8.6)	3.67 q-like (8.5)	3.66 q-like (8.7)	3.62 q-like (8.7)	3.67 m	3.67 q (8.7)
2	1.93 dd (10.5, 7.8)	1.93 m	1.93 m	1.94 m	1.90 dd (10.2, 6.3)	1.23 m	1.22 m
	1.21 m	1.22 m	ca. 1.22 m	ca. 1.21 m	ca. 1.22 m	2.25 m	1.93 m
3	1.22 m	1.22 m	ca. 1.22 m	ca. 1.23 m	ca. 1.23 m	1.22 m	1.20 m
4	2.05 m	2.06 m	ca. 2.05 m	ca. 2.05 m	ca. 2.02 m	2.05 m	2.05 m
5	0.92 qd (12.7, 3.2)	0.93 qd (12.7, 3.2)	0.93 qd (12.7, 3.2)	0.93 qd (12.7, 3.0)	0.88 qd (12.7, 3.2)	0.92 qd (12.7, 3.2)	0.93 qd (12.7, 3.3)
						2.02 m	2.05 m
6	1.31 m	1.32 m	1.32 m	1.32 m	1.30 m	1.31 m	1.33 m
	2.13 m	2.14 m	2.14 m	2.15 m	2.08 m	2.13 m	2.15 m
7	3.19 sextet-like (7.0)	3.20 sextet-like (7.2)	3.20 sextet-like (7.0)	3.19 sextet-like (7.2)	3.12 sextet-like (7.2)	3.19 m	3.20 sextet-like (7.1)
14	4.98 br d (9.3)	4.97 d (9.1)	4.99 br d (9.2)	4.93 d (9.2)	4.93 br d (9.3)	4.96 d (9.1)	4.98 br d (11.5)
16	1.67 s	1.67 s	1.67 s	1.67 s	1.64 s	1.66 s	1.67 d (1.0)
17	1.71 s	1.71 s	1.72 s	1.72 s	1.68 s	1.72 s	1.72 d (1.5)
18	1.02 d (6.0)	1.02 d (5.9)	1.02 d (6.0)	1.03 d (5.9)	1.00 d (5.6)	1.02 d (5.9)	1.02 d (7.5)
19	1.25 d (6.8)	1.27 d (6.8)	1.26 d (6.8)	1.25 d (6.8)	1.18 d (6.6)	1.27 d (1.8)	1.26 d (8.5)
20	2.07 s	2.05 s	2.08 s	2.10 s	1.97 s	2.06 s	2.09 s
1′	5.11 d (3.7)	5.14 d (3.8)	5.18 d (4.0)	5.12 d (3.7)	5.10 d (2.5)	5.18 d (3.6)	5.22 d (3.6)
2′	4.03 dd (9.5, 3.7)	4.04 dd (10.1, 3.8)	4.30 ddd (10.4, 4.0, 3.0[a])	5.24 dd (10.4, 3.7)	4.17 br d (7.3)	4.10 dd (9.9, 3.6)	4.33 dd (10.0, 3.8)
3′	4.13 br d (9.5)	4.35 dd (10.1, 3.3)	5.29 dd (10.4, 3.0)	4.26 dd (10.4, 3.2)	4.12 br d (7.3)	4.32 dd (9.9, 3.4)	5.31 dd (10.0, 3.8)
4′	3.89 br	5.21 br d (3.3)	4.06 br s	3.97 br d (3.2)	4.08 br s	5.24 m	4.27 m
5′	4.52 q (6.7)	4.55 q (6.6)	4.58 q (6.6)	4.56 q (6.6)	4.25 d (12.6)	4.36 br d (13.0)	4.42 dd (16.0, 1.5)
					3.78 d (12.6)	3.89 dd (13.0, 1.9)	3.87 dd (16.0, 3.0)
6′	1.33 d (6.7)	1.17 d (6.6)	1.33 d (6.6)	1.39 d (6.6)			
Ac		2.19 s	2.21 s	2.23 s		2.16 s	2.22 s

[a] The coupling is due to hydroxyl group present at C-2′.

m/z 244 the aglycone after loosing an isopropylidene unit. Its molecular formula, $C_{26}H_{38}O_6$, was determined by HREIMS. The UV spectrum showed maximum absorptions at 213, 232, 276, and 285 nm due to the presence of a substituted benzene ring. The ^{1}H and ^{13}C NMR data of **1** (Tables 1 and 2) suggested that **1** belongs to pseudopterosin family.[1–4] The ^{1}H NMR spectrum of **1** showed signals of two singlet methyls at δ 1.67 (H_3-16) and 1.71 (H_3-17), a singlet methyl substituted on an aromatic ring at δ 2.07 (H_3-20), two doublet methyls at δ 1.02 (H_3-18) and 1.25 (H_3-19) and an olefinic proton at δ 4.98 (H-14) for the aglycone part. The ^{13}C NMR spectrum of **1** showed 26 signals, among which 20 resonances including six aromatic carbons at δ 126.8, 127.8, 129.2, 136.6, 143.2, and 145.2 were assigned to the aglycone. Further analysis of ^{1}H signals, assisted with H–H COSY spectra, allowed assigning all proton signals. In particular, the chemical shifts and coupling patterns of H-1 (δ 3.66, q-like, J=8.5 Hz), H-7 (δ 3.19, sextet-like, J=7.0 Hz) and H-14 (δ 4.98, br d, J=9.3 Hz) suggested 1S^*,3S^*,4R^*,7S^* configuration for the aglycone, since the data were close to the values reported for the aglycone derivative with the known configuration.[2,11]

The sugar portion showed signals of an anomeric proton, H-1′ (δ 5.11), a doublet methyl (δ 1.33) assignable to H_3-6′ and four oxymethine protons. Decoupling experiments and correlations in the H–H COSY spectrum established the assignments of H-2′ (δ 4.03), H-3′ (δ 4.13), H-4′ (δ 3.89), and H-5′ (δ 4.52). $J_{H\text{-}2',H\text{-}3'}$ and $J_{H\text{-}2',H\text{-}3'}$ values were 3.7 and 9.5 Hz, respectively, and H-4′ was observed as a broad singlet. These data evidenced axial–axial relationships for H-2′ and H-3′ and equatorial orientation of H-1′ and H-4′, suggesting α-fucose as a sugar structure. Furthermore, the ^{13}C data for the sugar moiety of **1** were in good agreement with those of a fucose-substituted pseudopterosin, pseudopterosin-E[2] which is a C-1 epimer of **1**. Thus, the sugar moiety was determined as α-fucopyranoside. That the sugar was linked to C-10 rather than C-9 was initially deduced from comparison of the ^{13}C data of **1** with those of compound **2**.

We then investigated the absolute configuration of the aglycone and fucose moieties of **1**, since **1** was available in good quantity and not acetylated. It should be noted that the occurrence of an antipode of pseudopterosin aglycone was reported in pseudopterosins K and L (1*S*,3*R*,4*S*,7*R*-aglycone, compared to an usual 1*R*,3*S*,4*R*,7*S*-aglycone).[2] For this purpose, **1** was benzylated and the resulting 9-benzyl ether derivative was hydrolyzed under acidic conditions to give the aglycone 9-benzyl ether (Scheme 1). Fortunately, Lazerwith et al.[11] reported the synthesis of the same ether of the aglycone with known 1*S*,3*S*,4*R*,7*S* absolute configuration together with the NMR and optical data. The NMR data of the aglycone 9-benzyl ether derived from **1** were in



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Scheme 1. Conversion of pseudopterosin-P (**1**) to the C-9 benzyl ether derivative.

Table 2. ^{13}C NMR (500 MHz, $CDCl_3$) spectral data of compounds **1–7**

Carbon No.	1	2	3	4	5	6	7
1	37.3	37.3	37.3	37.3	37.3	37.3	37.3
2	40.2	40.2	40.2	40.1	40.2	40.2	40.2
3	33.9	33.9	33.9	33.9	33.9	33.9	33.9
4	44.6	44.7	44.6	44.7	44.6	44.7	44.7
5	27.8	27.8	27.8	27.8	27.8	27.8	27.8
6	31.7	31.8	31.8	31.9	31.7	31.8	31.8
7	28.4	28.4	28.5	28.6	28.4	28.5	28.5
8	126.8	126.9	127.0	126.7	126.8	126.9	127.1
9	145.2	145.2	145.0	144.5	145.0	145.2	145.0
10	143.2	143.2	143.1	143.0	143.1	143.1	142.9
11	127.8	127.8	127.6	127.3	127.9	127.8	127.6
12	136.6	136.7	136.6	136.6	136.6	136.8	136.7
13	129.2	129.3	129.2	129.8	129.3	129.2	129.2
14	131.3	131.4	131.4	131.2	131.3	131.3	131.4
15	128.1	128.2	128.2	128.4	128.1	128.2	128.2
16	25.4	25.4	25.4	25.4	25.4	25.4	25.5
17	17.5	17.5	17.5	17.5	17.5	17.5	17.5
18	20.1	20.1	20.1	20.0	20.0	20.1	20.1
19	23.3	23.3	23.2	23.1	23.3	23.2	23.2
20	13.5	13.6	13.5	13.7	13.8	13.9	13.8
1′	103.0	103.0	102.8	101.3	103.8	103.1	103.1
2′	70.4	69.5	70.4	72.3	69.5[a]	70.0	68.1
3′	69.6	69.1	74.3	68.8	69.5[a]	68.2	73.3
4′	72.2	73.6	67.7	71.4	69.4[a]	71.5	67.5
5′	67.3	66.3	67.1	67.4	64.0	61.9	63.7
6′	16.2	16.3	16.1	16.1			
Ac		20.8	20.8	21.0		21.1	21.1
		171.9	171.7	170.9		171.3	171.6

Assignments for compound **2** and **6** were based on ^{1}H–^{1}H COSY, DEPT, HMQC and HMBC spectra, while the other compounds were assigned from their analogy and based on ^{1}H–^{1}H COSY and DEPT spectra.

[a] Assignments may be reversed.

excellent agreement with those reported.[11] This unequivocally determined the relative stereochemistry at the chiral centers of **1**. Further, the sign and magnitude of the α value for the ether were similar to the reported values, thus establishing the absolute configuration of the aglycone as 1*S*,3*S*,4*R*,7*S*. Conversion of **1** to the known benzyl ether also proved the position of glycosylation.

Fucose was identified by TLC in the aqueous phase of the above acidic hydrolysis. Chirality of the fucose sample was analyzed by the method of Hara et al.[12] GLC analysis of the trimethylsilyl ether of the corresponding methyl 2-(polyhydroxyalkyl)-thiazolidine-4(*R*)-carboxylate derivative revealed that the fucose is in L-form. The results agree with earlier findings in which fucose-bearing pseudopterosins utilize the L-form of fucose.[2,3,11] The structure of compound **1** was, therefore, established to be as shown in Figure 1, which depicts the correct absolute configuration.

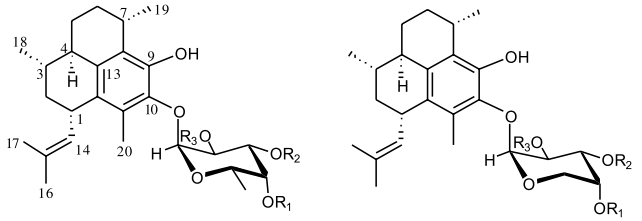

Figure 1. New pseudopterosins isolated from *Pseudopterogorgia elisabethae* from Providencia island.

Pseudopterosin Q (**2**) showed a molecular ion at *m*/*z* 488 and intense fragment ions at *m*/*z* 300 and 244 in EI-MS. The former fragment ion corresponds to the pseudopterosin aglycone, suggesting a loss (188 mass unit) of a monoacetylated deoxyhexose. The ion at *m*/*z* 244 could be due to a loss of an isopropylidene unit from the aglycone. The molecular formula of **2** was established as $C_{28}H_{40}O_7$ by HREIMS. The general characteristics of the UV and NMR data (Tables 1 and 2) suggested that **2** belongs to the pseudopterosin family too. The ^{1}H and ^{13}C NMR spectra of **2** resembled those of **1**, but with an additional signal for an acetyl group. It is obvious from the similarity of the NMR data for the aglycone part of **1** and **2** that compound **2** has the aglycone with the same stereochemistry as in compound **1**.

The ^{1}H NMR spectrum of **2** exhibited signals of an anomeric proton (δ 5.14), a doublet methyl assignable to H_3-6′ (δ_H 1.17) and an acetyl methyl (δ 2.19) along with four oxymethine proton signals for the sugar moiety. The anomeric proton was coupled to H-2′ (δ 4.04) with J=3.8 Hz, which in turn coupled to H-3′ (δ 4.35) with J=10.1 Hz. H-3′ further coupled to H-4′ (δ 5.21) with J=3.3 Hz. The downfield shift of H-4′ evidenced that the acetoxy group was attached to C-4 of the sugar. The large coupling constant between H-2′ and H-3′ indicated axial–axial relationships for these protons, while H-1′ and H-4′ must bear equatorial orientation. These data established an α-glycosidic linkage. H-5′ (δ 4.55, q, J=6.6 Hz), coupled to H_3-6, was sharpened by a decoupling experiment irradiating H-4′, although the J value between H-4′ and H-5′ was nearly zero. Further, an NOE correlation was observed from H-3′ to H-5′, indicating an axial orientation of H-5′. Thus, the sugar moiety was unambiguously established as 4-*O*-acetyl-α-L-fucopyranoside (L configuration of the sugar was assigned by converting **2** to peracetylated derivative (vide infra)). The ^{13}C NMR signals for the sugar, assigned by HMQC spectrum, were in good agreement with those of pseudopterosin J which has an 4-*O*-acetyl-α-fucopyranoside moiety.[2] Finally, the sugar was linked to the C-10 position on the basis of an HMBC correlation from the anomeric proton to C-10 (δ_C 143.2). The structure of compound **2** was established to be as shown in Figure 1, which depicts the correct absolute configuration. The ^{13}C signals were completely assigned with the aid of the HMBC spectrum (Fig. 2). Pseudopterosin-Q is a regioisomer of pseudopterosin-J[2] which is glycosylated at C-9. Originally assigned 1*R*,3*S*,4*R*,7*R* stereochemistry of pseudopterosin-J was revised to 1*S*,3*S*,4*R*,7*S* by synthetic work.[11]

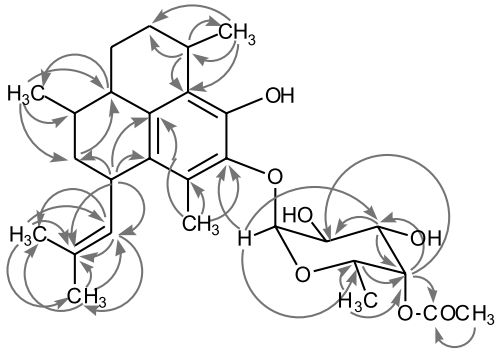

Figure 2. HMBC correlations from H to C for pseudopterosin-Q (**2**).

Pseudopterosin-R (**3**) showed a molecular ion at *m*/*z* 488 and intense fragment ions at *m*/*z* 300 and 244 in EI-MS. The molecular formula, $C_{28}H_{40}O_7$, was deduced from HREIMS. Analysis of the ^{1}H and ^{13}C NMR data (Tables 1 and 2) indicated that the aglycone structure of **3** is identical to that of **2**. It became also clear from ^{13}C NMR data that the C-10 phenol is glycosidated. Compound **3** showed an anomeric proton at δ 5.18 (d) which was coupled to H-2′ (δ 4.30) with J=3.0 Hz. The latter was coupled to H-3′ (δ 5.29) with J=10.4 Hz, which was then coupled to H-4′ (δ 4.06) with J=3.0 Hz. H-5′ (δ 4.58, q, 6.6 Hz) was coupled to a doublet methyl at δ 1.33. $J_{H\text{-}4',H\text{-}5'}$ value was nearly zero. The acetyl methyl signal resonated at δ 2.21. These data established that the sugar moiety at C-10 of **3** is 3-*O*-acetyl-α-fucopyranoside. Chirality of 3-*O*-acetyl-fucose was determined to be L, since **3** and **1** furnished the same peracetate (vide infra). Hence, the structure of **3** was established to be as shown in Figure 1. Pseudopterosin-R is a regioisomer of pseudopterosin-I[2] which is glycosylated at C-9 (initially reported 1*R*,3*S*,4*R*,7*R* configuration was revised to 1*S*,3*S*,4*R*,7*S*[11]).

Pseudopterosin-S (**4**) showed a molecular ion at *m*/*z* 488 in EI-MS and its molecular formula was determined to be $C_{28}H_{40}O_7$ by HREIMS. The NMR data revealed that compound **4** is an isomer of **2** and **3** in terms of the position of the acetyl group. Signals of an anomeric proton, a doublet methyl and acetyl methyl were observed at δ 5.12

(d, J=3.7 Hz), 1.39 and 2.23, in that order. The H–H COSY spectrum allowed us to connect oxymethine protons to form the network: H-1′–H-2′ (δ 5.24, dd, J=10.4, 3.7 Hz)–H-3′ (δ 4.26, dd, J=10.4, 3.2 Hz)–H-4′ (δ 3.97, J=3.2 Hz). H-5′ (δ 4.56, q, J=6.6 Hz) was coupled to the methyl doublet. It is therefore clear that the sugar moiety at C-10 of **4** is 2-*O*-acetyl-α-L-fucopyranoside (L configuration of the sugar was assigned by converting **3** to peracetylated derivative (vide infra)). Hence, compound **4** was elucidated to be as shown in Figure 1. Pseudopterosin-S is a regioisomer of pseudopterosin-H[2] which is glycosylated at C-9 (initially assigned 1*R*,3*S*,4*R*,7*R* configuration was revised to 1*S*,3*S*,4*R*,7*S*[11]).

Pseudopterosin-T (**5**) showed a molecular ion peak at *m*/*z* 432 and intense fragment ions at *m*/*z* 300 and 244. The loss of 132 mass units suggested the presence of a pentose. Its molecular formula, $C_{25}H_{36}O_6$, was determined by HREIMS. Comparison of the NMR data of **5** with those of **1** indicated that **5** has the same aglycone as in **1**, but the structure of the sugar moiety substituted at C-10 is different from **1**. The ^{1}H NMR spectrum of **5** exhibited an anomeric proton at δ 5.10 in addition to the five signals assignable to the sugar moiety. The H–H COSY spectrum correlated these signals: H-1′ (d, J=2.5 Hz)–H-2′ (δ 4.17, br d, J=7.3 Hz)–H-3′ (δ 4.12, br d, J=7.3 Hz)–H-4′ (δ 4.08, br s)–H-5′a (δ 4.25, d, J=12.5 Hz)/H-5′b (δ 3.78, d, J=12.5 Hz). These data clearly indicated that H-2′ and H-3′ have an axial orientation while H-1′ and H-4′ must take an equatorial position and that the anomeric configuration is β. The data further indicated that sugar is β-arabinopyranoside. In order to establish the chirality of arabinose, **5** was subjected to acidic hydrolysis. Arabinose was identified by TLC in the hydrolysate. Analysis of the sample in the same manner as described for fucose revealed that the arabinose is in D-form. Hence, the structure of **5** was established to be as shown in Figure 1.

Pseudopterosin-U (**6**) showed a molecular ion at *m*/*z* 474 and intense fragment ions at *m*/*z* 300 and 244. The loss of 174 mass units could be due to a mono-acetylated pentose. The molecular formula of **6** was determined to be $C_{27}H_{38}O_7$ by HREIMS. Comparison of the NMR data of **6** and **5** indicated that **6** is a mono-acetyl derivative in the sugar moiety of **5**.

The ^{1}H signals for the sugar moiety of **6** were correlated by H–H COSY spectrum: H-1′ (5.18, d, J=3.6 Hz)–H-2′ (δ 4.10, dd, J=9.9, 3.6 Hz)–H-3′ (δ 4.32, dd, J=9.9, 3.4 Hz)–H-4′ (δ 5.24, m)–H-5′a (δ 4.36, br d, J=13.0 Hz)/H-5′b (δ 3.89, dd, J=13.0, 1.9 Hz). These data clearly indicated that sugar is 4-*O*-acetyl-β-D-arabinopyranoside. D configuration of the sugar was assigned by converting **6** to peracetylated derivative (vide infra). HMBC correlations (Fig. 3) corroborated the sugar structure and C-10 substitution of the sugar. Hence, the structure of compound **6** was established to be as shown in Figure 1.

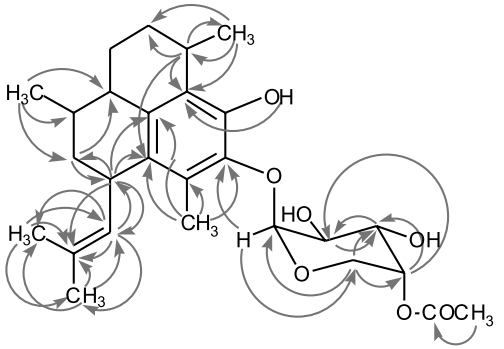

Figure 3. HMBC correlations from H to C for pseudopterosin-U (**6**).

Pseudopterosin-V (**7**) had the same molecular formula ($C_{27}H_{38}O_7$) as for **6**, and the mass spectral pattern was essentially identical to that of **6**. These data, together with ^{1}H NMR data, indicated that **7** is an isomer in terms of the position of acetyl group. The H–H COSY spectrum of **7** showed coupling networks: H-1′ (δ 5.22)–H-2′ (δ 4.33)–H-3′ (δ 5.31)–H-4′ (δ 4.27)–H-5′a (δ 4.42)/H-5′b (δ 3.87). These data clearly indicated that the sugar structure is 3-*O*-acetyl-β-D-arabinopyranoside. D configuration of the sugar was assigned by converting **6** to peracetylated derivative (vide infra). Hence, the structure of **7** was established to be as depicted in Figure 1.

It should be mentioned that Jacobs et al. reported in their patent the isolation of pseudopterosins M, N and O,[13] which are listed in SciFinder as 2-*O*-acetyl-xyloside, 3-*O*-acetyl-xyloside and 4-*O*-acetyl-xyloside at C-10 of 1*R**,3*S**,4*R**,7*S**-aglycone. They recently published details of these compounds, reporting that pseudopterosins M, N and O are acetyl-arabinoside derivatives (the structures shown in the paper are not acetyl-arabinoside but acetyl-xyloside derivatives).[3] Our ^{1}H and ^{13}C NMR data for compounds **6** and **7** are not consistent with the values reported for pseudopterosins M and O.[14]

Compounds **1**–**4** yielded a common peracetylated derivative upon acetylation, which secured the stereochemical (absolute configuration) identity for the aglycone and sugar moieties (L-fucose derivatives) among the four pseudopterosins. The ^{1}H NMR spectrum of the tetra-acetate showed a unique pattern due to the presence of two conformers as illustrated in Figure 4. When recorded at 20 °C, the spectrum showed two sets (ca. 45:55 ratio) of signals in some peaks which might correspond to two conformers. For example, the signal for H-7 was clearly observed at δ 2.70 and δ 3.18 as broad peaks. When measured at 60 °C,[15] the two H-7 signals turned to one very broad signal, and one of the acetate signals was similarly very broad, suggesting that the two conformers were not rapidly interchanged at this temperature. Compounds **5**–**7** furnished the other common peracetylated derivative, confirming the absolute stereochemistry of the aglycone and sugar moieties (D-arabinose derivatives). When the ^{1}H NMR spectrum of the acetate was recorded at 20 °C, the signal for H-7 appeared very broad around at δ 2.8–3.1, also the H_3-19 and one of the acetates H_3 were not clear due to their broad and complex signals. At 60 °C, the spectrum became clearer except for the some broadness of H-7 (Fig. 4). The 9-benzyl ether of pseudopterosin-P (see Scheme 1) did not show such broadening of the ^{1}H NMR signals. It is, therefore, conceivable that these ^{1}H NMR behaviors are due to restricted rotation of the glycosidic bond caused by acetylation of the C-10 hydroxyl as well as the hydroxyl groups at the sugar moiety. Furthermore, higher energy

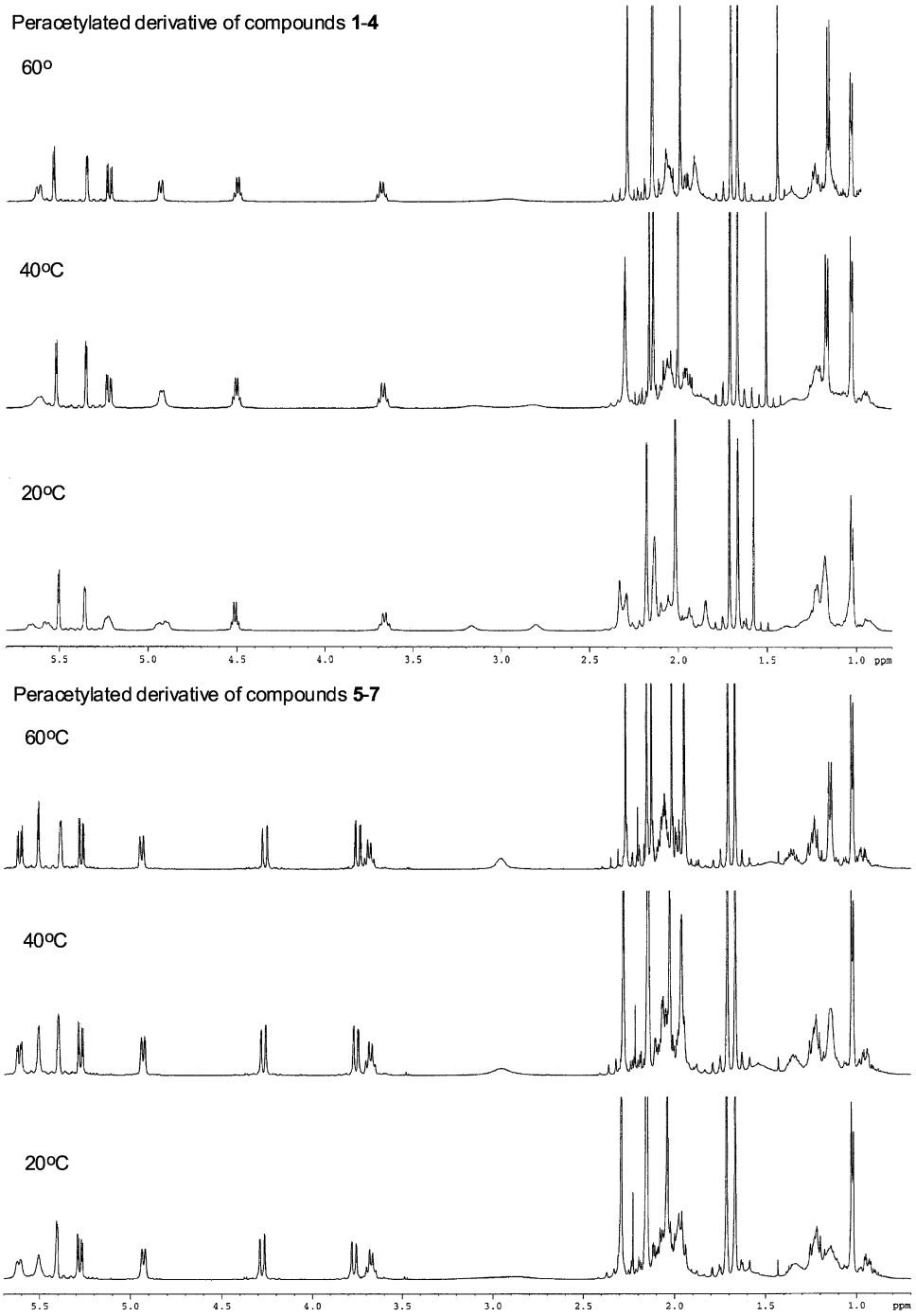

Figure 4. ^{1}H NMR spectra of the peracetylated derivatives of compounds **1**–**4** and of compounds **5**–**7**, at different temperature.

barrier for the rotation of the fucose derivative, compared to that of the arabinose derivative, allowed us to detect two distinct conformers at 20 °C.

Cumulative NMR data for pseudopterosins including the present study provided a simple clue to differentiate C-10 glycosylation from C-9 glycosylation. The chemical shift for C-11 in ^{13}C NMR spectra showed the most diagnostic difference: C-11 appears at δ 121–122 for C-9 glycosylated compounds, whereas it resonates at δ 126–127 for C-10 glycosylated pseudopterosins. Fortunately, there are no disturbing ^{13}C signals in this area in pseudopterosin molecules, and this rule seems to be applicable, irrespective of C-1 stereochemistry of the aglycone.

In addition to the new pseudopterosins reported in this paper, new *seco*-type pseudopterosins were isolated as minor constituents. Further isolation and structure analysis of these compounds are in progress in our laboratory.

Our preliminary results in the neutrophil degranulation inhibition assay have revealed interesting activity of the new pseudopterosins reported here, but varying effects in neutrophil activation or inhibition depending on

concentration tested. Therefore, determination of antiinflammatory activity will be matter of further research and results will be published elsewhere.

3. Experimental

3.1. General

Optical rotations were measured on a JASCO DIP-360 polarimeter. UV spectra were recorded on a Shimadzu UV-1600PC spectrophotometer. ^{1}H NMR and ^{13}C NMR (one- and two-dimensional) spectra were recorded on a Bruker DRX500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer in $CDCl_3$ solution. ^{1}H chemical shifts are expressed with tetramethylsilane as an internal standard ($\delta=0.00$), while ^{13}C chemical shifts are referenced to the solvent signal ($\delta=77.0$). EI-MS and HREIMS were obtained on a JEOL JMS-700 spectrometer. HPLC-MS on APCI mode was carried out on a Shimadzu QP-8000α spectrometer with a Thermo Hypersil-Keystone RP-18 (100×2 mm i.d., 3 μm) column. Preparative HPLC was conducted with a Merck-Hitachi instrument with a UV/VIS L-4250 detector (detected at 230 nm) using a Nucleosil 120 10 C-18 (300×8 mm i.d., 10 μm) column with a 30 min gradient of acetonitrile–water (70–100%) to 100% acetonitrile as mobile phase at a flow rate of 1 ml/min. Final HPLC purification was performed with a Shimadzu LC-6A apparatus equipped with a UV detector (detected at 230 nm) under a Shimadzu Shim-Pack CLC-ODS (15×6 mm i.d., 5 μm) using MeOH/water (9:1) as mobile phase at a flow rate of 1 ml/min. The following adsorbents were used for purification: column chromatography, Merck Kieselgel 60; preparative TLC, Merck Kieselgel 60 F_{254}. TLC plates were visualized by dipping with 5% phosphomolybdic acid in EtOH followed by heating.

3.2. Animal material

Fragments of several *Pseudopterogorgia elisabethae* colonies were collected by SCUBA at a range depth of 20–30 m at various sites around the island of Providencia. Sample collection never implied removing whole colonies, only a terminal fragment of each individual colony was cut off the main gorgonian axis with sharp scissors. Gorgonian fragments were air-dried and stored in the freezer. Samples were kept frozen until the moment of extraction. Animals were identified as *Pseudopterogorgia elisabethae* by M. Puyana, and voucher specimens were deposited at the invertebrate collection of Museo de Historia Natural Marina Colombiano (MHNMC) at Instituto de Investigaciones Marinas de Punta de Betín (INVEMAR), coded as INV CNI 1612, INV CNI 1613 and INV CNI 1614.

3.3. Extraction and separation of pseudopterosins

Dried gorgonian tissue (10 g) were repeatedly extracted with a CH_2Cl_2/MeOH (1:1) mixture. The resultant extract was filtered and concentrated by rotary evaporation obtaining a dark green oily extract (4 g). This crude extract was subjected to silica gel column chromatography using CH_2Cl_2 and EtOAc mixtures of increasing polarity, and finally pure EtOAc, to yield eight fractions. Pseudopterosins were present, as shown by HPLC-MS in APCI mode, in fraction 6 which eluted with EtOAc/CH_2Cl_2 (6:4) and in fraction 8 which eluted with EtOAc. Fraction 6 was subjected first to preparative HPLC using a Nucleosil 120 10 C-18 column with a solvent gradient of acetonitrile–water to yield pure compounds **2** (6 mg), **3** (2 mg), **4** (1.5 mg), **6** (4.5 mg) and **7** (1.5 mg). On the other hand, fraction 8 was subjected to preparative HPLC, as mentioned above, and then for final purification to HPLC on a Shimadzu Shim-Pack CLC-ODS with MeO–H_2O as solvent system to yield compounds **1** (5 mg) and **5** (6 mg) and pseudopterosins G (4 mg), and K (7 mg). Structures of the known three compounds were determined by comparison of the spectral data with reported values.[2,4]

3.3.1. Pseudopterosin P (1). White powder; $[\alpha]_D^{25}$ −29° (*c*, 0.52, MeOH); UV λ_{max} (MeOH) 213 (ε 24,300), 232 (shoulder), 276 (shoulder), 285 (ε 1400) nm; EI-MS *m/z* (relative intensity): 446 (M^+, 2), 300 (4.7), 285 (8), 244 (100), 229 (78); HREIMS *m/z*: 446.2669 (M^+), $C_{26}H_{38}O_6$ requires 446.2668; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.2. Pseudopterosin Q (2). White powder; $[\alpha]_D^{25}$ −53° (*c*, 0.56, MeOH); UV λ_{max} (MeOH) 214 (ε 23,700), 232 (shoulder), 276 (shoulder), 285 (ε 1670) nm; EI-MS *m/z* (relative intensity): 488 (M^+, 8), 300 (71), 285 (9), 244 (100), 229 (38); HREIMS 488.2762 (M^+), $C_{28}H_{40}O_7$ requires 488.2774; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.3. Pseudopterosin R (3). White powder; $[\alpha]_D^{25}$ −34° (*c*, 0.28, MeOH); UV λ_{max} (MeOH) 208 (ε 25,900), 234 (shoulder), 276 (shoulder), 285 (ε 1150) nm; EI-MS *m/z* (relative intensity): 488 (M^+, 2), 300 (40), 285 (10), 244 (100), 229 (56); HREIMS *m/z*: 488.2779 (M^+), $C_{28}H_{40}O_7$ requires 488.2774; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.4. Pseudopterosin S (4). White powder; $[\alpha]_D^{25}$ −48° (*c*, 0.18, MeOH); UV λ_{max} (MeOH) 208 (ε 20,500), 232 (shoulder), 276 (shoulder), 284 (ε 1200) nm; EI-MS *m/z* (relative intensity): 488 (M^+, 1), 300 (30), 285 (7), 244 (100), 229 (48); HREIMS *m/z*: 488.2773 (M^+), $C_{28}H_{40}O_7$ requires 488.2774; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.5. Pseudopterosin T (5). White powder; $[\alpha]_D^{25}$ −38° (*c*, 0.89, MeOH); UV λ_{max} (MeOH) 212 (ε 15,100), 232 (shoulder), 276 (shoulder), 285 (ε 1770) nm; EI-MS *m/z* (relative intensity): 432 (M^+, 22), 300 (94), 285 (32), 244 (100), 229 (88); HREIMS *m/z*: 432.2544 (M^+), $C_{25}H_{36}O_6$ requires 432.2512; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.6. Pseudopterosin U (6). White powder; $[\alpha]_D^{25}$ −90° (*c*, 0.88, MeOH); UV λ_{max} (MeOH) 211 (ε 21,900), 232 (shoulder), 276 (shoulder), 285 (ε 2020) nm; EI-MS *m/z* (relative intensity): 474 (M^+, 13), 300 (91), 285 (11), 244 (100), 229 (32); HREIMS *m/z*: 474.2626 (M^+), $C_{27}H_{38}O_7$ requires 474.2618; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.3.7. Pseudopterosin V (7). White powder; $[\alpha]_D^{25}$ −63°

(*c*, 0.31, MeOH); UV λ_{max} (MeOH) 207 (ε 21,100), 232 (shoulder), 274 (shoulder), 285 (ε 2130) nm; EI-MS *m/z* (relative intensity): 474 (M^+, 15), 300 (91), 285 (8), 244 (92), 229 (13); HREIMS *m/z*: 474.2582 (M^+), $C_{27}H_{38}O_7$ requires 474.2618; ^{1}H NMR: see Table 1; ^{13}C NMR: see Table 2.

3.4. Conversion of Pseudopterosin P (1) to the C-9 benzyl ether derivative

Potassium carbonate (8.8 mg) was added to a solution of compound **1** (8 mg, combined amount from two extraction processes) in dry acetone (0.5 ml). The mixture was stirred at room temperature under nitrogen for 10 min. Benzyl bromide (5.0 µl) was added to this suspension and the mixture was heated at reflux for 7 h. Solvent was removed by flushing nitrogen and the residue was partitioned between $CHCl_3$ and water. The water layer was washed with $CHCl_3$ once more, and the combined $CHCl_3$ layer was dried over Na_2SO_4 and concentrated to dryness. The crude benzyl ether (8 mg) was dissolved in MeOH (0.5 ml) and 3 N-HCl (0.5 ml) and the solution was allowed to react at 50 °C under nitrogen for 3 h. The solution was cooled to room temperature, diluted with water, and extracted with $CHCl_3$ (3×10 ml). The $CHCl_3$ layer was washed with 5% aq $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated to give a crude aglycone benzyl ether, which was chromatographed on silica gel with hexane/ether (10:1) to furnish pure aglycone benzyl ether (3 mg). $[\alpha]_D = +83$ (*c*, 0.24, $CHCl_3$) [lit. +103[11]]; ^{1}H NMR δ: 0.97, 1.03 (d, 3H), 1.25 (m, 2H), 1.34 (d, 3H), 1.36 (m, 1H), 1.67 (s, 3H), 1.74 (s, 3H), 2.01 (m, 1H), 2.06 (s, 3H), 2.10 (m, 3H), 3.24 (sextet, J=7.3 Hz, 1H), 3.74 (m, 1H), 4.73 (d, J=11.2 Hz, 1H), 4.97 (d, J=11.2 Hz, 2H), 5.51 (s, 1H), 7.42 (m, 5H); ^{13}C NMR δ: 12.1, 17.7, 20.1, 23.8, 25.6, 27.8, 29.3, 31.6, 36.4, 37.1, 40.2, 43.8, 75.3, 121.0, 127.9, 128.3, 128.5, 128.7, 131.0, 131.2, 131.8, 135.1, 137.3, 142.3, 145.3. These data were in good agreement with reported values.[11]

3.5. Analysis of the sugar portion of Pseudopterosins P (1) and T (5)

The water layer of the acidic treatment of the C-9 benzyl ether of compound **1** was freeze-dried. Fucose was identified by TLC (CH_2Cl_2/MeOH/H_2O, 8:7:1 and visualized with *p*-anisaldehyde reagent) analysis of the residue. Chirality of the sugar was determined according to the protocol of Hara et al.[12] To the dried sugar sample dissolved in pyridine (0.2 ml) was added L-cysteine methyl ester hydrochloride (2 mg), and the mixture was allowed to react at 60 °C for 1.5 h. The solvent was evaporated by flushing nitrogen and the residue was treated with hexamethyldisilazane–trimethylchlorosilane (HMDS–TMCS) (0.1 ml) at 60 °C for 1 h. The mixture was partitioned between hexane (0.3 ml) and water (0.3 ml) and an aliquot of the hexane layer was injected to GC [column, DB-1, 0.25 mm×30 m, oven temp 200 °C]. The derivatives from D-fucose and L-fucose had retention times of 13.4 and 15.2 min, respectively, and the sample from compound **1** eluted at 15.2 min.

Compound **5** (4 mg) was hydrolyzed in MeOH (0.5 ml) and 3 N-HCl (0.5 ml) at 50 °C under nitrogen for 3 h. The mixture was diluted with chloroform and water. The water layer was washed with chloroform once more and then lyophilized. TLC analysis of the residue indicated the presence of arabinose. Chirality of the sugar was examined as described for fucose. Retention times of the D- and L-arabinose derivatives were 11.5 and 10.4 min in the same GC conditions as described above. The derivative of compound **5** was detected at 11.5 min.

3.5.1. Conversion of compounds 1–4 and compounds 5–7 to the peracetylated derivatives. Each compound (1–2 mg) was treated with pyridine (40 µl) and acetic anhydride (20 µl) at room temperature overnight. Addition of methanol followed by evaporation of the solvent gave an oily residue, which was partitioned with ether and water. The ether layer was washed with 2 N-HCl, satd $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated and analyzed by ^{1}H NMR. The peracetylated derivatives of compounds **1**–**4** showed identical behavior on TLC (hexane/EtOAc, 4:1). ^{1}H NMR (recorded at 60 °C) δ: 1.03 (d, J=7.0 Hz, H_3-18), 1.16 (d, J=6.5 Hz, H_3-19 and H_3-6′), 1.67 (d, J=1.0 Hz, H_3-16), 1.70 (d, J=1.1 Hz, H_3-17), 1.90 (broad, Ac), 1.99 (s, Ac), 2.146 (s, Ac), 2.151 (s, Ac), 2.29 (s, H_3-20), 2.96 (very broad, H-7), 3.68 (q-like, J=8.5 Hz, H-1), 4.50 (q-like, J=6.6 Hz, H-5′), 4.93 (br d, J=8.9 Hz, H-14), 5.20 (dd, J=10.9, 3.4 Hz, H-2′), 5.35 (d, J=3.3 Hz, H-4′), 5.54 (d, J=3.4 Hz, H-1′), 5.62 (br d, J=10.9 Hz, H-3′). HRFABMS *m/z*: 615.3156 (MH^+), $C_{34}H_{47}O_{10}$ requires 615.3169.

Compounds **5**–**7** were similarly converted to the peracetylated derivatives. Identity of them was confirmed by TLC (hexane/EtOAc 4:1) and ^{1}H NMR. ^{1}H NMR (recorded at 60 °C) δ: 1.03 (d, J=5.9 Hz, H_3-18), 1.15 (d, J=6.8 Hz, H_3-19), 1.67 (d, J=1.0 Hz, H_3-16), 1.70 (d, J=1.1 Hz, H_3-17), 1.95 (s, Ac), 2.02 (s, Ac), 2.13 (s, Ac), 2.15 (s, Ac), 2.27 (s, H_3-20), 2.96 (br, H-7), 3.69 (q-like, J=8.7 Hz, H-1), 3.75 (dd, J=14.2, 2.3 Hz, H-5a), 4.27 (dd, J=14.2, 1.5 Hz, H-5b), 4.94 (d, J=9.1 Hz, H-14), 5.28 (dd, J=10.6, 3.2 Hz, H-2′), 5.39 (m, H-4′), 5.51 (d, J=3.2 Hz, H-1′), 5.61 (dd, J=10.5, 3.5 Hz, H-3′). HRFABMS *m/z*: 623.2864 (MNa^+), $C_{33}H_{44}O_{10}Na$ requires 623.2832.

Acknowledgements

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14. Direct comparison of compounds **6** and **7** with pseudopterosins M and O were not possible, since authentic samples were not available to us.
15. Look and Fenical (Ref. 4) reported on the ^{1}H NMR measurement of *seco*-pseudopterosin peracetate derivatives at 60 °C ($CDCl_3$), probably due to the broadening of the signals at room temperature. Their results may rule out the possibility that the presently observed two conformers are associated with the aglycone moiety.

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Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones skeleton via intramolecular electrophilic cyclization

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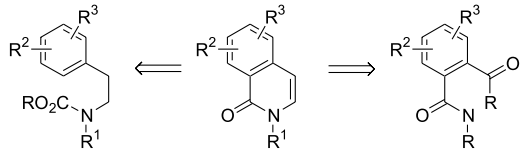
Abstract—An original alternative approach to isoquinolines based on the installation of a benzene nucleus on a performed heterocyclic ring. Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones via intramolecular electrophilic cyclization of 3,4-disubstituted lactams is reported.

1. Introduction

The isoquinolone subunit is one of the most important pharmacophores that is widely found in biologically active molecules[1] and natural products.[2] This has encouraged the development of a number of approaches for the synthesis of the isoquinoline ring system and related heterocyclic compounds, including isoquinolones. Bischler–Napieralski,[3] Pictet–Spengler,[4] and Pomeranz–Fritsch[5] reactions have been powerful methods for the synthesis of isoquinolines. Other procedures like the Curtius rearrangement of cinnamic acids[6] or methanolysis of 2-alkynylbenzonitriles[7] to isoquinolones ring system were also reported. Although these classical methods have been frequently employed in the synthesis of isoquinoline or isoquinolone alkaloids, an electron-donating group on the aromatic ring was still required, such as alkoxy groups. Relatively strong acidic conditions were employed to cyclize β-phenethylamines or benzamide analog (Scheme 1). The substrates that lack of electron-donating groups often failed to cyclize or gave low yields.[8]



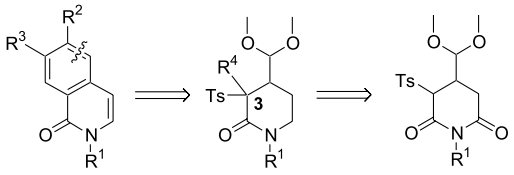
Scheme 1. Preparation of isoquinolone derivatives from β-phenethylamines and benzamide analog.

2. Result and discussion

Recently, we developed a facile stepwise [3+3] annulation reaction between *N*-benzyl-α-sulfonyl acetamide and different α- or β-, aryl- or alkyl- substituted acyclic α,β-unsaturated alkyl esters had lead to the corresponding glutarimides in good yields. This method has been used for the synthesis of natural products and potential biological drugs.[9]

2.1. Retrosynthesis of 3,4-dihydroisoquinoline-1(2*H*)-ones

Continuing our investigation on the application of the synthesis of alkaloids, we disclose our preliminary finding regarding a valuable alternative route for the preparation of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one and 3,4-dihydroisoquinoline-1(2*H*)-one analogues. The key step of the target structure construction was intramolecular electrophilic cyclization of a suitably substituted lactam (Scheme 2).



Scheme 2. Retrosynthesis of 3,4-dihydroisoquinoline-1(2*H*)-ones.

Keywords: Stepwise [3+3] annulation; 3,4-Dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones; Electrophilic cyclization.

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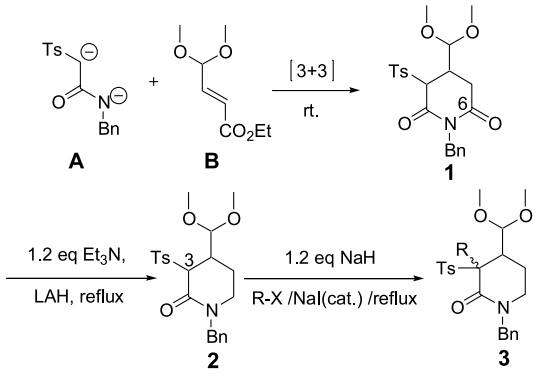
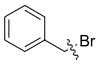
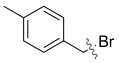
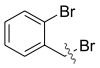
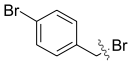
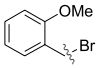
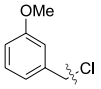
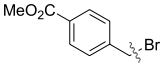
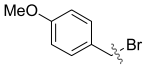
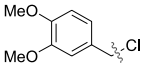
2.2. Synthesis of 3,4-disubstituted-δ-lactam

Our synthetic studies commenced with the construction of glutarimides **1**, which were easily prepared via stepwise [3+3] annulation of *N*-benzyl α-sulfonylacetamide A with α,β-unsaturated ester[9] B, followed by regioselective reduction[10] of C6 carbonyl (Scheme 3). Reaction of δ-lactam **2** with excess NaH and various alkyl halides provided alkylated products **3** (Table 1).



Scheme 3.

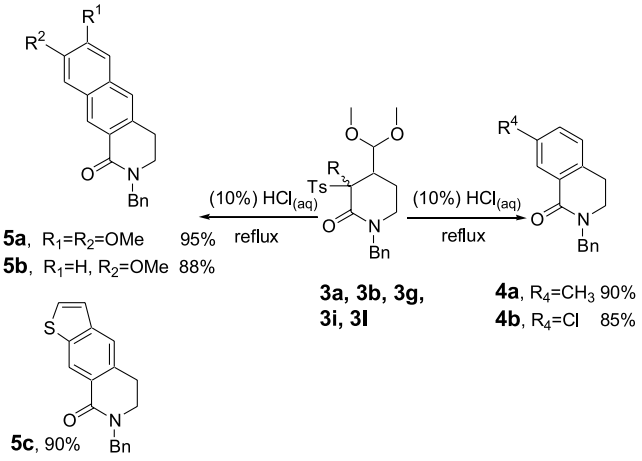
Table 1. Treatment of **2** with 1.5 equiv NaH and various alkyl halides

Entry	Alkyl halides (R–X)	Product (yield, %)
1		**3a** 87
2		**3b** 90
3		**3c** 90
4		**3d** 85
5		**3e** 80
6		**3f** 87
7		**3g** 86[a]
8		**3h** 81
9		**3i** 83
10		**3j** 75[a]
11		**3k** 86
12		**3l** 85

Reagents and conditions: Alkyl halides (1.5 equiv), NaH (1.2 equiv), solvent THF, reflux temperature.
[a] The compound decomposed during the separation on the silica gel. The yield was crude yield.

2.3. Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones

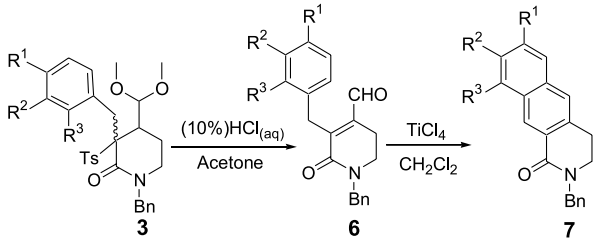
With the desired lactams **3** in hand, we started to focus on the intramolecular electrophilic cyclization. In the case of lactams **3a**, **3b**, **3g**, **3i**, **3l**, we accomplished the cyclization by dissolving the lactams in 10% aqueous hydrochloric acid and acetone followed by heating the resulting solution at reflux temperature. The corresponding 3,4-dihydroisoquinoline-1(2*H*)-ones **4a–b**, and 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones **5a–c** were obtained in good yield (Scheme 4).



Scheme 4. Intramolecular electrophilic cyclization.

For entries 1–7 (R_2=H), only hydrolyzed products **6** were found. However, treatment of compounds **6** with $TiCl_4$[11] in CH_2Cl_2 at reflux temperature for 4 h, the desired 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one derivatives **7a–g** were obtained in good yield (Table 2). The structures of

Table 2. Hydrolysis of acetal and intramolecular electrophiliccyclization



Entry	Alkyl groups				Hydrolyzed product[a] (yield, %)[b]	Cyclized product[c] (yield, %)[b]
		R^1	R^2	R^3		
1	**3c**	H	H	H	**6a** (91)	**7a** (87)
2	**3d**	CH_3	H	H	**6b** (85)	**7b** (85)
3	**3e**	H	H	Br	**6c** (83)	**7c** (81)
4	**3f**	Br	H	H	**6d**[d] (85)	**7d**[d] (80)
5	**3h**	H	H	OMe	**6e** (87)	**7e** (83)
6	**3k**	OMe	H	H	**6f** (87)	**7f**[d] (82)
7	**3j**	CO_2Me	H	H	**6g** (90)	**7g**[d] (60)

[a] All reaction were carried out under reflux temperature of acetone.
[b] Isolated yields.
[c] Dichloromethane.
[d] The structures were confirmed by single crystal X-ray analysis.

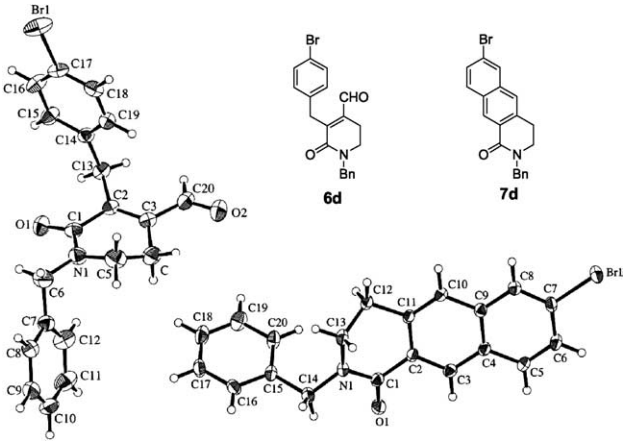
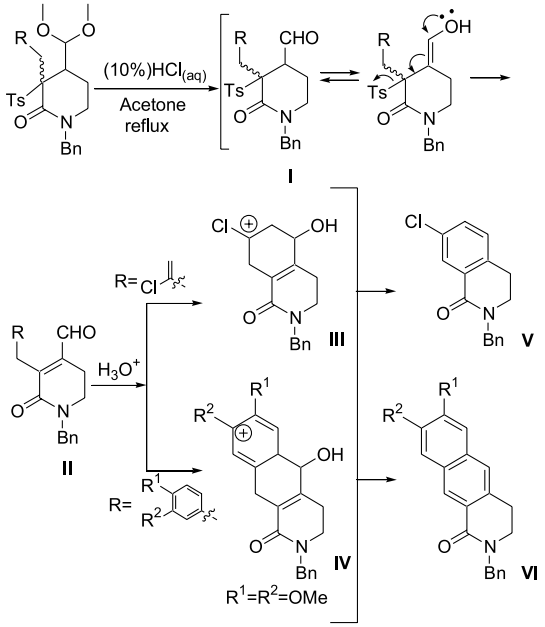


Figure 1. X-ray structures of **6d** and **7d**.

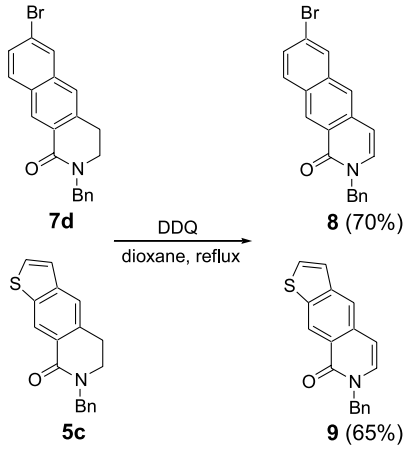
6d and **7d** were confirmed by single crystal X-ray analysis (Fig. 1).[12]

To account for these results, we propose a mechanism which involves (1) hydrolysis of the acetal to aldehyde **I**, (2) elimination of *p*-toluenesulfinic acid to the α?β-unsaturated lactam **II**, (3) intramolecular electrophilic cyclization forming the cation intermediates **III** or **IV** and (4) deprotonation and dehydration (Scheme 5). When R^2 substituents can stabilize the carbon cation either by electron donation or resonance, the target core structure would form easily in acidic aqueous solution. Otherwise, a Lewis acid has to be employed to promote the reaction (Scheme 5).



Scheme 5. Proposed mechanism for cyclization.

Finally, in the presence of DDQ,[13] **5c** and **7d** could be oxidized to the corresponding isoquinolones **8** and **9** in good yields (Scheme 6).



Scheme 6.

3. Conclusion

In conclusion, we developed an easy and alternative approach to synthesize substituted 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one and 3,4-dihydroisoquinoline-1(2*H*)-one derivatives based on the construction of benzene ring on a preformed δ-lactam ring. This method is different from the traditional procedures, which start from a substituted benzene ring to the fused pyridine. It is noteworthy that in entry 7 (Table 2), the cyclization still occurred in the presence of a strong electron-withdrawing group (i.e. $-CO_2Me$) and provided **7g** in reasonable yield. Further application of this methodology in the synthesis of alkaloids is currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were determined with Fargo micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on Varian unity INOVA-500 spectrometer. ^{1}H NMR spectra were recorded at indicated field strength as solution in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are reference to $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded at indicated field strength as solution in $CDCl_3$ unless otherwise indicated. Mass spectra were recorded by Brucker APEX II. Elemental analyses were performed using a Perkin–Elmer 2400(II) CHN analyzer. Infrared spectra (IR) were measured with a Shimadzu IR-408 series FT-IR spectrophotometer. X-ray data were performed by Rigaku AFC6S diffractometer.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous magnesium sulfate before concentration under vacuum.

4.2. Procedure for alkylation of lactam 2

A solution of lactam **2** (500 mg, 1.2 mmol) in THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (96 mg, 2.4 mmol, 60%) in tetrahydrofuran (20 mL). After the reaction mixture was stirred at room temperature for 15 min, alkyl halides were added. The resulting mixtures were refluxed for 3–4 h, quenched with NH_4Cl (1 mL), filtered and concentrated under reduced pressure. The residue was diluted with water (10 ml) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=3:1) afforded the pure products.

4.2.1. 1-Benzyl-4-dimethoxymethyl-3-(2-methyl allyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3a). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J=8.5 Hz, 2H), 7.36–7.24 (m, 7H), 5.16 (d, J=7.0 Hz, 1H),4.9 (d, J=15.0 Hz, 1H), 4.89 (s, 1H), 4.80 (s, 1H), 4.23 (d, J=15.0 Hz, 1H), 3.53 (s, 3H), 3.47–3.43 (m, 1H), 3.42 (s, 3H), 3.27 (dt, J=12.5, 4.5 Hz 1H), 3.19 (d, J=13.0 Hz, 1H), 2.92 (d, J=13.0 Hz, 1H), 2.8 (ddt, J=13.5, 13.0, 7.0 Hz, 1H), 2.59 (ddd, J=13.5, 10.0, 7.5 Hz 1H), 2.41 (s, 3H), 1.99 (ddt, J=14.0, 7.0, 3.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.81, 144.35, 139.92, 136.37, 136.03, 130.66 (2C), 128.64 (2C), 128.69 (2C), 127.92 (2C), 127.42, 117.07, 104.72, 75.2, 56.04, 53.82, 51.49, 46.93, 42.36, 40.74, 23.61, 21.67, 20.88; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{26}H_{33}NO_5S$ 472.2079. Found 472.2106.

4.2.2. 1-Benzyl-3-(2-chloro allyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3b). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J=8.0 Hz, 2H), 7.36–7.25 (m, 7H), 5.33 (d, J=12.5 Hz, 1H), 5.18 (d, J=8.0 Hz, 1H), 4.89 (d, J=15.0 Hz, 1H), 4.23 (d, J=15.0 Hz, 1H), 3.57 (d, J=13.5 Hz, 1H), 3.54 (s, 3H), 3.44–3.4 (m, 2H), 3.39 (s, 3H), 3.32–3.25 (m, 2H), 2.74 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.64 (ddd, J=12.0, 8.0, 2.5 Hz 1H), 2.41 (s, 3H), 1.99 (ddt, J=11.5, 8.0, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.01, 144.65, 136.42, 136.37, 135.63, 130.56 (2C), 128.73 (2C), 128.43 (2C), 127.92 (2C), 127.32, 119.18, 104.63, 74.74, 55.81, 52.78, 51.54, 46.65, 42.23, 42.11, 21.67, 21.27; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{25}H_{31}NO_5SCl$ 492.1533. Found 492.1606.

4.2.3. 1,3-Dibenzyl-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3c). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3014, 1641; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 2H), 7.30–7.25 (m, 7H), 7.19–7.14 (m, 5H), 5.31 (d, J=8.0 Hz, 1H), 4.60 (d, J=14.5 Hz, 1H), 4.48 (d, J=14.5 Hz, 1H), 3.78 (d, J=12.0 Hz, 1H), 3.65 (s, 3H), 3.52 (d, J=12.0 Hz, 1H), 3.35 (s, 3H), 3.22 (dd, J=5.5, 1.5 Hz, 1H), 2.9 (dt, J=12.0, 4.5 Hz, 1H), 2.71 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.43 (s, 3H), 2.44 (ddd, J=13.0, 8.0, 3.0 Hz, 1H), 1.86 (ddt, J=14.0, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.38, 144.50, 136.20, 136.17, 135.33, 131.66 (2C), 130.73 (2C), 128.73 (2C), 128.52 (2C), 128.02 (2C), 127.68 (2C), 127.30, 126.77, 104.86, 77.44, 56.11, 52.88, 51.44, 46.65, 41.33, 38.61, 21.70, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{33}NO_5S$ 508.2079. Found 508.2064.

4.2.4. 1-Benzyl-3-(4-bromobenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3f). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3034, 1656; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=9.0 Hz, 2H), 7.31–7.26 (m, 7H), 7.17 (d, J=9.0 Hz, 2H), 7.12 (d, J=7.0 Hz, 2H), 5.30 (d, J=8.0 Hz, 1H), 4.56 (d, 15.0 Hz, 1H), 4.50 (d, J=15.0 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 3.66 (s, 3H), 3.42 (d, J=12.5 Hz, 1H), 3.37 (s, 3H), 3.21 (dd, J=8.0, 1.5 Hz, 1H), 2.89 (dt, J=12.5, 5.0 Hz 1H), 2.71 (ddt, J=13.5, 13.0, 5.0 Hz 1H), 2.46–2.41 (m, 1H), 2.44 (s, 3H), 1.88 (ddt, J=14.0, 12.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.13, 144.68, 136.04, 135.91, 134.37, 133.54 (2C), 130.11 (2C), 130.74 (2C), 128.80 (2C), 128.58 (2C), 127.62 (2C), 127.42, 120.99, 105.01, 77.17, 56.23, 53.17, 51.54, 46.74, 41.33, 37.91, 21.72, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{32}NO_5SBr$ 586.1185. Found 586.1166.

4.2.5. 1-Benzyl-3-(2-bromobenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3e). 80% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 2H), 7.51 (dd, J=8.0, 1.0 Hz, 1H), 7.40–7.33 (m, 7H), 6.95 (dt, J=7.5, 1.0 Hz, 1H), 6.87 (dt, J=7.5, 1.0 Hz, 1H), 6.61 (d, J=8.0 Hz, 1H), 5.19 (d, J=5.5 Hz, 1H), 4.79 (d, J=14.5 Hz, 1H), 4.61 (d, J=14.5 Hz, 1H), 4.12 (d, J=15.0 Hz, 1H), 3.56–3.53 (m, 1H), 3.50 (d, J=15.0 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.33–3.27 (m, 1H), 2.86 (ddt, J=13.5, 13.0, 6.0 Hz, 1H), 2.51 (ddd, J=13.0, 6.0, 3.0 Hz, 1H), 2.43 (s, 3H), 1.92 (ddt, J=14.0, 6.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.01, 144.75, 136.14, 135.67, 135.58, 133.27, 130.97, 128.91 (2C), 128.83 (2C), 128.67 (2C), 128.52 (2C), 127.72, 127.66, 127.08, 126.25, 104.58, 75.61, 56.03, 55.15, 52.11, 47.07, 42.22, 38.44, 21.68, 20.01; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{32}NO_5SBr$ 586.1185. Found 586.1179.

4.2.6. 1-Benzyl-4-dimethoxymethyl-3-(2-methoxy benzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3h). 81% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3016, 1628; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J=8.0 Hz, 2H), 7.39–7.24 (m, 9H), 7.14 (d, J=2.5 Hz, 1H), 6.69 (d, J=9.0 Hz, 1H), 5.16 (d, J=3.0 Hz, 1H), 4.95 (d, J=14.5 Hz, 1H), 4.35 (d, J=14.5 Hz, 1H), 3.92 (d, J=13.5 Hz, 1H), 3.78 (s, 3H), 3.52 (s, 3H), 3.42 (d, J=14.0 Hz, 1H), 3.38 (s, 3H), 3.37–3.32 (m, 1H), 3.08–3.04 (m, 1H), 2.83 (ddt, J=14.0, 13.5, 6.0 Hz, 1H), 2.42 (s, 3H), 2.27 (dt, J=12.5, 3.5 Hz, 1H), 1.84 (ddt, J=14.0, 6.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.79, 156.8, 144.45, 136.39, 136.29, 133.55, 130.79(2C), 128.7 (2C), 128.64(2C), 128.56 (2C), 128.55, 127.65 (2C), 127.33, 126.22, 112.75, 112.12, 104.39, 57.17, 55.51, 51.31, 46.73, 44.19, 31.54, 21.65, 19.53; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{36}NO_6S$ 538.2185. Found 538.2259.

4.2.7. 1-Benzyl-4-dimethoxymethyl-3-(3-methoxy benzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3i). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3017, 1633; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.32–7.25 (m, 7H), 7.17 (d, J=7.0 Hz, 1H), 7.09 (t, J=8.0 Hz,

1H), 6.9 (s, 1H), 6.73 (d, J=8.0 Hz, 1H), 5.32 (d, J=8.0 Hz, 1H), 4.69 (d, J=14.5 Hz, 1H), 4.45 (d, J=14.5 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.52 (d, J=12.5 Hz, 1H), 3.35 (s, 3H), 3.23 (dd, J=13.0, 5.0 Hz, 1H), 2.93 (dt, J=13.0, 5.0 Hz, 1H) 2.73 (ddt, J=13.5, 13.5, 5.0 Hz, 1H), 2.48 (ddd, J=8.5, 7.5, 2.5 Hz 1H), 2.44 (s, 3H), 1.86 (ddt, J=13.5, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.41, 159.23, 144.45, 136.82, 136.27, 136.13, 130.66 (2C), 128.83, 128.73 (2C), 128.52 (3C), 127.51 (2C), 127.22, 124.01, 116.78, 112.7, 104.63, 56.04, 55.01, 52.68, 51.34, 46.55, 41.23, 38.61, 21.67, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{36}NO_6S$ 538.2185. Found 538.2263.

4.2.8. 4-[1-Benzyl-4-dimethoxymethyl-2-oxo-3-(toluene-4-sulfonyl)piperidin-3-ylmethyl]benzoic acid methyl ester (3j). 75% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3026, 1714, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 2H), 7.55 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 7.32–7.27 (m, 5H), 7.17 (d, J=8.0 Hz, 2H), 5.31 (d, J=8.5 Hz, 1H), 4.65 (d, J=15.0 Hz, 1H), 4.42 (d, J=15.0 Hz, 1H), 3.89 (s, 3H), 3.86 (d, J=12.0 Hz, 1H), 3.66 (s, 3H), 3.54 (d, J=12.0 Hz, 1H), 3.33 (s, 3H), 3.24 (dt, J=5.5, 4.0 Hz, 1H), 2.89 (dt, J=12.5, 5.0 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.44 (s, 3H), 2.32 (ddd, J=11.5, 8.0, 3.0 Hz, 1H), 1.86 (ddt, J=13.5, 8.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.04, 164.18, 144.73, 141.01, 136.05, 135.88, 131.74 (2C), 130.76 (2C), 129.22 (2C), 128.82 (2C), 128.63, 128.59 (2C), 127.65 (2C), 127.45, 104.77, 77.17, 56.17, 52.68, 52.03, 51.53, 46.70, 41.32, 38.55, 21.74, 21.11.; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{31}H_{35}NO_7S$ 566.2134. Found ($M^+ + 1$) 566.2145.

4.2.9. 1-Benzyl-4-dimethoxymethyl-3-(4-methylbenzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3d). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1656, 1223; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=8.0 Hz, 2H), 7.31–7.27 (m, 5H), 7.19 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 5.32 (d, J=7.5 Hz, 1H), 4.62 (d, J=14.5 Hz, 1H), 4.49 (d, J=14.5 Hz, 1H), 3.74 (d, J=12.5 Hz, 1H), 3.66 (s, 3H), 3.48 (d, J=12.5 Hz, 1H), 3.37 (s, 3H), 3.22 (dd, J=5.5, 1.5 Hz, 1H), 2.90 (dt, J=12.5, 4.5 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.46 (ddd, J=13.0, 8.0, 3.0 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 1.87 (ddt, J=14.0, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.42, 144.44, 136.27, 136.24 (2C), 132.09, 131.52 (2C), 130.73 (2C), 128.75 (2C), 128.71 (2C), 128.48 (2C), 127.69 (2C), 127.27, 104.85, 77.48, 56.13, 52.93, 51.40, 46.65, 41.32, 38.21, 21.70, 21.05, 21.00; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{35}NO_5S$ 522.2236. Found ($M^+ + 1$) 522.2261.

4.2.10. 1-Benzyl-3-(3,4-dimethoxybenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3l). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3015, 1640, 1203; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.0 Hz, 2H), 7.33–7.24 (m, 5H), 7.21 (d, J=8.0 Hz, 2H), 6.90 (dd, J=8.0, 2.0 Hz, 1H), 6.86 (d, J=2.0 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 5.32 (d, J=8.0 Hz, 1H), 4.77 (d, J=15.0 Hz, 1H), 4.33 (d, J=15.0 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.72 (d, J=12.0 Hz, 1H), 3.66 (s, 3H), 3.47 (d, J=12.0 Hz, 1H), 3.37 (s, 3H), 3.23 (dd, J=11.0, 4.5 Hz, 1H), 2.93 (dt, J=12.5, 5.0 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.49 (ddd, J=13.0, 7.5, 2.5 Hz, 1H), 2.44 (s, 3H), 1.87 (ddt, J=13.5, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.61, 148.24, 147.73, 144.49, 136.30, 136.09, 130.70 (2C), 128.79 (2C), 128.60 (2C), 127.59, 127.38 (2C), 127.33, 124.17, 114.55, 110.57, 104.89, 77.52, 56.06, 55.68, 55.65, 53.01, 51.28, 46.67, 41.33, 38.19, 21.73, 21.12.; HRMS m/z (ESI, $M^+ + 1$–$C_2H_6O_2$) calcd for $C_{30}H_{35}NO_5S$ 506.2236. Found ($M^+ + 1$) 506.2259.

4.3. Procedure for hydrolysis of lactam 3 to 1,2,3,4-tetrahydroisoquinoline derivatives 4 and 5

To a solution of lactam **3** (400 mg, 0.8 mmol) in acetone (20 mL) was added 10% aqueous HCl (1 mL). The resulting mixture was refluxed for 12 h and then evaporated. The residue was dissolved with dichloromethane and the mixture was basified with 2 N aqueous sodium hydroxide in an ice bath. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, and evaporated to give crude product. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.3.1. 2-Benzyl-7-chloro-3,4-dihydro-2*H*-isoquinolin-1-one (4b). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1656; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J=2.5 Hz, 1H), 7.38 (dd, J=8.0, 2.5 Hz, 1H), 7.36–7.27 (m, 5H), 7.11 (d, J=8.0 Hz, 1H), 4.79 (s, 2H), 3.48 (t, J=6.5 Hz, 2H), 2.90 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.39, 137.10, 136.27, 133.15, 131.62, 130.89, 128.69 (2C), 128.47, 128.35, 128.06 (2C), 127.57, 50.54, 45.20, 27.51; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{16}H_{14}NOCl$ 272.0764. Found 272.0758.

4.3.2. 2-Benzyl-7-methyl-3,4-dihydro-2*H*-isoquinolin-1-one (4a). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.33–7.27 (m, 5H), 7.23 (dd, J=6.5, 1.0 Hz, 1H), 7.05 (d, J=6.5 Hz, 1H), 4.79 (s, 2H), 3.46 (t, J=6.5 Hz, 2H), 2.89 (t, J=6.5 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.81, 137.47, 136.76, 135.05, 132.43, 129.08, 128.81, 128.60 (2C), 128.01 (2C), 127.38, 126.80, 50.45, 45.51, 27.67, 21.06; HRMS m/z (EI, M^+) calcd for $C_{17}H_{17}NO$ 251.1310. Found 251.1316.

4.3.3. 2-Benzyl-7,8-dimethoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (5a). 95% Yield; white solid; mp 189–191 °C; IR ($CHCl_3$, cm^{-1}) 3030, 1653, 1235; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.43 (s, 1H), 7.36–7.28 (m, 5H), 7.22 (s, 1H), 7.06 (s, 1H), 4.85 (s, 2H), 4.01 (s, 3H), 4.01 (s, 3H) 3.53 (t, J=6.5 Hz, 2H), 3.06 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.98, 151.18, 149.49, 137.52, 132.85, 131.15, 128.62 (2C), 128.03 (2C), 127.87, 127.78, 127.39, 125.75, 123.50, 107.34,105.38, 55.92, 55.89, 50.57, 45.72, 28.44; HRMS m/z (EI, M^+) calcd for $C_{22}H_{21}NO_3$ 347.1521. Found 347.1516. Compound **5a** was recrystallized from ethyl acetate.

4.3.4. 2-Benzyl-8-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (5b). 88% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1629, 1494; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.68 (d, J=9.0 Hz, 1H), 7.52 (s, 1H), 7.36–7.18 (m, 7H), 4.58 (s, 2H), 3.93 (s, 3H), 3.53 (t, J=6.3 Hz,

2H), 3.06 (t, J=6.3 Hz, 2H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.00, 158.79, 138.63, 134.48, 131.67, 129.84(2C), 129.59, 129.23(3C), 128.85, 128.62, 126.05, 122.14, 114.93, 107.97, 56.54, 51.78, 47.01, 29.55; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1409.

4.3.5. 7-Benzyl-6,7-dihydro-5*H*-1-thia-7-aza-cyclopenta[*b*]naphthalen-8-one (5c). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.7 (s, 1H), 7.59 (s, 1H), 7.58 (s, 1H), 7.34–7.25 (m, 6H), 4.84 (s, 2H), 3.52 (t, J=6.5 Hz, 2H), 3.05 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.71, 141.95, 138.42, 137.45, 133.78, 130.02, 128.63 (2C), 128.02 (2C), 127.42, 125.93, 123.45, 123.21, 121.26, 50.52, 45.67, 28.55; HRMS *m/z* (EI, M^+) calcd for $C_{18}H_{15}NOS$ 239.0874. Found 239.871.

4.4. Procedure for hydrolysis of lactam 3 to 1-benzyl-3-substituted-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde 6

To a solution of lactam **3** (400 mg, 0.8 mmol) in acetone (20 mL) was added 10% aqueous HCl (1 mL). The resulting mixture was refluxed for 12 h and then evaporated. The residue was dissolved with dichloromethane, and the mixture was basified with 2 N aqueous sodium hydroxide in an ice bath. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, and evaporated to give the crude product. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.4.1. 1,3-Dibenzyl-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6a). 91% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1635, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.31–7.19 (m, 10H), 4.66 (s, 2H), 4.29 (s, 2H), 3.31 (t, J=7.0 Hz, 2H), 2.54 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.43, 164.53, 145.48, 139.08, 138.68, 136.65, 128.77 (2C), 128.70 (2C), 128.50 (2C), 127.89 (2C), 127.63, 126.56, 50.87, 43.96, 30.27, 20.86; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{19}NO_2$ 305.1416. Found 305.3708.

4.4.2. 1-Benzyl-3-(4-methylbenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6b). 85% Yield; mp 126–128 °C; white solid; IR ($CHCl_3$, cm^{-1}) 3022, 1656; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.31–7.10 (m, 9H), 4.65 (s, 2H), 4.23 (s, 2H), 3.30 (t, J=7.0 Hz, 2H), 2.52 (t, J=7.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.52, 164.56, 145.73, 138.89, 136.70, 136.13, 135.60, 129.45 (2C), 128.68 (2C), 128.38 (2C), 127.90 (2C), 127.61, 50.84, 43.95, 29.85, 20.99, 20.84; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_2$ 319.1572. Found 319.1569.

4.4.3. 1-Benzyl-3-(2-bromobenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6c). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.56 (dd, J=8.0, 1.0 Hz, 1H), 7.31–7.20 (m, 7H), 7.11–7.08 (m, 1H), 4.67 (s, 2H), 4.36 (s, 2H), 3.55 (t, J=7.0 Hz, 2H), 2.55 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.42, 164.42, 143.91, 140.04, 138.17, 136.66, 132.99, 130.30, 128.70 (2C), 128.23, 127.92 (2C), 127.67 (2C), 124.25, 50.83, 43.96, 31.06, 21.09; HRMS *m/z* (EI) calcd for $C_{20}H_{18}BrNO_2$ 383.0521. Found (M^+) 383.0518.

4.4.4. 1-Benzyl-3-(4-bromo-benzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6d). 85% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 1655, 1227; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.42 (d, J=8.0 Hz, 2H), 7.31–7.18 (m, 5H), 7.14 (d, J=8.0 Hz, 2H), 4.65 (s, 2H), 4.22 (s, 2H), 3.31 (t, J=7.0 Hz, 2H), 2.54 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.07, 164.32, 144.88, 139.26, 137.62, 136.53, 131.82 (2C), 130.32 (2C), 128.74 (2C), 127.87 (2C), 127.72, 120.52, 50.89, 43.93, 29.81, 20.91; LRMS *m/z* (EI, 30 eV): 383 (M^+, 1%), 354 (2%), 288 (8%), 91 (100%). Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.45; H, 4.61; N, 4.05. Compound **6d** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **6d** were grown by slow diffusion of *n*-hexane into a solution of **6d** in ethyl acetate to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P2_1/n$(#14), a=14.142(3) Å, b=9.276(3) Å, c=19.066(4) Å, β=92.99(2)°, V=179.2(9) Å^3, Z=4, D_{calc}=1.425 g/cm^3, absorption coefficient 22.8 cm^{-1}, F(000)=784, 2θ range (8.8–13.8°).

4.4.5. 1-Benzyl-3-(2-methoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6e). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.36–7.18 (m, 7H), 6.92 (dd, J=0.5, 0.5 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H) 4.65 (s, 2H), 4.25 (s, 2H), 3.76 (s, 3H) 3.24 (t, J=7.0 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.30, 164.73, 157.06, 144.56, 138.18, 136.77, 130.91, 128.56 (2C), 127.88, 127.75 (2C), 127.44, 126.44, 120.67, 110.23, 54.84, 50.72, 43.95, 25.21, 20.72; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_3$ 335.1521. Found 335.1517.

4.4.6. 1-Benzyl-3-(4-methoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6f). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3032, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.30–7.16 (m, 7H), 6.84 (d, J=8.5 Hz, 2H), 4.65 (s, 2H), 4.21 (s, 2H), 3.79 (s, 3H), 3.30 (t, J=7.0 Hz, 2H), 2.52 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.49, 164.58, 158.28, 145.87, 138.75, 136.67, 130.59, 129.57 (2C), 128.70 (2C), 127.88 (2C), 127.63, 114.17 (2C), 55.27, 50.86, 43.98, 29.42, 20.85; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_3$ 335.1521. Found (M^+) 335.1519.

4.4.7. 4-(1-Benzyl-4-formyl-2-oxo-1,2,5,6-tetrahydropyridin-3-ylmethyl)benzoic acid methyl ester (6g). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1683, 1652, 1611; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.97 (dd, J=7.0, 2.0 Hz, 2H), 7.33–7.28 (m, 5H), 7.19 (dd, J=7.0, 2.0 Hz, 2H), 4.65 (s, 2H), 4.33 (s, 2H), 3.91 (s, 3H), 3.32 (t, J=7.0 Hz, 2H), 2.55 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.04, 166.85, 164.30, 144.52, 144.05, 139.58, 136.52, 130.09 (2C), 128.75 (2C), 128.56, 128.52 (2C), 127.90 (2C), 127.74, 52.09, 50.90, 43.92,

30.40, 20.96; HRMS *m/z* (EI, M^+) calcd for $C_{22}H_{21}NO_4$ 363.1471. Found 363.1465.

4.5. Procedure for preparation of 1,2,3,4-tetrahydro-isoquinolone derivatives 7

To solution of lactam **6** (200 mg, 0.66 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (124 mg, 0.66 mmol). The resulting mixture were refluxed for 12 h and then evaporated. The residue was dilute with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.5.1. 2-Benzyl-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7a). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3020, 1662, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.96 (dd, J=8.5, 2.0 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.56 (dd, J=9.0, 2.0 Hz, 1H), 7.50 (s, 1H), 7.38–7.28 (m, 6H), 4.86 (s, 2H), 3.58 (t, J=6.5 Hz, 2H), 3.11 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.34, 137.19, 135.77, 135.58, 130.93, 130.59, 129.47 (2C), 129.16, 128.70 (2C), 128.08 (2C), 127.85, 127.55, 124.20, 122.25, 50.70, 45.48, 28.58; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{17}NO$ 287.1310. Found 287.1315.

4.5.2. 2-Benzyl-7-methyl-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7b). 85% Yield; white solid; mp 123–125 °C; IR ($CHCl_3$, cm^{-1}) 3022, 1656; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.86 (d, J=8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.36–7.30 (m, 6H), 4.86 (s, 2H), 3.53 (t, J=6.5 Hz, 2H), 3.09 (t, J=6.5 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.87, 137.93, 137.42, 135.12, 134.35, 130.41, 129.30, 129.15, 128.64 (2C), 128.27, 128.05 (2C), 127.43, 126.59, 126.01, 124.37, 50.63, 45.65, 28.63, 21.91; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO$ 301.1467. Found 301.1462.

4.5.3. 2-Benzyl-9-bromo-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7c). 81% Yield; white solid; mp 146–148 °C; IR ($CHCl_3$, cm^{-1}) 3022, 1227; ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.76 (dd, J=7.7, 1.0 Hz, 1H), 7.73 (d, J=8.5 Hz, 1H), 7.59 (s, 1H), 7.29–7.37 (m, 6H), 4.87 (s, 2H), 3.56 (t, J=6.0 Hz, 2H), 3.12 (t, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.20, 137.25, 135.97, 135.33, 131.09, 130.01, 128.90, 128.73, 128.69 (2C), 128.11 (2C), 127.53, 126.53, 126.94, 125.71, 124.30, 50.77, 45.46, 28.37; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{16}NOBr$ 365.0415. Found 365.0408.

4.5.4. 2-Benzyl-7-bromo-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7d). 80% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.96 (d, J=2.0 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.56 (dd, J=9.0, 2.0 Hz, 1H), 7.50 (s, 1H), 7.38–7.28 (m, 5H), 4.86 (s, 2H), 3.58 (t, J=6.5 Hz, 2H), 3.11 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.34, 137.19, 135.77, 135.58, 130.93, 130.59, 129.47 (2C), 129.16, 128.70 (2C), 128.08 (2C), 127.85, 127.55, 124.20, 122.25, 50.70, 45.48, 28.58; LRMS *m/z* (EI, 30 eV): 365 (M^+, 20%), 274 (9%), 91 (100%). Anal. Calcd for $C_{20}H_{16}BrNO$: C, 65.59; H, 4.40; N, 3.82. Found: C, 65.45; H, 4.36; N, 4.16. Compound **7d** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7d** were grown by slow diffusion of *n*-hexane into a solution of **7d** in ethyl acetate to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P2_1/c$(#14), a=14.350(3) Å, b=7.859(2) Å, c=14.201(4) Å, β=99.34(2)°, V=1580.4(7) Å^3, Z=4, D_{calc}=1.539 g/cm^3, absorption coefficient 26.12 cm^{-1}, F(000)=744, 2θ range (8.63–14.15°).

4.5.5. 2-Benzyl-9-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7e). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3020,1232; ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.51 (s, 1H), 7.43 (t, J=8.0 Hz, 1H), 7.31–7.25 (m, 6H), 6.01 (dd, J=8.0, 2.5 Hz, 1H), 4.86 (s, 2H), 4.00 (s, 3H), 3.52 (t, J=6.5 Hz, 2H), 3.08 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.82, 156.74, 137.52, 136.40, 135.94, 134.92, 128.61 (2C), 128.25, 128.09 (2C), 127.40, 126.65, 124.62, 124.25, 119.09, 103.74, 55.49, 50.68, 45.62, 28.59; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1418.

4.5.6. 2-Benzyl-7-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7f). 82% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 16215, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.85 (d, J=9.0 Hz, 1H), 7.46 (s, 1H), 7.37–7.26 (m, 5H), 7.14 (dd, J=9.0, 2.5 Hz, 1H), 7.07 (d, J=2.5 Hz, 1H), 4.85 (s, 2H), 3.92 (s, 3H), 3.53 (t, J=6.5 Hz, 2H), 3.08 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.89, 159.30, 137.49, 136.40, 135.02, 130.93, 129.34, 128.63 (2C), 128.06 (2C), 127.65, 127.41, 125.32, 123.85, 118.86, 105.01, 55.32, 50.59, 45.62, 28.67; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1409. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.23; H, 6.39; N, 4.81. Compound **7f** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7f** were grown by slow diffusion of *n*-hexane into a solution of **7f** in ethyl acetate to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group *Pbca*, a=12.0504(16) Å, b=8.0388(11) Å, c=33.425(4) Å, α=90.00°, β=90.00°, γ=90.00°, Z=8, D_{calc}=1.302 g/cm^3, absorption coefficient 0.83 cm^{-1}, F(000)=1344.

4.5.7. 2-Benzyl-1-oxo-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-7-carboxylic acid methyl ester (7g). 60% Yield; yellow solid; mp 147–149 °C; IR ($CHCl_3$, cm^{-1}) 3018, 1721, 1629; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.55 (s, 1H), 8.06 (dd, J=8.5, 1.5 Hz, 1H), 8.01 (d, J=8.5 Hz, 1H), 7.70 (s, 1H), 7.36–7.29 (m, 5H), 4.87 (s, 2H), 3.99 (s, 3H), 3.57 (t, J=6.5 Hz, 2H), 3.13 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.99, 164.21, 137.13, 135.17, 134.17, 133.88, 130.03, 129.58, 129.47, 129.21, 129.14, 128.70 (2C), 128.07 (2C), 127.56, 126.54, 125.26, 52.36, 50.75, 45.50, 28.53; HRMS *m/z* (EI, M^+) calcd for $C_{22}H_{19}NO_3$ 345.1359, found 345.1366. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.20; H, 5.41; N, 4.48. Compound **7g** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7g** were grown by slow diffusion of *n*-hexane into a solution of **7g** in ethyl acetate to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group $P1(\#1)$, $a=8.818(4)$ Å, $b=12.692(4)$ Å, $c=8.517(3)$ Å, $\alpha=107.82(2)°$, $\beta=107.86(3)°$, $\gamma=82.04(3)°$, $V=862.7(5)$ Å^3, $Z=2$, $D_{calc}=1.330$ g/cm^3, absorption coefficient 0.88 cm^{-1}, $F(000)=364$, 2θ range (9.2–17.6°).

4.6. Procedure for preparation of isoquinolone derivatives 8 and 9

To a solution of **5c** (110 mg, 0.30 mmol) in 1,4-dioxane (15 mL) was added DDQ (275 mg, 1.2 mmol). The resulting mixture was refluxed for 24 h and then evaporated. The residue was dilute with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.6.1. 2-Benzyl-7-bromo-2*H*-benzo[*g*]isoquinolin-1-one (8). 70% Yield; white solid; mp 170–172 °C; IR ($CHCl_3$, cm^{-1}) 3029, 1625, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.08 (d, $J=2.0$ Hz, 1H), 7.91 (d, $J=9.0$ Hz, 1H), 7.85 (s, 1H), 7.56 (dd, $J=9.0$, 2.0 Hz, 1H), 7.35–7.29 (m, 5H), 7.03 (d, $J=7.5$ Hz, 1H), 6.58 (d, $J=7.5$ Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.56, 136.77, 136.05, 133.86, 131.13, 130.92, 130.11, 129.54, 129.49, 129.41, 128.84 (2C), 127.96 (2C), 127.89, 124.98, 123.13, 122.66, 106.38, 51.53; HRMS *m/z* (EI, M$^+$) calcd for $C_{20}H_{14}NOBr$ 363.0259. Found 363.0255. Compound **8** was recrystallized from ethyl acetate.

4.6.2. 7-Benzyl-7,8-dihydrothieno[3,2-*g*]isoquinoline-8-one (9). 65% White solid; yield; mp 150–152 °C; IR ($CHCl_3$, cm^{-1}) 3030, 1640; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.95 (s, 1H), 7.68 (d, $J=5.0$ Hz, 1H), 7.42 (d, $J=5.0$ Hz, 1H), 7.35–7.29 (m, 5H), 7.04 (d, $J=7.5$ Hz, 1H), 6.59 (d, $J=7.5$ Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.36, 142.91, 138.74, 137.01, 132.99, 131.31, 129.95, 128.80 (2C), 127.92 (2C), 127.78, 123.35, 123.31, 122.80, 120.00, 106.79, 51.57; HRMS *m/z* (EI, M$^+$) calcd for $C_{18}H_{13}NOS$ 291.0718. Found 291.0712. Compound **9** was recrystallized from ethyl acetate

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Supplementary data

Experimental procedures and photocopies of spectral data for (^{1}H NMR in $CDCl_3$) were supported.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.015.

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Concise synthesis of quinazoline alkaloids, luotonins A and B, and rutaecarpine

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Abstract—The total synthesis of luotonin A was achieved in excellent yield by using a Pd-assisted biaryl coupling reaction of *N*-(bromoquinolinyl)methylquinazolinone with Cy_3P and KOAc. The successive treatment of luotonin A with NBS and aq. $AgNO_3$ gave luotonin B in good yield. Although the Pd-assisted coupling reaction of *N*-(2-bromoindolyl)ethylquinazolinone with Cy_3P and KOAc yielded rutaecarpine in poor yield, *N*-acetate under the same reaction conditions yielded the desired rutaecarpine directly in excellent yield.

1. Introduction

Palladium-assisted aryl–aryl coupling reactions have been used to synthesize many condensed aromatic compounds.[1] Recently, we reported that intramolecular aryl–aryl coupling reactions using Pd reagents were a very versatile way to synthesize polycyclic heteroaromatic compounds, including phenanthridine, benzo[c]phenanthridine, and pyrrolophenanthridine alkaloids.[2] In order to examine the utility of this methodology, we subsequently designed a concise plan for synthesizing luotonins A (**1**) and B (**2**), and rutaecarpine (**3**), as shown in Figure 1; this plan involves the aryl–aryl coupling reaction of 2-bromoaromatic heterocycles-quinazolinone (**A**) to alkaloid (**B**) with a Pd reagent as the key reaction. This paper presents the details of these results.[3]

2. Results and discussion

Luotonins A (**1**) and B (**2**) are novel quinazoline–quinoline alkaloids isolated from the aerial parts of *Peganum nigellastrum* Bunge.[4] These alkaloids are cytotoxic against mouse leukemia P-388 cells in vitro and inhibit DNA topoisomerases I and II.[4–6] *P. nigellastrum* is a Chinese traditional medicine that is used to treat rheumatism, abscesses, and inflammation.[7] The biological activities of these alkaloids and their structural similarity to camptothecin have focused attention on the synthesis of **1** and **2**.[8]

3-[(2-Bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone (**4**), the key intermediate in the synthesis of **1**, was synthesized as follows. *N*-alkylation of 4(3*H*)-quinazolinone with potassium *tert*-butoxide and 2-bromo-3-(bromomethyl)quinoline[9] gave **4** in 92% yield. The biaryl coupling reaction of **4** using the Pd reagent in DMF under reflux was examined, and the results are summarized in Table 1. Biaryl coupling reactions using our novel method[2d,e] (run 7), using DBU[2m] (run 9), using cesium carbonate (run 11), and using silver carbonate (run 3) as the base were not fruitful. However, using tricyclohexylphosphine (Cy_3P) as the ligand and KOAc as the base, the coupling reaction proceeded smoothly to give luotonin A (**1**)[4] in 86% yield (see run 5). Interestingly, even in the absence of a phosphorus ligand, the reaction proceeded to yield **1** in 61% yield (see run 14).[10,11]

Subsequently, the conversion of **1** to **2** was examined. Bromination of **1** with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobisisobutyronitrile (AIBN) under irradiation from a tungsten lump, followed by solvolysis with silver nitrate in aqueous acetone,[12] gave luotonin B (**2**)[4] in 66% yield.

Rutaecarpine (**3**) is an indolopyridoquinazoline alkaloid that has been isolated from rutaceous plants, such as *Evodia rutaecarpa*,[13] and has long been used to treat inflammation-related disorders in traditional oriental medical practice.[14] In addition to its anti-inflammatory activity,[15] there are

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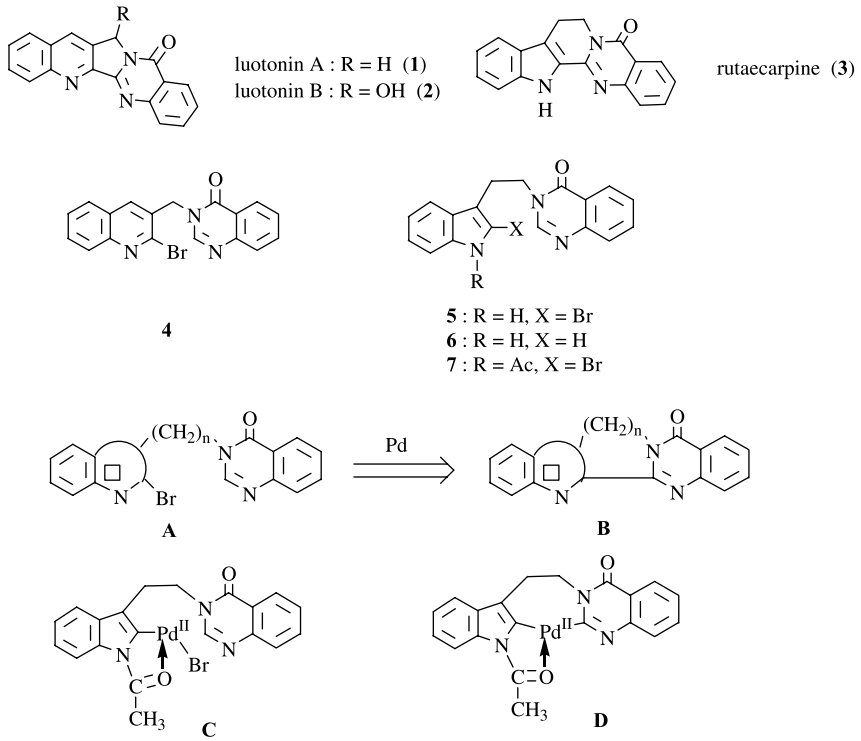

Figure 1.

Table 1. Results of coupling reactions of 3-[(2-bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone (**4**) to luotonin A (**1**)[a]

Run	Pd (equiv)	Ligand (L/Pd)	Additive (equiv)	Base (equiv)	Time (min)	Result (%)
1	$Pd(OAc)_2$ (0.1)	(*o*-Tol)$_3$P (2)	—	K_2CO_3 (2.0)	50	nr[b]
2	$Pd_2(dba)_3$ (0.1)	(*o*-Tol)$_3$P (2)	—	K_2CO_3 (2.0)	20	22
3	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	Ag_2CO_3 (2.0)	60	nr[b]
4	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	K_2CO_3 (2.0)	20	64
5	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	KOAc (2.0)	30	86
6	$Pd(OAc)_2$ (0.05)	Cy_3P (2)	—	KOAc (2.0)	30	61[c]
7	$Pd(OAc)_2$ (1.0)	(*n*-Bu)$_3$P (1), DPPP (1)[d]	—	Ag_2CO_3 (2.0)	30	22
8	$Pd(OAc)_2$ (0.1)	(*n*-Bu)$_3$P (2)	—	K_2CO_3 (2.0)	30	55
9	$Pd(OAc)_2$ (0.1)	(*n*-Bu)$_3$P (2)	—	DBU (2.0)	60	nr[b]
10	$Pd(OAc)_2$ (0.1)	(*t*-Bu)$_3$P (2)	—	K_2CO_3 (2.0)	10	24
11	$Pd(OAc)_2$ (0.1)	(*t*-Bu)$_3$P (2)	—	Cs_2CO_3 (2.0)	30	24
12	$Pd(OAc)_2$ (0.1)	—	Bu_4NCl (1)	KOAc (5.0)	20	41
13	$Pd(OAc)_2$ (0.1)	—	—	K_2CO_3 (2.0)	60	33
14	$Pd(OAc)_2$ (0.1)	—	—	KOAc (2.0)	30	61

[a] All reactions were carried out in DMF under argon atmosphere and reflux.
[b] nr: no reaction.
[c] Starting material was recovered in 5% yield.
[d] See Ref. 2(d) and (e).

reports that **3** has cytotoxic,[16] antiplatelet aggregation,[17] vasorelaxation,[18] and anti-anoxic[19] activities. Owing to its pharmaceutical activities, attention is still focused on the development of new synthetic methods for **3**.[20]

3-[2-(2-Bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**5**), the key intermediate in the synthesis of **3**, was synthesized as follows. 3-(2-Bromoethyl)indole[21] was brominated with NBS in CH_2Cl_2 and then reacted with 4(3*H*)-quinazolinone in the presence of K_2CO_3 in DMF to give **5** in 59% yield. The Pd-assisted coupling reaction of **5** using the Pd reagent in DMF under reflux was examined, and the results are summarized in Table 2. Even using equimolar $Pd(OAc)_2$ in the presence of Cy_3P and KOAc, the coupling reaction gave **3** and the debromo compound (**6**) in poor yields (run 5 in Table 2). Then, we envisioned that formation of the intermediate (**C**) via oxidative addition of *N*-acetate (**7**) to Pd (0) and coordination of the carbonyl group to Pd (II) would help the biaryl coupling reaction and/or bulkyness of *N*-acetyl group might facilitate access of reaction sites. The coupling reaction of 3-[2-(*N*-acetyl-2-bromoindol-3-yl)-ethyl]-4(3*H*)-quinazolinone (**7**), which was prepared by acetylation of **5** in 82% yield, was examined, and the results are summarized in Table 3. The coupling reaction using (*n*-Bu)$_3$P and K_2CO_3 or using $PdCl_2(PPh_3)_2$ gave **3** directly in moderate yield (runs 3 and 11 in Table 3). The reaction using Cy_3P and KOAc proceeded smoothly to yield **3** in 89% yield, (run 4 in Table 3) indicating that the coupling

Table 2. Results of coupling reactions of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**5**)[a]

Run	Pd (equiv)	Ligand (L/Pd)	Additive (equiv)	Base (equiv)	Time (h)	Result (%)		
						3	**6**	**1**
1	$Pd(OAc)_2$ (0.1)	(*o*-Tol)$_3$P (2)	—	K_2CO_3 (2.0)	12	—	7	47
2	$Pd_2(dba)_3$ (0.1)	(*o*-Tol)$_3$P (2)	—	K_2CO_3 (2.0)	5		Decomp.	
3	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	Ag_2CO_3 (2.0)	5		Decomp.	
4	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	KOAc (2.0)	3	12	51	—
5	$Pd(OAc)_2$ (1.0)	Cy_3P (2)	—	KOAc (2.0)	1.5	24	8	—
6	$Pd(OAc)_2$ (0.1)	DPPP (1)	(*n*-Bu)$_3$P (1)[b]	Ag_2CO_3 (2.0)	2		Decomp.	
7	$Pd(OAc)_2$ (0.1)	(*n*-Bu)$_3$P (2)	—	KOAc (2.0)	6	18	27	—
8	$Pd(OAc)_2$ (0.1)	(*t*-Bu)$_3$P (2)	—	Cs_2CO_3 (2.0)	9	5	49	14
9	$Pd(OAc)_2$ (0.1)	—	Bu_4NCl (1)	KOAc (5.0)	6	9	59	—
10	$PdCl_2(PPh_3)_2$ (0.1)	—	—	NaOAc (2.0)	4.5	17	46	—

[a] All reactions were carried out in DMF under argon atmosphere and reflux.
[b] See Ref. 2(d) and (e).

Table 3. Results of coupling reactions of 3-[2-(*N*-acetyl-2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**7**)[a]

Run	Pd (equiv)	Ligand (L/Pd)	Additive (equiv)	Base (equiv)	Time (min)	Result (%)		
						3	**6**	**5**
1	$Pd(OAc)_2$ (0.1)	(*o*-Tol)$_3$P (2)	—	KOAc (2.0)	60	15	9	59
2	$Pd_2(dba)_3$ (0.1)	Cy_3P (2)	—	Ag_2CO_3 (2.0)	60		Decomp.	
3	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	K_2CO_3 (2.0)	60	44	22	—
4	$Pd(OAc)_2$ (0.1)	Cy_3P (2)	—	KOAc (2.0)	60	89	—	—
5	$Pd(OAc)_2$ (1.0)	DPPP (1)	(*n*-Bu)$_3$P (1)[b]	Ag_2CO_3 (2.0)	30		Decomp.	
6	$Pd(OAc)_2$ (0.1)	(*t*-Bu)$_3$P (2)	—	Cs_2CO_3 (2.0)	60	—	16	61
7	$Pd(OAc)_2$ (0.1)	(*n*-Bu)$_3$P (2)	—	K_2CO_3 (2.0)	60	31	—	40
8	$Pd(OAc)_2$ (0.1)	(*n*-Bu)$_3$P (2)	—	KOAc (2.0)	60	78	—	—
9	$Pd(OAc)_2$ (0.1)	—	Bu_4NCl (1)	KOAc (5.0)	30	16	63	12
10	$Pd(OAc)_2$ (0.1)	—	—	KOAc (2.0)	60	17	—	—
11	$PdCl_2(PPh_3)_2$ (0.1)	—	—	NaOAc (2.0)	60	56	—	—

[a] All reactions were carried out in DMF under argon atmosphere and reflux.
[b] See Ref. 2(d) and (e).

reaction occurred first and then hydrolysis took place, or *N*-acetyl group of palladacycle intermediate (**D**) might be susceptible to hydrolysis by the coordination of carbonyl group to Pd^{II} and then coupling reaction occurred. The use of KOAc as base gave **3** generally in a good to excellent yields, while the reaction using Ag_2CO_3 as a base caused the decomposition of **5** and **7**. (see runs 3 and 6 in Table 2, and runs 2 and 5 in Table 3).

In conclusion, the concise syntheses of quinazoline alkaloids **1**–**3** were accomplished by applying a strategy involving a biaryl coupling reaction using Pd reagent with Cy_3P and KOAc in DMF under reflux.

3. Experimental

3.1. General

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on JASCO A-102 or FT/IR 350 spectrophotometers, and ^{1}H NMR spectra in deuteriochloroform were recorded on Varian Mercury 300 or VXR-500 spectrometers. NMR spectra data are reported in parts per million downfield from the internal standard tetramethylsilane (δ 0.0) and the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out with Merck silica gel (230–400 mesh). All the experiments were carried out in an argon atmosphere, unless otherwise noted, and the extract was washed with brine, dried over anhydrous K_2CO_3, and filtered, and the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

3.1.1. 3-[(2-Bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone (4). A mixture of 4(3*H*)-quinazolinone (194 mg, 1.33 mmol) and *t*-BuOK (179 mg, 1.60 mmol) in DMF (12 mL) was stirred at rt for 1 h, and then 2-bromo-3-(bromomethyl)quinoline (400 mg, 1.33 mmol) was added to the reaction mixture. After stirring for 1.5 h, the reaction mixture was diluted with aqueous 5% Na_2CO_3 solution to bring the solution to pH 10 before extracting it with AcOEt. The extract was washed with brine. The residue was recrystallized from $CHCl_3$–hexane to give **4** (451 mg, 92%) as colorless needles, mp 203–205 °C. IR (KBr) cm^{-1}: 1670. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.43 (2H, s), 7.55 (1H, ddd, J=7.0, 7.0, 1.0 Hz), 7.56 (1H, ddd, J=7.0, 7.0, 1.0 Hz), 7.75 (1H, ddd, J=7.0, 7.0, 1.0 Hz), 7.76–7.84 (3H, m), 8.01 (1H, br d, J=8.0 Hz), 8.22 (1H, s), 8.32 (1H, dd, J=8.0, 1.0 Hz), 8.37 (1H, s). MS (FAB positive ion mode) *m*/*z*: 366

(M+1), 368 (M+3). Anal. Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47. Found: C, 59.01; H, 3.67; N, 11.35.

3.2. General procedure for the coupling reaction of 3-[(2-bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone (4)

The Pd-assisted coupling reaction of **4** (55 mg, 0.15 mmol) in dry DMF (2 mL) was carried out under the reaction conditions indicated in Table 1 with reflux in an argon atmosphere. The reaction mixture was diluted with AcOEt, and the precipitates were removed by filtration. The residue was dissolved in $CHCl_3$ (7 mL) and subjected to column chromatography on silica gel. Elution with hexane–acetone (3:1) gave **1**.

3.2.1. Luotonin A (1). Colorless needles (from $CHCl_3$), mp 283–285 °C [lit.,[4] 252 °C (dec); lit.,[8c] 281–283 °C]. The ^{1}H NMR and IR spectra of the synthetic sample agreed with those of authentic luotonin A.

3.2.2. Luotonin B (2). A solution of **1** (114 mg, 0.40 mmol), NBS (71.2 mg, 0.40 mmol), and AIBN (32.8 mg, 0.20 mmol) in dry CH_2Cl_2 (10 mL) and dry CCl_4 (10 mL) was refluxed for 1 h under irradiation from a tungsten lamp (300 W). The reaction mixture was concentrated in vacuo. A mixture of the residue and $AgNO_3$ (68.0 mg, 0.40 mmol) in 50% aqueous acetone (5 mL) was stirred for 1 h under reflux and then concentrated to dryness in vacuo. CH_2Cl_2 was added, and insoluble materials were removed by filtration. The CH_2Cl_2 solution was evaporated in vacuo. Recrystallization from CH_2Cl_2 gave **2** (79 mg, 66%) as colorless prisms, mp 271–274 °C (lit.,[8c] 237–240 °C). Anal. Calcd for $C_{18}H_{11}N_3O_2 \cdot 1/2H_2O$: C, 70.91; H, 3.77; N, 13.78. Found: C, 70.98; H, 4.11; N, 13.82. The ^{1}H NMR and IR spectra of synthetic sample agreed with those of authentic sample.

3.2.3. 3-[2-(2-Bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (5). A mixture of 3-(2-bromoethy)lindole (896 mg, 4.0 mmol) and NBS (712 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred for 5 min at rt. The reaction mixture was diluted with AcOEt and then washed with aqueous sodium thiosulfate. The residue was dissolved in DMF (20 mL), and 4(3*H*)-quinazolinone (584 mg, 4.0 mmol) and K_2CO_3 (552 mg, 4.0 mmol) were added. The reaction mixture was stirred for 1 h at rt and then heated for 30 min at 70 °C with stirring. The mixture was diluted with water and extracted with AcOEt. The residue was dissolved in $CHCl_3$ and subjected to chromatography on silica gel. Elution with hexane–ether (1:1) gave **5** (868 mg, 59%) as amorphous. IR (KBr) cm^{-1}: 3200, 1660, 1610. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.24 (2H, t, J=6.9 Hz), 4.26 (2H, t, J=6.9 Hz), 7.07 (1H, ddd, J=7.0, 7.0, 1.2 Hz), 7.15 (1H, ddd, J=7.0, 7.0, 1.2 Hz), 7.24 (1H, br d, J=7.0 Hz), 7.42 (1H, s), 7.48–7.54 (2H, m), 7.62 (1H, dd, J=7.0, 1.2 Hz), 7.73 (1H, ddd, J=7.0, 7.0, 1.2 Hz), 8.36 (1H, dd, J=7.0, 1.2 Hz), 8.59 (1H, br s). MS (FAB positive ion mode) *m/z*: 368 (M+1), 370 (M+3). Anal. Calcd for $C_{18}H_{14}BrN_3O$ $1/2H_2O$: C, 57.31; H, 4.01; N, 11.14. Found: C, 57.76; H, 3.94; N, 10.73.

3.3. General procedure for the coupling reaction of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (5)

The Pd-assisted coupling reaction of **5** (121 mg, 0.33 mmol) in dry DMF (2 mL) was carried out under the reaction conditions indicated in Table 2 with reflux in an argon atmosphere. The reaction mixture was diluted with AcOEt, and the precipitates were removed by filtration. The residue was dissolved in $CHCl_3$ (7 mL) and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (1:1) gave **3**, and successive elution with the same solvent gave **6**.

3.3.1. Rutaecarpine (3). Colorless needles (from AcOEt), mp 256–258 °C (lit.,[22] 259 °C). The ^{1}H NMR and IR spectra of synthetic sample agreed with those of authentic sample.

3.3.2. 3-[2-(Indol-3-yl)ethyl-4(3*H*)-quinazolinone (6). Colorless needles (from ether), mp 167–170 °C (lit.,[22] 164–165 °C). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.45; H, 5.41; N, 14.32.

3.3.3. 3-[2-(*N*-Acetyl-2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (7). A solution of **5** (3.68 g, 10.0 mmol), Et_3N (4.05 g, 40.0 mmol), DMAP (61 mg, 0.50 mmol), and acetyl chloride (1.56 g, 20.0 mmol) in CH_2Cl_2 (40 mL) was stirred for 4 h at rt. The reaction mixture was diluted with CH_2Cl_2 and washed with 1*N* HCl. The residue was dissolved in CH_2Cl_2 (7 mL) and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (1:2) gave **7** (3.36 g, 82%) as colorless needles (from AcOEt), mp 159–161 °C. IR (KBr) cm^{-1}: 1670. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.81 (3H, s), 3.28 (2H, t, J=6.9 Hz), 4.26 (2H, t, J=6.9 Hz), 7.20–7.28 (1H, m), 7.33 (1H, ddd, J=8.0, 8.0, 1.5 Hz), 7.51–7.59 (2H, m), 7.65 (1H, s), 7.66 (1H, br d, J=8.0 Hz), 7.76 (1H, ddd, J=8.0, 8.0, 1.5 Hz), 8.26 (1H, br d, J=8.0 Hz), 8.35 (1H, br d, J=8.0 Hz). Anal. Calcd for $C_{20}H_{16}BrN_3O_2$: C, 58.55; H, 3.93; N, 10.24. Found: C, 58.28; H, 3.87; N, 10.12.

3.4. General procedure for the coupling reaction of 3-[2-(*N*-acetyl-2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (7)

The Pd-assisted coupling reaction of **7** (82 mg, 0.20 mmol) in dry DMF (2 mL) was carried out under the reaction conditions indicated in Table 3 with reflux in an argon atmosphere. The reaction mixture was diluted with AcOEt, and the precipitates were removed by filtration. The residue was dissolved in CH_2Cl_2 (7 mL) and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (1:1) gave **3**, and successive elution with the same solvent gave **5** and **6**.

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Total synthesis of *cis*-solamin and its inhibitory action with bovine heart mitochondrial complex I

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Abstract—A convergent total synthesis of *cis*-solamin (**1a**) and its diastereomer (**1b**) was accomplished. A key reaction of this approach was the use of $VO(acac)_2$-catalyzed diastereoselective epoxidation of (*Z*)-bis-homoallylic alcohol **3** followed by spontaneous cyclization for the *cis*-THF ring formation. By comparison of the optical rotation of the two possible diastereomers, it is suggested that the absolute configuration of natural *cis*-solamin is **1a**. Inhibitory action of synthetic **1a** and **1b** with bovine heart mitochondrial complex I are reported.

1. Introduction

Annonaceous acetogenins, which have been isolated from a number of plants of *Annonaceae*, have attracted much attention in recent years due to their broad spectrum of biological activities such as cytotoxic, antitumor, antimalarial, antimicrobial, immunosuppressive, pesticidal, and antifeedant effects. Since the first annonaceous acetogenin, uvaricin was found from the plant of *Uvaria accuminata* in 1982,[1] more than 350 related compounds have been isolated in the past of 20 years.[2] The common structural features of annonaceous acetogenins are characterized by a terminal α,β-unsaturated γ-lactone ring and a C-32 or 34 long aliphatic side chain connected with some oxygen containing moieties, such as THF, THP, and/or epoxide rings and several hydroxyl groups. Consequently, significant effort has been devoted toward the total synthesis of annonaceous acetogenins.[3]

cis-Solamin (**1**) is a mono-THF acetogenin, isolated from the roots of *Annona muricata* in 1998.[4] The relative stereochemistry of the THF-diol part of **1** was determined to be *threo–cis–threo* by Laurens et al.[4] and the (*S*)-configuration of the secondary methyl group of the γ-lactone moiety is well known, it follows that the absolute configuration of **1** is (15*R*, 16*R*, 19*S*, 20*S*, 34*S*) or (15*S*, 16*S*, 19*R*, 20*R*, 34*S*) (Fig. 1).

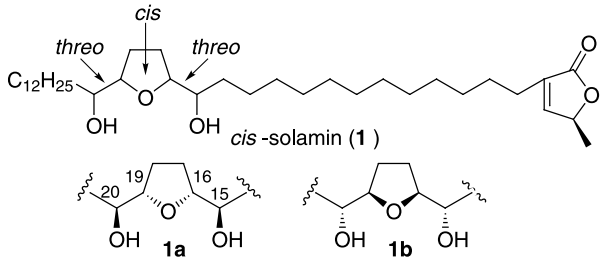

Figure 1. Structures of (15*R*, 16*R*, 19*S*, 20*S*, 34*S*)-*cis*-solamin (**1a**) and (15*S*, 16*S*, 19*R*, 20*R*, 34*S*)-*cis*-solamin (**1b**).

The two possible structures, **1a** and **1b**, would be difficult to distinguish by ^1H or ^{13}C NMR spectroscopic data, because the THF moiety and γ-lactone moiety are separated by 13 carbon long chain. X-ray analysis would be also very hard due to the waxy nature of this compound. To establish the absolute configuration and evaluate biological activity, we planned to synthesize the two candidates **1a** and **1b**, employing a $VO(acac)_2$ catalyzed diastereoselective

Keywords: Annonaceous acetogenin; Antitumor; Mitochondrial complex I.
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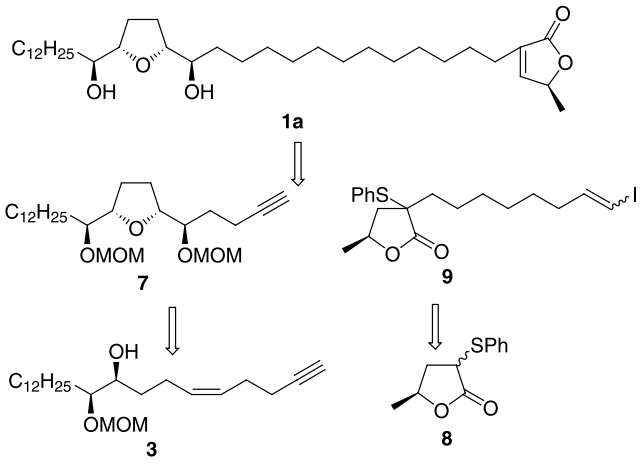
epoxidation in the presence of peroxide followed by a cyclization strategy.[5]

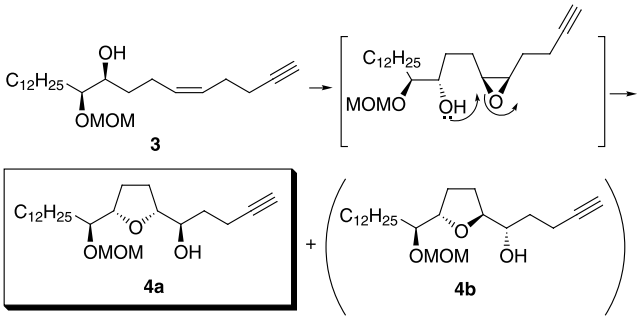
2. Results and discussion

Our synthetic strategy is outlined in Scheme 1. The key step for constructing THF ring formation is $VO(acac)_2$ catalyzed diastereoselective epoxidation[6,7] followed by spontaneous cyclization in the presence of molecular sieves 4 Å. The starting material is (*Z*)-bis-homoallylic alcohol **3**, whose enantiomer had been synthesized earlier by us.[7]



Scheme 1. Synthetic strategy of *cis*-solamin (**1a**).

The results of diastereoselective epoxidation of **3** (Scheme 2) and cyclization are summarized in Table 1.



Scheme 2. Diastereoselective epoxidation of **3** and cyclization.

The results shown indicate the following. TBHP-$VO(acac)_2$ in the presence of 4 Å molecular sieves can serve as the most effective system in the diastereoselective epoxidation. Cumene hydroperoxide also served as a good oxidant. On the other hand, Ti and Mo catalysts were ineffective. Halogenic solvents, especially 1,2-dichloroethane, gave a good stereoselectivity and yield.

Determination of the relative stereochemistry of **4a** and **4b** was performed by applying Cassady's method as we have previously reported (Fig. 2).[7,8]

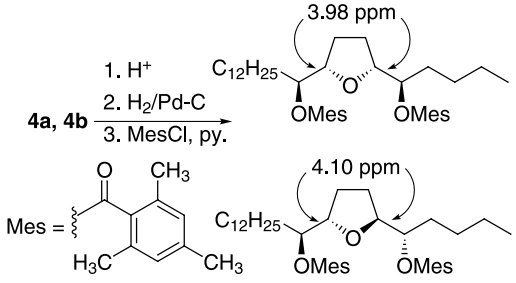


Figure 2. Determination of the relative stereochemistry of **4a** and **4b** by applying Cassady's method.[8]

Diastereomers **4a** and **4b** were separated by silica gel column chromatography (benzene–AcOEt=20:1) after hydroxyl group of **4a** and **4b** had been protected as a benzoate ester to give **5a** and **5b**. The differences of ^1H NMR chemical shifts of compounds **5a** and **5b** were shown in Figure 3. This indicates that the *threo–cis–threo* and the *threo–trans–threo* relationships of the THF core part can be differentiated by ^1H NMR (Fig. 3).

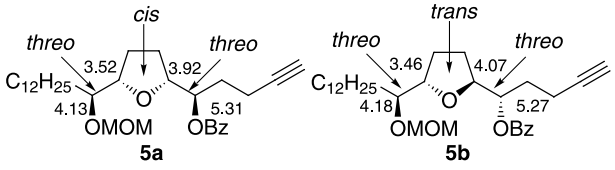


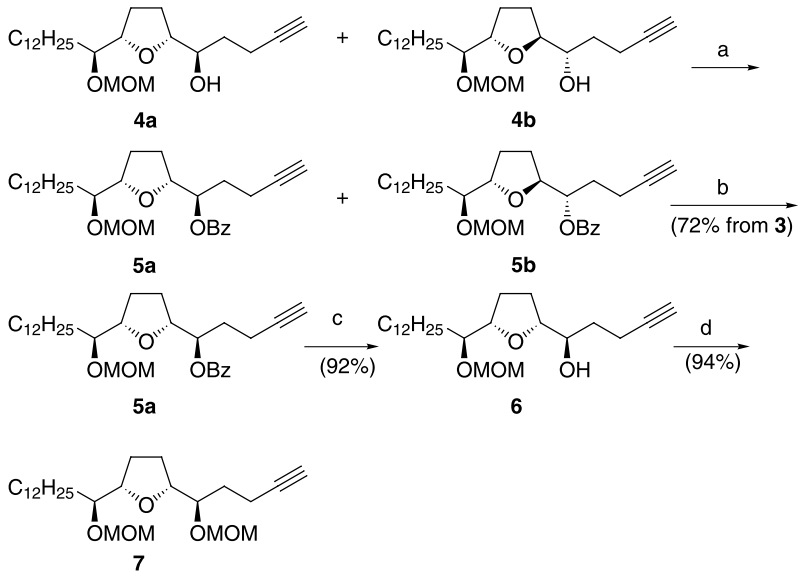
Figure 3. Differences between the characteristic chemical shifts of the oxymethine proton of compounds **5a** and **5b**.

Hydrolysis of the benzoate ester **5a** gave **6** and protection of the hydroxyl group as MOM ether afforded tetrahydrofuran moiety **7** (Scheme 3).

Table 1. Epoxidation and subsequent cyclization of bis-homoallyl alcohol **3**[a]

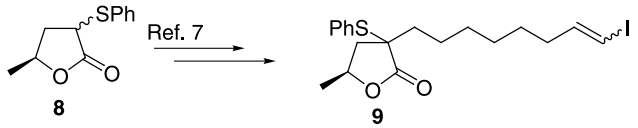
Reagent	Solvent	Additive	Yield (**4a**+**4b**)	**4a**:**4b**
*m*CPBA	CH_2Cl_2	—	83	37:63
TBHP–10 mol% $Ti(O\text{-}iPr)_4$	CH_2Cl_2	—	24	49:51
TBHP–10 mol% $MoO_2(acac)_2$	CH_2Cl_2	—	Trace	—
TBHP–5 mol% $VO(acac)_2$	C_6H_5Cl	—	Trace	—
TBHP–5 mol% $VO(acac)_2$	CH_2Cl_2	—	43	78:22
TBHP–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	—	51	87:13
Cummene hydroperoxide–5 mol% $VO(acac)_2$	CH_2Cl_2	—	78	83:17
Cummene hydroperoxide–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$		77	85:15
Cummene hydroperoxide–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	MS 4 Å	83	85:15
TBHP–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	MS 4 Å	75	89:11

[a] Determination of the relative stereochemistry of **4a** and **4b** was performed by applying Cassady's methods as we have previously reported.[8]



Scheme 3. Reagents and conditions: (a) BzCl, pyridine; (b) separation; (c) NaOH, MeOH; (d) MOMCl, *i*-Pr_2NEt.

As shown in Scheme 4, the γ-lactone part **9** was constructed as we had reported earlier starting from γ-lactone **8**.[7,9]

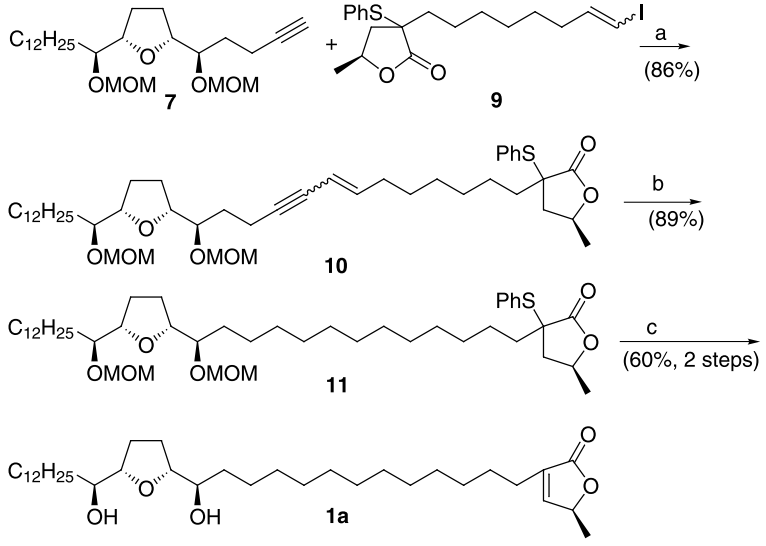


Scheme 4. Synthesis of γ-lactone part.

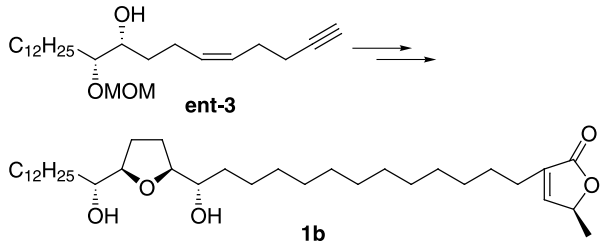
Both segments were coupled by Sonogashira cross-coupling reaction[10] mediated by $Cl_2Pd(PPh_3)_2$/CuI in the Et_3N solvent system to give compound **10**. When THF or benzene was used as a solvent the yield of coupled product got lower. Diimide reduction with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded saturated product **11** in good yield.[3g] When ethylene glycol dimethyl ether was used, some partially unsaturated compound was observed. Catalytic hydrogenation with $ClRh(PPh_3)_3$ under 1 atm of H_2 atmosphere in benzene–EtOH (4:1) also sometimes gave some minor amount of unsaturated product. Oxidation of the sulfur with *m*-CPBA followed by thermal elimination and deprotection of the MOM ethers with $BF_3 \cdot Et_2O$ in dimethyl sulfide afforded the candidate **1a** (Scheme 5).

The other candidate **1b** was also synthesized from the enantiomer of compound **3** using the same procedure as that employed for **1a** (Scheme 6).

The two synthetic samples (**1a**, **1b**) could not be differentiated by the spectral data (^1H, ^{13}C NMR). On the other hand, their specific rotation showed different values. While the specific rotation of synthetic **1a** ($[\alpha]_D^{21} = +26$, *c* 0.45, MeOH) is similar to the reported value of the naturally occurring *cis*-solamin ($[\alpha]_D = +22$, *c* 0.55, MeOH), that of **1b** ($[\alpha]_D^{21} = +42$, *c* 0.50, MeOH) showed a much higher value. As shown in Table 2, the ^1H NMR spectra of the



Scheme 5. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N; (b) *p*-$TsNHNH_2$, ethylene glycol diethyl ether, NaOAc; (c) (i) *m*CPBA, toluene, (ii) reflux; (iii) $BF_3 \cdot Et_2O$/dimethyl sulfide.



Scheme 6.

Table 2. [1]H NMR chemical shifts of the bis-(*R*)- and (*S*)-MTPA esters of **1a** and **1b**[a]

MTPA ester	15-H	16-H	19-H	20-H
(*R*)-MTPA-**1a**	5.06	3.87	4.08	4.92
(*S*)-MTPA-**1a**	5.06	3.86	4.09	4.93
δ (*S*)-(*R*)-**1a**		−0.01	0.01	0.01
Abs. confign.	*R*	*R*	*S*	*S*
(*R*)-MTPA-**1b**	5.06	3.86	4.09	4.93
(*S*)-MTPA-**1b**	5.06	3.87	4.08	4.92
δ (*S*)-(*R*)-**1b**		0.01	−0.01	−0.01
Abs. confign.	*S*	*S*	*R*	*R*

[a] Proton chemical shifts are referenced to $CHCl_3$ (δ 7.25). Each proton was assigned by H–H COSY experiment.

carbinol centers of the corresponding bis-(*R*)- and (*S*)-MTPA esters of synthetic **1a** and **1b** showed a slight chemical shift difference. According to the sign of $\Delta\delta_H[=(\delta_S-\delta_R)]$ values of each carbinol center, the absolute configuration of **1a** was assigned as C-15*R*, C-16*R*, C-19*S*, and C-20*S*. Similarly, the absolute configuration of **1b** was assigned as C-15*S*, C-16*S*, C-19*R*, and C-20*R*.[11] This indicates that if natural **1** is available, we can determine stereochemistry of *cis*-solamin by applying advanced Mosher methodology.[12]

The inhibition of mitochondrial complex I was determined by NADH oxidase assay using bovine-heart submitochondrial particles (Table 3).

Table 3. Inhibition activity of mitochondrial complex I

Sample	IC_{50} (nM)
1a	2.2
1b	2.1
(10*R*)-corossoline	1.5
(10*S*)-corossoline	2.0
(17*R*, 18*R*, 21*R*, 22*S*)-reticulation-1	16
(17*S*, 18*S*, 21*S*, 22*R*)-reticulation-1	17
bullatacin	0.8

The inhibitory potency in terms of IC_{50} of bullatacin, one of the most potent natural acetogenins, was 0.8 nM as a control. Under the same experimental conditions, the IC_{50} of **1a** and **1b** were 2.2 and 2.1 nM, respectively. The inhibitory potencies were almost identical to those of (10*R*)- and (10*S*)-corossoline which had been synthesized by us.[13] This indicates that the stereochemistry around the hydroxylated THF rings and the presence of 10-OH group in the spacer region are not essential for the potent activity. This observation is consistent with the results of Miyoshi et al. who revealed that the stereochemistry around the hydroxylated THF rings and the presence of a polar substituent(s) in the spacer moiety were of minor importance for the activity.[14–17] The length of the spacer of compounds **1a**, **1b**, (10*R*)-, and (10*S*)-corossoline is 13 carbon atoms in common. Compared to both possible diastereomers of reticulatain-1, which has a spacer of 15 carbon atoms, the inhibitory activities of the four compounds are about eight-times stronger (Fig. 4).[14]

Thus, the length of spacer moiety is critically important for the inhibitory action. This observation is also consistent with the results of Takada et al. which demonstrated that an optimal length of the spacer is about 13 carbon atoms.[18]

In summary, the first total synthesis of *cis*-solamin (**1a**) and its diastereomer **1b** was accomplished using $VO(acac)_2$-catalyzed diastereselective epoxidation followed by spontaneous cyclization. On the basis of the present data, it is strongly suggested that the natural *cis*-solamin is **1a**.

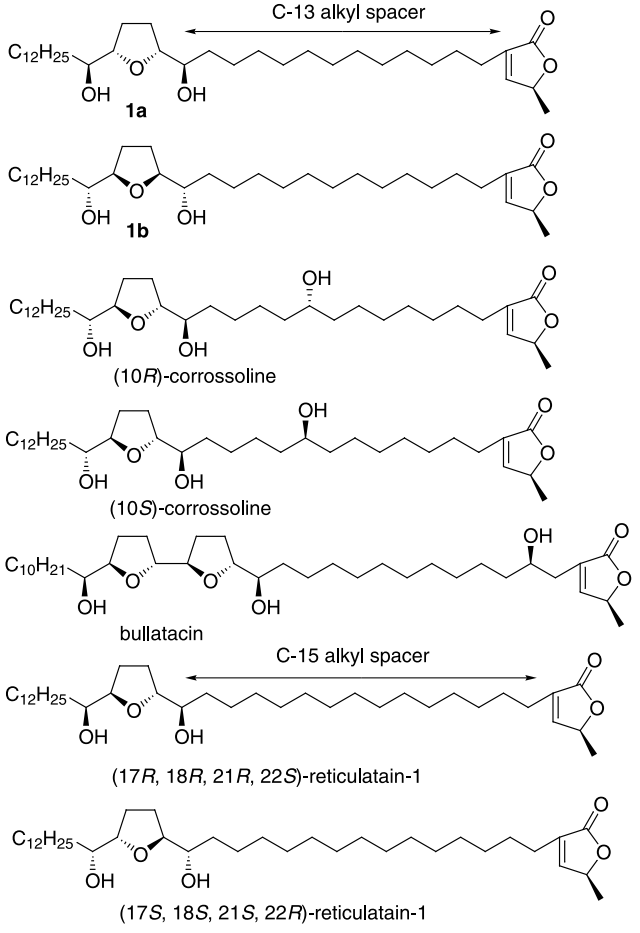


Figure 4. The structure of biological tested compounds.

Inhibitory action of these compounds was examined with bovine heart mitochondrial complex I. Both compounds showed almost same activity.

3. Experimental

3.1. General

All melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DR 500 FT NMR spectrometer in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hertz. Mass spectra were obtained on JEOL JMS 700 mass spectrometer. IR spectra were recorded with JASCO IR-810 infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

3.1.1. (*Z*,9*S*,10*S*)-10-(Methoxymethoxy)docos-5-en-1-yn-9-ol (3). This compound was prepared as we reported previously starting from (+)-muricatacin.[7] $[\alpha]_D^{27}=+9.3$ (*c* 1.5, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3450, 3300, 3000, 2920, 2850, 2100, 1650, 1470, 1455, 1100, 1040, 920, 720, 630; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.26–1.58 (24H, m), 1.94 (1H, t, $J=2.4$ Hz), 2.19–2.32 (6H, m), 2.40 (1H, br., –OH), 3.35 (1H, m), 3.41 (3H, s), 3.52 (1H, m), 4.70 (2H, s), 5.47 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 18.83, 22.71, 23.56, 25.22, 26.34, 29.37, 29.60, 29.63 (2×C), 29.67, 29.69, 29.84, 31.11, 31.94, 33.23, 55.85, 68.37, 72.25, 83.44, 84.20, 97.12, 128.19, 130.91 ppm; HREIMS calcd for $C_{24}H_{44}O_3$ [M^+] 380.3290, found 380.3286. Anal. Calcd for $C_{24}H_{44}O_3$: C, 75.74; H, 11.65. Found: C, 75.34; H, 11.60.

3.1.2. Determination of the ratio of 4a and 4b. This experiment was carried out as we reported previously.[7] The ^{1}H NMR showed that the ratio of **4a** and **4b** was 89:11.

3.1.3. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Benzoyloxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (5a). To a solution of mixture **4a** and **4b** (909 mg, 2.3 mmol) in pyridine (10 mL) was added benzoyl chloride (0.18 mL, 3.5 mmol) at 0 °C. After being stirred in an ice bath for 1 h and then at 23 °C for 5 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. Drying over $MgSO_4$ and subsequent evaporation of the extract afforded a crude product, which was purified by preparative TLC (benzene–AcOEt=20:1) furnished **5a** (828 mg, 72% from **3**) as a colorless oil. $[\alpha]_D^{27}=+4.1$ (*c* 0.95, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3300, 3060, 2920, 2850, 2100, 1720, 1600, 1450, 1270, 1170, 1040, 920, 720; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.7$ Hz), 1.20–1.65 (22H, m), 1.70–2.10 (6H, m), 1.93 (1H, t, $J=2.5$ Hz), 2.29 (2H, m), 3.36 (3H, s), 3.54 (1H, m), 3.92 (1H, m), 4.13 (1H, m), 4.65 (1H, d, $J=6.5$ Hz), 4.83 (1H, d, $J=6.5$ Hz), 5.31 (1H, m), 7.44 (2H, m), 7.56 (1H, m), 8.07 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 14.21, 15.10, 22.70, 25.36, 27.68, 27.94, 29.37, 29.64 (2×C), 29.65, 29.66, 29.68, 29.70, 29.83, 30.44, 31.30, 31.94, 55.68, 68.86, 74.51, 79.49, 79.96, 82.55, 83.37, 96.78, 128.39, 129.80, 130.22, 133.00, 166.21 ppm; HREIMS calcd for $C_{31}H_{48}O_5$ [M^+] 500.3502, found 500.3505. Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 73.90; H, 9.48.

3.1.4. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Hydroxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (6). To a solution of **5a** (219 mg, 0.44 mmol) in MeOH (10 mL) was added NaOH (50 mg). After the mixture had been stirred for 5 h, the solvent was evaporated and the mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and concentrated to afford crude product, which was chromatographed over silica gel with hexane–AcOEt (4:1) to give **6** as a colorless oil (169 mg, 92%). $[\alpha]_D^{24}=+12.0$ (*c* 1.70, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3450, 3320, 2950, 2930, 2850, 2120, 1460, 1070, 620; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.20–1.45 (21H, m), 1.45–2.00 (7H, m), 1.93 (1H, t, $J=2.4$ Hz), 2.30–2.40 (2H, m), 3.08 (1H, br., –OH), 3.37 (3H, s), 3.46 (1H, m), 3.54 (1H, m), 3.86 (1H, m), 4.00 (1H, m), 4.70 (1H, d, $J=6.5$ Hz), 4.73 (1H, d, $J=6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 15.04, 22.70, 25.44, 28.09, 28.15, 29.37, 29.62 (2×C), 29.66 (2×C), 29.69 (2×C), 29.85, 31.94, 33.59, 55.89, 68.31, 72.49, 80.36, 81.28, 82.09, 84.40, 96.50 ppm; HREIMS calcd for $C_{24}H_{44}O_4$ [M^+] 396.3240, found 396.3242. Anal. Calcd for $C_{24}H_{44}O_4$: C, 70.87; H, 10.98. Found: C, 70.73; H, 11.22.

3.1.5. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Methoxymethoxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (7). An ice-cooled mixture of alcohol **6** (169 mg, 0.43 mmol) and chloromethyl methyl ether (caution) (0.07 mL, 0.9 mmol) in CH_2Cl_2 (5 mL) was treated with *i*-Pr_2NEt (0.17 mL, 1.0 mmol) and the resulting mixture was allowed to warm to 24 °C and stirred for 24 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and saturated aqueous NH_4Cl was added to it. The mixture was extracted with ether and the extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexane–AcOEt=5:1) afforded **7** (176 mg, 94%) as a colorless oil. $[\alpha]_D^{17}=+9.1$ (*c* 0.84, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3320, 2930, 2850, 2120, 1470, 1150, 1100, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.20–1.55 (24H, m), 1.60–1.85 (4H, m), 1.95 (1H, t, $J=2.6$ Hz), 2.25–2.35 (2H, m), 3.38 (3H, s), 3.40 (3H, s), 3.49 (1H, m), 3.64 (1H, m), 3.89 (2H, m), 4.67 (1H, d, $J=6.5$ Hz), 4.69 (1H, d, $J=6.5$ Hz), 4.81 (1H, d, $J=6.5$ Hz), 4.82 (1H, d, $J=6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 14.79, 22.70, 25.42, 27.48, 27.69, 29.37, 29.62, 29.65, 29.66, 29.68, 29.70, 29.84, 30.32, 31.36, 31.94, 55.72, 55.88, 68.55, 78.63, 79.80, 81.48, 82.02, 84.19, 96.71, 97.10 ppm; HREIMS calcd for $C_{26}H_{48}O_5$ [M^+] 440.3502, found 440.3505. Anal. Calcd for $C_{26}H_{48}O_5$: C, 72.68; H, 11.18. Found: C, 72.39; H, 11.08.

3.1.6. (1‴*S*,2″*R*,3*RS*,5*S*,5″*S*,7′*E*,13′*R*)-3-{13′-Methoxymethoxy-13′-[5″-(1‴-methoxymethoxytridecyl)tetrahydrofuran-2″-yl]tridec-7′-en-9′-ynyl}-5-methyl-3-(phenylsulphanyl)tetrahydrofuran-2-one (10). To a solution of the vinyl iodide **9** (60 mg, 0.14 mmol) in Et_3N (0.5 mL) was added $Cl_2Pd(PPh_3)_2$ (2.8 mg, 0.007 mmol) and the resulting solution was stirred for 1 h. The acetylenic ether **7** (60 mg, 0.14 mmol) along with CuI (1.4 mg, 0.014 mmol) were then added to the mixture, which after

being stirred for a further 8 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane–AcOEt=4:1) to give **10** (87 mg, 86%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2920, 2850, 2200, 1765, 1460, 1430, 1150, 1100, 1040, 920, 745, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.19 (2.4H, d, J=6.2 Hz), 1.39 (0.6H, d, J=6.2 Hz), 1.20–1.95 (39H, m), 2.00–2.10 (2H, m), 2.20–2.55 (3H, m), 3.38 (3H, s), 3.39 (3H, s), 3.49 (1H, m), 3.62 (1H, m), 3.86–3.93 (2H, m), 4.46–4.65 (1H, m), 4.67 (1H, d, J=6.5 Hz), 4.69 (1H, d, J=6.5 Hz), 4.81 (1H, d, J=6.5 Hz), 4.82 (1H, d, J=6.5 Hz), 5.40–5.45 (1H, m), 5.96–6.05 (1H, m), 7.30–7.45 (3H, m), 7.50–7.60 (2H, m); HRFABMS calcd for $C_{45}H_{72}O_7SNa$ [$(M+Na)^+$] 779.4896, found 778.4894.

3.1.7. (1‴*S*,2″*R*,3*RS*,5*S*,5″*S*,13′*R*)-3-{13′-Methoxymethoxy-13′-[5″-(1‴-methoxymethoxytridecyl)tetrahydrofuran-2″-yl]tridecyl}-5-methyl-3-(phenylsulphanyl)-tetrahydrofuran-2-one (11). To a refluxing solution of **10** (15 mg, 0.2 mmol) and *p*-toluenesulfonylhydrazide (2.62 g, 13.4 mmol) in diethoxyethane (15 mL) was added sodium acetate (1.36 g, 16.6 mmol) in water (20 mL) over a 4 h period at 120 °C. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed over silica gel (hexane–AcOEt=4:1) to give **11** (13 mg, 89%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2920, 2850, 1765, 1460, 1430, 1150, 1100, 1040, 920, 740; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.19 (2.4H, d, J=6.2 Hz), 1.38 (0.6H, d, J=6.2 Hz), 1.20–1.90 (49H, m), 1.95–2.10 (2H, m), 2.32 (0.2H, dd, J=13.9, 5.5 Hz), 2.52 (0.8H, dd, J=13.9, 7.5 Hz), 3.38 (3H, s), 3.39 (3H, s), 3.49 (2H, m), 3.89 (2H, m), 4.46–4.65 (1H, m), 4.67 (1H, d, J=6.5 Hz), 4.69 (1H, d, J=6.5 Hz), 4.81 (1H, d, J=6.5 Hz), 4.82 (1H, d, J=6.5 Hz), 7.30–7.45 (3H, m), 7.50–7.60 (2H, m); HRFABMS calcd for $C_{45}H_{78}O_7SNa$ [$(M+Na)^+$] 785.5366, found 785.5368.

3.1.8. *cis*-Solamin (1a). To a solution of **11** (10 mg, 13.6 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (80%, 5.4 mg, 25 mmol) at 0 °C. After the mixture had been stirred at this temperature for 10 min, $Na_2S_2O_3$/$NaHCO_3$ (1:1, 1.0 mL) was added. After stirring at 23 °C for 1 h, the mixture was extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and subsequent concentration gave an oil, which was then dissolved in toluene (2.0 mL) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture gave an oil, which was dissolved in dimethyl sulfide (0.5 mL) at 0 °C and $BF_3{\cdot}Et_2O$ was added. After the mixture had been stirred for 10 min at this temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with AcOEt. The mixture was washed with water and brine. Drying over $MgSO_4$ and evaporation of the solvent gave a colorless solid, which was purified by silica gel chromatography (AcOEt) gave **1a** (3.4 mg, 60%) as a colorless solid. Mp 66–68 °C; $[\alpha]_D^{21}=+26$ (*c* 0.45, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 1320, 1110, 1080, 1030, 960, 840, 750, 715; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (48H, m), 1.41 (3H, d, J=6.6 Hz), 2.27 (2H, t, J=7.3 Hz), 2.39 (2H, br., –OH), 3.41 (2H, m), 3.81 (2H, m), 4.99 (1H, dq, J=6.7, 1.6 Hz), 6.98 (1H, d, J=1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 19.23, 22.70, 25.20, 25.73, 27.43, 28.15 (2×C), 29.20, 29.31, 29.37, 29.51 (2×C), 29.61, 29.64, 29.66 (2×C), 29.68, 29.69, 29.84, 29.72 (2×C), 30.32, 31.94, 32.54, 34.00 (2×C), 34.16, 74.39, 77.40, 82.70, 134.40, 148.83, 173.89 ppm; HREIMS calcd for $C_{35}H_{64}O_5$ [M^+] 564.4753, found 564.4720.

3.1.8.1. Diastereomer of *cis*-solamin (1b). Mp 63–66 °C; $[\alpha]_D^{21}=+42$ (*c* 0.50, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 1320, 1110, 1080, 1030, 960, 840, 750, 715; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (48H, m), 1.41 (3H, d, J=6.6 Hz), 2.00 (1H, br., –OH), 2.27 (2H, t, J=7.3 Hz), 2.35 (1H, br., –OH), 3.42 (2H, m), 3.81 (2H, m), 4.99 (1H, dq, J=6.7, 1.6 Hz), 6.98 (1H, d, J=1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 19.24, 22.70, 25.20, 25.73, 27.44, 28.16 (2×C), 29.20, 29.32, 29.37, 29.52 (2×C), 29.61, 29.63, 29.65 (2×C), 29.68, 29.70, 29.72 (2×C), 30.32, 31.94, 32.54, 34.00 (2×C), 34.16, 74.40, 77.40, 82.70, 134.41, 148.83, 173.90 ppm; HRFABMS calcd for $C_{35}H_{64}O_5Na$ [$M+Na^+$] 587.4651, found 587.4650.

3.1.9. Preparation of the bis-(*R*)-MTPA ester of 1a. To a stirred solution of **1a** (1.0 mg, 1.8 μmol) in CH_2Cl_2 (0.2 mL) was sequentially added Et_3N (0.4 mg, 2.5 μmol), DMAP (0.1 mg, 0.8 μmol), and (*S*)-MTPACl (~5 μL, 27 mmol) at room temperature. After the mixture was stirred for 8 h, saturated aqueous $NaHCO_3$ and Et_2O were added. This mixture was stirred vigorously for 1 h. The organic phase was extracted with Et_2O and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was purified with preparative TLC (hexane–AcOEt=4:1) to give bis-(*R*)-MTPA ester of **1a** (1.2 mg, 90%) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87 (1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.1. Bis-(*S*)-MTPA ester of 1a. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86 (1H, m), 4.09 (1H, m), 4.93 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.2. Bis-(*R*)-MTPA ester of 1b. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86 (1H, m), 4.09 (1H, m), 4.93 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.3. Bis-(*S*)-MTPA ester of 1b. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87 (1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98

(1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J= 1.4 Hz), 7.35–7.65 (10H, m) ppm.

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Diastereoselective addition of organozinc reagents to 2-alkyl-3-(arylsulfanyl)propanals

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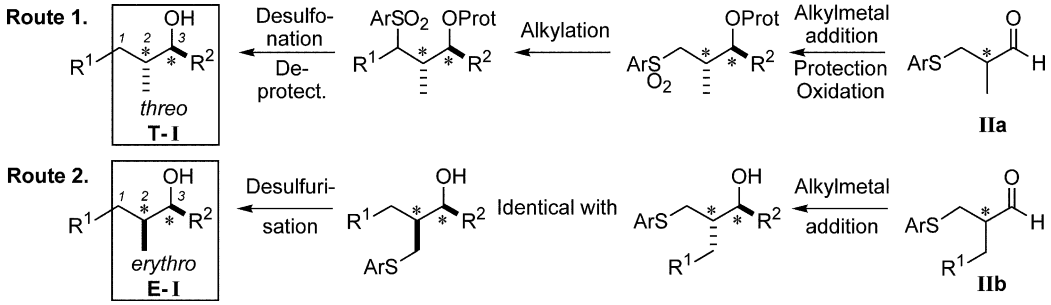
Abstract—The preparation of compounds incorporating the 3-hydroxy-2-methyl-1-alkyl moiety of high diastereomeric purity is described. Such compounds can serve as potential building blocks for the preparation of several kinds of natural products. Diastereoselective synthesis of two potential pine sawfly pheromone components, one the pure racemic *threo*-isomer of 3-methylpentadecan-2-ol and the other the racemic *erythro*-isomer of 3-methyltridecan-2-ol are described. The diastereoselective addition of R_2Zn (R = Me, Et and *n*-Bu) to several 2-alkyl-3-(arylsulfanyl)propanals in the presence of a Lewis acid and CH_2Cl_2 as solvent was studied. An excellent diastereomeric ratio (95/5 *anti*-Cram/Cram) was obtained with 2-[(phenylsulfanyl)methyl]pentanal, 2-[(phenylsulfanyl)methyl]decanal and 2-[(phenylsulfanyl)-methyl]dodecanal and Me_2Zn in the presence of $TiCl_4$.

1. Introduction

A number of natural products, for example, pheromones[1] and antibiotics[2] contain the 3-hydroxy-2-methyl-1-alkyl moiety **I** (either as the *threo*- or *erythro*-form, **T-I** and **E-I**, respectively; Scheme 1). Various approaches are available for the diastereo- and enantioselective synthesis of compounds containing such moieties.[1–3]

The nucleophilic addition of an organometallic reagent to a carbonyl group is one of the most powerful and reliable methods for carbon–carbon bond formation known in organic synthesis. When the carbonyl compound has diastereotopic faces, diastereoselective addition reactions are possible. They usually proceed according to Cram's rule giving the so-called Cram-product [called *erythro*-product (**E**) in this paper].[4] However, for carbonyl compounds incorporating a suitably placed heteroatom (for example O, N or S in the α-, β-, or γ-position), chelation of the organometallic reagent with the carbonyl oxygen and the heteroatom can occur. In such cases, the addition usually proceeds according to Cram's cyclic model, which leads to the so-called *anti*-Cram-product [*threo*-product (**T**)].[4,5]

We are interested in the development of highly stereoselective, preparative methods for a class of natural products



Scheme 1. Generalised synthetic routes to compounds of type **I** containing the stereoisomerically pure 3-hydroxy-2-methyl-1-alkyl moiety. For both routes 1 and 2: R^1 = alkyl group; R^2 = Me, Et or *n*-Bu. *: Marks stereogenic centres (relative or absolute configurations).

Keywords: Diastereoselective additions; Dimethylzinc; Titanium tetrachloride; Chelation; Pheromones.
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Table 1. Diastereomeric ratios (dr) obtained when reacting Me_2Zn (2 M in toluene, 1.6 equiv) with aldehydes **1a–g** (1 equiv) mixed with added $TiCl_4$ (1 equiv) at −78; +10 °C in CH_2Cl_2[a]

Entry	Aldehyde	R^1	Dr[b] *threo/erythro*	Product	Yield (%)[c]
1	**1a**	Ph	95/05	**2a**	90
2	**1b**	*p*-Tolyl	94/06	**2b**	75
3	**1c**	*p*-ClC_6H_4	90/10	**2c**	32[d]
4	**1d**	*p*-$MeOC_6H_4$	80/20	**2d**	33[d]
5	**1e**	*o*-$MeOC_6H_4$	30/70	**2e**	43[e]
6	**1f**	*t*-Bu	81/19	**2f**	29[e]
7	**1g**	*n*-Bu	94/06	**2g**	44[e]

[a] A small amount (~4 vol%) of toluene from the reagent, the volume of the solvent was 8 mL/0.47 mmol of **1**.
[b] Diastereomeric ratio was determined by GC analysis on the butyrate, derived from the products **2a–g** and/or by ^1H NMR spectroscopy.
[c] Isolated yields after reactions to full conversion.
[d] Product recovery incomplete.
[e] Low yield due to formation of by-products.

containing the 3-hydroxy-2-methyl-1-alkyl moiety **I** (Scheme 1, R^1=methyl branched alkyl group or alkyl group, R^2=Me), namely the pine sawfly pheromones.[1] If an efficient and highly diastereoselective addition of an alkyl moiety to chiral aldehydes of type **II** could be accomplished, we would have easy access to useful synthons for further transformation into targets of type **I** (Scheme 1).

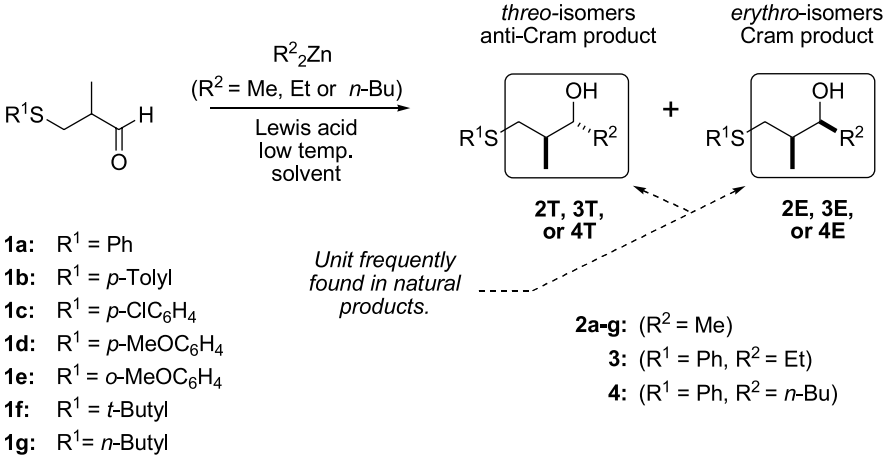
We have earlier screened the reactions of various methylmetal reagents with an aldehyde having a sulfur atom in the β-position, with the sulfur and the carbonyl oxygen serving as chelating centres.[6] Thus, addition of dimethylzinc to 2-methyl-3-(phenylsulfanyl)propanal (**1a**) in the presence of $TiCl_4$ furnished 3-methyl-4-(phenylsulfanyl)butan-2-ol (**2a**) in good yield and high diastereomeric ratio (90%, 95/5 *anti*-Cram/Cram, see entry 1, Table 1).[6] We have also shown that it is possible to prepare stereoisomerically pure 3-methyl-4-(phenylsulfanyl)butan-2-ol (**2a**) from dimethylzinc addition to enantiopure 2-methyl-3-(phenylsufanyl)propanal (**1a**) followed by purification by enzyme catalysed acylation.[7]

In this paper, we describe our efforts to improve the diastereoselectivity in this type of reaction. We have also studied how the diastereoselectivities of additions of other alkylzinc derivatives compare with those of dimethylzinc. Another objective was to see if it was possible to diastereoselectively prepare not only derivatives of type **T-I** via the general Route 1 (Scheme 1) but also **E-I**-ones. In the latter case an alternative sequence of reactions was envisaged (Route 2, Scheme 1).

2. Results and discussion

We first varied the substituents on the sulfur atom in 2-methylpropanals of type **IIa** (Scheme 1) and studied how this affected the diastereoselectivity in methylmetal additions. Therefore, a series of aldehydes **1** were prepared and reacted with dialkylzincs in the presence of various Lewis acids (Scheme 2). Aldehydes **1a–e** with various aryl groups at sulfur and aldehydes **1f** and **1g** with a *tert*-butyl and a *n*-butyl group, respectively, at sulfur were chosen as substrates representing different electronic and steric effects.

The results of the reactions of the arylsulfanylaldehydes **1a–e** with dimethylzinc catalysed by $TiCl_4$ (Table 1) revealed, that an electron withdrawing substituent as well as a donating one in the arylsulfanyl moiety, led to decreased yields and diastereoselectivities (compare entries 3 and 4). The steric effect, however, is more evident (compare entries 6 and 7; products **2f** with a bulky *tert*-butyl group vs **2g** with an *n*-butyl group; dr 81/19 vs 94/06). A probable explanation is that the bulky *tert*-butyl group in **1f** partially hinders chelation between the bulky Lewis acid ($TiCl_4$), sulfur and the carbonyl oxygen. The remarkably



Scheme 2. Diastereoselective addition of R_2Zn (R=Me, Et or *n*-Bu) to racemic aldehydes **1a–g**.

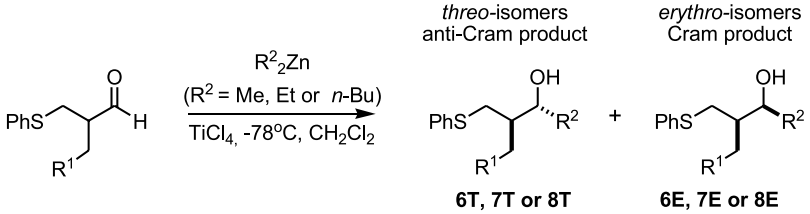
high, and reversed diastereoselectivity observed for the reaction with substrate **1e** to give product **2e** (compare entry 5 with entry 4) with the *erythro* diastereomer in excess (*threo*/*erythro*; 30/70) could probably be explained by assuming that the Lewis acid preferred chelation between oxygen in the 2-methoxyphenyl group and sulfur rather than between sulfur and the carbonyl oxygen. This would lead to an extremely bulky substituent in the aldehyde substrate, which would favour the Cram-product, that is, the *erythro*-one, in excess. In conclusion, when aldehydes **1b–g** were used as substrates, neither the diastereomeric ratios nor the yields in $TiCl_4$-catalysed dimethylzinc additions could be improved by variation of the substituents on sulfur.

Thus, addition of Me_2Zn to 2-methyl-3-(phenylsulfanyl)-propanal (**1a**) seems to be the most efficient way to a synthetic equivalent for the synthon **2aT** (*threo*-configuration, see Scheme 2) leading to targets of type **T-I** (Route 1, Scheme 1). However, as pointed out above, many natural products also contain the stereoisomerically pure 3-hydroxy-2-methyl-1-alkyl moiety having *erythro*-configuration (**E-I**, shown in Scheme 1, where R^2=Me). Therefore, we were interested to see if we were able to achieve similar diastereoselectivities in methylmetal additions to appropriate aldehydes of type **IIb** (Scheme 1), but in this case furnishing ultimately the desired *erythro*-isomers, **E-I**.

Our previous work shows, that addition of various methylmetal reagents to 2-methyl-3-(phenylsulfanyl)propanal (**1a**), in some cases in the presence of Lewis acids, actually furnish the Cram-products (*erythro*-products), albeit in poor diastereoselectivities.[6] Therefore, we decided to develop an alternative sequence of reactions for achieving the desired products of type **E-I** (Route 2, Scheme 1). Replacement of the methyl group in 2-methyl-3-(phenylsulfanyl)propanal (**1a**, Scheme 2) with an alkyl chain, either straight or methyl-branched, leads to aldehydes of type **5** (Scheme 3). Provided that the *anti*-Cram addition of a methylmetal reagent (e.g., Me_2Zn) to **5**, in the presence of $TiCl_4$, proceeds with a high diastereoselectivity, we shall have easy access to synthons of type **6T**. Removal of the phenylsulfanyl group will lead to a methyl group and will furnish the desired target of type **E-I** (Route 2, Scheme 1).

To investigate such an approach, we prepared three aldehydes of type **5** (Scheme 3) with increasing length of the alkyl chain attached to position 2, one with a moderately long chain (**5a**) and the other two with relatively long chains (**5b** and **5c**). The latter was used in one of the pheromone syntheses described below). First, a crossed aldol condensation of a straight chain aldehyde (pentanal, decanal, or dodecanal) with formaldehyde furnished the corresponding 2-alkylpropenals. Each of them was reacted with thiophenol in a Michael addition reaction. Exposure of the resulting aldehydes **5a–c** to Me_2Zn in the presence of $TiCl_4$ furnished the expected products **6a–c** in good yields and in very good diastereoselectivities (95/5; see entries 1–3, Table 2) in favour of the *threo*-products **6T** (*anti*-Cram-product), independent of the chain length of R^1. The diastereoselectivities observed with aldehydes **1a**, **5a–c** and Me_2Zn are very similar, indicating that exchanging the 2-methyl with longer alkyl groups has limited influence on the reaction. Desulfurisation of the products **6T** by treatment with Raney-Nickel yielded the corresponding compounds of type **E-I** (Route 2, Scheme 1, R^2=Me) with a preserved diastereomeric ratio of 95/5 (*erythro*/*threo*). In order to demonstrate the importance of using a combination of Me_2Zn and $TiCl_4$ in these reactions, MeLi was added in the absence of Lewis acid (entry 4, Table 2). This gave a poor *threo*/*erythro*-diastereoselectivity of 60/40 (*anti*-Cram/Cram). Furthermore, an experiment was performed in which Me_2Zn was added to 2-methylundecanal, in the presence of $TiCl_4$. This yielded a selectivity of 58/42 (*anti*-Cram/Cram). This confirmed the importance of the presence of a good chelating group/atom in the proximity of the electrophilic carbonyl group.

Because the additions of Me_2Zn to the aldehydes **1a**[6] and **5a–c** provided the desired products **2a** and **6a–c** in very good diastereoselectivities, we were interested in exploring if an equally efficient diastereoselective addition of either an ethyl or a *n*-butyl moiety to these aldehydes would be possible (Schemes 2 and 3).



dr: from 81/19 up to 95/5 (T/E)

5a: $R^1 = C_2H_5$
5b: $R^1 = n\text{-}C_7H_{15}$
5c: $R^1 = n\text{-}C_9H_{19}$

6a: $R^1 = C_2H_5$, R^2 = Me
7a: $R^1 = C_2H_5$, R^2 = Et
8a: $R^1 = C_2H_5$, $R^2 = n$-Bu
6b: $R^1 = n\text{-}C_7H_{15}$, R^2 = Me
7b: $R^1 = n\text{-}C_7H_{15}$, R^2 = Et
8b: $R^1 = n\text{-}C_7H_{15}$, $R^2 = n$-Bu
6c: $R^1 = n\text{-}C_9H_{19}$, R^2 = Me

Scheme 3. Diastereoselective addition of R_2Zn (R=Me, Et or *n*-Bu) to racemic aldehydes **5a–c**.

Table 2. Diastereomeric ratios (dr) obtained when reacting alkylmetal reagents (1.5 equiv) with aldehydes **5a–5c** (1 equiv; 0.56 mmol) mixed with added $TiCl_4$ (1.1 equiv) at −78; +10 °C in CH_2Cl_2[a]

Entry[b]	Substrate	Reagent[c]	Major product	R^1	R^2	Dr[d] *threo/erythro*
1	**5a**	Me_2Zn	**6aT**	C_2H_5	Me	95/05
2	**5b**	Me_2Zn	**6bT**	n-C_7H_{15}	Me	95/05
3	**5c**	Me_2Zn	**6cT**	n-C_9H_{19}	Me	95/05
4	**5a**	MeLi[e]	**6aT**	C_2H_5	Me	60/40

[a] The volume of the solvent was 8 mL/0.56 mmol of **5**.
[b] Yields were in range of 80–95%.
[c] The solvents from the reagents are Me_2Zn (2 M in toluene) and MeLi (1.3 M in Et_2O). The solvent from the organometallic reagent constitute about 10 vol% of the reaction media.
[d] Diastereomeric ratio was determined by GC analysis on the trifluoroacetate, derived from the products **6a–6c** and/or by ^{1}H NMR spectroscopy.
[e] No Lewis acid present, Et_2O as solvent.

Whereas Me_2Zn failed to react with the aldehyde **1a** in the absence of Lewis acid,[6] the more reactive (see references cited in Ref. 6) Et_2Zn or Bu_2Zn did react with aldehyde **1a** (conversion <5%) in the absence of Lewis acid. Traces of the desired products **3** or **4**, respectively, were formed [*threo*-products, (*anti*-Cram) in excess]. When Et_2Zn and Bu_2Zn were added to the aldehyde **1a** with $TiCl_4$-catalysis as used for the addition of Me_2Zn, the *anti*-Cram selectivities obtained were lower (65/35; *anti*-Cram/Cram; **3T/3E** and 77/23; *anti*-Cram/Cram; **4T/4E**, respectively, entries 1 and 2, Table 3) than that with Me_2Zn.

A possible explanation for these results is that the $TiCl_4$-chelated substrate underwent a certain degree of alkylzinc to alkyltitanium exchange prior to the alkyl addition to the aldehyde. This should result in some intramolecular addition[8] (e.g., 1,3-intramolecular migration) that would result in a lower diastereoselectivity. In order to see if the selectivity in the addition could be increased, the effects of several variables were further studied. The effect of temperature on the outcome of the reaction was almost negligible, addition of Et_2Zn at −100 °C up to −23 °C gave diastereomeric ratios ranging from 65/35 to 68/32 (*threo/erythro*). Varying the added amount of Bu_2Zn (from 1 up to 10 equiv) had no significant effect [dr from 74/26 to 77/23 (*threo/erythro*)]. Increasing the concentration of $TiCl_4$, from 0.5 to 2.4 equiv (compare entries 2–4, 13, and 14, Table 3), changed the diastereoselectivity from 55/45 (0.5 equiv) to 77/23 (1.2 equiv) (*threo/erythro*). Variations of the concentrations of substrates and reactants did not influence the selectivity much. However, it was clear that the nucleophile should not be added neat to the reaction (compare entries 1, 9, 12 and 15, Table 3). The choice of solvent was important. Reactions in ether solvents, for example, THF or Et_2O, gave a low diastereoselectivity, whereas those in dichloromethane gave the highest one (compare entries 2, 5, 6, 10 and 11, Table 3). Replacing the appropriate dialkylzinc with *n*-BuLi, EtMgCl or BuZnBr in the reaction of the aldehyde **1a** in the presence of $TiCl_4$, resulted in poor diastereoselectivity probably due to

Table 3. Diastereomeric ratios (dr) obtained when reacting alkylmetal reagents with aldehyde **1a** (1 equiv; 0.56 mmol) mixed with added $TiCl_4$ at −78; +10 °C in CH_2Cl_2[a]

Entry[b]	$TiCl_4$ (equiv)	Reagent[c] (equiv)	Conv. (%)	Product	Dr[d] *threo/erythro*
1	(1.2)	Et_2Zn (1.6)	85	**3**	65/35
2	(1.2)	Bu_2Zn (1.6)	90	**4**	77/23
3	(2.4)	Bu_2Zn (1.6)	27	**4**	70/30
4	(0.8)	Bu_2Zn (1.6)	100	**4**	75/25
5	(1.2)[e]	Bu_2Zn (1.6)	90	**4**	57/43
6	(1.2)[f]	Bu_2Zn (1.6)	82	**4**	52/48
7	(1.2)	EtMgCl (1.6)	54	**3**	52/48
8	(1.2)	*n*-BuLi (1.6)	76	**4**	61/39
9	(1.2)	Et_2Zn, (1.6), neat	40	**3**	52/48
10	(1.2)[g]	Et_2Zn (1.6)	94	**3**	62/38
11	(1.2)[h]	Et_2Zn (1.6)	99	**3**	64/36
12	(1.2)[i]	Et_2Zn (1.6)	100	**3**	67/33
13	(0.5)[j]	Bu_2Zn (1.6)	70	**4**	55/45
14	(1.0)	Bu_2Zn (1.0)	84	**4**	77/23
15	(1.2)	Et_2Zn (1.6)[k]	90	**3**	67/33
16	(1.2)	BuZnBr (1.6)	66	**4**	53/47

[a] The volume of the solvent was 8 mL/0.56 mmol of **1a**, unless otherwise stated.
[b] Yields were in range of 15–90%, according to GC.
[c] The solvents from Et_2Zn (1 M) and *n*-BuLi (1.6 M) are *n*-hexane, Bu_2Zn (1 M in *n*-heptane), EtMgCl (2 M) and BuZnBr (0.5 M) in THF. The solvent from the organometallic reagent constitute about 10 vol% of the reaction media.
[d] Diastereomeric ratio was determined by GC analysis on the alcohol products **3** and **4** and/or by ^{1}H NMR spectroscopy.
[e] THF as solvent.
[f] Et_2O as solvent.
[g] CH_2Cl_2/*n*-hexane as solvent (1:1).
[h] CH_2Cl_2/benzene as solvent (1:1).
[i] Double amount of solvent (16 mL).
[j] Double amount of **1a**, due to difficulties in measuring the volume of $TiCl_4$, 20 mL of solvent.
[k] Molarity of 0.2 M in CH_2Cl_2/*n*-hexane; 4/1.

Table 4. Diastereomeric ratios (dr) obtained when reacting Bu_2Zn (1 M in *n*-heptane, 1.6 equiv) with aldehyde **1a** (1 equiv) mixed with various Lewis acids at −78 °C; +10 °C in CH_2Cl_2

Entry	Lewis acid (equiv)	Conv. (%)	Dr[a] *threo/erythro*	Product
1	Ti(O-*i*-Pr)$_4$ (1.1)	0	—	—
2	TiCl(O-*i*-Pr)$_3$ (1.1)	55	55/45	**4**
3	$BF_3{\cdot}OEt_2$ (1.1)	91	46/54	**4**
4	$SnCl_4$ (1.1)	0	—	—
5	LiCl (1.1)	0	—	—
6	$ZrCl_4$ (1.2)	96	46/54	**4**
7	$CeCl_3$ (1.2)	0	—	—
8	Cp_2HfCl_2 (1.2)	95	40/60	**4**
9	$LaCl_3$ (1.2)	0	—	—
10	Cp_2TiCl_2 (1.2)	100	35/65	**4**
11	Cp_2ZrCl_2 (1.2)	89	41/59	**4**

[a] Diastereomeric ratio was determined by GC analysis and/or by ^{1}H NMR spectroscopy on the alcohol product **4**.

decomposition of the cyclic chelate (compare entries 1, 7 and 2, 8 and 16, Table 3). Albeit the yield of the desired product **3** was very low, the best selectivity was obtained when $RTiCl_3$ was added to aldehyde **1a** furnishing **3** in diasteromeric ratios up to 90/10 (*threo/erythro*) along with large amounts of by-products from reduction and elimination.

The results described above indicated that, with Et_2Zn and Bu_2Zn in the presence of the substrate and $TiCl_4$, high diastereoselectivities are not easily obtained. However, chelation seems to have some importance for the outcome of these reactions (compare entries 1 and 2 with entries 7 and 8, respectively).

The influence of the nature of the Lewis acid was also studied. Thus, additions of Bu_2Zn to aldehyde **1a** in the presence of various Lewis acids (Table 4) gave no improvements in terms of the diastereoselectivity or yield. It is worth noting, though, that most of the Lewis acids investigated furnished a slight excess of the Cram product (*erythro*-isomer of **4**). Probably the reaction proceeded via an open chain intermediate resulting in a poor selectivity. R_2Zn (R = Et and *n*-Bu) was also reacted with the aldehydes **5a–b** (Table 5). The diastereoselectivities were substantially increased with these substrates, from a selectivity of 65/35 (Et_2Zn) and 77/23 (Bu_2Zn) (products **3** and **4**, Scheme 2, entries 1 and 2, Table 3) to 87/13 (Et_2Zn) and 87/13 (Bu_2Zn) (products **7a** and **8a**, Scheme 3, entries 1 and 2, Table 5). This indicates that, apart from the effects of chelation, sterical interaction within the substrate also plays an important role in the outcome of the addition.

Finally, using the methods previously described in this and our previous paper[6] as starting points, we have synthesised two compounds, ($2R^*$,$3S^*$)-3-methylpentadecan-2-ol, (**11**, *rac-threo*-isomer), and ($2R^*$,$3R^*$)-3-methyltridecan-2-ol, (**12**, *rac-erythro*-isomer) (Scheme 4). The former is a pheromone component of *Gilpinia socia* and *G. frutetorum*.[9] Both the racemates of **11** and the corresponding *erythro*-isomer have been resolved efficiently by esterification with vinyl acetate or propionate mediated by a lipase from *Pseudomonas* sp. (Amano PS).[10]

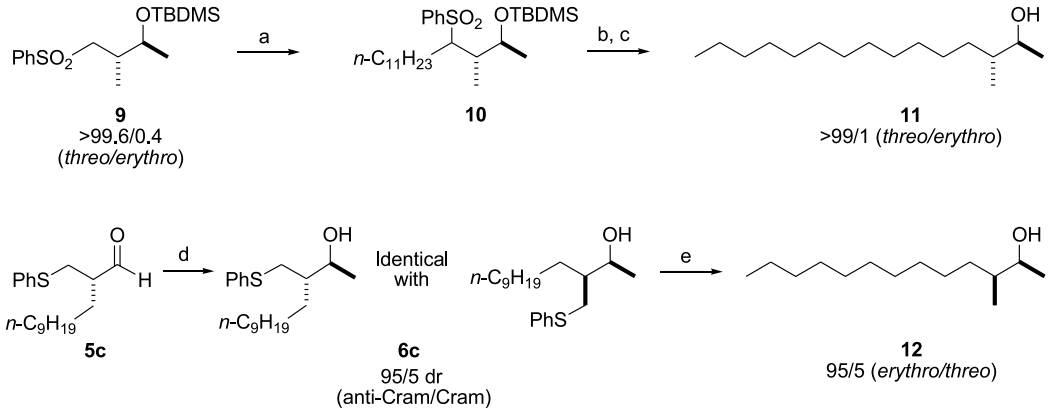
The first synthetic target **11** with *threo*-stereochemistry was prepared from compound **2a**. Oxidation of this to the sulfone followed by recrystallisation of the corresponding 3,5-dinitrobenzoate, hydrolysis and subsequent silylation gave *rac-tert*-butyl-[1,2-dimethyl-3-(phenylsulfonyl)propoxy]-dimethyl-silane, (**9**,[6] *threo/erythro* > 99.6/0.4, Scheme 4). The carbanion of **9** was prepared as earlier reported by us.[6] Alkylation of this with 1-iodoundecane yielded compound **10**. The phenylsulfone moiety and the protective group were removed by treatment with Raney-Ni in 1,4-dioxane under reflux followed by HCl in methanol, to give the desired ($2R^*$,$3S^*$)-3-methylpentadecan-2-ol (**11**, *threo/erythro*, >99/1).

The second synthetic target **12** with *erythro*-stereochemistry was prepared from 3-[(phenylsulfanyl)-methyl]tridecan-2-ol, (**6c**, Scheme 3). Thus, treatment of this compound with Raney-Ni in EtOH at room temperature furnished ($2R^*$,$3R^*$)-3-methyltridecan-2-ol, (**12**, *erythro/threo*, 95/5).

Table 5. Diastereomeric ratios (dr) obtained when reacting alkylmetal reagents (1.5 equiv) with aldehydes **5a–b** (1 equiv; 0.56 mmol) mixed with added $TiCl_4$ (1.1 equiv) at −78; +10 °C in CH_2Cl_2[a]

Entry[b]	Substrate	Reagent[c] (equiv)	Major product	R^1	R^2	Dr[d] *threo/erythro*
1	**5a**	Et_2Zn	**7aT**	C_2H_5	Et	87/13
2	**5a**	Bu_2Zn	**8aT**	C_2H_5	*n*-Bu	87/13
3	**5b**	Et_2Zn	**7bT**	*n*-C_7H_{15}	Et	86/14
4	**5b**	Bu_2Zn	**8bT**	*n*-C_7H_{15}	*n*-Bu	81/19

[a] The volume of the solvent was 8 mL/0.56 mmol of **5**.
[b] Yields were in range of 55–85%.
[c] The solvents from the reagents are Et_2Zn (1 M in *n*-hexane) and Bu_2Zn (1 M in *n*-heptane). The solvent from the organometallic reagent constitute about 10 vol% of the reaction media.
[d] Diastereomeric ratio was determined by GC analysis on the trifluoroacetate, derived from the products **7a–8b** and/or by ^{1}H NMR spectroscopy.



Scheme 4. Synthesis of two potential pine sawfly pheromone components; *threo*-**11** and *erythro*-**12**. Reagents and conditions: (a) 1. THF, DMPU, −40 °C, *n*-BuLi (2.1 equiv), up to 0 °C, cool to −40 °C. 2. 1-Iodoundecane (1.2 equiv, neat), up to 20 °C (93%). (b) Ra-Ni, 1,4-dioxane, reflux (73%). (c) HCl in MeOH, 20 °C (74%). (d) 1. CH_2Cl_2, −78 °C, $TiCl_4$. 2. Me_2Zn. (e) Ra-Ni, EtOH, H_2, 20 °C, 5 days (86%).

3. Experimental

3.1. General experimental procedure

Commercially available chemicals were used without further purification unless otherwise stated Me_2Zn was purchased as a 2.0 M solution in toluene, Et_2Zn (1.0 M) and *n*-BuLi (1.6 M) in *n*-hexane, Bu_2Zn (1.0 M in *n*-heptane), MeLi (1.6 M in Et_2O), EtMgCl (2.0 M) and BuZnBr (0.5 M) in THF. Raney nickel (W-2 type) and $TiCl_4$ were obtained from Fluka and J. T. Baker, respectively. Et_2O ($LiAlH_4$), THF (K, benzophenone), DMPU and CH_2Cl_2 (CaH_2) were distilled from the indicated drying agents and used immediately. Preparative liquid chromatography (LC) was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) employing a gradient technique using an increasing concentration of distilled ethyl acetate in distilled cyclohexane as eluent. The progress was followed by GC or thin layer chromatography (TLC) which was performed on silica gel plates (Merck 60 F_{254}, precoated aluminium foil) eluted with ethyl acetate (20–60%) in cyclohexane and developed by spraying with vanillin in sulphuric acid and heated at 120 °C. NMR spectra were recorded on a Bruker DMX 250 (250 MHz ^{1}H and 62.9 MHz ^{13}C) spectrometer using $CDCl_3$ as solvent and TMS as internal reference. The diastereomeric ratio (dr) of the alcohols **3** and **4**, the corresponding trifluoroacetates of the alcohols **6a**–**8b** and of the corresponding butyrates of the alcohols **2a**–**g** were determined using a capillary column Factor Four, 30 m, 0.32 mm i.d., d_f=0.25 μm, carrier gas N_2, and/or by ^{1}H NMR spectroscopy. The diastereomeric ratio (dr) of **9** was determined using a capillary column EC-1, 30 m, 0.32 mm i.d., d_f=0.25 μm, carrier gas N_2. Mass spectra were recorded on a Saturn 2000 instrument, operating in the EI mode, coupled to a Varian 3800 GC instrument. Infrared absorption spectra were recorded neat, (KBr plates, Perkin–Elmer 16PC FT-IR). Boiling points are uncorrected, and are given as air-bath temperatures (bath temperature/mbar) in a bulb-to-bulb (Büchi-GKR-51) apparatus. The elemental analyses (C and H) were performed by Mikrokemi AB, SE-752 28 Uppsala, Sweden. 2-Methyl-3-(phenylsulfanyl)propanal (**1a**), 3-methyl-4-(phenylsulfanyl)butan-2-ol (**2a**) and *tert*-butyl-[1,2-dimethyl-3-(phenylsulfonyl)propoxy]-dimethyl-silane (**9**) were prepared using the same procedure as reported by us previously.[6]

3.2. Preparation of starting materials

3.2.1. 3-(*tert*-Butylsulfanyl)-2-methylpropanal (1f). Following the procedure described by Vedejs et al.[11] a mixture of *tert*-butylthiol (5.0 g, 55.4 mmol) and methacrolein (3.88 g, 55.4 mmol) was refluxed with triethylamine (0.5 mL) as catalyst over night. This crude mixture was distilled, furnishing a colourless oil (5.5 g, 62%), 92% pure by GC. Bp 70–80 °C/12 mm Hg. The physical and spectroscopic properties were in accordance with those described in the literature.[11]

3.2.2. 2-Methyl-3-[(4-methylphenyl)sulfanyl]propanal (1b). Similarly, *p*-toluenethiol (5.0 g, 40.3 mmol), methacrolein (2.82 g, 40.3 mmol) and triethylamine (0.5 mL) furnished a colourless oil (3.78 g, 48%) after distillation, 90% pure by GC. Bp 110 °C/0.8 mbar. ^{1}H NMR: δ 1.21 (3H, d, J=7.1 Hz), 2.32 (3H, s), 2.51–2.65 (1H, m), 2.87 (1H, dd, J=7.1, 13.4 Hz), 3.25 (1H, dd, J=6.6, 13.4 Hz), 7.03–7.20 (2H, m), 7.26–7.39 (2H, m), 9.65 (1H, d, J=1.4 Hz). ^{13}C NMR: δ 13.4, 21.0, 35.5, 45.9, 129.9 (2C), 130.9 (2C), 131.5, 137.0, 203.1. MS (EI): *m*/*z* 194 (100) (M^+), 165 (3), 137 (10), 124 (47), 91 (28). IR: 3021, 2969, 2922, 2870, 2817, 2729, 1749, 1734, 1718, 1706, 1700, 1684, 1654, 1647, 1636, 1559, 1540, 1534, 1522, 1516, 1508, 1491, 1473, 1464, 1458, 1436, 1419, 1397, 1092, 1017, 928, 804 cm^{-1}. Anal. Calcd for $C_{11}H_{14}OS$: C 68.0; H 7.3. Found: C 67.9; H 7.2.

3.2.3. 3-[(4-Chlorophenyl)sulfanyl]-2-methylpropanal (1c). Similarly, 4-chlorothiophenol (7.0 g, 48.4 mmol), methacrolein (3.39 g, 48.4 mmol) and triethylamine (0.5 mL) furnished a colourless oil (5.0 g, 48%) after distillation, 97% pure by GC. Bp 118 °C/0.6 mbar. ^{1}H NMR: δ 1.23 (3H, d, J=7.2 Hz), 2.53–2.68 (1H, m), 2.89 (1H, dd, J=7.1, 13.3 Hz), 3.28 (1H, dd, J=6.5, 13.3 Hz), 7.28–7.41 (4H, m), 9.66 (1H, d, J=1.4 Hz). ^{13}C NMR: δ 13.5, 34.9, 45.8, 129.3 (2C), 131.3, (2C), 132.7, 134.0, 202.6. MS (EI): *m*/*z* 216 (36) ($M^{37}Cl)^+$, 214 (100) ($M^{35}Cl)^+$, 185 (2), 157 (5), 144 (14), 109 (8). IR: 2970, 2932, 2876, 2816, 2724, 1724, 1560, 1477, 1458, 1438,

1389, 1096, 1011, 929, 814, 745 cm^{-1}. Anal. Calcd for $C_{10}H_{11}ClOS$: C 55.9; H 5.2. Found: C 55.5; H 5.1.

3.2.4. 3-[(4-Methoxyphenyl)sulfanyl]-2-methylpropanal (1d). Similarly, 4-methoxy-benzenethiol (5.0 g, 35.7 mmol), methacrolein (2.5 g, 35.7 mmol) and triethylamine (0.5 mL) furnished a colourless oil (5.4 g, 72%) after distillation, 98% pure by GC. Bp 125 °C/0.5 mbar. ^{1}H NMR: δ 1.20 (3H, d, J=7.1 Hz), 2.50–2.59 (1H, m), 2.82 (1H, dd, J=7.1, 13.4 Hz), 3.18 (1H, dd, J=6.7, 13.4 Hz), 3.80 (3H, s), 6.78–6.88 (2H, m), 7.34–7.40 (2H, m), 9.64 (1H, d, J=1.5 Hz). ^{13}C NMR: δ 13.4, 36.9, 45.9, 55.3, 114.7 (2C), 125.3, 134.0 (2C), 159.3, 203.2. MS (EI): *m/z* 210 (100) (M^+), 153 (4), 140 (12). IR: 2966, 2935, 2836, 2720, 1724, 1592, 1570, 1495, 1459, 1442, 1406, 1373, 1286, 1247, 1174, 1105, 1031, 928, 827, 639, 626 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C 62.8; H 6.7. Found: C 62.8; H 6.8.

3.2.5. 3-[(2-Methoxyphenyl)sulfanyl]-2-methylpropanal (1e). Similarly, 2-methoxy-benzenethiol (10 g, 71.3 mmol), methacrolein (5.87 g, 71.3 mmol) and triethylamine (0.5 mL) furnished a colourless oil (9.0 g, 60%) after distillation, 98% pure by GC. Bp 128 °C/0.5 mm Hg. ^{1}H NMR: δ 1.23 (3H, d, J=7.1 Hz), 2.55–2.64 (1H, m), 2.89 (1H, dd, J=7.2, 13.1 Hz), 3.27 (1H, dd, J=6.5, 13.1 Hz), 3.89 (3H, s), 6.86–6.95 (2H, m), 7.20–7.33 (2H, m), 9.68 (1H, d, J=1.3 Hz). ^{13}C NMR: δ 13.5, 33.1, 45.9, 55.8, 110.7, 121.1, 123.1, 128.2, 131.1, 158.0, 203.2. MS (EI): *m/z* 210 (100) (M^+), 153 (3), 140 (21). IR: 3063, 2967, 2935, 2874, 2836, 2724, 1724, 1578, 1478, 1464, 1433, 1392, 1374, 1295, 1274, 1245, 1182, 1162, 1133, 1072, 1043, 1024, 929, 792, 750, 718, 685 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C 62.8; H 6.7. Found: C 62.8; H 6.7.

3.2.6. 3-(Butylsulfanyl)-2-methylpropanal (1g). Similarly, 1-butanethiol (5.0 g, 55.4 mmol), methacrolein (3.88 g, 55.4 mmol) and triethylamine (0.5 mL) furnished a colourless oil (5.3 g, 60%) after distillation, 95% pure by GC. Bp 62–70 °C/1.0 mbar. ^{1}H NMR: δ 0.92 (3H, d, J=7.2 Hz), 1.21 (3H, d, J=6.8 Hz), 1.33–1.69 (5H, m), 2.50–2.61 (3H, m), 2.82–2.97 (1H, m), 9.69 (1H, d, J=1.4 Hz). ^{13}C NMR: δ 13.6, 13.7, 22.0, 31.6, 32.5, 32.8, 46.3, 203.5. MS (EI): *m/z* 160 (43) (M^+), 132 (63), 103 (14), 89 (18), 56 (100). IR: 2959, 2932, 2873, 2718, 1725, 1654, 1560, 1458, 1438, 1420, 1376, 1275, 1225, 1099, 927 cm^{-1}. Anal. Calcd for $C_8H_{16}OS$: C 60.0; H 10.1. Found: C 60.3; H 9.9.

3.2.7. 2-[(Phenylsulfanyl)methyl]pentanal (5a). A mixture of valeraldehyde (4.9 g, 56.4 mmol), 37% aqueous formaldehyde (9.2 g, 0.11 mol) and diethylamine hydrochloride (9.4 g, 84.6 mmol) was stirred at 40 °C for 12 h, followed by the addition of triethylamine (3 mL) and thiophenol (7.0 g, 63.6 mmol) and the reaction was allowed to stir at 70 °C over night. Organic and aqueous phases were extracted. The aqueous phase was extracted with *n*-hexane (3×15 mL) and the combined hexane extract was washed with HCl (20 mL, 2 M, aq.), brine (20 mL), dried ($MgSO_4$), filtered and the solvent was evaporated off. A Colourless oil (5.5 g, 47%) was obtained after chromatography and distillation, 93% pure by GC, which was used immediately without further purification (see Section 3.3.3). Bp 130 °C/0.4 mbar. ^{1}H NMR: δ 0.90 (3H, t, J=7.2 Hz), 1.25–1.38 (2H, m), 1.52–1.76 (2H, m), 2.52–2.59 (1H, m), 3.01 (1H, dd, J=6.0, 13.3 Hz), 3.21 (1H, dd, J=7.7, 13.3 Hz), 7.17–7.37 (5H, m), 9.64 (1H, d, J=2.1 Hz). ^{13}C NMR: δ 14.0, 19.8, 30.6, 32.8, 50.8, 126.6, 129.1 (2C), 130.0 (2C), 135.5, 203.1. MS (EI): *m/z* 208 (100) (M^+), 123 (8), 110 (13).

3.2.8. 2-[(Phenylsulfanyl)methyl]decanal (5b). Similarly, decyl aldehyde (7.6 g, 48.6 mmol) furnished **5b** as a colourless oil (5.1 g, 38%), 84% pure by GC, which was used immediately without further purification (see Section 3.3.3). Bp 210 °C/0.5 mbar. ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz), 1.17–1.32 (12H, m), 1.54–1.77 (2H, m), 2.49–2.60 (1H, m), 3.01 (1H, dd, J=6.0, 13.3 Hz), 3.22 (1H, dd, J=7.7, 13.3 Hz), 7.17–7.38 (5H, m), 9.65 (1H, d, J=2.2 Hz). ^{13}C NMR: δ 14.1, 22.6, 26.5, 28.5, 29.2, 29.3, 29.6, 31.8, 32.8, 51.0, 126.6, 129.1 (2C), 130.0 (2C), 135.5, 203.2. MS (EI): *m/z* 278 (35) (M^+), 123 (17), 110 (100).

3.2.9. 2-[(Phenylsulfanyl)methyl]dodecanal (5c). Similarly, dodecyl aldehyde (6.6 g, 36.0 mmol) furnished **5c** as a colourless oil (2.5 g, 23%), 94% pure by GC, which was used immediately without further purification (see Section 3.3.3). ^{1}H NMR: δ 0.88 (3H, t, J=6.9 Hz), 1.24 (16H, br s), 1.54–1.77 (2H, m), 2.49–2.61 (1H, m), 3.01 (1H, dd, J=6.0, 13.3 Hz), 3.22 (1H, dd, J=7.7, 13.3 Hz), 7.18–7.39 (5H, m), 9.65 (1H, d, J=2.2 Hz. MS (EI): *m/z* 306 (28) (M^+), 123 (12), 110 (100).

3.3. General procedures for the alkylmetal addition reactions

3.3.1. 3-Methyl-4-[(4-methylphenyl)sulfanyl]butan-2-ol (2b), 4-[(4-chlorophenyl)sulfanyl]-3-methylbutan-2-ol (2c), 4-[(4-methoxyphenyl)sulfanyl]-3-methylbutan-2-ol (2d), 4-[(2-methoxyphenyl)sulfanyl]-3-methylbutan-2-ol (2e), 4-(*tert*-butylsulfanyl)-3-methylbutan-2-ol (2f) and 4-(butylsulfanyl)-3-methylbutan-2-ol (2g). Entries 2–7, Table 1. The appropiate aldehyde (0.47 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 mL) and cooled to −78 °C. $TiCl_4$ (50 μL, 0.47 mmol) was added dropwise via a syringe. An orange viscous solution was obtained and this was kept at −78 °C. After stirring for 0.5 h, Me_2Zn [0.38 mL, 2 M in toluene, 0.75 mmol] was added dropwise followed by stirring at −78 °C. After stirring over night, at which point the temperature had reached 10 °C, water (5 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3×15 mL) and the combined Et_2O extract was washed with $NaHCO_3$ (20 mL, sat. aq.), dried (Na_2SO_4), filtered and the solvent was evaporated off. A colourless oil was obtained after LC.

3.3.2. 2-Methyl-1-(phenylsulfanyl)pentan-3-ol (3) and 2-methyl-1-(phenylsulfanyl)heptan-3-ol (4). Tables 3 and 4. The Lewis acid (from 0.28 mmol up to 1.34 mmol; see specific entries in Tables 3 and 4) was added to a precooled, −78 °C, solution of 2-methyl-3-(phenylsulfanyl)propanal (**1a**, 0.1 g, 0.56 mmol) in freshly distilled dry solvent (8.0 mL). An orange viscous solution was obtained and this was kept at −78 °C. After stirring for 1 h, the alkylmetal reagent solution (from 0.56 mmol up to 0.90 mmol; see specific entries in Tables 3 and 4) was added. After stirring over night, at which point the temperature had reached 10 °C, water (5 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O

(3×15 mL) and the combined Et_2O extract was washed with $NaHCO_3$ (20 mL, sat. aq.), dried (Na_2SO_4), filtered and the solvent was evaporated off, furnishing the product.

3.3.3. 3-[(Phenylsulfanyl)methyl]hexan-2-ol (6a, $R^1=C_2H_5$, $R^2=Me$), 4-[(phenylsulfanyl)methyl]heptan-3-ol (7a, $R^1=C_2H_5$, $R^2=Et$), 4-[(phenylsulfanyl)methyl]nonan-5-ol (8a, $R^1=C_2H_5$, $R^2=n$-Bu), 3-[(phenylsulfanyl)methyl]undecan-2-ol (6b, $R^1=n$-C_7H_{15}, $R^2=Me$), 4-[(phenylsulfanyl)methyl]dodecan-3-ol (7b, $R^1=n$-C_7H_{15}, $R^2=Et$), 6-[(phenylsulfanyl)methyl]tetradecan-5-ol (8b, $R^1=n$-C_7H_{15}, $R^2=n$-Bu) and 3-[(phenylsulfanyl)methyl]tridecan-2-ol (6c, $R^1=n$-C_9H_{19}, $R^2=Me$). *(a)* Tables 2 and 5, *with the exception of entry 4* (Table 2). $TiCl_4$ (0.07 mL, 0.62 mmol) was added to a precooled, −78 °C, solution of the appropiate aldehyde (0.56 mmol) in freshly distilled dry CH_2Cl_2 (8.0 mL). An orange viscous solution was obtained and this was kept at −78 °C. The mixture was stirred at that temperature for 1 h, followed by the addition of the R_2Zn solution (0.84 mmol; see specific entries in Table 2). After stirring over night, at which point the temperature had reached 10 °C, water (5 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3×15 mL) and the combined Et_2O extract was washed with $NaHCO_3$ (20 mL, sat. aq.), dried (Na_2SO_4), filtered and the solvent was evaporated off, furnishing the product.

(b) Entry 4 (Table 2). The differences from above are; no Lewis acid is present, the alkylmetal reagent is MeLi (1.3 M in Et_2O) and the reaction is performed in Et_2O.

3.4. Description of specific compounds

3.4.1. 3-Methyl-4-[(4-methylphenyl)sulfanyl]butan-2-ol (2b). Entry 2, Table 1, *threo/erythro*, **2bT/2bE**, 94/06. LC furnished a colourless oil. Bp 120 °C/0.4 mbar. ^{1}H NMR: δ 1.00 (0.18H, d, J=6.9 Hz), 1.02 (2.82H, d, J=6.8 Hz), 1.17 (3H, d, J=6.3 Hz), 1.64 (1H, d, –OH, J=4.8 Hz), 1.68–1.84 (1H, m), 2.31 (3H, s), 2.76 (1H, dd, J=8.0, 12.8 Hz), 3.04–3.12 (0.06H, m), 3.14 (0.94H, dd, J=4.8, 12.8 Hz), 3.75 (0.94H, dquint, J=4.9, 6.3 Hz), 3.91–4.00 (0.06H, m), 7.08–7.11 (2H, m), 7.25–7.30 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.6*, 15.4, 20.3, 21.0, 38.1, 39.1*, 40.1, 69.6*, 71.1, 129.7 (2C), 129.8 (2C), 133.0, 136.0. MS (EI): m/z 210 (100) (M^+), 193 (8), 165 (3), 137 (6), 124 (10), 91 (5). IR: 3385, 2975, 2932, 1654, 1560, 1508, 1492, 1458, 1420, 1400, 1377, 1320, 1124, 1087, 1025, 1012, 932, 846, 811, 668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}OS$: C 68.5; H 8.6. Found: C 68.7; H 8.7.

3.4.2. 4-[(4-Chlorophenyl)sulfanyl]-3-methylbutan-2-ol (2c). Entry 3, Table 1, *threo/erythro*, **2cT/2cE**, 90/10. LC furnished a colourless oil. Bp 135 °C/1.1 mbar. ^{1}H NMR: δ 1.02 (0.3H, d, J=6.9 Hz), 1.03 (2.7H, d, J=6.8 Hz), 1.19 (0.3H, d, J=6.4 Hz), 1.20 (2.7H, d, J=6.3 Hz), 1.49 (1H, d, –OH, J=4.8 Hz), 1.70–1.81 (1H, m), 2.75 (1H, dd, J=8.3, 12.8 Hz), 3.08–3.15 (0.1H, m), 3.20 (0.9H, dd, J=4.4, 12.8 Hz), 3.74 (0.9H, dquint, J=4.9, 6.3 Hz), 3.91–4.03 (0.1H, m), 7.22–7.30 (4H, m). ^{13}C NMR: δ 15.4, 20.6, 37.5, 40.2, 71.1, 129.0 (2C), 130.2 (2C), 131.7, 135.6. MS (EI): m/z 232 (36) ($M^{37}Cl)^+$, 230 (100) ($M^{35}Cl)^+$, 213 (8), 185 (3), 157 (7), 144 (16), 108 (14), 86 (11), 71 (21). Anal. Calcd for $C_{11}H_{15}ClOS$: C 57.3; H 6.6. Found: C 57.7; H 6.7.

3.4.3. 4-[(4-Methoxyphenyl)sulfanyl]-3-methylbutan-2-ol (2d). Entry 4, Table 1, *threo/erythro*, **2dT/2dE**, 80/20. LC furnished a colourless oil. Bp 165 °C/0.8 mbar. ^{1}H NMR: δ 0.99 (0.6H, d, J=6.9 Hz), 1.01 (2.4H, d, J=6.8 Hz), 1.16 (3H, d, J=6.3 Hz), 1.60 (1H, d, –OH, J=5.6 Hz), 1.64–1.80 (1H, m), 2.72 (1H, dd, J=7.9, 12.8 Hz), 2.98–3.06 (0.2H, m), 3.07 (0.8H, dd, J=4.8, 12.8 Hz), 3.72–3.78 (0.8H, m), 3.79 (3H, s), 3.86–4.03 (0.2H, m), 6.81–6.87 (2H, m), 7.33–7.39 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.6*, 15.3, 20.3, 39.6*, 39.7, 40.1, 55.3, 69.6*, 71.1, 114.6 (2C), 126.9, 132.8 (2C), 158.8. MS (EI): m/z 226 (100) (M^+), 209 (6), 181 (3), 153 (9), 140 (32), 125 (13), 107 (6). IR: 3422, 2970, 1595, 1578, 1497, 1458, 1304, 1252, 1174, 1089, 1026, 829, 668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_2S$: C 63.7; H 8.0. Found: C 64.3; H 8.0.

3.4.4. 4-[(2-Methoxyphenyl)sulfanyl]-3-methylbutan-2-ol (2e). Entry 5, Table 1, *threo/erythro*, **2eT/2eE**, 30/70. LC furnished a colourless oil. Bp 150 °C/0.5 mbar. ^{1}H NMR: δ 1.03 (2.1H, d, J=6.9 Hz), 1.05 (0.9H, d, J=6.8 Hz), 1.19 (2.1H, d, J=6.4 Hz), 1.20 (0.9H, d, J=6.3 Hz), 1.58 (1H, d, –OH, J=4.9 Hz), 1.71–1.86 (1H, m), 2.77 (0.7H, dd, J=7.3, 12.5 Hz), 2.75–2.83 (0.3H, m), 3.08 (0.7H, dd, J=6.5, 12.5 Hz), 3.09–3.16 (0.3H, m), 3.75–3.85 (0.3H, m), 3.90 (3H, s), 3.96–4.07 (0.7H, m), 6.84–6.96 (2H, m), 7.15–7.34 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.8, 15.7*, 20.2, 20.3*, 35.8, 35.9*, 39.0, 40.1*, 55.8, 69.7, 71.1*, 110.5, 121.1, 124.8, 127.0, 127.2*, 129.3, 129.6*, 157.3. MS (EI): m/z 226 (100) (M^+), 209 (8), 181 (3), 153 (6), 140 (23), 125 (8), 107 (3). IR: 3367, 2973, 1586, 1479, 1436, 1379, 1274, 1240, 1132, 1071, 1021, 793, 755 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_2S$: C 63.7; H 8.0. Found: C 64.1; H 8.1.

3.4.5. 4-(*tert*-Butylsulfanyl)-3-methylbutan-2-ol (2f). Entry 6, Table 1, *threo/erythro*, **2fT/2fE**, 81/19. LC furnished a colourless oil. ^{1}H NMR: δ 1.00 (3H, d, J=6.9 Hz), 1.19 (3H, d, J=6.3 Hz), 1.33 (9H, s), 2.18 (1H, s, –OH), 1.67–1.81 (1H, m), 2.41–2.48 (0.19H, m), 2.50 (0.81H, dd, J=7.2, 11.7 Hz), 2.69 (1H, dd, J=5.3, 11.7 Hz), 3.69–3.79 (0.81H, m), 3.86–3.98 (0.19H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 14.1*, 16.0, 20.2*, 20.4, 30.9 (3C), 31.0*, 31.9, 32.0*, 39.8*, 40.7, 42.0, 70.3*, 71.5. MS (EI): m/z 176 (53) (M^+), 159 (7), 131 (8), 119 (12), 103 (14), 87 (54), 71 (36), 57 (100).

3.4.6. 4-(Butylsulfanyl)-3-methylbutan-2-ol (2g). Entry 7, Table 1, *threo/erythro*, **2gT/2gE**, 94/06. LC furnished a colourless oil. Bp 95 °C/1.4 mbar. ^{1}H NMR: δ 0.92 (3H, t, J=7.2 Hz), 0.99 (3H, d, J=6.9 Hz), 1.18 (3H, d, J=6.3 Hz), 1.33–1.86 (5H, m), 1.95 (1H, d, –OH, J=4.4 Hz), 2.39–2.56 (3H, m), 2.68 (1H, dd, J=5.4, 12.7 Hz), 3.74 (0.94H, dquint, J=4.5, 6.3 Hz), 3.90–3.96 (0.06H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.7, 15.7, 20.4, 22.0, 31.7, 32.5, 36.0*, 36.3, 39.3*, 40.3, 70.1*, 71.5. MS (EI): m/z 176 (65) (M^+), 159 (19), 131 (12), 103 (14), 87 (34), 71 (100), 57 (11). IR: 3356, 2977, 2937, 2877, 1706, 1458, 1448, 1379, 1345, 1321, 1294, 1125, 1100,

1048, 1007, 948, 907, 846 cm^{-1}. Anal. Calcd for $C_9H_{20}OS$: C 61.3; H 11.4. Found: C 61.1; H 11.3.

3.4.7. 2-Methyl-1-(phenylsulfanyl)pentan-3-ol (3). Entry 1, Table 3; *threo/erythro*, **3T/3E**, 65/35. LC furnished a colourless oil. Bp 140 °C/0.5 mbar. ^1H NMR: δ 0.91–0.99 (3H, m), 1.00 (1.05H, d, $J=6.7$ Hz), 1.05 (1.95H, d, $J=6.9$ Hz), 1.33–1.67 (3H, m), 1.75–1.90 (1H, m), 2.80 (0.65H, dd, $J=8.4$, 12.8 Hz), 2.85 (0.35H, dd, $J=7.1$, 13.0 Hz), 3.10 (0.35H, dd, $J=6.9$, 12.8 Hz), 3.23 (0.65H, dd, $J=4.2$, 12.7 Hz), 3.44–3.51 (0.65H, m), 3.66–3.73 (0.35H, m), 7.13–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 10.0, 10.6*, 13.1*, 15.9, 26.9, 27.4*, 36.9, 37.4*, 37.8*, 38.4, 74.8*, 76.5, 125.7, 128.8 (2C), 128.9 (2C), 137.1. MS (EI): *m/z* 210 (100) (M^+), 193 (28), 163 (8), 123 (25), 110 (32), 100 (30). IR: 3406, 3058, 2964, 2932, 2876, 1584, 1480, 1458, 1438, 1378, 1302, 1272, 1245, 1186, 1091, 1069, 1026, 972, 897, 738, 690 cm^{-1}. Anal. Calcd for $C_{12}H_{18}OS$: C 68.5; H 8.6. Found: C 68.5; H 8.8.

3.4.8. 2-Methyl-1-(phenylsulfonyl)pentan-3-ol (sulfonyl of 3). *m*-Chloroperbenzoic acid (0.57 g, 2.54 mmol) was added to a solution of **3** (0.21 g, 1.01 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The mixture was allowed to reach room temperature over night, $NaHCO_3$ (10 mL, sat. aq.) was added and the aqueous phase was extracted with Et_2O (3× 15 mL) and the combined Et_2O extract was washed with $NaHCO_3$ (15 mL, sat. aq.), brine (15 mL), dried (Na_2SO_4), filtered and the solvent was evaporated off, furnishing a yellowish oil (0.20 g, 81%) after LC (EtOAc gradient in cyclohexane), 99% pure by GC. Bp 235 °C/0.6 mbar. (*threo/erythro*, 65/35). ^1H NMR: δ 0.91 (1.95H, t, $J=7.4$ Hz), 0.94 (1.05H, t, $J=7.4$ Hz), 1.02 (1.05H, d, $J=7.0$ Hz), 1.14 (1.95H, d, $J=6.9$ Hz), 1.27–1.57 (2H, m), 1.85 (1H, br s, OH), 2.09–2.20 (0.65H, m), 2.26–2.35 (0.35H, m), 2.94 (0.65H, dd, $J=8.5$, 14.2 Hz), 2.97 (0.35H, dd, $J=6.9$, 14.1 Hz), 3.32–3.47 (1.65H, m), 3.65–3.71 (0.35H, m), 7.53–7.69 (3H, m), 7.91–7.95 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 9.79, 10.6*, 13.6*, 17.4, 26.5*, 27.2, 33.4*, 34.1, 58.6, 59.6*, 74.8*, 76.4, 127.8 (2C), 129.3 (2C), 133.6, 140.0. MS (EI): *m/z* 243 (34) $(M+H)^+$, 225 (32), 213 (12), 200 (30), 182 (7), 143 (75), 125 (43), 100 (19), 78 (100), 59 (90). The ^1H NMR and ^{13}C NMR spectral data were similar to those reported in the literature for the *erythro*-isomer.[12]

3.4.9. 2-Methyl-1-(phenylsulfanyl)heptan-3-ol (4). Entry 3, Table 3; *threo/erythro*, **4T/4E**, 70/30. LC furnished a colourless oil. Bp 180 °C/0.9 mbar. ^1H NMR: δ 0.88–0.93 (3H, m), 1.00 (0.9H, d, $J=6.9$ Hz), 1.05 (2.1H, d, $J=6.9$ Hz), 1.23–1.58 (7H, m), 1.74–1.88 (1H, m), 2.79 (0.7H, dd, $J=8.4$, 12.7 Hz), 2.84 (0.3H, dd, $J=7.1$, 12.9 Hz), 3.10 (0.3H, dd, $J=6.9$, 12.8 Hz), 3.22 (0.7H, dd, $J=4.3$, 12.7 Hz), 3.51–3.58 (0.7H, m), 3.74–3.79 (0.3H, m), 7.12–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.2*, 14.1, 15.9, 22.7*, 22.7, 28.0, 28.4*, 33.7, 34.2*, 36.9, 37.7*, 38.7, 73.3*, 75.1, 125.7, 128.9 (4C), 137.1. MS (EI): *m/z* 238 (100) (M^+), 221 (14), 163 (15), 151 (14), 128 (34), 123 (57), 110 (100), 86 (88), 69 (49), 58 (47). IR: 3406, 3059, 2957, 2932, 2871, 1584, 1481, 1466, 1458, 1438, 1378, 1272, 1115, 1090, 1026, 1001, 978, 897, 737, 690, 670 cm^{-1}. Anal. Calcd for $C_{14}H_{22}OS$: C 70.5; H 9.3. Found: C 70.6; H 9.4.

3.4.10. 2-Methyl-1-(phenylsulfonyl)heptan-3-ol (sulfonyl of 4). Oxidation of **4** was performed as above to give a colourless oil after LC. Bp 260 °C/1.2 mbar (*threo/erythro*, 70/30). ^1H NMR: δ 0.85–0.92 (3H, m), 1.02 (0.9H, d, $J=7.0$ Hz), 1.15 (2.1H, d, $J=6.9$ Hz), 1.18–1.48 (6H, m), 1.82 (1H, br s, OH), 2.06–2.21 (0.7H, m), 2.25–2.34 (0.3H, m), 2.90–3.01 (1H, m), 3.33–3.46 (1.7H, m), 3.73–3.79 (0.3H, m), 7.53–7.69 (3H, m), 7.91–7.95 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 13.7*, 14.0, 17.4, 22.6, 27.7, 28.3*, 33.3*, 33.7*, 34.1, 34.5, 58.5, 59.5*, 73.3*, 75.0, 127.8 (2C), 129.3 (2C), 133.6, 140.0. MS (EI): *m/z* 271 (7) $(M+H)^+$, 253 (11), 228 (10), 213 (12), 170 (4), 156 (7), 143 (42), 125 (23), 87 (48), 78 (40), 69 (100). IR: 3510, 3066, 2957, 2933, 2872, 1466, 1459, 1448, 1406, 1381, 1304, 1147, 1086, 999, 986, 749, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3S$: C 62.2; H 8.2. Found: C 62.5; H 8.1.

3.4.11. 3-[(Phenylsulfanyl)methyl]hexan-2-ol (6a, $R^1=C_2H_5$, $R^2=Me$). Entry 1, Table 2; *threo/erythro*, **6aT/6aE**, 95/05. LC furnished a colourless oil. ^1H NMR: δ 0.90 (3H, t, $J=6.9$ Hz), 1.20 (3H, d, $J=6.3$ Hz), 1.17–1.55 (4H, m), 1.61–1.71 (1H, m), 1.71 (1H, s, –OH), 2.86–3.15 (2H, m), 3.94 (0.95H, app. quint, $J=6.2$ Hz), 4.02–4.16 (0.05H, m), 7.13–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 14.3, 15.3*, 19.7, 20.2, 20.6, 31.3*, 31.8, 34.5, 34.7*, 43.9*, 44.5, 68.8*, 69.1, 125.8, 128.9 (2C), 129.0 (2C), 137.1. MS (EI): *m/z* 224 (100) (M^+), 207 (20), 123 (27), 110 (50), 85 (15).

3.4.12. 4-[(Phenylsulfanyl)methyl]heptan-3-ol (7a, $R^1=C_2H_5$, $R^2=Et$). Entry 1, Table 5; *threo/erythro*, **7aT/7aE**, 87/13. LC furnished a colourless oil. Bp 190 °C/2.8 mbar. ^1H NMR: δ 0.90 (3H, t, $J=7.0$ Hz), 0.95 (3H, t, $J=7.2$ Hz), 1.27–1.62 (6H, m), 1.64 (1H, s, –OH), 1.67–1.77 (1H, m), 2.98 (1H, dd, $J=6.5$, 12.6 Hz), 3.12 (1H, dd, $J=5.0$, 12.6 Hz), 3.62 (0.87H, dt, $J=4.5$, 8.4 Hz), 3.78 (0.13H, dt, $J=3.2$, 6.6 Hz), 7.13–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 10.4, 10.8*, 14.3, 20.2, 20.7*, 26.8*, 27.3, 30.7*, 32.2, 34.3, 35.2*, 42.4*, 42.6, 74.3*, 74.5, 125.8, 128.9 (2C), 129.0 (2C), 137.2. MS (EI): *m/z* 308 (100) (M^+), 291 (28), 249 (12), 169 (65), 123 (53), 110 (82). MS (EI): *m/z* 238 (100) (M^+), 221 (58), 123 (5), 110 (8). IR: 3416, 3059, 2959, 2931, 2872, 1584, 1480, 1464, 1438, 1378, 1304, 1090, 1069, 1026, 998, 973, 738, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{22}OS$: C 70.5; H 9.3. Found: C 70.5; H 9.5.

3.4.13. 4-[(Phenylsulfanyl)methyl]nonan-5-ol (8a, $R^1=C_2H_5$, $R^2=n$-Bu). Entry 2, Table 5; *threo/erythro*, **8aT/8aE**, 87/13. LC furnished a colourless oil. Bp 195 °C/0.3 mbar. ^1H NMR: δ 0.90 (6H, t, $J=7.0$ Hz), 1.21–1.55 (10H, m), 1.61 (1H, s, –OH), 1.63–1.75 (1H, m), 2.97 (1H, dd, $J=6.5$, 12.6 Hz), 3.10 (1H, dd, $J=5.0$, 12.6 Hz), 3.70 (0.87H, dt, $J=4.6$, 7.6 Hz), 3.83–3.90 (0.13H, m), 7.13–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 14.1, 14.3, 20.3, 20.7*, 22.7, 28.3, 28.5*, 30.7*, 32.2, 33.6*, 34.1, 34.3, 35.2*, 42.8*, 43.0, 72.7*, 73.0, 125.8, 128.9 (2C), 129.0 (2C), 137.2. MS (EI): *m/z* 266 (100) (M^+), 249 (73), 123 (5), 110 (11). IR: 3422, 3059, 2957, 2931, 2871, 1584, 1480, 1466, 1458, 1438, 1378,

1089, 1026, 738, 690 cm^{-1}. Anal. Calcd for $C_{16}H_{26}OS$: C 72.1; H 9.8. Found: C 72.0; H 10.0.

3.4.14. 3-[(Phenylsulfanyl)methyl]undecan-2-ol (6b, R^1=*n*-C_7H_{15}, R^2=Me). Entry 2, Table 2; *threo*/*erythro*, **6bT/6bE**, 95/05. LC furnished a colourless oil. ^{1}H NMR: δ 0.88 (3H, t, J=6.8 Hz), 1.21 (3H, d, J=6.3 Hz), 1.18–1.48 (14H, m), 1.60–1.68 (1H, m), 1.67 (1H, s, –OH), 2.86–3.15 (2H, m), 3.94 (0.95H, app. quint, J=6.2 Hz), 4.05–4.20 (0.05H, m), 7.14–7.38 (5H, m). MS (EI): *m*/*z* 294 (100) (M^+), 277 (18), 184 (21), 163 (13), 123 (51), 110 (83), 85 (29), 71 (42).

3.4.15. 4-[(Phenylsulfanyl)methyl]dodecan-3-ol (7b, R^1=*n*-C_7H_{15}, R^2=Et). Entry 3, Table 5; *threo*/*erythro*, **7bT/7bE**, 86/14. LC furnished a colourless oil. Bp 270 °C/0.8 mbar. ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz), 0.95 (3H, t, J=7.4 Hz), 1.26 (12H, br s), 1.37–1.60 (4H, m), 1.67 (1H, s, –OH), 1.61–1.75 (1H, m), 2.97 (1H, dd, J=6.5, 12.6 Hz), 3.12 (1H, dd, J=4.9, 12.6 Hz), 3.62 (0.86H, dt, J=4.3, 8.4 Hz), 3.78 (0.14H, dt, J=3.2, 6.5 Hz), 7.13–7.37 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 10.4, 10.8*, 14.1, 22.7, 26.8*, 27.1, 27.3, 27.5*, 28.4*, 29.3, 29.5, 29.9 (2C), 31.9, 34.3, 35.2*, 42.7*, 42.9, 74.3*, 74.5, 125.8, 128.9 (2C), 129.0 (2C), 137.0*, 137.2. MS (EI): *m*/*z* 308 (100) (M^+), 291 (28), 249 (12), 169 (65), 123 (53), 110 (82). IR: 3422, 3059, 2957, 2926, 2855, 1584, 1480, 1459, 1438, 1376, 1088, 1026, 738, 690 cm^{-1}. Anal. Calcd for $C_{19}H_{32}OS$: C 74.0; H 10.5. Found: C 74.4; H 10.7.

3.4.16. 6-[(Phenylsulfanyl)methyl]tetradecan-5-ol (8b, R^1=*n*-C_7H_{15}, R^2=*n*-Bu). Entry 4, Table 5; *threo*/*erythro*, **8bT/8bE**, 81/19. LC furnished a colourless oil. Bp 300 °C/0.35 mbar. ^{1}H NMR: δ 0.85–0.93 (6H, m), 1.26 (16H, br s), 1.30–1.49 (4H, m), 1.58 (1H, s, –OH), 1.61–1.73 (1H, m), 2.97 (1H, dd, J=6.5, 12.6 Hz), 3.11 (1H, dd, J=5.0, 12.6 Hz), 3.71 (0.81H, dt, J=4.6, 7.4 Hz), 3.84–3.90 (0.19H, m), 7.13–7.39 (5H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ 14.0*, 14.1 (2C), 22.6*, 22.7 (2C), 27.1, 27.5*, 28.3, 28.4*, 28.5*, 29.2*, 29.3, 29.5, 29.8, 29.9, 31.8*, 31.9, 34.2, 34.3, 43.0*, 43.2, 72.8*, 73.0, 125.8, 128.9 (2C), 129.0 (2C), 129.7*, 137.2. MS (EI): *m*/*z* 336 (100) (M^+), 319 (62), 110 (11).

3.4.17. 3-[(Phenylsulfanyl)methyl]tridecan-2-ol (6c, R^1=*n*-C_9H_{19}, R^2=Me). Entry 3, Table 2; *threo*/*erythro*, **6cT/6cE**, 95/05. A yellowish oil which was used without further purification (see Section 3.4.19). ^{1}H NMR: δ 0.88 (3H, t, J=6.8 Hz), 1.21 (3H, d, J=6.3 Hz), 1.18–1.48 (18H, m), 1.59–1.68 (1H, m), 1.59 (1H, s, –OH), 2.86–3.15 (2H, m), 3.94 (0.95H, app. quint, J=6.2 Hz), 4.01–4.14 (0.05H, m), 7.14–7.37 (5H, m). ^{13}C NMR: δ 14.1, 20.7, 22.7, 26.9, 27.0, 29.4, 29.6 (3C), 29.9, 31.9, 34.5, 44.7, 69.2, 125.8, 128.9 (2C), 129.0 (2C), 137.1. MS (EI): *m*/*z* 322 (100) (M^+), 305 (8), 277 (14), 212 (25), 197 (13), 163 (13), 123 (50), 110 (85), 71 (55).

3.4.18. (2R^*,3S^*)-3-Methylpentadecan-2-ol (11). To a solution of **9**, *threo*/*erythro*>99.6/0.4 (0.38 g, 1.11 mmol) and DMPU (1.34 mL, 11.1 mmol) in dry degassed THF (10 mL) a solution of *n*-BuLi (1.50 mL, 2.33 mmol, 1.55 M) was added at −40 °C. After 5 min the reaction was allowed to reach 0 °C followed by cooling to −40 °C. 1-Iodoundecane (0.31 mL, 1.33 mmol) was added neat and the reaction was allowed to reach room temperature overnight. The reaction was quenched with NH_4Cl (10 mL, sat. aq.) and the aqueous phase was extracted with Et_2O (4×15 mL) and the combined Et_2O extract was washed with HCl (10 mL, 2 M, aq.), brine (20 mL), dried (Na_2SO_4). filtered and the solvent was evaporated off. A colourless oil of (1R^*,2R^*)-[3-(phenylsulfonyl)1,2-dimethyl-tetradecyloxy]-*tert*-butyl-dimethyl-silane (**10**) (0.54 g, 93%) was obtained after chromatography, 95% pure by GC with a diastereomeric ratio of 84/16, which was used without further purification. ^{1}H NMR: δ 0.00 (2.52H, s), 0.02 (2.52H, s), 0.14 (0.48H, s), 0.20 (0.48H, s), 0.84 (7.56H, s), 0.88 (1.44H, s), 0.80–0.92 (3H, m), 0.96 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=6.1 Hz), 1.08–1.30 (18H, m), 1.58–2.10 (3H, m), 3.46–3.59 (1.84H, m), 4.38–4.48 (0.16H, m), 7.50–7.65 (3H, m), 7.85–7.91 (2H, m). ^{13}C NMR (asterisk denotes minor diastereomer peaks): δ −4.67, −4.16*, −3.60, −3.30*, 11.7*, 11.8, 14.3, 18.1, 22.0, 22.5*, 22.8, 24.3, 26.0 (3C), 26.1*, 26.8*, 28.1*, 28.9*, 29.1, 29.4, 29.5, 29.6, 29.7, 29.8, 30.2, 32.1, 39.7, 44.1*, 63.0*, 64.2, 70.4*, 71.2, 128.7 (2C), 129.0*, 129.1 (2C), 133.3*, 133.4, 139.6, 140.5*. MS (EI): *m*/*z* 439 (100), 365 (88), 355 (23), 297 (10), 217 (4), 199 (22), 159 (25), 135 (18), 103 (28). A suspension of a large excess of Raney Ni (W-2) in 1,4-dioxane (3 mL) was added to a refluxing solution of **10** (0.02 g, 0.04 mmol) in 1,4-dioxane (1.5 mL). The reaction was refluxed for 2 h. Raney-Ni was filtered off through a pad of Celite-silica gel and the solids were rinsed with CH_2Cl_2. The filtrate was concentrated and distilled (bp 145 °C/1.7 mbar) to give *tert*-butyl-(1,2-dimethyl-tetradecyloxy)-dimethyl-silane (0.01 g, 73%) as a colourless oil; purity of >99% (GC). ^{1}H NMR: δ 0.03 (3H, s), 0.03 (3H, s), 0.82 (3H, d, J=6.7 Hz), 0.81–0.91 (3H, m), 0.88 (9H, s), 1.02 (3H, d, J=6.2 Hz), 1.13–1.46 (23H, m), 3.64 (1H, dq, J=5.0, 6.2 Hz). ^{13}C NMR: δ −4.8, −4.4, 14.1, 14.4, 18.1, 19.3, 22.7, 25.9 (3C), 27.4, 29.4, 29.7 (5C), 30.0, 31.9, 32.7, 40.3, 72.0. MS (EI): *m*/*z* 355 (8) $(M-H)^+$, 341 (42), 299 (100), 159 (37), 103 (22), 75 (30). This compound (0.01 g, 0.03 mmol) was subjected to a solution of HCl in MeOH (1.5 mL, 3 vol%) at room temperature and allowed to stir over night. The reaction was quenched with water (4 mL) and the aqueous phase was extracted with Et_2O (4×15 mL) and the combined Et_2O extract was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent was evaporated off. A colourless oil of **11** (0.06 g, 74%) was obtained after chromatography and distillation (bp 110 °C/0.5 mbar), 98% pure by GC. ^{1}H NMR: δ 0.87 (3H, d, J=6.8 Hz), 0.81–0.91 (3H, m), 1.12 (3H, d, J=6.3 Hz), 1.16–1.55 (24H, m), 3.66 (1H, dq, J=5.6, 6.2 Hz). ^{13}C NMR: δ 14.1, 14.5, 19.3, 22.7, 27.3, 29.4, 29.7 (5C), 30.0, 31.9, 32.5, 40.0, 71.8. MS (EI): *m*/*z* 241 (34) $(M-H)^+$, 224 (18), 194 (27), 182 (8), 166 (19), 155 (21), 138 (33), 125 (69), 111 (100), 97 (75), 85 (91), 71 (62), 57 (50), 45 (63). The ^{1}H NMR was similar to that reported in the literature for the diastereomerically pure *threo* isomer[13] and for the enantiomerically pure *erythro* isomer, (2*S*,3*S*)-3-methylpentadecan-2-ol,[14] except for the peak at 3.66 ppm, where our alcohol displayed a doublet of quartets (J=5.6, 6.2 Hz), whereas a doublet of quartets (J=4.2, 6.4 Hz) at 3.69 ppm was reported.

3.4.19. (2R^*,3R^*)-3-Methyltridecan-2-ol (12). A solution

of **6c** (0.08 g, 0.25 mmol) in absolute EtOH (5 mL, saturated with H_2) was added via a syringe to a suspension of a large excess of Raney-Ni (W-2) in EtOH (5 mL, saturated with H_2). The reaction was then allowed to stir for 5 days under an atmosphere of H_2. The work-up procedure was performed as above and a colourless oil of **12** (0.05 g, 86%) was obtained after chromatography and distillation (bp 120 °C/0.9 mbar, lit.[15] 100 °C/0.2 Torr), 96% pure by GC. ^{1}H NMR: δ 0.87 (3H, t, J=7.0 Hz), 0.88 (3H, d, J=6.6 Hz), 1.15 (3H, d, J=6.4 Hz), 1.09–1.49 (19H, m), 1.33 (1H, s, –OH), 3.60–3.67 (0.05H, m), 3.71 (0.95H, dq, J=4.3, 6.3 Hz). ^{13}C NMR: δ 14.1 (2C), 20.3, 22.7, 27.4, 29.4, 29.7 (3C), 30.0, 31.9, 32.7, 39.8, 71.4. MS (EI): m/z 213 (8) $(M-H)^+$, 199 (12), 183 (8), 166 (17), 154 (10), 139 (15), 125 (22), 111 (41), 97 (42), 83 (34), 71 (38), 57 (62), 45 (100). The ^{1}H NMR was similar to those reported in the literature for the diastereomerically pure *erythro* isomer of 3-methylpentadecan-2-ol,[13] for the diastereomerically pure *erythro* isomer of (2R^*,3R^*)-3-methylnonan-2-ol[16] and for the enantiomerically pure *erythro* isomer, (2*S*,3*S*)-3-methylpentadecan-2-ol.[14]

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Synthesis and crystal structures of 2,3,12,13-tetraalkoxy-21,23-dithiaporphyrins and 2,3-dialkoxy-21-monothiaporphyrins

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Abstract—The tetraalkoxy and dialkoxy substituted 21,23-dithiaporphyrins and 21-monothiaporphyrins, respectively, having methoxy, butoxy, octyloxy and dodecyloxy substituents at β-thiophene carbons were synthesized and characterized. The X-ray structure was solved for tetrabutoxy substituted 21,23-dithiaporphyrin and it exhibited a more planar structure compared with unsubstituted S_2TPP, whereas the dimethoxy substituted 21-monothiaporphyrin showed a saddle shaped structure similar to unsubstituted STPPH.

1. Introduction

Thiaporphyrins are a class of compounds in which one or two inner nitrogens of the porphyrin ring are replaced by sulfur atoms (N_3S and N_2S_2 cores).[1,2] The physico-chemical properties and metal coordination chemistry of thiaporphyrins are quite different from normal porphyrins (N_4 core). One of the interesting feature of thiaporphyrins is that they stabilize metals in unusual oxidation states such as copper and nickel in the +1 oxidation state, which is not possible with N_4 porphyrins.[1] Porphyrins have two reactive positions—the β- and *meso*-positions at which suitable substituent(s) can be introduced to tune the electronic properties of the porphyrin for specific applications. The β-functionalization of porphyrins is of considerable chemical interest since the β-substituents are in direct conjugation with the porphyrin ring and small changes in the substituents at β-positions alters the properties of porphyrin macrocycle. There are several reports on both electron releasing and electron withdrawing substituents at β-pyrrole carbons of N_4 porphyrin systems.[3] Porphyrins with electron withdrawing substituents at β-pyrrole carbons are found to be robust catalysts for alkene epoxidation and alkane hydroxylation reactions.[4] Interestingly, reports on β-substituted thiaporphyrins rarely exploit their potential for various applications. Thiaporphyrins possess two reactive β-positions: β-thiophenes and β-pyrroles at which substituents can be introduced to alter the properties of thiaporphyrins. In our recent communication, we reported the preliminary details of the synthesis of 2,3,12,13-tetraalkoxy-21,23-dithiaporphyrins with methoxy, butoxy, octyloxy and dodecyloxy substituents at β-thiophene carbons.[5] In this paper, we report the detailed synthesis of series of 21,23-dithiaporphyrins and 21-monothiaporphyrins having alkoxy substituents at β-thiophene carbons. The β-substituted porphyrins synthesised were (Chart 1) 2,3,12,13-tetramethoxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (**1**), 2,3,12,13-tetrabutoxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (**2**), 2,3,12,13-tetraoctyloxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (**3**), 2,3,12,13-tetradodecyloxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (**4**), 2,3-dimethoxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin (**5**), 2,3-dibutoxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin (**6**), 2,3-dioctyloxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin (**7**) and 2,3-didodecyloxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin (**8**). The X-ray structure was solved for **2** and indicates that it is more planar than parent 5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (S_2TPP)[1] whereas the structure solved for **5** is almost saddle-shaped similar to that of 5,10,15,20-tetraphenyl-21-monothiaporphyrin (STPPH).[1]

2. Results and discussion

2.1. Thiophenes (13–16) and thiophene diols 17–20

The required thiophenes were prepared according to the literature[6] with some modifications as outlined in Scheme 1.

Keywords: Monothiaporphyrin; Dithiaporphyrin; STPPH.
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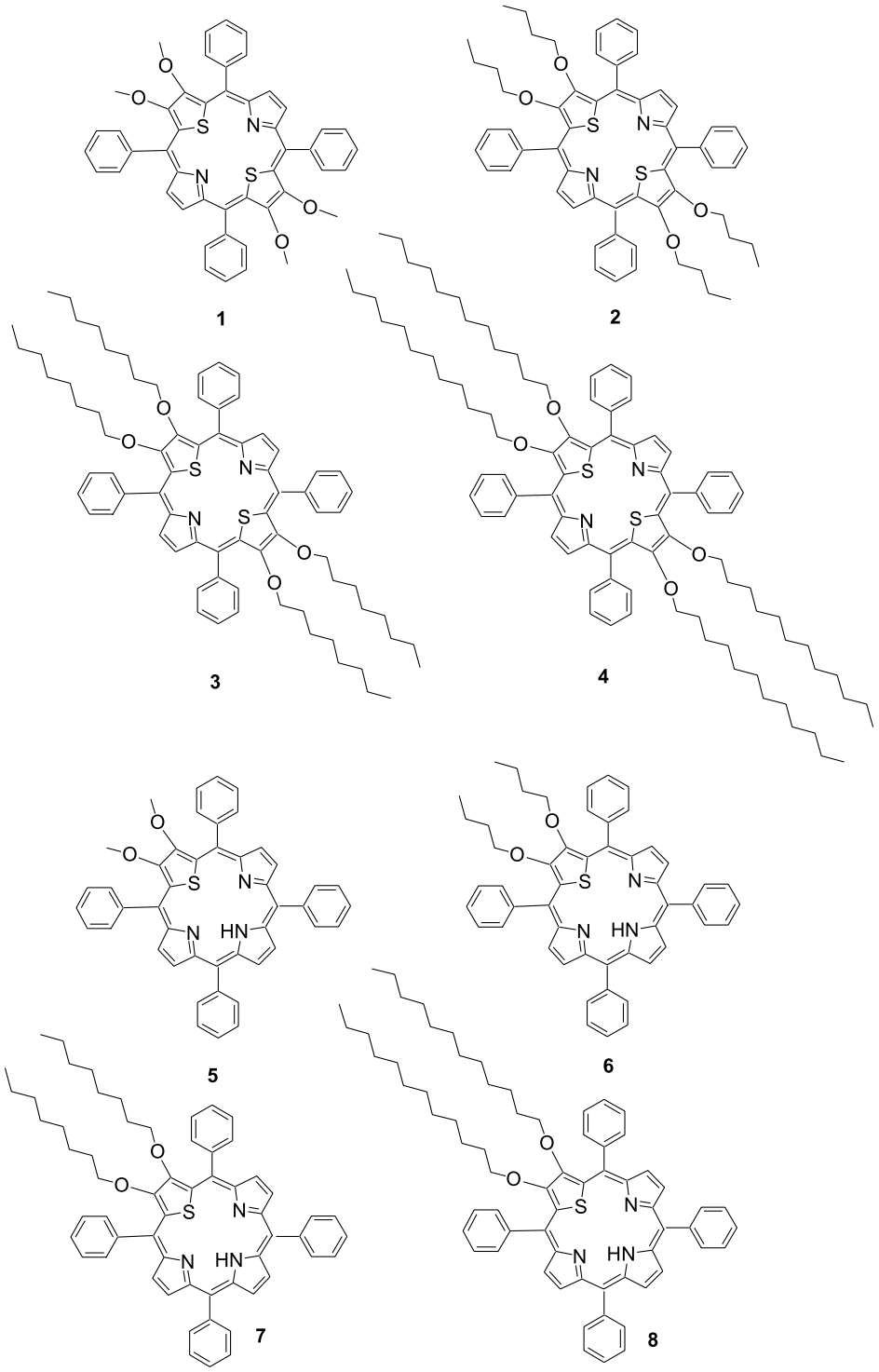
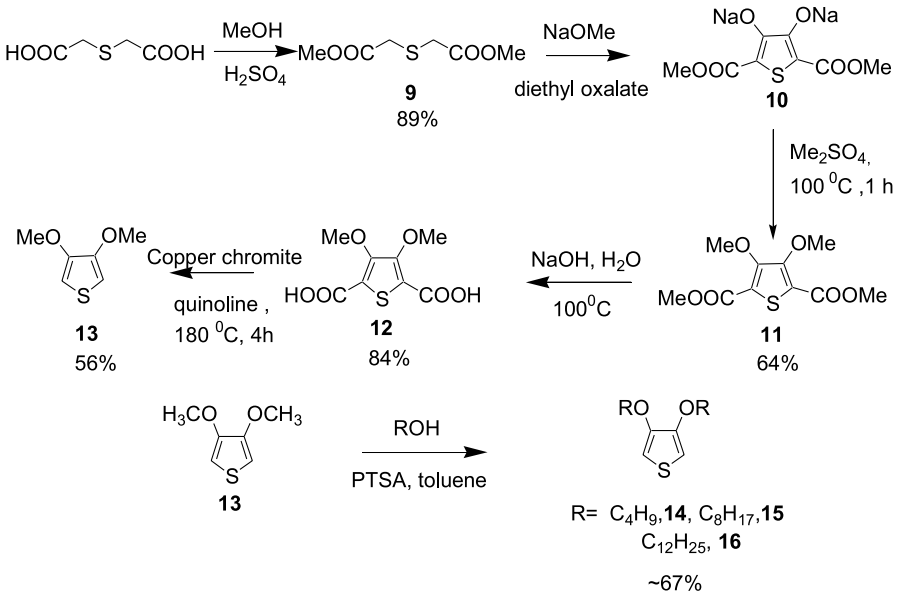
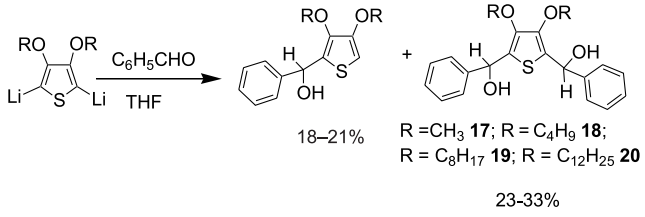


Chart 1.

The thiodiglycolic acid was first esterified and afforded dimethylthiodiglycollate **9** as a yellow liquid. Compound **9** was condensed with diethyloxalate in the presence of sodium methoxide and the resultant precipitate of disodium salt **10** was filtered and dried. The disodium salt **10** was then refluxed with dimethyl sulfate at 100 °C for 1 h. The excess dimethylsulfate was removed in vacuo and gave **11** as white solid in 64% yield. The demethylation of **11** was carried out by refluxing with 10% NaOH for 1 h followed by work-up, which resulted in product **12** as a white solid in 84% yield. The decarboxylation of **12** proceeded smoothly with copper chromite at 180 °C for 4 h. The brown coloured crude liquid obtained after standard work up was purified by column chromatography and afforded 3,4-dimethoxythiophene **13** as a colourless liquid in 56% yield. 3,4-Dibutoxy **14**, 3,4-dioctyloxy **15**, and 3,4-didodecyloxy **16** substituted thiophenes were prepared under *trans*-etherification conditions in ~67% yields by treating **13** with 1-butanol, 1-octanol and 1-dodecanol, respectively, in the presence of *p*-toluenesulfonic acid in toluene.[6b]



Scheme 1. Synthetic scheme for thiophenes **13**–**16**.

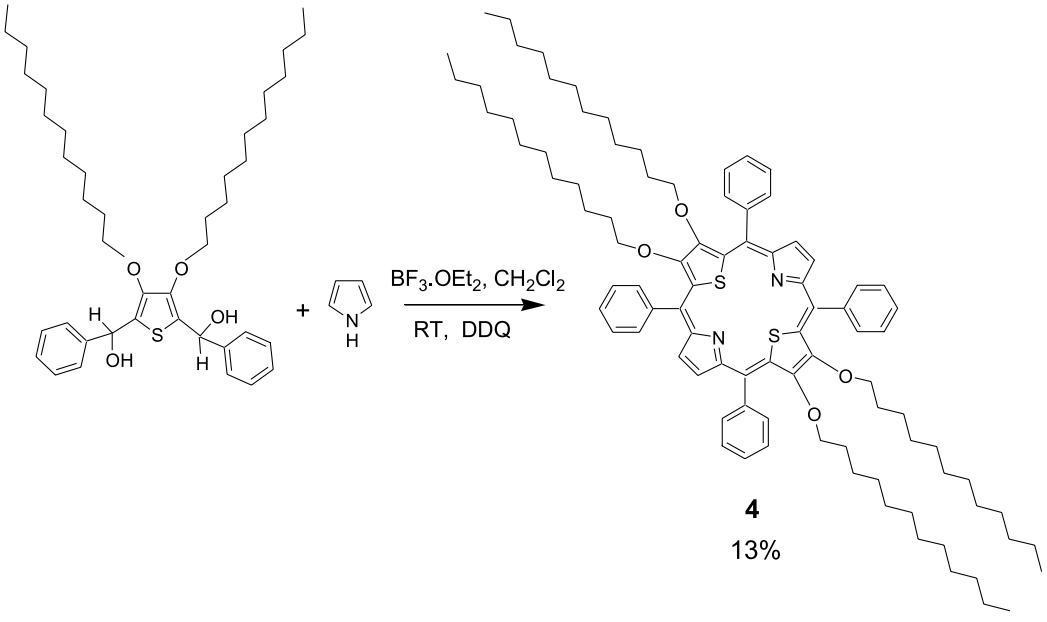


Scheme 2. General synthetic scheme for diols **17**–**20**.

The unknown thiophene diols **17**–**20** were prepared according to the method of Ulman and Manassen.[7] One equivalent of 3,4-disubstituted-2,5-dilithiothiophene was condensed with 2.5 equiv of benzaldehyde in ice cold dry THF (Scheme 2). The TLC analysis showed the formation of required diol with some amount of mono-ol (18–21%). The diol reaction mixtures were purified by silica gel column chromatography using petroleum ether/ethyl acetate mixture as eluant and afforded pure diols **17**–**20** as white soft solids in 23–33% yields. The diols **17**–**20** were characterized by NMR, IR, mass and elemental analysis. All four diols showed a broad peak at ~2.80 ppm for OH and a sharp peak at ~6.00 ppm for –CH in ^{1}H NMR and broad peak of OH at ~3300 cm^{-1} in IR confirmed the compounds.

2.2. 21,23-Dithiaporphyrins with alkoxy substituents at β-thiophene carbons 1–4

21,23-Dithiaporphyrins **1**, **2**, **3** and **4** were synthesized by condensing 1 equiv of corresponding diol **17**, **18**, **19** and **20**, respectively, with 1 equiv of pyrrole in CH_2Cl_2 in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ followed by



Scheme 3. Synthetic scheme for N_2S_2 porphyrin **4**.

Table 1. ^{1}H NMR chemical shifts (δ in ppm) of selected protons of porphyrins **1–8** recorded in $CDCl_3$

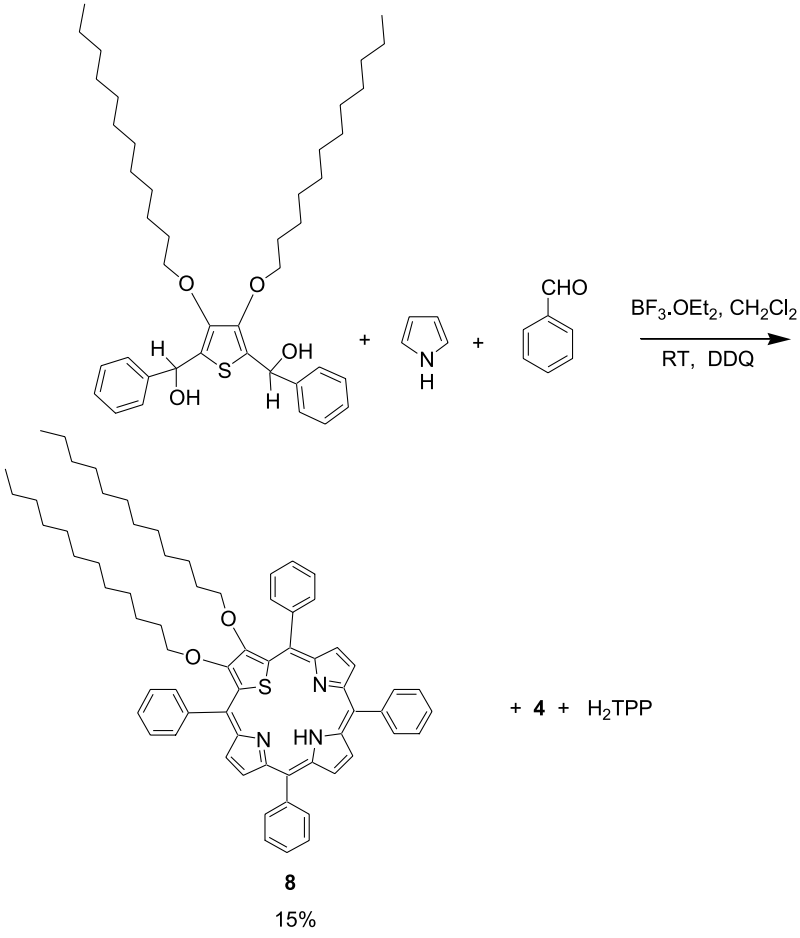
Porphyrin	NH	Pyrrole
S_2TPP	—	8.67 (s)
1	—	8.38 (s)
2	—	8.30 (s)
3	—	8.30 (s)
4	—	8.30 (s)
STPPH	−2.66(s)	8.61 (d), 8.72 (d), 8.88 (s)
5	−2.58 (s)	8.47(d), 8.52 (d), 8.85 (s)
6	−2.57 (s)	8.41 (d), 8.50 (d), 8.85 (s)
7	−2.59 (s)	8.40 (d), 8.48 (d), 8.83 (s)
8	−2.58 (s)	8.42 (d), 8.50 (d), 8.84 (s)

oxidation with DDQ (Scheme 3). TLC analysis showed a single yellow spot for the required 21,23-dithiaporphyrin with small amount of polymeric compound (2–5%) on the baseline. The crude porphyrins were purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (1:1) and afforded the porphyrins **1–4** in 8–14% yields. Porphyrins **1** and **2** are purple crystalline solids and **3** and **4** were waxy purple solids. The β-alkoxy 21,23-dithiaporphyrins **1–4** were characterized by NMR, mass, absorption, emission and elemental analysis. The ^{1}H NMR data of selected protons compared with unsubstituted 5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (S_2TPP) is presented in Table 1. The β-thiophene protons which usually appear at

Table 2. Absorption and emission data of porphyrins **1–8** in toluene

Porphyrin	Soret band λ, nm (log ε)		Q-bands λ, nm (log ε)			λem.		
		IV	III	II	I	$Q(0,0)$	$Q(0,1)$	ϕ[a]
S2TPP	435 (5.40)	514 (4.41)	547 (3.84)	633 (3.34)	696 (3.65)	706	781	0.0076
1	439 (5.40)	517 (4.31)	552 (sh)	639 (3.28)	703 (3.61)	711	788	0.0107
2	441 (5.04)	519 (4.22)	555 (sh)	639 (3.40)	705 (3.58)	713	787	0.0133
3	441 (5.14)	519 (4.53)	557 (sh)	640 (3.28)	705 (3.74)	713	787	0.0094
4	441 (5.24)	519 (4.41)	553 (sh)	640 (2.71)	705 (3.78)	713	789	0.0080
STPPH	429 (5.27)	513 (4.23)	547 (3.64)	618 (3.27)	675 (3.47)	678	760	0.0168
5	430 (5.49)	513 (4.49)	546 (sh)	617 (3.56)	677 (3.78)	684	750	0.0042
6	431 (5.36)	514 (4.39)	547 (sh)	617 (3.48)	678 (3.68)	685	752	0.0047
7	431 (5.30)	515 (4.39)	551 (sh)	620 (3.43)	680 (3.61)	684	752	0.0036
8	431 (5.50)	515 (4.54)	549 (sh)	618 (3.60)	678 (3.84)	685	752	0.0035

[a] The fluorescence quantum yields were estimated by taking 5,10,15,20-tetraphenyl porphyrin $\phi=0.11$ as the standard.



Scheme 4. Synthetic scheme of N_3S porphyrin **8**.

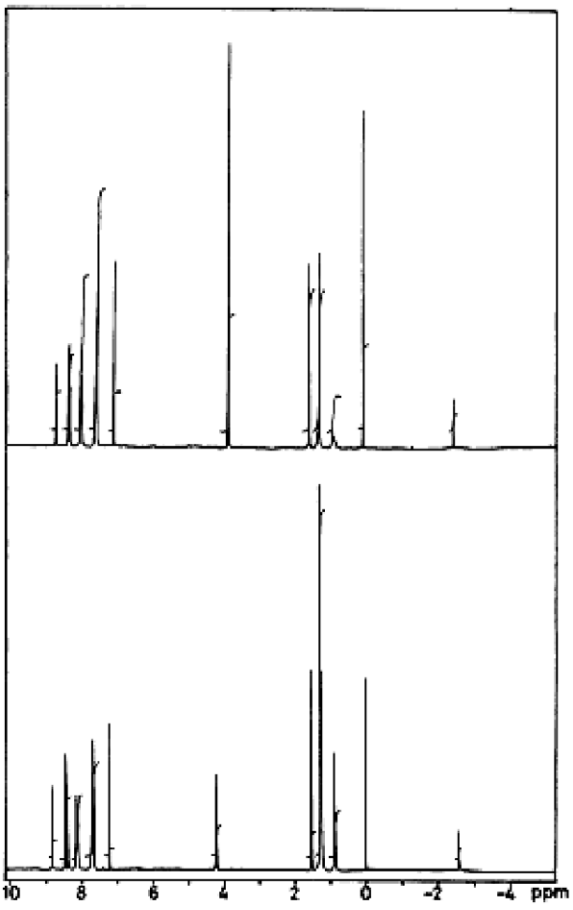


Figure 1. ^{1}H NMR spectra of N_3S porphyrin **5** (top) and **8** (bottom) recorded in $CDCl_3$.

9.68 ppm in S_2TPP[1]were absent in **1–4** due to the substitution of alkoxy groups at β-thiophene carbons. The pyrrole protons appeared as singlet indicating the symmetric nature of porphyrins **1–4**. However, the proton signal of pyrrole which appears at ~8.30 ppm in S_2TPP[1] was upfield shifted in **1–4** by 0.35 ppm. The mass spectra of **1–4** showed corresponding molecular ion peaks confirming the products. The absorption spectra of **1–4** showed three clear Q-bands and a strong Soret band, which were bathochromically shifted (8–10 nm) compared to the parent S_2TPP (Table 2). The fluorescence bands of **1–4** also experienced similar red shifts compared to S_2TPP. However, the quantum yields of **1–4** were slightly increased with alkoxy substituents at β-thiophene carbons compared to S_2TPP (Table 2).

2.3. 21-Monothiaporphyrins with alkoxy substituents at β-thiophene carbons 5–8

21-Monothiaporphyrins **5–8** were prepared using the same diols **17–20**. One equivalent of corresponding diol **17–20** was condensed with 2 equiv of benzaldehyde and 3 equiv of pyrrole in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ followed by oxidation with DDQ (Scheme 4). The condensation resulted in the formation of a mixture of three porphyrins with three different porphyrin cores:[8] N_4, N_3S and N_2S_2. The mixture of three porphyrins was separated by silica gel column chromatography using petroleum ether/dichloromethane mixture as eluant. The desired N_3S porphyrin **5–8** always moved as the second band and afforded **5–8** in 8–15% yields. Porphyrins **5** and **6** are purple crystalline solids and **7** and **8** are soft brownish solids. The presence of corresponding strong molecular ion peaks in the mass spectra confirmed the porphyrins **5–8**. The ^{1}H NMR spectra of porphyrins **5** and **8** are presented in Figure 1 and data of selected protons are tabulated in Table 1. In ^{1}H NMR, the thiophene protons which usually appear at 9.81 ppm as a singlet in STPPH were absent due to substitution of thiophene protons by alkoxy groups. The three pyrroles in **5–8** appeared as three separate doublets like STPPH, indicating the less symmetric nature of porphyrins **5–8**. However, the pyrrole protons of **5–8** were upfield shifted compared to STPPH (Table 1). The NH proton of **5–8** appeared as a singlet and slightly downfield shifted compared to STPPH. Absorption and emission bands were also slightly red shifted compared to STPPH.[1]

2.4. Crystal-structure analysis of N_2S_2 porphyrin 2 and N_3S porphyrin 5

The structures of **2** (CCDC No. 191919) and **5** (CCDC No. 221893) were elucidated by single crystal X-ray diffraction analysis. A single crystal of **2** suitable for X-ray analysis was obtained by slow evaporation of CH_2Cl_2 solution over a period of one week and crystallized in a triclinic P-1 unit cell. The aerial and side views of **2** are presented in Figure 2 and the selected parameters and bond lengths and bond

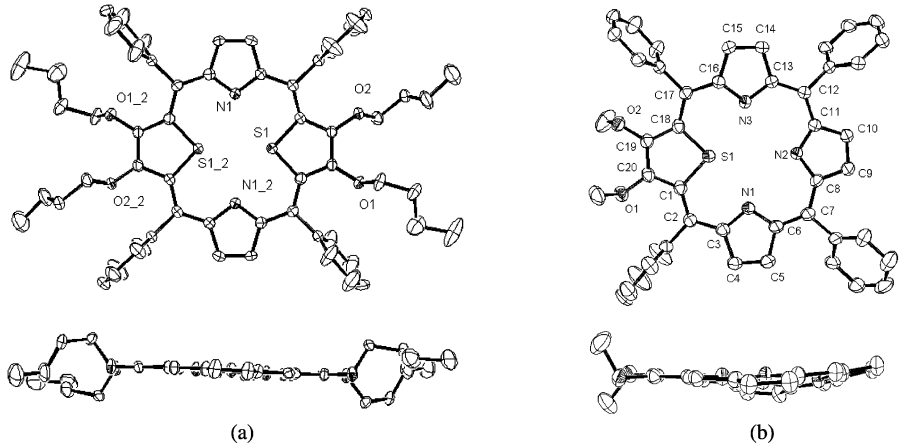


Figure 2. X-ray structure of (a) N_2S_2 porphyrin **2** and (b) N_3S porphyrin **5**. Top: aerial view; bottom: side view.

Table 3. Crystal data and collection parameters for **2** and **5**

Parameters	**2**	**5**
Empirical formula	$C_{30}H_{30}NO_2S$	$C_{46}H_{33}N_3O_2S$
Formula weight	468.61	691.81
Dimensions (mm^3)	0.47×0.18×0.12	0.25×0.20×0.18
Crystal system	Triclinic	Triclinic
a (Å)	8.6153(9)	10.4122(7)
b (Å)	12.0456(13)	12.5830(9)
c (Å)	12.2567(14)	14.3020(10)
α (deg)	97.985(2)	78.568(2)
β (deg)	90.840(2)	75.1600(10)
γ (deg)	97.106(2)	84.1140(10)
V ($Å^3$)	1249.3(2)	3375(5)
Space group	*P*-1	*P*-1
Z value	2	2
Residuals: *R*1	0.0694	0.0543
T (K)	150(2)	150(2)

angles are presented in Tables 3 and 4. The ORTEP structure of **2** is perfectly symmetrical but slightly disordered and half of the molecules are observed with the other half generated from symmetry. Disorder was noted with the butoxy groups, which were placed into two positions in a ratio of 74/26. Interestingly, porphyrin **2** is more planar compared to S_2TPP indicating that the presence of the butoxy substituents at β-thiophene carbons induced more planarity in **2** compared to the parent S_2TPP. In the structure of S_2TPP, the four five-membered rings are slightly deviated from the plane of the four *meso* carbons whereas in the structure of **2**, the four five membered rings were in the same plane with four *meso* carbons with negligible deviation. The non-bonded S···S′ distance was slightly increased and the N···N′ distance was decreased in **2** compared to S_2TPP.[1] Furthermore, the presence of substituents at β-positions also resulted in the decrease of the C_α–C_β and C_β–C_β distances of the thiophene rings in **2** compared to S_2TPP.[1] The average distance between the porphyrin cores in the layered packing structure is 4.702 Å. There was no complete organized overlap packing on the *n*-butoxy chain for the β-substituents but the tail-to-tail organization between the dithiaporphyrin rings was clearly evident from the packing diagram.

Porphyrin **5** with two methoxy substituents at β-thiophene carbons crystallized in a triclinic P-1 unit cell with two molecules in the unit cell. The crystal was obtained by slow evaporation of CH_2Cl_2/CH_3OH solution over a period of 10 days. The structure of **5** was slightly saddle-shaped similar to that of β-unsubstituted 5,10,15,20-tetraphenyl-21-thiaporphyrin (STPPH) suggesting that the two methoxy groups at β-thiophene carbons did not alter the structure of the porphyrin (Fig. 2). The average bond distance of 1.741(3) is in the normal range of carbon–sulfur bond distances. One of the methoxy groups on the β-thiophene carbon was tilted upward and the other methoxy group was tilted downward. The porphyrin core is saddle-shaped with a mean deviation of 0.16 Å for the atoms in the porphyrin core. The packing of **5** showed a twisted layer structure with a distance of 3.464 Å between N(1) of one molecule and C(21) of the neighbouring molecule. The C_α–S, C_β–C_β distances of **5** is almost similar to that of STPPH. The important feature of the structure is the presence of intramolecular hydrogen-bonded interactions in the cavity (Table 5).

3. Conclusions

In conclusion, we synthesized and characterized 2,3,12,13-tetraalkoxy substituted 21,23-dithiaporphyrins and 2,3-dialkoxy substituted 21-monothiaporphyrins. The spectral properties were moderately altered by introducing alkoxy substituents at β-thiophene carbons. Interestingly, the crystal structure solved for the butoxy substituted 21,23-dithiaporphyrin is more planar than the unsubstituted parent S_2TPP. However, the crystal structure solved for methoxy substituted 21-monothiaporphyrin exhibited a saddle-shaped structure as shown by the unsubstituted parent STPPH (Fig. 2). Porphyrins bearing long chain alkoxy groups have been shown to be good liquid crystalline

Table 4. Selected X-ray structural data for porphyrins **2** and **5**

Compound	Bond lengths		Bond angles (Å)		Non-bonded distances (Å)	
2	S1–C12	1.741(3)	C9–C10–C11	113.5(3)	S1···S1A	3.100
	C11–C12	1.438(4)	C10–C11–C12	113.6(3)	N1···N1A	4.574
	C10–C11	1.383(4)	C11–C12–S1	109.5(2)		
	N1–C20	1.357(4)	S1–C9–C10	110.5(2)		
	C20–C21	1.450(5)	C11–C12–C13	126.7(3)		
	C21–C22	1.339(5)	C9–S1–C12	92.89(15)		
			C20–N1–C1A	105.9(3)		
			N1–C20–C21	110.9(3)		
			C12–C13–C20	122.5(3)		
			C13–C20–C21	125.7(3)		
			N1–C20–C13	123.4(3)		
			C21–C22–C1A	107.0(3)		
5	S1–C18	1.738(3)	C1–S1–C18	92.69(15)	S1···N2	3.598
	C18–C19	1.429(4)	S1–C18–C19	110.3(3)	N1···N3	4.343
	C19–C20	1.380(5)	C18–C19–C20	113.3 (3)		
	N3–C16	1.350(4)	C19–C20–C1	114.0(3)		
	C16–C15	1.455(5)	S1–C1–C20	109.7(3)		
	C15–C14	1.337(4)	C16–C17–C18	121.8(5)		
	C16–C17	1.422(4)	N3–C16–C15	111.2 (3)		
	C17–C18	1.400(5)	C16–C15–C14	106.5 (3)		
			C15–C14–C13	105.9 (3)		
			C14–C13–N3	111.4 (2)		
			C13–N3–C16	104.9 (3)		
			C13–C12–C11	125.8 (3)		

Table 5. Intramolecular hydrogen bonding data for N_3S porphyrin **5**

		Distance (Å)		Angle (deg)
N2···H2A···S1	0.8600	2.7650	3.598(2)	163.48
N2···H2A···N1	0.8600	2.4927	2.985(4)	117.18
N2···H2A···N3	0.8600	2.4771	2.971(3)	117.28

materials[9] and the porphyrins reported in this paper are potential liquid crystalline materials.

4. Experimental

4.1. General

4.1.1. Dimethyl thiodiglycollate 9. In a 500 ml round bottom flask, thiodiglycolic acid (100 g, 0.666 mol) was dissolved in dry methanol (250 ml) and conc. sulphuric acid (10 ml) was added drop wise to it. The resulting mixture was refluxed for 24 h. The excess methanol was evaporated and the residue was taken in ethyl acetate, washed with saturated sodium bicarbonate solution until the aqueous layer was neutral. The organic layer wad dried over sodium sulfate and the solvent was removed on a rotary evaporator to afford a light yellow liquid (106 g, 89%). ^{1}H NMR ($CDCl_3$, δ, ppm): 3.4 (s, 4H), 3.7 (s, 6H); Anal. Calcd: C, 40.44; H, 5.66; S, 17.99. Found: C, 40.32; H, 5.85; S, 17.88.

4.1.2. 3,4-Dimethoxy-2,5-dimethoxycarboxy thiophene 11. A solution of 10.5 g of sodium metal in 100 ml of dry methanol was cooled at 0–5 °C. To this a solution of 26.7 g of **9** and 26.7 g of diethyloxalate was added and stirred. The temperature was maintained below 30 °C. The sodium salt was precipitated as a yellow solid. The reaction was completed by warming the reaction mixture to reflux for 2 h. After cooling, the solid was filtered and dried. The sodium salt of diol diester **10** (15 g, 54.3 mmol) was taken in 65 ml of freshly distilled dimethyl sulfate and the mixture was heated at 100 °C for 1 h. The excess dimethyl sulfate was distilled at low pressure and the crude product was dissolved in ethyl acetate (100 ml) and washed with cold 5% NaOH solution (50 ml). The organic layer was dried over sodium sulfate and solvent was evaporated to afford compound **11** as a pure light yellow solid (9.1 g, 64%). Mp: 85 °C; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.9 (s, 6H), 4.1 (s, 6H); Anal. Calcd: C, 46.15; H, 4.65; S, 12.32. Found: C, 46.46; H, 4.42; S, 12.51.

4.1.3. 3,4-Dimethoxy thiophene-2,5-dicarboxylic acid 12. In a 100 ml round bottom flask **11** (9 g, 34.6 mmol) was taken and 10% NaOH (50 ml) was added to it. The mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and conc. HCl was added to it with stirring. The precipitate thus formed was collected in a Buchner funnel and dried in a oven to give **12** as a white solid (6.8 g, 84%). Mp: >250 °C (lit. value[6a]: decomposed above 250 °C); ^{1}H NMR ($CDCl_3$, δ, ppm): 3.9 (s, 6H); Anal. Calcd: C, 41.38; H, 3.47; S, 13.81. Found: C, 41.59; H, 3.52, S, 13.94, (lit. value[6a]: S, 13.79).

4.1.4. 3,4-Dimethoxythiophene 13. A 100 ml dry three-necked round bottom flask was charged with **12** (9 g, 43.3 mmol), copper chromite (0.56 g, 4% mol) and dry quinoline (30 ml). The mixture was heated at 160 °C for 4 h under argon atmosphere. The reaction mixture was vacuum distilled and the pink liquid obtained was dissolved in 50 ml of ethyl acetate and washed repeatedly with 5% HCl and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to give a crude brown coloured liquid. The crude compound was purified by silica gel column chromatography using ethyl acetate/petroleum ether mixture (5:95) to afford **13** as colourless liquid (3.1 g, 56%). ^{1}H NMR ($CDCl_3$, δ, ppm): 3.8 (s, 6H), 6.2 (s, 2H); Anal. Calcd: C, 49.98; H, 5.59; S, 22.24. Found: C, 50.15; H, 5.45; S, 22.47.

4.1.5. 3,4-Dibutoxythiophene 14. In a 100 ml dry three-necked round bottom flask, **13** (2.0 g, 13.8 mmol) was taken with 50 ml of dry toluene. To this solution *n*-butanol (3.5 g, 47.29 mmol) was added along with 0.20 g *p*-toluenesulfonic acid. The mixture was allowed to stir at 90 °C for 28 h. Excess solvent was evaporated and the crude compound was purified by column chromatography using petroleum ether as eluent. 2.0 g (66%) of pure compound **14** was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.10 (s, 2H), 3.90 (t, $J=7.99$ Hz 4H), 1.80 (m, 4H), 1.46 (m, 4H), 0.96 (t, $J=6.39$ Hz, 6H); Anal. Calcd: C, 63.12; H, 8.83; S, 14.04. Found: C, 63.39; H, 8.67; S, 14.17.

4.1.6. 3,4-Dioctyloxythiophene 15. Stirring of **13** (2.0 g, 13.8 mmol) in 50 ml of dry toluene, *n*-Octanol (3.9 g, 30 mmol) and *p*-toluenesulfonic acid (0.20 g) under same reaction conditions mentioned for **14** yielded **15** as yellow oil in 67% yield (3.1 g). ^{1}H NMR ($CDCl_3$, δ, ppm): 6.10 (s, 2H), 3.9 (t, $J=5.94$ Hz, 4H), 1.80 (m, 4H), 1.30 (m, 20H), 0.80 (t, $J=3.99$ Hz, 6H); Anal. Calcd: C, 70.53; H, 10.65; S, 9.42. Found: C, 70.92; H, 10.87; S, 9.58.

4.1.7. 3,4-Didodecyloxythiophene 16. Compound **16** was synthesized under similar reaction conditions mentioned for **14** by stirring **13** (2.0 g, 13.8 mmol) in 50 ml of dry toluene with *n*-dodecanol (5.6 g, 30.36 mmol) and *p*-toluenesulfonic acid (0.20 g) at 90 °C. Column chromatography of crude compound afforded **16** as yellow oil (4.2 g, 67%). ^{1}H NMR ($CDCl_3$, δ, ppm): 6.10 (s, 2H), 3.98 (t, $J=5.99$ Hz, 4H), 1.80 (m, 4H), 1.15 (m, 36H), 0.80 (t, $J=4.23$ Hz, 6H); Anal. Calcd: C, 74.27; H, 11.58; S, 7.08. Found: C, 74.53; H, 11.79; S, 7.20.

4.1.8. 2,5-Bis-(phenylhydroxymethyl)-3,4-dimethoxythiophene 17. In a 100 ml three-necked round bottom flask fitted with a gas inlet tube, a reflux condenser and a rubber septum, dry and distilled *n*-hexane (25 ml) was placed. *N*, *N*′,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (1.40 ml, 9.45 mmol) and *n*-BuLi (7.0 ml 15% solution in hexane) were injected and stirred for 10 min. A sample of **13** (540 mg, 3.75 mmol) was then added and solution was refluxed gently for 1 h. A white curdy solution of 2,5-dilithiated salt of **13** was formed. In another three-necked

round bottom flask, fitted with a gas inlet, outlet and rubber septum, benzaldehyde (1.1 ml, 10.7 mmol) was dissolved in 15 ml dry THF. The solution was cooled in an ice bath and nitrogen was bubbled for 15 min. The 2,5-dilithiated salt of **13** was added slowly to benzaldehyde solution in THF through siphon apparatus over 15 min. After addition was complete, the mixture was allowed to reach the room temperature. An ice-cooled saturated NH_4Cl solution was added and extracted with ether (3×50 ml). The organic layers were combined and washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator to obtain a crude brown oil. TLC analysis indicated the formation of the required diol **17** and small amounts of mono-ol. The crude diol was subjected to silica gel column chromatography using petroleum ether/ethyl acetate mixture as eluent. The mono-ol was collected first as oily compound using petroleum ether/ethyl acetate (8:2) in 21% yield (0.210 g) and the diol **17** was collected as white crystalline compound using petroleum ether/ethyl acetate (7:3) in 23% yield (0.295 g). Mp: 126–127 °C; IR (KBr, cm^{-1}): 3299 (OH); ^1H NMR ($CDCl_3$, δ in ppm): 2.60 (s, 2H, OH), 3.77 (s, 6H, OCH_3), 6.11 (s, 2H, CH), 7.27–7.43 (m, 10H, phenyls); FAB-MS: $C_{20}H_{20}O_4S$ calcd av. mass, 356.10. Obsd *m/z* 356 (M^+); Anal. Calcd: C, 67.39, H, 5.66. S, 9.00. Found: C, 67.58; H, 5.79, S, 9.25.

4.1.9. 2,5-Bis-(phenylhydroxymethyl)-3,4-dibutyloxythiophene 18. The 2,5-dilithiated salt of **14** was prepared by refluxing the mixture of TMEDA (0.35 ml, 2.3 mmol), *n*-Buli (2.2 ml of 15% solution in *n*-hexane) and **14** (0.230 mg, 1 mmol) in *n*-hexane (15 ml). The 2,5-dilithiated salt of **14** was then added slowly to the ice-cooled solution of benzaldehyde (0.270 ml, 2.65 mmol) in dry THF (5 ml) and refluxed for 1 h. After standard work-up as mentioned for diol **17**, the crude compound was purified by silica gel column chromatography. The fast moving mono-ol was collected as the first band with petroleum ether/ethyl acetate (9:1) in 21% yield (0.210 g) and the desired diol **18** was obtained as white crystalline solid in 28% yield (0.125 g). Mp: 92–94 °C; IR (KBr, cm^{-1}): 3313(OH); ^1H NMR ($CDCl_3$, δ in ppm): 0.94 (t, $J=7.34$ Hz, 6H, CH_3), 1.45 (q, $J=7.71$ Hz, 4H, CH_2), 1.60–1.67 (m, 4H, CH_2), 2.61 (d, $J=3.2$ Hz, 2H, OH), 3.90–3.94 (m, 4H, OCH_2), 6.03 (d, $J=3.0$ Hz, 2H, CH), 7.28–7.43 (m, 10H, phenyl); ^{13}C NMR ($CDCl_3$, δ in ppm): 13.91, 14.26, 18.95, 19.23, 19.34, 31.90, 69.62, 72.71, 73.26, 74.36, 126.23, 127.26, 128.32, 142.4, 145.7; FAB-MS: $C_{26}H_{32}O_4S$ calcd av. mass, 440.5. Obsd *m/z* 440 (M^+); Anal. Calcd: C, 70.88; H, 7.32; S, 7.28. Found: C, 71.23; H, 7.47; S, 7.36.

4.1.10. 2,5-Bis-(phenylhydroxymethyl)-3,4-dioctyloxythiophene 19. A mixture of **15** (0.420 g, 1.2 mmol), TMEDA (0.450 ml, 3.03 mmol) and *n*-BuLi (2.5 ml, 1.6 M solution in hexane) in *n*-hexane (10 ml) was refluxed to afford the 2,5-dilithiated salt of **15**. The dilithiated salt of **15** was added slowly to an ice-cooled solution of benzaldehyde (0.33 ml, 3.23 mmol) in dry THF (10 ml). The crude compound was subjected to silica gel column chromatography using petroleum ether/ethyl acetate mixture as eluent. The mono-ol was obtained as oil in 21% yield (0.130 g) using petroleum ether/ethyl acetate (8:2) and diol **19** as white solid in 28% yield (0.190 g) using petroleum ether/ethyl acetate mixture (8:2). Mp: 128–129 °C; IR (KBr, cm^{-1}): 3310 (OH); ^1H NMR ($CDCl_3$, δ in ppm): 0.88 (t, $J=6.89$ Hz, 6H, CH_3), 1.27 (s, 24H, CH_2), 2.68 (s, 2H, OH), 3.83–3.93 (m, 4H, OCH_2), 6.03 (s, 2H, CH), 7.26–7.43 (m, 10H, phenyl); FAB-MS: $C_{34}H_{48}O_4S$ calcd av. mass, 552.8. Obsd *m/z* 552 (M^+); Anal. Calcd: C, 73.87; H, 8.75; S, 5.80. Found: C, 73.45; H, 9.01; S, 5.95.

4.1.11. 2,5-Bis-(phenylhydroxymethyl)-3,4-bis-(didodecyloxy)thiophene 20. The 2,5-Dilithiated salt of **16** was prepared by refluxing TMEDA (0.56 ml, 3.80 mmol), *n*-BuLi (3.0 ml 15% solution in hexane) and **16** (0.680 g, 1.5 mmol) in *n*-hexane (6 ml). Benzaldehyde, (0.40 ml, 3.92 mmol) in dry THF (10 ml) was added slowly to the 2,5-dilithiated salt of **16** and refluxed for 1 h. After standard work-up, the crude diol was purified by colomn chromatography using petroleum ether/ethyl acetate mixture as eluent. The oily mono-ol (18%) was collected as the first band with petroleum ether/ethyl acetate (9:1) and white crystalline solid diol **20** was collected in 9:1 petroleum ether/ethyl acetate solvent mixture (0.345 g, 33%). Mp: 54–56 °C; IR (KBr, cm^{-1}): 3308 (OH); ^1H NMR ($CDCl_3$, δ in ppm): 0.88 (t, $J=6.92$ Hz, 6H, CH_3), 1.26 (s, 36H, CH_2), 1.65 (q, $J=7.62$ Hz, 4H, CH_2), 2.65 (d, $J=3.66$ Hz, 2H, OH), 3.90 (q, $J=6.67$ Hz, 4H, OCH_2,), 6.03 (d, $J=3.66$ Hz, 2H, CH), 7.28–7.43 (m, 10H, phenyl); FAB-MS: $C_{42}H_{64}O_4S$ calcd av. mass, 665.02. Obsd *m/z* 665 (M^+); Anal. Calcd: C, 75.85; H, 9.70; S, 4.82. Found: C, 75.63; H, 9.87; S, 4.75.

4.1.12. 2,3,12,13-Tetramethoxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin 1. A solution of 1 equiv of diol **17** (0.50 g, 1.41 mmol) and 1 equiv of pyrrole (0.15 ml, 2.16 mmol) were condensed in CH_2Cl_2 (140 ml) in the presence of catalytic amount of $BF_3\cdot OEt_2$ (50 µl of 2.5 M solution in CH_2Cl_2). The reaction mixture was stirred for 1 h under nitrogen. The progress of the reaction was monitored with UV–visible spectroscopy at regular intervals by taking aliquots of the reaction mixture and oxidised with DDQ. After completion of the reaction, DDQ (0.250 g, 1.10 mmol) was added as an oxidant and the reaction stirred at room temperature for 1 h in air. A few drops of triethylamine were added to neutralize the reaction mixture. TLC analysis showed the formation the required compound as the sole product. The solvent was removed under vacuo and the crude reaction mixture was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (2:8) and afforded **1** as a purple solid in 14% yield (0.150 g). Mp: >300 °C; IR (KBr, cm^{-1}): 701, 2867, 2952, 3425; ^1H NMR ($CDCl_3$, δ in ppm): 3.86 (s, 12H, OCH_3), 7.69–7.77 (m, 12H, *m,p*-phenyl), 8.12 (q, $J=3.66$ Hz, 8H, *o*-phenyl), 8.38 (s, 4H, pyrrole); FAB-MS calcd av. for $C_{48}H_{36}N_2O_4S_2$: 768.9. Obsd *m/z*: 769. Anal. Calcd: C, 74.97; H, 4.72; N, 3.64; S, 8.34. Found: C, 75.26; H, 4.92; N, 3.71; S, 7.98.

4.1.13. 2,3,12,13-Tetrabutyloxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin 2. Samples of diol **18** (0.650 g, 1.47 mmol) and pyrrole (0.15 ml, 2.16 mmol) were dissolved in 150 ml dichloromethane taken in a 250 ml one-necked round bottom flask and stirred under an argon atmosphere for 15 min. $BF_3\cdot OEt_2$ (50 µl of 2.5 M solution) was added to initiate the condensation. After 1 h DDQ (0.260 g, 1.14 mmol) was added and the reaction mixture

stirred for 1 h in air. After standard work up, the crude compound was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (2:8) as eluent to afford purple compound **2** in 8% yield (0.110 g). Mp: > 250 °C; IR (KBr, cm^{-1}): 701, 2866, 2955, 3414; ^1H NMR ($CDCl_3$, δ in ppm): 0.87 (t, $J=6.59$ Hz, 12H, CH_3), 1.20–1.25 (m, 16H, CH_2), 4.11 (t, $J=6.22$ Hz, 8H, OCH_2), 7.67–7.69 (m, 12H, *m*,*p*-phenyl), 8.13 (q, $J=3.66$ Hz, 8H, *o*-phenyl), 8.30 (s, 4H, pyrrole); ^{13}C NMR ($CDCl_3$, δ in ppm): 13.89, 14.14, 19.12, 29.76, 31.68, 53.48, 74.39, 120.18, 126.46, 127.34, 128.47, 133.22, 134.04, 137.57, 142.40, 153.92, 157.46; LD-MS $C_{60}H_{60}N_2O_4S_2$ calcd av. mass: 937.26. Obsd *m*/*z*: 937.64; Anal. Calcd: C, 76.89; H, 6.45; N, 2.99; S, 6.84. Found: C, 76.69; H, 6.58; N, 3.10; S, 6.95.

4.1.14. 2,3,12,13-Tetraoctyloxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin 3. In a one-necked 250 ml round bottom flask, samples of diol **19** (0.50 g, 0.91 mmol) and pyrrole (0.090 ml, 1.3 mmol) were dissolved in 100 ml CH_2Cl_2 and stirred at room temperature under an inert atmosphere. $BF_3\cdot OEt_2$ (40 μl of 2.5 M solution in dichloromethane) was added to start the cyclization. After stirring for 1.5 h DDQ (154 mg, 0.678 mmol) was added and stirred for additional 1 h in air. A few drops of triethylamine were added to neutralize the reaction mixture. Column chromatography on silica gel, using petroleum ether/CH_2Cl_2 (1:2) as an eluent afforded the desired porphyrin **3** as purple waxy solid (13%, 0.13 g). Mp: 216–217 °C; IR (KBr, cm^{-1}): 701, 2856, 2923, 3434; ^1H NMR ($CDCl_3$, δ in ppm): 0.91 (t, $J=$ 6.95 Hz, 12H, CH_3), 1.25 (m, 48H, CH_2), 4.11 (q, $J=$ 6.22 Hz, 8H, OCH_2), 7.67–7.69 (m, 12H, *m*,*p*-phenyl), 8.11 (q, $J=3.29$ Hz, 8H, *o*-phenyl),), 8.30 (s, 4H, pyrrole); ^{13}C NMR ($CDCl_3$, δ in ppm): 14.21, 22.79, 25.94, 29.36, 29.78, 31.93, 74.68, 126.46, 127.37, 131.45, 132.15, 133.05, 133.21, 134.05, 142.43, 153.96, 157.28; LDMS $C_{76}H_{92}N_2O_4S_2$ calcd mass 1161.6. Obsd *m*/*z* 1162.5; Anal. Calcd: C, 78.58; H, 7.98; N, 2.41; S, 5.52. Found: C, 78.46; H, 8.06; N, 2.58; S, 5.69.

4.1.15. 2,3,12,13-Tetradodecyloxy-5,10,15,20-tetraphenyl-21,23-dithiaporphyrin 4. A solution of diol **20** (0.400 g, 0.58 mmol) and pyrrole (0.050 ml, 0.73 mmol) in CH_2Cl_2 was stirred under an inert atmosphere. After 15 min, $BF_3\cdot OEt_2$ (30 μl of 2.5 M solution in dichloromethane) was added and the reaction was stirred for 1 h. DDQ (0.102 g, 0.45 mmol) was added and stirred for an additional 1 h in air. After work up, the crude porphyrin was purified by column chromatography using petroleum ether/CH_2Cl_2 (6:4) as eluent and afforded a waxy purple solid of **4** in 13% yield (0.260 g). Mp: 195–196 °C; IR (KBr, cm^{-1}): 702, 2860, 2927, 3442; ^1H NMR ($CDCl_3$, δ in ppm): 0.90 (t, $J=6.59$ Hz, 12H, CH_3), 1.25–1.28 (m, 80H, CH_2), 4.11 (t, $J=6.22$ Hz, 8H, OCH_2), 7.67–7.69 (m, 12H, *m*, *p*-phenyl), 8.10–8.13 (m, 8H, *o*-phenyl), 8.30 (s, 4H, pyrrole); ^{13}C NMR ($CDCl_3$, δ in ppm): 14.22, 22.80, 25.97, 29.50, 29.74, 32.05, 74.70, 126.47, 127.39, 131.47, 133.07, 133.22, 134.07, 142.45, 153.98, 157.30; LD-MS $C_{92}H_{124}N_2O_4S_2$ calcd mass 1386.1. Obsd *m*/*z*: 1386.0; Anal. Calcd: C, 79.72; H, 9.02; N, 2.02; S, 4.63. Found: C, 79.96; H, 8.93; N, 2.23; S, 4.84.

4.1.16. 2,3-Dimethoxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin 5. A mixture of **17** (0.200 g, 0.560 mmol), benzaldehyde (0.120 ml, 1.17 mmol) and pyrrole (0.120 ml, 1.73 mmol) were dissolved in dichloromethane (50 ml) and stirred at room temperature for 15 min. $BF_3\cdot OEt_2$ (30 μl of 2.5 M stock solution in dichloromethane) was added to initiate the reaction. After 1.5 h stirring DDQ (0.095 g, 0.42 mmol) was added to oxidise the porphyrinogen. The TLC analysis of the crude porphyrin showed the formation of three porphyrins as expected. The mixture of three porphyrins were separated by silica gel column chromatography using petroleum ether/dichloromethane as solvent mixture. The desired N_3S porphyrin **5** moved as the second band with petroleum ether/CH_2Cl_2 (1:1). Removal of solvent under reduced pressure gave **5** as purple solid in 10% yield (0.039 g). Mp: > 300 °C; IR (KBr, cm^{-1}): 701, 2854, 2927, 3463; ^1H NMR ($CDCl_3$, δ in ppm): −2.58 (s, 1H, NH), 3.92 (s, 6H, OCH_3), 7.70–7.74 (m, 12H, *m*,*p*-phenyl), 8.11–8.18 (m, 8H, *o*-phenyl), 8.47 (d, $J=4.76$ Hz, 2H, pyrrole), 8.52 (d, $J=4.76$ Hz, 2H, pyrrole), 8.85 (s, 2H, pyrrole); FAB-MS: $C_{46}H_{33}N_3O_2S$ calcd 691.84. Obsd *m*/*z*: 692; Anal. Calcd: C, 79.86; H, 4.81; N, 6.07; S, 4.63. Found: C, 79.51; H, 5.06; N, 6.47; S, 4.92.

4.1.17. 2,3-Dibutoxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin 6. A solution of diol **18** (0.30 g, 0.68 mmol), benzaldehyde (0.15 ml, 1.47 mmol) and pyrrole (0.14 ml, 2.02 mmol) in dichloromethane (80 ml) was treated with $BF_3\cdot OEt_2$ (50 μl of 2.5 M solution of dichloromethane). After 1 h, DDQ (0.120 g, 0.528 mmol) was added and stirring was continued for another 1 h. Column chromatography on silica gel using with petroleum ether and CH_2Cl_2 (1:1) gave the desired compound **6** as the second band (0.042 g, 8%). Mp: > 300 °C; IR (KBr, cm^{-1}): 709, 2861, 2927, 3460; ^1H NMR ($CDCl_3$, δ in ppm): −2.57 (s, 1H, NH), 1.27 (s, 14H, CH_2CH_3), 4.21–4.24 (s, 4H, OCH_2), 7.70–7.76 (m, 12H, *m*,*p*-phenyl), 8.11–8.18 (m, 8H, *o*-phenyl), 8.41 (d, $J=4.76$ Hz, 2H, pyrrole), 8.50 (d, $J=4.39$ Hz, 2H, pyrrole), 8.85 (s, 2H, pyrrole); FAB-MS: $C_{52}H_{45}N_3O_2S$ calcd 776.84. Obsd *m*/*z*: 776; Anal. Calcd: C, 80.48; H, 5.85; N, 5.41; S, 4.13. Found: C, 80.83; H, 6.02; N, 5.77; S, 4.43.

4.1.18. 2,3-Dioctyloxy-5,10,15,20-tetraphenyl-21-monothiaporphyrin 7. A mixture of **19** (0.200 g, 0.362 mmol), benzaldehyde (0.090 ml, 0.797 mmol) and pyrrole (0.080 ml, 1.21 mmol) in dry CH_2Cl_2 (40 ml) was condensed in the presence of $BF_3\cdot OEt_2$ (30 μl of 2.5 M solution in dichloromethane) followed by oxidation with DDQ (0.062 g, 0.27 mmol). Purification was achieved by silica gel column chromatography using petroleum ether/CH_2Cl_2 mixture (1:1) giving the desired N_3S as second band. The solvent was removed in vacuo to afford **7** as soft purple solid (0.032 g, 9.9%). Mp: >225 °C; IR (KBr, cm^{-1}): 703, 2852, 2923, 3434; ^1H NMR ($CDCl_3$, δ in ppm): and −2.59 (s, 1H, NH), 1.42 (s, 30H, CH_2CH_3), 4.2 (s, 4H, OCH_2), 7.68–7.73 (m, 12H, *m*,*p*-phenyl), 8.11–8.29 (m, 8H, *o*-phenyl), 8.40 (d, $J=4.88$ Hz, 2H, pyrrole), 8.48 (d, $J=3.66$ Hz, 2H, pyrrole), 8.83 (s, 2H, pyrrole); FAB-MS: $C_{60}H_{61}N_3O_2S$ calcd 888.21. Obsd *m*/*z*: 889; Anal. Calcd: C, 80.13; H, 6.92; N, 4.73; S, 3.61. Found: C, 80.38; H, 6.74; N, 4.98; S, 3.45.

4.1.19. 2,3-Didodecyloxy-5,10,15,20-tetraphenyl-21-monothia porphyrin 8. A solution of diol **20** (0.210 g, 0.304 mmol), benzaldehyde (0.065 ml, 0.637 mmol) and

pyrrole (0.070 ml, 1.01 mmol) in CH_2Cl_2 (30 ml) was treated with $BF_3 \cdot OEt_2$ (25 μl of 2.5 M solution). After 1 h stirring, DDQ (0.060 g, 0.26 mmol) was added and stirring was continued for another hour. Chromatography on silica gel using petroleum ether/CH_2Cl_2 (7:3) gave the desired N_3S porphyrin **8** as a waxy purple solid in 15% yield (0.450 g). Mp: >225 °C; IR (KBr, cm^{-1}): 704, 2853, 2923, 3453; ^1H NMR ($CDCl_3$, δ in ppm): −2.58 (s, 1H, NH), 0.90 (s, 6H, CH_3), 1.27 (s, 40H, CH_2), 4.19 (s, 4H, OCH_2), 7.67–7.73 (m, 12H, *m*,*p*-phenyl), 8.10–8.15 (m, 8H, *o*-phenyl), 8.42 (d, J=4.76 Hz, 2H, pyrrole), 8.50 (d, J=4.76 Hz, 2H, pyrrole), 8.84 (s, 2H, pyrrole); ^{13}C NMR ($CDCl_3$, δ in ppm): 14.2, 22.78, 26.00, 29.74, 32.04, 74.73, 123.96, 126.45, 127.30, 127.86, 128.43, 133.06, 133.38, 134.42, 134.84, 138.71, 142.25, 142.50, 153.53, 154.18, 158.71; FAB-MS: $C_{68}H_{77}N_3O_2S$ calcd 1000.42. Obsd *m*/*z*: 1001; Anal. Calcd: C, 81.64; H, 7.76; N, 4.20; S, 3.21. Found: C, 81.76; H, 7.52; N, 4.60; S, 3.53.

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Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tet.2004.09.008

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Semiconductor-mediated oxidative dimerization of 1-naphthols with dioxygen and *O*-demethylation of the enol-ethers by SnO_2 without dioxygen

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Abstract—Oxidative dimerization of 1-naphthols **1** with dioxygen in the presence of a semiconductor, such as SnO_2, ZrO_2, or activated charcoal, as a catalytic mediator takes place selectively to give the corresponding 2,2′-binaphthols **2** or 2,2′-binaphthyl-1,1′-quinones **3** in excellent yields without light irradiation. The catalytic activity of SnO_2 could be fully restored by appropriate reactivation treatment after the oxidation. In addition, SnO_2 without dioxygen catalyzes selective *O*-demethylation of the enol-ethers **3** to **4**.

1. Introduction

Aryl–aryl bond formation is one of the most important tools of modern organic synthesis. These bonds are found in natural biaryls such as binaphthoquinones, binaphthols, lignans, alkaloids, flavonoids, and coumarins,[1] as well as in many pharmaceuticals and agrochemicals.

In general, the methods for construction of aryl–aryl bonds (biaryl frameworks) can be classified into two types: (i) the oxidative (biomimetic) coupling of various aromatic compounds using an electrochemical[2a–i] or a chemical method[2j–m,3,4] and (ii) a transition-metal-catalyzed coupling of aryl halides, for example, the palladium-catalyzed Still and Suzuki reactions.[2j] Oxidative coupling of hydroxyarenes (so-called oxidative dimerization of hydroxyarenes) commonly involves oxidative dehydrogenation and subsequent C–C or C–O coupling of the resulting arenyl radical.

We have focused on the oxidative dimerization of naphthols as a means to construct biaryl frameworks, aiming at biomimetic synthesis of natural products such as binaphthoquinones and binaphthols. Various methods have been developed for the preparation of binaphthols and their derivatives by the oxidative coupling of naphthols using a range of oxidants, such as metal salts, Ag(I), Pb(IV), Fe(III), Mn(III), Cu(II), etc., in homogeneous solution.[2j–m] In most cases, however, the coupling reactions are not catalytic, but require more-than-stoichiometric amounts of oxidants. There are some exceptions employing such catalyst systems as oxovanadium (IV)–amino acid complex, Ru (II)–salen complex, etc., under dioxygen (O_2) as coupling reagents.[2j,3] In the oxidation of naphthols, the use of homogeneous oxidants often leads to poor selectivity and low yield of the desired products, accompanied with side reactions, so that the reactions are difficult to control. Recently, solid Lewis acids,[4] such as $FeCl_3$ have been used as heterogeneous catalysts, either alone or in binary combinations such as $CuSO_4/Al_2O_3$ and $FeCl_3$/montmorillonite, with aerial oxygen or dioxygen for oxidative coupling of 2-naphthols.

The replacement of current stoichiometric oxidations for the production of fine chemicals with environmentally benign catalytic oxidations is one of the major tasks in green chemistry. Dioxygen seems to be an ideal oxidant for such purposes, as well as for biomimetic synthesis of natural products, because the supply is ample, and the molecule is environmentally friendly and nontoxic. In addition, dioxygen participates in many metabolic processes in mammalians and plants.[5]

Recently, much attention has been focused on the use of various semiconductor catalysts,[6a,b] particularly TiO_2,[6c] to achieve a variety of organic reactions and syntheses based on the concept of green chemistry.[7] Semiconductors (SC) are usually used as sensitizers in heterogeneous photocatalytic oxidations. They are particularly useful from an

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environmental viewpoint, because they are almost nontoxic, stable, and inexpensive. Several such reactions have been reported, including oxygenations and oxidative cleavage.[6] From practical and environmental viewpoints, SC should be advantageous as heterogeneous catalysts, and it is expected that dioxygen can be effectively used for the facile regeneration of such catalysts in a catalytic cycle. However, to our knowledge, there has been no report to date on oxidative dimerization of 1-naphthols (NPOH) with dioxygen using SC in the absence of light irradiation.

In a previous communication,[8c] we reported that semiconductors efficiently mediate the oxidative dimerization of 1-naphthols (**1**; NPOH) to the corresponding 2,2′-binaphthyls in the presence of dioxygen (O_2). Here, we present the results of a detailed study of the oxidative reaction of NPOH **1** with various SC/O_2 systems.

2. Results and discussion

We investigated the oxidation of NPOH **1a–d**, **f** (including precursors for the synthesis of natural products) and the naphthol ether **1e** using several SCs[6] [TiO_2, Nb_2O_5, SnO_2, ZrO_2, activated charcoal (Act-C),[9] etc.] and solvents saturated with dioxygen [CH_2Cl_2, MeCN, $MeNO_2$, etc.] without light irradiation. We found that the nature of the major products depended upon the substrates (NPOH) in oxidation with the SC/O_2 system. In particular, there was a difference between oxidation of **1a–c** having a methoxyl group and oxidation of **1f** having a methyl group at the C-4 position. Three types of reactions in the presence of semiconductors were found: (1) the oxidative dimerization of NPOH **1a–c** to 2,2′-binaphthyls **2** and **3** under O_2, (2) selective demethylation of 2,2′-binaphthyl-1,1′-quinones **3a–c** (enol-ethers) to 1′-hydroxy-2,2′-binaphthyl-1,4-quinones **4** without O_2, and (3) the oxidative conversion of **1f** to the naphthol trimers **8** and **9** under O_2.

2.1. Oxidative dimerization of NPOH 1a–1e with various SC/O_2 systems

Preliminary experiments on the oxidative dimerization were done with NPOH **1a** as a substrate using several SCs[6] and solvents saturated with dioxygen under various conditions, and the results are shown in Table 1. The best result was obtained with Act-C in CH_2Cl_2 (entry 1). That is, the reaction of **1a** using the Act-C/O_2 reagent system in the presence of O_2 in CH_2Cl_2 afforded selectively the so-called Russig's Blue,[10a] 2,2′-binaphthyl-1,1′-quinone (**3a**; BNPQ), in excellent yield. A similar result was obtained in the dark.

With the ZrO_2/O_2 system in CH_2Cl_2, BNPQ **3a** was obtained as a major product along with the *ortho*-naphthoquinone[5a] as a by-product (entry 2). However, good results were not obtained with the Nb_2O_5/O_2 or the TiO_2/O_2 system (entries 3 and 4). Furthermore, with the SnO_2/O_2 system in CH_2Cl_2, 2,2′-binaphthol (**2a**; BNPOH) and 1′-hydroxy-2,2′-binaphthyl-1,4-quinone (**4a**; HBNPQ) were obtained in yields of 67% and 28%, respectively (entry 5). A solvent effect of MeCN was only observed in the reaction with the SnO_2/O_2 system. When MeCN was used in place of CH_2Cl_2 under similar conditions, **4a** was not obtained at all, and in this case **2a** and **3a** were obtained in yields of 64 and 28%, respectively (entry 6). The reason for this is discussed below. The catalyst (SnO_2) could be easily recovered by simple filtration and washing with CH_2Cl_2, followed by drying at 130 °C for 12 h under reduced pressure before re-use. The recovered SnO_2 showed almost unchanged catalytic reactivity, since repeated reaction (five times) with **1a** using the recovered SnO_2 in MeCN under identical conditions gave similar results to that of entry 6 in all cases. However, recovered ZrO_2 and Act-C did not re-acquire full catalytic activity after the above reactivation treatment.

Similar reactions were explored using **1b** or **1c**,[11] which can be precursors for the synthesis of binaphthyl natural products (Table 1).[10]

In the case of **1b**, the best result was obtained with the ZrO_2/O_2 system in MeCN for 0.75 h, affording **3b** selectively in excellent yield (entry 9). The reaction with the SnO_2/O_2 system under similar conditions gave a complex mixture containing a substantial amount of **2b**. In order to isolate **2b**, we performed column chromatography of the reaction mixtures under various conditions. However, all the attempts were unsuccessful, producing mainly solid mixtures of **2b** and **3b**. Therefore, the mixture of **2b** and **3b** was treated with benzyl bromide/K_2CO_3 to give **5** (81%) as a major product together with nonreacted **3b** (2%) (entry 10).

In the case of **1c**, the best result was obtained with the SnO_2/O_2 system in MeCN. This oxidative coupling was very sluggish, but selectively afforded **2c** in good yield (entry 13). In all experiments with **1c** using various semiconductors, a longer period of reaction was required for completion of the reaction, in comparison with the cases of **1a**, **b**. This may be owing to the influence of the hydrogen-bond formation[12] between the hydroxyl proton (at C1) and the methoxyl group (at C8) in **1c**, as shown in Scheme 1, though this remains to be confirmed.

When the α-naphthol **1d** without substituents other than a hydroxyl group at the C-1 position was used, the oxidative biaryl coupling reaction did not proceed at all (entries 14–16). In the case of the naphthol-ether **1e** with the SnO_2/O_2 system, the reaction also did not proceed under similar conditions (entry 17). No reaction of **1a** with ZrO_2 under air took place at all under similar conditions (entry 18). Finally, the reaction of **1b** with the well-known oxidant Ag_2O in chloroform was examined, but gave only a mixture of the coupling product and its oxidized quinone (entry 19).

Noteworthy features of the above reactions were as follows. The hydroxyl group in **1a–c** was required for the formation of the binaphthyl derivatives, based on the result of entry 17. The SC-mediated oxidation of **1a–c** in the presence of O_2 made it possible to control the synthesis in the direction of either **3** or **2**. For example, the reaction of **1a** or **1b** with the Act-C/O_2 or the ZrO_2/O_2 system afforded the corresponding **3a** or **3b**, respectively, in excellent yield, while the reaction of **1c** with the SnO_2/O_2 system gave **2c** in high yield. The SC was essential for the catalysis of the present oxidation, since the reaction did not proceed in its absence. The resulting

Table 1. Semiconductor-mediated oxidative dimerization of naphthols **1** in the presence of dioxygen (O_2)[a]

Entry	NPOH	Reagent	Solvent	Temperature (°C)	Time (h)	Product (isolated yield, %)					
						2	**3**	**4**	**5**	**6**	**7**
1	**1a**	Act-C[b]	CH_2Cl_2[c]	23[c]	16		95	Trace			
2	**1a**	ZrO_2	CH_2Cl_2	23	1.5		75			17	
3	**1a**	Nb_2O_5	CH_2Cl_2	23	3.5		51			43	
4	**1a**	TiO_2	CH_2Cl_2	23	0.5	4	15	18		20	
5	**1a**	SnO_2	CH_2Cl_2	23	72	67		28			
6	**1a**	SnO_2	MeCN	70	29	64	28				
7	**1a**	SnO_2	$MeNO_2$	23	72	81	6				
8	**1b**	Act-C[b]	MeCN	70	24		44		20[d]	11	9
9	**1b**	ZrO_2	MeCN	70	0.75		96				
10[e]	**1b**	SnO_2	CH_2Cl_2	23	24		2	3	81[d]		
11	**1c**	Act-C[b]	MeCN	70	72	64	16	Trace			
12[e]	**1c**	ZrO_2	MeCN	70	70	68	14	Trace			
13[e]	**1c**	SnO_2	MeCN	70	136	86					
14	**1d**	Act-C[b]	MeCN	70	285	No reaction					
15	**1d**	ZrO_2	MeCN	70	24						2[f]
16	**1d**	SnO_2	MeCN	70	312	No reaction					
17	**1e**	SnO_2	CH_2Cl_2	23	72	No reaction					
18[g]	**1a**	ZrO_2	CH_2Cl_2	23	1.5	No reaction					
19[h]	**1b**	Ag_2O	$CHCl_3$	23	0.5		34		30[d]	8	
20	**2a**	SnO_2	CH_2Cl_2	23	22	29	49	14			
21	**2a**	ZrO_2[i]	MeCN	70	0.75		93				

[a] General procedure: a slurry of semiconductor powder [Act-C (1 g),[b] SnO_2 (5 g), ZrO_2 (5 g), Nb_2O_5 (5 g), or TiO_2 (1 g)] and **1a** (0.25 mmol) in a dioxygen-saturated solvent (MeCN, CH_2Cl_2, or $MeNO_2$) was vigorously stirred at an appropriate temperature (23 or 70 °C) under normal laboratory light. Similar results were obtained in the dark. These semiconductors are commercially available (Wako Pure Chemical Industries, Ltd., in Japan).

[b] In our previous communication, we erroneously reported that when MeCN was used as a solvent at 70 °C, BNPQ **3a** was obtained in this reaction of **1a**.[8c] The solvent (MeCN) and the temperature (70 °C) should have been given as CH_2Cl_2 and 23 °C.

[c] With activated charcoal.

[d] Yield from **1b**.

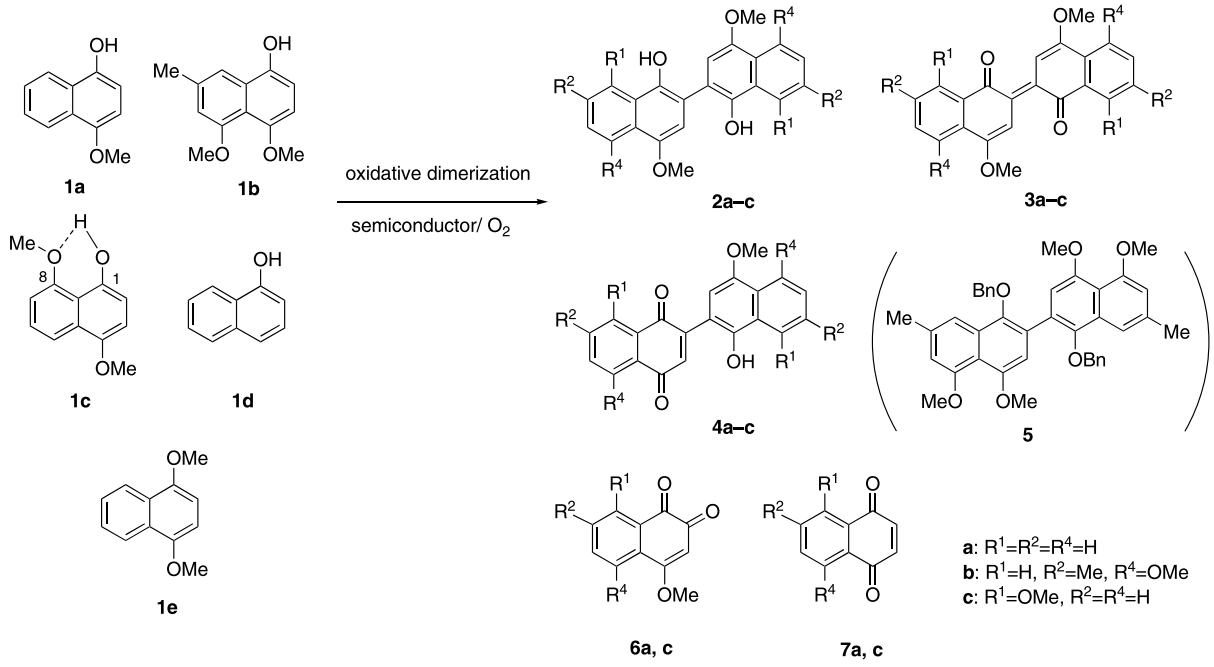
[e] Unreacted NPOHs **1** were also recovered: entry 10, **1b** (14%); entry 12, **1c** (8%); entry 13, **1c** (12%).

[f] **7a** (2%) along with a polymeric compound.

[g] This reaction was carried out under air. CH_2Cl_2 as a solvent was used without any treatment.

[h] With Ag_2O (1.5 equiv) under air.

[i] In our previous communication, we erroneously reported that when SnO_2 was used as a reagent, BNPQ **3a** was obtained in this reaction of **2a**.[8c] SnO_2 should have been written as ZrO_2.

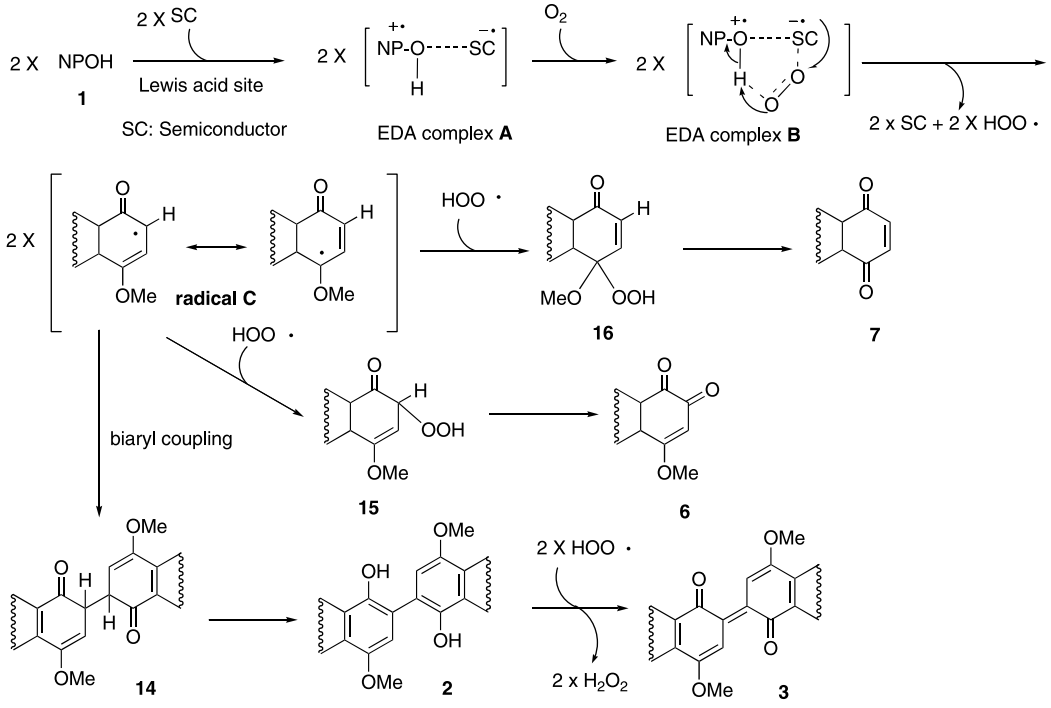


Scheme 1.

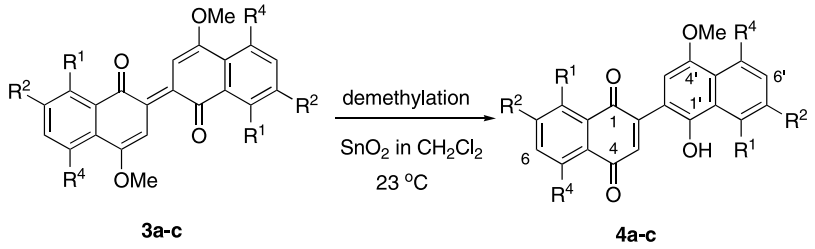
products **2**, **3**, and **4** would be useful synthetic intermediates for naturally occurring diosindigo B, biramentaceone and violet-quinone.[10b,c]

In order to confirm the formation mechanism of **3** in the present oxidation, the reaction of **2a** with the ZrO_2/O_2 system in MeCN was carried out to give **3a** in high yield (entry 21 in Table 1). No reaction occurred in the absence of O_2 under similar conditions. The above results indicate that the products **3** are produced via **2** by the oxidation of **1**.

The proposed mechanism for the SC-mediated oxidative dimerization of NPOH **1** using O_2 is illustrated in Scheme 2. This is analogous to that proposed for the oxidative reaction of 1-naphthols with the $SnCl_4/O_2$ system reported previously by us.[8d] This reaction is initiated by the formation of the electron donor–acceptor (EDA) complex **A** between **1** and a Lewis acid site on the SC surface.[13a] Subsequent processes proceed on the SC surface. The SC, such as SnO_2, ZrO_2 or Act-C, plays an important role in the present oxidation. That is, it acts not only as a characteristic Lewis



Scheme 2.



Scheme 3.

Table 2. Demethylation of the enol-ethers **3** to **4** with various reagents in the absence of O_2[a]

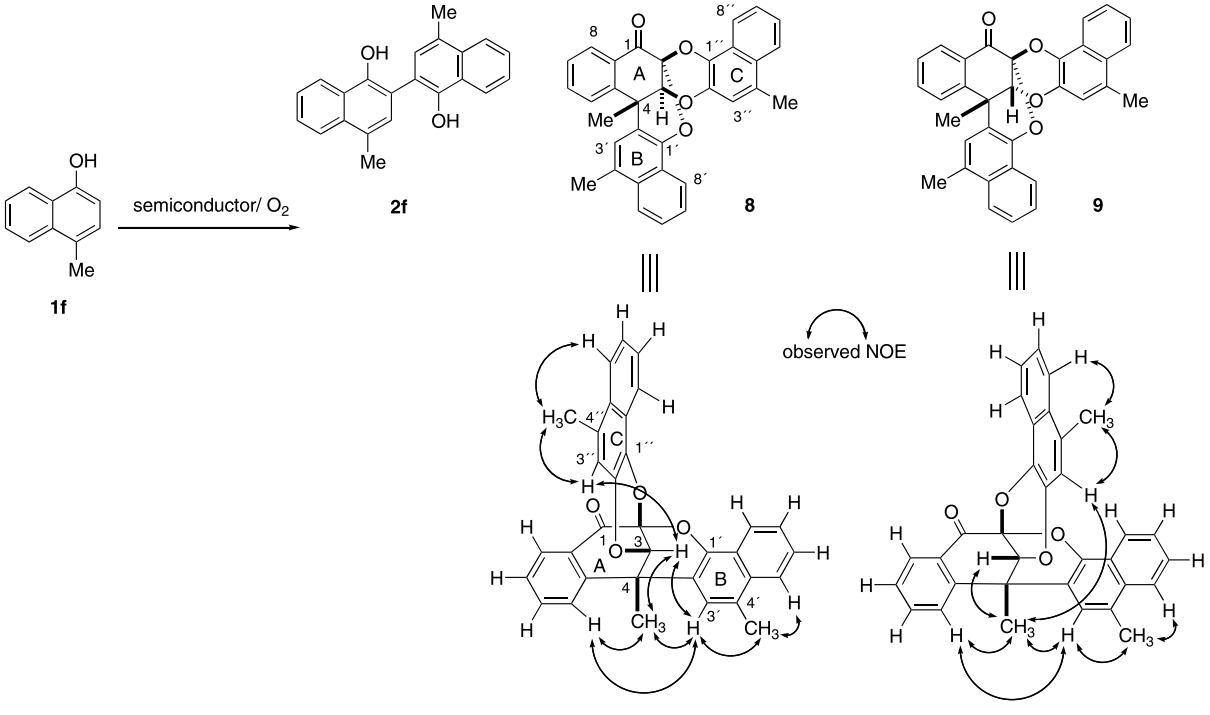
Entry	Substrate	Reagent	Solvent	Time (h)	Product (%)[b]
1	**3a**	SnO_2	CH_2Cl_2	19	**4a** (96)
2	**3a**	SnO_2	MeCN	72	No reaction
3	**3b**	SnO_2	CH_2Cl_2	2	**4b** (95)
4	**3c**	SnO_2	CH_2Cl_2	2	**4c** (93)
5[c]	**3a**	ZrO_2	CH_2Cl_2	72	**4a** (12)
6	**3a**	Act-C	CH_2Cl_2	72	No reaction
7[d]	**3a**	HCl	CH_2Cl_2	8	**4a** (91)

[a] General procedure: a slurry of semiconductor powder [SnO_2 (5 g), ZrO_2 (5 g) or Act-C (1 g)] and **3** (0.25 mmol) in an argon-saturated solvent (CH_2Cl_2, or MeCN) was vigorously stirred at 23 °C under normal laboratory light. Similar results were obtained in the dark.
[b] Isolated yield.
[c] Together with the recovered **3a** (40%).
[d] Using 10% HCl aq.

acid catalyst, but also as a mediator for electron transfer. Alternatively, O_2 may act as a one-electron acceptor from the anion-radical species ($SC^{\cdot -}$) and a one-proton acceptor from the cation-radical species ($NPOH^{\cdot +}$) within complex **B**. Finally, the resulting hydroperoxy radicals act as a two-hydrogen acceptor from **2**. Alternatively, *o*-naphthoquinone **6** and *p*-naphthoquinone **7** can be formed through coupling between the hydroperoxy radical and the *ortho*-radical **C** or the *para*-radical **C**.[13b,c]

2.2. Selective demethylation of BNPQ 3 to HBNQ 4 with various SCs without O_2

Next, to throw light on whether HBNPQ **4** is formed by acid-induced demethylation or oxidative demethylation of the enol-ethers **3** in the reaction of **1** in CH_2Cl_2 (entries 4, 5, and 9 in Table 1), the reactions of **3a–c** with various reagents in the absence of O_2 in CH_2Cl_2 or MeCN were examined (Scheme 3). The results are summarized in



Scheme 4.

Table 3. Oxidation of NPOH **1f** with various SC/O_2 systems[a]

Entry	NPOH	Reagent	Time (h)	Product (%)[b]			
				2f	**8**	**9**	**1f**[c]
1	**1f**	ZrO_2	6		14	14	-
2[d]	**1f**	ZrO_2	6				99
3	**1f**	SnO_2	144		22	22	-
4	**1f**	Act-C	144		6	6	-
5	**1f**	TiO_2	6				-[e]
6	**1f**	Nb_2O_5	24	24	10	10	8

[a] General procedure: a slurry of semiconductor powder [SnO_2 (5 g), ZrO_2 (5 g) or Act-C (1 g)] and **1f** (0.25 mmol) in a dioxygen-saturated MeCN was vigorously stirred at 70 °C under normal laboratory light. Similar results were obtained in the dark.
[b] Isolated yield.
[c] Recovered **1f**.
[d] In an argon-saturated MeCN in the absence of O_2.
[e] Complex mixture.

Table 2. With SnO_2 in CH_2Cl_2, selective demethylation of **3a–c** proceeded efficiently to give **4a–c** under mild conditions in high yield (entries 1, 3, and 4). Similar results were obtained in the dark. These results indicate that the formation of **4** from **3** does not require dioxygen and light, but requires SnO_2.

Alternatively, the formation of the hydroxyl group (at C-1′) in **4** from **3** requires a proton (H^+) or a hydrogen source. This suggests the participation of a Brønsted acid (Sn–OH) site on the SnO_2 surface, because proton sources, such as water (H_2O) and acids were not used in the work-up after the reaction according to general procedure described in Table 2. Early infrared studies (IR spectroscopy) of the adsorption of carbon monoxide (CO) on the SnO_2 surface explicitly showed the existence of Sn–OH sites on the SnO_2

Table 4. ^{13}C and ^1H NMR spectral data (δ/ppm) for compounds **8**,[a] **9**,[a] **10**[a] and **11**[a]

Carbon no.	**8**		**9**		**10**		**11**	
	^{13}C	^1H[b]	^{13}C	^1H[b]	^{13}C	^1H[b]	^{13}C	^1H[b]
1	186.4		186.4		70.7	5.13 bs	70.6	5.10 bs
2	109.2		109.2		114.8		114.6	
3	89.0	5.17 s	89.1	5.17 s	89.8	5.10 s	90.0	5.08 s
4	50.4		50.4		51.0		50.9	
4a	145.2		145.2		138.6		138.7	
5	127.3	7.74 bd (7.9)	127.2	7.73 bd (8.2)	126.8	7.80 bd (8.2)	126.8	7.79 bd (7.9)
6	135.4	7.67 m	135.4	7.65 dt (1.2, 6.7)	129.3	7.47 m	129.4	7.47 dt (1.2, 6.1)
7	111.9	7.32 m	127.4	7.32 dt (1.2, 6.7)	127.4	7.31 m	127.4	7.32 dt (1.2, 6.1)
8	128.1	8.00 dd (1.2, 6.7)	128.0	7.99 dd (1.2, 6.7)	129.6	7.55 bd (7.6)	129.8	7.52 bd (7.6)
8a	129.0		129.07		134.3		134.4	
1′	151.9		151.6		151.5		151.4	
2′	127.2		127.1		127.1		127.2	
3′	120.1	7.42 bs	120.1	7.41 bs	120.8	7.45 bs	120.7	7.41 bs
4′	128.6		128.7		128.2		128.1	
4a′	133.1		133.1		132.8		132.7	
5′	124.4	7.88 m	124.4	7.88 m	124.3	7.88 bd (8.6)	124.2	7.83 bd (9.2)
6′	126.4	7.46 bs	126.4	7.47 m	126.0	7.43 m	125.9	7.36 m
7′	125.7	7.47 m	125.7	7.48 m	125.3	7.34 m	125.2	7.21 m
8′	122.4	8.04 m	122.5	8.08 m	122.0	7.72 bd (8.2)	121.7	7.65 bd (8.2)
8a′	120.8		120.9		120.6		120.6	
1″	138.2		139.8		139.5		139.6	
2″	142.7		141.1		142.7		142.5	
3″	127.4	7.93 bs	111.0	7.00 bs	111.7	6.88 bs	111.0	7.05 bs
4″	130.3		129.11		128.8		128.7	
4a″	128.6		129.0		128.4		128.4	
5″	125.0	7.30 bd (8.6)	124.5	7.93 bd (8.9)	125.0	7.92 bd (8.6)	124.5	7.85 bd (9.2)
6″	119.9	7.69 bt (8.2)	124.2	7.42 m	123.6	7.36 m	123.6	7.27 m
7″	126.1	7.41 m	126.2	7.54 bt (7.0)	125.8	7.43 m	125.6	7.25 m
8″	123.8	7.36 m	121.0	8.18 bd (8.6)	120.1	7.80 bd (8.2)	120.3	7.52 bd (7.6)
8a″	119.8		120.2		119.7		120.1	
4-Me	26.2	2.23 bs	26.1	2.19 bs	29.7	1.97 bs	29.4	1.97 bs
4′-Me	19.6	2.67 bs	19.5	2.66 bs	19.4	2.66 bs	19.54 or 19.50	2.652 bs
4″-Me	19.6	2.69 bs	19.6	2.64 bs	19.6	2.57 bs	19.54 or 19.50	2.654 bs
1-OH						2.84 bs		2.90 bs

[a] Data recorded in $CDCl_3$ at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR). Assignments were based on ^1H–^1H COSY, ^1H–^{13}C COSY, HMBC and NOESY spectra.
[b] Coupling constants (J in Hz) are given in parentheses.

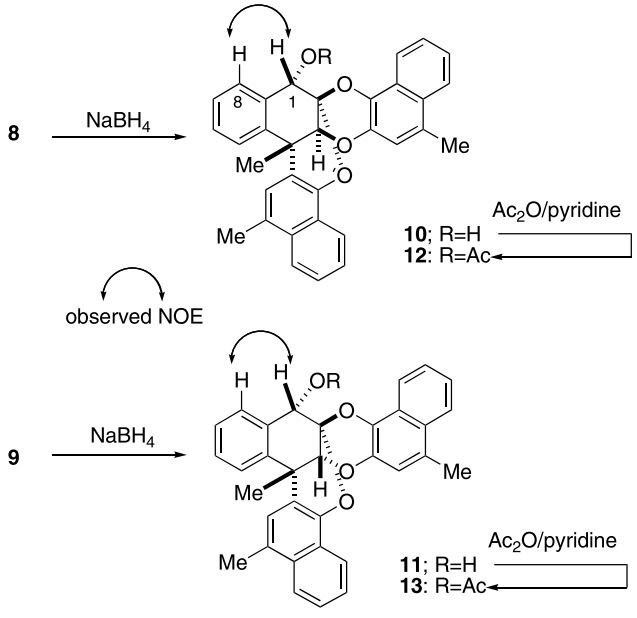
surface.[14b] Indeed, the reaction of **3a** with HCl as a Brønsted acid in place of SnO_2 gave **4a** in good yield (entry 7). Accordingly, **4** is concluded to be formed by demethylation of **3** at Sn–OH sites on the SnO_2 surface.

In order to examine the reason why MeCN has the solvent effect described above, the reaction of **3a** using MeCN in place of CH_2Cl_2 as a solvent was carried out under similar conditions. Surprisingly, this reaction did not proceed at all (entry 2). In the above case, as well as in the case of entry 6 in Table 1, **4a** was presumably not obtained because the interaction between the Sn–OH sites and the carbonyl group in **3a** is blocked by the MeCN molecules, which bind to the Sn–OH sites; Yates and co-workers[13c] observed the adsorption of MeCN on Brønsted acid sites of a metal oxide surface, such as TiO_2, by means of IR spectroscopy. The reaction with ZrO_2 under similar conditions gave **4a** in low yield, while no reaction occurred with Act-C. These results indicate that the formation of **4** by the reaction of **1** or **3** can be well controlled when ZrO_2 or Act-C catalyst and MeCN are employed.

2.3. Oxidative conversion of NPOH 1f to the naphthol trimers 8 and 9 with various SC/O_2 systems

Interestingly, when we used NPOH **1f** having a methyl group (at C4) with various SC/O_2 systems, a unique reaction took place to afford the novel naphthol trimer **8** and **9** in all cases, that is, the tricyclic adduct with two ether linkages formed between ring A and ring C (Scheme 4 and Table 3). The best result was obtained in the reaction with the SnO_2/O_2 system in MeCN at 70 °C (entry 3).

The structure of **8** was elucidated by means of detailed analyses of the ^1H and ^{13}C NMR spectra with the aid of various 2D NMR experiments (Table 4),[15] and also by chemical transformation to **10** as shown in Scheme 5. In addition, the structure **8** was also supported by its mass spectral fragmentation pattern (Fig. 1).



Scheme 5.

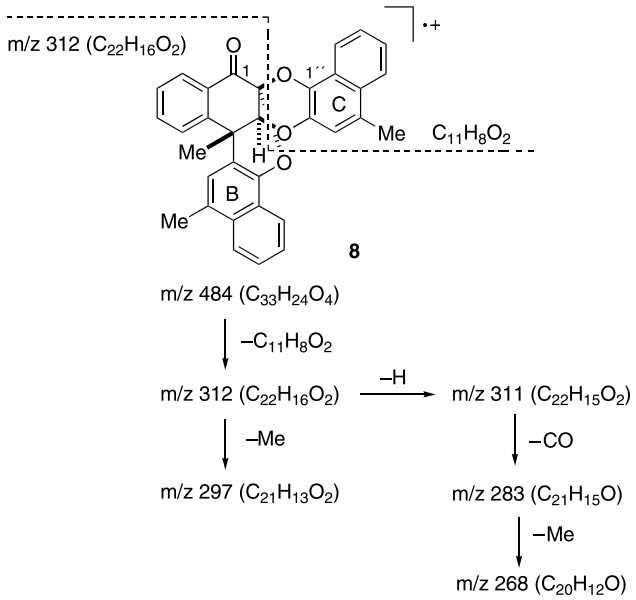


Figure 1. Characteristic peaks in the mass spectrum of **8**.

The regiosubstitution was determined by means of a NOESY experiment on **8**, showing NOE effects between 3-H (ring A) and 3″-H (ring C), and between 4-Me (ring A) and 3′-H (ring B), which correspond to the linkages between the units, C3–O–C1″, C2–O–C2″ and C4–C2′–C1′, C2–O–C2′ (Scheme 4). In addition, this linkage between ring A and ring B was confirmed by observation of the long-range correlations of 4-CH_3 and C2′, and 3′-H and C4 in the HMBC spectrum of **8** (Table 5).

The relative configuration in ring A was also confirmed by the NOESY experiment on **8**: NOE correlations were observed between 3-H and 3″-H, and 3-H and 3′-H, showing that structure **8** has the *trans*-configuration between C-3 and C-4 in ring A (Scheme 4).

The reduction of **8** with $NaBH_4$ yielded only one product **10** having a secondary hydroxyl group; the hydride attacked from the less hindered β-face to produce the C1α-hydroxyl group (Scheme 5). The relative stereostructure of the C1 position in ring A was characterized by observation of the NOE correlations between 1-H and 8-H in **10** (Scheme 5). Furthermore, on acetylation with acetic anhydride and pyridine, **10** afforded a monoacetate **12**. The structure of **9** was elucidated by similar analysis, and also by chemical transformation to **11**. In addition, the mass spectra of **9** showed a fragmentation pattern similar to that of **8**.

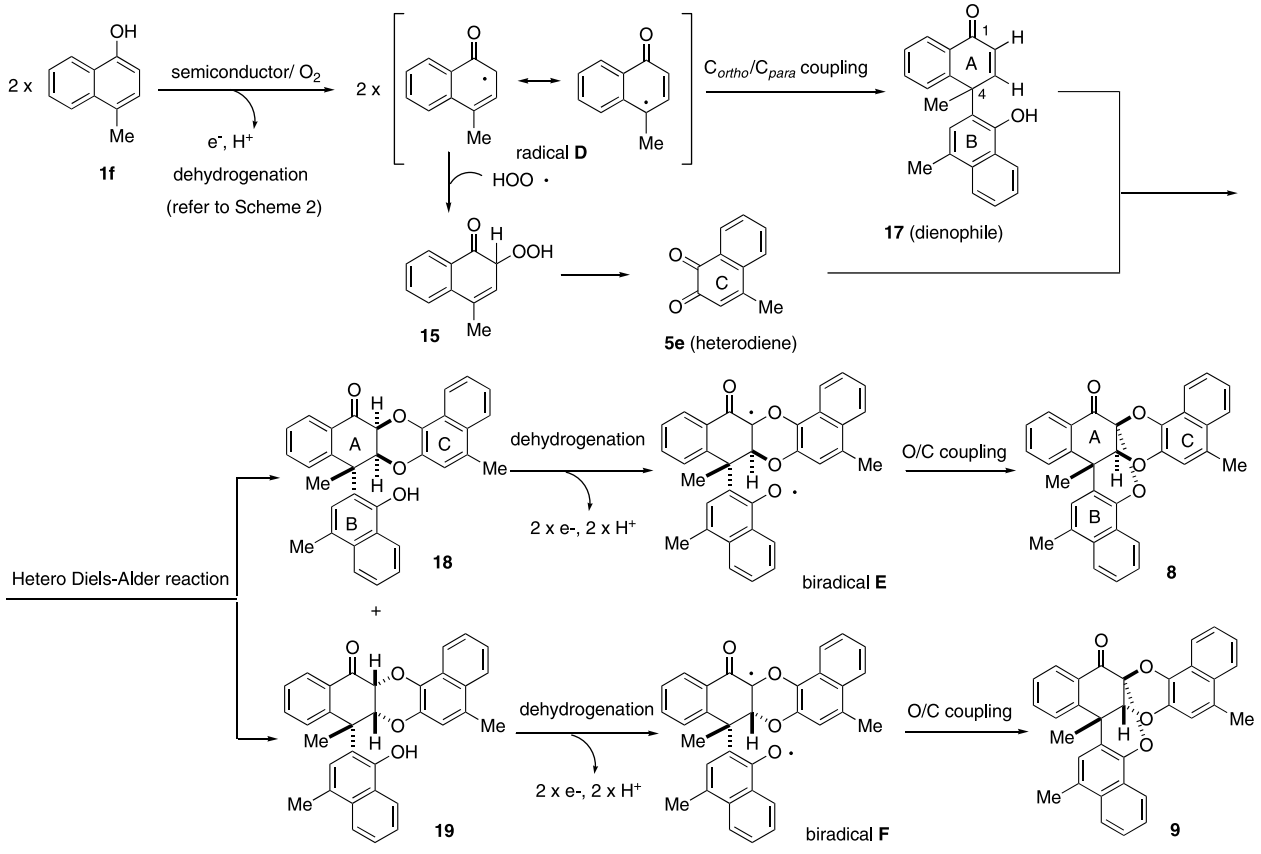
The oxidative conversion of **1f** to **8** and **9** can be explained in terms of oxidative dehydrogenation, followed by *C*/*C* and *O*/*C* radical couplings and the hetero Diels–Alder (HDA) cycloaddition[16] as illustrated in Scheme 6. This HDA reaction is analogous to that reported previously by Moujir et al.[17a] Firstly, the *p*-napthoquinone methide **17** is formed by C_{ortho}/C_{para} coupling of the radical **D** generated by the oxidative dehydrogenation of **1h** with the SC/O_2 system. On the other hand, the radical **D** reacts with the hydroperoxy radical[13b,c] generated from dioxygen (O_2) to give the *o*-napthoquinone **5e** (refer to Scheme 4). Subsequently, the HDA reaction of **17** with **5e** takes place

Table 5. Long-range heteronuclear correlations (HMBC) for **8**, **9**, **10** and **11**

^{1}H position	**8**	**9**	**10**	**11**
1	—	—	C-8a	C-2, C-4a, C-8a
1-OH	—	—	—	—
3	C-1, C-2, C-4, C-4a, C4-Me	C-1, C-2, C-4, C-4a, C4-Me	C-1, C-2, C-4, C-4a, C4-Me, C-2′	C-1, C-2, C-4a, C4-Me
4-Me	C-3, C-4, C-4a, C-2′	C-3, C-4, C-4a, C-2′	C-3, C-4, C-4a, C-2′	C-3, C-4, C-4a, C-2′
5	C-4, C-8a	C-4, C-7, C-8a	C-4, C-7, C-8a	C-4, C-7, C-8a
6	C-4a	C-4a, C-8	C-4a, C-8	C-4a, C-8
7	C-6	C-5, C-6, C-8a	C-5, C-8a, C-8	C-5, C-8a
8	C-1, C-4a, C-6	C-1, C-4a, C-6	C-1, C-4a, C-6	C-1, C-4a, C-6
3′	C-4, C-1′, C-4a′, C4′-Me	C-4, C-1′, C-4a′, C4′-Me	C-4, C-4a′, C4′-Me	C-4, C-1′, C-4a′, C4′-Me
4′-Me	C-3′, C-4a′	C-3′, C-4a′	C-3′, C4′, C-4a′	C-3′, C-4a′
5′	C-4a′, C-7′, C-8a′	C-7′, C-8a′	C-4′, C-7′, C8a′	C-4′, C-7′
6′	—	—	C-8′	C-4a′, C-8′
7′	C-8′	C-5′, C-8′	C-5′, C8a′	C-5′
8′	C-4a′, C-6′	C-1″, C-4a″, C-6″	C-1′, C-4a′, C-6′	C-1′, C-4a′, C-6′
3″	C-1″, C-2″, C-4a″, C4″-Me	C-1″, C-2″, C-4a″, C4″-Me	C-1″, C-2″, C-4a″, C4″-Me	C-1″, C-2″, C-4a″, C4″-Me
4″-Me	C-4″	C-3″, C-4a″	C-3″, C-4″	C-3″, C-4″
5″	C-4″, C-6″, C-7″	C-4″, C-7″, C-8a″	C4″, C-7″, C-8a″	C-7″, C-8a″
6″	C-8″	C-4a″, C-8″	C-4a″, C-8″	C-4a″, C-8″
7″	C-5″, C-6″	C-5″, C-8a″	C-5″, C8a″	C-5″
8″	C-6″	C-1″, C-4a″, C-6″	C-1″, C-6″	C-6″

regioselectively to form the bicyclic *cis*-fused adducts **18** and **19**.

Although the reason for the regioselective formation of **18** and **19** is unclear, a possible explanation is as follows. In general, the HDA reaction proceed preferentially through the *endo*-mode rather than the corresponding *exo*-mode in the transition state.[16g] The *p*-napthoquinone methide **17** has two π-faces, *syn* and *anti*, with respect to the NPOH group at the C4-position in ring A (Fig. 2).[16b,d] Among four possible transition modes (I)–(IV), in the formation of the *anti*-adduct **18** and the *syn*-adduct **19**, both the *anti* (I) and *syn* (III) transition states can be operative, respectively (Fig. 2). Alternatively, the regioisomers **20** and **21** were not formed at all in this reaction since the *anti* (II) and *syn* (IV) orientations are not possible in the transition state because of steric repulsion between the *o*-naphthoquinone ring (ring C) and the methyl group or the NPOH group at the C4 position in ring A.



Scheme 6.

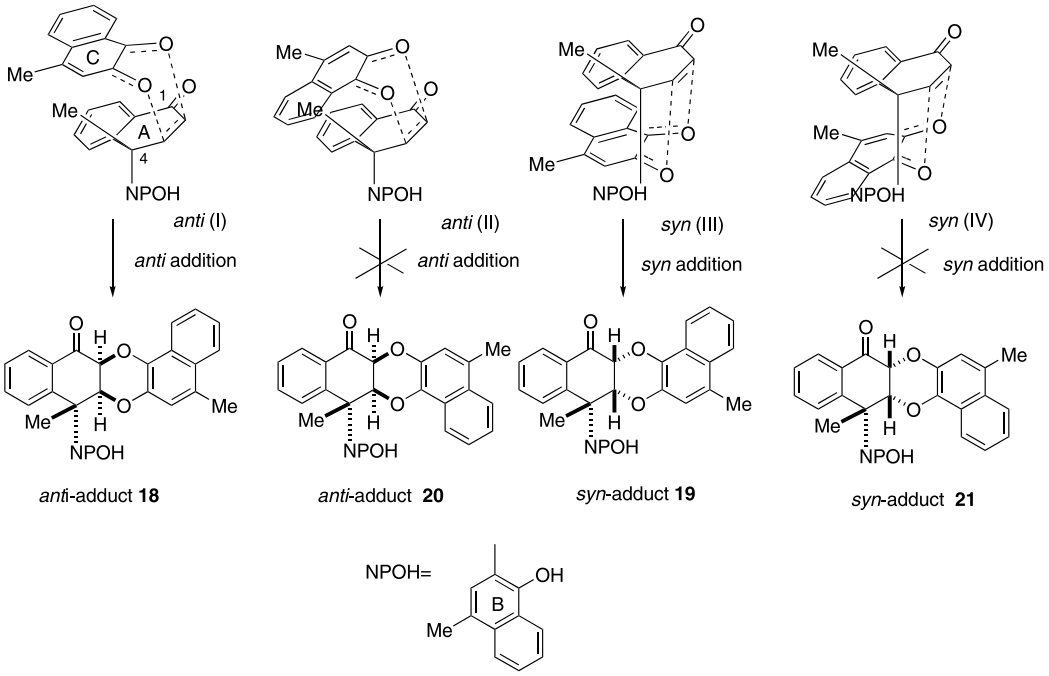


Figure 2. Four possible transition states in the hetero Diels–Alder reaction of *p*-napthoquinone methide **17** with *o*-napthoquinone **5e**.

Finally, the tricyclic bridged adduct **8** or **9** is formed by intramolecular O/C radical coupling in the biradical **E** or **F**, which is generated by oxidative dehydrogenations of both the enolate (ring A) and the naphthol sites (ring B) in **18** or **19**, respectively (Scheme 6).

This proposed HDA reaction of *p*-napthoquinone methide **17** with *o*-napthoquinones **5e**[16a–c] is attractive because of its potential application to quinoid natural products synthesis, and its possible involvement in the biosynthesis of natural products including triterpene dimers or trimers with various biological activities.[17]

In the results described above, a noteworthy difference in the major product between oxidation with **1a–c** and oxidation with **1f** as a substrate was observed. Oxidation of **1a–c** with the SC/O_2 system afforded the corresponding BNPOH **2** or BNPQ **3**, whereas in the case of **1f**, the naphthol trimers **8** and **9** were obtained as the major products. Although the reason for this difference is unclear, some structural difference of the electron donor–acceptor (EDA) complex formed between the semiconductors and **1a–c** or **1f** in the reaction process may be involved.

3. Conclusion

In this study, we found that heterogeneous SC, such as SnO_2, ZrO_2 and Act-C, are efficient solid oxidation catalysts for the oxidative dimerization of NPOH **1a–c** to 2,2′-binaphthyl derivatives **2** or **3** using dioxygen as an oxidant. In particular, SnO_2 is a useful and convenient catalyst for the selective synthesis of 2,2′-binaphthols **2** and for selective *O*-demethylation of the enol-ethers **3a–c** to **4**. The SnO_2-mediated oxidations appear to be environmentally friendly, since the reagent is nontoxic and can be recycled.

4. Experimental

4.1. General

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer, and ^1H and ^{13}C NMR spectra with JEOL JNM-AL300 and JNM-alpha 500 spectrometers, with tetramethylsilane as an internal standard ($CDCl_3$, CD_3COCD_3 or CD_3SOCD_3 solution). Mass spectra were recorded on a JEOL JMS-D300 or Shimadzu QP-5000 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Merck Kieselgel 60 (230–400 mesh), Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for flash column chromatography, column chromatography and thin-layer chromatography (TLC), respectively. Each organic extract was dried over $MgSO_4$ or Na_2SO_4. The semiconductors, such as ZrO_2 and activated charcoal powders, are commercially available (Wako Pure Chemical Industries, Ltd., Japan).

4.2. Synthesis of 1-naphthols 1a–h

Naphthols **1b**,[18a,b] **1c**,[18d–f] **1e**,[8b] and **1f**[8a] were synthesized according to the protocol reported previously, and **1a** and **1d** are commercially available (Tokyo Kasei Chemical Industries, Ltd., Japan).

4.3. General procedure for oxidative dimerization of NPOHs 1a–g with semiconductors in the presence of dioxygen (O_2) (the SC/O_2 system)

A slurry of semiconductor powder [Act-C (1 g), SnO_2 (5 g), ZrO_2 (5 g), Nb_2O_5 (5 g), or TiO_2 (1 g)] and the selected substrate **1** (0.28 mmol) in a dioxygen (O_2)-saturated solvent or an argon-saturated solvent (MeCN, CH_2Cl_2 or CH_3NO_2; 15 ml) was vigorously stirred at 23 or 70 °C under

normal laboratory light. Then, the reaction mixture was stirred in a sealed tube until disappearance of the substrate (1-naphthols and 2,2′-binaphthyls), except in cases where the starting material was recovered. The insoluble reagent was filtered off and washed with the solvents used, and then the filtrate was evaporated. The residue was subjected to flash column chromatography on silica gel.

4.4. Oxidative dimerization of 1a with the SC/O_2 system

Oxidation of **1a** (50 mg, 0.29 mmol) was carried out according to the general procedure for the oxidative dimerization of NPOHs **1** with the SC/O_2 system described above. The crude product was subjected to flash column chromatography on silica gel with the designated solvents as follows: CH_2Cl_2–hexane (3:1; for **3a** and **6a** in Table 1); CH_2Cl_2–hexane (1:2; for **2a**, **3a**, **4a** and **6a** in Table 1); CH_2Cl_2–hexane (1:2; for **2a** and **4a** in Table 1); CH_2Cl_2–hexane (1:2; for **2a** and **3a** in Table 1); yields are listed in Table 1. Similar results were obtained when the reactions were carried out in the dark.

4.4.1. 4,4′-Dimethoxy[2,2′]binaphthalenyl-1,1′-diol (2a). Colorless needles (benzene), mp 223–224 °C. LR-MS *m/z*: 346 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8b]

4.4.2. 4,4′-Dimethoxy[2,2′]binaphthalenylidene-1,1′-dione (3a). Deep blue needles (benzene), mp 257–258 °C. LR-MS *m/z*: 344 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8b]

4.4.3. 1′-Hydroxy-4′-methoxy[2,2′]binaphthalenyl-1,4-dione (4a). Deep violet needles (benzene), mp 189 °C. LR-MS *m/z*: 330 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8a]

4.4.4. 4-Methoxy-1,2-naphthoquinone (6a). Yellow needles (MeOH–hexane), mp 192–193 °C. LR-MS *m/z*: 188 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8a]

4.5. Oxidative dimerization of 1b with various reagents

Method A (entry 19) (with Ag_2O). A solution of **1b** (100 mg, 0.46 mmol) in $CHCl_3$ (10 ml) containing 1.5 equiv of Ag_2O (160 mg, 0.69 mmol) was stirred at 23 °C in an air atmosphere for 30 min. The solvent was removed and the residue was subjected to flash column chromatography on silica gel using CH_2Cl_2–AcOEt (20:1, v/v) as an eluent to give a mixture of **2b** and **3b**, and 4,5-dimethoxy-7-methyl-1,2-naphthoquinone (**6b**). Benzyl bromide (268 μl, 2.26 mmol) was added to a solution of the mixture of **2b** and **3b**, and anhydrous K_2CO_3 (312 mg, 2.26 mmol) in dry DMF (5 ml), and the solution was stirred vigorously at 23 °C for 15 min. The reaction mixture was poured into ice-water, neutralized with 10% HCl, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and concentrated. The residue was subjected to flash column chromatography on silica gel. The eluate with hexane–AcOEt (10:1, v/v) gave 1,10-dibenzyloxy-4,5,40,50-tetramethoxy[2,20]binaphthalenyl-1,10-diol (**5**) and 4,5,4′,5′-tetramethoxy-7,7′-dimethyl[2,2′]binaphthalenylidene-1,10-dione (**3b**). Yields are listed in Table 1.

Method B (entry 8) (with the Act-C/O_2 system). Oxidation of **1b** (50 mg, 0.23 mmol) with Act-C (1 g) in MeCN was carried out at 70 °C for 24 h according to the general procedure for the oxidative dimerization of NPOHs **1** with the SC/O_2 system. Benzylation of the resulting products was carried out by the same procedure under the conditions described above (method A) for benzylation of a mixture of **2b** and **3b**. The crude product was purified by flash column chromatography on silica gel. The eluate with CH_2Cl_2–hexane (1:2, v/v) gave **5**, **3b**, **6b** and **7b**. Yields are listed in Table 1.

Method C (entry 9) (with the ZrO_2/O_2 system). Oxidation of **1b** (50 mg, 0.23 mmol) with ZrO_2 (5 g) in MeCN was carried out at 70 °C for 0.75 h according to the general procedure for the oxidative dimerization of NPOHs **1** with the SC/O_2 system. The crude product was purified by recrystallization from benzene to yield **3b** (96%).

Method D (entry 10) (with the SnO_2/O_2 system). Oxidation of **1b** (50 mg, 0.23 mmol) with SnO_2 (5 g) in CH_2Cl_2 was carried out at 23 °C for 24 h according to the general procedure for the oxidative dimerization of NPOHs **1** with the SC/O_2 system. Benzylation of the resulting oxidative products was carried out by the same procedure under the conditions described above (method A) for benzylation of a mixture of **2b** and **3b**. The crude product was purified by flash column chromatography on silica gel. The eluate with hexane–AcOEt (10:1, v/v) gave **5**, **3b**, and **4b**. Yields are listed in Table 1. Similar results were obtained when the reactions were carried out in the dark.

4.5.1. 4,5,4′,5′-Tetramethoxy-7,7′-dimethyl[2,2′]binaphthalenylidene-1,1′-dione (3b). Deep blue powder (benzene), mp 236.5–237.0 °C (lit.[8a] 236.5–237 °C). IR (KBr) cm^{-1}: 1589, 1302, 1053. ^1H NMR ($CDCl_3$) δ: 2.43 (6H, s, 7 and 7′-Me), 3.92 (6H, s, 5 and 5′-OMe), 4.05 (6H, s, 4 and 4′-OMe), 6.98 (2H, br s, 6 and 6′-H), 7.70 (2H, br s, 8 and 8′-H), 8.37 (2H, s, 3 and 3′-H). ^{13}C NMR ($CDCl_3$) δ: 21.8 (and *′-Me*), 56.1 (4 and 4′-O*Me*), 56.9 (5 and 5′-O*Me*), 103.2 (C3 and C3′), 118.0 (C4a and C4a′), 118.2 (C6 and C6′), 121.7 (C8 and C8′), 130.3 (C8a and C8a′), 133.6 (C2 and C2′), 140.3 (C7 and C7′), 156.1 (C4 and C4′), 159.5 (C5 and C5′), 188.9 (C1 and C1′). LR-MS *m/z*: 432 (M^+). HR-MS calcd for $C_{26}H_{24}O_6$: 432.1566. Found: 432.1563. Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.35; H, 5.56.

4.5.2. 1′-Hydroxy-5,4′,5′-trimethoxy-7,7′-dimethyl[2,2′]-binaphthalenyl-1,4-dione (4b). Green granules (hexane–AcOEt), mp 168.5–169.5 °C. IR (KBr) cm^{-1}: 3418, 2920, 1643, 1599. ^1H NMR ($CDCl_3$) δ: 2.52 (6H, s, 7 and 7′-Me), 3.93 (3H, s, 5′-OMe), 3.98 (3H, s, 4′-OMe), 4.03 (3H, s, 5-OMe), 6.55 (1H, s, 3′-H), 6.81 (1H, d, J=1.5 Hz, 6′-H), 7.01 (1H, s, 3-H), 7.17 (1H, d, J=0.6 Hz, 6-H), 7.70 (1H, dd, J=0.6, 0.92 Hz, 8-H), 7.86 (1H, dd, J=0.6, 0.92 Hz, 8′-H), 8.60 (1H, s, 1′-OH). ^{13}C NMR ($CDCl_3$) δ: 22.1 (C7 or C7′-*Me*), 22.3 (C7 or C7′-*Me*), 56.4 (C4′-O*Me*), 56.5 (C5-O*Me*), 57.3 (C5′-O*Me*), 107.0 (C3′), 110.6 (C6′), 114.8 (C2′), 115.7 (C8′), 117.0 (C4a or C4a′), 117.7 (C4a or

C4a′), 119.0 (C6), 121.3 (C8), 129.8 (C8a′), 134.4 (C8a), 136.6 (C7′), 141.3 (C3), 144.8 (C1′), 146.4 (C7), 146.5 (C2), 151.04 (C4′), 156.5 (C5′), 159.6 (C5), 183.6 (C1), 188.3 (C4). LR-MS *m/z*: 418 (M^+). HR-MS calcd for $C_{25}H_{22}O_6$: 418.1417. Found: 418.1432. Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.78; H, 5.35.

4.5.3. 1,1′-Dibenzyloxy-4,5,4′,5′-tetramethoxy[2,2′]-binaphthalenyl-1,1′-diol (5). Pale yellow powder (AcOEt), mp 203.5–204.0 °C (lit.[8a] 203.5–204 °C). IR (KBr) cm^{-1}: 2922, 1604. ^1H NMR ($CDCl_3$) δ: 2.50 (6H, s, 7 and 7′-Me), 3.91 (6H, s, 4 and 4′-OMe), 4.02 (6H, s, 5 and 5′-OMe), 4.71 (4H, s, 2×–CH_2–Ar), 6.78 (2H, d, J= 1.29 Hz, 6 and 6′-H), 7.17 (2H, s, 3 and 3′-H), 7.20–7.30 (10H, m, Ar-H), 7.67 (2H, d, J=1.29 Hz, 8 and 8′-H). ^{13}C NMR ($CDCl_3$) δ: 22.2 (7- and 7′-Me), 56.55 (5-OMe), 56.62 (4 and 4′-OMe), 75.1 (–CH_2–Ar), 108.3 (C3 and C3′), 109.1 (C6 and C6′), 114.5 (C8 and C8′), 116.2 (C2 and C2′), 127.5 (C4a and C4a′), 127.9 (Ar-C), 128.1 (Ar-C), 128.4 (Ar-C), 132.1 (C8a and C8a′), 136.7 (C7 and C7′), 137.3 (Ar-C), 145.2 (C1 and C1′), 152.8 (C4 and C4′), 157.1 (C5 and C5′). LR-MS *m/z*: 614 (M^+). HR-MS: calcd for $C_{40}H_{38}O_6$: 614.2658. Found: 614.2642. Anal. Calcd for $C_{40}H_{38}O_6$: C, 78.15; H, 6.23. Found: C, 78.13; H, 6.20.

4.5.4. 4,5-Dimethoxy-7-methyl-1,2-naphthoquinone (6b). Orange powder ($CHCl_3$–hexane), mp 175.0–176.0 °C. IR, ^1H and ^{13}C NMR data were described previously by us.[8a]

4.5.5. 5-Methoxy-7-methyl-1,4-naphthoquinone (7b). Yellow needles (benzene), mp 169.5–170 °C (lit.[18e] 164–166 °C). IR (KBr) cm^{-1}: 1651, 1559. ^1H NMR ($CDCl_3$) δ: 2.48 (3H, s, 7-Me), 4.00 (3H, s, 5-OMe), 6.84 (2H, s, 2 and 3-H), 7.11 (1H, s, 6-H), 7.55 (1H, s, 8-H). HR-MS calcd for $C_{12}H_{10}O_3$: 202.0627. Found: 202.0614.

4.6. Oxidative dimerization of 1c with the SC/O_2 system

Oxidation of **1c** (50 mg, 0.25 mmol) was carried out according to the general procedure for the oxidative dimerization of NPOHs. The crude product was subjected to flash column chromatography on silica gel with the designated solvents as follows: hexane–AcOEt (3:1; for **2c**, **3c** and **4c** in Table 1); hexane–AcOEt (3:1; for **2c** in Table 1); hexane–AcOEt (1:1; for **3c** in Table 1). Yields for **2c**, **3c** and **4c** are listed in Table 1. Similar results were obtained when the reactions were carried out in the dark.

4.6.1. 4,4′,8,8′-Tetramethoxy-2,2′-di-1,1′-naphthol (2c). Colorless needles ($CHCl_3$–hexane), mp 207–209 °C. LR-MS *m/z*: 406 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8b]

4.6.2. 4,8,4′,8′-Tetramethoxy[2,2′]binaphthalenylidene-1,1′-dione (3c). Deep purple needles ($CHCl_3$–hexane), mp 261–262 °C. LR-MS *m/z*: 404 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8b]

4.6.3. 1′-Hydroxy-4′,8,8′-trimethoxy[2,2′]binaphthalenyl-1,4-dione (4c). Deep purple needles (hexane–AcOEt), mp 120–122 °C. IR (KBr) cm^{-1}: 3394, 1607. ^1H NMR ($CDCl_3$) δ: 3.95 (3H, s, OMe), 3.99 (3H, s, OMe), 4.01 (3H, s, OMe), 6.72 (1H, s, 3′-H), 6.86 (1H, d, J= 7.9 Hz, 7′-H), 7.04 (1H, s, 3-H), 7.30 (1H, d, J=8.2 Hz, 7-H), 7.37 (1H, t, J=7.9, 8.5 Hz, 6′-H), 7.66 (1H, t, J=7.6, 8.2 Hz, 6-H), 7.76 (1H, dd, J=0.9, 7.6 Hz, 5-H), 7.86 (1H, dd, J=1.1, 8.5 Hz, 5′-H), 9.41 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 55.9 (C4′-O*Me*), 56.1 (C8-O*Me*), 56.5 (C8′-O*Me*), 105.6 (C7′), 107.1 (C3′), 114.9 (C2′), 115.3 (C8a′), 115.9 (C5′), 117.8 (C7), 118.6 (C5), 121.1 (C8a), 126.3 (C6′), 128.9 (C4a′), 134.35 (C3), 134.38 (C6), 134.41 (C4a), 146.3 (C1′), 147.8 (C4′), 150.9 (C2), 156.4 (C8′), 159.6 (C8), 183.2 (C1), 185.3 (C4). LR-MS *m/z*: 390 (M^+). HR-MS calcd for $C_{23}H_{18}O_6$: 390.1100. Found: 390.1170. Anal. Calcd for $C_{23}H_{18}O_6$: C, 70.76; H, 4.65. Found: C, 70.56; H, 4.62.

4.7. Oxidation of 1d with the SC/O_2 system

The reaction of **1d** (50 mg, 0.35 mmol) was carried out according to the general procedure for the oxidative dimerization of NPOHs. The crude product was subjected to flash column chromatography on silica gel with CH_2Cl_2–hexane (2:1, v/v) to yield 1,4-naphthoquinone **7a**, as yellow needles (ethanol), mp 125–126 °C (lit.[18g] 128 °C). Yields are listed in Table 1. Similar results were obtained when the reactions were carried out in the dark. IR (KBr) cm^{-1}: 1659, 1587. ^1H NMR (DMSO-d_6) δ: 7.08 (2H, s, 2 and 3-H), 7.88 (2H, dd, J=3.3, 5.8 Hz, 6 and 7-H), 7.99 (2H, dd, J= 3.3, 5.8 Hz, 5 and 8-H). LR-MS *m/z*: 158 [M^+].

4.8. Oxidation of 1e with the SC/O_2 systems

These reactions did not proceed.

4.8.1. General procedure for demethylation of BNPQ 3a–c to HBNPQ 4a–c with semiconductors in the absence of O_2. A slurry of semiconductor powder [SnO_2 (5 g), ZrO_2 (5 g), or Act-C (1 g)] and the selected substrate **3** (0.15 mmol) in a argon-saturated solvent (MeCN or CH_2Cl_2; 15 ml) was vigorously stirred at 23 °C under normal laboratory light. Then, the reaction mixture was stirred in a sealed tube until disappearance of the substrate (2,2′-binaphthyls), except in cases where the starting material was recovered. The insoluble reagent was filtered off and washed with solvents used, and then the filtrate was evaporated. The residue was subjected to flash column chromatography on silica gel with the designated solvents as follows: hexane–CH_2Cl_2 (1:1; for **4a** in Table 2); CH_2Cl_2–AcOEt (20:1; for **4b** in Table 2); hexane–AcOEt (1:1; for **4c** in Table 2). Yields for **4a–c** are listed in Table 2. Similar results were obtained when the reactions were carried out in the dark.

4.8.2. The reaction of 3a with HCl. A solution of **3a** (1.0 g, 2.91 mmol) and 10% HCl (1.1 ml) in CH_2Cl_2 (100 ml) was stirred at 23 °C for 8 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to flash column chromatography on silica gel using CH_2Cl_2–hexane (1:1, v/v) as an eluent to give **4a** (91%).

4.9. Oxidation of 1f with the SC/O_2 system

The reaction of **1f** (50 mg, 0.32 mmol) was carried out

according to the general procedure for the oxidative dimerization of NPOHs. The crude product was subjected to flash column chromatography on silica gel with the designated solvents as follows: CH_2Cl_2–hexane (1:2; for **2f**, **8** and **9** in Table 3); CH_2Cl_2–hexane (1:2; for **8** and **9** in Table 3). Yields are listed in Table 3. Similar results were obtained when the reactions were carried out in the dark.

4.9.1. 4,4′-Dimethyl[2,2′]binaphthalenyl-1,1′-diol (2f). White amorphous powder ($CHCl_3$–hexane), mp 219–220 °C. LR-MS *m/z*: 314 (M^+). IR, ^1H and ^{13}C NMR data were described previously by us.[8b]

4.9.2. Compound 8. Yellow powder ($CHCl_3$–hexane), mp over 300 °C. IR (KBr) cm^{-1}: 1717, 1651, 1601. ^1H and ^{13}C NMR spectral data are listed in Table 4. HR-MS calcd for $C_{33}H_{24}O_4$: 484.1668. Found: 484.1675. Anal. Calcd for $C_{33}H_{24}O_4$: C, 81.80; H, 4.99. Found: C, 81.90; H, 5.01.

4.9.3. Compound 9. Pale yellow powder ($CHCl_3$–hexane), mp over 300 °C. IR (KBr) cm^{-1}: 1717, 1608. ^1H and ^{13}C NMR spectral data are listed in Table 4. HR-MS calcd for $C_{33}H_{24}O_4$: 484.1668. Found: 484.1693. Anal. Calcd for $C_{33}H_{24}O_4$: C, 81.80; H, 4.99. Found: C, 81.85; H, 4.96.

4.9.4. Reduction of 8 with $NaBH_4$. To a solution of **8** (30 mg, 0.06 mmol) in CH_2Cl_2 (10 ml) and MeOH (5 ml) was added dropwise a solution of $NaBH_4$ (20 mg, 0.53 mmol) in MeOH (2 ml) at 0 °C and the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel. The eluate with CH_2Cl_2–hexane (1:1, v/v) gave 28 mg (93%) of **10**, as colorless crystals (benzene–hexane), mp 278.5–279.5 °C. IR (KBr) cm^{-1}: 3562, 1653, 1612. ^1H and ^{13}C NMR spectal data are listed in Table 4. HR-MS calcd for $C_{33}H_{26}O_4$: 486.1824. Found: 486.1807. Anal. Calcd for $C_{33}H_{26}O_4$: C, 81.46; H, 5.39. Found: C, 81.36; H, 5.40.

4.9.5. Reduction of 9 with $NaBH_4$. Reduction of **9** (50 mg, 0.10 mmol) was carried out at 23 °C for 15 min by the same procedure under the conditions described above for the reduction of **8**. The crude product was purified by flash column chromatography on silica gel. The eluate with CH_2Cl_2–hexane (1:1, v/v) gave 49 mg (98%) of **11**, as colorless crystals (benzene–hexane), mp 246–247 °C. IR (KBr) cm^{-1}: 3457, 1651, 1617. ^1H and ^{13}C NMR spectral data are listed in Table 4. HR-MS calcd for $C_{33}H_{26}O_4$: 486.1824. Found: 486.1801. Anal. Calcd for $C_{33}H_{26}O_4$: C, 81.46; H, 5.39. Found: C, 81.56; H, 5.42.

4.9.6. Acetylation of 10 with Ac_2O/pyridine. Acetic anhydride (1.5 ml) was added to a solution of **10** (40 mg, 0.08 mmol) in pyridine (0.5 ml) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto crushed ice and stirred at room temperature for 1 h, and the whole was extracted with $CHCl_3$. The organic layer was washed with diluted HCl, and H_2O, then dried, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel. The eluate with CH_2Cl_2–hexane (1:1, v/v) gave 38 mg (87%) of **12**, as colorless plates (benzene–hexane), mp 271.5–272.0 °C. IR (KBr) cm^{-1}: 1746, 1661, 1620. ^1H NMR ($CDCl_3$) δ: 1.75 (3H, s, Me), 2.00 (3H, s, Me), 2.58 (3H, s, Me), 2.62 (3H, s, Me), 5.15 (1H, s, 3-H), 6.44 (1H, s, 1-H), 6.95 (1H, s, Ar-H), 7.21–7.52 (8H, m, Ar-H), 7.71 (1H, br d, J=8.3 Hz, Ar-H), 7.85–7.90 (4H, m, Ar-H). HR-MS calcd for $C_{35}H_{28}O_5$: 528.1929. Found: 528.1916.

4.9.7. Acetylation of 11 with Ac_2O/pyridine. Acetylation of **11** (45 mg, 0.09 mmol) was carried out at 23 °C for 2 h by the same procedure under the conditions described above for acetylation of **10**. The crude product was purified by flash column chromatography on silica gel. The eluate with CH_2Cl_2–hexane (1:1, v/v) gave 40 mg (82%) of **13** as colorless plates (benzene–hexane), mp 261.0–262.0 °C. IR (KBr) cm^{-1}: 1746, 1653, 1617. ^1H NMR ($CDCl_3$) δ: 1.75 (3H, s, Me), 1.99 (3H, s, Me), 2.61 (3H, s, Me), 2.62 (3H, s, Me), 5.11 (1H, s, 3-H), 6.39 (1H, s, 1-H), 6.99 (1H, br s, Ar-H), 7.21–7.41 (7H, m, Ar-H), 7.47–7.53 (1H, m, Ar-H), 7.61–7.65 (1H, m, Ar-H), 7.82–7.88 (4H, m, Ar-H). HR-MS calcd for $C_{35}H_{28}O_5$: 528.1929. Found: 528.1958.

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Iridium-catalyzed hydroboration of alkenes with pinacolborane

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Abstract—Hydroboration of terminal and internal alkenes with pinacolborane (1.2 equiv) was carried out at room temperature in the presence of an iridium(I) catalyst (3 mol%). Addition of dppm (2 equiv) to $[Ir(cod)Cl]_2$ gave the best catalyst for hydroboration of aliphatic terminal and internal alkenes at room temperature, resulting in addition of the boron atom to the terminal carbon of 1-alkenes with more than 99% selectivities. On the other hand, a complex prepared from dppe (2 equiv) and $[Ir(cod)Cl]_2$ resulted in the best yields for vinylarenes such as styrene. These complexes exhibited higher levels of catalyst activity and selectivity than those of corresponding rhodium complexes.

1. Introduction

Hydroboration of alkenes and alkynes is the most convenient method for preparation of alkyl- and 1-alkenylboron compounds. Since most H-B reagents can be added to double or triple C–C bonds without any assistance of catalysts,[1] catalyzed hydroboration did not attract much attention until Männig and Nöth reported in 1985 that the Wilkinson complex $[RhCl(PPh_3)_3]$ catalyzes the addition of catecholborane to alkenes and alkynes at room temperature.[2] Subsequent extensive works revealed that the catalyzed hydroboration is a more interesting strategy for accelerating the slow reaction with (dialkoxy)-boranes, such as catecholborane[3] and pinacolborane,[4] and for achieving the different chemo-, regio-, diastereo- and enantioselectivities, relative to the uncatalyzed reaction.[5] Among them, $RhCl(PPh_3)_3$ is the most-extensively studied catalyst for hydroboration of alkenes with catecholborane, which provides an internal hydroboration product (**3**) for styrene with selectivity exceeding 99%.[6] Such a high internal selectivity characteristic for rhodium catalysts and vinylarenes system is accounted for by a catalytic cycle proceeding through a π-benzylrhodium intermediate.[7] Thus, $[RhCl(cod)]_2/4PPh_3$,[8] $Rh(\eta^3\text{-}2\text{-methallyl})(dppb)$,[7] $[Rh(cod)_2]BF_4/2PPh_3$[6] and $[Rh(cod)_2]BF_4/dppb$[6] selectively gave an internal product (**3**), whereas other metal complexes such as $[Cp^*IrCl_2]_2$,[9] $RuCl_2(PPh_3)_4$,[10] Cp_2TiMe_2,[11] and Cp^*Sm[12] afforded terminal hydroboration products (**2**) for styrene.

Catecholborane has been used in most of the reactions studied, but pinacolborane has recently been found to be an excellent alternative because it is a more stable and an easily prepared and stored hydroboration reagent. The high stability of the resulting pinacol organoboronates to moisture and chromatography is also convenient for isolation and handling. Much bulkier pinacolborane increases the terminal selectivity for styrene due to its steric hindrance. For example, the hydroboration of styrene with pinacolborane in the presence of $RhCl(PPh_3)_3$ yields a mixture of **2**/**3**=41/59, and $Rh(CO)(PPh_3)_2Cl$ and $CpNi(PPh_3)Cl$ selectively afford a terminal product (**2**>99%).[13] In contrast to such alterable selectivity for vinylarenes depending upon metal catalysts and hydroboration reagents, the boron atom is selectively added to the terminal carbon of aliphatic 1-alkenes. Representative metal complexes such as $Rh(PPh_3)_3Cl$,[14] $[Rh(nbd)(dppb)]BF_4$,[14] $Cp^*Sm(THF)$,[12] SmI_3[15] and Cp_2ZrHCl[16] have been reported to yield terminal products (**2**) for both catecholborane and pinacolborane. Thus, selectivity and activity of representative metal catalysts have been studied extensively; however, there is little information on the corresponding iridium complexes.[9,14b] We report here that neutral iridium(I)–phosphine complexes such as $[Ir(cod)Cl]_2$/2dppm and $[Ir(cod)Cl]_2$/2dppe are excellent catalysts for hydroboration of terminal and internal alkenes possessing an aliphatic or aromatic substituent on the vinylic carbon with pinacolborane (Eq. 1). Most catalysts employed were prepared in situ from an air-stable cyclooctadiene complex and a phosphine ligand since previous studies using air-sensitive $RhCl(PPh_3)_3$ has resulted in different regioselectivities between complexes handled under argon and air.[17]

Keywords: Hydroboration; Pinacolborane; Iridium; Rhodium.
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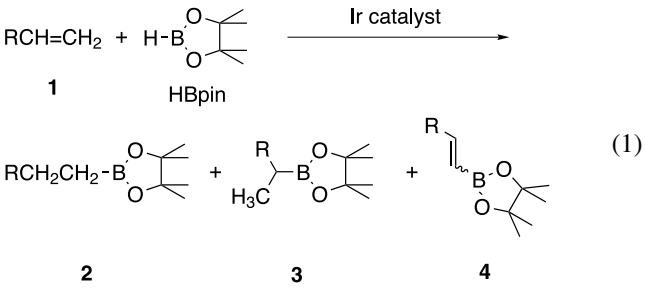


(1)

2. Results and discussion

2.1. Iridium-catalyzed hydroboration of alkenes

Various neutral and cationic rhodium(I) complexes are effective for catalyzing hydroboration of styrene and other arylethenes with catecholborane (HBcat) at room temperature. The reaction selectively provides an internal hydroboration product (**3**) when $RhCl(PPh_3)_3$,[8,17] $RhCl(CO)(PPh_3)_2$[4,13] and $[Rh(cod)_2]BF_4$/dppb[6] are used. The formation of dehydrogenative coupling products (**4**) has been reported in the hydroboration of arylethenes with phosphine-free catalysts such as $[RhCl(p\text{-}MeOC_6H_4\text{-}CH{=}CH_2)_2]_2$[18] and $[RhCl(cod)]_2$.[19] Among the representative rhodium catalysts screened for styrene, pinacolborane (HBpin) showed a high terminal selectivity, giving **2** in the presence of $RhCl(CO)(PPh_3)_2$ (Table 1, entry 2).[13] This regioselectivity is completely opposite to that of catecholborane, which selectively provided **3** in the presence of $RhCl(PPh_3)_3$, $[Rh(cod)_2]BF_4/2PPh_3$ or $[Rh(cod)_2]BF_4$/dppb.[6,8,17] Other neutral and cationic rhodium complexes effective for catecholborane[5] resulted in a mixture of **2**, **3** and **4** or a mixture of **2** and **4** for styrene (entries 1 and 3–10). Iridium complexes have rarely been used as catalysts for hydroboration, but they are catalysts that show a high terminal selectivity in hydroboration of styrene with catecholborane.[9,14b] Indeed, most neutral and cationic iridium–phosphine complexes mainly afforded a terminal boron product (**2**) also for pinacolborane (entries 12–24). Among them, a combination of $[IrCl(cod)]_2$ and dppe, dppp or dppb was recognized to be the best catalyst for achieving high yields and high selectivities (entries 13–15). Analogous catalysts prepared from a cationic iridium(I) precursor also predominated the formation of **2**, but they were less selective than were neutral complexes (entries 17–24).

Effects of rhodium and iridium catalysts on hydroboration of 1-octene with pinacolborane are summarized in Table 2.

Table 1. Hydroboration of styrene with pinacolborane[a]

Entry	Catalyst	Yield/%[b]	**2**	**3**	**4**
1	$RhCl(PPh_3)_3$	26	66	34	4
2	$Rh(CO)(PPh_3)_2Cl$	76	94	0	6
3	$[Rh(cod)Cl]_2$	48	75	2	23
4	1/2$[Rh(cod)Cl]_2$/dppm	74	29	47	24
5	1/2$[Rh(cod)Cl]_2$/dppe	67	50	37	13
6	1/2$[Rh(cod)Cl]_2$/dppp	68	44	56	0
7	$[Rh(cod)_2]BF_4$	28	42	32	26
8	$[Rh(cod)_2]BF_4$/dppm	73	38	42	20
9	$[Rh(cod)_2]BF_4$/dppe	79	37	56	7
10	$[Rh(cod)_2]BF_4$/dppb	51	39	31	30
11	$[Ir(cod)Cl]_2$	80	62	8	30
12	1/2$[Ir(cod)Cl]_2$/dppm	66	99	0	1
13	1/2$[Ir(cod)Cl]_2$/dppe	93	100	0	0
14	1/2$[Ir(cod)Cl]_2$/dppp	97	100	0	0
15	1/2$[Ir(cod)Cl]_2$/dppb	94	98	0	2
16	$[Ir(cod)_2]PF_6$	19	67	11	22
17	$[Ir(cod)_2(PPh_3)_2]PF_6$	26	76	12	12
18	$[Ir(cod)_2(PMePh_2)_2]PF_6$	63	100	0	0
19	$[Ir(cod)_2]PF_6/2PCy_3$	63	94	0	6
20	$[Ir(cod)_2]PF_6/2P^tBu_3$	46	80	7	13
21	$[Ir(cod)]PF_6$/dppm	63	96	0	4
22	$[Ir(cod)_2]PF_6$/dppe	12	24	41	35
23	$[Ir(cod)_2]PF_6$/dppp	26	60	13	27
24	$[Ir(cod)_2]PF_6$/dppb	25	67	12	21

[a] A mixture of styrene (1 mmol), pinacolborane (1.2 mmol), catalyst (0.03 mmol based on the metals) in toluene was stirred for 24 h at room temperature.
[b] Isolated yields by chromatography.

Table 2. Hydroboration of 1-octene with pinacolborane[a]

Entry	Catalyst	Yield/%[b]
1	$RhCl(PPh_3)_3$	18
2	$Rh(CO)(PPh_3)_2Cl$	63
3	1/2$[Rh(cod)Cl]_2$/dppm	56
4	1/2$[Rh(cod)Cl]_2$/dppe	71
5	1/2$[Rh(cod)Cl]_2$/dppp	82
6	$[Ir(cod)Cl]_2$	50
7	1/2$[Ir(cod)Cl]_2/3PCy_3$	78
8	1/2$[Ir(cod)Cl]_2$/dppm	89
9	1/2$[Ir(cod)Cl]_2$/dppe	86
10	1/2$[Ir(cod)Cl]_2$/dppp	53
11	1/2$[Ir(cod)Cl]_2$/dppb	78

[a] A mixture of 1-octene (1 mmol), pinacolborane (1.2 mmol), and catalyst (0.03 mmol based on the metals) in CH_2Cl_2 was stirred for 24 h at room temperature.
[b] Isolated yields of **2** by chromatography on silica gel. Formations of **3** and **4** were not observed.

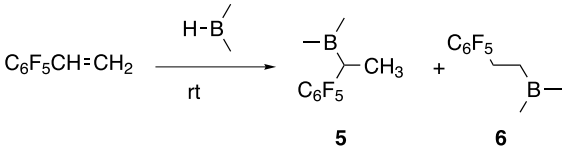
Table 3. Iridium-catalyzed hydroboration of terminal alkenes with pinacolborane[a]

Entry	Alkene	Product no.	Yield/%[b] dppm	Yield/%[b] dppe
1	$CH_3(CH_2)_5CH{=}CH_2$	**2a**	89	—
2	$CH_3C(=O)CH_2CH_2CH{=}CH_2$	**2b**	68	—
3	$BrCH_2CH_2CH{=}CH_2$	**2c**	77	—
4	$PhOCH_2CH{=}CH_2$	**2d**	89	—
6	$NCCH_2CH{=}CH_2$	**2e**	15	—
7	$PhCH{=}CH_2$	**2f**	66	93
9	4-$CH_3OC_6H_4CH{=}CH_2$	**2g**	76	80
10	4-$CH_3C_6H_4CH{=}CH_2$	**2h**	77	99
11	$C_6F_5CH{=}CH_2$	**2i**	60	82
12	2-NaphthylCH=CH_2	**2j**	84	91
13	4-PyridylCH=CH_2	**2k**	21	—

[a] Alkene (1 mmol) and pinacolborane (1.2 mmol) were added to a solution of $[Ir(cod)Cl]_2$ (0.015 mmol) and dppm or dppe (0.03 mmol) in CH_2Cl_2. The resulting mixture was stirred for 24 h at room temperature.
[b] Isolated yields of the terminal addition products (**2**) by Kugelrohr distillation or by chromatography over silica gel. The internal addition product (**3**) and the dehydrogenative coupling product (**4**) were less than 0.6% in each reactions.

In contrast to styrene, which was more prone to yield internal addition products (**3**) or dehydrogenative coupling products (**4**), all rhodium(I) and iridium(I) catalysts selectively provided a terminal hydroboration product (**2**) for 1-octene without accompanying **3** or **4**. Addition of dppp (2 equiv to $[Rh(cod)Cl]_2$) afforded the best rhodium catalyst, giving **2** (R=*n*-C_6H_{13}) in 82% yield (entry 5). Among the iridium complexes examined, $[Ir(cod)Cl]_2$ and dppm or dppe was recognized to be the best combination for obtaining **2**, with yields of 89 and 86%, respectively (entries 8 and 9).

Iridium-catalyzed hydroboration of representative terminal alkenes are summarized in Table 3. Since pinacol alkylboronates are thermally stable and insensitive to silica gel, they were easily isolated by chromatography or Kugelrohr distillation. Addition of dppm to $[IrCl(cod)]_2$ worked well for aliphatic terminal alkenes, whereas dppe was a better ligand than dppm for aromatic alkenes (entries 7–12). However, both catalysts failed to catalyze hydroboration of nitrile and pyridine derivatives in high yields due to their strong coordination ability to the metal catalysts (entries 6 and 13). It has been reported that hydroboration of the terminal double bond of 1-hexen-5-one with catecholborane is much faster than reduction of the carbonyl group in the presence of $RhCl(PPh_3)_3$; thus giving hydroboration product (**2**) and 1-hexen-5-ol in a ratio of 83/17.[3] Such a carbonyl group also remained perfectly intact in the iridium-catalyzed hydroboration with pinacolborane (entry 2). All aliphatic and aromatic terminal alkenes selectively gave terminal products (**2**) even for pentafluorophenylethene (entry 11). Pentafluorophenylethene, which is inert to uncatalyzed hydroboration with 9-BBN or $HBSia_2$ (Sia=1,2-dimethylpropyl), has previously been hydroborated with catecholborane in the presence of $RhCl(PPh_3)_3$ (Eq. 2). Catecholborane predominantly afforded the internal product (**5/6**=79/21), and bulkier pinacolborane effected to further increase the terminal product in a ratio of **5/6**=29/71.[20] Thus, both iridium(I)–dppm and –dppe complexes shown in entry 11 were found to be the best catalysts for obtaining a perfect *anti*-Markovnikov addition product.



borane	catalyst	**5**/%	**6**/%	ref
HBcat	$RhCl(PPh_3)_3$	79	21	[20]
HBpin	$RhCl(PPh_3)_3$	29	71	[20]
HBpin	$[IrCl(cod)]_2$/2dppe	0	100	present

(2)

Iridium(I)-catalyzed hydroboration of internal alkenes with pinacolborane is shown in Table 4. Hydroboration of both (*E*)- and (*Z*)-4-octene resulted in the formation of pinacol 1-alkylboronates (entries 1 and 2). The corresponding reaction of (*Z*)-2-butene and (*Z*)-1-phenylpropene also resulted in isomerization to the terminal carbon (entries 3 and 4). Such isomerization to the terminal carbon, which is popular in catalyzed hydrometallation of internal alkenes, is greatly dependent on catalysts and borane reagents

Table 4. Iridium-catalyzed hydroboration of internal alkenes with pinacolborane[a]

Entry	Alkene	Product no.	Yield/%[b]
1	(*E*)-4-Octene	**2a**	77[c]
2	(*Z*)-4-Octene	**2a**	78[c]
3	(*Z*)-$CH_3CH{=}CHCH_3$	**2l**	65[d]
4	(*Z*)-$PhCH{=}CHCH_3$	**2m**	75[e]
5	Cyclohexene	**2n**	74
6	Norbornene	**2o**	66[f]
7	1-*t*-Butyl-4-methylenecyclohexane	**2p**	97
8	*t*-$BuMe_2SiOCH_2C(CH_3){=}CH_2$	**2q**	73
9	2-Methy-2-butene	**2r**	5 (36)[g]

[a] A mixture of alkene (1 mmol), pinacolborane (1.2 mmol), $[Ir(cod)Cl]_2$ (0.015 mmol) and dppm (0.03 mmol) in CH_2Cl_2 was stirred for 24 h at room temperature.
[b] Isolated yields.
[c] Pinacol 1-octylboronate.
[d] Pinacol 1-butylboronate. dppb (0.03 mmol) was used in place of dppm.
[e] Pinacol 3-phenylpropylboronate.
[f] *exo* Isomer was selectively given.
[g] $[Ir(cod)Cl]_2$ (0.015 mmol) was used in the absence of phosphine ligand.

employed. It has been reported that such isomerization is slow in hydroboration with catecholborane using a neutral or cationic rhodium(I) catalyst[17] and that the use of much bulkier pinacolborane is more prone to afford the isomerized pinacol 1-alkylboronates[13,16] (Eq. 3). The reaction also took place smoothly for cyclic alkenes such as cyclohexene and norbornene (entries 5 and 6) and for 1,1-disubstituted alkenes (entries 7 and 8). Hydroboration of trisubstituted alkenes such as 2-methyl-2-butene was very slow as was reported in related metal-catalyzed hydroboration. All attempts at finding a practical catalyst for trisubstituted alkenes failed, though a phosphine-free $[IrCl(cod)]_2$ exhibited a higher level of catalyst activity than that of phosphine complexes (entry 9).

$$(E)\text{-}C_3H_7CH{=}CHC_3H_7 \xrightarrow[2.\ H_2O_2,\ OH^-]{1.\ \text{hydroboration}} \text{1-octanol + 2-octanol + 3-octanol + 4-octanol} \quad (3)$$

borane	catalyst	1-ol	2-ol	3-ol	4-ol	ref
HBcat	$RhCl(PPh_3)_3$	0	0	0	100	[17]
HBcat	$[Rh(nbd)(dppb)]BF_4$	4	2	7	87	[17]
HBpin[a)]	$RhCl(PPh_3)_3$	100	0	0	0	[13,16]
HBpin[a)]	$[IrCl(cod)]_2$/2dppp	100	0	0	0	present

a) Isolated as the pinacol ester.

3. Experimental

3.1. Reagents

Pinacolborane purchased from Aldrich was purified by distillation before use or it can be synthesized from $BH_3 \cdot SMe_2$ (BMS) and pinacol.[4] $RhCl(PPh_3)_3$,[21] $Rh(CO)(PPh_3)_2Cl$,[22] $[RhCl(cod)]_2$,[23] $[Rh(cod)_2]BF_4$,[24,26] $[IrCl(cod)]_2$,[25] $[Ir(cod)_2]PF_6$,[24,26] $[Ir(cod)(PPh_3)_2]PF_6$, and $[Ir(cod)(PMePh_2)_2]PF_6$[24,27] were prepared by the reported procedures. All phosphine ligands of dppm ($Ph_2PCH_2PPh_2$), dppe ($Ph_2PCH_2CH_2PPh_2$), dppp ($Ph_2PCH_2CH_2CH_2PPh_2$), dppb ($Ph_2P(CH_2)_4PPh_2$), PCy_3 (Cy=cyclohexyl), and $P(t\text{-}Bu)_3$ were commercially available.

3.2. Iridium-catalyzed hydroboration of alkenes (Tables 3 and 4)

The catalytic hydroboration of alkenes with pinacolborane was carried out by the following general procedure. A round-bottom flask charged with $[Ir(cod)Cl]_2$ (0.015 mmol, 1.5 mol%) and dppm or dppe (0.03 mmol) was flushed with argon. CH_2Cl_2 (3 ml), pinacolborane (1.2 mmol), and alkene (1.0 mmol) were added successively at room temperature. The mixture was then stirred at room temperature for the period shown in Tables 3 and 4. The reaction was quenched with methanol (1 ml) and water (3 ml), the product was extracted with ether, and dried over $MgSO_4$. Chromatography on silica gel with CH_2Cl_2 gave a pinacol 1-alkylboronate.

The spectral data of compounds synthesized in Tables 3 and 4 are followed.

3.2.1. 2-Octyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2a). ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, J=7.8 Hz, 2H), 0.87 (t, J=6.8 Hz, 3H), 1.24 (s, 12H), 1.21–1.29 (m, 10H), 1.38–1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 24.0, 24.8, 29.2, 29.4, 31.9, 32.4, 82.8; MS (EI) m/z 41 (81), 59 (58), 69 (50), 85 (82), 129 (100), 183 (10), 225 (52), 240 (3); HRMS calcd for $C_{14}H_{29}BO_2$; 240.2261, found: 240.2265.

3.2.2. 2-(5-Oxohexyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2b). ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, 2H, J=7.8 Hz), 1.24 (s, 12H), 1.30–1.45 (m, 2H), 1.54–1.62 (m, 2H), 2.13 (s, 3H), 2.42 (t, 2H, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.7, 26.3, 29.6, 43.5, 82.8, 209.1; MS (EI) m/z 43 (100), 55 (39), 69 (15), 83 (25), 111 (12), 168 (9), 211 (1), 241 (0.2); HRMS calcd for $C_{12}H_{23}BO_3$; 226.1740, found: 226.1750.

3.2.3. 2-(4-Bromobutyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2c). ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, 2H, J=7.8 Hz), 1.25 (s, 12H), 1.55 (tt, J=7.5, 7.8 Hz, 2H), 1.87 (tt, J=6.8, 7.5 Hz, 2H), 3.40 (t, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.8, 33.6, 35.3, 83.0; MS (EI) m/z 41 (85), 55 (66), 69 (42), 83 (100), 96 (25), 129 (34), 163 (19), 183 (66), 247 (27), 262 (0.8); HRMS calcd for $C_{10}H_{20}BBrO_2$; 262.0740, found: 262.0729.

3.2.4. 2-(3-Phenoxypropyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2d). ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J=7.8 Hz, 2H), 1.28 (s, 12H), 1.90 (tt, J=6.7, 7.8 Hz, 2H), 3.95 (t, J=6.7 Hz, 2H), 6.89–6.93 (m, 3H), 7.24–7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.8, 69.4, 83.0, 114.5, 120.3, 129.3, 159.1; MS (EI) m/z 41 (49), 57 (38), 69 (24), 83 (41), 94 (100), 101 (28), 119 (19) 169 (16), 189 (33), 262 (17); HRMS calcd for $C_{15}H_{23}BO_3$; 262.1740, found: 262.1738.

3.2.5. 2-(3-Cyanopropyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2e). ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J=7.8 Hz, 2H), 1.24 (s, 12H), 1.78 (tt, J=7.2, 7.8 Hz, 2H), 2.37 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 24.5, 24.8, 83.3, 129.0; MS (EI) m/z 43 (100), 59 (72), 68 (36), 85 (78), 96 (81), 109 (15), 137 (19), 180 (64), 194 (4); HRMS calcd for $C_{10}H_{18}BNO_2$; 195.1431, found: 195.1429.

3.2.6. 2-(2-Phenylethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2f). ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J=8.1 Hz, 2H), 1.22 (s, 12H), 2.75 (t, J=8.1 Hz, 2H), 7.13–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 29.9, 83.1, 125.5, 128.0, 128.1, 144.4; MS (EI) m/z 41 (72), 59 (33), 69 (19), 84 (100), 91 (82), 105 (40) 132 (38), 175 (17), 232 (6); HRMS calcd for $C_{14}H_{21}BO_2$; 232.1635, found: 232.1649.

3.2.7. 2-(2-(4-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2g). ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J=8.1 Hz, 2H), 1.22 (s, 12H), 2.69 (t, J=8.1 Hz, 2H), 3.78 (s, 3H), 6.79–6.82 (m, 2H), 7.12–7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 29.0, 55.2, 83.0, 113.5,

128.8, 136.5, 157.5; MS (EI) *m/z* 41 (53), 59 (15), 69 (10), 84 (45), 91 (15), 121 (100) 134 (46), 161 (11), 262 (14); HRMS calcd for $C_{15}H_{23}BO_3$; 262.1740, found: 262.1718.

3.2.8. 2-(2-(4-Methylphenyl)ethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=8.1 Hz, 2H), 1.23 (s, 12H), 2.30 (s, 3H), 2.70 (t, J=8.1 Hz, 2H), 7.05–7.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.8, 29.4, 83.0, 127.8, 128.8, 134.8, 141.3; MS (EI) *m/z* 41 (67), 59 (21), 69 (16), 84 (100), 105 (63), 118 (23), 146 (16), 189 (6), 246 (9); HRMS calcd for $C_{15}H_{23}BO_2$; 246.1791, found: 246.1781.

3.2.9. 2-(2-Pentafluorophenylethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J=8.1 Hz, 2H), 1.23 (s, 12H), 2.79 (t, J=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 24.7, 83.3, 117.1, 138.0, 138.6, 140.5, 143.7, 146.1; MS (EI) *m/z* 43 (100), 59 (91), 69 (21), 85 (47), 129 (28), 181 (30) 222 (23), 307 (21), 322 (6); HRMS calcd for $C_{14}H_{16}BF_5O_2$; 322.1164, found: 322.1185.

3.2.10. 2-(2-(2-Naphthyl)ethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2j). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=8.1 Hz, 2H), 1.22 (s, 12H), 2.92 (t, J=8.1 Hz, 2H), 7.36–7.43 (m, 3H), 7.64 (s, 1H), 7.73–7.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 30.1, 83.1, 124.9, 125.7, 125.7, 127.3, 127.4, 127.5, 127.7, 131.9, 133.6, 142.0; MS (EI) *m/z* 41 (50), 59 (15), 69 (14), 84 (71), 115 (37), 141 (100), 154 (69), 166 (18), 182 (18), 282 (26); HRMS calcd for $C_{18}H_{23}BO_2$; 282.1791, found: 282.1774.

3.2.11. 2-(2-(4-Prydyl)ethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J=8.1 Hz, 2H), 1.25 (s, 12H), 2.74 (t, J=8.1 Hz, 2H), 7.11–7.16 (m, 2H), 8.42–8.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 29.2, 83.3, 123.5, 149.2, 153.4; MS (EI) *m/z* 41 (52), 59 (59), 93 (39), 106 (29), 133 (100), 147 (40), 218 (43), 233 (50); HRMS calcd for $C_{13}H_{20}BNO_2$; 233.1587, found: 233.1576.

3.2.12. 2-(1-Butyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2l). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, J=7.7 Hz, 2H), 0.88 (t, J=7.2 Hz, 3H), 1.25 (s, 12H), 1.27–1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 24.7, 25.3, 26.1, 82.7; MS (EI) *m/z* 43 (16), 59 (24), 85 (50), 129 (62), 169 (100), 184 (3); HRMS calcd for $C_{10}H_{21}BO_2$; 184.1635, found: 184.1638.

3.2.13. 4,4,5,5-Tetramethyl-2-(3-phenyl-propyl)-[1,3,2]-dioxaborolane (2m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J=7.8 Hz, 2H), 1.24 (s, 12H), 1.73 (tt, J=7.8, 7.9 Hz, 2H), 2.60 (t, J=7.9 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.1, 38.6, 82.9, 125.5, 128.1, 128.5, 142.7; MS (EI) *m/z* 41 (22), 59 (10), 85 (100), 91 (62), 118 (93), 127 (24), 146 (13), 173 (12), 231 (11), 246 (32); HRMS calcd for $C_{15}H_{23}BO_2$; 246.1791, found: 246.1796.

3.2.14. 2-(Cyclohexyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–1.04 (m, 1H), 1.23 (s, 12H), 1.26–1.36 (m, 4H), 1.54–1.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.7, 27.1, 28.0, 82.7; MS (EI) *m/z* 43 (23), 69 (44), 82 (30), 85 (26), 110 (30), 124 (100), 129 (23), 195 (38); HRMS calcd for $C_{12}H_{23}BO_2$; 210.1791, found: 210.1773.

3.2.15. (*exo*)-2-(Bicyclo-[2,2,1]-hept-2-yl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2o). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.94 (m, 1H), 1.23 (s, 12H), 1.14–1.40 (m, 4H), 1.42–1.68 (m, 4H), 2.22–2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 29.3, 32.2, 32.2, 36.6, 38.1, 38.7, 82.8; MS (EI) *m/z* 41 (100), 55 (42), 67 (34), 84 (33), 108 (12), 136 (14), 207 (15), 222 (0.6); HRMS calcd for $C_{13}H_{23}BO_2$; 222.1791, found: 222.1813.

3.2.16. 2-(4-*tert*-Butyl-cyclohexylmethyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2p). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69–1.02 (m, 4H), 0.82 (s, 9H), 1.25 (s, 12H), 1.39–1.57 (m, 5H), 1.69–1.78 (m, 2H), 2.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.8, 27.5, 28.6, 32.8, 36.3, 48.6, 82.7; MS (EI) *m/z* 41 (27), 57 (61), 85 (100), 87 (24), 95 (24), 101 (55), 129 (39), 167 (24), 223 (20), 265 (13), 280 (11); HRMS calcd for $C_{17}H_{33}BO_2$; 280.2574, found: 280.2584.

3.2.17. 2-[3-(*tert*-Butyldimethylsilyloxy)-2-methyl-propyl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2q). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.002 (s, 6H), 0.55 (dd, J=8.8, 15.6 Hz, 1H), 0.82–0.85 (m, 1H), 0.86 (s, 9H), 0.87 (d, J=6.5 Hz, 2H), 1.22 (s, 12H), 1.76–1.89 (m, 1H), 3.28 (dd, J=7.2, 9.6 Hz, 1H), 3.40 (dd, J=5.7, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.35, 18.3, 19.0, 24.8, 26.0, 32.2, 70.0, 82.8; MS (EI) *m/z* 75 (24), 115 (23), 101 (11), 115 (23), 157 (100), 257 (23), 299 (2), 313 (0.2); HRMS calcd for $C_{12}H_{26}BO_3Si$ (–*tert*-butyl); 274.1744, found: 274.1753.

3.2.18. 2-(1,2-Dimethyl-propyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2r). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J=6.8 Hz, 6H), 0.90 (d, J=6.6 Hz, 3H), 1.23–1.28 (m, 1H), 1.25 (s, 12H), 1.42–4.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 22.2, 24.8, 32.9, 82.8; MS (EI) *m/z* 41 (16), 57 (38), 69 (16), 83 (35), 87 (37), 99 (34), 129 (100), 183 (52), 198 (17); HRMS calcd for $C_{11}H_{23}BO_2$; 198.1791, found: 198.1791.

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Asymmetric Kumada–Corriu cross-coupling reaction with $Pd_2(dba)_3$ and an N–Ar axially chiral mimetic-type ligand catalyst

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Abstract—A catalyst comprised of $Pd_2(dba)_3 \cdot CHCl_3$ and an N–Ar axially chiral mimetic-type ligand, (*S*)-*N*-[2-(diphenylphosphanyl)naphthalene-1-yl]-2-(piperidinylmethyl)piperidine, provides good enantioselectivities for the asymmetric Kumada–Corriu cross-coupling reaction of 1-phenylethylmagnesium chloride and *E*-β-bromostyrene derivatives with which it is more difficult to achieve high enantioselectivity. Furthermore, in the case of styrene derivatives bearing both vinyl and aryl bromide groups, the chemoselective asymmetric cross-coupling reaction of the vinyl bromide group is observed. This N–Ar axially chiral mimetic-type ligand allows easy synthesis of a wide variety of analogues, and starting from the initial ligand, the enantioselectivity of coupling products is improved by modifying the structure in the ligand.

1. Introduction

Catalytic asymmetric carbon–carbon bond formation with metal–chiral ligand complexes, is one of the most important reactions in synthetic organic chemistry. The development of new chiral ligands for use in asymmetric catalysis has continued to undergo rapid growth. For testing the new ligands, standard palladium-catalyzed asymmetric allylic substitution with the use of (*E*)-1,3-diphenyl-2-propenyl acetate as the substrate and dimethyl malonate as the pronucleophile, has been quite often examined.[1] A large number of ligands, which exhibit enantioselectivity of more than 90%, have been reported.[1] However, there are some successful examples of other catalytic asymmetric reactions with these new ligands.[2] Therefore, it is very important to develop versatile chiral ligands, which afford good enantioselectivity in a variety of reactions.

We have recently developed a novel chiral ligand **1** mimicking N–Ar axial chirality, in which a chiral carbon center induces a preferred conformation **2a** by rotation around an N–Ar bond which is fixed by formation of a chelate structure with metal (Figs. 1 and 2).[3] Among the designed ligands **1**, **1i** has been found to exhibit 99% ee in the standard palladium-catalyzed asymmetric allylic substitution.[3] These results prompted us to explore further application of the ligand **1**. Our interest in this ligand focused on its use in the asymmetric Kumada–Corriu cross-coupling reaction[4] of 1-phenylethylmagnesium chloride with alkenyl halides, which has met with success using Kumada's P,N-ligands.[5] Some ligands have been developed for the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride with alkenyl halides, but the best substrate exhibiting more than 80% ee was vinyl bromide.[6] One type of substrate with which it has been more difficult to achieve high selectivity is a styrene derivative such as

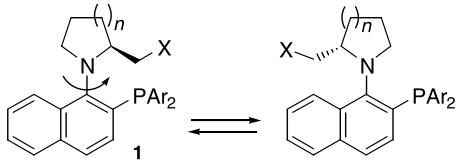

Figure 1.

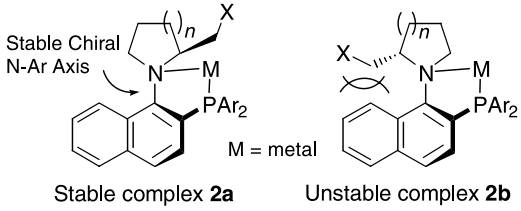

Figure 2.

Keywords: Kumada–Corriu cross-coupling reaction; N–Ar Axially chiral mimetic-type ligand; Enantioselectivity.
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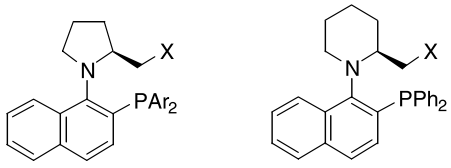
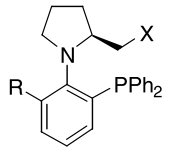
E-β-bromostyrene.[7] There are, to date, only two examples by Knochel[8] and Saigo[9] that give good enantioselectivity with *E*-β-bromostyrene. Herein we would like to report our investigation of this reaction using *E*-β-bromostyrene derivatives as substrates with the ligand **1** mimicking N–Ar axial chirality.[10] The results obtained with the ligand **1** are, to the best of our knowledge, the third best enantioselectivity in the reported literature. Additionally, the ligand **1** is appealing, because it allows easy synthesis of a wide variety of analogues.

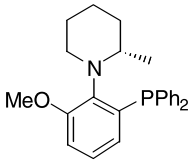


1a: X=OMOM, Ar=Ph
1b: X=OBn, Ar=Ph
1c: X=O*t*-Bu, Ar=Ph
1d: X=pyrrolidinyl, Ar=Ph
1e: X=NBn_2, Ar=Ph
1f: X=OBn, Ar=*p*-tolyl
1g: X=pyrrolidinyl, Ar=*p*-tolyl
1h: X=pyrrolidinyl, Ar=2-naphthyl

1i: X=pyrrolidinyl
1j: X=piperidinyl



1k: X=OBn, R=Me
1l: X=pyrrolidinyl, R=OMe



1m

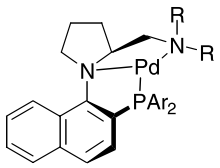
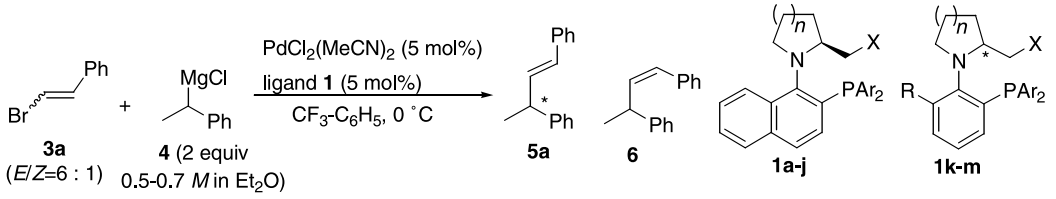


Figure 3. Internal coordination of the pendant nitrogen group.

2. Results and discussion

We began to screen a variety of the ligands **1** in the asymmetric cross-coupling reaction of 1-phenylethylmagnesium chloride (**4**) with β-bromostyrene (*E*/*Z*=6:1, **3a**). The results are shown in Table 1. Reactions were carried out with $PdCl_2(CH_3CN)_2$ (5 mol%), the ligand **1** (5 mol%), and 1-phenylethylmagnesium chloride (**4**) (2 equiv, 0.5–0.7 mol/L in Et_2O) in α,α,α-trifluorotoluene[11] at 0 °C. The use of other solvents such as toluene, chlorobenzene, THF, Et_2O, isopropyl ether, *t*-butyl methyl ether, dioxane, DME, and CH_2Cl_2, gave less satisfactory results. First, the effect of a pendant substituent X with the pyrrolidine-based ligands **1a–e** was examined.[12] As shown in entries 1–5, the pendant substituent played an important role. The ligands **1a–c** possessing a pendant oxygen group exhibited faster reaction rate than **1d** and **1e** possessing a pendant nitrogen group. Among the oxygen-containing ligands **1a–c**, the ligand **1b** bearing the pendant BnO group, gave better results (entry 2, 66% yield, 66% ee). The ee of **5a** was determined by HPLC analysis (Daicel Chiralcel OD), and its absolute configuration was determined by comparison with the reported **5a**.[8] The inhibition of the reactivity observed with the ligands **1d** and **1e** possessing

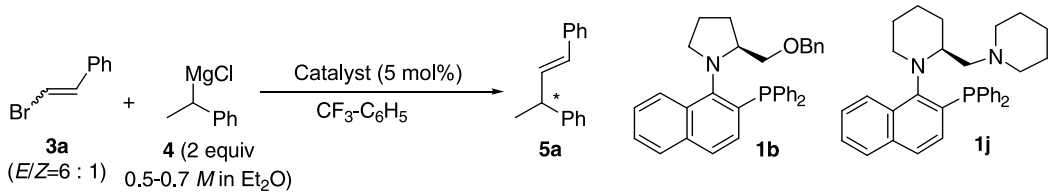
Table 1. Initial ligand screening[a]



Entry[b]	Ligand **1**	X	*n*	Ar	R	Time (h)	Yield of **5a** (%)	ee[c] of **5a** (%)	Absolute configuration
1	**1a**	OMOM	1	Ph	—	1	59	7	*R*
2	**1b**	OBn	1	Ph	—	1	66	66	*S*
3	**1c**	O*t*-Bu	1	Ph	—	1	42	47	*S*
4	**1d**	Pyrrolidinyl	1	Ph	—	24	35	62	*S*
5	**1e**	NBn_2	1	Ph	—	24	20	9	*R*
6	**1i**	Pyrrolidinyl	2	Ph	—	1	53	61	*S*
7[d]	**1i**	Pyrrolidinyl	2	Ph	—	24	25	52	*S*
8	**1j**	Piperidinyl	2	Ph	—	1	58	66	*S*
9	**1f**	OBn	1	*p*-Tolyl	—	24	15	9	*S*
10	**1g**	Pyrrolidinyl	1	*p*-Tolyl	—	24	37	65	*S*
11	**1h**	Pyrrolidinyl	1	2-Naphthyl	—	24	43	56	*S*
12	**1k**	OBn	1	Ph	Me	24	42	63	*S*
13	**1l**	Pyrrolidinyl	1	Ph	MeO	24	26	69	*S*
14	**1m**	H	2	Ph	MeO	1	52	7	*S*

[a] The reactions were performed using 5 mol% of $PdCl_2(MeCN)_2$ and the ligand **1**, a 6:1 mixture of *E*- and *Z*-β-bromostyrene **3a**, and 2 equiv of the Grignard reagent **4** in CF_3–C_6H_5 at 0 °C.
[b] In all entries, a small amount of **6** was obtained with no enantioselectivity (for example, **1d** afforded **6** with 2% yield and 0% ee).
[c] Determined by HPLC analysis.
[d] 1-Phenylethylmagnesium bromide was used.

Table 2. Further screening of reaction conditions with the ligand **1b** and **1j**[a]

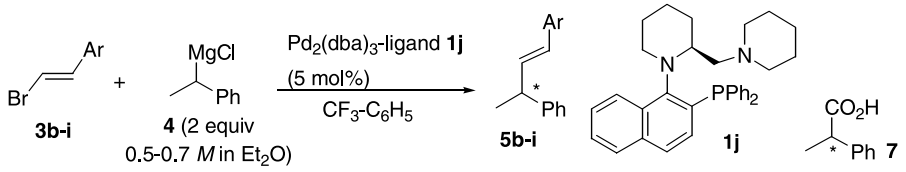


Entry[b]	Catalyst	Additive	Temperature (°C)	Time (h)	Yield of **5a** (%)	ee[c] of **5a** (%)	Absolute configuration
1	$PdCl_2(MeCN)_2$/**1b**	—	−10	24	NR[d]	—	—
2	$PdCl_2(MeCN)_2$/**1j**	—	−10	12	66	71	*S*
3	$PdCl_2(MeCN)_2$/**1j**	—	−20	24	NR[d]	—	—
4	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	—	−20	2	67	74	*S*
5[e]	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	—	−30	7	64	76	*S*
6	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	LiCl[f]	−30	12	61	73	*S*
7	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	LiI[f]	−30	24	9	47	*S*
8	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	$ZnCl_2$[f]	−30	24	Trace	—	—
9	$Pd_2(dba)_3\cdot CHCl_3$/ **1j**	—	−40	24	Trace	—	—
10	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ /**1j**	—	0	1	68	58	*S*
11	$Ni(cod)_2$/**1j**	—	0	15	56	0	—

[a] The reactions were performed using 5 mol% of metal complex and the ligand **1**, a 6:1 mixture of *E*- and *Z*-β-bromostyrene **3a**, and 2 equiv of the Grignard reagent **4** in CF_3–C_6H_5.
[b] In all entries, a small amount of **6** was obtained.
[c] Determined by HPLC analysis.
[d] No reaction occurred.
[e] The use of 7.5–10 mol% of the ligand **1j** gave the same results.
[f] One molar equivalent of the additive was used.

the pendant nitrogen substituent, a strong coordinating group, is considered to be due to the internal coordination of the pendant nitrogen group to palladium (Fig. 3). Molecular modeling studies suggested that the piperidine based-ligand **1i** avoids such a problem, because coordination of the pendant nitrogen group to the internal palladium seemed to be torsionally unfavorable. As expected, replacement of the piperidine ring on the naphthalene ring enhanced the reaction rate, and the chemical yield was increased from 35 to 53% (entries 4 vs 6). The use of 1-phenylethylmagnesium bromide in place of the corresponding chloride decreased both chemical yield and enantioselectivity (entries 6 vs 7). Furthermore, employing the piperidine-based ligand **1j** possessing the pendant piperidinyl group gave better results (58% yield, 66% ee) than **1i** (entries 6 vs 8). The effects of the diarylphosphino groups, the aromatic parts and so on were also examined (entries 9–14), but their replacements gave less satisfactory results.

Table 3. Substrate generality[a]

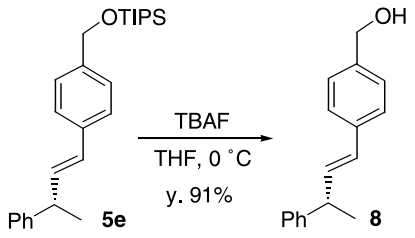


Entry	Ar	Temperature (°C)	Time (h)	Yield of **5** (%)	ee[b] of **5** (%)	Absolute configuration
1	4-Me-C_6H_4– (**3b**)	−20	4	73[c] (**5b**)	78	*S*
2	4-*i*-Pr-C_6H_4– (**3c**)	−20	6	75[c] (**5c**)	80	*S*
3	4-Cl-C_6H_4– (**3d**)	−10	2	80[c] (**5d**)	71	*S*
4	4-TIPSOCH_2-C_6H_4– (**3e**)	−10	18	61[d] (**5e**)	73	*S*
5	4-MeO-C_6H_4– (**3f**)	0	24	NR[e]	—	—
6	3-MeO-C_6H_4– (**3g**)	0	24	NR[e]	—	—
7	2-Br-C_6H_4– (**3h**, *E*/*Z*=17:1)	−20	24	22[c,f] (**5h**)	60	*S*
8[g]	3-Br-C_6H_4– (**3i**, *E*/*Z*=23:1)	−20	9	65[c] (**5i**)	70	*S*

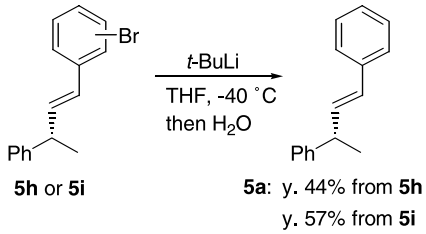
[a] The reactions were performed using 2.5 mol% of $Pd_2(dba)_3\cdot CHCl_3$, 5 mol% of the ligand **1j**, an *E*-isomer of the bromostyrene **3** except for **3h** and **3i**, and 2 equiv of the Grignard reagent **4** in CF_3–C_6H_5.
[b] Determined by HPLC analysis.
[c] The desired product **5** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield was calculated on the basis of ^1H NMR analysis of the mixture.
[d] Yield of **8** after desilylation.
[e] No reaction occurred.
[f] Remainder of mass balance was the unreacted starting bromostyrene **3h**.
[g] Since the use of (*E*)-1-bromo-2-(4-bromophenyl)ethene as a substrate gave a mixture of the cross-coupling product and a small amount of unknown impurities, the chemical yield and ee of the cross-coupling product could not be determined.

Thus, in terms of both chemical yield and enantioselectivity, the two ligands **1b** and **1j** were chosen as candidates for the next screening. The effect of temperature on the reaction was examined (entries 1–3, Table 2). In the case of the ligand **1b**, lowering the temperature from 0 to −10 °C resulted in no reaction (entry 1). On the other hand, in the case of the ligand **1j**, the enantioselectivity was improved (entry 2: 71% ee). Further intensive screening of other palladium and nickel complexes (entries 4, 10 and 11) established that $Pd_2(dba)_3 \cdot CHCl_3$ is the most effective complex. Thus, the reaction was found to proceed at lower temperature (< −10 °C), and the best enantioselectivity (76% ee) was observed at −30 °C (entry 5). The use of the additives such as LiCl, LiI, and $ZnCl_2$ with the best catalyst gave less satisfactory results (entries 6–8).

Using the best $Pd_2(dba)_3$-ligand **1j** catalyst, we examined the cross-coupling reaction with several *E*-β-bromostyrenes as shown in Table 3. Styrene derivatives bearing *p*-methyl (**3b**), *p*-isopropyl (**3c**), *p*-chloro (**3d**) and *p*-triisopropylsilyloxymethyl (**3e**) groups were found to be employable, giving the corresponding products in good enantioselectivities (entries 1–4, up to 80% ee). Unfortunately, the reaction with **3f** and **3g** bearing an electron-donating group did not proceed (entries 5 and 6).[13] The coupling product **5e** with 73% ee was transformed into lipoxygenase inhibitor[14] **8**, as shown in Scheme 1. The ee of **5b–e** were determined by HPLC analysis (Daicel Chiralcel OD), and their absolute configurations were determined by HPLC analysis (Daicel Chiralpak AD) after conversion of **5b–e** to the commercially available carboxylic acid **7**. Finally, the asymmetric cross-coupling reaction with the styrene derivatives **3h** and **3i** bearing both vinyl and aryl bromide groups was examined as shown in entries 7 and 8, because it is important to control the chemoselectivity in the Pd-catalyzed Grignard cross-coupling.[15] The styrene derivatives **3h** and **3i** underwent the selective substitution of the vinyl bromide group to give the corresponding mono-coupling product **5h** and **5i**, respectively, although conversion of the reaction with *ortho*-substituted bromostyrene **3h** was low. Their ee and absolute configurations were determined by HPLC analysis after conversion to **5a** as shown in Scheme 2.



Scheme 1. Conversion to lipoxygenase inhibitor **8**.



Scheme 2. Debromination of **5h** and **5i**.

Based on the previous ^1H and ^{31}P NMR study[3] of the Pd-ligand **1d** complex, which is similar to the Pd-ligand **1j** complex, and the absolute configuration of the product **5** obtained by using the Pd-ligand **1j** catalyst, enantiomeric induction in the present system can be understood by assuming the transition state in Figure 4. At first, oxidative addition of the styryl bromide **3** to the Pd-ligand **1j** complex occurs. Next, the pendant nitrogen group of **1j** coordinates with the Mg atom of the Grignard reagent **4** (Fig. 4). This coordination allows to undergo enantiomerselective transmetalation, thus giving the observed *S*-product.

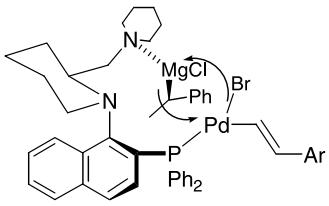


Figure 4. Possible model for asymmetric induction.

3. Conclusion

We have shown that an N–Ar axially chiral mimetic-type ligand is efficient in the asymmetric Kumada–Corriu cross-coupling reaction[16–18] of 1-phenylethylmagnesium chloride with *E*-β-bromostyrene derivatives. Starting from the initial ligand, the enantioselectivity was improved by modifying the structure in the ligand. These findings validate the usefulness of ligand tuning for optimization. Further application to other catalytic asymmetric reactions is now in progress.

4. Experimental

4.1. General

IR spectra were measured on a SHIMADZU FTIR-8100 and 84005 diffraction grating IR spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-EX-270 NMR spectrometer, operating at 270 MHz for ^1H NMR and at 68 MHz at ^{13}C NMR. ^1H and ^{13}C NMR spectra were reported in δ units, parts per million (ppm) downfield from tetramethylsilane ($\delta=0$). EI and FAB MS spectra were measured on a JEOL JMS-SX-102A instrument. Specific rotations (in deg cm^3 g^{-1} L^{-1}) were determined on a JASCO DIP-1000 digital polarimeter.

1-Methoxy-2-(diarylphosphinyl)naphthalene,[19] (*S*)-2-(benzyloxymethyl)pyrrolidine,[20] (*S*)-2-(*t*-butoxymethyl)-pyrrolidine[21] and 1,1-dibromo-2-(2-bromophenyl)ethene[22] were prepared according to the known procedure. (*S*)-2-Methylpiperidine and 1-bromo-2-phenylethene (*E*/*Z*=6:1) were commercially available. The syntheses of the ligands **1b**, **1d**, **1e**, **1g**, **1h** and **1i** were previously reported by us.[3] The known (*E*)-1-bromo-2-arylethene shown below were prepared according to our published procedure.[23] Their physical data were comparable to those of the corresponding literature: (*E*)-1-bromo-2-(4-tolyl)ethene[24] (**3b**), (*E*)-1-bromo-2-(4-isopropylphenyl)ethene[23] (**3c**), (*E*)-1-bromo-2-(4-chlorophenyl)ethene[24] (**3d**), (*E*)-1-bromo-2-(4-hydroxymethylphenyl)ethene,[23] (*E*)-1-bromo-2-(4-methoxyphenyl)-ethene[24] (**3f**), (*E*)-1-bromo-2-(3-methoxyphenyl)ethene[24]

(**3g**). 2,3-Diphenylbutane, and optically active and racemic 2-phenylpropionic acid were commercially available.

All reagents were available from commercial sources and used without further purification. In general, all reactions were performed under an argon atmosphere. α,α,α-Trifluorotoluene was distilled from Na under a nitrogen atmosphere. THF, Et_2O, DME, and 1,4-dioxane, were distilled from Na/benzophenone ketyl under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere. Other solvents were available from commercial sources and used without further purification. Silica gel column chromatography was performed on Fuji silysia PSQ 60B, unless otherwise noted.

4.1.1. (*S*)-2-(Piperidinylmethyl)piperidine. The title compound was prepared according to the similar procedure reported.[25] The physical data were comparable to the commercially available racemate. $[\alpha]_D^{26}=+33°$ (*c* 8.17, dioxane).

4.2. Representative procedure for the synthesis of ligand 1

4.2.1. (*S*)-*N*-[2-(Diphenylphosphanyl)naphthalen-1-yl]-2-(piperidinylmethyl)piperidine (1j). First step: to a stirred solution of (*S*)-2-(piperidinylmethyl)piperidine (700 mg, 3.84 mmol) in THF (4.0 mL) was gradually added BuLi (2.53 mL, 4.00 mmol, 1.58 M solution in hexane) at −30 °C, and the mixture was stirred for 2 h at the same temperature. To this solution was then added a solution of 1-methoxy-2-(diphenylphosphinoyl)naphthalene (680 mg, 1.90 mmol) in THF (2.0 mL) at −30 °C. The whole mixture was stirred for 1 h at the same temperature, quenched with water and extracted with EtOAc. The organic extracts were successively washed with saturated aq. NH_4Cl and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel column (Fuji Silysia Chromatorex NH, EtOAc/hexane=1:5) gave a mixture (724 mg) of 1-(*S*)-*N*-[2-(diphenylphosphonyl)naphthalen-1-yl]-2-(piperidinylmethyl)piperidine and small amounts of impurities. This mixture was used for the next step without further separation. IR (neat): $\nu=1308$, 1254, 1192, 1161 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.75$–1.15 (m, 8H), 1.24–1.45 (m, 2H), 1.60–1.94 (m, 7H), 2.46 (dd, $J=13.3$, 5.9 Hz, 1H), 2.92 (brd, $J=11.1$ Hz, 1H), 3.36 (dd, $J=11.1$, 11.1 Hz, 1H), 3.51–3.62 (br, 1H), 6.97 (dd, $J=12.1$, 8.6 Hz, 1H), 7.35–7.57 (m, 10H), 7.65–7.87 (m, 4H), 8.23 (d, $J=8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$): 24.29, 24.90, 25.47, 25.63, 31.38, 54.80, 56.09, 60.55, 62.23, 125.15, 125.42, 125.62, 126.21, 127.02, 127.95, 128.13, 128.65, 129.02, 129.22, 129.77, 130.74, 131.09, 131.23, 131.37, 131.94, 132.07, 134.15, 134.65, 135.09, 135.22, 135.66, 136.22, 136.63, 155.14. FABMS: $m/z=509$ ($M^+ +1$). Second step: the above mixture was dissolved in *p*-xylene (7.0 mL), and Et_3N (2.10 mL, 15.1 mmol) and $HSiCl_3$ (1.4 mL, 14 mmol) were added at 0 °C. The whole mixture was heated at 140 °C for 2 h. After being cooled to rt, the reaction mixture was carefully poured into 10% NaOH, and the whole mixture was extracted with EtOAc. The organic extracts were successively washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by silica gel column (Fuji Silysia Chromatorex NH, hexane/EtOAc=20:1) gave (*S*)-*N*-[2-(diphenylphosphanyl)naphthyl]-2-(pyrrolidinylmethyl)piperidine (**1j**) (505 mg, 54% in 2 steps) as a colorless amorphous. $[\alpha]_D^{28}=+115°$ (*c* 1.60, dioxane). IR (nujol): $\nu=1300$, 1275, 1206, 1159 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.83$–2.22 (m, 18H), 2.66 (brd, $J=11.5$ Hz, 1H×4/5), 3.01 (brd, $J=11.2$ Hz, 1H×1/5), 3.30 (brdd, $J=11.5$, 10.6 Hz, 1H×4/5), 3.45–3.53 (br, 1H×1/5), 3.55–3.73 (br, 1H×4/5), 4.13–4.28 (br, 1H×1/5), 6.89 (dd, $J=8.6$, 2.4 Hz, 1H×4/5), 7.09 (dd, $J=8.6$, 3.8 Hz, 1H×1/5), 7.14–7.57 (m, 13H), 7.72–7.77 (m, 1H×1/5), 7.81 (dd, $J=6.3$, 3.5 Hz, 1H×4/5), 8.05 (dd, $J=6.3$, 3.5 Hz, 1H×4/5), 8.63 (dd, $J=6.3$, 3.5 Hz, 1H×1/5). ^{13}C NMR ($CDCl_3$): 24.05, 24.29, 24.41, 25.27, 25.71, 25.93, 26.02, 27.47, 29.75, 31.59, 32.34, 54.10, 54.32, 54.93, 55.10, 57.17, 57.38, 59.20, 61.70, 62.50, 62.59, 124.80, 124.94, 125.49, 125.57, 125.78, 125.95, 126.02, 126.71, 127.44, 127.90, 127.97, 128.00, 128.13, 128.17, 128.27, 128.37, 128.63, 129.50, 131.91, 132.72, 133.00, 133.29, 133.54, 133.80, 133.95, 134.10, 134.26, 134.54, 134.66, 135.01, 135.19, 136.92, 137.40, 137.60, 138.35, 138.54, 138.81, 139.00, 139.63, 139.87, 150.99, 151.30, 153.92, 154.28. FABMS: $m/z=493$ ($M^+ +1$). Anal. Calcd for $C_{33}H_{37}N_2P$: C, 80.46; H, 7.57; N, 5.69. Found: C, 80.27; H, 7.56; N, 5.85.

4.2.2. (*S*)-*N*-[2-(Diphenylphosphanyl)naphthalen-1-yl]-2-(methoxymethoxymethyl)pyrrolidine (1a). The representative 2-step procedure was used to afford the title ligand **1a** (yield 35%) as a colorless viscous oil. $[\alpha]_D^{24}=+98°$ (*c* 0.41, THF). IR (neat): $\nu=1374$, 1362, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 55 °C): $\delta=1.93$–2.06 (br, 3H), 2.30–2.46 (br, 1H), 3.15 (s, 3H), 3.20–3.32 (br, 2H), 3.38 (d, $J=6.3$ Hz, 2H), 4.16–4.28 (br, 1H), 4.34 (s, 2H), 7.07 (dd, $J=1.5$, 3.2 Hz, 1H), 7.24–7.34 (br, 10H), 7.44 (dd, $J=1.5$, 3.2 Hz, 2H), 7.57 (d, $J=7.6$ Hz, 1H), 7.80 (dd, $J=1.5$, 3.2 Hz, 1H), 7.99–8.12 (br, 1H). ^{13}C NMR ($CDCl_3$): 25.15, 30.32, 54.72, 55.07, 63.43, 63.55, 71.83, 96.66, 124.44, 125.72, 126.24, 126.32, 128.11, 128.19, 128.23, 128.32, 128.62, 130.92, 133.43, 133.59, 133.73, 133.89, 135.59. FABMS: $m/z=456$ ($M^+ +1$). Anal. Calcd for $C_{29}H_{30}NO_2P$: C, 76.46; H, 6.64; N, 3.07. Found: C, 76.75; H, 6.48; N, 3.11.

4.2.3. (*S*)-*N*-[2-(Diphenylphosphanyl)naphthalen-1-yl]-2-(*t*-butoxymethyl)pyrrolidine (1c). The representative 2-step procedure was used to afford the title ligand **1c** (yield 44%) as a colorless amorphous. $[\alpha]_D^{27}=+115°$ (*c* 2.26, dioxane). IR (neat): $\nu=1374$, 1362, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 50 °C): $\delta=0.93$ (s, 9H), 1.91–2.06 (m, 3H), 2.26–2.43 (br, 1H), 3.09–3.31 (m, 4H), 4.00–4.14 (br, 1H), 7.05 (br d, $J=8.4$ Hz, 1H), 7.21–7.33 (m, 10H), 7.43 (br dd, $J=4.2$, 4.2 Hz, 2H), 7.57 (d, $J=8.4$ Hz, 1H), 7.77–7.84 (br, 1H), 7.96–8.12 (br, 1H). ^{13}C NMR ($CDCl_3$): 25.05, 27.54, 30.33, 54.70, 54.76, 64.04, 64.12, 65.65, 72.17, 124.67, 125.52, 126.15, 126.22, 128.04, 128.08, 128.15, 128.25, 128.36, 128.65, 130.73, 133.38, 133.50, 133.67, 133.80, 135.68, 139.02, 139.25, 150.32, 150.65. FABMS: $m/z=468$ ($M^+ +1$). Anal. Calcd for $C_{31}H_{34}NOP$: C, 79.63; H, 7.33; N, 3.00. Found: C, 79.39; H, 7.35; N, 3.24. The physical data of the coupling product in the first step, (*S*)-*N*-[2-(diphenylphosphinoyl)naphthalen-1-yl]-2-(*t*-butoxymethyl)pyrrolidine, with small amounts of inseparable impurities are shown below. This mixture was used for the second step, the reduction reaction, without further separation. IR (neat): $\nu=1387$, 1364, 1196, 1115 cm^{-1}. ^1H

NMR ($CDCl_3$): δ=0.89 (s, 9H), 1.70–1.82 (m, 3H), 2.04–2.20 (br, 1H), 2.71–2.89 (br, 1H), 2.96–3.05 (m, 1H), 3.11 (dd, J=9.1, 4.1 Hz, 1H), 3.23–3.35 (br, 1H), 4.16–4.31 (br, 1H), 7.16 (dd, J=12.7, 8.6 Hz, 1H), 7.37–7.60 (m, 9H), 7.65–7.81 (m, 4H), 7.84 (d, J=7.8 Hz, 1H), 8.23 (br d, J=7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): 24.60, 27.35, 29.45, 54.02, 64.32, 64.50, 71.93, 124.78, 124.98, 125.41, 126.02, 127.38, 127.87, 128.06, 128.49, 129.31, 129.50, 130.79, 130.83, 130.88, 130.92, 131.21, 131.35, 131.63, 131.77, 133.72, 133.92, 135.25, 135.48, 136.72, 136.75, 152.08, 152.14. FABMS: m/z=484 (M^++1).

4.2.4. (*S*)-*N*-[2-(Di-*p*-tolylphosphanyl)naphthalen-1-yl]-2-(benzyloxymethyl)pyrrolidine (1f). The representative 2-step procedure was used to afford the title ligand **1f** (yield 48%) as a colorless viscous oil. $[\alpha]_D^{24}$=+81° (c 0.47, THF). IR (neat): ν=1374, 1308, 1113 cm^{-1}. ^{1}H NMR ($CDCl_3$, 50 °C): δ=1.90–2.09 (br, 3H), 2.22–2.45 (m, 7H), 3.20–3.41 (m, 4H), 4.10–4.30 (br, 3H), 6.98–8.25 (m, 19H). ^{13}C NMR ($CDCl_3$): 21.32, 25.24, 30.26, 54.63, 63.22, 63.32, 72.88, 74.61, 125.58, 126.04, 126.15, 127.02, 127.22, 127.90, 127.98, 129.01, 129.11, 133.44, 133.58, 133.74, 133.88, 137.84, 137.95, 138.81. FABMS: m/z=530 (M^++1). Anal. Calcd for $C_{36}H_{36}NOP$: C, 81.64; H, 6.85; N, 2.64. Found: C, 81.35; H, 6.70; N, 2.65. The physical data of the coupling product in the first step, (*S*)-*N*-[2-(di-*p*-tolylphosphinoyl)naphthalen-1-yl]-2-(benzyloxymethyl)pyrrolidine, with small amounts of inseparable impurities are shown below. This mixture was used for the second step, the reduction reaction, without further separation. IR (neat): ν=1383, 1310, 1186, 1113 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.56–1.73 (br, 1H), 1.78–1.94 (m, 2H), 2.12–2.29 (br, 1H), 2.36 (s, 6H), 2.80–2.99 (br, 1H), 3.11–3.27 (m, 2H), 3.28–3.46 (br, 1H), 4.11 (s, 2H), 4.27–4.48 (br, 1H), 7.03 (br d, J=6.8 Hz, 2H), 7.11–7.32 (m, 8H), 7.36–7.67 (m, 7H), 7.83 (d, J=8.1 Hz, 1H), 8.14–8.24 (br, 1H). ^{13}C NMR ($CDCl_3$): 21.58, 24.81, 29.57, 54.21, 63.38, 72.56, 73.88, 124.80, 124.99, 125.47, 125.73, 126.88, 126.95, 127.43, 127.87, 128.69, 128.75, 128.83, 128.88, 128.93, 129.50, 129.69, 130.34, 130.81, 131.34, 131.48, 131.67, 131.81, 132.40, 136.72, 138.71, 141.19, 141.23, 141.27, 151.86. FABMS: m/z=546 (M^++1).

4.2.5. (*S*)-*N*-[2-(Diphenylphosphanyl)-6-methylphenyl]-2-(benzyloxymethyl)pyrrolidine (1k). The representative 2-step procedure was used to afford the title ligand **1l** (yield 50%) as a colorless viscous oil. $[\alpha]_D^{24}$=+50° (c 0.647, THF). IR (neat): ν=1095 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.49–1.90 (m, 3.5H), 1.99–2.20 (m, 1.2H), 2.27 (s, 3H), 2.60–2.80 (m, 0.6H), 2.85 (dd, J=7.6, 7.6 Hz, 0.9H), 3.09–3.36 (m, 2H), 3.64–3.80 (m, 0.8H), 4.27 (s, 2H), 6.61–6.84 (br, 0.8H), 7.01 (dd, J=7.4, 7.4 Hz, 1H), 6.97–7.40 (16.2H). FABMS: m/z=466 (M^++1). EIMS: m/z=344 (M^+−CH_2OBn, bp), 91. HRMS (M^+−CH_2OBn): calcd for $C_{23}H_{23}NP$: 344.1568; found: 344.1549. The physical data of the coupling product in the first step, (*S*)-*N*-[2-(diphenylphosphinoyl)-6-methylphenyl]-2-(benzyloxymethyl)pyrrolidine, with small amounts of inseparable impurities are shown below. This mixture was used for the second step, the reduction reaction, without further separation. IR (neat): ν=1454, 1418, 1200, 1113 cm^{-1}. ^{1}H NMR ($CDCl_3$, 50 °C): δ=1.30–1.51 (br, 1H), 1.54–1.72 (m, 2H), 1.90–2.05 (m, 2H), 2.29 (s, 3H), 2.43–2.68 (br, 1H), 2.88–3.04 (br, 1H), 3.12–3.23 (m, 2H), 4.22 (s, 2H), 6.89–7.02 (m, 2H), 7.06–7.13 (m, 2H), 7.15–7.49 (m, 9H), 7.61–7.76 (m, 5H). FABMS: m/z=482 (M^++1).

4.2.6. (*S*)-*N*-[2-(Diphenylphosphanyl)-6-methoxylphenyl]-2-(pyrrolidinylmethyl)pyrrolidine (1l). The representative 2-step procedure was used to afford the title ligand **1l** (yield 31%) as a colorless viscous oil. The physical data were comparable to those reported.[18a]

4.2.7. (*S*)-*N*-[2-(Diphenylphosphanyl)-6-methoxylphenyl]-2-methylpiperidine (1m). The representative 2-step procedure was used to afford the title ligand **1m** (yield 30%) as a colorless amorphous. $[\alpha]_D^{25}$=−23° (c 3.51, dioxane). IR (neat): ν=1283, 1258 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.67 (d, J=6.3 Hz, 3H), 1.03–1.35 (m, 4H), 1.48 (brd, J=8.3 Hz, 1H), 1.60–1.68 (br, 1H), 2.46 (brd, J=11.1 Hz, 1H), 2.94 (ddd, J=11.1, 11.1, 3.3 Hz 1H), 3.20–3.32 (m, 1H), 3.77 (s, 3H), 6.36 (brd, J=8.1 Hz 1H), 6.81 (d, J=8.1 Hz, 1H), 7.02 (dd, J=8.1, 8.1 Hz, 1H), 7.22–7.36 (m, 10H). ^{13}C NMR ($CDCl_3$): 20.03, 20.08, 25.40, 25.84, 35.20, 52.41, 54.98, 55.18, 111.90, 124.71, 126.09, 126.11, 127.77, 127.82, 127.87, 127.92, 133.87, 134.12, 134.18, 134.42, 138.04, 138.22, 138.91, 139.12, 141.67, 141.79, 141.82, 141.97, 158.83, 158.86. FABMS: m/z=390 (M^++1). Anal. Calcd for $C_{25}H_{28}NOP$: C, 77.10; H, 7.25; N, 3.60. Found: C, 76.96; H, 7.33; N, 3.41. The physical data of the coupling product in the first step, (*S*)-*N*-[2-(diphenylphosphinoyl)-6-methoxylphenyl]-2-methylpiperidine, with small amounts of inseparable impurities are shown below. This mixture was used for the second step, the reduction reaction, without further separation. IR (nujol): ν=1283, 1267, 1190 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.52 (d, J=6.4 Hz, 3H), 0.83–1.00 (m, 1H), 1.08–1.34 (m, 4H), 1.79–1.91 (br, 1H), 2.87–2.95 (m, 2H), 3.16–3.30 (m, 1H), 3.80 (s, 3H), 6.62 (ddd, J=13.5, 7.3, 1.6 Hz, 1H), 6.99–7.10 (m, 2H), 7.36–7.50 (m, 6H), 7.73–7.83 (m, 4H). ^{13}C NMR ($CDCl_3$): 19.75, 24.88, 25.42, 34.06, 54.29, 55.19, 55.85, 115.59, 115.62, 125.50, 125.73, 125.88, 126.06, 127.62, 127.73, 127.80, 127.90, 130.48, 130.50, 130.52, 130.54, 131.19, 131.32, 131.56, 131.69, 133.53, 134.00, 135.07, 135.55, 144.08, 144.15, 159.84, 159.99. FABMS: m/z=406 (M^++1).

4.2.8. (*E*)-1-Bromo-2-(4-triisopropylsilyloxymethylphenyl)ethene (3e). To a stirred solution of (*E*)-1-bromo-2-(4-hydroxymethylphenyl)ethene (134 mg, 0.632 mmol) and imidazole (94.2 mg, 1.37 mmol) in DMF (0.6 mL) was gradually added TIPSCl (240 mg, 1.24 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at rt and purified directly by silica gel column (hexane) to gave 1-bromo-2-(4-triisopropylsilyloxymethylphenyl)ethene (**3e**) (230 mg, 99%) as a colorless oil. IR (neat): ν=1462, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.97–1.24 (m, 3H), 1.09 (d, J=5.6 Hz, 18H), 4.81 (s, 2H), 6.74 (d, J=14.0 Hz, 1H), 7.09 (d, J=14.0 Hz, 1H), 7.26 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=12.00, 18.01, 64.63, 105.68, 125.73, 125.87, 134.23, 136.82, 141.71. EIMS: m/z=370 (M^+), 368 (M^+), 325 (bp), 195. HRMS: m/z calcd for $C_{18}H_{29}^{79}BrOSi$: 368.1171; found: 368.1180.

4.3. Representative procedure for the stereoselective synthesis of (*E*)-1-bromo-2-arylethene (3)[23]

4.3.1. 1-Bromo-2-(2-bromophenyl)ethene (3h). To a stirred solution of 1,1-dibromo-2-(2-bromophenyl)ethene (580 mg, 1.72 mmol) and EtOAc (302 mg, 3.44 mmol) in THF (5.7 mL) was gradually added $LiAlH_4$ (130 mg, 3.44 mmol) at −40 °C. The mixture was stirred for 8 h at the same temperature and quenched with a small amount of acetone. To the mixture was then added $Na_2SO_4 \cdot 10H_2O$. The whole mixture was stirred for 1 h at rt and filtered to remove white precipitates. After concentration, purification by silica gel column (hexane) gave 1-bromo-2-(2-bromophenyl)ethene (**3h**) (283 mg, 65%) as a 17:1 mixture of *E*- and *Z*-isomers. a colorless oil. IR (neat): ν=1605, 1462, 1435 cm^{-1}. ^1H NMR ($CDCl_3$): δ=6.76 (d, J=14.0 Hz, 1H), 7.15 (ddd, J=7.7, 7.7, 1.6 Hz, 1H), 7.27 (ddd, J=7.7, 7.7, 1.2 Hz, 1H), 7.39 (dd, J=7.7, 1.6 Hz, 1H), 7.43 (d, J=14.0 Hz, 1H), 7.55 (dd, J=7.7, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=109.14, 122.63, 126.95, 127.53, 129.44, 132.99, 135.78, 136.03. EIMS: m/z=264 (M^+), 262 (M^+), 260 (M^+), 181 (bp), 75. HRMS: m/z calcd for $C_8H_6^{79}Br_2$: 259.8836; found: 259.8839.

4.3.2. 1,1-Dibromo-2-(3-bromophenyl)ethene. The published procedure[26] was used to afford the title dibromoalkene (yield 99%) as a pale yellow oil. IR (neat): ν=1589, 1560, 1470 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.23 (dd, J=7.6, 7.9 Hz, 1H), 7.41 (s, 1H), 7.43 (d, J=7.9 Hz, 1H), 7.47 (d, J=7.6 Hz, 1H), 7.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=91.37, 122.31, 126.85, 129.79, 131.01, 131.34, 135.24, 137.08. EIMS: m/z=344 (M^+), 342 (M^+), 340 (M^+, bp) 338 (M^+), 261, 180. HRMS: m/z calcd for $C_8H_5^{79}Br_3$: 337.7941; found: 337.7953.

4.3.3. (*E*)-1-Bromo-2-(3-bromophenyl)ethene (3i). The above representative procedure was used to afford the title bromoalkene (yield 65%, *E*/*Z*=23: 1) as a colorless oil. IR (neat): ν=1605, 1593, 1562, 1475, 1470 cm^{-1}. ^1H NMR ($CDCl_3$): δ=6.80 (d, J=14.0 Hz, 1H), 7.04 (d, J=14.0 Hz, 1H), 7.18–7.24 (m, 2H), 7.38–7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=108.13, 122.82, 124.61, 128.85, 130.17, 131.03, 135.62, 137.75. EIMS: m/z=264 (M^+), 262 (M^+, bp), 260 (M^+), 102, 75. HRMS: m/z calcd for $C_8H_6^{79}Br_2$: 259.8836; found: 259.8823.

4.4. Representative procedure for the cross-coupling with $PdCl_2(MeCN)_2$-the ligand 1j catalyst (entry 2, Table 2)

1-Phenylethylmagnesium chloride (2.10 mL, 1.50 mmol, 0.70 mol/L in Et_2O) was added to the mixture of $PdCl_2(MeCN)_2$ (9.3 mg, 0.036 mmol) and the ligand **1j** (18.2 mg, 0.0369 mmol) in α,α,α-trifluorotoluene (2.10 mL) at 0 °C, and the solution was stirred at the same temperature for 30 min (CAUTION: stirring at 0 °C for 30 min for the favorable complexation of Pd and ligand **1j** is needed.). To the solution was added β-bromostyrene (*E*/*Z*=6:1, **3a**) (133 mg, 0.727 mmol) at −10 °C. The resulting solution was stirred for 6 h at −10 °C. After usual work-up, purification by silica gel column (hexane) afforded (*S*)-(*E*)-1,3-diphenyl-1-butene (**5a**) (105 mg, 69%, 71% ee) as a colorless oil. The ee was determined by HPLC analysis (Daicel chiralcel OD, hexane/*i*-PrOH=100:1, 0.3 mL/min, 254 nm): t_R/min=34.9 (*S*), 37.1 (*R*). The absolute configuration was determined by comparison of the reported specific rotation.[8] The physical data were comparable to those reported.[8]

4.5. Representative procedure for the cross-coupling reaction with $Pd_2(dba)_3$-the ligand 1j catalyst (entry 5, Table 2)

1-Phenylethylmagnesium chloride (2.10 mL, 1.50 mmol, 0.70 mol/L in Et_2O) was added to the mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (19.1 mg, 0.0180 mmol) and the ligand **1j** (18.2 mg, 0.0369 mmol) in α,α,α-trifluorotoluene (2.10 mL) at −30 °C, and the solution was stirred at the same temperature for 30 min. To the solution was added β-bromostyrene (*E*/*Z*=6:1, **3a**) (133 mg, 0.727 mmol) at −30 °C. The resulting solution was stirred for 7 h at −30 °C. After usual work-up, purification by silica gel column (hexane) afforded (*S*)-(*E*)-1,3-diphenyl-1-butene (**5a**) (96.9 mg, 64%, 76% ee) as a colorless oil. The ee was determined by HPLC analysis with Daicel chiralcel OD. The absolute configuration was determined by comparison of the reported specific rotation.[8] The physical data were comparable to those reported.[8]

4.5.1. (*S*)-(*E*)-1-(4-Tolyl)-3-phenyl-1-butene (5b). Yield 73%, 78% ee. The desired product **5b** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield of **5b** was calculated on the basis of ^1H NMR analysis of the mixture. The protons of these compounds were assigned, respectively, by comparison with the authentic sample (±)-**5b**, which was prepared by Wittig olefination of 2-phenylpropionaldehyde with $Ph_3P{=}CH$(4-tolyl), and commercially available 2,3-diphenylbutane. The ee was determined by HPLC analysis with Daicel chiralcel OD (hexane/*i*-PrOH=200:1), and its absolute configuration was determined by HPLC analysis with Daicel Chiralpak AD (hexane/*i*-PrOH/TFA=9:1:0.1) after conversion ((i) OsO_4, NMO, *t*-BuOH–H_2O, (ii) RuO_2, $NaIO_4$, CCl_4-MeCN–H_2O, 0 °C) of **5b** to 2-phenylpropionic acid **7** of known configuration. Physical data of the authentic sample (±)-(*E*)-**5b**. A colorless oil. IR (neat): ν=1603, 1456, 967 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.46 (d, J=6.9 Hz, 3H), 2.32 (s Hz, 3H), 2.87 (sept, J=6.9 Hz, 1H), 3.57–3.68 (m, 1H), 6.33–6.37 (m, 2H), 7.06–7.35 (m, 9H). EIMS: m/z= 222 (M^+), 207 ($M^+ - CH_3$, bp). HRMS (M^+): calcd for $C_{17}H_{18}$ 222.1409; found: 222.1401.

4.5.2. (*S*)-(*E*)-1-(4-Isopropylphenyl)-3-phenyl-1-butene (5c). Yield 75%, 80% ee. The desired product **5c** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield of **5c** was calculated on the basis of ^1H NMR analysis of the mixture. The protons of these compounds were assigned, respectively, by comparison with the authentic sample (±)-**5c**, which was prepared by Wittig olefination of 2-phenylpropionaldehyde with $Ph_3P{=}CH$(4-*i*-Pr-C_6H_4), and commercially available 2,3-diphenylbutane. The ee was determined by HPLC analysis with Daicel chiralcel OD (hexane/*i*-PrOH=200:1), and its absolute configuration was determined by HPLC analysis with Daicel Chiralpak AD (hexane/*i*-PrOH/TFA=9:1:0.1) after conversion of **5c** to 2-phenylpropionic acid **7** of known

configuration. Physical data of the authentic sample (±)-(*E*)-**5c**. A colorless oil. IR (neat): ν=1603, 1453, 968 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.23 (d, J=6.9 Hz, 3H×2), 1.45 (d, J=7.1 Hz, 3H), 2.87 (sept, J=6.9 Hz, 1H), 3.62 (dt, J=6.9, 6.9 Hz, 1H), 6.28–6.46 (m, 2H), 7.10–7.34 (m, 9H). ^{13}C NMR ($CDCl_3$): 21.34, 24.04, 33.88, 42.56, 126.00, 126.04, 126.44, 127.20, 128.23, 128.33, 134.21, 135.08, 145.66, 147.72. EIMS: m/z=250 (M^+), 207 (bp). HRMS (M^+): calcd for $C_{19}H_{22}$ 250.1722; found: 250.1715.

4.5.3. (*S*)-(*E*)-1-(4-Chlorophenyl)-3-phenyl-1-butene (5d). Yield 80%, 71% ee. The desired product **5d** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield of **5d** was calculated on the basis of ^1H NMR analysis of the mixture. The protons of these compounds were assigned, respectively, by comparison with the known **5d**[27] and commercially available 2,3-diphenylbutane. The ee was determined by HPLC analysis with Daicel chiralcel OD (hexane/*i*-PrOH=200:1), and its absolute configuration was determined by HPLC analysis with Daicel Chiralpak AD (hexane/*i*-PrOH/TFA=9:1:0.1) after conversion of **5d** to 2-phenylpropionic acid **7**.

4.5.4. (*S*)-(*E*)-1-(4-Hydroxymethylphenyl)-3-phenyl-1-butene (8). The ee of **5e** was determined by HPLC analysis with Daicel chiralpak AD (hexane/*i*-PrOH=20:1), and its absolute configuration was determined by HPLC analysis with Daicel Chiralpak AD (hexane/*i*-PrOH/TFA=9:1:0.1) after conversion of **5e** to 2-phenylpropionic acid of known configuration. Since the desired product **5e** was obtained as a mixture with 2,3-diphenylbutane, the desilylation was performed without further separation. The solution of the above mixture and TBAF (187 mg, 0.717 mmol) in THF (1.2 mL) were stirred for 1 h at 0 °C, and purified directly by silica gel column (EtOAc/hexane=1:2) to gave (*S*)-(*E*)-1-(4-hydroxymethylphenyl)-3-phenyl-1-butene (**8**) (81 mg, 61%, 2 steps, 73% ee) as a pale yellow oil. $[\alpha]_D^{23}=-36°$ (*c* 2.08, THF). IR (neat): ν=1491, 1451, 1011 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.46 (d, J=7.1 Hz, 3H), 1.68–1.76 (br, 1H), 3.58–3.67 (m, 1H), 4.63 (s, 2H), 6.34–6.43 (m, 2H), 7.17–7.35 (m, 9H). ^{13}C NMR ($CDCl_3$): δ=21.26, 42.59, 65.12, 126.14, 126.23, 127.12, 127.20, 128.03, 128.40, 135.29, 136.98, 139.52, 145.46. EIMS: m/z=238 (M^+), 115 (bp). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.27; H, 7.68.

4.5.5. (*S*)-(*E*)-1-(2-Bromophenyl)-3-phenyl-1-butene (5h). Yield 22%, 60% ee. The desired product **5h** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield of **5h** was calculated on the basis of ^1H NMR analysis of the mixture. The protons of these compounds were assigned, respectively, by comparison with the known **5h**[28] and commercially available 2,3-diphenylbutane. The ee and absolute configuration were determined by HPLC analysis with Daicel chiralcel OD and OD-H (hexane/*i*-PrOH=400:1) after conversion (*t*-BuLi, THF, −40 °C) of **5h** to **5a**.

4.5.6. (*S*)-(*E*)-1-(3-Bromophenyl)-3-phenyl-1-butene (5i). Yield 65%, 70% ee. The desired product **5i** was obtained as a mixture with 2,3-diphenylbutane. The chemical yield of **5i** was calculated on the basis of ^1H NMR analysis of the mixture. The protons of these compounds were assigned, respectively, by comparison with the authentic sample (±)-**5i**, which was prepared by Wittig olefination of 2-phenylpropionaldehyde with Ph_3P=CH(3-Br-C_6H_4), and commercially available 2,3-diphenylbutane. The ee and absolute configuration were determined by HPLC analysis with Daicel chiralcel OD and OD-H (hexane/*i*-PrOH=400:1) after conversion (*t*-BuLi, THF, −40 °C) of **5i** to **5a** of known configuration. Physical data of the authentic sample (±)-**5i**. A colorless oil. IR (neat): ν=1591, 1558, 1493, 1474, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.46 (d, J=6.9 Hz, 3H), 3.63 (dq, J=6.9, 6.9 Hz, 1H), 6.27–6.44 (m, 2H), 7.08–7.37 (m, 8H), 7.50 (s, 1H). EIMS: m/z=288 (M^+), 286 (M^+), 207 (bp), 192, 130. HRMS (M^+): calcd for $C_{16}H_{15}^{79}Br$: 286.0357; found: 286.0369.

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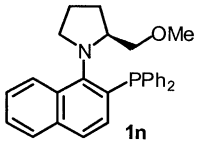

1n

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A highly stereoselective construction of 1,2-*trans*-β-glycosidic linkages capitalizing on 2-azido-2-deoxy-D-glycosyl diphenyl phosphates as glycosyl donors

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Abstract—The scope of TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycopyranosyl diphenyl phosphates is investigated. The 3,4,6-tri-*O*-benzyl-protected glucosyl and galactosyl donors and the 4,6-*O*-benzylidene-protected galactosyl donor each react with a range of acceptor alcohols in the presence of a stoichiometric amount of TMSOTf in propionitrile at −78 °C to afford 1,2-*trans*-β-linked disaccharides in high yields with α:β ratios ranging from 9:91 to 1:>99, regardless of the anomeric composition of the donor used. The use of propionitrile as a solvent at −78 °C has proven to be among the best choice for the highest levels of β-selectivity reported to date for this type of glycosidation. A plausible reaction mechanism, which features a large equilibrium preference for α-glycosyl-nitrilium ions over β-nitrilium ions, is proposed based on byproducts formed through their intermediacy and accounts for the observed excellent β-selectivities.

1. Introduction

The rapidly growing significance of glycosides and oligosaccharides as constituents of biologically important compounds such as antitumor antibiotics and glycoconjugates has mandated the rational design and development of stereocontrolled glycosidation reactions.[1] Since 2-acetamido-2-deoxy-D-glycopyranosides, mainly found in β-glycosidic linkage, are ubiquitous building blocks of glycolipids, glycoproteins, proteoglycans and peptidoglycans, numerous procedures for synthesizing 1,2-*trans*-β-linked 2-acetamido-2-deoxy-D-glycosides have been reported.[2] In terms of efficiency and practicality, direct glycosidation using 2-acetamido-2-deoxyglycosyl donors should constitute an ideal procedure for the stereocontrolled construction of these linkages. In practice, however, the reactions of these donors generally lead to the predominant formation of oxazoline derivatives via a neighboring group participation and subsequent elimination of an amide proton. Although oxazolines can react with acceptor alcohols in the presence of Brϕnsted or Lewis acids to afford 1,2-*trans*-glycosides with the natural 2-acetamido group (i.e. oxazoline method), the harsh reaction conditions for this conversion have precluded its wide application for synthesizing complex oligosaccharides.[3]

To overcome this problem, Lemieux and co-workers introduced the use of 2-deoxy-2-phthalimidoglycosyl donors as a reliable method for synthesizing 2-acetamido-2-deoxy-β-glycosides.[4] The phthalimido method generally gives high yields and virtually complete β-selectivity with most glycosyl acceptors as demonstrated with numerous complex oligosaccharide syntheses. However, removing the phthaloyl group requires basic conditions at elevated temperatures, which often cause the product to partially decompose. Therefore, a variety of different 2-amino protecting groups with an anchimeric assistance such as *N*-2,2,2-trichloroethoxycarbonyl (Troc),[5a–c] *N*-allyloxycarbonyl (Alloc),[5c] *N*-benzyloxycarbonyl (Cbz),[5c] *N*-trichloroacetyl (TCA),[5d] *N*-tetrachlorophthaloyl (TCP),[5e–g] *N*-dithiasuccinoyl (Dts),[5h,i] *N*,*N*-diacetyl,[5j] *N*-4,5-dichlorophthaloyl (DCPhth),[5k] *N*-dimethylmaleoyl (DMM),[5l] *N*,*N*-dibenzyl,[5m] and *N*-thiodiglycoloyl (TDG)[5n] have been investigated.

An alternative approach to 2-acetamido-2-deoxy-β-glycopyranosides involves using 2-azido-2-deoxyglycopyranosyl donors. Although the azido group as a latent amino functionality is incapable of neighboring group participation, modest to high levels of β-selectivity were observed with 2-azido-2-deoxyglycosyl trichloroacetimidates,[6–8] *S*-xanthates,[9] isopropenyl carbonate,[10] 2-pyridinecarboxylates,[11]

Keywords: 2-Azido-2-deoxyglycopyranosyl diphenyl phosphate; β-Selective glycosidation; α-Nitrilium ion.
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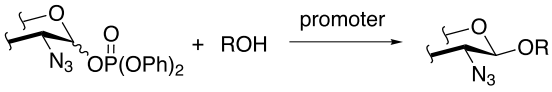
dibutyl phosphates,[12] and phenylthio glycosides.[13] Of these, glycosidation of 2-azido-2-deoxyglycosyl trichloroacetimidates in the presence of $BF_3 \cdot OEt_2$ in CH_2Cl_2–hexane[7] or in the presence of TMSOTf in acetonitrile[8] is the method of choice for a highly stereoselective construction of 2-azido-2-deoxy-β-glycosides.[14]

We recently developed glycosyl donors that incorporate various phosphorus-containing leaving groups. The glycosidations constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages with or without a participating group at C2.[15] The exceptionally high levels of β-selectivity observed with 2,3,4,6-tetra-*O*-benzyl-protected glycosyl diphenyl phosphates,[15a] *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidates,[15d] and diethyl phosphites[15e] suggested that these leaving groups would also be promising candidates for constructing 2-azido-2-deoxy-β-glycosidic linkages. In this article, the scope, limitations, and mechanism of TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycosyl diphenyl phosphates (Eq. (1)) are documented.[16] In addition, a comparative study with TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycosyl trichloroacetimidates is described.



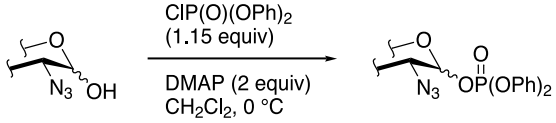
(1)

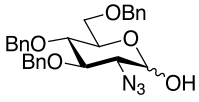
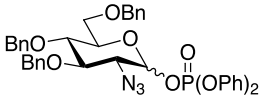
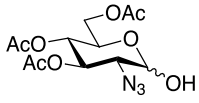
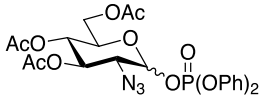
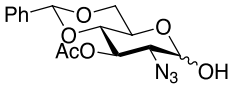
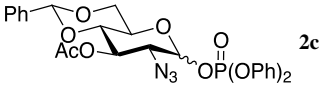
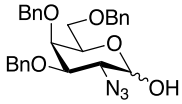
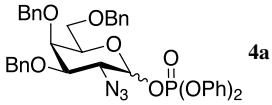
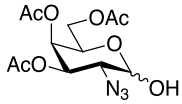
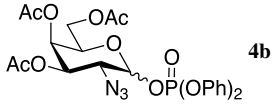
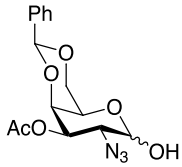
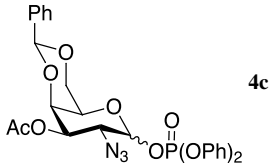
2. Results and discussion

2.1. Preparation of 2-azido-2-deoxy-D-glycosyl donors

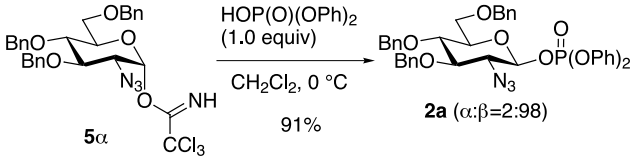
2-Azido-2-deoxy-D-glycosyl donors were prepared according to the standard procedures used for 2,3,4,6-tetra-*O*-benzyl-protected glycosyl donors. Application of Sabesan's phosphorylation method[17] [$ClP(O)(OPh)_2$, DMAP, CH_2Cl_2, 0 °C] to the corresponding glycopyranoses **1a–c** and **3a–c** afforded 2-azido-2-deoxyglycosyl diphenyl phosphates **2a–c** and **4a–c** in good to high yields (Table 1). Diphenyl phosphate **2a** with α:β ratio of 2:98 was obtained by coupling 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucosyl trichloroacetimidate (**5**α)[7b] with diphenyl phosphoric acid in CH_2Cl_2 at 0 °C (Eq. (2)).[18]

Table 1. Preparation of 2-azido-2-deoxyglycosyl diphenyl phosphates



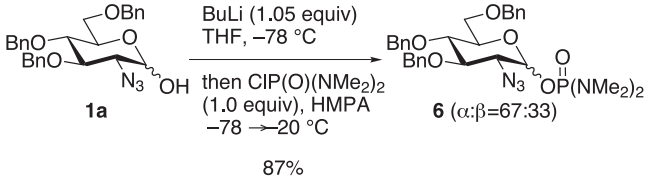
Entry	Glycopyranose	Phosphate	Yield %	α:β[a]
1	 **1a** (α:β=56:44)	 **2a**	97	72:28
2	 **1b** (α:β=61:39)	 **2b**	99	46:54
3	 **1c** (α:β=52:48)	 **2c**	99	31:69
4	 **3a** (α:β=68:32)	 **4a**	79	58:42
5	 **3b** (α:β=44:56)	 **4b**	97	24:76
6	 **3c** (α:β=63:37)	 **4c**	75	67:33

[a] Determined by 109 MHz ^{31}P NMR using 85% H_3PO_4 as an external standard.



(2)

Tetramethylphosphorodiamidate **6** was prepared by condensing a lithium alkoxide derived from **1a** with bis(dimethylamino)phosphorochloridate in THF-HMPA (Eq. (3)).[15d] On the other hand, 2-azido-2-deoxyglucosyl



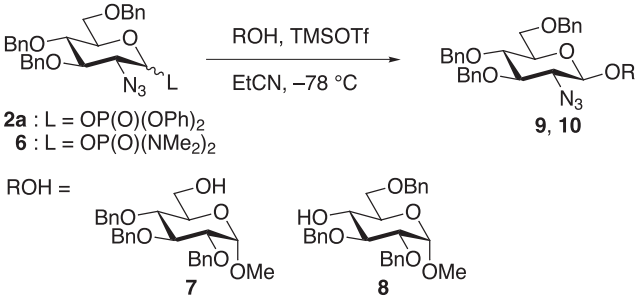
(3)

diethyl phosphite was inaccessible since it decomposed upon concentration in vacuo, although the reaction of **1a** with diethyl chlorophosphite and triethylamine proceeded in CH_2Cl_2 at 0 °C. The obtained 2-azido-2-deoxyglycosyl donors were purified by silica gel column chromatography, and stored without decomposition in the freezer (at −30 °C) for several months.

2.2. Reaction optimization

At the outset of this study, glycosidations of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucosyl diphenyl phosphate **2a** (α:β=72:28 or 2:98) and *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate **6** (α:β=67:33) were explored with *O*-6- or *O*-4-unprotected glycosides **7** or **8** (1.1 equiv each) as highly reactive and less reactive acceptor alcohols, respectively (Table 2). The addition of a 1.0 M solution of TMSOTf (1.5 equiv) in CH_2Cl_2 to a cooled solution (−78 °C) of the donor and acceptor in propionitrile afforded a disaccharide and the α:β ratio was assayed by HPLC (Zorbax® Sil column). As expected from previous work,[15a] TMSOTf-promoted glycosidations of the diphenyl phosphate **2a** with **7** or **8** in propionitrile at −78 °C proceeded smoothly to give disaccharides **9** and **10** in high yields with excellent β-selectivities, regardless of the anomeric composition of the donor (entries 1–4) (Fig. 1). The reactions of phosphorodiamidate **6** under the same conditions exhibited virtually the same β-selectivities as those found with **2a** (entries 5 and 6), although longer reaction times were required. In either case, the reaction did not go to completion when a substoichiometric amount of TMSOTf was used. Upon further examining these reactions, we were somewhat surprised to find a small amount (5–7%) of the hydrolysis-prone α-imidate **11**, which has an R_f value comparable to disaccharide **9**, was produced as a byproduct when alcohol **7** was used as an acceptor (entries 1, 2 and 5). It must be mentioned that imidate byproducts such as **11** are formed regardless of the nature of 2-azido-2-deoxyglycosyl donors whenever the reactions with highly reactive *O*-6-unprotected glycoside alcohols are conducted in propionitrile (vide infra). Fortunately, their formation did not prevent the isolation of products since the imidates were

Table 2. TMSOTf-Promoted glycosidation of 2-azido-2-deoxyglycosyl donors **2a**[a] and **6**[b]



Entry	Donor		ROH	Time, h	Glycoside		
		α:β[c]				Yield, %	α:β[d]
1	**2a**	72:28	**7**	1.5	**9**	84[e]	1:99
2	**2a**	2:98	**7**	1.5	**9**	85[e]	1:99
3	**2a**	72:28	**8**	2	**10**	90	6:94
4	**2a**	2:98	**8**	2	**10**	92	7:93
5	**6**	67:33	**7**	2.5	**9**	81[e]	2:98
6	**6**	67:33	**8**	3	**10**	85	7:93

[a] Donor **2a**/ROH/TMSOTf molar ratio=1.0/1.1/1.5.
[b] Donor **6**/ROH/TMSOTf molar ratio=1.0/1.1/1.8.
[c] Determined by 109 MHz ^{31}P NMR using 85% H_3PO_4 as an external standard.
[d] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 13 or 17% AcOEt in hexane; flow rate 1.0 mL/min).
[e] α-Imidate **11** was obtained in 5–7% yield.

easily hydrolyzed upon an acidic aqueous work-up. The ^1H NOE between H1′ and CH_2 of ethyl group established the *anti* stereochemistry of **11**. In contrast, such a byproduct was not detected when less reactive alcohol **8** was used. While the phosphorodiamidate **6** has a greater shelf-stability than the diphenyl phosphate **2a**, we selected the phosphate method due to the ease in preparing this type of donor.

Examining solvents other than propionitrile for the reaction of diphenyl phosphate **2a** (α:β=72:28) with *O*-6-unprotected glycoside **7** showed that similar high levels of β-selectivity could be achieved in CH_2Cl_2 and toluene (Table 3, entries 1–5). A further solvent survey with *O*-4-unprotected glycoside **8** revealed that propionitrile was optimal for this glycosidation and has a beneficial effect on the stereoselectivity as well as the reaction rate (entries 6–8). Consistent with the proposal by Schmidt,[8] an

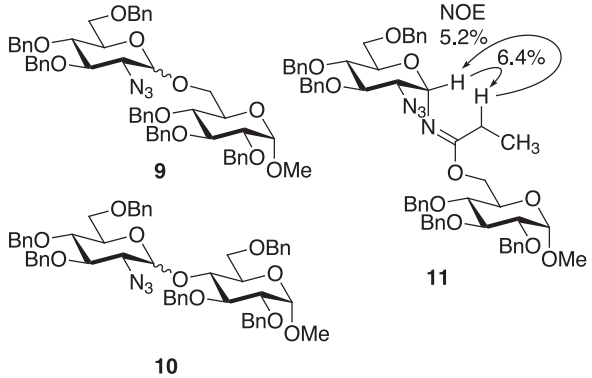
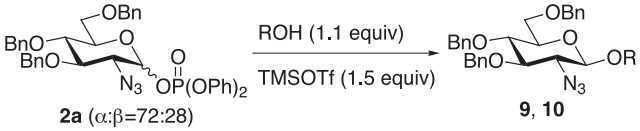


Figure 1. Products of glycosidation reactions of diphenyl phosphate **2a** with **7** and **8**.

Table 3. Effect of solvent in TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycosyl diphenyl phosphate **2a**



2a (α:β=72:28) **9**, **10**

Entry	ROH	Solvent	Temp.[a] °C	Time, h	Glycoside		
						Yield, %	α:β[b]
1	**7**	EtCN	−78	1.5	**9**	84	1:99
2	**7**	CH_2Cl_2	−78	4	**9**	88	1:99
3	**7**	Toluene	−65	2	**9**	90	4:96
4	**7**	EtOAc	−65	2	**9**	89	11:89
5	**7**	Et_2O	−30	1	**9**	88	38:62
6	**8**	EtCN	−78	2	**10**	90	6:94
7	**8**	CH_2Cl_2	−78	8	**10**	84	10:90
8	**8**	Toluene	−65	8	**10**	81	24:76

[a] Temperature limit for smooth reaction.
[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 13% or 17% AcOEt in hexane; flow rate 1.0 mL/min).

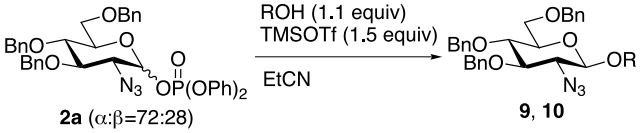
exceptionally high order of β-selectivity in propionitrile can be explained by the intermediacy of 2-azido-2-deoxy-α-D-glucosyl-nitrilium ion associated with triflate as a counter-ion (vide infra).

As expected the temperature profile of the glycosidation in propionitrile revealed a descending β-selectivity with ascending temperature (Table 4). The temperature effect was more pronounced with less reactive alcohol **8** (entries 4 vs 5) than with **7**.

2.3. Glycosidations of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxyglycosyl diphenyl phosphates 2a and 4a

With the optimal reaction conditions determined, glycosidations of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy glycosyl diphenyl phosphates **2a** (α:β=72:28) and **4a** (α:β=58:42) in the D-gluco and D-galacto series were explored with a range of suitably protected glycoside alcohols (Fig. 2). The results are compiled in Tables 5 and 6. In all cases,

Table 4. Temperature profile of TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycosyl diphenyl phosphate **2a**



2a (α:β=72:28) **9**, **10**

Entry	ROH	Temp, °C	Time, h	Glycoside		
					Yield, %	α:β[a]
1	**7**	−78	1.5	**9**	84	1:99
2	**7**	−45	0.5	**9**	89	3:97
3	**7**	−10	0.1	**9**	92	8:92
4	**8**	−78	2	**10**	90	6:94
5	**8**	−45	0.5	**10**	88	13:87

[a] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 13% or 17% AcOEt in hexane; flow rate 1.0 mL/min).

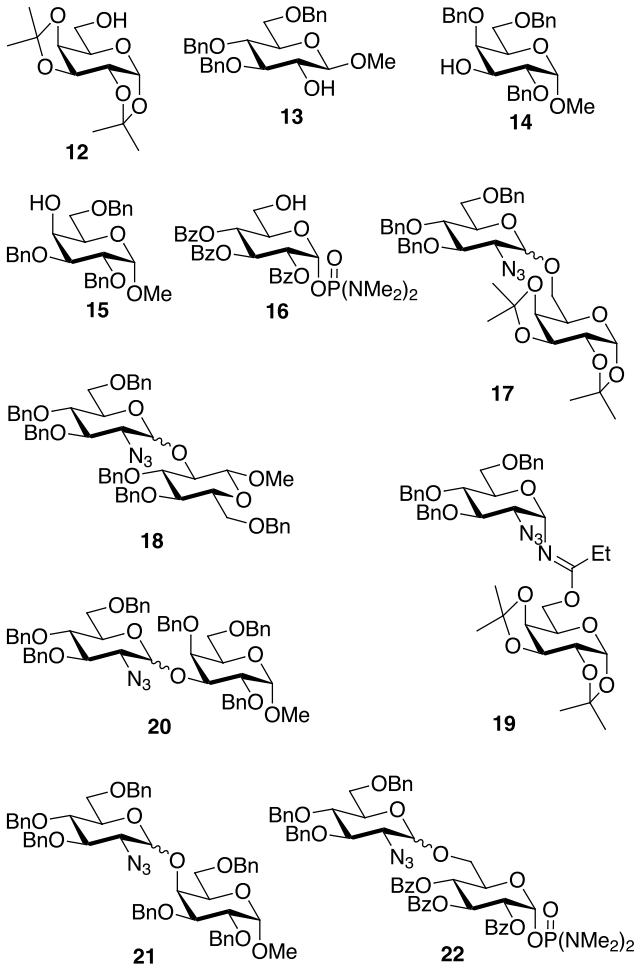
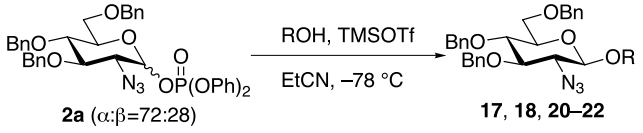


Figure 2. Acceptor alcohols and products in Table 5.

TMSOTf-promoted glycosidations in propionitrile at −78 °C offered a facile and high-yielding entry to 1,2-*trans*-β-linked disaccharides, wherein the α:β ratios ranged from 9:91 to 1:>99.

Table 5. TMSOTf-promoted glycosidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxyglucosyl diphenyl phosphate **2a** with acceptor alcohols[a,b]

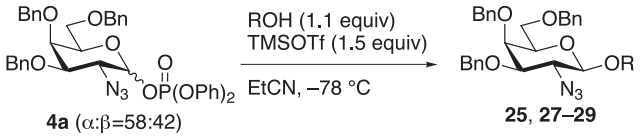


2a (α:β=72:28) **17**, **18**, **20–22**

Entry	ROH	Time, h	Glycoside		
				Yield, %	α:β[c]
1	**12**	1.5	**17**	79[d]	2:98
2	**13**	2	**18**	91	9:91
3	**14**	2	**20**	89	1:>99
4	**15**	2	**21**	90	5:95
5[e]	**16**	2	**22**	88	7:93[f]

[a] The reaction was carried out on 0.1 mmol scale.
[b] Donor **2a**/ROH/TMSOTf molar ratio=1.0/1.1/1.5 unless otherwise noted.
[c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17∼20% AcOEt in hexane or 14% THF in hexane; flow rate 1.0 mL/min), unless otherwise stated.
[d] α-Imidate **19** was obtained in 9% yield.
[e] The reaction was performed with 2.0 equiv of TMSOTf.
[f] Determined by 500 MHz ^{1}H NMR.

Table 6. TMSOTf-promoted glycosidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxygalactosyl diphenyl phosphate **4a** with acceptor alcohols[a]



4a (α:β=58:42) **25**, **27–29**

Entry	ROH	Time, h	Glycoside		
				Yield, %	α:β[b]
1	**7**	0.2	**25**	86[c]	4:96
2	**8**	0.5	**27**	90	4:96
3	**23**	0.3	**28**	81	6:94
4	**24**	0.5	**29**	86	8:92

[a] The reaction was carried out on 0.1 mmol scale.
[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% AcOEt in hexane or 17% THF in hexane; flow rate 1.0 mL/min).
[c] Propionate **26** was obtained in 5% yield.

Seeberger and co-workers reported that TMSOTf-promoted coupling of 2-azido-2-deoxyglucosyl dibutyl phosphate with glycoside alcohols **12** or **13** in acetonitrile at −40 °C produced disaccharides **17** and **18** in modest yields with α:β ratios of 1:5 and 1:4, respectively.[12] Clearly, the present method is superior to the dibutyl phosphate method in terms of product yield and stereoselectivity (Table 5, entries 1 and 2). Here again, a small amount (9%) of α-imidate byproduct **19** was detected when *O*-6-unprotected glycoside **12** was used. It is also noteworthy that glycosylation of *O*-3-unprotected galactose derivative **14** exclusively formed disaccharide **20**β, which corresponds to GlcNAcβ1→3Gal, a constituent of biologically important gangliosides such as sialyl Lewis^x (entry 3). Since the fully benzoylated glucosyl tetramethylphosphorodiamidate is unaffected at temperatures below −5 °C by these reaction conditions,[19] chemoselective glycosidation was uneventfully realized using *O*-6-unprotected glucosyl phosphorodiamidate **16** as a disarmed acceptor (entry 5). It is interesting to note that 2-azido-2-deoxygalactosyl diphenyl phosphate **4a** is even more reactive than the corresponding glucosyl donor **2a**, as manifested by much shorter reaction times (Table 6). When alcohols **7** and **8** were used, donor **4a** displayed somewhat lower and higher β-selectivities, respectively, than donor **2a**. In the former reaction, 5% of *O*-6-propionyl-protected glycoside **26**, due to the hydrolysis of the imidate byproduct (not shown), was obtained. The effectiveness of the present method was also demonstrated by synthesizing LacdiNAc equivalent **29**, which was achieved by glycosylation of *O*-4-unprotected glucosamine derivative **24** in 86% yield with an α:β ratio of 8:92 (entry 4) (Fig. 3).

2.4. Glycosidations of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxyglycosyl diphenyl phosphates 2b and 4b

While 2-azido-3,4,6-tri-*O*-benzyl-2-deoxyglycosyl donors **2a** and **4a** performed well, attempts to employ 3,4,6-tri-*O*-acetyl-protected glycosyl donors **2b** and **4b** met with less success. 2-Azido-2-deoxyglucosyl diphenyl phosphate **2b** was activated by TMSOTf at −65 °C in propionitrile, but the reaction with alcohol **7** predominantly formed imidates **30** with an α:β ratio of 85:15 (Table 7, entry 1). Although some of the β-imidate partially decomposed during column

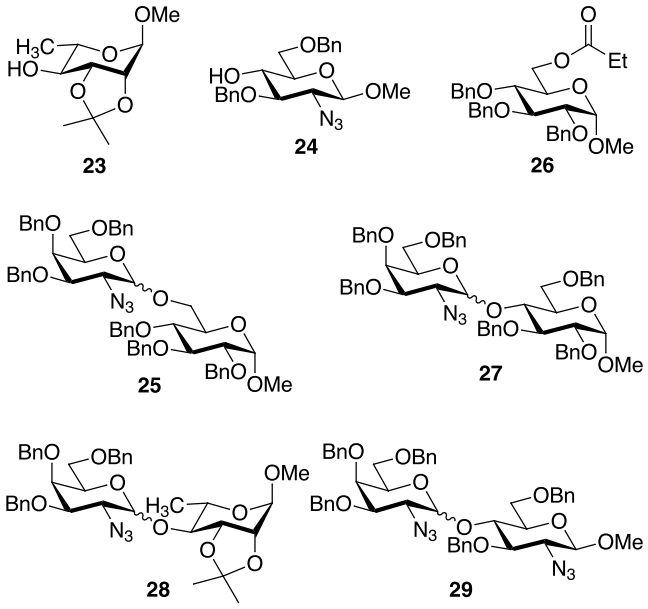
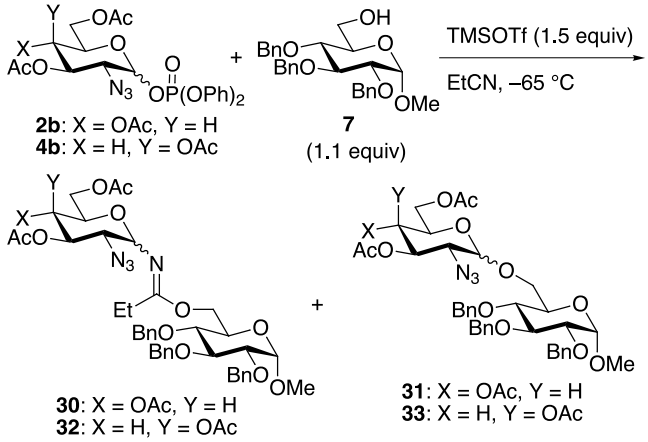


Figure 3. Acceptor alcohols and products in Table 6.

chromatography on silica gel, α-imidate **30**α was safely isolated in 79% yield. In this reaction, the corresponding disaccharide **31** with an α:β ratio of 14:86 was obtained in only 4% yield. Likewise, the reaction of 2-azido-2-deoxygalactosyl diphenyl phosphate **4b** with **7** afforded imidate **32** (α:β=88:12) as a major product, along with 9%

Table 7. TMSOTf-promoted glycosidation of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxyglycosyl diphenyl phosphates **2b** and **4b** with alcohol **7**[a,b]



Entry	Donor	Time, h	Imidate		Glycoside		
				α:β[c]		Yield, %	α:β[c]
1	**2b**	4	**30**[d]	85:15	**31**	4	14:86
2	**4b**	3	**32**[e]	88:12	**33**	9	3:97

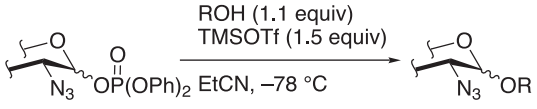
[a] The reaction was carried out on 0.1 mmol scale.
[b] The anomeric α:β ratio of the phosphates: **2b**, 46:54; **4b**, 24:76.
[c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 29% AcOEt–THF (1:1) in hexane or 20% THF in hexane; flow rate 1.0 mL/min).
[d] Only α-imidate **30**α could be isolated in 79% yield after chromatographic separation.
[e] Only α-imidate **32**α could be isolated in 68% yield after chromatographic separation.

of disaccharide **33** (α:β=3:97), wherein the α-imidate **32α** was isolated in 68% yield (entry 2). These disappointing results are attributed to the electron-withdrawing effect of the ester functionality, which deactivates the anomeric reactivity of nitrilium ion intermediates and favors a nucleophilic attack by alcohol **7** on a nitrilium carbon leading to imidates **30** and **32** (vide infra). Although the fully acyl-protected 2-azido-2-deoxyglycosyl donors are not suitable for the present coupling reaction, other donors with partially acyl protection should not be excluded (vide infra).

2.5. Glycosidations of 2-azido-4,6-*O*-benzylidene-2-deoxyglycosyl diphenyl phosphates 2c and 4c

It is well documented that 4,6-*O*-benzylidene-protected glycosyl donors exhibit reduced reactivities[20] and different stereoselectivities[21] compared to the fully benzylated ones. Therefore, we were driven to investigate glycosidations of 2-azido-4,6-*O*-benzylidene-2-deoxyglycosyl diphenyl phosphates. 2-Azido-2-deoxyglucosyl donor **2c** was activated with TMSOTf at −45 °C in propionitrile, but the reaction with **7** gave disaccharide **35** in only 6% yield with an α:β ratio of 8:92 and considerable amounts of imidates **36** (α:β=91:9); the α-imidate **36α** was isolated in 84% yield (Table 8, entry 1). In stark contrast, 2-azido-2-deoxygalactosyl diphenyl phosphate **4c** underwent a smooth coupling with a range of alcohols even at −78 °C to provide disaccharides **37**, **39**, **40** in good yields with excellent β-selectivities (entries 2–4), although a small amount (10%) of α-imidate **38** was produced as a byproduct of the reaction with **7**. It is noteworthy that glycosylation of diol **34** produced 1,2-*trans*-β-linked disaccharide **40** with essentially perfect regioselectivity and excellent stereoselectivity (α:β=1:99 and 2:98) (entries 4 and 5).[22] The difference in reaction mode between these donors may be explained by considering that 2-azido-2-deoxyglucosyl donor **2c** is a *trans*-fused bicyclic compound whereas 2-azido-2-deoxygalactosyl donor **4c** has a relatively flexible, *cis*-decaline-like architecture (Fig. 4). The greater conformational rigidity of **2c** relative to **4c** would serve to torsionally disarm the nitrilium ion intermediate with respect to formation of the *O*-glycosidic linkage.[20,23]

Table 8. TMSOTf-promoted glycosidation of 2-azido-4,6-*O*-benzylidene-2-deoxyglycosyl diphenyl phosphates **2c** and **4c** with acceptor alcohols[a]



2c, **4c** → **35**, **37**, **39**, **40**

Entry	Donor	ROH	Time, h	Glycoside		
					Yield, %	α:β[b]
1[c]	**2c**[d]	**7**	4	**35**	6[e]	8:92
2	**4c**[f]	**7**	3	**37**	78[g]	3:97
3	**4c**[f]	**8**	3	**39**	90	4:96
4	**4c**[f]	**34**	2	**40**	80	1:99
5	**4c**[h]	**34**	2	**40**	82	2:98

[a] The reaction was carried out on 0.1 mmol scale.
[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 20 or 60% AcOEt in hexane; flow rate 1.0 mL/min).
[c] The reaction was carried out at −45 °C.
[d] α:β=31:69.
[e] α-Imidate **36α** was obtained in 84% yield.
[f] α:β=95:5.
[g] α-Imidate **38** was obtained in 10% yield.
[h] α:β=0:100.

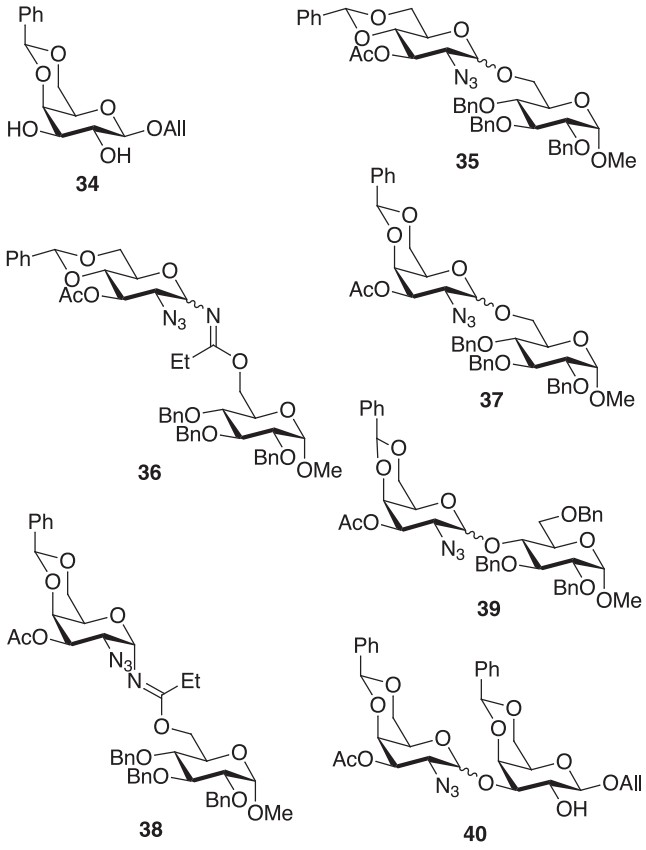
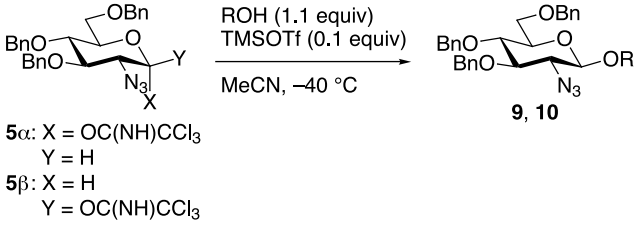


Figure 4. Acceptor alcohols and products in Table 8.

2.6. Comparative study

While high yields and excellent β-selectivities were achieved in the reactions of glycosyl diphenyl phosphates **2a**, **4a**, and **4c** with a range of acceptor alcohols, limitations of the phosphate method were recognized with donors **2b**, **2c**, and **4b**. To verify the effectiveness of the phosphate method, the scope of TMSOTf-promoted glycosidations of the corresponding trichloroacetimidates was examined. Although the exceptional power of the trichloroacetimidate method developed by Schmidt has been well demonstrated in numerous aminosugar-containing oligosaccharide syntheses,[24] a systematic investigation has yet to be described. The glycosidations were performed under frequently used conditions [cat. TMSOTf, acetonitrile, −40 °C].[8,22,24] Table 9 summarizes the results. TMSOTf (0.1 equiv)-catalyzed glycosidations of trichloroacetimidates **5α**[7b] or **5β**[25] with alcohols **7** and **8** proceeded to completion within 20 min, yielding high levels of β-selectivity similar to those of **2a** in propionitrile at −45 °C (entries 1 and 2 vs entry 2 in Table 4, and entries 3 and 4 vs entry 5 in Table 4). The stereochemical outcome observed was independent of the anomeric configuration of the donor similar to the phosphates. Somewhat surprisingly, evidence of the formation of imidate byproduct such as **11** could not be detected when alcohol **7** was used. Instead, a small amount

Table 9. TMSOTf-catalyzed glycosidation of 2-azido-2-deoxyglucosyl trichloroacetimidates **5**α and **5**β with alcohols **7** and **8** in acetonitrile[a]



Entry	Donor	ROH	Time, h	Glycoside		
					Yield, %	α:β[b]
1	**5**α	**7**	0.1	**9**	82[c]	3:97
2	**5**β	**7**	0.1	**9**	85	3:97
3	**5**α	**8**	0.3	**10**	50[d]	10:90
4	**5**β	**8**	0.3	**10**	68[e]	11:89
5[f]	**5**α	**8**	0.3	**10**	51[g]	12:88
6[f]	**5**β	**8**	0.3	**10**	84	12:88

[a] The reaction was carried out on 0.1 mmol scale.
[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% AcOEt in hexane; flow rate 1.0 mL/min).
[c] β-Trichloroacetamide **41** was obtained in 4% yield.
[d] Amide **41** and lactol **1a** were obtained in 28% and 4% yields, respectively.
[e] Amide **41** and lactol **1a** were obtained in 10% and 5% yields, respectively.
[f] In the presence of MS4A.
[g] Amide **41** was obtained in 35% yield.

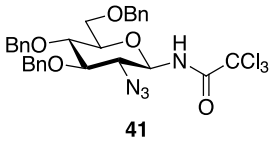


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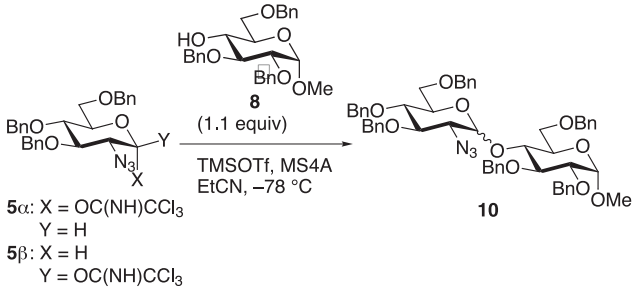
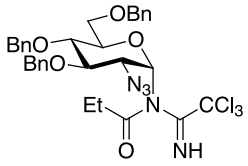
Table 10. TMSOTf-promoted glycosidation of 2-azido-2-deoxyglucosyl trichloroacetimidates **5**α and **5**β with alcohol **8** in propionitrile[a]



Entry	Donor	TMSOTf, equiv	Time, h	Glycoside **10**	
				Yield, %	α:β
1	**5**α	0.2	1	15	8:92[b]
2	**5**β	0.2	1	39	8:92[b]
3	**5**α	1.5	0.3	54[c]	7:93[d]
4	**5**β	1.5	0.3	85	9:91[d]

[a] The reaction was carried out on 0.1 mmol scale.
[b] Determined by 500 MHz ^{1}H NMR.
[c] Amidine **42** was obtained in 20% yield.
[d] Determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% AcOEt in hexane; flow rate 1.0 mL/min).



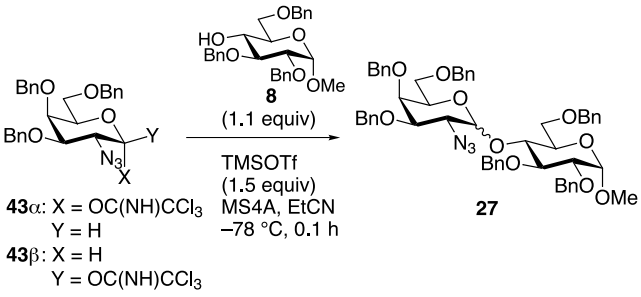
42

(4%) of β-trichloroacetamide **41** was obtained as a byproduct of the reaction of **5**α with **7** (entry 1), whereas **41** was not formed from **5**β (entry 2).[26] A moderate product yield in the reaction of **5**α with less reactive alcohol **8** was due to the formation of β-trichloroacetamide **41** (28%) and lactol **1a** (4%) (entry 3). The yield of byproduct **41** decreased to 10% with **5**β, thereby allowing a higher product yield (entry 4). A significant improvement in product yield (68→84%) was achieved when the reaction of **5**β with **8** was carried out in the presence of MS4A, whereas the beneficial effect was not observed with **5**α (entries 5 and 6). Although discrepancies between the behavior of α- and β-glycosyl trichloroacetimidates were observed in some cases,[27] the reason is currently unclear.

Next, glycosidation of trichloroacetimidates **5**α or **5**β with alcohol **8** in propionitrile at −78 °C were explored in order to determine whether the β-selectivity (α:β=12:88–10:90) observed in acetonitrile at −40 °C could be enhanced to the ratio (α:β=6:94) achieved with the phosphate method. Although the goal in terms of stereoselectivity could be virtually achieved using 0.2 equiv of TMSOTf, product yields were not preparatively useful (Table 10, entries 1 and 2). When using 1.5 equiv of TMSOTf, product yields from **5**α and **5**β were improved to 54 and 85%, respectively, without affecting the stereoselectivity (entries 3 and 4). α-Amidine byproduct **42** was obtained in 20% yield when **5**α was used, but β-trichloroacetamide **41** was not formed from either **5**α or **5**β. It is noteworthy that the formation of an amidine byproduct has not been reported in glycosidation reactions using trichloroacetimidates as glycosyl donors. It is also interesting that the reaction of **5**α with **8** in acetonitrile at −40 °C gave β-trichloroacetamide **41** as a major byproduct, whereas the same reaction in propionitrile at −78 °C afforded α-amidine **42** as a major one, but the reason is unclear. These results again demonstrated the superiority of donor **5**β over **5**α. From the results with **4a**, 2-azido-2-deoxygalactosyl trichloroacetimidates **43**α[7a] and **43**β[28] are anticipated to have greater reactivities than the corresponding glucosyl donors **5**α and **5**β. Indeed, the reactions with alcohol **8** in propionitrile at −78 °C in the presence of 1.5 equiv of TMSOTf proceeded to completion within 5 min (Table 11). Although virtually the same β-selectivities as those observed with phosphate **4a** were achieved, the product yields (48% from **43**α and 66% from **43**β) were unsatisfactory (Table 11 vs entry 2 in Table 6), due to the inevitable formation of β-trichloroacetamide **44** (37% from **43**α and 7% from **43**β) and α-amidine **45** (7% from **43**α and 7% from **43**β).

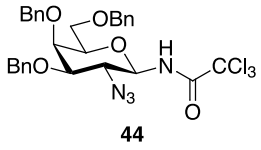
Two key findings emerged from this comparative study. (1) 2-Azido-2-deoxyglycosyl trichloroacetimidates generally exhibit higher reactivities than the corresponding diphenyl phosphates. (2) Only using β-imidates gives coupling products in good to high yields and with exceptionally

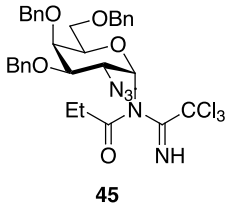
Table 11. TMSOTf-promoted glycosidation of 2-azido-2-deoxygalactosyl trichloroacetimidates **43**α and **43**β with alcohol **8** in propionitrile[a]



Entry	Donor	Glycoside **27**		**44**	**45**
		Yield, %	α:β[b]	Yield, %	Yield, %
1	**43**α	48	4:96	37	7
2	**43**β	66	4:96	7	7

[a] The reaction was carried out on 0.1 mmol scale.
[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% AcOEt in hexane; flow rate 1.0 mL/min).

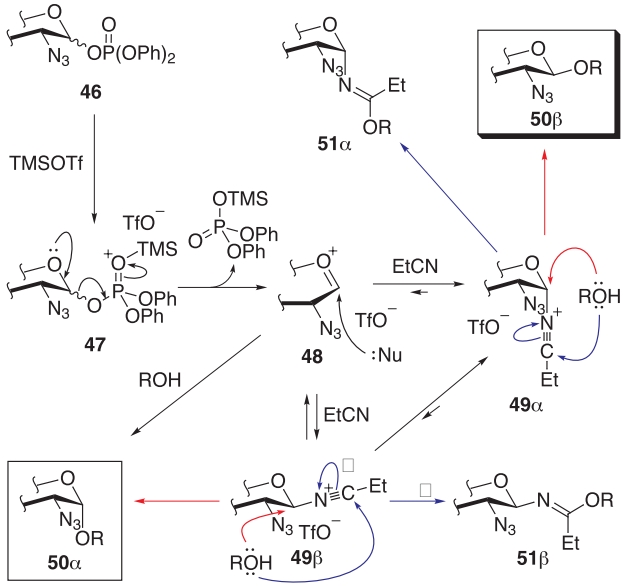




high levels of β-selectivity comparable to those found with an anomeric mixture of diphenyl phosphates, when the reactions are conducted in the presence of 1.5 equiv of TMSOTf in propionitrile at −78 °C.[29]

2.7. Mechanistic considerations

The beneficial effect of nitrile as a solvent on 1,2-*trans*-β-glycosidations without neighboring participation observed by Noyori and co-workers in 1984[30] is now a well-appreciated phenomenon in carbohydrate chemistry. In 1990 Fraser-Reid[31] and Schmidt[8] separately proposed that the β-selectivity could be given by an S_N2-like displacement at the anomeric carbon of kinetically formed α-nitrilium ion, which has been widely accepted.[32] It is evident that the so-called 'nitrile effect' plays a pivotal role in the TMSOTf-promoted glycosidations with 2-azido-2-deoxyglycosyl diphenyl phosphates since propionitrile at −78 °C is an excellent solvent for high levels of β-selectivity.[33] Scheme 1 outlines the possible reaction pathways. Diphenyl phosphate **46** is activated by silylation on the phosphoryl oxygen atom to cleave off the phosphate group, producing oxocarbenium ion **48** as a common intermediate. Intermediate **48** is rapidly trapped by propionitrile to form an anomeric mixture of nitrilium ions **49**α and **49**β associated with triflate as a counterion. In this step, the α-nitrilium ion **49**α preferentially forms over **49**β because of the stereoelectronically favored axial attack of propionitrile from the α-face.[34] In addition, **49**α benefits from anomeric stabilization.[35] On the kinetic and thermodynamic grounds, the equilibrium between these nitrilium ions would heavily lie to **49**α. The S_N2-like displacement by acceptor alcohols at the anomeric carbon of **49**α and **49**β affords glycosides **50**β and **50**α,

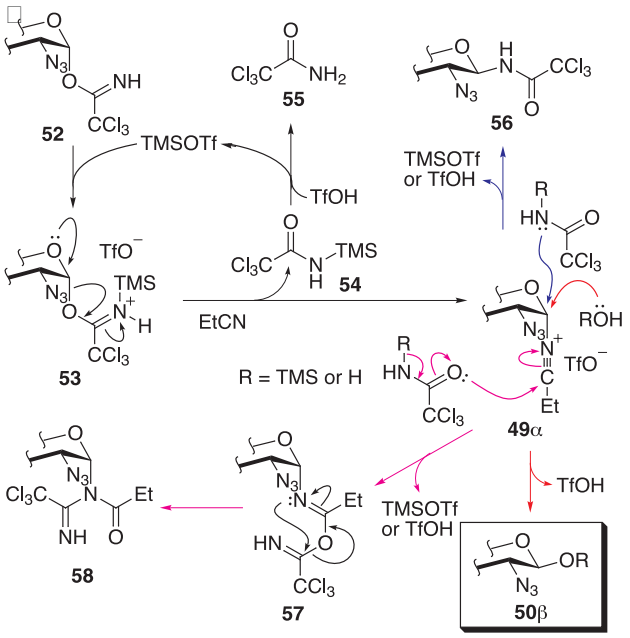


Scheme 1. A mechanistic rationale for TMSOTf-promoted glycosidation of 2-azido-2deoxyglycosyl diphenyl phosphates.

respectively, whereas capture of **49**α and **49**β by alcohols at the nitrilium carbon leads to the formation of imidate byproducts **51**α and **51**β, respectively. The chemoselectivity depends on the anomeric reactivity of glycosyl-nitrilium ions **49** influenced by the choice of protecting groups on 2-azido-2-deoxy-sugar components as well as the reactivity of acceptor alcohols, as is demonstrated by the foregoing experimental results. The exclusive formation of disaccharides was realized when the 3,4,6-tri-*O*-benzyl-protected glucosyl and galactosyl donors **2a** and **4a**, and the 4,6-*O*-benzylidene-protected galactosyl donor **4c** were used, although a small amount of imidates was produced as byproducts in the reaction with highly reactive *O*-6-unprotected glycoside alcohols. Hence, the high levels of β-selectivity observed here are attributed to a large equilibrium preference for **49**α as well as a high propensity of **49**α for an S_N2-like displacement.[6c] The stereochemical reaction course via a common oxocarbenium ion **48** is consistent with the fact that the stereoselectivities are irrespective of the anomeric configuration of the diphenyl phosphates used. Actually, it was found that glycosidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucosyl diphenyl phosphate **2a** ($\alpha:\beta = 2:98$) competes with the anomerization to α-phosphate via an internal return of the departing diphenyl phosphate group under the present reaction conditions. Of prime importance in terms of a mechanism is that only α-imidates **11**, **19**, and **38** were obtained as byproducts (5–10%) in the reaction of **2a** or **4c** with *O*-6-unprotected alcohols. Assuming that the much less stable β-nitrilium ion **49**β would have a reactivity comparable to **49**α toward the imidate formation, these results, along with the ^1H NMR analysis of the crude reaction mixture, which did not detect traces of β-imidates or their hydrolysates, provide evidence that α-nitrilium ion **49**α exclusively forms at least in these reactions. Along with the finding that the proportion of 1,2-*cis*-α-linked disaccharides slightly increased with less reactive alcohols compared to highly reactive ones, it seems likely that their formation would arise from the kinetically favored α-axial attack of alcohols

on the transient, solvent separated oxocarbenium ion **48** rather than the S_N2-like displacement of any **49**β. While the corresponding imidate byproduct could not be detected due to its increased hydrolytic lability for 3,4,6-tri-*O*-benzyl-protected galactosyl donor **4a**, highly efficient glycosidations of **4a** are also assumed to proceed in a similar manner as those of **2a** and **4c**. On the other hand, the behaviors of 3,4,6-tri-*O*-acetyl-protected glycosyl donors **2b** and **4b**, and 4,6-*O*-benzylidene-protected glucosyl donor **2c** are quite different from those of glycosyl donors **2a**, **4a** and **4c** mentioned above. Those reactions with alcohol **7** produced an anomeric mixture of imidates **30** (α:β=85:15), **32** (α:β=88:12), and **36** (α:β=91:9) as main products, along with small amounts of disaccharides **31**, **33**, and **35** with α:β ratios of 14:86, 3:97, and 8:92, respectively. It is interesting to note that the α:β ratios of imidates **30** and **36** in the D-gluco series are opposite to those of the corresponding disaccharides **31** and **35**, respectively. These relationships strongly suggest that glycosidations with electronically or torsionally disarmed 2-azido-2-deoxyglucosyl diphenyl phosphates proceed via an S_N2-like displacement, where the glucosyl-nitrilium ions **49** would be too stable to generate the solvent separated oxocarbenium ion **48**. However, this is not the case with 3,4,6-tri-*O*-acetyl-protected galactosyl diphenyl phosphate **4b** probably because the galactosyl nitrilium ions **49** may exhibit greater anomeric reactivities to allow for a dynamic equilibrium than the glucosyl counterparts.[20c,d]

Since TMSOTf-promoted glycosidations of 2-azido-2-deoxyglycosyl trichloroacetimidates exhibit essentially the same high β-selectivities as those found with diphenyl phosphates under identical conditions, the stereochemical reaction course seems to be analogous to that proposed with the phosphate method in Scheme 1. However, the product yields in the trichloroacetimidate method highly depends on the anomeric configuration of the starting donor and the reactivity of acceptor alcohols. Substantial amounts of β-trichloroacetamides and α-amidines were frequently obtained as byproducts when α-trichloroacetimidates were used as glycosyl donors. Although the striking difference between the behavior of α- and β-trichloroacetimidates currently cannot be explained, the formation of β-trichloroacetamides **56** and α-amidines **58** can be rationalized by the mechanism shown in Scheme 2. In glycosidations with trichloroacetimidates, the departing trichloroacetamide (**55**) and/or its TMS derivative **54** competes as a nucleophile with acceptor alcohols. No such reactions were observed in the phosphate method due to the low nucleophilicity of the diphenyl phosphate. The S_N2-like displacement by the amide nitrogen atom of **54** or **55** at the anomeric carbon of α-nitrilium ion **49**α leads to β-amides **56** with inversion of configuration, whereas the capture of **49**α by the amide oxygen atom of **54** or **55** at the nitrilium carbon followed by rearrangement produces α-amidines **58**. The stereocontrolled formation of β-amides **56** and α-amidines **58** again demonstrates the virtually exclusive intermediacy of α-nitrilium ion **49**α in glycosidations of the 3,4,6-tri-*O*-benzyl-protected glucosyl and galactosyl donors.



Scheme 2. Potential pathways in the TMSOTf-promoted glycosidation of 2-azido-2-deoxyglycosyl trichloroacetimidates.

3. Conclusion

The effectiveness of the diphenyl phosphate group as a leaving group of 2-azido-2-deoxyglycosyl donors has been demonstrated. We found that coupling of the 3,4,6-tri-*O*-benzyl-protected glucosyl and galactosyl donors and the 4,6-*O*-benzylidene-protected galactosyl donor with a range of glycoside alcohols in the presence of 1.5 equiv of TMSOTf in propionitrile at −78 °C proceeds smoothly to give 1,2-*trans*-β-linked disaccharides in high yields with α:β ratios ranging from 9:91 to 1:>99, regardless of the anomeric composition of the starting donor. The use of propionitrile as a solvent at −78 °C proved to be the best choice for the highest levels of β-selectivity reported to date for this type of glycosidation. However, limitations of the phosphate method were recognized for 3,4,6-tri-*O*-acetyl-protected glucosyl and galactosyl donors and 4,6-*O*-benzylidene-protected glucosyl donor. These results indicate that the properly choosing of protecting groups on 2-azido-2-deoxy-sugar components is crucial for the success in the present method. It has also been experimentally demonstrated that highly efficient and β-selective glycosidations proceed through intermediate α-glycosyl-nitrilium ions followed by an S_N2-like displacement, which is based on the finding that only α-imidates formed through their intermediate were small amounts of byproducts when highly reactive *O*-6-unprotected glycoside alcohols were used as a glycosyl acceptor. A comparative study with the corresponding trichloroacetimidates under the present reaction conditions demonstrated that similar high levels of β-selectivity are observed, but the phosphate method generally gives higher product yields than the trichloroacetimidate method. The latter method is frequently accompanied by side-products that originate from the departing trichloroacetamide, particularly when α-imidates are used. While the discrepancy in reaction mode between α- and β-trichloroacetimidates remains to be elucidated, only using β-trichloroacetimidates ensures a successful result. Thus, the present method would be a

potent alternative to Schmidt's trichloroacetimidate procedure.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were recorded on a JASCO P-1030 digital polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker ARX500 (500 MHz) spectrometer with tetramethylsilane (δ_H 0.00) as an internal standard. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL AL400 (100 MHz) or Bruker ARX500 (126 MHz) spectrometers with $CDCl_3$ (δ_C 77.0) as an internal standard. Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on JEOL EX270 (109 MHz) or Bruker ARX500 (202 MHz) spectrometers with H_3PO_4 (δ_P 0.00) as an external standard. Fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS HX110 spectrometer in the Center for Instrumental Analysis, Hokkaido University.

Column chromatography was carried out on Kanto silica gel 60 N (40–50 μm or 63–210 μm) or Wakogel C-200 (75–150 μm). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating. HPLC analyses were performed on a JASCO PU-980 and UV-970 (detector, $\lambda=254$ nm). Retention times (t_R) and peak ratios were determined with a Shimadzu Chromatopac C-R6A. Hexane was HPLC grade, and filtered and degassed prior to use.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Dehydrated stabilizer free THF was purchased from Kanto Chemical Co., Inc. Dichloromethane and propionitrile were distilled from P_2O_5, and redistilled from calcium hydride prior to use. Molecular sieves 4 Å was finely ground in mortar and heated in vacuo at 220 °C for 12 h.

All reactions were conducted under an argon atmosphere. Lactols **1a**,[7b] **1b**,[7a] **3a**,[7a] **3b**[36] and **3c**[37] were prepared according to literature procedures. For full characterization, most of the authentic α-glycosides were prepared by glycosidations of diphenyl phosphates with acceptor alcohols in Et_2O at 0 °C, followed by chromatographic separation from the β-glycosides. Glycosides **31**, **33** and **35** were prepared by reactions of diphenyl phosphates with alcohol **7** in CH_2Cl_2 at −30 °C, followed by column chromatography.

4.2. Preparation of 2-azido-2-deoxy-D-glycosyl donors

4.2.1. Typical procedure for preparation of 2-azido-2-deoxyglycopyranosyl diphenyl phosphate: 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl diphenyl phosphate (2a). Diphenylphosphoryl chloride (0.55 mL, 2.66 mmol) was added to a stirred solution of **1a**[7b] (1.10 g, 2.31 mmol) and DMAP (564 mg, 4.62 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 0.5 h, the reaction was quenched with crushed ice, followed by stirring at room temperature for 15 min. The mixture was poured into a two-layer mixture of Et_2O (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the whole was extracted with AcOEt (40 mL). The organic layer was washed with brine (2× 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (1.70 g), which was purified by column chromatography (silica gel 30 g, 2:1 hexane/AcOEt with 2% Et_3N) to give diphenyl phosphate **2a** (1.59 g, 97%, $\alpha:\beta=72:28$) as a colorless oil. The anomeric $\alpha:\beta$ ratio of the diphenyl phosphate was determined by ^{31}P NMR.

Data for α-anomer (**2aα**): TLC $R_f=0.42$ (2:1 hexane/AcOEt); $[\alpha]_D^{14}=+38.1°$ (c 1.14, $CHCl_3$) ($\alpha:\beta=85:15$); IR (film) 3022, 2872, 2870, 2116, 1591, 1491, 1288, 1059, 1188, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.35 (brd, $J=10.9$ Hz, 1H, H-6a), 3.61 (ddd, $J=3.4$, 9.8, 3.3 (J_{H-P}) Hz, 1H, H-2), 3.64 (dd, $J=1.0$, 10.9 Hz, 1H, H-6b), 3.79–3.85 (m, 2H, H-4, H-5), 3.88 (m, 1H, H-3), 4.43 (d, $J=11.1$ Hz, 1H, OC*H*Ph), 4.536 (d, $J=11.1$ Hz, 1H, OC*H*Ph), 4.537 (d, $J=10.9$ Hz, 1H, OC*H*Ph), 4.78 (d, $J=10.9$ Hz, 1H, OC*H*Ph), 4.82 (d, $J=10.7$ Hz, 1H, OC*H*Ph), 4.86 (d, $J=10.7$ Hz, 1H, OC*H*Ph), 5.98 (dd, $J=3.4$, 6.1 (J_{H-P}) Hz, 1H, H-1), 7.15–7.35 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 63.5 (d, $J_{C-P}=8.6$ Hz), 67.4, 73.2, 73.5, 75.1, 75.6, 80.0, 97.3 (d, $J_{C-P}=6.3$ Hz, C-1), 120.1 (d, $J_{C-P}=5.0$ Hz), 120.3 (d, $J_{C-P}=5.0$ Hz), 125.4, 125.5, 127.7, 127.77, 127.83, 127.9, 128.0, 128.1, 128.4, 128.45, 128.48, 129.7, 129.8, 137.6, 137.66, 137.70, 150.38 (d, $J_{C-P}=7.5$ Hz), 150.44 (d, $J_{C-P}=7.5$ Hz); ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.3; FAB-HRMS m/z calcd for $C_{39}H_{39}N_3O_8P$ $(M+H)^+$ 708.2474, found 708.2476; Anal. calcd for: $C_{39}H_{38}N_3O_8P$: C, 66.19; H, 5.41; N, 5.94, found C, 66.06; H, 5.54; N, 5.82. Data for β-anomer (**2aβ**): TLC $R_f=0.38$ (2:1 hexane/AcOEt); $[\alpha]_D^{22}=+2.69°$ (c 1.33, $CHCl_3$) ($\alpha:\beta=5:95$); IR (film) 3022, 2872, 2870, 2116, 1591, 1491, 1288, 1059, 1188, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.47–3.54 (m, 3H, H-2, H-4, H-5), 3.63 (dd, $J=1.7$, 11.1 Hz, 1H, H-6a), 3.73 (dd, $J=3.6$, 11.1 Hz, 1H, H-6b), 3.76 (t, $J=9.1$ Hz, 1H, H-3), 4.45 (d, $J=12.0$ Hz, 1H, OC*H*Ph), 4.55 (d, $J=12.0$ Hz, 1H, OC*H*Ph), 4.58 (d, $J=10.9$ Hz, 1H, OC*H*Ph), 4.78 (d, $J=10.9$ Hz, 1H, OC*H*Ph), 4.82 (d, $J=11.0$ Hz, 1H, OC*H*Ph), 4.86 (d, $J=11.0$ Hz, 1H, OC*H*Ph), 5.15 (dd, $J=7.3$, 7.3 (J_{H-P}) Hz, 1H, H-1), 7.16–7.34 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.5 (d, $J_{C-P}=9.2$ Hz), 67.9, 73.6, 75.0, 75.7, 75.9, 82.9, 98.2 (d, $J_{C-P}=5.5$ Hz, C-1), 120.1 (d, $J_{C-P}=5.0$ Hz), 120.5 (d, $J_{C-P}=5.0$ Hz), 125.5, 125.6, 127.68, 127.71, 127.8, 127.9, 128.0, 128.1, 128.4, 128.46, 128.48, 129.6, 129.8, 137.6, 137.7, 137.9, 150.3, (d, $J_{C-P}=7.5$ Hz), 150.5 (d, $J_{C-P}=7.5$ Hz); ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.5; FAB-HRMS m/z calcd for $C_{39}H_{39}N_3O_8P$ $(M+H)^+$ 708.2474, found 708.2490.

4.2.2. 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranosyl diphenyl phosphate (2b). The reaction was performed according to the typical procedure (10 mL CH_2Cl_2, 0 °C, 0.5 h) employing lactol **1b**[7a] (754 mg, 2.28 mmol), diphenylphosphoryl chloride (0.66 mL, 3.19 mmol), and DMAP (557 mg, 4.56 mmol). The crude product (1.53 g) was purified by column chromatography (silica gel 40 g, 1.5:1 hexane/AcOEt with 1% Et_3N) to give diphenyl phosphate **2b** (1.28 g, 99%, α:β=46:54) as a pale yellow syrup. TLC R_f=0.50 (1:1 hexane/AcOEt); $[\alpha]_D^{18}$=+48.0° (*c* 1.35, $CHCl_3$) (α:β=46:54); IR (film) 2116, 1753, 1591, 1489, 1188, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 1.5H, CH_3CO), 2.02 (s, 1.5H, CH_3CO), 2.03 (s, 1.5H, CH_3CO), 2.04 (s, 1.5H, CH_3CO), 2.08 (s, 1.5H, CH_3CO), 2.10 (s, 1.5H, CH_3CO), 3.64 (m, 0.5H, H-2β), 3.72 (ddd, *J*=3.4, 10.4, 3.3 (J_{H-P}) Hz, 0.5H, H-2α), 3.76 (m, 0.5H, H-5β), 3.80 (dd, *J*=2.1, 12.6 Hz, 0.5H, H-6aα), 4.00 (dd, *J*=2.3, 12.5 Hz, 0.5H, H-6aβ), 4.03 (ddd, *J*=2.1, 3.9, 10.4 Hz, 0.5H, H-5α), 4.17 (dd, *J*=3.9, 12.6 Hz, 0.5H, H-6bα), 4.22 (dd, *J*=4.8, 12.5 Hz, 0.5H, H-6bβ), 5.02–5.11 (m, 1.5H, H-4α, H-3β, H-4β), 5.24 (dd, *J*=7.8, 7.8 (J_{H-P}) Hz, 0.5H, H-1β), 5.45 (dd, *J*=9.9, 10.4 Hz, 0.5H, H-3α), 6.01 (dd, *J*=3.4, 6.4 (J_{H-P}) Hz, 0.5H, H-1α), 7.20–7.38 (m, 10H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.36, 20.38, 20.41, 20.5, 60.8, 60.9 (d, J_{C-P}=8.9 Hz), 61.2, 63.9 (d, J_{C-P}=9.8 Hz), 67.4, 67.6, 69.7, 70.3, 72.4, 72.5, 96.1 (d, J_{C-P}=5.5 Hz, C-1α), 97.6 (d, J_{C-P}=5.0 Hz, C-1β), 119.88, 119.92, 120.0, 120.15, 120.19, 120.23, 120.3, 125.56, 125.62, 129.6, 129.7, 129.8, 150.0, 150.06, 150.10, 150.12, 150.15, 150.16, 169.36, 169.39, 169.5, 169.7, 170.2; ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.6 (β), −13.2 (α); FAB-HRMS *m*/*z* calcd for $C_{24}H_{27}N_3O_{11}P$ $(M+H)^+$ 564.1383, found 564.1379; Anal. calcd for: $C_{24}H_{26}N_3O_{11}P$: C, 51.16; H, 4.65; N, 7.46, found C, 51.16; H, 4.71; N, 7.60.

4.2.3. 3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose (1c). Tetrabutylammonium fluoride in THF (1.0 M, 2.50 mL, 2.50 mmol) was added to a stirred solution of *tert*-butyldimethylsilyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[38] (850 mg, 1.89 mmol) in THF (10 mL)—AcOH (0.16 mL) at 0 °C. After stirring for 15 min, saturated aqueous $NaHCO_3$ (3 mL) was added, and the whole was extracted with AcOEt (50 mL). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (2× 10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.02 g), which was purified by column chromatography (silica gel 30 g, 2:1 hexane/AcOEt) to give lactol **1c** (621 mg, 98%, α:β=52:48) as a white amorphous. The anomeric α:β ratio of the lactol was determined by ^1H NMR. TLC R_f=0.23 (2:1 hexane/AcOEt); $[\alpha]_D^{23}$=−7.49° (*c* 1.02, $CHCl_3$) (α:β=52:48); IR (KBr) 3468, 2868, 2112, 1726, 1452, 1371, 1259, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.33 (dd, *J*=3.6, 10.3 Hz, 0.5H, H-2α), 3.37 (br, 0.5H, O*H*), 3.45 (dd, *J*=8.0, 10.0 Hz, 0.5H, H-2β), 3.49 (ddd, *J*=5.0, 9.6, 10.4 Hz, 0.5H, H-5β), 3.63 (dd, *J*=9.5, 9.6 Hz, 1H, H-4α, H-4β), 3.73 (dd, *J*=10.3, 10.4 Hz, 0.5H, H-6axα), 3.77 (dd, *J*=10.4, 10.6 Hz, 0.5H, H-6axβ), 3.97 (br, 0.5H, O*H*), 4.19 (ddd, *J*=5.0, 9.5, 10.3 Hz, 0.5H, H-5α), 4.28 (dd, *J*=5.0, 10.4 Hz, 0.5H, H-6eqα), 4.32 (dd, *J*=5.0, 10.6 Hz, 0.5H, H-6eqβ), 4.77 (d, *J*=8.0 Hz, 0.5H, H-1β), 5.17 (dd, *J*=9.5, 10.0 Hz, 0.5H, H-3β), 5.35 (brd, *J*=3.6 Hz, 0.5H, H-1α), 5.48 (s, 0.5H, C*H*Ph), 5.50 (s, 0.5H, C*H*Ph), 5.64 (dd, *J*=9.6, 10.3 Hz, 0.5H, H-3α), 7.34–7.38 (m, 3H, Ar-H), 7.40–7.45 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 62.2, 62.7, 65.7, 66.5, 68.3, 68.8, 69.1, 71.3, 78.6, 79.4, 93.1 (C-1α), 96.6 (C-1β), 101.5, 101.7, 126.1, 126.2, 128.2, 129.2, 136.6, 136.8, 170.0, 170.1; FAB-HRMS *m*/*z* calcd for $C_{15}H_{18}N_3O_6$ $(M+H)^+$ 336.1196, found 336.1193.

4.2.4. 3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosyl diphenyl phosphate (2c). The reaction was performed according to the typical procedure (8 mL, CH_2Cl_2, 0 °C, 0.5 h) employing lactol **1c** (621 mg, 1.85 mmol), diphenylphosphoryl chloride (0.50 mL, 2.41 mmol), and DMAP (476 mg, 3.90 mmol). The crude product (1.14 g) was purified by column chromatography (silica gel 40 g, 2:1 hexane/AcOEt with 1% Et_3N) to give diphenyl phosphates **2c**β (714 mg, 68%, white solid) and **2c**α (324 mg, 31%, colorless syrup). Data for α-anomer (**2c**α): mp 103.0–105.0 °C (AcOEt–hexane); TLC R_f=0.20 (2:1 hexane/AcOEt); $[\alpha]_D^{22}$=+48.1° (*c* 1.50, $CHCl_3$); IR (film) 2868, 2114, 1753, 1589, 1489, 1371, 1219, 1186, 954 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.60–3.66 (m, 3H, H-2, H-4, H-6ax), 3.89–3.95 (m, 2H, H-5, H-6eq), 5.45 (s, 1H, C*H*Ph), 5.58 (t, *J*=9.9 Hz, 1H, H-3), 5.99 (dd, *J*=3.5, 6.5 (J_{H-P}) Hz, 1H, H-1), 7.21 (m, 2H, Ar-H), 7.25–7.31 (m, 4H, Ar-H), 7.35–7.42 (m, 9H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 61.7 (d, J_{C-P}= 8.9 Hz), 64.6, 68.0, 68.9, 78.4, 96.9 (d, J_{C-P}=5.5 Hz, C-1), 101.1, 119.9 (d, J_{C-P}=5.0 Hz), 120.2 (d, J_{C-P}=5.0 Hz), 125.6, 126.0, 128.1, 129.1, 129.7, 129.8, 136.5, 150.1, (d, J_{C-P}=5.0 Hz), 150.2 (d, J_{C-P}=5.0 Hz), 169.4; ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.0; FAB-HRMS *m*/*z* calcd for $C_{27}H_{27}N_3O_9P$ $(M+H)^+$ 568.1485, found 568.1467. Data for β-anomer (**2c**β): TLC R_f=0.39 (2:1 hexane/AcOEt); $[\alpha]_D^{22}$=−52.8° (*c* 1.50, $CHCl_3$); IR (film) 2868, 2114, 1755, 1589, 1489, 1371, 1219, 1186, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 3.56 (ddd, *J*= 4.9, 9.6, 10.2 Hz, 1H, H-5), 3.63 (m, 1H, H-2), 3.65 (dd, *J*= 9.6, 10.3 Hz, 1H, H-4), 3.67 (dd, *J*=10.2, 10.4 Hz, 1H, H-6ax), 4.23 (dd, *J*=4.9, 10.4 Hz, 1H, H-6eq), 5.22 (dd, *J*= 8.9, 10.3 Hz, 1H, H-3), 5.31 (dd, *J*=7.7, 7.9 (J_{H-P}) Hz, 1H, H-1), 5.46 (s, 1H, C*H*Ph), 7.20–7.27 (m, 6H, Ar-H), 7.34–7.41 (m, 9H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5, 64.7 (d, J_{C-P}=8.8 Hz), 66.8, 67.7, 71.1 (d, J_{C-P}=1.1 Hz), 77.7, 98.0 (d, J_{C-P}=5.0 Hz, C-1), 101.4, 119.8 (d, J_{C-P}= 5.0 Hz), 120.1 (d, J_{C-P}=5.0 Hz), 125.5, 125.6, 125.9, 128.1, 129.0, 129.6, 129.7, 136.4, 150.05, (d, J_{C-P}= 6.3 Hz), 150.11 (d, J_{C-P}=6.3 Hz), 169.2; ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.8; FAB-HRMS *m*/*z* calcd for $C_{27}H_{27}N_3O_9P$ $(M+H)^+$ 568.1485, found 568.1468; Anal. calcd for $C_{27}H_{26}N_3O_9P$: C, 57.15; H, 4.62; N, 7.40, found C, 57.22; H, 4.61; N, 7.49.

4.2.5. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl diphenyl phosphate (4a). The reaction was performed according to the typical procedure (10 mL CH_2Cl_2, 0 °C, 0.5 h) with lactol **3a**[7a] (1.10 g, 2.31 mmol), diphenylphosphoryl chloride (0.63 mL, 3.02 mmol), and DMAP (567 mg, 4.63 mmol). The crude product (1.68 g) was purified by column chromatography (silica gel 40 g, 3:1 hexane/AcOEt with 2% Et_3N) to give diphenyl phosphate **4a** (1.30 g, 79%, α:β=58:42) as a colorless syrup. TLC

R_f=0.45 (α), 0.31 (β) (2:1 hexane/AcOEt); $[\alpha]_D^{22}$=+55.3° (*c* 1.50, $CHCl_3$) (α:β=90:10); IR (film) 3032, 2872, 2114, 1591, 1489, 1290, 1188, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (dd, *J*=5.4, 9.0 Hz, 0.6H, H-6aα), 3.39 (dd, *J*=2.7, 10.4 Hz, 0.4H, H-3β), 3.45 (dd, *J*=4.7, 8.5 Hz, 0.4H, H-6aβ), 3.56 (dd, *J*=8.1, 9.0 Hz, 0.6H, H-6bα), 3.58 (dd, *J*=8.0, 8.5 Hz, 0.4H, H-6bβ), 3.61 (dd, *J*=4.7, 8.0 Hz, 0.4H, H-5β), 3.86 (dd, *J*=2.5, 10.5 Hz, 0.6H, H-3α), 3.90 (dd, *J*=8.0, 10.4 Hz, 0.4H, H-2β), 3.92 (d, *J*=2.7 Hz, 0.4H, H-4β), 4.01 (dd, *J*=5.4, 8.1 Hz, 0.6H, H-5α), 4.05 (brs, 0.6H, H-4α), 4.10 (ddd, *J*=3.3, 10.5, 3.2 (J_{H-P}) Hz, 0.6H, H-2α), 4.36 (d, *J*=12.6 Hz, 0.6H, OC*H*Ph), 4.38 (d, *J*=12.6 Hz, 0.6H, OC*H*Ph), 4.39 (d, *J*=11.6 Hz, 0.4H, OC*H*Ph), 4.41 (d, *J*=11.6 Hz, 0.4H, OC*H*Ph), 4.52 (d, *J*=11.2 Hz, 0.6H, OC*H*Ph), 4.55 (d, *J*=11.4 Hz, 0.4H, OC*H*Ph), 4.64 (d, *J*=11.7 Hz, 0.4H, OC*H*Ph), 4.65 (d, *J*=11.4 Hz, 0.6H, OC*H*Ph), 4.69 (d, *J*=11.7 Hz, 0.4H, OC*H*Ph), 4.71 (d, *J*=11.4 Hz, 0.6H, OC*H*Ph), 4.85 (d, *J*=11.2 Hz, 0.6H, OC*H*Ph), 4.87 (d, *J*=11.4 Hz, 0.4H, OC*H*Ph), 5.09 (dd, *J*=8.0, 7.2 (J_{H-P}) Hz, 0.4H, H-1β), 5.94 (dd, *J*=3.3, 5.7 (J_{H-P}) Hz, 0.6H, H-1α), 7.11–7.39 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.4 (d, J_{C-P}=8.4 Hz), 63.1 (d, J_{C-P}=9.1 Hz), 67.4, 67.5, 71.5, 72.0, 72.4, 72.5, 73.30, 73.34, 74.2, 74.6, 74.8, 77.0, 77.2, 80.4 (d, J_{C-P}=2.4 Hz), 97.8 (d, J_{C-P}=5.9 Hz, C-1α), 98.3 (d, J_{C-P}=5.2 Hz, C-1β), 119.9 (d, J_{C-P}=5.0 Hz), 120.0 (d, J_{C-P}=5.0 Hz), 120.1 (d, J_{C-P}=5.0 Hz), 120.4 (d, J_{C-P}=5.0 Hz), 125.2, 125.3, 125.4, 125.5, 127.60, 127.64, 127.67, 127.73, 127.8, 127.86, 127.89, 128.15, 128.18, 128.3, 128.4, 129.4, 129.5, 129.6, 129.7, 137.08, 137.12, 137.5, 137.9, 138.0, 150.2 (d, J_{C-P}=7.5 Hz), 150.30 (d, J_{C-P}=7.5 Hz), 150.31 (d, J_{C-P}=7.5 Hz), 150.36 (d, J_{C-P}=7.5 Hz); ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.32 (β), −13.25 (α); FAB-HRMS *m/z* calcd for $C_{39}H_{39}N_3O_8P$ $(M+H)^+$ 708.2474, found 708.2451; Anal. calcd for $C_{39}H_{38}N_3O_8P$: C, 66.19; H, 5.41; N, 5.94, found C, 66.35; H, 5.59; N, 5.85.

4.2.6. 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl diphenyl phosphate (4b). The reaction was performed according to the typical procedure (10 mL CH_2Cl_2, 0 °C, 0.5 h) with lactol **3b**[36] (994 mg, 3.00 mmol), diphenylphosphoryl chloride (0.81 mL, 3.90 mmol), and DMAP (953 mg, 7.80 mmol). The crude product (1.96 g) was purified by column chromatography (silica gel 40 g, 2:1 hexane/AcOEt) to give diphenyl phosphate **4b** (1.64 g, 97%, α:β=24:76) as a colorless syrup. Data for α-anomer (**4b**α): TLC R_f=0.58 (10:1 CH_2Cl_2/acetone); $[\alpha]_D^{24}$=+74.2° (*c* 1.50, $CHCl_3$); IR (film) 2116, 1753, 1591, 1489, 1371, 1226, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.90 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.14 (s, 3H, CH_3CO), 3.86 (dd, *J*=6.4, 11.3 Hz, 1H, H-6a), 3.96 (ddd, *J*=3.3, 11.0, 3.2 (J_{H-P}) Hz, 1H, H-2), 4.06 (dd, *J*=6.8, 11.3 Hz, 1H, H-6b), 4.29 (dd, *J*=6.4, 6.8 Hz, 1H, H-5), 5.30 (dd, *J*=3.2, 11.0 Hz, 1H, H-3), 5.46 (brd, *J*=3.2 Hz, 1H, H-4), 6.04 (dd, *J*=3.3, 6.1 (J_{H-P}) Hz, 1H, H-1), 7.21 (m, 2H, Ar-H), 7.25–7.28 (m, 4H, Ar-H), 7.34–7.38 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4, 20.47, 20.50, 57.4 (d, J_{C-P}=8.7 Hz), 60.8, 66.7, 68.4, 68.7, 96.7 (d, J_{C-P}=5.5 Hz, C-1), 120.0 (d, J_{C-P}=5.0 Hz), 120.2 (d, J_{C-P}=5.0 Hz), 125.60, 125.63, 129.7, 129.8, 150.2 (d, J_{C-P}=6.3 Hz), 150.3 (d, J_{C-P}=6.3 Hz), 169.6, 169.8, 170.1; ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.1; FAB-HRMS *m/z* calcd for $C_{24}H_{27}N_3O_{11}P$ $(M+H)^+$ 564.1383, found 564.1368. Data for β-anomer (**4b**β): TLC R_f=0.42 (10:1 CH_2Cl_2/acetone); $[\alpha]_D^{24}$=+5.60° (*c* 1.50, $CHCl_3$); IR (film) 2116, 1753, 1591, 1489, 1371, 1226, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.16 (s, 3H, CH_3CO), 3.82 (dd, *J*=8.2, 10.7 Hz, 1H, H-2), 3.97 (dt, *J*=0.6, 6.5 Hz, 1H, H-5), 4.02 (dd, *J*=6.5, 11.0 Hz, 1H, H-6a), 4.10 (dd, *J*=6.5, 11.0 Hz, 1H, H-6b), 4.87 (dd, *J*=3.3, 10.7 Hz, 1H, H-3), 5.24 (dd, *J*=8.2, 7.4 (J_{H-P}) Hz, 1H, H-1), 5.36 (dd, *J*=0.6, 3.3 Hz, 1H, H-4), 7.22 (m, 2H, Ar-H), 7.26–7.28 (m, 4H, Ar-H), 7.34–7.37 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4, 20.5, 60.7, 61.0 (d, J_{C-P}=9.4 Hz), 65.9, 71.2 (d, J_{C-P}=1.6 Hz), 71.8, 98.1 (d, J_{C-P}=5.3 Hz, C-1), 120.0 (d, J_{C-P}=3.4 Hz), 120.3 (d, J_{C-P}=3.4 Hz), 125.6, 125.7, 129.7, 129.8, 150.2 (d, J_{C-P}=8.8 Hz), 150.3 (d, J_{C-P}=8.8 Hz), 169.5, 169.8, 170.2; ^{31}P NMR (109 MHz, $CDCl_3$) δ −13.5; FAB-HRMS *m/z* calcd for $C_{24}H_{27}N_3O_{11}P$ $(M+H)^+$ 564.1383, found 564.1385; Anal. calcd for: $C_{24}H_{26}N_3O_{11}P$: C, 51.16; H, 4.65; N, 7.46, found C, 51.02; H, 4.72; N, 7.47.

4.2.7. 3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl diphenyl phosphate (4c). The reaction was performed according to the typical procedure (6 mL CH_2Cl_2, 0 °C, 0.5 h) employing lactol **3c**[37] (350 mg, 1.04 mmol), diphenylphosphoryl chloride (0.28 mL, 1.36 mmol), and DMAP (254 mg, 2.08 mmol). The crude product (530 mg) was purified by column chromatography (silica gel 25 g, 2:1→1:1 hexane/AcOEt with 1% Et_3N) to give diphenyl phosphates **4c**α (295 mg, 50%) and **4c**β (147 mg, 25%) as white amorphous. Data for α-anomer (**4c**α): TLC R_f=0.44 (1:1 hexane/AcOEt); $[\alpha]_D^{24}$=+152.5° (*c* 1.50, $CHCl_3$); IR (KBr) 3069, 2922, 2116, 1747, 1591, 1489, 1224, 1188, 958, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.66 (brs, 1H, H-5), 3.83 (dd, *J*=1.0, 13.0 Hz, 1H, H-6a), 3.95 (dd, *J*=0.9, 13.0 Hz, 1H, H-6b), 4.20 (ddd, *J*=3.2, 11.0, 3.2 (J_{H-P}) Hz, 1H, H-2), 4.42 (brd, *J*=5.4 Hz, 1H, H-4), 5.23 (dd, *J*=3.3, 11.0 Hz, 1H, H-3), 5.46 (s, 1H, C*H*Ph), 6.10 (dd, *J*=3.2, 6.0 (J_{H-P}) Hz, 1H, H-1), 7.18 (m, 2H, Ar-H), 7.25–7.38 (m, 11H, Ar-H), 7.46 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 57.0 (d, J_{C-P}=8.6 Hz), 64.3, 68.3, 69.4, 72.6, 97.6 (d, J_{C-P}=5.0 Hz, C-1), 100.6, 120.0 (d, J_{C-P}=5.0 Hz), 120.2 (d, J_{C-P}=5.0 Hz), 125.4, 125.5, 126.0, 128.1, 129.1, 129.67, 129.72, 137.1, 150.2, (d, J_{C-P}=4.4 Hz), 150.3 (d, J_{C-P}=4.4 Hz), 170.2; ^{31}P NMR (202 MHz, $CDCl_3$) δ −12.9; FAB-HRMS *m/z* calcd for $C_{27}H_{27}N_3O_9P$ $(M+H)^+$ 568.1485, found 568.1501; Anal. calcd for: $C_{27}H_{26}N_3O_9P$: C, 57.15; H, 4.62; N, 7.40, found C, 57.20; H, 4.64; N, 7.39. Data for β-anomer (**4c**β): TLC R_f=0.28 (1:1 hexane/AcOEt); $[\alpha]_D^{26}$=+73.8° (*c* 1.50, $CHCl_3$); IR (KBr) 3069, 2905, 2118, 1749, 1591, 1491, 1371, 1294, 1186, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3CO), 3.56 (brs, 1H, H-5), 3.95 (dd, *J*=1.3, 12.5 Hz, 1H, H-6a), 4.00 (dd, *J*=8.2, 10.8 Hz, 1H, H-2), 4.17 (dd, *J*=1.2, 12.5 Hz, 1H, H-6b), 4.34 (d, *J*=3.3 Hz, 1H, H-4), 4.78 (dd, *J*=3.3, 10.8 Hz, 1H, H-3), 5.25 (dd, *J*=8.2, 6.7 (J_{H-P}) Hz, 1H, H-3), 5.49 (s, 1H, C*H*Ph), 7.18 (m, 2H, Ar-H), 7.24–7.43 (m, 11H, Ar-H), 7.51 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 60.5 (d, J_{C-P}=10.1 Hz), 67.0, 68.3, 72.0, 72.2 (d, J_{C-P}=1.5 Hz), 98.2 (d, J_{C-P}=5.0 Hz, C-1), 100.8, 120.0 (d, J_{C-P}=5.0 Hz), 120.7 (d, J_{C-P}=5.0 Hz), 125.5, 126.2, 128.2, 129.2, 129.6, 129.7, 137.4, 150.2 (d, J_{C-P}=6.3 Hz), 150.3 (d, J_{C-P}=7.5 Hz),

170.1; ^{31}P NMR (202 MHz, $CDCl_3$) δ −13.1; FAB-HRMS *m/z* calcd for $C_{27}H_{27}N_3O_9P$ $(M+H)^+$ 568.1485, found 568.1470.

4.2.8. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl diphenyl phosphate (2a) (α:β=2:98). Diphenyl phosphate (207 mg, 0.83 mmol) was added to a stirred solution of **5**α[7b] (514 mg, 0.83 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After 0.1 h, the mixture was poured into a two-layer mixture of Et_2O (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole was extracted with AcOEt (30 mL). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (735 mg), which was purified by column chromatography (silica gel 15 g, 2:1 hexane/AcOEt with 2% Et_3N) to give diphenyl phosphate **2a** (507 mg, 86%, α:β=2:98) as a colorless oil. The anomeric α:β ratio of the product was determined by ^{31}P NMR.

4.2.9. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (6). Butyllithium in hexane (1.56 M, 0.3 mL, 0.468 mmol) was added to a stirred solution of **1a** (212 mg, 0.446 mmol) in THF (5.0 mL) at −78 °C. After 15 min, a solution of bis(dimethylamino)phosphoryl chloride (0.067 mL, 0.450 mmol) in HMPA (0.5 mL) was added, and the mixture was allowed to warm to −20 °C over 30 min. After stirring at this temperature for 2 h, the reaction was quenched with crushed ice, followed by stirring at 0 °C for 30 min. The mixture was poured into a two-layer mixture of Et_2O (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole was extracted with AcOEt (20 mL). The organic layer was washed with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the yellow residue (301 mg), which was purified by column chromatography (silica gel 8 g, 1:1→1:2 hexane/AcOEt) to give diamidate **6** (238 mg, 87%, α:β=67:33) as a colorless oil. The anomeric α:β ratio of the product was determined by ^{31}P NMR. TLC R_f=0.31 (AcOEt); $[\alpha]_D^{22}$=+13.9° (*c* 1.27, $CHCl_3$) (α:β=67:33); IR ($CHCl_3$) 3034, 2932, 2114, 1454, 1305, 1215, 995 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (d, J_{H-P}=10.1 Hz, 4.2H, N(C*H*$_3$)$_2$), 2.63 (d, J_{H-P}=10.4 Hz, 1.8H, N(C*H*$_3$)$_2$), 2.66 (d, J_{H-P}=10.2 Hz, 4.2H, N(C*H*$_3$)$_2$), 2.69 (d, J_{H-P}=10.3 Hz, 1.8H, N(C*H*$_3$)$_2$), 3.44–3.52 (m, 0.9H, H-2β, H-3β, H-5β), 3.61 (ddd, *J*=3.4, 10.1, 1.4 (J_{H-P}) Hz, 0.7H, H-2α), 3.64–3.69 (m, 1H, H-6aα, H-6aβ), 3.71–3.79 (m, 2H, H-4α, H-6bα, H-4β, H-6bβ), 3.88 (dd, *J*=9.0, 10.1 Hz, 0.7H, H-3α), 3.94 (ddd, *J*=1.8, 3.1, 10.0 Hz, 0.7H, H-5α), 4.49 (d, *J*=12.0 Hz, 0.7H, OC*H*Ph), 4.51 (d, *J*=12.1 Hz, 0.3H, OC*H*Ph), 4.561 (d, *J*=12.1 Hz, 0.3H, OC*H*Ph), 4.562 (d, *J*=10.7 Hz, 0.7H, OC*H*Ph), 4.60 (d, *J*=10.9 Hz, 0.3H, OC*H*Ph), 4.61 (d, *J*=12.0 Hz, 0.7H, OC*H*Ph), 4.80 (d, *J*=10.9 Hz, 0.3H, OC*H*Ph), 4.81 (d, *J*=10.7 Hz, 0.7H, OC*H*Ph), 4.83 (d, *J*=10.3 Hz, 0.3H, OC*H*Ph), 4.86 (d, *J*=10.8 Hz, 0.7H, OC*H*Ph), 4.87 (d, *J*=10.3 Hz, 0.3H, OC*H*Ph), 4.90 (d, *J*=10.8 Hz, 0.7H, OC*H*Ph), 5.00 (dd, *J*=7.5, 7.6 (J_{H-P}) Hz, 0.3H, H-1β), 5.75 (dd, *J*=3.4, 7.9 (J_{H-P}) Hz, 0.7H, H-1α), 7.10–7.17 (m, 3H, Ar-H), 7.26–7.38 (m, 12H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.3, 36.36, 36.41, 36.45, 36.48, 64.2 (d, J_{C-P}=7.3 Hz), 67.2 (d, J_{C-P}=7.9 Hz), 68.2, 68.3, 72.7, 73.5, 73.6, 75.0, 75.2, 75.3, 75.5, 75.6, 77.4, 77.9, 80.4, 83.0, 93.5 (d, J_{C-P}=4.0 Hz, C-1α), 96.1 (d, J_{C-P}=4.5 Hz, C-1β), 127.66, 127.72, 127.8, 127.88, 127.91, 128.06, 128.11, 128.3, 128.4, 128.45, 128.47, 137.7, 137.76, 137.81, 137.87, 137.94; ^{31}P NMR (109 MHz, $CDCl_3$) δ 19.41 (α), 20.01 (β); FAB-HRMS *m/z* calcd for $C_{31}H_{41}N_5O_6P$ $(M+H)^+$ 610.2795, found 610.2795.

4.3. Glycosidations of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxyglucosyl diphenyl phosphate 2a

4.3.1. Typical procedure for glycosidation of 2-azido-2-deoxyglucopyranosyl donors: methyl 4-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (10). TMSOTf in CH_2Cl_2 (1.0 M, 0.15 mL, 0.15 mmol) was added to a stirred solution of diphenyl phosphate **2a** (α:β=72:28) (70.8 mg, 0.10 mmol) and alcohol **8** (51.1 mg, 0.11 mmol) in EtCN (1.5 mL) at −78 °C. After stirring at this temperature for 2 h, the reaction was quenched with Et_3N (0.1 mL). The reaction mixture was poured into a two-layer mixture of AcOEt (2 mL) and $NaHCO_3$ (3 mL), and the whole was extracted with AcOEt (20 mL). The organic layer was successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (108.9 mg), from which an anomeric mixture of disaccharide **10** (82.6 mg, 90%, α:β=6:94) was obtained as a colorless oil after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt). The anomeric ratio of the disaccharide was determined by HPLC analysis [column, Zorbax® Sil, 4.6×250 mm; eluent, 7:1 hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm; t_R (α-anomer)=56.6 min, t_R (β-anomer)=63.5 min]. The α- and β-glycosides were separated by flash column chromatography with 6:1 hexane/AcOEt.

The following work-up may be employed in those cases where the highly reactive primary alcohol (**7** or **12**) was used as an acceptor. It serves only to remove the imidate as its hydrolyzed product. After the reaction was quenched with Et_3N (0.1 mL), the mixture was diluted with AcOEt (20 mL). The whole was successively washed with 10% aqueous HCl (5 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo to yield the crude product containing propionated acceptor alcohol.

Data for β-anomer (**10**β): TLC R_f=0.49 (2:1 hexane/AcOEt); $[\alpha]_D^{15}$=−11.4° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3009, 2910, 2870, 2112, 1496, 1454, 1361, 1277, 1087, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (ddd, *J*=1.7, 4.3, 9.6 Hz, 1H, H-5′), 3.24 (dd, *J*=8.9, 9.8 Hz, 1H, H-3′), 3.31 (dd, *J*=8.0, 9.8 Hz, 1H, H-2′), 3.38 (s, 3H, OC*H*$_3$), 3.47–3.50 (m, 2H, H-2, H-6′a), 3.59 (dd, *J*=8.9, 9.6 Hz, 1H, H-4′), 3.62 (dd, *J*=1.7, 11.1 Hz, 1H, H-6′b), 3.70 (dd, *J*=1.6, 10.9 Hz, 1H, H-6a), 3.78 (ddd, *J*=1.6, 3.2, 9.8 Hz, 1H, H-5), 3.89 (dd, *J*=8.9, 9.5 Hz, 1H, H-3), 3.92 (dd, *J*=3.2, 10.9 Hz, 1H, H-6b), 3.96 (dd, *J*=8.9, 9.8 Hz, 1H, H-4), 4.26 (d, *J*=8.0 Hz, 1H, H-1′), 4.35 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.40 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.47 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.54 (d, *J*=11.0 Hz, 1H, OC*H*Ph), 4.58 (d, *J*=

12.1 Hz, 1H, OC*H*Ph), 4.59 (d, J=3.6 Hz, 1H, H-1), 4.67 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.74 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.76 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.781 (d, J=11.4 Hz, 1H, OC*H*Ph), 4.782 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.02 (d, J=11.4 Hz, 1H, OC*H*Ph), 7.17–7.36 (m, 30H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.3, 66.9, 68.2, 68.6, 69.7, 73.3, 73.47, 73.51, 74.7, 75.19, 75.24, 75.4, 77.9, 79.1, 80.3, 83.3, 98.3 (C-1), 100.9 (C-1′), 127.0, 127.4, 127.5, 127.65, 127.67, 127.70, 127.72, 127.8, 127.95, 127.98, 128.1, 128.2, 128.3, 128.36, 128.42, 128.5, 137.8, 137.9, 138.0, 138.3, 138.4, 139.5; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4083; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.45; H, 6.45; N, 4.55. Data for α-anomer (**10α**): TLC R_f=0.54 (2:1 hexane/AcOEt); $[\alpha]_D^{15}=+39.1°$ (c 0.78, $CHCl_3$); IR ($CHCl_3$) 3013, 2910, 2870, 2112, 1602, 1454, 1361, 1221, 1049, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 (dd, J=3.9, 10.4 Hz, 1H, H-2′), 3.34 (brd, J=11.0 Hz, 1H, H-6′a), 3.38 (s, 3H, OCH_3), 3.52 (dd, J=1.4, 11.0 Hz, 1H, H-6′b), 3.57 (dd, J=3.6, 9.6 Hz, 1H, H-2), 3.65 (dd, J=1.9, 11.0 Hz, 1H, H-6a), 3.66–3.70 (m, 2H, H-4′, H-5′), 3.72 (dd, J=4.3, 11.0 Hz, 1H, H-6b), 3.79 (ddd, J=1.9, 4.3, 10.0 Hz, 1H, H-5), 3.86 (m, 1H, H-3′), 3.91 (dd, J=8.6, 10.0 Hz, 1H, H-4), 4.08 (dd, J=8.6, 9.6 Hz, 1H, H-3), 4.25 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.45 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.49 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.50 (s, 2H, OCH_2Ph), 4.61 (d, J=3.6 Hz, 1H, H-1), 4.62 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.74 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.75 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.83 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.85 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.86 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.10 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.73 (d, J=3.9 Hz, 1H, H-1′), 7.12 (m, 2H, Ar-H), 7.20–7.35 (m, 28H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.3, 63.3, 67.9, 69.3, 69.5, 71.4, 73.27, 73.31, 73.5, 74.9, 75.0, 75.3, 78.1, 80.1, 80.5, 82.0, 97.69 (C-1′), 97.73 (C-1), 127.2, 127.4, 127.45, 127.53, 127.66, 127.71, 127.8, 127.9, 128.1, 128.26, 128.32, 128.4, 128.5, 137.8, 137.9, 138.0, 138.1, 138.2, 138.7; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4083.

4.3.2. Methyl 6-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (9). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 1.5 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **9** (77.0 mg, 84%, α:β=1:99) was obtained as a white solid from the crude product (108.7 mg) after flash column chromatography (silica gel 6 g, 6:1 hexane/AcOEt with 1% Et_3N), along with α-imidate **11** (5.3 mg, 5%) as a colorless oil. The anomeric ratio of the disaccharide was determined by HPLC analysis [column, Zorbax® Sil, 4.6×250 mm; eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm; t_R (β-anomer)=24.1 min, t_R (α-anomer)=34.7 min]. The α- and β-glycosides were separated by flash column chromatography with 3:1 hexane/Et_2O. Data for β-anomer (**9β**): TLC R_f=0.46 (2:1 hexane/AcOEt), 0.30 (1:1 hexane/Et_2O); mp 119.0–120.0 °C (colorless fine needles from AcOEt–hexane); $[\alpha]_D^{19}=-5.27°$ (c 1.15, $CHCl_3$); IR ($CHCl_3$) 3009, 2930, 2868, 2112, 1496, 1454, 1359, 1265, 1222, 1068, 763 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (m, 1H, H-5′), 3.38 (s, 3H, OCH_3), 3.40 (dd, J=8.7, 9.8 Hz, 1H, H-3′), 3.45 (dd, J=7.7, 9.8 Hz, 1H, H-2′), 3.55 (dd, J=3.5, 9.6 Hz, 1H, H-2), 3.575 (dd, J=8.7, 9.4 Hz, 1H, H-4′), 3.576 (dd, J=8.9, 10.0 Hz, 1H, H-4), 3.64–3.71 (m, 3H, H-6a, H-6′a, H-6′b), 3.81 (ddd, J=1.6, 4.3, 10.0 Hz, 1H, H-5), 4.00 (dd, J=8.9, 9.6 Hz, 1H, H-3), 4.12 (dd, J=1.6, 10.9 Hz, 1H, H-6b), 4.16 (d, J=7.7 Hz, 1H, H-1′), 4.51 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.55 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.57 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.62 (d, J=3.5 Hz, 1H, H-1), 4.65 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.66 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.77–4.80 (m, 3H, OC*H*Ph×3), 4.84 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.86 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.93 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.98 (d, J=11.0 Hz, 1H, OC*H*Ph), 7.17 (m, 2H, Ar-H), 7.24–7.36 (m, 28H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 66.4, 68.4, 68.7, 69.7, 73.4, 74.8, 75.0, 75.2, 75.6, 75.7, 77.75, 77.79, 79.8, 82.1, 83.3, 98.2 (C-1), 102.1 (C-1′), 127.5, 127.59, 127.63, 127.7, 127.8, 127.85, 127.87, 128.0, 128.06, 128.14, 128.3, 128.35, 128.42, 128.44, 137.9, 138.1, 138.2, 138.4, 138.8; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4080; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.67; H, 6.44; N 4.49. Data for α-anomer (**9α**): TLC R_f=0.44 (2:1 hexane/AcOEt), 0.26 (1:1 hexane/Et_2O); $[\alpha]_D^{24}=+84.7°$ (c 1.18, $CHCl_3$); IR (film) 3030, 2922, 2106, 1496, 1454, 1359, 1207, 1049, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (dd, J=3.5, 10.1 Hz, 1H, H-2′), 3.37 (s, 3H, OCH_3), 3.51–3.55 (m, 2H, H-2, H-6′a), 3.56 (dd, 1H, J=9.2, 9.4 Hz, H-4), 3.63 (dd, J=3.3, 10.7 Hz, H-6′b), 3.67–3.71 (2H, m, H-6a, H-4′), 3.74–3.78 (2H, m, H-5, H-5′), 3.83 (dd, J=4.6, 11.4 Hz, 1H, H-6b), 3.92 (dd, J=8.8, 10.1 Hz, 1H, H-3′), 4.00 (t, J=9.2 Hz, 1H, H-3), 4.43 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.49 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.56–4.61 (m, 3H, H-1, OC*H*Ph×2), 4.66 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.78 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.79 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.80 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.83 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.86 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.94 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.98 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.01 (d, J=3.5 Hz, 1H, H1′), 7.13 (m, 2H, Ar-H), 7.24–7.37 (m, 28H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 63.5, 66.4, 68.1, 69.9, 70.7, 73.4, 73.5, 74.9, 75.2, 75.8, 77.2, 77.7, 78.2, 79.8, 80.0, 82.0, 97.9 (C-1), 98.2 (C-1′), 127.5, 127.6, 127.7, 127.76, 127.80, 128.0, 128.1, 128.29, 128.31, 128.4, 137.7, 137.8, 137.95, 138.04, 138.2, 138.6; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4109.

Data for methyl 6-*O*-[1-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)iminopropyl]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**11**): TLC R_f=0.49 (2:1 hexane/AcOEt); $[\alpha]_D^{20}=+47.5°$ (c 0.40, $CHCl_3$); IR (film) 3030, 2922, 2106, 1664, 1496, 1454, 1359, 1211, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, J=7.6 Hz, 3H, CH_2CH_3), 2.36 (dq, J=14.6, 7.6 Hz, 1H, C*H*CH$_3$), 2.38 (dq, J=14.6, 7.6 Hz, 1H, C*H*CH$_3$), 3.37 (s, 3H, OCH_3), 3.52 (dd, J=4.1, 10.0 Hz, 1H, H-2′), 3.54 (dd, J=3.6, 9.5 Hz, 1H, H-2), 3.56 (dd, J=1.7, 10.7 Hz, 1H, H-6′a), 3.62 (dd, J=9.0, 10.0 Hz, 1H, H-4), 3.73 (dd, J=3.5, 10.7 Hz, 1H, H-6′b), 3.78 (dd, J=9.0, 9.9 Hz, 1H, H-4′), 3.87 (ddd, J=1.8, 4.1, 10.0 Hz, 1H, H-5), 4.00 (dd, J=9.0, 9.5 Hz, 1H, H-3), 4.08 (ddd, J=1.7, 3.5, 9.9 Hz, 1H, H-5′), 4.09 (dd, J=9.0, 10.0 Hz, 1H, H-3′), 4.23 (dd, J=4.1, 12.3 Hz, 1H, H-6a), 4.30 (dd, J=1.8, 12.3 Hz, 1H, H-6b), 4.46 (d, J=

12.2 Hz, 1H, OC*H*Ph), 4.51 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.59 (d, J=10.6 Hz, 1H, OC*H*Ph), 4.60 (d, J=3.6 Hz, 1H, H-1), 4.62 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.66 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.73 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.789 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.790 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.80 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.84 (d, J=10.6 Hz, 1H, OC*H*Ph), 4.97 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.20 (d, J=4.1 Hz, 1H, H-1′), 7.12–7.18 (m, 3H, Ar-H), 7.22–7.37 (m, 27H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.7, 22.9, 55.1, 64.2, 64.7, 68.7, 71.2, 73.4, 73.5, 75.09, 75.14, 75.2, 75.9, 77.8, 78.9, 80.0, 80.9, 82.1, 83.2 (C-1′), 98.1 (C-1), 127.6, 127.68, 127.74, 127.76, 127.79, 127.87, 127.91, 128.0, 128.1, 128.35, 128.41, 128.5, 137.9, 138.0, 138.07, 138.13, 138.2, 138.7, 168.8; FAB-HRMS *m/z* calcd for $C_{58}H_{65}N_4O_{10}$ $(M+H)^+$ 977.4700, found 977.4721.

4.3.3. 6-*O*-(2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (17).[12a] The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 1.5 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **12** (28.6 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **17** (56.8 mg, 79%, α:β=2:98) was obtained as a colorless oil from the crude product (91.4 mg) after column chromatography (silica gel 8 g, 7:1 hexane/AcOEt with 1% Et_3N), along with α-imidate **19** (7.2 mg, 9%) as a colorless syrup. The anomeric ratio of the product was determined by HPLC analysis [eluent, 6:1 hexane/THF; flow rate, 1.0 mL/min; t_R (α-anomer)=8.9 min, t_R (β-anomer)=9.6 min]. The α- and β-glycosides were separated by flash column chromatography with 30:1 toluene/acetone. Data for β-anomer (**17**β): TLC R_f=0.39 (3:1 hexane/AcOEt), 0.49 (10:1 toluene/acetone); $[\alpha]_D^{16}$=−47.9° (c 2.45, $CHCl_3$) (α:β=2:98); IR (film) 2986, 2906, 2110, 1454, 1381, 1211, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H, CC*H*$_3$), 1.33 (s, 3H, CC*H*$_3$), 1.44 (s, 3H, CC*H*$_3$), 1.54 (s, 3H, CC*H*$_3$), 3.40–3.44 (m, 3H, H-2′, H-4′, H-5′), 3.63 (m, 1H, H-3′), 3.70 (dd, J=4.1, 11.1 Hz, 1H, H-6′a), 3.73 (dd, J=2.2, 11.1 Hz, 1H, H-6′b), 3.79 (m, 1H, H-6a), 4.04–4.09 (m, 2H, H-5, H-6b), 4.28 (dd, J=1.2, 7.8 Hz, 1H, H-4), 4.31 (dd, J=2.4, 5.0 Hz, 1H, H-2), 4.41 (m, 1H, H-1′), 4.53 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.54 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.60 (dd, J=2.4, 7.8 Hz, 1H, H-3), 4.61 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.78 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.79 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.89 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.54 (d, J=5.0 Hz, 1H, H-1), 7.16 (m, 2H, Ar-H), 7.25–7.36 (m, 13H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 25.0, 25.97, 26.02, 66.4, 67.6, 68.5, 68.8, 70.5, 70.7, 71.2, 73.5, 74.96, 75.02, 75.5, 77.7, 83.1, 96.3 (C-1), 102.4 (C-1′), 108.7, 109.3, 127.6, 127.76, 127.79, 127.82, 128.0, 128.35, 128.38, 128.41, 138.0, 138.06, 138.08; FAB-HRMS *m/z* calcd for $C_{39}H_{47}N_3O_{10}Na$ $(M+Na)^+$ 740.3159, found 740.3195; Anal. calcd for: $C_{39}H_{47}N_3O_{10}$: C, 65.26; H, 6.60; N, 5.85, found C, 65.26; H, 6.60; N, 5.83. Data for α-anomer (**17**α): TLC R_f=0.41 (3:1 hexane/AcOEt), 0.53 (10:1 toluene/acetone); $[\alpha]_D^{17}$=+42.2° (c 0.49, $CHCl_3$); IR ($CHCl_3$) 2924, 2106, 1454, 1381, 1255, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H, CC*H*$_3$), 1.34 (s, 3H, CC*H*$_3$), 1.43 (s, 3H, CC*H*$_3$), 1.53 (s, 3H, CC*H*$_3$), 3.33 (dd, J=3.5, 10.3 Hz, 1H, H-2′), 3.66 (dd, J=1.8, 10.8 Hz, 1H, H-6′a), 3.72 (dd, J=6.7, 10.3 Hz, 1H, H-6a), 3.73–3.80 (m, 2H, H-4′, H-6′b), 3.81 (dd, J=6.4, 10.3 Hz, 1H, H-6b), 3.88 (m, 1H, H-5′), 3.98–4.01 (m, 2H, H-5, H-3′), 4.31 (dd, J=2.3, 5.0 Hz, 1H, H-2), 4.32 (dd, J=1.8, 8.0 Hz, 1H, H-3), 4.48 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.53 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.61 (dd, J=2.3, 8.0 Hz, 1H, H-3), 4.64 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.79 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.85 (d, J=11.5 Hz, 1H, OC*H*Ph), 4.87 (d, J=11.5 Hz, 1H, OC*H*Ph), 4.99 (d, J=3.5 Hz, 1H, H-1′), 5.51 (d, J=5.0 Hz, 1H, H-1), 7.16 (m, 2H, Ar-H), 7.24–7.37 (m, 13H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 24.9, 26.0, 26.1, 63.4, 66.2, 66.9, 68.2, 70.6, 70.66, 70.69, 70.8, 73.5, 74.9, 75.3, 78.3, 79.9, 96.3 (C-1), 98.3 (C-1′), 108.6, 109.3, 127.70, 127.73, 127.8, 127.9, 128.0, 128.38, 128.43, 137.9, 138.1; FAB-HRMS *m/z* calcd for $C_{39}H_{47}N_3O_{10}Na$ $(M+Na)^+$ 740.3159, found 740.3134.

Data for 6-*O*-[1-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)iminopropyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**19**): TLC R_f=0.43 (3:1 hexane/AcOEt); $[\alpha]_D^{24}$=+4.68° (c 0.28, $CHCl_3$); IR (film) 2924, 2106, 1658, 1462, 1213, 1072 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.32 (s, 6H, CC*H*$_3$×2), 1.44 (s, 3H, CC*H*$_3$), 1.50 (s, 3H, CC*H*$_3$), 2.34 (dq, J=15.0, 7.6 Hz, 1H, C*H*CH$_3$), 2.38 (dq, J=15.0, 7.6 Hz, 1H, C*H*CH$_3$), 3.57 (dd, J=4.2, 10.0 Hz, 1H, H-2′), 3.58 (dd, J=1.8, 10.8 Hz, 1H, H-6′a), 3.74 (dd, J=3.5, 10.8 Hz, 1H, H-6′b), 3.78 (t, J=9.5 Hz, 1H, H-4′), 4.05 (ddd, J=1.6, 5.3, 7.1 Hz, 1H, H-5), 4.10 (dd, J=9.5, 10.0 Hz, 1H, H-3′), 4.10–4.14 (m, 2H, H-6a, H-5′), 4.27 (dd, J=1.6, 7.9 Hz, 1H, H-4), 4.31 (dd, J=2.4, 5.0 Hz, 1H, H-2), 4.33 (dd, J=5.3, 11.2 Hz, 1H, H-6b), 4.47 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.53 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.60 (dd, J=2.4, 7.9 Hz, 1H, H-3), 4.62 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.85 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.89 (d, J=11.7 Hz, 1H, OC*H*Ph), 5.22 (d, J=4.2 Hz, 1H, H-1′), 5.55 (d, J=5.0 Hz, 1H, H-1), 7.17 (m, 2H, Ar-H), 7.24–7.38 (m, 13H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.7, 23.0, 24.4, 25.0, 26.0, 26.1, 29.7, 64.0, 65.0, 66.1, 68.7, 70.7, 71.2, 71.3, 73.5, 75.0, 75.3, 79.0, 80.8, 83.4 (C-1′), 96.3 (C-1), 108.6, 109.5, 127.65, 127.70, 127.76, 127.80, 127.9, 128.1, 128.3, 128.38, 128.43, 138.0, 138.1, 138.2, 168.0; FAB-HRMS *m/z* calcd for $C_{42}H_{53}N_4O_{10}$ $(M+H)^+$ 773.3762, found 773.3770.

4.3.4. Methyl 2-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (18).[12b] The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 2 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **13** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **18** (83.6 mg, 91%, α:β=9:91) was obtained as a colorless oil from the crude product (107.4 mg) after column chromatography (silica gel 5 g, 5:1 hexane/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=12.6 min, t_R (β-anomer)=16.3 min]. The α- and β-glycosides were separated by flash column chromatography with 6:1 hexane/AcOEt. Data for β-anomer (**18**β):[12b] TLC R_f=0.61 (2:1 hexane/AcOEt); mp 83.5–84.5 °C (colorless needles from AcOEt–hexane); $[\alpha]_D^{28}$=−17.9° (c 1.00, $CHCl_3$); IR (KBr) 3030, 2908,

2868, 2112, 1496, 1452, 1359, 1269, 1062, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.34 (m, 1H, H-5′), 3.39 (dd, J= 9.1, 9.5 Hz, 1H, H-3′), 3.46 (dd, J=8.1, 9.5 Hz, 1H, H-2′), 3.48 (s, 3H, OCH_3), 3.49 (m, 1H, H-5), 3.64–3.78 (m, 7H, H-3, H-4, H-6a, H-6b, H-4′, H-6′a, H-6′b), 3.80 (dd, J=7.2, 8.9 Hz, 1H, H-2), 4.37 (d, J=7.2 Hz, 1H, H-1), 4.53–4.59 (m, 4H, OC*H*Ph×4), 4.61–4.66 (m, 2H, OC*H*Ph×2), 4.71 (d, J=8.1 Hz, 1H, H-1′), 4.78 (d, J=10.5 Hz, 1H, OC*H*Ph), 4.79 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.81 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.85 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.89 (d, J= 10.6 Hz, 1H, OC*H*Ph), 4.95 (d, J=10.6 Hz, 1H, OC*H*Ph), 7.16–7.19 (m, 4H, Ar-H), 7.22–7.38 (m, 26H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.3, 66.6, 68.3, 68.8, 73.5, 73.6, 74.8, 75.0, 75.2, 75.3, 75.4, 77.8, 78.3, 78.9, 83.4, 85.1, 101,1 (C-1′), 102.4 (C-1), 127.5, 127.6, 127.65, 127.67, 127.72, 127.77, 127.81, 127.90, 127.94, 128.0, 128.3, 128.4, 137.9, 138.0, 138.2, 138.3, 138.4; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4072; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.58; H, 6.49; N, 4.61. Data for α-anomer (**18**α):[12b] TLC R_f=0.66 (2:1 hexane/AcOEt); $[\alpha]_D^{28}$ = +67.4° (c 1.00, $CHCl_3$); IR (film) 3030, 2918, 2864, 2104, 1496, 1454, 1359, 1211, 1126, 1055, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.26 (d, J=1.6 Hz, 2H, H-6′), 3.34 (dd, J=3.7, 10.4 Hz, 1H, H-2′), 3.48 (ddd, J=2.0, 3.7, 9.4 Hz, 1H, H-5), 3.57 (s, 3H, OCH_3), 3.61 (dd, J=9.0, 9.2 Hz, 1H, H-3), 3.64–3.76 (m, 5H, H-2, H-4, H-6a, H-6b, H-4′), 3.91 (dd, J=8.9, 10.4 Hz, 1H, H-3′), 3.98 (m, 1H, H-5′), 4.28 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.38 (d, J= 7.4 Hz, 1H, H-1), 4.43 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.53 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.55 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.56 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.64 (d, J= 12.2 Hz, 1H, OC*H*Ph), 4.72 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.74 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.79 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.85 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.87 (d, J= 11.3 Hz, 1H, OC*H*Ph), 4.91 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.58 (d, J=3.7 Hz, 1H, H-1′), 7.06–7.08 (m, 4H, Ar-H), 7.12–7.18 (m, 3H, Ar-H), 7.22–7.36 (m, 23H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.2, 63.3, 67.6, 68.5, 70.4, 73.4, 73.5, 74.8, 74.9, 75.3, 75.8, 76.3, 77.2, 78.1, 78.5, 80.0, 83.1, 96.7 (C-1′), 104.5 (C-1), 127.4, 127.50, 127.54, 127.6, 127.68, 127.73, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 137.69, 137.72, 137.8, 137.91, 137.94, 138.3; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4110.

4.3.5. Methyl 3-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (20). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 2 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **14** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **20** (81.7 mg, 89%, α:β=1:>99) was obtained as a colorless oil from the crude product (108.5 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=29.9 min, t_R (β-anomer)=36.3 min]. The α- and β-glycosides were separated by flash column chromatography with 20:1 toluene/AcOEt. Data for β-anomer (**20**β): TLC R_f=0.42 (2:1 hexane/AcOEt), 0.28 (10:1 toluene/AcOEt); $[\alpha]_D^{16}$ = −7.13° (c 1.17, $CHCl_3$); IR ($CHCl_3$) 3024, 2914, 2870, 2112, 1454, 1358, 1273, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H, OCH_3), 3.38–3.43 (m, 3H, H-2′, H-4′, H-5′), 3.48 (dd, J= 6.6, 9.5 Hz, 1H, H-6a), 3.51 (dd, J=6.2, 9.5 Hz, 1H, H-6b), 3.66–3.71 (m, 2H, H-3′, H-6′a), 3.74 (dd, J=3.9, 11.0 Hz, 1H, H-6′b), 3.93 (dd, J=6.2, 6.6 Hz, 1H, H-5), 4.00 (brd, J=3.0 Hz, 1H, H-4), 4.06 (dd, J=3.6, 10.1 Hz, 1H, H-2), 4.19 (dd, J=3.0, 10.1 Hz, 1H, H-3), 4.38 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.46 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.49 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.57–4.61 (m, 5H, H-1, OC*H*Ph×4), 4.73 (m, 1H, H-1′), 4.80 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.81 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.88 (d, J= 10.9 Hz, 1H, OC*H*Ph), 4.90 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.95 (d, J=11.4 Hz, 1H, OC*H*Ph), 7.18 (m, 2H, Ar-H), 7.20–7.38 (m, 26H, Ar-H), 7.42 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.3, 67.1, 68.5, 69.1, 69.2, 73.4, 73.5, 73.6, 74.7, 75.05, 75.14, 75.5, 77.2, 77.4, 77.7, 83.0, 98.3 (C-1), 102.7 (C-1′), 127.5, 127.59, 127.64, 127.7, 127.79, 127.82, 127.84, 127.9, 128.2, 128.3, 128.35, 128.40, 128.42, 128.5, 137.95, 138.03, 138.10, 138.12, 138.4, 138.7; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4136; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.67; H, 6.49; N, 4.56. Data for α-anomer (**20**α): TLC R_f=0.44 (2:1 hexane/AcOEt), 0.33 (10:1 toluene/AcOEt); $[\alpha]_D^{24}$ = +66.5° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 3022, 2914, 2870, 2112, 1454, 1358, 1209, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (s, 3H, OCH_3), 3.50–3.57 (m, 4H, H-6a, H-6b, H-2′, H-6′a), 3.62 (dd, J=2.8, 11.1 Hz, 1H, H-6′b), 3.79 (dd, J=9.4, 9.6 Hz, 1H, H-4′), 3.90 (dd, J=6.5, 6.6 Hz, 1H, H-5), 3.99-4.03 (m, 2H, H-2, H-4), 4.05 (dd, J=9.4, 9.8 Hz, 1H, H-3′), 4.16–4.19 (m, 2H, H-3, H-5′), 4.35 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.41 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.489 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.490 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.562 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.564 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.60 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.70 (d, J= 3.6 Hz, 1H, H-1), 4.72 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.77 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.87 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.06 (d, J= 11.2 Hz, 1H, OC*H*Ph), 5.21 (d, J=3.5 Hz, 1H, H-1′), 7.11 (m, 2H, Ar-H), 7.18–7.20 (m, 3H, Ar-H), 7.22–7.35 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 63.7, 68.1, 68.8, 69.0, 70.5, 73.3, 73.4, 74.4, 74.7, 74.8, 75.1, 75.3, 78.3, 80.2, 94.7 (C-1′), 98.4 (C-1), 127.5, 127.55, 127.62, 127.71, 127.74, 127.8, 128.0, 128.1, 128.2, 128.25, 128.28, 128.36, 128.39, 137.87, 137.92, 138.1, 138.3, 138.6; FAB-HRMS m/z calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4097.

4.3.6. Methyl 4-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (21). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 2 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **15** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **21** (82.5 mg, 90%, α:β=5:95) was obtained as a colorless oil from the crude product (100.6 mg) after column chromatography (silica gel 8 g, 4:1 hexane/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=12.4 min, t_R (β-anomer)=15.5 min]. The α- and β-glycosides were separated by flash column

chromatography with 15:1 toluene/AcOEt. Data for β-anomer (**21**β): TLC R_f=0.46 (2:1 hexane/AcOEt), 0.34 (10:1 toluene/AcOEt); $[\alpha]_D^{19}$=+3.32° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3020, 2930, 2868, 2114, 1454, 1358, 1277, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.27 (ddd, *J*=1.9, 3.9, 9.9 Hz, 1H, H-5′), 3.34 (dd, *J*=8.8, 9.8 Hz, 1H, H-3′), 3.37 (s, 3H, OC*H*$_3$), 3.40 (dd, *J*=7.6, 9.8 Hz, 1H, H-2′), 3.58–3.65 (m, 4H, H-6a, H-4′, H-6′a, H-6′b), 3.73 (dd, *J*=4.7, 10.5 Hz, 1H, H-6b), 3.90–3.94 (m, 2H, H-3, H-5), 4.13 (dd, *J*=3.7, 10.1 Hz, 1H, H-2), 4.16 (brd, *J*=3.0 Hz, 1H, H-4), 4.37 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.44 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.48 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.52 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.54 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.64 (d, *J*=3.7 Hz, 1H, H-1), 4.67 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.69 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.73 (d, *J*=7.6 Hz, 1H, H-1′), 4.77–4.80 (m, 2H, OC*H*Ph×2), 4.84 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.91 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.92 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 7.15 (m, 2H, Ar-H), 7.24–7.37 (m, 28H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.3, 66.6, 68.9, 69.4, 70.2, 73.2, 73.4, 73.5, 73.8, 74.3, 74.8, 75.0, 75.5, 76.6, 77.7, 78.4, 83.1, 98.8 (C-1), 101.6 (C-1′), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.80, 127.82, 127.9, 128.0, 128.2, 128.27, 128.32, 128.36, 128.42, 128.44, 137.9, 138.05, 138.14, 138.58, 138.61, 138.9; FAB-HRMS *m/z* calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4102; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.68; H, 6.55; N, 4.55. Data for α-anomer (**21**α): TLC R_f=0.43 (2:1 hexane/AcOEt), 0.40 (10:1 toluene/AcOEt); $[\alpha]_D^{18}$=+44.5° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3018, 2930, 2870, 2114, 1454, 1358, 1277, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.03 (dd, *J*=1.7, 11.1 Hz, 1H, H-6′a), 3.28 (dd, *J*=2.0, 11.1 Hz, 1H, H-6′b), 3.35 (dd, *J*=3.6, 9.2 Hz, 1H, H-2′), 3.36 (s, 3H, OC*H*$_3$), 3.54 (dd, *J*=10.4, 12.9 Hz, 1H, H-5), 3.75 (dd, *J*=9.4, 10.1 Hz, 1H, H-4′), 3.83–3.92 (m, 5H, H-2, H-3, H-6a, H-6b, H-3′), 4.18 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.20 (d, *J*=2.9 Hz, 1H, H-4), 4.23 (ddd, *J*=1.7, 2.0, 10.1 Hz, 1H, H-5′), 4.43 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.46 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.52 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.55 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.69–4.74 (m, 4H, H-1, OC*H*Ph×3), 4.77 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.80–4.82 (m, 2H, OC*H*Ph×2), 4.86 (d, *J*=10.6 Hz, 1H, OC*H*Ph), 4.94 (d, *J*=3.6 Hz, 1H, H-1′), 7.13 (m, 2H, Ar-H), 7.17–7.37 (m, 28H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.4, 64.1, 67.3, 67.5, 68.9, 70.7, 73.16, 73.19, 73.3, 73.6, 74.8, 74.9, 75.27, 75.33, 78.2, 80.4, 98.5, 98.6, 127.4, 127.5, 127.6, 127.66, 127.73, 127.8, 127.95, 127.99, 128.03, 128.26, 128.31, 128.33, 128.4, 128.5, 137.6, 137.9, 138.1, 138.2, 138.4, 138.7; FAB-HRMS *m/z* calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4136.

4.3.7. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (22). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 2 h) employing diphenyl phosphate **2a** (70.8 mg, 0.10 mmol), alcohol **16** (68.9 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.20 mL, 0.20 mmol). An anomeric mixture of disaccharide **22** (95.0 mg, 88%, α:β=7:93) was obtained as a colorless oil from the crude product (126.0 mg) after column chromatography (silica gel 8 g, 1:2 hexane/AcOEt). The anomeric ratio of the product was determined by ^1H NMR [integration of H1′, β-anomer (4.27 ppm), α-anomer (4.94 ppm)]. The α- and β-glycosides were separated by flash column chromatography with 1:2 hexane/AcOEt. Data for β-anomer (**22**β): TLC R_f=0.37 (1:3 hexane/AcOEt); $[\alpha]_D^{16}$=+2.06° (*c* 1.66, $CHCl_3$); IR ($CHCl_3$) 3018, 2978, 2114, 1730, 1452, 1358, 1107, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.61 (d, J_{H-P}=10.4 Hz, 6H, N(C*H*$_3$)$_2$), 2.71 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 3.34 (dd, *J*=7.9, 9.8 Hz, 1H, H-2′), 3.36 (ddd, *J*=2.2, 4.1, 9.8 Hz, 1H, H-5′), 3.44 (dd, *J*=8.9, 9.8 Hz, 1H, H-3′), 3.58 (dd, *J*=8.9, 9.8 Hz, 1H, H-4′), 3.62 (dd, *J*=2.2, 11.2 Hz, 1H, H-6′a), 3.65 (dd, *J*=4.1, 11.2 Hz, 1H, H-6′b), 3.76 (dd, *J*=5.1, 11.1 Hz, 1H, H-6a), 4.14 (dd, *J*=2.5, 11.1 Hz, 1H, H-6b), 4.27 (d, *J*=7.9 Hz, 1H, H-1′), 4.45 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.48 (ddd, *J*=2.5, 5.1, 10.1 Hz, 1H, H-5), 4.540 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.541 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.78 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.79 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.89 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 5.39 (ddd, *J*=3.3, 10.3, 1.5 (J_{H-P}) Hz, 1H, H-2), 5.72 (dd, *J*=9.7, 10.2 Hz, 1H, H-4), 6.15 (dd, *J*=3.3, 8.1 (J_{H-P}) Hz, 1H, H-1), 6.19 (dd, *J*=9.7, 10.3 Hz, 1H, H-3), 7.16 (m, 2H, Ar-H), 7.25–7.52 (m, 22H, Ar-H), 7.87 (m, 2H, Ar-H), 7.94–7.97 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.4 (d, J_{C-P}=3.8 Hz), 36.5 (d, J_{C-P}=4.0 Hz), 66.3, 68.2, 68.4, 69.2, 70.0, 70.8, 71.5 (d, J_{C-P}=6.4 Hz), 73.4, 74.9, 75.1, 75.6, 77.6, 83.2, 92.0 (d, J_{C-P}=3.9 Hz, C-1), 102.1 (C-1′), 127.6, 127.7, 127.79, 127.84, 128.0, 128.29, 128.32, 128.33, 128.38, 128.42, 128.95, 129.03, 129.1, 129.7, 129.8, 129.9, 133.16, 133.22, 133.4, 137.87, 137.89, 138.0, 165.2, 165.4, 165.9; ^{31}P NMR (109 MHz, C_6D_6) δ 19.7; FAB-HRMS *m/z* calcd for $C_{58}H_{63}N_5O_{14}P$ $(M+H)^+$ 1084.4109, found 1084.4150; Anal. calcd for: $C_{58}H_{62}N_5O_{14}P$: C, 64.26; H, 5.76; N, 6.46, found C, 64.33; H, 5.83; N, 6.41. Data for α-anomer (**22**α): TLC R_f=0.25 (1:3 hexane/AcOEt); $[\alpha]_D^{17}$=+84.8° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3026, 2934, 2114, 1730, 1452, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.60 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 2.69 (d, J_{H-P}=10.0 Hz, 6H, N(C*H*$_3$)$_2$), 3.35 (dd, *J*=3.6, 10.2 Hz, 1H, H-2′), 3.45 (dd, *J*=1.4, 10.9 Hz, 1H, H-6′a), 3.58 (dd, *J*=3.2, 10.9 Hz, 1H, H-6′b), 3.65–3.72 (m, 3H, H-6a, H-4′, H-5′), 3.92 (dd, *J*=5.0, 11.3 Hz, 1H, H-6b), 4.02 (dd, *J*=8.4, 10.2 Hz, 1H, H-3′), 4.37 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.48 (ddd, *J*=1.9, 5.0, 10.3 Hz, 1H, H-5), 4.50 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.51 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.80 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.86 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.88 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.94 (d, *J*=3.6 Hz, 1H, H-1′), 5.38 (ddd, *J*=3.4, 10.3, 1.5 (J_{H-P}) Hz, 1H, H-2), 5.72 (dd, *J*=9.8, 10.3 Hz, 1H, H-4), 6.13 (dd, *J*=3.4, 8.1 (J_{H-P}) Hz, 1H, H-1), 6.16 (dd, *J*=9.8, 10.3 Hz, 1H, H-3), 7.18 (m, 2H, Ar-H), 7.24–7.50 (m, 22H, Ar-H), 7.87 (m, 2H, Ar-H), 7.93–7.95 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.4 (d, J_{C-P}=3.5 Hz), 36.6 (d, J_{C-P}=3.6 Hz), 63.4, 66.7, 68.1, 68.7, 70.1, 70.5, 70.8, 71.5 (d, J_{C-P}=6.5 Hz), 73.4, 74.9, 75.4, 78.2, 80.0, 92.2 (d, J_{C-P}=3.9 Hz, C-1), 98.4 (C-1′), 127.6, 127.7, 127.8, 128.1, 128.29, 128.33, 128.34, 128.38, 128.44, 128.9, 129.0, 129.1, 129.7, 129.8, 129.9, 133.2, 133.3, 133.4, 137.8, 138.0, 138.2, 165.0, 165.4, 166.0; ^{31}P NMR (109 MHz, C_6D_6) δ 19.4; FAB-HRMS *m/z* calcd for $C_{58}H_{63}N_5O_{14}P$ $(M+H)^+$ 1084.4109, found 1084.4100.

4.4. Glycosidations of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxygalactosyl diphenyl phosphate 4a

4.4.1. Methyl 6-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (25).[9] The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.2 h) employing diphenyl phosphate **4a** (70.8 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **25** (79.4 mg, 86%, α:β=4:96) was obtained as a white solid from the crude product (108.0 mg) after column chromatography (silica gel 7 g, 5:1 hexane/AcOEt), along with propionate **26** (2.7 mg, 5%) as a colorless oil. The anomeric ratio of **25** was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=20.5 min, t_R (β-anomer)=27.2 min]. The α- and β-glycosides were separated by flash column chromatography with 6:1 hexane/AcOEt. Data for β-anomer (**25**β):[9] mp 93.5–94.5 °C (colorless needles from AcOEt–hexane); TLC R_f=0.42 (2:1 hexane/AcOEt); $[\alpha]_D^{23}$=+0.79° (*c* 1.00, $CHCl_3$); IR (KBr) 3030, 2912, 2856, 2110, 1496, 1454, 1358, 1284, 1105, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.29 (dd, *J*=2.8, 10.4 Hz, 1H, H-3′), 3.36 (s, 3H, OC*H*$_3$), 3.44 (dd, *J*=6.1, 7.7 Hz, 1H, H-5′), 3.51–3.55 (m, 3H, H-2, H-4, H-6′a), 3.61 (dd, *J*=7.7, 9.9 Hz, 1H, H-6′b), 3.64 (dd, *J*=5.0, 10.9 Hz, 1H, H-6a), 3.79 (ddd, *J*=1.8, 5.0, 10.1 Hz, 1H, H-5), 3.85 (dd, *J*=8.2, 10.4 Hz, 1H, H-2′), 3.87 (m, 1H, H-4′), 3.98 (t, *J*=9.3 Hz, 1H, H-3), 4.07 (dd, *J*=1.8, 10.9 Hz, 1H, H-6b), 4.09 (d, *J*=8.2 Hz, 1H, H-1′), 4.40 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.43 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.53 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.60 (d, *J*=3.5 Hz, 1H, H-1), 4.639 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.640 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.66 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.70 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.77 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.80 (d, *J*=10.0 Hz, 1H, OC*H*Ph), 4.86 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.90 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.97 (d, *J*=10.0 Hz, 1H, OC*H*Ph), 7.24–7.38 (m, 30H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.1, 63.2, 68.27, 68.34, 69.8, 72.2, 72.4, 73.4, 73.52, 73.53, 74.6, 74.8, 75.7, 77.8, 79.9, 80.9, 82.1, 98.0 (C-1), 102.5 (C-1′), 127.5, 127.6, 127.8, 127.85, 127.86, 128.0, 128.05, 128.13, 128.2, 128.3, 128.42, 128.44, 128.5, 137.6, 137.8, 138.2, 138.4, 138.5, 138.8; FAB-HRMS *m*/*z* calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4093; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.62; H, 6.51; N 4.55. Data for α-anomer (**25**α):[9] TLC R_f=0.48 (2:1 hexane/AcOEt); $[\alpha]_D^{21}$=+83.3° (*c* 1.00, $CHCl_3$); IR (film) 3030, 2916, 2108, 1496, 1454, 1358, 1259, 1159, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (s, 3H, OC*H*$_3$), 3.49 (dd, *J*=6.1, 9.2 Hz, 1H, H-6′a), 3.51 (dd, *J*=9.0, 9.9 Hz, 1H, H-4), 3.53 (dd, *J*=3.6, 9.6 Hz, 1H, H-2), 3.56 (dd, *J*=7.9, 9.2 Hz, 1H, H-6′b), 3.69 (dd, *J*=1.2, 11.2 Hz, 1H, H-6a), 3.75 (ddd, *J*=1.2, 4.9, 9.9 Hz, 1H, H-5), 3.80 (dd, *J*=4.9, 11.2 Hz, 1H, H-6b), 3.83 (dd, *J*=3.5, 10.7 Hz, 1H, H-2′), 3.89 (dd, *J*=2.5, 10.7 Hz, 1H, H-3′), 3.93 (dd, *J*=6.1, 7.9 Hz, 1H, H-5′), 3.992 (br, 1H, H-4′), 3.994 (dd, *J*=9.0, 9.6 Hz, 1H, H-3), 4.37 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.44 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.53 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.56 (d, *J*=11.0 Hz, 1H, OC*H*Ph), 4.58 (d, *J*=3.6 Hz, 1H, H-1), 4.649 (d, *J*=11.4 Hz, 1H, OC*H*Ph), 4.654 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.71 (d, *J*=11.4 Hz, 1H, OC*H*Ph), 4.78 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.80 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.87 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.88 (d, *J*=11.0 Hz, 1H, OC*H*Ph), 4.980 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.982 (d, *J*=3.5 Hz, 1H, H-1′), 7.22–7.39 (m, 30H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.0, 59.8, 66.7, 68.6, 69.6, 69.9, 72.0, 73.35, 73.37, 73.39, 74.8, 74.9, 75.7, 76.6, 77.9, 80.0, 82.0, 97.9, 98.6, 127.6, 127.65, 127.66, 127.71, 127.72, 127.8, 127.87, 127.90, 128.0, 128.06, 128.07, 128.2, 128.36, 128.40, 128.5, 137.5, 137.9, 138.1, 138.27, 138.29, 138.8; FAB-HRMS *m*/*z* calcd for $C_{55}H_{59}N_3O_{10}Na$ $(M+Na)^+$ 944.4098, found 944.4079.

Data for methyl 2,3,4-tri-*O*-benzyl-6-*O*-propionyl-α-D-glucopyranoside (**26**): TLC R_f=0.45 (2:1 hexane/AcOEt); $[\alpha]_D^{25}$=+27.1° (*c* 1.00, $CHCl_3$); IR (film) 3030, 2918, 1738, 1454, 1190, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, *J*=7.7 Hz, 3H, CH_2CH_3), 2.30 (m, 2H, CH_2CH_3), 3.36 (s, 3H, OC*H*$_3$), 3.47 (dd, *J*=8.9, 10.1 Hz, 1H, H-4), 3.53 (dd, *J*=3.5, 9.6 Hz, 1H, H-2), 3.82 (ddd, *J*=3.0, 3.9, 10.1 Hz, 1H, H-5), 4.01 (dd, *J*=8.9, 9.6 Hz, 1H, H-3), 4.26 (dd, *J*=3.9, 12.0 Hz, 1H, H-6a), 4.29 (dd, *J*=3.0, 12.0 Hz, 1H, H-6b), 4.56 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.60 (d, *J*=3.5 Hz, 1H, H-1), 4.66 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.79 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.83 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.88 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 5.00 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 7.26–7.36 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.0, 27.3, 55.1, 62.8, 68.6, 73.3, 75.0, 75.7, 77.4, 79.9, 82.0, 97.9 (C-1), 127.6, 127.8, 127.87, 127.92, 127.94, 128.0, 128.3, 128.38, 128.39, 137.8, 138.0, 138.5, 174.0; FAB-HRMS *m*/*z* calcd for $C_{31}H_{36}O_7Na$ $(M+Na)^+$ 543.2359, found 543.2333; Anal. calcd for: $C_{31}H_{36}O_7$: C, 71.52; H 6.97, found C, 71.40; H, 6.93.

4.4.2. Methyl 4-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (27).[10] The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.5 h) employing diphenyl phosphate **4a** (70.8 mg, 0.10 mmol), alcohol **8** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **27** (82.8 mg, 90%, α:β=4:96) was obtained as a colorless oil from the crude product (110.6 mg) after column chromatography (silica gel 5 g, 5:1 hexane/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=15.3 min, t_R (β-anomer)=22.8 min]. The α- and β-glycosides were separated by flash column chromatography with 6:1 hexane/AcOEt. Data for β-anomer (**27**β):[10] TLC R_f=0.49 (2:1 hexane/AcOEt); $[\alpha]_D^{25}$=−3.12° (*c* 2.51, $CHCl_3$); IR (film) 3030, 2868, 2112, 1496, 1454, 1361, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.13 (dd, *J*=2.8, 10.3 Hz, 1H, H-3′), 3.21 (dd, *J*=5.2, 8.2 Hz, 1H, H-5′), 3.30 (dd, *J*=5.2, 9.2 Hz, 1H, H-6′a), 3.37 (s, 3H, OC*H*$_3$), 3.47 (dd, *J*=3.7, 9.4 Hz, 1H, H-2), 3.48 (dd, *J*=8.2, 9.2 Hz, 1H, H-6′b), 3.70 (dd, *J*=1.5, 10.9 Hz, 1H, H-6a), 3.74 (dd, *J*=8.1, 10.3 Hz, 1H, H-2′), 3.76 (m, 1H, H-5), 3.849 (dd, *J*=8.9, 9.4 Hz, 1H, H-4), 3.852 (brd, *J*=2.8 Hz, 1H, H-4′), 3.91 (dd, *J*=9.3, 9.4 Hz, 1H, H-3), 3.94 (dd, *J*=3.2, 10.9 Hz, 1H, H-6b), 4.14 (d, *J*=8.1 Hz, 1H, H-1′), 4.22 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.33 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.43 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=11.3 Hz, 1H, OC*H*Ph), 4.58 (d, *J*=3.7 Hz, 1H, H-1), 4.61 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.62 (d, *J*=

12.1 Hz, 1H, OC*H*Ph), 4.66 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.68 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.74 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.80 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.88 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.96 (d, J=10.7 Hz, 1H, OC*H*Ph), 7.13–7.38 (m, 30H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 63.8, 67.9, 68.3, 69.7, 72.1, 73.2, 73.3, 73.4, 73.6, 74.7, 75.4, 76.7, 79.1, 80.1, 81.0, 98.3 (C-1), 101.2 (C-1′), 127.5, 127.62, 127.64, 127.68, 127.71, 127.76, 127.78, 127.83, 127.86, 127.91, 127.93, 128.0, 128.2, 128.32, 128.34, 128.4, 137.6, 138.0, 138.4, 138.6, 139.4; FAB-HRMS m/z calcd for $C_{55}H_{60}N_3O_{10}$ $(M+H)^+$ 922.4278, found 922.4290; Anal. calcd for: $C_{55}H_{59}N_3O_{10}$: C, 71.64; H, 6.45; N, 4.56, found C, 71.42; H, 6.54; N, 4.52. Data for α-anomer (**27**α):[10] TLC R_f=0.55 (2:1 hexane/AcOEt); $[\alpha]_D^{23}$=+47.5° (c 0.35, $CHCl_3$); IR (film) 3030, 2868, 2112, 1496, 1454, 1361, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (s, 3H, OC*H*$_3$), 3.39 (m, 1H, H-6′a), 3.47 (dd, J=8.0, 8.6 Hz, 1H, H-6′b), 3.55 (dd, J=3.5, 9.6 Hz, 1H, H-2), 3.63 (dd, J=4.0, 11.1 Hz, 1H, H-6a), 3.66 (dd, J=2.2, 11.1 Hz, 1H, H-6b), 3.76–3.85 (m, 5H, H-4, H-5, H-2′, H-3′, H-5′), 3.96 (brs, 1H, H-4′), 4.05 (dd, J=8.4, 9.6 Hz, 1H, H-3), 4.23 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.30 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.43 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.49 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.56 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.58 (d, J=3.5 Hz, 1H, H-1), 4.60 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.61 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.66 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.75 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.87 (d, J=10.6 Hz, 1H, OC*H*Ph), 5.06 (d, J=10.6 Hz, 1H, OC*H*Ph), 5.70 (d, J=2.8 Hz, 1H, H-1′), 7.20–7.39 (m, 30H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.3, 59.5, 68.5, 69.5, 69.7, 70.0, 72.1, 73.0, 73.1, 73.3, 73.5, 73.7, 74.8, 75.0, 80.4, 81.9, 97.7, 98.1, 127.39, 127.42, 127.67, 127.73, 127.8, 127.9, 128.0, 128.16, 128.21, 128.24, 128.3, 128.35, 128.37, 128.47, 128.49, 137.6, 137.8, 138.0, 138.2, 138.4, 138.6; FAB-HRMS m/z calcd for $C_{55}H_{60}N_3O_{10}$ $(M+H)^+$ 922.4278, found 922.4301.

4.4.3. Methyl 4-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (28). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.3 h) employing diphenyl phosphate **4a** (70.8 mg, 0.10 mmol), alcohol **23** (24.0 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **28** (55.0 mg, 81%, α:β=6:94) was obtained as a colorless oil from the crude product (82.5 mg) after column chromatography (silica gel 7 g, 7:1 hexane/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 5:1 hexane/THF; flow rate, 1.0 mL/min; t_R (α-anomer)=6.3 min, t_R (β-anomer)=7.4 min]. The α- and β-glycosides were separated by flash column chromatography with 8:1 hexane/AcOEt. Data for β-anomer (**28**β): TLC R_f=0.57 (2:1 hexane/AcOEt); $[\alpha]_D^{24}$=−33.8° (c 1.47, $CHCl_3$); IR (film) 2934, 2112, 1454, 1367, 1221, 1091, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J=5.6 Hz, 3H, H-6), 1.33 (s, 3H, CC*H*$_3$), 1.44 (s, 3H, CC*H*$_3$), 3.34 (dd, J=3.0, 10.4 Hz, 1H, H-3′), 3.36 (s, 3H, OC*H*$_3$), 3.47 (m, 1H, H-5′), 3.53 (dd, J=5.3, 9.1 Hz, 1H, H-6′a), 3.60–3.66 (m, 3H, H-4, H-5, H-6′b), 3.73 (dd, J=8.1, 10.4 Hz, 1H, H-2′), 3.86 (d, J=3.0 Hz, 1H, H-4′), 4.09 (d, J=5.6 Hz, 1H, H-2), 4.25 (dd, J=5.6, 5.8 Hz, 1H, H-3), 4.42 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.45 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.57 (d, J=11.4 Hz, 1H, OC*H*Ph), 4.67 (d, J=12.6 Hz, 1H, OC*H*Ph), 4.70 (d, J=12.6 Hz, 1H, OC*H*Ph), 4.71 (d, J=8.1 Hz, 1H, H-1′), 4.84 (s, 1H, H-1), 4.89 (d, J=11.4 Hz, 1H, OC*H*Ph), 7.25–7.39 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.7, 26.4, 27.8, 54.8, 63.4, 64.1, 68.4, 72.6, 73.48, 73.50, 74.7, 76.0, 78.2, 78.5, 80.7, 97.9 (C-1), 100.5 (C-1′), 109.2, 127.6, 127.75, 127.78, 127.83, 128.1, 128.2, 128.4, 128.5, 137.76, 137.80, 138.5; FAB-HRMS m/z calcd for $C_{37}H_{46}N_3O_9$ $(M+H)^+$ 676.3236, found 676.3252; Anal. calcd for: $C_{37}H_{45}N_3O_9$: C, 65.76; H, 6.71; N, 6.22, found C, 65.65; H, 6.69; N, 6.17. Data for α-anomer (**28**α): TLC R_f=0.63 (2:1 hexane/AcOEt); $[\alpha]_D^{23}$=+80.8° (c 0.99, $CHCl_3$); IR (film) 2986, 2934, 2112, 1496, 1454, 1367, 1221, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H, CC*H*$_3$), 1.34 (d, J=6.3 Hz, 3H, H-6), 1.37 (s, 3H, CC*H*$_3$), 3.32 (dd, J=6.4, 10.1 Hz, 1H, H-4), 3.35 (s, 3H, OC*H*$_3$), 3.50 (dd, J=4.6, 8.4 Hz, 1H, H-6′a), 3.67 (dd, J=8.4, 9.5 Hz, 1H, H-6′b), 3.69 (dq, J=10.1, 6.3 Hz, 1H, H-5), 3.89 (dd, J=3.4, 10.7 Hz, 1H, H-2′), 3.95 (dd, J=2.5, 10.7 Hz, 1H, H-3′), 4.07–4.10 (m, 2H, H-2, H-3), 4.16 (brs, 1H, H-4′), 4.24 (dd, J=4.6, 9.5 Hz, 1H, H-5′), 4.40 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.50 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.57 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.64 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.72 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.83 (s, 1H, H-1), 4.89 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.98 (d, J=3.4 Hz, 1H, H-1′), 7.24–7.40 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.5, 26.4, 27.9, 54.8, 60.1, 64.8, 67.5, 69.0, 71.9, 73.1, 73.5, 74.9, 76.0, 76.9, 80.4, 97.9, 98.8, 109.1, 127.5, 127.8, 127.9, 128.0, 128.2, 128.45, 128.49, 137.6, 138.0, 138.6; FAB-HRMS m/z calcd for $C_{37}H_{46}N_3O_9$ $(M+H)^+$ 676.3234, found 676.3232.

4.4.4. Methyl 2-azido-4-*O*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (29). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.5 h) employing diphenyl phosphate **4a** (70.8 mg, 0.10 mmol), alcohol **24** (43.9 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **29** (73.7 mg, 86%, α:β=8:92) was obtained as a colorless oil from the crude product (100.3 mg) after column chromatography (silica gel 6 g, 30:1 toluene/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=10.2 min, t_R (β-anomer)=14.8 min]. The α- and β-glycosides were separated by flash column chromatography with 30:1 toluene/AcOEt. Data for β-anomer (**29**β): TLC R_f=0.53 (2:1 hexane/AcOEt), 0.53 (10:1 toluene/AcOEt); $[\alpha]_D^{22}$=−39.7° (c 0.93, $CHCl_3$); IR (film) 3030, 2868, 2110, 1496, 1454, 1361, 1280, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (dd, J=2.8, 10.4 Hz, 1H, H-3′), 3.23 (dd, J=5.1, 8.4 Hz, 1H, H-5′), 3.29 (dd, J=5.1, 9.0 Hz, 1H, H-6′a), 3.35 (dd, J=7.6, 9.8 Hz, 1H, H-2), 3.38 (dd, J=8.3, 9.8 Hz, 1H, H-3), 3.43 (ddd, J=1.2, 3.5, 9.8 Hz, 1H, H-5), 3.48 (dd, J=8.4, 9.0 Hz, 1H, H-6′b), 3.55 (s, 3H, OC*H*$_3$), 3.75 (dd, J=8.2, 10.4 Hz, 1H, H-2′), 3.80 (dd, J=1.2, 11.1 Hz, 1H, H-6a), 3.87 (d, J=2.8 Hz, 1H, H-4′), 3.92 (dd, J=3.5, 11.1 Hz, 1H, H-6b), 4.01 (dd, J=8.3, 9.8 Hz, 1H, H-4), 4.12 (d, J=7.6 Hz, 1H, H-1), 4.23 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.25 (d, J=8.2 Hz, 1H, H-1′), 4.32 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.47 (d, J=12.1 Hz, 1H,

OC*H*Ph), 4.51 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.62 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.65 (d, J=10.3 Hz, 1H, OC*H*Ph), 4.68 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.69 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.89 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.98 (d, J=10.3 Hz, 1H, OC*H*Ph), 7.12–7.38 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.1, 63.8, 65.8, 67.7, 68.0, 72.20, 72.22, 73.2, 73.3, 73.4, 74.8, 74.9, 75.3, 76.1, 80.8, 81.4, 101.1 (C-1′), 102.8 (C-1), 127.4, 127.5, 127.66, 127.74, 127.8, 127.9, 128.0, 128.2, 128.3, 128.35, 128.39, 128.5, 137.6, 137.9, 138.1, 138.2, 138.6; FAB-HRMS m/z calcd for $C_{48}H_{53}N_6O_9$ $(M+H)^+$ 857.3874, found 857.3879; Anal. calcd for: $C_{48}H_{52}N_6O_9$: C, 67.27; H, 6.12; N, 9.81, found C, 67.36; H, 6.15; N, 9.89. Data for α-anomer (**29**α): TLC R_f=0.59 (2:1 hexane/AcOEt), 0.67 (10:1 toluene/AcOEt); $[\alpha]_D^{22}=+27.4°$ (c 1.07, $CHCl_3$); IR (film) 3030, 2868, 2110, 1496, 1454, 1361, 1280, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39–3.42 (m, 2H, H-2, H-6′a), 3.46 (dd, J=6.4, 9.0 Hz, 1H, H-6′b), 3.49 (m, 1H, H-5), 3.51 (dd, J=9.1, 9.5 Hz, 1H, H-3), 3.57 (s, 3H, OCH_3), 3.66 (dd, J=5.0, 11.0 Hz, 1H, H-6a), 3.74 (dd, J=2.3, 11.0 Hz, 1H, H-6b), 3.76 (dd, J=2.3, 10.9 Hz, 1H, H-3′), 3.81 (dd, J=3.7, 10.9 Hz, 1H, H-2′), 3.83 (dd, J=9.1, 9.2 Hz, 1H, H-4), 3.86 (t, J=6.4 Hz, 1H, H-5′), 3.95 (brs, 1H, H-4′), 4.22 (d, J=8.0 Hz, 1H, H-1), 4.28 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.36 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.46 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.49 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.572 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.574 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.64 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.80 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.84 (d, J=10.4 Hz, 1H, OC*H*Ph), 5.00 (d, J=10.4 Hz, 1H, OC*H*Ph), 5.63 (d, J=3.7 Hz, 1H, H-1′), 7.21–7.39 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.0, 59.5, 66.7, 68.5, 69.6, 70.2, 72.0, 72.9, 73.3, 73.4, 73.5, 74.6, 74.76, 74.78, 83.7, 97.9 (C-1′), 102.9 (C-1), 127.5, 127.6, 127.7, 127.78, 127.80, 127.9, 128.2, 128.3, 128.4, 128.49, 128.51, 137.5, 137.7, 137.8, 138.2, 138.3; FAB-HRMS m/z calcd for $C_{48}H_{53}N_6O_9$ $(M+H)^+$ 857.3874, found 857.3863.

4.5. Glycosidations of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxyglycosyl diphenyl phosphates 2b and 4b

4.5.1. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[1-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranosyl)iminopropyl]-α-D-glucopyranoside (30). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −65 °C, 4 h) employing diphenyl phosphate **2b** (56.3 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). A mixture of imidate **30** and disaccharide **31** (79.7 mg) was obtained as a colorless oil from the crude product (106.9 mg) after short column chromatography (silica gel 3 g, 2:1 hexane/AcOEt with 1% Et_3N). The anomeric ratio of the products was determined by HPLC analysis [eluent, 5:1:1 hexane/AcOEt/THF; flow rate, 1.0 mL/min; t_R (**30**α)=9.6 min, t_R (**31**α)=10.3 min, t_R (**31**β)=11.1 min, t_R (**30**β)=11.8 min]. The mixture was purified by flash column chromatography (silica gel 6 g, 3:1 hexane/AcOEt with 1% Et_3N) to give α-imidate **30**α (65.5 mg, 79%) as a colorless oil, along with an anomeric mixture of disaccharide **31** (3.4 mg, 4%, α:β=14:86) as a colorless oil. The α- and β-glycosides of disaccharide **31** were separated by flash column chromatography with 15:1 toluene/acetone. Data for α-anomer (**30**α): TLC R_f=0.46 (1:1 hexane/AcOEt); $[\alpha]_D^{23}=+87.7°$ (c 2.01, $CHCl_3$); IR (film) 2922, 2106, 1751, 1660, 1454, 1367, 1228, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J=7.6 Hz, 3H, CH_2CH_3), 2.01 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.35 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.41 (s, 3H, OCH_3), 3.52 (dd, J=4.1, 10.2 Hz, 1H, H-2′), 3.55 (dd, J=3.5, 9.6 Hz, 1H, H-2), 3.61 (dd, J=8.9, 10.1 Hz, 1H, H-4), 3.90 (ddd, J=1.5, 4.0, 10.1 Hz, 1H, H-5), 3.95 (m, 1H, H-6a), 4.01 (dd, J=8.9, 9.6 Hz, 1H, H-3), 4.22–4.26 (m, 3H, H-6b, H-5′, H-6′a), 4.42 (dd, J=1.7, 12.3 Hz, 1H, H-6′b), 4.60 (d, J=3.5 Hz, 1H, H-1), 4.61 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.67 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.84 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.85 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.08 (t, J=9.6 Hz, 1H, H-4′), 5.22 (d, J=4.1 Hz, 1H, H-1′), 5.63 (dd, J=9.6, 10.2 Hz, 1H, H-3′), 7.26–7.38 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.6, 20.6, 20.69, 20.73, 23.0, 55.2, 62.1, 62.2, 64.6, 68.0, 68.7, 69.2, 71.4, 73.4, 75.1, 75.8, 77.6, 80.0, 82.0, 83.0 (C-1′), 98.1 (C-1), 127.6, 127.8, 127.9, 128.0, 128.06, 128.11, 128.39, 128.44, 137.9, 138.1, 138.6, 169.7, 169.9, 170.3, 170.6; FAB-HRMS m/z calcd for $C_{43}H_{53}N_4O_{13}$ $(M+H)^+$ 833.3609, found 833.3600; Anal. calcd for: $C_{43}H_{52}N_4O_{13}$: C, 62.01; H, 6.30; N, 6.73, found C, 61.85; H, 6.23; N, 6.64. Data for β-anomer (**30**β): TLC R_f=0.40 (1:1 hexane/AcOEt); $[\alpha]_D^{21}=+9.07°$ (c 0.45, $CHCl_3$); IR (film) 2924, 2112, 1751, 1657, 1454, 1365, 1230, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, J=7.4 Hz, 3H, CH_2CH_3), 2.01 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.34 (dq, J=14.6, 7.4 Hz, 1H, C*H*CH_3), 2.36 (dq, J=14.6, 7.4 Hz, 1H, C*H*CH_3), 3.37 (s, 3H, OCH_3), 3.515 (dd, J=8.4, 9.4 Hz, 1H, H-2′), 3.523 (dd, J=9.0, 10.1 Hz, 1H, H-4), 3.54 (dd, J=3.6, 9.5 Hz, 1H, H-2), 3.75 (ddd, J=2.1, 5.6, 9.7 Hz, 1H, H-5′), 3.87 (ddd, J=1.8, 4.7, 10.1 Hz, 1H, H-5), 4.01 (dd, J=9.0, 9.5 Hz, 1H, H-3), 4.09 (dd, J=2.1, 12.3 Hz, 1H, H-6′a), 4.18 (dd, J=5.6, 12.3 Hz, 1H, H-6′b), 4.30 (dd, J=1.8, 12.2 Hz, 1H, H-6a), 4.42 (dd, J=4.7, 12.2 Hz, 1H, H-6b), 4.51 (d, J=8.4 Hz, 1H, H-1′), 4.56 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.61 (d, J=3.6 Hz, 1H, H-1), 4.67 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.80 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.87 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.00 (dd, J=8.2, 9.7 Hz, 1H, H-4′), 5.04 (dd, J=8.2, 9.4 Hz, 1H, H-3′), 7.26–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8, 20.6, 20.68, 20.74, 23.9, 55.1, 62.6, 64.6, 65.8, 68.8, 73.0, 73.4, 73.7, 75.1, 75.9, 78.0, 80.0, 82.1, 87.8 (C-1′), 98.0 (C-1), 127.7, 127.8, 127.88, 127.93, 128.07, 128.09, 128.41, 128.43, 128.5, 138.1, 138.2, 138.7, 169.7, 170.1, 170.6, 171.9; FAB-HRMS m/z calcd for $C_{43}H_{53}N_4O_{13}$ $(M+H)^+$ 833.3609, found 833.3580.

Data for methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranosyl)-α-D-glucopyranoside (**31**). Data for β-anomer (**31**β): TLC R_f=0.40 (1:1 hexane/AcOEt), 0.52 (5:1 toluene/acetone); $[\alpha]_D^{17}=-1.41°$ (c 1.58, $CHCl_3$); IR (film) 2930, 2112, 1753, 1454, 1365, 1228, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 3.38 (s, 3H, OCH_3), 3.52 (dd, J=9.2, 10.1 Hz, 1H, H-4), 3.52–3.55 (m, 2H, H-2, H-2′), 3.57 (ddd, J=2.4, 3.6, 9.5 Hz, 1H, H-5′), 3.70 (dd, J=4.7, 10.9 Hz, 1H, H-6a), 3.82 (ddd, J=1.7, 4.7, 10.1 Hz, 1H, H-5), 4.00 (dd, J=9.2, 9.3 Hz, 1H, H-3), 4.090 (dd, J=1.7, 10.9 Hz, 1H, H-6b), 4.094 (dd, J=

2.4, 12.1 Hz, 1H, H-6′a), 4.22 (dd, J=3.6, 12.1 Hz, 1H, H-6′b), 4.23 (d, J=8.1 Hz, 1H, H-1′), 4.61 (d, J=3.5 Hz, 1H, H-1), 4.62 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.65 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.79 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.94 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.96–5.00 (m, 3H, H-3′, H-4′, OC*H*Ph), 7.26–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5, 20.61, 20.63, 55.3, 61.8, 63.8, 68.4, 68.7, 69.7, 71.7, 72.6, 73.4, 74.8, 75.7, 77.6, 79.8, 82.0, 98.2 (C-1), 102.0 (C-1′), 127.6, 127.7, 127.90, 127.93, 128.1, 128.2, 128.35, 128.43, 128.5, 138.1, 138.3, 138.7, 169.5, 169.9, 170.5; FAB-HRMS *m/z* calcd for $C_{40}H_{47}N_3O_{13}Na$ $(M+Na)^+$ 800.3007, found 800.3033; Anal. calcd for: $C_{40}H_{47}N_3O_{13}$: C, 61.77; H, 6.09; N, 5.40, found C, 61.64; H, 6.08; N, 5.31. Data for α-anomer (**31**α): TLC R_f=0.42 (1:1 hexane/AcOEt), 0.56 (5:1 toluene/acetone); $[\alpha]_D^{20}=+119.6°$ (*c* 1.28, $CHCl_3$); IR (film) 3030, 2932, 2108, 1751, 1454, 1367, 1226, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 3.30 (dd, J=3.4, 10.7 Hz, 1H, H-2′), 3.39 (s, 3H, OCH_3), 3.53 (dd, J=3.5, 9.8 Hz, 1H, H-2), 3.54 (dd, J=8.7, 10.2 Hz, 1H, H-4), 3.68 (m, 1H, H-6a), 3.77–3.81 (m, 2H, H-5, H-6b), 3.92 (ddd, J=2.2, 4.3, 10.1 Hz, 1H, H-5′), 3.99 (dd, J=2.2, 12.5 Hz, 1H, H-6′a), 4.01 (dd, J=8.7, 9.8 Hz, 1H, H-3), 4.15 (dd, J=4.3, 12.5 Hz, 1H, H-6′b), 4.59 (d, J=3.5 Hz, 1H, H-1), 4.62 (d, J=11.5 Hz, 1H, OC*H*Ph), 4.66 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.78 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.97 (d, J=11.5 Hz, 1H, OC*H*Ph), 4.99 (d, J=11.2 Hz, 1H, OC*H*Ph), 5.00 (dd, J=9.4, 10.1 Hz, 1H, H-4′), 5.04 (d, J=3.4 Hz, 1H, H-1′), 5.40 (dd, J=9.4, 10.7 Hz, 1H, H-3′), 7.26–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.57, 20.64, 20.7, 55.2, 61.0, 61.7, 66.7, 67.5, 68.5, 69.9, 70.3, 73.4, 74.9, 75.7, 77.5, 80.0, 82.0, 97.95 (C-1′), 98.04 (C-1), 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.37, 128.42, 138.1, 138.3, 138.7, 169.6, 169.9, 170.5; FAB-HRMS *m/z* calcd for $C_{40}H_{47}N_3O_{13}Na$ $(M+Na)^+$ 800.3007, found 800.3034.

4.5.2. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-[1-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl)iminopropyl]-α-D-glucopyranoside (32). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −65 °C, 3 h) employing diphenyl phosphate **4b** (56.3 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). A mixture of imidate **32** and disaccharide **33** (80.3 mg) was obtained as a colorless oil from the crude product (102.4 mg) after short column chromatography (silica gel 3 g, 2:1 hexane/AcOEt with 1% Et_3N). The anomeric ratio of the products was determined by HPLC analysis [eluent, 4:1 hexane/THF; flow rate, 1.0 mL/min; t_R (**32**α)=19.3 min, t_R (**33**α)=21.7 min, t_R (**33**β)=26.6 min, t_R (**32**β)=30.4 min]. The mixture was purified by flash column chromatography (silica gel 6 g, 4:1 hexane/acetone with 1% Et_3N) to give α-imidate **32**α (56.4 mg, 68%) as a colorless oil, along with an anomeric mixture of disaccharide **33** (6.8 mg, 9%, α:β=3:97) as a white solid. The α- and β-glycosides of disaccharide **33** were separated by flash column chromatography with 1:1 hexane/Et_2O. Data for α-anomer (**32**α): TLC R_f=0.47 (1:1 hexane/AcOEt); $[\alpha]_D^{22}=+72.7°$ (*c* 1.50, $CHCl_3$); IR (film) 2916, 2108, 1751, 1662, 1454, 1371, 1228, 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.99 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 2.35 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.40 (s, 3H, OCH_3), 3.55 (dd, J=3.6, 9.6 Hz, 1H, H-2), 3.60 (dd, J=9.0, 10.0 Hz, 1H, H-4), 3.81 (dd, J=4.0, 10.8 Hz, 1H, H-2′), 3.88 (ddd, J=1.6, 4.3, 10.0 Hz, 1H, H-5), 3.97 (dd, J=6.8, 11.3 Hz, 1H, H-6′a), 4.01 (dd, J=9.0, 9.6 Hz, 1H, H-3), 4.04 (dd, J=6.6, 11.3 Hz, 1H, H-6′b), 4.23 (dd, J=4.3, 12.1 Hz, 1H, H-6a), 4.36 (dd, J=1.6, 12.1 Hz, 1H, H-6b), 4.39 (ddd, J=0.7, 6.6, 6.8 Hz, 1H, H-5′), 4.59 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.61 (d, J=3.6 Hz, 1H, H-1), 4.68 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.81 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.83 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.85 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.24 (d, J=4.0 Hz, 1H, H-1′), 5.44 (dd, J=0.7, 3.3 Hz, 1H, H-4′), 5.47 (dd, J=3.3, 10.8 Hz, 1H, H-3′), 7.26–7.38 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.6, 20.6, 20.66, 20.70, 23.0, 55.2, 58.6, 62.0, 64.5, 67.0, 68.0, 68.7, 69.3, 73.4, 75.2, 75.8, 77.7, 80.0, 82.0, 83.4 (C-1′), 98.1 (C-1), 127.6, 127.8, 127.9, 128.00, 128.02, 128.1, 128.4, 128.5, 138.0, 138.1, 138.7, 169.8, 170.0, 170.1, 170.3; FAB-HRMS *m/z* calcd for $C_{43}H_{53}N_4O_{13}$ $(M+H)^+$ 833.3609, found 833.3626; Anal. calcd for: $C_{43}H_{52}N_4O_{13}$: C, 62.01; H, 6.30; N, 6.73, found C, 61.95, H, 6.14, N, 6.69. Data for β-anomer (**32**β): TLC R_f=0.45 (1:1 hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (dd, J=7.0, 7.3 Hz, 3H, CH_2CH_3), 2.01 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 2.35 (dq, J=14.4, 7.3 Hz, 1H, C*H*CH$_3$), 2.38 (dq, J=14.4, 7.0 Hz, 1H, C*H*CH$_3$), 3.38 (s, 3H, OCH_3), 3.545 (dd, J=3.6, 9.7 Hz, 1H, H-2), 3.546 (dd, J=8.9, 9.9 Hz, 1H, H-4), 3.80 (dd, J=8.3, 10.9 Hz, 1H, H-2′), 3.88 (ddd, J=2.1, 4.5, 9.9 Hz, 1H, H-5), 3.94 (dd, J=6.5, 6.7 Hz, 1H, H-5′), 4.01 (dd, J=8.9, 9.7 Hz, 1H, H-3), 4.10 (dd, J=6.5, 11.4 Hz, 1H, H-6′a), 4.12 (dd, J=6.7, 11.4 Hz, 1H, H-6′b), 4.35 (dd, J=2.1, 12.1 Hz, 1H, H-6a), 4.39 (dd, J=4.5, 12.1 Hz, 1H, H-6b), 4.50 (d, J=8.3 Hz, 1H, H-1′), 4.57 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.61 (d, J=3.6 Hz, 1H, H-1), 4.67 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.80 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.85 (dd, J=3.4, 10.9 Hz, 1H, H-3′), 4.86 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.98 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.38 (d, J=3.4 Hz, 1H, H-4′), 7.25–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8, 20.6, 20.66, 20.68, 23.8, 55.1, 61.8, 62.8, 64.7, 66.8, 68.7, 71.3, 72.5, 73.4, 75.2, 75.9, 78.1, 80.1, 82.1, 88.3 (C-1′), 98.0 (C-1), 127.67, 127.69, 127.9, 128.06, 128.08, 128.38, 128.42, 128.5, 138.1, 138.2, 138.7, 169.9, 170.2, 170.4, 171.8; FAB-HRMS *m/z* calcd for $C_{43}H_{53}N_4O_{13}$ $(M+H)^+$ 833.3609, found 833.3614.

Data for methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl)-α-D-glucopyranoside (**33**).[9] Data for β-anomer (**33**β):[9] TLC R_f=0.42 (1:1 hexane/AcOEt), 0.24 (1:3 hexane/Et_2O); mp 145.0–146.0 °C (colorless needles from AcOEt–hexane); $[\alpha]_D^{24}=-9.46°$ (*c* 1.00, $CHCl_3$); IR (KBr) 3032, 2926, 2114, 1751, 1454, 1369, 1242, 1076 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 3.39 (s, 3H, OCH_3), 3.53 (dd, J=8.8, 10.2 Hz, 1H, H-4), 3.54 (dd, J=3.5, 9.6 Hz, 1H, H-2), 3.70 (dd, J=4.8, 11.0 Hz, 1H, H-6a), 3.72 (dd, J=8.1, 10.9 Hz, 1H, H-2′), 3.77 (dd, J=6.8, 7.0 Hz, 1H, H-5′), 3.83 (ddd, J=1.5, 4.5, 10.2 Hz, 1H, H-5), 4.01 (dd, J=8.8, 9.6 Hz, 1H, H-3), 4.07–4.14 (m, 3H, H-6b, H-6′a, H-6′b), 4.22 (d, J=8.1 Hz, 1H, H-1′), 4.62 (d, J=3.5 Hz,

1H, H-1), 4.63 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.65 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.76 (dd, J=3.3, 10.9 Hz, 1H, H-3′), 4.80 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.82 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.94 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.30 (d, J=3.3 Hz, 1H, H-4′), 7.27–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.56, 20.58, 20.61, 55.3, 60.9, 61.1, 66.3, 68.8, 69.7, 70.6, 71.3, 73.4, 75.7, 77.7, 79.8, 82.0, 98.2 (C-1), 102.4 (C-1′), 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.45, 128.46, 138.1, 138.3, 138.7, 169.8, 170.0, 170.3; FAB-HRMS m/z calcd for $C_{40}H_{47}N_3O_{13}Na$ $(M+Na)^+$ 800.3007, found 800.2985; Anal. calcd for: $C_{40}H_{47}N_3O_{13}$: C, 61.77; H, 6.09; N, 5.40, found C, 61.75; H, 6.09; N, 5.30. Data for α-anomer (**33**α):[9] TLC R_f=0.43 (1:1 hexane/AcOEt), 0.31 (1:3 hexane/Et_2O); $[\alpha]_D^{25}=+96.4°$ (c 1.01, $CHCl_3$); IR (film) 2928, 2110, 1751, 1454, 1371, 1228, 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO), 3.38 (s, 3H, OCH_3), 3.51 (dd, J=9.0, 9.9 Hz, 1H, H-4), 3.52 (dd, J=3.5, 9.7 Hz, 1H, H-2), 3.62 (dd, J=3.4, 11.2 Hz, 1H, H-2′), 3.70 (m, 1H, H-6a), 3.75–3.79 (m, 2H, H-5, H-6b), 3.96–4.02 (m, 2H, H-3, H-6′a), 4.05 (dd, J=6.0, 10.9 Hz, 1H, H-6′b), 4.09 (dd, J=6.0, 6.9 Hz, 1H, H-5′), 4.59 (d, J=3.5 Hz, 1H, H-1), 4.61 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.66 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.79 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.81 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.94 (d, J=11.3 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.06 (d, J=3.6 Hz, 1H, H-1′), 5.28 (dd, J=3.3, 11.2 Hz, 1H, H-3′), 5.39 (brd, J=3.3 Hz, 1H, H-4′), 7.26–7.37 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5, 20.6, 55.2, 57.5, 61.6, 66.6, 66.7, 67.6, 68.0, 69.9, 73.4, 74.9, 75.7, 77.6, 80.0, 82.0, 97.9, 98.1, 127.6, 127.7, 127.85, 127.94, 128.1, 128.3, 128.4, 138.1, 138.2, 138.6, 169.7, 169.9, 170.2; FAB-HRMS m/z calcd for $C_{40}H_{47}N_3O_{13}Na$ $(M+Na)^+$ 800.3007, found 800.3007.

4.6. Glycosidations of 2-azido-4,6-*O*-benzylidene-2-deoxyglycosyl diphenyl phosphates 2c and 4c

4.6.1. Methyl 6-*O*-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (35). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −45 °C, 4 h) employing diphenyl phosphate **2c** (56.7 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). A mixture of disaccharide **35** and imidate **36** (80.3 mg) was obtained as a colorless oil from the crude product (104.6 mg) after short column chromatography (silica gel 3 g, 3:1 hexane/AcOEt with 1% Et_3N). The anomeric ratio of the products was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (**36**α)=17.4 min, t_R (**35**β)=21.5 min, t_R (**36**β)=25.4 min, t_R (**35**α)=30.6 min]. The mixture was purified by flash column chromatography (silica gel 8 g, 5:1 hexane/AcOEt with 1% Et_3N) to give α-imidate **36** (70.4 mg, 84%) as a white amorphous, along with an anomeric mixture of disaccharide **35** (5.0 mg, 6%, α:β=8:92) as a white solid. The α- and β-glycosides of disaccharide **35** were separated by flash column chromatography with 6:1 hexane/AcOEt. Data for β-anomer (**35**β): TLC R_f=0.38 (2:1 hexane/AcOEt); mp 149.0–149.5 °C (colorless needles from AcOEt–hexane); $[\alpha]_D^{23}=-35.5°$ (c 1.01, $CHCl_3$); IR (film) 2928, 2112, 1753, 1454, 1369, 1222, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 3.38 (s, 3H, OCH_3), 3.41 (ddd, J=5.0, 9.4, 10.1 Hz, 1H, H-5′), 3.53 (dd, J=8.0, 9.8 Hz, 1H, H-2′), 3.54 (dd, J=3.5, 9.4 Hz, 1H, H-2), 3.56 (dd, J=9.1, 9.3 Hz, 1H, H-4), 3.59 (dd, J=9.4, 9.7 Hz, 1H, H-4′), 3.75 (dd, J=4.2, 10.4 Hz, 1H, H-6a), 3.76 (dd, J=10.1, 10.5 Hz, 1H, H-6′ax), 3.80 (ddd, J=1.4, 4.2, 9.3 Hz, 1H, H-5), 4.01 (dd, J=9.1, 9.4 Hz, 1H, H-3), 4.08 (dd, J=1.4, 10.4 Hz, 1H, H-6b), 4.30 (dd, J=5.0, 10.5 Hz, 1H, H-6′eq), 4.35 (d, J=8.0 Hz, 1H, H-1′), 4.61 (d, J=3.5 Hz, 1H, H-1), 4.64 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.65 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.80 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.83 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.95 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.15 (dd, J=9.7, 9.8 Hz, 1H, H-3′), 5.46 (s, 1H, C*H*Ph), 7.28–7.36 (m, 18H, Ar-H), 7.41 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 55.3, 64.8, 66.4, 68.4, 68.8, 69.6, 71.3, 73.4, 74.9, 75.7, 77.6, 78.5, 79.7, 82.0, 98.2 (C-1), 101.5, 102.4 (C-1′), 127.6, 127.77, 127.80, 127.9, 128.0, 128.15, 128.23, 128.4, 128.45, 128.49, 129.1, 136.7, 138.1, 138.2, 138.7, 169.7; FAB-HRMS m/z calcd for $C_{43}H_{47}N_3O_{11}Na$ $(M+Na)^+$ 804.3109, found 804.3135; Anal. calcd for: $C_{43}H_{47}N_3O_{11}$: C, 66.06; H, 6.06; N, 5.37, found C, 65.94; H, 6.13; N, 5.27. Data for α-anomer (**35**α): TLC R_f=0.32 (2:1 hexane/AcOEt); mp 152.0–153.0 °C (colorless fine needles from AcOEt/hexane); $[\alpha]_D^{21}=+106.9°$ (c 0.76, $CHCl_3$); IR (film) 2926, 2112, 1753, 1454, 1369, 1222, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 3.21 (dd, J=3.6, 10.4 Hz, 1H, H-2′), 3.39 (3H, s, OCH_3), 3.54 (dd, J=3.5, 9.7 Hz, 1H, H-2), 3.55 (dd, J=8.9, 10.5 Hz, 1H, H-5), 3.58 (dd, J=9.5, 9.8 Hz, 1H, H-4′), 3.69 (m, 1H, H-6a), 3.70 (dd, J=10.2, 10.3 Hz, 1H, H-6′ax), 3.77–3.83 (m, 2H, H-5, H-6b), 3.91 (ddd, J=4.9, 9.8, 10.2 Hz, 1H, H-5′), 4.01 (dd, J=8.9, 9.7 Hz, 1H, H-3), 4.20 (dd, J=4.9, 10.3 Hz, 1H, H-6′eq), 4.59 (d, J=3.5 Hz, 1H, H-1), 4.63 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.65 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.77 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.82 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.95 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.99 (d, J=11.0 Hz, 1H, OC*H*Ph), 5.02 (d, J=3.6 Hz, 1H, H-1′), 5.48 (s, 1H, C*H*Ph), 5.53 (dd, J=9.5, 10.4 Hz, 1H, H-3′), 7.26–7.36 (m, 18H, Ar-H), 7.42 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9, 55.3, 61.8, 62.7, 66.9, 68.7, 68.8, 69.9, 73.5, 75.1, 75.7, 77.5, 79.5, 80.0, 82.1, 98.1 (C-1), 99.1 (C-1′), 101.7, 127.5, 127.86, 127.87, 127.93, 128.1, 128.2, 128.37, 128.43, 128.5, 129.1, 136.9, 138.1, 138.8, 169.7; FAB-HRMS m/z calcd for $C_{43}H_{47}N_3O_{11}Na$ $(M+Na)^+$ 804.3109, found 804.3134.

Data for methyl 6-*O*-[1-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosyl)iminopropyl]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**36**α): TLC R_f=0.40 (2:1 hexane/AcOEt); $[\alpha]_D^{20}=+81.0°$ (c 2.30, $CHCl_3$); IR (film) 2926, 2106, 1753, 1660, 1454, 1369, 1224, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J=7.6 Hz, 3H, CH_2CH_3), 2.15 (s, 3H, CH_3CO), 2.35 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.397 (dd, J=4.2, 10.0 Hz, 1H, H-2′), 3.399 (s, 3H, OCH_3), 3.52 (dd, J=3.6, 9.7 Hz, 1H, H-2), 3.63 (dd, J=8.8, 10.5 Hz, 1H, H-4), 3.64–3.70 (m, 2H, H-4′, H-6′ax), 3.88 (ddd, J=1.6, 4.1, 10.5 Hz, 1H, H-5), 4.00 (dd, J=8.8, 9.7 Hz, 1H, H-3), 4.14–4.20 (m, 2H, H-5′, H-6′eq), 4.23 (dd, J=4.1, 12.3 Hz, 1H, H-6a), 4.53 (dd, J=1.6, 12.3 Hz, 1H, H-6b), 4.617 (d, J=10.5 Hz, 1H, OC*H*Ph), 4.619 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.64 (d, J=3.6 Hz, 1H, H-1), 4.74

(d, J=12.1 Hz, 1H, OC*H*Ph), 4.83 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.84 (d, J=10.5 Hz, 1H, OC*H*Ph), 4.97 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.21 (d, J=4.2 Hz, 1H, H-1′), 5.52 (s, 1H, C*H*Ph), 5.76 (dd, J=9.5, 10.0 Hz, 1H, H-3′), 7.23 (m, 1H, Ar-H), 7.25–7.36 (m, 17H, Ar-H), 7.44 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.7, 20.9, 23.0, 55.2, 62.7, 63.3, 64.4, 68.9, 69.2, 69.8, 73.2, 75.2, 75.8, 77.6, 80.1, 80.3, 82.1, 84.1 (C-1′), 97.9 (C-1), 101.5, 126.1, 127.6, 127.79, 127.83, 128.0, 128.1, 128.2, 128.38, 128.40, 128.5, 129.0, 137.1, 138.0, 138.2, 138.7, 169.7, 170.4; FAB-HRMS m/z calcd for $C_{46}H_{53}N_4O_{11}$ $(M+H)^+$ 837.3711, found 837.3727; Anal. calcd for: $C_{46}H_{52}N_4O_{11}$: C, 66.02; H, 6.26; N, 6.69, found C, 65.90; H, 6.27; N, 6.66.

4.6.2. Methyl 6-*O*-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (37).[9] The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 3 h) employing diphenyl phosphate **4c** (56.7 mg, 0.10 mmol), alcohol **7** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **37** (60.6 mg, 78%, α:β=3:97) was obtained as a white solid from the crude product (98.4 mg) after column chromatography (silica gel 6 g, 40:1→30:1 CH_2Cl_2/AcOEt with 0.5% Et_3N), along with α-imidate **38** (8.5 mg, 10%) as a colorless oil. The anomeric ratio of the product was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=29.5 min, t_R (β-anomer)=79.6 min]. The α- and β-glycosides were separated by flash column chromatography with 4:1 hexane/AcOEt. Data for β-anomer (**37**β):[9] TLC R_f=0.20 (2:1 hexane/AcOEt), 0.40 (10:1 CH_2Cl_2/AcOEt); mp 149.0–150.0 °C (colorless fine needles from AcOEt–hexane); $[\alpha]_D^{23}=+31.1°$ (c 1.01, $CHCl_3$); IR (KBr) 3032, 2918, 2114, 1745, 1454, 1367, 1246, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.37 (brs, 1H, H-5′), 3.39 (s, 3H, OCH_3), 3.53 (dd, J=8.2, 10.1 Hz, 1H, H-4), 3.55 (dd, J=3.6, 9.7 Hz, 1H, H-2), 3.71 (dd, J=5.1, 11.1 Hz, 1H, H-6a), 3.85 (ddd, J=1.7, 5.1, 10.1 Hz, 1H, H-5), 3.95 (dd, J=8.0, 10.7 Hz, 1H, H-2′), 3.99–4.02 (m, 2H, H-3, H-6′a), 4.16 (dd, J=1.7, 11.1 Hz, 1H, H-6b), 4.23 (d, J=8.0 Hz, 1H, H-1′), 4.27–4.29 (m, 2H, H-4′, H-6′b), 4.62 (d, J=3.6 Hz, 1H, H-1), 4.64 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.65 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.68 (dd, J=3.5, 10.7 Hz, 1H, H-3′), 4.78 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.93 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.99 (d, J=11.0 Hz, 1H, OC*H*Ph), 5.48 (s, 1H, C*H*Ph), 7.25–7.38 (m, 18H, Ar-H), 7.47 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9, 55.3, 60.3, 66.3, 68.6, 68.8, 69.9, 72.5, 72.6, 73.4, 74.9, 75.7, 77.9, 79.9, 82.1, 98.1 (C-1), 100.9, 102.5 (C-1′), 126.2, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.36, 128.44, 129.1, 137.5, 138.1, 138.4, 138.8, 170.5; FAB-HRMS m/z calcd for $C_{43}H_{47}N_3O_{11}Na$ $(M+Na)^+$ 804.3108, found 804.3094; Anal. calcd for: $C_{43}H_{47}N_3O_{11}$: C, 66.06; H, 6.06; N, 5.37, found C, 66.07; H, 5.92; N, 5.41. Data for α-anomer (**37**α):[9] TLC R_f=0.34 (2:1 hexane/AcOEt), 0.53 (10:1 CH_2Cl_2/AcOEt); $[\alpha]_D^{22}=+153.1°$ (c 1.00, $CHCl_3$); IR (KBr) 3032, 2914, 2110, 1745, 1496, 1454, 1371, 1228, 1145, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.38 (s, 3H, OCH_3), 3.52–3.56 (m, 2H, H-2, H-4), 3.56 (brs, 1H, H-5′), 3.70 (m, 1H, H-6a), 3.77–3.81 (m, 2H, H-5, H-6b), 3.88 (d, J=12.5 Hz, 1H, OC*H*Ph), 3.90 (dd, J=3.1, 11.0 Hz, 1H, H-2′), 4.01 (t, J=9.2 Hz, 1H, H-3), 4.13 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.38 (d, J=3.1 Hz, 1H, H-4′), 4.59 (d, J=3.6 Hz, 1H, H-1), 4.60 (d, J=11.6 Hz, 1H, OC*H*Ph), 4.66 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.79 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, J=10.9 Hz, 1H, OC*H*Ph), 4.96 (d, J=11.6 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.12 (d, J=3.1 Hz, 1H, H-1′), 5.22 (dd, J=3.1, 11.0 Hz, 1H, H-3′), 5.47 (s, 1H, C*H*Ph), 7.27–7.36 (m, 18H, Ar-H), 7.47 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9, 55.1, 57.2, 62.3, 66.6, 69.0, 69.3, 69.9, 73.3, 73.4, 74.8, 75.7, 77.8, 80.0, 82.0, 98.0 (C-1), 98.6 (C-1′), 100.7, 126.1, 127.56, 127.63, 127.9, 128.0, 128.07, 128.14, 128.3, 128.4, 129.0, 137.5, 138.1, 138.4, 138.7, 170.5; FAB-HRMS m/z calcd for $C_{43}H_{47}N_3O_{11}Na$ $(M+Na)^+$ 804.3108, found 804.3093.

Data for methyl 6-*O*-[1-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl)iminopropyl]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**38**): TLC R_f=0.34 (2:1 hexane/AcOEt); $[\alpha]_D^{22}=+104.2°$ (c 0.31, $CHCl_3$); IR (film) 3032, 2908, 2108, 1743, 1662, 1454, 1373, 1228, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J=7.6 Hz, 3H, CH_2CH_3), 2.15 (s, 3H, CH_3CO), 2.36 (q, J=7.6 Hz, 2H, CH_2CH$_3$), 3.39 (s, 3H, OCH_3), 3.55 (dd, J=3.6, 9.6 Hz, 1H, H-2), 3.59 (dd, J=8.9, 10.1 Hz, 1H, H-4), 3.87 (ddd, J=1.7, 4.5, 10.1 Hz, 1H, H-5), 3.92 (brs, 1H, H-5′), 3.94 (dd, J=1.6, 12.6 Hz, 1H, H-6′a), 4.01 (dd, J=8.9, 9.6 Hz, 1H, H-3), 4.09 (dd, J=4.0, 10.9 Hz, 1H, H-2′), 4.12 (dd, J=1.5, 12.6 Hz, 1H, H-6′b), 4.20 (dd, J=4.5, 12.2 Hz, 1H, H-6a), 4.36 (dd, J=1.7, 12.2 Hz, 1H, H-6b), 4.43 (d, J=3.5 Hz, 1H, H-4′), 4.59 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.60 (d, J=3.6 Hz, 1H, H-1), 4.67 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.84 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.86 (d, J=11.0 Hz, 1H, OC*H*Ph), 4.99 (d, J=10.8 Hz, 1H, OC*H*Ph), 5.33 (d, J=4.0 Hz, 1H, H-1′), 5.41 (dd, J=3.5, 10.9 Hz, 1H, H-3′), 5.50 (s, 1H, C*H*Ph), 7.26–7.39 (m, 18H, Ar-H), 7.51 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8, 21.1, 22.9, 55.2, 58.3, 62.9, 64.4, 68.8, 69.5, 70.7, 73.4, 73.7, 75.2, 75.9, 77.9, 80.0, 82.1, 83.6 (C-1′), 98.2 (C-1), 100.8, 126.2, 127.66, 127.73, 127.9, 127.97, 128.04, 128.1, 128.2, 128.4, 128.5, 129.0, 137.7, 138.1, 138.2, 138.7, 169.4, 170.6; FAB-HRMS m/z calcd for $C_{46}H_{53}N_4O_{11}$ $(M+H)^+$ 837.3711, found 837.3692.

4.6.3. Methyl 4-*O*-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (39). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 3 h) employing diphenyl phosphate **4c** (56.7 mg, 0.10 mmol), alcohol **8** (51.1 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **39** (70.1 mg, 90%, α:β=4:96) was obtained as a colorless oil from the crude product (97.7 mg) after column chromatography (silica gel 6 g, 15:1 toluene/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=28.6 min, t_R (β-anomer)=60.0 min]. The α- and β-glycosides were separated by flash column chromatography with 3:1 hexane/AcOEt. Data for β-anomer (**39**β): TLC R_f=0.23 (2:1 hexane/AcOEt), 0.21 (5:1 toluene/AcOEt); $[\alpha]_D^{27}=+24.2°$ (c 1.17, $CHCl_3$); IR (film) 3032, 2903, 2114, 1747, 1454, 1367, 1232, 1047, 912 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H,

CH_3CO), 2.97 (brs, 1H, H-5′), 3.39 (s, 3H, OCH_3), 3.53 (dd, J=3.6, 9.4 Hz, 1H, H-2), 3.72 (dd, J=1.6, 10.8 Hz, 1H, H-6a), 3.78 (m, 1H, H-5), 3.81 (dd, J=8.1, 10.7 Hz, 1H, H-2′), 3.85 (dd, J=1.7, 12.5 Hz, 1H, H-6′a), 3.92 (dd, J=9.0, 9.4 Hz, 1H, H-3), 3.98 (dd, J=9.0, 9.8 Hz, 1H, H-4), 3.99 (dd, J=2.5, 10.8 Hz, 1H, H-6b), 4.192 (dd, J=1.0, 12.5 Hz, 1H, H-6′b), 4.194 (d, J=3.7 Hz, 1H, H-4′), 4.25 (d, J=8.1 Hz, 1H, H-1′), 4.42 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.47 (dd, J=3.7, 10.7 Hz, 1H, H-3′), 4.60 (d, J=3.6 Hz, 1H, H-1), 4.63 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.72 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.78 (d, J=10.6 Hz, 1H, OC*H*Ph), 4.81 (d, J=12.1 Hz, 1H, OC*H*Ph), 5.10 (d, J=10.6 Hz, 1H, OC*H*Ph), 5.46 (s, 1H, C*H*Ph), 7.17–7.22 (m, 3H, Ar-H), 7.25–7.35 (m, 13H, Ar-H), 7.45–7.47 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.9, 55.3, 60.9, 66.2, 68.2, 68.6, 69.7, 72.5, 72.8, 73.4, 73.6, 75.9, 77.4, 79.2, 80.3, 98.3 (C-1), 100.9, 101.2 (C-1′), 127.8, 127.9, 128.06, 128.08, 128.10, 128.11, 128.2, 128.35, 128.40, 128.5, 129.0, 137.7, 138.0, 138.4, 139.1, 170.4; FAB-HRMS *m/z* calcd for $C_{43}H_{48}N_3O_{11}$ $(M+H)^+$ 782.3289, found 782.3281; Anal. calcd for: $C_{43}H_{47}N_3O_{11}$: C, 66.06; H, 6.06; N, 5.37, found C, 65.94; H, 6.13; N, 5.27. Data for α-anomer (**39**α): TLC R_f=0.35 (2:1 hexane/AcOEt), 0.38 (5:1 toluene/AcOEt); $[\alpha]_D^{24}=+99.5°$ (*c* 1.24, $CHCl_3$); IR (film) 3032, 2908, 2110, 1743, 1496, 1454, 1369, 1228, 1143, 1101, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 3.40 (s, 3H, OCH_3), 3.54 (brs, 1H, H-5′), 3.57 (dd, J=3.5, 9.6 Hz, 1H, H-2), 3.61 (dd, J=1.2, 12.6 Hz, 1H, H-6′a), 3.63 (dd, J=1.4, 11.2 Hz, 1H, H-6a), 3.75 (dd, J=4.2, 11.2 Hz, 1H, H-6b), 3.80 (ddd, J=1.4, 4.2, 9.8 Hz, 1H, H-5), 3.85 (dd, J=3.6, 11.2 Hz, 1H, H-2′), 3.87 (brd, J=12.6 Hz, 1H, H-6′b), 3.94 (dd, J=8.7, 9.8 Hz, 1H, H-4), 4.08 (dd, J=8.7, 9.6 Hz, 1H, H-3), 4.29 (d, J=3.3 Hz, 1H, H-4′), 4.53 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.59 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.60 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.61 (d, J=3.5 Hz, 1H, H-1), 4.73 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.85 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.10 (d, J=10.9 Hz, 1H, OC*H*Ph), 5.20 (dd, J=3.3, 11.2 Hz, 1H, H-3′), 5.38 (s, 1H, C*H*Ph), 5.85 (d, J=3.6 Hz, 1H, H-1′), 7.26–7.38 (m, 18H, Ar-H), 7.43 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0, 55.3, 57.0, 62.7, 69.0, 69.1, 69.45, 69.48, 73.1, 73.3, 73.4, 73.5, 74.8, 80.6, 81.9, 97.8, 98.0, 100.6, 126.1, 127.3, 127.36, 127.39, 127.7, 128.0, 128.1, 128.2, 128.3, 128.48, 128.50, 129.0, 137.5, 137.9, 138.0, 138.7, 170.5; FAB-HRMS *m/z* calcd for $C_{43}H_{48}N_3O_{11}$ $(M+H)^+$ 782.3289, found 782.3306.

4.6.4. Allyl 3-*O*-(3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-D-galactopyranosyl)-4,6-*O*-benzylidene-β-D-galactopyranoside (40).[22b]

The glycosidation was performed according to the typical procedure [1.55 mL EtCN–CH_2Cl_2 (30:1), −78 °C, 2 h] employing diphenyl phosphate **4c** (56.7 mg, 0.10 mmol), alcohol **34** (33.9 mg, 0.11 mmol), and TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol). An anomeric mixture of disaccharide **40** (50.1 mg, 80%, α:β=1:99) was obtained as a colorless film from the crude product (87.4 mg) after column chromatography (silica gel 6 g, 5:1 toluene/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 1:1.5 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer)=9.4 min, t_R (β-anomer)=14.6 min]. The α- and β-glycosides were separated by flash column chromatography with 1:1 hexane/AcOEt. Data for β-anomer (**40**β):[22b] TLC R_f=0.36 (1:3 hexane/AcOEt), 0.36 (3:1 toluene/acetone); $[\alpha]_D^{21}=+24.2°$ (*c* 1.00, $CHCl_3$); IR (KBr) 3514, 2870, 2116, 1745, 1454, 1369, 1236, 1051, 916 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 3.03 (br, 1H, O*H*), 3.40 (brs, 1H, H-5), 3.46 (brs, 1H, H-5′), 3.86 (dd, J=3.5, 10.0 Hz, 1H, H-3), 3.99 (dd, J=8.0, 10.8 Hz, 1H, H-2′), 4.03 (dd, J=1.5, 12.5 Hz, 1H, H-6′a), 4.05 (dd, J=1.1, 12.5 Hz, 1H, H-6a), 4.11 (dd, J=7.8, 10.0 Hz, 1H, H-2), 4.14 (m, 1H, C*H*CH=CH_2), 4.27 (brd, J=12.5 Hz, 1H, H-6′b), 4.28 (d, J=3.6 Hz, 1H, H-4′), 4.31 (brd, J=12.5 Hz, 1H, H-6b), 4.37 (d, J=7.8 Hz, 1H, H-1), 4.38 (d, J=3.5 Hz, 1H, H-4), 4.42 (m, 1H, C*H*CH=CH_2), 4.73 (dd, J=3.6, 10.8 Hz, 1H, H-3′), 4.98 (1H, d, J=8.0 Hz, H-1′), 5.20 (1H, dd, J=0.9, 10.6 Hz, CH_2CH=C*H*), 5.32 (1H, dd, J=1.2, 17.3 Hz, CH_2CH=C*H*), 5.49 (s, 1H, C*H*Ph), 5.57 (s, 1H, C*H*Ph), 5.95 (m, 1H, CH_2CH=CH_2), 7.28–7.37 (m, 6H, Ar-H), 7.49 (m, 2H, Ar-H), 7.54 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 60.1, 66.2, 66.6, 68.9, 69.0, 69.9, 70.2, 71.9, 72.5, 75.9, 78.9, 100.5, 100.7, 101.6 (C-1), 102.0 (C-1′), 117.8, 126.06, 126.09, 127.9, 128.1, 128.5, 129.0, 133.7, 137.4, 137.6, 170.3; FAB-HRMS *m/z* calcd for $C_{31}H_{36}N_3O_{11}$ $(M+H)^+$ 626.2350, found 626.2353; Anal. calcd for: $C_{31}H_{35}N_3O_{11}$: C, 59.51; H, 5.64; N, 6.72, found C, 59.32; H, 5.64; N, 6.62. Data for α-anomer (**40**α): TLC R_f=0.55 (1:3 hexane/AcOEt), 0.44 (3:1 toluene/acetone); $[\alpha]_D^{23}=+165.1°$ (*c* 0.36, $CHCl_3$); IR (film) 3510, 2922, 2864, 2110, 1743, 1452, 1369, 1244, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 2.63 (br, 1H, O*H*), 3.44 (brs, 1H, H-5), 3.80 (dd, J=3.7, 9.8 Hz, 1H, H-3), 3.93 (dd, J=3.4, 11.2 Hz, 1H, H-2′), 3.98 (dd, J=7.8, 9.8 Hz, 1H, H-2), 4.04 (dd, J=1.1, 12.6 Hz, 1H, H-6′a), 4.11 (dd, J=1.1, 12.5 Hz, 1H, H-6a), 4.14 (m, 1H, C*H*CH=CH_2), 4.19 (brs, 1H, H-5′), 4.24 (dd, J=1.2, 12.6 Hz, 1H, H-6′b), 4.32 (d, J=3.7 Hz, 1H, H-4), 4.36 (d, J=7.8 Hz, 1H, H-1), 4.37 (dd, J=1.3, 12.5 Hz, 1H, H-6b), 4.44 (dddd, J=1.0, 1.1, 5.1, 12.7 Hz, 1H, C*H*CH=CH_2), 4.50 (d, J=3.3 Hz, 1H, H-4′), 5.23 (dd, J=1.0, 11.1 Hz, 1H, CH_2CH=C*H*), 5.30 (d, J=3.4 Hz, 1H, H-1′), 5.32 (m, 1H, CH_2CH=C*H*), 5.40 (dd, J=3.3, 11.2 Hz, 1H, H-3′), 5.52 (s, 1H, C*H*Ph), 5.58 (s, 1H, C*H*Ph), 5.96 (dddd, J=5.1, 6.0, 11.1, 17.1 Hz, 1H, CH_2CH=CH_2), 7.30–7.40 (m, 6H, Ar-H), 7.49 (m, 2H, Ar-H), 7.55 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0, 56.7, 62.8, 66.7, 69.1, 69.2, 69.4, 70.0, 72.3, 73.5, 76.8, 95.8 (C-1′), 100.7, 101.0, 101.9 (C-1), 118.0, 126.1, 126.2, 128.0, 128.2, 128.8, 129.1, 133.8, 137.6, 170.4; FAB-HRMS *m/z* calcd for $C_{31}H_{36}N_3O_{11}$ $(M+H)^+$ 626.2350, found 626.2372.

4.7. Comparative study

4.7.1. TMSOTf-catalyzed glycosidation of 2-azido-2-deoxyglucopyranosyl trichloroacetimidate 5α with alcohol 8 in acetonitrile (Table 9, entry 5).

The glycosidation was performed according to the typical procedure (1.5 mL MeCN, −40 °C, 0.3 h) employing trichloroacetimidate **5**α[7b] (62.0 mg, 0.10 mmol), alcohol **8** (51.1 mg, 0.11 mmol), TMSOTf (1.0 M in CH_2Cl_2, 0.015 mL, 0.015 mmol), and pulverized molecular sieves 4 Å (60 mg). An anomeric mixture of disaccharide **10** (47.2 mg, 51%, α:β=12:88) was obtained as a white solid from the crude product (118.5 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt with 1% Et_3N),

along with β-trichloroacetamide **41** (21.7 mg, 35%) as a white solid.

Data for *N*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)trichloroacetamide (**41**):[26b] TLC R_f=0.59 (2:1 hexane/AcOEt); mp 129.5–131.0 °C (colorless needles from Et_2O–hexane); $[\alpha]_D^{23}=-3.79°$ (*c* 1.00, $CHCl_3$); IR (KBr) 3360, 3032, 2893, 2108, 1699, 1520, 1454, 1363, 1277, 1128, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (dd, *J*=9.4, 9.6 Hz, 1H, H-2), 3.54 (ddd, *J*=1.8, 2.9, 10.2 Hz, 1H, H-5), 3.62 (dd, *J*=8.9, 9.6 Hz, 1H, H-3), 3.71 (dd, *J*=1.8, 11.0 Hz, 1H, H-6a), 3.75 (dd, *J*=2.9, 11.0 Hz, 1H, H-6b), 3.79 (dd, *J*=8.9, 10.2 Hz, 1H, H-4), 4.49 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.56 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.60 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.80 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.88 (s, 2H, OCH_2Ph), 4.97 (dd, *J*=9.3, 9.4 Hz, 1H, H-1), 7.08 (d, *J*=9.3 Hz, 1H, N*H*), 7.15 (m, 2H, Ar-H), 7.25–7.35 (m, 13H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 65.8, 67.8, 73.6, 75.0, 75.7, 77.0, 77.2, 80.4 (C-1), 83.8, 92.0, 127.7, 127.89, 127.90, 128.0, 128.05, 128.14, 128.45, 128.51, 137.4, 137.5, 137.7, 161.7; FAB-HRMS *m/z* calcd for $C_{29}H_{30}N_4O_5Cl_3$ $(M+H)^+$ 619.1282, found 619.1271; Anal. calcd for: $C_{29}H_{29}N_4O_5Cl_3$: C, 56.19; H, 4.72; N, 9.04, found C, 56.04; H, 4.62; N, 8.89.

4.7.2. TMSOTf-promoted glycosidation of 2-azido-2-deoxyglucopyranosyl trichloroacetimidate 5α with alcohol 8 in propionitrile (Table 10, entry 3). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.3 h) employing trichloroacetimidate **5α**[7b] (62.0 mg, 0.10 mmol), alcohol **8** (51.1 mg, 0.11 mmol), TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol), and pulverized molecular sieves 4 Å (60 mg). An anomeric mixture of disaccharide **10** (49.6 mg, 54%, α:β=7:93) was obtained as a colorless oil from the crude product (125.4 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt with 1% Et_3N), along with α-amidine **42** (13.6 mg, 20%) as a colorless oil.

Data for *N*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-*N*-(2,2,2-trichloro-1-iminoethyl)propionamide (**42**): TLC R_f=0.50 (2:1 hexane/AcOEt); $[\alpha]_D^{22}=-11.4°$ (*c* 1.61, $CHCl_3$); IR ($CHCl_3$) 3020, 2926, 2868, 2118, 1635, 1577, 1221, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (dd, *J*=7.4, 7.5 Hz, 3H, CH_2CH_3), 2.61 (m, 2H, CH_2CH_3), 3.61 (brd, *J*=10.8 Hz, 1H, H-6a), 3.66 (m, 1H, H-5), 3.76 (dd, *J*=3.4, 10.8 Hz, 1H, H-6b), 3.79 (dd, *J*=8.2, 9.4 Hz, 1H, H-4), 3.82 (dd, *J*=8.2, 9.5 Hz, 1H, H-3), 3.89 (dd, *J*=4.9, 9.5 Hz, 1H, H-2), 4.47 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.54 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.59 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.80 (d, *J*=10.9 Hz, 1H, OC*H*Ph), 4.92 (d, *J*=10.3 Hz, 1H, OC*H*Ph), 4.94 (d, *J*=10.3 Hz, 1H, OC*H*Ph), 5.46 (d, *J*=4.9 Hz, 1H, H-1), 7.16 (m, 2H, Ar-H), 7.26–7.36 (m, 13H, Ar-H), 11.0 (br, 1H, N*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.6, 26.9, 62.0, 68.0, 72.0, 73.6, 75.1, 76.1, 77.6, 78.8, 81.3, 95.8, 127.7, 127.86, 127.91, 128.0, 128.1, 128.2, 128.45, 128.50, 128.6, 137.2, 137.4, 137.5, 174.5, 179.8; FAB-HRMS *m/z* calcd for $C_{32}H_{35}N_5O_5Cl_3$ $(M+H)^+$ 674.1704, found 674.1691; Anal. calcd for: $C_{32}H_{34}N_5O_5Cl_3$: C, 56.94; H, 5.08; N, 10.39; Cl, 15.76, found: C, 57.34; H, 5.18; N, 10.31; Cl, 15.41.

4.7.3. TMSOTf-promoted glycosidation of 2-azido-2-deoxygalactopyranosyl trichloroacetimidate 43α with alcohol 8 in propionitrile (Table 11, entry 1). The glycosidation was performed according to the typical procedure (1.5 mL EtCN, −78 °C, 0.1 h) employing trichloroacetimidate **43α**[7a] (62.0 mg, 0.10 mmol), alcohol **8** (51.1 mg, 0.11 mmol), TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol), and pulverized molecular sieves 4 Å (60 mg). An anomeric mixture of disaccharide **27** (43.8 mg, 48%, α:β=4:96) was obtained as a white solid from the crude product (123.4 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt with 1% Et_3N), along with β-trichloroacetamide **44** (23.0 mg, 37%) and α-amidine **45** (4.5 mg, 7%) as colorless oils.

Data for *N*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)trichloroacetamide (**44**): TLC R_f=0.59 (2:1 hexane/AcOEt); $[\alpha]_D^{24}=+21.1°$ (*c* 1.20, $CHCl_3$); IR (film) 3323, 3032, 2872, 2114, 1724, 1520, 1454, 1361, 1286, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (dd, *J*=2.8, 9.8 Hz, 1H, H-3), 3.56–3.61 (m, 2H, H-6a, H-6b), 3.68 (t, *J*=6.6 Hz, 1H, H-5), 3.86 (dd, *J*=9.5, 9.8 Hz, 1H, H-2), 4.00 (brd, *J*=2.8 Hz, 1H, H-4), 4.43 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.47 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.57 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.69 (d, *J*=11.6 Hz, 1H, OC*H*Ph), 4.74 (d, *J*=11.6 Hz, 1H, OC*H*Ph), 4.87 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.91 (dd, *J*=9.3, 9.5 Hz, 1H, H-1), 7.07 (d, *J*=9.3 Hz, 1H, N*H*), 7.27–7.40 (m, 15H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 62.5, 67.7, 71.9, 72.4, 73.5, 75.0, 75.5, 80.4 (C-1), 81.6, 92.0, 127.87, 127.92, 128.1, 128.3, 128.35, 128.44, 128.5, 137.1, 137.5, 137.9, 161.6; FAB-HRMS *m/z* calcd for $C_{29}H_{30}N_4O_5Cl_3$ $(M+H)^+$ 619.1282, found 619.1276; Anal. calcd for: $C_{29}H_{29}N_4O_5Cl_3$: C, 56.19; H, 4.72; N, 9.04, found C, 55.98; H, 4.69; N, 8.93.

Data for *N*-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-*N*-(2,2,2-trichloro-1-iminoethyl)propionamide (**45**): TLC R_f=0.43 (2:1 hexane/AcOEt); $[\alpha]_D^{20}=+4.32°$ (*c* 1.05, $CHCl_3$); IR (film) 3342, 3032, 2874, 2118, 1637, 1574, 1454, 1367, 1211, 1080 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.5 Hz, 3H, CH_2CH_3), 2.55 (dq, *J*=15.3, 7.5 Hz, 1H, $CHCH_3$), 2.59 (dq, *J*=15.3, 7.5 Hz, 1H, $CHCH_3$), 3.50 (dd, *J*=6.1, 9.2 Hz, 1H, H-6a), 3.56 (dd, *J*=7.1, 9.2 Hz, 1H, H-6b), 3.76–3.79 (m, 2H, H-3, H-5), 4.02 (brs, 1H, H-4), 4.34 (dd, *J*=5.1, 10.5 Hz, 1H, H-2), 4.40 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.45 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.51 (d, *J*=11.2 Hz, 1H, OC*H*Ph), 4.77 (d, *J*=10.6 Hz, 1H, OC*H*Ph), 4.79 (d, *J*=10.6 Hz, 1H, OC*H*Ph), 4.57 (d, *J*=11.2 Hz, 1H, OC*H*Ph), 5.44 (d, *J*=5.1 Hz, 1H, H-1), 7.24–7.42 (m, 15H, Ar-H), 11.0 (br, 1H, N*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.5, 26.9, 58.2, 68.2, 70.8, 72.5, 72.7, 73.6, 75.0, 78.8, 79.0, 95.9, 127.85, 127.91, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 136.8, 137.4, 137.9, 174.4, 180.1; ESI-HRMS *m/z* calcd for $C_{32}H_{34}N_5O_5Cl_3Na$ $(M+Na)^+$ 696.1523, found 696.1537.

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Lundurines A–D, cytotoxic indole alkaloids incorporating a cyclopropyl moiety from *Kopsia tenuis* and revision of the structures of tenuisines A–C

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Abstract—The leaf extract of the Borneo *Kopsia*, *K. tenuis*, provided several new indoles with a novel hexacyclic carbon skeleton, incorporating a cyclopropyl moiety. Two of these, displayed appreciable in vitro cytotoxicity against B16 melanoma cells, as well as the circumvention of drug-resistance in drug-resistant KB cells. The structures of tenuisines A–C were revised from a dimeric to a monomeric structure, based on new LSIMS data, and in conjunction with the preparation of the methyl iodide salt of tenuisine A.

1. Introduction

Plants of the genus *Kopsia* have proven to be rich sources of novel alkaloids with intriguing carbon skeletons as well as interesting biological activities.[1–17] We previously reported the structure of lundurine A from the Borneo species *K. tenuis*.[14] This novel dihydroindole derivative is distinguished by the presence of a cyclopropyl moiety embedded within the hexacyclic ring system. We also reported the structures of tenuisines A–C, which were characterized as bisindoles, distinguished by the presence of an element of symmetry giving rise to homotropic behaviour of the NMR spectra,[15,16] and tenuiphylline,[16] a novel bisindole constituted from a lapidilectine B-type unit[17] linked to a rearranged venalstonine-like unit, which at that time was as yet unknown. We have since then isolated such compounds, which constitute a new subclass of the monoterpenoid indoles, to which we have given the trivial name kopsifolines A–F.[2,3] We now report the results of a detailed investigation of the alkaloidal constituents of *K. tenuis* which was undertaken with a view to address several issues. Firstly, we wish to report full structure elucidation for lundurines B, C, and D in addition to lundurine A. Secondly, in view of our preliminary finding of the anti-melanoma activity of lundurine B,[8] we were interested to uncover more analogues to gain some structure-activity insights, as well as to determine the IC_{50} values of the biologically active compounds. Thirdly, a detailed study involving a separate sample would provide some idea of the seasonal variation of the alkaloid composition, and finally, we needed to confirm the structures of tenuisines A–C. We now report the results to which these issues were addressed.

2. Results and discussion

The leaf extract of *K. tenuis* provided in addition to lundurines A–C (**1**–**3**), another new lundurine alkaloid, lundurine D (**4**). In addition, tenuisines A–C were also isolated, but the previously isolated novel bisindole, tenuiphylline,[16] was not obtained in the present study. Lundurine A (**1**) was obtained as a colourless oil, with $[\alpha]_D = -90$ (*c* 0.09, $CHCl_3$). The UV spectrum was characteristic of a dihydroindole chromophore with absorption maxima at 208, 250, and 298 nm, while the IR spectrum showed bands due to carbamate (1704 cm^{-1}) and conjugated lactam (1686 cm^{-1}) functions. The EIMS of **1** showed a molecular ion at *m/z* 366, which analyzed for $C_{21}H_{22}N_2O_4$, requiring 12 degrees of unsaturation while the mass fragments which were observed at *m/z* 351, 338, and 307 are due to loss of methyl, ethylene, and methyl ester groups, respectively. The ^{13}C NMR spectrum (Table 2) gave

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a total of 21 carbon resonances (two methyls, five methylenes, six methines, and eight quaternary carbons) in agreement with the molecular formula. In addition to the eight signals associated with the dihydroindole moiety, the ^{13}C NMR spectrum is notable for the presence of two methoxy groups, one associated with an aromatic methoxy substituent (δ 55.7), and the other with a carbamate function (δ 52.9), two carbonyl resonances, one due to carbamate (δ 154.8) and the other due to a lactam (δ 169.8), and two olefinic methines (δ 125.1 and 154.1). The ^{1}H NMR spectrum of **1** (Table 1) showed the presence of three aromatic hydrogens, the coupling pattern and carbon shift values indicating substitution by a methoxy group at C(10). This is further confirmed by the NOE observed between the H(9) doublet at δ 6.72 and H(6). The downfield shift of the olefinic hydrogens coupled with the observed vicinal coupling of 6 Hz for these hydrogens (instead of the usual 10 Hz in six-membered rings), suggested that the double bond constitutes part of a five membered ring lactam. This conclusion receives additional support from the absence of peaks normally associated with the aminomethylene hydrogens at C(3), the presence of the lactam resonance at δ 169.8, as well as the marked downfield shift of the H(15) olefinic resonance to δ 6.88, characteristic of a β-H of an α,β-unsaturated carbonyl moiety. The COSY spectrum showed the remaining partial structures to be made up of two CH_2CH_2 and one $CHCH_2$ fragment. The methine associated with the latter fragment was observed as a doublet at high field at δ 1.13, highly suggestive of a cyclopropyl or cyclobutyl ring. Based on the NMR spectral data, three structures can be assembled, two incorporating cyclobutyl rings, and one incorporating a cyclopropyl ring. These can be distinguished by considering the HMBC data, from the observed three-bond correlation from the methylene H(17) to C(15), which ruled out structures **5** and **6**, but is consistent with structure **1**. Other HMBC correlations are in complete accord with **1**.

Lundurine B **2** was obtained as a light yellowish oil with $[\alpha]_D = -34$ (*c* 0.16, $CHCl_3$). The UV spectrum was similar to that of **1** showing absorption maxima at 211, 252 and 299 nm. In contrast to **1**, the IR spectrum of **2** showed only one carbonyl band due to a carbamate function at 1704 cm^{-1}. The EIMS of **2** showed a molecular ion at *m/z* 352, which analyzed for $C_{21}H_{24}N_2O_3$, differing from **1** by replacement of an oxygen atom with two hydrogens. The ^{13}C NMR spectrum (Table 2) showed signals due to two methyls, six methylenes, six methines, and seven quaternary carbons, the spectrum being in all respects rather similar to that of **1**, except for the notable absence of the lactam carbonyl resonance and its replacement by an aminomethylene resonance at δ 64.6, and the marked upfield shifts for C(5), and C(15), when compared to **1**, all of which are consistent with replacement of the lactam carbonyl at

Table 1. ^{1}H NMR spectral data of **1**, **2**, **3**, **4**, **8**, **9**, and **10**[a]

Position	1	2	3	4	8	9	10
3a	—	3.45 dt (14.8, 2.1)	2.55 m	3.47 dt (15, 1.8)	3.18 m	3.17 m	—
3b	—	4.00 dt (14.8, 1.9)	3.12 br t (7)	4.09 br d (15)	3.80 m	3.82 m	—
5a	3.53 ddd (15, 12, 4)	2.87 dt (13, 4.4)	2.86 dt (13, 4)	2.93 br d (12.2)	2.91 td (13, 9)	3.87 m	3.19 dd (16.1, 12.2)
5b	4.30 dt (15, 4)	3.12 td (13, 2.4)	3.03 td (13, 2)	3.15 td (12.2, 2.0)	3.24 dd (13, 9)	3.25 m	4.57 dd (16.1, 6.7)
6a	2.64 m	2.31 m	2.34 m	2.40 m	2.15 m	2.11 m	2.28 m
6b	2.64 m	2.57 ddd (15.7, 4.4, 2.4)	2.61 m	2.56 ddd (15.7, 4.2, 2.0)	2.70 dd (15.2, 9)	2.71 d (15, 8)	2.89 dd (16, 6.7)
9	6.72 d (2.6)	6.82 d (2.6)	6.80 d (2.4)	6.81 s	6.94 s	6.88 s	6.97 s
11	6.68 dd (8.7, 2.6)	6.65 dd (8.8, 2.6)	6.65 dd (8.8, 2.4)	—	6.90 d (8.6)	—	6.95 m
12	7.46 d (8.7)	7.52 br s	7.53 br s	7.44 br s	7.48 d (8.6) 7.93 br d (8.6)	7.74 br s 7.20 br s	7.52 br d (8.1) 7.96 br s
14	6.09 d (5.8)	5.62 dt (6.0, 1.9)	1.63 m 1.63 m	5.63 dt (6, 1.8)	5.73 d (6.4)	5.75 m	6.11 d (5.9)
15	6.88 d (5.8)	5.40 dt (6.0, 2.1)	1.71 m 1.71 m	5.42 dt (6, 2.0)	5.53 d (6.4)	5.54 m	6.86 d (5.9)
16	1.13 d (5.5)	1.05 dd (5.3, 1.1)	1.00 d (5.4)	1.03 br d (5.2)	3.43 m 3.29 m	3.45 m 3.31 m	4.02 br d (12.2)
17a	1.85 d (14.6)	1.94 dd (14.5, 5.3)	1.93 dd (15, 5.4)	1.95 dd (15, 5.2)	1.99 m	1.99 m	2.06 m
17b	2.47 dd (14.6, 5.5)	2.36 m	2.36 d (15)	2.37 br d (15)	2.25 dd (13, 7)	2.18 m	2.68 br t (13)
18a	2.74 ddd (15.4, 12.5, 7)	2.26 dd (14.6, 5.8)	2.30 m	2.33 td (14.6, 5.6)	1.71 m	1.67 m	1.88 m
18b	2.91 dd (15.2, 9.1)	2.53 m	2.49 m	2.51 m	2.62 m 1.71 m 2.42 m	2.58 m 1.71 m 2.41 m	2.44 m
19a	1.58 dd (13.7, 7, 1.2)	1.43 ddt (13.0, 5.8, 2.0)	1.55 m	1.51 m	1.99 m	2.03 m	1.65 m
19b	2.13 m	1.75 m	1.62 m	1.75 m	2.05 m	2.07 m	2.22 m
10-OMe	3.79 s	3.78 s	3.78 s	3.87 s	3.80 s	3.88 s	3.83 s
11-OMe	—	—	—	3.87 s	—	3.91 s	—
NCO_2Me	3.88 s	3.86 s	3.86 s	3.88 s	3.88 s	3.88 s	3.93 s

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

Table 2. ^{13}C NMR spectral data of **1**, **2**, **3**, **4**, **8**, **9**, and **10**[a]

Position	**1**	**2**	**3**	**4**	**8**	**9**	**10**
2	50.1	48.1	48.7	47.4	74.0 73.7	74.1 74.6	72.8
3	169.8	64.6	58.6	64.5	61.7	61.7	171.5
5	36.1	50.2	48.7	50.4	47.1	47.3	34.7
6	27.9	28.5	27.9	27.9	29.8	29.7	29.2
7	33.6	33.4	33.4	33.7	90.5 91.1	91.7 91.8	91.4
8	139.4	139.0	138.9	127.9	130.8 129.3	119.1 120.0	127.9
9	108.9	109.7	109.6	106.9	109.9 107.4	107.0 107.2	109.6
10	156.1	155.8	155.7	147.9	156.0	151.4 151.3	156.3
11	111.2	111.3	111.3	144.8	116.4	145.7	116.7
12	116.3	116.2	116.1	101.0	116.4 116.7	100.0 100.3	117.2
13	135.0	136.2	136.1	136.1	134.5	136.5 135.0	134.9
14	125.1	124.6	23.5	124.0	126.4 126.9	127.1 126.8	127.7
15	154.1	137.6	42.7	136.9	135.9 135.6	135.7 135.9	155.0
16	26.0	28.2	27.9	27.7	44.7 45.6	45.8 44.9	39.5
17	30.6	27.6	29.3	27.6	38.5	38.8	31.2
18	20.5	19.8	20.3	19.8	21.8 22.9	23.0 21.9	21.1
19	28.9	34.5	35.1	35.0	25.1	25.0	28.7
20	65.6	67.6	60.0	66.8	67.4	67.2	64.1
10-OMe	55.7	55.7	55.7	56.1	55.7	56.1	55.8
11-OMe	—	—	—	56.4	—	56.4	—
NCO_2Me	154.8	154.9	154.9	154.7	52.7	52.9	52.7
NCO_2Me	52.9	52.7	52.7	52.8	152.7 152.1	152.2 152.4	152.9
CO (lactone)	—	—	—	—	177.4 177.1	177.1 177.4	178.0

[a] $CDCl_3$, 400 MHz; assignments based on COSY and HMQC.

position 3 by a methylene. Accordingly, the ^1H NMR spectrum of **2** showed additional signals due to the C(3) aminomethylene hydrogens, as well as corresponding upfield shifts of the olefinic hydrogen signals. The COSY spectrum gave similar fragments as **1** except for the $NCH_2CH{=}CH$ unit in place of $C(=O)CH{=}CH$. In view of the above spectral data the structure of lundurine B is as shown in **2**.

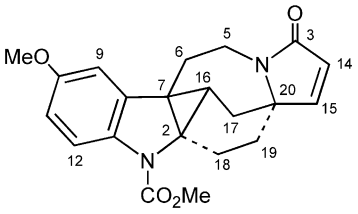
Lundurine C **3** was obtained as a light yellowish oil with $[\alpha]_D = -25$ (*c* 0.07, $CHCl_3$). The UV spectrum was similar to that of the previous two compounds, showing absorption maxima at 203, 253, and 299 nm. As in the case of **2**, the IR spectrum showed a carbonyl band at 1704 cm^{-1} due to a carbamate function. The EIMS of **3** showed a molecular ion at *m/z* 354, which analyzed for $C_{21}H_{26}N_2O_3$, differing from **2** by addition of two hydrogens. The ^1H and ^{13}C NMR spectral data were largely similar to that of **2**, except for the absence of the 14,15-olefinic resonances, which have been replaced by methylenes, resulting in corresponding upfield shifts of both the ^1H (δ 1.63, 1.71) and ^{13}C (δ 23.5 and 42.7) resonances. The COSY spectrum of **3** gave similar fragments as **2** except for the replacement of the NCH_2-$CH{=}CH$ unit by a $NCH_2CH_2CH_2$ unit. The main change therefore involve the pyrrolidine ring, in which the 14,15-unsaturation has been removed, as shown in structure **3**.

Lundurine D **4** was obtained as a light yellowish oil with $[\alpha]_D = -22$ (*c* 0.01, $CHCl_3$). The UV spectrum (215, 255, and 302 nm) was similar to that of **2**, while the IR spectrum showed a similar carbamate carbonyl band at 1705 cm^{-1}. The EIMS of **4** showed a molecular ion at *m/z* 382, which analyzed for $C_{22}H_{26}N_2O_4$, suggesting additional methoxy substitution. This was readily confirmed by the ^1H and ^{13}C NMR spectral data which were essentially similar to that of **2**, except for the additional aromatic methoxy substituent, which was placed at C(11), from the observation of two aromatic singlets at δ 6.81 and 7.44.

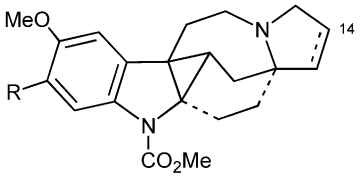
A key piece of evidence in support of the structure of the lundurines which is characterized by a cyclopropyl moiety fused to the dihydroindole chromophore, is provided by measurement of the $^1J_{C-H}$ coupling constant for C(16) which yielded a value of 164.1 Hz in the case of lundurine A **1** and 162.1 Hz in the case of lundurine B **2**, values which are characteristic of cyclopropyl rings.[18,19] The structure is also consistent with the NOE/NOESY data of **2**, which showed clear NOE interactions between H(5α)/H(3β), H(5β)/H(3β), H(9)/H(6β), H(17α)/H(5β), H(9)/ArOMe, H(11)/ArOMe, H(17β)/H(15), and H(19β)/H(15). The lundurines represent the first examples of a new structural subclass of the monoterpenoid indoles, which are characterized by a novel hexacyclic carbon skeleton, incorporating a cyclopropyl unit.

We previously reported the structures of tenuisines A–C

which were also obtained from the same plant.[15,16] The structure elucidation led to two possible structures, one, a hexacyclic dihydroindole incorporating a five membered lactone ring (**8**–**10**),[14] similar to the prototype compound in the series, lapidilectine B **7**.[17] Alternatively, a bisindole from the union of two identical units of the monomeric alkaloid, as shown in structures **11**–**13**. The dimeric structure for tenuisines A–C, as represented in structures **11**–**13**, where two identical monomeric units are linked via carboxyl linkages from C(16) of one half to C(7) of the other, is distinguished by the presence of a C_2 axis passing through the two halves, which would result in homotropic behaviour of the NMR spectra. We were prompted in our earlier report to adopt the dimeric structure, since the FABMS of tenuisines A–C gave very strong peaks corresponding to a dimeric compound.[16] For example, in the case of tenuisine A, the FABMS showed a strong MH^+ peak at *m/z* 793 (60% of base peak), although the EIMS showed only the *m/z* 396 peak. Similarly ESIMS gave the MH^+ peak at *m/z* 793. Since the formulation of a dimeric structure for the tenuisines rested principally on the FAB- and ESI-MS data (in hindsight, techniques which are prone



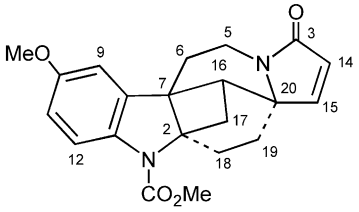
1



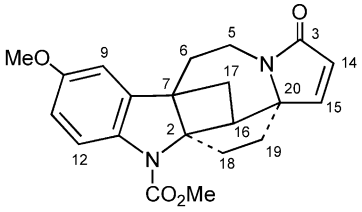
2 R = H, $\Delta^{14,15}$

3 R = H

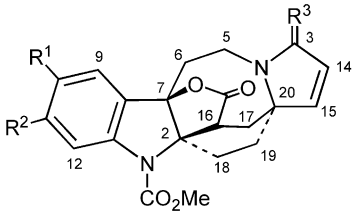
4 R = OMe, $\Delta^{14,15}$



5



6

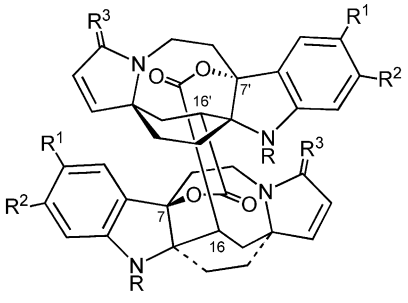


7 R^1 = H, R^2 = H, R^3 = H_2

8 R^1 = OMe, R^2 = H, R^3 = H_2

9 R^1 = OMe, R^2 = OMe, R^3 = H_2

10 R^1 = OMe, R^2 = H, R^3 = O



11 R = CO_2Me, R^1 = OMe, R^2 = H, R^3 = H_2

12 R = CO_2Me, R^1 = OMe, R^2 = OMe, R^3 = H_2

13 R = CO_2Me, R^1 = OMe, R^2 = H, R^3 = O

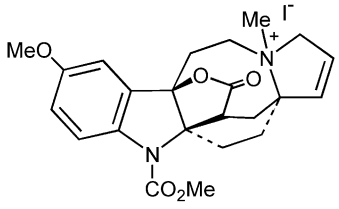


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Table 3. Cytotoxic effects of **1–4**

Compound	IC_{50} value (μg/ml)			
	B16 melanoma	KB/S[a]	KB/VJ300[a]	KB/VJ300[b]
Lundurine A **1**	>25	>25	>25	8.8
Lundurine B **2**	2.8	19	15.5	4.6
Lundurine C **3**	>25	>25	>25	14.2
Lundurine D **4**	7.2	>25	>25	4.6

[a] KB/S and KB/VJ300 are vincristine-sensitive and -resistant human oral epidermoid carcinoma cell line, respectively.[24]
[b] With added vincristine 0.1 μg/ml.

to artefact formation), we decided to reinvestigate the structures of the tenuisines in order to establish whether the monomeric or dimeric version represents the correct constitution of the tenuisines. In the present study, the LSIMS spectra of tenuisines A–C were obtained, which this time clearly showed that the compounds are monomeric. Thus the LSIMS spectrum of tenuisine A showed the MH^+ peak at *m/z* 397 as the base peak, with no significant peak attributable to a dimeric species (*m/z* 793 peak <2% of base peak). HRLSIMS measurement of the *m/z* 397 peak analyzed for $C_{22}H_{25}N_2O_5$. The same results were obtained for the LSIMS spectra of tenuisines B (MH^+ *m/z* 427, base, $C_{23}H_{26}N_2O_6+H$) and C (MH^+ *m/z* 411, 77%; M^+ *m/z* 410, base, $C_{22}H_{22}N_2O_6$). Thus the LSIMS mass-spectra of the tenuisines clearly indicated that the compounds are monomers. To obtain further confirmation of this, tenuisine A was converted to its methyl iodide salt **14** and the positive ion LSIMS spectrum of the salt was obtained, which yielded an M^+ ion at *m/z* 411 as the base peak and which analyzed for $[C_{23}H_{27}N_2O_5]^+$, with no evidence of any higher mass fragments. The ^1H NMR spectrum of the salt (see Section 3) showed an additional 3H singlet due to the methyl substituent on the quaternary *N*(4) at *δ* 3.47, and furthermore, the signals of the C(5) and C(3) hydrogens have been shifted downfield compared to the spectrum of tenuisine A, indicating that they are now adjacent to a quaternary nitrogen. Other than this, the spectrum of the salt was essentially similar to that of tenuisine A. As noted previously,[15,16,20] the ^1H NMR spectra of the tenuisines are complicated by the existence of equilibrating rotamers due to the carbamate group at the indolic nitrogen. In any case, we have now demonstrated that the dimeric structures originally attributed to tenuisines A–C (**11**–**13**) require revision to the monomeric version as shown in structures **8**–**10**. The tenuisines are therefore congeners of lapidilectine B,[17] previously obtained from another Malayan *Kopsia*. Comparison of the present results with that of the previous study[14,16] showed a seasonal dependence of the alkaloidal composition. Lundurine D was not detected in the previous sample, while the novel bisindole tenuiphylline, which was found in the previous sample, was not detected in the present study.

Lundurines B **2** and D **4** showed appreciable in vitro cytotoxicity towards B16 melanoma cells, in contrast to lundurines A **1** and C **3** which were practically inactive (Table 3). Of the two active lundurine derivatives, lundurine B displayed the highest potency (IC_{50} 2.8 μg/ml). It would appear from the observed values that the presence of the pyrrolidine 14,15-double bond is necessary (cf. **2** versus **3**), although oxygenation of C(3) has the effect of abolishing the cytotoxic effect altogether, despite the presence of the 14,15-unsaturation (cf. **2** versus **1**). Surprisingly, lundurines B and D (**2** and **4**) did not display appreciable cytotoxicity towards KB cells, but were found instead to be effective in circumventing multidrug-resistance (MDR) in vincristine-resistant KB cells.[8,9]

3. Experimental

3.1. General

UV spectra were recorded on a Shimadzu UV-3101PC spectrophotometer. IR spectra were recorded on a Perkin–Elmer RX1 FT-IR spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter or an Atago Polax-D polarimeter. ESIMS was obtained on a Perkin–Elmer API 100 instrument. HREIMS, LSIMS, and HRLSIMS measurements were carried out at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JMN-LA400 spectrometer at 400 and 100 MHz, respectively. Assignments are confirmed by COSY, HMQC, HMBC, NOESY, and NOE experiments. All solvents were of analytical grade and were distilled before use.

3.2. Collection, extraction, and isolation

Details of collection of plant material and the deposition of voucher specimens have been described previously.[16] Extraction of the ground leaf material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere.[21] The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH, followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for centrifugal TLC were Et_2O–hexane (5:1), Et_2O–MeOH (100:1), Et_2O, $CHCl_3$–MeOH (100:1), and EtOAc. The yields (g kg^{-1}) of the alkaloids were as follows: **1** (0.004), **2** (0.037), **3** (0.010), **4** (0.006), **8** (0.027), **9** (0.006), and **10** (0.001).

3.2.1. Lundurine A 1. $[\alpha]_D=-90$ ($CHCl_3$, *c* 0.09); IR (dry film) ν_{max} 1704 and 1686 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 208 (4.71), 250 (4.34), and 298 (3.80). EIMS, *m/z* (rel. int.): 366 [M^+] (100), 351 (10), 338 (9), 337 (9), and 307 (10). HREIMS found, *m/z* 366.1530, calcd for $C_{21}H_{22}N_2O_4$, 366.1579. ^1H and ^{13}C NMR: see Tables 1 and 2, respectively. HMBC: H-5 to C-3, C-6, C-20; H-6 to C-2, C-7, C-16; H-9 to C-7, C-10, C-11, C-13; H-11 to C-9, C-10, C-13; H-12 to C-10; H-14 to C-3, C-15, C-20; H-15 to

C-3, C-14, C-20; H-16 to C-2, C-7, C-8, C-18, C-20; H-17 to C-2, C-7, C-15, C-16, C-20; H-18 to C-2, C-19, C-20; H-19 to C-2, C-17, C-20.

3.2.2. Lundurine B 2. $[\alpha]_D=-34$ ($CHCl_3$, *c* 0.16); IR (film) ν_{max} 1704 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 211 (4.43), 252 (4.07), and 299 (3.92). EIMS, *m/z* (rel. int.): 352 [M^+] (100), 337 (12), 324 (15), 323 (45), 309 (10), and 293 (15). ^1H and ^{13}C NMR spectral data, see Tables 1 and 2, respectively. HMBC: H-3 to C-5, C-14, C-15; H-5 to C-3, C-6, C-7, C-20; H-6 to C-2, C-5, C-7; H-9 to C-7, C-10, C-11, C-13; H-11 to C-9, C-10, C-13; H-14 to C-3, C-15, C-20; H-15 to C-3, C-14, C-20; H-16 to C-2, C-6, C-7, C-8, C-17, C-20; H-17 to C-2, C-7, C-19, C-20; H-18 to C-7, C-19, C-20; 10-OMe to C-10; NCO_2Me to NCO_2Me.

3.2.3. Lundurine C 3. $[\alpha]_D=-25$ ($CHCl_3$, *c* 0.07); IR (film) ν_{max} 1704 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 203 (4.71), 253 (4.42), and 299 (3.92). EIMS, *m/z* (rel. int.): 354 [M^+] (100), 339 (12), 326 (12), 326 (20), 325 (43), 311 (6), and 295 (47). ^1H and ^{13}C NMR spectral data, see Tables 1 and 2, respectively.

3.2.4. Lundurine D 4. $[\alpha]_D=-22$ ($CHCl_3$, *c* 0.01); IR (dry film) ν_{max} 1705 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 215 (4.38), 255 (3.94), and 302 (3.71). EIMS, *m/z* (rel. int.): 382 [M^+] (100), 367 (23), 353 (32), 339 (10), and 323 (15). HREIMS found, *m/z* 382.1881, calcd for $C_{22}H_{26}N_2O_4$, 382.1893. ^1H and ^{13}C NMR: see Tables 1 and 2, respectively. HMBC: H-3 to C-5, C-14, C-15; H-6 to C-2, C-16; H-9 to C-7, C-10, C-11, C-13; H-14 to C-3, C-15, C-20; H-15 to C-3, C-14, C-20; H-16 to C-8, C-20; H-17 to C-19; H-18 to C-2, C-19; 10-OMe to C-10; 11-OMe to C-11; NCO_2Me to NCO_2Me.

3.2.5. Tenuisine A 8. $[\alpha]_D=+77$ ($CHCl_3$, *c* 0.76); IR (dry film) ν_{max} 1750 and 1700 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 206 (4.46), 247 (3.99), and 304 (3.64). EIMS, *m/z* (rel. int.): 396 [M^+] (100), 325 (88), 293 (21), 246 (91), 186 (9), 94 (32), and 40 (15). HREIMS found, *m/z* 396.1685, calcd for $C_{22}H_{24}N_2O_5$, 396.1685. LSIMS, *m/z* (rel. int.): 397 [MH^+] (100), 353 (11), and 246 (7). HRLSIMS found, *m/z* 397.1753, calcd for $C_{22}H_{24}N_2O_5+H$, 397.1763. ^1H and ^{13}C NMR: see Tables 1 and 2, respectively. HMBC: H-5 to C-6, C-7, C-20; H-6 to C-2, C-5, C-7, C-8; H-9 to C-7, C-10; H-11 to C-10; H-12 to C-10, C-11, C-13; H-14 to C-3, C-15, C-20; H-15 to C-3, C-14, C-20; H-16 to C-7; H-17 to C-2, C-16, C-19, C-20, CO (lactone); H-19 to C-17; 10-OMe to C-10; NCO_2Me to NCO_2Me.

3.2.6. Tenuisine B 9. $[\alpha]_D=+51$ ($CHCl_3$, *c* 0.09); IR (dry film) ν_{max} 1754 and 1704 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 214 (4.48), 252 (4.08), and 300 (3.70). EIMS, *m/z* (rel. int.): 426 [M^+] (100), 353 (61), 323 (21), 276 (84), 216 (16), 165 (23), 83 (53), and 40 (65). HREIMS found, *m/z* 426.1794, calcd for $C_{23}H_{26}N_2O_6$, 426.1791. LSIMS, *m/z* (rel. int.): 427 [MH^+] (100), 383 (12), and 262 (20). HRLSIMS found, *m/z* 427.1883, calcd for $C_{23}H_{26}N_2O_6+H$, 427.1869. ^1H and ^{13}C NMR: see Tables 1 and 2, respectively.

3.2.7. Tenuisine C 10. $[\alpha]_D=+87$ ($CHCl_3$, *c* 0.06); IR (dry film) ν_{max} 1770, 1694, and 1682 cm^{-1}; UV (EtOH), λ_{max} nm (log ε): 203 (4.41), 247 (4.10), and 304 (3.55). EIMS, *m/z* (rel. int.): 410 [M^+] (100), 338 (13), 244 (19), 198 (7), 154 (15), 122 (13), and 43 (16). HREIMS found, *m/z* 410.1483, calcd for $C_{22}H_{22}N_2O_6$, 410.1478. LSIMS, *m/z* (rel. int.): 411 [MH^+] (77), 410 [M^+] (100), 367 (61), 317 (15), 244 (28), and 211 (14). HRLSIMS found, *m/z* 410.1469, calcd for $C_{22}H_{22}N_2O_6$, 410.1478. ^1H and ^{13}C NMR: see Tables 1 and 2, respectively.

3.2.8. Conversion of tenuisine A 8 to its methyl iodide salt 14. Tenuisine A **8** (0.05 mmol, 20 mg) was added to iodomethane to stand at room temperature, until TLC indicated almost complete conversion to the salt. Excess methyl iodide was then removed by distillation under reduced pressure giving a residue which on recrystallisation from chloroform–methanol gave the methyl iodide salt **14** (16 mg, 59%). LSIMS, *m/z* (rel. int.): 411 [M^+] (100), 371 (7), 291 (30), and 219 (23). HRLSIMS found, *m/z* 411.1922, calcd for $C_{23}H_{27}N_2O_5$, 411.1920. ^1H (400 Hz; CD_3OD/$CDCl_3$; Me_4Si) δ 2.1–2.5 (2×H-17, 2×H-18, 2×H-19, overlapped with broad solvent peak), 2.82 (1H, br dd, *J*=17, 12 Hz, H-6), 3.13 (1H, br dd, *J*=17, 6.6 Hz, H-6), 3.42 (1H, m, H-16), 3.47 (3H, s, $N(4)^+$-Me), 3.66 (1H, br t, *J*=13 Hz, H-5), 3.81 (3H, s, 10-OMe), 3.94 (3H, s, NCO_2Me), 3.97 (1H, m, H-16), 4.73 (1H, m, H-5), 4.76 (2H, m, H-3), 5.74 (1H, br s, H-15), 6.08 (1H, d, *J*=6.6 Hz, H-14), 6.97 (1H, d, *J*=8 Hz, H-11), 7.05 (1H, s, H-9), 7.47 (1H, br d, *J*=8 Hz, H-12), 7.92 (1H, br s, H-12).

3.3. Cytotoxicity assays

Cytotoxicity assays were carried out by a slight modification of the method described previously.[22] Human oral epidemoid carcinoma KB cells, P-gp expressing multidrug resistant cell line KB/VJ300 cells, and mouse malignant B16 melanoma cells were maintained in culture flasks in Eagle's MEM, supplemented with 10% fetal calf serum and kanamycin (60 μg/ml). These cells (1.5×10^5/ml) were seeded in 0.2 ml of culture medium/well in 96-well plates (Corning Glass Works). The cells were treated in triplicate with graded concentrations of 5 μl test samples and were then incubated in a 5% carbon dioxide atmosphere at 37 °C for 72 h. The MTT assay was used to measure the cytotoxicity effect.[23] The activity was shown as the IC_{50} value, which was the concentration (μg/ml) of test compound to give 50% inhibition of the cell growth.

Acknowledgements

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Synthesis of novel, boron-containing cavitands derived from calix[4]resorcinarenes and their molecular recognition of biologically important polyols in Langmuir films

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Abstract—An efficient synthetic route for the synthesis of cavitands derived from calix[4]resorcinarene and its tetrabromo derivative was elaborated. A large-scale preparation was achieved in excellent yield, by replacing the high-boiling solvents with acetone. The tetrabromocavitands were transformed into tetra-boronic acid cavitands via lithiation with butyllithium and reaction with triethylborate. Two lipophilic cavitands bearing four boronic acid residues were demonstrated to form stable Langmuir monolayers at the water–air interface. These cavitand receptors differ in bridging unit between oxygen atoms, i.e. one contains a one-carbon unit and the other a two-carbon unit. L-sorbose, D-galactose, D-glucose, and D-cellobiose were selected for molecular recognition studies using the Langmuir techniques. The unsubstituted tetra-*n*-undecyl calix[4]resorcinarene was used as a reference receptor compound. Differences in surface potential were diagnostic of the different types of binding forces, which can occur.

1. Introduction

Cavitands are molecular receptors derived from calix[4]resorcinarenes by linking oxygen atoms with small carbon or heteroatom units, mainly phosphorous-containing compounds. The carbon units may be one, two or three atom-long aliphatic chains,[1] or even heterocyclic systems.[2,3] This covalent reinforcement of the cone conformation in calix[4]resorcinarene has profound implications on the complexing properties of the new molecular receptor. The preorganised cavitand is no longer susceptible to conformational changes in solution. Therefore, a more defined pattern of molecular interactions can be expected. On the other hand, this type of receptor has limited possibilities for further derivatisation, when compared to the initial calix[4]resorcinarene. The conceivable way to introduce further functionalities is the formation of tetrabromocalix[4]resorcinarene followed by the formation of cavitand structure. The typical procedure used for cavitand formation is the alkylation of phenolic hydroxyl groups with chlorobromomethane, 1,2-dibromoethane, or 1,3-dibromopropane in the presence of anhydrous potassium carbonate or caesium carbonate in DMF, DMA, DMSO or *N*-methylpirolidinone.[4,5] In this way the cavitands formed possess, respectively, one, two, or three carbon units between oxygen atoms, which also reflects the depth and size of their cavities. The tetrabromocavitands open a way to a number of derivatives by replacement of bromine atoms by strong nucleophiles, such as thiols, or phosphines. Alternatively, their lithiation with *n*-butyllithium at low temperature followed by reaction with electrophiles such as esters, orthoesters, carboxamides, ketones, aldehydes, nitriles and sulphonyl chlorides, gives rise to a vast variety of derivatives. Some of the emerging derivatives can be elaborated further to form a novel class of receptors.

Molecular recognition is one of the main topics in supramolecular chemistry. Its importance is appreciated in sensors, and other analytical tools used in electrochemistry, spectroscopy and thermochemistry.[1–4] We have been interested in molecular recognition involving molecular receptors based on calix[4]resorcinarenes. This class of receptors is particularly interesting with respect to their various non-covalent interactions with the 'guest' molecules. Moreover, there are many possibilities for their functionalisation with desired functional groups, which change their complexing abilities. The importance of calixarenes as molecular receptors has been widely recognised.[6–8]

Boronic acid derivatives are known to form complexes, or

Keywords: Boronic acids; Cavitands; Resorcinarenes; Langmuir films; Molecular recognition; Surface pressure; Surface potential.
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esters with polyols of biological relevance.[9,10] Such boronic acid-appended lipophilic cavitands would be suitable receptors for molecular recognition studies of carbohydrates and related compounds.

The Langmuir technique[11–16] is a particularly sensitive tool to detect minute differences in molecular recognition. In the present work, we focused on boron-containing cavitands with a preorganised molecular cavity. This preorganisation is advantageous over more conformationally flexible calix[4]resorcinarenes. That is, the preorganised cavitand receptor is not susceptible to conformational changes upon variations of the subphase, or subphase components, thus a more definite picture of molecular interactions may be deduced, in contrast to the flexible and pH-sensitive calix[4]resorcinarenes. A possible disadvantage of the preorganised receptors may originate from the lack of change of the surface area per molecule upon complexation that may lead to mis-interpretation, as if there were no complexes being formed.

Hence, it was interesting for us to investigate cavitands, appended with four boronic acid residues, which form a convergent binding site for polyols of biological importance, and sugars in particular.

2. Results and discussion

So far, the synthesis of cavitands was a rather tedious task, due to the relatively low yields of cyclisation, time-consuming work-up by chromatography and the use of high-boiling point solvents (DMSO, DMF, DMA, *N*-methylpyrrolidinone) which are hard to remove after cyclisation. Thus, their large-scale synthesis was always limited, although there were some attempts to improve the yield.[4,5] We found that these inconvenient solvents can be replaced by dry acetone, and the remaining conditions for the cyclisations remained virtually the same. However, acetone is more environmentally acceptable solvent and the final work-up is much easier. In the case of tetrabromo-calix[4]resorcinarenes the yields were always around 70%, while for calix[4]resorcinarenes the yields were lower, in the range of 45–50%, and tedious chromatographic separation was required. Improved purity of the products is associated with the reaction temperature. A shorter reaction time was required at 100 °C in an autoclave, but always at the expense of the purity of the product. The reaction temperature was therefore 65 °C. The cavitands can be crystallised from alcohols to give white, crystalline solids. The tetra-bromo-derivatives are very useful synthons in which bromine atoms can be replaced by lithium, and reaction with triethylborate then afforded the tetraboronic ester derivatives that can be easily hydrolysed with water. These so far unknown boron derivatives can be used in molecular recognition studies involving polyols, and also they are very promising synthons giving an access to a range of derivatives obtained by their coupling with aromatic, or heteroaromatic halides under Suzuki conditions[8]. Figure 1 shows the synthetic pathways involved in our work.

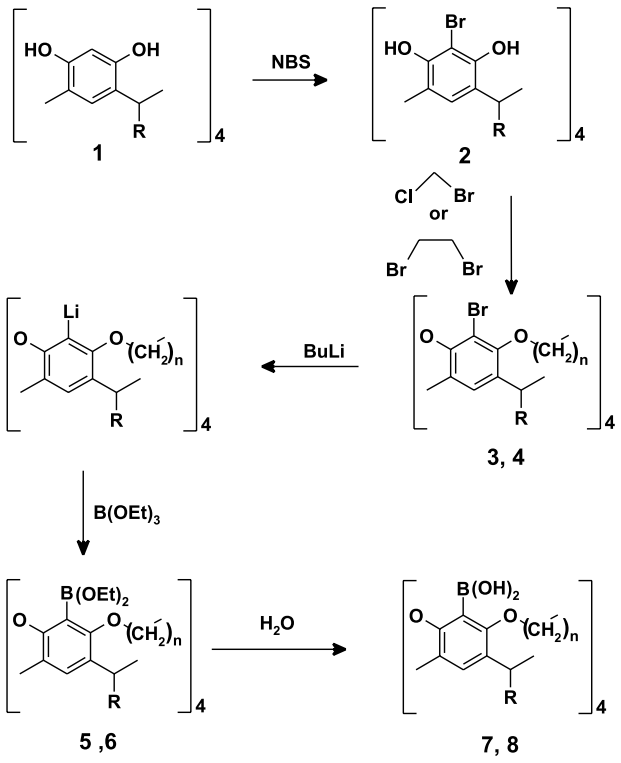

Figure 1. Synthetic route to boron-containing cavitands, $n=1$ or 2, R= $C_{11}H_{23}$.

2.1. Langmuir studies

The Langmuir technique was used to investigate the molecular recognition of carbohydrates by the three molecular receptors, namely, tetra-*n*-undecylcalix[4]resorcinarene **1** and two tetraboronic acid-cavitands **7** and **8**. Resorcinarene **1** was used as a reference receptor because its complexing abilities towards sugars have been described.[17–22] This receptor is conformationally flexible and can adopt conformations suitable for sugars, contrary to cavitands with a greater degree of molecular rigidity.

We selected several sugars as substrates. L-Sorbose, D-galactose D-glucose, D-cellobiose, shown in Figure 2, possess different configurations of hydroxyl groups and hence different molecular volumes.

Surface pressure and surface potential isotherms were recorded on pure water and on subphases containing selected carbohydrates. Corresponding surface characteristics are given in Table 1. Figure 3 illustrates the surface pressure isotherms.

Generally, the three investigated receptors formed stable monolayers of liquid condensed type.[23] The values of collapse pressure and compressibility modulus for resorcinarene **1** were lower than those for both boron cavitands. This means the monolayers formed by the latter boronated receptors were more stable.

Receptor **1**, as a more flexible molecule, can adopt conformations suitable for the steric requirements of sugars.

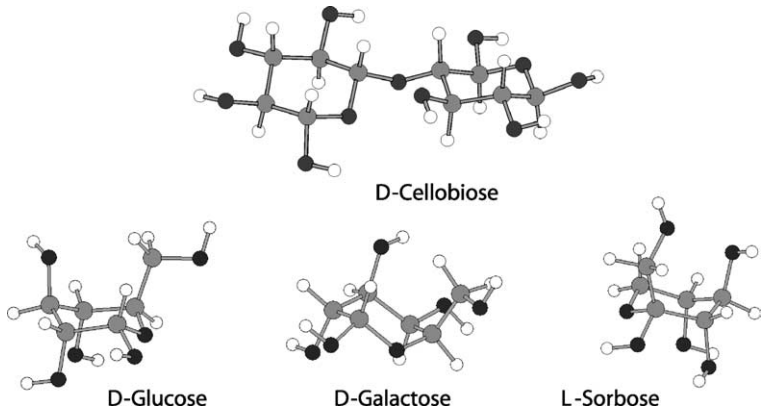

Figure 2. Structural formulae of the investigated sugars. Grey circles denote carbon, black oxygen and white hydrogen atoms.

This is manifested in different values of area per molecule, estimated from isotherms registered on pure water and subphases containing sugars. In contrast, the surface pressure isotherms registered for boron cavitands differ slightly. Only surface pressure isotherms for receptor **7** registered on a subphase containing either D-cellobiose or D-galactose differ from that registered on pure water. This can be explained in such a way that L-sorbose and D-glucose form esters inside the cavity of the receptor **7** and the area per molecule is therefore the same as for the free cavitand. The cavity of **8** is larger than that of **7**. So, sugars can be accommodated within the cavity of the former and do not interact with neighbouring molecules, which manifests in very modest differences in the surface pressure isotherms. Receptor **8** can accommodate inside cavity even disaccharide D-cellobiose and, as a consequence, differences in surface pressure isotherms are rather small. Figure 4 presents the molecular modelling (HyperChem 5.0, MM^+) of all receptors with L-sorbose inside the cavity. For the calculation we assumed that complexes with 1:1 stoichiometry were formed.

Calculated cross-sectional areas for free receptors are 76, 132, and 153 $Å^2$ for **1**, **7** and **8**, respectively. The cross-sectional area increased for resorcinarene **1** complex with L-sorbose (108 $Å^2$), whereas for both cavitands remained the same (**7**–132 $Å^2$, and **8**–156 $Å^2$). That is in agreement with the observation that change of area per molecule **1** can only be observed for, when the subphase contained L-sorbose. There is a need for some comments on differences in calculated and estimated areas per molecule. The resorcinarene cross-section areas are smaller than those observed from monolayer π-A isotherm. This means that the estimated area from monolayer is determined by hydrocarbon chains attached to resorcinarene head-group. As was described earlier, hydrophobic substituents are not perpendicular to water surface but form an angle about 66 degrees.[13] The limiting area per molecule for both cavitands is in agreement with the cross-section area for head-group calculated from molecular modelling. We can conclude that the head-groups determine the area occupied by receptor **7** and **8** on the air/water interface.

Contrary to surface pressure isotherms the surface potential isotherms indicated more profound changes. Surface potential values measured for maximum packing in monolayer are collected in Table 1.

Presumably, the presence of the sugar in the receptor cavity induces changes in the electron density distribution that has a profound effect on the surface potential.

Due to the character of the interaction between receptors and sugars there are opposite changes observed in values of

Table 1. Surface parameters for investigated receptor monolayers at the air/water interface

Receptor	Sugar	A_0 [$Å^2$]	π_{col} [mN m^{-1}]	C_s^{-1} [mN m^{-1}]	ΔV [mV]
1	—	150	48	163	125
	D-Galactose	158	30	135	550
	D-Glucose	138	48	217	250
	D-Cellobiose	171	46	215	200
	L-Sorbose	133	33	185	1100
7	—	129	52	256	700
	D-Galactose	120	38	245	600
	D-Glucose	128	49	299	360
	D-Cellobiose	152	49	287	250
	L-Sorbose	129	52	321	350
8	—	155	52	251	60
	D-Galactose	151	52	247	35
	D-Glucose	151	57	279	30
	D-Cellobiose	161	51	218	100
	L-Sorbose	155	53	239	25

A_0—limiting area per molecule, estimated by drawing a tangent to the surface pressure isotherm from the most condensed region to zero ordinate, π_{col}—surface pressure at which monolayer collapsed, C_s^{-1}—compressibility modulus, calculated from equation $-A(d\pi/dA)_T$, ΔV—value of surface potential at maximally packed monolayer.

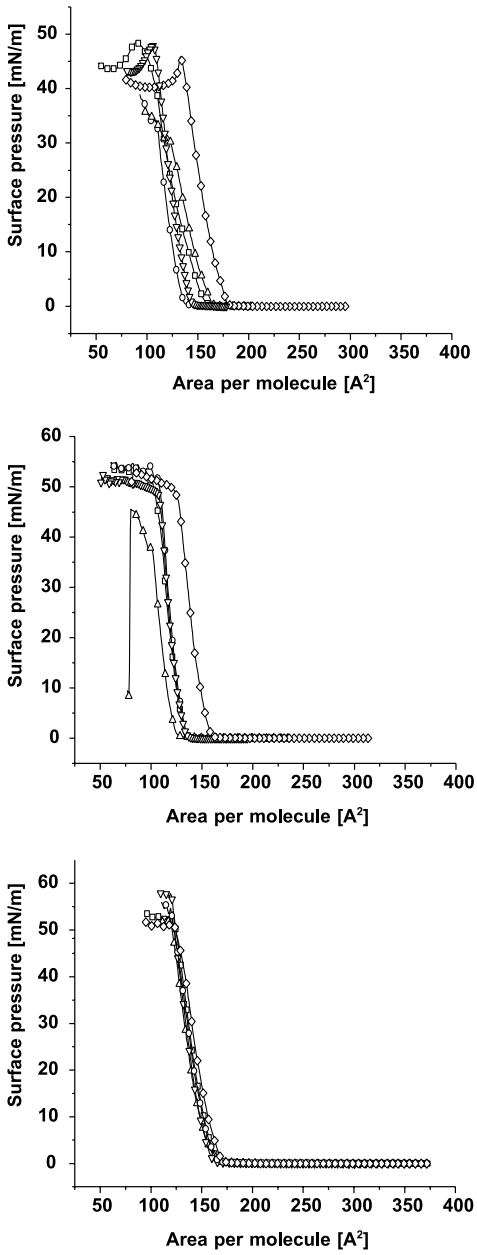

Figure 3. Langmuir π-A isotherms for monolayers formed by resorcinarene **1** (upper), and boronic acid cavitands **7** and **8** (middle and lower, respectively). Symbols correspond to isotherms registered on a subphase consisting: pure water-squares, L-sorbose-circles, D-galactose-up triangles, D-cellobiose-diamonds and D-glucose-down triangles.

surface potential. The resorcinarene **1** formed complexes with carbohydrates via hydrogen bonding.[6,7] The resulting complex is more polar than the receptor itself and that is manifested in an increased surface potential in comparison to the surface potential for a receptor **1** monolayer formed on pure water. The boronic acid derivatives bound the sugars via esterification (see Fig. 5). The formed species are less polar than boronic acid derivatives themselves. The surface potential decreased for monolayers of boronic acid cavitands registered on subphases containing sugars. Only modest changes in the surface potentials for the films of compound **8** were observed. That is, a sugar molecule may occupy the cavity of the **8**, which is larger than those of the other two receptors. If these sugars are accommodated within this larger cavity, then they do not interact with neighbouring molecules, contrary to the inclusion complexes of the two other, more compact receptors.

It is known that boronic acid derivatives form esters with sugars. Figure 5 shows structural formulas of some selected examples of boronic acid ester with hexoses.[24] It turns out that not only 1,2-diols form derivatives, but also 1,3-diols, provided that the resulting ester forms a six-membered ring free of steric strain.

This fact implies that the interaction of tetraboronic acid receptors with sugars can be fairly complicated, depending on the conformation and configuration of the selected sugar. We performed conductometric and spectrophotometric titrations of both cavitands with glucose to establish the stoichiometry of complexes formed. These studies were conducted in water/tetrahydrofuran solutions to obtain relatively good solubility receptors and sugars. What we observed was multimolecular equilibria, but it was difficult to draw explicit conclusions.[25]

3. Conclusion

Our results indicate the recognition of carbohydrates by boron acid-containing cavitands using the Langmuir technique. From these data it is difficult to draw conclusions about the stoichiometry and stereochemistry of complexes. The most reliable method to reveal the nature of complexes formed between boronic receptors and carbohydrates in the solid state would be X-ray structural study. Actually, we attempted to grow crystals of the complexes. The second

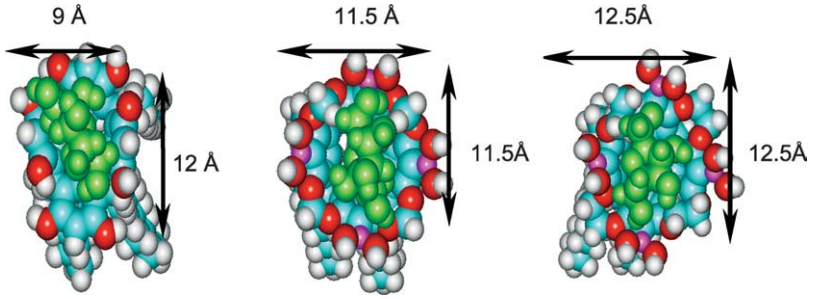

Figure 4. Molecular modelling of complexes between L-sorbose and **1**, **7** and **8**, respectively. HyperChem 5.0, MM^+. Colours of receptor atoms: blue-carbon, red-oxygen, white-hydrogen, magenta-boron, sugar atoms in green.

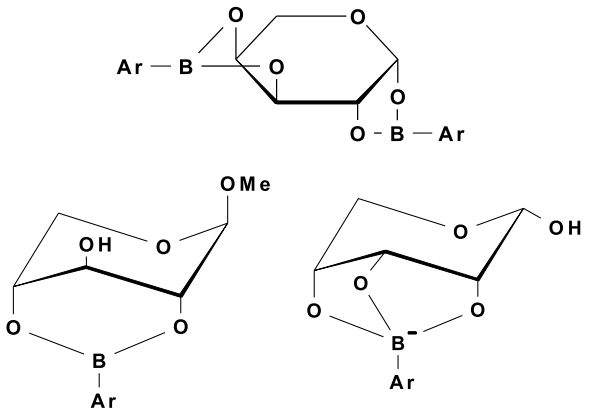

Figure 5. Structural formulae of hexose esters with boronic acid derivatives.

step is the synthesis of boron acid cavitands with no alkyl chains to improve the solubility of these derivatives in polar solvents. That would allow for the investigation not only at the interface but also in solution.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich or Merck and used as received, except for tetrahydrofuran (distillation over lithium aluminum hydride), acetone (drying over potassium carbonate). The lipophilic tetra-*n*-undecylcalix[4]resorcinarene was prepared according to Aoyama.[6,7] The novel compounds were characterised by ^{1}H and ^{13}C NMR (Varian Gemini 200 MHz), IR (Perkin–Elmer) and (Mariner Biospectrometer Workstation) mass spectra. For the alkylation of the phenolic oxygens in the initial calix[4]resorcinarene we have used bromochloromethane, or 1,2-dibromoethane. *Caution*! All works with lithium aluminum hydride and butyllithium are potentially hazardous and should be performed by experienced chemists protected with gloves, glasses and well-ventilated hood. Particular care should be observed while transferring the butyllithium, which is highly pyrophoric.

4.1.1. Synthesis of tetrabromo calix[4]resorcinarene (2). The synthesis was performed according to the literature procedure.[1,5] The calix[4]resorcinarene **1** (22 g, 0.02 mol) was dissolved in THF (200 mL) and NBS (14.3 g, 0.08 mol) was added with stirring under argon for 2 h. THF was evaporated at reduced pressure, and the light-yellow residue was recrystallised from methanol to give **2** as white crystals. Yield 85%. Mp >250 °C. All analytical data correspond to those previously reported.[5]

4.1.2. Improved synthesis of tetrabromocavitands (3,4). Dry tetrabromocalix[4]resorcinarene **2** (35 g, 0.0246 mol) was dissolved in 1000 mL of dry acetone in reactor, flushed with argon. To the stirred solution, finely ground and calcined potassium carbonate (54 g, 0.39 mol) was added portionwise to maintain efficient stirring, followed by the addition of 1,2-dibromoethane (19.3 mL, 0.22 mol) and tetra-*n*-butylammonium iodide (0.01 g). The suspension was stirred in the reactor for 24 h at 50–60 °C. An additional amount of 1,2-dibromoethane (10 mL, 0.115 mol) and tetra-*n*-butylammonium iodide (0.05 g) was added, and stirring was maintained for an additional 24 h at the same temperature. After cooling, the mixture was filtered through Celite and evaporated. The residue was dissolved in chloroform (500 mL), shaken with water (200 mL). The water layer was extracted with chloroform (300 mL) and the combined extracts were evaporated under reduced pressure. The brown residue was extracted with acetonitrile and crystallised from acetonitrile to give white crystals of **4**, which were recrystallised from *n*-propanol to give long white needles. Yield 70%. Mp: 62–64 °C. ^{1}H NMR, ($CDCl_3$, TMS): δ 0.87 (t, $J=6$ Hz, 12H, CH_3–$C_{10}H_{21}$), 1.24 (m, 72H, –$(CH_2)_9$–), 2.03 (m, 8H, –CH_2–CH–), 3.75 (m, 8H, *out* AA′XX′, –CH_2CH_2–), 4.44 (m, 8H, *in* AA′XX′, –CH_2CH_2–), 5.26 (t, $J=7$ Hz, 4H, Ar-C*H*-Ar), 7.23 (s, 4H, Ar-*H*). Anal. Calcd for $C_{80}H_{116}O_8Br_4$: C 62.99%, H 7.66%; found: C 62.14%, H 7.34%. MS *m*/*z* calcd 1525, found: 1526 $(M+H)^+$.

The cavitand **3** was prepared analogously, using bromochloromethane as alkylating agent. Yield 60%. Mp: 78–80 °C. ^{1}H NMR ($CDCl_3$, TMS): δ 0.88 (t, $J=6$ Hz, 12H, CH_3–$C_{10}H_{21}$), 1.26 (m, 72H, –$(CH_2)_9$–), 2.20 (m, 2H, –CH_2–CH–), 4.44 (m, 4H, *in* O–CH_2–O), 4.72 (t, $J=7$ Hz, 4H, Ar-C*H*-Ar), 5.26 (m, 4H, *out* O–CH_2–O), 7.10 (s, 4H, Ar-*H*). Anal. Calcd for $C_{76}H_{108}O_8Br_4$: C 62.13%, H 7.41%; found: C 62.49%, H 7.71%. MS *m*/*z* calcd: 1469, found: 1470 $(M+H)^+$. The ^{13}C NMR (100 MHz), IR (KBr) spectra have been reported.[5]

4.1.3. Synthesis of boron-containing cavitands (5,6,7,8). Compound **3** (4 g, 2.74 mmol) was dissolved in dry THF under argon and cooled to –78 °C. BuLi in hexane (1.6 M, 16 mL, 5.5 mmol) was added via syringe, and stirring at low temperature was maintained for 1 h, followed by addition of triethylborate (1.35 mL, 12.5 mmol). After 1 h, the mixture was brought to room temperature, filtered, evaporated to dryness, and the residue was crystallised from methanol, to give **5** as white needles. Yield 70%. The hydrolysis of ethoxy groups in **5** was effected in THF solution by addition of water, stirring for 1 h, evaporation and crystallisation from methanol to give **7** as white crystals. Yield 80%.

The cavitands **6** and **8** was prepared analogously, using cavitand **4**. Yield for **6** 75% and 80% for **8**. All compounds have mp >250 °C.

Boroncavitand **5**. ^{1}H NMR ($CDCl_3$, TMS): δ 0.88 (t, $J=$ 6 Hz, 12H, CH_3–$C_{10}H_{21}$), 1.26 (m, 84H, –$(CH_2)_9$–, and $BOCH_2CH_3$), 2.20 (m, 8H, –CH_2–CH–), 3.63 (m, 16H, BO–CH_2–), 4.44 (m, 4H, outer of O–CH_2–O), 4.72 (m, 4H, Ar-C*H*-Ar), 5.72 (m, 4H, inner of O–CH_2–O), 7.15 (s, 4H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ 154.9, 136.4, 124.9, 115.7, 73.2, 34.4, 34.0, 32.6 (two coincident resonances), 30.4 (two coincident resonances), 28.6, 23.3, 14.8. IR (KBr, cm^{-1}): 3643, 3494, 3404, 2958, 2920, 2850, 1513, 1490, 1460, 1444. Anal. Calcd for $C_{92}H_{148}B_4O_{16}$: C 71.13%, H 9.60%; found: C 71.24%, H 9.77%. MS *m*/*z* calcd: 1553, found: 1554 $(M+H)^+$.

Boroncavitand **7**. ^{1}H NMR ($CDCl_3$, TMS): δ 0.88 (t, $J=$ 6 Hz, 12H, CH_3–$C_{10}H_{21}$), 1.25 (m, 72H, –$(CH_2)_9$–), 2.27

(m, 8H, –CH_2–CH–), 2.88 and 2.96 (s, 2×4H, B-OH), 4.39 (m, 4H, *out* O–CH_2–O), 4.72 (t, J=7 Hz, 4H, Ar-CH-Ar), 5.72 (m, 4H, *in* O–CH_2–O), 6.97 (s, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 153.2, 136.2, 128.7, 115.1, 71.7, 37.0, 32.6, 30.4 (two coincident resonances), 28.5, 23.3, 14.8. IR (KBr, cm^{-1}): 3431, 2924, 2854, 1619, 1570, 1478, 1452, 1440, 1082. Anal. Calcd for $C_{76}H_{116}B_4O_{16}$: C 68.63%, H 8.80%; found: C 68.88%, H 9.01%. MS *m*/*z* calcd: 1329, found: 1330 $(M+H)^+$.

Boroncavitand **6**. ^{1}H NMR ($CDCl_3$, TMS): δ 0.87 (t, J= 6 Hz, 12H, CH_3–$C_{10}H_{21}$), 1.24 (m, 84H, –(CH_2)$_9$–, and BOCH_2CH_3), 2.05 (m, 8H, –CH_2–CH–), 3.47 (m, 8H, *out* AA′XX′, –CH_2CH_2–), 3.64 (m, 16H, BO–CH_2–), 5.13 (m, 8H, *in* AA′XX′, –CH_2CH_2–), 4.76 (t, J=7 Hz, 4H, Ar-CH-Ar), 6.67 (s, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 154.9, 136.4, 124.9, 115.7, 73.2, 34.4, 34.0, 32.6 (two coincident resonances), 30.4 (two coincident resonances), 28.6, 23.3, 14.8. IR (KBr, cm^{-1}): 3643, 3494, 3404, 2958, 2922, 2855, 1516, 1490, 1462, 1454. Anal. Calcd for $C_{96}H_{156}B_4O_{16}$: C 71.64%, H 9.77%; found: C 71.58%, H 9.69%. MS *m*/*z* calcd: 1609, found: 1610 $(M+H)^+$.

Boroncavitand **8**. ^{1}H NMR ($CDCl_3$, TMS): δ 0.87 (t, J= 6 Hz, 12H, CH_3–$C_{10}H_{21}$), 1.24 (m, 84H, –(CH_2)$_9$–), 2.04 (m, –CH_2–CH–), 3.49 (m, 8H, *out* AA′XX′, –CH_2CH_2–), 5.13 (m, 8H, *in* AA′XX′, –CH_2CH_2–), 5.33 (t, J=7 Hz, 4H, Ar-CH-Ar), 6.78 (s, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 153.2, 136.2, 128.7, 115.7, 71.7, 34.5, 32.6, 30.4 (two coincident resonances), 28.5, 23.3, 14.8. IR (KBr, cm^{-1}): 3431, 2924, 2854, 1629, 1578, 1488, 1462, 1445, 1092. Anal. Calcd for $C_{80}H_{124}B_4O_{16}$: C 69.37%, H 9.02%; found: C 69.42%, H 9.12%. MS *m*/*z* calcd: 1385, found: 1386 $(M+H)^+$.

4.2. Langmuir films

Surface pressure (π) and surface potential (ΔV) vs. area per molecule (A) isotherms were recorded, using a computer-controlled NIMA 601BAM trough with Wilhelmy plate type microbalance. Surface potential and surface pressure measurements were performed simultaneously as a function of area per molecule. The instrument was placed in a laminar hood in which temperature was kept constant at 20 ± 1 °C. The procedures of cleaning the trough and monolayer spreading have been described earlier.[8–12] The accuracy of measurements was ±0.1 mN m^{-1} for surface pressure, ±1 Å^2 molcule^{-1} for molecular area per molecule and ±5 mV for surface potential. All chemicals were of analytical grade. The spread solutions were prepared daily by dissolving 5 mg of the studied compound in 5 mL of chloroform (Aldrich). Water used as the subphase was purified with a Millipore-Q water purification system. Concentration of sugars in water subphase was 10^{-2} mol dm^{-3}.

4.3. Molecular modelling

Calculations were performed on PC by means of the MM^+ (molecular mechanics) method from a HyperChem® software package, version 5.0 (Hypercube, Inc.). The geometry of the receptors and their complexes with sorbose was optimised in the gas phase.

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Antibiotics from Australian terrestrial invertebrates. Part 1: Antibacterial trinervitadienes from the termite *Nasutitermes triodiae*

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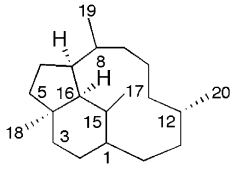
Abstract—The antibacterial activity of an extract of the Australian termite *Nasutitermes triodiae* (Isoptera: Termitidae) (Froggatt) is due to the presence of a group of trinervitanes, diterpenes unique to termite genera within the subfamily Nasutitermitinae. The major active components are novel hydroxylated 1(15),8(19)-trinervitadienes and the known 1(15),8(9)-trinervitadiene-2β,3α-diol. This constitutes the first observation of hydroxylation of the trinervitane skeleton at the 5- and 18-positions, and of the substantial antimicrobial activity of trinervitane diterpenes.

1. Introduction

During screening of extracts from Australian terrestrial invertebrates for biological activity, an extract from a species of termite, the so-called 'cathedral termite' *Nasutitermes triodiae* (Isoptera: Termitidae) (Froggatt), was observed to have significant antimicrobial activity against the Gram positive bacterium *Bacillus subtilis*. The extract furthermore was moderately cytotoxic, with intermediate levels of growth-inhibitory activity against two mammalian cell types, a non-secreting mouse myeloma cell line and a human-derived small cell lung carcinoma cell line. Bioassay-directed examination of the extract has shown that the antibacterial activity, but probably not the cytotoxicity, is due to the presence of several trinervitadienes, diterpenoid metabolites characterised by their trinervitane carbon skeleton **1**.



1

Diterpenes of the trinervitane group are unique to termites, and to date have been found only in species belonging to 10 genera within the subfamily Nasutitermitinae of the family Termitidae. They are components of the defensive secretions of the nozzle-like frontal gland or 'nasus' of nasute termite soldiers, and have been assumed to increase the efficacy of the secretion by increasing its viscosity and reducing monoterpene evaporation.[1–3] There has been no previous report, however, of antimicrobial or other pharmacological activity associated with trinervitanes, unlike the monoterpene components of the soldier secretion, which are known to be toxic to insects[1,3,4] and have antifungal properties.[5] We describe here the isolation from *N. triodiae* and the structural characterisation of the novel trinervitadienes **2**–**4** and the known trinervitadiene **7**. We also assess the antibacterial and cytotoxic activity of these metabolites and of the fully acetylated derivative **6**.

2. Results

Mixed adult castes, mainly soldiers, of *N. triodiae* were collected near Mount Molloy approximately 100 km northwest of Cairns in Queensland, Australia. They were freeze-dried, powdered, and then extracted with methanol–water (70% v/v). Fractionation by gradient elution on preparative HPLC gave a discrete group of fractions, detected by UV absorption and evaporative light scattering, which had marked activity against *B. subtilis* and eluted between 22 and 26 min. After further purification the active materials

Keywords: Antibacterial; Diterpene; *Nasutitermes triodiae*; Termite; Trinervitane; Trinervitadiene.
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were subjected to detailed analysis, leading to their identification as the following trinervitadienes.

2.1. 1(15),8(19)-Trinervitadiene-3α,5α,18-triol (2) from fraction 23

Fraction 23 contained the triol **2**, ESMS of which showed ions at *m/z* 343 and 663 corresponding to sodiated mono- and dimeric forms of molecular weight 320 amu. EIMS showed no molecular ion at this mass, but rather daughter ions due to the loss of one, two and three molecules of water at *m/z* 302, 284 and 266 amu. HREIMS established the composition of the first of these daughter ions as $C_{20}H_{30}O_2$, corresponding to a parent molecular formula $C_{20}H_{32}O_3$. Since the ^{13}C NMR spectrum (Table 1) showed only four trigonal carbons as olefinic resonances between δ 110 and 150 ppm, the triol must be tricyclic. APT and HMQC spectroscopy defined two weakly coupled olefinic hydrogen resonances, δ 4.99 and 4.86, as a methylene group $=CH_2$, the remaining three olefinic carbon resonances being fully substituted.

These data suggested that the triol has the trinervitane skeleton **1** in the 1(15),8(19)-diene form, which occurs as its hydroxylated and esterified derivatives in a number of termite metabolites. No unesterified trihydroxy derivative of this diene, however, has been reported previously as a natural product. One such triol, the 2β,3α,13α-triol, has been prepared by hydrolysis of its triacetate isolated from *N. rippertii*[6] but its ^1H NMR spectroscopy characteristics differ from those of the present triol, which is thus a novel compound.

The ^1H NMR spectrum of the triol **2** showed four midfield resonances at δ 3.95 and 3.80, and 4.16 and 4.68, established by HMQC spectroscopy as connected to a hydroxylated methylene $-CH_2OH$ and two hydroxylated methine –CHOH– carbons at δ 64.2, 70.1, and 74.8, respectively. All four proton resonances were unresolved multiplets, but COSY data showed that the δ 3.95 and 3.80 signals were mutually coupled only, implying a neo-pentyl alcohol segment. The presence of such a segment, necessarily at the 6,5-ring junction if the carbon skeleton **1** is correct, was confirmed by NMR spectroscopic data showing vinylic (C-17) and secondary (C-20) methyl groups but no resonance corresponding to the tertiary methyl group (C-18) normally present at C-4. HMQC and COSY data established that the δ 4.16 methine signal formed part of an essentially isolated three-spin system $-CH(OH)CH_2-$ with adjacent methylene protons at δ 2.40 and 2.18. The δ 4.68 methine signal was coupled to adjacent methylene protons at δ 2.18 and 1.84, which in turn formed a linear five-spin system $-CH(OH)CH_2CHCH-$ with methine protons at δ 3.47 and 2.55. These three- and five-spin systems clearly constitute the C-2,3 and C-5,6,7,16 segments of the 6- and 5-membered rings, respectively, of the skeleton **1**. The former segment is oriented so as to position the alcohol function at C-3, in accordance with the observed downfield shifts of δ 2.40 and 2.18 expected for the two methylene protons if they occupy the allylic C-2 site. This orientation is confirmed by homoallylic coupling seen in the COSY spectrum between both these C-2 protons and the vinylic methyl protons at δ 1.68. HMQC and COSY data also displayed the two hydrocarbon segments $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2CH_2-$ of the medium ring, although there

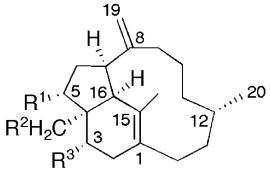
Table 1. ^{13}C and ^1H NMR spectroscopic data for 1(15),8(19)-trinervitadiene-3α,5α,18-triol (**2**) and 1(15),8(19)-trinervitadiene-3α,5α-diol (**3**)

Position	3α,5α,18-Triol (**2**)		3α,5α-Diol (**3**)	
	C	H	C	H
1	127.9		127.7	
2	36.6	2.40 (m)	36.8	2.29 (dd, 6, 16.5)
		2.18 (m)		1.95 (m)
3	70.1	4.16 (bs)	68.7	3.97 (dd, 11.0, 6.5)
4	53.3		49.9	
5	74.8	4.68 (d, 3.5)	76.9	4.27 (d, 4.0)
6	36.3	2.18 (m)	36.6	2.16 (m)
		1.84 (m)		1.75 (m)
7	49.2	3.47 (m)	49.0	3.46 (m)
8	149.7		150.2	
9	27.2	1.92 (m)	27.0	1.98 (m)
		1.83 (m)		1.80 (m)
10	23.8	1.59 (m)	23.9	1.58 (m)
		1.59 (m)		1.58 (m)
11	31.9	1.21 (m)	32.0	1.20 (m)
		0.91 (m)		0.93 (m)
12	27.3	1.31 (m)	27.2	1.36 (m)
13	32.0	1.43 (m)	32.1	1.36 (m)
		1.43 (m)		1.44 (m)
14	27.8	2.40 (m)	27.9	2.41 (m)
		1.68 (m)		1.70 (m)
15	126.4		126.7	
16	51.9	2.55 (d, 11.5)	55.6	2.70 (d, 10.5)
17	21.0	1.68 (s)	21.2	1.71 (s)
18	64.2	3.95 (d, 11.0)	12.4	0.98 (s)
		3.80 (bs)		
19	113.3	4.99 (s)	112.9	4.98 (s)
		4.86 (s)		4.85 (s)
20	21.8	0.88 (d, 7.0)	21.8	0.89 (d, 6.5)

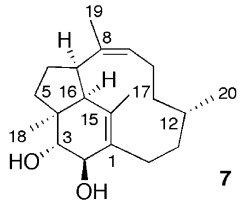
were no clear correlations linking or orienting these segments.

Conclusive proof of the 1(15),8(19)-trinervitadiene carbon skeleton, and of the location and orientation of all the above segments, followed from the numerous long range H,C correlations observed in HMQC spectroscopy. In particular, the 6,5-ring substitution follows from 3-bond couplings between CH_2-2, C-4 and C-15, CH_2-18 and C-5, CH(OH)-5 and C-3, C-7 and C-16, CH_2-6 and C-8 and C-16, CH-7 and C-15, and CH-16 and C-3, C-8, C-17 and C-18. The points of attachment of the medium ring to the 6,5-system follow from reciprocal 3-bond H,C couplings between CH-7, CH_2-9 and CH_2-19, CH_2-2 and CH_2-14, and 3-bond H,C coupling from CH_2-14 to C-15. Coupling from CH_2-11 to C-13 and from CH_3-20 to C-11 and C-13 confirmed the orientation and linkage of the $–CH_2CH_2CH_2–$ and $–CH(CH_3)CH_2CH_2–$ segments of the medium ring. The metabolite was thus identified as 1(15),8(19)-trinervitadiene-3,5,18-triol (**2**), without regard to stereochemistry.

The relative stereochemistry of this triol **2** was studied by NOESY and GOESY spectroscopy. Both techniques showed mutual Overhauser enhancements between CH_2-18, H-16 and H-7, confirming the *cis*,*cis*-ring junction stereochemistry, with these substituents assumed to be α-oriented in accordance with the normal trinervitane carbon skeleton **1**. Mutual Overhauser effects were also observed between H-3 and H-5, but not between either of these protons and CH_2-18, defining them as β-oriented and thus the two secondary hydroxyl groups as α-oriented. The secondary methyl group at C-12, the remaining stereogenic centre, was confirmed as α-oriented in accord with the skeleton **1** from the Overhauser effects between H-12 and the β-protons at C-2 and C-6. The resulting relative configuration depicted for the triol **2** is assumed to represent also the absolute configuration, since all determinations to date of absolute configurations of trinervitanes have led to the same 6,5,11-ring junction chirality shown in skeleton **1**.[7,8]



2: R^1, R^2, R^3 = OH
3: R^1, R^3 = OH ; R^2 = H
4: R^1 = OAc; R^2, R^3 = OH
5: R^1 = OH; R^2, R^3 = OAc
6: R^1, R^2, R^3 = OAc



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2.2. 1(15),8(19)-Trinervitadiene-3α,5α-diol (3) from fraction 24

Further chromatography of fraction 24 gave the pure diol **3** as the major component. ESMS and EIMS established its molecular formula as $C_{20}H_{32}O_2$, containing one less oxygen atom than the triol **2**. Detailed analysis of its one- and two-dimensional ^{13}C and ^1H NMR spectra (similar to that described above for the triol **2**) led to the assignments recorded in Table 1, where they are compared with corresponding data for the triol **2**. The diol retains the spin systems $–CH(OH)CH_2–$, $–CH(OH)CH_2CHCH–$, $–CH_2CH_2CH_2–$ and $–CH(CH_3)CH_2CH_2–$ of the triol, on the same 1(15),8(19)-trinervitadiene skeleton. The only major spectral differences occur in the chemical shifts and multiplicity of both C and H at the 18 position, where the diol **3** clearly lacks the primary hydroxyl function of the triol **2**. Expected minor differences also occur in chemical shifts at the 2, 3, 4, 5 and 16 positions, which flank the 18 position, while other resonances are virtually unchanged.

The metabolite thus has the 1(15),8(19)-trinervitadiene-3,5-diol structure (**3**), without regard to stereochemistry. NOESY and GOESY correlations (similar to those detailed above for the triol **2**) confirmed the expected relative stereochemistry of the trinervitane carbon skeleton, and established the 3α,5α-diol configuration shown in structure **3**. As with the triol **2**, this structure **3** is also assumed to represent the absolute configuration. Three $C_{20}H_{32}O_2$ diols with the same 1(15),8(19)-trinervitadiene skeleton have been reported previously, from termites of the subfamily Nasutitermitinae, but in each case carry vicinal 2,3-diol functionality with distinctively different NMR spectroscopy characteristics.[6,7,9–11]

2.3. 1(15),8(9)-Trinervitadiene-2β,3α-diol (7) from fraction 26

Fraction 26 was separated by further chromatography into two major components, the less polar of which was shown by ESMS and EIMS to have the molecular formula $C_{20}H_{32}O_2$, isomeric with the diol **3**. Unlike the 1(15),8(19)-trinervitadiene-diol **3** (Table 1), however, this diol **7** lacked the distinctive C-19 exomethylene $=CH_2$ signals in its ^1H NMR spectrum, which were replaced instead by those of a vinylic methyl system $–CH_3C=CH–$ at δ 1.56 (d, 2.0) and 5.29 (qdd, 2.0, 6.0, 11.0). Together with the continued presence of resonances typical of CH_3-17, CH_3-18 and CH_3-20 at δ 1.69 (bs), 0.97 (s) and 0.85 (d, 7.0), these data suggested a trinervitane skeleton **1** in the 1(15),8(9)-diene form. Two $C_{20}H_{32}O_2$ diols with this diene skeleton, carrying 2,3-diol functionality and differing from each other only in the configuration of the diol, have been reported previously from genera in the subfamily Nasutitermitinae. Comparison of their ^1H NMR spectroscopic data[7,11–13] with that of the present diol established its structure as 1(15),8(9)-trinervitadiene-2β,3α-diol (**7**).

2.4. 1(15),8(19)-Trinervitadiene-3α,5α,18-triol 5-acetate (4) from fraction 26

The more polar component of fraction 26 had the molecular formula $C_{22}H_{34}O_4$. Its EI mass spectrum showed a daughter ion at *m*/*z* 302 arising by loss of 60 amu from the molecular ion at *m*/*z* 362, indicating an acetate ester, possibly of the triol **2**. This was supported by its ^1H NMR spectrum (Table 2), which displayed the indicative CHOH-3, CH-7, CH_3-17, CH_2OH-18, $=CH_2$-19, and CH_3-20 resonances of the 1(15),8(19)-trinervitadiene-3,5,18-triol (**2**) (cf. Table 1).

Table 2. ^{1}H NMR spectroscopic data for 1(15),8(19)-trinervitadiene-3α,5α,18-triol 5-acetate (**4**), 3,18-diacetate (**5**) and 3,5,18-triacetate (**6**)

Position	5-Acetate (**4**)	3,18-Diacetate (**5**)	3,5,18-Triacetate (**6**)
3	4.14 (m)	5.38 (dd 11.0, 6.0)	5.36 (dd, 11.0, 6.5)
5	5.72 (d, 4.0)	4.08 (bs)	5.22 (d, 4.0)
7	3.40 (m)	3.50 (m)	3.43 (m)
16		2.73 (d, 12.0)	2.90 (d, 12.0)
17	1.67 (s)	1.71 (s)	1.71 (s)
18	3.85 (d, 13.0)	4.31 (d, 12.5)	4.54 (d, 11.5)
	3.40 (d, 13.0)	4.34 (d, 12.5)	4.04 (d, 11.5)
19	5.02 (d, 2.0)	5.02 (s)	5.02 (s)
	4.90 (d, 2.0)	4.90 (s)	4.92 (s)
20	0.88 (d, 6.0)	0.89 (d, 6.5)	0.89 (d, 6.5)
OAc	2.18 (s)	2.08 (s)	2.09 (s)
		2.05 (s)	2.06 (s)
			1.98 (s)

The acetate ester, seen as a methyl singlet at δ 2.18, is clearly attached at the 5-position, resulting in a marked downfield shift of that methine doublet signal from δ 4.68 to δ 5.72.

The structure and stereochemistry of this triol monoacetate **4** were confirmed by partially acetylating the triol **2** over a period of 3 h, and isolating from the acetylation mixture a major component with identical retention time and ^{1}H NMR spectrum to the natural metabolite. Four trinervitadiene-triol monoacetates with the molecular formula $C_{22}H_{34}O_4$ have been reported previously, from termites in the subfamily Nasutitermitinae. They are all 1(15),8(19)-diene-2β,3α-diols, and carry the acetoxy substituent at the 9α-, 9β-, 17- or 20-positions.[7,9,12,14–16]

2.5. Synthetic 1(15),8(19)-trinervitadiene-3α,5α,18-triol 3,18-diacetate (5) and 3,5,18-triacetate (6)

In addition to the monoacetate **4**, a less polar diacetate $C_{24}H_{36}O_5$ was also isolated from the partial acetylation of the natural triol **2**. Comparison of its ^{1}H NMR spectrum (Table 2) with that of the parent triol **2** (Table 1) showed two singlet acetoxy resonances, and large downfield shifts of the methine and methylene resonances at the 3- and 18-positions from δ 4.16, 3.95 and 3.80 to δ 5.38, 4.34 and 4.31. This product is thus the 3,18-diacetate **5**. Only one trinervitadiene-triol diacetate, the 1(15),8(19)-diene-2β,3α,9α-triol 2,3-diacetate from several termite genera in the subfamily Nasutitermitinae, has been reported previously.[7]

Acetylation of the triol **2** for 3 days gave the 3,5,18-triacetate **6**, $C_{26}H_{38}O_6$. Its ^{1}H NMR spectrum (Table 2), in addition to three singlet acetoxy resonances, showed all four methine and methylene ^{1}H NMR signals at the 3-, 5- and 18-positions shifted markedly downfield compared to those of the triol **2** (Table 1). Three trinervitadiene-triol triacetates have been reported previously from five termite species in the subfamily Nasutitermitinae. They are all esters of 1(15),8(19)-diene-2β,3α-diols, with the third acetoxy substituent at the 9α-, 13α- or 14α-position.[6,9,16,17]

2.6. Antimicrobial activity and cytotoxicity of the trinervitadienes

The pure trinervitadienes showed significant antimicrobial activity, and were the principal active components of the total termite extract. The 1(15),8(9)-trinervitadiene-2β,3α-diol (**7**) was most potent, with a MIC against the Gram positive bacterium *B. subtilis* estimated as $\leq$25 μg/mL. The 1(15),8(19)-trinervitadiene-3α,5α,18-triol (**2**) and 3α,5α-diol (**3**) were somewhat less active, with MIC values $\leq$50 μg/mL. Acetylation of the triol **2** reduced its activity; the mono- and triacetates **4** and **6** showed MIC values $>$50 μg/mL. The total termite extract, and thus also these components, showed no activity against the Gram negative bacterium *Escherichia coli*. No inhibition of mammalian cell proliferation was observed when the triol **2** was tested against the non-secreting mouse myeloma cell line SP2/0 at concentrations up to 30 μg/mL, and against the human-derived small cell lung carcinoma line NCI-H460 at concentrations up to 100 μg/mL. Accordingly it is probable that the moderate cytotoxicity of the total termite extract, observed at a concentration of 60 μg/mL against the former cell line, is due to components other than these trinervitadienes. Several monoterpenes, known to be toxic to various insect species,[3,4] have been reported in extracts of *N. triodiae*,[3,18] and may be responsible for the observed cytotoxicity.

3. Discussion and conclusions

The trinervitane diterpenoids previously isolated from termite genera within the subfamily Nasutitermitinae share the carbon skeleton **1**, and, as far as has been studied, the same absolute chirality at the 6,5,11-ring junctions. They commonly carry alkene functionality at the 1(15),8(19)- or 1(15),8(9)-positions of the skeleton **1**, less commonly at the 15(17)-, 11(12)- or 1(2)-positions. One or more oxygen substituents are invariably present, frequently at the 2-, 3- or 9-positions, but sometimes at the 11-, 13-, 14-, 17-, or 20-positions. The present trinervitanes are the first to carry oxygenation at the C-5 or C-18 sites, and are also the first to be reported from an Australian termite.

Everaerts and co-workers[19] did not observe trinervitanes in the defensive secretion from soldiers of New Guinean isolates of the present termite species, *N. triodiae*. This may reflect intraspecific variation which is known to occur in termite colonies,[12,20] but their use of pentane rather than methanol–water for extraction and GC rather than LC for analysis may have precluded their finding the relatively polar, non-volatile trinervitadiene alcohols.

There has been no previous report of antimicrobial activity associated with the trinervitanes. Several general points emerge regarding structure–activity relationships. The more potent antibacterial compounds **7**, **2** and **3** all carry unesterified polar diol or triol functionality on the exposed side of the 6,5-ring system. Esterification of the triol **2** to the mono- or triacetate **4** or **6** reduces but does not abolish activity. Whether the second alkene is at the 8(19)-position as in compounds **2**–**6** or the 8(9)-position as in **7** does not appear to be critical, perhaps because the conformation of the overhanging medium ring is not substantially altered.

Trinervitane diterpenes from nasute termite soldier secretions have previously been classified as 'defensive compounds', the sole function of which is to protect the colony against attack by predators. The present discovery that these compounds have marked antimicrobial activity, however, raises the possibility that they also serve to suppress microbial parasites within the colony. The recent demonstration that Formosan subterranean termites (*Coptotermes formosanus*) fumigate their nests with naphthalene[21,22] provides a precedent for this suggestion.

4. Experimental

4.1. Spectroscopy

Electrospray and electron impact mass spectra were recorded with VG Quattro II and VG Autospec spectrometers. NMR spectra were acquired on a Varian Inova-500 spectrometer at 500 MHz for ^{1}H and 125.75 MHz for ^{13}C, except for the ^{13}C spectrum of compound **2** which was acquired on a Varian Gemini-300 at 75.43 MHz. Data refer to solutions in $CDCl_3$, using solvent peaks (7.26 for ^{1}H, 76.9 for ^{13}C) as internal reference. Proton signal multiplicity and coupling constants (Hz) are given in parentheses in Tables. Where individual proton multiplets are unresolved chemical shifts are approximate. APT, HMQC, COSY, HMBC, NOESY and GOESY spectra were acquired using standard parameters.

4.2. Chromatography

HPLC was carried out on a System Gold, Model 126, Beckman Instruments, Inc., USA. Columns were obtained from YMC Co Ltd, Japan, through Sapphire Biosciences, Sydney.

4.3. Bioassay

Antimicrobial activity was detected by saturating a 1/4 in. diameter filter paper disk (Bacto Laboratories Pty Ltd, Australia) with a methanolic solution of material to be assayed (insect extract, HPLC fraction, or pure compound), evaporating the solvent in a cool air stream and placing the disk onto a bacteriological plate inoculated with *B. subtilis* (ATCC strain 6633; 9.2 mL of a log phase culture with $Abs_{600\ nm}$ 1.0 per 200 mL of Luria–Bertani medium containing 1.5% w/v agar). The plate was incubated at 28 °C for 24 h and the diameter of the clearing zone measured. In some cases, HPLC fractions were tested by evaporating to dryness, redissolving in methanol and spotting the methanolic solution (10 μL) directly onto the bacteriological plate and proceeding as described.

Minimum inhibitory concentrations with *B. subtilis* ATCC strain 6633 were determined using the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution test.[23] The test was standardised using penicillin G and gentamicin with *Staphylococcus aureus* ATCC strains 29213 and 25923 and *Enterococcus faecalis* ATCC strain 29212. Results of standardisation were assessed according to Ferraro et al.[24]

Effects on mammalian cell growth were determined by exposing cultures of two mammalian neoplastic cell lines, SP2/0-Ag8 a non-secreting mouse myeloma cell line derived from Balb/C mice (Australian Tissue Culture Collection CRL 1581), and NCI-H460 a human-derived small cell lung carcinoma line, to methanolic solutions of material to be assayed (*N. triodiae* extracts or pure compound) for 19 h at 37 °C. Cells were grown in wells of sterile 96-well tissue culture cluster plates by standard methods. Cell growth was estimated using the Cell Proliferation Reagent WST-1 (Roche Diagnostics) according to the manufacturer's instructions and proliferation data were compared with those from untreated control wells.

4.4. Isolation of trinervitadienes 2, 3, 4 and 7

N. triodiae Froggatt (Isoptera: Termitidae) adults (mixed castes, mainly soldiers, 11.59 g wet weight) were collected near Mount Molloy, Queensland, Australia and frozen in a dry-shipper containing liquid nitrogen. The material was stored at −80 °C before being freeze-dried to constant weight (1.39 g). The sample was ground to a powder, dispersed in methanol–water (70% v/v, 4 mL/g wet biomass) by blending for 2–5 min and sonication for 10 min at 0 °C, and shaken at room temperature overnight. The sample was centrifuged for 10 min at 4500 rpm, and the residue washed by sonication for 10 min with further solvent (2 mL/g wet biomass). The combined supernatants (47 mL) were centrifuged at 16,000 rpm for 30 min, and then stored at −80 °C. The extract was syringe filtered (0.2 μm) before use.

A portion of the methanolic extract (10 mL, corresponding to 2.47 g wet weight and containing 98 mg of solute) was purified in batches (0.5 mL) by semi-preparative reverse-phase HPLC on a YMC ODS-AQ capped C18 column (250×10 mm). Elution conditions were water (containing trifluoroacetic acid 0.05% v/v) for 2 min, then a linear gradient to 100% acetonitrile from 2–22 min, followed by acetonitrile from 22–35 min. The flow rate was 4 mL/min, the absorbance of the effluent was monitored at 230 nm, and fractions were collected each minute. Corresponding fractions from all batches were pooled and evaporated to dryness under nitrogen. Fractions 23, 24 and 26 showed activity in disk assays against *B. subtilis*. These were subjected to analytical HPLC on a YMC ODS-AQ capped C18 column (250×3 mm), using similar elution conditions to the preparative procedure but with flow rate 0.55 mL/min.

Fraction 23 contained a single component **2** (15 mg), but the

two later fractions were mixtures. Further chromatography of fraction 24 in four portions on the same semi-preparative HPLC column, using isocratic elution with acetonitrile–tetrahydrofuran–water (containing 0.05% v/v trifluoroacetic acid) 42:28:30, yielded the pure major compound **3** (4 mg) as the only antibacterial component, eluting between 14–17 min. Fraction 26 loaded in two portions and eluted isocratically with acetonitrile–water (containing 0.05% v/v trifluoroacetic acid) 80:20, gave two major antibacterial components **4** (0.5 mg) and **7** (1.5 mg), with retention times 12–13 and 14–15 min.

All compounds were obtained as colourless gums on evaporation of eluents.

4.4.1. 1(15),8(19)-Trinervitadiene-3α,5α,18-triol (2). ^{13}C and ^{1}H NMR spectroscopic data are recorded in Table 1; ESMS *m/z* 343 and 663 (MNa^+ and M_2Na^+, M 320); EIMS *m/z* 302 (M^+-H_2O), 284 (M^+-2H_2O), 266 (M^+-3H_2O); HREIMS found *m/z* 302.2243 (M^+-H_2O), $C_{20}H_{30}O_2$ requires 302.2246.

The MIC against *B. subtilis* was estimated as $\leq$50 μg/mL. No inhibitory effect on the proliferation of NCI-H460 cells was observed at concentrations up to 100 μg/mL, or on the proliferation of SP2/0 cells up to 30 μg/mL.

4.4.2. 1(15),8(19)-Trinervitadiene-3α,5α-diol (3). ^{13}C and ^{1}H NMR spectroscopic data are recorded in Table 1; ESMS *m/z* 327 (MNa^+, M 304); EIMS *m/z* 304 (M^+), 286 (M^+-H_2O); HREIMS found *m/z* 304.2403 (M^+), $C_{20}H_{32}O_2$ requires 304.2402.

The MIC against *B. subtilis* was estimated as $\leq$50 μg/mL.

4.4.3. 1(15),8(9)-Trinervitadiene-2β,3α-diol (7). ESMS *m/z* 327 and 631 (MNa^+ and M_2Na^+, M 304); EIMS *m/z* 304 (M^+), 286 (M^+-H_2O), 271 (M^+-H_2O, CH_3), 268 (M^+-2H_2O), and 253 (M^+-2H_2O, CH_3); HREIMS found *m/z* 304.2404 (M^+), $C_{20}H_{32}O_2$ requires 304.2402. ^{1}H NMR spectroscopic data are identical with those published for this diol.[7,12,13]

The MIC against *B. subtilis* was estimated as $\leq$25 μg/mL.

4.4.4. 1(15),8(19)-Trinervitadiene-3α,5α,18-triol 5-acetate (4). ^{1}H NMR spectroscopic data are recorded in Table 2; ESMS *m/z* 345, 363, 385 and 747 (MH^+-H_2O, MH^+, MNa^+ and M_2Na^+, M 362); EIMS *m/z* 362 (M^+), 344 (M^+-H_2O), 302 (M^+-AcOH), 284 (M^+-H_2O, AcOH); HREIMS found *m/z* 362.2460 (M^+), $C_{22}H_{34}O_4$ requires 362.2457; found *m/z* 344.2350 (M^+-H_2O), $C_{22}H_{32}O_3$ requires 344.2351.

The MIC against *B. subtilis* was estimated as $>$50 μg/mL.

4.4.5. Partial acetylation of 1(15),8(19)-trinervitadiene-3α,5α,18-triol (2). The triol (**2**) (1 mg) and acetic anhydride (10 μL) in dry pyridine (100 μL) were kept for 3 h at room temperature. The reaction was diluted with water, extracted with dichloromethane, and the extract subjected to preparative HPLC on the semi-preparative column using gradient elution in acetonitrile–water from 50:50 to 100:0 over 35 min. UV-absorbing material eluting between 16.5–19 min contained two major components, and was rechromatographed on the analytical HPLC column in the same solvent gradient. The first major fraction, with R_t 18 min, matched the natural triol monoacetate (**4**) in ^{1}H NMR spectrum and R_t on analytical HPLC. The fraction (0.2 mg) with R_t 19 min was homogeneous by analytical HPLC and ^{1}H NMR spectroscopy, and contained 1(15),8(19)-trinervitadiene-3α,5α,18-triol 3,18-diacetate (**5**): ^{1}H NMR spectroscopic data are recorded in Table 2; ESMS *m/z* 427 and 831 (MNa^+ and M_2Na^+, M 404); EIMS *m/z* 404 (M^+), 386 (M^+-H_2O), 344 (M^+-AcOH), 326 (M^+-H_2O, AcOH), 284 ($M^+-2AcOH$), 266 (M^+-H_2O, 2AcOH); HREIMS found *m/z* 404.2567 (M^+), $C_{24}H_{36}O_5$ requires 404.2563.

4.4.6. 1(15),8(19)-Trinervitadiene-3α,5α,18-triol 3,5,18-triacetate (6). The triacetate (**6**) was synthesised by acetylation of the natural triol (**2**). The triol (**2**) (1 mg) and acetic anhydride (30 μL) in dry pyridine (100 μL) were kept for 3 days at room temperature. The reaction was diluted with water, extracted with dichloromethane, and the extract subjected to preparative HPLC under the standard conditions. The major fraction was collected and filtered through a short silica column in dichloromethane to afford the triacetate **6** (1 mg), which chromatographed as a single peak with R_t 28 min under the standard analytical HPLC conditions. ^{1}H NMR spectroscopic data are recorded in Table 2; ESMS *m/z* 469 (MNa^+, M 446); EIMS *m/z* 386 (M^+-AcOH), 326 ($M^+-2AcOH$), 266 ($M^+-3AcOH$); HREIMS found *m/z* 386.2449 (M^+-AcOH), $C_{24}H_{34}O_4$ requires 386.2457.

The MIC against *B. subtilis* was estimated as $>$50 μg/mL.

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Synthesis, separation and configuration determination of diastereoisomers of (*R*,*S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides

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Abstract—For synthesizing title compounds, first we carried out the Ferrier's rearrangement involving tri-*O*-acetyl-D-glucal **1** and alcohols **2a–e** using Montmorillonite K-10 as a catalyst. This reaction gave diastereoisomeric mixture of **3a–e** and **4a–e**. Basic hydrolysis of each pair of diastereoisomeric mixture furnished title compounds **5a–e** and **6a–e**, which were separated very carefully over a silica gel column yielding all diastereoisomers in the pure form. One of them **5d** was subjected to a single crystal X-ray analysis to determine the correct configuration at the asymmetric carbon atom of the aglycone. The methyl signals of the diastereomers helped to assign the configuration of each diastereoisomer. Molecular orbital calculations of **5d** using the semi-empirical method (AM1) has been performed to compare its results with the crystallographic data. We have also determined the rotational barrier of C(8) and O(9) bond in both (*R*) and (*S*) enantiomers of compounds **5a** and **6a**.

1. Introduction

The incorporation of heterocyclic moieties in carbohydrates has been gaining impetus.[1–3] Because of our interest in the synthesis 1,2,4-oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles, we wished to unite the oxadiazole part with the carbohydrate framework. One of the reasons to undertake such program was that 1,2,4-oxadiazole derivatives manifest a wide range of biological activities[4–6] including antiinflammatory property.[7] In 1996, various 4,5-dihydro-1,2,4-oxadiazoles (Δ^2-1,2,4-oxadiazolines) have been found to possess anti-HIV activity.[8] Yu and co-workers have reported the preparation, spectroscopic and X-ray diffraction studies of two diastereoisomeric spiroheterocyclic Δ^2-1,2,4-oxadiazolines having a spiral junction at C-3 of fructopyranose.[9] The spiroheterocyclic compounds have extensive applications as drugs as well.[10] A literature search revealed that only a few attempts have been made to combine an oxadiazole moiety with a sugar framework.[9,11–14] Further, no work appeared in the literature which describes the synthesis of unsaturated glycosides having an 1,2,4-oxadiazole part as an aglycone. Therefore, this paper gives a detailed account of the preparation, separation and configuration differentiation of the diastereomers of **5a–e** and **6a–e**. Overall, there are 10 new unsaturated glycosides having a stereocenter in the aglycone moiety also. To the best of our knowledge, these have not yet been recorded in the literature.

2. Results and discussion

Racemic 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanols **2a–e** were used to carry out Ferrier's rearrangement.[15] Reaction of these alcohols individually with tri-*O*-acetyl-D-glucal **1** gave diastereomers **3a–e** and **4a–e**, respectively (Scheme 1). Each diastereomeric pair showed only one spot on a thin-layer chromatogram. However, the ^{1}H NMR spectrum of each set presented two methyl doublets in the region δ 1.21–1.40 ppm in the ratio of 2:3 indicating the presence of diastereomers. Each methyl doublet has another overlapping doublet of smaller intensity (~40%) suggesting them as a mixture of

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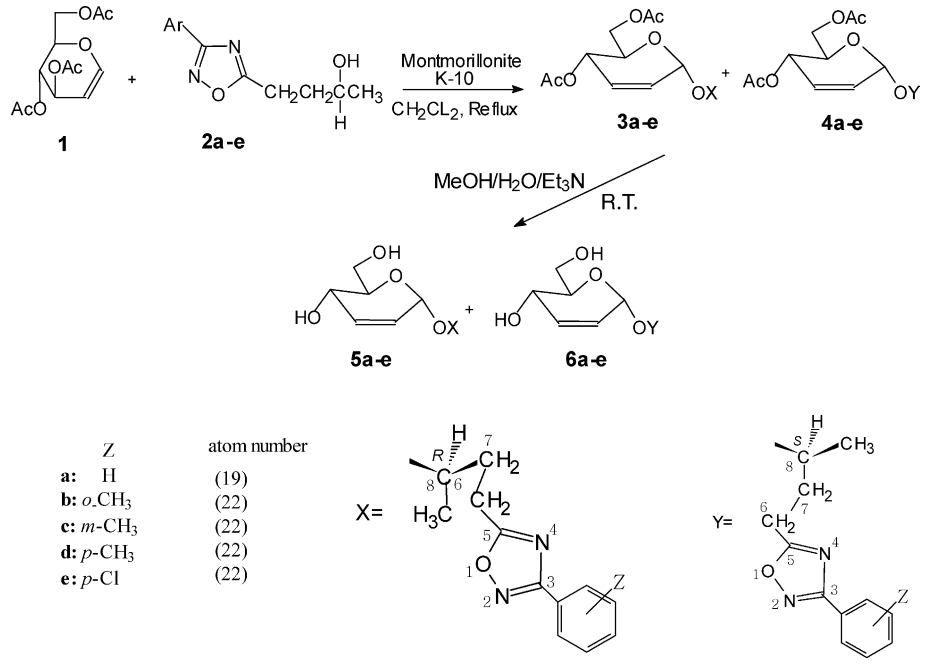
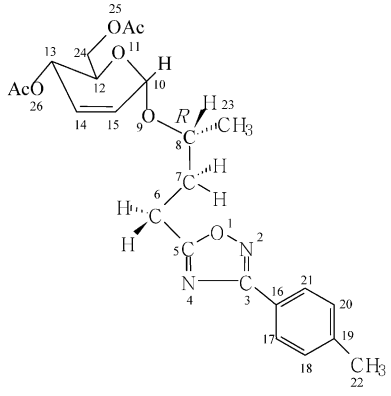
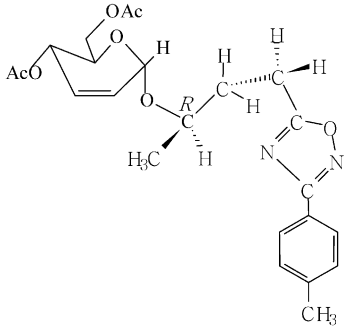


Scheme 1.

conformational isomers. This observation requires some clarifications. Since the reaction has been carried out in methylene chloride, each diastereoisomer formed conformational isomer as shown below for **5d** and **5d′**. The two conformational isomers of each diastereoisomer are visible when the temperature is not higher. There is a small barrier to rotation between C(8) and O(9) which causes this to happen (see the section dealing with M.O. calculations). When the compound is deacetylated, separated and purified, only one conformational isomer is observed for **5a** and **6a**. Apparently, during the work-up rotation along the C(8) and O(9) bond occurred to provide the most stable conformation which shows only one doublet for the methyl group for each diastereoisomer.



5d (conformational isomer of higher proportion)



5d′ (conformational isomer of smaller proportion)

Next, we hydrolyzed the diacetylated sugars using the method of Fraser-Reid and collaborators,[16] which furnished diols **5a–e** and **6a–e** again as a mixture of diastereoisomers. Thin-layer chromatography displayed two spots of very close R_f values. However, it was possible to separate them by a very careful liquid chromatography over silica gel. The diastereoisomer which is in smaller proportion, in each case, crystallized. All of them gave the methyl doublet at δ 1.35 ppm, and the anomeric proton appeared at δ 5.13 ppm. The other set of diastereoisomers (larger quantity) are liquids and it was not possible to crystallize them. All five of them produced a methyl doublet at δ 1.25 ppm, and the anomeric proton absorbed at δ 5.16 ppm. One of the diastereoisomers (either **5d** or **6d**) which had better crystals was subjected to X-ray crystallography. It turned out that it has the configuration (*R*) at the carbon atom containing the methyl group in the aglycone moiety. This diastereoisomer is designated as **5d**. Therefore the other diastereoisomer must possess configuration (*S*) for the same carbon atom (C-8) in **6d**. It is presumed that, all compounds **6a–e** possess configuration (*S*) at the asymmetric carbon atom of the aglycone while **5a–e** have configuration (*R*) at the same stereocenter.

Pure **5a** and **6a** were reacetylated individually and their spectra recorded. This was done just to make correct assignments of their chemical shifts in the ^{1}H NMR spectra, which are give in Section 4.

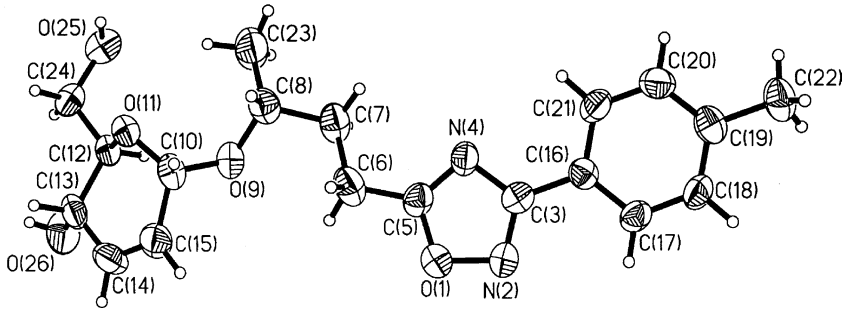


Figure 1. Ortep diagram of compound 1-(*R*)-methy-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]]propryl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **5d**.

2.1. Structure, configuration and conformation of 5d

The crystallographic data provided the precise information regarding the configuration (at C-8) and also about the molecular conformation of **5d**. As expected, the configurations at C(10), C(12) and C(13) are (*S*), (*R*) and (*S*), respectively. It is interesting to know that the C(8)–H bond is found approximately parallel to those on C(10) and C(13), and antiparallel to the one on C(12). The ortep diagram is shown in Figure 1.

There is another feature which needs comment. This concerns the hydrogen bonding between the molecules. Each hydroxyl oxygen atom, O(25) and O(26), is involved in two hydrogen bonds, one as a donor and one as acceptor. O(25) donates a hydrogen bond to O(26) of a parallel molecular in an adjacent cell, O(26) donates a hydrogen bond to O(25) of a molecule generated by a two-fold screw rotation in the [010] direction. The result is that molecules are linked into slabs normal to the [010] direction; the two slabs that pass through one unit cell are not linked together. The other oxygen and nitrogen atoms are not involved in hydrogen bond (see Figs. 2 and 3).

2.2. Semi-empirical molecular orbital calculations of compounds 5d and 6d

The semi-empirical calculations (AM1) showed that compound **5d** has a torsion angle H(15)–C(15)–C(10)–H(10) of −43.2° which clearly shows that the anomeric proton is disposed equatorially. The ring oxygen atom is a little above the plane of C(10)-C(15)-C(14)-C(13). The C(12) atom is slightly below the plane just described. The enthalpy of formation of this compounds is −112.04 kcal/mol. A comparison of some selected dihedral angles of **5d** with its crystallographic data are given in Table 1, which shows that the experimental and calculated values are somewhat closer. The calculations further demonstrate that the *p*-tolyl ring and the 1,2,4-oxadiazole rings are coplanar (torsion angle N(2)–C(3)–C(16)–C(17)=10.61°). The bond distances between C(13)–C(12) and C(12)–O(11) are 1.54 Å and 1.43 Å, respectively.

Figure 4 depicts the most stable conformation of **5d** obtained by the AM1 level of calculation.

Next, we examined the stable conformation of **6d** using the same method as described for **5d**. The dihedral angle H(15)–C(15)–C(10)–H(10) is −46.20° which clearly indicates the disposition of H-10 equatorially. The other interesting feature is that C(23)–C(8)–C(7) and C(6) form an angle of −165.9°. The heterocyclic and the *p*-tolyl rings are at the lower level of the pyranose ring as exhibited in Figure 5. In this case also, the *p*-tolyl ring and 1,2,4-oxadiazole ring are almost coplanar. Selected bond lengths, bond angles and torsion angles of **5d** and **6d** are given in Table 2.

In order to determine the rotational barrier of the C(8) and O(9) bond, diastereoisomers **5a** and **6a** were chosen.

The rotational impediment along the C(8) and O(9) bond in **5a** is approximately 4.0 kcal/mol, whereas in **6a** it approximates about 8.0 kcal/mol. Although the semi-empirical method is less sophisticated, the barrier seems reasonable. Figure 6 represents the structures of **5a** and **6a**. The numbering of the atoms of these molecules here has been slightly modified.

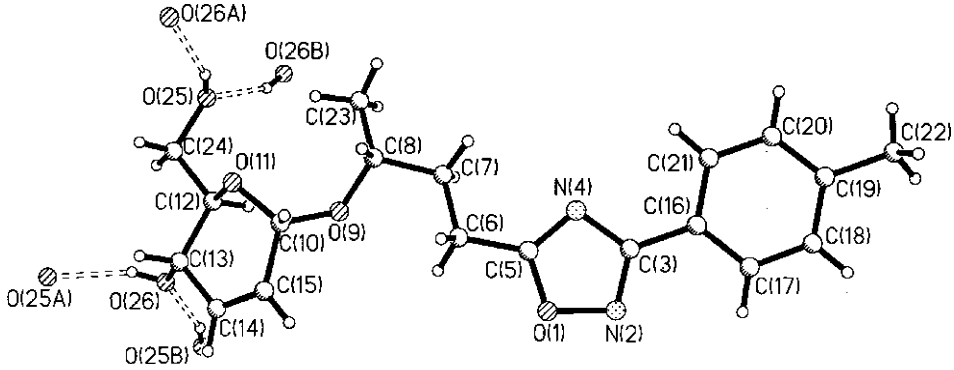


Figure 2. Compound 1-(*R*)-methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propryl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **5d** showing the hydrogen bonds between O(25A) and H-26, H(25B) and O(26), O(26A) and H(25), and O(25) and H(26B).

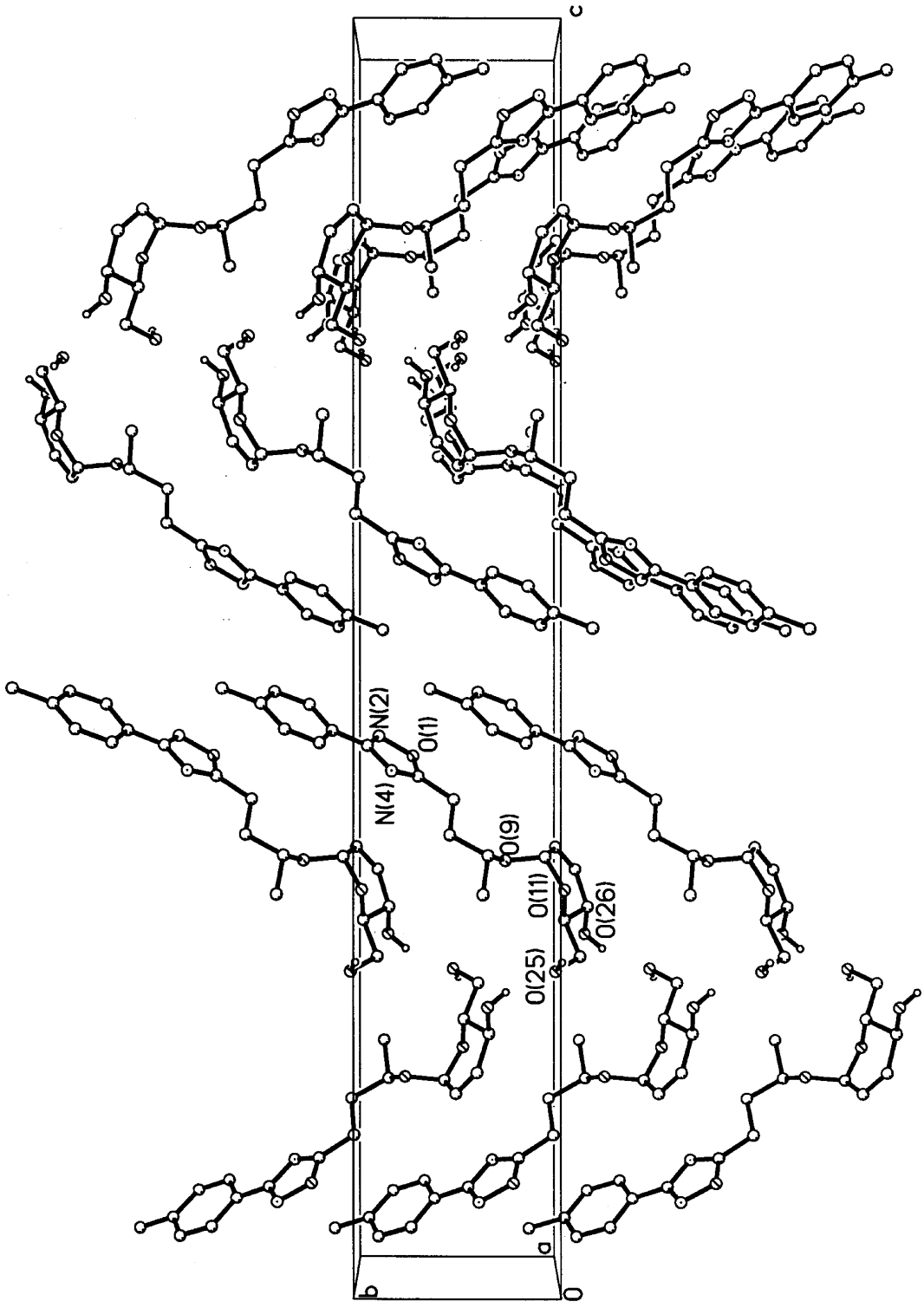


Figure 3. Unit cell depicting the packing of 1-(*R*)-methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propryl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **5d** molecules in the crystal.

Table 1. Comparison of the calculated and experimental torsion angles of **5d**

Torsion angle (°C)	X-ray	AM1 method
C(10)–O(11)–C(12)–C(13)	67.70	62.07
C(10)–C(15)–C(14)–C(13)	2.10	1.48
C(15)–C(14)–C(13)–C(12)	19.0	10.25
C(14)–C(13)–C(12)–O(11)	−52.1	−40.16
C(10)–O(11)–C(12)–C(24)	−170.3	−177.67
O(26)–C(13)–C(14)–C(15)	140.7	128.64
O(9)–C(10)–O(11)–C(12)	77.3	71.62
O(9)–C(10)–C(15)–C(14)	−115.6	−97.12

Point Apparatus, series IA-9100, Electrothermal Ltd., England. IR spectra were recorded as KBr films on a Brucker IFFS66 series Fourier transform spectrophotometer. The 300 MHz ^{1}H NMR spectra were recorded with a Varian Unity Plus spectrophotometer or a Brucker DRX 300 using $CDCl_3$ as solvent and TMS as an internal standard. Elemental analyses were performed in the Department of Fundamental Chemistry, Federal University of Pernambuco, Recife (Brazil). Thin-layer chromatography (TLC) was carried out on plates coated with silica gel 60

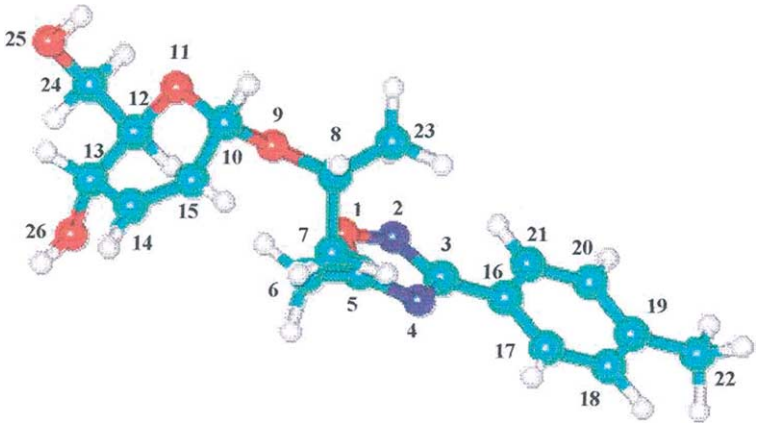


Figure 4. Stable conformation of (1*R*)-1-methyl-3-[(*p*-tolyl)-1,2-4-oxadiazol-5-yl]propyl 2,3-didesoxy-α-D-*erythro*-hex-2-enopyranoside **5d** obtained by the AM1 method.

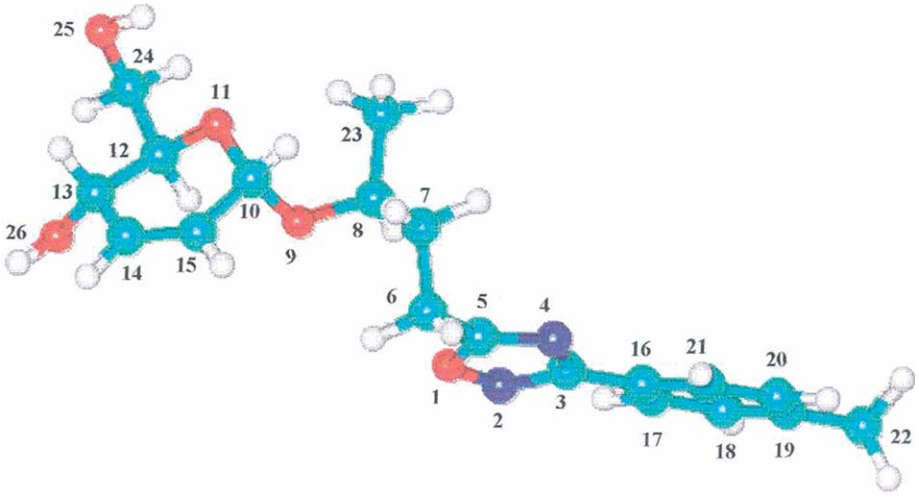


Figure 5. Stable conformation of (1*S*)-1-methyl-3-[(*p*-tolyl)-1,2-4-oxadiazol-5-yl]propyl 2,3-didesoxy-α-D-*erythro*-hex-2-enopyranoside **6d** obtained by the AM1 method.

3. Conclusion

In summary, the glycosides **5a–e** and **6a–e** have been synthesized and diastereoisomers have been separated by chromatography. Also the configuration of compound **5d** was proved by X-ray crystallography.

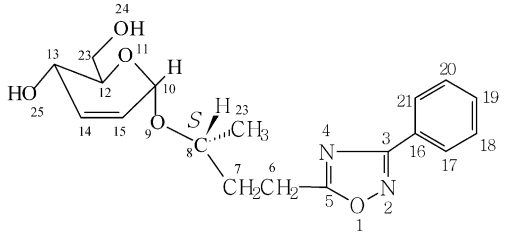
4. Experimental

Melting points were determined with a Digital Melting

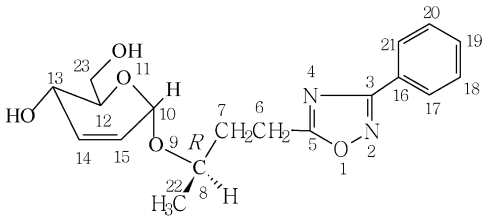
followed by the exposure of the plates in a chamber containing iodine vapors, which revealed the spots. The solvent system for running the TLC plates was a mixture of 0.5:9.5 ethyl acetate–dichlromethane. For compounds **5e** and **6e**, the solvent system for the development of the plate was $CHCl_3$/AcOEt/MeOH, 8.5:1.0:0.5. Optical rotaions were measured with a Prkin–Elmer 141 and 241 polarimeters at the Université Claude Bernard Lyon 1, Villeurbanne (France), and at the University of São Carlos, São Carlos, São Paulo (Brazil), respectively.

Table 2. Selected bond lengths, bond angles and torsion angles of **5d** and **6d** obtained by AM1 calculations

Atoms	AM1	
	Configuration at C(8) (*R*)	Configuration at C(8) (*S*)
Bond length (Å)		
C(10)–O(9)	1.42	1.42
C(10)–O(11)	1.41	1.42
C(10)–O(15)	1.50	1.50
C(14)–O(15)	1.33	1.33
O(9)–C(8)	1.43	1.43
C(5)–C(6)	1.48	1.48
C(5)–N(4)	1.33	1.33
C(5)–O(1)	1.43	1.43
N(2)–C(3)	1.36	1.36
O(1)–C(2)	1.31	1.31
C(3)–C(16)	1.46	1.46
Bond angle (°)		
H(15)–C(15)–C(10)	115.8	115.3
C(10)–O(11)–C(12)	113.7	114.4
H(10)–C(10)–O(11)	105.4	104.7
O(9)–C(10)–H(10)	111.1	113.4
C(10)–O(9)–C(8)	115.6	117.0
O(9)–C(8)–C(23)	106.8	113.5
C(23)–C(8)–C(7)	112.3	111.2
C(6)–C(5)–N(4)	134.1	133.6
C(6)–C(5)–O(1)	116.4	116.9
Torsion angle (°)		
O(9)–C(10)–O(11)–C(12)	71.6	71.2
C(10)–O(11)–C(12)–C(13)	62.1	60.6
C(10)–O(9)–C(8)–C(23)	−131.8	−44.5
C(23)–C(8)–C(7)–C(6)	−75.3	−165.9
H(10)–C(10)–C(15)–H(15)	−43.2	−46.2
C(10)–O(9)–C(8)–C(7)	106.4	81.3



6a



5a

Figure 6. Structures of **5a** and **6a**.

AM1 method: Semi-empirical molecular orbital calculations were carried out employing the AM1 method.[17] The MOPAC 93 program[18,19] was used for the calculations. Geometry optimization could be achieved in all cases, the gradient norm being ≤ 0.2.

4.1. General procedure for the preparation of 4-[3-aryl-1,2,4-oxadiazol-5-yl]-2-butanol 2a–e

Sodium borhydride (7.66 mmol) was added to a solution of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanones[21] (16.15 mmol) dissolved in methanol (57 mL) under stirring at room temperature. After an hour of agitation, thin layer chromatography showed the disappearance of the starting material and the formation of a new product. Later, most of the solvent was evaporated and the residue was treated with a saturated aqueous sodium chloride solution and extracted with ethyl acetate (3×30 mL). Drying (Na_2SO_4) and solvent evaporation afforded of the crude product. Liquid chromatography over silica gel using hexane–ethyl acetate (9:1) gave chromatographically pure **2a–e**.[22]

4.2. General procedure for the preparation of (*R* e *S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides 3a–e and 4a–e

The reaction of **2a–e** with compound **1** were conducted according to the method of Toshima et al.[20] The details are given below.

4.2.1. (*R* e *S*)-1-Methyl-3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*eryhtro*-hex-2-enopyranoside 3a and 4a. Yield 68%, $R_f=0.58$ (dichromethane–ethyl acetate, 9:1); IR ν_{max} (KBr): 1743, 1368, 1231, 1034, 722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.12–8.02 (m, 2H, H-17 and H-21), 7.54–7.42 (m, 3H, H-18, H-19 and H-20), 6.00–5.72 (m, 2H, H-14 and H-15), 5.23 (dd, 1H,

J=9.6 Hz, 3.0 Hz, H-13), 5.16 and 5.13 (2bs, each 1H, H-10), 4.30–4.16 (m, 2H, H-23 and H-23′), 4.16–3.84 (m, 2H, H-12 and H-8), 3.20–3.00 (m, 2H, H-6 and H-6′), 2.18–2.02 (m, 2H, H-7 and H-7′), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.36 and 1.34 (2d, each 3H, J=6.3 Hz, H-22), 1.25 and 1.24 (2d, each 3H, J= 6.0 Hz, H-22).

4.2.2. 1-(*R* and *S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3b and 4b). Yield 53%; IR ν_{max} (KBr): 1743, 1370, 1223, 1053, 741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.94–7.80 (m, 1H, H-21), 7.38–7.15 (m, 3H, H-18, H-19 and H-20), 5.86–5.60 (m, 2H, H-14 and H-15′), 5.25 (dd, 1H, J=9.6 and 2.7 Hz, H-13), 5.15 and 5.12 (2s, each 1H, H-10), 4.24 (m, 2H, H-24 and H-24′), 4.10–3.78 (m, 2H, H-12 and H-8), 3.18–3.01 (m, 2H, H-6 and H-6′), 2.60 (s, 3H, Ar-CH_3), 2.09–2.04 (m, 2H, H-7 and H-7′), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.38 (2d, each 3H, J=6.3 Hz, H-23), 1.24 (2d, each 3H, J=6.0 Hz, H-23).

4.2.3. 1-(*R* and *S*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3c and 4c). Yield 83%; IR ν_{max} (KBr): 1744, 1575, 1369, 1034, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00–7.81 (m, 2H, H-17 and H-21), 7.41–7.24 (m, 2H, H-19 and H-20), 6.00–5.78 (m, 2H, H-14 and H-15), 5.36–5.20 (m, 1H, H-13), 5.16 and 5.12 (2d, each 1H, H-10), 4.36–4.18 (m, 2H, H-24 and H-24′), 4.18–4.10 (m, 1H, H-12), 4.06–3.80 (m, 1H, H-8), 3.22–2.90 (m, 2H, H-6 and H-6′), 2.42 (bs, 3H, Ar-CH_3), 2.15–2.02 (m, 2H, H-7 and H-7′), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.35 (d, 3H, J=6.3 Hz, H-23), 1.25 (d, 3H, J=6.3 Hz, H-23).

4.2.4. 1-(*R* and *S*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3d and 4d). Yield 92%; IR ν_{max} (KBr): 1744, 1370, 1034, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.97 and 7.94 (2d, each 2H, J=8.4 Hz, H-17 and H-21), 7.29 and 7.28 (2d, each 2H, J=8.4 Hz, H-18 and H-20), 6.00–5.54 (m, 2H, H-14 and H-15), 5.28 and 5.25 (2bd, each 1H, J=9.9 and 9.0 Hz, H-13), 5.16 and 5.13 (2bs, each 1H, H-10), 4.40–4.20 (m, 2H, H-24 and H-24′), 4.20–3.85 (m, 2H, H-12 and H-8), 3.28–2.95 (m, 2H, H-6 and H-6′), 2.41 (s, 3H, Ar-CH_3), 2.22–2.02 (m, 2H, H-7 and H-7′), 2.08 and 2.07 (2s, 3H, OAc), 1.35 (d, 3H, J=6.0 Hz, H-23), 1.23 (d, 3H, J=6.0 Hz, H-23).

4.2.5. 1-(*R* and *S*)-Methyl-[3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3e and 4e). Yield 58%; IR ν_{max} (KBr): 1744, 1475, 1035, 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00–7.99 (2d, each 2H, J=8.7 Hz, H-17 and H-21), 7.45–7.44 (2d, each 2H, J=8.7 Hz, H-18 and H-20), 5.97–5.73 (m, 2H, H-14 and H-15), 5.28 and 5.21 (2ddd, each 1H, J=9.5 Hz, 3.3 Hz, 1.5 Hz, H-13), 5.15 and 5.11 (2bs, each 1H, H-10), 4.25–4.16 (m, 2H, H-24 and H-24′), 4.15–3.82 (m, 2H, H-12 and H-8), 3.20–3.10 (m, 2H, H-6 and H-6′), 2.10–2.02 (m, 2H, H-7 and H-7′), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.35 (d, 3H, J=6.3 Hz, H-23), 1.23 (d, 3H, J=6.0 Hz, H-23).

4.3. General procedure for the preparation of (*R* and *S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 5a–e and 6a–e

The hydrolysis of **3a–e** and **4a–e** were conducted according to the method of Fraser-Reid et al.[16] The products were purified by chromatography using dichlromethane–ethyl acetate (9.5:0.5) to give **5a–e** as a crystalline solids and **6a–e** as a syrup.

4.3.1. 1-(*R*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5a). R_f=0.12, yield 45%; mp 105.3–106.5 °C; $[\alpha]_D^{27}=+10\pm1°$ (c=1.5, CH_2Cl_2); IR ν_{max} (KBr): 3407, 1594, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–8.04 (ddd, 2H, J=1.8, 5.4, 10.2 Hz, H-17 and H-21), 7.48 (dd, 3H, J=1.8, 10.2 Hz, H-18, H-19 and H-20), 5.94 (d, 1H, J=10.5 Hz, H-14), 5.74 (ddd, 1H, J=10.5, 2.4, 2.1 Hz, H-15), 5.08 (s, 1H, H-10), 4.22 (dd, 1H, J=3.6, 7.5 Hz, H-13), 3.91–3.71 (m, 4H, H-12, H-23, H-23′ and H-8), 3.04 (m, 2H, H-6 and H-6′), 2.10–2.02 (m, 2H, H-7 and H-7′), 1.97 (s, 1H, OH), 1.90 (s, 1H, OH), 1.32 (d, 3H, J=6.3 Hz, H-22). Anal. Calcd for ($C_{18}H_{22}O_5N_2\cdot3/4H_2O$): C, 60.07; H, 6.58; N, 7.78. Found: C, 60.32; H, 6.39; N, 7.46.

4.3.2. 1-(*S*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6a). R_f=0.15, colorless thick liq., yield 53%; $[\alpha]_D^{27}=+57\pm1°$ (c=1.5, CH_2Cl_2); IR ν_{max} (KBr): 3353, 1594, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–8.04 (ddd, 2H, J=1.8, 5.1, 10.2 Hz, H-17 and H-21), 7.51–7.46 (dd, 3H, J=1.8, 10.2 Hz, H-18, H-19 and H-20), 5.95 (dd, 1H, J=1.5, 10.2 Hz, H-14), 5.70 (ddd, 1H, J=10.2, 2.1, 1.5 Hz, H-15), 5.04 (d, 1H, J=1.5 Hz, H-10), 4.10 (d, 1H, J=7.2 Hz, H-13), 3.94–3.74 (m, 4H, H-12, H-23, H-23′ and H-8), 3.31–3.01 (m, 2H, H-6 and H-6′), 2.58 (s, 1H, OH), 2.12–2.04 (m, 2H, H-7 and H-7′), 1.97 (s, 1H, OH), 1.20 (d, 3H, J=6.0 Hz, H-22). Anal. Calcd for ($C_{18}H_{22}O_5N_2\cdot3/4H_2O$): C, 60.07; H, 6.58; N, 7.78. Found: C, 60.32; H, 6.39; N, 7.46.

4.3.3. 1-(*R*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5b). R_f=0.08, yield 33%; mp 124.3–125 °C; $[\alpha]_D^{28}=+19.8°$ (c=0.5, $CHCl_3$); IR ν_{max} (KBr): 3400, 1595, 1365, 1059, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.93 (d, 1H, J=7.5 Hz, H-21), 7.41–7.27 (dd, 3H, J=1.8, 7.8 Hz, H-18, H-19 and H-20), 5.97 (dd, 1H, J=10.5, 1.8 Hz H-14), 5.68 (tt, 1H, J=10.5, 1.8, 2.1 Hz, H-15), 5.25 (td, 1H, J=1.8 Hz, H-13), 5.08 (bs, 1H, H-10), 4.22–3.72 (m, 4H, H-12, H-24, H-24′ and H-8), 3.07 (m, 2H, H-6 and H-6′), 2.61 (s, 3H. $ArCH_3$), 2.12–2.04 (m, 2H, H-7 and H-7′), 1.98 (s, 2H, OH), 1.33 (d, 3H, J=6.3 Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.93; H, 6.71; N, 7.40.

4.3.4. 1-(*S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6b). R_f=0.08, colorless syrup, yield 33%; $[\alpha]_D^{27}=+18°$ (c=0.4, $CHCl_3$); IR ν_{max} (KBr): 3350, 1594, 1026, 1370, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.93 (d, 1H, J=7.2 Hz, H-21), 7.41–7.30 (m, 3H, H-18, H-19 and H-20), 5.96 (d, 1H, J=10.2 Hz, H-14), 5.68 (tt, 1H, J=

10.2, 1.5 Hz, H-15), 5.18 (td, 1H, $J=3.0$ Hz, H-13), 5.06 (s, 1H, H-10), 4.10–3.75 (m, 4H, H-12, H-24, H-24′ and H-8), 3.07 (m, 2H, H-6 and H-6′), 2.61 (s, 3H. $ArCH_3$), 2.23 (s, 2H, OH), 2.10–1.97 (m, 2H, H-7 and H-7′), 1.23 (d, 3H, $J=$ 6.0 Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.95; H, 6.65; N, 7.43.

4.3.5. 1-(*R*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5c). $R_f=0.09$, yield 43%; mp 127.3–128.9 °C; $[\alpha]_D^{27}=+17.6°$ ($c=0.8$, $CHCl_3$); IR ν_{max} (KBr): 3352 (OH), 1574, 1351, 1027, 738 cm^{-1}; H NMR (300 MHz, $CDCl_3$) δ: 7.88–7.84 (dd, 2H, $J=1.5$, 9.6 Hz, H-17 and H-21), 7.39–7.30 (d, 2H, $J=7.8$ Hz, H-19 and H-20), 5.95 (d, 1H, $J=9.9$ Hz, H-14), 5.75 (ddd, 1H, $J=9.9$, 3.0, 1.2 Hz, H-15), 5.08 (s, 1H, H-10), 4.23 (sl, 1H, H-13), 4.01–3.77 (m, 4H, H-12, H-24, H-24′and H-8), 3.01–3.10 (m, 2H, H-6 and H-6′), 2.62 (s, 1H, OH), 2.42 (s, 3H, Ar-CH_3), 2.10–2.02 (m, 2H, H-7 and H-7′), 1.32 (d, 3H, $J=6.0$ Hz, H-10). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.98; H, 6.77; N, 7.48.

4.3.6. 1-(*S*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6c). Colorless syrup, $R_f=0.14$, yield 48%; $[\alpha]_D^{27}=+18.5°$ ($c=1.2$, $CHCl_3$); IR ν_{max} (KBr): 3406 (OH), 1596, 1366, 1059, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92–7.84 (dd, 2H, $J=4.5$, 10.8 Hz, H-17 and H-21), 7.40–7.30 (d, 3H, $J=7.8$ Hz, H-19 and H-20), 5.95 (d, 1H, $J=$ 10.2 Hz, H-15), 5.69 (dd, 1H, $J=10.2$, 2.7 Hz, H-14), 5.05 (s, 1H, H-10), 4.11 (sl, 1H, H-14), 3.93–3.80 (m, 4H, H-12, H-24, H-24′and H-8), 3.00–3.16 (m, 2H, H-6 and H-6′), 2.85 (s, 1H, OH), 2.42 (s, 3H, Ar-CH_3), 2.18–1.97 (m, 2H, H-7 and H-7′), 1.24 (d, 3H, $J=6.0$ Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.94; H, 6.88; N, 7.45.

4.3.7. 1-(*R*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5d). $R_f=0.19$, yield 42%; mp 128.9–129.5 °C; $[\alpha]_D^{27}=+14\pm1°$ ($c=0.7$, CH_2Cl_2); IR ν_{max} (KBr): 3335 (OH), 1588, 1365, 1026, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, 2H, $J=8.1$ Hz, H-17 and H-21), 7.30 (dd, 2H, $J=$ 8.7 Hz, H-18 and H-20), 5.92 (d, 1H, $J=10.2$ Hz, H-14), 5.72 (ddd, 1H, $J=10$, 2 Hz, e $J=2$, 7, 2.1 Hz, H-15), 5.22 (d, 1H, $J=7.5$ Hz, H-13), 5.07 (s, 1H, H-10), 3.96–3.71 (m, 4H, H-12, H-24, H-24′ and H-8), 3.03 (m, 2H, H-6 and H-6′) 2.41 (s, 3H, Ar-CH_3), 2.09–2.02 (m, 2H, H-7 and H-7′), 1.32 (d, 3H, $J=6.3$ Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.89; H, 6.68; N, 7.71.

4.3.8. 1-(*S*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]-propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6d). $R_f=0.22$, colorless syrup, yield 30%; $[\alpha]_D^{25}=+79°$ ($c=0.7$, CH_2Cl_2); IR ν_{max} (KBr): 3414 (OH), 1590, 1365, 1026, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95–7.92 (d, 2H, $J=8.4$ Hz, H-2″ and H-21), 7.29–7.26 (dd, 2H, $J=$ 7.8, 2.1 Hz, H-18″ and H-20″), 5.95 (dd, 1H, $J=10.2$, 1.8 Hz, H-14), 5.68 (dd, 1H, $J=10$, 2 Hz, e $J=2$, 7 Hz, H-15), 5.05 (s, 1H, H-10), 4.10 (d, 1H, $J=9.3$ Hz, H-13), 3.92–3.73 (m, 4H, H-12, H-24, H-24′and H-8), 3.20–3.00 (m, 2H, H-6 and H-6′), 2.96 (s, 2H, OH), 2.41 (s, 3H, Ar-CH_3), 2.12–2.04 (m, 2H, H-7 and H-7′), 1.22 (d, 3H, $J=$ 6.0 Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 63.89; H, 7.24; N, 7.56.

4.3.9. 1-(*R*)-Methyl-[3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5e). $R_f=0.27$, yield 30%; mp 132.7–133.8 °C; $[\alpha]_D^{25}=+13.14°$ ($c=0.7$, $CHCl_3$); IR ν_{max} (KBr): 3404 (OH), 1589, 1474, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–7.99 (dd, 2H, $J=8.4$, 3.0 Hz, H-17 and H-21), 7.47–7.44 (dd, 2H, $J=7.8$, 1.2 Hz, H-18 and H-20), 5.90 (d, 1H, $J=10.5$ Hz, H-14), 5.74 (ddd, 1H, $J=10$, 5 Hz, e $J=1.8$, 1.5 Hz, H-15), 5.07 (s, 1H, H-10), 4.22 (d, 1H, $J=$ 7.5 Hz, H-13), 3.95–3.67 (m, 4H, H-12, H-24, H-24′and H-8), 3.09–3.01 (m, 2H, H-6 and H-6′), 2.09–2.02 (m, 2H, H-7 and H-7′), 1.70 (bs, 2H, OH), 1.32 (d, 3H, $J=6.3$ Hz, H-23). Anal. Calcd for ($C_{18}H_{24}O_5N_2Cl$): C, 56.77; H, 5.56; N, 7.36. Found: C, 56.88; H, 5.78; N, 7.14.

4.3.10. 1-(*S*)-Methyl-3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6e). $R_f=0.40$, colorless syrup, yield 35%; $[\alpha]_D^{25}=+33.7°$ ($c=0.6$, $CHCl_3$); IR ν_{max} (KBr): 3404 (OH), 1589, 1564, 1474, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–7.98 (dd, 2H, $J=1.5$, 8.1 Hz, H-17 and H-21), 7.47–7.38 (dd, 2H, $J=8.4$, 2.1 Hz, H-18 and H-20), 6.34 (dd, 1H, $J=9.8$, 1.8 Hz, H-14), 5.90 (dd, 1H, $J=9.8$ Hz, e $J=$ 3.3 Hz, H-15), 5.06 (s, 1H, H-10), 4.12 (d, 1H, $J=6.9$ Hz, H-13), 3.98–3.65 (m, 4H, H-12, H-24, H-24′and H-8), 3.13–303 (m, 2H, H-6 and H-6′), 2.96 (s, 2H, OH), 2.10–1.92 (m, 2H, H-7 and H-7′), 1.28 (d, 3H, $J=6.0$ Hz, H-23). Anal. Calcd for ($C_{18}H_{24}O_5N_2Cl$): C, 56.77; H, 5.56; N, 7.36. Found: C, 56.31; H, 5.70; N, 6.96.

4.4. General procedure for the acetylation of (*R*) and (*S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (5a and 6a)

To the pure dihydroxy compounds **5a** or **6a** (0.07 g, 0.21 mmol) in dry pyridine (2.0 mL), in a 10 mL round-bottom flask and cooled to 0 °C was added Ac_2O (1.0 mL). Stirring at rt overnight gave mixture of 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides **3a** and **4a**. Purification was achieved by column chromatography over silica gel. Elution with 1:9 EtOAc–*n*-hexane gave **5a** or **6a** in pure forms.

4.4.1. 1-(*R*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]-propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3a). $R_f=0.61$, liq., yield 90%; $[\alpha]_D^{25}=43°$ ($c=0.49$, $CHCl_3$); IR ν_{max} (KBr): 1743, 1571, 1368, 1231, 1034, 722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.09–8.06 (dd, 2H, $J=3.3$, 9.6 Hz, H-17 and H-21), 7.53–7.49 (m, 3H, H-18, H-19 and H-20), 5.80 (d, 1H, $J=10.2$ Hz, H-14), 5.85 (ddd, 1H, $J=10.2$, 2.7, 2.0 Hz, H-15), 5.31 (dd, 1H, $J=9.6$, 1.5 Hz, H-13) 5.14 (bs, 1H, H-10), 4.60–4.40 (m, 2H, H-23 or H-23′), 4.35 (m, 1H, H-8), 3.82 (dd, 1H, $J=9.7$, 5.4 Hz, H-12), 3.06 (t, 2H, $J=7.5$ Hz, H-6 and H-6′), 2.15–2.00 (m, 2H, H-7 and H-7′), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.36 (d, 3H, $J=6.3$ Hz, H-22). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 61.39 H, 6.09 N, 6.51. Found: C, 61.37 H, 6.07 N, 6.28.

4.4.2. 1-(*S*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]-propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4a). $R_f = 0.65$, mp 63.6 °C (from *n*-hexane–ether), 96%; $[\alpha]_D^{25} = 69°$ ($c = 0.91$, $CHCl_3$); IR ν_{max} (KBr): 1744, 1571, 1369, 1232, 1034, 722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10–8.06 (m, 2H, H-17 and H-21), 7.54–7.46 (m, 3H, H-18, H-19 and H-20), 5.90 (d, 1H, $J=$ 10.2 Hz, H-14), 5.80 (ddd, 1H, $J=10.2$, 2.7, 2.2 Hz, H-15), 5.30 (dd, 1H, $J=9.7$, 1.5 Hz, H-13) 5.18 (sl, 1H, H-10), 4.28 (dd, 1H, $J=13.1$, 5.4 Hz, H-23 or H-23′), 4.20 (dd, 1H, $J=$ 13.1 Hz, $J \leq 1.0$ Hz, H-23 or H-23′), 4.15 (m, 1H, H-8), 4.04 (dd, 1H, $J=9.7$, 5.4 Hz, H-12), 3.01–3.20 (m, 2H, H-6 and H-6′), 2.20–2.06 (m, 2H, H-7 and H-7′), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.26 (d, 3H, $J=6.0$ Hz, H-22). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 61.39 H, 6.09 N, 6.51. Found: C, 61.58 H, 6.14 N, 6.26.

5. Supplementary material

Details of the crystallographic data (CCDC) for compound **5d** has been deposited with the Cambridge Crystallographic Data Center. These data may be acquired from the Director of CCDC, 12 Union Road, Cambridge CB2 1DEZ, UK (Tel.: +44-1223-336408, fax: +44-1223-33-6033; e-mail: deposit@ccdc.cam.ac.uk or www: http//www.ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.08.075

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Synthesis of α-substituted iminodiacetate ligands: α-hexadienyl derivatives for the selection of lipoxygenase mimics☆

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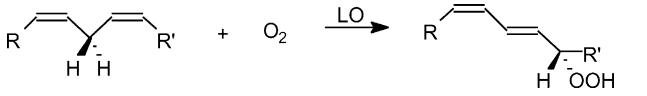
Abstract—Derivatives of iminodiacetic acid (IDA) are important as ligands for metal ions, having numerous applications in separations, sensing, catalysis and medicine. This report describes the preparation of two types of IDA derivatives (**1**, **2**) that could be covalently attached to a polymer or protein surface via a variable length spacer chain. The parent compounds **1** (R′=H) were easily prepared via *N*-alkylation of dimethyl iminodiacetate with esters of 6-bromo-hexanoic acid and subsequent selective ester hydrolysis. Metal complexes of IDA derivatives having an α-dienyl side chain are required for the selection of histidine-rich proteins with potential lipoxygenase activity. The α-hexadienyl side chain of IDA derivative **2** was selectively introduced in the reaction of (2,4-hexadienyl acetate)$Fe(CO)_3$ with a glycine-derived TMS–enol ester. Subsequent demetallation, followed by *N*-carboxymethylation, *N*-deacylation, *N*-alkylation with a trichloroethyl 6-halohexanoate, and TCE–ester cleavage provided the desired α-hexadienyl IDA derivative **2**. Amide formation with IDA acid **1b** demonstrates the feasibility of conjugating the IDA ligands to polymers and proteins while Ni(II)-complexation with the derived IDA triacid **1e** shows the complexing ability of the tethered IDA ligand.

1. Introduction

Metalloenzymes catalyze a variety of important hydrolytic, redox and carbon–carbon bond-forming reactions, some of which have no efficient synthetic counterparts. In order to gain a better understanding of the catalytic mechanisms of metalloenzymes and to develop comparable abiotic catalysts for synthetic utilization, there have been intensive studies of metal complexes that simulate the structural and functional features of metalloenzymes. A common feature of the active site of many metalloenzymes is a bis- or tris-imidazole (from histidine) ligand set.[1] Accordingly, numerous synthetic poly(amine)- and some poly(imidazole)–metal complexes have been investigated as structural and electronic models for these metalloenzymes.[2] A class of poly(histidine)-ligated metalloenzymes of special interest because of their unique and mechanistically intriguing reactions are the lipoxygenases (LO).[3] These iron enzymes catalyze the regio-, stereo- and enantioselective hydroperoxidation of unsaturated fatty acids (Eq. 1).



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The exceptionally high catalytic activity and selectivity of typical enzymes is thought to result in large measure from the substrate-binding and the co-catalytic functionality of the active site's protein environment (as well as transition state stabilization). In an effort to incorporate these features into semi-synthetic metalloenzyme mimics we are investigating various strategies for implanting poly(imidazole)–metal centers in protein matrices. Our initial efforts in this area provided a hybrid esterase protein with high activity by incorporation of a bis(imidazole)-copper cofactor into the combining site of the 38C2 aldolase antibody.[4]

In an approach to poly(imidazole)–metal-proteins that would include a substrate or transition-state binding site at the metal center we are seeking to select metal/substrate-binding proteins from libraries, either directly (by panning) or via immunization/antibody production. For this purpose we envision employing a strongly, but minimally coordinated metal center that can bind effectively to accessible bis/tris-histidine sites on peptides/proteins. Inclusion of a substrate/transition state element situated near to the metal could select/elicit proteins with complementary binding sites. The strong metal binding affinity of iminodiacetate

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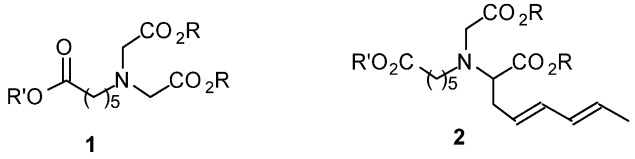
(IDA) ligands[5] and the proven use of M(IDA) complexes for the purification of histidine-tagged proteins by immobilized metal-affinity chromatography (IMAC)[6] has prompted us to seek α-functionalized IDA ligands for the selection of his-rich metal-binding proteins having complementary substrate-binding capability. In the context of our search for LO mimics we have targeted his-phillic IDA derivatives that possess an α-tethered dienyl chain **2** to simulate the putative planar dienyl radical intermediate of the LO enzyme-catalyzed reactions (Fig. 1). In this contribution we describe the first synthesis of such compounds, featuring a new and potentially general method for the α-alkylation of IDA esters.



2. Results and discussion

Two classes of IDA-derivatives were sought, the parent compounds **1** and the α-hexadienyl derivatives **2**, both of which include a nitrogen-linked spacer chain functionalized to enable covalent attachment to a polymer support (for protein binding/selection) or to a protein (for immunization) via amide formation. To allow orthogonal functionalization/deprotection of the three carboxyl functions we used the 2,2,2-trichloroethyl (TCE) ester-derived spacer. The mixed triester **1a** was efficiently synthesized by *N*-alkylation of IDA ester **3** by TCE-6-bromohexanoate **4a**, itself prepared from inexpensive 6-bromohexanoic acid (Fig. 2). Removal of the TCE group of **1a** to afford acid diester **1b** was easily accomplished under standard reducing conditions. To establish the capability of conjugating the *N*-tethered IDA ligands via an amide linkage, the monoacid **1b** was shown to be converted easily to the benzyl amide **1c** using standard amine/carbodiimide methodology. To initially assess the metal-binding ability of the new IDA ligands, the triacid **1e** was prepared by *N*-alkylation of diester **3** to produce triester **1d** and subsequent hydrolysis. The triacid **1e** formed a green nickel complex upon treatment with aqueous $NiCl_2$ which is tentatively formulated as Ni(**1e**-H)$(H_2O)_n$ based on its mass spectrum (ES).

Our original plan for synthesizing the dienyl IDA derivatives **2** was to install the α-dienyl unit via alkylation of an IDA-derived enolate with a simple dienyl electrophile such as sorbyl bromide **5** (Eq. 2). Although seemingly straightforward, in fact, there are very few literature precedents for either the alkylation of IDA ester enolates[7] or for selective nucleophilic substitutions on the bromide **5**.[8] To test this approach, alkylation of the BOC-protected IDA ester **6** was investigated. Treatment of **6** with LDA (THF) followed by benzyl bromide did afford a modest yield of the benzyl derivative **7**. The reported dienyl bromide **5** needed for the synthesis of **8** was produced only in about 80% isomeric purity from the corresponding alcohol under a variety of conditions.[9a,b] Finally, use of bromide **5** (1.2 equiv, 80% purity) in the reaction with the enolate from **6** afforded only 10–15% yield of the alkylated

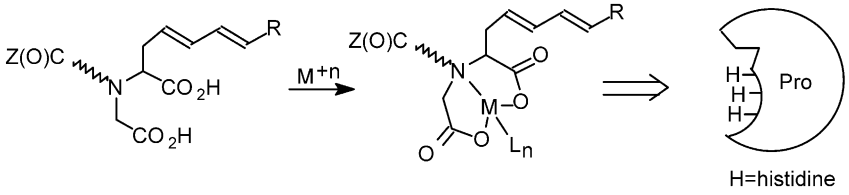


Figure 1.

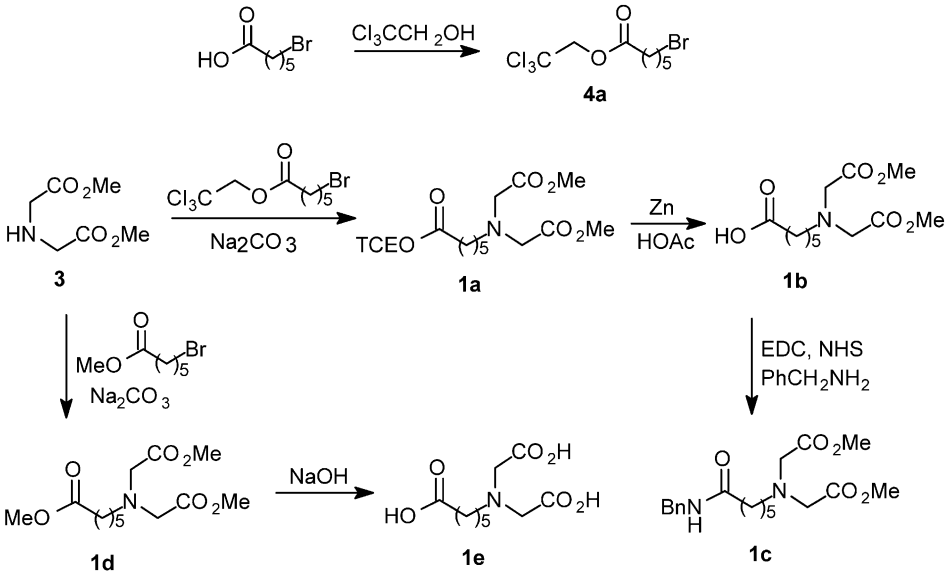
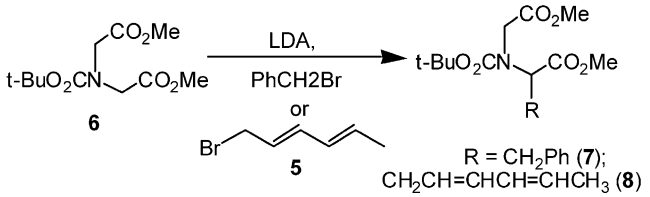


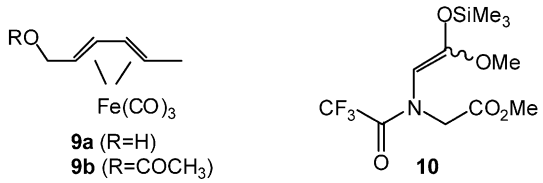
Figure 2.

product(s), which was primarily a non-conjugated regioisomer (rather than **8**) judging by ^{1}H NMR.



(2)

Seeking a more effective and regioselective dienylation method we evaluated an approach based on the electrophilic reactivity of $[(pentadienyl)Fe(CO)_3]^+$ complexes with mild carbon nucleophiles.[10] The readily available (*E*,*E*)-dienyl acetate complex **9b** was selected as the electrophilic component. The initially targeted nucleophilic partner for **9b**, IDA–TMS derivative **10**, proved to be extremely labile and difficult to prepare efficiently. Therefore, we turned to the known glycine derivative **11**[11] as the coupling partner for complex **9b** (Fig. 3). The reaction between **9b** and **11** proceeded readily and regiospecifically at −78 °C in the presence of TMS–OTf to afford the dienyl glycine derivative **12** in excellent yield as a 1:1 diastereomeric mixture (stereounits at the dienyl-iron and α-amino centers). Careful comparison of the ^{1}H NMR spectra of **12** with **9b** and its precursor alcohol **9a** revealed characteristic *trans* coupling constants for protons of the coordinated diene unit (J=8.5 Hz) and highly shielded terminal vinyl protons (0.5–1.2 ppm) in each case, showing that the *E*,*E*-diene sterochemistry is preserved throughout. Demetallation of complex **12** with Ce(IV) cleanly produced the corresponding free dienyl glycine derivative **13** as a single regio- and diastereoisomer (with removal of the stereoinducing –$Fe(CO)_3$ unit). The latter could be converted to the dienyl IDA-derivative **14** upon treatment with methyl bromoacetate under basic conditions.[12] We were pleased to find that the trifluoroacetamide **14** could be selectively deprotected by $NaBH_4$ in methanol (rt, 51%) with no reduction of the ester functions. Attachment of the hexanoate chain by *N*-alkylation of the secondary amine **15** with the TCE bromoester **4a** was found to be very sluggish and inefficient under a variety of conditions.[13] Some improvement was found using the corresponding iodide **4b** (X=I), enabling the preparation of the triester **2a** in moderate yield. The desired acid diester **2b** was obtained when **2a** was treated with excess zinc in glacial acetic acid.[14]



To further demonstrate the synthetic potential of the alkylation of amino acid TMS enol ethers by electrophilic metal complexes, we also examined the reaction between **11** and the dienyl aldehyde complex **16** (Eq. 3). The anticipated product (after demetallation) could be useful for selecting/eliciting metal-binding proteins having a complementary lipoxygenase late transition state/product binding site. In the event, the dienyl alcohol complex **17** was obtained as a partly separable mixture of diastereomers (71% combined), accompanied by a small amount of the dehydrated complex **18** (single isomer, undetermined geometry). These results suggest that the coupling of electrophilic metal complexes with glycine–TMS enol compounds could provide a rather general entry to α-alkylated amino acid and iminodiacetate derivatives.

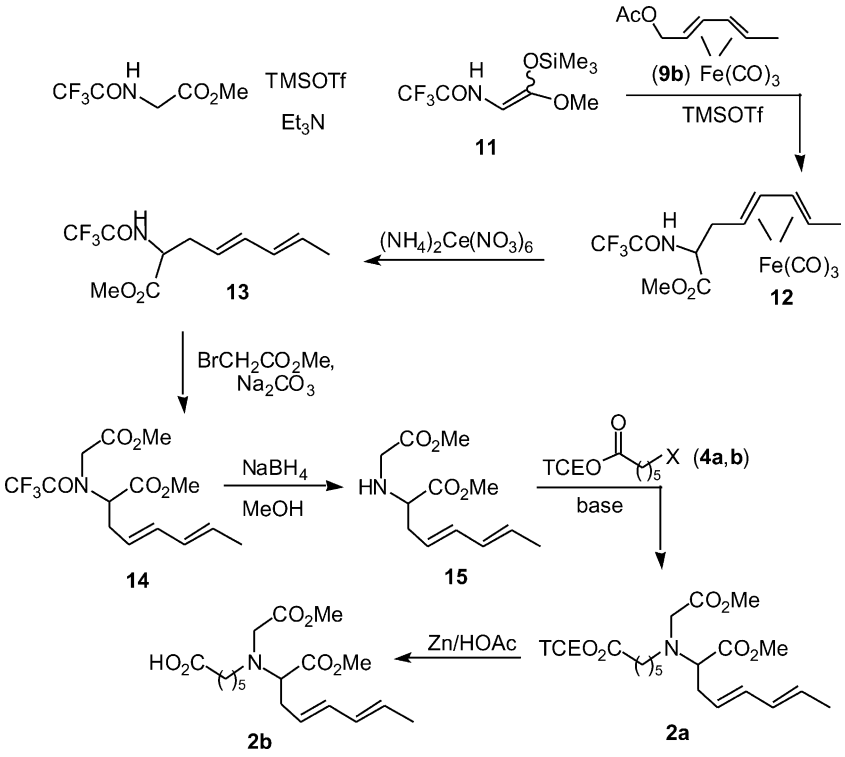
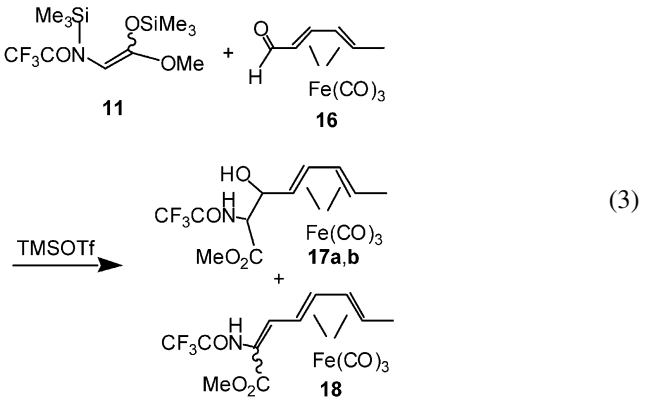


Figure 3.



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3. Summary/conclusions

Preparative methods have been developed to access iminodiacetate derivatives with a functional spacer chain for immobilization and an α-dienyl chain which may be useful for selecting complementary metal binding peptides/proteins with lipoxygenase activity. The α-hexadienyl side chain of IDA derivatives **2** was selectively introduced in the reaction of (2,4-hexadienyl acetate)$Fe(CO)_3$ with a glycine-derived TMS–enol ester. Amide formation with IDA acid **1b** demonstrates the feasibility of conjugating the IDA ligands to polymers and proteins while Ni(II)-complexation with triacid **1e** shows the complexing ability of the tetthered IDA ligand.

Studies of the surface modification and protein conjugation by IDA derivatives **1b** and **2b** are underway. These results, together with investigations of the binding/selection of peptides and proteins by immobilized complexes of the ligands, will be reported in due course.

4. Experimental

4.1. General information

All moisture sensitive reactions were carried out under a dry N_2 atmosphere. All reaction temperatures (°C), except room temperature (rt), correspond to the external bath temperatures.

The following compounds were prepared by reported methods: dimethyl iminodiacetate,[15] dimethyl *N*-*t*-Boc-iminodiacetate,[15] *N*-trifluoroacetyl glycine methyl ester,[16] 2,4-hexadienyl bromide,[9a] (*E*,*E*-2,4-hexadienol)$Fe(CO)_3$,[17] (*E*,*E*-2,4-hexadienyl acetate)$Fe(CO)_3$,[18] (*E*,*E*-2,4-hexadienal)$Fe(CO)_3$[19] and methyl 6-bromohexanoate.[20]

Analytical TLC plates were pre-coated with silica gel 60 F(254). Visualization was accomplished using short wavelength UV light and/or exposing the plate to an iodine chamber. Flash column chromatography (FCC) was performed using 200–400 mesh silica gel with nitrogen pressure. Preparative thin-layer chromatography was performed using Partisil PK6F silica gel plates (Whatman). Triethylamine was dried by distillation from CaH_2 before use. Tetrahydrofuran (THF) and diethyl ether were distilled over Na/benzophenone; dichloromethane and acetonitrile were distilled from CaH_2. Dimethylformamide (DMF) used was purchased as pre-dried. All other reagents/chemicals were obtained commercially and were used without any purification.

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian 300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS (^1H, ^{13}C) or CF_3Cl (^{19}F). Infra-red spectra were recorded on a FTS 135-BioRad FT-IR spectrometer and reported in wavenumbers (cm^{-1}). Mass spectra are recorded on a Micro-mass (Q-TOF) spectrometer using electrospray time-of -flight (ES-TOF). All new compounds were judged to be >95% pure by NMR and TLC.

4.1.1. TCE bromoester 4a. To a solution of 6-bromohexanoic acid (1.00 g, 5.13 mmol) in 50 mL CCl_4 was added *p*-$TsOH\cdot H_2O$ (1.95 g, 10.3 mmol) and 2,2,2-trichloroethanol (2.46 mL, 25.6 mmol) under N_2 and the reaction mixture was refluxed for 12 h using a Dean–Stark apparatus to remove water. After cooling, 10 mL of water was added and the organic phase was separated. The organic phase was further washed with water (2×10 mL), dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford **4a** as an oil (1.30 g, 78.0%), which was pure enough to use directly in the next reaction.

δ 1.52–1.53 (m, 2H), 1.71–1.73 (m, 2H), 1.85–1.90 (m, 2H), 2.47 (t, J=7.4 Hz, 2H), 3.39 (t, J=6.8 Hz, 2H), 4.72 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1 27.7, 32.5, 33.6, 33.9, 74.1, 95.2, 171.9. IR ($CHCl_3$, cm^{-1}): 1755, 2666, 2946. MS (+ESI): calcd 325 (M); found 348 (M+23), 350, 352. HRMS (+ES): calcd 346.8984 (M^+Na); found 346.8982 (M+Na), 348.8925, 350.8921.

4.1.2. TCE triester 1a. To a solution of **3** (0.085 g, 0.53 mmol) in 5 mL acetonitrile was added anhydrous Na_2CO_3 (10 equiv, 0.560 g, 5.28 mmol), followed by addition of a solution of **4a** (1.5 equiv, 0.257 g, 0.792 mmol) in 1 mL acetonitrile under N_2 and the mixture was vigorously stirred at reflux. After 2 days, the solvent was rotary evaporated and the residual solid was triturated with ethyl acetate (3×50 mL) and the mixture filtered. The filtrate was rotary evaporated to give a gummy material which was purified by flash column chromatography using mixtures of ethyl acetate and hexane as eluant to give **1a** as a colorless oil (0.120 g, 56.1%).

^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (m, 2H), 1.50 (m, 2H), 1.70 (m, 2H), 2.42 (t, J=8 Hz, 2H), 2.69 (t, J=8 Hz, 2H), 3.54 (s, 4H), 3.69 (s, 6H), 4.72 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 26.6, 27.6, 33.9, 51.7, 54.2, 54.9, 73.9, 95.2, 171.8, 172.1. IR ($CHCl_3$, cm^{-1}): 1443, 1744, 2952. MS (+ESI): calcd 405 (M); found: 428 (M+23), 406 (M+1), 408, 410.

4.1.3. IDA acid 1b. To a solution of **1a** (0.116 g, 0.286 mmol) in glacial acetic acid (4 mL) under N_2 was added Zn powder (−100 mesh, 1.86 g, 28.6 mmol) and the mixture was stirred vigorously at rt. After 10 h, 50 mL of ethyl acetate was added and the mixture was filtered through a Celite pad. The residue was washed well with excess ethyl

acetate. The combined washings were concentrated by rotary evaporation and the residual acetic acid was removed under high vacuum at 50–60 °C leaving a white solid. To this material was added 50 mL of ethyl acetate and the solution was washed with saturated aqueous $NaHCO_3$ solution (3×10 mL). The organic phase was separated and the aqueous phase was acidified to pH 4 with conc. HCl and then again extracted with ethyl acetate (3×25 mL). The combined ethyl acetate fractions were dried over anhydrous $MgSO_4$, filtered and rotary evaporated to give **1b** as a gum (0.052 g, 66.1%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (m, 2H), 1.47 (m, 2H), 1.62 (m, 2H), 2.32 (t, J=7 Hz, 2H), 2.69 (t, J=7 Hz, 2H), 3.54 (s, 4H), 3.69 (s, 6H), 9.30 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 26.6, 27.4, 33.9, 51.6, 54.1, 54.7, 171.6, 179.3. IR ($CHCl_3$, cm^{-1}): 1699, 1713, 1716, 1732, 1738, 1742. MS (+ESI): calcd 275 (M); found 276 (M+1), 298 (M+23); (−ESI): 274 (M−1). HRMS (+ESI): calcd 298.1267 (M^++Na); found 298.1245 (M^++Na).

4.1.4. Amide 1c. To a solution of **1b** (0.052 g, 0.189 mmol) in 1 mL dry DMF was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.036 g, 0.188 mmol) and *N*-hydroxysuccinimide (0.022 g, 0.19 mmol) under N_2 at room temperature, and the reaction mixture was stirred for 24 h to make the NHS–ester of **1b**. Then a solution of benzylamine (0.024 g, 0.23 mmol) in 0.5 mL dry DMF was added to the active ester solution and the reaction mixture was stirred for another 8 h at room temperature. DMF was removed under vacuum at 40–50 °C to give a gummy material which was purified by preparative TLC (1:2 ethyl acetate/hexane) to afford **1c** as a gum (0.042 g, 61%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (m, 2H), 1.50 (m, 2H), 1.65 (m, 2H), 2.20 (t, J=8 Hz, 2H), 2.68 (t, J=8 Hz, 2H), 3.51 (s, 4H), 3.67 (s, 6H), 4.41 (d, J=6 Hz, 2H), 4.49 (d, J=6 Hz, 2H), 5.75 (br, s), 5.85 (br, s), 7.23–7.31 (m, 5H). IR ($CHCl_3$, cm^{-1}): 1617, 1674, 1695, 1700, 1743, 2934, 2985, 3054, 3314, 3441. MS (+ESI): calcd: 364; found: 365 (M+1).

4.1.5. IDA triester 1d. To a solution of dimethyl iminodiacetate **3** (0.322 g, 2.00 mmol) in 15 mL of dry acetonitrile under N_2 was added a mixture of methyl 6-bromohexanoate (0.627 g, 3.00 mmol) in 0.5 mL acetonitrile and anhydrous Na_2CO_3 (2.21 g, 20.8 mmol). The reaction mixture was stirred at 80–85 °C for 2 days. Acetonitrile was removed by rotary evaporation and the residue was triturated with ethyl acetate (3×40 mL) and filtered. The combined organic washings were rotary evaporated to give a gummy material which was purified by FCC using a mixture of ethyl acetate and hexane (1:15, 1:10, 1:5) to give the desired **1d** as an oil (0.335 g, 58.0%).

^{1}H NMR (300 MHz, CD_3OD): δ 1.20–1.28 (m, 2H), 1.30–1.40 (m, 2H), 1.45–1.55 (m, 2H), 2.22 (t, J=8 Hz, 2H), 2.57 (t, J=8 Hz, 2H), 3.43 (s, 4H), 3.55 (s, 3H), 3.58 (s, 6H). IR ($CHCl_3$, cm^{-1}): 1265, 1731, 2952. MS (+ESI): calcd 289; found 312 (M+23), 313 (M+1+23), 290 (M+1). HRMS (+ESI): calcd 312.1424 (M^++Na); found 312.1419.

4.1.6. Triacid 1e. To a solution of the triester **1d** (0.20 g, 0.70 mmol) in 1 mL methanol was added 1 mL of 2 N NaOH and the solution was stirred at rt for 5 h. After complete disappearance of the starting material (tlc), the reaction was quenched with 2 N HCl adjusting the pH to 5 at 0–5 °C. Water and methanol were removed by rotary evaporation and the solid obtained was dried under vacuum, triturated with methanol (5×25 mL), and the mixture was filtered. The filtrate was rotary evaporated and vacuum dried to give **1e** as a hygroscopic white solid (0.127 g, 73.4%).

^{1}H NMR (300 MHz, D_2O): δ 1.3–1.4 (m, 2H), 1.55–1.61 (m, 2H), 1.65–1.75 (m, 2H), 2.33 (t, J=8 Hz, 2H), 3.19 (t, J=8 Hz, 2H), 3.73 (s, 4H). ^{13}C NMR (75 MHz, D_2O): 23.4, 23.7, 25.0, 33.6, 55.8, 56.9, 170.2, 178.2. MS (+ESI): calcd 247 (M); found 270 (M+23), 293 (270+23), 317 (293+23+1); (−ESI): found 246 (M−1). HRMS (ES+) calcd 270.0953 (M^++Na); found: 270.0966.

4.1.7. Ni complex of 1e. To a solution of the triacid **1e** (0.100 g, 0.405 mmol) in 1.5 mL of distilled water was added a solution of $NiCl_2\cdot 6H_2O$ (0.096 g, 0.41 mmol) in 0.5 mL of distilled water. The pH of the reaction medium was adjusted to pH 7 by dropwise addition of 1 M NaOH and then the mixture was stirred at room temperature for 4 h, followed by heating at 60–65 °C for another 4 h. After cooling to room temperature, the solution was poured onto a small crystallization plate. After vacuum evaporation of the water at rt and drying under high vacuum, 0.143 g of a light green solid (including NaCl) was obtained. The MS of this material showed a major ion cluster at 326/328 for ^{58,60}Ni(**1e**-H)+Na^+, consistent with a formulation of Ni(**1e**-H)$(H_2O)_n$ (n=0–3).

MS (+ESI): calcd 357 [M(^{58}Ni)]; found 326 [M(^{58}Ni–$3H_2O$+Na)], 328 [M(^{60}Ni–$3H_2O$+Na)]; (−ESI): found 302 (^{58}Ni–$3H_2O$), 304 (^{60}Ni–$3H_2O$). HRMS (+ES): calcd 326.0102 (M^+–$3H_2O$+Na); found 326.0176.

4.1.8. Alkylation of 6 with benzyl bromide and sorbyl bromide. To a solution of diisopropylamine (0.167 mL, 1.19 mmol) in 4.5 mL of anhydrous tetrahydrofuran under N_2 at 0 °C was added *n*-BuLi (0.75 mL, 1.19 mmol) and the reaction mixture was stirred for 20 min. The reaction mixture was then cooled to −78 °C whereupon a solution of **6** (0.300 g, 1.19 mmol) in 1 mL of tetrahydrofuran was added dropwise over a period of 7–10 min. The reaction mixture was then stirred at that temperature for 3 h. Then a solution of benzyl bromide (0.204 g, 1.19 mmol) in 5.4 mL tetrahydrofuran was added dropwise at −78 °C and the mixture was stirred for another 7 h while warming to rt. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and then extracted with ethyl acetate (3×25 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification of the crude material by FCC (ethyl acetate–hexane) gave the benzylated product **7** as a gum (0.191 g, 45.5%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9H), 3.00 (complex m, 2H), 3.15 (complex m, 2H), 3.64 (s, 6H), 3.73 (d, J=3 Hz, 2H), 4.00 and 4.10 (m, 1H, isomeric mixture), 7.19–7.25 (m, 5H). MS (+ESI): calcd: 351 (M); found: 374 (M+23).

When the same methodology was used for alkylation of **6** with 2,4-hexadienyl bromide **5** (1.2 equiv), a mixture of isomeric dienyl products was obtained in low yield with the 2,4-dienyl isomer **8** as a minor component.

4.1.9. TMS–enol ester 11. To a stirred solution of *N*-trifluoroacetyl glycine methyl ester (0.550 g, 2.97 mmol) in 10 mL of dry ether was added anhydrous Et_3N (3.70 mL, 26.5 mmol) under N_2 at rt and the temperature was lowered to 0 °C. To this stirred solution was added trimethylsilyl trifluoromethanesulfonate (1.10 mL, 6.15 mmol) dropwise. After complete addition the mixture was stirred at rt for 8 h. The ethereal phase was separated carefully from the lower salt phase. The salt phase was further washed with 10 mL of dry ether. The combined organic phase was rotary evaporated. Drying under high vacuum afforded **11** as a light red liquid (0.770 g, 94.9%) that was used for the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.26 (s, 9H), 0.27 (s, 9H), 3.61 (s, 3H), 5.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.3, 0.5, 54.6, 88.4, 117.9 (q, $J_{C-F}=203$ Hz), 134.8 (q, $J_{C-F}=29$ Hz), 159.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.2.

4.1.10. (*E*,*E*)-Dienyl complex 12. To a solution of **11** (0.762 g, 2.79 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C was added a solution of **9b** (0.876 g, 2.33 mmol) in 1 mL CH_2Cl_2 under N_2. To this stirred solution was added TMSOTf (84 μL, 20 mol%) and the reaction mixture was stirred while monitoring reaction progress by tlc. After disappearance of **9b**, the reaction was quenched with 2 mL of water and allowed to warm to rt. The mixture was diluted with 25 mL CH_2Cl_2 and the organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent rotovapped. Purification of the crude material by FCC using hexane–ethyl acetate as the eluant afforded **12** as a yellow gum (0.810 g, 85.8%).

^{1}H NMR (300 MHz, $CDCl_3$): (1:1 diastereomeric mixture) δ 0.52–0.58 (m, 0.5H), 0.66–0.72 (m, 0.5H), 1.10–1.17 (m, total 1H), 1.37 (d, $J=6.0$ Hz, 3H), 2.03–2.31 (m, 2H), 3.80 and 3.82 (2s, 3H), 4.57–4.64 (m, 1H), 4.89–4.93 (dd, $J=5.0$, 8.5 Hz, 1H), 4.98–5.24 (m, 1H), 6.95 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 35.9, 36.8, 52.4, 53.3, 53.4, 53.7, 53.8, 58.6, 58.7, 83.4, 83.8, 86.4, 86.5, 116.0 (q, $J_{C-F}=289$ Hz), 157.0 (q, $J_{C-F}=21$ Hz), 170.7, 170.8, 211.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.7, −75.8. IR ($CHCl_3$, cm^{-1}): 1214, 1440, 1719, 1734, 1971, 2044, 2856, 2923, 2958, 3327, 3405. MS (+ESI): calcd 405 (M); found 428 (M^++Na), 429 (M+23+1), 344 (428-3CO), 288.10; MS (−ESI): 404 (M−1). HRMS (+ES): calcd 428.0020 (M^++Na); found 428.0019.

4.1.11. (*E*,*E*)-Dienyl ester 13. To a stirred solution of complex **12** (0.802 g, 1.98 mmol) in 30 mL acetone at −78 °C was added ceric ammonium nitrate (1.63 g, 2.97 mmol) under N_2 and the reaction mixture was slowly allowed to warm to −10 °C. Stirring was continued at this temperature for 5 h whereupon the starting material was consumed (tlc). Acetone was removed by rotary evaporation and the residue was dried under vacuum. Ethyl acetate (75 mL) was added to the residue followed by addition of 20 mL of water. The ethyl acetate phase was separated and the aqueous part was further washed with ethyl acetate (2× 25 mL). The combined organic phase was washed with water (3×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give a red gummy material. Purification by FCC using a mixture of hexane/ethyl acetate as the eluant afforded **13** as a gum (0.310 g, 59.1%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (d, $J=7.5$ Hz, 3H), 2.60 (m, 2H), 3.78 (s, 3H), 4.61 (m, 1H), 5.30 (m, 1H), 5.62 (m, 1H), 6.00 (m, 2H), 6.80 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 34.7, 52.4, 52.9, 115.6 (q, $J_{C-F}=216$ Hz), 122.1, 130.1, 130.6, 135.7, 156.7 (q, $J_{C-F}=28$ Hz), 170.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.9. IR ($CHCl_3$, cm^{-1}): 1178, 1212, 1696, 1700, 1733, 2361, 3326. MS (+ESI): calcd 265 (M); found 288 (M+23), 266 (M+1). HRMS (+ES): calc. 288.0823 (M^+Na); found 288.0790.

4.1.12. Dienyl IDA ester 14. To a solution of **13** (0.305 g, 1.15 mmol) in 7 mL of dry DMF was added NaH (0.033 g, 1.38 mmol) under N_2 and the mixture was stirred at rt for 10 min. Then a solution of methyl bromoacetate (0.22 mL, 2.3 mmol) in 1 mL dry DMF was added dropwise and the reaction mixture was stirred at 80 °C while monitoring by tlc. After disappearance of the starting materials (12 h), the mixture was cooled to 40 °C and the DMF was removed under reduced pressure. The residue was triturated with ethyl acetate (3×50 mL) and the solution was filtered. The organic phase was rotary evaporated to give a gummy material that was purified by FCC using hexane/ethyl acetate to afford **14** (ca. 1.4:1 amide rotomeric mixture) as a gum (0.190 g, 49.0%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (d, $J=6.6$ Hz, 3H), 2.50–2.70 (m, 2H), 3.69 and 3.70 (2s, 3H), 3.73 (s, 3H), 4.10 and 4.20 (complex m, 2H), 4.62 (m, 1H), 5.30–5.40 (m, 1H), 5.60–5.70 (m, 1H), 5.85–6.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 32.2, 33.5, 45.7, 52.4, 52.8, 115.0, 122.8, 130.0, 130.6, 135.2, 157.5, 167.7, 169.4. ^{19}F (282 MHz, $CDCl_3$): δ −68.15, −69.43. IR ($CHCl_3$, cm^{-1}): 1695, 1699, 1749, 2957. MS (+ESI): calcd 337 (M); found 360 (M+23), 338 (M+1), 268 (M−CF_3), 697 [(M×2)+23].

4.1.13. IDA amine 15. To a stirred solution of the *N*-trifluoroacetyl derivative **14** (0.186 g, 0.551 mmol) in 5 mL dry methanol was added $NaBH_4$ (0.052 g, 1.38 mmol) in portions under N_2 at −5 °C. The reaction was stirred at rt while monitoring its progress by tlc. After 5.5 h, the reaction was quenched with glacial acetic acid at 0 °C by lowering the pH to 6. Methanol was rotary evaporated, 50 mL of ethyl acetate was added, and the solution was washed with 20 mL of water. The aqueous phase was further extracted with ethyl acetate (3×25 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and rotary evaporated. Purification of the crude material by column chromatography on silica with ethyl acetate/hexane gave the **15** as a gum (0.068 g, 51.2%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, $J=7$ Hz, 3H), 2.30 (br, 1H), 2.40–2.46 (m, 2H), 3.36 (s, 2H), 3.41 (m, 1H), 3.68 (s, 6H), 5.40 (m, 1H), 5.60 (m, 1H), 6.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 36.3, 48.9, 51.9, 60.5, 125.1, 128.8, 131.1, 134.1, 172.2, 174.1. IR ($CHCl_3$, cm^{-1}): 1739, 1742, 2953, 3019, 3338. MS (+ESI): calcd 241 (M); found

264 (M+23), 242 (M+1). HRMS (+ESI): calcd 264.1211 (M^++Na); found 264.1232.

4.1.14. 2,2,2-Trichloroethyl-6-iodohexanoate 4b. To a solution of 2,2,2-trichloroethyl-6-bromohexanoate (0.500 g, 1.53 mmol) in 5 mL acetone was added NaI (0.230 g, 1.53 mmol) at room temperature under N_2 and the reaction mixture was stirred for 10 h during which time the starting material was completely consumed (tlc). The solvent was removed by rotary evaporation and the crude material was triturated with CH_2Cl_2 (5×15 mL) and then filtered. The filtrate was concentrated by rotary evaporation and then dried under vacuum to afford the desired iodo compound **4b** as an oil which was spectroscopically pure (0.540 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 2.47 (t, J=7.35 Hz 2H), 3.17 (t, J=6.9 Hz, 2H), 4.73 (s, 2H). IR ($CHCl_3$, cm^{-1}): 801, 1754, 2856, 2929. MS (ESI+): calcd 372 (M^+), 395 (M^++23); found 372.9 (M^++1), 374.9 [(M^++1)+2], 376.9 [(M^++1)+4], 394.9 (M^++23).

4.1.15. IDA TCE ester 2a. To a solution of **15** (0.065 g, 0.27 mmol) in 5 mL of dry acetonitrile was added anhydrous Na_2CO_3 (0.285 g, 2.69 mmol) followed by addition of bromide **4a** (0.13 g, 0.40 mmol) under N_2, and the reaction mixture was stirred at 90 °C while monitoring its progress by tlc. After 3d, the acetonitrile was removed by rotary evaporation, and the residue was triturated with ethyl acetate (3×25 mL) and filtered. Ethyl acetate was removed by rotary evaporation and the residue was purified by preparative thin layer chromatography (1:2 ethyl acetate/hexane) to afford **2a** as a gum (0.037 g, 28%). The corresponding reaction with iodoester **4b** gave **2a** in 38% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.50 (m, overlapping, 4H), 1.60–1.70 (m, 2H), 1.70 (t, J=7 Hz, 3H), 2.30 (m, 2H), 2.40–2.50 (m, overlapping, 4H), 3.40 (m, 1H), 3.66 (s, 6H), 4.05 (t, J=3 Hz, 2H), 4.73 (s, 2H), 5.40–5.60 (m, 2H), 6.00–6.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 23.9, 27.6, 32.3, 33.4, 33.7, 36.3, 48.9, 51.92, 60.5, 73.9, 95.0, 125.1, 128.8, 131.1, 134.1, 171.8, 172.2, 174.1. IR ($CHCl_3$, cm^{-1}): 1712, 1730, 1742, 2926. MS (+ESI): calcd 485 (M); found 508 (M+23), 509, 510, 511, 512, 513, 514, 515.

4.1.16. IDA acid 2b. To a solution of **2a** (0.035 g, 0.072 mmol) in 2 mL glacial acetic acid under N_2 was added Zn powder (−100 mesh, 0.47 g, 7.2 mmol) and the reaction mixture was stirred vigorously at rt for 14 h. The mixture was then diluted with 50 mL of ethyl acetate and filtered through a Celite pad. The combined filtrate was concentrated by rotary evaporation and the acetic acid left was removed under high vacuum. To the residue was added 40 mL of ethyl acetate; the solution was then washed with aqueous $NaHCO_3$ solution (3×5 mL). The organic phase was separated and the aqueous phase was acidified to pH 4 with conc. HCl and then again extracted with ethyl acetate (3×30 mL). The combined ethyl acetate phase was dried over $MgSO_4$, filtered and concentrated to give **2b** as a gum after vacuum drying (0.010 g, 39%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (m, 2H), 1.55 (m, 2H), 1.65 (t, J=7 Hz, 2H), 1.73 (d, J=7 Hz, 3H), 2.35 (t, J=7 Hz, 2H), 2.51 (m, 2H), 2.73 (t, J=8 Hz, 2H), 3.47 (d, J=6 Hz, 1H), 3.58 (s, 2H), 3.71 and 3.73 (2s, 6H), 5.40–5.50 (m, 1H), 5.60–5.70 (m, 1H), 6.00–6.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, low concentration): 18.1, 23.8, 27.6, 29.7, 32.4, 33.5, 35.8, 48.5, 52.2, 60.3, 124.3, 129.3, 130.9, 134.7, 177.7. IR ($CHCl_3$, cm^{-1}): 1731, 1735, 2253. MS (+ESI): calcd: 355 (M); found: 394 (M+K); (− ESI) 354 (M−1).

4.1.17. (*E*,*E*)-Dienyl alcohol complex 17. To a solution of **11** (0.100 g, 0.29 mmol) in 5 mL of dry CH_2Cl_2 under N_2 at −78 °C was added a solution of aldehyde complex **16** (0.045 g, 0.190 mmol) in 1 mL dry CH_2Cl_2 followed by addition of TMSOTf (0.1 mL). The reaction mixture was stirred at this temperature for 2.5 h, whereupon the aldehyde was completely consumed (tlc). The reaction was quenched with 1 mL of water and then extracted with CH_2Cl_2 (3× 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotary evaporation. Purification of the residue by preparative TLC (1:1 diethyl ether/hexane) afforded triene complex **18** (0.016 g, 20.9%), and dienyl alcohol complexes **17a**,**a′** (0.034 g, 42.5%) and **17b** (0.023 g, 28.7%).

Compound **17a**,**a′**. (1.3:1 diastereomeric mixture) ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 and 0.95 (m, 1H), 1.25 (m, 1H), 1.41 (d, J=6 Hz, 3H), 1.85 and 2.10 (br s, 1H), 3.78, 3.79 and 3.80 (s, 3H), 3.60 and 3.90 (m, 1H), 4.70 (m, 1H), 5.15 (m, 2H), 7.05 and 7.20 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.6, −75.7, −75.8. MS (+ESI): calcd: 421 (M); found: 444 (M+23), 404 (M−OH), 865 (2M+23).

Compound **17b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (m, 1H), 1.23 (m, 1H), 1.40 (d, J=6 Hz, 3H), 2.30 (br s, 1H), 3.78 (s, 3H), 4.20 (m, 1H), 4.69 (d, J=6 Hz, 1H), 5.10 (m, 1H), 5.30 (m, 1H), 7.0 (d, J=15 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.1, 53.0, 57.8, 59.2, 73.1, 86.8, 169.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.6. IR ($CHCl_3$, cm^{-1}): 1179, 1215, 1726, 1758, 1974, 2045, 2349, 3343 (br). MS (+ESI): calcd: 421 (M); found: 444 (M+23), 445 (M+1+23), 865 (2M+23), 866 (2M+23+1).

Compound **18**. (single diastereomer) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (m, 1H), 1.48 (d, J=6 Hz, 3H), 2.85 (m, 1H), 3.74 (s, 3H), 5.20 (m, 2H), 6.40 (d, J=12 Hz, 1H), 7.23 (br, s, 1H). ^{19}F NMR ($CDCl_3$): −75.3, −75.7. MS (+ESI): calcd: 403; found: 426 (M+23), 427 (M+1+23), 404 (M+1), 829 (2M+23).

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The nitration of some 4,6-dimethoxyindoles

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Abstract—A range of 3-substituted-4,6-dimethoxyindoles bearing electron-withdrawing groups in either the 2- or 7-position, can be nitrated using nitric acid adsorbed on silica, to give 7-nitro and 2-nitro-indoles, respectively. A 1-cyano-indole gives regioselectively the 2-nitro-indole with loss of the cyano group.

1. Introduction

Indoles have long been known to be sensitive to acids and therefore their nitration requires care in the design of experimental conditions.[1–3] While the 3-position is the preferred site for electrophilic attack, in strong acid nitration occurs on the 3*H*-indolium salt to give the 5-nitroindole under the directing influence of the iminium moiety. However, the 3,6-dinitroindole can be obtained via the 3-nitroindole under more neutral conditions. The nitration of indoles containing hydrogen at C2 does not lead to well-defined products but usually gives only polymeric material presumably resulting from initial oxidative attack at C2 or at the 2,3-double bond.[4–7] While the nitration of 2-unsubstituted indoles in acidic conditions is unsuccessful, gramine and tryptophan undergo nitration with concentrated nitric acid in acetic acid.[8,9] The success of these nitrations has been attributed to protonation of the side chain amino group, with the resulting positive charge preventing oxidative attack through electrostatic repulsion. Indoles bearing a 3-aryl group can undergo nitration in that ring rather than the indole ring.[10] Also, *ipso*-nitration can occur at C3 with the displacement of acyl and hydroxymethyl groups.[11]

Recently, nitric acid absorbed onto silica has been used to mononitrate some activated indoles in reasonable chemical yields and with moderate regioselectivity, provided they also contained an electron-withdrawing group at N1 or C2.[12]

Keywords: Indole; Nitration; Nitric acid.
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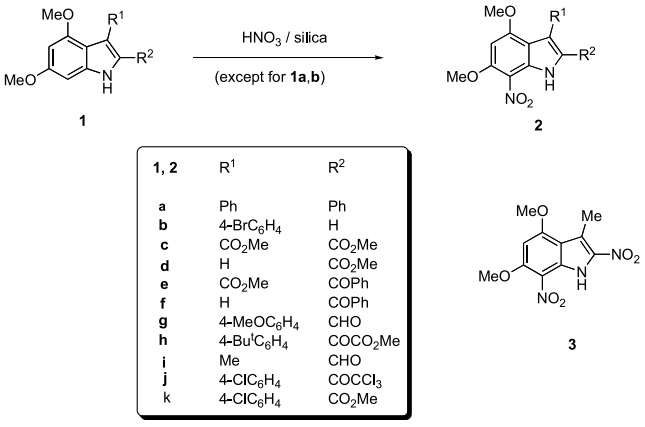
2. Results and discussion

We were interested in the nitration of 4,6-dimethoxyindoles for a variety of purposes, including their potential as a source of amino indoles. Initial studies involved 4,6-dimethoxy-2,3-diphenylindole **1a** and the 4′-bromophenyl analog **1b**. Investigated reaction conditions included a mixture of concentrated nitric and sulfuric acids at 0 °C, fuming nitric acid in tetrahydrofuran at −10 °C, copper(II) nitrate and acetic anhydride in tetrahydrofuran at 0 °C, concentrated nitric acid in acetic anhydride at −10 °C, and concentrated nitric acid supported on silica gel at room temperature: in all cases complex mixtures containing both mono- and poly-nitrated products were obtained. Clearly electron-withdrawing substituents were desirable and a survey was carried out on a range of such indoles, using the nitric acid on silica reagent. These reactions proceeded extremely quickly, usually in less than 10 s, at room temperature in dichloromethane, and gave good yields of mononitrated compounds. Some of the precursor indoles **1a**,[13] **1b**,[14,15] **1c**,[13] **1d**,[13] **1g**,[16] **1i**,[17] **4b**[16] and **6b**[15] have been reported previously, but details of the synthesis of **1e**, **1f**, **1g**, **1h**, **1j**, **4a**, **4b**, **4c**, **6a** and **6c** are provided here. Indoles **1e** and **1f** were prepared using the *N*-phenacyl isatin ring-opening and recyclisation strategy developed by Black and Wong.[18] The indole glyoxylic ester **1h** was obtained by the reaction of the new 3-(4-*tert*-butylphenyl)-4,6-dimethoxy-indole with oxalyl chloride followed by methanol, and indoles **1j** and **4c** by the reaction of 3-(4-chlorophenyl)-4,6-dimethoxyindole with trichloroacetyl chloride. Indoles **6** were formed by phenylsulfonylation, acetylation and cyanation, respectively, of the related indoles.

Thus the indoles **1c–j** with electron-withdrawing groups at C2 (and sometimes also C3) gave the 7-nitro compounds

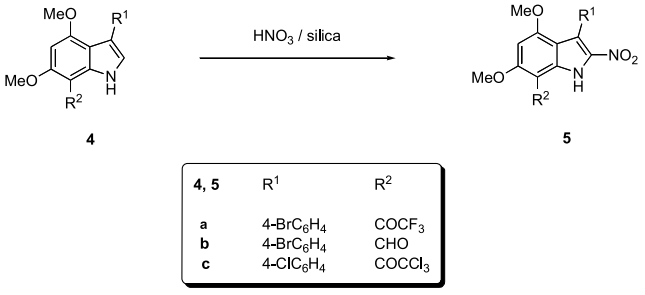


1, 2	R^1	R^2
a	Ph	Ph
b	4-BrC_6H_4	H
c	CO_2Me	CO_2Me
d	H	CO_2Me
e	CO_2Me	COPh
f	H	COPh
g	4-$MeOC_6H_4$	CHO
h	4-$Bu^tC_6H_4$	$COCO_2Me$
i	Me	CHO
j	4-ClC_6H_4	$COCCl_3$
k	4-ClC_6H_4	CO_2Me

Scheme 1.

2c–**j**, respectively, in yields of 60–96%. Reaction of the 2-formyl-3-methyl indole **1i** produces not only the 7-nitro derivative **2i** in 68% yield, reaction for a longer time leads to the 2,7-dinitro-derivative **3** in 45% yield, through an *ipso*-substitution of the 2-formyl group (Scheme 1).

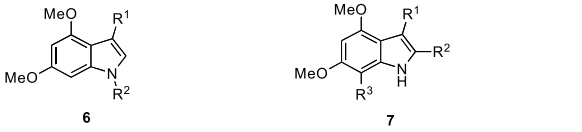
The presence of electron-withdrawing groups at C7, as in indoles **4a**–**c**, leads to formation of the 2-nitro-indoles **5a**–**c** respectively in 70–85%. Until recently 2-nitro-indoles were relatively unknown and only the 3-methyl- and 3-phenyl-2-nitro-indoles had been obtained in low yield and with undesirable 3-substitution.[19] 2-Nitroindoles have been synthesized directly through the thermolysis of β-substituted-*o*-azidostyrenes: 2-nitroindole itself was obtained in three steps from 2-nitrobenzaldehyde in 40% overall yield.[20,21] The ability to nitrate specifically at the 2-position is a new approach to 2-nitro-indoles that is extremely quick, clean and high yielding (Scheme 2).



4, 5	R^1	R^2
a	4-BrC_6H_4	$COCF_3$
b	4-BrC_6H_4	CHO
c	4-ClC_6H_4	$COCCl_3$

Scheme 2.

Indoles **6a**–**c**, substituted with electron-withdrawing groups at N1, reacted extremely rapidly with nitric acid on silica to give mixtures of mono- and dinitro-indoles, with consequent reduced yields of isolated products. ^{1}H NMR spectra of the crude reaction mixtures indicated that partial hydrolysis of the N-substituent had occurred, and therefore complete removal of this substituent was effected by formal hydrolysis. It was difficult to characterize all of these products fully because of their variable stability. The *N*-phenylsulfonylindole **6a** gave a 75% yield of the rather unstable 2,7-dinitro-indole **7a**, while the *N*-acetylindole **6b** gave an approximately equal mixture of 2- and 7-nitro-indoles **7b** and **2b**, respectively, the former being less stable than the latter. Significantly, the *N*-cyanoindole **6c** showed a clear regiochemical preference for formation of the 2-nitro-indole **7c**, possibly as the result of hydrogen bonding of the cyano group on to free hydroxyl groups on the silica surface.



6	R^1	R^2
a	Ph	SO_2Ph
b	4-BrC_6H_4	$COCH_3$
c	4-ClC_6H_4	CN

7	R^1	R^2	R^3
a	Ph	NO_2	NO_2
b	4-BrC_6H_4	NO_2	H
c	4-ClC_6H_4	NO_2	H

In an attempt to slow down the nitration reactions, a nitrosation approach was investigated, as the nitrosonium cation is less reactive than the nitronium cation: any nitroso product could be subsequently oxidized to the related nitro compound. The reactions of indoles with nitrous acid and other nitrosating agents have been well studied.[1,22,23] Preferred attack is at C3 and the 3-nitroso-indole is usually isolated as its tautomeric isomer, the 3-oximino-3*H*-indole, which can be oxidized to the related 3-nitro-indole. The nitrosation of 3-aryl-4,6-dimethoxyindoles was examined under both acidic (sodium nitrite in acetic acid) and basic (*iso*-pentyl nitrate and potassium carbonate in dimethylformamide) conditions. The reaction failed completely under basic conditions, giving unchanged starting material. However, the reaction using acidic conditions furnished a complex mixture, which was suggested by ^{1}H NMR spectroscopy to contain 7-substituted products, and by mass spectral analysis to contain both nitroso- and nitro-indole derivatives.

3. Conclusion

The use of nitric acid on silica is very effective for the nitration of 4,6-dimethoxyindoles bearing an electron-withdrawing group either at C2, C7 or N1. When such a group is positioned at C7, an entry to the very rare 2-nitro-indoles is provided.

4. Experimental

4.1. General information

Melting points (uncorrected) were measured using a Mel-Temp melting point apparatus. Microanalyses were performed by the Microanalysis Unit of the Australian National University, Canberra or the University of Otago, New Zealand. Infrared spectra were recorded as Nujol mulls on a Perkin–Elmer 298 or a Perkin–Elmer 580B spectrometer. Ultraviolet–visible spectra were recorded in methanol (unless otherwise stated) on a Hitachi UV-3200 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F (300 MHz) spectrometer or at 500 MHz with a Bruker AM-500 spectrometer. ^{1}H NMR data are reported as follow: chemical shift measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling

constant (J) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). ^{13}C NMR chemical shifts are reported in ppm downfield from TMS and identifiable carbons are given. The EI and ES mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 210 °C. MALDI (matrix assisted laser desorption) mass spectra were recorded on a Finnigan MAT Lasermat 2000 for high molecular weight compounds. The principal ion peaks m/z are reported together with their percentage intensities relative to the base peak (where possible). Kieselgel 60H (Merck, Art 7736) was employed for flash chromatography and thin-layer chromatography (TLC) was performed on DC Aluminium Foil Kieselgel F_{254} (Merck, Art 5554). Preparative thin layer chromatography was performed on 3 mm plates using Merck silica gel 7730 $60GF_{254}$. Solvents and reagents were purified by literature methods. Petroleum ether refers to the hydrocarbon fraction of boiling range 60–80 °C. Compounds were detected by short and long ultraviolet light and with iodine vapor.

4.2. Preparation of indoles

4.2.1. 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione. 4,6-Dimethoxyisatin (5.0 g, 24.1 mmol) was added to a solution of NaOH (1.0 g, 25 mmol) in methanol (150 mL) and the mixture was refluxed for 1 h. The methanol was evaporated and the reddish-purple residue was suspended in dry DMF (50 mL). A solution of phenacyl bromide (4.8 g, 24.1 mmol) in DMF (10 mL) was added and the reaction mixture was heated at 100 °C for 16 h. On cooling, the dark solution was poured onto a mixture of ice and 10% HCl (50 mL). The yellow precipitate was collected, dried and chromatographed with DCM. The title 1-phenacyl isatin was obtained as a yellow solid (3.9 g, 50%), mp 210–212 °C (from EtOH). (Found: C, 66.4; H, 4.6; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.7; N, 4.3%). ν_{max}: 1745, 1715, 1700, 1635, 1600, 1440, 1390, 1215, 1170 cm^{-1}. λ_{max}: 215 nm (ε 18,300 cm^{-1} M^{-1}), 249 (25,200), 352 (13,300). ^{1}H NMR spectrum ($CDCl_3$): δ 3.85, 3.96 (6H, 2s, OMe), 5.10 (2H, s, CH_2), 5.82 (1H, d, J=2.0 Hz, H5), 6.02 (1H, d, J=2.0 Hz, H7), 7.50–7.68 (3H, m, aryl), 7.99–8.02 (2H, m, aryl). ^{13}C NMR spectrum ($CDCl_3$): δ 46.31 (CH_2), 56.08, 56.26 (OMe), 90.77 (C5), 91.96 (C7), 128.12, 128.98, 134.03 (aryl CH), 100.98, 134.03, 153.29, 160.17, 161.27 (aryl C), 170.03, 176.53, 191.22 (CO). Mass spectrum: m/z 325 (M, 10%), 192 (60), 105 (100), 77 (40).

4.2.2. 2-Benzoyl-4,6-dimethoxyindole-3-carboxylic acid. 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione (4.0 g, 12.3 mmol) was added to 20% aqueous NaOH (90 mL) and the mixture refluxed for 12 h. On cooling, the alkaline solution was diluted with water (300 mL), cooled in an ice bath and slowly acidified with conc. HCl. The precipitate was collected and dried to yield the title 2-benzoyl indole (3.0 g, 76%) as a light yellow solid, mp 206–207 °C. (Found: C, 66.0; H, 4.6; N, 4.2. $C_{18}H_{15}NO_5$ requires C, 66.4; H, 4.6; N, 4.3%). ν_{max}: 3375, 3125, 1685, 1660, 1635, 1620, 1580, 1530, 1510, 1420, 1390, 1340, 1280, 1260, 1240, 1215, 1200, 1175, 1140 cm^{-1}. λ_{max}: 218 nm (ε 16,000 cm^{-1} M^{-1}), 256 (14,000), 351 (10,000). ^{1}H NMR spectrum ($CDCl_3$): δ 3.38, 4.01 (6H, 2s, OMe), 6.37 (1H, d, J=2.0 Hz, H5), 6.53 (1H, d, J=2.0 Hz, H7), 7.35–7.53 (3H, m, aryl), 7.80–7.83 (2H, m, aryl), 10.08 (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.73, 56.26 (OMe), 87.81 (C5), 95.19 (C7), 128.36, 129.20, 133.24 (aryl CH), 110.85, 130.11, 137.07, 137.51, 137.89, 152.50, 159.62 (aryl C), 164.71, 190.40 (CO). Mass spectrum: m/z 325 (M, 10%), 307 (10), 281 (70), 266 (20), 105 (100).

4.2.3. Methyl 2-benzoyl-4,6-dimethoxyindole-3-carboxylate (1e). 2-Benzoyl-4,6-dimethoxyindole-3-carboxylic acid (2.0 g, 6.1 mmol) in diethyl ether (50 mL) was treated with an excess of diazomethane solution by slow addition over 30 min. The resulting solution was evaporated and the residue recrystallised from methanol to yield **1e** as a light yellow solid (2.1 g, 98%), mp 144–145 °C (from methanol). (Found: C, 67.3; H, 5.0; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.0; N, 4.1%). ν_{max}: 3300, 1720, 1620, 1600, 1575, 1565, 1520, 1500, 1425, 1400, 1355, 1330, 1275, 1210 cm^{-1}. λ_{max}: 219 nm (ε 18,000 cm^{-1} M^{-1}), 257 (17,500), 353 (12,500). ^{1}H NMR spectrum ($CDCl_3$): δ 3.27, 3.79, 3.84 (9H, 3s, OMe), 6.20 (1H, d, J=2.0 Hz, H5), 6.44 (1H, d, J=2.0 Hz, H7), 7.42–7.54 (3H, m, aryl), 7.76–7.79 (2H, m, aryl), 9.92 (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 51.66, 55.48, 55.60 (OMe), 85.92 (C5), 94.25 (C7), 128.29, 128.45, 132.15 (aryl CH), 111.74, 115.51, 131.30, 138.25, 138.74, 155.33, 161.04 (aryl C), 165.88, 187.86 (CO). Mass spectrum: m/z 340 (M+1, 10%), 339 (M, 45), 278 (30), 105 (80), 77 (100).

4.2.4. 2-Benzoyl-4,6-dimethoxyindole (1f). 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione (4.0 g, 12.3 mmol) was added to 20% aqueous NaOH (90 mL) and the mixture refluxed for 12 h. On cooling, the alkaline solution was diluted with water (300 mL) and extracted with chloroform. The extract was dried and concentrated to yield the pale yellow 2-benzoyl indole **1f** (2.8 g, 80%), mp 173–175 °C. (Found: C, 71.4; H, 5.6; N, 4.7. $C_{17}H_{15}NO_5$. 0.25 H_2O requires C, 71.4; H, 5.5; N, 4.9%). ν_{max}: 3310, 1635, 1615, 1590, 1570, 1510, 1490, 1390, 1290, 1220, 1200, 1150 cm^{-1}. λ_{max}: 219 nm (ε 13,500 cm^{-1} M^{-1}), 254 (13,500), 356 (17,500). ^{1}H NMR spectrum ($CDCl_3$): δ 3.85, 3.91 (6H, 2s, OMe), 6.18 (1H, d, J=1.9 Hz, H5), 6.48 (1H, d, J=0.8 Hz, H3), 7.20 (1H, d, J=1.9 Hz, H7), 7.47–7.58 (3H, m, aryl), 7.95–7.97 (2H, m, aryl), 9.51 (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.31, 55.54 (OMe), 85.98 (C5), 92.86 (C7), 111.32 (C3), 128.29, 129.01, 131.88 (aryl CH), 114.40, 132.49, 138.18, 139.62, 155.51, 161.24 (aryl C), 186.06 (CO). Mass spectrum: m/z 282 (M+1, 10%), 281 (M, 70), 266 (20), 238 (20), 149 (45), 105 (85), 77 (100).

4.2.5. 4,6-Dimethoxy-3-(4-methoxyphenyl)indole-7-carbaldehyde, 4,6-dimethoxy-3-(4-methoxyphenyl)indole-2-carbaldehyde (1g) and 4,6-dimethoxy-3-(4-methoxyphenyl)indole-2,7-dicarbaldehyde. To a stirred solution of 4,6-dimethoxy-3-(4-methoxyphenyl)indole (2.0 g, 7.1 mmol) in anhydrous chloroform (10 mL) at −50 °C was added dropwise an ice-cold solution of phosphoryl chloride (1.0 mL, 10.7 mmol) in DMF (2 mL). The mixture was stirred at this temperature for 1 h, then allowed to come to room temperature. Ice water (10 mL) was added and the

mixture stirred vigorously for 1 h, then made strongly alkaline with 10% NaOH and stirred vigorously for a further 4 h. The mixture was extracted with DCM (3×100 mL), the organic layer collected, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography (DCM).

The first band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-7-carbaldehyde (1.1 g, 50%) as yellow needles, mp 199–201 °C (from DCM/petroleum ether). (Found: C, 69.2; H, 5.5; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). ν_{max}: 3408, 1635, 1599, 1550, 1509, 1361, 1321, 1245, 1213, 1177, 1084, 981, 836 cm^{-1}. λ_{max}: 232 nm (ε 2800 $cm^{-1}\,M^{-1}$), 258 (3500), 333 (1200), 368 (1000). ^1H NMR spectrum ($CDCl_3$): δ 3.88, 3.90, 3.99 (9H, 3s, OMe), 6.17 (1H, s, H5), 6.96 (2H, d, J=8.8 Hz, aryl), 7.06 (1H, d, J=2.5 Hz, H2), 7.53 (2H, d, J=8.8 Hz, aryl), 10.42 (1H, s, CHO), 10.52 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$): 55.27, 55.35, 56.32 (OMe), 86.62, 113.19, 121.21, 130.47 (aryl CH), 104.45, 110.29, 118.42, 127.94, 137.62, 158.18, 161.42, 163.00 (aryl C), 188.25 (CHO). Mass spectrum: *m/z* 312 (M+1, 20%), 311 (M, 100), 296 (50), 97 (20), 69 (25), 57 (35).

The second band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-2-carbaldehyde **1g** (0.2 g, 10%) as yellow crystals, mp 215–216 °C (from DCM/petroleum ether). (Found: C, 69.2; H, 5.6; N, 4.4. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). ν_{max}: 3302, 1618, 1579, 1535, 1501, 1368, 1268, 1217, 1132, 802 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): δ 3.74, 3.87, 3.88 (9H, 3s, OMe), 6.16 (1H, d, J=2.0 Hz, H5), 6.42 (1H, d, J=2.0 Hz, H7), 6.96 (2H, d, J=8.7 Hz, aryl), 7.48 (2H, d, J=8.7 Hz, aryl), 9.12 (1H, sb, NH), 9.50 (1H, s, CHO). ^{13}C NMR spectrum (DMSO-d_6): 55.32, 55.37, 55.59 (OMe), 86.62, 93.24, 113.06, 132.73 (aryl CH), 111.62, 124.95, 129.42, 131.30, 140.29, 156.67, 158.99, 161.06 (aryl C), 180.96 (CHO). Mass spectrum: *m/z* 312 (M+1, 20%), 311 (M, 100), 296 (20).

The third band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-2,7-dicarbaldehyde (0.5 g, 20%) as yellow crystals (Found: C, 67.4; H, 5.2; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.1; N, 4.1%). ν_{max}: 3419, 1649, 1592, 1544, 1241, 1217, 990, 799, 608 cm^{-1}. λ_{max}: 248 nm (ε 3150 $cm^{-1}\,M^{-1}$), 311 (1900), 348 (2250), 361 (2050), 373 (1850). ^1H NMR spectrum ($CDCl_3$): δ 3.86, 3.87, 3.83 (9H, 3s, OMe), 6.13 (1H, s, H5), 6.95 (2H, d, J=8.7 Hz, aryl), 7.42 (2H, d, J=8.7 Hz, aryl), 9.55 (1H, s, 2-CHO), 10.34 (1H, s, 7-CHO), 10.86 (1H, sb, NH). ^{13}C NMR spectrum (DMSO-d_6) 55.43, 56.59, 57.28 (OMe), 89.42, 113.38, 132.68 (aryl CH), 103.19, 111.19, 123.63, 129.12, 131.43, 137.68, 159.42, 163.76, 166.49 (aryl C), 181.24, 187.27 (CHO). Mass spectrum: *m/z* 340 (M+1, 20%), 339 (M, 100), 32 (25), 28 (100).

4.2.6. Methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-7-yl] glyoxylate and methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-2-yl] glyoxylate (1h). 3-(4-*tert*-Butylphenyl)-4,6-dimethoxyindole (1.0 g, 3.2 mmol) was dissolved in anhydrous diethyl ether (30 mL). Oxalyl chloride (0.39 mL, 4.0 mmol) was added in one portion. The mixture was stirred for 3 h at room temperature. The resulting orange-red precipitate was filtered off. This solid was then added to a solution of excess methanol in diethyl ether (20 mL). The mixture was stirred for 1 h. Water was then added and the mixture extracted with DCM. The organic layer was washed until neutral, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give ester **1h** as a light yellow solid (45 mg, 35%), mp 177–178 °C (from methanol). (Found: C, 70.0; H, 6.4; N, 3.3. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.4; N, 3.5%). ν_{max}: 3320, 3260, 1755, 1630, 1600, 1570, 1520, 1490, 1340, 1310, 1280, 1240, 1210, 1200, 1160, 1130, 1070 cm^{-1}. λ_{max}: 214 nm (ε 31,800 $cm^{-1}\,M^{-1}$), 259 (22,500), 348 (24,000). ^1H NMR spectrum ($CDCl_3$): δ 1.36 (9H, s, Bu^t), 3.21, 3.64, 3.85 (9H, 3s, OMe), 6.10 (1H, d, J=1.9 Hz, H5), 6.41 (1H, d, J=1.9 Hz, H7), 7.37, 7.40 (4H, 2dd, J=14.0, 8.7 Hz, aryl), 9.47 (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 31.24 (CH_3-Bu^t), 34.55 (C-Bu^t), 51.85, 55.15, 55.54 (OMe), 85.58 (C5), 93.54 (C7), 123.93, 130.65 (aryl CH), 113.37, 127.39, 130.21, 130.59, 140.09, 150.38, 157.20, 162.29 (aryl C), 164.43, 177.56 (CO). Mass spectrum: *m/z* 396 (M+1, 30%), 395 (M, 90), 338 (20), 280 (100), 265 (25).

The filtrate containing 2-indol-7-ylglyoxyloyl chloride was evaporated under pressure. The residue was re-dissolved in diethyl ether (10 mL) and excess methanol was added. The mixture was allowed to stir for 1 h. The resulting precipitate was dissolved in DCM, washed with water until neutral, and dried to yield the methyl-[3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-7-yl]-glyoxylate as a yellow solid (38 mg, 30%), mp 196–197 °C (from methanol). (Found: C, 69.6; H, 6.2; N, 3.3. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.4; N, 3.5%). ν_{max}: 3390, 1725, 1620, 1590, 1570, 1550, 1540, 1500, 1430, 1350, 1320, 1310, 1260, 1210, 1170, 1150, 1120, 1085, 1060 cm^{-1}. λ_{max}: 211 nm (ε 23,500 $cm^{-1}\,M^{-1}$), 256 (24,000), 340 (12,300). ^1H NMR spectrum ($CDCl_3$): δ 1.37 (9H, s, Bu^t), 3.94 (9H, s, OMe), 6.17 (1H, s, H5), 7.11 (1H, d, J=2.3 Hz, H2), 7.47, 7.64 (4H, 2dd, J=33.5, 8.3 Hz, aryl), 10.53 (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 31.34 (CH_3-Bu^t), 34.39 (C-Bu^t), 52.13, 55.48, 57.09 (OMe), 87.22 (C5), 121.82 (C2), 124.85, 128.95 (aryl CH), 100.67, 110.80, 119.03, 132.05, 138.34, 148.90, 162.03, 162.35 (aryl C), 166.44, 184.62 (CO). Mass spectrum: *m/z* 396 (M+1, 10%), 395 (M, 50), 336 (100).

4.2.7. 3-(4-Chlorophenyl)-4,6-dimethoxy-7-trichloroacetylindole (4c) and 3-(4-chlorophenyl)-4,6-dimethoxy-2-trichloroacetylindole (1j). Trichloroacetyl chloride (2.0 mL, 17.9 mmol) was added dropwise to a solution of 3-(4-chlorophenyl)-4,6-dimethoxyindole (1.0 g, 3.5 mmol) in chloroform (20 mL). After completion of the addition, the solution was refluxed under N_2 overnight. The mixture was allowed to cool to room temperature, then water (20 mL) was added. The organic layer was extracted with DCM (2× 20 mL) and the organic layer was dried ($MgSO_4$), the solvent evaporated off under reduced pressure. Column chromatography of the residue (DCM/petroleum ether) gave the orange **4c** as the first fraction (1.0 g, 66%), mp 178 °C (DCM/petroleum ether). (Found: C, 50.0; H, 3.0; N, 3.1. $C_{18}H_{13}Cl_4NO_3$ requires C, 49.9; H, 3.0; N 3.2%). ν_{max}: 3380, 1610, 1580, 1560, 1340, 1245, 1215, 1080 cm^{-1}. λ_{max}: 212 nm (ε 14,000 $cm^{-1}\,M^{-1}$), 256 (12,600), 343 (8000). ^1H NMR spectrum ($CDCl_3$): δ 3.43, 3.99 (6H, 2s, OMe), 6.23 (1H, s, H5), 7.08 (1H, d, J=2.0 Hz, H2),

7.35–7.48 (4H, m, aryl), 10.29 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.45, 55.62 (OMe), 87.69 (C5), 121.84 (C2), 127.79, 130.74, (aryl CH), 98.65 (CCl_3), 110.80, 118.53, 132.05, 133.81, 139.78, 160.38, 161.39 (aryl C), 182.36 (CO). Mass spectrum: *m/z* 435 (M+2, $Cl^{37/37}$, 7%), 433 (M, $Cl^{35/35}$, 15), 316 (33), 314 (100).

The second fraction produced the yellow **1j** (0.30 g, 17%), mp 214 °C (DCM/petroleum ether). (Found: C, 49.9; H, 2.9; N, 3.3. $C_{18}H_{13}Cl_4NO_3$ requires C, 49.9; H, 3.0; N, 3.2%). ν_{max}: 3400, 1670, 1615, 1570, 1380, 1350, 1250, 1210, 1150 cm^{-1}. λ_{max}: 210 nm (ε 21,200 cm^{-1} M^{-1}), 281 (14,300), 360 (9600). ^{1}H NMR spectrum ($CDCl_3$): δ 3.63, 3.88 (6H, 2s, OMe), 6.13 (1H, d, J=2.0 Hz, H5), 6.45 (1H, d, J=2.0 Hz, H7), 7.36 – 7.48 (4H, m, aryl), 8.95 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.26, 55.70 (OMe), 87.57 (C5), 93.96 (C7), 127.34, 131.63, (aryl CH), 113.20, 120.67, 132.41, 132.86, 133.31, 139.13, 156.62, 161.47 (aryl C), 96.25 (CCl_3), 170.64 (CO). Mass spectrum: *m/z* 435 (M+2, $^{37/37}$Cl, 10%), 433 (M, $^{35/35}$Cl, 25), 314 (35), 279 (90), 264 (50), 150 (100).

4.2.8. 3-(4-Bromophenyl)-4,6-dimethoxyindole-7-carbaldehyde (4b). To a stirred solution of 3-(4-bromophenyl)-4,6-dimethoxyindole (1.50 g, 6.8 mmol) in anhydrous chloroform (10 mL) at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (0.63 mL, 6.8 mmol) in DMF (1.5 mL). The mixture was stirred at this temperature for 1 h, then allowed to come to room temperature. Ice water (10 mL) was added and the mixture stirred vigorously for 1 h, then made strongly alkaline with 10% NaOH and stirred vigorously for a further 4 h. The mixture was extracted with DCM (3×100 mL), the organic layer collected, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was column chromatographed (DCM) to give **4b** as yellow crystals (1.14 g, 70%), mp 218–220 °C (from DCM/petroleum ether). (Found: C, 57.0; H, 4.2; N, 3.7. $C_{17}H_{14}BrNO_3$ requires C, 56.7; H, 3.9; N, 3.9%). ν_{max}: 3400, 1640, 1590, 1350, 1330, 1210, 1090, 980, 800 cm^{-1}. λ_{max}: 233 nm (ε 2250 cm^{-1} M^{-1}), 252 (2250), 267 (1500), 332 (1250), 363 (1000). ^{1}H NMR spectrum ($CDCl_3$): δ 3.93, 4.00 (6H, 2s, OMe), 6.20 (1H, s, H5); 7.09 (1H, d, J= 2.2 Hz, H2); 7.44 (2H, d, J=8.6 Hz, aryl); 7.49 (2H, d, J= 8.6 Hz, aryl); 10.39 (1H, s, CHO); 10.54 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): 55.44, 56.40 (OMe), 86.82, 121.83, 130.76, 131.03 (aryl CH), 104.50, 109.96, 117.73, 120.03, 134.42, 137.77, 161.27, 163.13 (aryl C), 188.37 (CHO). Mass spectrum: *m/z* 362 (M+1, ^{81}Br, 20%), 361 (M, ^{81}Br, 100), 360 (M+1, ^{79}Br, 22), 359 (M, ^{79}Br, 100), 265 (35).

4.3. Preparation of nitric acid on silica gel

Silica gel (60H, Merck, 60 g) was added to nitric acid (8 M, 140 mL) and the resulting suspension stirred at room temperature for 2 h. The suspension was filtered and the silica gel allowed to dry in air for one week, then stored in an airtight container. The nitric acid content of the gel was determined by titration to be approximately 20%.

4.4. General procedure for the nitration of C-substituted indoles

To a solution of indole (100 mg) in DCM (20 mL) was added HNO_3 supported on silica gel (0.50 g). The mixture was quickly shaken for 10 seconds and immediately filtered. The solvent was removed and the residue recrystallised from methanol.

4.4.1. Dimethyl-4,6-dimethoxy-7-nitroindole-2,3-dicarboxylate (2c). Indole **1c** (100 mg, 0.34 mmol) gave the yellow nitrated indole **2c** (110 mg, 96%), mp 267–268 °C (from methanol). (Found: C, 49.6; H, 4.0; N, 8.1. $C_{14}H_{14}N_2O_8$ requires C, 49.7; H, 4.2; N, 8.3%). ν_{max}: 3460, 1740, 1710, 1630, 1590, 1555, 1520, 1500, 1450, 1420, 1345, 1320, 1290, 1250, 1225, 1200, 1120 cm^{-1}. λ_{max}: 205 nm (ε 18,700 cm^{-1} M^{-1}), 229 (22,300), 295 (14,700), 356 (13,200). ^{1}H NMR spectrum ($CDCl_3$): δ 3.94, 3.97, 4.03, 4.09 (12H, 4s, OMe), 6.27 (1H, s, H5), 10.52 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 52.43, 52.71, 56.45, 57.31 (OMe), 88.99 (C5), 111.22, 115.35, 123.71, 124.92, 131.76, 159.16, 159.68 (aryl C), 160.03, 165.43 (CO). Mass spectrum: *m/z* 339 (M+1, 10%), 338 (M, 100), 306 (50), 275 (35), 248 (65), 215 (40), 202(40).

4.4.2. Methyl-4,6-dimethoxy-7-nitroindole-2-carboxylate (2d). Indole **1d** (100 mg, 0.43 mmol) gave the yellow nitrated indole **2d** (95 mg, 80%), mp 230–231 °C (from methanol). (Found: C, 50.3; H, 4.3; N, 9.8. $C_{12}H_{12}N_2O_6\cdot 0.25H_2O$ requires C, 50.6; H, 4.4; N, 9.8%). ν_{max}: 3485, 1710, 1620, 1580, 1535, 1510, 1310, 1300, 1250, 1220, 1170, 970 cm^{-1}. λ_{max}: 209 nm (ε 12,000 cm^{-1} M^{-1}), 225 (13,700), 292 (13,000), 356 (9000). ^{1}H NMR spectrum (DMSO-d_6): δ 3.86, 4.06, 4.08 (9H, 3s, OMe), 6.59 (1H, s, H5), 7.19 (1H, d, J=2.6 Hz, H3), 10.94 (1H, sb, NH). ^{13}C NMR spectrum (DMSO-d_6): δ 52.39, 57.12, 58.03 (OMe), 90.25 (C5), 107.17 (C3), 79.53, 113.45, 126.74, 132.64, 158.40, 160.09 (aryl C), 160.84 (CO). Mass spectrum: *m/z* 281 (M+1, 10%), 280 (M, 100), 248 (55), 218 (40), 201 (15), 190 (25).

4.4.3. Methyl-2-benzoyl-4,6-dimethoxy-7-nitroindole-3-carboxylate (2e). Indole **1e** (100 mg, 0.29 mmol) gave the yellow nitrated indole **2e** (102 mg, 90%), mp 188–190 °C (from methanol). (Found: C, 58.8; H, 4.1; N, 7.3. $C_{19}H_{16}N_2O_7$. 0.25 H_2O requires C, 58.7; H, 4.3; N, 7.2%). ν_{max}: 3430, 3410, 1730, 1635, 1620, 1590, 1575, 1540, 1490, 1395, 1300, 1275, 1255, 1240, 1210, 1190, 1175 cm^{-1}. λ_{max}: 208 nm (ε 31,500 cm^{-1} M^{-1}), 245 (25,000), 337 (21,800). ^{1}H NMR spectrum (DMSO-d_6): δ 3.36, 4.02, 4.07 (9H, 3s, OMe), 6.65 (1H, s, H5), 7.51–7.56 (2H, m, aryl), 7.64–7.73 (3H, m, aryl), 11.92 (1H, sb, NH). ^{13}C NMR spectrum (DMSO-d_6): δ 51.96, 57.26, 58.08 (OMe), 91.28 (C5), 129.04, 129.11, 133.64 (aryl CH), 79.53, 110.50, 113.24, 131.80, 135.61, 137.69, 157.93, 159.98 (aryl C), 164.19, 187.23 (CO). Mass spectrum: *m/z* 385 (M+1, 15%), 384 (M, 100), 352 (20), 385 (25), 323 (25).

4.4.4. (4,6-Dimethoxy-7-nitroindol-2-yl)-phenylmethanone (2f). Indole **1f** (100 mg, 0.36 mmol) gave the yellow nitrated indole **2f** (87 mg, 75%), mp 239–240 °C (from methanol). ν_{max}: 3460, 1620, 1575, 1565, 1515, 1410, 1310, 1290, 1250, 1215, 1190, 1170, 1110 cm^{-1}. λ_{max}: 309 nm (ε 22,500 cm^{-1} M^{-1}), 230 (17,500), 241 (16,900), 336 (21,800). ^{1}H NMR spectrum ($CDCl_3$): δ 4.08, 4.11 (6H, 2s, OMe), 6.26 (1H, s, H5), 7.22 (1H, d, J=2.6 Hz, H3), 7.49–7.64 (3H, m, aryl), 7.93–7.96 (2H, m, aryl), 10.73 (1H,

sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 56.18, 57.36 (OMe), 88.39 (C5), 110.68 (C3), 128.51, 129.05, 132.43 (aryl CH), 114.36, 133.76, 133.99, 137.64, 159.48, 159.48, 160.95 (aryl C), 185.60 (CO). Mass spectrum: *m/z* 327 (M+1, 15%), 326 (M, 100), 250 (35), 207 (20).

4.4.5. 4,6-Dimethoxy-3-(4-methoxyphenyl)-7-nitroindole-2-carbaldehyde (2g). Indole **1g** (100 mg, 0.32 mmol) gave the yellow nitrated indole **2g** (103 mg, 90%), mp 272–274 °C (from methanol). (Found: C, 59.3; H, 4.6; N, 7.9. $C_{18}H_{16}N_2O_6$. 0.5 H_2O requires C, 59.2; H, 4.7; N, 7.7%). ν_{max}: 3450, 1650, 1620, 1580, 1570, 1550, 1510, 1490, 1440, 1420, 1340, 1300, 1260, 1230, 1210, 1180 cm^{-1}. λ_{max}: 204 nm (ε 15,900 cm^{-1} M^{-1}), 249 (16,000), 325 (11,400), 377 (9500). ^{1}H NMR spectrum ($CDCl_3$): δ 3.89, 4.10 (9H, 2s, OMe), 6.23 (1H, s, H5), 6.98, 7.42 (4H, 2dd, J=34.3, 8.7 Hz, aryl), 9.57 (1H, s, CHO), 10.65 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.34, 55.94, 57.33 (OMe), 88.54 (C5), 113.19, 132.39 (aryl CH), 112.44, 112.97, 118.63, 123.33, 130.26, 131.97, 134.11, 159.76, 162.42 (aryl C), 181.35 (CO). Mass spectrum: *m/z* 357 (M+1, 20%), 356 (M, 100).

4.4.6. Methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxy-7-nitroindol-2-yl] glyoxylate (2h). Indole **1h** (100 mg, 0.25 mmol) gave the yellow nitrated indole **2h** (111 mg, 84%), mp 284–285 °C (from methanol). (Found: C, 62.7; H, 5.4; N, 6.3. $C_{23}H_{24}N_2O_7$ requires C, 62.7; H, 5.5; N, 6.4%). ν_{max}: 3450, 1740, 1630, 1580, 1560, 1520, 1510, 1490, 1440, 1420, 1340, 1320, 1290, 1230, 1210, 1150 cm^{-1}. λ_{max}: 206 nm (ε 8000 cm^{-1} M^{-1}), 245 (5900), 339 (6000). ^{1}H NMR spectrum ($CDCl_3$): δ 1.29 (9H, s, Bu^t), 3.74, 3.85, 4.04 (9H, 3s, OMe), 6.23 (1H, s, H5), 7.20, 7.35 (4H, 2dd, J=48.7, 8.7 Hz, aryl), 9.08 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 31.21 (CH_3-Bu^t), 34.61 (C-Bu^t), 52.05, 55.94, 57.26 (OMe), 88.52 (C5), 124.17, 130.48 (aryl CH), 113.04, 118.33, 128.29, 128.89, 129.96, 134.11, 151.10, 160.12, 162.53 (aryl C), 163.54, 177.43 (CO). Mass spectrum: *m/z* 441 (M+1, 15%), 440 (M, 85), 343 (25), 325 (100), 307 (25).

4.4.7. 4,6-Dimethoxy-3-methyl-7-nitroindole-2-carbaldehyde (2i). Indole **1i** (100 mg, 0.46 mmol) gave the yellow nitrated indole **2i** (78 mg, 60%), mp 243–245 °C (from methanol). ν_{max}: 3440, 3370, 3320, 1650, 1640, 1615, 1570, 1550 1450, 1430, 1410, 1300, 1280, 1220, 1200, 970 cm^{-1}. λ_{max}: 207 nm (ε 16,600 cm^{-1} M^{-1}), 230 (17,000), 323 (18,900), 360 (16,400). ^{1}H NMR spectrum (DMSO-d_6): δ 2.63 (3H, s, CH_3), 4.04, 4.06 (6H, 2s, OMe), 6.47 (1H, s, H5), 9.99 (1H, s, CHO), 11.13 (1H, sb, NH). ^{13}C NMR spectrum (DMSO-d_6): δ 10.93 (CH_3), 57.18, 57.97 (OMe), 89.81 (C5), 113.57, 124.13, 131.85, 133.39, 159.45, 163.02 (aryl C), 182.45 (CHO). Mass spectrum: *m/z* 265 (M+1, 15%), 264 (M, 100), 246 (30), 188 (50), 173 (40).

4.4.8. 4,6-Dimethoxy-3-methyl-2,7-dinitroindole (3). To a solution of indole **1i** (100 mg, 0.46 mmol) in DCM (20 mL) was added HNO_3 supported on silica gel (0.50 g). The mixture was stirred for 10 min and then filtered. The solvent was removed and the residue triturated in methanol to give the yellow dinitrated indole **3** (58 mg, 45%), mp 274–276 °C. (Found: C, 47.3; H, 4.0; N, 14.7. $C_{11}H_{11}N_3O_6$ requires C, 47.0; H, 3.9; N, 14.9%). ν_{max}: 3400, 1620, 1580, 1530, 1500, 1420, 1390, 1340, 1310, 1280, 1240, 1200 cm^{-1}. λ_{max}: 204 nm (ε 9500 cm^{-1} M^{-1}), 234 (7100), 363 (8500). ^{1}H NMR spectrum (DMSO-d_6): δ 2.72 (3H, s, CH_3), 4.06, 4.07 (6H, 2s, OMe), 6.54 (1H, s, H5), 11.41 (1H, sb, NH). Mass spectrum: *m/z* 282 (M+1, 20%), 281 (M, 50), 263 (50), 251 (100), 234 (20).

4.4.9. 3-(4-Chlorophenyl)-4,6-dimethoxy-7-nitro-2-trichloroacetylindole (2j). The title compound was prepared from 2-trichloroacetylindole **1j** (0.20 g, 0.46 mmol) and conc. HNO_3 supported on silica gel (0.80 g). The nitro compound **2j** (0.16 g, 72%) was obtained as a yellow solid, mp 202 °C (DCM/petroleum ether). (Found: C, 44.7; H, 2.5; N, 5.9. $C_{18}H_{12}Cl_4N_2O_5$. 0.3 H_2O requires C, 44.8; H, 2.6; N, 5.8%). ν_{max}: 3410, 1700, 1620, 1560, 1530, 1350, 1290, 1220, 1200, 980, 845 cm^{-1}. λ_{max}: 242 nm (ε 28,400 cm^{-1} M^{-1}), 202 (24,900), 294 (12,600), 369 (12,500). ^{1}H NMR spectrum ($CDCl_3$): δ 3.80, 4.11 (6H, 2s, OMe), 6.21 (1H, s, H5), 7.31–7.40 (4H, m, aryl), 11.29 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 56.09, 57.46 (OMe), 88.91 (C5), 127.67, 131.41 (aryl CH), 95.49 (CCl_3), 112.73, 118.22, 122.21, 127.58, 131.88, 133.45, 133.89, 160.52, 162.14 (aryl C), 171.15 (CO). Mass spectrum: *m/z* 480 (M+2, $^{37/37}$Cl, 7%), 478 (M, 10), 375 (98), 361 (30), 359 (100).

4.4.10. Methyl 3-(4-chlorophenyl)-4,6-dimethoxy-7-nitroindole-2-carboxylate (2k). The mixture of indole **2j** (670 mg, 1.40 mmol) in methanol (20 mL) was treated with triethylamine (4 drops), then heated under reflux for 1 h. The mixture was allowed to cool to room temperature and the resulting precipitate was filtered, washed with methanol and dried to give the ester **2k** (430 mg, 78%) as a yellow solid, mp 240 °C (methanol/DCM). (Found: C, 55.4; H, 3.9; N, 7.0. $C_{18}H_{15}ClN_2O_6$ requires C, 55.3; H, 3.9; N, 7.2%). ν_{max}: 3460, 1700, 1680, 1580, 1325, 1285, 1225, 1200, 980, 800 cm^{-1}. λ_{max}: 242 nm (ε 62,800 cm^{-1} M^{-1}), 203 (61,600), 368 (28,000), 294 (27,000). ^{1}H NMR spectrum ($CDCl_3$): δ 3.79, 3.80, 4.09 (9H, 3s, OMe), 6.20 (1H, s, H5), 7.34 (4H, s, aryl), 10.64 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 51.97, 55.87, 57.33 (OMe), 88.55 (C5), 127.20, 132.05 (aryl CH), 112.84, 122.71, 124.50, 127.09, 131.75, 132.47, 133.39, 159.02, 160.77 (aryl C), 161.72 (CO). Mass spectrum: *m/z* 392 (M+2, $^{37/37}$Cl, 7%), 390 (M, $^{35/35}$Cl, 21), 358 (20).

4.4.11. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindol-7-yl]-2,2,2-trifluoroethanone (5a). Indole **4a** (100 mg, 0.23 mmol) gave the yellow nitrated indole **5a** (94 mg, 85%), mp 232–234 °C (from methanol). (Found: C, 45.8; H, 2.6; N, 5.6. $C_{18}H_{12}N_2O_5BrF_3$ requires C, 45.7; H, 2.6; N, 5.9%). ν_{max}: 3390, 1720, 1630, 1600, 1580, 1490, 1440, 1420, 1400, 1360, 1320, 1300, 1230, 1200, 1190, 1170, 1160, 1120 cm^{-1}. λ_{max}: 232 nm (ε 23,800 cm^{-1} M^{-1}), 351 (16,900). ^{1}H NMR spectrum ($CDCl_3$): δ 3.82, 4.05 (6H, 2s, OMe), 6.20 (1H, s, H5), 7.47, 7.64 (4H, 2dd, J=78.4, 8.2 Hz, aryl) 11.30 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.91, 56.67 (OMe), 88.99 (C5), 130.57, 131.84 (aryl CH), 99.26, 104.96, 111.74, 118.72, 119.00, 122.45, 127.14, 129.89, 131.56, 164.57 (aryl C), 165.73 (CO). Mass spectrum: *m/z* 475 (M+2, 10%), 474 (M+1, 95), 472 (85), 458 (20), 442 (20), 403 (100), 403 (90), 392 (35), 149 (75).

4.4.12. 3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindole-7-carbaldehyde (5b). Indole **4b** (100 mg, 0.28 mmol) gave the yellow nitrated indole **5b** (90 mg, 80%), mp 288–290 °C (from methanol). (Found: C, 50.4; H, 3.3; N, 3.9. $C_{17}H_{13}N_2O_5Br$ requires C, 50.4; H, 3.2; N, 6.9%). ν_{max}: 3400, 3355, 1650, 1600, 1575, 1530, 1510, 1485, 1450, 1400, 1360, 1290, 1230, 1220 cm^{-1}. λ_{max}: 205 nm (ε 16,100 cm^{-1} M^{-1}), 240 (19,900). ^1H NMR spectrum ($CDCl_3$): δ 3.80, 4.04 (6H, 2s, OMe), 6.18 (1H, s, H5), 7.47, 7.64 (4H, 2dd, J=70.8, 8.2 Hz, aryl), 10.35 (1H, s, CHO), 11.21 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.70, 56.41 (OMe), 88.32 (C5), 130.48, 131.97 (aryl CH), 103.53, 118.66, 122.28, 126.46, 130.21, 132.25, 134.26, 163.47, 166.41 (aryl C), 187.56 (CHO). Mass spectrum: *m/z* 407 (M+2, 15%), 406 (M+1, 100), 404 (100), 376 (20), 374 (25), 368 (20).

4.4.13. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-nitro-7-trichloroacetylindole (5c). To a solution of 7-trichloroacetylindole **4c** (0.13 g, 0.3 mmol) in DCM (10 mL) was added conc. HNO_3 supported on silica gel (0.50 g). The mixture was stirred for 10 min. After completion of the reaction, the silica was filtered off. The filtrate was concentrated and the residue chromatographed (DCM/petroleum ether) to give compound **5c** (0.10 g, 70%) as a yellow solid, mp 243 °C (from DCM/petroleum ether). (Found: C, 45.2; H, 2.3; N, 5.1. $C_{18}H_{12}Cl_4N_2O_5$. $0.1H_2O$ requires C, 45.1; H, 2.6; N, 5.8%). ν_{max}: 3400, 1650, 1580, 1485, 1290, 1235, 1220, 1160, 980, 840, 800, 720 cm^{-1}. λ_{max}: 227 nm (ε 20,900 cm^{-1} M^{-1}), 203 (16,400). ^1H NMR spectrum ($CDCl_3$): δ 3.80, 4.04 (6H, 2s, OMe), 6.21 (1H, s, H5), 7.36 – 7.41 (4H, m, aryl), 11.03 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.90 (OMe), 89.25 (C5), 127.73, 131.72 (aryl CH), 97.78, 98.23, 112.20, 119.20, 129.71, 134.23, 135.51, 136.68, 163.67, 163.90 (aryl C), 165.49 (CO). Mass spectrum: *m/z* 478 (M, 3%), 361 (30), 359 (100).

4.5. Preparation of N-substituted indoles

4.5.1. 4,6-Dimethoxy-3-phenyl-1-phenylsulfonylindole (6a). 4,6-Dimethoxy-3-phenylindole (5.84 g, 23 mmol) in anhydrous THF (100 mL) and the solution cooled in an ice-ethanol bath. *n*-Butyllithium (1.6 M, 15.9 mL, 24.4 mmol) was added dropwise over 5 min and the solution stirred under N_2 for 1 h. Phenylsulfonyl chloride (4.10 g, 23 mmol) was added slowly over 5 min and the mixture stirred at room temperature for 2 h. The reaction mixture was poured into ice water (200 mL) and extracted with diethyl ether (3× 100 mL). The organic extract was dried ($MgSO_4$), concentrated and the residue purified by column chromatography (DCM/hexane) to give **6a** as a white powder (6.85 g, 76%), mp 157–159 °C. (Found: C, 67.1; H, 5.0; N, 3.5. $C_{22}H_{19}NO_4S$ requires C, 67.2; H, 4.9; N, 3.6%). ν_{max}: 1590, 1340, 1200, 1180, 1170, 1140, 1100, 810, 800, 750, 720, 680 cm^{-1}. λ_{max}: 230 nm (ε 15,900), 246 (14,300), 287 (3500), 304 (1900). ^1H NMR spectrum ($CDCl_3$): δ 3.72, 3.90 (6H, 2s, OMe), 6.35 (1H, d, J=2.1 Hz, H5), 7.22 (1H, d, J=2.1 Hz, H2), 7.23–7.56 (9H, m, H7 and aryl), 7.91–7.94 (2H, m, aryl). ^{13}C NMR spectrum ($CDCl_3$): δ 55.18, 55.83 (OMe), 89.87 (C5), 95.24 (C7), 121.54 (C2), 126.80, 127.07, 127.64, 129.31, 129.55, 133.86 (aryl CH), 113.03, 124.70, 133.86, 137.53, 138.09 (aryl C), 154.70, 159.25 (C4, C6). Mass spectrum: *m/z* 394 (M+1, 4%), 393 (M, 15), 253 (20), 252 (100).

4.5.2. 3-(4-Chlorophenyl)-4,6-dimethoxy-indole-1-carbonitrile (6c). The 3-(4-chlorophenyl)-4,6-dimethoxyindole (1.0 g, 3.5 mmol) was added to a suspension of sodium hydride (1.1 equiv) in DMF (10 mL) at room temperature under N_2. *p*-Nitrophenylisocyanate (0.69 g, 4.2 mmol) was added slowly to the sodium salt of the indole and the mixture was further stirred at room temperature for 1 h. Water was added and extraction with ethyl acetate, followed by drying and evaporation of the solvent yielded the cyanoindole **6c** (0.93 g, 85%) as white crystals, mp 214–215 °C (from methanol). (Found: C, 65.1; H, 4.1; N, 8.9. $C_{17}H_{13}N_2O_2Cl$ requires C, 65.3; H, 4.2; N, 9.0%). ν_{max}: 3130, 2215, 1615, 1590, 1560, 1550, 1500, 1450, 1430, 1300, 1260, 1240, 1200 cm^{-1}. λ_{max}: 210 nm (ε 21,800 cm^{-1} M^{-1}), 245 (27,000). ^1H NMR spectrum ($CDCl_3$): δ 3.77, 3.89 (6H, 2s, OMe), 6.38 (1H, d, J=2.1 Hz, H5), 6.70 (1H, d, J=2.1 Hz, H7), 6.98 (1H, s, H2), 7.35, 7.46 (4H, dd, J=33.3, 8.2 Hz, aryl). ^{13}C NMR spectrum ($CDCl_3$): δ 55.34, 55.88 (OMe), 87.28 (C5), 95.90 (C7), 107.47 (CN), 120.43 (C2), 127.94, 130.70 (aryl CH), 110.12, 123.96, 131.39, 133.46, 139.65, 155.15, 160.15 (aryl C). Mass spectrum: *m/z* 314 (M+2, 35%), 312 (M, 100), 262 (30).

4.6. General procedure for the nitration of N-substituted indoles

To a solution of indole (100 mg) in dichloromethane (20 mL) was added HNO_3 supported on silica gel (0.50 g). The mixture was quickly shaken for 10 s and immediately filtered. The solvent was removed and the residue was run on preparative TLC plates with DCM to separate out the different bands. The crude nitrated indole fractions were then hydrolysed in methanol with excess NaOH. Each fraction was again run on a preparative TLC plate with DCM to yield the deprotected nitrated indole products.

4.6.1. 4,6-Dimethoxy-2,7-dinitro-3-phenylindole (7a). Indole **6a** (100 mg, 0.25 mmol) gave the yellow nitrated indole **7a** (65 mg, 75%), mp 221–223 °C. ν_{max}: 3420, 1620, 1605, 1570, 1555, 1515, 1490, 1430, 1410, 1355, 1330, 1310, 1280, 1270, 1220, 1195, 1170 cm^{-1}. λ_{max}: 207 nm (ε 16,000 cm^{-1} M^{-1}), 242 (11,800), 357 (11,300). ^1H NMR spectrum ($CDCl_3$): δ 3.78, 4.11 (6H, 2s, OMe), 6.24 (1H, s, H5), 7.42 (5H, s, aryl) 10.97 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.97, 57.29 (OMe), 89.28 (C5), 127.39, 128.22, 130.02 (aryl CH), 111.76, 130.21, 130.54, 144.21, 149.70, 153.13, 160.20, 162.69 (aryl C). Mass spectrum: *m/z* 344 (M+1, 15%), 343 (100), 313 (25), 267 (20), 105 (85), 77 (90).

4.6.2. 3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindole (7b). Indole **6b** (100 mg, 0.27 mmol) gave the yellow nitrated indole **7b** (35 mg, 35%), mp 211–213 °C ν_{max}: 3390, 1620, 1570, 1520, 1490, 1420, 1340, 1290, 1250, 1210, 1180, 1150, 1120 cm^{-1}. λ_{max}: 215 nm (ε 25,300 cm^{-1} M^{-1}), 261 (13,500), 385 (10,800). ^1H NMR spectrum ($CDCl_3$): δ 3.64, 3.87 (6H, 2s, OMe), 6.17 (1H, d, J=2.1 Hz, H5), 6.38 (1H, d, J=2.1 Hz, H7), 7.30, 7.52 (4H, 2dd, J=57.9, 8.7 Hz, aryl) 9.25 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.16, 55.64 (OMe), 85.50 (C5), 94.48

(C7), 130.27, 132.10 (aryl CH), 111.99, 119.81, 122.06, 130.69, 134.67, 135.81, 157.23, 162.69 (aryl C). Mass spectrum: *m/z* 379 (M+2, 10%), 378 (M+1, 100), 376 (90), 346 (40), 315 (30), 253 (25).

4.6.3. 3-(4-Bromophenyl)-4,6-dimethoxy-7-nitroindole (2b). Indole **6b** (100 mg, 0.27 mmol) also gave the yellow nitrated indole **2b** (40 mg, 40%), mp 218–220 °C. (Found: C, 50.2; H, 3.6; N, 7.2. $C_{16}H_{13}N_2O_4Br$. 0.25 H_2O requires C, 50.3; H, 3.6; N, 7.4%). ν_{max}: 3420, 1610, 1570, 1550, 1535, 1500, 1450, 1440, 1360, 1350, 1320, 1300, 1280, 1250, 1230, 1210 cm^{-1}. λ_{max}: 213 nm (ε 23,000 cm^{-1} M^{-1}), 263 (14,800), 283 (7400). ^1H NMR spectrum ($CDCl_3$): δ 3.93, 4.08 (6H, 2s, OMe), 6.26 (1H, s, H5), 7.13 (1H, d, J= 2.6 Hz, H2), 7.38–7.51 (4H, m, aryl), 10.31 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.59, 57.22 (OMe), 88.26 (C5), 121.80 (C2), 130.64, 131.04 (aryl CH), 118.98, 120.44, 130.64, 131.80, 133.34, 133.60, 156.84, 160.23 (aryl C). Mass spectrum: *m/z* 379 (M+2, 35%), 377 (M, 100), 347 (25).

4.6.4. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-nitroindole (7c). Indole **6c** (100 mg, 0.32 mmol) gave the yellow nitrated indole **7c** (53 mg, 50%), mp 216–217 °C. (Found: C, 57.2; H, 3.9; N, 8.3. $C_{16}H_{13}N_2O_4Cl \cdot 0.25H_2O$ requires C, 57.0; H, 4.0; N, 8.3%). ν_{max}: 3370, 1620, 1590, 1580, 1570, 1535, 1520, 1490, 1455, 1440, 1385, 1335, 1280, 1270, 1240, 1200, 1170, 1140, 1120 cm^{-1}. λ_{max}: 220 nm (ε 15,700 cm^{-1} M^{-1}), 260 (18,900), 385 (15,700). ^1H NMR spectrum ($CDCl_3$): δ 3.64, 3.87 (6H, 2s, OMe), 6.16 (1H, d, J=1.6 Hz, H5), 6.38 (1H, d, J=1.6 Hz, H7), 7.35, 7.42 (4H, m, aryl), 9.26 (1H, sb, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.15, 55.64 (OMe), 85.51 (C5), 94.48 (C7), 127.34, 131.82 (aryl CH), 112.06, 119.84, 130.19, 133.76, 135.82, 153.86, 157.23, 162.69 (aryl C). Mass spectrum: *m/z* 334 (M+1, 35%), 333 (M, 20), 332 (100), 302 (50), 271 (45).

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Electrochemical dimerization of phenacyl bromides *N*-acylhydrazones—a new way to 1-*N*-acylamino-2,5-diaryl-pyrroles

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Abstract—Cathodic reduction of phenacyl bromides *N*-acyl hydrazones lead to dimeric 1,4-diaryl-1,4-butanedione di-*N*-acylhydrazones, which give the corresponding 1-*N*-acylamino-2,5-diarylpyrroles in good yields.

1. Introduction

1-Aminopyrroles and *N*-substituted-1-aminopyrroles are a class of useful intermediates in organic chemistry which possess a wide range of the properties expected for *N*,*N*-disubstituted hydrazines.[1] Furthermore, 1-*N*-carbalkoxyaminopyrroles undergo efficient Diels–Alder reaction with electron deficient olefins.[2] Some 1-*N*-substitutedaminopyrroles and their derivatives have shown antibacterial activity.[3] 1-*N*-Aminoacetamido-2,5-dialkylpyrroles have exhibited analgesic and anesthetic properties.[4] 1-*N*-Carbalkoxyaminopyrroles have been used in synthesis of anxiolytic agents.[5] Systems based on the reaction of iron salts with heterocyclic hydrazines have been used in photothermographic processes.[6]

Recent advances in electroorganic chemistry have provided organic chemists with a new versatile synthetic device of a great promise.[7] Despite the long history of electroorganic chemistry, most of the electroorganic reactions that could provide product selectivity have been developed within the last twenty five years.[8] Research of various applications has spread gradually to cover many areas of fundamental and industrial organic chemistry.

Among them the cathodic reduction of α-halocarbonyl compounds has proved to be a very good tool in organic synthesis.[9] We have prepared electrochemically in such manner several classes of compounds such as 4-aryl-2-methylfurans,[10] imidazo[2,1-*b*][1,3,4]-oxadiazines,[11] [1,3]oxathiolan-5-ones,[12] tetrahydrofuran-2-ols,[13] 3-chloro-1,4-disubstituted-2(1*H*)-quinolinones.[14]

Several years ago, we reported the cathodic reduction of phenacyl bromide semicarbazones leading to the dimeric semicarbazones which were converted into either 1,4-diaryl-1,4-butanediones and 2,5-diarylfuranes[15] or 3,6-diarylpyridazines.[16]

In the present study we wish to report a facile and convenient way to 1-*N*-acylamino-2,5-diarylpyrroles starting from phenacyl bromides **1a**–**f**, which first were converted into phenacyl bromide *N*-acylhydrazones **2a**–**f**. The electrochemical reduction of phenacyl bromide *N*-acylhydrazones led to the dimeric 1,4-diaryl-1,4-butanedione di-*N*-acylhydrazones **3a**–**f**. Heating of dimers **3a**–**f** gave the corresponding 1-*N*-acylamino-2,5-diarylpyrroles **4a**–**f**. Our syntheses are summarized in Scheme 1.

2. Results and discussion

Acylhydrazones **2a**–**f** were obtained in nearly quantative yields using a modified known procedure.[17] Electroreduction of **2a**–**f** was accomplished in a divided cell on the mercury cathode. The first step in this process apparently involves two-electron cleavage of the carbon–bromine bond with the formation of anion A and bromide anion (Scheme 2).[18] Subsequent nucleophilic attack of anion A on the molecule of starting substrate **2a**–**f** lead to dimeric

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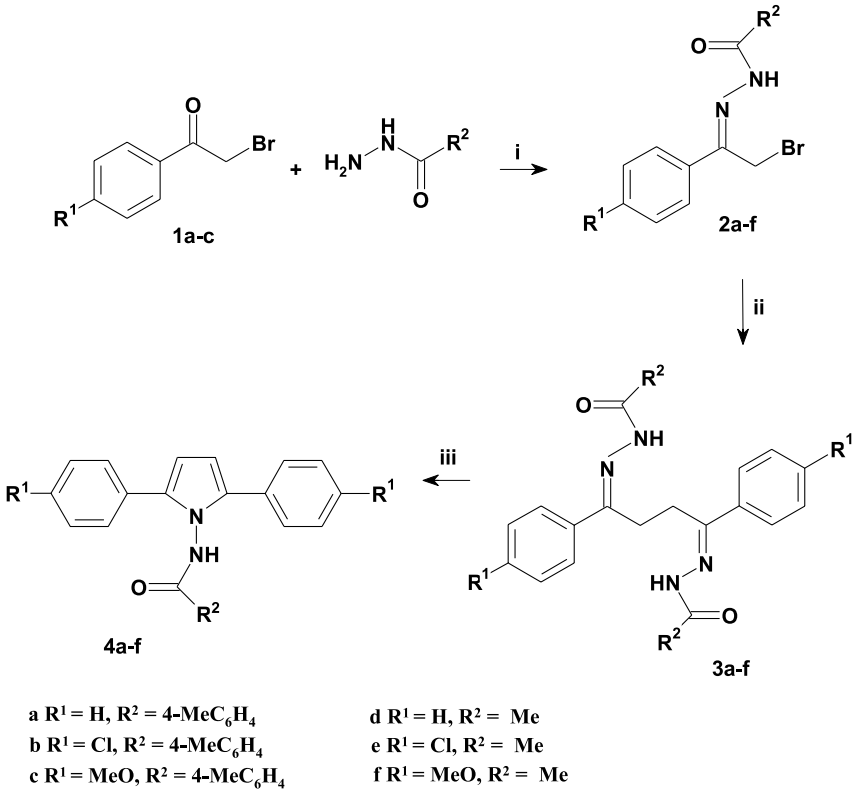
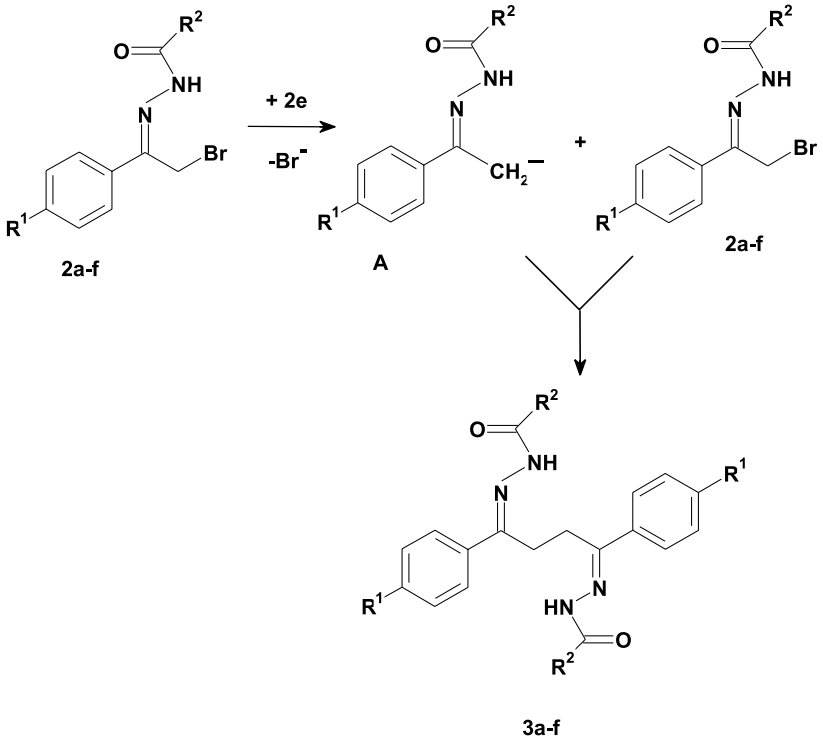


Scheme 1. (i) H^+, MeOH/H_2O; (ii) electrochemical dimerization; Hg-cathode, solvent–DMF, supporting electrolyte $LiClO_4$, divided cell; (iii) DMF reflux 1 h, or AcOH/EtOH, reflux 4 h.

compounds **3a–f** (Table 1). Similar dimers were obtained earlier by reduction of phenacyl bromides semicarbazones in a divided cell.[15,16] Further heating of **3a–c** in refluxing dimethylformamide (method A, Table 1) resulted in the formation of cyclic pyrroles **4a–c** in good yield. In contrast to **3a–c**, dimers **3d–f** were stable in boiling dimethylformamide. It should be mentioned that dimers of phenacyl bromides semicarbazones, that is, 1,4-diaryl-1,4-butanedione disemicarbazones in boiling dimethylformamide were converted into 3,6-diarylpyridazines.[16] Cyclization of **3d–f**



Scheme 2.

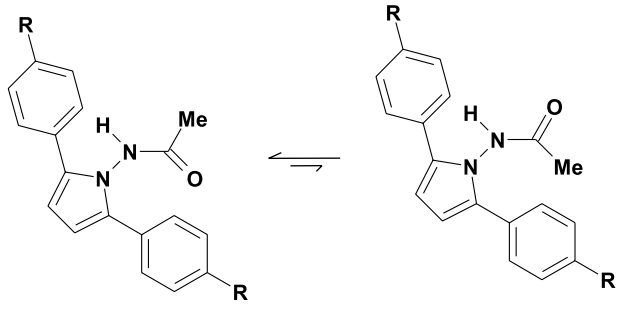
Table 1. Synthesis of 1-*N*-acylamino-2,5-diarylpyrroles

N-Acyl hydrazones	Di-*N*-acyl hydrazones	Yield (%)[a]	Method of cyclization	Pyrrole	Yield (%)[a]
2a	**3a**	69	**A** and **B**	**4a**	73 and 71
2b	**3b**	64	**A** and **B**	**4b**	76 and 72
2c	**3c**	62	**A** and **B**	**4c**	63 and 65
2d	**3d**	81	**B**	**4d**	87
2e	**3e**	85	**B**	**4e**	78
2f	**3f**	82	**B**	**4f**	72

[a] Isolated yields.

into the corresponding pyrroles **4a–f** was achieved in good yields by refluxing in the mixture of acetic acid/ethanol (1:1) (method B, Table 1). Dimers **3a–c** were also transformed into pyrroles **4a–c** using method B.

The ^{1}H NMR and ^{13}C NMR spectra of pyrroles **4d–f** showed the presence of two isomers for each compound (Scheme 3). The ratio of isomers depends on the solvent (Table 2). It is known that in a few cases single bond rotation is so slow that (*E*)- and (*Z*)-isomers can be detected on the NMR time scale even where no double bond exists,[19] for example, thioamides and certain amides,[20] because resonance gives the single bond some double bond character and slows rotation.[21]



4d-f

d R = H, e R = Cl, f R = OMe

Scheme 3.

Table 2. Ratio of isomer in 1-*N*-acetylamino-2,5-diarylpyrroles[a]

1-*N*-Acetyl-aminopyrrole	$CDCl_3$	Acetone-d_6	DMSO-d_6
4d	4:3	5:1	7:1
4e	2:1	7:1	10:1
4f	6:5	7:2	6:1

[a] ^{1}HMR data at 25 °C.

Table 3. ^{1}H NMR characteristic signals in $CDCl_3$ for isomers of 1-*N*-acetylamino-2,5-diarylpyrroles[a]

1-*N*-Acetyl-aminopyrrole	NH	CH═	CH_3
4d	7.77; *8.29*	6.35; *6.41*	1.89; *1.38*
4e	7.77; *8.26*	6.32; *6.61*	1.92; *1.36*
4f	7.64; *8.11*	6.25; *6.30*	1.90; *1.39*

[a] Signals of minor isomer in italics.

The (*Z*)-structures of **4d–f** main isomer were established by NOE experiments which show the close proximity of the amide proton and the methyl group (Table 3). For **4a–c** the ^{1}H NMR spectra show a single absorption for the NH, olefinic, and methyl protons due to the rapid interconversion of the *Z* and *E* isomers. This could be because conjugation between the carbonyl group and the benzene ring weakens the double bond character of the carbon–nitrogen bond.

As to our knowledge only one 1-*N*-acylamino-2,5-diarylpyrrole, namely 1-*N*-acetylamino-2,5-diphenylpyrrole is known in the chemical literature.[22,23] In both cases it was synthesized by action of acetyl anhydride on 1-amino-2,5-diphenylpyrrole.

3. Conclusion

Thus the electrochemical dimerization of phenacyl bromides *N*-acylhydrazones into dimeric 1,4-diaryl-1,4-butanedione di-*N*-acylhydrazones and further cyclization of dimers gives 1-*N*-acylamino-2,5-diarylpyrroles in good yields. This constitutes a facile and efficient method for the transformation of phenacyl bromides into 1-*N*-acylamino-2,5-diarylpyrroles, which are convenient and useful intermediates for organic chemistry and synthesis of pharmacology active agents.

The procedure uses inexpensive reagents, it is easily carried out, and the work up is very simple.

4. Experimental

The electrolyses were carried out using an Amel potentiostat Model 552 with electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett–Packard Model 5988A mass-selective detector equipped with a Hewlett–Packard Ms Chem Station. IR spectra of the compounds were recorded as dispersions in KBr on a Perkin–Elmer Model 583 spectrometer. ^{1}H and ^{13}C NMR spectra for **2a–f** and **3a–f** were recorded in $CDCl_3$ on Varian Unity 300 (300 MHz) spectrometer, for **4a–f** on Varian Unity 500-PLUS (500 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard. All melting points were measured on a Reichert Thermovar microhot stage apparatus and are uncorrected.

4.1. General procedure for the preparation of phenacyl bromides *N*-acylhydrazones 2a–f

Phenacyl bromides (20 mmol) were slowly added in solid

state (**1a** as a solution in 20 ml of MeOH) to a solution of hydrazone (40 mmol) and 2 ml of 5% HCl in 60 ml of a mixture of MeOH/H_2O under rapid stirring below 5 °C. The stirring was maintained for 24 h to complete the reaction. The quantitatively precipitated solid was isolated by filtration. The precipitate was washed consequently with chloroform and hexane (**2a–c**) or with hexane only (**2d–f**) and used for the next reaction without further purification.

4.1.1. Phenacyl bromide *N*-(4-methylbenzoyl)hydrazone 2a. Yield 6.09 g (92%), mp 133–134 °C. ^{1}H NMR ($CDCl_3$): δ 2.34 and 2.41 (s, 3H), 4.34 and 4.42 (s, 2H), 7.15–7.80 (m, 9H), 9.03 and 9.18 (bs, 1H). IR: 3469, 3299, 3028, 1655, 1535, 1468, 1272, 1178, 831, 770. Anal. Calcd for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.56; Br, 24.12; N, 8.46. Found: C, 57.83; H, 4.65; Br, 23.89; N, 8.37.

4.1.2. 4-Chlorophenacyl bromide *N*-(4-methylbenzoyl)-hydrazone 2b. Yield 6.87 g (94%), mp 144–146 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 and 2.42 (s, 3H), 4.36 and 4.44 (s, 2H), 7.20–7.80 (m, 8H), 9.11 and 9.25 (bs, 1H). IR: 3466, 3154, 3009, 1646, 1506, 1455, 1280, 1129, 995, 830, 752. Anal. Calcd for $C_{16}H_{14}BrClN_2O$: C, 52.56; H, 3.86; Br, 21.85; Cl, 9.70; N, 7.66. Found: C, 52.37; H, 3.72; Br, 21.89; Cl, 9.53; N, 7.51.

4.1.3. 4-Methoxyphenacyl bromide *N*-(4-methyl-benzoyl)hydrazone 2c. Yield 6.57 g (91%), mp 118–120 °C. ^{1}H NMR ($CDCl_3$): δ 2.35 and 2.41 (s, 3H), 3.82 and 3.86 (s, 3H), 4.32 and 4.41 (s, 2H), 6.90–7.80 (m, 8H), 9.15 and 9.36 (bs, 1H). IR: 3467, 3153, 2995, 1640, 1609, 1455, 1249, 1174, 829, 751. Anal. Calcd for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; Br, 22.12; N, 7.75. Found: C, 56.63; H, 4.85; Br, 21.89; N, 7.53.

4.1.4. Phenacyl bromide *N*-acetylhydrazone 2d. Yield 4.49 g (88%), mp 126–128 °C. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 4.29 (s, 2H,), 7.41 (m, 3H), 7.75 (m, 2H), 9.35 (bs, 1H). IR: 3466, 3199, 3044, 1669, 1553, 1260, 1119, 1003, 776, 690. Anal. Calcd for $C_{10}H_{11}BrN_2O$: C, 47.08; H, 4.35; Br, 31.32; N, 10.98. Found: C, 47.22; H, 4.39; Br, 31.13; N, 10.72.

4.1.5. 4-Chlorophenacyl bromide *N*-acetylhydrazone 2e. Yield 5.38 g (93%), mp 146–148 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 4.27 (s, 2H,), 7.37 (d, 2H, J=8.7 Hz), 7.68 (d, 2H, J=8.7 Hz), 9.43 (bs, 1H). IR: 3468, 3189, 3081, 1669, 1599, 1378, 1336, 1094, 1009, 834. Anal. Calcd for $C_{10}H_{10}BrClN_2O$: C, 41.48; H, 3.48; Br, 27.60; Cl, 12.24; N, 9.67. Found: C, 41.32; H, 3.55; Br, 27.38; Cl 12.05; N, 9.46.

4.1.6. 4-Methoxyphenacyl bromide *N*-acetylhydrazone 2f. Yield 4.84 g (85%), mp 133–135 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.82 (s, 3H), 4.27 (s, 2H,), 6.91 (d, 2H, J=8.8 Hz), 7.81 (d, 2H, J=8.8 Hz), 9.38 (bs, 1H). IR: 3467, 3153, 2995, 1640, 1609, 1455, 1249, 1174, 829, 751. Anal. Calcd for $C_{11}H_{13}BrN_2O_2$: C, 46.34; H, 4.60; Br, 28.02; N, 9.82. Found: C, 46.17; H, 4.55; Br, 27.88; N, 9.56.

4.2. General procedure for the electrochemical dimerization of phenacyl bromides *N*-acylhydrazones 3a–f

Anhydrous lithium perchlorate (10 mmol) was dissolved in 40 ml of dry dimethylformamide. 20 ml of this solution was placed in the cathode compartment and the other 20 ml in the anode compartment of the divided (porous glass diaphragm) electrolytic cell. Then the corresponding phenacyl bromide hydrazone (5 mmol) was added to the cathode compartment. For prevention of the accumulation of electrogenerated acid, anhydrous sodium carbonate (3 g) was placed in the anode compartment. The electrolyses were carried out under controlled cathodic potential at −1 V versus SCE. The charge consumed was 1 F/mol in all cases. At the end of the electrolysis, the cathodic solution was poured onto ice water (150 ml). In the case of **3d–f** the cathodic solution was evaporated under reduced pressure up to 10 ml before this operation. After 12 h, the precipitated solid isolated by filtration was washed with chloroform and used for the next reaction without further purification. Analytically pure samples of **3a–f** were obtained by crystallization from dimethylsulphoxide–methanol.

4.2.1. 1,4-Diphenyl-1,4-butanedione di-*N*-(4-methyl-benzoyl)hydrazone 3a. Yield 0.87 g (69%), mp 192–194 °C. ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 6H), 3.12 (s, 4H,), 7.20–7.80 (m, 18H,), 10.82 (bs, 2H). IR: 3336, 3249, 1651, 1524, 1471, 1274, 1116, 918, 829, 744, 692. Anal. Calcd for $C_{32}H_{30}N_4O_2$: C, 76.47; H, 6.02; N, 11.15. Found: C, 76.21; H, 5.92; N, 10.97.

4.2.2. 1,4-Di-(4-chloro)phenyl-1,4-butanedione di-*N*-(4-methylbenzoyl)hydrazone 3b. Yield 0.91 g (64%), mp 219–221 °C. ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 6H), 3.12 (s, 4H,), 7.20–7.85 (m, 16H), 10.72 (bs, 2H). IR: 3466, 3232, 1647, 1521, 1487, 1271, 1091, 833, 744, 669. Anal. Calcd for $C_{32}H_{28}Cl_2N_4O_2$: C, 67.25; H, 4.94; Cl, 12.41; N, 9.80. Found: C, 67.11; H, 4.82; Cl, 12.18; N, 9.67.

4.2.3. 1,4-Di-(4-methoxy)phenyl-1,4-butanedione di-*N*-(4-methylbenzoyl)hydrazone 3c. Yield 0.87 g (62%), mp 215–217 °C. ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 6H), 3.05 (s, 4H,), 3.76 (s, 6H), 6.80–7.80 (m, 16H), 10.61 (bs, 2H). IR: 3473, 3261, 1651, 1608, 1498, 1257, 1176, 1022, 829, 747. Anal. Calcd for $C_{34}H_{34}N_4O_2$: C, 72.58; H, 6.09; N, 9.96. Found: C, 72.31; H, 5.91; N, 9.78.

4.2.4. 1,4-Diphenyl-1,4-butanedione di-*N*-acetylhydrazone 3d. Yield 0.71 g (81%), mp 192–194 °C. ^{1}H NMR (DMSO-d_6): δ 1.99 and 2.15 (s, 6H), 2.89 and 2.92 (s, 4H,), 7.30–7.60 (m, 10H), 10.75 (bs, 2H). IR: 3428, 3227, 1658, 1459, 1383, 1128, 1006, 862, 769, 687. Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.41; H, 6.25; N, 15.78.

4.2.5. 1,4-Di-(4-chloro)phenyl-1,4-butanedione di-*N*-acetylhydrazone 3e. Yield 0.89 g (85%), mp 242–244 °C. ^{1}H NMR (DMSO-d_6): δ 1.97 and 2.13 (s, 6H), 2.89 and 2.91 (s, 4H,), 7.30–7.55 (m, 8H), 10.73 (bs, 2H). IR: 3446, 3235, 1668, 1533, 1490, 1322, 1091, 1011, 845, 668. Anal. Calcd for $C_{20}H_{20}Cl_2N_4O_2$: C, 57.29; H, 4.81; Cl, 16.91; N, 13.36. Found: C, 57.11; H, 4.91; Cl, 16.76; N, 13.15.

4.2.6. 1,4-Di-(4-methoxy)phenyl-1,4-butanedione di-*N*-acetylhydrazone 3f. Yield 0.84 g (82%), mp 210–212 °C. ^{1}H NMR (DMSO-d_6): δ 1.98 and 2.14 (s, 6H), 2.83 and 2.85 (s, 4H,), 3.77 (s, 6H), 6.90–7.80 (m, 8H), 10.67 (bs, 2H). IR: 3447, 3222, 1651, 1513, 1334, 1258, 1102, 1029, 833, 668. Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.38; H, 6.38; N, 13.65. Found: C, 64.17; H, 6.36; N, 13.49.

4.3. General procedure for the cyclization of di-*N*-acylhydrazones 3a–f

Cyclization. Method A. The di-*N*-acylhydrazones **3a–c** (1 mmol) were refluxed 1 h in 4 ml of dry dimethylformamide, then the solvent was evaporated under reduced pressure and the residue was crystallized from ethanol or chloroform–hexane. Isolated yields are presented in Table 1.

Cyclization. Method B. The di-*N*-acylhydrazones **3a–f** (1 mmol) were refluxed 1 h in 4 ml of a mixture of AcOH/EtOH (1:1), then the solvent was evaporated under reduced pressure and the residue was crystallized from ethanol or chloroform–hexane. Isolated yields are presented in Table 1.

4.3.1. 1-*N*-(4-Methylbenzoyl)amino-2,5-diphenylpyrrole 4a. Mp 276–278 °C. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 6.41 (s, 2H), 7.20 (d, 2H, J=8.1 Hz,), 7.24 (m, 2H), 7.32 (m, 4H), 7.46 (d, 2H, J=8.1 Hz,), 7.52 (m, 4H), 8.18 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 108.2, 127.1, 127.3, 128.1, 128.4, 129.3, 129.5, 131.8, 134.9, 136.7, 143.0, 167.6. MS *m/z* (relative intensity) EI: 352 (M^+, 26), 233(9), 218(7), 194(3), 130(2), 119(100), 115(5), 102(7), 91(39), 65(12). IR: 3449, 3219, 3015, 1654, 1532, 1304, 1287, 915, 746, 695. Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.66; H, 5.77; N, 7.82.

4.3.2. 1-*N*-(4-Methylbenzoyl)amino-2,5-di(4-chlorophenyl)pyrrole 4b. Mp 335–337 °C (dec). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 6.49 (s, 2H), 7.27 (d, 2H, J=8.3 Hz,), 7.41 (d, 4H, J=8.5 Hz), 7.56 (d, 4H, J=8.5 Hz), 7.63 (d, 2H, J=8.3 Hz), 11.71 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 20.5, 107.4, 126.6, 127.8, 128.0, 128.4, 128.6, 129.6, 130.9, 133.8, 141.9, 164.9. MS *m/z* (relative intensity) EI: 422 (M^++2, 6), 420 (M^+, 8), 303(1), 301(1), 288(1), 286(1), 267(1), 119(100), 91(25), 65(6). IR: 3481, 3209, 3009, 1648, 1528, 1483, 1285, 1090, 832, 771. Anal. Calcd for $C_{24}H_{18}Cl_2N_2O$: C, 68.42; H, 4.31; Cl, 16.83; N, 6.65. Found: C, 68.51; H, 4.39; Cl, 16.73; N, 6.51.

4.3.3. 1-*N*-(4-Methylbenzoyl)amino-2,5-di(4-methoxyphenyl)pyrrole 4c. Mp 267–269 °C (dec). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 3.72 (s, 6H), 6.29 (s, 2H), 6.90 (d, 4H, J=8.8 Hz), 7.27 (d, 2H, J=8.3 Hz), 7.45 (d, 4H, J=8.8 Hz), 7.65 (d, 2H, J=8.3 Hz). 11.53 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 20.4, 59.7, 105.8, 113.3, 123.9, 126.8, 127.9, 128.3, 128.5, 128.7, 134.0, 141.8, 165.2. MS *m/z* (relative intensity) EI: 412 (M^+, 30), 293(16), 278(23), 235(5), 224(8), 133(9), 119(100), 91(85), 65(32). IR: 3460, 3207, 3003, 1648, 1566, 1464, 1296, 1172, 834, 772. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.63; H, 5.81; N, 6.85.

4.3.4. 1-*N*-Acetylamino-2,5-diphenylpyrrole 4d. Mp 206–208 °C. ^{1}H NMR ($CDCl_3$) two isomers: δ 1.38 and 1.89 (s, 3H), 6.35 and 6.41 (s 2H), 7.27–7.45 (m, 10H), 7.77 and 8.29 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 18.7, 20.0, 108.1, 108.2, 127.3, 127.4, 127.7, 128.0, 128.4, 128.7, 128.9, 129.9, 130.8, 131.6, 135.7, 136.3, 169.6, 174.3. MS *m/z* (relative intensity) EI: 276 (M^+, 100), 233(39), 218(26), 204(12), 130(65), 115(17), 102(58), 77(32), 63(18). IR: 3463, 3184, 3028, 1668, 1543, 1449, 1270, 965, 756, 619. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.13; H, 5.81; N, 9.95.

4.3.5. 1-*N*-Acetylamino-2,5-di(4-chlorophenyl)pyrrole 4e. Mp 280–282 °C. ^{1}H NMR ($CDCl_3$) two isomers: δ 1.36 and 1.92 (s, 3H), 6.32 and 6.41 (s, 2H), 7.35–7.40 (m, 8H), 7.77 and 8.26 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 18.5, 20.9, 108.5, 108.7, 128.2, 128.8, 129.0, 129.1, 129.3, 129.4, 133.5, 134.3, 135.7, 136.6, 169.8, 174.5. MS *m/z* (relative intensity) EI: 346 (M^++2, 63), 344 (M^+, 100), 303(23), 301(28), 288(18), 286(25), 164(30), 130(57), 101(14), 75(12). IR: 3445, 3248, 3015, 1674, 1596, 1484, 1096, 1008, 828, 764. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O$: C, 62.62; H, 4.09; Cl, 20.54; N, 8.11. Found: C, 62.53; H, 3.98; Cl, 20.43; N, 7.95.

4.3.6. 1-*N*-Acetylamino-2,5-di(4-methoxyphenyl)pyrrole 4f. Mp 220–222 °C. ^{1}H NMR ($CDCl_3$) two isomers: δ 1.39 and 1.90 (s, 3H), 3.81 (s, 6H), 6.25 and 6.30 (s, 2H), 6.89 (m, 4H), 7.35 (m, 4H), 7.64 and 8.11 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 18.7, 21.0, 55.3, 107.2, 113.8, 114.2, 123.3, 123.5, 124.4, 128.1, 129.1, 129.4, 134.9, 135.6, 169.7, 174.5. MS *m/z* (relative intensity) EI: 336 (M^+, 63), 321(4), 293(43), 278(57), 160(13), 132(80), 117(24), 102(10), 89(33), 63(14). IR: 3461, 3132, 2931, 1682, 1611, 1503, 1251, 1179, 1034, 836. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.32; H, 6.04; N, 8.17.

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Cycloadditions [3+2] et [4+2] de l'α-nitrososstyrène sur le 2-hydroxyméthylène indanone et ses dérivés

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Résumé—La préférence de la cycloaddition [3+2] devant la réaction d'hétéro-Diels–Alder des dérivés 2-hydroxymethylène indanones avec l'α-nitrososstyrène est décrite. Les nouvelles structures spiro-pyrroles-1′-oxyde et spiro-1′,2′-oxazines sont rapportées. La stéréospécificité et la régiospécicficité des réactions sont discutées.

Abstract—The preferred [3+2] cycloaddition before hetero-Diels–Alder reaction of 2-hydroxymethylene indanones derivatives with α-nitrososstyrene is described. New fused spiro-pyrroles-1′-oxide and spiro-1′,2′-oxazines structures are reported. The stereospecificity and regiospecificity of the cycloadditions are discussed.

Les premières réactions d'hétéro-Diels–Alder utilisant les α-nitrosoalcènes comme hétérodiènes ont été réalisées par Gilchrist et al.[1,2] En les opposant à des systèmes diéniques conjugués, les auteurs ont obtenu des dérivés 1,2-oxaziniques avec une haute régiosélectivité. D'autres travaux ont décrit les mêmes observations.[3–10]

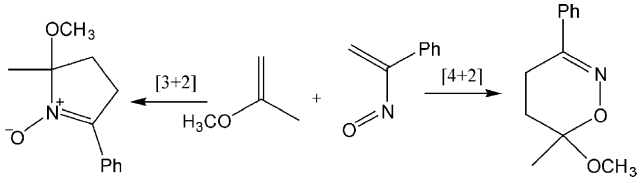

Schéma 1.

En étudiant l'action de l'α-nitrososstyrène sur le 2-méthoxypropène, Davies et al.[2b] ont mis en évidence la cycloaddition [3+2] dans une proportion de 10% par rapport à la cycloaddition [4+2] (Schéma 1).

Dans le cadre des travaux réalisés au laboratoire, Tahdi et al.[10] ont étudié l'action des α-nitrosoalcènes sur le dérivé 2H-pyrrole et ont montré la concurrence entre les deux hétérocycloadditions [4+2] et [3+2] (Schéma 2).

Afin d'étendre l'étude réactionnelle et stéréochimique de la cycloaddition moyennant l'hétérodiène α-nitrososstyrène **2**, le présent travail traite l'action des diénophiles cétone α,β-énoliques exocycliques, à comportements électroniques et stériques particuliers. Il s'agit du 2-hydroxyméthylène

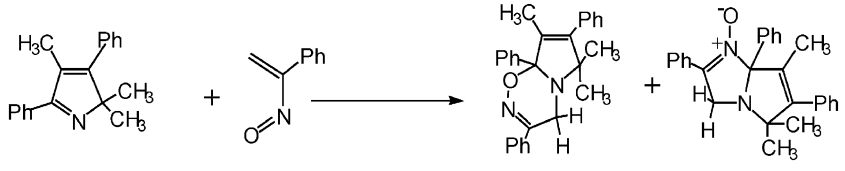

Schéma 2.

Mots Clés: α-Nitrosoalcène; Hétéro-Diels–Alder; Cycloaddition [3+2].
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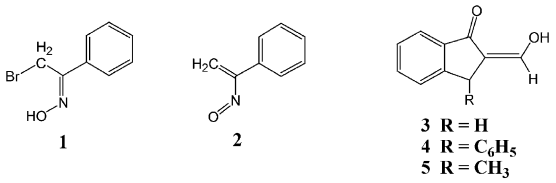

Figure 1.

indan-1-one **3** à faces énantiotopiques et de ses dérivés substitués **4** et **5** à faces diastéréotopiques (Fig. 1).

Le protocole opératoire retenu pour cette hétérocycloaddition consiste à mener la réaction dans le dichlorométhane anhydre, avec le diénophile et l'oxime de l'α-bromoacétophénone **1** en quantités stœchiométriques et le carbonate de sodium anhydre en excès. Le mélange réactionnel est agité à température ambiante pendant 24 heures. La séparation et la purification de la plupart des produits ont été possibles par recristallisation fractionnée.

L'α-nitrososstyrène **2**, issu in situ de l'oxime de l'α-bromoacetophénone **1** et opposé aux diénophiles **3**, **4** et **5**, a conduit, d'une façon reproductible et dans des proportions non équivalentes, à deux cycloadduits isomères et isolables (**6** 78%, **7** 22%) et (**8** 80%, **9** 20%) dans les cas respectifs des dérivés **3** et **4** et à deux composés non isomères et isolables **10** (78%) et **11** (22%) dans le cas **5**. Ces nouveaux produits formés se sont avérés être, d'après les analyses spectroscopiques, des spiro-pyrroles-1′-oxyde dans les cas, **6**, **8** et **10**, des spiro-1′,2′-oxazines dans les cas **7** et **9** et d'une oxime dans le cas **11** (Schéma 3).

1. Resultats et discussion

Les spectres protoniques des divers cycloadduits synthétisés, montrant plus particulièrement un singulet et un système AB relatifs au proton anomérique H-$C_{6'}$ (H–$C_{5'}$) et aux deux protons H_2–$C_{4'}$ (H_2–$C_{3'}$), attestent le caractère régiospécifique de la cycloaddition entre les diénophiles **3**, **4** et **5** et l' α-nitrososstyrène **2**.

La structure pyrrole-1′-oxyde, assignée aux produits **6**, **8** et **10**, se particularise de la structure 1′,2′-oxazine des produits **7** et **9** d'après les données de la R.M.N. protonique. En effet, la présence du multiplet centré à 8.3 ppm, intégrant deux protons, correspondants aux protons *ortho* aromatiques déblindés, caractérisent le système pyrrole-1′-oxyde porteur d'un groupement phényle en $C_{2'}$.[2b,10]

La structure pyrrole-1′-oxyde a été également confortée par voie chimique[2b] via la cycloaddition dipolaire entre le cycloadduit **6** et le dimethylacétylènedicarboxylate. La structure du nouvel hétérocycle **12** formé a été établie sur la base de ses données spectroscopiques (Schéma 4).

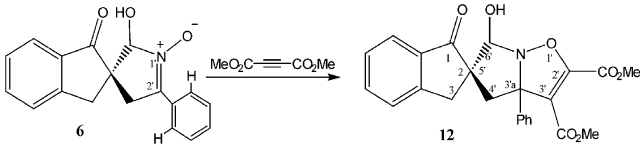

Schéma 4.

Le fait d'avoir obtenu dans les deux cas de diénophiles, **3** à faces énantiotopiques et **4** à faces diastéréotopiques, deux cycloadduits isomères, isolables et stables en les traitant séparément dans les conditions de la réaction (étude approuvée par la RMN ^{1}H et ^{13}C: réalisée en fonction du temps et en milieu acide), confirme la non épimérisation au niveau du carbone anomérique des cycloadduits formés et l'approche stéréospécifique, contrôlée par le carbone asymétrique C_3 du cycle indanonique.[11] En outre, la formation de deux cycloadduits de structures différentes et dans des proportions inégales: pyrrole-1′-oxyde majoritaire et 1′,2′-oxazine minoritaire, est en faveur des caractères concerté et privilégié de la cycloaddition [3+2] avec le s-*trans* α-nitrososstyrène et des caractères concerté et défavorisé de la cycloaddition [4+2] avec le s-*cis* α-nitrososstyrène (Schéma 5).

Il est à noter que les spectres RMN ^{1}H et ^{13}C des deux cycloadduits isomères **6** et **7**, contrairement à ceux des autres cycloadduits synthétisés, révèlent chacun un mélange de deux stéréoisomères (**6**$_1$, **6**$_2$) et (**7**$_1$, **7**$_2$) dans des proportions similaires (80%, 20%) dans le cas où le solvant de dissolution est le $DMSOd_6$ et de (52%, 48%) relatives à **7**$_1$ et **7**$_2$ dans le cas de $CDCl_3$ (le produit **6** étant insoluble dans ce solvant). Ces proportions restent inaltérées avec le temps et en milieu acide, ce qui atteste la non épimérisation des cycloadduits au niveau de leur carbone anomérique et renforce plutôt leur équilibre conformationnel (Schéma 6).

La structure des deux steréoisomères conformères a été

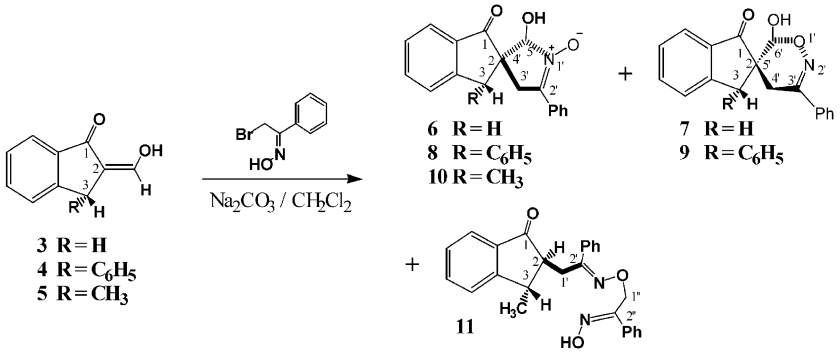

Schéma 3.

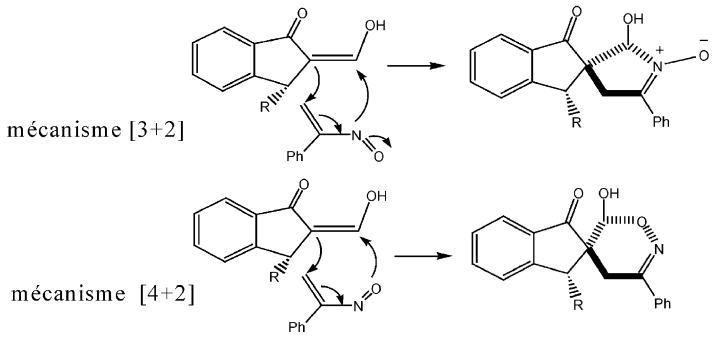

Schéma 5.

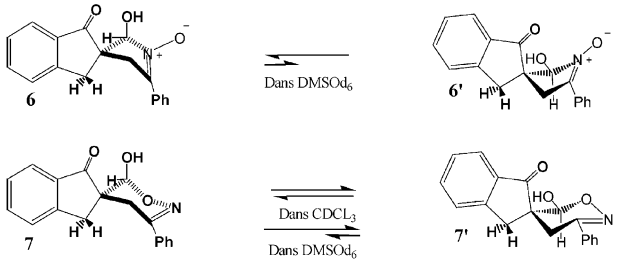

Schéma 6.

résolue sur la base des positions pseudoaxiale ou pseudo-équatoriale du groupement hydroxyle porté par le carbone $C_{5'}$ ($C_{6'}$) à caractère anomérique. En effet, les données de la RMN ^{13}C et en accord avec les études menées sur les carbohydrates[12] et sur certaines oxazines,[13] montrent que le carbone avec un groupement hydroxyle en position axiale résonne à champ fort par rapport à son homologue avec un groupement hydroxyle en position équatoriale. Ainsi le spectre RMN ^{13}C relatif aux deux conformères $\mathbf{6_1}$ et $\mathbf{6_2}$ ($\mathbf{7_1}$ et $\mathbf{7_2}$) indiquant huit signaux dans la région des carbones sp^3, montre un déplacement chimique à 96.6 ppm (92.7 ppm) attribuable au carbone anomérique $C_{5'}$ ($C_{6'}$) de $\mathbf{6_1}$ ($\mathbf{7_1}$) et celui à 99.8 ppm (95.7 ppm) au même carbone de $\mathbf{6_2}$ ($\mathbf{7_2}$).

Il est à noter que les spectres RMN ^1H et ^{13}C du cycloadduit **10**, enregistrés dans le $DMSOd_6$, montre une stabilité avec le temps, alors qu'en présence de traces d'acide et en fonction du temps, une instabilité a eu lieu. La complexité des produits formés, suite vraisemblablement à une réaction d'épimérisation au niveau du carbone anomérique, préconise en quelque sorte la formation particulière de l'oxime **11**.

L'oxime **11** précipite dans l'éthanol sous forme de cristaux après récupération du cycloadduit **10**. Sa structure a été établie sur la base de ses données spectroscopiques et confirmée par diffraction des rayons X. L'ORTEP (Fig. 2) montre, d'une part, la disposition *trans* des hydrogènes en position C_2 et C_3 exhortant ainsi le caractère stéréospécifique de l'hétérocycloaddition et d'autre part, la configuration *Z* des deux fonctions imines, confortant l'addition de deux molécules de α-nitrososstyrène dans la configuration transoïde.

Afin d'établir par voie chimique le mécanisme réactionnel gérant la formation de l'oxime **11**, deux chemins réactionnels ont été conçus. Dans un premier temps, la quantité de l'oxime **1** est réduite de moitié par rapport au diénophile **5**, il n'en résulte que le pyrrole-1′-oxyde **10**; quand l'oxime **1** est prise en excès, le produit **11** est formé majoritairement. Dans un deuxième temps, le cycloadduit **10** est soumis à l'action de l'oxime **1** dans les conditions opératoires de la cycloaddition, le produit obtenu est l'oxime **11**.

De ces deux réactions, le pyrrole-1′-oxyde **10** pourrait être l'intermédiaire réactionnel qui, suite à une rupture de sa liaison anomérique $C_{5'}$-N, réagit avec le s-*trans* nitososstyrène **2** et conduit à l'oxime **11** après une déformylation ou une oxydation par l'oxygène de l'air et décarboxylation (Schéma 7).

Par comparaison avec les diénophiles **3** et **4**, le comportement du diénophile **5** vis-à-vis de l'α-nitrososstyrère est dû probablement, suite à l'analyse de leur modèle moléculaire, aux gênes stériques plus importants causées par le groupement méthyle porté par C_3 indanonique. Ceci peut

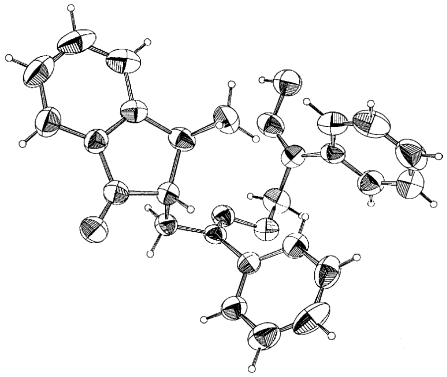

Figure 2. L'ORTEP du produit **11**.

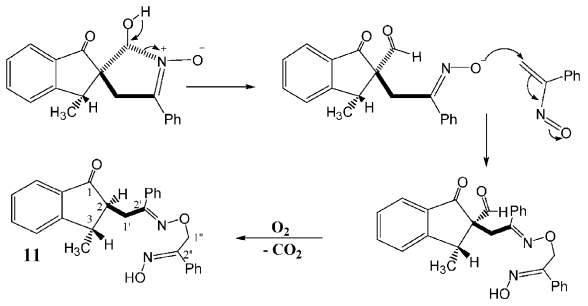

Schéma 7.

approuver l'exclusivité de la cycloaddition [3+2], l'instabilité du cycloadduit **10** en milieu acide et renforce en quelque sorte la réactivité privilégiée de l'α-nitrososstyrène sous sa forme transoïde: un comportement inédit par rapport à ce qui est décrit dans la littérature.[2b,10]

2. Conclusion

- L'obtention de deux cycloadduits, isomères, stables, isolables et dans des proportions distinctes: pyrrole-1′-oxyde majoritaire et 1′,2′-oxazine minoritaire, approuve la préférence de la cycloaddition [3+2] devant la réaction d'hétéro-Diels–Alder: deux mécanismes proposés dans l'élaboration d'une nouvelle classe spiranique. Il s'agit des indanone-spiro-1′,2′-oxazine et indanone-spiro-pyrrole-1′-oxyde qui font à notre connaissance des systèmes récents non décrits dans la littérature.
- L'aspect hautement concerté, stéréo et régiosélectif des deux hétérocycloadditions découlent des données spectroscopiques et sont confirmés par le spectre de diffraction des RX de l'oxime **11**.
- La synthèse de l'oxime **11** crée un phénomène inédit et le fait de l'avoir obtenu à partir du pyrrole-1′-oxyde **10**, constitue une preuve en soi pour la réaction d'épimérisation proposée lors de l'instabilité de **10**.
- Le choix judicieux des cétone α,β-hydroxyméthylènes exocycliques comme diénophiles, assujettis aux deux effets électroniques mésomères inverses, se sont avérés être une contribution aux caractères électroniques de la réaction d'hétéro-Diels–Alder et de la réaction dipolaire [3+2].
- La sélection des diénophiles indanoniques, à faces énantiotopiques et à faces diastéréotopiques, et de l'hétérodiène α-nitrsostyrène sous ses formes s-*cis* et s-*trans*, constitue un apport important dans le domaine stéréochimique de l'hétérocycloaddition [4+2] et [3+2].
- Le comportement stérique des systèmes indanoniques semble le facteur major dans l'orientation conformationnelle de l'hétérodiène: l'approche transoïde s'avère privilégiée devant la cisoïde.

3. Partie expérimentale

Les points de fusion ont été pris au moyen d'un appareil Buchi 510. Les spectres RMN ^{1}H et ^{13}C ont été enregistrés avec des appareils Brücker respectivement (300 MHz) et (75 Hz). Les spectres ont été enregistrés dans $CDCl_3$ avec le TMS comme référence interne. Les déplacements chimiques sont donnés en ppm et les constantes de couplage en Hertz. Les spectres de masse ont été enregistrés avec un spectromètre Varian MAT 311. Les spectres IR ont été pris avec un appareil PERKIN ELMER 577. Les produits étant dispersés en phase solide dans KBr à 5%. Les chromatographies sur couche mince ont été réalisées avec des plaques d'oxyde d'alumine: réf. 5554, prêtes à l'emploi, avec indicateur de fluorescence. L'éluant utilisé est un mélange de cyclohexane et d'acétate d'éthyle (9/1). Les analyses élémentaires ont été effectuées par le service central de microanalyse de C.N.R.S. de Lyon. La préparation des diénophiles a été réalisée selon le protocole opératoire décrit par W. S. Johnson et al.[14] Les oximes de l′α-bromocétone sont synthétisées selon les méthodes décrites par Korten[15] et Smith.[16]

3.1. Mode opératoire général

A une solution de 4×10^{-3} mol de diénophile dans 40 ml de dichlorométhane anhydre, sont ajoutés 4×10^{-3} mol de l'oxime de l'α-bromocétone et 10^{-1} mol de carbonate de sodium anhydre. Le mélange réactionnel est maintenu sous agitation à température ambiante. L'évolution de la réaction est suivie par chromatographie sur couche mince (support: alumine 0.2 mm; Eluant: cyclohexane/acétate d'éthyle 9/1) jusqu'à épuisement du diénophile. Le mélange réactionnel est filtré sur papier filtre. Le solide récupéré, lavé au dichlorométhane puis à l'eau, donne un seul produit relativement pur (cycloaddition [3+2]). Les phases organiques, séchées sur le chlorure de calcium, sont évaporées sous pression réduite. Le résidu obtenu suit une recristallisation fractionnée dans un solvant approprié (cycloaddition [4+2] majoritaire+cycloaddition [3+2]).

3.1.1. 5′-Hydroxy-2′-phénylindanone-2-spiro-4′ (3′H)-pyrrole-1′-oxyde: 6. 6′-Hydroxy-3′-phénylindanone-2-spiro-5′ (4′H)-1′,2′-oxazine: 7. L'oxime de l′α-bromoacétophénone (4×10^{-3} mol: 0.84 g), le 2-hydroxyméthylène-indan-1-one (4×10^{-3} mol: 0.6 g) donne le mélange de la nitrone **6** et de l'oxazine **7**: Rdt=45%. Par recristallisation fractionnée dans le benzène, les cycloadduits **6** et **7** sont séparés purs; nitrone **6**: Rdt=78%. F=240–242 °C; IR, ν cm^{-1}=1690 (C=O); 2400–3600 (OH); Anal. $C_{18}H_{15}NO_3$ calcd: C, 73.71; H, 5.15; Tr.: C, 73.68; H, 5.23; ms, *m/z*: Th. 293.1052($M^{\cdot+}$); Tr. 293.1084 ($M^{\cdot+}$), 276 (M^+–OH, 100%); conformère $\mathbf{6_1}$ (80%); RMN ^{1}H (DMSO-d_6): δH_3=3.03–3.79 (AB.2H, J=17.5 Hz); $\delta H_{3'}$=3.25–3.33 (AB.2H, J=17.1 Hz); $\delta H_{5'}$=5.24 (d.1H, $J_{H5'-OH}$=3.9);

δH_{Ar} (m, 9H)=7.49–8.38; RMN ^{13}C (DMSO-d_6): δC_1= 206.12; δC_2=53.51; δC_3=34.21; $\delta C_{2'}$=154.10; $\delta C_{3'}$= 37.31; $\delta C_{5'}$=96.61; δC_{Ar}=123.39–136.04; conformère **6_2** (20%); RMN ^1H (DMSO-d_6): δH_3=3.15–3.54 (AB.2H, J= 17.4 Hz); $\delta H_{3'}$=3.25–3.33 (AB.2H, J=17.1 Hz); $\delta H_{5'}$= 5.42 (d.1H, $J_{H5'-OH}$=3.7 Hz); δH_{Ar} (m.9H)=7.49–8.18; RMN ^{13}C (DMSO-d_6): δC_1=204.23; δC_2=52.01; δC_3= 34.58; $\delta C_{2'}$=152.09; $\delta C_{3'}$=44.55; $\delta C_{5'}$=99.81; δC_{Ar}= 123.39–136.04; oxazine **7**: Rdt=22%. F=170–172 °C (benzène); IR, ν cm^{-1}=1690 (C=O); 2400–3600 (OH); Anal. $C_{18}H_{15}NO_3$ calcd: C, 73.71; H, 5.15; Tr.: C, 73.82; H, 5.19; ms, *m/z*: Th. 293.1052 ($M^{\cdot +}$); Tr. 293.1055 ($M^{\cdot +}$), 276 (M^+ −OH, 100%); conformère **7_1** (52%); RMN ^1H ($CDCl_3$): δH_3=2.67–3.21 (AB.2H; $J_{H3,H3}$=18.1 Hz); $\delta H_{4'}$=2.38–3.31 (AB.2H, $J_{H4',H4'}$=17.9 Hz); $\delta H_{6'}$=5.22 (s.1H); δH_{Ar} (m.9H)=7.2–7.8; RMN ^{13}C ($CDCl_3$): δC_1= 205.85; δC_2=47.57; δC_3=33.43; $\delta C_{3'}$=154.06; $\delta C_{4'}$= 37.70; $\delta C_{6'}$=95.45; δC_{Ar}=124.15–136.03; conformère **7_2** (48%); RMN ^1H ($CDCl_3$): δH_3=2.97–3.34 (AB.2H, $J_{H3–H3}$=17.7 Hz); $\delta H_{4'}$=2.81–3.70 (AB.2H; $J_{H4',H4'}$= 17.7 Hz); δOH=4.25 (s.1H); $\delta H_{6'}$=5.42 (s.1H); δH_{Ar} (m, 9H)=7.2–7.8; RMN ^{13}C ($CDCl_3$): δC_1=205.73; δC_2= 48.93; δC_3=25.56; $\delta C_{3'}$=154.55; $\delta C_{4'}$=33.86; $\delta C_{6'}$= 91.52; δC_{Ar}=124.15–136.03; conformère **7_1** (78%); RMN ^1H (DMSO-d_6): δH_3=2.86–3.42 (AB.2H, $J_{H3,H3}$= 17.4 Hz); $\delta H_{4'}$=2.91–3.03 (AB.2H, $J_{H4',H4'}$=18.2 Hz); $\delta H_{6'}$=5.15 (d.1H, $J_{H6'-OH}$=4.6 Hz); δH_{Ar} (m, 9H)= 7.20–7.80; RMN ^{13}C (DMSO-d_6): δC_1=206.23; δC_2= 49.02; δC_3=32.91; $\delta C_{3'}$=154.37; $\delta C_{4'}$=33.67; $\delta C_{6'}$= 95.69; δC_{Ar}=128.28–140.86; conformère **7_2** (22%); RMN ^1H (DMSO-d_6): δH_3=2.94–3.09 (AB.2H, $J_{H3,H3}$= 18.3 Hz); $\delta H_{4'}$=2.90–3.47 (AB.2H, $J_{H4'-H4'}$=17.5 Hz); $\delta H_{6'}$=5.02 (d.1H, $J_{H6'-OH}$=4.3 Hz); δH_{Ar} (m, 9H)= 7.20–7.80; RMN ^{13}C (DMSO-d_6): δC_1=207.70; δC_2= 48.61; δC_3=25.21; $\delta C_{3'}$=151.85; $\delta C_{4'}$=37.78; $\delta C_{6'}$= 92.68; δC_{Ar}=124.15–136.03.

3.1.2. 5′-Hydroxy-3,2′-diphénylindanone-2-spiro-4′ (3′H)-pyrrole-1′-oxyde: 8. 6′-Hydroxy-3,3′-diphénylindanone-2-spiro-5′ (4′H)-1′,2′-oxazine: 9. L'oxime de l'α-bromoacétophénone (4×10^{-3} mol: 0.84 g) et le 2-hydroxyméthylène-3-phénylindane-1-one (4.0×10^{-3} mol: 0.94 g) conduit au mélange de la nitrone **8** et de l'oxazine **9**: Rdt=43% La nitrone **8** cristallise dans l'éthanol, l'oxazine **9** dans le benzène. nitrone **8**: Rdt=82%. F= 252–253 °C (éthanol); IR, ν cm^{-1}=1690 (C=O), 2400–3600 (OH); Anal. $C_{24}H_{19}NO_3$ calcd: C, 78.03; H, 5.18; Tr.: C, 78.12; H, 5.09; ms, *m/z*: 369 (M^+); 352 (M^+ −OH, 100%); RMN ^1H (DMSO-d_6): δH_3=4.93 (s.1H); $\delta H_{3'}$= 3.33–3.44 (AB.2H, J=17.9 Hz); $\delta H_{5'}$=4.57 (d.1H, $J_{H5'-OH}$=5.1 Hz); δH_{Ar}=7.28–8.36 (m, 14H); RMN ^{13}C (DMSO-d_6): δC_1=204.26; δC_2=58.22; δC_3=53.08; $\delta C_{2'}$=154.70; $\delta C_{3'}$=33.98; $\delta C_{5'}$=96.50; δC_{Ar}=123.89–138.73. oxazine **9**: Rdt=8%. F=180–182 °C (éthanol); IR, ν cm^{-1}: 1690 (C=O); 2400–3600 (OH); Anal. $C_{24}H_{19}NO_3$ calcd: C, 78.03; H, 5.18; Tr.: C, 77.96; H, 5.27; ms, *m/z*: 369 (M^+); 352 (M^+–OH, 100%); RMN ^1H (DMSO-d_6): δH_3= 4.60 (s.1H); $\delta H_{4'}$=2.93–3.25 (AB.2H, J=17.80 Hz); $\delta H_{6'}$=4.60 (s.1H); δH_{Ar}=7.10–7.90 (m, 14H); RMN ^{13}C (DMSO-d_6): δC_1=203.30; δC_2=55.69; δC_3=54.33; $\delta C_{3'}$=153.87; $\delta C_{4'}$=28.19; $\delta C_{6'}$=93.93; δC_{Ar}=125.46–137.15.

3.1.3. 5′-Hydroxy-3-méthyl-2′-phénylindanone-2-spiro-4′ (3′H)-pyrrole-1′-oxyde: 10 2-[2′-[O-(2′ ′-hydroxyimino-2′ ′-phényléthyl)oxyimino]-2′-phényléthyl]-3-méthylindan-1-one: 11. (a) L'oxime de l'α-bromoacétophénone (4.0×10^{-3} mol: 0.84 g), le 2-hydroxyméthylène-3-méthylindan-1-one (4.0×10^{-3} mol: 0.70 g) donne le mélange de la nitrone **10** et de l'oxime **11**: Rdt=45%. Par recristallisation fractionnée dans l'éthanol, les produits **10** (Rdt: 78%) et **11** (Rdt: 22%) sont séparés purs. (b) L'oxime de l'α-bromoacétophénone (2×10^{-3} mol: 0.42 g), le 2-hydroxyméthylène-3-méthylindan-1-one (4.0×10^{-3} mol: 0.70 g) donne la nitrone **10**: Rdt=35%. (c) L'oxime de l'α-bromoacétophénone (1×10^{-3} mol: 0.30 g), la nitrone **10** (2.0×10^{-3} mol: 0.35 g) donne l'oxime **11**: Rdt=15%. nitrone **10**. F=170–172 °C (éthanol); IR, ν cm^{-1}: 1690(C=O), 2400–3600(OH); Anal. $C_{19}H_{17}NO_3$ calcd: C, 74.25; H, 5.58; Tr.: C, 74.32; H, 5.45; ms, *m/z*: 307(M^+); 290(M^+–OH, 100%); RMN ^1H (DMSO-d_6): δCH_3=1.60 (d.3H, $J_{CH3–H3}$=7.00 Hz)); δH_3=3.60 (q.1H, $J_{H3–CH3}$ = 7.00 Hz); $\delta H_{5'}$=5.50 (d.1H, $J_{H5'-OH}$=3.2 Hz); $\delta H_{3'}$= 3.17–3.28 (AB.2H, J=17.0 Hz); δH_{ar} =7.2–8.4 (m, 9H); RMN ^{13}C (DMSO-d_6): δC_1=204.26; δC_2=56.02; δC_3= 40.85; δCH_3=14.23; $\delta C_{5'}$=95.02; $\delta C_{3'}$=33.25; $\delta C_{2'}$= 156.35; δC_{Ar}=122.84–135.56; le produit **11**. F=159–160 °C (éthanol); IR, ν cm^{-1}: 1705(C=O), 2400–3600(OH); Anal. $C_{26}H_{24}N_2O_3$ calcd: C, 75.71; H, 5.86; Tr.: C, 75.68; H, 5.81; ms, *m/z*: 412 (M^+); RMN ^1H (DMSO-d_6): δCH_3=1.26(d.3H, $J_{CH3–H3}$=7.4 Hz); δH_3= 3.21(qd.1H, $J_{H3–CH3}$=7.4 Hz, $J_{H3–H2}$=3.6 Hz); δH_2= 2.30(td.1H, $J_{H2–H3}$=3.6 Hz, $J_{H2–H1'cis}$=9.9 Hz, $J_{H2–H1'trans}$=3.6 Hz); $\delta H_{1'cis}$=3.16(dd.1H, $J_{H1'cis-H2}$=9.9 Hz, $J_{H1'cis–H1'trans}$=15.4 Hz), $\delta H_{1'trans}$=2.63(dd.1H, $J_{H1'trans–H2}$=3.6 Hz, $J_{H1'cis–H1'trans}$=15.4 Hz); $\delta H_{1'\ '}$=4.79–4.87(AB.2H, J=12.8 Hz); δOH=11.25(s.1H); δH_{Ar}= 7.0–7.7(m, 14H); RMN ^{13}C (DMSO-d_6): δC_1=205.70; δC_2=38.75; δCH_3=20.22; δC_3=35.63; $\delta C_{1'}$=52.53; $\delta C_{2'}$=156.30; $\delta C_{1'\ '}$=74.50; δ $C_{2'\ '}$=158.40.

3.2. Analyse par diffraction des rayons X du composé 11

L'enregistrement est réalisé sur un diffractomètre automatique ENRAF-NOMIUS CAD4, radiation: Mo Kα, Max 2θ (°): 50, mode de balayage: ω. La structure a été résolue par les méthodes directes, puis affinée par matrice entière; $\omega=1/\sigma(F_o)^2=[\sigma^2(1)+(0.04F_o^2)^2]^{-1/2}$. $C_{26}N_2O_3H_{24}$. M=412.5, triclinic, $P-1$, Z=2, a=10.023(3) Å, b=11.646(1) Å, c= 11.750(2) Å, α=110.78(1), β=98.45(2), γ=114.44(2)°, V=1095.5(5) $Å^{-3}$, Z=2, Dx=1.25 Mg m^{-3}, 1(Mo Kα)= 0.71069 Å, μ=0.75 cm^{-1}, F(000)=436, T=293 K, R= 0.043, $R\omega$=0.038 et $S\omega$=1.50 (résidu d'intensité $\Delta\rho$<à 0.14 e $Å^{-3}$) pour 353 variables et 2322 observations.

3.2.1. 6′-Hydroxy-2′,3′-diméthoxycarbonyl-3′a-phénylindanone-2-spiro-5′ [4′H]-pyrrolo-[1,2-*b*]-isoxazole: 12. A une solution de (5.1×10^{-3} mol: 0.15 g) de la nitrone **6** dans un mélange de 20 ml de dichlorométhane anhydre et 1 ml de diméthylsulfoxide, sont ajoutées (5.1×10^{-3} mol: 0.73 g) du diméthylacéthylène-dicarboxylate. Le mélange réactionnel est maintenu sous agitation à température ambiante durant 48 heures. L'évaporation du solvant réactionnel et la recristallisation du résidu obtenu dans l'éther donne le diester pur **12**: Rdt=45%. F=224–225 °C (ether); IR, ν cm^{-1}=1684 (C_1=O), 1764 (CO_2Me),

1709(CO_2Me), 1650(C=C); 3225–3550(OH); Anal. $C_{24}H_{21}NO_7$ calcd: C, 66.20; H, 4.86; Tr.: C, 66.27; H, 4.78; ms, *m/z*: 435 (M^+); RMN ^1H (DMSO-d_6): $\delta CO_2CH_3(1)=3.70$ (s, 3H); $\delta CO_2CH_3(2)=3.86$ (s, 3H); $\delta H_{4'}=2.53$–3.58 (AB, 2H, $J_{H4'-H4'}=17.0$ Hz); $\delta H_{5'}=2.70$–3.30 (AB, 2H, $J_{H3-H3}=13.7$ Hz); $\delta H_{6'\ '}=5.36$ (d, 1H, $J_{H6'-OH'}=4.5$ Hz); $\delta OH=3.35$ (s, 1H); δH_{Ar} (m, 9H)= 7.25–756; RMN ^{13}C (DMSO-d_6): $\delta C_1=205.01$; $\delta C_2=$ 51.99; $\delta C_3=46.01$; $\delta C_{4'}=33.66$; $\delta C_{5'a}=75.40$; $\delta C_{6'}=$ 96.23; δCO_2-(1)=162.13, δCO_2-(2)=159.28; δ-$OCH_3(1)=54.89$, δ-$OCH_3(2)=53.27$; $\delta C_{Ar}=114.63$–153.84.

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Corrigendum

Corrigendum to "A novel synthesis of substituted quinolines using ring-closing metathesis (RCM): its application to the synthesis of key intermediates for anti-malarial agents" [Tetrahedron 60 (2004) 3017]

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The authors regret that the base for allylation of compound **59** in Scheme 4 should be K_2CO_3 and the base and reaction temperature for allylation of compound **64** in Scheme 5 should be K_2CO_3 and 80 °C, respectively. The experimental details for compound **60** and **65** are correct.

In experimental section, (1) preparation for compound **10**, Ar atmosphere was incorrect. The actual condition is H_2 atmosphere. (2) The IR spectra for compound **11**, **43a**, **43b**, **43c**, **45** were taken by neat condition but KBr pellet.

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