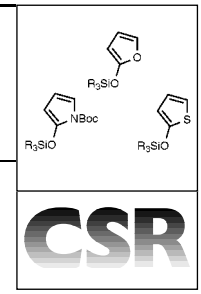
The synthetic utility of furan-, pyrrole- and thiophene-based 2-silyloxy dienes



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The aim of this review is to highlight the utility of a remarkable triad of 2-silyloxy diene synthons derived from furan, pyrrole and thiophene in organic synthesis. These heterocycles, in reacting with a number of carbonyl-related compounds (aldehydes, imines, heteroatom-stabilized carbenium ions), act as vinylogous nucleophile modules giving rise to a myriad of functionality-rich aldol-type constructs. These, in turn, represent invaluable synthetic platforms onto which a limitless number of functional elements and chosen chirality may be introduced. Eleven syntheses, amongst the most appealing of 1991–1999, have been chosen to illustrate the potentiality of silyloxy diene chemistry.

Giovanni Casiraghi was born and raised in Monza, Italy. He received his graduate education at the University of Pavia where he received the Laurea degree in Chemistry in 1964. He pursued his research as a Shell-sponsored Postdoctoral Fellow in the laboratories of Professor S. Pietra at the University of Pavia. In 1968 he joined Professor G. Casnati's group at the University of Parma, where he rose through the ranks to become Full Professor of Organic Chemistry in 1985. From 1986–1991 he served in the Department of Chemistry of the University of Sassari and in 1992 he accepted an appointment in the Faculty of Pharmacy of the University of Parma, as Chair in Organic Chemistry, establishing an active research laboratory engaged in both synthetic organic and bioorganic chemistry. G. Casiraghi's research interests focus on method- and target-oriented synthesis, molecular design and recognition, and the biological actions of organic molecules.

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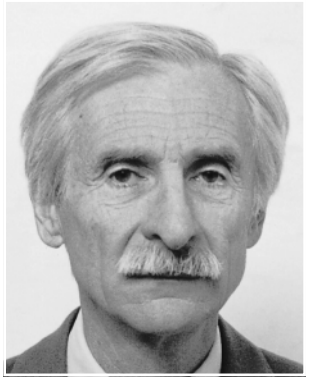


Giovanni Casiraghi

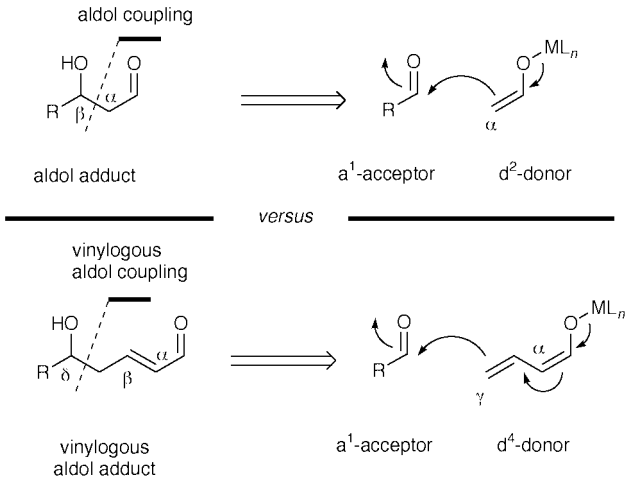
Franca Zanardi

Gloria Rassu

Lucia Battistini

1 Introduction

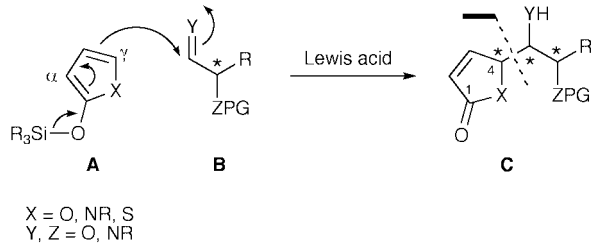
The immense diversity, biological relevance, and structural complexity of Nature's molecules have long inspired and fascinated organic chemists.[1] Here, being faced with the task of creating such complex structures, the synthetic practitioner, while exploiting the arsenal of existing transformations, is strongly stimulated to improve experienced maneuvers and to design truly novel methods and techniques. In the art of forming molecules by synthesis, the aldol reaction and its variants—imino aldol, Mannich, nitro-aldol, aza-aldol, *etc*.—are, undoubtedly, invaluable methods of carbon–carbon bond formation.[2] Indeed, by simply coupling enolate synthons (d^2-donors) to proper carbonyl frames (a^1-acceptors), a variety of β-hydroxy carbonyl constructs are formed (Scheme 1). In the vinylogous



Scheme 1

version of this construction, a carbonyl framework is connected to the γ-carbon of a dienolate synthon (d^4-donor), generating a δ-hydroxy-α,β-unsaturated carbonyl compound. Here, the precious functionality of the common aldols is flanked by a reactive conjugated double bond, which can easily undergo further manipulation. Thus, these vinylogous adducts, *vis-à-vis* the 'normal' adducts, have potentially greater synthetic application.

Five-membered heterocyclic silyloxy dienes **A** (Scheme 2) are the basis of a vast programme aimed at achieving molecular diversity. These molecules originate from furan, pyrrole, and



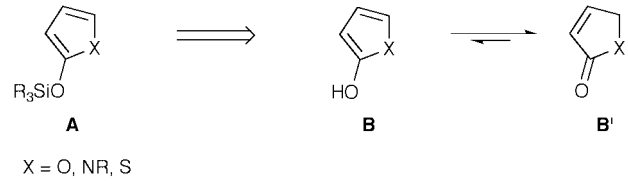
Scheme 2

thiophene and constitute a chemically affined ensemble of vinylogous d^4-nucleophiles. Adducts of type **C** may be traced to heterocyclic silyloxy dienes **A** and carbonyl precursors **B** *via* the regio- and stereoselective Lewis acid-assisted vinylogous cross-aldol reaction (vinylogous Mukaiyama-aldol addition). Functional groups and chirality may readily be introduced into **C** to give a near limitless number of target constructs. In fact, the wide assortment of independent variables within the donor and acceptor molecules **A** and **B**, *i.e.* the ternary heteroatom variable X and the ancillary variables Y and Z, together with the high functionalization potential of carbons 1–4, and the flexibility with which chirality can be established, all favour the successful realization of a varied inventory of natural and synthetic biosubstances.

This review hopes to emphasize the synthetic utility and charm of the vinylogous aldol addition exploiting furan-, pyrrole- and thiophene-based 2-silyloxy dienes. After briefly dealing with the chemical nature, preparation and basic reactivity of these heterocycles, the total syntheses of 11 chiral, nonracemic molecules of biological relevance carried out by various research teams including our own, during the period 1991–1999, will be reviewed and compared. The examples are grouped together on the basis of the pivotal chemical maneuver involved: the vinylogous aldol addition (Section 3.1), the vinylogous imino-aldol addition (Mannich-type addition) (Section 3.2) and the vinylogous addition to cyclic heteroatom-stabilized carbenium ions (Section 3.3). For a recent overview on this topic, the reader is referred to a monograph, comprehensively covering published material through end-1996.[3]

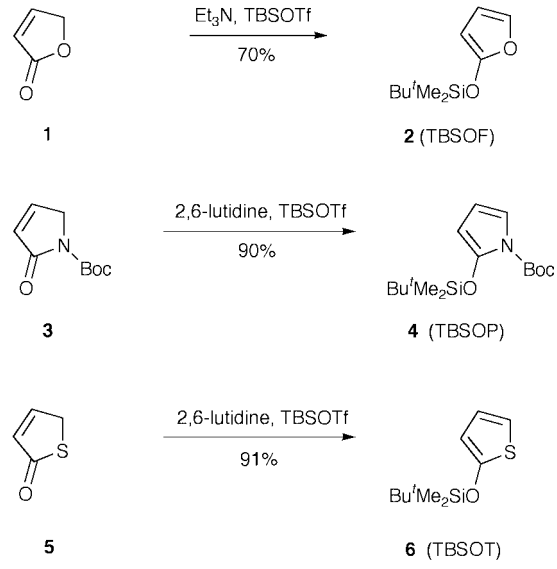
2 Background

The five-membered 2-silyloxy dienes **A** (Scheme 3), the basic modules in this account, can be chemically envisioned as stable



Scheme 3

silyl derivatives of 2-hydroxyfuran, 2-hydroxypyrrole and 2-hydroxythiophene, **B**, respectively. These compounds represent the less favoured enolic forms of the corresponding α,β-unsaturated 2-oxo heterocycles **B′**. Hence, the general strategy to access the 2-silyloxy diene reagents **A** simply entails deprotonation of readily available unsaturated 2-oxo precursors **B′** with a suitable base, followed by silylation. For prototypical 2-[(*tert*-butyldimethylsilyl)oxy]furan **2** (TBSOF), an optimum, scalable procedure involves treatment of furan-2(5*H*)-one **1** with a slight molar excess of triethylamine, followed by *tert*-butyldimethylsilyloxy trifluoromethanesulfonate (Scheme 4).

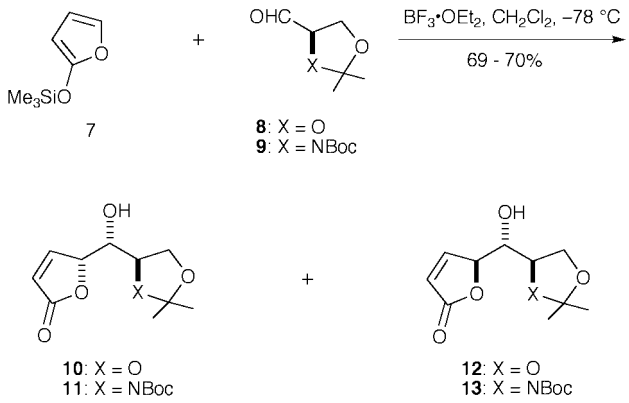


Scheme 4

TBSOF **2**, together with *N*-*tert*-butoxycarbonyl-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole **4** (TBSOP) and 2-[(*tert*-butyldi-

methylsilyl)oxy]thiophene **6** (TBSOT), readily available from their respective precursors **3** and **5**, are quite stable products which can be purified using conventional techniques (distillation and/or flash chromatography) and stored in a refrigerator for several months. 2-Silyloxy dienes **2**, **4** and **6**, as well as many related substituted derivatives and variants, are ambident carbon nucleophiles, their peculiar reactivity residing in alkylation or aldol type reactions involving the nucleophile C3 (α position) or C5 (γ position) carbon centers. In truth, the pivotal nucleophilic reactivity is restricted to Lewis acid-assisted reactions at the remote C5 site.

The first report mentioning the synthesis and use of 2-silyloxyfurans, including the parent compound 2-[(trimethylsilyl)oxy]furan (TMSOF) appeared more than 20 years ago (1977) and focused on cycloadditive reactions with maleic anhydride.[4] After this first report, sporadic studies have appeared, focused mainly on the use of furan-derived silyloxy dienes in Lewis acid-promoted additions to achiral aldehydes, ketones, and acetals.[3] The first application in a chiral nonracemic domain was communicated in 1989,[5] highlighting the regio- and diastereoselective vinylogous aldol addition of silyloxyfuran **7** to chiral pool-derived 2,3-*O*,*O*-isopropylidene-D-glyceraldehyde **8** or *N*-*tert*-butoxycarbonyl-2,3-*N*,*O*-isopropylidene-D-serinal **9** leading to butenolide adducts **10** and **12**, or **11** and **13** (Scheme 5). In fact, this work has acted as the springboard for a long-term synthetic programme where a few research groups and ourselves have been engaged.



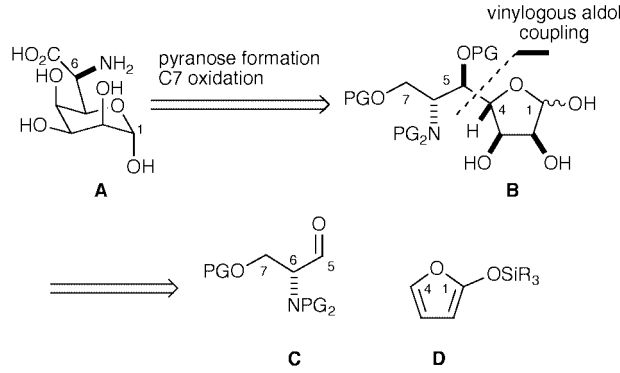
Scheme 5

3 Application in synthesis

This section, the core of the work, illustrates 11 synthetic transformations aimed at the assembly of chiral nonracemic biologically relevant targets including carbohydrates, polyhydroxylated alkaloids, non-proteinogenic amino acids and annonaceous acetogenin compounds. Despite the limited number of examples, this selection hopefully underlines the key merits of the vinylogous additions of silyloxy diene reagents, namely, the malleability and reliability of the technique. The syntheses are subdivided into three subsections, according to the nature of the electrophilic acceptor involved in the aldol coupling. Special emphasis will be placed on the basic homologative steps, while transformations exploiting trivial chemistry will be only marginally disclosed.

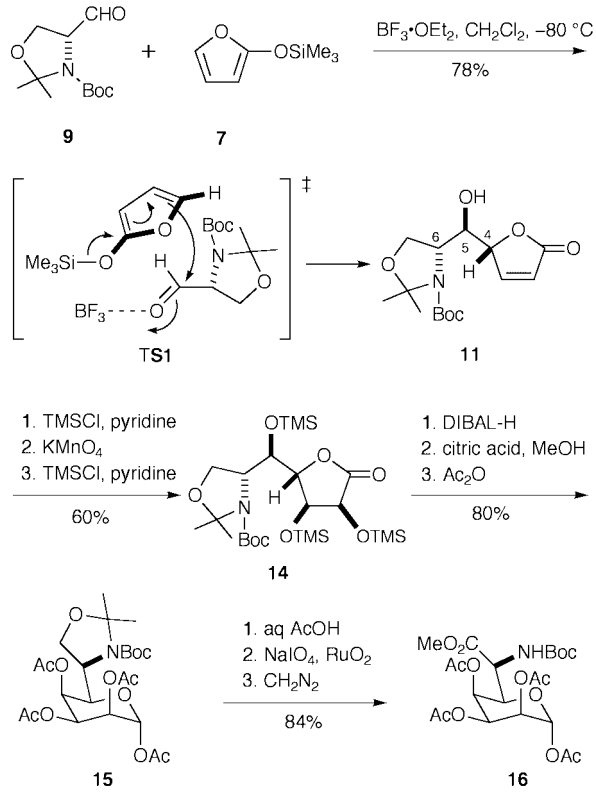
3.1 Vinylogous aldol addition

The opening target is a seven-carbon, terminal *C*-glycopyranosyl-α-amino acid of type **A** (Scheme 6), reminiscent of the sugar-core component of a rare class of nucleoside antibiotics, including amipurimycin and the miharamycins. Retrosynthetically,[6] the pyranose target **A** is traced to furanose **B** through a simple reaction sequence encompassing furanose-to-pyranose enlargement and oxidation of the C7 hydroxymethyl terminus to a carboxylic function. Disconnection of **B** along the indicated bond (C4–C5) allows us to identify two key precursors, 2-silyloxyfuran **D** and serine-derived chiron **C**. Thus, according to a 'resource-effective' concept, none of the carbons of the precursor synthons are sacrificed; the four-carbon nucleophile **D** furnishes the C1-to-C4 frame of the target pyranose ring, and the three-carbon serinal **C** becomes the C5–C7 amino acid portion.



Scheme 6

Central to the success of the synthesis (Scheme 7) was the vinylogous aldol addition between TMSOF **7** and readily available *N*-*tert*-butoxycarbonyl-2,3-*N*,*O*-isopropylidene-D-serinal **9**. Under BF_3 etherate assistance, the coupling maneuver proved highly regio- and diastereoselective, leading to the seven-carbon butenolide **11** in a 78% yield and a 94% diastereomeric excess. Mechanistically, a Felkin–Diels–Alder-like transition state **TS1** may be invoked to account for the observed stereochemical behaviour, resulting in a product with a 4,5-*syn*-5,6-*anti* relative configuration.



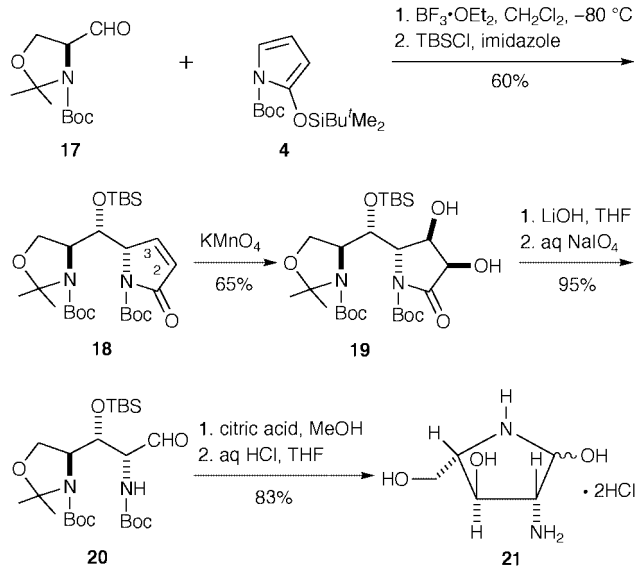
Scheme 7

After protection of the free secondary hydroxy group, exposure of the butenolide double bond to $KMnO_4$, under solid–

liquid phase transfer conditions, stereoselectively installed the C2–C3 diol function providing **14**, after proper protection. Expansion of the furan moiety to a pyranose ring required three further manipulations, selective reduction of the lactone carbonyl to a lactol (DIBAL-H), followed by desilylation and reprotection; sugar **15** was obtained in an 80% yield for these three steps. Unmasking of the terminal amino acidic portion was finally effected by sequential deacetonidation (aq. AcOH) and oxidation ($NaIO_4$, RuO_2), providing an amino acid which was isolated as the methyl ester **16**. To expand the scope of this chemistry, the synthesis was adapted to the preparation of certain enantiomeric and diastereomeric analogues, by changing *N-tert*-butoxycarbonyl-2,3-*N,O*-isopropylidene-D-serinal **9** with its enantiomer or by subjecting the butenolide precursor **11** to base-promoted C4 epimerization.

Chiral nonracemic amino sugars and, in particular, the aza-sugars have become increasingly important pharmacological products, their prominent activity being the inhibition of glycoside processing enzymes. Exploitation of pyrrole-based 2-silyloxy dienes of type **4** succeeded in introducing the nitrogen heteroatom into a given carbon sequence. This was the case for the synthesis of 2,4-diamino-2,4-dideoxy-L-arabinofuranose **21**—the pyrrolidinose form of the sugar component of the naturally occurring antifungal antibiotic prumycin—starting from TBSOP **4** and L-serine aldehyde **17**.[7]

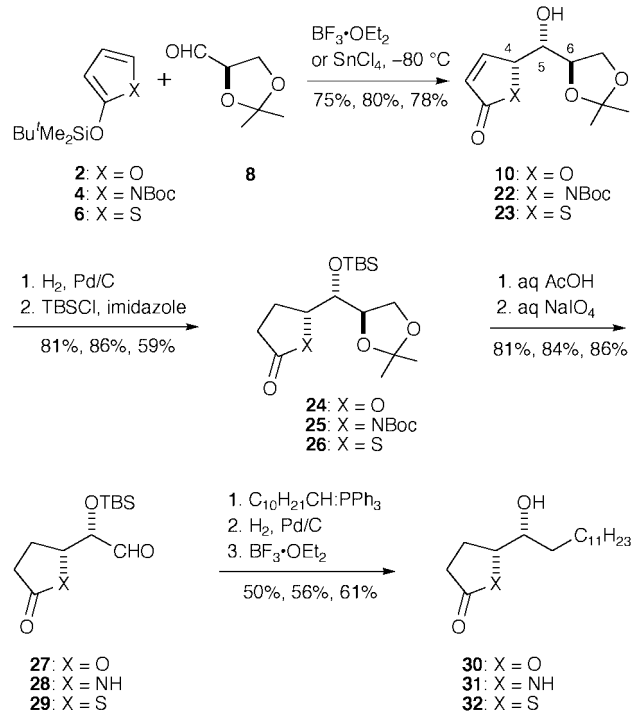
As portrayed in Scheme 8, the BF_3 etherate-promoted vinylogous Mukaiyama-aldol addition proved rather selective giving, after silylation, a 60% yield of the 4,5-*syn*-5,6-*anti*



Scheme 8

configured lactam **18**, accompanied by a 20% yield of its C4 epimeric counterpart (not shown). At first, the formyl function of the requisite five-carbon D-amino sugar **20** was implemented by oxidative cleavage of the C2–C3 bond within the seven-carbon matrix **18**. Thus, selective dihydroxylation of the double bond provided diol **19**, whose ring was hydrolytically opened to a carboxylate and then cleaved by periodate treatment to aldehyde **20**. Deacetonidation and acidic removal of all the protective groups spontaneously produced the target diamino sugar **21**, isolated here in its stable pyrrolidinose form.

A pre-eminent objective of our laboratory is to exploit the heteroatom diversity within the triad of furan-, pyrrole- and thiophene-based 2-silyloxy dienes as a ternary variable to assemble collections of important, naturally occurring compounds and isosterically affined variants. An extremely simple example of this concept is the parallel synthesis of both enantiomers of the annonaceous acetogenin-related metabolite muricatacin and their nitrogen and sulfur mimics.[8] As for the (*R,R*)-muricatacin series (Scheme 9), the Lewis acid-assisted vinylogous addition of 2,3-*O,O*-isopropylidene-D-glyceraldehyde **8** to the silyloxy diene triad TBSOF **2**, TBSOP **4** and



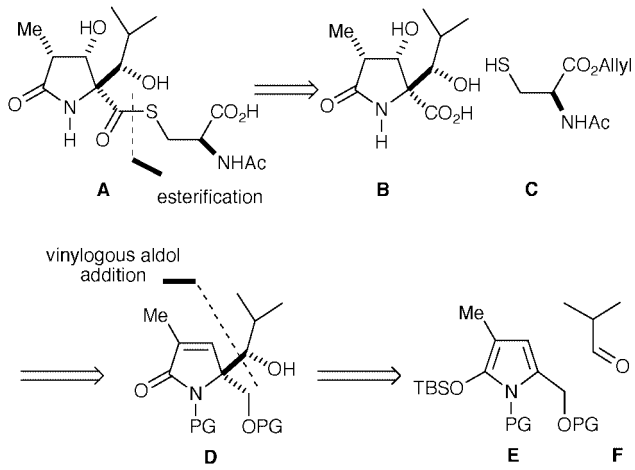
Scheme 9

TBSOT **6** gave the expected 4,5-*syn*-5,6-*anti* adducts **10**, **22** and **23**. According to independent, parallel routes, the above three matrices were processed to the corresponding saturated derivatives **24**, **25** and **26**, which were, in turn, elaborated into hydroxy aldehydes **27**, **28** and **29** by conventional chemistry. The muricatacin targets **30**, **31** and **32** were elaborated *via* Wittig elongations with a C_{11} ylide, followed by hydrogenation and deprotection. The common reactivity of the three silyloxy dienes, barely affected by heteroatom diversity, demonstrates the practicality and synthetic malleability of this strategy.

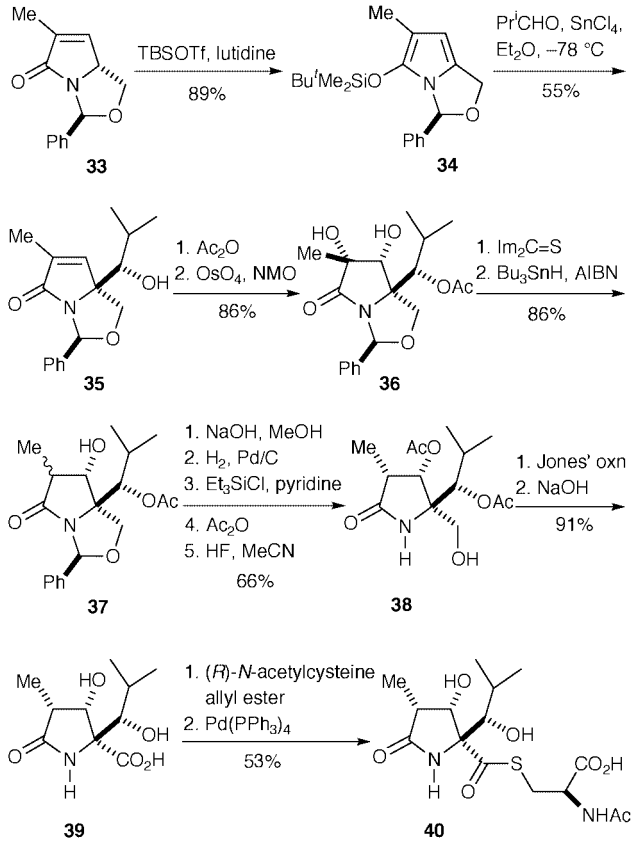
A remarkable exploitation of 2-[(trimethylsilyl)oxy]furan **7** and TBSOP **4** to access enantiomerically enriched (+)-(*S,S*)-muricatacin *ent*-**30** and (+)-(*S,S*)-azamuricatacin *ent*-**31** (not shown) was recently devised by Figadère *et al.*, utilizing enantioselective vinylogous aldolization protocols.[9,10] In both cases, the chiral $Ti(OPr^i)_4$–(*R*)-Binol system (20 mol%) was employed to catalyze the crucial vinylogous aldol maneuver with fairly good margins of enantioselection efficiency (80–90% ee).

Pyrrole-based 2-silyloxy dienes possess a ring nitrogen to which a chiral auxiliary can conveniently be attached. This inspired the clever, total synthesis of (+)-lactacystin **40** carried out by J. Baldwin's group in 1994.[11] Lactacystin is a naturally occurring microbial metabolite from *Streptomyces* species that exhibits potent neurotrophic and proteasome-mediated peptidase inhibitory activities. Retrosynthetically (Scheme 10), (+)-lactacystin **A** derives from pyroglutamic acid **B** and cysteine **C** *via* simple esterification. The core amino acid portion **B** is, in turn, related to the unsaturated lactam **D**, which can be disconnected along the indicated bond to afford the readily available 2-silyloxypyrrole **E** and isobutyraldehyde **F**.

Following this scheme, the key silyloxypyrrole chiron **34** was first prepared, *via* enolization/silylation of bicyclic oxazolidine **33**, in turn obtained from (*R*)-glutamate (Scheme 11). The residing glutamate chirality was transmitted to the benzylidene *N,O*-acetal carbon, according to the Seebach concept of 'self-regeneration of stereocenters'.[12] Indeed, enolization of **33** resulted in annihilation of the original C5 stereocenter, but the chirality memory remained imprinted on the acetal moiety.



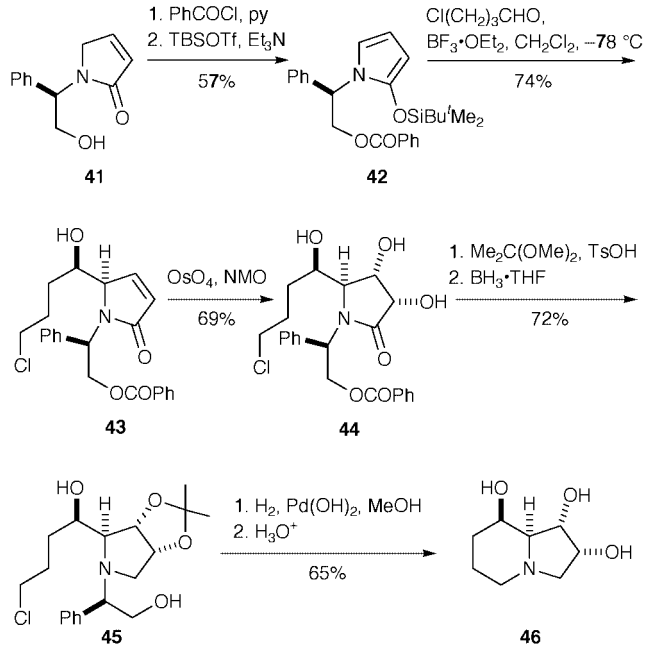
Scheme 10



Scheme 11

In the pivotal event, the quaternary carbon center within **35** was installed by $SnCl_4$-promoted vinylogous addition between **34** and isobutyraldehyde. Here, the major isomer **35** was obtained with surprising π-facial selectivity by addition of the aldehyde carbonyl to the same face as the phenyl substituent. As usual (*vide supra*), simple diastereoselection favouring a *threo* (*syn*) relationship between the two newly created C4 and C5 stereocenters was manifested.[13] A multistep sequence comprising, *inter alia*, double bond dihydroxylation, Barton–McCombie regioselective deoxygenation, chirality adjustment and removal of the chiral auxiliary unit, allowed transformation of **35** to **38** *via* **36** and **37**. All that remained was the oxidation of the primary hydroxymethyl function to a carboxylic acid, **39**, and its junction to *N*-acetylcysteine ultimately giving rise to (+)-lactacystin **40**.

The opportunity of chiralizing a silyloxy pyrrole reagent by joining an appropriately shaped nonracemic appendage to the free nuclear nitrogen was grasped by Royer *et al.* during a recent investigation of azasugar synthesis.[14] As an example, a chiral approach to a swainsonine-related indolizidine triol, **46**, is illustrated in Scheme 12, using commercially available *N*-substituted pyrrolinone **41** as the key source of chirality.



Scheme 12

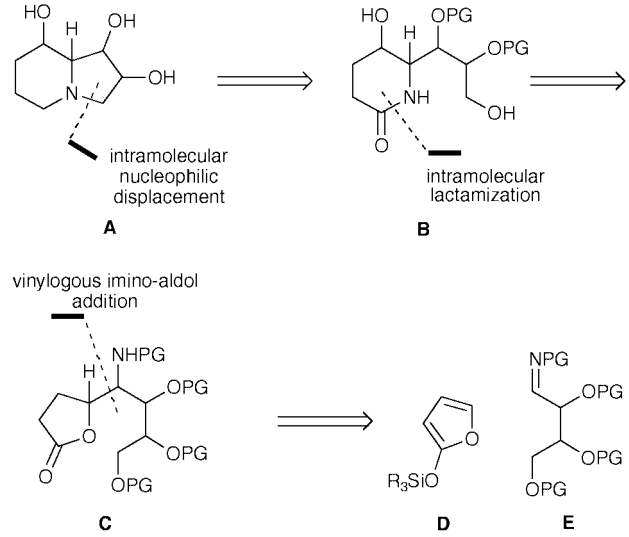
Chiral silyloxy pyrrole **42** was first prepared by a conventional enol-silylation protocol, and then reacted with 4-chlorobutanal. The lactam adduct **43** was obtained *via* a vinylogous aldol addition in the presence of boron trifluoride in a fairly good yield and useful diastereoselectivity (80% de). The major *syn* (*threo*)-configured isomer **43** was then *cis*-dihydroxylated to afford the densely functionalized intermediate **44**, which was eventually elaborated into 1,2,8-trihydroxyindolizidine **46** [(−)-8a-*epi*-swainsonine] *via* the multistep sequence shown.

Based on the chiral auxiliary principle, Royer recently completed total syntheses of both *threo* and *erythro* isomers of aza-muricatacin (*vide supra*) by exploiting, as the key move, a similar vinylogous aldolization maneuver.[15]

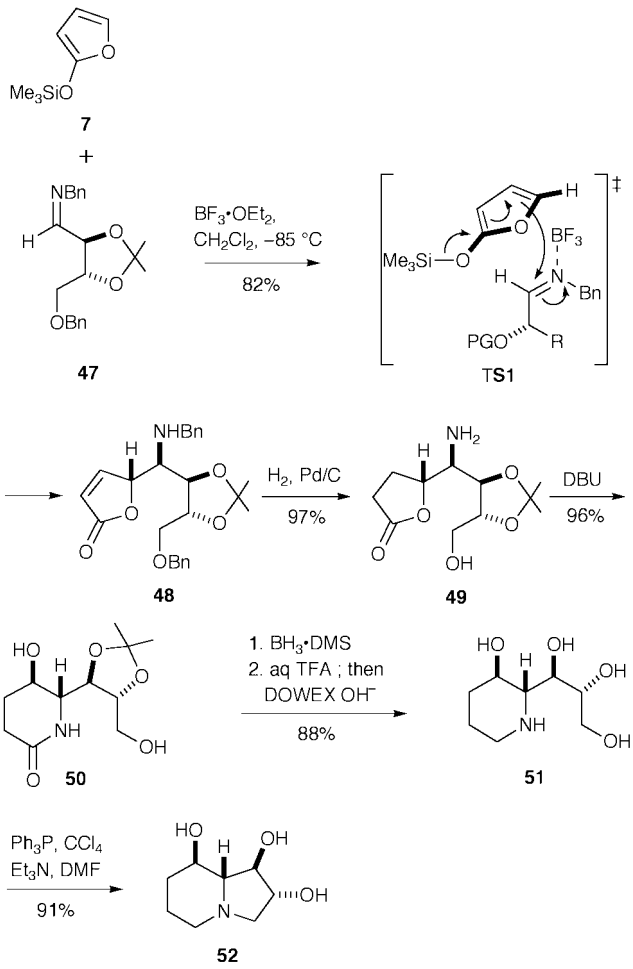
3.2 Vinylogous imino-aldol (Mannich-type) addition

Chiral nitrogen-containing compounds are widely encountered in Nature, and the nitrogen frames within these molecules are often recognized as having a decisive role in bioactivity. These constructs may be obtained from nonracemic imine precursors and enolate-derived synthons.[16] The diastereoselective synthesis of swainsonine congeners, executed by us in 1993, cleverly illustrates this strategy.[17] The plan is delineated in Scheme 13, and simply entails a vinylogous imino-aldol addition between the furan **D** and imine **E**, followed by γ-lactone to δ-lactam ring expansion giving **B**, and annulation to the swainsonine target **A**.

For the total synthesis of (−)-1-*epi*-swainsonine **52** (Scheme 14), the opening move was the vinylogous Mannich-type addition of 2-silyloxy furan **7** to the orthogonally protected D-threose *N*-benzylimine **47**. Here, the vinylogous imino-aldol reaction proved highly diastereoselective (BF_3 as the promoter) producing an 82% yield of a single, 4,5-*anti*-5,6-*anti* configured product **48**. Unlike the usual behaviour of the above discussed vinylogous aldol additions to aldehydes (Section 3.1), which invariably favour a *syn* (*threo*) simple diastereoselection, here, reversal of the stereochemistry occurs with an *anti* (*erythro*)



Scheme 13

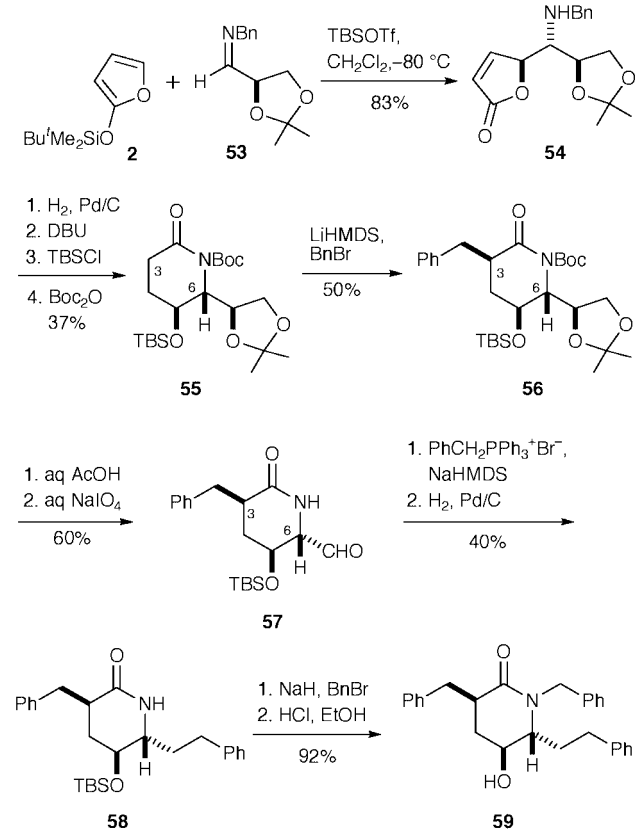


Scheme 14

adduct **48** almost exclusively being formed, possibly *via* an open-chain transition state **TS1**.

Exposure of **48** to catalytic hydrogen resulted in clean saturation of the double bond and concomitant removal of the *N*-benzyl protective groups. The amino-butanolide **49** so formed was then treated with DBU at reflux, allowing conversion of the γ-lactone **49** into the δ-lactam **50**. Carbonyl lactam reduction and deprotection gave polyhydroxylated piperidine **51**, which was finally cyclized to (−)-1-*epi*-swainsonine **52** by exposure to PPh_3–CCl_4–Et_3N reagent mixture in DMF. Overall, this synthesis comprises only six steps, with a good 61% overall yield.

The high potency of seven-membered cyclic urea-based compounds[18] and the recently introduced tetrahydropyrimidinone variants[19] against HIV-protease enzymes, stimulated our interest in planning a total synthesis of scantily investigated piperidinone mimics to evaluate a possible HIV-protease inhibitory action. As an example, we selected nonracemic piperidinone **59** as our synthetic target.[20] The proposed route (Scheme 15) uses the basic chemistry we employed to obtain the swainsonine congeners (*vide supra*), that is, vinylogous imino-aldol coupling and DBU-assisted γ-lactone to δ-lactam ring enlargement.



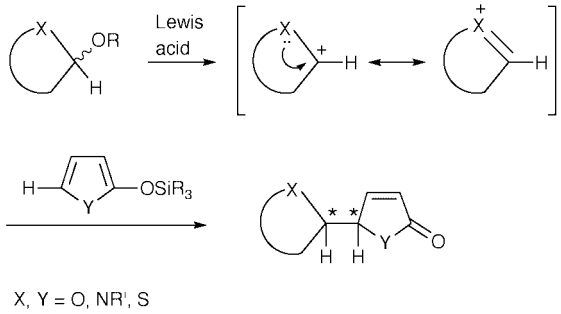
Scheme 15

Silyl triflate-catalyzed addition of TBSOF **2** to D-glyceraldehyde imine **53** gave, as expected, a high yield of the 4,5-*anti*-5,6-*anti* configured vinylogous Mannich adduct **54** (>90% de), which was converted to lactam **55** by hydrogenation, base-promoted ring expansion and protection. The requisite benzyl binding element at C3 was then installed by lactam enolate alkylation to provide piperidinone **56**, bearing an exocyclic protected glycerol unit at C6. Elaboration of the external glycerol unit into a phenylethyl moiety was achieved by simple chemistry involving oxidative fragmentation to aldehyde **57** and Wittig elongation to **58**. Benzylation of the free lactam nitrogen and removal of the silyl protective group finally afforded novel piperidinone **59**, endowed with many of the crucial binding elements and stereochemistry present in known clinically interesting HIV-protease inhibitors.

3.3 Vinylogous addition to cyclic heteroatom-stabilized carbenium ions

Cyclic oxonium species and nitrogen and sulfur analogues have long been recognized as excellent electrophilic synthons to be

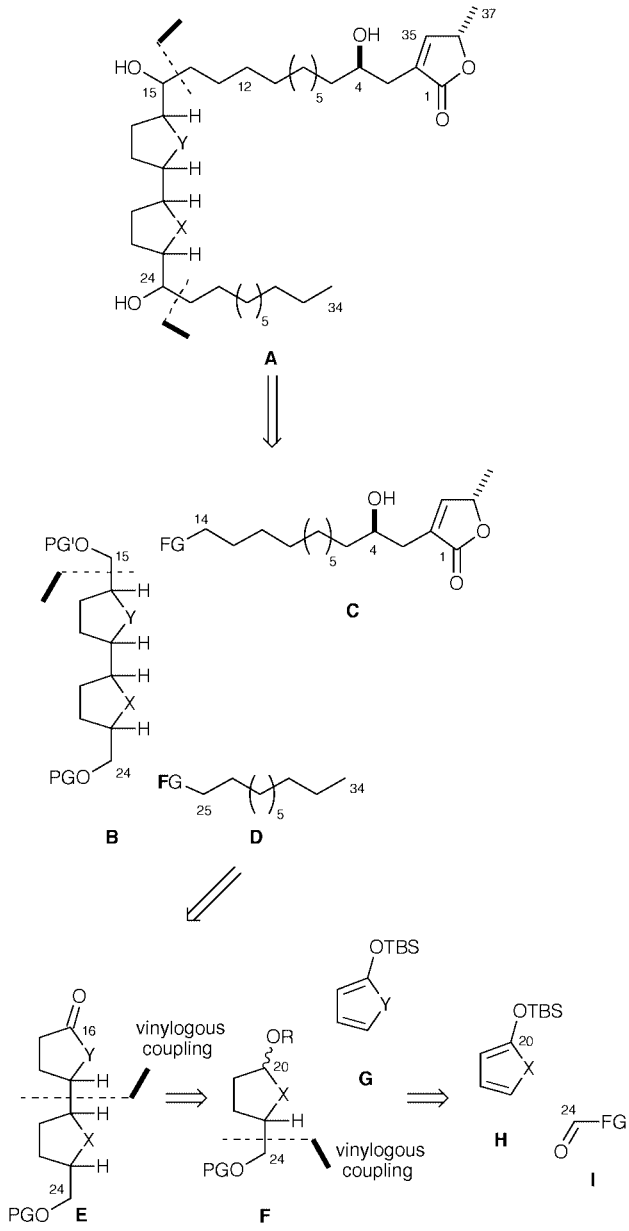
coupled to a variety of carbon nucleophiles, including the heterocyclic silyloxy dienes of this report (Scheme 16). This



Scheme 16

process—a sort of *C*-glycosylation—produces useful intermediates that can be eventually elaborated into a huge number of target constructs. The presence of two ternary heteroatom variables, X and Y, coupled with two stereocenters (binary variables) at the carbon–carbon juncture represents a special asset, *vis-à-vis* the issues of synthetic flexibility and diversity generation. To validate the basic concept of this synthetic tactic, we embarked on a wide programme aimed at the construction of the core motifs of annonaceous acetogenins and their heteroatom variants.

The relevance of the annonaceous acetogenins resides in their spectacular cytotoxicity against (*inter alia*) a wide range of human tumor cell lines, as well as *in vivo* antitumor activity against murine leukemias and human carcinoma implanted in athymic mice.[21] As shown retrosynthetically in Scheme 17,[22] disconnection of a generic C_{37} binuclear acetogenin **A** at the indicated bonds leads to three fragments: the α,ω-orthogonally protected C15–C24 core unit **B**, the C1–C14 butenolide frame **C** and the C25–C34 alkyl chain **D**. The core segment is easily traced to **E** by one-carbon elongation, while disconnection of **E** at the bond connecting the two heterocycles gives monocyclic lactol **F** and silyloxy diene **G**. Ultimately, **F** originates from vinylogous aldol coupling of silyloxy diene **H** and aldehyde **I**. Indeed, if viable with each member of the silyloxy diene triad (X, Y = O, NBoc, S), this technique ought to produce, at least in principle, 3^2 binuclear scaffolds of different heteroatom composition.

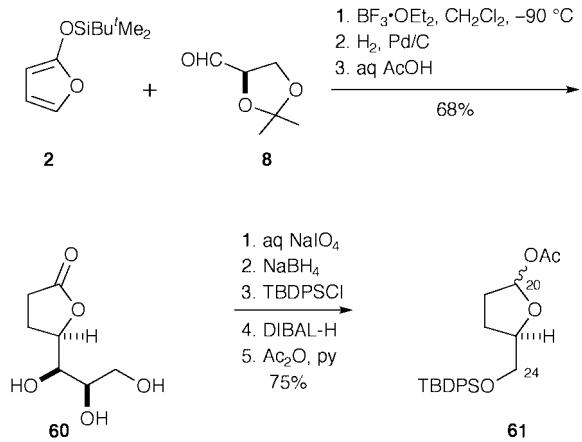


Scheme 17

As for the series {X = O, Y = O, NBoc, S}, this synthesis commenced with the vinylogous coupling between 2-silyloxy furan **2** and D-glyceraldehyde derivative **8** (Scheme 18). The aldol addition provided, after hydrogenation and deprotection, the seven-carbon butanolide **60**, which was quickly transformed to the C20–C24 key subunit **61** by two-carbon shortening. Lactol **61** gave rise to the six binuclear adducts **62**–**67** in Scheme 19, *via* parallel vinylogous additions involving oxygen, nitrogen, and sulfur silyloxy dienes **2**, **4** and **6**. Parallelling this basic chemistry, adaptation of this flexible methodology to the remaining two series {X = NBoc, Y = O, NBoc, S}, and {X = S, Y = O, NBoc, S} resulted in the completion of a repertoire of 18 scaffolds encompassing the core units of naturally occurring annonaceous acetogenins, as well as non-natural variants bearing pyrrolidine and thiolane nuclei.

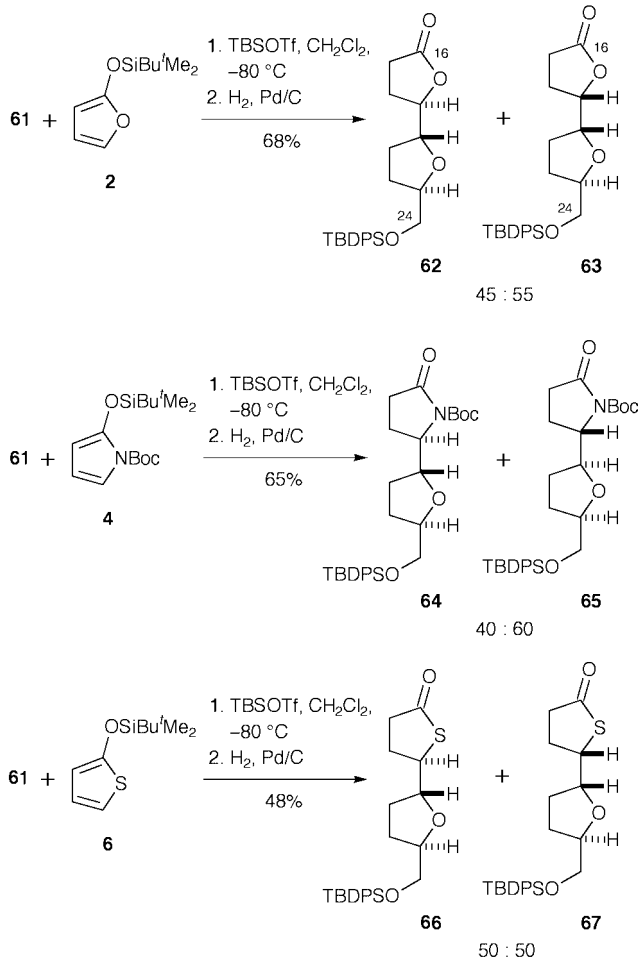
Figadère *et al.*[23] used a similar strategy to obtain oligotetrahydrofuranic lactones related to annonaceous acetogenins by exploiting 2-[(trimethylsilyl)oxy]furan **7** as the basic module. Here, the authors succeeded in the replicative construction of a series of trinuclear and tetranuclear THF-fragments equipped with diverse stereochemical arrangements.

In order to complete a synthesis of an annonacin A-type acetogenin, **74**, Hanessian and Grillo[24] required diastereoselective joining of L-glutamic acid-derived lactol **68** to 2-[(trimethylsilyl)oxy]furan **7** (Scheme 20). In this case, the 4*S*,5*S*-*threo* adduct **69** was preferentially formed, accompanied



Scheme 18

by minor amounts of its 4*R*-epimer. For the major isomer, a Diels–Alder-like *exo* approach, **TS1**, can be postulated, accounting for the observed 4,5-*threo* stereocontrol. The facial



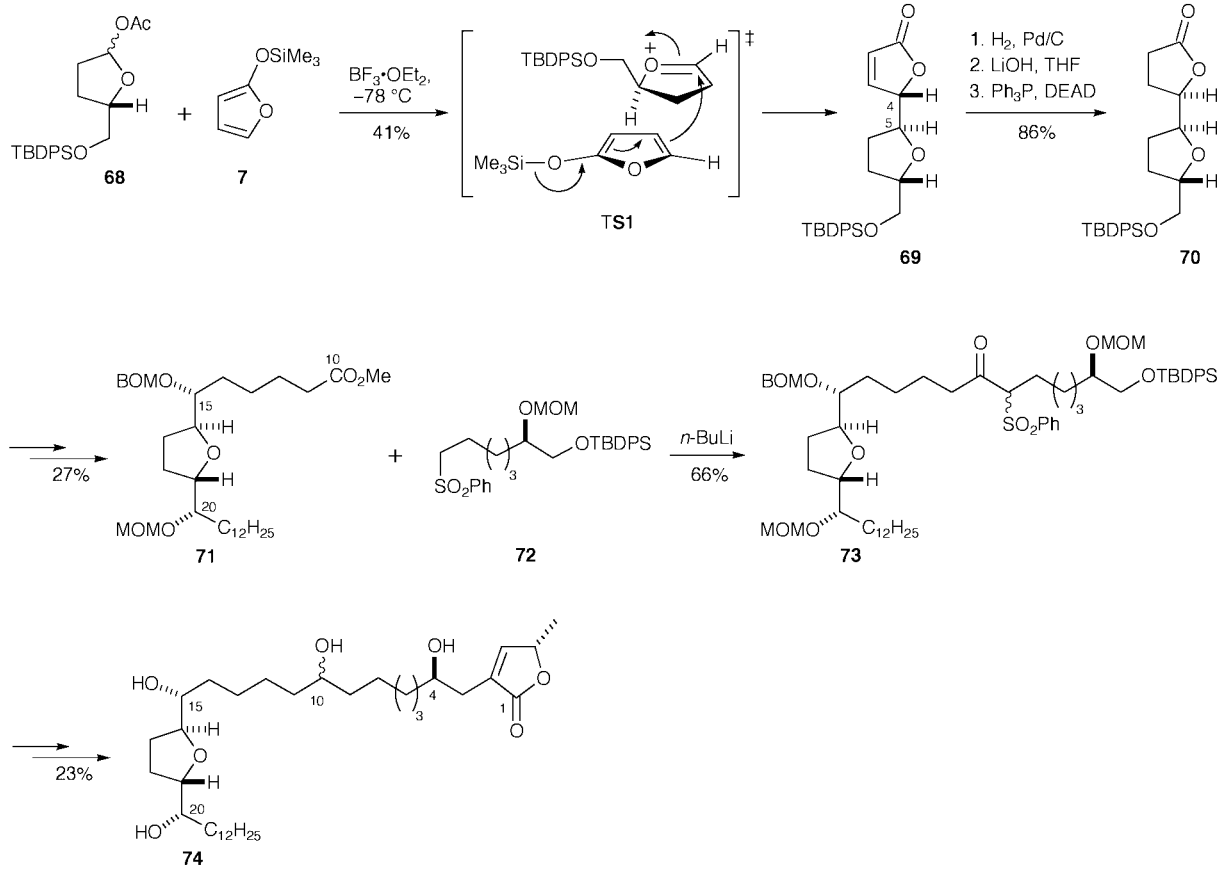
Scheme 19

selectivity could be dictated by the hydroxymethyl appendage of the oxonium species generated from **68**, with the nucleophile approaching the less encumbered α-face of the acceptor. After adjustment of the C4 chirality, lactone **69** was cleanly elaborated to the 2,6-disubstituted tetrahydrofuran segment **71**, encompassing the C10–C32 frame of the acetogenin target **74**. The butenolide frame at the right-hand side of the molecule was finally installed onto **71** by a clever multistep sequence where *S*-lactaldehyde was used as the source of the chiral unsaturated γ-lactone terminal.

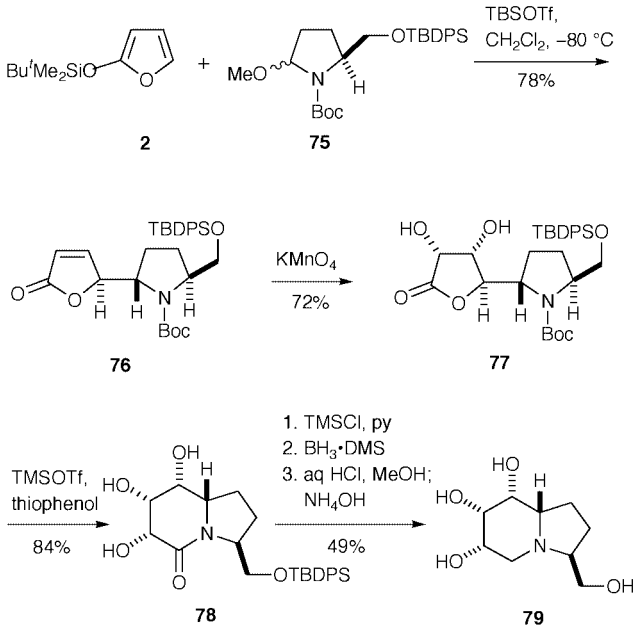
It is fitting to conclude this section on the use of heteroatom-stabilized carbenium ions with the discussion of two examples highlighting the vinylogous Mannich addition of 2-silyloxyfurans to five-membered cyclic iminium acceptors.[25] The first example is the total synthesis of the uncommon alkaloid 1,2-dideoxy-6,7-dihydroxyhomoaustraline **79** (Scheme 21), recently completed in our laboratories.[26] The key intermediary scaffold **76** was constructed by TBSOTf-catalyzed Mannich addition between 2-[(*tert*-butyldimethylsilyl)oxy]furan **2** and the nonracemic hemiaminal **75**.

Two additional hydroxy functions were then installed by selective *cis,anti*-dihydroxylation of the double bond within **76**, to afford **77** as a single reaction component. Removal of the *N*-Boc protective group cleanly ensured spontaneous intramolecular δ-lactam formation to indolizidinone **78**, which was finally elaborated to homoaustraline **79** by carbonyl reduction and silyl deprotection.

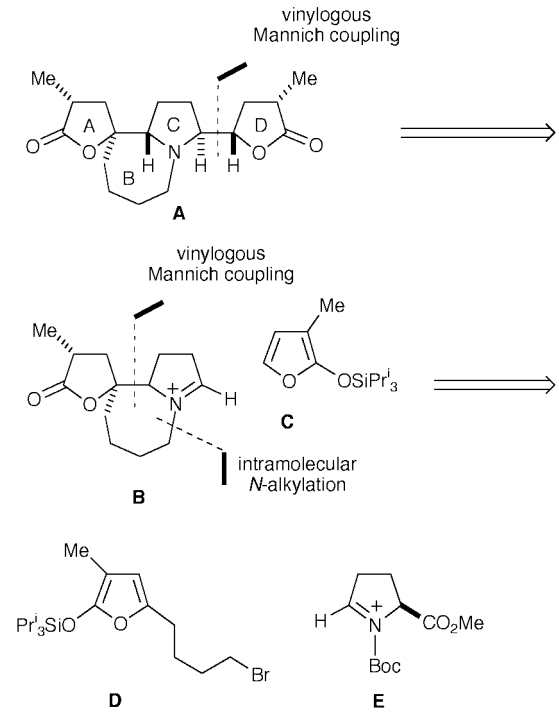
The last, brilliant synthesis targets the alkaloidal metabolite (+)-croomine **86**, a complex molecule extracted from plants belonging to the Stemonaceae family. The analysis of the alkaloid by Martin and Barr is portrayed in Scheme 22.[27] The plan emphasizes two sequential vinylogous Mannich couplings involving two 2-silyloxyfuran modules, **C** and **D**, and two iminium species, **B** and **E**. In fact, the unique structure of croomine, featuring three adjacently linked five-membered heterocycles—a pyrrolidine core flanked by two 3-methyl-



Scheme 20



Scheme 21



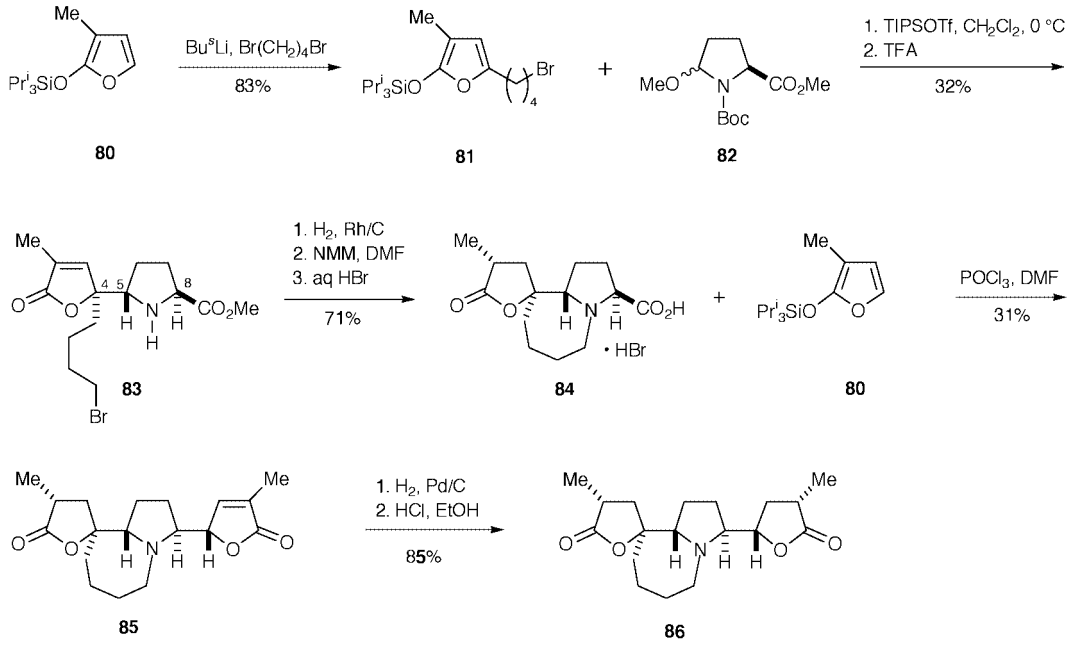
Scheme 22

furan-2-one moieties—seems to be created *ad hoc* to exalt the synthetic potentiality of silyloxy diene-based chemistry.

The synthesis began with alkylation of silyloxyfuran **80** to give the bromo-derivative **81** (Scheme 23). Next, the first Mannich addition was carried out using the hemiaminal **82** as the iminium source, to afford the binuclear proline derivative **83** with a spectacular margin of diastereoselection, favouring a 4,5-*threo*-5,8-*trans* relative stereodisposition. The seven-membered ring within the croomine precursor **84** was assembled by intramolecular bromine nucleophilic displacement by the free pyrrolidine nitrogen. Intermediate **84** then underwent a second vinylogous Mannich addition using the same silyloxyfuran precursor **80**. Exposure of **84** to $POCl_3$ in DMF resulted in decarboxylation, with formation of a transient iminium ion, which was trapped *in situ* by enoxysilane **80** to afford the tetranuclear construct **85** with acceptable diastereoselectivity. The synthesis ended with stereoselective hydrogenation delivering (+)-croomine **86**, which was identical in all respects to the natural compound.

4 Conclusions and perspectives

The vinylogous aldol addition has numerous applications, and the use of 2-silyloxy dienes as the reacting nucleophiles makes this reaction particularly apt for generating molecular diversity during synthesis. The examples illustrated herein only partially cover the entire work exploiting heterocyclic silyloxy dienes which can be found disseminated in the literature of the last decade.[3] The major contribution concerns the asymmetric synthesis based on the chiron concept, *i.e.* the use of nonracemic aldehyde, imine, and cyclic *O,O*- and *N,O*-acetal precursors derived from the chiral pool. Scarce attention has been paid to additions involving ketones, epoxides and Michael-type acceptors, as well as to the true catalytic executions of the basic vinylogous reaction. We hope to see this Lewis acid-assisted vinylogous aldolization involving silyloxy dienes both adapted to new acceptor and donor components, and applied to the



Scheme 23

chemical synthesis of important, chiral nonracemic targets of growing structural complexity.

5 Acknowledgements

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