Pure Appl. Chem., Vol. 72, No. 9, pp. 1645–1648, 2000.

Vinylogous aldol reaction of heterocyclic silyloxy dienes. Application in synthesis*

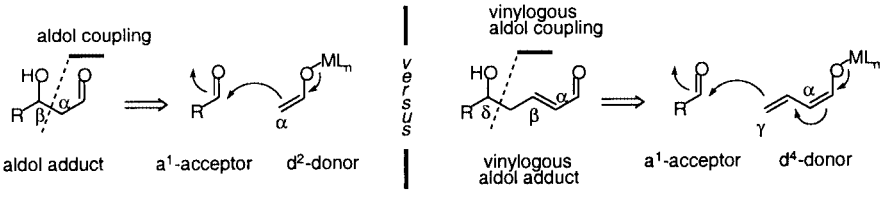
Giovanni Casiraghi†, Franca Zanardi, and Gloria Rassu

Dipartimento Farmaceutico dell'Università, I-43100 Parma, Italy and Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici del CNR, I-07100 Sassari, Italy

Abstract: A versatile, readily accessible triad of 2-enoxy silane synthons derived from furan, pyrrole, and thiophene is presented. These heterocycles, in reacting with carbonyl and carbonyl-related acceptors, act as vinylogous nucleophile modules, giving rise to diverse, functionality-rich, γ-substituted α,β-unsaturated carbonyl constructs. These, in turn, are invaluable platforms onto which further functional elements and chirality may be introduced. A couple of appealing applications—the variable construction of a repertoire of carbasugars and a library of annonaceous acetogenin segments—have been chosen to illustrate the viability of this vinylogous aldol approach.

INTRODUCTION

Vinylogy, the transmission of electronic effects through a conjugate system, thoroughly permeates organic and bioorganic chemistry with a number of synthetic and biosynthetic events being guided by this concept. Owing to the intrinsic polar nature of its mechanism, the aldol reaction—a cornerstone of synthetic and biosynthetic organic chemistry—is a prime candidate for vinylogous extension. In the vinylogous version of this construction (Scheme 1), a carbonyl framework is connected to the γ-carbon of a dienolate synthon, generating a vinylogous aldol motif (i.e., a δ-hydroxy-α,β-unsaturated carbonyl structure). Here, the precious functionality of the common aldols is flanked by a reactive conjugated double bond, which can easily undergo further manipulation. Thus, the remarkable increase in educt complexity qualifies the vinylogous aldol reaction and its close variants (imino-aldol, Mannich, nitro-aldol, etc.) as strategic maneuvers in the multistep synthesis of a variety of functional molecular frameworks and targets [1].

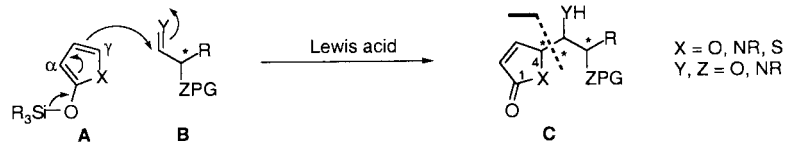


Scheme 1

*Lecture presented at the 13th International Conference on Organic Synthesis (ICOS-13), Warsaw, Poland, 1–5 July 2000. Other presentations are published in this issue, pp. 1577–1797.

†Corresponding author

Decisive evolution of the aldol addition has been pioneered by Mukaiyama, who first found that stable enoxy silanes quickly react with carbonyl acceptors in the presence of Lewis acids to give aldol and aldol-related products. The aim of this account is to highlight the merits of the vinylogous version of this basic process, as applied to a unique triad of vinylogous enoxy silane synthons, the five-membered heterocycles denoted as **A** in Scheme 2.



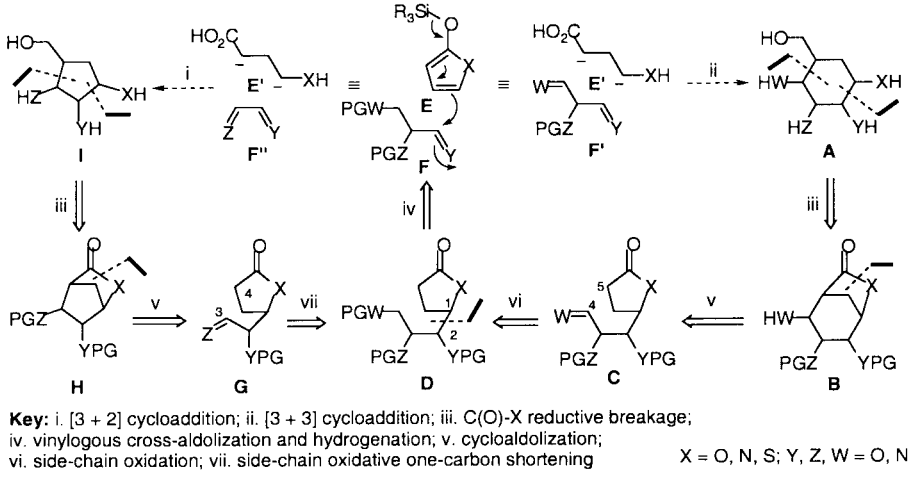
Scheme 2

Here, densely functionalized adducts of type **C** are simply traced to **A** (a d^4 donor) and **B** (an a^1 acceptor) via the regio- and stereoselective vinylogous Mukaiyama aldolization. The wide assortment of variables within the donor and acceptor molecules, the high functionalization potential of carbons 1–4 within **C**, and the flexibility with which chirality can be established, imply that, at least in theory, a wide assortment of natural and synthetic compounds may be assembled by adopting this chemistry. In truth, the heterocyclic enoxy silanes in this account did not fall short of our expectations, and their use in vinylogous aldolization has evolved into an elegant platform for notable ventures in organic synthesis [2].

APPLICATION IN SYNTHESIS

Carbasugars and relatives

Carbasugars, also known as pseudo-sugars, are a family of sugar analogs that are currently attracting great interest among organic and medicinal chemists. Owing to close topological resemblance to the parent furanoses and pyranoses (the sugar ring oxygen is here replaced by a methylene), it is not surprising that their basic biological function may be attributed to the inhibition of glycoside processing enzymes.

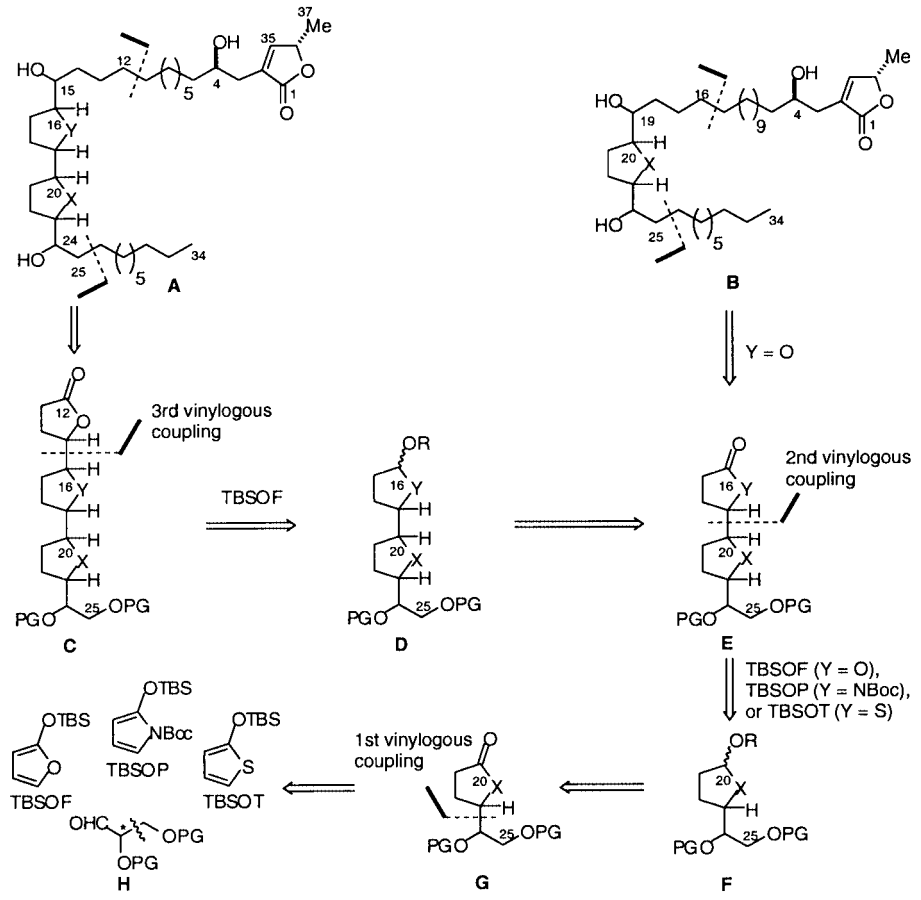


Scheme 3

To access the carbasugar constructs of both 5a and 4a ring structures, we addressed the flexible retrosynthetic plan contemplated in Scheme 3, where carbapyranoses **A** or carbafuranoses **I** were assembled by conjoining two complementary subunits, the butyric acid-based α,γ-dianion **E'** and malondialdehyde- **F'** or glyoxal-related fragment **F"**. Here, two common retrons, the enoxy silane **E** and the chiral glyceraldehyde-related unit **F,** are envisioned as synthetic equivalents of dianion **E'** and dialdehydes **F'** or **F"**, respectively. The route we hoped to pursue involves formation of the divergent intermediary adduct **D** via implementation of the C1–C2 juncture before the annulation processes (**C** → **B** or **G** → **H**; C4-C5 or C3–C4 junctures), which ultimately produce pseudopyranoses **A** or pseudofuranoses **I**. Two formal [3+3] or [3+2] cycloadditive maneuvers featuring a sequential vinylogous cross aldolization-cycloaldolization protocol are central to these constructions. This project was then put into practice in the form of stereocontrolled synthesis of a diverse repertoire of chiral, nonracemic carbasugars, including pseudo-β-D-gulopyranose, pseudo-β-D-xylofuranose, 1-deoxy-1-amino-pseudo-β-D-gulopyranose, and 1-deoxy-1-amino-pseudo-β-D-xylofuranose.

Annonaceous acetogenins and variants thereof

The annonaceous acetogenins are a class of C_{35} or C_{37} plant metabolites isolated, as to date, only from the archaic family of the *Annonaceae*. The relevance of this compound class mainly resides in their spectacular citotoxicity against a variety of human tumor cell lines, as well as antitumor activity.



Scheme 4

The structural hallmark of the majority of annonaceous acetogenins is an oxygenated core consisting of one or two adjacent tetrahydrofuran rings, carrying two alkyl chains. The synthesis of these chiral constructs and their analogs provides a challenging application for the vinylogous aldolization using the heterocyclic silyl dienol ethers of this report. As shown in the plan delineated in Scheme 4, disconnection of the generic C_{37} binuclear acetogenin **A** along the bonds C11–C12 and C25–C26 defines the subtarget lactone **C** as the basic scaffold of the C12–C25 core backbone, which contains the two adjacently linked heterocycles. Attachment of the methyl butenolide frame and the saturated aliphatic chain at the north and south orthogonally masked termini (or vice-versa) guarantees formation of the acetogenin targets. Installation of the lactone moiety within **C** may arise via a vinylogous juncture of the silyloxy furan TBSOF to the "anomeric" carbon of the binuclear intermediate **D**. The C16–C25 unit **D**, in turn, originates from **E**, an intermediate common to the synthesis of mononuclear annonaceous acetogenins of type **B**. Disconnection of **E** along the bond C19–C20 reveals the mononuclear lactol-type synthon **F**, which, in the forward sense, leads to **E** via vinylogous coupling with one of the three silyloxy diene heterocycles TBSOF, TBSOP, or TBSOT. Lactol **F** readily traces back to **G**, which may derive from the vinylogous Mukaiyama aldol addition between glyceraldehyde **H** and one of the silyloxy diene modules already mentioned.

On the whole, this synthesis, which exploits a readily available triad of four-carbon modules and uses a uniform and reiterative chemistry, outlines the stepwise elongation of the easily accessible three-carbon "chiron" **H** via three sequential vinylogous additions. The choice of the heteroatoms combined in the first and the second vinylogous aldol couplings, the chirality of the chosen aldehyde starter **H** (*R* vs *S*) and the chirality transmittal during the molecular growth (*erythro* vs *threo*, *cis* vs *trans*) all ensure the generation of ample chemical diversity during this synthesis.

The realization of this uniformed plan allowed us to assemble a library of advanced bis-tetrahydrofuran, pyrrolidine, and thiolane scaffolds encompassing the core portion of a variety of annonaceous acetogenins and their nitrogen and sulfur analogs. In practice, the utility of this construction was demonstrated by the preparation of eight bis-tetrahydrofuran units, two bis-pyrrolidine units, and four bis-thiolane units of type **C**, along with a number of intermediary subunits of type **E**.

CONCLUSION

Here, the vinylogy concept perceived by Claisen more than 70 years ago [3], has been adapted to the aldol reaction and has set the foundations for the heterocyclic dienoxy silanes to become an emblematic and valuable reactant ensemble. For reasons of concision, the synthetic examples illustrated herein have been somewhat limited, and thus the reader might not be able to fully savor this chemistry. Nonetheless, several recent articles, extensively covering this subject matter, are available (ref. 2). On the whole, although much progress has been made by us and other groups over the past ten years, it can be seen that the major contribution has come from asymmetric syntheses based on the chiron concept. Instead, the catalytic asymmetric executions of this vinylogous aldolization, as well as the vinylogous additions to Michael acceptors (a rare example of a double vinylogous reaction), remain only marginally explored.

In the years to come, we hope to see this vinylogous aldolization involving 2-silyloxy dienes being both exploited by an ever-growing number of organic synthesis practitioners, and applied to the chemical synthesis of increasingly important constructs.

REFERENCES

1. G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu. *Chem. Rev.* **100**, 1929–1972 (2000).
2. G. Rassu, F. Zanardi, L. Battistini, G. Casiraghi. *Chem. Soc. Rev.* **29**, 109–118 (2000).
3. L. Claisen. *Ber.* **59**, 144–153 (1926).