

Catalytic, Asymmetric Hypervinylogous Mukaiyama Aldol Reactions of Extended Furan-Based Silyl Enolates

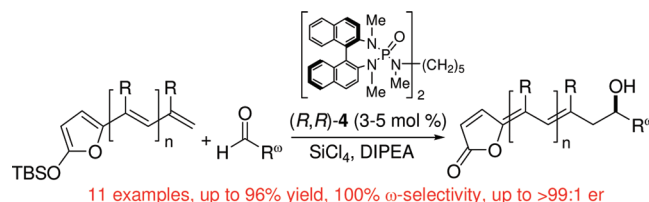
Claudio Curti,^{*,†} Lucia Battistini,[†] Andrea Sartori,[†] Alessio Lodola,[†] Marco Mor,[†]
Gloria Rassu,[‡] Giorgio Pelosi,[§] Franca Zanardi,[†] and Giovanni Casiraghi^{*,†}

Dipartimento Farmaceutico, Università degli Studi di Parma, Parco Area delle Scienze 27A,
I-43124 Parma, Italy, Istituto di Chimica Biomolecolare del CNR, Traversa La Crucca 3,
I-07100 Li Punti, Sassari, Italy, and Dipartimento di Chimica Generale ed Inorganica,
Chimica Analitica, Chimica Fisica, Università degli Studi di Parma,
Parco Area delle Scienze 17A, I-43124 Parma, Italy

claudio.curti@unipr.it; giovanni.casiraghi@unipr.it

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ABSTRACT



Virtually perfect transmittal of the enolate reactivity up to five conjugated double bonds from the origin allows a series of furan-based silyloxypolyenes to add to aldehyde carbonyls at the most distant point of the molecule. Denmark's axially chiral bisphosphoramidate/SiCl₄ combination catalyzes these scantily precedented, long-range Mukaiyama-type vinylogous aldol reactions efficiently, providing a palette of extended γ -alkylidene butenolide carbinols with complete ω -site selectivity and good to excellent levels of enantioselectivity.

Since Fuson, 76 years ago,¹ limpidly formulated the principle of vinylogy, much progress has been made in this area, including the development of the vinylogous extensions of several enabling carbon–carbon bond-forming reactions. Thus, for example, the aldol reaction-based

technology, whose utility in assembling acetate- or propionate-derived polyketide arrays is amply documented,² has been adapted to a vinylogous extension, providing a reliable construction tool, with which high levels of expediency and atom efficiency were attained.^{3,4} Used originally to forge α,β -unsaturated δ -hydroxycarbonyls, the majority of studies in this field have focused on single vinylogous aldol techniques, leaving the application of more extended adaptations, giving densely unsaturated remote hydroxycarbonyls, substantially unexplored. Rare examples include the development of catalytic, asymmetric bisvinylogous Mukaiyama aldol reactions of sorbic acid derived, open-chain silyloxytriene nucleophiles by List et al.⁵ and Denmark et al.,⁶ the ZnCl₂-promoted, doubly vinylogous aldol additions to acetals by Wilk et al.,⁷ and the elegant phenylogous aldolization and cycloaldolization reactions by Jacobi

[†] Dipartimento Farmaceutico, Università degli Studi di Parma.

[‡] Istituto di Chimica Biomolecolare del CNR, Sassari.

[§] Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, Università degli Studi di Parma.

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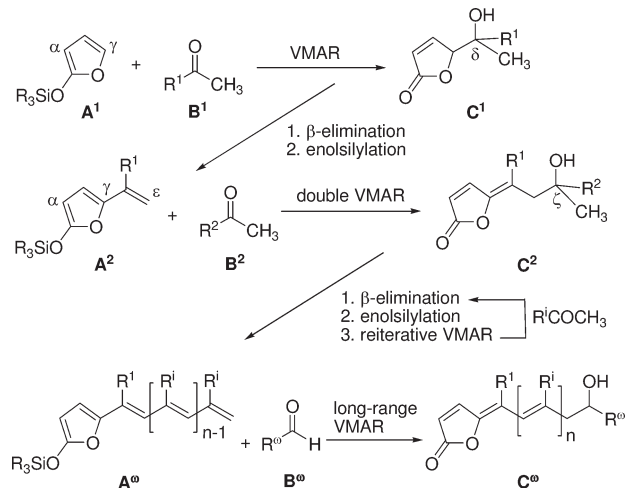
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Scheme 1. Single, Double, and Long-Range Vinylogous Mukaiyama Aldol Reaction (VMAR) Trail of Furan-Based Silicon Enolates with Generic Carbonyl Acceptors

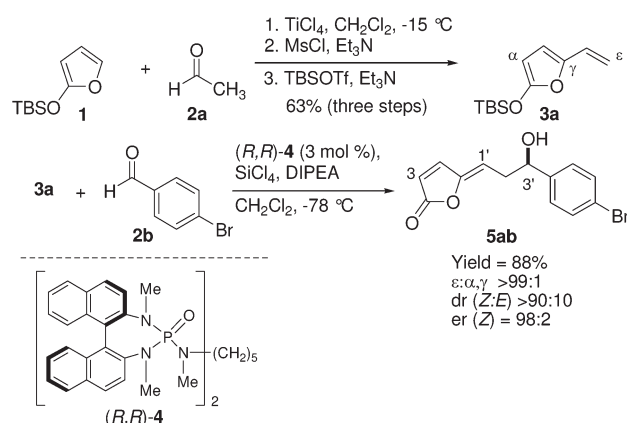


et al.^{8,9} Scheme 1 visualizes a vinylogous Mukaiyama aldol reaction (VMAR) trail, as applied to elongation of furan-based silicon enolate homologues, a compound progeny whose common origin is the popular 2-trialkylsilyloxyfuran nucleophile **A**¹. Specifically, in the initial stage, a VMAR coupling of dienoxysilane **A**¹ to methyl carbonyl **B**¹ produces δ -hydroxycarbonyl **C**¹, which can be elaborated to trienoxyasilane **A**² via β -elimination and enolsilylation. Reiteration of this maneuver using donor **A**² and acceptor **B**² enables the polyene chain to grow to arrive at $\alpha,\beta,\gamma,\delta$ -unsaturated ζ -hydroxycarbonyl **C**², the fruit of a double VMAR. Further, n -time iteration of the elimination–enolization–VMAR sequence then furnishes polyenolate **A** ^{ω} , which is finally coupled to a stopper carbonyl **B** ^{ω} terminating the chain growth, and forming the polyene ω -hydroxycarbonyl **C** ^{ω} , which can be viewed as a sort of hyperextended aldol. This assemblage, predicated on multiple execution of VMAR elongation stages, follows a reiterative pattern in a sequence reminiscent of the iterative homologation observed in biosynthetic polyketide assembly.² As a proof of concept, this paper reports, for the first time, the execution of this synthetic proposal, aiming at the following goals: (i) to find the conditions for an efficient, catalytic asymmetric double VMAR to be established; (ii) to validate the asymmetric reaction protocol with diverse donor and acceptor components; and (iii) to adapt the procedure for assembling hyperextended chiral nonracemic ω -hydroxyvinylene butenolides and to explore whether the reactivity of the enolate homologues could propagate along a long-range conjugated vinylene system.

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(9) Of note, extended conjugated systems have been used also as vinylogous acceptors in 1,6-asymmetric additions. For a recent example, see: Murphy, J. J.; Quintard, A.; McArdle, P.; Alexakis, A.; Stephens, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 5095.

Scheme 2. Preparation of Furan Silyloxytriene **3a** and Its Asymmetric Double VMAR Coupling to Aldehyde **2b**



Initial studies focused on the asymmetric double VMAR of 5-vinyl silyloxyfuran model **3a**, which was in turn obtained from easily accessible 2-*tert*-butyldimethylsilyloxyfuran (**1**) and acetaldehyde (**2a**) via sequential VMAR, β -elimination, and silylenolization as shown in Scheme 2. Remarkably, the reaction between **3a** and 4-bromobenzaldehyde (**2b**), carried out in the presence of the Denmark's bisphosphoramidate (*R,R*)-**4** (3.0 mol %), SiCl_4 (1.1 equiv), and DIPEA (10 mol %) in CH_2Cl_2 at -78°C , performed efficiently, and the desired 5-(3'-hydroxyalkylidene)butenolide **5ab** was obtained as a single ε -regioisomer, in 88% isolated yield, >90:10 *Z/E* diastereoselectivity, and 98:2 er (96% ee) for the 3'-*R*-configured isomer.

The choice of the specific catalyst system, which was earlier discovered and exploited by Denmark in the late 1990s,¹⁰ originated from the ability of this chiral Lewis base–Lewis acid combination to propel similar aldol and vinylogous aldol transformations with superior levels of chemical and stereochemical efficiency.^{11,12}

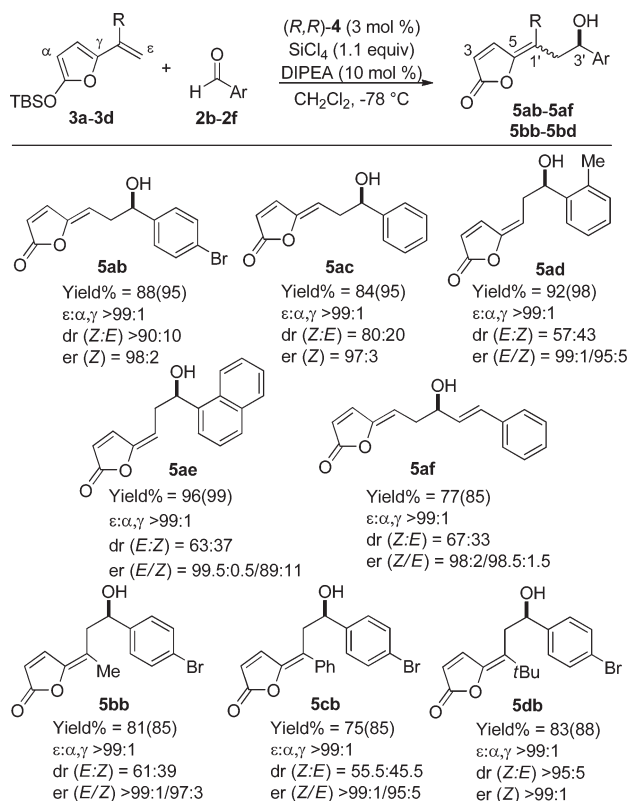
With conditions for an efficient, asymmetric double VMAR established, we sought to explore the scope of the reaction with respect to the nature of both the electrophilic and nucleophilic components (Scheme 3). Invariably, neutral, electron-rich, and electron-poor aromatic aldehydes proved to be excellent substrates, which afforded the expected bisvinylogous aldols **5ab**–**5ae** in high yields, with complete ε -site selectivities and with excellent enantioselectivities in the range 97:3/99:1 er. As for aromatic aldehydes, cinnamaldehyde **2f** still enabled the reaction to occur with

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(11) Denmark, S. E.; Heemstra, J. R., Jr. *J. Org. Chem.* **2007**, *72*, 5668 and references therein.

(12) (a) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428. (b) Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011.

(13) Aliphatic representatives such as 2-methylpropanal and cyclohexanal proved reluctant to react, with marginal production of the respective aldol products.

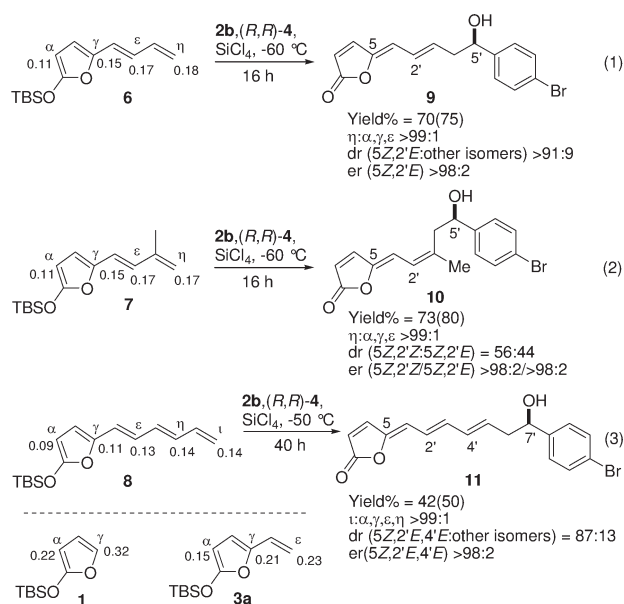
Scheme 3. Scope of the Catalytic, Asymmetric Double VMAR^a

^aAll reactions were carried out using 100 mg of nucleophile **3**, 1.1 equiv of aldehyde **2**, 3.0 mol % (R,R) -**4**, 1.1 equiv of SiCl_4 , 10 mol % DIPEA in CH_2Cl_2 (0.1 M) at -78°C for 12 h. Yields refer to isolated products (conversions in parentheses); dr determined by ^1H NMR analysis; er determined by HPLC on chiral stationary phases (see the SI).

great stereocontrol (>98:2 er), furnishing the expected aldol adducts **5af** in a good isolated yield.¹³

We further determined the scope of the reaction with respect to the nucleophile, using 4-bromobenzaldehyde (**2b**) as a probe (Scheme 3, compounds **5ab**, **5bb**, **5cb**, and **5db**). The reaction was notably successful with both unsubstituted and substituted trienoxy furans **3a** ($R = \text{H}$), **3b** ($R = \text{Me}$), and **3c** ($R = \text{Ph}$), and even with highly demanding *tert*-butyl substituted furan **3d** ($R = t\text{-Bu}$). The structure could be varied, and good yields, complete ϵ -site selectivities, and excellent enantioselectivities were attained in all cases. Remarkably, both the nature of the R group in the nucleophile and the electronic properties and steric demand of the aromatic rings in the electrophiles impacted the geometry of the newly formed double bond connecting the butenolide ring. While good *Z*-selectivity was attained for **5ab** and **5ac** ($R = \text{H}$), the geometrical selectivity was eroded for **5ad**, **5ae**, **5af**, **5bb**, and **5cb**, where slightly unbalanced mixtures of *Z*- and *E*-isomers were obtained. However, for **5db** carrying a bulky substituent at the C1'-position ($R = t\text{-Bu}$), reversal of the double-bond

(14) Due to CIP nomenclature change in the priority of the exocyclic double bond substituents, **5ab**–**5af**, **5cb**, and **5db** have the same *Z* configuration but opposite location of the double-bond substituents.

Scheme 4. HVMAR of Extended Silyloxyfuran Nucleophiles **6–8**, and Related Atomic Fukui Indices^a

^aAll reactions were carried out using 100 mg nucleophile **6**, **7** or **8**, 1.5 equiv aldehyde **2b**, 5.0 mol % (R,R) -**4**, 1.1 equiv SiCl_4 , 10 mol % DIPEA in CH_2Cl_2 (0.1 M). Yields refer to combined isolated products (conversions in parentheses); dr determined by ^1H NMR analysis; er values were determined by conversion of the carbinols into the corresponding (–)-menthyloxycarbonyl derivatives and subsequent ^1H NMR analysis (see the SI).

geometry was manifested, and the *Z*-configured isomer solely formed.^{14,15}

Having documented the scope of the double VMAR with respect to the donor and acceptor components and validated their efficiency in terms of yields, regiocontrol, and enantiocontrol, subsequent studies focused upon demonstrating the challenging, yet unprecedented, hypervinylogous aldol strategy (HVMAR), as applied to three prototypical polyene nucleophiles namely, the silyloxy tetraenes **6** and **7**, and the silyloxy pentaene **8**, using the optimized double VMAR conditions developed with silyloxytrienes **3a–3d** (Scheme 4).

A matter of concern with the elongated reactants **6–8** might be the concomitant activation of more than one nucleophilic site in the molecule, the α,γ,ϵ , and η positions for tetraenes **6** and **7** and the $\alpha,\gamma,\epsilon,\eta$, and ι positions for pentaene **8**. To support the rationale for a favored activation of the most remote site of the chain, density functional theory (DFT) and Fukui function calculations were performed,¹⁶ paralleling the recent study by List and co-workers with open-chain silyloxydiene and triene compounds.⁵

(15) The complete *Z*-selectivity of compound **5db** with respect to **5bb** and **5cb** could not be easily rationalized by simply assuming a preferred *s*-cis conformation of nucleophile **3d** in the transition state; in fact, internal energy calculations revealed that *s*-trans conformers of **3a–3d** scaffolds are the most stable (see Table S2 in the SI). Probably, concurrence of both steric and electronic issues related to the *t*-Bu group determines the diastereocontrol.

(16) For a detailed description of DFT and Fukui index calculations, see the SI.

Atomic Fukui indices¹⁶ at the carbon atoms of the reacting polyenes **6–8** (see figures on the structures in Scheme 4) were in line with the data obtained by List, foreseeing a preferential electrophilic attack of the aldehydes at the terminal carbon atom of the silyloxy nucleophiles. As for simple furan **1** and the related bisvinyllogous furan candidate **3a** above disclosed, for which exclusive attack at the most distant point has been validated, the calculations for higher homologues **6–8** also point to the terminal positions as the most reactive sites, though the values of the competing nucleophilic positions are more leveled as compared to **3a**. Interestingly, as the polyene chain grows in length, the Fukui indices of the terminal methylenes decrease in the series, a possible foreshadowing of a decreased reactivity of these very remote sites. However, other issues could impact the practicality and selectivity of the reactions, including the diverse steric congestion of the competing nucleophilic sites of the donors, the nature of the acceptors, and the mutual, often unpredictable disposition of the reactants and catalyst in the transition states.

Encouraged by the computational results, we turned our attention toward finding the experimental proof of the concept. In practice, under our optimized conditions, HVMAR between tetraene **6** and brominated aldehyde **2b** was shown to work well and, as was our hope and as predicted by DFT calculations, θ -hydroxylated butenolide **9** formed in acceptable yield and with complete η -site selectivity, as a mixture of geometrical isomers in which the *5Z,2'E* isomer highly predominated (>91:9 dr). Remarkably, the enantioselectivity proved very good (>98:2 er) as demonstrated by HPLC and ¹H NMR analyses of the corresponding (–)-menthyloxycarbonyl derivative;¹⁷ this highlights once more the superior ability of Denmark's catalyst system even with these elongated vinyl nucleophiles. Similarly, chiral catalyst (*R,R*)-**4**/SiCl₄ was successfully tried out with 3'-substituted tetraene **7** and the hyperextended pentaene **8**, in asymmetric HVMAR additions to **2b**. To our delight, the same reactivity and remarkable enantiocontrol were observed for methyl-substituted furan **7**, affording carbinol **10** in 73% isolated yield, which was obtained as a 56:44 mixture of *5Z/2'Z* and *5Z/2'E* isomers (>98:2 er for both).

Noteworthy, unsubstituted *all-trans* furan pentaene **8** also proved to be a pertinent partner, providing the expected hypervinyllogous aldol **11** cleanly with complete ι -site selectivity, while maintaining the excellent enantiocontrol exerted by its lower counterparts (>98:2 er). However, as predicated by our DFT studies, the reduced reactivity of extended substrate **8** required a higher reaction temperature and a prolonged reaction time for the process to be acceptably productive.

The geometry of all γ -alkylidene butenolide adducts in this study was firmly established as shown by direct

inspection of their high resolution 1D and 2D NMR spectra, including detailed ¹H–¹H NOESY experiments and proton coupling constant measurements.¹⁸ As for the assignment of the absolute configuration of the sole stereogenic carbon in the butenolide products, we assumed that all compounds were invariably *R*-configured as indicated, based on the experienced stereoreduction trend dictated by the chiral ligand in the catalyst, featuring a preferential attack of the incoming nucleophiles at the *Re*-face of the aldehyde carbonyls.^{10–12} To validate this assumption, derivatization of butenolide **5db** to the corresponding crystalline menthyl derivative allowed us to definitely confirm its three-dimensional disposition via single crystal X-ray analysis (Figure S1 in the Supporting Information (SI)). By assuming that the sense of stereocontrol exerted by the catalyst was the same for all the substrates, the *R*-absolute configuration for the remaining butenolide candidates in this study was assigned by analogy.¹⁹

To conclude, we have successfully developed a reliable catalytic, asymmetric bisvinyllogous and hypervinyllogous Mukaiyama-type aldol methodology using easily available extended furan-based silyloxy polyenes. We have demonstrated, for the first time, a perfect relay of the enolate reactivity over a distance of up to five conjugated double bonds and named this phenomenon “hypervinyllogy”. These novel extended and overextended aldolizations displayed excellent enantiocontrol (up to >99:1 er), complete selectivity at the most remote nucleophilic site of the substrates, and good to moderate control of the product geometries. Our findings contrast with the results obtained by List et al.⁵ with open-chain bisvinyllogous silyl nucleophiles, where variable mixtures of ϵ - and α -substituted adducts were formed. The extended enantioenriched polyene alcohols formed are rich in functionality and varied in shape, with a butenolide skeleton flanked by diverse conjugated double bonds, a chiral secondary hydroxyl, and several prochiral centers. This is a prelude for a number of significant skeletal transformations and challenging opportunity in asymmetric synthesis. Work is planned to address this goal.

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Supporting Information Available. Experimental procedures, characterization data, chiral HPLC traces, NMR spectra for new compounds, crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(17) For extended butenolides **9–11**, for which no conditions for direct measurement of the enantiomeric purity via chiral HPLC analysis were found, the er values were calculated indirectly via ¹H NMR and HPLC analyses of the corresponding (–)-menthyloxycarbonyl derivatives; see the SI for details.

(18) See the SI for details.

(19) A detailed ¹H NMR investigation on (–)-menthyloxycarbonyl derivatives of (*E*)-**5cb** and (*Z*)-**5cb** allowed us to argue that both candidates possess the same 3'*R*-configuration; see the SI for details. Thanks are due to a reviewer for bringing this issue to our attention.