Modular Approach toward the Construction of the Core Motifs of Annonaceous Acetogenins and Variants Thereof

Franca Zanardi,* Lucia Battistini, Gloria Rassu, Luigi Pinna, Marco Mor, Nicola Culeddu, and Giovanni Casiraghi*

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

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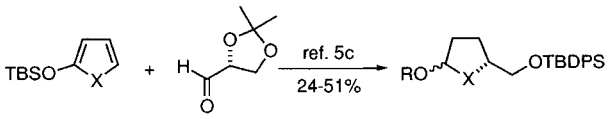
Adjacently linked tetrahydrofuran units constitute the core motifs of widely encountered naturally occurring compounds, as the acetogenins of the *Annonaceae*[1] and certain ionophore antibiotics.[2] The annonaceous acetogenins consist of polyoxygenated, long-chain fatty acids usually incorporating one or two tetrahydrofuran rings and are particularly attractive due to their extremely interesting pharmacological profiles and useful plant-protecting actions.[1]

Most of the recently introduced strategies toward acetogenin compounds have been addressed to the linear synthesis of structurally defined targets,[3] while the development of parallel, unified methodologies aimed at preparation of collections of structurally and stereochemically diverse acetogenin analogues has yet to meet such success.[4] Since molecular diversity represents a pivotal concern to access potentially bioactive candidates, we became interested in developing a unified, modular strategy that could possibly secure the construction of a series of oligotetrahydrofurans, as well as related nonnatural sulfur and nitrogen, homogeneous and mixed variants, en route to ensembles of annonaceous acetogenins and their altered congeners. We opted to investigate this domain by using the "silyloxy diene methodology",[5,6] a well experienced protocol based on the exploitation of a triad of oxygen-, sulfur-, and nitrogen-based heterocyclic silyloxy dienes, namely, 2-[(*tert*-butyldimethylsilyl)oxy]furan, TBSOF; 2-[(*tert*-butyldimethylsilyl)oxy]-thiophene, TBSOT; and *N*-(*tert*-butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole, TBSOP.

As part of this program, we report here the viability of the above project in a chiral, nonracemic domain, en route to a series of bis-tetrahydrofuran, bis-thiolane, and bis-pyrrolidine precursors, as well as a number of related mixed dinuclear templates derived from the combination of the three heteroatoms of choice, oxygen, sulfur, and nitrogen.

Scheme 1.



TBSOF: X = O
TBSOT: X = S
TBSOP: X = NBoc

1

2a: X = O; R = Ac
2b: X = S; R = Ac
2c: X = NBoc; R = Me

We first focused on the preparation of the key electrophilic modules **2a**−**c**, which were readily obtained in 51%, 24%, and 26% yields by starting from the respective precursors TBSOF, TBSOT, and TBSOP and 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) according to a previously reported, diastereoselective procedure (Scheme 1).[5c,7] Having the proper building blocks at hand, namely, the three electrophiles **2a**−**c** as well as the three silyloxy diene nucleophiles TBSOF, TBSOT, and TBSOP, we were ready to construct a collection of dinuclear core units systematically, by adopting a uniformed coupling protocol based on a Lewis acid-mediated Mukaiyama aldolization.[8]

As depicted in Chart 1, addition of TBSOF to activated lactol **2a** in the presence of 0.6 equiv of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in CH_2Cl_2 at −80 °C afforded a separable 45:55 mixture of two unsaturated lactone intermediates (not shown), which were individually hydrogenated to provide the corresponding saturated counterparts *threo,trans*-**O**,**O** and *erythro,trans*-**O**,**O** in 68% combined yield for the two steps.[9] By extending this chemistry, the entire collection of dinuclear scaffolds comprising all the possible heteroatom combinations (3^2) was easily assembled as indicated, consisting of 18 (16 shown) constitutionally and/or stereochemically diverse congeners.

Inspection of the results in Chart 1 reveals that, under standard conditions, the nine processes behave similarly irrespective of the heteroatom composition, providing acceptable yields of the expected adducts. *threo,trans*-Configured compounds formed in all reactions, often accompanied by substantial quantities of the corresponding C-4 epimeric *erythro,trans* derivatives and/or *threo,cis* compounds. When oxygen- and sulfur-containing modules **2a** and **2b** were coupled to TBSOF and TBSOT (reactions 1, 2, 4, and 5), *threo,trans* and *erythro,trans* adducts were obtained in almost equimolecular ratios, while reactions involving the *N*-Boc protected counterpart **2c** (reactions 7, 8, and 9) showed a more diastereoselective character favoring *threo,trans* adducts. Furthermore, formation of 5,8-*cis* disposed isomers was scantily observed (reactions 3, 6, and 9) when nitrogen silyloxy diene TBSOP was employed. Indeed, the presence of the *N*-Boc protective group within the nucleophile and/or the electrophile modules influences the stereochemical outcome of the process on some extent, as compared to the behavior of the reactions involving the O,O, S,S, S,O, and O,S heteroatom combinations, where formation of C-4 epimerizable *threo,trans* and *erythro,trans* unsaturated adducts preferentially formed.

The stereochemical assignment for the whole compound collection in Chart 1 followed upon extensive ^{1}H NMR

* To whom correspondence should be addressed at Università di Parma.

(1) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275. Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Hertz, W., Eds.; Springer-Verlag: Wien, New York, 1997; Vol. 70, p 81.

(2) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1983; Vols. 1 and 2.

(3) Total syntheses: Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989. Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996.

(4) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640 and previous papers cited therein.

(5) (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. (b) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168. (d) Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. *J. Org. Chem.* **1997**, *62*, 4513. (e) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567. (f) Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697. (g) Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963.

(6) Concurrent with ourselves, the group of Figadère developed a similar (silyloxy)furan-based approach, where the scope was limited to assembly of "natural" oligo-THF motifs. See: Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428.

(7) The enantiomeric excesses of **2a**−**c** were judged to be 96%, 92%, and 98%, respectively, based on Mosher ester analyses of suitable hydroxymethyl intermediates. See ref 5c.

(8) This coupling maneuver can be regarded as a *C*-glycosylation reaction, with the silyloxy dienes as acceptors and lactols as donors.

(9) For dinuclear compounds listed in Chart 1, we opted to utilize an immediately explicative naming based on the heteroatom composition and stereochemistry instead of the usual arabic numbering.

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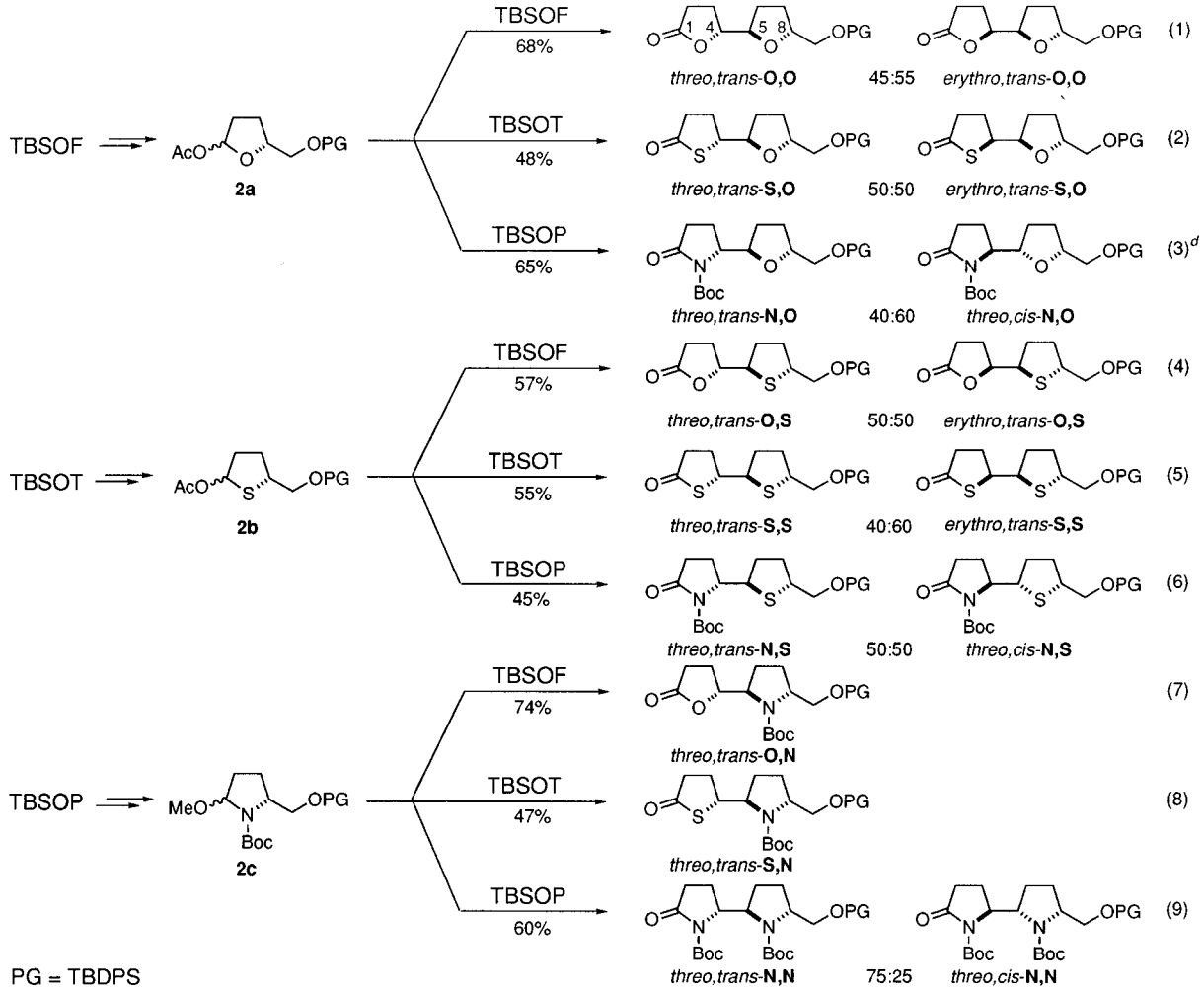
Chart 1. Diastereoselective Synthesis of Dinuclear Templates Related to Annonaceous Acetogenin Core Units[a–c]



[a] General Procedures. Reactions 1, 3, 4, and 6: (a) **2**, dry CH_2Cl_2, −80 °C; then silyl enol ether, TBSOTf (0.6 equiv); (b) SiO_2 chromatographic separation of unsaturated isomers; (c) H_2, THF, AcONa. Reactions 2 and 5: (a) **2**, dry CH_2Cl_2, −80 °C; then silyl enol ether, TBSOTf (0.6 equiv); (b) H_2, THF, AcONa; (c) SiO_2 chromatographic separation of saturated isomers. Reactions 7, 8, and 9: (a) **2**, dry CH_2Cl_2, TBSOTf (0.6 equiv), −80 °C; then silyl enol ether; (b) SiO_2 chromatographic separation of unsaturated isomers; (c) H_2, THF, AcONa. Further details in Supporting Information. [b] The isomeric ratios were determined by integration of proper resonances in the ^1H NMR spectra of the coupling reaction mixtures. [c] The yields quoted refer to combined yields of isomeric products for the two coupling/hydrogenation steps starting from **2**. [d] Two minor isomers isolated, namely, *erythro,trans*-**N**,**O** (18%) and *erythro,cis*-**N**,**O** (11%).

investigations, as well as chirooptical[10] and analogy studies. *threo,trans*-**O**,**O** and *erythro,trans*-**O**,**O** constructs were related to known substances,[4,6] while the *threo,trans*-**O**,**N** derivative was the enantiomer of a reported, well-characterized synthetic intermediate.[5e] For a given series, the isomeric unsaturated components were subjected to base-catalyzed epimerization, which directly assessed their C-4 epimeric relationship.

The $^1H-^1H$ coupling constants between the H-4 and H-5 protons within both unsaturated and saturated products as well as the H-4 chemical shift values guided us to assign the 4,5-*threo*/*erythro* relative disposition, with *erythro* compounds exhibiting larger J values than the corresponding *threo* counterparts ($J_{4,5\text{-}erythro} \approx 5-10$ Hz; $J_{4,5\text{-}threo} \approx 3-8$ Hz) and upfield H-4 resonances.[11,12]

To conclude, the chemistry disclosed herein traces a simple, highly efficient pathway to various dinuclear fragments related to annonaceous acetogenins based on the exploitation of three readily available modules, TBSOF, TBSOT, and TBSOP, and which embodies divergence, flexibility, and reiteration capability for structural diversity.

Supporting Information Available: Experimental procedures including physical and spectroscopic data for the whole compound series and molecular modeling details (12 pages).

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(10) As a rule, (4*R*)-configured 2,3-unsaturated butenolides and relative compounds are dextrorotatory, while (4*S*)-configured counterparts are levorotatory. See: Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807.

(11) 4,5-*Erythro* butenolides and congeners were also distinguished from their 4,5-*threo* counterparts by the downfield chemical shift of the H-3 proton. See: Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037. Figadère, B.; Chaboche, C.; Peyrat, J.-F.; Cavé, A. *Tetrahedron Lett.* **1993**, *34*, 8093.

(12) The H-4−H-5 anti disposition was found to be energetically favorable for the *erythro* isomers, as compared to the *threo* ones, and this behavior was magnified for S,S-derivatives. For some representative dinuclear fragments (X, X′ = O,O and S,S), a molecular mechanics calculation was performed (Sybyl 6.3, Tripos Inc. St. Louis MO), simulating a rotation around the C-4−C-5 bond. The calculation of the relative populations of *anti* and *gauche* conformations allowed the prediction of the mean J values, which were in good accordance with the experimental ones, thus confirming the discussed assignments. In particular, the calculated and observed J values were: 4,5-*threo*-O,O: 4.4 Hz (obsd 2.5 Hz), 4,5-*erythro*-O,O: 6.4 (6.1), 4,5-*threo*-S,S: 7.7 (8.3), 4,5-*erythro*-S,S: 9.8 (10.5).