

Chemoenzymatic Synthesis of *trans*-Tetrahydrofuran Cores of Annonaceous Acetogenins from Bromobenzene

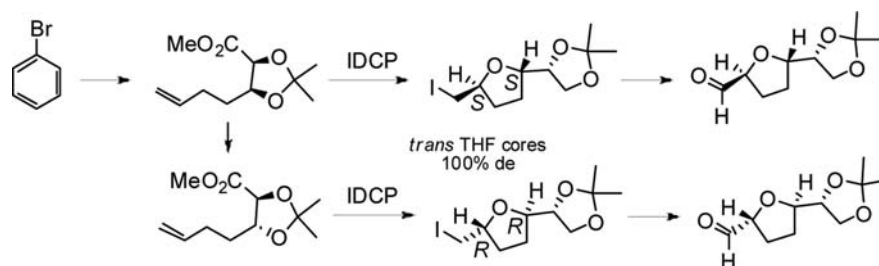
Juan Carlos Ramos, Margarita Brovetto,* and Gustavo A. Seoane*

Departamento de Química Orgánica, Facultad de Química, Universidad de la República,
C.C. 1157 Montevideo, Uruguay

mbrovetto@fq.edu.uy; gseoane@fq.edu.uy

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ABSTRACT



Two types of *trans*-THF cores, present in acetogenins, have been synthesized by an intramolecular iodoetherification reaction. The starting alkenol was obtained in a few steps from a chiral *cis*-diol resulting from microbial oxidation of bromobenzene. The cyclization gave complete stereoselectivity for *trans*-THF cores with either (S,S) or (R,R) configurations at the THF chiral carbons.

Annonaceous acetogenins are a large family of natural products isolated from tropical plants belonging to the *Annonaceae* family, comprising more than 430 members,^{1,2}

displaying an ample array of biological activity such as antitumor, pesticidal, antimalarial, immunosuppressive, and antifeedant activities.^{3–5} Structurally, acetogenins are characterized by one to three tetrahydrofuran (THF) ring(s) flanked by two α -hydroxylated, long hydrocarbon chains, one of them containing an α,β -unsaturated γ -lactone residue at the end, which is essential for activity (Figure 1). The THF core has been considered the site for mitochondrial membrane recognition, and SAR studies have shown that bis-*trans*-THF acetogenins are among the most potent compounds of this family,^{3a,4c} the cytotoxicity being modulated by the stereochemistry of the THF core.⁶ Although many synthetic methodologies have been developed for the preparation of mono- and bis-THF cores of

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these compounds;⁷ there is still interest in the development of new methodologies for synthetic routes with high selectivity and divergency.

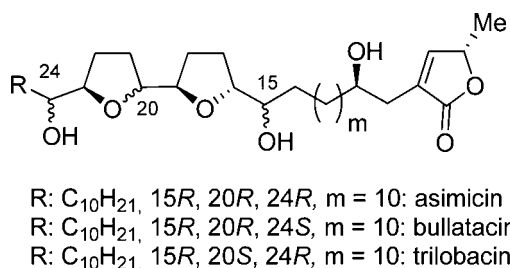


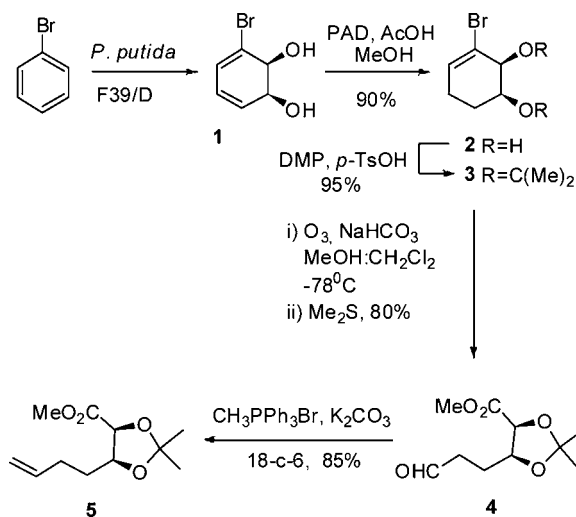
Figure 1. Representative structure of annonaceous acetogenins.

Our group has been working on the enantioselective synthesis of THF rings, in connection with our ongoing efforts to prepare marine natural products.⁸ Also, as part of a continuous program to employ microbially derived and enantiomerically pure *cis*-cyclohexadienediols such as **1** as synthons for organic synthesis, herein we present an efficient synthetic sequence that enables the preparation of *trans*-THF cores with either (*S,S*) or (*R,R*) configuration at the THF chiral carbons, in arrangements similar to those found in natural acetogenins.

The sequence for both THF cores started with the toluene dioxygenase-mediated oxidation of bromobenzene to produce enantiopure *cis*-diol **1**, using *Pseudomonas putida* F39/D as a whole-cell biocatalytic system (Scheme 1).^{9,10} Reduced diol **2** was obtained in 90% through selective hydrogenation with diimide generated in situ.¹¹ Protection of the diol functionality as acetonide followed by ozonolysis in the presence of NaHCO₃, using DMS in the reductive step, afforded ester–aldehyde **4** in 76% combined yield.⁸

Wittig reaction of **4** using Bodan conditions⁸ gave alkenol **5**, which is a common precursor in both synthetic routes for (*R,R*) and (*S,S*) *trans*-THF rings. Compound **5**

Scheme 1



was obtained in an overall yield of 58% through a five-step sequence starting from bromobenzene.

For the key cyclization step we chose the simple halocyclization methodology¹² over protected 3-butenylcarbinol **5**. The reaction can be performed on a free alkenol, but it is known that the presence of protecting groups on the alcohol dramatically affects the stereochemical outcome.¹³ In particular, the presence of cyclic protecting groups at the *vic*-diol system in these structures induces a complete *trans* diastereoselectivity in the formation of THF rings.^{12a,b} Pursuing the idea of using conformationally restricted alkenols as a template for the *trans* selective halocyclization, we performed the reaction under different conditions, changing the halonium source, base, solvent, temperature, and also using complexing agents for the diol system.¹⁴ After some experimentation with different halonium sources (NIS, NBS, I₂), best results in terms of yield and selectivity were obtained with iodonium dicollidine perchlorate (I(Coll)₂ClO₄, IDCP) for the protected *vic*-diol **5**. Thus, treatment of **5** with IDCP in wet acetonitrile at different temperatures, led to the formation of diastereomeric mixtures of THF rings with high *trans* selectivity, but contaminated with variable amounts of iodohydrin **7** (Table 1, entries 1–3).

To diminish the formation of this compound, the reaction was carried out at lower temperature and also in the absence of water. However, under these conditions the reaction did not proceed (entries 4–5). Regarding the

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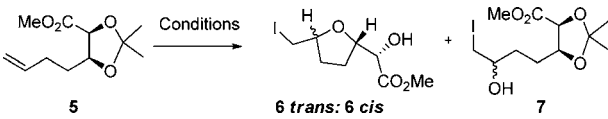
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(14) Cyclization studies were carried out using compound **5** and its deprotected diol, with different halonium sources (NIS, NBS, I₂, IDCP), bases (K₂CO₃, DBU, NaH, KHMDS), carbonate counterions (Na₂CO₃, Cs₂CO₃, CaCO₃, PbCO₃, CdCO₃), complexing diol sources (CuCl₂, PhB(OH)₂, CuSO₄, montmorillonite), solvents (MeCN, toluene, THF, DMF, CH₂Cl₂, hexanes), and temperatures (–20 °C to rt) (see Supporting Information).

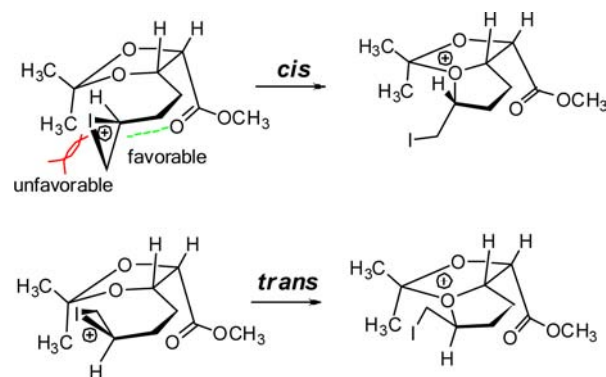
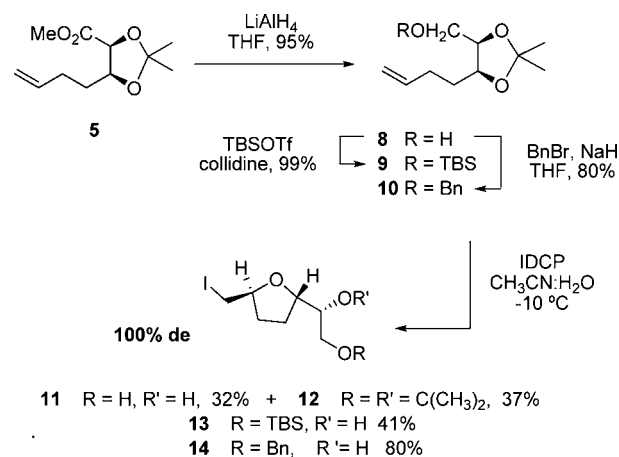
Table 1. Cyclization Studies


entry	conditions	time (h)	yield	6 <i>trans</i> :6 <i>cis</i> :7 ^a
1	IDCP, CH ₃ CN:H ₂ O (99:1), rt	0.2	70%	10:1:5
2	IDCP, CH ₃ CN:H ₂ O (99:1), -10 °C	24	70%	10:1:3
3	IDCP, CH ₃ CN:H ₂ O (99:1), -20 °C	48	65%	10:1:2
4	IDCP, CH ₃ CN:H ₂ O (95:5), -40 °C	48	No reaction	
5	IDCP, CH ₃ CN -20 °C → rt	48	No reaction	

^a Determined by ¹H NMR

stereochemical assignments, they are not easy for 2,5-disubstituted THFs, due to the small NOE enhancements observed in these systems; hence, we decided to take advantage of the functionalities present in the substituents and use chemical means for this task. Thus, treatment of the isomeric mixture of THFs with DBU in CH₂Cl₂ led to the cyclization of the *cis*-isomer to obtain a bicyclic compound, leaving the *trans*-isomer unchanged and confirming the high *trans* selectivity of the THF-forming cyclization (see Supporting Information). Despite previous reports on this type of system that mentioned a complete stereoselection,^{12a,b} with our compound both *cis*- and *trans*-THF rings were obtained, suggesting that the iodonium intermediate was formed through electrophilic attack on both faces of the double bond. These results, together with halocyclization studies performed in our laboratory using I₂-K₂CO₃ on compound **5** and its deprotected analogue¹⁴ which gave always diastereomeric mixtures, led us to believe that there is a stabilizing interaction (involving electron-deficient and electron-rich orbitals) between the iodonium and the carbonyl group of the ester, respectively.¹⁵ Inspection of models for both modes of cyclization is in agreement with such type of interaction taking place only in the conformation leading to the *cis*-isomer, decreasing the net unfavorable steric hindrance produced by the protecting group of the diol and thus lowering the overall *trans* selectivity of the reaction (Figure 2).

We reasoned that the stabilizing interaction would be eliminated by reduction of the ester, allowing a complete selectivity in the formation of the preferred *trans*-THF ring. With this hypothesis in mind, the ester group in compound **5** was reduced using LiAlH₄ and then protected with different groups to try the cyclization (Scheme 2).

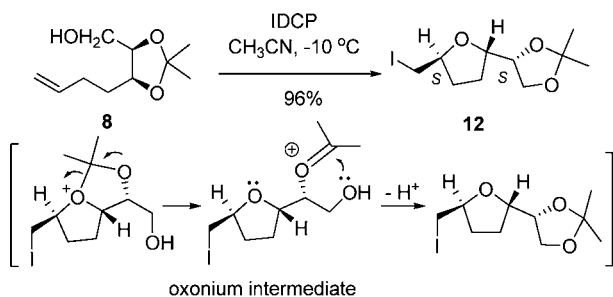
**Figure 2.** Proposed rationale for the diminished *trans* selectivity observed when an ester group is present.**Scheme 2**

To our delight, upon reduction of the ester group the reaction of the alcohol substrate with electrophilic iodine generated the *trans*-THF ring with complete stereoselectivity. This selectivity was also maintained for the different protecting groups tested (**8–10**), although the cyclization yields varied. Best results were obtained using the benzyl ether, yielding 80% of the *trans*-THF **14**. Interestingly, when cyclization was performed on the unprotected alcohol **8**, diol **11** was formed in 32%, and not surprisingly, acetonide **12** was also obtained in 37% yield, resulting from acetonide migration. This result, coupled to the need of a suitable protection for the terminal *vic*-diol system, led us to test the cyclization in the absence of water (Scheme 3). In these conditions (*S,S*)-*trans*-THF **12** was obtained as a single isomer in 96% yield, resulting from intramolecular attack of the primary OH to the oxonium cation formed during the cyclization. The reasons to explain the lack of reactivity of **5** compared to that of **8** are not clear.

At this point we were able to synthesize (*S,S*)-*trans*-THF **12** with complete stereoselectivity and 47% overall yield, in six steps from bromodiols **1**.

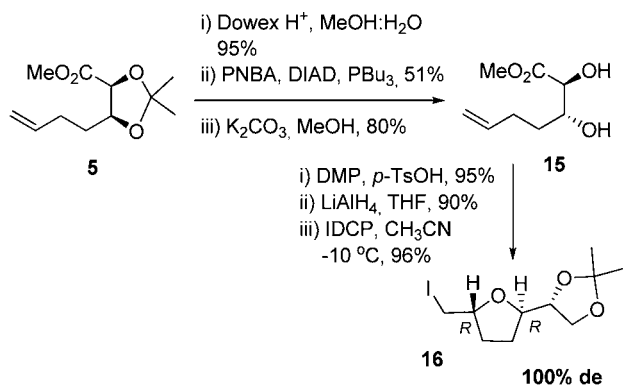
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Scheme 3



On the other hand, for the (*R,R*)-*trans*-THF rings an inversion of configuration at the alcohol participating in the cyclization is necessary. Thus, deprotection of the diol functionality in compound **5**, followed by Mitsunobu inversion¹⁶ and further hydrolysis of the resulting *p*-nitrobenzoate ester, afforded diol **15** in 39% yield for the three steps. It is noteworthy that the inversion protocol, performed on the free diol, gave exclusively the product of inversion at the C3-OH, probably due to the inductive effect of the ester group lowering the nucleophilicity of the α -OH. Also, best yields were obtained using the more reactive tributyl phosphine and DIAD, compared to triphenyl phosphine and DEAD.

Scheme 4

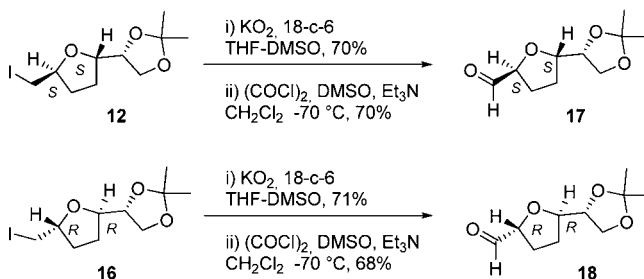


Under those conditions, the sequence performed on the free diol afforded a higher overall yield than that using a compound monoprotected selectively on the α -OH. After inversion, the *syn*-diol was reprotected as acetonide, the ester group was reduced, and the cyclization with IDCP in CH₃CN gave the *trans*-THF in high yield (96%) with complete stereoselectivity (Scheme 4). The entire sequence for (*R,R*)-*trans*-THF cores of type **16** can be performed with complete stereoselectivity and 20% overall yield in 10 steps from bromodiol **1**.

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With both *trans*-THF cores in hand, the next step is the conversion of the iodomethyl substituent in a formyl group, needed to prepare the α -hydroxyalkyl chain of the acetogenins via an organometallic addition. Therefore, alcohol formation by reaction with potassium superoxide in DMSO,¹⁷ in both (*S,S*)-*trans*-THF **12**, and (*R,R*)-*trans*-THF **16**, followed by Swern oxidation afforded aldehydes **17** and **18** in 49% overall yield (Scheme 5). The aldehydes can be used not only to form the side chain of the annonaceous acetogenins but also to prepare an adjacent THF ring by addition of an homoallylic residue and further halocyclization of the resulting 3-butenylcarbinol in an iterative fashion.

Scheme 5



In conclusion, we have developed a highly stereoselective synthesis of both *trans*-THF cores present in acetogenins, starting from a chiral *cis*-diol obtained from microbial oxidation of bromobenzene. As THF rings of type **17** and **18** can be functionalized at both substituents to form α -hydroxyalkyl chains, our strategy can be easily applicable to the synthesis of a series of natural acetogenins. Also, the extension of this methodology to the preparation of bis- and tris-THF cores present in acetogenins is currently being developed in our laboratory.

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Supporting Information Available. ¹H and ¹³C NMR spectra of compounds **3–18** and experimental procedures for **4** to **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.