Toward Chemical Libraries of Annonaceous Acetogenins. Total Synthesis of Trilobacin

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To date, more than 230 different acetogenins have been isolated from 26 plants of the Annonaceae.[1] Taking into consideration that the number of plants within this family exceeds 2300, one may conclude that isolation and full characterization of the entire naturally occurring repertoire of the Annonaceous acetogenins will require a formidable effort. Many of these compounds have shown remarkable cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities.[2] For example, studies with human solid-tumor cell lines show that trilobacin, **1** is over 1 billion times more potent cytotoxic agents than adriamycin.[3] The urgent need for a comprehensive biological screening of such compounds led us to design synthetic approaches that will generate large chemical libraries of isomeric acetogenins.[4,5]

A dominant structural feature that appears in more than 40% of the Annonaceous acetogenins, particularly in those showing the highest antitumor activity, is a linear 10-carbon skeleton (i.e., carbons 15−24 in **1**) that comprises two adjacent tetrahydrofuran rings flanked by two hydroxyl groups. Having six stereogenic carbinol centers, this unit alone may appear in the form of as many as 64 stereoisomers. To date, only four different diastereomers of this fragment have been identified in naturally occurring bis-THF acetogenins. Here, we present an efficient methodology to produce 32 such stereoisomers. We demonstrate this approach by the actual synthesis of eight diastereomers, **10**−**17**, and by the use of one of them in the first total synthesis of **1**.

Our previously described synthetic approach to the bis-THF acetogenins[4,6] is based on selective placement of the oxygen functions onto a naked, unsaturated carbon skeleton.[7,8] This was achieved using the Sharpless asymmetric dihydroxylation (AD) reaction,[9] the ligand-assisted Kennedy oxidative-cyclization with rhenium oxide,[10] and the Mitsunobu inversion of alcohols.[11] Here, we combine these principles with the advantages of convergent synthesis. We start with two fragments, each containing two stereogenic centers; one is a phosphonium salt and the other is an aldehyde. Referring to the structure of **1**, the phosphonium salt contains stereogenic centers 23 and 24, and the aldehyde contains centers 15 and 16.

The phosphonium salts **4a**−**d** (Scheme 1A) and aldehydes **7a**−**d** (Scheme 1B) were prepared using the AD reaction with alkenes **2** and **5**, respectively. For example, reaction of **2** with AD-mix-β produced the (*R*,*R*) lactone **3a** in 96% ee (>99.5% ee after recrystallization). The latter was converted to either (*R*,*R*) phosphonium salt, **4a**, or, using the Mitsunobu inversion, to the (4*R*,5*S*) diastereomer, **4b**. The two other enantiomers, **4c,d**, were prepared from **2** in 94% ee (>99.5% ee after recrystallization) using AD-mix-α. All stereoisomeric aldehydes, **7a**−**d**, were similarly prepared in very high ee (Scheme 1B).

Coupling of all four Wittig reagents **4a**−**d** with the four aldehydes **7a**−**d** can produce 16 stereoisomeric *Z*-alkenes. This strategy is demonstrated here by the synthesis of four of such alkenes, **8a**−**d** (Scheme 2). Oxidative cyclization with Re_2O_7/lutidine affords the corresponding trans-substituted tetrahydrofurans **9a**−**d**. Conversion of **9a** to the corresponding mesylate followed by acid-catalyzed acetonide-cleavage and ring closure produces tricyclic lactone **10**. Alternatively, Mitsunobu inversion of the free alcohol's configuration within **9a**, prior to its activation and ring-closure, gives rise to lactone **11**. Similarly, isomers **12** and **13** were obtained from **9b**, isomers **14** and **15** from **9c**, and isomers **16** and **17** from **9d**.[12,13] Since products **14**−**17** are epimers of **10**−**13** at the free hydroxyl position, their interconversion is possible by the Mitsunobu reaction. We have confirmed this idea by an alternative synthesis of diastereomers **14** and **15** from **10** and **11**, respectively.

Altogether, by using two diastereomeric Wittig reagents **4a,b** and two diastereomeric aldehydes **7a,b** we have synthesized eight diastereomers of the desired tricyclic skeleton, **10**−**17**. Consequently, combinatorial coupling of all four Wittig reagents **4a**−**d** with all four aldehydes, **7a**−**d**, should create a library of 32 out of 64 possible stereoisomeric skeletons.

The recently corrected structure of trilobacin, **1**,[3b] exhibits two very unusual features: an erythro junction between the two adjacent THF rings and a cis stereochemistry in the B ring. This structure suggests that our synthetic lactone **11** is the appropriate precursor of **1**. Thus, lactone **11** was converted to the primary Wittig salt **20** (Scheme 3). Treatment of the latter with BuLi

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(12) Compounds **10**, **13**, **14**, and **17** can be obtained by tandem oxidative cyclization with the appropriate stereoisomer of 5-hydroxytricosa-8,12-dien-1,4-olide. Significantly higher yields were obtained with a modified perrhenate reagent $CF_3CO_2ReO_3/(CF_3CO)_2O$ rather than with Re_2O_7/H_5IO_6 (ref 6).

(13) Chemical purity of all compounds was verified by TLC, ^1H NMR, ^{13}C NMR, and HRMS. For physical data of **10**−**17** see the supporting information.

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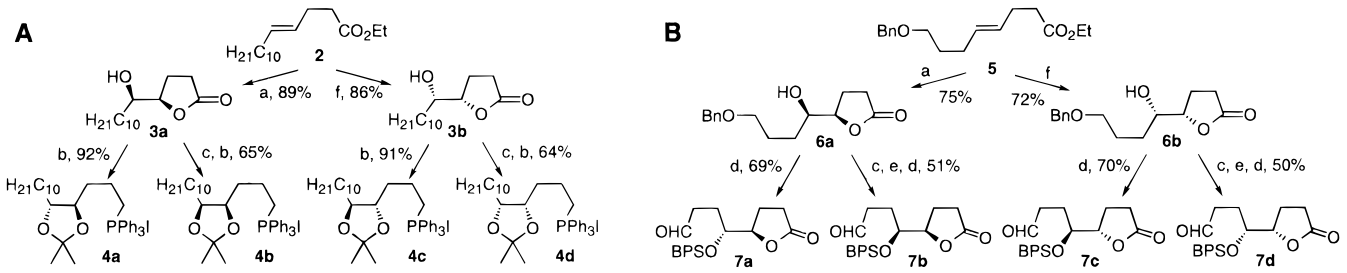
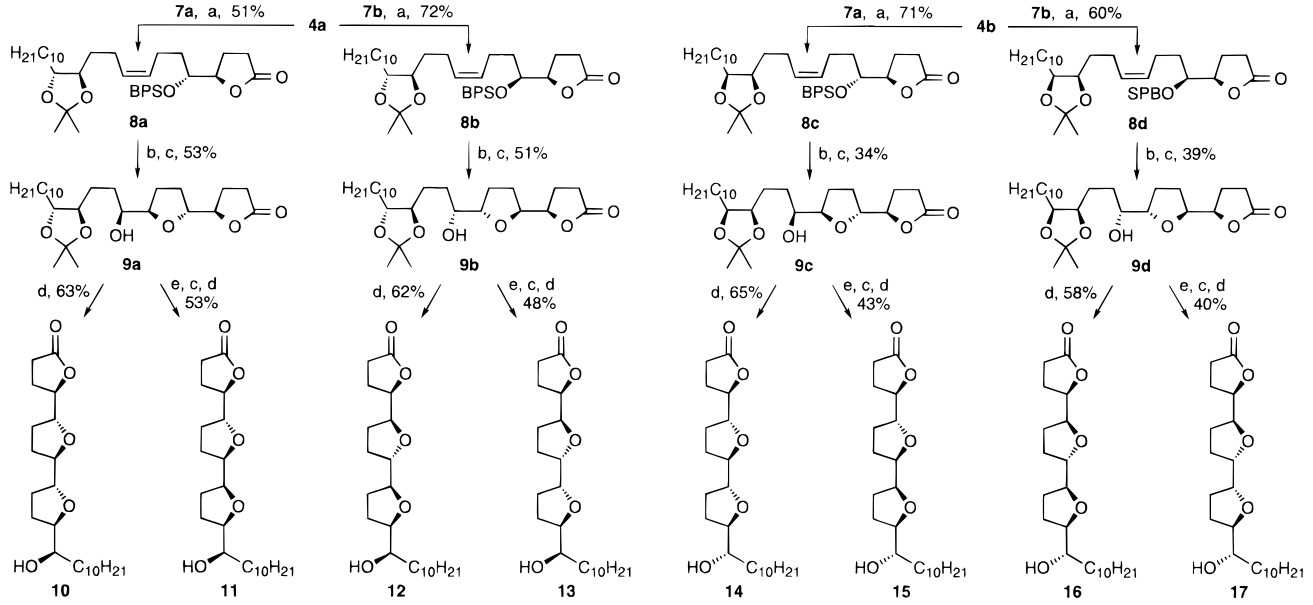
Scheme 1. Synthesis of All Possible Stereoisomeric Starting Building Blocks[a]



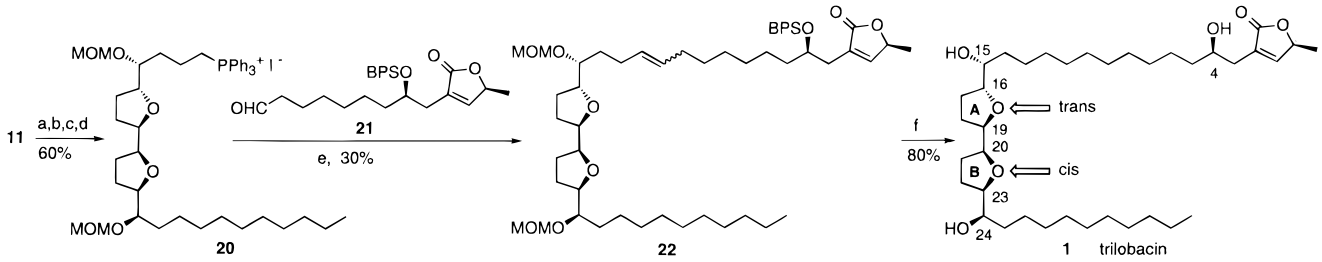
[a] Key: (a) (i) AD-mix-β, methanesulfonamide, *t*-BuOH, H_2O, 0 °C, 24 h, (ii) aqueous KOH, MeOH then 3 N HCl, (iii) TsOH, CH_2Cl_2, rt, 1 h; (b) (i) LAH, Et_2O−THF, 0 °C to reflux, 2 h; (ii) TsOH, acetone, C_6H_6 azeotropic distillation, 24 h, (iii) PPh_3, I_2, imidazole, toluene, rt, 3 h, (iv) PPh_3, $NaHCO_3$, CH_3CN, reflux, 4 h; (c) *p*-nitrobenzoic acid, PPh_3, DEAD, C_6H_6, 16 h; (d) (i) *tert*-butyldiphenylchlorosilane (BPSCl), imidazole, DMF, rt, 16 h; (ii) Pd−C (10%), MeOH, propionic acid, H_2, 24 h, (iii) PCC, Celite, CH_2Cl_2, 2 h; (e) (i) aqueous KOH, EtOH, reflux, 16 h, then 3 N HCl, (ii) TsOH, CH_2Cl_2, 1 h; (f) (i) AD-mix-α, methanesulfonamide, *t*-BuOH, H_2O, 0 °C, 24 h, (ii) aqueous KOH, MeOH then 3 N HCl, (iii) TsOH, CH_2Cl_2, rt, 1 h.

Scheme 2. Synthesis of Eight Representative Bis-THF Stereoisomers[a]



[a] Key: (a) (i) $KN(SiMe_3)_2$, THF, −78 °C, 2 h, then aldehyde **7a** or **7b** in THF−HMPA, −78 °C to rt, 16 h; (b) (i) TBAF, THF, rt, 2 h, (ii) Re_2O_7, lutidine, CH_2Cl_2, 4 h; (c) dimethoxypropane, acetone, TsOH, 1 h; (d) (i) MsCl, CH_2Cl_2, −20 to 0 °C, 1 h, (ii) TsOH, MeOH−H_2O, rt, 16 h, (iii) pyridine, 100 °C, 2 h; (e) (i) *p*-nitrobenzoic acid, PPh_3, DEAD, C_6H_6, 16 h, (ii) aqueous KOH, EtOH, reflux, 16 h, then 3 N HCl, (iii) TsOH, CH_2Cl_2, 1 h.

Scheme 3. Final Steps of Trilobacin Synthesis[a]



Key: (a) (i) LAH, Et_2O−THF, 0 °C to reflux, 2 h; (ii) BMSCl, diisopropylethylamine, DMAP, CH_2Cl_2, rt, 12 h, then MOMCl, 12 h; (b) TBAF, THF, 0 °C to rt, 1 h; (c) PPh_3, I_2, imidazole, CH_2Cl_2, rt, 1 h; (d) PPh_3, $NaHCO_3$, CH_3CN, 45 °C, 24 h; (e) *n*-BuLi, THF, 0 °C, 0.5 h, then aldehyde **21** in THF 0 °C to rt, 1 h; (f) (i) $Rh(PPh_3)_3Cl$ (10%) C_6H_6, EtOH, H_2, rt, 2 h, (ii) acetyl chloride, MeOH, ether, reflux, 6 h.

and then with aldehyde **21**[4] followed by hydrogenation and deprotection afforded **1**, which was found to be identical (^{1}H NMR, $[\alpha]_D$, IR, MS) to the naturally occurring trilobacin.

In conclusion, the convergent synthetic strategy outlined here provides a useful entry to a 32-member chemical library of stereoisomeric bis-THF acetogenins. This approach is demonstrated here by the first total synthesis of trilobacin.

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Supporting Information Available: Physical data of **10**−**17** (2 pages).

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