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The First Total Synthesis of 15-*epi*-Annonin I

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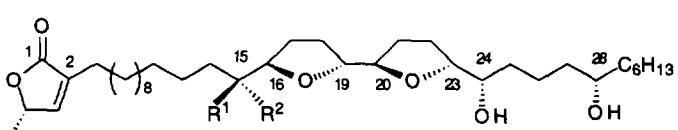
Abstract: The first total synthesis of the 15-epimer **1b** of the naturally occurring acetogenin annonin I **1a** is described. All stereogenic centres in the bis-THF subunit are controlled via successive Sharpless asymmetric epoxidations (AE). Alkyl side chains were attached directly to the core using alkyne-epoxide couplings. Copyright © 1996 Published by Elsevier Science Ltd

The Annonaceous acetogenins are natural products isolated from the plant family *Annonaceae*. About 150 of these compounds of polyketide origin are known up to date[1] and show a broad scope of biological activities such as cytotoxic, antitumor, fungicidal, pesticidal and insecticidal effects. Biochemical studies have demonstrated the potent inhibition of mitochondrial NADH-ubiquinone reductase (complex I) by Annonaceous acetogenins.[2-4] Another explanation for the strong biological activity could lie in the binding ability towards metallic cations.[5] Since the structure-activity relationship is not yet unraveled nor all the absolute configurations of the isolated compounds are known, it would be helpful to obtain these substances and their analogues for systematic biological screening. Among the 19 Annonaceous acetogenins that were isolated from *Annona squamosa* Born et. al. found annonin I **1a**[6] to be the most potent compound concerning cytotoxic and insecticidal activitiy. Annonin I (= squamocin) is a even more potent complex I inhibitor than rotenone.[2a,7]

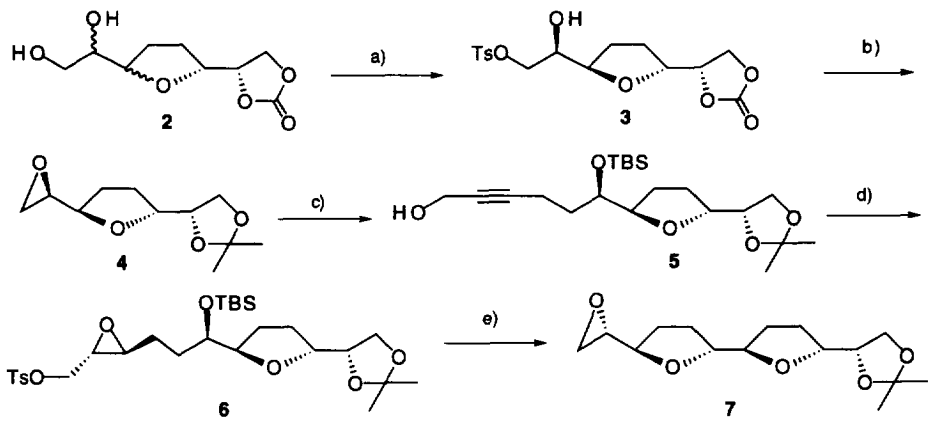
1a shows, like bullatacin[8], *threo/trans/threo/trans/erythro* configuration from C-15 to C-24, but differs in the position of the hydroxyl function in the alkyl chains. Seven total syntheses of bis-THF ring acetogenins have been reported up to present.[9] Our synthetic strategy allows the selective variation of each stereogenic centre thus enabling us to synthesize all possible stereoisomers following the same route. With the aim to prepare interesting substances for biological assays we set out to synthesize 15-*epi*-annonin I **1b** possessing a hitherto unique *erythro/trans/threo/trans/erythro* configuration at the C_2 symmetric THF core.



1a: R^1 = H; R^2 = OH
1b: R^1 = OH; R^2 = H

We started our approach with a diastereomeric mixture of mono-THF building block **2** which we previously have published as a 85:15 mixture in favour of the *trans* isomer.[10] Separation of the diastereomers was accomplished by flash column chromatography of the primary tosylates obtained via a dibutylstannylation / tosylation sequence.[11] The desired major *threo/trans/erythro* compound **3** was isolated in 72% yield. Treatment with DBU gave the crystalline epoxide in 98% yield. Saponification of the carbonate group with NaOMe/MeOH and acetalization of the resulting diol gave **4** (90%, 2 steps).

Scheme 1

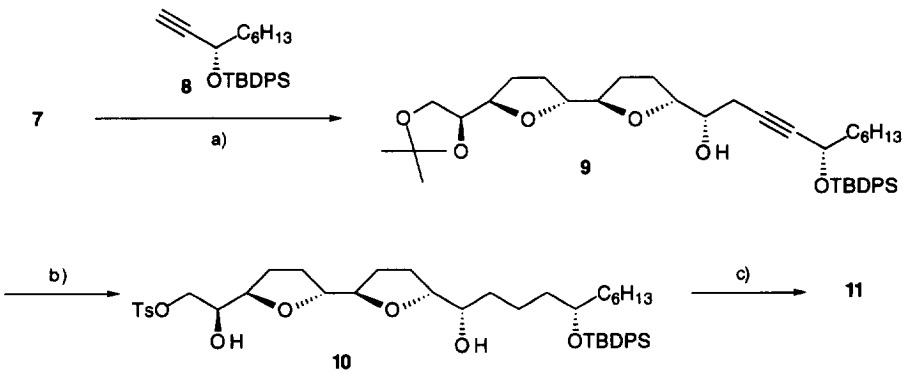


a) i) $Bu_2Sn(OMe)_2$, toluene then TsCl, 5% NEt_3; ii) separation of diastereomers; b) i) DBU, CH_2Cl_2; ii) NaOMe, MeOH; iii) 2,2-dimethoxypropane, acetone, PPTS; c) i) propargylmagnesium bromide, ether, 0°C; ii) TBSOTf, py, CH_2Cl_2; iii) t-BuLi, THF, $(CH_2O)_n$, -78°C to rt; d) i) Red-Al®, ether, rt; ii) (+)-DIPT, CH_2Cl_2, -25°C; iii) TsCl, NEt_3; e) i) H_2SiF_6, CH_3CN, rt; ii) 2,2-dimethoxypropane, acetone, PPTS; iii) K_2CO_3, MeOH.

To obtain the required allylic alcohol for the envisaged Sharpless asymmetric epoxidation a four-carbon extension was necessary. Selective nucleophilic opening of the epoxide with propargylmagnesium bromide afforded an alkyne (91%) that was, after protection of the alcohol as its t-butyldimethylsilyl (TBS) ether (98%), subjected to hydroxymethylation with t-BuLi / paraformaldehyde to yield the propargylic alcohol **5** (82%). The formation of a *cis* or a *trans* allylic alcohol is optional, thereby the configuration of the resulting second THF ring can be manipulated at this stage. A *trans* allylic alcohol was installed by treatment of **5** with Red-Al® in ether (85%) which smoothly underwent Sharpless epoxidation with L-(+)- diethyl tartrate (92%).[12] The resulting epoxy alcohol was converted to **6** with TsCl (96%). Epoxide cascade was performed by hexafluorosilicic acid to produce the bis-THF moiety in excellent 96% isolated yield. Under these cyclization conditions, we obtained a triol which was reprotected as an acetonide (93%) and furnished epoxide **7** after treatment with K_2CO_3 (99%) (scheme 1).

Borontrifluoride mediated opening[13] of **7** with 2 equivalents of alkyne **8**[14] gave alcohol **9** (75%). After hydrogenation on Pd/C (95%), liberation of the vicinal diol and selective monotosylation furnished the epoxide precursor **10** (82%, 2 steps).

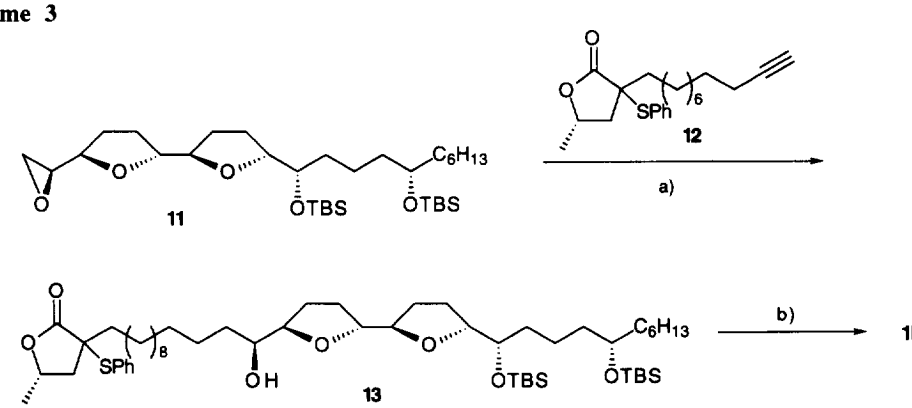
Scheme 2



a) 2 equiv **8**, THF, t-BuLi, **7** then $BF_3{\cdot}OEt_2$, -78°C, 30 min; b) i) cat. Pd/C, EtOAc, 1 atm H_2, rt; ii) 80% AcOH then $Bu_2Sn(OMe)_2$, toluene, TsCl, 5% NEt_3; c) i) TBAF, THF, rt ii) TBSCl, $AgNO_3$, py, THF, rt.

Reaction of **10** with 4 equiv. of TBAF simultaneously resulted in desilylation and epoxide formation to yield an epoxy alcohol which was protected as bis-TBS ether **11** (85%) (scheme 2). The lactone **12**[15] was attached to subunit **11** again by opening the epoxide with an alkyne in the presence of $BF_3{\cdot}OEt_2$ (60%).[13] Hydrogenation with Wilkinson's catalyst in benzene (95%) gave **13** which was desulfurized by oxidation with MMPP (magnesium monoperoxophthalate) and subsequent thermal elimination to complete the butenolide (74%, 2 steps). Finally, removal of the silyl protecting groups (89%) gave 15-*epi*-annonin I **1b**[16] as a white amorphous solid with mp. 81-83°C (scheme 3).

Scheme 3



a) i) 6 equiv **12**, THF, t-BuLi, **11** then $BF_3{\cdot}OEt_2$, -78°C, 30 min; ii) $(Ph_3P)_3RhCl$, H_2, benzene, rt; b) i) MMPP, H_2O/EtOH/$CHCl_3$, rt; ii) toluene, reflux, 1h; iii) Lewatit S100®, MeOH.

In conclusion, the modular synthetic approach presented here led to the first total synthesis of a bis-THF Annonaceous acetogenin bearing two hydroxyl groups in the alkyl chain. Deriving benefit from the highly flexible Sharpless AE methodology, it is possible to establish each of the stereocentres in the core seperately, thus providing a versatile access to a large variety of acetogenines for the purpose of systematical biological

testing and structure-activity relationship studies. Full experimental details and the total synthesis of annonin I **1a** will be reported shortly.

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14. Compound **8** was prepared by kinetic resolution of the corresponding γ-chloro allylic alcohol, subsequent dehydrohalogenation (Ito, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1990**, *31*, 6399-6402) and protection as its t-butyldiphenylsilyl (TBDPS) ether.

15. Compound **12** was prepared from 11-iodo-undecyne and (4S)-methyl-2-(phenylthio)-γ-butyrolactone similar to the procedure reported in ref. 9a.

16. Selected physical data for **1b**: $[\alpha]_D^{20}$= +18.3° (c 0.65, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3H), 1.22-1.60 (m, 40H), 1.40 (d, J = 6.7 Hz, 3H), 1.81 (m, 2H), 1.90 (m, 2H), 2.00 (m, 2H), 2.26 (ddt, J=1.6/ 7.3/ 8.2 Hz, 2H), 3.60 (m, 1H), 3.88-3.92 (m, 4H), 3.94 (m, 2H), 4.99 (qq, J = 1.6/ 6.7 Hz, 1H), 6.98 (q, J = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.10, 19.24, 22.08, 22.64, 24.45, 24.60, 25.20, 25.66, 26.09, 27.43, 28.79, 28.81, 29.21, 29.33, 29.38, 29.53, 29.57, 29.60, 29.61, 29.62, 29.69, 31.87, 32.42 (2C), 37.34, 37.52, 71.23 (2C), 71.87, 77.45, 82.76, 82.82, 83.06, 83.09, 134.43, 148.92, 173.92.

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