Pergamon

Tetrahedron Letters 39 (1998) 1493–1496

TETRAHEDRON LETTERS

Total Synthesis of the *threo, trans, threo*-mono-Tetrahydrofuran Annonaceous Acetogenin Longifolicin

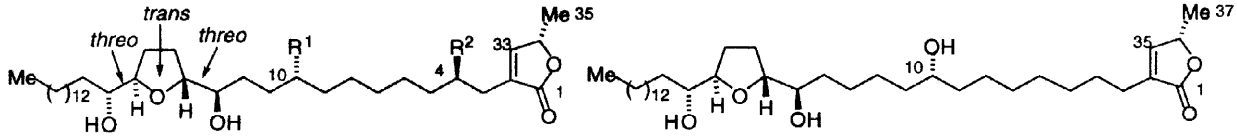
James A. Marshall and Hongjian Jiang

Department of Chemistry, University of Virginia, Charlottesville, VA 22901

Received 1 December 1997; revised 15 December 1997; accepted 16 December 1997

Abstract: An enantioselective synthesis of the C_{35} *threo, trans, threo*-mono-tetrahydrofuran annonaceous acetogenin longifolicin through use of chiral long-chain α-and γ-OMOM allylic stannanes and *(E)*-ethyl 3-formyl-2-propenoate as the starting materials is described. The synthesis is structurally definitive and potentially applicable to other members of this family of cytotoxic acetogenins.

In recent years a significant number of acetogenins have been identified in several genera of tropical and subtropical plants of the Annonaceae family.[1] Most members feature a core tetrahydrofuran or *bis*-2,2′-tetrahydrofuran array embedded near the center of a long-chain fatty acid with a butenolide terminus. Structural types can be further divided based on the total chain length and the core unit stereochemistry, as illustrated for longifolicin[2], goniothalamicin,[3] and longicoricin,[2] representative of the mono tetrahydrofuran C_{35} and C_{37} *threo, trans, threo* subgroups.



R^1 = OH, R^2 =H, Longifolicin
R^1 = R^2 = OH, Goniothalamicin

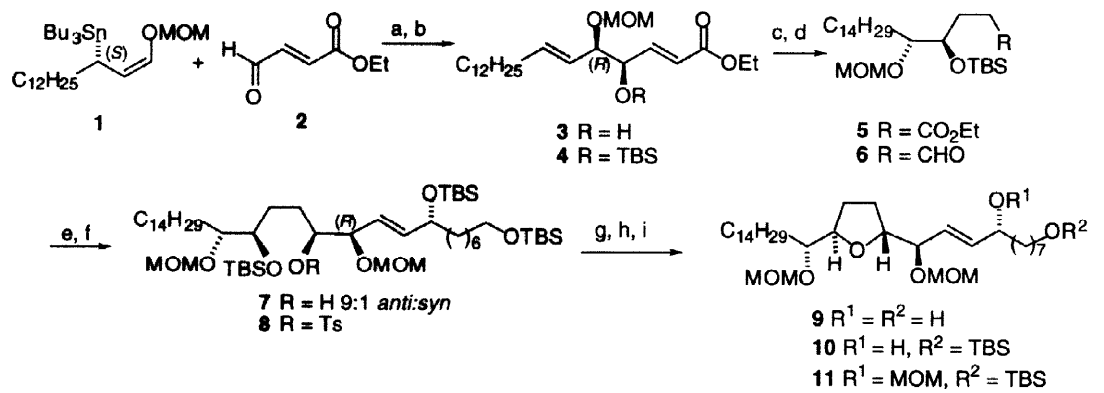
Longicoricin

The diverse biological activities of these compounds[4] and the problems associated with their purification and structure elucidation[5] have provided the stimulus for synthetic efforts in this area.[6] Pursuant to our interest in developing nonracemic α- and γ-oxygenated allylic stannanes as reagents for the synthesis of *syn* and *anti* 1,2-diol derivatives, we formulated a bidirectional strategy for the synthesis of the *bis* -tetrahydrofuran acetogenins.[7]. The present study was directed toward the mono-tetrahydrofuran *threo, trans, threo* C_{35}

0040-4039/98/$19.00
PII: S0040-4039(98)00007-0

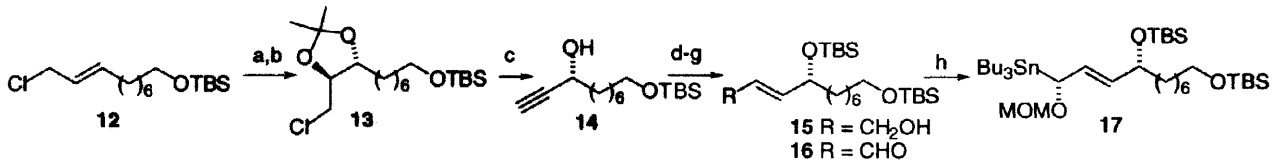
acetogenin longifolicin.[2] The approach, with minor modification, could also apply to the C_{37} analogue, longicoricin.[3]

Addition of the *(S)*-γ-OMOM allylic stannane **1**[8] to enal **2** in the presence of BF_3•OEt_2 afforded a 9:1 *syn:anti* mixture favoring the *syn* adduct **3** in 89% yield. Conversion to the TBS ether **4** and subsequent hydrogenation and reduction with *i*-Bu_2AlH afforded the aldehyde **6** in high yield. This underwent *anti* - selective addition of an allylic indium derivative prepared *in situ* from the *(R)*-γ-OMOM allylic stannane **17** and $InBr_3$ in ether at -30 °C affording the adduct as a separable 9:1 mixture favoring the *anti* isomer **7**.[7] The use of $InCl_3$ in EtOAc for this transformation by our previouse procedure[7] gave the adduct in only 25% yield. Alcohol **7** was converted to the tosylate **8** and treated with TBAF in THF to give the tetrahydrofuran product **9** in 79 % yield.



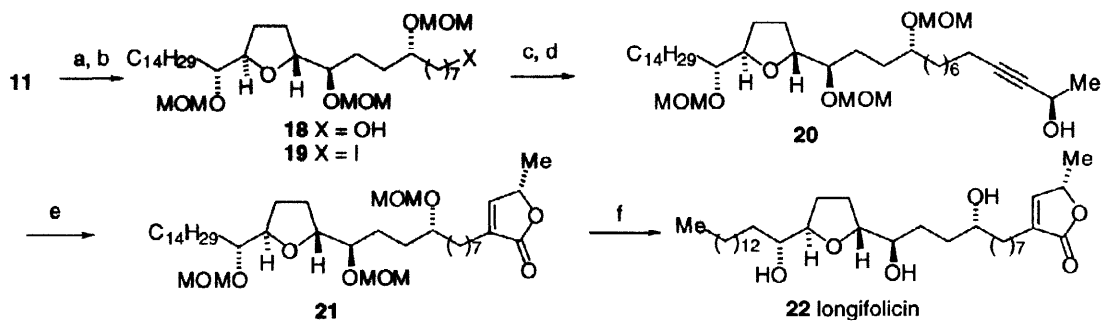
a) BF_3•OEt_2 , CH_2Cl_2 , -78 °C (89%); b) TBSCl, imidazole (93%); c) H_2/Rh-Al_2O_3 (100%); d) *i*-Bu_2AlH, hexanes (87%) e) **17**,$InBr_3$,Et_2O, -30 °C (72%); f) *p*-TsCl, py (96%); g) TBAF, THF, 45 °C (79%); h) TBSCl, Im (83%); i) MOMCl, *i*-Pr_2NEt (92%)

The preparation of stannane **17** commenced with the allylic chloride **12**.[10] Asymmetric dihydroxylation[11] and treatment of the resulting *syn*-diol with 2,2-dimethoxypropane and PPTS gave the acetonide **13**. This was converted to the alkynol **14** of > 90% ee by *n*-BuLi in 95% yield.[12] Conversion to the enal **16** was effected by sequential protection as the TBS ether and addition of paraformaldehyde to the derived lithio acetylide. Reduction of the resulting propargylic alcohol with Red-Al yielded the *(E)*-allylic alcohol **15** which was oxidized to aldehyde **16** with MnO_2. The final four steps leading to stannane **17**, addition of Bu_3SnLi, *in situ* oxidation with 1,1′-(azodicarbonyl)dipiperidine (ADD), enantioselective reduction with BINAL-H, and protection with MOMCl, were accomplished without purification of intermediates.[9]



a) AD-mix β (93%); b) $Me_2C(OMe)_2$, PPTS (84%), c) BuLi, -35 °C (95%); d)TBSCl, Im (95%); e) $(CH_2O)_n$, BuLi (80%); f) Red-Al (81%); g) MnO_2 (92%); h) Bu_3SnLi, THF; ADD; *(S)*-BINAL-H; MOMCl, $(i\text{-}Pr)_2NEt$ (28%-four steps).

The final stage of the synthesis entailed attachment of a butenolide moiety to the tetrahydrofuran intermediate **11**. This was achieved through introduction of a chiral propargylic alcohol segment and application of our allenyl Pd hydrocarbonylation methodology.[7] Thus, hydrogenation of the unsaturated TBS ether **11** then TBS cleavage afforded alcohol **18**. The derived iodide **19**[13] was treated with the lithio derivative of *(R)*-3-butyn-2-ol TBS ether.[14] After TBS cleavage the propargylic alcohol was converted to the trifluoroacetate and subjected to 1 mol % $Pd(PPh_3)_4$ in aqueous THF under 1 atm. of CO followed by 10 mol % $AgNO_3$ in ether affording butenolide **21** in 62% yield. The MOM protecting groups were cleaved with aqueous HCl in methanol-THF to give longifolicin (**22**) in high yield. The ^1H and ^{13}C NMR spectra were identical to those of an authentic sample. Furthermore, the rotation ($[\alpha]_D$ + 13.5, c 0.37, CH_2Cl_2) and mp (79-80 °C) were in close agreement with the reported values ($[\alpha_D]$ + 13.0, c 0.001, CH_2Cl_2; mp 83 °C).[2]



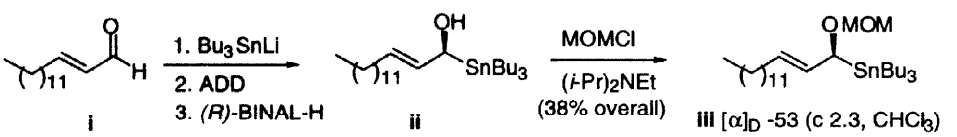
a) H_2/Rh-Al_2O_3 (100%); b) TBAF, THF (98%); c) I_2, Ph_3P, Im (90%); d)*(R)*- LiCCCH(OTBS)Me, HMPA ; TBAF, THF (90% two-steps); e) $(CF_3CO)_2O$, py ; $Pd(PPh_3)_4$, CO, H_2O, THF; $AgNO_3$, Et_2O (62% three-steps); f) HCl-THF-MeOH, 1:2:2 (97%)

The present synthesis confirms the structural assignment of longifolicin. It also demonstrates the potential of long chain chiral α and γ-oxygenated allylic stannanes for efficient and convergent assemblage of mono-tetrahydrofuran acetogenins. With minor modifications the present approach should be applicable to all members of this family and related analogues, including core unit stereoisomers.[7]

Acknowledgements. This work was supported by a research grant from the National Institutes of Health (GM R0139998). We thank Professor Jerry McLaughlin for his continued assistance in providing spectral data and helpful insight regarding biological testing data and its interpretation.

References and Notes

1. Review: Cavé, A.; Figadere, B.; Laurens, A.; Cortes, D. in *Progress in the Chemistry of Natural Products*, Herz, W.; Kirby, G.W.; Moore, R.E.; Steglich, W.; Tamm, Ch, Ed. Springer -Verlag, Vienna, 1997; pp 81-288.
2. Ye, Q.; Alfonso, D.; Evert D.; McLaughlin, J.L. *Bioorg. Med. Chem.* **1996**, *4*, 537.
3. Gu, Z.-M.; Zeng, L.; Fang, X.-P.; Colman-Saizarbitoria, T.; Huo, M.; McLaughlin, J.L. *J. Org. Chem.* **1994**, *59*, 5162.
4. Most notable is the selective cytotoxicity of many of these compounds toward tumor cells. *Cf.* Zeng, L.; Ye, Q.; Oberlies, N.H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J.L. *Nat. Prod. Reports* **1996**, 275. Longifolicin exhibits ED_{50} values of 10^{-5}-10^{-7} μg/mL for lung, breast, and prostate human tumor cell lines
5. Virtually all of the acetogenins (>250) isolated to date are oils or waxy solids unsuitable for X-ray structure analysis. They occur in minute amounts as mixtures of structurally similar isomers requiring multiple chromatographic purifications.[1,4]
6. Reviews: Figadere, B. *Accts. Chem. Res.* **1995**, *28*, 359. Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**,1447. Marshall, J.A.; Hinkle K.W.; Hagedorn, C.E. *Israel J. Chem.* **1997**, *37*, 97. See also Hoye, R.R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *37*, 7001 and references cited therein.
7. a) Marshall, J.A.; Hinkle, K.W. *J. Org. Chem.* **1997**, *62*, 5989. b) Marshall, J.A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996.
8. This stannane was prepared from 1-tetradecene by the following sequence:[9]



ADD = 1,1'-(azodicarbonyl)dipiperidine

9. *Cf.* Marshall, J.A.; Welmaker, G.S.; Gung, B.W. *J. Am. Chem. Soc.* **1991**, *113*, 647.
10. Prepared from 1,8-octanediol by the sequence 1) NaH, TBSCl, THF; 2) Swern oxidation; 3) NaH, $(EtO)_2POCH_2CO_2Et$; 4) *i*-Bu_2AlH; 5) LiCl, MsCl, 2,6-lutidine as described in reference 7b.
11. Vanhessche, K.P.M.; Wang, Z.-M.; Sharpless, K.B. *Tetrahedron Lett.* **1994**, *35*, 3469.
12. Yadav, J.S.; Chander, M.C.; Rao, C.S.; *Tetrahedron Lett.* **1989**, *30*, 5455.
13. Garegg, P.J.; Samuelsson, B. *J. Chem. Soc., Perkin I* **1980**, 2866.
14. The alcohol of 97% ee is available from DMS Fine Chemicals Inc., Saddlebrook N.J.