Tetrahedron Letters,Vol.29,No.7,pp 741-744,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

SYNTHESIS OF A POSSIBLE KALLOLIDE A PRECURSOR VIA [2,3] WITTIG RING CONTRACTION OF A MACROCYCLIC FURAN DIETHER

James A. Marshall* and David J. Nelson
Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208

Summary: Treatment of the macrocyclic furan diether **16** with Li 2,2,6,6-tetramethylpiperidide in hexane-THF affords the *cis* alcohol **17**, a possible precursor of the pseudopterane diterpene kallolide A.

Recently Fenical *et al.* described the isolation and structure elucidation of kallolide A (III), a novel pseudopterane macrocyclic furano lactone diterpene possessing marked antiinflammatory activity.[1] In connection with studies on new approaches to macrocyclic natural products, we foresaw an assemblage of the essential kallolide A ring system via the [2,3] Wittig ring contraction I → II.[2] Accordingly, the macrocyclic propargylic ether I serves as the carbocyclic precursor with the connecting chain R-R' representing either the requisite β-isopropenyl alcohol moiety or, alternatively, an allylic ether that might be convertible to this moiety via a second [2,3] Wittig rearrangement (Fig. 1).

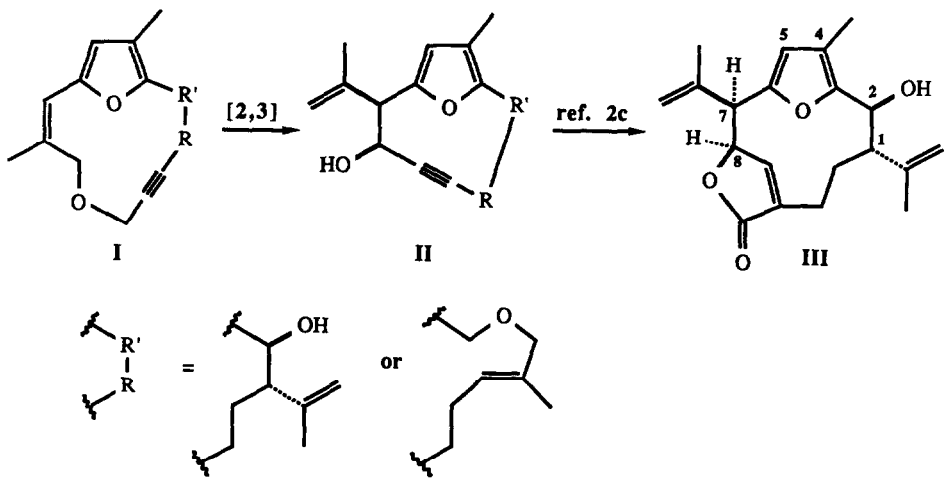


Figure 1. [2,3] Wittig ring contraction strategy for kallolide A (III)

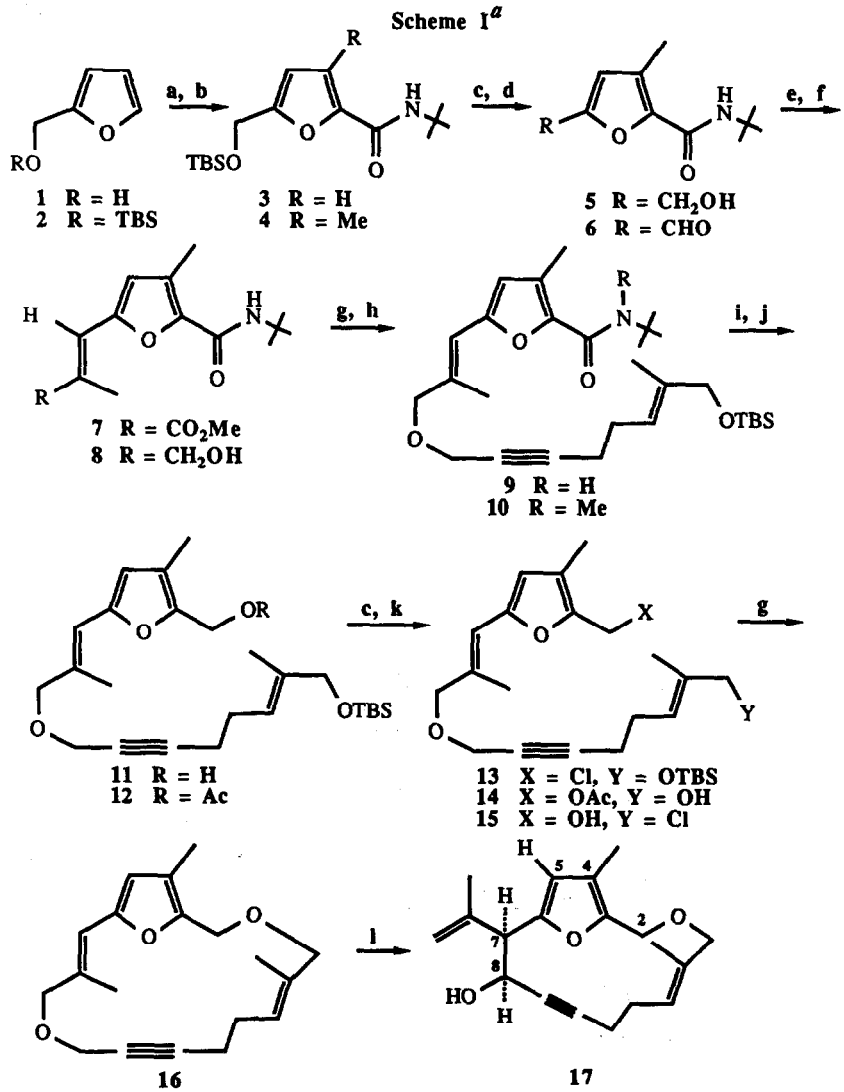
Furfuryl alcohol (1) was the starting point for this investigation. The TBS[3] ether **2** underwent smooth α'-metalation with *n*-BuLi in hexane. Subsequent *in situ* trapping with *t*-BuNCO afforded the crystalline amide **3**, mp 103-104°C, in 61% yield.[4] Directed metalation at the 3-position with 2 equivalents of *n*-BuLi and subsequent treatment with CH_3I yielded the crystalline methylated furanamide **4**, mp 83-84°C, in 69% yield.[4] Silyl ether cleavage with TBAF-HOAc[3] followed by Swern-Wittig homologation[5] led to the crystalline (*E*)-conjugated ester **7**, mp 154-155°C, in 80% overall yield. The chemical shift of the olefinic H_β proton at 7.37 ppm confirmed the assigned stereochemistry.[6]

Selective reduction of the ester **7** with DIBAH[3] yielded the alcohol **8** (96%), mp 107-108°C. Etherification of the derived magnesium salt with allylic chloride **24**, prepared as outlined in Scheme II, afforded the ether **9** in 89% yield. Attempted reduction of the amide function in **9** with a variety of reducing agents failed to give the desired alcohol **11**.[7] This transformation was eventually effected by

treatment of the *N*-methyl amide **10** with a reagent prepared by adding one mole equivalent of water to a solution of $LiAlH_4$ in THF, whereupon alcohol **11** was obtained in 55% yield along with the related tertiary amine as the principal by product.

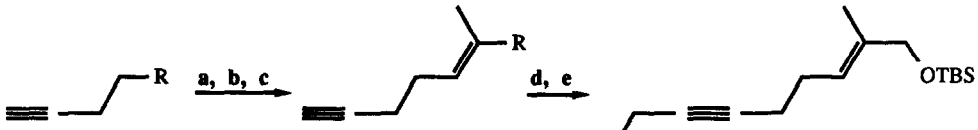
Attempts to prepare the chloride **13** were unsuccessful owing to its extreme lability. Accordingly, alcohol **11** was converted to the acetate **12** (96%) and then by TBS cleavage (94%), treatment with MsCl-LiCl[8] (54%) and acetate cleavage (84%) to chloro alcohol **15**. This unstable chloride cyclized to the diether **16** upon treatment with EtMgBr in THF-HMPA[2a] in 15% yield. This cyclization reaction has not yet been optimized. A major problem is the lability of the furan ring.

Scheme I[a]



a) *n*-BuLi, THF; *t*-BuNCO; (b) *n*-BuLi (2x), THF; CH_3I; (c) Bu_4NF, HOAc, THF; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (e) $Ph_3P{=}C(CH_3)CO_2CH_3$, CH_2Cl_2; (f) *i*-Bu_2AlH, CH_2Cl_2; (g) EtMgBr, THF, HMPA, 24; (h) KOH, DMSO, CH_3I; (i) $LiAlH_4 \cdot H_2O$, THF, inverse addition; (j) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2; (k) LiCl, 2,6-lutidine, MsCl, DMF; K_2CO_3, MeOH; (l) Li 2,2,6,6-tetramethylpiperidide, hexane-THF (10:1), -78 to -23°C.

Scheme II[a]



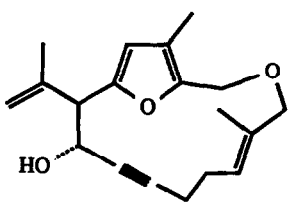
18 R = CH_2OH
19 R = CHO

20 R = CO_2Me
21 R = CH_2OH
22 R = CH_2OTBS

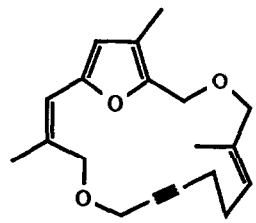
23 X = OH
24 X = Cl

(a) $Ph_3P{=}C(CH_3)CO_2CH_3$, CH_2Cl_2; (b) *i*-Bu_2AlH, Et_2O; (c) TBSCl, Et_3N, DMAP, CH_2Cl_2; (d) *n*-BuLi, THF; $(CH_2O)_n$; (e) LiCl, 2,6-lutidine, MsCl, DMF.

[2,3] Wittig rearrangements of acyclic (*E*)-crotyl propargylic ethers generally afford anti homoallylic alcohols whereas the (*Z*)-isomers lead to syn diastereomers, although exceptions are known.[9] On this basis, we expected the anti isomer **25** from the (*E*)-ether **16**. Attainment of the desired syn stereochemistry (*cf.* III) would require Mitsunobu inversion of alcohol **25**,[10,2c] or rearrangement of **26**, the (*Z*)-isomer of **16**, obtainable through proper choice of reagent in the Horner-Emmons homologation of aldehyde **6**.[11] In the event, treatment of ether **16** with Li 2,2,6,6-tetramethylpiperidide at -78 to -20°C afforded a single diastereomeric product according to high field ^1H NMR analysis. Irradiation of the carbinyl proton (H-8) caused nOe enhancement of the allylic proton (H-7) and the furan proton (H-5); irradiation of H-7 caused nOe enhancement of H-8 and H-5. Similar nOe phenomena have been found for kallolide A.[1] These observations require a syn relationship as depicted in **17**.[12,13] This finding considerably simplifies implementation of the [2,3] Wittig approach as it enables the more readily available and better behaved (*E*)-allylic ethers (*e.g.* **16**) to be employed as rearrangement precursors. Presumably, conformational constraints engendered by the macrocyclic furan diether ring system of **16** direct the [2,3] Wittig rearrangement along a pathway differing from that followed by acyclic analogs of **16**.[9] Chelation by the transannular oxygen centers may also play a role in this process.



25



26

Unfortunately, the isolated yield of rearranged alcohol **17** was only 12% (two trials) owing in large measure to the instability of the furan ring system of **16** and **17**. However, *no isomeric compounds were detected in the rearrangement reaction*, so if the instability problems can be overcome, the route should be efficient. Future work will be directed toward a solution to this problem and to the preparation of **17** in homochiral form[2e] and its further elaboration to kallolide A.

Acknowledgement. Support from the National Institute of General Medical Sciences through research grant 5-RO1 GM 29475 is gratefully acknowledged. Funds for the AM-300 NMR spectrometer used in this work were provided by NSF instrument grant CHE-8411172. Model studies on acyclic analogs of ether **16** were conducted by Dr. Scott Rothenberger to whom we are most grateful.

References and Notes

1. Look, S. A.; Burch, M. T.; Fenical, W.; Oi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.

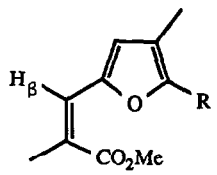
2. (a) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. (b) Takehashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315. (c) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *Tetrahedron Lett.* **1987**, *28*, 723. (d) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883. (e) Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323. (f) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860.

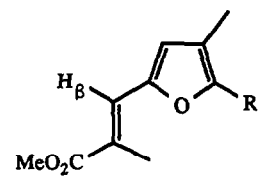
3. Abbreviations: DIBAH = di-(isobutyl)aluminum hydride; DMAP = 4-(dimethylamino)pyridine; DMF = *N,N*-dimethylformamide; DMSO = dimethyl sulfoxide; HMPA = hexamethylphosphorictriamide; 2,6-lutidine = 2,6-dimethylpyridine; MsCl = methanesulfonyl chloride; nOe = nuclear Overhauser effect; TBAF = tetra-*n*-butylammonium fluoride; TBS = *t*-butyldimethylsilyl; THF = tetrahydrofuran.

4. Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 1777; Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362.

5. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

6. The following chemical shifts were observed for Hβ in the isomeric α-furfurylidene propionic esters i-iv:





i (R = H) 6.50 ppm **iii (R = H) 7.45 ppm**
ii (R = CH_2OTBS) 6.48 ppm **iv (R = CH_2OTBS) 7.38 ppm**

S. D. Rothenberger and D. J. Nelson, unpublished results.

7. Some of the reducing agents examined: Red-Al, 1.2 equiv at 0°C → 80% of amine; DIBAH, 2.2 equiv at 25°C → 62% amine; $LiEt_3BH$, 2.2 equiv at 0°C → no reaction; $LiAlH_4$, 0.25 equiv at 25° → 30-50% of alcohol **11**. For a discussion, see Nelson, D. J. *Master's Thesis.* University of South Carolina, 1988.

8. Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

9. Nakai, T.; Mikimi, K. *Chem. Rev.* **1986**, *86*, 885. S. D. Rothenberger and D. J. Nelson, unpublished results.

10. Mitsunobu, O. *Synthesis* **1981**, 1.

11. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

12. Dreiding models show that the furan H is roughly equidistant from H-7 and H-8 in a conformation where the dihedral angle of H-7 and H-8 is near 0°.

13. We are indebted to Dr. S. L. Crooks for carrying out the nOe experiments and for assistance with molecular modeling via Still's MacroModel program.

(Received in USA 22 July 1987)