Pergamon

Tetrahedron Letters 41 (2000) 1347–1350

TETRAHEDRON LETTERS

A new synthesis of 3-carboxy-2,5-disubstituted furans and their conversion to 5-vinyl derivatives

James A. Marshall * and Dong Zou

Department of Chemistry, University of Virginia, Charlottesville, VA 22904, USA

Received 8 November 1999; accepted 29 November 1999

Abstract

A new route to the title compounds is described. The key transformation involves treatment of a 2-(4-keto-2-alkynyl)-3-ketobutanoate with silica gel or Et_3N to effect ring closure and subsequent double bond isomerization.

Keywords: cyclization; furans; diones; isomerization.

Cembranes are a large group of macrocyclic diterpenes isolated from diverse sources including pine trees, soft coral, and ants.[1] A subgroup of these compounds contains a furan ring and a butenolide embedded within a 12- or 14-membered carbocycle. Some of the more structurally and biologically interesting members of this subgroup feature a 3-carboxy-2,5-furan system (Fig. 1).[2a]

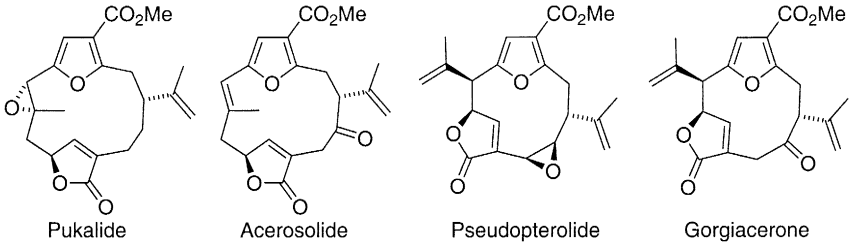
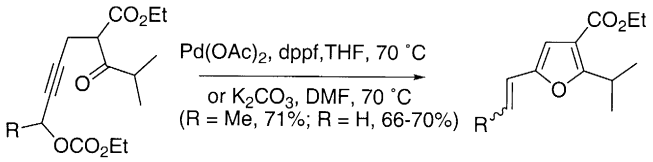


Fig. 1. Representative furanocembrane and pseudopterolide natural products

A number of synthetic routes to 3-methyl-2,5-dialkyl and 3-methyl-2-alkyl-5-vinyl substituted furans have been reported.[2a–c] However, general routes to the 3-carboxy 5-vinyl analogues are less common.[3,4] A recent method utilizes the Pd(0) or base-catalyzed ring closure of an α-propargylic β-keto ester to prepare prototype 2-isopropyl-3-carboxy-5-vinyl furans (Eq. (1)).[5]

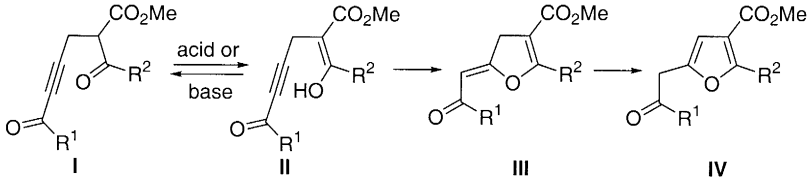
* Corresponding author. Tel: +00 804-924-7997; fax: +00 804-924-7993; e-mail: jam5x@virginia.edu (J. A. Marshall)

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02290-X



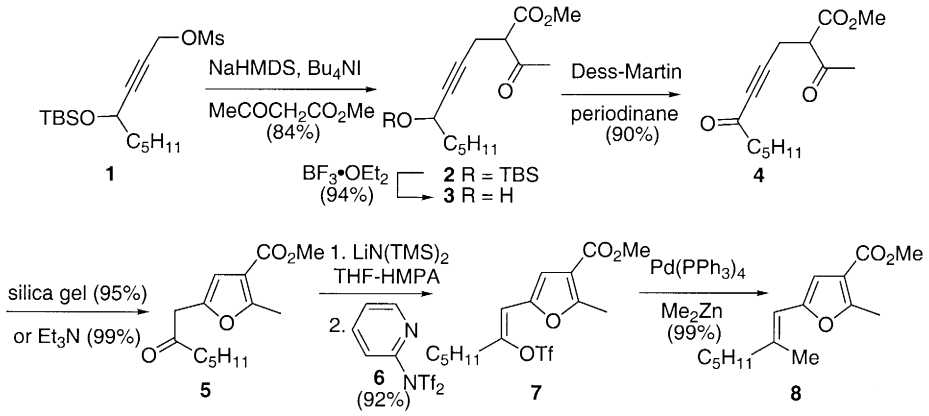
(1)

We have developed a mild and potentially versatile synthesis of 3-carboxy furans and effected the transformation of these intermediates to 5-vinylfurans with structural features required for the construction of furanocembrane (14-membered) and pseudopterane (12-membered) natural products (Fig. 1).[2a] The essence of our approach is detailed in Eq. (2). Accordingly, a β-keto ester such as **I** was expected to undergo acid- or base-catalyzed enolization and ensuing intramolecular 1,4-addition to the alkynone to afford a vinylic ketone **III**. Subsequent double bond isomerization would afford the furan **IV**. The carbonyl substituent of this intermediate could then be further transformed to a vinylic substituent with the desired substitution pattern.



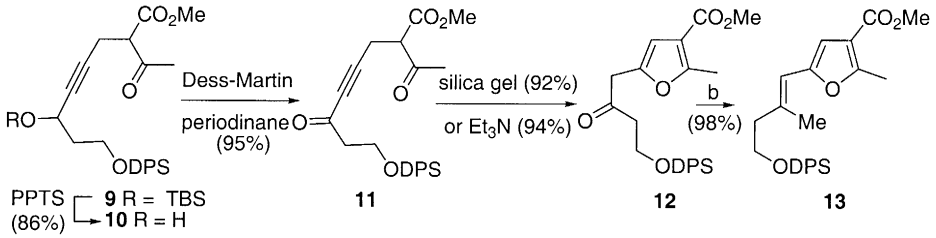
(2)

Our initial studies were conducted with β-keto ester **2** obtained by alkylation of methyl acetoacetate with mesylate **1** (Scheme 1).[6] Deprotection and Dess–Martin oxidation[7] afforded diketone **4** in high overall yield. Upon brief exposure to silica gel in hexane, diketone **4** was converted to furan **5** in near quantitative yield. This cyclization could also be effected, in quantitative yield, by exposure of diketone **4** to Et_3N in hexanes. Methylation was achieved via the enol triflate **7**[8] through treatment with Me_2Zn in the presence of $Pd(PPh_3)_4$. The stereochemistry of the vinylfuran **8** was confirmed through NOE measurements. None of the (*Z*)-isomer could be detected. The direct sp^2–sp^3 coupling leading to vinylfuran **8** is noteworthy for its efficiency.[9]



Scheme 1. (a) TBS=*t*-$BuMe_2Si$, NaHMDS=$NaN(TMS)_2$

A second application of the new methodology is outlined in Scheme 2. This sequence starts from the β-keto ester **9**[10] and proceeds via diketone **11** along the lines described in Scheme 1. As before, cyclization to the keto furan **12** proceeds in high yield by treatment with silica gel or Et_3N.



Scheme 2. (a) DPS=*t*-BuPh$_2$Si, PPTS=pyridinium *p*-toluenesulfonate; (b) (i) LiN(TMS)$_2$, THF–HMPA; (ii) 2-(C$_5$H$_4$N)NTf$_2$ (**6**), (90%); (iii) Pd(PPh$_3$)$_4$, Me$_2$Zn (95%)

The foregoing route to 3-carboxyfurans should be well suited to the synthesis of furanocembranes such as pukalide. In fact, preliminary findings on a 'furan last'[2] approach show great promise.[11] These studies are currently in progress and will be reported in due course.

1. Representative procedures

*1.1. 2-Methyl-3-carbomethoxy-5-(2-ketoheptyl)furan (**5**)*

Silica gel procedure: To a stirred solution of 100 mg of ketone **4** in 10 mL of hexanes was added 1 g of silica gel. The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated and the residue was purified by flash column chromatography with 10% EtOAc-hexanes as eluent to afford 95 mg (95%) of furano ketone **5**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.42 (s, 1H), 3.80 (s, 3H), 3.63 (s, 2H), 2.53 (s, 2H), 2.44 (t, 2H), 2.53 (m, 2H), 1.26 (m, 5H), 0.86 (t, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 250.8, 164.3, 158.9, 146.3, 114.1, 108.9, 51.2, 41.9, 41.8, 31.2, 23.2, 22.4, 13.8, 13.7. Anal. calcd for C$_{14}$H$_{20}$O$_4$: C, 66.65; H, 7.99. Found: C, 66.43; H, 8.00.

Et$_3$N procedure: To a solution of 90 mg of ketone **4** in 10 mL of hexanes was added 0.05 mL of Et$_3$N at room temperature. The mixture was stirred at room temperature for 5 min and quenched with brine. The mixture was extracted with ether twice and the combined ether extracts were dried over MgSO$_4$ and filtered through silica gel. The filtrate was concentrated to afford 89 mg (99%) of furano ketone **5**.

1.2. 2-Methyl-3-carbomethoxy 5-[(E)*-2-methyl-1-heptenyl]furan (**8**)*

To a solution of 30 mg (0.12 mmol) of furano ketone **5** in 1.2 mL of anhydrous THF at −78°C was added 0.3 mL of HMPA and 0.13 mL (0.13 mmol) of 1.0 M LHMDS in hexanes. The mixture was stirred for 15 min and a solution of 71 mg (0.24 mmol) of Commin's reagent **6**[7] in THF was added. The cooling bath was removed and, after 1 h, water and ether were added. The mixture was extracted with ether three times and the combined extracts were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with 10% EtOAc-hexanes as eluent to afford 44 mg (95%) of triflate **7**. ^{1}H NMR (CDCl$_3$): δ 6.77 (s, 1H), 5.98 (s, 1H), 3.82 (s, 3H), 2.60 (s, 3H), 2.46 (t, 2H), 1.59 (m, 2H), 1.35 (m, 4H), 0.93 (m, 3H) ppm.

To a stirred solution of 35 mg of triflate **7** in 1 mL of THF at 0°C was added 4 mg of Pd(PPh$_3$)$_4$. The mixture was stirred for 15 min and 0.27 mL of Me$_2$Zn (1.0 M solution in heptane) was added. The mixture was allowed to warm to rt slowly and stirred for 24 h. The reaction was quenched with water and the mixture was extracted with ether twice. The combined ether layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash column chromatography with 5% EtOAc-hexanes as eluent to afford 22 mg (99%) of furan **8**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.39 (s, 1H), 5.99 (s, 1H), 3.82

(s, 3H), 2.56 (s, 3H), 2.14 (t, 2H), 1.94 (s, 3H), 1.49 (m, 2H), 1.40–1.20 (m, 4H), 0.89 (t, 3H) ppm. Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.99.

Acknowledgements

Financial support was provided by research grant GM29475 from the National Institutes of General Medical Sciences.

References

1. Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A.; *Progress in the Chemistry of Organic Natural Products* **1979**, *36*, 286.
2. (a) Marshall, J. A. *Recent Res. Devel. in Organic Chem.* **1997**, 1. (b) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (c) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687.
3. Access to these compounds has typically involved the synthesis of a 5-formyl derivative and subsequent Wittig-type condensation[4a] or Pd(0)-catalyzed coupling of a 5-furanylzinc halide or tributylstannane with a vinylic halide[4b] to install the vinyl substituent.
4. (a) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910. Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem*. **1996**, *61*, 5729. (b) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283. (c) Paterson, I.; Brown, R. E.; Urch, C. J. *Tetrahedron Lett*. **1999**, *40*, 5807.
5. Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132.
6. This mesylate was prepared from 1-octyn-3-ol (Aldrich 12,728-0) by the sequence (1) silylation; TBSCl, imidazole (99%) (2) formylation; BuLi $(CH_2O)_n$ (89%) (3) mesylation; MsCl, Et_3N (94%).
7. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
8. Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77.
9. Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229. Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Organic Lett.* **1999**, *1*, *in press.*
10. The β-keto ester was prepared from 1,3-propanediol by the sequence (1) silylation; *t*-$BuPh_2SiCl$ (DPSCl), imidazole (64%) (2) Swern oxidation; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (84%) (3) acetylide addition; $LiC{\equiv}CCH_2OPMB$, THF (96%) (4) silylation; TBSCl, imidazole (95%) (5) PMB cleavage; DDQ, CH_2Cl_2, H_2O (81%) (6) mesylation; MsCl, Et_3N (95%) (7) alkylation; $MeCOCH_2CO_2Me$, NaHMDS, Bu_4NI, THF (62%).
11. The following example (Zou, D.; VanDevender, E. A., unpublished) is illustrative: