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Synthesis of the Cyclohexan Subunit of Baconipyrones A and B from Furan

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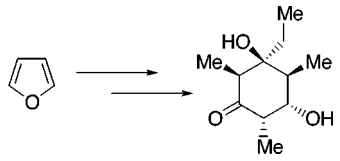
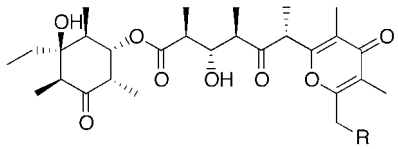
ABSTRACT

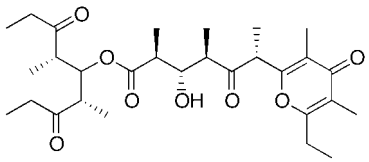


The synthesis of the cyclohexan subunit of the siphonariid metabolites baconipyrones A and B from furan is described. A key step included the alkylative ring opening of 7-oxanorbornenic sulfone 4 and oxidative desulfonylation of compound 8.

Pulmonate molluscs of the genus *Siphonaria* are a source of secondary metabolites of the polypropionate class.[1] Among these, baconipyrones A and B isolated in 1989 by Faulkner et al.[2] (Figure 1), constitute an exception to the normal polypropionic skeleton[3] since they do not contain the expected carbon sequence typical of this polyketide family.[4] To date no total synthesis of baconipyrones A anb B has been published, albeit the total synthesis of (−)-baconipyrone C (Figure 1) has been recently reported by Paterson et al.[5]



baconipyrone A (R=Me)
baconipyrone B (R=H)



baconipyrone C

Figure 1.

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(1) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep*. **1998**, *15*, 477, and references therein.

(2) Manker, C. D.; Faulkner, D. J.; Stout, J. T.; Clardy, J. *J. Org. Chem*. **1989**, *54*, 5371.

(3) For an interesting report on noncontiguous polypropionates from marine molluscs, see: Brecknell, D. J.; Collet, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497.

(4) According to Davies-Coleman et al.[3] "baconipyrones are proposed to be rearrangement products generated from a siphonariid precursor..." or "are generated as artifacts during the extraction."

(5) Paterson, I.; Chen, D. Y.; Aceña, J. L.; Franklin, A. S. *Org. Lett*. **2000**, *2*, 1513.

(6) Paterson, I.; Franklin, A. S. *Tetrahedron Lett*. **1994**, *35*, 6925.

(7) Black, K. A.; Vogel, P. *J. Org. Chem*. **1986**, *51*, 5341. Compound **1** has been synthesized in optically pure form ($[\alpha]_D = +235.0$) starting from (+)-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl camphanate. In this preliminary account racemic **1** has been used.

(8) For a review on the use of 7-oxanorbornenic derivatives (Diels−Alder adducts of furan) as synthetic intermediates, see: Arjona, O.; Cossy, J.; Plumet, J.; Vogel, P. *Tetrahedron* **1999**, *55*, 13521

(9) The referee suggests a possible improvement of the yield of this process by application of a procedure previously described: Warm, A.; Vogel, P. *J. Org. Chem*. **1986**, *51*, 5348. We thank the referee for this valuable suggestion, which will be tested soon.

(10) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett*. **1980**, *21*, 1357. (b) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem*. **1987**, *52*, 188. (c) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem*. **1985**, *50*, 3946.

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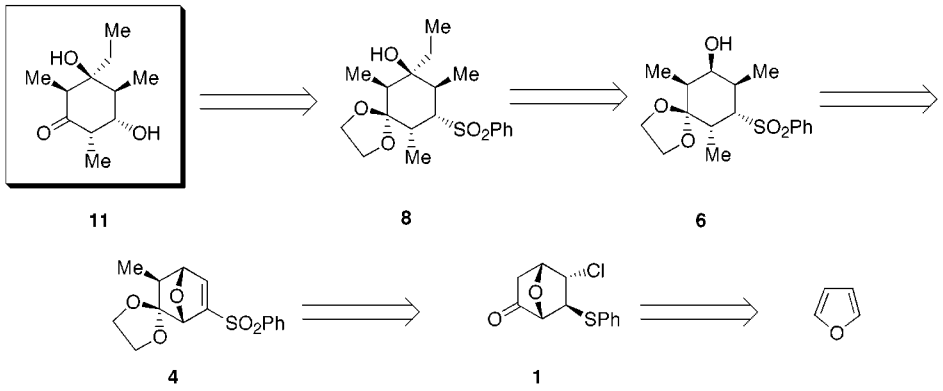
Scheme 1



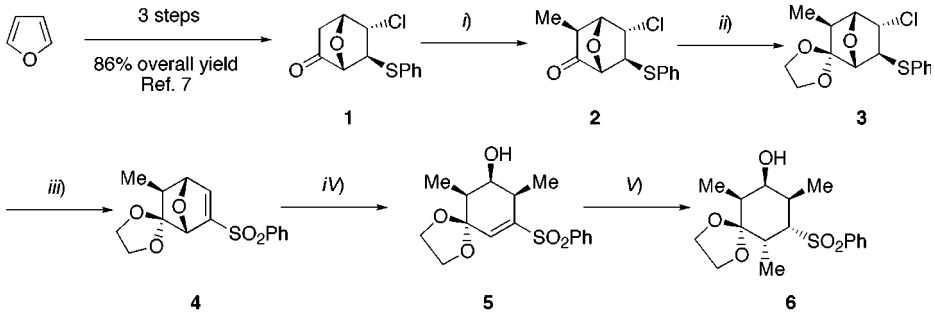
Previously, an enantiocontrolled synthesis of the γ-pyrone subunit of these compounds was also reported by the same authors.[6]

In this paper we wish to account for the synthesis of the cyclohexan subunit of baconipyrones A and B from furan via the oxanorbornenic derivative **1** (Scheme 1). The synthetic plan was designed as follows. Methylation of **1**, followed by protection of the carbonyl group, oxidation of the phenylsulfenyl moiety and dehydrochlorination would provide the vinyl sulfone **4**. Stereoselective *exo*-alkylative ring opening of **4**, followed by 1,4-addition of MeLi to the resulting cyclohenenyl sulfone will provide **6**, with the correct configuration of the three methyl groups. The relative configuration of the ethyl group in **8**, *trans* to the α,α′ dimethyl groups, could be obtained by oxidation of the hydroxyl group followed by addition of ethylmagnesium bromide. Finally, the oxidative desulfonylation of **8**, followed by stereocontrolled reduction of the resulting hydroxyl group and deprotection of the ketal functionality would give rise to the desired compound **11**.

Compound **1** was prepared in three steps (86% overall yield) from furan according to the procedure previously described by P. Vogel et al.[7] starting from furan.[8] Alkylation of **1** with lithium bis(trimethylsilyl)amide (LHMDS) and IMe gives ketone **2** in 40% overall yield. In this reaction 45% of starting **1** was recovered and recycled.[9] Using other reaction conditions (*t*-BuOK, IMe), substantial amounts of α,α′-dialkylated ketone were obtained as byproduct. Protection of the carbonyl group as ethylenacetal using 1,2-bis-(trimethylsilyloxy)-ethane in the presence of TMSOTf[10] affords **3**, which after oxidation of the phenylsulfide moiety with monoperoxyphthalic acid magnesium salt (MMPP) followed by dehydrochlorination with DBU yields vinyl sulfone **4** in 82% overall yield (two steps). The S_N2' ring opening of **4** using MeLi in THF[11] gives cyclohexenyl sulfone **5**, which after Michael addition of MeLi followed by hydrolysis with a saturated aqueous NH_4Cl solution affords sulfone **6** (Scheme 2).[12]

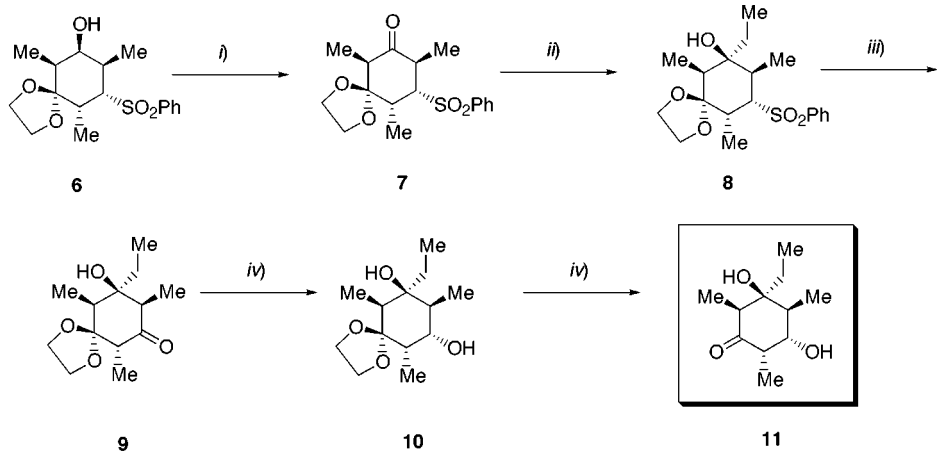
With sulfone **6** in our hands, the synthetic sequence was completed as follows (Scheme 3). Swern's oxidation of **6** followed by addition of EtMgBr to the ketone **7** gives alcohol **8** with total stereoselectivity. Oxidative desulfonylation of **8** to afford ketone **9** appeared to be a critical step of this synthetic route. After considerable experimentation, the best conditions were those reported by Yamada et al.[13] (LDA, THF/DMPU, followed by treatment with oxygen). Under these conditions 54% of ketone **9** was obtained. Reduction of the carbonyl group with $BH_3{\cdot}SMe_2$ yielded the desired

Scheme 2



Scheme 2. Key: *i*) LHMDS, IMe, -78°C, THF, 40%; *ii*) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 91%.; *iii*) a) MMPP, MeOH, 0°C, 96%; b) DBU, CH_2Cl_2, 0°C, 85%; *iv*) MeLi, THF, -78°C, 95%; *v*) MeLi, THF, -78°C to 0°C, then NH_4Cl aq., 81%.

Scheme 3



Scheme 3. Key: *i*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 82%; *ii*) EtMgBr, Et_2O, 0°C, 70%; *iii*) a) LDA, THF:DMPU, -20°C; b) O_2, -20°C, 54%; *iv*) $BH_3{\cdot}SMe_2$, THF, 0°C, 74%; *v*) $CeCl_3{\cdot}7H_2O$, NaI, CH_3CN, 65°C, 87%.

equatorial alcohol **10** as the only diastereomer. Finally, deprotection of **10** with $CeCl_3{\cdot}7H_2O$ in the presence of NaI[14] afforded **11**.

In summary, the cyclohexan subunit of baconipyrones A and B has been synthesized starting from furan in 15 steps and 4% overall yield. Considering that the remaining fragment of these compounds, conveniently functionalized, was obtained by Paterson et al.[5] using methodologies based on the aldol reaction, the way for the total synthesis of baconipyrones A and B is now opened.

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Supporting Information Available: Copies of NMR spectra for key compounds **6**, **8**, **9**, **10** and **11** and description of all experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906.

(12) This transformation can be achieved without isolation of the intermediate vinyl sulfone **5**. In this case the overall yield for the transformation of **4** into **6** is 59%.

(13) Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett.* **1984**, *25*, 3239.

(14) Marcantoni, E.; Nobili, F. *J. Org. Chem.* **1997**, *62*, 4183.