Palladium Catalyzed Synthesis of the Furanoterpene Ircinin-4

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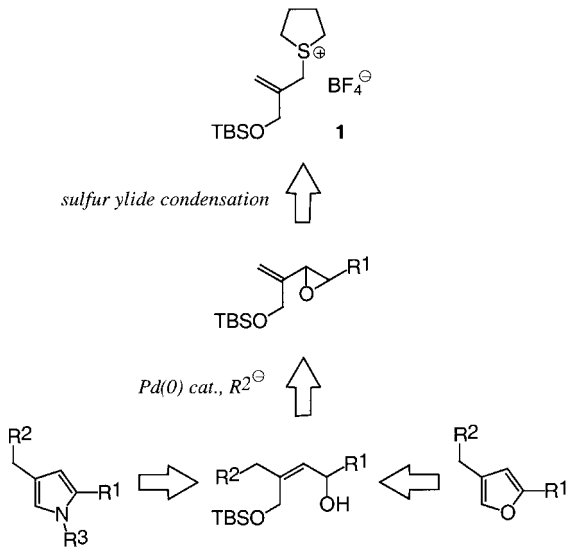
Abstract: A flexible entry into 2,4-disubstituted furan derivatives is outlined employing sulfonium salt **1** as a well accessible starting material. Condensation of the sulfur ylide derived from **1** with aldehydes, palladium catalyzed opening of the vinyloxirane thus formed, and a final oxidative cyclization of the furan ring constitute the key steps of this method. Its utility is exemplified by the first total synthesis of the marine natural product ircinin-4 (**2**).

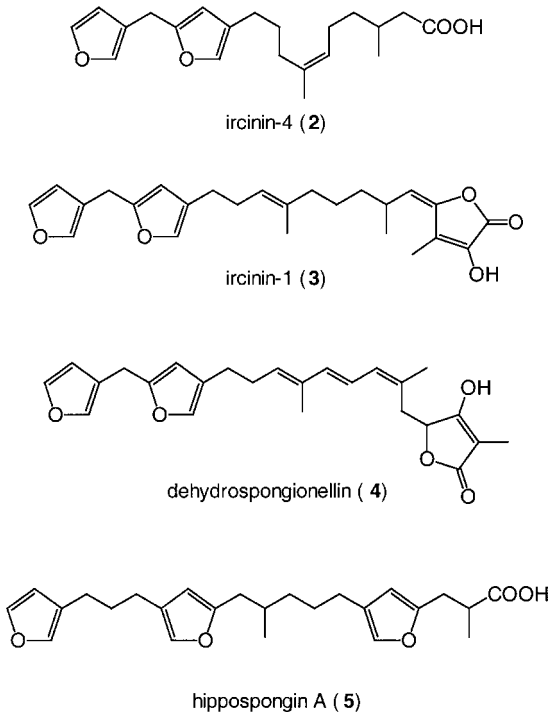
Key words: furan, palladium, sulfur ylide, terpene, marine natural product

The central role of heterocycles in life sciences and natural product chemistry provides a constant drive for the development of even more efficient methods for their preparation. In this context, we have recently identified the functionalized sulfonium salt **1** as a valuable building block for the formation of pyrroles and have demonstrated its utility by a concise approach to the complex anti-tumor alkaloid roseophilin.[1] Quite obviously, the underlaying strategy (Scheme 1) may serve as a more general platform for the formation of different types of heterocycles. The first total synthesis of ircinin-4 (**2**) outlined below now extends this concept to the furan series.



Scheme 1

2,4-Disubstituted furan derivatives are particularly difficult to make by conventional methods.[2] This structural motif, however, is present in various physiologically active natural products such as **2**-**5** isolated from marine sources (Scheme 2).[3,4] Among them, the ircinin family of furanoterpenes produced by the mediterranean sponges *Ircinia oros* and *I. fasciculata* deserves mentioning due to issues related to their biosynthesis[5] and, more importantly, because of the interesting biological effects exerted by these compounds. Specifically, they exhibit high activity in the brine shrimp assay and one member of this series turned out to be a selective inhibitor of phospholipase A_2.[3]



Scheme 2

As part of our program aiming at the synthesis of bioactive natural products by organometallic means[6] we decided to probe the envisaged entry into furans by an application to this class of secondary metabolites. Since no preparative studies on ircinin-4 (**2**) have been reported so far, we chose this particular compound as our prime target. As shown in Scheme 3, **2** may be readily assembled via alkylation of the side chain surrogate **7** with the furanylmethylfuran derivative **6** which itself can be traced back to substrate **1**. If successful, this convergent approach can be easily adapted to the synthesis of other furanoterpene dervatives as well.

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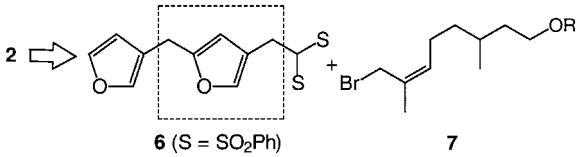
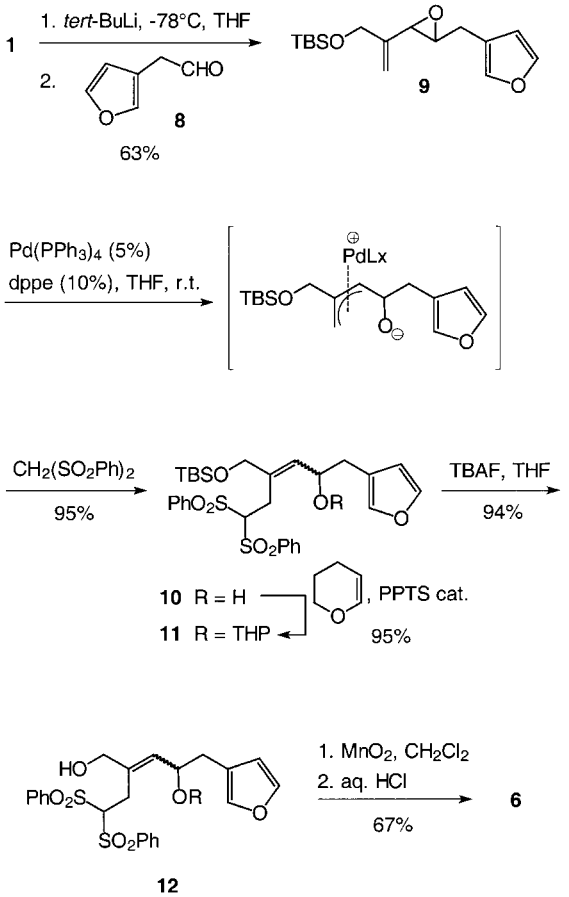


Scheme 3

Our synthesis of segment **6** (Scheme 4) starts from 3-furylacetaldehyde **8**[7] which reacts with the sulfur ylide formed from **1** by deprotonation with *tert*-BuLi[1] to afford the desired epoxide **9** in 63% yield. Treatment of this compound with catalytic amounts of $Pd(PPh_3)_4$ selectively activates its vinyloxirane entity without affecting the adjacent allyl ether site.[8] The alkoxide unit of the resulting functionalized π-allylpalladium complex deprotonates admixed bis(phenylsulfonyl)methane which, in turn, attacks the electrophilic organopalladium species in a regioselective manner at the terminal C-atom to afford allylic alcohol **10**[9] in very high yield. Attempts to transform this compound directly into the desired furanylmethylfuran **6** by oxidation of its *secondary* alcohol and subsequent dehydrative cylization resulted in rather poor yields.[10] A viable alternative, however, was found by reversing the oxidation pattern: thus, temporary protection of the –OH group of **10** as a THP acetal **11**[11] followed by fluoride induced cleavage of the TBS group sets the stage for a selective oxidation of the *primary* allylic alcohol.



Scheme 4

Exposure of this derivative **12** to MnO_2 and subsequent treatment of the resulting aldehyde with aq. HCl cleanly provides the desired furanylmethylfuran derivative **6** which was isolated in 67% yield. The structural integrity of this key building block was deduced from NMR, MS and IR data as well as from an X-ray analysis (Figure 1).[12,13]

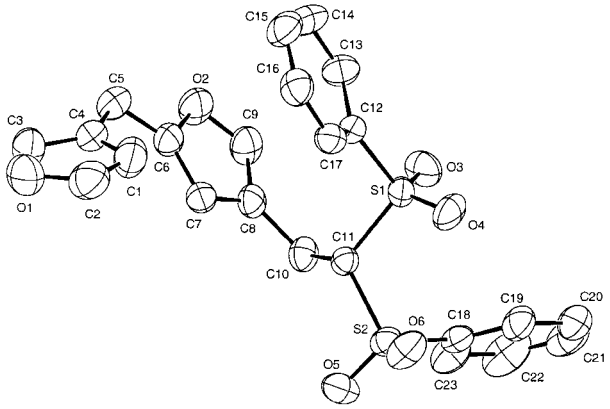
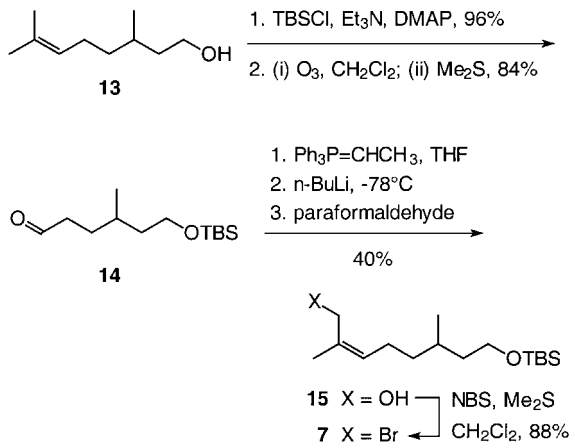


Figure 1. Structure of compound **6** in the crystal. Selected bond length [Å], bond angles [°] and torsion angles [°] (estimated standard deviations are given in parentheses): O(1)-C(2) 1.352(4); O(1)-C(3) 1.361(5); O(2)-C(6) 1.375(3); O(2)-C(9) 1.372(3); C(4)-C(5) 1.496(4); C(5)-C(6) 1.490(4); C(8)-C(10) 1.502(3); C(10)-C(11) 1.526(3); S(1)-C(11) 1.818(2); S(2)-C(11) 1.826(2); C(2)-O(1)-C(3) 105.8(3); C(6)-O(2)-C(9) 106.7(2); C(4)-C(5)-C(6) 113.9(2); C(11)-S(1)-C(12) 105.2(1); C(11)-S(2)-C(18) 107.5(1); S(1)-C(11)-S(2) 112.6(1); C(1)-C(4)-C(5)-C(6) 51.0; C(4)-C(5)-C(6)-C(7) 5.4; C(9)-C(8)-C(10)-C(11) 118.3; C(8)-C(10)-C(11)-S(1) –71.4; C(8)-C(10)-C(11)-S(2) 159.0

β-Citronellol **13** serves as an obvious starting material for the preparation of the required side chain **7** (Scheme 5). For this purpose, **13** was converted into aldehyde **14** by two routine steps[14] in excellent yield on a multigram scale; the latter was then subjected to the modified Wittig reaction for the preparation of trisubstituted olefins.[15] Thus, reaction of **14** with ethylidenetriphenylphosphorane followed by treatment of the resulting betaine with *n*-BuLi at –78°C forms a deeply red colored β-oxido phosphonium ylide which was quenched



Scheme 5

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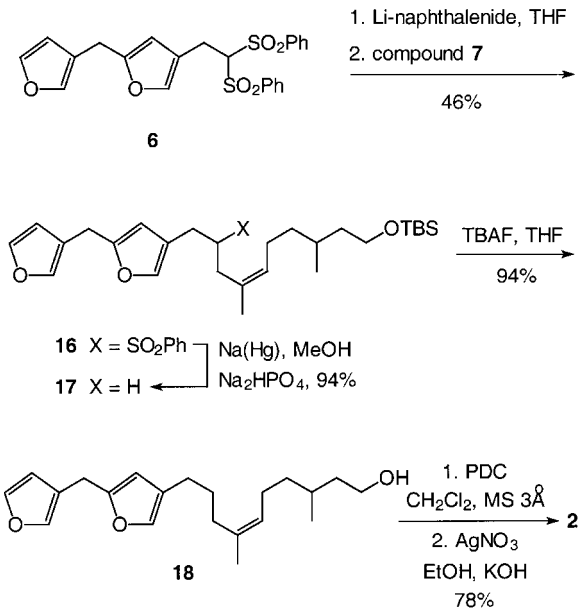
with excess paraformaldehyde to deliver (*Z*)-configurated allyl alcohol **15** as a single isomer. Although the chemical yield was moderate, the preparative ease and the stereospecific course render this transformation sufficiently attractive for our purposes. **15** was then converted into bromide **7** under standard conditions.[12,16]

Reductive metalation of bis-sulfone **6** with lithium naphthalenide[17] followed by addition of the allylic bromide **7** provides the desired coupling product **16**; despite considerable experimentation, however, the yield did not exceed 46% (Scheme 6). The remaining sulfone group was then removed with Na(Hg) (6% *w/w*) in buffered MeOH as the reaction medium (**16**→**17**)[18] and the silyl ether was cleaved with TBAF in aqueous THF. Due to the inherent lability of the furan rings towards oxidation, the conversion of the resulting alcohol **18**[12] to the target must be carried out under carefully controlled conditions and was best achieved by a two step protocol comprising treatment with PDC in CH_2Cl_2[19] followed by oxidation of the resulting crude aldehyde with $AgNO_3$ in ethanolic KOH solution.[20] The analytical and spectroscopic data of ircinin-4 (**2**) thus formed are in full agreement with those reported in the literature.[12,3a]



Scheme 6

Further studies on the scope of this new approach to furan derivatives are in progress and will be reported in due course.

Acknowledgement

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(5) Note that ircinin-4 (**2**) contains 21 (!) C-atoms. This raises the question whether its biosynthesis proceeds by degradation of a sesterterpene or by addition of a C-1 unit to a diterpenoid precursor. Arguments in favor of the former possibility are launched in: Minale, L.; Cimino, G.; De Stefano, S.; Sodano, G. *Fortschritte der Chemie Organischer Naturstoffe* **1976**, *33*, 1-72.

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(9) Compounds **9**-**12** are obtained as mixtures of stereoisomers. Since all of them converge into product **6**, the synthesis depicted in Scheme 4 was carried out with these mixtures and no attempts were made to isolate the individual compounds.

(10) For related furan syntheses see: (a) Cyclization of γ-hydroxy-α,β-unsaturated aldehydes formed in situ by reduction of γ-hydroxy-α,β-unsaturated nitriles: Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett*. **1981**, *22*, 2187-2190. (b) Oxidation of 2-butene-1,4-diol derivatives: Nishiyama, H.; Sasaki, M.; Itoh, K. *Chem. Lett*. **1981**, 1363-1366.

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(12) Selected analytical and spectroscopic data of key compounds: **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.83 (m, 4H), 7.68-7.59 (m, 2H), 7.54-7.45 (m, 4H), 7.35 (t, *J* = 1.7 Hz, 1H), 7.22 (m, 1H), 6.90 (m, 1H), 6.23 (m, 1H), 5.61 (m, 1H), 4.54 (t, *J* = 5.4 Hz, 1H), 3.60 (s, 2H), 3.28 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 142.9, 139.7, 139.2, 138.1, 134.5, 129.4, 129.0, 120.7, 120.3, 111.1, 106.3, 84.1, 23.9, 21.7. MS: *m/z* (rel intensity) 456 (19), 316 (16), 315 (74), 314 (19), 252

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(14), 251 (71), 174 (10), 173 (15), 172 (10), 170 (12), 169 (87), 168 (100), 141 (31), 125 (23), 117 (16), 116 (10), 115 (30), 91 (18), 81 (60), 78 (11), 77 (62), 53 (11), 51 (14). IR: 3108, 3065, 2921, 1614, 1584, 1551, 1501, 1482, 1450, 1433, 1380, 1340, 1313, 1238, 1199, 1186, 1155, 1142, 1109, 1080, 1022, 979, 950, 929, 873, 832, 818, 791, 764, 726, 692, 654, 617, 604, 558, 532, 508 cm^{-1}. HR-MS ($C_{23}H_{20}O_6S_2$): *calcd.* 456.07013; *found* 456.06868. Anal. *calcd*. for $C_{23}H_{20}O_6S_2$: C, 60.51; H, 4.42; *found*: C, 60.38; H, 4.46.

7: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (dt, *J* = 7.4, 1.3Hz, 1H), 3.96 (s, 2H), 3.69-3.55 (m, 2H), 2.16-1.94 (m, 2H), 1.84-1.77 (m, 3H), 1.63-1.13 (m, 5H), 0.90-0.84 (m, 12H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.0, 131.3, 61.3, 39.8, 36.6, 32.3, 29.1, 26.0, 25.5, 21.8, 19.5, 18.3, -5.3. MS: *m/z* (rel intensity) 137 (30), 95 (39), 81 (100), 75 (18), 73 (18), 69 (24), 67 (12), 57 (25), 55 (12). IR: 3030, 2956, 2928, 2857, 1733, 1662, 1472, 1463, 1380, 1361, 1256, 1205, 1099, 1034, 1006, 939, 897, 836, 810, 775, 731, 639 cm^{-1}. Anal. *calcd.* for $C_{16}H_{33}BrOSi$: C, 55.00; H, 9.52; *found*: C, 55.11; H, 9.39.

18: ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.38 (m, 1H), 7.30 (m, 1H), 7.11 (m, 1H), 6.34 (m, 1H), 5.94 (m, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 3.73 (bs, 2H), 3.70-3.55 (m, 2H), 2.40-2.30 (m, 2H), 2.10-1.85 (m, 4H), 1.67 (m, 3H), 1.67-1.46 (m, 4 H), 1.42-1.08 (m, 4 H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 154.2, 143.0, 139.8, 137.5, 134.9, 126.2, 125.7, 121.7, 111.3, 107.3, 61.0, 40.1, 37.6, 31.4, 29.4, 28.4, 25.3, 24.9, 24.1, 23.1, 19.4. MS: *m/z* (rel intensity) 330 (25), 229 (13), 175 (25), 174 (10), 163 (12), 162 (100), 81 (31), 55 (13), 41 (18). HR-MS ($C_{21}H_{30}O_3$): *calcd.* 330.21950; *found* 330.22000.

2: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (t, *J* = 1.6 Hz, 1H), 7.27 (m, 1H), 7.08 (m, 1H), 6.30 (m, 1H), 5.88 (m, 1H), 5.09 (t, *J* = 7.1 Hz, 1H), 3.71 (bs, 2H), 2.37-2.25 (m, 2H), 2.18-1.84 (m, 6H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.64-1.49 (m, 2 H), 1.42-1.13 (m, 3 H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 154.6, 142.9, 139.7, 137.4, 135.3, 125.9, 125.0, 121.3, 111.2, 107.3, 41.1, 36.9, 31.4, 29.9, 28.2, 25.2, 24.8, 24.1, 23.3, 19.5. MS: *m/z* (rel intensity) 344 (23), 229 (12), 175 (25), 163 (12), 162 (100), 81 (24). HR-MS ($C_{21}H_{28}O_4$): *calcd.* 344.19876; *found* 344.19637.

(13) Crystal structure analysis of compound **6**: colorless crystals grown from EtOAc; $C_{23}H_{20}O_6S_2$; M_r = 456.51 g·mol^{-1}; crystal size 0.63 x 053 x 0.42 mm; a = 12.0473(7), b = 15.7355(10), c = 12.0565(6) Å, V = 2141.1(2) Å^3; β = 110.480(5)°; T = 293 K; d_{cal} = 1.416Mg·m^{-3}; Z = 4, space group: monoclinic, ***P*2$_1$/n** (No. 14); θ range for data collection: 2.06 to 27.41°; 5106 collected reflections, 4882 unique reflections, refinement method: full matrix least squares on F_2; final R indices: R(F) = 0.039, wR_2 = 0.143. The complete set of data has been deposited at the Cambridge Crystallographic Data Center, Cambridge, U.K., under the deposition number CCDC 103522.

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