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Stannylfuranones in Synthesis: Highly Enantioselective Preparation of (+)-Hamabiwalactone B

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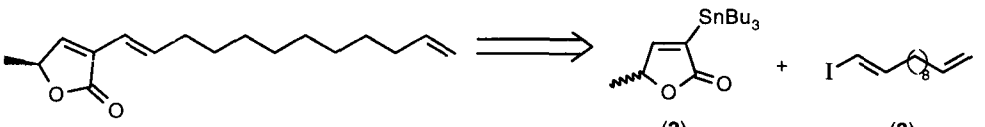
Abstract

An unambiguous and highly enantioselective total synthesis of the naturally-occurring 2(5H)-furanone hamabiwalactone B has been achieved. The key step is a Stille coupling of novel stannylfuranone **2** with (*E*)-iodoalkene **3**. The enantiomeric purity of the synthetic natural product was ≥99%, as judged by chiral HPLC.

Keywords: Stille reaction, 2(5H)-Furanone, hamabiwalactone, *Litsea Japonica*.

Many natural and bioactive compounds contain the 2(5H)-furanone subunit [1]; we have developed methodology to allow synthesis of such compounds *via* palladium-catalyzed cross-coupling of 3- and 4-tributylstannyl 2(5H)-furanones with aryl iodides [2]. We herein report the first preparation of a 3-tributylstannyl 2(5H)-furanone bearing an asymmetric centre and describe how this compound was used to synthesize and confirm the stereochemistry of hamabiwalactone B (Figure 1), a 2(5H)-furanone isolated from the roots of *Litsea Japonica*



(+)-Hamabiwalactone B (**1**) (**2**) (**3**)

isolated from *Litsea Japonica*
$[\alpha]_D$ +2, absolute configuration unknown

Figure 1

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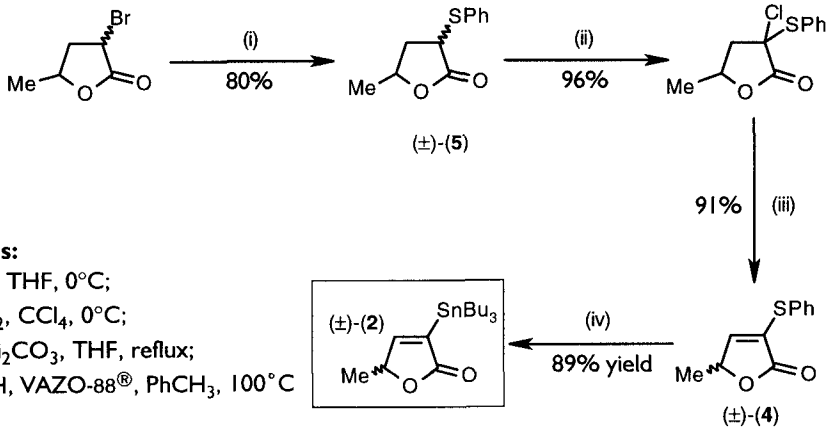
(Japanese name *Hamabiwa*) which grows in the southern part of Japan [3]. The absolute stereochemistry of the single asymmetric centre of (+)-hamabiwalactone B was unknown prior to our studies towards its synthesis and, furthermore, the optical rotation of this compound (+2.2 [c 0.32, $CHCl_3$]) was so low as to suggest that the isolation process may have compromised the stereogenic integrity of the asymmetric centre, given the relatively high acidity of the C5-proton.

Using the disconnection shown in Figure 1, we first turned our attention to the synthesis of racemic stannane **2**. Thus, by utilizing the previously-described desulfurative-stannylation reaction of sulfanyl 2(5H)-furanones [2], we sought to prepare (±)-5-methyl-3-tributylstannylfuran-2(5H)-one **2** from 5-methyl-3-phenylsulfanyl-2(5H)-furanone **4** [4]. The reaction sequence which allowed us to realize this synthetic aspiration is shown in Scheme 1.

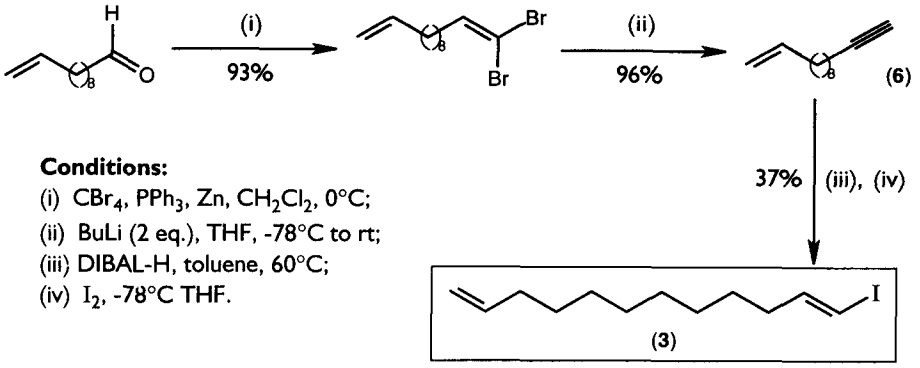


Scheme 1

2-Bromo-γ-valerolactone was reacted with sodium thiophenoxide in THF at 0°C, to give lactone **5**, a colourless oil which could be converted to furanone **4** in excellent yield *via* sequential chlorination-dehydrochlorination. Desulfurative stannylation of **4** gave the previously-unreported stannylfuranone **2** in 89% yield.

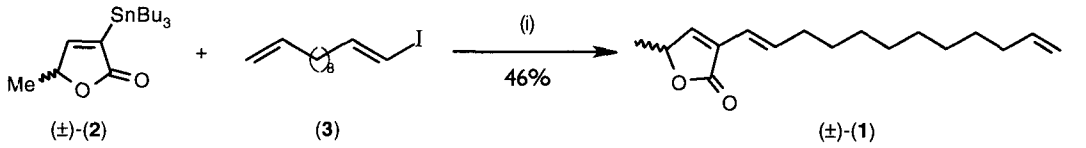
With the synthesis of stannylfuranone **2** complete, we turned our attention towards preparation of the required coupling partner, (*E*)-iodo-1,11-dodecadiene **3** [5], as shown in Scheme 2. Thus, 10-undecenal was homologated to dodeca-11-ene-1-yne [6] *via* Corey-Fuchs reaction [7] in excellent yield. Sequential stereoselective *cis*-hydroalumination of **6** by DIBAL-H and reaction of the vinyl alane so produced with elemental iodine gave **3**; despite extensive variation of the reaction conditions, the final step of the reaction sequence always proceeded in mediocre yield. Nevertheless, we were able to prepare significant amounts of key intermediate **3** using this synthetic sequence.

Our initial studies on coupling of **2** and **3** were unfruitful, and considerable optimization



Scheme 2

of the reaction conditions were required. The most efficient reaction conditions employed tris(dibenzylideneacetone)dipalladium(II), triphenylarsine and copper (I) iodide in DMF at ambient temperature over 20 hours; using this protocol, a 46% yield of (±)-hamabiwalactone B was obtained (Scheme 3). Our synthetic material exhibited data consistent with those previously reported [3].

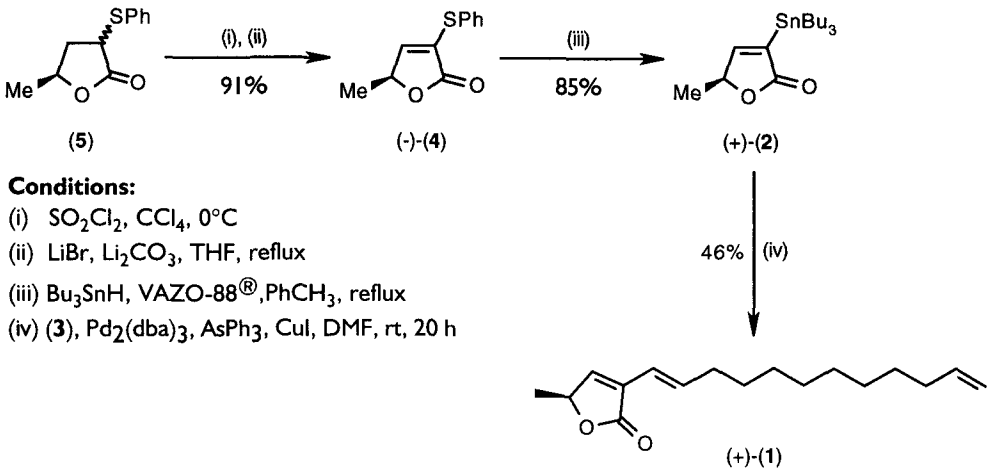


Conditions: (i) $Pd_2(dba)_3$ (0.25 mol%), $AsPh_3$ (20 mol%)$_3$, CuI (10 mol%), DMF, rt, 20 h

Scheme 3

Having demonstrated the validity of our synthetic design, we next attempted the first enantioselective synthesis of hamabiwalactone-B. (+)-(S)-5-Methyl-3-tributylstannylfuran-2(5H)-one (+)-**2** [8], was prepared from (-)-(S)-5-methyl-3-phenylsulfanyl-2(5H)-furanone (-)-**4** [9] itself prepared from (2RS, 4S)-4-methyl-2-phenylsulfanyl-γ-butyrolactone [10] **5** (stereochemically homogenous at C4 but a 1:1 mixture of absolute configurations at C2) by a sequence of reactions identical to those shown in Scheme 1 (Scheme 4).

When (+)-**2** was reacted with iodoalkene **3** under the conditions previously optimized in the racemic synthesis, (+)-hamabiwalactone B was obtained [11]. This compound exhibited $[\alpha]_D^{23}$ +29.4 (c 0.2 $CHCl_3$), an optical rotation of significantly greater magnitude than that reported for the natural product (+2.2 [c 0.32, $CHCl_3$]), but very similar to those reported for a range of other furanones bearing a C_{12}-substituent in the 3-position [12]. Analysis of synthetic hamabiwalactone-B using chiral HPLC [13] confirmed the stereogenic purity of our material to be ≥99%, thereby establishing the absolute stereochemistry of the single asymmetric centre of the natural product as (S).



Scheme 4

Thus, we have achieved a highly enantioselective synthesis of (+)-hamabiwalactone-B and established the absolute configuration of its single stereogenic centre. Synthesis of similar naturally-occurring 2(5H)-furanones is underway in our laboratories.

Acknowledgements

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[8] Data for (+)-**2**: $[\alpha]_D^{23}$ +27.9 (c 1.0 $CHCl_3$) ν_{max} (neat) 2953, 2869, 2850, 1735, 1582, 1463, 1147, 1115; δ_H ($CDCl_3$) 0.85-0.89 (9H, m), 0.97-1.34 (12H, m), 1.38 (3H, d, *J* 6.6), 1.42-1.60 (6H, m), 5.05 (1H, br q, *J* 6.6), 7.44 (1H, dd, *J* 1.1 and 11.0 coupling to ^{119}Sn, ^{117}Sn 9.9); δ_C ($CDCl_3$) 9.6, 13.6, 19.2, 27.1, 28.8, 81.2, 134.7, 166.6, 177.8; m/z (CI) (Found $(M\text{-}Bu)^+$, 331.0726 (100%), $C_{13}H_{23}O_2Sn$ requires 331.0720, 270 (70), 216 (43), 176 (20)

[9] Data for (-)-**4**: $[\alpha]_D^{24}$ -26.6 (c 1.0 $CHCl_3$), ν_{max} (bromoform) 1757, 1596; δ_H ($CDCl_3$) 1.38 (3H, d, *J* 6.6), 5.03 (1H, dq, *J* 1.5 and 6.6), 6.53 (1H, d, *J* 1.5), 7.42-7.43 (3H, m), 7.54-7.57 (2H, m); m/z (EI) (Found M^+, 206.0406 (64%), $C_{11}H_{10}O_2S$ requires 206.0402)

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[11] Data for (+)-**1**: $[\alpha]_D^{23}$ +29.4 (c 0.2 $CHCl_3$); ν max (neat) 1755, 1656, 1641, 1624; δH ($CDCl_3$) 1.28 (12H, br. s), 1.42 (3H, d, *J* 6.6), 2.04 (2H, app. dd, *J* 7.2 and 14.2), 2.16 (2H, app. dd, *J* 7.2 and 14.2), 4.91-5.05 (3H, m), 5.81 (1H, ddt, *J* 6.6, 10.3 and 16.9), 6.09 (1H, d, *J* 15.8), 6.79 (1H, dt, *J* 7 and 15.8), 7.03 (1H, d, *J* 1.5); δC ($CDCl_3$) 19.3, 28.8, 28.9, 29.2, 29.4, 29.7, 29.8, 33.4, 33.8, 76.9, 114.1, 118.3, 129.4, 138.9, 139.2, 146.8, 172.0; m/z (EI) (Found (M)+, 262.1945 (9%), $C_{17}H_{26}O_2$ requires 262.1930), 217 (6), 150 (10), 137 (30), 93 (58)

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[13] Column: Chiralcel OB (25cmx4.6mm); Mobile Phase: Hexane/ isopropyl alcohol (90:10); Detector: UV λ 250nm , Ab 0.64 Å; Flow: 2ml/ min; Load: 10μl of 1mg/ml solution in mobile phase.