Total synthesis of (−)-solavetivone using enantioselective copper-catalysed conjugate addition of Me_3Al to a cyclohexa-2,5-dienone intermediate

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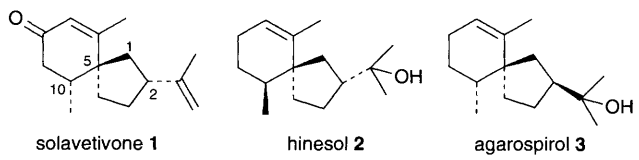
By applying a new enantioselective Cu-catalysed conjugate addition of Me_3Al, (−)-solavetivone 1 is synthesized stereoselectively from cyclohexa-2,5-dienone 4, prepared from a chiral compound 6 using a regioselective Hg^{II}-mediated cyclopropyl ring-opening, subsequent Pd^{II}-mediated spiroannulation of 7, and a stereoselective Pd^0-catalysed hydrogenation of an allylic formate 5 as key reactions.

(−)-Solavetivone **1**, a representative phytoalexin,[1] was isolated from potato tubers infected with the blight fungus *phtophthora infestans*[2a] or air-cured tobacco leaves.[2b] This compound was structurally classified as *trans*-spirovetivane characterized by the *trans*-configuration between a C(1)–C(5) bond and a methyl group at C(10) in the spiro[4.5]decane skeleton. Although the *trans*-spirovetivanes such as **1** possess inhibitory activity against several bacteria, *cis*-ones, represented by hinesol **2** and agarospirol **3** known as fragrant principles, have no biological activity (Scheme 1).[1c,d] From the viewpoint of evaluating the structure–activity relationship of the phytoalexins and identifying the defense mechanisms of plants, stereoselective construction of all the stereogenic centres in **1**–**3** (C-2, C-5 and C-10) is considered very important. While, thus far, considerable attention has been directed towards the synthesis of these two types of sesquiterpenes, most of the works are limited to racemic preparation, and stereocontrols for the C-2 and C-10 chiral centres still remain to be resolved.[3,4] Recently, one group succeeded in the asymmetric synthesis of (−)-solavetivone starting from (+)-dihydrocarvone, which already contains the C-2 chirality.[5] In the course of our studies directed towards the asymmetric synthesis of all the stereoisomers, *e.g.* **1**–**3**, by stereoselective chemical reactions, we reported an asymmetric construction of the quaternary carbon centre (C-5) and stereoselective introduction of the C(2)-chirality.[6] This time, we investigated a Pd^0-mediated Tsuji–Mandai reaction[7] of **5**, which possesses the three carbon units required for the isopropenyl group, in expectation of attaining higher stereoselectivity than previously reported,[6a] and also an enantioselective Cu-catalysed conjugate addition[8] of Me_3Al to cyclohexa-2,5-dienone **4** in the presence of a chiral ligand to control the C-10 chirality, which may open routes to both types of spirovetivanes (Scheme 2). Here we describe a second asymmetric synthesis of (−)-solvetivone from a chiral cyclopropyl sulfide **6**[6b] with two controlling stereogenic centres (C-2 and C-10) by using novel diastereoselective reactions recently developed in our laboratory.

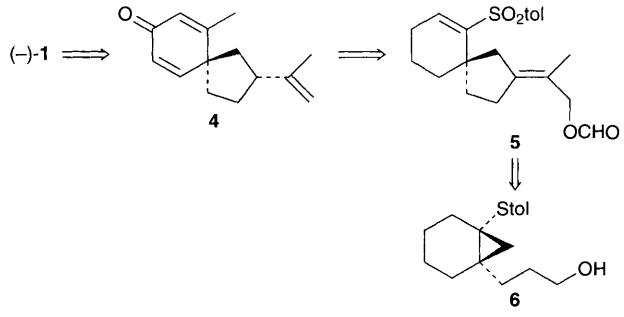
Our initial efforts were focused on constructing the spiro[4.5]decane skeleton and C-2 chiral centre (Scheme 3). For this purpose, conversion of **6** to the alkylmercury chloride **7** was achieved in 69% yield using a Swern oxidation, Wittig reaction with the appropriate phosphonium ester, and then regioselective ring-opening with mercury(II) trifluoroacetate.[6b] The spiroannulation reaction of **7** with Li_2PdCl_4 in the presence of $KHCO_3$† proceeded stereoselectively and gave the spirocyclic product **8** as a single isomer.[6a,9] The relative stereochemistry of **8** was determined by X-ray crystallographic analysis.‡ The key hydrogenation of the *exo*-cyclic alkene **8** was of some considerable concern, since a sulfenyl group at C-6 can behave as either a stereodirecting or a sterically demanding group. However, we assumed that if the sulfenyl group transforms into a sulfonyl group, then the appropriate (2*R*)-isomer could be formed due to the steric hindrance of the C-6 sulfonyl moiety (Fig. 1). Transformation of **8** into the targeted sulfone **5** was accomplished by the oxidation with MCPBA, reduction with DIBAL-H, and protection of the resulting alcohol as a formate. As expected, the subjection of the resulting formate **5** to a Tsuji–Mandai reaction[7] [1.0 equiv. $Pd(acac)_2$ and 1.0 equiv. PBu_3 in benzene at 60 °C, 2 h] proceeded stereoselectively and gave two diastereoisomers **9** and **10** in a 90 : 10 ratio, which were separated by HPLC.§

Completion of the synthesis of (−)-solavetivone is shown in Scheme 4. The successive treatment of **9** with Bu^tOOH under basic conditions and $MgBr_2$ gave a bromo ketone,[10] which was

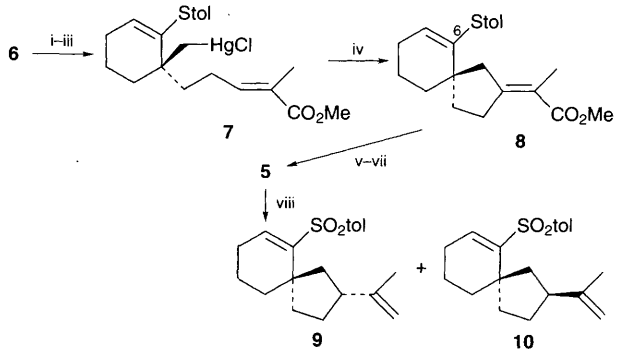


solavetivone **1** hinesol **2** agarospirol **3**

Scheme 1 *trans*- and *cis*-type spirovetivanes



Scheme 2 Retrosynthetic analysis of (−)-solavetivone



Scheme 3 *Reagents and conditions*: i, $(COCl)_2$, Me_2SO, CH_2Cl_2, −50 °C; then Et_3N, 90%; ii, $Ph_3PC(Me)CO_2Me$, toluene, reflux, 90%; iii, $Hg(TFA)_2$, NaOAc, CH_2Cl_2, room temp., then saturated NaCl, CH_2Cl_2, 85%; iv, Li_2PdCl_4, $KHCO_3$, THF, DMF, reflux, 49%; v, MCPBA, CH_2Cl_2, 0 °C, 97%; vi, DIBAL-H, CH_2Cl_2, −78 °C, 85%; vii, HCO_2H, Ac_2O, pyridine, 87%; viii, $Pd(acac)_2$, PBu_3, HCO_2H-Et_3N, benzene, reflux, 67%

then converted to the enone **11** by the reaction with DBU. 1,2-Addition of MeLi to **11** and subsequent oxidation of the resulting allylic alcohol with PCC furnished the enone **12** with concomitant 1,3-migration of a ketone moiety, which was subjected to Trost's alkenation reaction[11] to give the desired dienone **4**. It was assumed from previous papers that the diastereoselective 1,4-addition of a methyl group to **3** bearing no stereodirecting groups is difficult.[3b,4c,12] Therefore, we examined the enantioselective Cu-catalysed conjugate addition of Me_3Al to **4** in the presence of a chiral ligand (4*R*)-**A**, which had been developed in our laboratory.[8] Indeed, the 1,4-addition of Me_3Al to **4** under optimized conditions [5 mol% CuOTf·$1/2C_6H_6$, 20 mol% (4*R*)-**A**, 2.0 equiv. Me_3Al, 1.2 equiv. TBDMSOTf, THF, 0 °C; then Bu_4NF] proceeded diastereoselectively, and gave two diastereoisomers (−)-solavetivone **1** and (−)-10-episolavetivone **13**, a *cis*-spirovetivane, in a 81 : 19 ratio (total yield 93%).¶ Finally, chromatographic separation of these two compounds by HPLC gave enantiomerically pure (−)-solavetivone‡ in 72% yield, which was identical spectroscopically to an authentic sample reported previously.[2a,5]

In conclusion, we have established a stereoselective method for constructing all the stereogenic centres involved in the spirovetivane sesquiterpenes **1–3**, and as an example, succeeded in the asymmetric synthesis of (−)-solavetivone with high stereoselectivity. This synthetic approach should allow the stereo- and enantio-selective synthesis of all types of spirovetivane sesquiterpenes.

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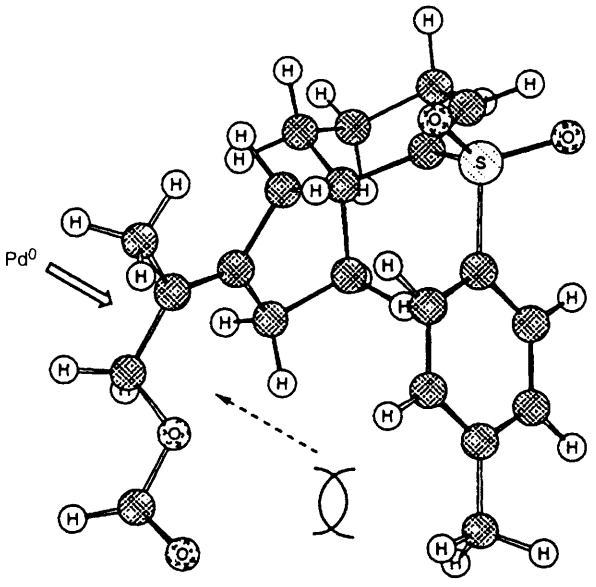
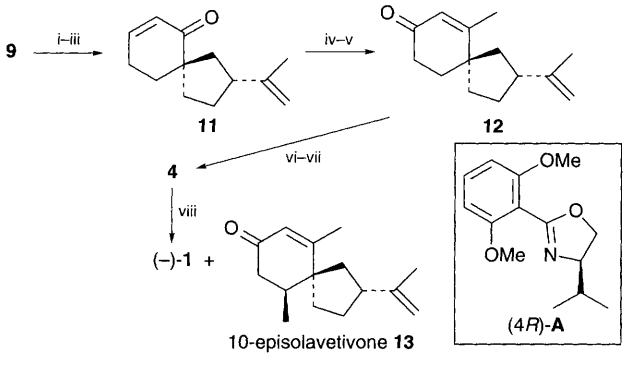


Fig. 1 The Pd^0-mediated hydrogenation of **5**



Scheme 4 *Reagents and conditions*: i, Bu^tOOH, KH, THF, −78 °C; then 0 °C, 95% (crude); ii, $MgBr_2$, Et_2O, 0 °C to room temp., 71%; iii, DBU, toluene, reflux, 72%; iv, MeLi, Et_2O, −78 °C, 91%; v, PCC, NaOAc, CH_2Cl_2, room temp., 77%; vi, LHMDS, THF, −78 °C; then $PhSSO_2Ph$, −78 °C, 86%; vii, $NaIO_4$, MeOH, H_2O, room temp.; then Et_3N, CCl_4, reflux, 75%; viii, CuOTf·$1/2C_6H_6$, (4*R*)-**A**, Me_3Al, TBDMSOTf, THF, 0 °C; Bu_4NF, room temp.; HPLC, 72%

Footnotes

† When the spiroannulation reaction of **7** was performed in the presence of triethylamine instead of $KHCO_3$, isomerization of the C=C double bond occurred and several regioisomers were produced along with the α,β-unsaturated ester **8** [see ref. 6(*a*)].

‡ *Physical and spectroscopic data* for **8**: mp 70 °C, $[\alpha]_D^{29}$ −21.2 (*c* 0.99, $CHCl_3$), HI-MS: Calcd for $C_{21}H_{16}O_2S$: 342.1651, Found: 342.1641. Details of the X-ray crystallographic analysis will be described in a full paper in the near future. For **1**: $[\alpha]_D^{24}$ −122 (*c* 0.63, EtOH), HI-MS: Calcd. for $C_{15}H_{22}O$: 218.1671, Found: 218.1654. For synthetic **1**[5]: $[\alpha]_D^{25}$ −135 (*c* 0.23, EtOH). For authentic **1**[2a]: $[\alpha]_D$ −119.

§ The Pd-mediated hydrogenation of sulfenyl and sulfinyl derivatives corresponding to **6** under similar conditions gave two diastereoisomers with poor stereoselectivities [2*R* (desired)/2*S* = 79/21 (76%) and 64/36 (82%), respectively].

¶ On the other hand, by the same 1,4-addition reaction using the antipodal ligand (4*S*)-**A**, (−)-10-episolavetivone was obtained as a major product [**1** : **13** = 37 : 63]. In this way, we were able to synthesize both *trans*- and *cis*-spirovetivanes by simply switching the chirality of the chiral ligand **A** of the enantioselective copper-catalysed conjugate addition, even though the latter diastereoselectivity was moderate.

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