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I_2–PPh_3 mediated spiroannulation of unsaturated β-dicarbonyl compounds. The first synthesis of (±)-negundoin A†

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An efficient and stereoselective spiroannulation of unsaturated enols is reported. Unsaturated β-dicarbonyl compounds undergo cyclization by reaction with catalytic I_2–PPh_3, affording the corresponding spiro enol ether derivatives, with complete regio- and stereoselectivity, under mild conditions. Utilizing this new methodology, the first total synthesis of the anti-inflammatory diterpene negundoin A and a naturally occurring trypanocidal aldehyde is reported.

Spirocompounds, with two rings joined at a single atom, are widely found in Nature. Among these, some spiroethers present particular interest due to their important biological properties. Spirodihydrobenzofuran derivatives, such as the complement inhibitor K-76,[1] the antagonist of endothelin and an inhibitor of HIV-1 protease stachybotrylactam,[2] or cytotoxic stypoldione (**1**),[3] are some representative bioactive spiroethers. A series of *nor*-diterpenes, bearing a characteristic tricyclic structure containing a spiro enol ether group with an α,β-unsaturated aldehyde, acid or ester, have recently been isolated from different species of the genus *Vitex*, which are widely used in folk medicine in some Asian countries. Representative examples are negundoin C (**2**), a potent anti-inflammatory aldehyde isolated from *V. negundo*, acid **3** (negundoin B) and ester **4** (negundoin A),[4] together with the trypanocidal aldehydes **5** and **6**, found in *V. trifolia*[5] (Fig. 1).

Only a few syntheses have been reported for some of these spirodihydrobenzofuran derivatives, *i.e.* K-76 and stachybotrylactam; in all cases, the key step is the spiroannulation of the suitable drimane (bicyclic sesquiterpene) phenol, under acidic conditions.[1b,c,6] To date, no syntheses for spiro enol ether derivatives, such as compounds **2–6**, have been reported.

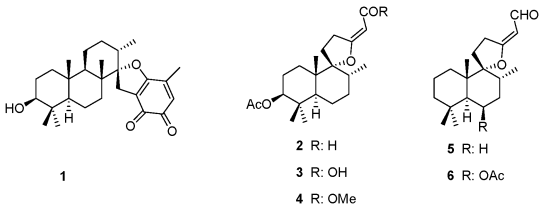
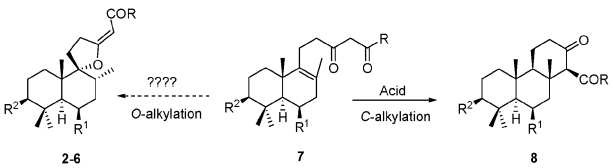


Fig. 1 Some bioactive natural spiro ethers.

Spiro tetrahydrofurylidene systems similar to that presented by negundoin A (**4**) have been previously elaborated by reaction of an oxirane with the dianion of a β-ketoester and the subsequent treatment with acid.[7,8] The construction of the spiro enol ether framework of compounds **2–6** could be achieved by spiro annulation of the enol derived from the corresponding unsaturated β-dicarbonyl compound **7** under suitable reaction conditions (Scheme 1). Alternatively, *O*-alkylation can take place affording the corresponding pyran derivative. Cyclization of β-dicarbonyl compound type **7** can also occur through the *C*-alkylation of the corresponding enol, leading to type **8** compounds. In some cases other C-cyclization processes can take place after the attack of an olefinic or an allyl carbon on the carbonyl group, affording the corresponding β-hydroxy carbonyl compound.[9] In most of the reactions described under acidic conditions processes involving C-cyclization have been reported.[10–12] Some examples of obtention of tetrahydrofurylidene derivatives by cyclization of unsaturated β-ketoesters catalyzed using $SnCl_4$[13] or Pd(II)[14] have been described. Under these conditions, alkyl 6-methyl-3-oxo-6-heptenoates afford



Scheme 1 Alternative cyclization processes for unsaturated β-dicarbonyl compounds.

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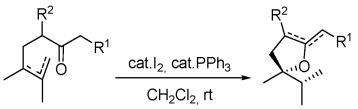
† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3cc45921g

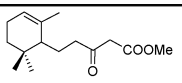
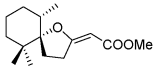
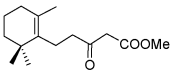
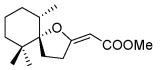
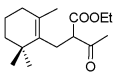
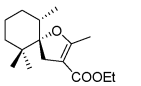
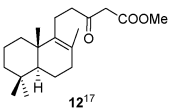
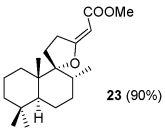
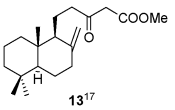
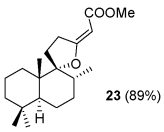
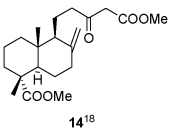
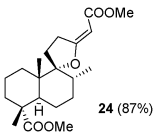
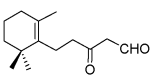
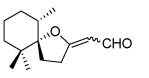
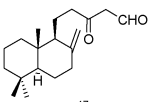
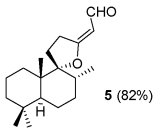
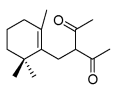
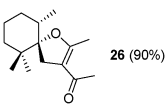
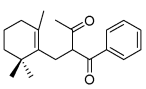
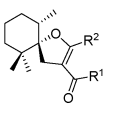
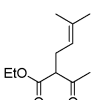
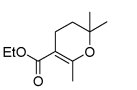
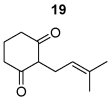
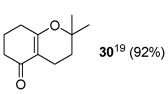
the corresponding spiro compound resulting from the favourable enol O-attack on the most substituted olefinic carbon. The stereoselectivity of these processes remains uncertain.[13a,14] However, the spiroannulation of unsaturated β-dicarbonyl compounds bearing a tetrasubstituted olefinic bond, such as compound **7**, to achieve compounds **2–6** involves certain difficulty due to the variety of possible alternative cyclizations discussed above. In order to search cyclization conditions favouring the required *O*-alkylation process, the behaviour of unsaturated β-ketoesters **9**, **10**, **12** and **13** under different cyclization conditions, including acidic ones, was studied. In most cases the cyclization process is not stereoselective, leading to a mixture of compounds, resulting from a *C*-alkylation reaction.[15]

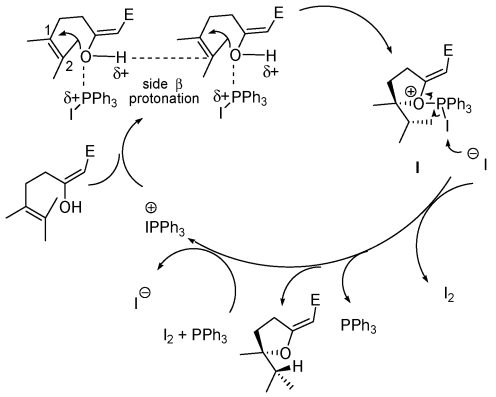
In the course of our investigations into the use of the I_2–PPh_3 system[16] we found that unsaturated β-ketoesters are efficiently transformed, in the presence of catalytic amounts of this reagent, into the corresponding spiro enol ethers. Thus, the β-ketoester **9** was converted with complete regio- and stereoselectivity into the spiro compound **21** by treatment with this system, in dichloromethane, at room temperature for 8 h (see Table 1). Ketoester **10** gave the same results under the above reaction conditions. Similarly, compound **11** was transformed in good yield into the spiro compound **22**. In order to optimize the reaction conditions and establish the scope of this reaction, some other β-ketoesters, β-ketoaldehydes and β-diketones were then studied. In all cases the corresponding spiro enol ethers were obtained with complete regio- and stereoselectivity. β-Ketoaldehydes (entries 7 and 8) show a similar behaviour. It should be noted that aldehyde **25** was the only spirane derivative obtained as a mixture of *E*–*Z* stereoisomers (4 : 1); the reason for this behaviour remains unclear. Compound **16** was transformed under the same reaction conditions into the spirane **5**, a trypanocidal aldehyde isolated from *V. trifolia*.[5] The optical rotation of synthetic aldehyde **5** ($[\alpha]_D$ +1.2; c 8.6, $CHCl_3$) and the spectroscopic properties were similar to those reported for the natural product. β-Diketones (entries 9 and 10) also produced the corresponding spiro enol ether derivatives. The relative stereochemistry of all the above spiro compounds was established on the basis of nOe experiments. On the other hand, β-ketoester **19** and β-diketone **20**, containing a prenyl substituent, afforded under the above conditions the corresponding enol ether bearing a dihydropyran ring. In order to rule out the participation of hydriodic acid in this I_2–PPh_3 mediated process, the behaviour of β-ketoester **9** against this acid reagent was investigated. Compound **9** remained unaltered after treating with 55% aq. HI in dichloromethane at room temperature for 48 h. Under reflux, decomposition was observed.

A first fact to be considered in rationalizing these results is the complete *anti* stereoselectivity of the addition process. When the I_2–PPh_3 system is utilized, an *anti* concerted process, precluding the formation of an intermediate carbocation, must take place. A possible mechanism, consistent with the experimental results, is postulated. The spirocyclization process is depicted in Scheme 2. Under the reaction conditions, the trisubstituted or exocyclic carbon–carbon double bond (compounds **9** and **13**; **14** and **16**) undergoes isomerization to the most stable tetrasubstituted derivatives. The enol hydroxyl group acts as a nucleophile and a proton donor simultaneously. The OH group, activated by the phosphonium ion $^{+}PPh_3I$, transfers the proton by

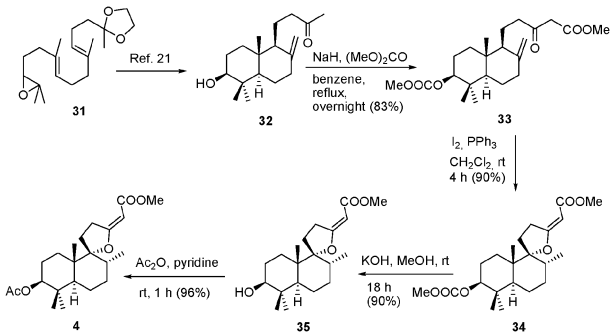
Table 1 I_2–PPh_3 mediated spiroannulation of some β-dicarbonyl compounds



Entry	β-Dicarbonyl compound	*t* (h)	Product
1	 **9**	8	 **21** (58%)
2	 **10**	8	 **21** (85%)
3	 **11**	5	 **22** (81%)
4	 **12**[17]	5	 **23** (90%)
5	 **13**[17]	5	 **23** (89%)
6	 **14**[18]	5	 **24** (87%)
7	 **15**	5	 **25a-b** (*E*/*Z* 4:1)(80%)
8	 **16**[17]	5	 **5** (82%)
9	 **17**	3	 **26** (90%)
10	 **18**	5	 **27** (R^1: Me; R^2: Ph) **28** (R^1: Ph; R^2: Me) 90% (2 : 1)
11	 **19**	5	 **29** (85%)
12	 **20**	5	 **30**[19] (92%)



Scheme 2 A possible mechanism for the I_2–PPh_3 mediated cyclization of β-dicarbonyl compounds.



Scheme 3 Synthesis of negundoin A (**4**).

the β side of the olefinic bond of the adjacent molecule. The latter undergoes the simultaneous intramolecular nucleophilic O-attack on carbon 1, affording intermediate I, which is a precursor of the spirane compound (Scheme 2). The complete regioselectivity of the cyclization process could be attributed to the preference for the transference of protons on the less hindered carbon 2. The preference for the β side proton transference could be attributed to the α side steric hindrance due to the keto ester moiety. As expected, compounds **19** and **20** afforded the dihydropyran ethers **29** and **30**, respectively, resulting from the OH attack on the most substituted olefinic carbon.

Utilizing the above spirocyclization of β-ketoesters, negundoin A (**4**) was synthesized (Scheme 3), utilizing the key intermediate hydroxyketone **32**, a terpenoid found in Copaiba oil,[20] which is easily prepared by the titanocene-catalyzed cyclization of (2*E*,5*E*)-9,10-epoxy-farnesyl acetone ketal (**31**).[21] The spectroscopic properties of synthetic negundoin A (**4**) were identical to those reported for the natural product.[4]

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