Asymmetric total synthesis of *ent*-heliespirones A & C†

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A concise 8-step synthetic route toward *ent*-heliespirones A & C is described. This synthetic strategy features a highly diastereoselective palladium-catalyzed Michael addition to form 3,5-*trans* lactone and a final biomimetic intramolecular oxa-spirocyclization.

In 1998, the first member of heliespirone family, heliespirone A, was isolated from cultivar sunflowers var. SH-222® by Macias' group. The primary structure was proposed based on extensive NMR spectra.[1] Eight years later, the same group reported two siblings in this family, heliespirones B & C namely, from the same species.[2] They revised the structure of heliespirone A at the same time by comparing its characterization data with those of heliespirones B & C and heliannuols B, D, E and F (Fig. 1).[3]

Heliespirones embrace a novel oxa-spirocyclic sesquiterpene skeleton and show potential allelopathic activity in the coleoptiles bioassay. The arresting bioactivity and unusual natural structure make them attractive synthetic targets; their total synthesis has not been reported yet. From a biogenetic view, heliespirones A & C might be achieved from heliannuol C *via* oxidation of the phenol ring and the following intramolecular *oxa*-Michael addition. Heliespirone B could be transformed from heliannuol A through a similar pathway.[2] Heliannuol C is one of the most active members of the heliannuol family, showing germination inhibition of lettuce and cress even in nM concentration.[3a,4] To the best of our knowledge, there have been only three total syntheses since the isolation of heliannuol C, which include two total syntheses of racemic heliannuol C and one enantioselective total synthesis.[5] Venkateswaran group developed a 12-step synthetic route to racemic heliannuol C, by employing a Claisen orthoester rearrangement and a Dieckmann cyclization from 6-hydroxycoumarin.[5a,b] A more concise racemic synthesis was elegantly attained through an aromatic Claisen rearrangement and the following biomimetic phenol epoxide cyclization in 7 steps by Vyvyan's group;[5c] however, the *direct* asymmetric version of such a strategy towards enantiopure heliannuol C has not been developed yet, since few methods on enantioselective aromatic Claisen rearrangement have been explored.[6] The only example of the enantioselective total synthesis of heliannuol C showed up with a linear 21-step synthetic route in 2003 and was featured with a lipase-catalyzed desymmetrization of the diol.[5d]

Although the transformation following the biogenetic pathway seems to be a straightforward way to reach heliespirones A & C enantioselectively from heliannuol C *via* a semi-synthetic way, we preferred a concise total synthesis toward them. Herein we would like to describe our achievements on the asymmetric total synthesis leading to *ent*-heliespirones A & C.

As illustrated in Fig. 2, *ent*-heliespirones A & C can be retrosynthetically derived from compound **I** *via* a biomimetic oxaspirocycliation. The precursor **I** might be achieved from intermediate **II** by transforming the primary alcohol to a terminal alkene. The two stereocenters of compound **III** are devised to be installed respectively through Michael addition to compound **IV** with reagent **V** in a substrate–controlling manner and Sharpless AD of compound **VI** in a chiral ligand–controlling manner, respectively.

Thus, the known compound **1**[7] was choosen as the starting material and was smoothly transformed to chiral diol **2** with 96% ee in 98% yield under Sharpless AD condition. Then diol **2** was converted to *Z*-disubstituted enester **3** with Lindlar catalyst in the presence of hydrogen, which was used without purification and further cyclized to form lactone **4** catalyzed by *para*-toluenesulfonic acid (Scheme 1).[8]

In order to install the C3 stereocenter with good selectivity, a 1,4-addition of an aryl ring to lactone **4** was studied carefully. First, various organocuprates **5a** were prepared by mixing aryl lithium, derived from bromide **5b**, with different copper salts including CuI, $CuBrSMe_2$, CuCN *etc*.[9] However, all efforts at promoting such a Michael addition, with or without a Lewis acid, proved sterile. Subsequently, the palladium-catalyzed 1,4-addition of bromide **5b**, with $Pd(PPh_3)_4$/TEA or $Pd(OAc)_2$/TEA/HCO_2H,[10] was attempted, but did not afford the desired adduct either. Inspired by the recent report on palladium-catalyzed C–H activation,[11] we applied $Pd(OAc)_2$ in TFA/DCM (4/1) to catalyze the coupling of lactone **4**

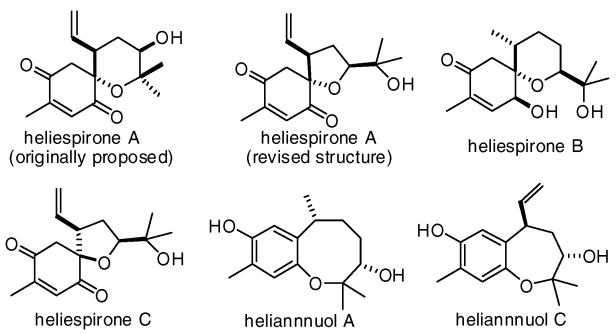

Fig. 1 Molecular structures of heliespirones and heliannuols A & C.

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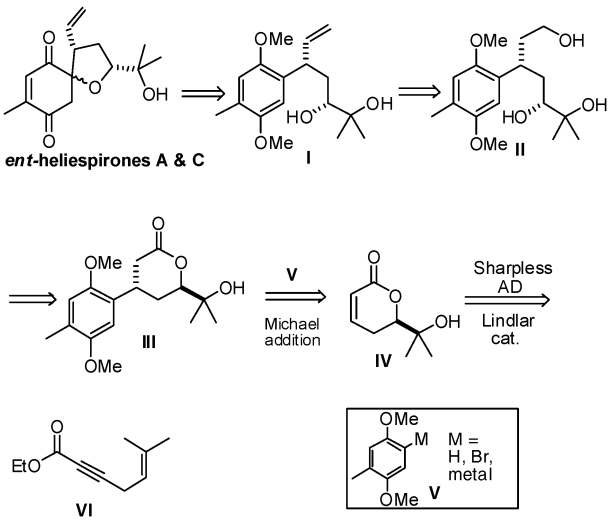
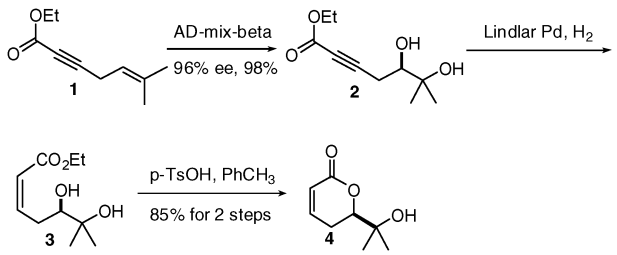


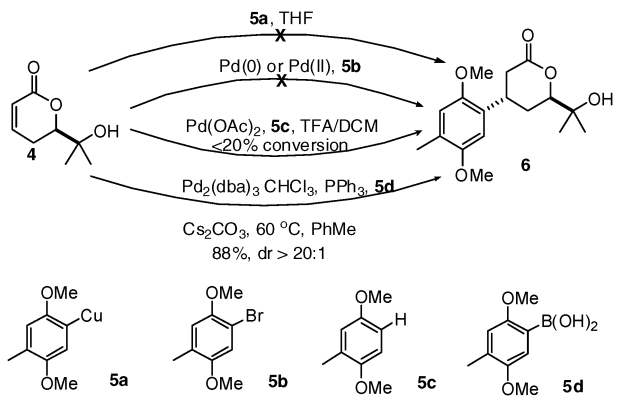
Fig. 2 Synthetic strategy towards heliespirones A & C.



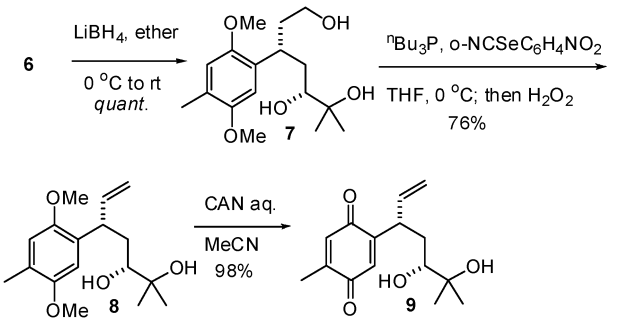
Scheme 1 Enantioselective construction of lactone **4**.

and 1,4-dimethoxy-2-methylbenzene (**5c**). To our delight, compound **6** with the proper stereochemistry was formed, but with less than 20% conversion. Failure to improve the conversion any further forced us to search for other effective methods. Eventually, addition of aryl boronic acid **5d**[12] to the α,β-unsaturated lactone **4** was successfully realized in 88% yield with more than 95% de by employing Ohta's method,[13] although no reaction occurred with $Pd(OAc)_2$/ bipyridine as the catalyst in HOAc–THF–H_2O solvent system (Scheme 2).[14]

The resultant adduct **6** was reduced with lithium borohydride to afford triol **7**, which was treated with *o*-nitrophenylselenocyanate and tributylphosphine,[15] followed by treatment with peroxide to produce compound **8**. Compound **8** was



Scheme 2 Diastereoselective construction of 1,4-adduct **6**.

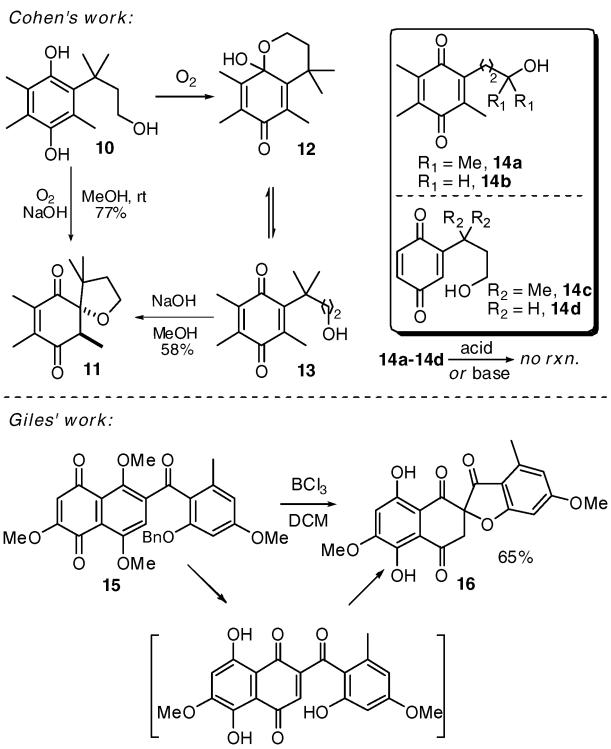


Scheme 3 Construction of quinone **9**.

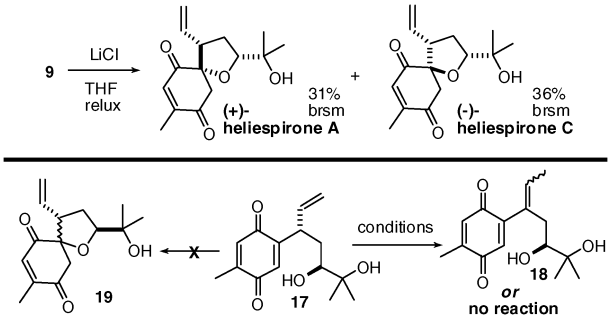
then oxidized to the corresponding key cyclisation precursor, quinone **9**(Scheme 3).

Thus, the biomimetic oxa-spirocyclization leading to heliespirones A & C needed to be investigated by following the synthetic plan. In general, the intramolecular *oxa*-Michael addition to quinone, resulting in a oxaspiro-[4,5]-dec-7-ene-6,9-dione, had been studied very rarely (Scheme 4). Cohen *et al*. reported that quinone **10**, with a so-called *trialkyl lock*, could be facilely transformed to oxaspiral cycle **11**; however, those isomeric unlocked quinones **14a–14d** did not show any reactivity under acid or alkali conditions.[16] Giles *et al*. described a formal intramolecular oxa-Michael addition using the substrate with a whole sp^2-hybridized carbon linker, which is structurally and inherently different from that in compound **9**.[17] Other groups found that the oxaspirocycle formed only as a side product in some cases.[18] So the intramolecular *oxa*-Michael addition of quinone **9** is actually not so reasonable as it appears at first glance.

In fact, a number of Brønsted acids, Lewis acids and Lewis bases were carefully evaluated, including $CeCl_3$, PPTS, TsOH,



Scheme 4 Previous work of intramolecular *oxa*-Michael addition.



Scheme 5 Completion of the total synthesis of *ent*-heliespirones A & C.

$LiClO_4$, DBU, *etc*. Finally, enantiopure *ent*-heliespirones A & C were fortunately obtained from **9** with lithium chloride as a mild Lewis acid in a satisfactory yield (Scheme 5).[19] It is very interesting that compound **17**,[20] the diastereoisomer of **9**, does not afford any oxacyclization product under all conditions. Either no reaction occurs, or the alkene rearrangement takes place giving compound **18**. It is noteworthy that **9** can turn into *ent*-heliespirones A & C automatically, albeit quite slowly, during standing at room temperature, which indicates that such a transformation should be a real process in nature. These findings show that the *trialkyl lock* is unnecessary for the intramolecular *oxa*-Michael addition of quinone to form oxaspiro-[4,5]-dec-7-ene-6,9-dione if the stereochemical requirement is matched. This could be a guide for total syntheses of other natural products with similar skeleton, such as conidione[21] and strongylophorines-6 & -7.[22]

In summary, we have completed the first total synthesis of *ent*-heliespirones A & C in eight steps from compound **1**. It features a highly enantioselective palladium-catalyzed addition of aryl boronic acid to an unsaturated lactone, and a biomimic intramolecular oxaspirocyclization of quinonyl alcohol. Applying this synthetic strategy in enantioselective syntheses of heliannuols C and E is under way in our laboratory.

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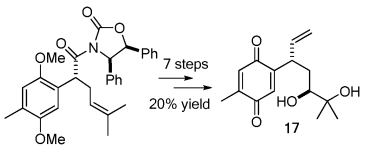
Notes and references

1 F. A. Macias, R. M. Varela, A. Torres and J. M. G. Molinillo, *Tetrahedron Lett*., 1998, **39**, 427–430.
2 F. A. Macias, J. L. G. Galindo, R. M. Varela, A. Torres, J. M. G. Molinillo and F. R. Fronczek, *Org. Lett*., 2006, **8**, 4513–4516.
3 For isolation of heliannuols B-D: (*a*) F. A. Macias, J. M. G. Molinillo, R. M. Varela and A. Torres, *J. Org. Chem*., 1994, **59**, 8261–8266; (*b*) For isolation of heliannuol E: F. A. Macias, R. M. Varela, A. Torres and J. M. G. Molinillo, *Tetrahedron Lett*., 1999, **40**, 4725–4728; (*c*) For isolation of heliannuol F:F. A. Macias, R. M. Varela, A. Torres and J. M. G. Molinillo, *J. Nat. Prod*., 1999, **62**, 1636–1639.
4 F. A. Macias, J. M. G. Molinillo, D. Chinchilla and J. C. G. Galindo, In *Allelopathy Chemistry and Mode of Action of Allelochemicals*, ed. F. A. Macias, J. M. G. Molinillo and J. C. G. Galindo, CRC: Boca Raton, 2004, ch. 5.
5 (*a*) B. Biswas, P. K. Sen and R. V. Venkateswaran, *Tetrahedron Lett*., 2006, **47**, 4019; (*b*) B. Biswas, P. K. Sen and R. V. Venkateswaran, *Tetrahedron*, 2007, **63**, 12026; (*c*) J. R. Vyvyan, J. M. Oaksmith, B. W. Parks and E. M. Peterson, *Tetrahedron Lett*., 2005, **46**, 2457; (*d*) K. Tomoyo, S. Mitsuru and K. Shishido, *Tetrahedron Lett*., 2003, **44**, 8505.
6 (*a*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc*., 1998, **120**, 815–816; (*b*) H. Ito, A. Sato and T. Taguchi, *Tetrahedron Lett*., 1997, **38**, 4815.
7 Compound **1** can be easily prepared by coupling ethyl propiolate with prenyl bromideL. W. Bieber and M. F. da Silva, *Tetrahedron Lett*., 2007, **48**, 7088–7090.
8 A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbaur, H. Kaehlig, E. Ohler and J. Mulzer, *J. Org. Chem*., 2003, **68**, 3026–3042.
9 (*a*) D. Kim, J. Lee, P. I. Shim, J. I. Lim, T. Doi and S. Kim, *J. Org. Chem*., 2002, **67**, 772–781; (*b*) J.-P. Lumb and D. Trauner, *Org. Lett*., 2005, **7**, 5865–5868.
10 (*a*) G. E. Stokker, *Tetrahedron Lett*., 1987, **28**, 3179–3182; (*b*) S. Cacchi, *Synthesis*, 1984, 575–577.
11 (*a*) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura and Y. Fujiwara, *Science*, 2000, **287**, 1992–1995; (*b*) C. Jia, D. Piao, T. Kitamura and Y. Fujiwara, *J. Org. Chem*., 2000, **65**, 7516–7522.
12 M. Yoshida, Y. Shoji and K. Shishido, *Org. Lett*., 2009, **11**, 1441–1443.
13 T. Yamamoto, M. Iizuka, H. Takenaka, T. Ohta and Y. Ito, *J. Organomet. Chem*., 2009, **694**, 1325–1332.
14 X. Lu and S. Lin, *J. Org. Chem*., 2005, **70**, 9651–9653.
15 (*a*) C. Ma, S. Schiltz, X. F. Le Gott and J. Prunet, *Chem. Eur. J*., 2008, **14**, 7314–7323; (*b*) D. L. Comins and A. Dehghani, *J. Org. Chem*., 1995, **60**, 794–795; (*c*) P. A. Grieco, S. Gilman and M. Nishizawa, *J. Org. Chem*., 1976, **41**, 1485–1486.
16 (*a*) R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc*., 1973, **95**, 8308–8313; (*b*) R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc*., 1972, **94**, 9175–9182.
17 C. B. de Koning and R. G. F. Giles, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3209.
18 (*a*) M. Kongkathip, B. Kongkathip, P. Siripong, C. Sangma, S. Luangkamin, M. Niyomdecha, S. Pattanapa, S. Piyaviriyagul and P. Kongsaeree, *Bioorg. Med. Chem*., 2003, **11**, 3179–3191; (*b*) D. Creed, H. Werbin and E. T. Strom, *J. Am. Chem. Soc*., 1971, **93**, 502–511.
19 The synthetic heliespirones A & C proved enantiomers of natural products. The characterization data of synthetic samples fit well with those of natural samples, and the NOE diffference spectrums were in accord with *ent*-heliespirones A & C. Please see electronic supplementary information† for details.
20 This compound was obtained in a different synthetic route starting from chiral auxiliary



21 L. Garrido, E. Zubia, M. J. Ortega and J. Salva, *J. Nat. Prod*., 2002, **65**, 1328.
22 J. Salva and D. J. Faulkner, *J. Org. Chem*., 1990, **55**, 1941.

