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A convenient two step protocol for the synthesis of cyclopentenones and indanones, including an asymmetric variant†

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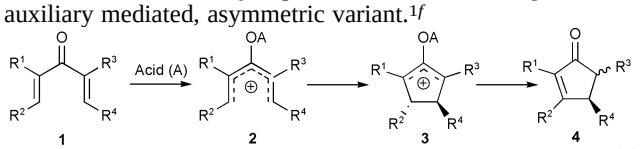
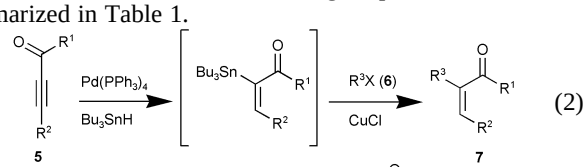
A one-pot palladium mediated hydrostannylation/cross-coupling protocol is used to give direct access to cross-conjugated dienones that can be utilized in Nazarov cyclizations to afford highly substituted cyclopentenones and indanones, including an asymmetric variant.

The prevalence of 5-membered carbocycles in natural products and other bioactive compounds has provided a major impetus for the development of efficient methods for their construction. Over the years the Nazarov reaction has been increasingly refined to meet this need.[1] Most usually, this reaction involves the use of cross-conjugated dienones **1**, treatment of which with a Lewis or Brønsted acid (A) induces the formation of a pentadienyl cation **2** that undergoes 4π-electrocyclization to give an allyl cation **3** followed by proton migration to give a cyclopentenone **4** (eqn. 1). The presence of an α-carbonyl group in **1** (R^3 = carbonyl) assists in the regioselective placement of the double bond in **4** and the relative stereochemistry of R^3 and R^4, *trans*-**4** preferred.[1d,e] In this work we describe a flexible approach to systems **1** and new, mild and efficient conditions for their conversion to cyclopentenones **4**, including a chiral auxiliary mediated, asymmetric variant.[1f]

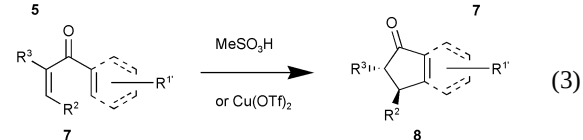


(1)

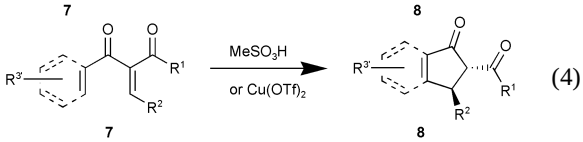
Readily available carboxyalkynes **5** are utilized in a one-pot, palladium mediated *syn*-hydrostannylation and copper co-catalyzed Stille–Scott cross-coupling with organic halides **6**, to afford direct access to stereo- and regio-selectively defined carboxyalkenes **7** (eqn. 2).[2] Suitable placement of an alkene or aromatic ring in **7** provides ready access to Nazarov precursors that can be cyclized to give cyclopentenones or indanones **8**, respectively (eqns. 3 and 4). The application of these reactions to a series of substrates **5** and **6** to give products **7** and **8** is summarized in Table 1.



(2)



(3)



(4)

Compounds **7** with extended conjugation were initially formed as a single isomer but then isomerized upon standing at rt to give a mixture of *E*- and *Z*-isomers (Table 1, entries 3 and 5–14). In the case of the oxazolidinone auxiliary containing system **7o** the kinetic product is also the exclusively formed thermodynamic product (entry 15).[3]

In the earlier studies on the Nazarov cyclization of α-carbonyl dienones **1** (R^3 = carbonyl), only low yields (< 40%) of the desired cyclopentenones **4** (R^3 = carbonyl) were obtained even under the most favoured conditions, involving trimethylsilyltriflate or trimethylsilyliodide as an acid source and heating to 120 °C in DMF (eqn. 1).[1d,e] In this work, we have found that methanesulphonic acid or cupric triflate in dichloromethane provides a superior set of conditions for converting such systems to cyclopentenones, generally giving moderate to high yields of product at rt (entries 5, 8, 9 & 15, Table 1). The obvious exception to this is **7g** (entry 7), which resisted cyclization to give the cyclopentenone **8g** even at elevated temperatures (entry 3). This is expected to arise from the absence of an additional substituent adjacent to dienone carbonyl in **7g**. Nazarov precursors **1** generally require R^1 and R^3 groups that are larger than hydrogen in order to help favour the correct conformation of **2** for cyclization (eqn. 1).[1c] Only the mild Lewis acid, cupric triflate, was effective in converting **7i** to **8i**, other Lewis acids ($BF_3{\cdot}Et_2O$ and $TiCl_4$) and $MeSO_3H$ led to rapid formation of very complex mixtures (entry 5). Most likely, the 1,5-relationship of the electron rich aryl group and the electron deficient double bond in **7i** provides for alternative reaction paths in the presence of strong acid. Cyclization of *gem*-diaroyl alkenes proceeds selectively through the aroyl unit most capable of stabilizing the intermediate pentadienyl cation (entry 12).

Nazarov cyclization of **7o** could be controlled to select for either one of the two β-phenyl diastereomers of the cyclopentenone product, *cis*-**8o** or *trans*-**8o** (entry 15). The *cis*- and *trans*-diastereomers of **8o** were distinguished from each other on the basis of the coupling constant of the two vicinal hydrogens attached to the cyclopentenone ring (*cis*: 7.8 Hz & *trans:* 2.1 Hz).[1e] They were both assigned the β-phenylcyclopentenone configuration on the basis of the observations of Pridgen *et al* involving a related, auxiliary controlled, Nazarov cyclization to give a homochiral indanone.[1f] They determined the absolute stereochemistry of their major product by converting it to a compound of known absolute stereochemistry. The kinetic product *cis*-**8o** was formed by reaction of **7o** with $MeSO_3H$ at −78 °C and warming to 0 °C and quenching (aqueous $NaHCO_3$) after 30 min. This material is stable indefinitely at rt in neutral or slightly basic solutions but epimerizes to *trans*-**8o** upon sustained exposure to acid at room temperature. Accordingly, when **7o** is reacted with $MeSO_3H$ or cupric triflate for several hours at rt, the thermodynamically more stable product, *trans*-**8o** is formed selectively. To the best of our knowledge, this is the first report of a selective formation of both the *cis*- and *trans*-diastereomers of a cyclopentenone from a Nazarov reaction. Since both enantiomers of the phenyl oxazolidinone auxiliary are readily available, this protocol provides access to all four possible stereoisomers of the cyclopentenone ring.

The polymethoxyaryl substituted enones **7j–m** and indanones **8j–m** are valuable analogues of our other potent tubulin polymerization inhibitors.[4]

† Electronic supplementary information (ESI) available: synthetic procedures and spectral data for all compounds **7** and **8**. See http://www.rsc.org/suppdata/cc/b2/b211845a/

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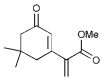
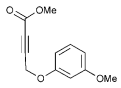
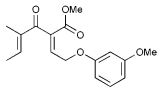
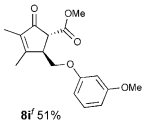
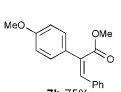
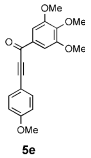
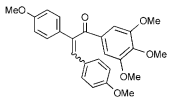
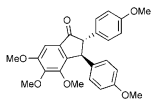
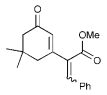
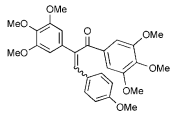
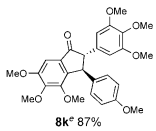
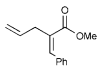
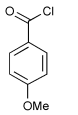
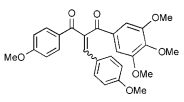
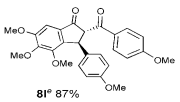
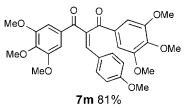
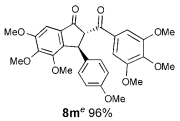
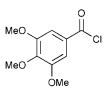
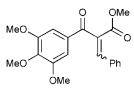
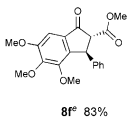
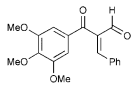
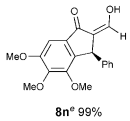
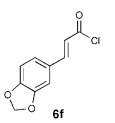
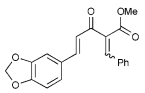
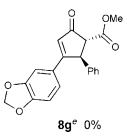
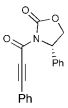
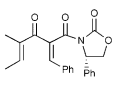
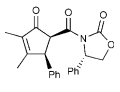
Table 1 One-pot hydrostannylation/cross-coupling of **5** and **6** to give **7** (eqn. 2) and Nazarov cyclization of **7** to give **8** [(eqn. 3) and (eqn. 4)]

Entry	Starting materials		Products		Entry	Starting materials		Products	
	5	**6**	**7**[a]	**8**[d]		**5**	**6**	**7**[a]	**8**[d]
1	 **5a**	 **6a**	 **7a**[b] 61%		9	 **5d**	**6d**	 **7i** 85%	 **8i**[f] 51%
2	 **5b**	 **6b**	 **7b** 75%		10	 **5e**	**6b**	 **7j**[c] 93%	 **8j**[f] 94%
3	**5b**	**6a**	 **7c**[c] 93%		11	**5e**	 **6g**	 **7k**[c] 81%	 **8k**[e] 87%
4	**5b**	 **6c**	 **7d** 83%		12	**5e**	 **6h**	 **7l**[c] 84%	 **8l**[e] 87%
5	**5b**	 **6d**	 **7e**[c] 87%	 **8e**[e] 90%	13	**5e**	**6e**	 **7m** 81%	 **8m**[e] 96%
6	**5b**	 **6e**	 **7f**[c] 70%	 **8f**[e] 83%	14	 **5f**	**6e**	 **7n** 48%	 **8n**[e] 99%
7	**5b**	 **6f**	 **7g**[c] 72%	 **8g**[e] 0%	15	 **5g**	**6d**	 **7o** 88%	 *cis*-**8o**[g] 73%
8	 **5c**	**6d**	 **7h**[c] 80%	**8h**[e] 88%					*trans*-**8o**[f] 76%

[a] Bu_3SnH, **5** and $Pd(PPh_3)_4$ 3 mol% in THF at 0 → 18 °C for 1–2 h, then **6** and CuCl 4–16 h. [b] Crude yield was virtually quantitative but product is quite unstable. [c] Initially formed as the kinetic product [(*Z*)-alkylidene isomer] but then slowly isomerizes to the thermodynamic mixture of double bond isomers. [d] Acid 1–2 eq. in CH_2Cl_2, 18 °C, 4–16 h. [e] Acid = $MeSO_3H$. [f] Acid = $Cu(OTf)_2$ [g] Acid = $MeSO_3H$, −78–0 °C then $NaHCO_3$ (aq).

Notes and references

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1 (*a*) K. L. Habermas, C. Santelli-Rouvier and M. Santelli, *Synthesis*, 1983, 429; (*b*) S. E. Denmark and T. K. Jones, *Org. React.*, 1994, **45**, 1; (*c*) S. E. Denmark in *Comprehensive Organic Synthesis*, Eds. B. M. Trost and I. Flemming, Pergamon, New York, 1991, Chapter 5.6.3, pp. 751–784; (*d*) J. P. Marino and R. J. Linderman, *J. Org. Chem.*, 1981, **46**, 3696; (*e*) J. F. P. Andrews and A. C. Regan, *Tetrahedron Lett.*, 1991, **32**, 7731; (*f*) L. N. Pridgen, K. Huang, S. Shilcrat, A. Tickner-Eldridge, C. De Brosse and R. C. Maltiwanger, *Synlett*, 1999, 1612; (*g*) C. Schultz-Fademrecht, M. A. Tius, S. Grimme, B. Wibbeling and D. Hoppe, *Angew. Chem., Int. Ed.*, 2002, **41**, 1532; (*h*) P. E. Harrington, M. Tsuyoshi, C. Chu and M. A. Tius, *J. Am. Chem. Soc.*, 2002, **124**, 10091and references cited therein. (*i*) Y. Wang, A. M. Arif and F. G. West, *J. Am. Chem. Soc.*, 1999, **121**, 876; (*j*) J. A. Bender, A. M. Arif and F. G. West, *J. Am. Chem. Soc.*, 1999, **121**, 7443; (*k*) C. C. Browder, F. P. Marmsäter and F. G. West, *Org. Lett.*, 2001, **3**, 3033.

2 (*a*) F. Bellina, A. Carpita, M. De Santis and R. Rossi, *Tetrahedron*, 1994, **50**, 12029; (*b*) X. Han, B. M. Stoltz and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 7600.

3 This is supported by the NOESY NMR† and is consistent with the observations of Prigden, *et al*. (ref. 1*f*).

4 (*a*) B. L. Flynn, P. Verdier-Pinard and E. Hamel, *Org. Lett.*, 2001, **3**, 651; (*b*) B. L. Flynn, E. Hamel and M. K. Jung, *J. Med. Chem.*, 2002, **45**, 2670.