

Michael Addition of Ortho-Lithiated Aryloxiranes to α,β -Unsaturated Malonates: Synthesis of Tetrahydroindenofuranones

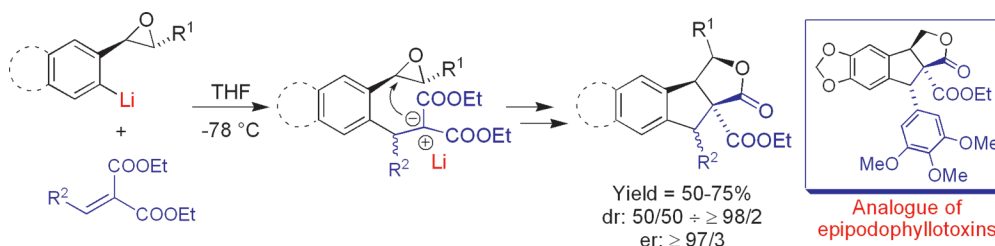
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ABSTRACT



A short and efficient synthesis of tetrahydroindenofuranones based on the Michael addition of ortho-lithiated aryloxiranes to alkylidene malonates followed by the nucleophilic oxirane ring-opening and subsequent lactonization is described. The methodology has been applied to the synthesis of a structural analogue of epipodophyllotoxins.

Functionalized organolithium compounds such as ortho-lithiated aryloxiranes and aziridines represent a class of particularly interesting reactive intermediates as their trapping with certain electrophiles, followed by the oxirane or aziridine ring-opening-promoted cyclization, can be a useful strategy for the construction of complex molecules in few synthetic steps.¹

Indeed, it has been recently found in our laboratory that addition of ortho-lithiated arylaziridines² or aryloxiranes³ to carbonyl compounds results in the formation of aminomethyl- or hydroxyalkylphthalanes, respectively.

Moreover, we had discovered that ortho-lithiated stilbene oxides add to α,β -unsaturated Fischer carbene complexes

leading to tetrahydronaphthols,⁴ through a highly stereoselective conjugate addition. Such unexpected regioselectivity, unusual for organolithiums which generally tend to give 1,2-addition, encouraged us to investigate the addition reaction of ortho-lithiated aryloxiranes to α,β -unsaturated carbonyl compounds.⁵

Herein, we report a short and efficient synthesis of tri- and disubstituted tetrahydroindenofuranone derivatives based on the conjugate addition of ortho-lithiated aryloxiranes to benzylidene and alkylidene malonates.⁶ Under optimized reaction conditions (*n*-BuLi, -78 °C, 15 min) for the

(4) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A.; Gasparrini, F. *Org. Lett.* **2005**, 7, 4895–4898.

(5) Preliminary experiments were conducted using methylcinnamate, chalcone, and *trans*-cinnamaldehyde: there was no reaction when ortho-lithiated *trans*-stilbene oxide was treated with methylcinnamate, and only 1,2-addition products were obtained in the case of chalcone and *trans*-cinnamaldehyde (see ref 3). For examples of Michael additions promoted by organolithium compounds, see: Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, 64, 2996–2997, and refs cited therein.

(1) For selected reviews on functionalized organolithium compounds, see: (a) Wu, G.; Huang, M. *Chem. Rev.* **2006**, 106, 2596–2616. (b) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, 7, 867–926.

(2) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, 7, 3749–3752.

(3) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A. *J. Org. Chem.* **2006**, 71, 3984–3987.

Table 1. Synthesis of Tetrahydroindenofuranones **4a–g**

entry	oxirane	malonate	product (yield %) ^a	entry	oxirane	malonate	product (yield %) ^a
1		5a : R ² = Ph	 4a (60), dr = 50/50 ^{b,c}	5		5a : R ² = Ph	 4e (75), dr = 77/23 ^{b,c}
2	"	5b : R ² = (CH ₃ O) ₃ C ₆ H ₂	 4b (50), dr = 60/40 ^{b,c}	6		5a : R ² = Ph	 4f (50), dr > 98/2 ^b
3	"	5c : R ² = <i>n</i> -Pr	 4c (50), dr = 67/33 ^{b,c}	7	"	5c : R ² = <i>n</i> -Pr	 4g (50), dr = 80/20 ^{b,c}
4		5b : R ² = (CH ₃ O) ₃ C ₆ H ₂	 4d (50), dr = 60/40 ^{b,c}				

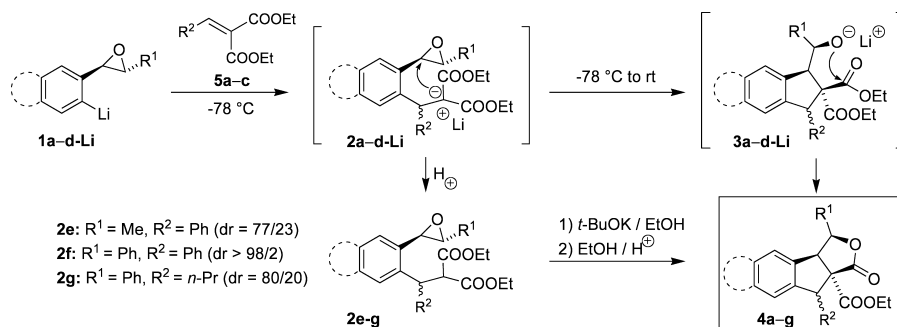
^a Isolated yields after column chromatography on silica gel. ^b Diastereomeric ratio calculated by ¹H NMR on the crude reaction mixture. ^c Separable mixture of diastereomers.

lithium–bromine exchange on the *o*-bromostyrene oxide **1a** (R¹ = H), we generated the organolithium **1a-Li** which reacted with benzylidene malonate **5a** (R² = Ph) to give the tetrahydroindenofuranone **4a** (60% yield) as an equimolar mixture of diastereomers (Table 1, entry 1). All this could be likely explained with a domino reaction that starts with the 1,4-addition of **1a-Li** to **5a** to give the intermediate **2a-Li** which then cyclizes on the oxirane ring via a stereospecific

intramolecular S_N2 (5-*exo*-tet mode), leading to **3a-Li**; successive lactonization furnishes **4a** (Scheme 1).

Similarly, **1a-Li** reacted smoothly with the electron-rich malonate **5b** [R² = 3,4,5-(CH₃O)₃C₆H₂] to give tricyclic product **4b** in 50% yield and with a small increase of the diastereomeric ratio (Table 1, entry 2). An aliphatic substituent on the β-carbon of the malonate was also tolerated, so that lithiated **1a** reacted with the enolizable malonate **5c**

Scheme 1



(R² = *n*-Pr) to give tetrahydroindenofuranone **4c** (50% yield) (Table 1, entry 3).

To extend the scope of the above domino process, we briefly investigated the substitution effect in the starting oxirane. Monosubstituted oxirane **1b-Li**, bearing a lithiated electron-rich aryl moiety (Table 1, entry 4), reacts with **5b** affording the expected product **4d** in moderate yield (50%).

In contrast, *trans*-disubstituted oxiranes **1c** (R¹ = Me) and **1d** (R¹ = Ph) react with aromatic and aliphatic malonates **5a** and **5c** providing, after stirring the reaction mixture overnight at room temperature, the uncyclized Michael adducts **2e–g** (Scheme 1). The substitution of oxiranes **1c,d** could be likely responsible, for steric reasons, for the unsuccessful intramolecular cyclization.

With the Michael adducts **2e–g** in hand, we checked the suitable experimental conditions for their cyclization to the corresponding tetrahydroindenofuranones. To this end, we first investigated the role of the cation in the ring-opening reaction: a solution of **2f** in THF was treated at room temperature with *t*-BuOK, but after 12 h stirring, only starting material was recovered. Similarly, treatment of **2f** with NaH in DMF did not furnish any expected product. After several attempts, we found that using EtOLi, EtONa, or *t*-BuOK in EtOH or *t*-BuOH at room temperature, tetrahydroindenofuranone **4f** was obtained as the sole diastereomer in a good yield (70% yield in the case of the *t*-BuOK/*t*-BuOH system, Table 1, entry 6).⁷ The same methodology was used to obtain products **4e,g** from the corresponding oxiranes **2e,g**.

We also checked the possibility of making the tetrahydroindenofuranone **4f** in one-pot simply by adding, to the ethereal reaction medium after completion of the Michael addition, a polar protic solvent such as EtOH. After stirring the reaction mixture for 3 days at room temperature, we obtained, after workup and purification by column chromatography on silica gel, the desired tetrahydroindenofuranone **4f** in 50% yield (dr > 98/2).⁸

Moreover, it is worth noting that the stereoselectivity of the conjugate addition of ortho-lithiated *trans*-1,2-disubstituted oxiranes **1c,d** to malonates was strongly improved in the case of adduct **4f** obtained as the sole diastereomer (Table 1, entry 6).⁹

(6) The Michael addition of aryllithiums to α,β -unsaturated malonates was reported by Kende and coworkers, as a key step in the racemic synthesis of an epipodophyllotoxin derivative. Such a methodology was employed in the construction of the tetrahydronaphthalene core starting from an ortho-bromobenzylether: Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826–2828.

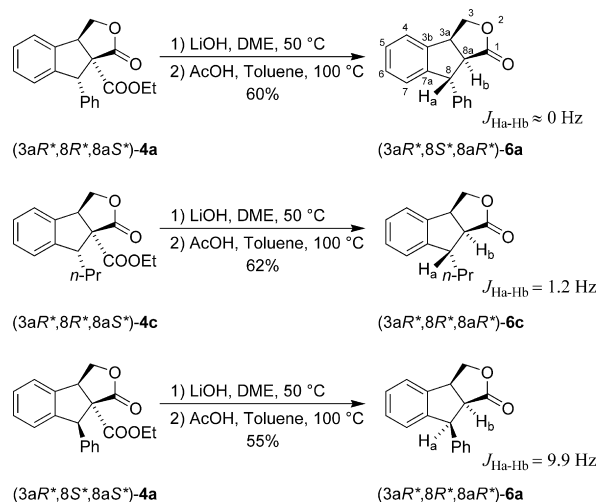
(7) After treating **2e–g** with *t*-BuOK, compounds **4e–g** were isolated as a mixture of ester and the corresponding carboxylic acid, because of a partial hydrolysis of the lactone and/or ethoxycarbonyl groups. Therefore, it was necessary to treat the crude with EtOH/H₂SO₄(cat) in order to obtain exclusively the desired indenofuranones **4e–g** (for details, see Supporting Information).

(8) The one-pot procedure was also employed for the synthesis of **4g** obtained in 50% yield (dr 80/20) after stirring the reaction mixture for one day.

(9) Starting from *cis*-**1d**, we thought that it would be possible to make epimeric tetrahydroindenofuranone *diast*-**4f** with the stereogenic center C3 “R”—instead of “S”—configured, as previously synthesized starting from *trans*-**1d**. All the attempts carried out by using ortho-lithiated *cis*-**1d** resulted in a very complex mixture of products containing only traces of a 60/40 diastereomeric mixture of *diast*-**4f**. After column chromatography, it was possible to isolate and characterize only the major diastereoisomer (for details, see Supporting Information).

The relative configuration of (3*aR**,8*R**,8*aS**)-**4a** and (3*aR**,8*R**,8*aS**)-**4c** was deduced after transformation in known compounds. Specifically, hydrolysis of the ester moiety with LiOH/DME and subsequent decarboxylation performed in toluene at 100 °C with a catalytic amount of AcOH gave, respectively, the tetrahydroindenofuranones (3*aR**,8*S**,8*aR**)-**6a** and (3*aR**,8*R**,8*aR**)-**6c** whose spectral data fitted quite well those reported by Muraoka and Momose (Scheme 2).¹⁰ By

Scheme 2



performing the hydrolysis–decarboxylation sequence on the second diastereomer (3*aR**,8*S**,8*aS**)-**4a**, formed in the reaction of **1a-Li** with **5a**, we obtained the tetrahydroindenofuranone (3*aR**,8*R**,8*aR**)-**6a** whose relative stereochemistry was assigned on the basis of the coupling constant value between the benzylic proton H_a and the vicinal proton H_b in the ¹H NMR, the ³J_{Ha-Hb} (9.9 Hz) being diagnostic of a dihedral angle H8–C8–C8a–H8a near zero.^{11,12}

This observation is in agreement with the nearly absent coupling (³J_{Ha-Hb} ≈ 0 Hz) in the epimeric compound (3*aR**,8*S**,8*aR**)-**6a** whose dihedral angle H8–C8–C8a–H8a value is nearly 90°.

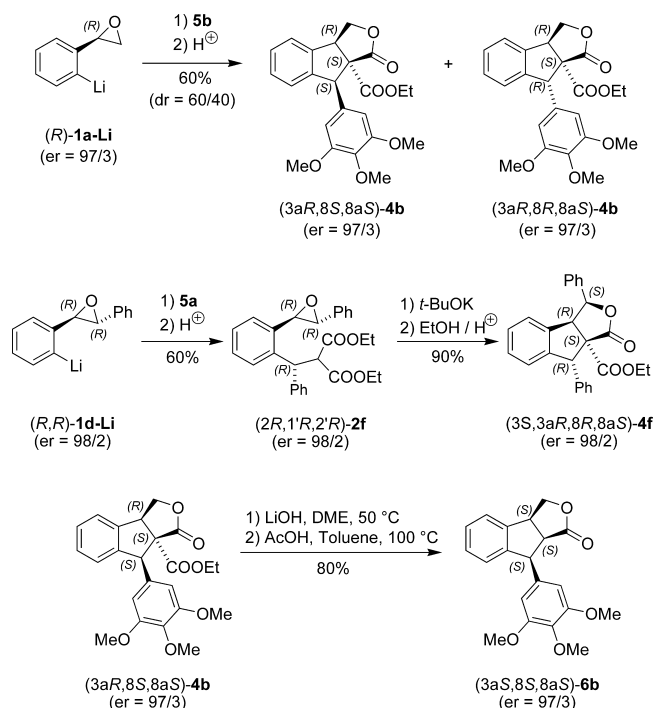
The relative configuration of tetrahydroindenofuranones **4b,d–f** was achieved by ¹H NMR analysis on the basis of the dibenzylic H8 chemical shift analogy with the reference product **4a**. Indeed, we noted that in the diastereoisomers bearing the ethoxycarbonyl group and the H8 on the same side, the resonance of the latter was downfield shifted of about 0.4–0.5 ppm with respect to the corresponding epimers, most probably because of the anisotropic effect of the carbonyl ester group. To support this assumption, we noted that both epimers of tetrahydroindenofuranone **6a**, in which the carbonyl anisotropic effect is missing, show a

(10) Muraoka, O.; Tanabe, G.; Kyohko, S.; Minematsu, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1833–1845.

(11) For all tetrahydroindenofuranones **4a–g** and **6a–c**, it is reasonable to assume that, for thermodynamic reasons, the γ -lactone ring may be fused to the indane system only in a *cis* fashion.

(12) Semiempirical calculations on the substituted indenofuranone systems confirm such values of dihedral angles.

Scheme 3



nearly equal value of chemical shift for the H8 resonance ($\Delta\delta < 0.1$ ppm).

The relative configuration of *(3R*,3aS*,8S*,8aR*)*-**4g** was established by detecting positive NOE effects, diagnostic of the spatially close hydrogen relationship, after applying selective 1H preirradiation within a double pulsed field gradient spin-echo NOE (DPFGSE-NOE) sequence.¹³

The possibility of making optically active tetrahydroindeno-furanones was also evaluated. Indeed, we found that

(13) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; p 264.

(14) To the best of our knowledge, the sole methodology described in the literature, concerning the construction of the tetrahydroindeno[1,2-c]furan-1-one skeleton, was based on the photochemical rearrangement of benzylfuranones, see: Muraoka, O.; Tanabe, G.; Sano, K.; Momose, T. *Heterocycles* **1992**, *34*, 1093–1096.

(R)-1a-Li and *(R,R)*-1d-Li add to malonate **5b** and **5a** with an excellent enantioselectivity leading to the formation of a separable mixture of diastereoisomers *(3aR,8S,8aS)*-**4b**, *(3aR,8R,8aS)*-**4b** (for both er = 97/3), and *(2R,1'R,2'R)*-**2f** (er = 98/2), respectively; the latter was then isolated and easily transformed, enantiospecifically, to the corresponding lactone *(3S,3aR,8R,8aS)*-**4f** (er = 98/2).

Compound *(3aR,8S,8aS)*-**4b** could be smoothly hydrolyzed and decarboxylated to give the corresponding tetrahydroindeno-furanone *(3aS,8S,8aS)*-**6b** (80%, er = 97/3), the configuration of all stereocenters remaining unaffected.

In conclusion, we have developed a simple and efficient domino process for the assembly of unusual tetrahydroindeno[1,2-c]furanone systems,¹⁴ based on the Michael addition of ortho-lithiated aryloxiranes to α,β -unsaturated malonates. Since organolithiums often give direct addition to the carbonyl group (1,2-addition), the complete regioselectivity of the process, toward 1,4-addition, is noteworthy.

The methodology can also be applied to the stereospecific synthesis of highly enantiomerically enriched tetrahydroindeno-furanone derivatives starting from chiral nonracemic ortho-bromo aryloxiranes. Moreover, the utility of the methodology has been underscored by preparing compound **4d** as a structural analogue of the natural antitumoral epipodophyllotoxins.^{15,16}

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Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) For the synthesis and biological evaluation of structural analogues of epipodophyllotoxins, see: Klein, L. L.; Yeung, C. M.; Chu, D. T.; McDonald, E. J.; Clement, J. J.; Plattner, J. J. *J. Med. Chem.* **1991**, *34*, 984992.

(16) For a recent strategy about the synthesis of Podophyllotoxin and its analogues, see: Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. *Org. Lett.* **2007**, *9*, 1199–1202.