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An Efficient Route to Tetrahydronaphthols via Addition of Ortho-Lithiated Stilbene Oxides to α,β-Unsaturated Fischer Carbene Complexes

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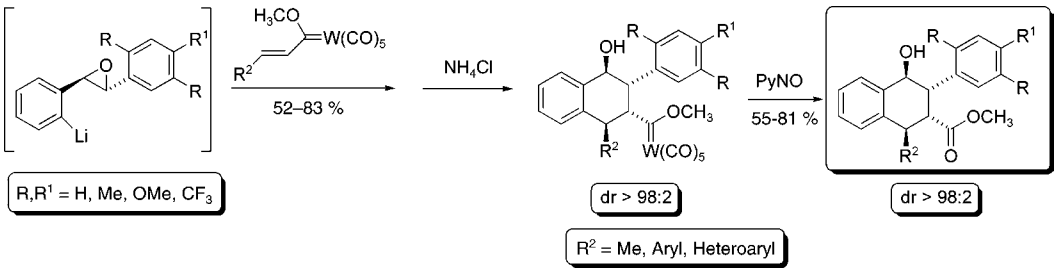
ABSTRACT



A stereoselective/stereospecific synthesis of polysubstituted tetrahydronaphthols based on the Michael addition of ortho-lithiated stilbene oxides to α,β-unsaturated Fischer carbene complexes followed by an unusual cyclization of the corresponding intermediate in a 6-*endo*-tet mode is described.

The tetrahydronaphthol moiety **A** (Scheme 1) is the core structure of many biologically active substances[1] among which (−)-podophyllotoxine, one of the well-known lignan natural products with antimitotic activity[2] whose semisynthetic derivatives such as etoposide (an effective topoisomerase II poison) and teniposide that are now in clinical use as anticancer agents.[3] (−)-Picropodophyllin[4] and (−)-neopodophyllotoxin[5] are also useful structural analogues. Thus, methods for the synthesis of tetrahydronaphthalene derivatives of this kind are of great interest and are widely being pursued.[6]

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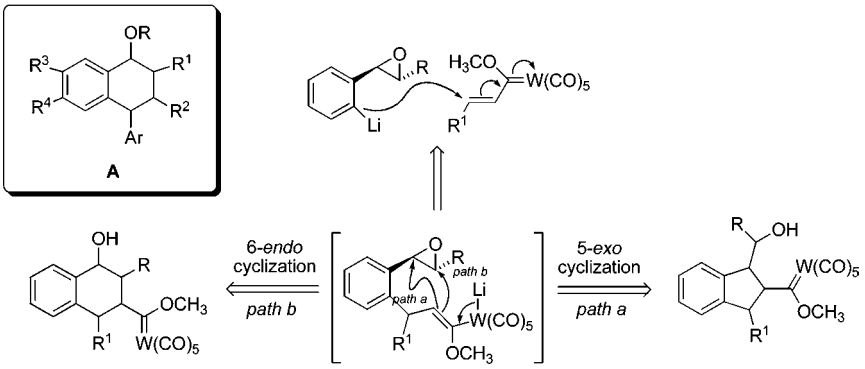
Scheme 1



In a project dealing with reactions of lithiated oxiranes with Fischer carbene complexes[7] we reasoned that addition of ortho-lithiated aryloxiranes to α,β-unsaturated Fischer carbene complexes might prove useful for the preparation of polysubstituted tetrahydronaphthols following a domino process of the kind shown in Scheme 1, if the oxirane ring-opening-promoted cyclization takes place in a 6-*endo* mode (path b).[8] A 5-*exo* process (path a) would, instead, lead to hydroxymethyl indane derivatives. Herein, we report a regio- and stereoselective synthesis of polysubstituted tetrahydronaphthols through the reaction of ortho-lithiated stilbene oxides with α,β-unsaturated Fischer carbene complexes.

First we concentrated on the generation of ortho-lithiated stilbene oxide: the bromo-lithium exchange of *ortho*-bromo-*trans*-stilbene oxide (±)-**1a** proved to be problematic and required specific conditions in terms of the lithiating agent: reduction to give *trans*-stilbene oxide mainly occurred with *n*-BuLi, *s*-BuLi, and *t*-BuLi. Ortho-lithiation did occur to give **1a-Li** when PhLi (0.9 equiv) was used, as proved by the capture with MeI (90%).[9] The addition of **3a** (0.75 equiv) to **1a-Li** led to the highly diastereoselective formation (dr > 98/2) of tetrahydronaphthol **4a**. A domino reaction, initiating with the 1,4-addition of **1a-Li** to **3a** to give the organolithium **2a-Li** and then **4a**, via simultaneous oxirane ring-opening and 6-*endo* mode cyclization, most likely takes place (Scheme 2).

The formation of **2a-Li** was proved by trapping it with an acidic quench to give **2a** (53%). The high electron-withdrawing nature of the metal carbonyl fragment in the α,β-unsaturated Fischer carbene complex **3a** reasonably explains the observed 1,4-addition, which contrasts with the behavior of other α,β-unsaturated carbonyl compounds.[10]

Similarly, **1a-Li** reacted with aromatic, heteroaromatic, and aliphatic Fischer carbene complexes **3b**−**h** to furnish tetrahydronaphthols **4b**−**h** (Table 1). Electron-donating as well as electron-withdrawing substituents in the β-phenyl ring were tolerated, such that lithiated **1b**−**d** reacted with **3c** and **3g** to give **4i**−**k**. The relative configuration of compounds **4a**−**k** was established by 2D-NOESY correlations and confirmed by the X-ray analysis in the case of **4g**.[11] It is worth pointing out that, in contrast with **1a-Li**, ortho-lithiated *cis*-stilbene oxide, when treated with **3g**, gave an inseparable mixture of several products, whatever the experimental conditions in terms of temperature, reaction time, and lithiating agent (*n*-BuLi, *s*-BuLi, PhLi).

The ease of oxidation of **4** to the corresponding esters was proven by the conversion of **4c**,**d**,**f**,**g**,**i**−**k** into **5c**,**d**,**f**,**g**,**i**−**k** upon treatment with pyridine *N*-oxide (PyNO) in THF (rt, 24−48 h).[12] The exclusive 6-*endo*-tet cyclization of the reaction of **1a-Li** with **3** is remarkable: it contrasts with many other cyclizations involving S_N2-type transition states in which the 5-*exo* mode cyclization predominates,[8,13] and no Lewis acid activation is needed as required for other cyclizations involving oxirane ring-opening. Indeed, it has been reported that either δ,ϵ-epoxy alcohols[14a] or epoxy-alkoxides[14b] cyclize predominantly in a 5-*exo* mode leading

(6) For the synthesis of podophyllotoxin and analogues see: refs 1a and 4 and the following: (a) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029−5041. (b) Ward, R. S. *Synthesis* **1992**, 719−730. (c) Clayden, J.; Kenworthy, N. M.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831−834. (d) Reynolds, A. R.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 12108−12109. (e) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487−2489. (f) Hadimani, S. B.; Tanpure, R. P.; Bhat, S. V. *Tetrahedron Lett.* **1996**, *37*, 4791−4794. (g) Klein, L. L.; Yeung, C. M.; Chu, D. T.; McDonald, E. J.; Clement, J. J.; Plattner, J. J. *J. Med. Chem.* **1991**, *34*, 984−992. (h) Choi, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796−5798. (i) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854−7858.

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(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−738.

(9) α-Lithiation competes with ortho-lithiation (1:2 ratio) when racemic *trans*-stilbene oxide was reacted with *s*-BuLi (1.5 equiv) in the presence of TMEDA (1.5 equiv), see: Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191−4194.

(10) The addition of **1a-Li** to methylcinnamate gave *trans*-stilbene oxide together with the unreacted methylcinnamate, whereas the reaction with chalcone and *trans*-cinnamaldehyde gave only the corresponding 1,2-addition products.

(11) Crystallographic data for compound **4g** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-279242). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (int.) +44-1223/336-033; E-mail deposit@ccdc.cam.ac.uk].

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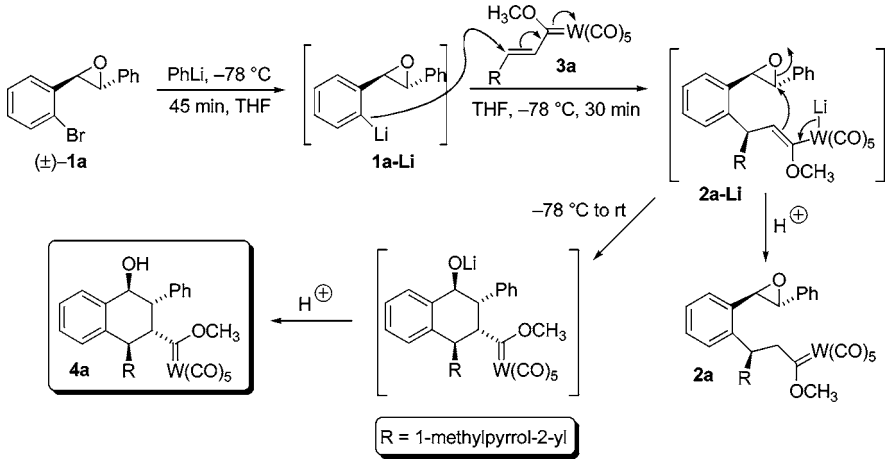
(13) In 1970, in an important and influential paper (Tenud, L.; Farouq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2054), Eschenmoser et al. defined the exocyclic and endocyclic modes of nucleophilic substitution pointing out that the endocyclic ones, although disfavored at "typical" tetrahedral carbons, may be allowed where the substitution center is an "sp^2-like" epoxide carbon. Therefore, the rules for opening three-membered rings, such as epoxides, seem really to lie between those for tetrahedral and trigonal systems.

Scheme 2

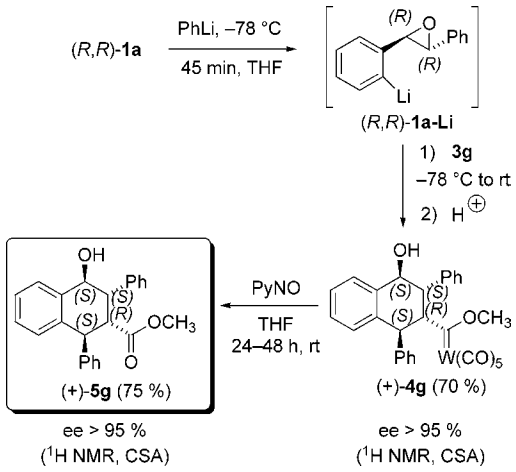


to tetrahydrofurans. Intramolecular 6-*endo*-tet selective cylizations are much less frequent and occur under specific experimental conditions such as antibody catalysis,[15] cooperative catalysis promoted by a dimeric [Co^{III}(salen)] complex,[16] or when unsaturated groups are present on the oxirane ring.[17] In the case of the reaction of **1a-Li** with **3**, the formation of tetrahydronaphthols **4** in a 6-*endo* mode could be ascribed to the geometric constraints imposed by the oxirane ring. Moreover, the structure of the tether between the nucleophilic site and the leaving group (C−O bond) as well as stereoelectronic and conformational restrictions may be playing an important role in controlling the size of the ring to be formed.

Optically pure (*R,R*)-*ortho*-bromo-*trans*-stilbene oxide **1a** was made available by chiral HPLC preparative chromatography (see experimental details in the Supporting Information) of the related racemate. The absolute configuration was indirectly secured by comparing its optical rotation {$[\alpha]_D$ +49 (*c* 1, $CHCl_3$)} with that of the (*S,S*)-enantiomer {$[\alpha]_D$ −49 (*c* 1, $CHCl_3$)}: the *S,S* configuration was assigned by converting it into the known (*S,S*)-*trans*-stilbene oxide {$[\alpha]_D$ −278 (*c* 0.6, EtOH)} by bromo-lithium exchange (PhLi, −78 °C, THF, 45 min) and acidic quenching.[18] With the optically pure (*R,R*)-**1a** in hand we used it for developing an asymmetric synthesis of tetrahydronaphthol **5g**.

Treating (*R,R*)-**1a** with PhLi generated (*R,R*)-**1a-Li**. The addition of **3g** resulted in the formation of optically pure tetrahydronaphthol (+)-**4g** (70%). The absolute configuration of the four stereocenters, (*S,R,S,S*), was established by 2D-NOESY correlations considering that there is retention of configuration at one benzylic carbon and inversion at the other one of the starting epoxide, which is that attacked by the nucleophilic carbon. Compound (+)-**4g** could be easily oxidized with PyNO to give the corresponding ester (+)-**5g** (75%), the configuration of all the stereocenters remaining unaffected. The ee values of (+)-**4g** and (+)-**5g** were measured by ^{1}H NMR in the presence of a chiral solvating agent (CSA) (see experimental details in the Supporting Information) (Scheme 3).

Scheme 3



In conclusion, we have developed an easy method of stereoselective (and stereospecific) synthesis of new and potentially bioactive polysubstituted tetrahydronaphthols based on the reaction of ortho-lithiated stilbene oxides and α,β-unsaturated Fischer carbene complexes in a MIRC (Michael-Initiated Ring Closure) process involving an un-

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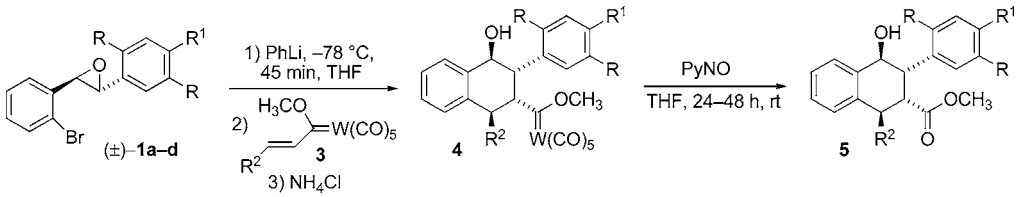
(17) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1995**, 1359−1362.

(18) The *S,S* configuration to the stilbene oxide was assigned on the basis of the negative sign of its rotation in EtOH {$[\alpha]_D$ −278 (*c* 0.6, EtOH anhyd)} compared to the positive one associated with the *R,R* isomer from the literature. In particular, as far as the latter rotation is concerned, large variations have been observed depending not only upon the nature of the solvent, but also upon the nature and the amount of the additive employed. It is surprising that the calculated $[\alpha]_D$ max for the *R,R* isomer in various EtOH commercially available has been found to range from +235 to +342! See: Solladié-Cavallo, A.; Diep-Vohuule, A.; Sunjic, V.; Vinkovic, V. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1783−1788.

Table 1. Preparation of Tetrahydronaphthol Carbenes **4a**−**k** and Carboxylates **5c**,**d**,**f**,**g**,**i**−**k**



stilbene oxide	R	R^1	R^2	carbene complex	**4** (% yield)[a,b]	**5** (% yield)[a]
1a	H	H	1-methylpyrrol-2-yl	**3a**	**4a** (53)	
1a	H	H	*p*-$MeOC_6H_4$	**3b**	**4b** (80)	
1a	H	H	*p*-ClC_6H_4	**3c**	**4c** (74)	**5c** (81)
1a	H	H	*p*-MeC_6H_4	**3d**	**4d** (72)	**5d** (55)
1a	H	H	*o*-MeC_6H_4	**3e**	**4e** (52)	
1a	H	H	2-furyl	**3f**	**4f** (63)	**5f** (59)
1a	H	H	Ph	**3g**	**4g** (71)	**5g** (76)
1a	H	H	Me	**3h**	**4h** (71)	
1b	H	Me	*p*-ClC_6H_4	**3c**	**4i** (83)	**5i** (79)
1c	OMe	H	Ph	**3g**	**4j** (81)	**5j** (69)
1d	H	CF_3	Ph	**3g**	**4k** (78)	**5k** (72)

[a] Isolated yields after column chromatography. [b] For all tetrahydronaphthol carbenes **4** dr >98/2 by ^1H NMR.

usual noncatalyzed 6-*endo*-tet cyclization. The synthetic application of the present methodology to target molecules is in progress in our lab.

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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra for compounds **2a**, **4a**−**k**, **5c**,**d**,**f**,**g**,**i**−**k**. Ortep view of compound **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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