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Sulfinyl-Directed Diastereoselective [5 + 2] Pyrone−Alkene Cycloadditions: A Practical Route to Enantiopure 8-Oxabicyclo[3.2.1]octane Derivatives

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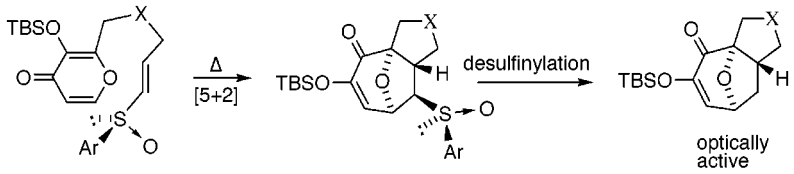
ABSTRACT



Introduction of a homochiral *p*-tolylsulfinyl group at an appropriate position in the alkene accelerates the thermal [5C + 2C] intramolecular cycloaddition to *β*-silyloxy-*γ*-pyrones and, most importantly, leads to excellent levels of diastereodifferentiation. The resulting adducts can be easily desulfinylated to give optically active 8-oxabicyclic[3.2.1]octane intermediates which by virtue of their rich functionalization might be susceptible to elaboration into enantiomerically pure natural products containing seven-membered carbocycles and tetrahydrofurans.

The great utility of 8-oxabicyclo[3.2.1]octane frameworks as versatile, stereochemically biased building blocks in organic synthesis[1] is currently encouraging the development of methods to prepare these bicycles as single enantiomers. Of the few approaches hitherto described, the most effective are based on the desymmetrization of meso derivatives[2] and on asymmetric versions of allyl cation−furan [4 + 3] cycloadditions.[3] Very recently an asymmetric [5C + 2C] cycloaddition of a carbonyl ylide to dimethylacetylenedicarboxylate[4] and an elegant [5 + 2] cycloaddition of pyranylmolybdenum *π*-complexes to electron-deficient alkenes[5] have also been reported. Whereas these efforts represent a significant contribution in the area, the development of a truly practical and general alternative for the assembly of enantiopure oxabicyclo[3.2.1]octane structures remains an important synthetic objective.

Our work in recent years has shown that the intramolecular thermal [5C + 2C] cycloaddition of *β*-alkoxy-*γ*-pyrones to alkenes is a remarkably practical method to assemble relatively complex 8-oxabicyclo[3.2.1]octane skeletons from simple, readily available precursors.[6] The particularly rich functionalization of the resulting adducts offers unique possibilities for gaining rapid access to a variety of valuable

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(2) (a) Cox, P. J.; Simpkims, N. S. *Synlett* **1991**, 321. (b) Williard, P. G.; Liu, Q. X. *J. Am. Chem. Soc.* **1993**, *115*, 3380. (c) Lautens, M.; Ma, S. *Tetrahedron Lett.* **1996**, *37*, 1727.

(3) (a) Lautens, M.; Aspiotis, R.; Colucci, J. *J. Am. Chem. Soc.* **1996**, *118*, 10930. (b) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353. (c) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1266. (d) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831. (e) Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 3394. (f) Ou, L.; Hu, Y.; Song, G.; Bai, D. *Tetrahedron* **1999**, *55*, 13999. See also ref 1g.

(4) (a) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. See also: (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471. (c) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185.

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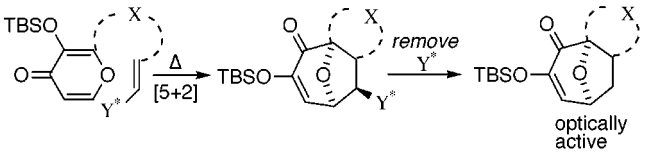
cyclic systems.[7] Therefore, the implementation of an asymmetric version of this cycloaddition showed itself as a meaningful, challenging goal.

We have already shown that incorporating a sulfoxide in the tether connecting the pyrone and the alkene leads to modest levels of diastereofacial selectivity (X = SO, Y = H, Scheme 1).[8]

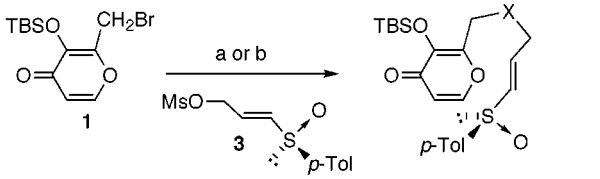
Scheme 1



Since this strategy is intrinsically limited by the presumable difficulty in preparing enantiorich precursors, we envisaged an alternative approach based on the introduction of a homochiral sulfoxide unit at the *trans* terminal position of the alkene (Y = SOAr).[9] Despite our concern about a potentially deleterious steric effect of this substituent on the cycloaddition rate, it was reasoned that the obligatory *endo* approach of the sulfoxide group to the pyrone might give rise to satisfactory levels of dissimilar facial interference. Herein we show that the approach is indeed successful, representing the first efficient application of a sulfur-based chiral auxiliary in an intramolecular homo Diels−Alder type of reaction.[10]

The feasibility of the strategy was tested on dinitrile **2a**, which was readily prepared in good yield from the known bromopyrone **1**[7b] by displacement with malononitrile and subsequent coupling with the enantiopure mesylate **3** (Scheme 2). This compound was prepared by mesylation of the

Scheme 2



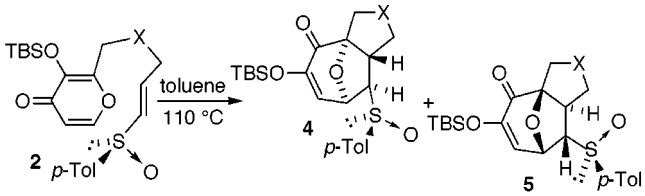
2a, X = $C(CN)_2$ (85%)
2b, X = $C(CO_2Et)_2$ (70%)
2c, X = S (70%)

For **2a** (E = CN) and **2b** (E = CO_2Et): (a) *i*) $CH_2(E)_2$, NaH, THF; *ii*) NaH, THF, **3**, rt.

For **2c**: (b) Ph_3SiSH, PPh_3, Cs_2CO_3, THF, rt.

corresponding alcohol ($[\alpha]^{20}_D$ = +234, *c* 1, $CHCl_3$, $[\alpha]^{20}_D$ lit = +233, *c* 1, $CHCl_3$), itself obtained by following a known procedure.[11] Remarkably, the cycloaddition of **2a** could be efficiently carried out by simple heating in toluene under reflux for 10 h (Table 1). These thermal conditions are

Table 1. Intramolecular [5 + 2] Thermal cycloaddition



entry	pyrone	X	yield, %[a]	**4**:**5**[b]	time, h
1	**2a**	$C(CN)_2$	98	**4a**:**5a** (91:9)	10
2	**2b**[c]	$C(CO_2Et)_2$	99	**4b**:**5b** (97:3)	3.5
3	**2c**[d]	S	95	**4c**:**5c** (93:7)	46

[a] Combined isolated yield after chromatography. [b] Ratio determined by ^1H NMR of the crude reaction mixture. [c] The cycloaddition of its alkene-unsubstituted analogue requires heating for 12 h at 110 °C. [d] The cycloaddition of its alkene-unsubstituted analogue requires heating for 40 h at 160 °C.

considerably milder than those needed to induce the reaction of its alkene-unsubstituted analogue (12 h at 160 °C or more than 60 h at 110 °C).[7c] This result indicates that the presence of the sulfinyl substituent does not hamper the reaction but actually accelerates it, probably by exerting a moderate electron-withdrawing effect which activates the alkene toward the cycloaddition. Most importantly, the diastereoselectivity of the reaction was notable (**4a**/**5a** 91:9, see Table 1), more than fulfilling our expectations in terms of the anticipated facial differentiating effect of the *endo*-placed arylsulfinyl group.

This high diastereoselectivity was also obtained with substrates bearing other type of pyrone−alkene linkers, such as dicarboxylate **2b** or sulfide **2c**, with their cycloaddition being again faster than that of their unsubstituted alkene analogues (Table 1).

(6) (a) Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585. (b) Mascareñas, J. L.; Pérez, I.; Rumbo, A.; Castedo, L. *Synlett* **1997**, 81. For a recent review, see: Mascareñas, J. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; Jai Press: Stamford, 1999; Vol 6, pp 1−54.

(7) (a) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620. (b) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L *J. Org. Chem.* **1999**, *64*, 966. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560.

(8) Rumbo, A.; Castedo, L.; Mascareñas, J. L. *Tetrahedron Lett.* **1997**, *38*, 5885.

(9) Vinyl sulfoxides have been used as chiral two-carbon components in other cycloadditions such as intermolecular [3 + 2] and [4 + 2] reactions, although to be useful as dienophiles in Diels−Alder reactions, the presence of an additional electron-activating group at the double bond is required. For [3 + 2] reactions, see: (a) Chaigne, F.; Gotteland, J.-P.; Malacria, M. *Tetrahedron Lett.* **1989**, *30*, 1807. For Diels−Alder applications, see: (b) Garcia Ruano, J. L.; Carretero, J. C.; Carreño, M. C.; Martin Cabrejas, L. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925.

(10) *p*-Tolyl vinyl sulfoxide has been used as chiral dipolarophile in intermolecular [5 + 2] cycloadditions to 3-oxodipyridinium betaines, although the reaction produces mixtures of regio- and stereoisomers: (a) Takahash, T.; Kitano, K.; Hagi, T.; Nihonmatsu, H.; Koizumi, T. *Chem. Lett.* **1989**, 597. (b) Araldi, G. L.; Prakash, K. R. C.; George, C.; Kozikowski, A. P. *Chem. Commun.* **1997**, 1875.

(11) This alcohol was synthesized from (+)-methyl *p*-tolyl sulfoxide in three steps and 43% overall yield by following the procedure described in Martín, L. M. Ph.D. Dissertation, Universidad Autonoma de Madrid, 1996. The product can be alternatively prepared from 2-propyn-1-ol in five steps and 33% overall yield according to the procedure described in Posner, T. *Tetrahedron Lett.* **1984**, *25*, 2627.

Diastereoisomeric products **4** and **5** were easily separated by flash chromatography, and their structures were established by ^{1}H NMR on the basis of the shielding (anisotropic effect of the aryl group) and deshielding (*syn*-axial effect of the sulfinylic oxygen) effects observed in the major and the minor diastereoisomers with respect to their sulfide homologues.[12] The hydrogens more affected are bold in the Figure 1.

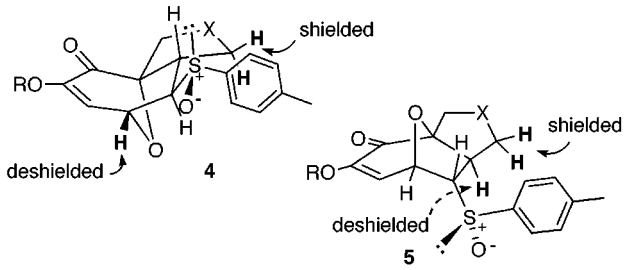


Figure 1.

The stereochemical outcome of the above reactions could be rationalized by assuming that the alkenyl sulfoxide unit adopts an *S-trans* conformation in order to avoid repulsive dipole−dipole interactions with the pyrone, disfavoring the approach from the face of the sulfoxide displaying the *p*-tolyl group (Figure 2).[13]

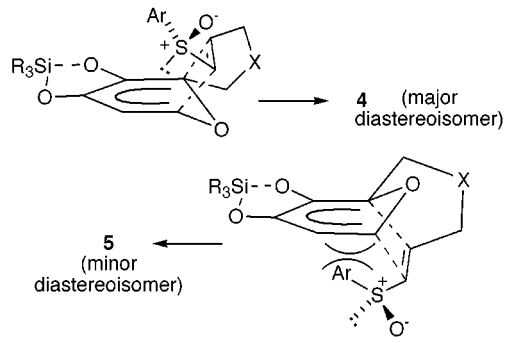
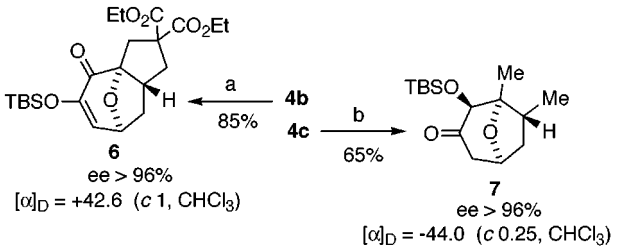


Figure 2.

It was now pertinent to demonstrate that the above cycloaddition occurred without racemization at the sulfur and hence that the cycloadducts could be desulfinylated to synthetically valuable enantiopure derivatives. Several attempts to remove the sulfoxide from dinitrile **4a** gave complex reaction mixtures, probably because of concomitant reactions of the reducing agents with the nitriles. However, treatment of diester **4b** with excess of Raney nickel in refluxing THF did afford the expected enantiomerically pure tricycle **6** (ee > 96%),[14] a class of building block with evident potential for obtaining synthetically appealing bicyclo[5.3.0] ring systems (Scheme 3).[15] On the other hand, similar

Scheme 3



(a) Raney Ni, THF, 60 °C. (b) Raney Ni, H_2, THF, 60 °C.

treatment of sulfoxide **4c** under an atmosphere of hydrogen gave optically active oxabicycle **7** (ee > 96%).[14]

We have already shown for the racemic case that this type of oxabicyclic α-silyloxyketone is particularly useful for obtaining stereochemically rich tetrahydrofurans.[7a,b]

In summary, attaching a *p*-tolylsulfinyl group at an appropriate position in the alkene leads to acceleration of its thermal [5C + 2C] intramolecular cycloaddition to β-silyloxy-γ-pyrones and, most importantly, leads to excellent levels of diastereodifferentiation. The ready availability and low cost of a variety of homochiral sulfinyl-containing cycloaddition precursors coupled with the polyfunctional nature of the oxabicyclic products augurs well for the application of the strategy to the enantioselective synthesis of natural products containing seven-membered carbocycles and tetrahydrofurans.

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Supporting Information Available: Characterization data and experimental procedures for the preparation of **2a**, **2b**, **2c**, **3**, **4a**, **4b**, **4c**, **5a**, **5b**, **5c**, **6**, and **7**, as well as the sulfide derivatives of **4** and **5**. ^{1}H NMR spectra relevant for deducing diastereo- and enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information for detailed NMR data of **4**, **5**, and their sulfide analogues. For a discussion on the NMR effects of the aryl sulfoxide group, see: (a) Carreño, M. C.; Garcia Ruano, J. L.; Martin, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120. (b) Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379.

(13) For conformational preferences of vinyl sulfoxides, see: (a) Arai, I.; Takayama, H.; Koizumi, T. *Tetrahedron Lett.* **1987**, *28*, 3689. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(14) Enantiomeric excess was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ using racemic mixtures as reference. Writing ee > 96% means that the other enantiomer was not detected at the NMR scale.

(15) We have recently discovered a practical method for opening the oxa bridge of these types of systems: Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Synthesis (Special issue)*, in press. For a discussion on the relevance of the bicyclo[5.3.0] ring systems, see: Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.