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A Sulfinyl-Directed Asymmetric [5C + 2C] Intramolecular Acetoxypyranone–Alkene Cycloaddition

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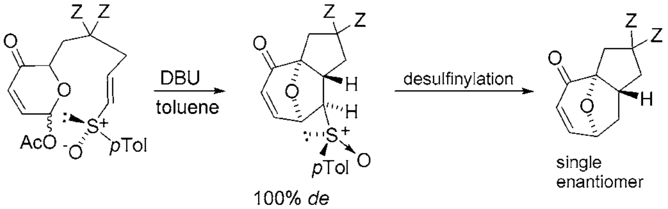
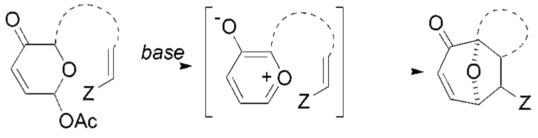
ABSTRACT



Introduction of a homochiral *p*-tolylsulfinyl group at the trans terminal position of an alkene induces a total diastereodifferentiation in the intramolecular cycloaddition of the latter to 3-oxidopyrylium ylide precursors. The cycloadducts can be readily desulfinylated to afford enantiomerically pure oxa-bridged bicyclo[5.3.0]decane ring systems. Theoretical calculations confirm that diastereoselectivity stems from the conformational preferences of the alkenylsulfoxide unit in the transition state of the reaction.

The 3-oxidopyrylium−alkene cycloaddition is a well-established method for constructing relatively complex 8-oxabicyclo[3.2.1]octanes from readily available 6-acetoxy-3-pyranone precursors (Scheme 1).[1] The synthetic relevance of this reaction and, in particular, that of its intramolecular version are demonstrated by its use as the key step in the synthesis of natural products as complex as phorbol or resiniferatoxin.[2] It is evident that the reaction would be of greater value if it could be carried out in an asymmetric fashion so that the products could be obtained in an enantiomerically enriched form.[3] Our recent discovery of the effectiveness of the sulfinyl group as chiral inducer in thermal intramolecular pyrone−alkene annulations[4] led us to find out whether the same stereogenesis strategy could be used in the above more classical oxidopyrylium−alkene cycloaddition.

Scheme 1



Herein we demonstrate that, indeed, attaching a chiral sulfoxide at the trans terminal position of an alkene allows for its mild, fully diastereoselective intramolecular cycloaddition to 6-acetoxy-3-pyranones. We also report preliminary theoretical calculations that explain the observed diasterereoselectivity.

The synthesis of an appropriate cycloaddition precursor was carried out as indicated in Scheme 2. The alkenylsulfinyl derivative **3** could be readily prepared by alkylating the

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(1) (a) Katrizky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827. (b) Sammes, P. G.; Street, L. J. *Gazz. Chim. Ital.* **1986**, *116*, 106. (c) Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9135.

(2) (a) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (b) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

(3) Intermolecular 3-oxidopyridinium−vinylsulfoxide cycloadditions have been previously reported, but they exhibit modest yields and relatively poor stereoselectivities: (a) Takahashi, 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. (c) Prakash, K. R. C.; Trzcinska, M.; Johnson, K. M.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1443.

(4) (a) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 1005; (b) **2001**, *3*, 623; (c) *Chem. Eur. J.* **2002**, *8*, 884.

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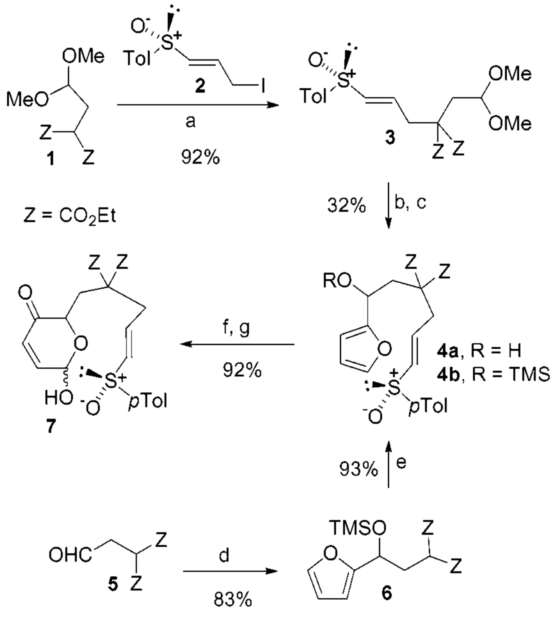
diethyl ester of 2-(2,2-dimethoxyethyl)-malonic acid (**1**)[5] with the enantiopure iodosulfinyl derivative **2**.[4c] However, coupling of the aldehyde resulting from acidic treatment with 2-lithiofuran gave only a 32% yield of the desired alcohol **4a**.

Scheme 2[a]



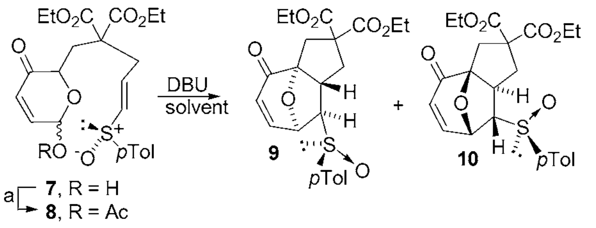
[a] Reaction conditions: (a) NaH, THF, 0 °C, **2**. (b) *p*-TsOH, acetone-H_2O. (c) *n*-BuLi, furan, THF, −78 °C, then **3**. (d) *n*-BuLi, furan, THF, −78 °C, then **5**, and after 10 min Et_3N and TMSCl. (e) NaH, THF, 0 °C, **2**. (f) TBAF, AcOH, THF, 0 °C. (g) NBS, THF−H_2O, 0 °C.

We therefore tried an alternative, more convergent approach to **4** that proved to be more efficient. Reaction of 2-lithiofuran with aldehyde **5**, followed by in situ silylation gave the expected trimethylsilyl ether **6** in 83% yield. This diester derivative was alkylated with iodide **2** to give the desired coupled product **4b** in 93% yield. The transformation of this furan derivative into the required pyranone **7** was achieved by careful removal of the TMS group followed by treatment of the resulting alcohol with NBS.

To carry out the cycloaddition reaction, the epimeric alcohols **7** were transformed into the acetates **8**, which upon treatment with DBU in CH_3CN, standard conditions for inducing the formation of the required 3-oxidopyrylium ylide, gave the expected [5 + 2] cycloadducts. The reaction was quite fast (5 min at rt) and led to an 85:15 mixture of the diastereoisomeric cycloadducts **9** and **10**, which could not be separated by standard chromatographic techniques.

As indicated in Table 1, the cycloaddition can be carried out at lower temperatures (even −30 °C), albeit the proportion of isomers is similar. Remarkably, with the use of CH_2Cl_2 or toluene as a solvent, the reaction is slower but completely stereoselective (entries 5−7, Table 1). The solvent choice thus seems to be important for full realization of the diastereoselectivity influence of the chiral sulfinyl group, with less polar solvents giving better results.

Table 1. Cycloaddition of **8**[a]



entry	solvent	T[a] (°C)	time (min)	**9**:**10**[b]	yield[c]
1	CH_3CN	20	5	85:15	77%
2	CH_3CN	0	5	85:15	75%
3	CH_3CN	−30	90	88:12	82%
4	DMF	0	15	85:15	72%
5	CH_2Cl_2	−30	150	100:0[d]	78%
6	toluene	−30	180	100:0	86%
7	toluene	0	60	100:0	81%
8	Et_2O	−30	180	96:4	80%

[a] Reactions were carried out using 1.1 equiv of DBU and 1 mM concentrations of **8**. [b] This ratio was determined by ^1H NMR of the crude reaction residue. [c] For both acetylation and cycloaddition steps. [d] The ratio 100:0 means that the minor diastereoisomer was not detected.

The structure of the major diastereoisomer **9** was initially established by ^1H NMR, on the basis of shielding and deshielding effects observed in comparison with the sulfide derivatives. Nonetheless, a definitive confirmation of the stereochemistry was obtained by X-ray crystallography of the alcohol produced by reduction of **9** with $NaBH_4/CeCl_3$ (Figure 1).

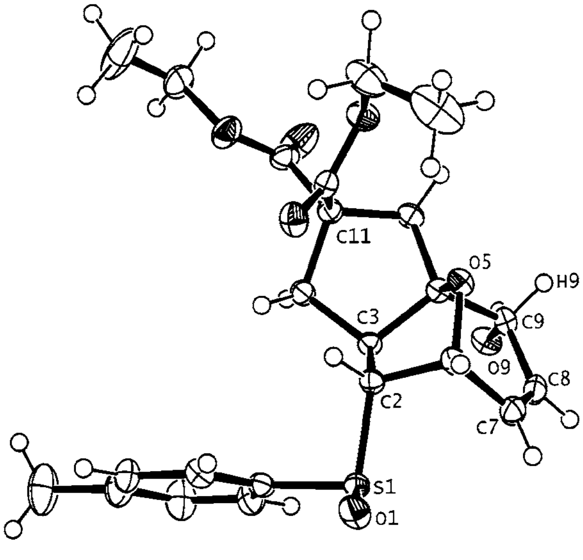


Figure 1.

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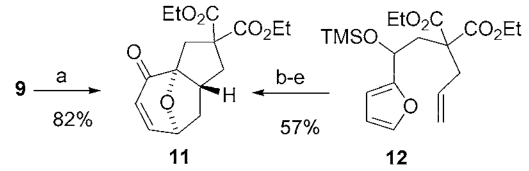
(5) Rahman, A.; Beisler, J. A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063.

Desulfinylation of the cycloadduct **9**, which was easily achieved by treatment with Raney Ni in refluxing THF, gave the expected enantiopure oxa-bridged carbobicycle (+)-**11** (ee > 97%).[6] The synthesis of this cycloadduct in racemic form was achieved from the furan derivative **12** (Scheme 3), itself prepared by coupling the anion of **6** with allyl bromide (99%).

Scheme 3[a]



[a] Reaction conditions: (a) Raney Ni, THF, 60 °C. (b) TBAF, AcOH, THF, 0 °C. (c) NBS, THF−H_2O, 0 °C. (d) AcCl, Et_3N, DMAP, CH_2Cl_2, −78 °C. (e) DBU, toluene, −30 °C, 210 min.

To obtain precise information on the origin of the facial stereoselectivity of the above cycloaddition reaction, we performed a theoretical investigation of the reaction course using DFT calculations. Previous studies by Domingo et al. have shown the validity of the B3LYP hybrid functional for obtaining accurate geometries and stationary point energies for related oxidopyrylium−alkene cycloadditions.[7] Energy minima and transition-state structures were explored in a model that lacked the diethylesters and with a phenyl instead of a *p*-tolyl group on the sulfur. A search of the potential energy surface[8] revealed two energy minima oxidopyrylium intermediates and four possible concerted and synchronical transition states, the two with the lower activation barriers being those represented in Figure 2.

S-Cis and *s*-trans correspond to the more stable conformations of the alkenylsulfinyl functionality in the oxidopyrylium ylide precursors.[9] As can be deduced from the diagram, transition state $\mathbf{TS_1}$, in which the alkenyl sulfoxide unit adopts an *s*-trans type of conformation, is about 3 kcal/mol more stable than $\mathbf{TS_2}$, which is the less energetic of the transition states leading to the opposed selectivity. Therefore, these theoretical results are in agreement with the observed experimental stereoselectivities and support our initial hypothesis[4] that the diastereofacial selectivity is largely due to the sulfinyl group preferring to adopt an *s*-trans conformation, most probably to avoid repulsive dipolar interactions with the oxidopyrylium. This is also consistent with the effect of the solvent polarity in the diastereoselectivity.

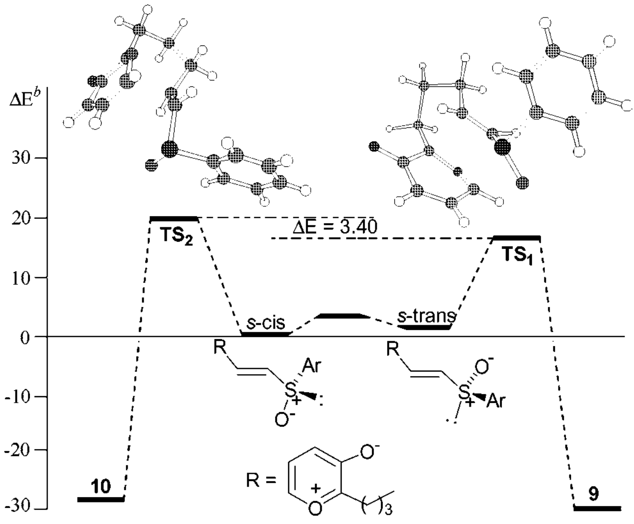


Figure 2. Reaction coordinate diagram for the cycloaddition. Models **10** and **9** do not include the diester present in **9** and **10**. Δ*E* is given in kcal/mol.

In conclusion, we have demonstrated that attaching a *p*-tolylsulfinyl group to the trans terminal position of an alkene allows a mild, highly diastereoselective [5 + 2] intramolecular cycloaddition of the alkene to 6-acetoxy-3-pyranone derivatives. The approach provides a facile entry to enantiopure oxa-bridged bicyclo[5.3.0]decanes, compounds of palpable synthetic interest. We have also shown that the observed diastereoselectivity is in agreement with the results of theoretical calculations.

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Supporting Information Available: Experimental procedures, spectroscopic data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Enantiomeric excess was determined by ^1H NMR in the presence of $Eu(hfc)_3$ using a racemic mixture as a reference.

(7) Domingo, L. C.; Zaragoza, R. J. *J. Org. Chem.* **2000**, *65*, 5480.

(8) Calculations were performed using the Gaussian 98 set of programs. Geometries were preoptimized by the semiempirical PM3 method. Stationary points were optimized at the B3LYP/6-31G* level of theory. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, version A-7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(9) Calculated C═C−S−O dihedral angle for *s*-cis: 9°. Calculated C═C−S−O dihedral angle for *s*-trans: 127°. This last conformer is 0.81 kcal/mol less stable than *s*-cis. For previous conformational studies of α,*β*-unsaturated sulfoxides, see: Tietze, L. F.; Schffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952.