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A Highly Enantioselective Approach to Functionalized [4.n.0] Bicyclic Compounds

Juan C. Carretero,* José L. García Ruano* and Luisa M. Martín Cabrejas

Departamento de Química (C-I), Universidad Autónoma
Cantoblanco, 28049-Madrid, Spain

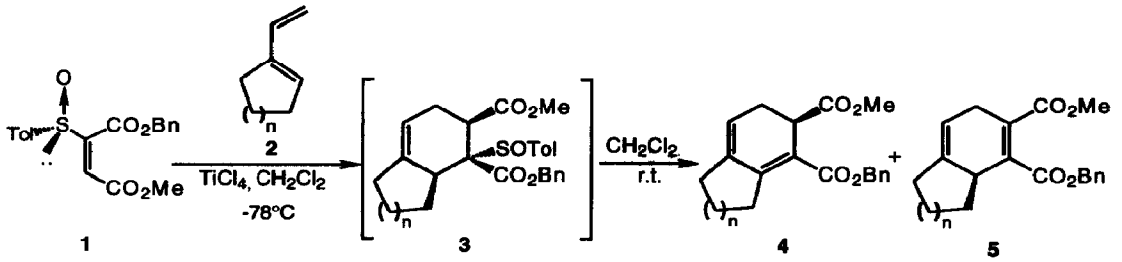
Abstract: The Diels-Alder reaction of benzyl, methyl (S)-2-(*p*-tolylsulfinyl) maleate with several 1-vinylcycloalkenes, catalyzed by $TiCl_4$, occurred with complete regio and stereoselectivity. The regioselectivity of the sulfinyl elimination from the adducts, as well as the stereoselectivity of the epoxidation and the hydroboration of the resulting [4.n.0] bicyclic compounds, increase with the size of the second ring.

During the last years the sulfinyl group has been widely used as chiral inductor in asymmetric Diels-Alder reactions. Although few papers concern to sulfinyl dienes,[1] most of the studies are related to the use of enantiomerically pure vinyl sulfoxides as dienophiles, using the ability of the sulfinyl group to control efficiently both regioselectivity and stereoselectivity of the cycloadditions.[2] In order to increase the low dienophilic reactivity of vinyl sulfoxides and the conformational restrictions around the C-S bond, other activating groups must be joined to the double bond. As a part of our research in this field,[3] we have recently described the great usefulness of benzyl, methyl (S)-(*p*-tolylsulfinyl) maleate (**1**) as a dienophile. Under $TiCl_4$ catalysis, dienophile **1** exhibits a high reactivity with both cyclic and acyclic dienes and reacts with almost complete *regio*, *endo* and π-facial selectivities.[4] Moreover, the resulting adducts undergo a spontaneous sulfinyl elimination at room temperature affording optically pure substituted cyclohexadienes.

These results suggested us the use of dienophile **1** to prepare optically pure [4.n.0] bicyclic compounds by reaction with 1-vinylcycloalkenes (**2**). We hereby report the Diels-Alder reactions of **1** with several dienes **2** and the subsequent sulfinyl elimination in the adducts to give bicyclic cyclohexadienes. We also describe some synthetic modifications (epoxidation and hydroboration) of the trisubstituted double bond of the cyclohexadienes **5** in order to control the stereochemistry of the ring fusion.

The Diels-Alder reactions of compound **1** with dienes **2a-2d**[5] were performed under the standard conditions ($TiCl_4$, CH_2Cl_2, -78°C).[6] Just after complete disappearance of dienophile **1**, the crude reaction mixtures were isolated and studied by ^{1}H-nmr. Their spectra shown the signals corresponding to a single bicyclic adduct (**3a-3d**). Like other related adducts,[4] compounds **3** underwent a spontaneous sulfinyl elimination at r.t. in CH_2Cl_2 solution, yielding bicyclic conjugated and/or no conjugated dienes (**4** and **5** respectively, Scheme 1), which were isolated and purified by column chromatography.[7] The e.e.'s of all compounds **4** and **5** were estimated as higher than 97% by ^{1}H-nmr in the presence of Pr(hfc)$_3$.[8] In Table 1 are summarized the main results obtained in these reactions.

The fact that only one adduct **3** was obtained in these cycloadditions proved that they have taken place with complete regio and stereoselectivity. The nature of the favoured regioisomers (Scheme 1), which was easily deduced from the ^{1}H-nmr spectra of compounds **3**[9] and **4**,[9] suggests that the regioselectivity is controlled by the sulfinyl group in the dienophile and the substituent on C-1 at diene.[10]



Scheme 1

Table 1. Diels-Alder reactions of vinylsulfoxide **1** with dienes **2a-2d.**

Diene	n	Reaction times (h)		**4/5** ratio[a]	Yield(%)[b]
		Cycloaddition	Elimination		
2a	1	5	6	81:19	**4a+5a** (86)[c]
2b	2	3	48	61:39	**4b** (63), **5b** (30)
2c	3	6	1	<5:>95	**5c** (83)[d]
2d	8	2	1	<5:>95	**5d** (93)[d]

[a] Determined by ^{1}H-nmr on the crude mixtures. [b] In purified product after cromatography. [c] The mixture of **4a+5a** could not be separated. [d] See ref.7.

In adducts **3c** and **3d** the elimination of the sulfinyl group was quite fast and completely regioselective affording exclusively the 1,4-dienes **5**. Compounds **3a** and **3b** gave a mixture of regioisomers **4** and **5**,[11] which indicates that these adducts (and therefore also **3c** and **3d**) must exhibit *endo* stereochemistry.[12] Finally, the π-facial selectivity in these cycloadditions must be almost complete, as it can be deduced from the very high optical purity of the products **4** and **5**. This result, that had also been observed in reactions of **1** with other cyclic and acyclic dienes,[4] can be explained by assuming that the *endo* approach of the diene to the less hindered face of the chelated species dienophile: $TiCl_4$, shown in fig.1, is strongly favoured.

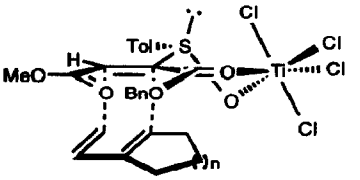


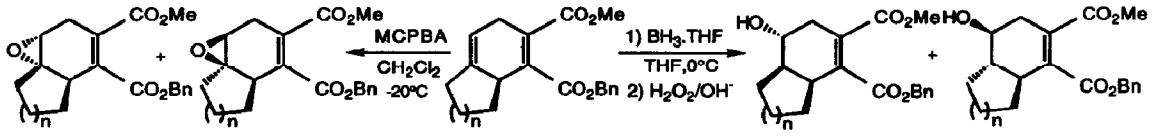
Fig. 1

As compounds **5** show two chemically well-differentiated double bonds and a chiral bridge carbon, they were selected as substrates for the preparation of functionalized [4.n.0] bicyclic systems with control of the stereochemistry at the ring fusion. Epoxidation and further reductive opening of the oxirane ring and hydroboration/oxidation processes have been the reactions used to functionalize the trisubstituted double bond of **5** because both processes are complementary from a stereochemical point of view. Moreover, in the case of the [4.4.0] bicyclo derivatives, the structure of the resulting alcohols is similar to that of the decalones used by Shea et al.[13] to prepare bridgehead enol lactones which are valuable intermediates in stereocontrolled syntheses.

The results obtained in the epoxidation (2 eq. of MCPBA, CH_2Cl_2, -20°C, 2 days, Scheme 2) and hydroboration/oxidation (2 eq. of BH_3.THF, THF, 0°C to r.t., 24 h, followed by treatment with H_2O_2/OH^-, Scheme 2) of compounds **5b-5d**[14] are shown in Table 2. The stereoselectivity of both reactions increases with the size of the saturated ring, being higher in the hydroboration. Compound **5d** evolved with complete stereoselectivity in both cases, yielding only one epoxide (**6d**) and a single alcohol (**7d**) in excellent yields. The same behaviour was exhibited by **5c** in the hydroboration but its epoxidation was not completely stereoselective (**6c/6'c** =9:1). Finally, **5b** afforded a 1:1 mixture of epoxides, whereas its hydroboration took place with a significant stereoselectivity (**7b/7'b** = 5/1).[15]

The *cis* -fused stereochemistry of the major alcohols (**7**) obtained by hydroboration was proposed on the basis of the ^{1}H-nmr data and n.o.e. experiments performed on **7d**.[16] Taking into account that both epoxidation and hydroboration are strongly dependent on steric factors, the stereochemistry of the ring fusion for the major

epoxide (**6**) should also be *cis*.. This assumption was confirmed as follows: reduction of **6d** with $NaBH_3CN$ in acidic conditions ($NaBH_3CN/BF_3.OEt_2$, THF, r.t., overnight) afforded the alcohol **8d**[16] in 77% yield, whose stereochemistry (assigned from its ^{1}H-nmr data and n.o.e. experiments) is in agreement with that expected from the well-known stereo and regioselectivity of this oxirane ring opening (attack of the hydride in a S_N2 process on the most substituted carbon[17]).



Scheme 2

Table 2. Epoxidation and hydroboration of cyclohexadienes **5**.

		Epoxidation		Hydroboration	
5	n	**6/6'** ratio[a]	Yield (%)[b]	**7/7'** ratio[a]	Yield (%)[b]
5b	2	**6b/6'b** (1:1)	70	**7b/7'b** (5:1)	69
5c	3	**6c/6'c** (9:1)	82	**7c/7'c** (>95:<5)	82
5d	8	**6d/6'd** (>95:<5)	93	**7d/7'd** (>95:<5)	83

[a] Determined by ^{1}H-nmr on the crude mixtures. [b] In purified product after cromatography.

In summary, we have reported an efficient procedure to prepare [4.n.0] bicyclic compounds in high optical purity. The application of this methodology is currently being studied to synthesize natural sesquiterpenoids.

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References and Notes

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2.- For some recent references on vinyl sulfoxides in asymmetric Diels-Alder reactions, see: a) Ronan, B.; Kagan H. B. *Tetrahedron: Asymmetry* **1991**, *2*, 75. b) Takahashi, T.; Kotsubo, H.; Koizumi, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1035. c) Fuji, K.; Tanaka, K.; Abe, H.; Itoh, A.; Node, M.; Taga, T.; Miwa, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1991**, *2*, 179. d) Arai, Y.; Matsui, M.; Koizumi, T.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 1983. e) Takahashi, T.; Kotsubo, H.; Iyobe, A.; Namiki, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3065.

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4.- a) Alonso, I.; Carretero, J.C.; García Ruano, J.L. *J. Org. Chem.* **1993**, *58*, 3231. b) *ibid.* **1994**, *59*, 1499.

5.- The dienes **2** were prepared from the corresponding commercially available cycloalkanones by addition of vinylmagnesium bromide (1.5 eq. from a solution 1.0 M in THF), followed by acid dehydratation of the resulting carbinol (0.3 eq. $KHSO_4$). Although diene **2d** was obtained as an inseparable 1:1 mixture of E/Z isomers, the Z-isomer does not react under the cycloaddition conditions. For previous preparations of 1-vinylcycloalkenes see : Junning, L.; Snyder, J.S. *J. Org. Chem.* **1990**, *55*, 4995.

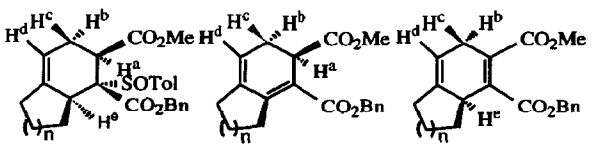
6.- General procedure for the preparation of **4** and **5**. A 1.0M solution of $TiCl_4$ in CH_2Cl_2 (0.67 mmol, 1,2 equiv) was added dropwise, under argon atmosphere, to a solution of dienophile **1** (200 mg, 0.56 mmol, 1.0 equiv) in 2.8 mL of dry CH_2Cl_2 at 78°C. The mixture was stirred for 10 min and 2-3 equiv of the corresponding 1-vinylcycloalkene **2** were added. The stirring was continued until **1** disappeared by t.l.c. (the reaction times are indicated in Table 1). Then, 10% $NaHCO_3$ (10ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x15 ml). The combined organic layers were washed with water (5 ml), dried (SO_4Mg) and carefully concentrated (without heating). The crude mixture of adducts was immediately analyzed by ^{1}H-nmr and then redissolved in CH_2Cl_2 (5 ml). This solution was allowed to stand at r.t. until the sulfinyl elimination was over (the reaction times are indicated in Table 1).

The solvent was concentrated, and the mixture of 1,3- and 1,4-cyclohexadienes **4** and **5** was readily purified by flash chromatography (eluent: CH_2Cl_2/hexane 1/1). The yields are shown in Table 1 (83-93%). Despite cyclohexadienes **4** and **5** remain unaltered for months when they are stored at -20°C under argon atmosphere, they show a significant trend to the aromatization at room temperature.

7.- At least 25% of **5c** and **5d** were obtained slightly contaminated with sulfenic acid derivatives as co-products. This contaminant does not affect further reactions.

8.- The racemic samples, (±)-**4** and (±)-**5** (prepared from (±)-1) required in the nmr studies, exhibited well-separated chemical shifts for both enantiomers in the presence of Pr(hfc)$_3$ (0.2 eq.).

9.- The ^{1}H-nmr data of the adducts **3**, 1,3-cyclohexadienes **4** and 1,4-cyclohexadienes **5** allowed to stablish unequivocally the regioselectivity of the cycloadditions. Values for δ (ppm) and J (Hz) in $CDCl_3$.



3 4 5

J_{bc} and J_{cc} ~ 2Hz

	δa	δb	δc	δd	δe	Jab	Jac
3	3.6-4.2	2.6-2.4	2.6-2.4	5.5-5.4	2.7-3.1	3.2	6.2
4	3.7-3.1	2.8-3.3	2.5-3.3	5.8-5.7	-	2.1	7.1
5	-	2.7-2.9	2.7-2.9	5.3-5.9	3.0-3.2	-	-

10.- This regioselectivity is just the opposite to that observed with Dane's diene.[4b]

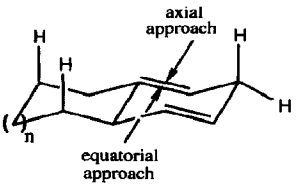
11.- Both stereochemical and stability factors must be responsible of the regular increase in the proportion of **5** with the size of second ring.

12.- Taking into account the *syn*-character of the pyrolytic sulfinyl elimination, the *exo*-adducts could only evolve into the no conjugated cyclohexadienes **5**.[4b]

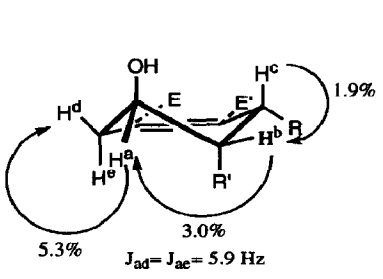
13.- a) R.C.; Burke L.D.; Cooper, D.K. *J. Am. Chem. Soc.* **1987**, *109*, 447. b) Shea, K.J.; Fruscella, W.M.; England, W.P. *Tetrahedron Lett.* **1987**, *28*, 5623. c) Shea, K.J.; Zandi, K.S.; Staab, A.J.; Carr, R.C. *Tetrahedron Lett.* **1990**, *31*, 5885.

14.- Compound **5a**, which was obtained as the minor isomer, was not studied because it could not be separated from **4a** (both compounds underwent fast aromatization at room temperature). The epoxidation of **5c** and **5d** has been directly performed on the crude mixtures, obtained after cycloaddition and sulfinyl eliminations, which substantially increases the yields (82% and 93% respectively).

15.- The stereoselectivity of these reactions (the equatorial approaches are favoured for both reagents) is the opposite to that observed for methylene cyclohexanes (the axial attacks are preferred, see: Trost, B. in *Comprehensive Organic Synthesis*. Pergamon Press **1993**, *Vol 7*, p. 364 and *Vol 8*, p. 707).This fact can be explained taking into account that the approach from the upper face (axial attack) must be hindered by steric interactions with the allylic CH_2 group in the pseudo-chair conformation addopted by the cyclohexadiene ring, which should be more severe in the hydroboration. The influence of the size of the saturated ring on the stereoselectivity of both reactions could be explained by assuming an increase in the steric hindrance of the *syn*-diaxial hydrogens on the axial approach as the ring becames larger.

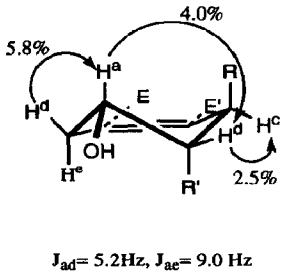


16.- Significant coupling constants and n.o.e.'s of compounds **7d** and **8d** in $CDCl_3$.



J_{ad}= J_{ae}= 5.9 Hz

7d



J_{ad}= 5.2Hz, J_{ae}= 9.0 Hz

8d

E =CO_2Me

E'=CO_2Bn

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