Tetrahedron Letters,Vol.30,No.30,pp 4003-4006,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS AND ASYMMETRIC DIELS-ALDER REACTIONS OF (S)-2-*p*-TOLYLSULFINYL-1,4-BENZOQUINONE

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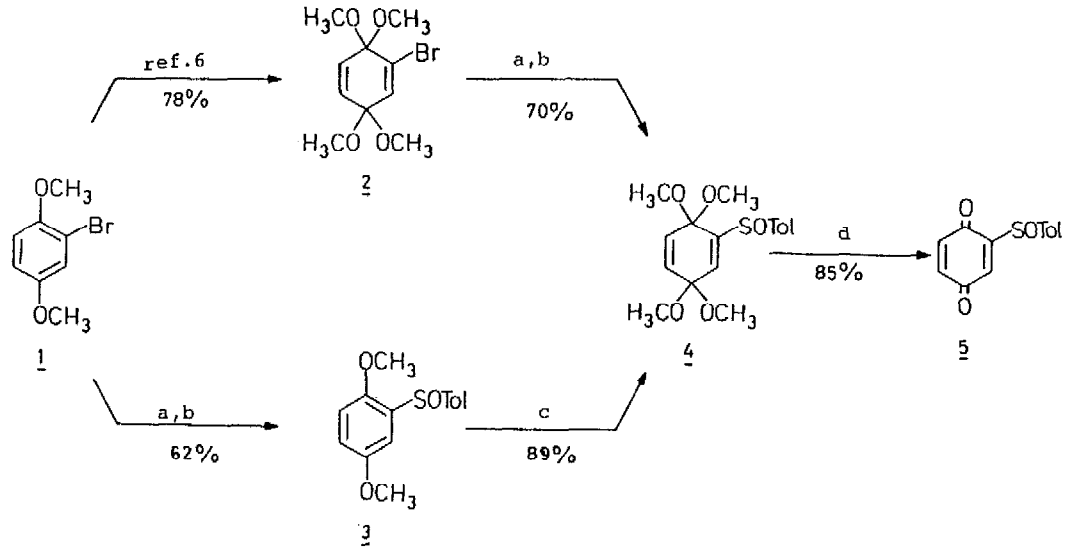
Optically pure (S)-2-*p*-tolylsulfinyl-1,4-benzoquinone (5) is readily obtained by deketalization of the corresponding quinone bisketal 4, synthesized by Andersen's type synthesis on 2-bromo-1,4-dimethoxybenzene (1) followed by anodic oxidation of the resulting sulfoxide. The Diels-Alder reaction of cyclopentadiene with 5 took place on C_5-C_6 dienophilic double bond showing high facial selectivity, which can be inverted by using different Lewis acids, and total *endo* selectivity.

The use of quinones as dienophiles has allowed the synthesis of some important natural products[1] such as certain anthracyclines and other acetate-derived compounds. Despite the success of these syntheses, to our knowledge, no simple chiral quinone has been reported.

We thought of using the sulfinyl group for the construction of this chiral quinone, because of the numerous applications of this group reported in the field of asymmetric synthesis,[2] and because it is well demonstrated both experimentally[3] and theoretically,[4] that it is able to differentiate the faces of the double bond.

In order to design a general method to obtain chiral 2-sulfinylquinones in high optical yield, we thought of applying Andersen's type synthesis,[5] the most widely and efficiently used method, to chiral sulfoxides. In this context, the synthesis of chiral 2-*p*-tolylsulfinyl-1,4-benzoquinone (5) was achieved from the corresponding bisketal 4, obtained by two alternative routes (Scheme 1).

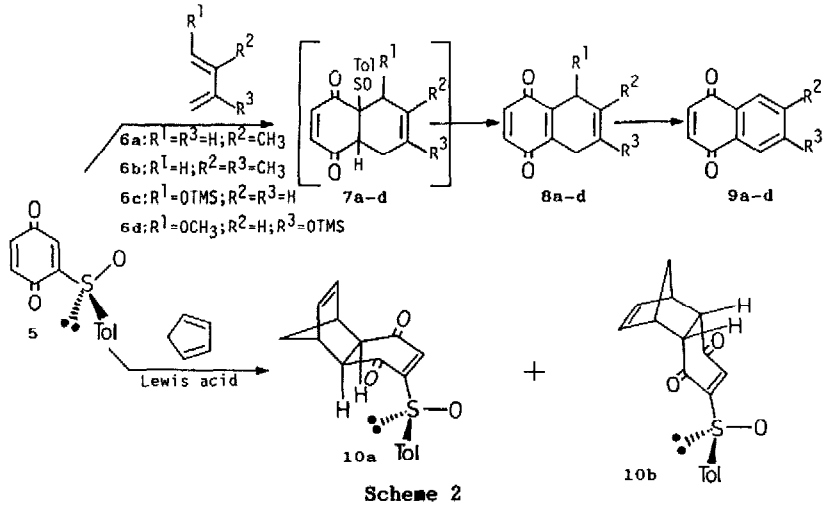
In the first route, compound 2, generated from 1, by the method described by Swenton,[6] was treated with *n*-buthyllithium and then with menthyl-(S)-*p*-toluenesulfinate[7] to afford a colorless oil, the spectroscopical parameters of which are in accordance with the structure of the bisketal 4.[8] The inversion in the order of these reactions also yields compound 4. Deketalization of 4 in the presence of *p*-toluenesulfonic acid allowed the obtention of (S)-2-*p*-tolylsulfinyl-1,4-benzoquinone (5) in high chemical and optical yields (≥98% e.e. by ^{1}H-NMR) as orange needles [m.p.=129-30°C (hexane); ^{1}H-NMR: 7.66 and 7.30 (AA'BB' Tolyl system, 4H), 7.43 (*d*, J = 2.2 Hz, H_3), 6.80 (*dd*, J = 2.2 and 10.2 Hz, H_5), 6.71 (*d*, J = 10.2 Hz, H_6), 2.39 (*s*, 3H, CH_3-Ar); ^{13}C-NMR: 184.6, 183.1, 154.6, 142.3, 137.9, 136.8, 135.9, 131.0, 129.7, 125.3, 20.9; $[\alpha]_D^{20}$ = +1099° (c = 1.0, $CHCl_3$)].



a) *n*-BuLi, THF, -78°C, 2h; b) (S)-*p*-Tol-SO$_2$Ment, THF, -78°C, 1h; c) E , KOH/MeOH, 0°C, 3h. d) p-TsOH, acetone, r.t., 6h.

Scheme 1

The reaction of 5 with acyclic dienes **6a-6d** (Scheme 2) afforded naphthoquinones **9a-9d** resulting from adducts 7 (non detected) by pirolysis of the sulfinyl group and further aromatization of the intermediates **8**. These intermediates were detected by ^{1}H-nmr in the crude reaction mixtures, but all attempts to isolate them were unsuccessful.



Scheme 2

The reaction of 5 with cyclopentadiene yielded two adducts **10a** and **10b**,[9] easily separated by chromatography (eluent, CH_2Cl_2/acetone : 20/1), resulting from reaction on the less activated dienophilic double bond (Scheme 2). The *endo* configuration of both adducts

was confirmed as follows: *i*) The oxidation of the adduct obtained from the reaction of 2-*p*-tolylsulfenyl-1,4-benzoquinone with cyclopentadiene,[10] afforded a mixture of racemic **10a** and **10b**. *ii*) **10b** was transformed by irradiation into a product **11**[11] (Figure 1) which exhibits a cage structure, only possible from *endo* adducts.[12]

Table 1. *Conditions and yields in reaction of 5 with cyclopentadiene*

Entry	Solvent	T°C	Lewis acid[a]	Yield	**10a:10b**	de
1	$CHCl_3$	-20	-	95	72:28	44
2	CH_2Cl_2	-78	-	64	75:25	50
3	CH_2Cl_2	-20	$Eu(fod)_3$(2)	58	89:11	79
4	CH_3CN	-20	$Eu(fod)_3$(2)	62	91:9	82
5	$CHCl_3$	20	$BF_3.OEt_2$(5)	80	13:87	74
6	$CHCl_3$	-20	$BF_3.OEt_2$(5)	89	10:90	80

[a] [Lewis acid]:[5] molar ratio

Thermal cycloadditions were carried out at different temperatures (20 to -78°C) using solvents of distinct polarity (C_6H_6, THF, $CHCl_3$, CH_2Cl_2, acetone, DMSO, CH_3CN and DMF). The results indicated that the amount of **10a** slightly raised when the temperature decreased and the solvent polarity increased. We used different Lewis acids in order to improve the stereoselectivity. As it can be seen in Table 1, the diastereoselectivity strongly depended on the nature and molar ratio of the catalyst, as well as on the temperature. The best results were achieved at -20°C in the presence of $Eu(fod)_3$ (entry 4) and BF_3 (entry 6). These acids gave opposite diastereoselection, and the absolute configuration of cycloadducts **11a** and **11b** could be inferred from the structure of the associated species, **12** and **13** (Figure 1), assuming a steric approach control.[13] The carbonyl and sulfinyl oxygens of the dienophile should be associate to Eu, forming the chelate **12**, in which the tolyl group shields the lower face of quinone ring, favoring the attack from the opposite face. On the contrary, BF_3 should be associate only to the sulfinylic oxygen (which increases its effective size) presumably adopting a conformation similar to **13**, in which the less hindered face is the opposite to that of the chelate **12**.

In conclusion, *p*-tolylsulfinyl group is a very efficient chiral inductor in asymmetric Diels-Alder reactions on the less activated double bond of **5**. The fact that the facial selectivity could be controlled by changing the Lewis acid catalyst makes the reaction very interesting from a synthetic point of view.

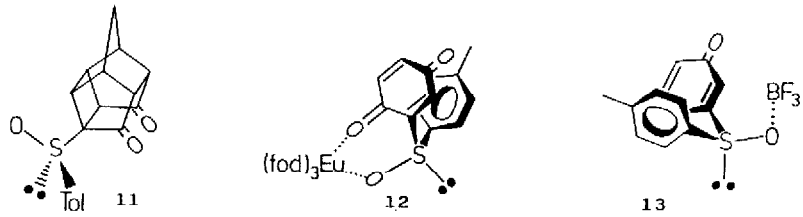


Figure 1

ACKNOWLEDGEMENTS

We thank *Dirección General de Investigación Científica y Técnica* (Grant PB86-0120) for financial support.

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(8) All new compounds described in this paper were fully characterized on the basis of their IR, ^{1}H-NMR (200 MHz, $CDCl_3$), ^{13}C-NMR (50.3 MHz, $CDCl_3$) spectral data and elemental analysis/MS.
(9) **10a**: yellow oil, ^{1}H-nmr: 7.55 and 7.29 (AA'BB' tolyl system, 4H), 7.17 (*s*, 1H), 5.85 (*dd*, 1H, J=2.9 and 5.6 Hz), 4.82 (*m*, 1H), 3.48 (*m*, 1H), 3.26 (*m*, 3H), 2.41 (*s*, 3H), 1.39 (*m*, 2H); ^{13}C-nmr: 196.5, 196.0, 161.0, 142.6, 138.1, 136.4, 135.2, 134.0, 129.8, 125.9, 50.0, 49.7, 49.5, 49.4, 49.2, 21.4; $[\alpha]^{20}$= 276° (c=1, $CHCl_3$); **10b**: yellow solid, m.p. 162-3^{0}C (hexane), ^{1}H-nmr: 7.62 and 7.28 (AA'BB' tolyl system, 4H), 7.23 (*s*, 1H), 6.13 (*t*, 2H, J=2.0 Hz), 3.54 (*m*, 2H), 3.23 and 3.12 (*AB* part of ABXY system, 2H, J=8.5 and 3.9 Hz), 2.38 (*s*, 3H), 1.57 and 1.40 (*AB* part of ABXY system, 2H, J=8.9 and 2.0 Hz); ^{13}C-nmr: 196.6, 195.7, 160.7, 142.5, 138.4, 137.0, 135.6, 135.2, 130.0, 125.7, 50.2, 49.4, 48.8, 48.6, 48.5, 21.3; $[\alpha]^{20}$=472° (c=1, $CHCl_3$).
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(11) **11**: ^{1}H-nmr: 7.64 and 7.33 (AA'BB' tolyl system, 4H), 3.71 (*m*, 1H), 3.13-2.26 (*m*, 6H), 2.15-1.92 (*m*, 2H). ^{13}C-nmr: 209.3, 205.4, 142.4, 135.9, 129.9, 125.4, 68.3, 56.0, 54.9, 44.3, 44.0, 43.9, 40.8, 40.7, 37.5, 21.5.
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(Received in UK 13 June 1989)