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Direct enantioselective approach to oxazolo[4,5-*e*]isoindoles from [(S)*R*]-1-aminosubstituted-4-(*p*-tolylsulfinyl)-1,3-butadienes

S. Blasco, M. C. Carreño, M. B. Cid, J. L. García Ruano and M. R. Martín *

Departamento de Química Orgánica (C-1), Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain

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Abstract

The enantioselective construction of [3a*S*,5a*R*,8a*R*,8b*R*]-1-(*p*-methoxyphenyl)-3a,7-dimethyl-3a,5a,8b,8a-tetrahydro-1*H*-oxazolo[4,5-*e*]isoindole-2,6,8-trione is achieved from enantiopure [(S)*R*]-(1*E*,3*E*)-2-methyl-1-(*p*-methoxyphenyl)amino-4-(*p*-tolylsulfinyl)-1,3-butadiene and *N*-methylmaleimide through a short sequence involving a Diels–Alder reaction, a sulfoxide–sulfenate rearrangement and intramolecular cyclization.

With the development of several general routes to enantiopure dienyl sulfoxides[1] has come an increasing attention to their use as chiral partners in asymmetric Diels–Alder reactions.[2] The synthesis of systems bearing a sulfoxide at C-1 and aryl or alkyl groups as well as alkoxy substituents in different positions of the butadiene framework has been successfully achieved. To date, no nitrogen substituents have been introduced in such enantiomerically pure dienes. In 1983, Overman reported the synthesis of racemic carbamate protected 1-amino-4-phenylsulfinyl-1,3-butadienes[3] and studied their Diels–Alder reactions with acrolein and phenyl vinyl ketone. While the regioselectivity was shown to be fully controlled by the acylamino substituents, the low π-facial diastereoselectivity achieved prevented further development of these reactions.

Our previous work devoted to the study of Diels–Alder reactions with enantiomerically pure (*R*)-1-(*p*-tolylsulfinyl)-1,3-butadiene derivatives has shown a high degree of stereocontrol in their cycloadditions with dienophiles such as *N*-methyl maleimide,[4] maleic anhydride[5]or 1,2,4-triazoline-3,5-dione.[6] In order to test the behaviour of amino substituted dienyl sulfoxides in cycloadditions with such kinds of dienophiles, we decided to focus on the enantiopure compound **4** bearing a nitrogen substituent at C-1 and a sulfoxide at C-4. We describe herein the synthesis of [(S)*R*] *N*-Boc 2-methyl-1-(*p*-methoxyphenyl)amino-4-(*p*-tolylsulfinyl)-1,3-butadiene **4** and the study of its Diels–Alder reactions with *N*-methyl maleimide and show that an unprecedented and stereoselective construction of the tetrahydro-1*H*-oxazolo[4,5-*e*]isoindole-2,6,8-trione skeleton can be achieved starting from **4** in a short sequence.

* Corresponding author. Fax: (34) 913973966; e-mail: rosario.martin@uam.es

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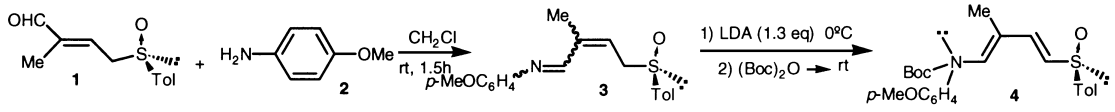
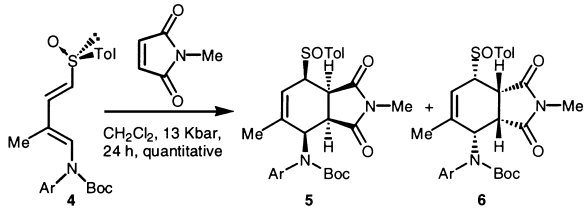
Enantiomerically pure derivative **4** was synthesized from [(S)*R*,2*E*]-2-methyl-4-(*p*-tolylsulfinyl)-2-butenal **1** which resulted from the acidic treatment (10% HCl) of [(S)*R*]-4-ethoxy-3-methyl-1-(*p*-tolylsulfinyl)-3-buten-2-ol, previously obtained by us from 3-ethoxy-methacrolein and (*R*)-methyl-*p*-tolylsulfoxide.[4] As shown in Scheme 1, aldehyde **1** was reacted with *p*-methoxyaniline **2**, to give imine **3** which was immediately transformed into the *N*-Boc protected diene **4** by successive treatment with LDA and $(Boc)_2O$. Compound **4** was isolated pure in a 66% overall yield from **1** and was shown to be enantiomerically pure {$[\alpha]_D^{20}$ +109 (c=1, $CHCl_3$); ee >98%}.[7]



Scheme 1.

With diene **4** in hand, we studied its Diels–Alder reactions with *N*-methyl maleimide. In CH_2Cl_2 at room temperature, reaction was very slow at normal pressure, but cycloaddition occurred in 24 h when the mixture was submitted to high pressure (13 Kbar). Under these conditions, diene **4** evolved into a 75:25 mixture of diastereoisomeric *endo* adducts **5** and **6** in quantitative yield (Scheme 2). Compounds **5** {$[\alpha]_D^{20}$ +179.1 (c=1, $CHCl_3$); ee >98% }[7] and **6** {$[\alpha]_D^{20}$ −1.7 (c=0.5, $CHCl_3$); ee >98%}[7] could be isolated diastereomerically pure by flash column chromatography.



Scheme 2.

The configurational assignment of adducts **5** and **6** was established on the basis of their ^1H NMR parameters and by comparison with those of other similar adducts previously obtained from reactions of a series of 1-dienyl sulfoxides,[4–6] by assuming an extended boat conformation for the cyclohexene ring in these adducts.[4–6,8] The most significant data are indicated in Fig. 1 and correspond to the chemical shifts of olefinic hydrogen H6 which is shielded in **5** (H6 and *p*-Tol 1,3-parallel) and deshielded in **6** (H6 and S–O 1,3-parallel) also due to the rigid disposition of the sulfinyl group shown. Similar effects are observed in the chemical shifts of H7a which is deshielded in **5** and shielded in **6** due to the influence of the sulfur substituents. Considering that the *R* configuration of the sulfoxide must not change in the Diels–Alder reaction, the absolute [3a*R*,4*R*,7*R*,7a*R*,(S)*R*] for the major diastereomer **5** and [3a*S*,4*S*,7*S*,7a*S*,(S)*R*] for the minor adduct **6** can be assigned.

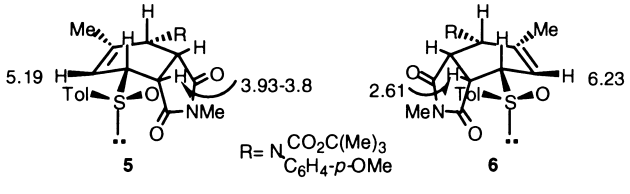


Figure 1.

Taking into account the behaviour reported by Overman for *N*-benzyloxycarbonyl-4-phenylsulfinyl-1,3-butadiene,[3] which reacted with α,β-unsaturated carbonyl compounds at 25°C, the low reactivity observed for *N*,*N*-disubstituted derivative **4**, also bearing a carbamate substituent at the nitrogen, suggests

that the methyl group at C-2 of the butadiene framework, as well as the increased size of the amine function due to the presence of the *p*-methoxyphenyl substituent, must be the origin of the different reactivity. It is likely that the *E* stereochemistry of the C1–C2 double bond (determined by NOE experiments) in **4** is forcing the lone electron pair at nitrogen to the *syn*-planar position indicated in Fig. 2 to avoid the strong 1,3-allylic interaction which would appear if the *p*-$MeOC_6H_4$ or Boc substituents were situated in such planar disposition.[9] Thus, in compound **4**, the lone electron pair cannot be delocalized into the 1,3-diene preventing the expected activation of this electron donor substituent and explaining the decreased reactivity observed for **4**, which is very similar to that observed for 1-dienyl sulfoxides lacking the amino substituent.[4–6]

The π-facial diastereoselectivity of these cycloadditions can be explained on the basis of the model previously proposed by us,[4] based on a steric and stereoelectronic approach control of the dienophile on the less hindered face of the diene adopting an *s-trans* conformation (Fig. 2). This *endo* transition state shows minimized electrostatic repulsions between the carbonyl and sulfinyl oxygens. Moreover, the orientation of the Ar (*p*-$MeOC_6H_4$) and Boc groups towards both faces of the diene system would explain the lower stereoselectivity observed in this case with respect to other 1-sulfinyldienes which evolve with a complete π-facial diastereoselectivity.

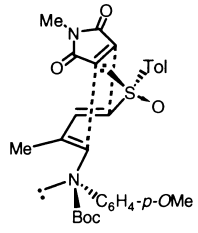
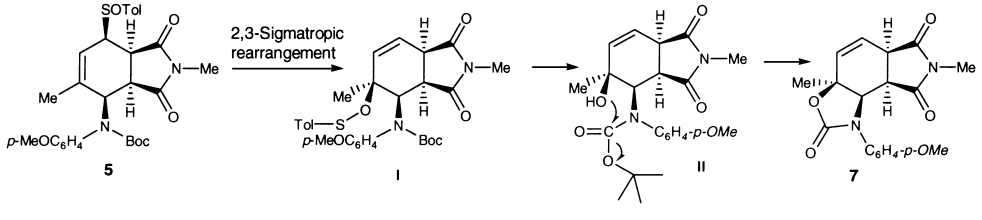


Figure 2.

When the crude mixture of **5** and **6** (75:25) resulting from the cycloaddition was kept at −20°C for a long time (41 days) we observed its spontaneous evolution to 1-(*p*-methoxyphenyl)-3a,7-dimethyl-3a,5a,8b,8a-tetrahydro-1*H*-oxazolo[4,5-*e*]isoindole-2,6,8-trione **7** (50% ee) which was cleanly formed. Starting from diastereomerically pure **5**, tricyclic derivative **7** was obtained in 46% isolated yield in enantiomerically pure form.[7] Formation of this tricyclic derivative could be explained on the basis of the mechanism depicted in Scheme 3 for the evolution of **5**. This allylic sulfoxide can evolve in a sterocontrolled manner through a sulfoxide–sulfenate rearrangement[10] to the sulfenate intermediate **I** easily transformed into the carbinol **II** by the cleavage of the S–O bond. The formation of all *cis*-substituted cyclohexenol **II** through this process had already been reported for adducts similar to **5**.[4,5] The evolution of **II** through an entropically favoured intramolecular attack to the vicinal CO carbonyl group of the Boc substituent would explain the formation of the oxazolidinone ring of **7** as a sole diastereomer.



Scheme 3.

Considering that the transformation of **5** and **6** in tricyclic derivative **7** through **I** and **II** must occur in a highly stereocontrolled manner according to the mechanism proposed above, the absolute configuration of the enantiomer **7** generated from the major adduct **5** must be [3a*S*,5a*R*,8a*R*,8b*R*].

Studies directed to improve the facial selectivity of these reactions are now in progress in order to further apply these good results to the synthesis of complex molecules.

Acknowledgements

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7. The enantiomeric excess of **4**, **5**, **6** and **7** was determined by ^{1}H NMR after complexation with (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as chiral solvating agent. Such determination required the synthesis of all racemic derivatives that was achieved from racemic **1**. Diene **4**: Yield 66% (from aldehyde 1). Mp 112–113°C. $[\alpha]_D^{20}$ +109 (c=1, $CHCl_3$). Anal. calcd for $C_{24}H_{29}NO_4S$: C 67.42, H 6.84, N 3.28, S 7.50. Found: C 67.21, H 6.90, N 3.32, S 7.78. IR (nujol): 1695, 1630, 1510, 1340, 1300, 1250, 1160, 1045. ^{1}H NMR: 7.49 and 7.28 (4H, *p*-tol), 7.07 and 6.83 (4H, *p*-methoxyphenyl), 7.06 (1H, H_1), 7.04 (d, 1H, H_3, $J_{3,4}$=15.0), 6.11 (d, 1H, H_4, $J_{3,4}$=15.0), 3.79 (s, 3H, CH_3O), 2.38 (s, 3H, CH_3Ar), 1.46 (s, 9H, *t*-butyl), 1.16 (d, 3H, CH_3, $J_{1,Me}$=1.2). ^{13}C NMR: 12.1 (CH_3), 21.3 (CH_3), 28.1 ($3CH_3$), 55.4 (CH_3O), 82.3 (C), 113.9 (CH), 119.5 (C), 124.6 (CH), 128.3 (CH), 129.3 (CH), 129.9 (CH), 133.7 (C), 135.8 (CH), 141.1 (C), 141.6 (C), 141.8 (CH), 153.3 (C), 157.9 (C). Adduct **5**: $[\alpha]_D^{20}$ +179.1 (c=1, $CHCl_3$). Mp 88–89°C. IR ($CHCl_3$): 1710, 1690, 1530, 1440, 1410, 1370, 1295, 1240, 1165. ^{1}H NMR: 7.67 and 7.31 (4H, *p*-tol), 7.32 and 6.82 (*p*-methoxyphenyl), 5.19 (bs, 1H, H_6), 3.93–3.80 (m, 2H, H_4 and H_{7a}), 3.78 (s, 3H, CH_3O), 3.42 (dd, 1H, H_{3a}, J=8.6, J=10.2), 3.31 (m, 1H, H_7), 2.98 (s, 3H, CH_3N), 2.39 (s, 3H, CH_3Ar), 1.81 (s, 3H, CH_3), 1.28 (s, 9H, *t*-butyl). ^{13}C NMR: 21.1 (CH_3), 21.5 (CH_3), 25.0 (CH_3N), 28.1 ($3CH_3$), 39.7 (CH), 42.8 (CH), 55.4 (CH_3O), 61.2 (CH), 61.4 (CH), 80.5 (C), 113.9 (CH), 115.0 (CH), 125.6 (CH), 128.3 (CH), 130.1 (CH), 137.1 (C), 141.0 (2C), 142.6 (C), 154.6 (C), 158.1 (C), 175.7 (C), 176.2 (C). MS (EI): 342 (9), 298 (44), 175 (89), 167 (92), 123 (79), 108 (80), 91 (90), 57 (100). Adduct **6**: Mp 114–115°C. $[\alpha]_D^{20}$ −1.7 (c=1, $CHCl_3$). Anal. calcd for $C_{29}H_{34}N_2O_6S$: C 64.66, H 6.36, N 5.20, S 5.95. Found: C 64.33, H 6.34, N 5.06, S 5.80. IR ($CHCl_3$): 1690. ^{1}H NMR: 7.75 and 7.36 (4H, *p*-tol), 7.30 and 6.86 (4H, *p*-methoxyphenyl), 6.23 (bs, 1H, H_6), 3.94 (bd, 1H, H_4, J_{4-3a}=10.2), 3.81 (s, 3H, CH_3O), 3.28 (dd, 1H, H_{3a}, J_{4-3a}=10.2, J_{3a-7a}=8.6), 3.20 (m, 1H, H_7), 2.98 (s, 3H, CH_3N), 2.61 (dd, 1H, H_{7a}, J_{3a-7a}=8.6, J_{7a-7}=5.5), 2.40 (s, 3H, CH_3Ar), 2.12 (s, 3H, CH_3), 1.32 (s, 9H, *t*-butyl). ^{13}C NMR: 20.8 (CH_3), 21.2 (CH_3), 25.0 (CH_3N), 27.9 ($3CH_3$), 41.4 (CH), 42.9 (CH), 55.2 (CH_3O), 60.5 (CH), 63.7 (CH), 80.3 (C), 113.7 (CH), 117.5 (CH), 125.3 (CH), 128.0 (CH), 129.7 (CH), 136.9 (C), 139.2 (C), 139.7 (C), 142.1 (C), 154.4 (C), 157.8 (C), 175.3 (C), 175.7 (C). MS (EI): 342 (2), 298 (35), 175 (84), 167 (82), 123 (77), 108 (77), 91 (98), 57 (100). Oxazolo[4,5-*e*]isoindole-2,6,8-trione **7**: Yield 46%. Mp 184–186°C. $[\alpha]_D^{20}$ −32.4 (c=0.5, $CHCl_3$). IR ($CHCl_3$): 1750, 1705. ^{1}H NMR: 7.14 and 6.89 (4H, *p*-methoxyphenyl), 6.18 (dd, 1H, H_5, $J_{5,4}$=10.2, $J_{5,5a}$=3.8), 5.90 (dd, 1H, H_4, $J_{4,5}$=10.2, $J_{4,5a}$=2.7), 4.62 (d, 1H, H_{8b}, $J_{8b,8a}$=4.3), 3.79 (s, 3H, CH_3O), 3.38 (m, 1H, H_{5a}), 3.22 (dd, 1H, H_{8a}, $J_{8a,8b}$=4.8, $J_{8a,5a}$=8.1), 2.38 (s, 3H, CH_3N), 1.66 (s, 3H, CH_3). ^{13}C NMR: 23.4 (CH_3), 24.4 (CH_3N), 39.0 (CH), 39.8 (CH), 55.4 (CH_3O), 59.7 (CH), 76.8 (C), 114.3 (CH), 121.7 (CH), 126.6 (CH), 128.9 (C),

129.5 (CH), 156.2 (C), 158.6 (C), 173.4 (C), 174.2 (C). MS (EI): 342 (M^+, 62), 298 (16), 205 (43), 187 (100), 175 (43), 134 (31), 108 (37), 91 (31), 77 (25). HRMS: calcd for $C_{18}H_{18}N_2O_5$: 342.1215. Found: 342.1210.

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