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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4015–4018

Desymmetrization of *meso* 7-aza-2,3-bis(phenylsulfonyl) bicyclo[2.2.1]hept-2-ene: a re-examination. Kinetic resolution of racemic 3-arylsulfonyl-7-aza-2-bromobicyclo[2.2.1]hepta-2,5-dienes

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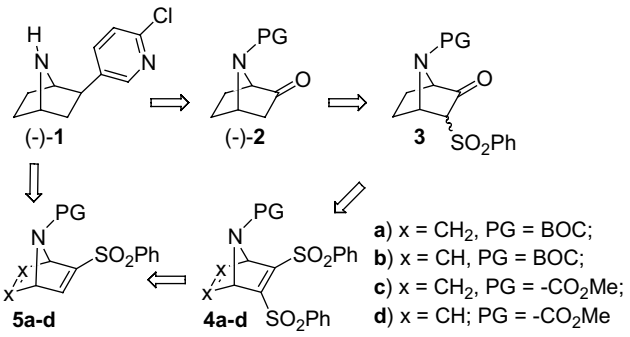
Received 7 February 2006; revised 5 April 2006; accepted 5 April 2006

Abstract—The inexpensive large scale preparation of *N*-methoxycarbonyl-7-aza-2,3-bis(phenylsulfonyl)bicyclo[2.2.1]hept-2-ene and the re-examination of its stereoselective desymmetrization are reported. Moreover, the kinetic resolution of N-protected 3-arylsulfonyl-7-aza-2-bromobicyclo[2.2.1]hepta-2,5-dienes promoted by (*R*,*R*)-hydrobenzoin is described, representing a new tool to fix the absolute stereochemistry of the 7-azabicyclo[2.2.1] skeleton.

Since Daly's pioneering work, *Epibatidine* **1** {*exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane}, has attracted intense synthetic interest because of its important biological properties.[1] In fact, this natural alkaloid shows exceptional non-opioid antinociceptive property and high binding affinity to nicotinic acetylcholine receptors.[1,2] The natural scarcity of epibatidine has prompted synthetic efforts devoted to its total synthesis both as racemate[3] and in optically active form;[4,5] because **1** exhibits high toxicity preventing its therapeutic use,[6] the preparation of structural analogues of epibatidine has been also extensively investigated.[7] Some strategies are based on the construction of racemic 7-azabicyclo[2.2.1]heptane-2-one **2**[3a,b,7a,8] and, in this context, Trudell's work evidences the importance of N-protected-7-aza-2-arylsulfonylbicyclo[2.2.1]heptane-3-one **3** as the key precursor of **1** (Scheme 1).[3b,7a–c,8a]

On the basis of our experience, we have explored the possibility to fix the absolute stereochemistry of the 7-azabicyclo[2.2.1] skeleton by the stereoselective desymmetrization of **4**, promoted by chiral diolates, according to our previously reported strategy.[9]



Scheme 1.

Although compound **4** could be achieved through the cycloaddition between bis(arylsulfonyl)ethyne and the proper protected pyrrole, the objective problems concerning the large scale preparation of the dienophile dramatically limit the synthetic use of this procedure.[8b] Moreover the reaction between the same pyrroles and either (*E*)- or (*Z*)-1,2-bis(phenylsulfonyl)chloroethylene, which have proven to be cheap synthetic equivalents of bis(arylsulfonyl)ethyne for [4+2] cycloadditions,[10] was unsuccessful. We also carried out a relevant number of experiments to prepare **4** by the β-metallation of sulfone **5** and the subsequent quenching of the vinyl anion with phenylsulfonylfluoride under the reported[11] as well as

Keywords: Desymmetrization; Kinetic resolution; Epibatidine; 7-Azabicyclo[2.2.1]heptane; Sulfones.
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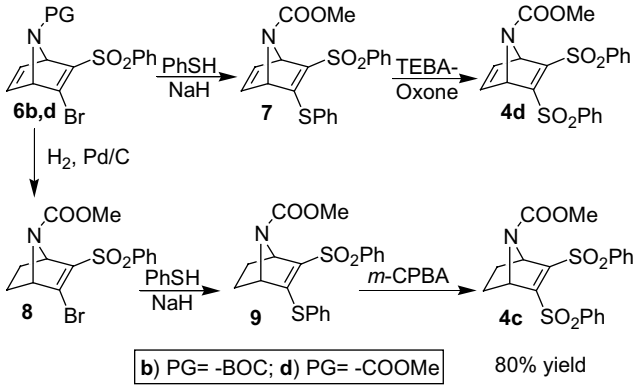
doi:10.1016/j.tetlet.2006.04.014

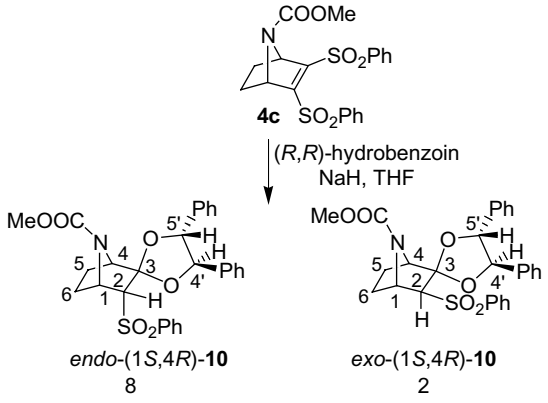
under different reaction conditions. Nevertheless we were unable to prepare **4** by this route, observing the quick and complete conversion of the polycyclic reagent to unidentified by-products whose NMR spectra suggest that an open-chain reaction is operative. Taking into account that Simpkins also encountered a similar difficulty attempting to metallate **5b**,[8b] we concluded that the preparation of **4** from **5** could not be easily realized.[11] Therefore, according to a protocol developed by our group, we conceived a strategy suitable for the preparation of alkenes **4** (Scheme 2) based on the efficient phenylsulfonylation of 2-bromo-3-phenylsulfonyl bridged alkenes **6**.[12] The preparation of reagents **6b**,**d**, which was adjusted over the Trudell's protocol,[8a] was realized by the [4+2] cycloaddition between N-protected pyrrole and 1-bromo-2-phenylsulfonylethyne in 65–70% average yield (after chromatographic purification). The *N*-Boc protected derivative **6b** revealed to be rather unstable under chromatographic conditions either on silica gel or on alumina, so we continued the research only considering the *N*-methoxycarbonyl substituted adduct **6d**.[13] The reaction between **6d** and an equivalent of freshly prepared thiophenol sodium salt in dry THF afforded **7**,[13] which was purified (flash chromatography) and collected in almost quantitative yield. The oxidation of **7** to **4d**, carried out under mild reaction conditions (TEBA–OXONE) in order to preserve the 5-double bond, requires very long reaction time (weeks) and the frequent renewal of the oxidizing reagent. In addition, compound **7** is strongly resistant to hydrogenation. More conveniently, **6d** was quantitatively hydrogenated to **8**[13] (H_2, 5% Pd/C, AcOEt, 1 h, rt), which was in turn transformed to **9**[13] (PhSH, NaH, THF) and finally oxidized to **4c**[13] (*m*-CPBA), which was collected in 80% overall yield.

The desymmetrization step (Scheme 3) has been realized by adding a THF solution of an equivalent of (*R*,*R*)-hydrobenzoin sodium salt to a THF solution of **4c** stirred at −78 °C under argon and at rt for an additional 4 h.

Among four possible stereoisomers, the NMR of the crude reveals the diastereoselective formation of (1*S*,4*R*)-**10** in an 8:2 *endo*/*exo* ratio (82% yield).[13] Deuterochloroform solution of **10**[11] has furnished completely unresolved NMR spectra of the crude, consequently, it has been impossible to attribute the signals as well as to correlate the pattern of signals to any structure. The phenomenon, frequently observed for polycyclic azasubstituted compounds, suggests a poor conformational stability due to the presence of the amidic moiety in apical position. Differently, the use of other solvents more polar than deuterochloroform, such as DMSO-d_6, gave a solution to this problem providing perfectly understandable spectra. By dissolving the samples in DMSO-d_6, all signals have been well resolved. Because of the difficulties to obtain suitable crystals for an X-ray structure determination, we chose to establish the absolute stereochemistry by NMR (COSY, NOESY, HMQC, HMBC), using the chiral 1,3-dioxolanic portion of absolute configuration (4′*R*,5′*R*) known as the intramolecular stereochemical marker. It should be noted, relatively to H_2 of structures *exo*-**10** and *endo*-**10** that the NMR signal does not show a measurable *J* coupling with the bridgehead H_1 either in $CDCl_3$ or as well in DMSO-d_6 solution. Consequently, the structure determination of *exo*-**10**[11] cannot be based on the observation of a missed coupling between H_2 and H_1. The NOESY map of *exo*-(1*S*,4*R*)-**10** shows a number of particularly diagnostic interactions involving, for instance, the aromatic proton (d, 7.94 ppm) at the position *ortho* to the sulfonyl group, which presents intense NOE allowing to unambiguously recognize both H_1 (br s, 4.57 ppm) and H_2 (br s, 4.14 ppm) as well as to discriminate H_4 (br s, 4.39 ppm) from H_1. Most importantly, the aforementioned aromatic proton shows NOE with the dioxolanic $H_{5'}$ (d, 4.25 ppm). Being connected to the dioxolanic carbon of absolute known configuration (5*R*), $H_{5'}$ is oriented towards the *exo* face of the norbornanic skeleton. Consequently, the latter interaction can be only justified by the phenylsulfonyl group oriented to the *exo* position, while H_2 occupies the *endo* one; this interpretation is also supported by the COSY map, which shows the complete absence of spin–spin correlation between H_1 and H_2 as it is expected, accordingly to the Karplus rules, taking into account the dihedral angle value between vicinal protons. Moreover, coherently with the proposed structure, a very diagnostic NOE between the bridgehead H_4 and the dioxolanic $H_{4'}$ is observed. It has been also noted the unfrequent NOE of the methoxy group in apical



Scheme 2.



Scheme 3.

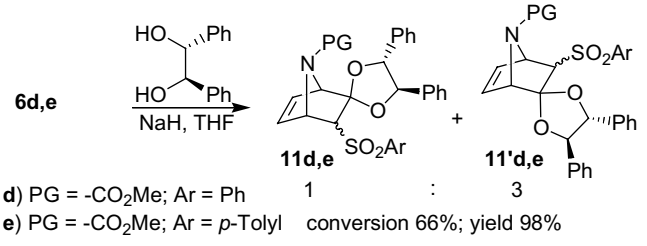
position with H_1, H_4 as well as with the previously cited aromatic proton; this effect is not observed considering H_5 and H_6. On these basis, seems reliable the propensity of the amidic groups to occupy the most hindered face. Based on similar consideration it was established the absolute configuration of the epimer at C_2 *endo*-(1*S*,4*R*)-**10**. In the present case the *exo* oriented position of H_2, which does not present measurable *J* coupling with H_1, was established by evaluating the COSY map, which shows the spin–spin correlation between H_1 and H_2. In addition, having at our disposal all the stereoisomers of **10** we have studied their chromatographic analytical separation by HPLC on a XTerra RP_{18} column (5 μm, 4.6 × 250 mm) (Waters) (CH_3CN–H_2O = 60/40, flow rate 0.8 mL/min, detection 254 nm) measuring for *exo*-**10** and *endo*-**10** $t_{R1} = 12.3$ min and $t_{R2} = 13.3$ min, respectively (for *exo*-**10**: lit.[11] $t_R = 3.56$ min).

Then this re-examined protocol represents a safe, quick and reproducible methodology useful for the multigram scale preparation (5 g) of **10**, in which the absolute configuration of (−)-epibatidine **1** is fixed. We have not further investigated both on the deprotection and the desulfonylation steps of **10** giving (−)-**2**, precursor of (−)-epibatidine.[4b,5e]

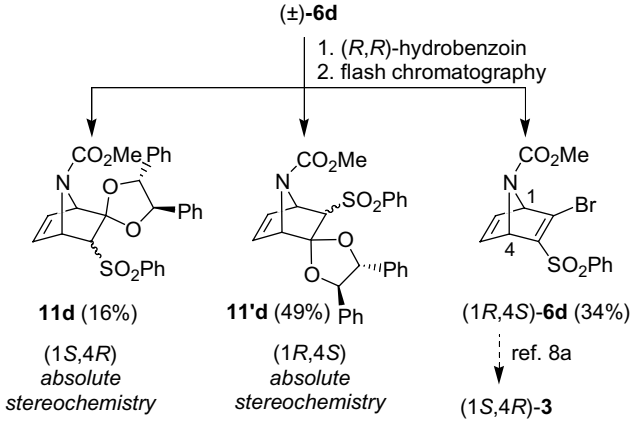
Successively, we resonated that a *meso* compound could be considered as an internal racemate, whereas the racemic mixture could represent a *meso* form in which the symmetry plane is external to the molecules.[14] From a kinetic point of view, the desymmetrization of a *meso* compound constitutes an internal resolution process. Based on these considerations we have explored on the kinetic resolution of racemic N-protected 3-arylsulfonyl-7-aza-2-bromobicyclo[2.2.1]hepta-2,5-dienes **6d**,**e**, constituting a promising strategy to prepare an optically active 7-azabicyclo[2.2.1] skeleton. Racemic mixtures of **6d**,**e** are prepared in multigram scale by [4+2] cycloaddition of *N*-CO_2Me protected pyrrole to 1-bromo-2-phenylsulfonyl-ethyne or 1-bromo-2-tolylsulfonyl-ethyne, respectively.[8a] The crude reaction mixtures were always carefully purified prior to its successive use as a standard practice (flash chromatography on silica gel, 65–70% yields). The kinetic resolution has been realized by treating a THF solution of **6d**,**e** with a THF solution of (*R*,*R*)-hydrobenzoin sodium salt (1:1 molar ratio) at −78 °C, then stirring under argon at rt for 24 h (Scheme 4). All reagents **6d**,**e** have shown to react in an almost identical fashion independently of the nature of the arylsulfonyl groups [conversion 66%, yield 98%, recovered starting material 34% (1*R*), recovered chiral auxiliary 34%]. On the basis of NMR maps, the reaction products are established to be a diastereoisomeric mixture of *endo*-(1*R*,4*S*)-**11′d**,**e** and *endo*-(1*S*,4*R*)-**11d**,**e** in a 3:1 ratio (by the NMR spectra of the crude). We have established the absolute stereochemistry of products **11d**,**e** and **11′d**,**e** by NMR spectroscopy[13] (DMSO-d_6) as previously described. The reaction mixture of dioxolanic derivatives **11d**,**e** and **11′d**,**e** has been separated by flash chromatography (silica gel, gradient of *n*-hexane–AcOEt up to 95:5 ratio, 65% yield). Under these conditions *endo*-(1*R*,4*S*)-**11′d**,**e** as well as *endo*-(1*S*,4*R*)-**11d**,**e** partially epimerize at the phenylsulfonyl substituted position 2 affording *exo*-(1*R*,4*S*)-**11′d**,**e** and *exo*-(1*S*,4*R*)-**11d**,**e**, respectively. All stereoisomers of **11d** and **11′d** were analyzed by HPLC as previously described: t_R (*endo*-**11′d**) 11.1 min, t_R (*exo*-**11′d**) 12.0 min, t_R (*exo*-**11d**) 12.6 min, t_R (*endo*-**11d**) 14.2 min.

Concerning the stereoselective aspects, it is noted that (*R*,*R*)-hydrobenzoin reacts with **6** showing opposite selectivity with respect to the reaction carried out on 2,3-bis(phenylsulfonyl) substituted **4c**. Furthermore, 1-bromo-2-phenylsulfonyl **6d** is, as expected, less reactive than the parent bis(phenylsulfonyl)substituted **4c**, requiring in fact longer reaction times (24 h vs 4 h) to reach completion, probably as the consequence of the changed steric and electronic situations (bromine vs $PhSO_2$– group). In addition, the impossibility to stabilize transient species through π–π interactions involving the aromatic rings of both the chiral auxiliary and the phenylsulfonyl group,[9d] makes the reaction of bromo derivatives less stereoselective. The comparison between **4c** and **6d** takes into account that the desymmetrization processes of 2,3-bis(phenylsulfonyl)bicyclo[2.2.1] systems are not influenced by the remote substituents at the positions 5,6.

Taking into account that racemic **6d** has proved to be itself a precursor of racemic ketosulfone **3**,[8a] the described asymmetric transformation of **6d** appears as a parallel kinetic resolution process, in which the recovered starting material 1*R*-**6d** (95 ee%, HPLC, Chiralcel OD-H) can be transformed[8a] to enantiopure N-protected-**3** (Scheme 5).



Scheme 4.



Scheme 5.

Acknowledgements

This work has been supported by Università Ca' Foscari di Venezia (ex 60% funds). Thanks are due to Dr. P. Volpato and Dr. A. Migatta for preliminary experiments.

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13. Compound **6d**: mp 154–155 °C (Et_2O–CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) 3.70 (br s, 3H, OMe), 5.21 (s, 1H, H_4), 5.69 (s, 1H, H_1), 6.97 (br s, 2H, H_5, H_6), 7.56–7.59, 7.63–7.69, 7.89–7.91 (series of m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) 53.2 (OMe), 69.3 (C1), 75.4 (C4), 127.7, 129.4, 134.1, 139.8, 154.6. Compound **7**: mp 162–163 °C (Et_2O–CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) 3.38 (br s, 3H, OMe), 4.80 (br s, 1H, H_4), 5.37 (br s, 1H, H_1), 6.65 (dd, $J = 5.3$, 2.6, 1H, H_5), 6.88 (dd, $J = 5.3$, 2.2, 1H, H_6), 7.43–7.67, 7.96–7.98 (series of m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) 52.9, 69.1, 71.4, 127.2, 129.2, 130.2, 133.5, 134.7, 138.5. 143.1. Compound **8**: mp 134–135 °C; ^1H NMR (300 MHz, $CDCl_3$) 1.24–1.50 (m, 2H, H_{5endo}, H_{6endo}), 1.95–2.03 (m, 2H, H_{5exo}, H_{6exo}), 4.76 (br s, 1H, H_1), 4.96 (br s, 1H, H_4), 3.47 (br s, 3H, OMe), 7.52–7.69, 7.95–7.98 (series of m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) 24.1 (C6), 26.6 (C5), 53.0 (OMe), 63.8 (C1), 69.7 (C2), 127.7, 129.4 (2C), 134.1, 134.3, 140.0. Compound **9**: ^1H NMR (300 MHz, $CDCl_3$) 1.25–1.39, 1.45–1.58, 1.77–1.85, 1.98–2.00 (series of m, 4H, H_{5exo}, H_{5endo}, H_{6exo}, H_{6endo}), 3.36 (s, 3H, OMe), 4.38 (br s, 1H, H_3), 4.92 (br s, 1H, H_2), 7.42–7.54, 7.59–7.71, 7.99–8.02 (series of m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, 2C omitted) 25.0, 27.7, 52.6, 64.1, 65.8, 127.2, 127.7, 129.2, 129.3, 129.6, 129.7 (2C), 133.5, 134.1 (2C), 141.2. Compound **4c**: mp 159–160 °C (*n*-hexane–AcOEt); ^1H NMR (300 MHz, $CDCl_3$) 1.35 (d, 2H, H_{5exo}, H_{6exo}), 2.08 (d, 2H, H_{5endo}, H_{6endo}), 3.38 (s, 3H, OMe), 5.10 (br s, 2H, H_1, H_4), 7.58 (t, $J = 7.6$ Hz, 4H, Ar), 7.70 (t, $J = 7.6$ Hz, 2H, Ar), 8.02 (d, $J = 7.6$ Hz, 4H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) 25.1 (C_5, C_6), 53.0 (OMe), 65.7 (C_1, C_4), 128.2 (4Ar C *o*- to SO_2), 129.4 (4Ar C *m*- to SO_2), 134.6 (2Ar C *p*- to SO_2), 139.3 (2Ar C–SO_2), 155.3 (C═O). Compound *exo*-**10**: ^1H NMR (300 MHz, DMSO-d_6) 1.60–1.90 (series of m, 4H, H_5, H_6), 3.57 (s, 3H, OMe), 4.14 (br s, 1H, H_2), 4.25 (d, 1H, 1/2 AX system, $J = 9.2$ Hz,$H_{5'}$), 4.39 (br s, 1H, H_4), 4.57 (br s, 1H, H_1), 4.83 (d, 1H, 1/2 AX system, $J = 9.2$ Hz, $H_{4'}$), 7.00–7.06, 7.10–717, 7.27–7.34 (series of m, 10H, Ar), 7.63 (t, 2H, $J = 7.5$ Hz, Ar, *meta* to SO_2), 7.73 (d, 1H, $J = 7.5$ Hz, Ar, *para* to SO_2), 7.94 (d, 2H, $J = 7.1$ Hz, Ar, *ortho* to SO_2). Compound *endo*-**10**: ^1H NMR (300 MHz, DMSO-d_6) 1.65–1.85 (series of m, 4H, H_5,H_6), 3.57 (s, 3H, OMe), 4.25 (d, 1H, 1/2 AX system, $J = 9.2$ Hz, $H_{5'}$), 4.40 (br s, 1H, H_4), 4.55 (d, $J = 7.2$ Hz, H_1), 4.83 (d, 1H, 1/2 AX system, $J = 9.2$ Hz, $H_{4'}$), 5.32 (br s, 1H, H_2), 7.02–7.11, 7.13–7.15, 7.30–7.33, 7.62–7.72, 7.93–7.96 (series of m, 15H, Ar); ^{13}C NMR (75 MHz, DMSO-d_6, mixture of *exo*–*endo* isomers in a 8:2 ratio) 22.6, 28.3, 52.8, 57.7, 62.7, 74.7, 84.7, 86.5, 127.4, 127.6, 128.9, 129.0, 129.1, 129.4, 129.6, 134.2, 135.1, 136.9, 140.0, 177.0. Compound *endo*-**11′d**: ^1H NMR (300 MHz, DMSO-d_6) 3.53 (s, 3H, OMe), 3.79 (s, 1H, H_2), 4.78 (d, 1H, 1/2 AX system, $J = 9.0$ Hz, $H_{5'}$), 4.85 (br s, 2H, H_1, H_4), 5.09 (d, 1H, 1/2 AX system, $J = 9.0$ Hz, $H_{4'}$), 6.63 (m, 1H, H_5), 6.72 (m, 1H, H_6), 7.20–7.47 (series of m, 10H, Ar), 7.52 (t, 2H, $J = 7.4$ Hz, Ar, *meta* to SO_2), 7.68 (d, 1H, $J = 7.4$ Hz, Ar, *para* to SO_2), 7.89 (d, 2H, $J = 7.4$ Hz, Ar, *ortho* to SO_2). Compound *endo*-**11d**: ^1H NMR (300 MHz, DMSO-d_6) 3.50 (s, 3H, OMe), 4.30 (br s, 1H, H_1), 4.83 (d, 1H, 1/2 AX system, $J = 9.0$ Hz, $H_{4'}$), 5.04 (br s, 1H, H_4), 5.07 (d, 1H, 1/2 AX system, $J = 9.0$ Hz, $H_{5'}$), 6.63 (m, 1H, H_5), 6.80 (m, 1H, H_6), 7.01–7.11, 7.13–7.20, 7.32–7.40 (series of m, 10H, Ar), 7.75 (t, 2H, $J = 7.6$ Hz, Ar, *meta* to SO_2), 7.83 (d, 1H, $J = 7.6$ Hz, Ar, *para* to SO_2), 8.05 (d, 2H, $J = 7.6$ Hz, Ar, *ortho* to SO_2).
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