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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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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.
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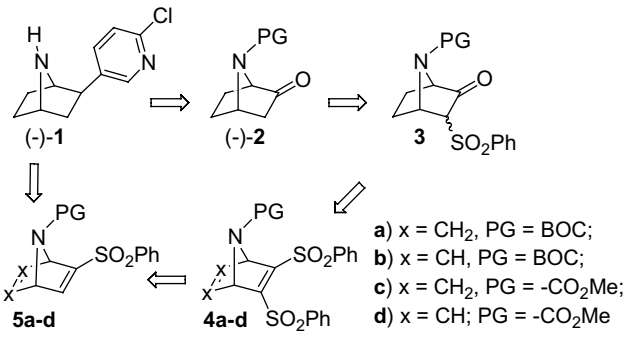
Since Daly's pioneering work, *Epibatidine* **1** {*exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane}, has attracted intense synthetic interest because of its important biological properties.[1] In fact, this natural alkaloid shows exceptional non-opioid antinociceptive property and high binding 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

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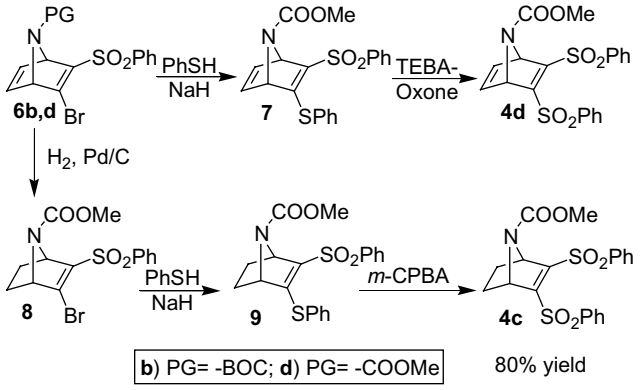
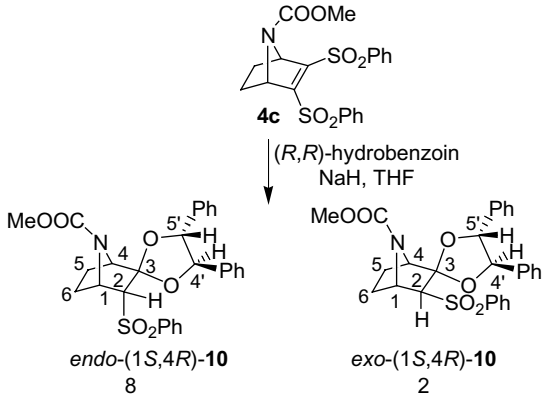
under different reaction conditions. Nevertheless we were unable to prepare **4** by this route, observing the quick and complete conversion of the polycyclic reagent to unidentified by-products whose NMR spectra suggest that an open-chain reaction is operative. Taking into account that Simpkins also 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.

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