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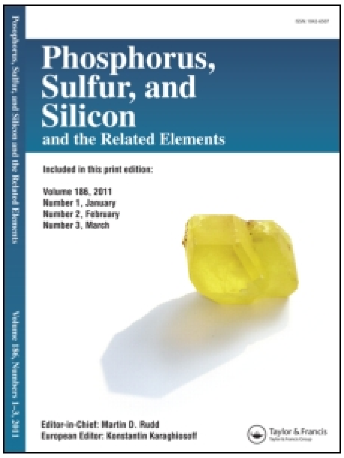

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Bis(Phenylsulfonyl)Alkenes: from Enantiopure Ketones to Fullerene Substructures

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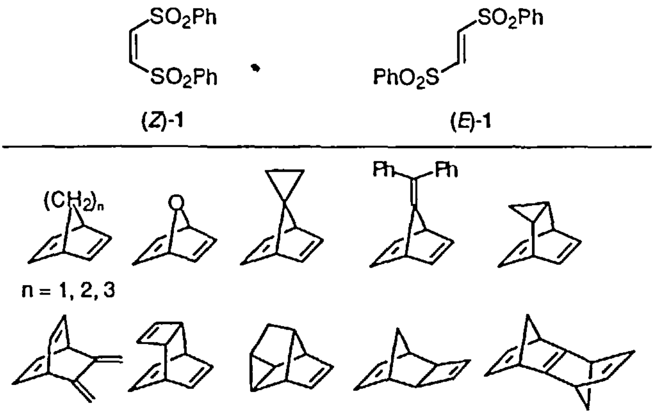
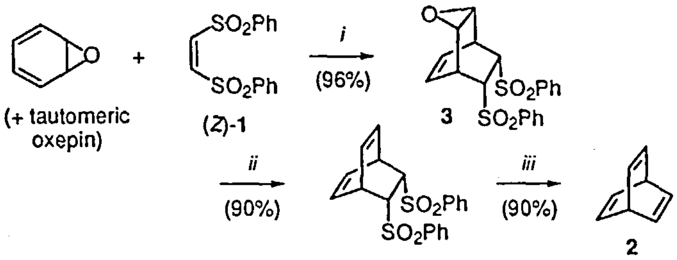
The synthetic potential of bis(phenylsulfonyl)alkenes, especially in view of their ability to function as equivalents of acetylene in cycloaddition reactions for the preparation of polycyclic molecules, is discussed. Differently from the bis(phenylsulfonyl)alkenes, bis(phenylsulfonyl)-acetylene has to be prepared and reacted *in situ* and affords polycyclic bis(phenylsulfonyl)alkenes upon Diels-Alder reaction. The same products arising from bis(phenylsulfonyl)acetylene can be more products arising from bis(phenylsulfonyl)acetylene can be more conveniently prepared by cycloaddition of (*E*)-1-chloro-1,2-bis(phenylsulfonyl)ethylene and dehydrochlorination with triethylamine. They react with enantiopure C_2-symmetric diols with complete enantiotopic discrimination, eventually leading to polycyclic enantiopure ketones of known configuration. The enantiopure ketones, transformed into bromoalkenes, are further transformed into bromotrimethylstannyl alkenes. Upon treatment with copper nitrate trihydrated, the latter undergo cyclotrimerisation to benzotrisnorbornadienes in high yield. These molecules are composed of five and six membered rings as the fullerenes and can function as host compounds, as a kind of calixarene. The rearrangements eventually leading to fullerenes substructures and fullerene C_{60} itself will be discussed.

Keywords: bis(arylsulfonyl)alkenes; bis(arylsulfonyl)acetylene

Double substitution of ethylene or acetylene with identical functional groups not only provides molecules with the highest degree of activation but also simplify operations and products identification because of the symmetry of the resulting molecules. Within this class of compounds, (Z)- and (*E*)-1,2-bis(phenylsulfonyl)ethylenes (**1**) have emerged amongst the most convenient acetylene equivalents in cycloaddition reactions[1] and have been used for the preparation of numerous molecules, some of which were not readily accessible by other conventional methods or were not available at all.[2]



A recent application is a new synthesis of barrelene 2 that makes it available in a sequence of steps that can be simply scaled up to grams quantities.[3] Barrelene is a peculiar molecule because it is the formal Diels-Alder adduct of acetylene to benzene, neither one reactive by its own in this sort of cycloaddition reactions.



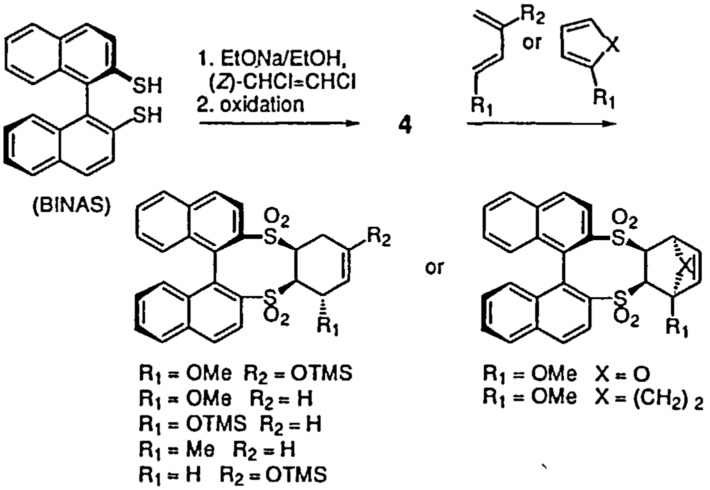
Reaction conditions: *i*. Benzene, 48 h, 80 °C. *ii*. WCl_6/BuLi, THF, 24 h, rt.
iii. Na/Hg, buffered MeOH

The use of oxepin, as an equivalent of benzene reacting as a diene in a cycloaddition reaction is noteworthy because oxepin is readily available and highly reactive. The epoxy functionality in 3 is readily removed from the adducts by established methodologies, in contrast to other functionalities that require reaction conditions not compatible with the system.

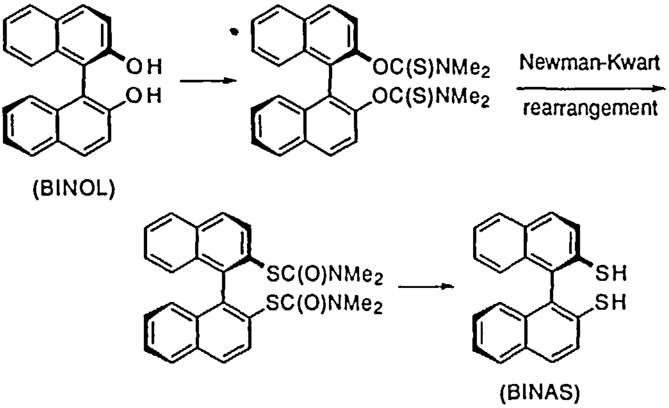
For sometime we have been seeking for a chiral variant of the bis(phenylsulfonyl)ethylenes (1). A reagent that allowed us to maintain all of the positive features of the achiral reagents still being chiral, is the dinaphthodithiocine tetroxide (4)[4] and that can be seen as an extended version of the previous dienophile as represented:

4

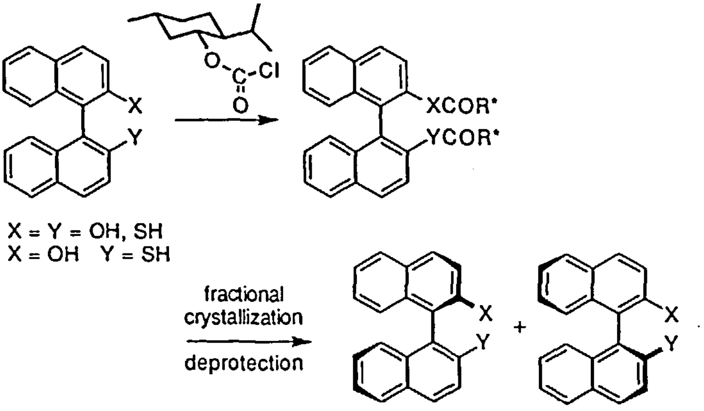
Dienophile 4 can be prepared by standard methodologies starting from 1,1'-binaphtho-2,2'dithiol (BINAS). It cycloadds to non symmetrical dienes under mild reaction conditions in most cases with total diastereoselectivity.[5]



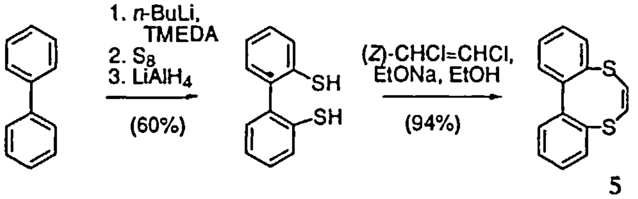
On the other hand, BINAS can be prepared in enantiopure form starting from enantiopure BINOL[6] that, in turn, can be prepared enantiopure by a number of routes. The crucial step, *i.e.* the Newman-Kwart rearrangement occurs with no loss of optical purity if carried out under proper reaction conditions.



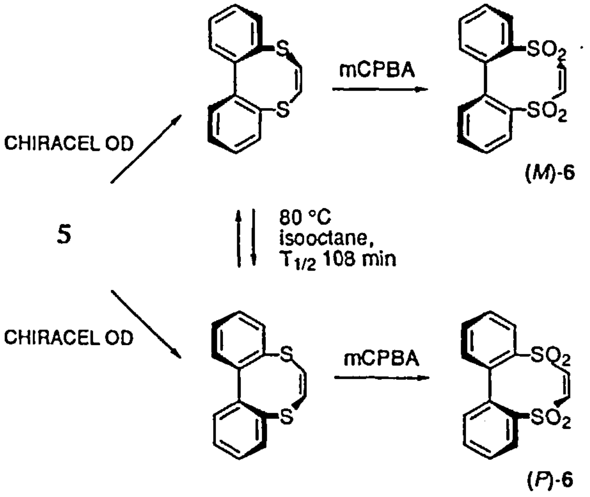
BINAS can also be resolved into its antipodes via separation of its diastereomeric menthyl carbonates.[7] The system is quite general and works equally well for the oxygen and sulfur analogs, as well as for the mixed system as represented below.



Seeking for an auxiliary of lower molecular weight we have investigated the biphenyl system. The relevant dithiocine 5 can be prepared from inexpensive starting material and features an interesting atropisomeric behaviour.[8]

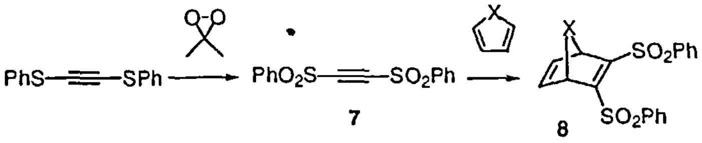


While dithiocine 5 can be racemized at 80 °C in isooctane and separated into its two antipodes by chiral HPLC, the oxidised material 6 is stable toward atropoisomerisation and can be indefinitely stored without loss of optical purity.

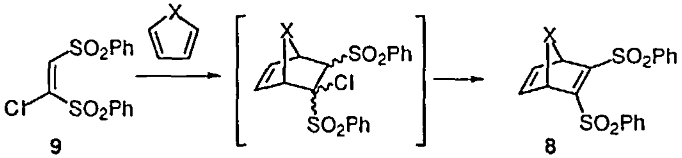


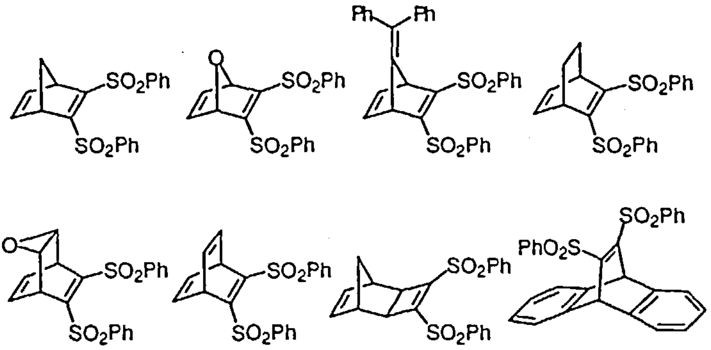
Deeming that an important issue is the ratio between the molecular weight of the auxiliary and that of the actually desired optically active product, other strategies leading to auxiliaries of lower molecular weight have been put forward[9] but they will be not described here.

Back to the realm of the achiral reagents, we have been looking for quite a long time to bis(phenylsulfonyl)acetylene 7. This elusive molecule could eventually be prepared and reacted *in situ* with cyclopentadiene or 1,3-cyclohexadiene to afford the Diels-Alder adduct 8.[10]

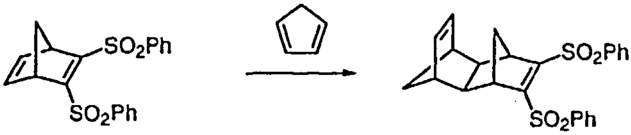


From a synthetic viewpoint, however, the reaction is unpractical and an alternative method, leading to multigram quantities of 8 was devised. The method uses (*E*)-chloro-1,2-bis(phenylsulfonyl)ethylene (9) as a surrogate of the unstable acetylene. After cycloaddition, an HCl molecule is eliminated with formation of the same adduct 8 that bis(phenylsulfonyl)acetylene itself would produce. The following set of molecules was prepared *via* this route.[11]

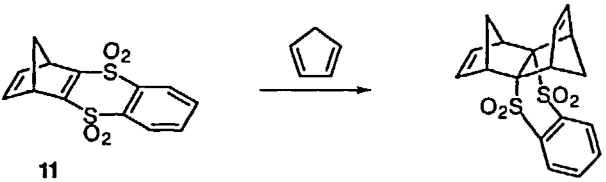




The reactivity in cycloaddition reactions of bis(phenylsulfonyl) alkenes other than the parent ones is rather poor, so that the synthetic equivalency of substituted bis(phenylsulfonyl)alkenes to substituted acetylene in cycloadition reactions is not feasable. To illustrate the poor reactivity of the class of doubly substituted vinyl sulfones is instructive the case shown below. 2,3-Bis(phenylsulfonyl)norbornadiene **10**, whose synthesis has just been described, reacts with cyclopentadiene to the unactivated double bond.[12]

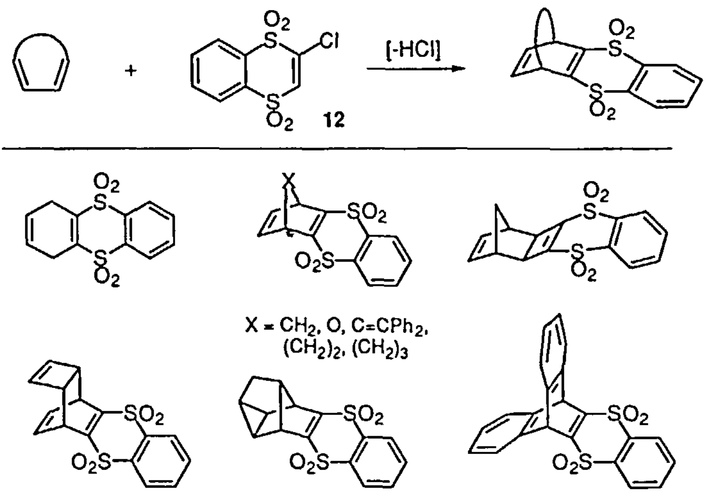


10

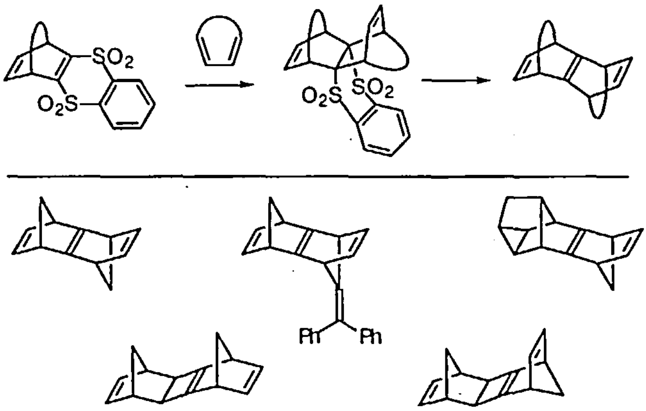


11

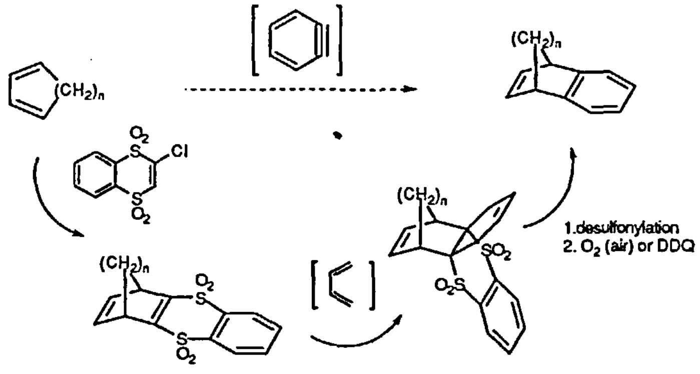
The poor dienophilic reactivity was imputed to the large steric hindrance imparted by the phenylsulfonyl groups and the inability of the molecule to adopt a proper orbital allignment for cycloaddition. Such steric impediments were expected not to be as crucial for the related 1,4-benzoditiin tetraoxide as reports in the literature[13] were supporting. Indeed the norbomadiene **11** derived from benzodithiin tetroxide, at variance with that substituted with two phenylsulfonyl groups **10**, is reactive at the functionalized double bond. The reaction is quite general and could be expanded to several dienes, thus forming the set of reactive bis(sulfonyl)alkenes shown below.[14]



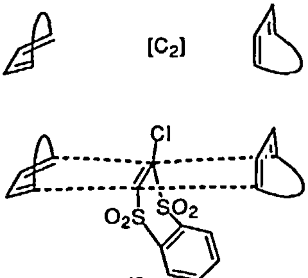
The Diels-Alder reactivity of such benzodithiin tetroxide derivatives allows for the synthesis of several other molecules that are nor readily accessible by other synthetic means. In the next scheme, the reactivity with another molecule of a diene and the desulfonylation reaction to the unsaturated hydrocarbon is reported.



In another perspective substituted benzodithiin tetroxides have been exploited as a mild equivalent of benzyne because its adducts to butadiene (as generated from 3-sulfolene) can be readily oxidized to the aromatic molecule.[16]

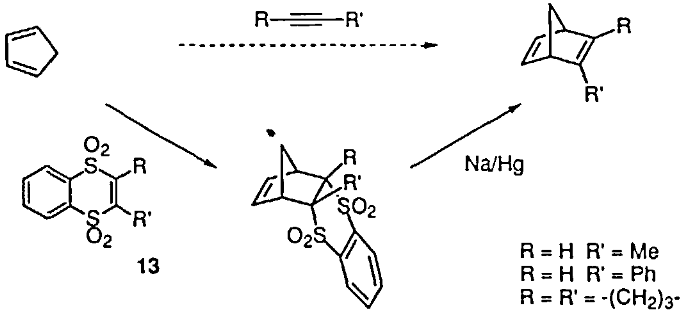


It is worth to note that in any reaction reported 2-chlorobenzodithiin tetroxide (12) can be view as a synthon of molecular C_2. As depicted below, infact, 12 behaves as a molecule of C_2 conjuncting two dienes systems via a double Diels-Alder reaction.[14]

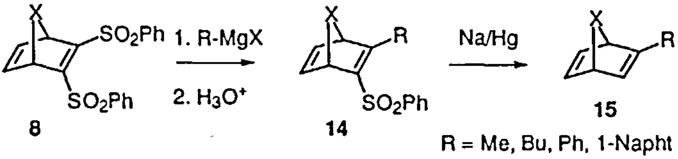


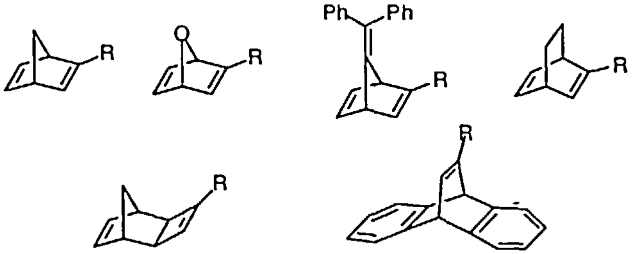
12

Having found in benzodithiin tetroxide a more reactive alternative of the bis(phenylsulfonyl) system, it was rather obvious to put forward a convenient equivalent to a substituted acetylene in a cycloaddition reaction. A set of 2- and 2,3-substituted derivatives 13 of such heterocyclic system was thus prepared, reacted with cyclopentadiene and desulfonylated in order to obtain the same molecules that would arise from the cycloaddition of a mono and disubstituted acetylene, if these would be reactive in cycloaddition reactions.[17]

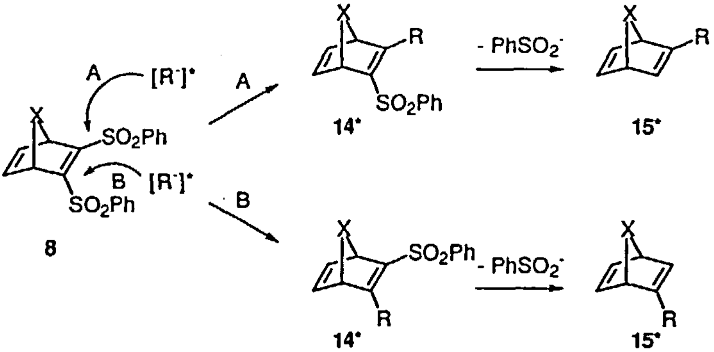


The class of bis(phenylsulfonyl)alkenes can be used for other synthetic manipulations other than cycloaddition reactions. The two phenylsulfonyl groups impart to the olefin a strong electrophilic character so that they react readly with numerous nucleophiles. Carbon nucleophiles, for example, react with **8** and lead to substituted vinyl sulfones **14** that can be desulfonylated to **15**, i.e. the formal adducts of a terminal acetylene to a diene.[18] This synthetic route is hence alternative to the use of the substituted benzodithiin tetroxides **13** just described.

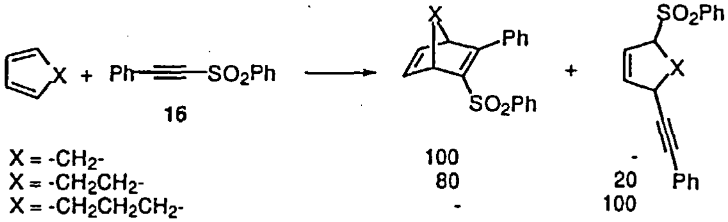




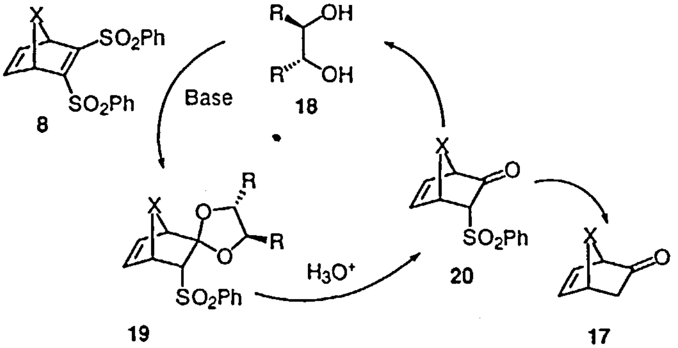
The mechanism of the reaction was not investigated in detail but it probably entails nucleophilic addition of the Grignard reagent followed by elimination of the phenylsulfinate anion.[19] On this basis, starting from a chiral nucleophilic carbon nucleophile it is possible to obtain selectively one or the other enantiomer depending on the side of attack of the carbanion. In view of the numerous chiral Michael addition reported in the literature[20] and the shield exerted by the sulfonyl groups, the bias to diastereoselection in generally good with the possibility to obtain chiral polycyclic hydrocarbons.[21]



The adducts of the carbon nucleophiles **14** correspond to the Diels-Alder adducts of a substituted phenylsulfonyl)acetlene ($R\text{-}C{\equiv}C\text{-}SO_2Ph$) to the diene. The reactivity of **16** was investigated in some detail. In general, the Diels-Alder reactivity is rather poor. Except for cyclopentadiene, the reaction takes place only upon heating and affords, beside the expected [4+2]-cycloadduct, the adduct derived from the addition of the two fragment from the $C\text{-}SO_2$ bond cleavage.[22]

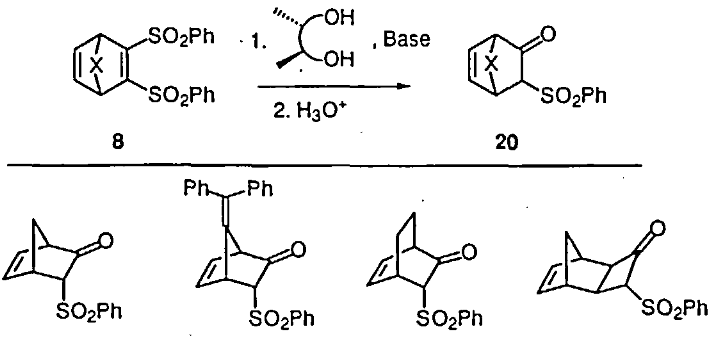


We have been also attracted by the possibility of generating optically active polycyclic ketones **17** from **8** by the following route.

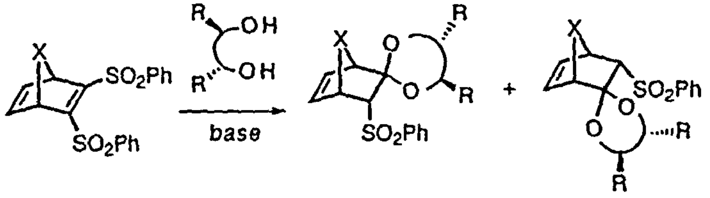


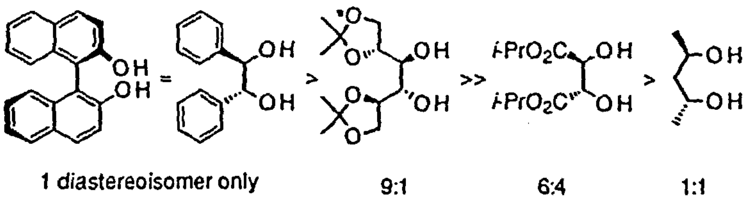
Double nucleophilic addition of the oxygen atoms of an enantiopure diol **18** to bis(phenylsulfonyl)alkene **8** affords the diastereomeric β-phenylsulfonyl acetal **19** that can be hydrolyzed to the ketosulfone **20** and finally desulfonylated to the desired ketone **17**. The later polycyclic ketones find widespread use in the total synthesis of numerous natural products and of compounds with biological activity.

The set of polycyclic bis(phenylsulfonyl)alkenes represented below was considered.[23]

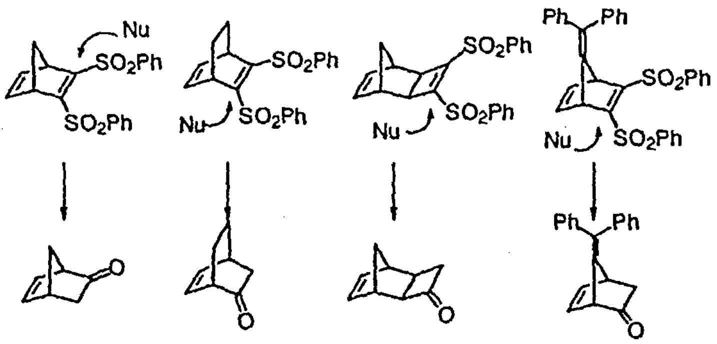


In all cases a single diastereoisomer was obtained with 1,1'-binaphtho-2,2'-diol and hydrobenzoin used as the diene, while poorer diastereomeric ratios were obtained with other diols as reported below.

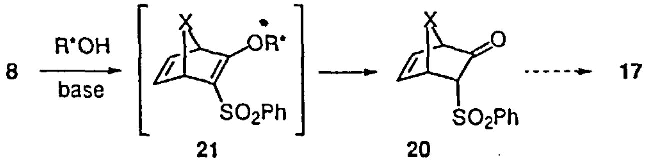




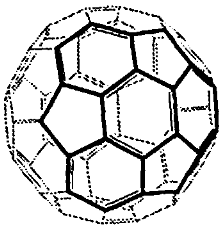
The use of the base is also of interest.[24] Sodium hidride in THF proved so far superior over other bases and different counterion. For example, deprotonation of the hydrobenzoin with *n*-butyllithium and Grignard reagents afford poorer diastereomeric ratio, while diethylzinc appears unreactive. The absolute configuration of the products was determined by X-ray structure analysis of the β-sulfonylacetals **19**. Being the configuration of hydrobenzoin known, the configuration of the following ketones was determined and a rational suggesting the attack by the diol nucleophile from the top or the bottom of the polycyclic bis(phenylsulfonyl)alkene (as rapresented) is suggested.



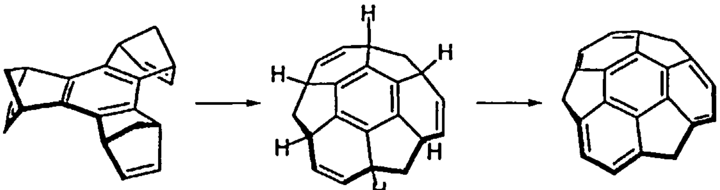
A practical improvement of the preparation of such polycyclic ketones entails the use of appropriate enantiopure alcohols instead of the diols **18**. They lead to enolethers **21** that undergo spontaneous hydrolysis to **20** during work-up and eventually to enantiopure ketones **17** in a reduced number of operations and in better overall yields.



In the meanwhile, in another area of research, we were investigating the possibility of preparing non-planar PAHs[25] and fullerene substructures. In our aim was the synthesis of the hitherto unknown C_{21} hydrocarbon **22** shown below in the surface of fullerene C_{60}. This molecule named "sumanene"[26] represents one of the smallest fullerene subunit featuring a clear cup-shaped geometry.

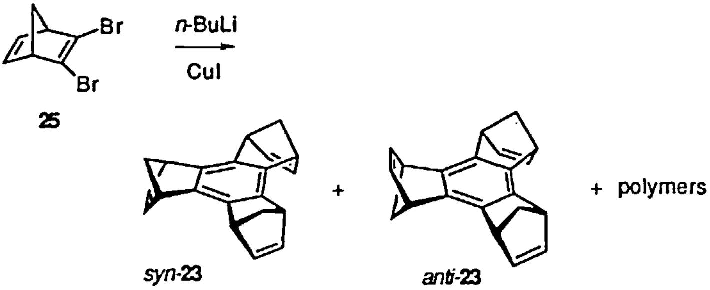


The strategy for its synthesis entails circumrearrangement of the molecule of benzotrinorbornadiene **23** to the esahydroderivative of sumanene **24** and final oxidation to sumanene **22** itself. From a thermodinamic point of view, the transformation of benzotrinorbornadiene **23** into esahydrosumanene **24** seems very favourable as determined computationally at the semiempirical level. Of course, the oxidation of the latter to the quite distorted aromatic sumanene **22** is quite endothermic.



23 **24** **22**

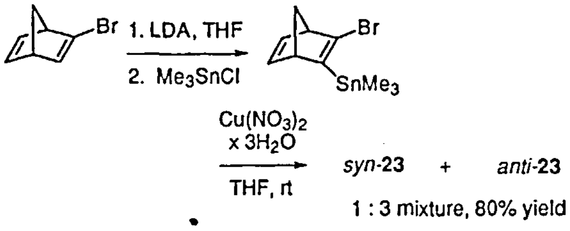
Although, all these transformations are yet to be accomplished, the scheme shown serves as a guideline of work and thus as the reason why we undertook a study aimed at the synthesis of the still hitherto unknown benzotrisnorborandiene 23. Following similar research in the area, we have investigated all possible cyclotrimerisation reactions known for polycyclic systems. The only route that proved viable for the synthesis of the desired molecule 23 is represented below and entails metal-halogen exchange from the dibromonorbornadiene 25 and treatment with copper(I) iodide as shown.[27]



25 *syn*-**23** *anti*-**23**

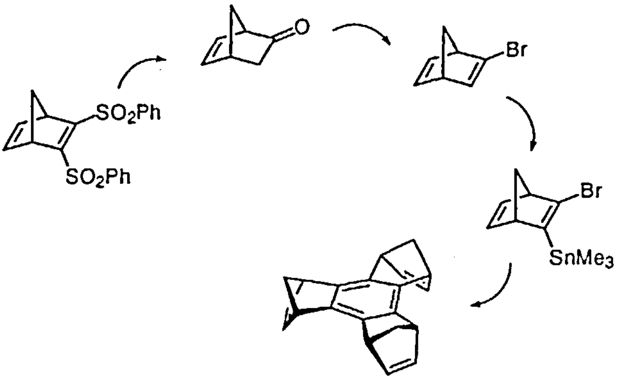
1 : 3 mixture, *ca.* 10% yield

Under these conditions, he product formes as a 1 : 3 *syn-anti* mixture of isomers in ca. 10% yield together with a large amount of polymeric material . Seeking for a more efficient preparation of 23 we prepared the bromostannyl derivative 26 that embodies into the same alkene both functionalities for the Stille coupling reaction. Upon treatment with copper nitrate trihydrated, bromostannylalkene 26 undergoes cyclotrimerisation to benzotrisnorbornadienes in high yield.[28]



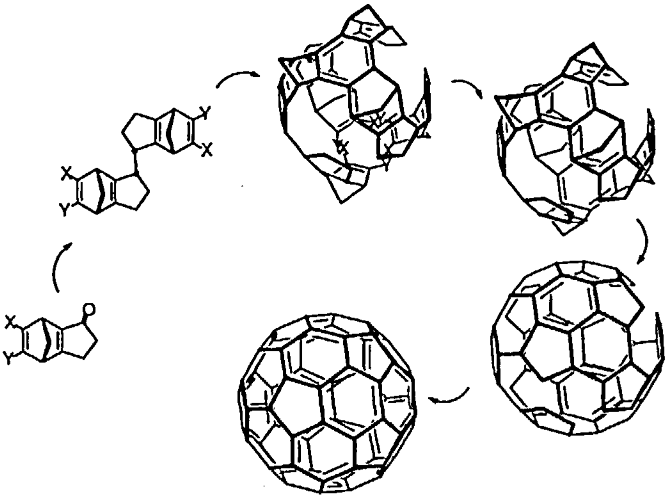
With racemic reagents, an almost statistical mixture of the *syn* -**23** plus the *anti* isomer (1 : 3) is formed while, using enantiopure substrates, the cyclotrimerisation reaction leads to *syn* structure only. In the cyclotrimerisation the chirality of the reagent is lost but the stereochemical information is retained in the generation of the single *syn* stereoisomer.

At this stage, the chemistry of bis(phenylsulfonyl)alkenes leading to enantiopure polycyclic ketones ties up conveniently because it allows for the synthesis of the bromoderivative *via* the Shapiro reaction. Being the bromonorbornadiene in enantiopure form, it is possible to eventually obtain the cyclotrimer **23** in its *syn* configuration only.



syn -**23**

It should be noticed that these final molecules are composed of five and six membered rings as the fullerenes and can function as host compounds, as kind of calixarenes. The rearrangement eventually leading to fullerenes substructures and fullerene C_{60} itself is still very speculative but it would represent a very short route of synthesis of this sort of molecules.



Acknowledgments

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