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A Convenient Synthesis of Dibenzo[a,c]cyclooctene Based on Thioenol Ether Reduction

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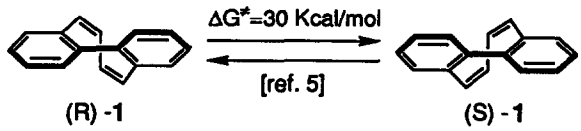
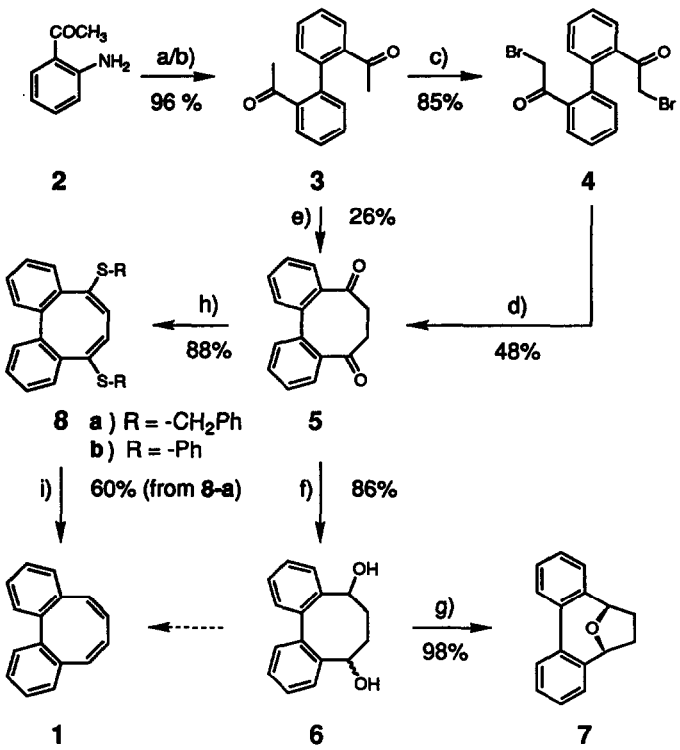
Abstract: *9,10,11,12-Tetrahydrodibenzo[a,c]cyclooctene-9,12-diol (6) is found to be reluctant to double bond forming elimination. It gives a bridged ether (7) instead. The corresponding diketone (5) reacts with benzyl mercaptan to provide the bis-thioenol ether (8-a). The latter, upon treatment with Raney nickel, gives the desired title diene 1. An alternative approach to 1, based on repeated carbene addition to phenanthrene, is also presented.*

The efficient synthesis and the properties of *o-o'*-bridged biphenyls continue to be of interest to many areas of chemistry[2,3]. The seemingly simple title hydrocarbon **1**, although known for nearly three decades[4], has only recently been resolved into its atropisomers (R)-**1** and (S)-**1**[5]. The chiral features of these antipodes, which are protected against racemization by an inversion barrier of $\Delta G^{\neq}$ = 30 kcal/mol, have not yet been exploited. In connection with our continuing studies of highly strained bicyclobutanes[6] we have demonstrated that the diene **1** undergoes a photo-Diels-Alder reaction with 4-methyl-3H-1,2,4-triazol-3,5(4H)-dione (MTAD). Thermally, **1** is inert towards the dienophile. Further studies on these lines are greatly hampered by the inefficiency of preparations of **1** according to literature procedures[4a,7b].



One of the first syntheses reported for **1** starts from the photoadduct of maleic anhydride and phenanthrene[4a]. It implies an oxidative bis-decarboxylation and a disallowed thermal ring opening. The method has been extended to derivatives of both maleic anhydride and phenanthrene[2a,8], but global yields are invariably low (1-6%). A somewhat better method was described by Wong and Sondheimer[7b]. It starts from 2,2'-bis(bromomethyl)-1,1'-biphenyl and avoids the disallowed ring opening. This method also has been extended to derivatives of the parent system[2a]. Global yields are in the range of 5-9%. In the present communication, we wish to report on a five-step synthesis of **1** which starts from the commercially available 2-aminoacetophenone **2**. The eight-membered ring is set up by intramolecular reductive coupling[7a]. The target diene **1** is obtained by this synthesis in 21% overall yield including the separation of the enantiomers (+)-**1** and (-)-**1**. Brief mention will be made at the end of this communication of an alternative approach towards **1**, which is based on ring expansion of phenanthrene *via* repeated carbene addition. It gives **1** in 14-16% yield.

For the initial biaryl formation (2 → 3) we have chosen reductive coupling of the diazonium salt derived from 2. The method had been shown to be very efficient in the analogous synthesis of diphenic acid[9] and proceeded in higher yield (96%) than the classical Ullmann reaction performed with the corresponding iodide (59%)[10]. The subsequent double bromination with phenyltrimethylammonium perbromide (PTAB) (3 → 4) as well as the zinc-copper promoted reductive cyclization providing the diketone 5, are known reactions[10]. The ring closure, with its modest 48% yield, is the weakest step in our synthesis. Our efforts to convert the diketone 3 directly into 5 by intramolecular oxidative coupling following Kobayashi's procedure[11] met with limited success. This procedure gave 5 in 26% yield only, and therefore does not present any advantage over the path *via* the dibromide 4.

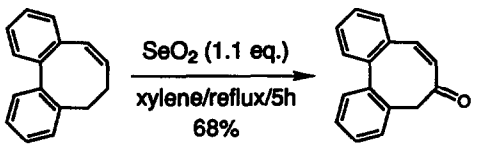


a/b) HNO_2/Cu(I) [ref.9] c) PTAB [ref.10] d) Zn-Cu/NaI/DMSO [ref.10]
e) LDA/$Cu(OTf)_2$/i-PrCN [ref.11] f) $NaBH_4$ g) TsOH/benzene
h) RSH/BF_3/AcOH [ref.14] i) Raney-Ni/acetone [ref.14]

Initially, we had planned to reduce the diketone 5 into its diol 6 (mixture of stereomers) and to reach the target diene 1 by standard elimination procedures. As expected, the reduction step (5 → 6) did not provide any problems. The difficulties started when the final elimination (6 → 1) was attempted. Most of the classical methods (*e.g.* TsOH/benzene) when applied to the diol 6, gave the bridged ether 7 as the main product[12,13].

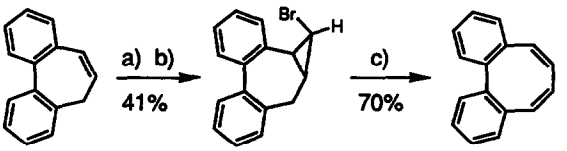
We could not find methods transforming 6 or 7 in acceptable yield into the desired diene 1. In order to overcome these difficulties, we resorted to a desulfurization method which had been used successfully in steroid chemistry[14]. The diketone 5 was found to react with two equivalents of benzyl mercaptan in the presence of BF_3 as a catalyst, to give the double thioenol ether 8-a in 88% yield[12,15]. Thiophenol reacts in

analogous fashion to give **8-b**(86% yield)[12]. Compounds **8-a** or **8-b** were readily desulfurized by treatment with Raney nickel in acetone to give the desired diene **1** in yields of 60% and 58% respectively[16]. This last step gives as a by-product the known 9,10-dihydro-dibenzo[a,c]cyclooctene **9**[5] in 15-20% yield. Careful tlc monitoring of the disappearance of starting material is required during the desulfurization in order to minimize this undesired overreduction. Compound **1** was separated into its antipodes by medium pressure chromatography on swollen microcrystalline triacetylcellulose (TAC)[5] with methanol/water (95/5) as eluent. This final chromatographic step results also in the separation from **9**. The compounds are eluted in the order (+)-**9**, (+)-**1**, (-)-**9**, and (-)-**1**. It must be mentioned however that compounds **1** and **9** have very similar retention times on ordinary silicagel columns. If one aims only at the isolation of racemic **1**, it is advantageous to first reflux the crude **1/9** mixture in p-xylene for 5h with selenium dioxide. This leaves **1** unchanged but converts **9** into the ketone **10**[12] . Final medium-pressure chromatography on silica gel with hexane/ether (95/5) as eluent gives pure **1**.



9 **10**

In addition to the synthesis described above, we have examined an entirely different approach towards **1** and wish to report briefly on that finding. Several laboratories[2a,17] had shown that phenanthrene can be readily expanded into 5H-dibenzo[a,c]cycloheptene **11**. The three step process consists of the addition of a dihalocarbene to phenanthrene with subsequent cyclopropyl-allyl rearrangement and reduction. Reported yields for **11** range from 45-60%. We found that the dibromocarbene adduct of **11** undergoes selective reduction with $LiAlH_4$ (Et_2O/0°C/48h) to give the *endo*-bromocyclopropane derivative **12**[12,18] in 47% yield. It is accompanied by the corresponding fully reduced cyclopropane derivative (14%). Heating of **12** in dry pyridine in a sealed Pyrex tube (185°C, 15h) results in the formation of **1** in 70% yield based on **12**. Note that a pyridinium salt resulting from a substitution path is obtained if this reaction is run at too low temperature (<175°C). This carbene route towards **1** is clearly a viable alternative to the other approaches.



11 **12** **1**

a) $CHBr_3$/t-BuOK/t-BuOH/pentane/-10°C/5h.
b) $LiAlH_4$/Et_2O/0°C/48h. c) Pyridine/185°C/14h.

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References and notes

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12. All new compounds gave correct elemental analyses and mass, IR, ^{1}H-NMR, and ^{13}C-NMR spectra consistent with the structures indicated.

13. Compd **7**: colourless oil, ^{1}H-NMR(200MHz,$CDCl_3$):1.97-2.30(m,4H);5,20-5.26(m,2H);7.11-7.81(m,8H).

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15. Compd **8-a**: colourless crystals. m.p.97-98°C.^{1}H-NMR(400MHz,$CDCl_3$): 3.61(s,4H); 5.97(s,2H); 7.0-7.5(m,18H).

16. A slurry of Raney nickel (*ca.* 1g; Fluka 83440) was prewashed 3x with acetone to remove water. The slurry with 30 ml acetone was deactivated by boiling under reflux for 2h. **8-a** (269mg, 0.6 mmole) in 15 ml acetone was added to the cold mixture and brought to reflux for 16h. The mixture was filtered over Celite and the solvent withdrawn under vacuum. The remaining mixture **1/9** was separated on TAC as indicated in the text.

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18. Compd. **12**: colourless crystals, m.p. 144-146°C. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.88(dddd, J=10.8, 9.6, 7.3, 6.0, 1H); 2.21(dd, J=9.6, 7.8, 1H); 2.72(dd, J=13.5, 10.8, 1H); 2.84(dd, J=13.5, 6.0, 1H); 3.39(dd, J=7.8, 7.3, 1H); 7.2-7.6(m, $8H_{arom.}$).

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