CHEMCOMM Communication
www.rsc.org/chemcomm

First asymmetric synthesis of dihydrobenzo[*c*]phenanthrene-1,4-quinones with helical chirality†

M. Carmen Carreño,* Susana García-Cerrada, M. Jesús Sanz-Cuesta and Antonio Urbano*

Departamento de Química Orgánica (C-I), Universidad Autónoma, Cantoblanco, 28049-Madrid, Spain. E-mail: carmen.carrenno@uam.es; antonio.urbano@uam.es; Fax: +34 91397 3966; Tel: +34 91397 3924

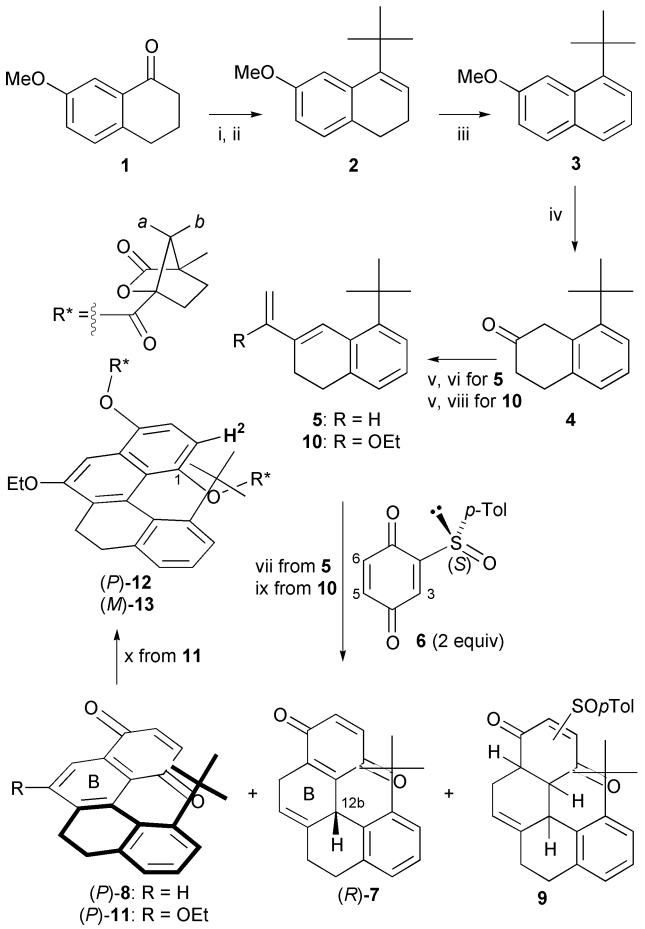
Received (in Cambridge, UK) 18th April 2001, Accepted 26th June 2001
First published as an Advance Article on the web 19th July 2001

The first enantioselective synthesis of 12-*tert*-butyl substituted 7,8-dihydrobenzo[*c*]phenanthrene-1,4-quinones having helical chirality is achieved with good chemical and optical yields through a domino Diels–Alder reaction–sulfoxide elimination–oxidation process starting from enantiopure (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone and 5-*tert*-butyl substituted 3-vinyl-1,2-dihydronaphthalenes as dienes.

Compounds with the benzo[*c*]phenanthrene framework, [4]-helicenes, posess helical chirality due to the distortion of the planarity caused by overcrowding of the substituents at 1 and 12 positions of the terminal rings.[1] When such substituents are large enough, these molecules can be resolved into their corresponding enantiomers. The first configurationally stable 1,12-dimethyl substituted [4]-helicene was prepared and resolved by Newman[2] in 1956. Since then, only a few derivatives have been resolved into their optical isomers either by chemical[3–6] or chromatographic[4,7] methods. Some of them have shown interesting properties in chiral catalysis,[5] chiral recognition in complexation with cyclodextrins,[8] chiral Langmuir Blodgett film formation,[9] charge-transfer complexation,[10] chiral macrocyclic anhydride and amide formation,[11] and as a part of the first rationally designed chemically powered molecular motor.[12] Moreover, a recent report has shown that a high non-planarity of helical benzo[*c*]phenanthrenes induced by a methyl group at C-12 lowers their DNA-damaging effects compared with the unsubstituted derivative.[13] Although the interest in synthesizing these helicenes in optically active form is evident, to the best of our knowledge, only a single asymmetric approach has been described so far for the enantioselective construction of a lactone-type chiral tetrahelicene.[14]

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[15] we have recently described the first asymmetric approach to [5]-helicenediquinones[16] based on the domino cycloaddition–sulfoxide elimination–oxidation process between enantiopure (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone and vinyl phenanthrenes. Nevertheless, due to the poor reactivity of these aromatic derivatives as dienes, Diels–Alder reactions took place only in reflux of solvents with high boiling points or under high pressure conditions, with low chemical and optical yields. Taking into account the low racemization barriers of [4]-helicenes (< 16 kJ mol^{-1} for tetrahelicene),[17] such an asymmetric approach would not be applicable unless milder conditions conducive to the formation of the tetracyclic skeleton could be found. Thus, we thought of using more reactive non-aromatic dienes such as vinyldihydronaphthalenes which would probably allow the cycloaddition step to proceed under milder conditions, thus avoiding the racemization processes. We also reasoned that the introduction of a bulky substituent such as the *tert*-butyl group at C-1 or C-12 positions of the [4]-helicene could notably increase the racemization barrier as well as induce a higher non-planarity of these helical molecules. In this communication, we report the first enantioselective approach to configurationally stable helically chiral 12-*tert*-butyl substituted 7,8-dihydrobenzo[*c*]-phenanthrene-1,4-quinones based on this strategy.

As outlined in Scheme 1, the synthesis of vinyldihydronaphthalene **5** started with the addition of *tert*-butyl magnesium chloride to commercially available 7-methoxy-1-tetralone (**1**),‡ followed by dehydration of the resulting tertiary carbinol with 10% H_2SO_4 (48% yield for the two steps). The dihydronaphthalene **2** obtained was fully aromatized to naphthalene **3** with DDQ in 99% yield. Birch reduction of **3** with Na in refluxing EtOH followed by acid hydrolysis of the resulting



Scheme 1 *Reagents and conditions*: i, *t*-BuMgCl 2 M, Et_2O, rt, 48 h, 56%; ii, 10% H_2SO_4, benzene, reflux, 1 h, 85%; iii, DDQ, CH_2Cl_2, rt, 10 min, 99%; iv, Na, EtOH, reflux, 5–8 h, 35% HCl, 99%; v, Tf_2NPh, KHMDS, THF, −78 °C, 2 h, 91%; vi, CH_2=$CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux, 2 h, 44%; vii, CH_2Cl_2, rt, 7 d, 54%; viii, CH_2=$C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux, 2 h, 50%; ix, CH_2Cl_2, −20 °C, 3 d, 57% for **11**; x, Zn, (−)-camphanoyl chloride, DMAP, Et_3N, CH_2Cl_2, reflux, 1 h, 42% for (*P*)-**12** and 40% for (*M*)-**13** from (±)-**11**, 78% for (*P*)-**12** from (+)-(*P*)-**11**.

† Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/cc/b1/b103447m/

 DOI: 10.1039/b1003447m

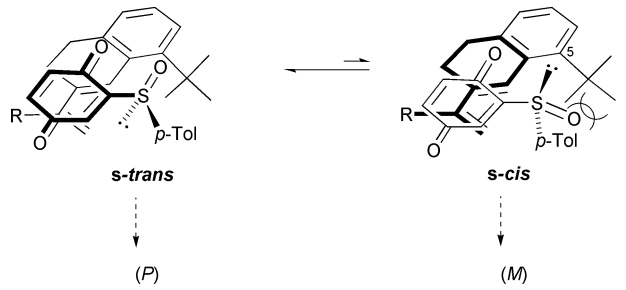


Fig. 1 *Endo* approaches of vinyldihydronaphthalenes on the s-*trans* and s-*cis* conformations of (*S*)-**6**.

vinyl ether gave 8-*tert*-butyl-2-tetralone (**4**) in 99% yield. Transformation of **4** into the corresponding enol triflate and Stille coupling with tributylvinylstannane afforded 5-*tert*-butyl-3-vinyl-1,2-dihydronaphthalene (**5**) in 40% yield for the two last steps.

The cycloaddition between diene **5** and enantiopure (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**6**)[18] at room temperature afforded a 25:15:60 mixture of **7**, **8** and **9** which could be separated by flash chromatography (54% overall yield). Compound **7** was formed by *endo*-cycloaddition of **5** to the sulfinyl substituted C-2=C-3 double bond of **6** followed by elimination of the sulfoxide. This derivative, having a stereogenic center at C-12b, showed a 72% ee§ {$[\alpha]_D^{20} = -240$ (*c* 0.024, $CHCl_3$)}. Compound **8**, resulting from full aromatization of the B ring of **7**, was isolated in optically active form {$[\alpha]_D^{20} = +371$ (*c* 0.017, $CHCl_3$)} with a 72% ee,§ confirming the expected helical chirality for this type of quinone. Although the dienophile **6** was used in excess (2 equiv.) to achieve the aromatization of the B ring of **7**, only a small amount of the desired derivative **8** was formed under these conditions. The major component of the crude reaction mixture was characterized as a mixture of regio- and diastereoisomers **9**, resulting from the cycloaddition of diene **5** to the unsubstituted C-5=C-6 double bond of **6**.¶

In accordance with our previous findings,[19] the increasing electron donating effects of diene substituents favored cycloadditions through the more polarized sulfinyl substituted C-2=C-3 double bond of **6**. We thus thought of using a more reactive diene such as **10**, bearing an oxygenated substituent at the vinylic moiety, with the aim of increasing the yield of the desired [4]-helicenequinone. Compound **10** was prepared in a similar way as derivative **5**, by using 1-ethoxyvinyltributylstannane for the Stille coupling step (46% yield for two steps from **4**, Scheme 1). Cycloaddition between **10** and **6** could be conducted at –20 °C, affording in 57% yield helically chiral derivative **11** showing an optical rotation value of $[\alpha]_D^{20} = +1077$ (*c* 0.019, $CHCl_3$) and 88% ee.§ Compound **11** resulted from the exclusive attack of **10** on the sulfinyl substituted C-2=C-3 double bond of **6**, elimination of the sulfoxide and full aromatization of the B ring. This result evidenced that the use of the electron rich diene **10** not only completely reversed the chemoselectivity of the process, but also facilitated the aromatization of the B ring of the non-isolated intermediate, the 6-EtO derivative of (*R*)-**7**. Moreover, the lower temperature used in the cycloaddition step improved the diastereoselectivity of the whole process.[20]

The (*R*) absolute configuration at C-12b, the only stereogenic center of **7**, as well as the (*P*) absolute configuration of helical quinones **8** and **11** were initially established considering the preferred formation of a Diels–Alder adduct resulting from the *endo*-approach of **5** and **10** to the lower face of (*S*)-**6** adopting the s-*trans* conformation (Fig. 1). This should be the most favoured situation from the steric point of view since, when the dienophile reacts through the most stable s-*cis* rotamer, the approach of the diene from the less encumbered upper face gives rise to a transition state where a severe unfavourable interaction between the bulky *tert*-butyl group at C-5 of dienes and the sulfinylic oxygen of (*S*)-**6** appears. This configurational assignment was confirmed for **11** by applying, for the first time for a [4]-helicene, the methodology described by Katz[21] based on the different O=C–C–O conformations of (*M*)- and (*P*)-helicenyl camphanates‖ which bring about a different polarity and NMR behaviour of each diastereoisomer. Thus, we prepared di-(−)-camphanates (*P*)-**12** and (*M*)-**13** from racemic **11** and diastereoisomer (*P*)-**12** from enantiomerically enriched (+)-**11** (Scheme 1). The lower R_f (0.34) shown by diastereoisomer (*P*)-**12** on silica gel (eluent EtOAc–hexane 1:2) with respect to that of (*M*)-**13** (R_f = 0.42), as well as the existence of differentiated NOESY enhancements between H-2 and the methyl groups *a* and *b* of the inside camphanates (OR* at C-1, Scheme 1) in (*M*) and (*P*) isomers are consistent with the data reported[21] for determining the absolute configuration of these derivatives.

In summary, we have synthesized for the first time helically chiral 12-*tert*-butyl-substituted tetrahelicenequinones under very mild conditions from enantiopure (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone and vinyldihydronaphthalenes. The presence of the bulky *tert*-butyl group at C-12 makes the system stable enough to be isolated in optically active form.

We thank DGICYT (PB98-0062) for financial support and Comunidad Autónoma de Madrid for a fellowship to S. G.-C.

Notes and references

‡ The IUPAC name for 1-tetralone is 3,4-dihydronaphthalene-1-(2*H*)-one.

§ The ee were determined by HPLC using chiral columns *Daicel Chiralpack* AS for **7** and **8**, and *Daicel Chiralcel* OD for **11**. The racemic derivatives necessary for such evaluation were prepared from racemic **6**.

¶ The major isomer of this mixture could be isolated pure by crystallysation, but its exact structure has not been elucidated.

‖ The IUPAC name for camphanic acid is 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid.

1 M. S. Newman and W. B. Wheatley, *J. Am. Chem. Soc.*, 1948, **70**, 1913.
2 M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, 1956, **78**, 450.
3 M. S. Newman, R. G. Mentzer and G. Slomp, *J. Am. Chem. Soc.*, 1963, **85**, 4018.
4 J. Cheung, L. D. Field, T. W. Hambley and S. Sternhell, *J. Org. Chem.*, 1997, **62**, 62.
5 H. Okubo, M. Yamaguchi and Ch. Kabuto, *J. Org. Chem.*, 1998, **63**, 9500.
6 G. Bringmann, M. Heubes, M. Breuning, L. Göbel, M. Ochse, B. Schöner and O. Schupp, *J. Org. Chem.*, 2000, **65**, 722.
7 H. Scherübl, U. Fritzsche and A. Mannschreck, *Chem. Ber.*, 1984, **117**, 336.
8 K. Kano, H. Kamo, S. Negi, T. Kitae, R. Takaoka, M. Yamaguchi, H. Okubo and M. Hirama, *J. Chem. Soc., Perkin Trans. 2*, 1999, 15.
9 F. Feng, T. Miyashita, H. Okubo and M. Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 10166; H. Okubo, F. Feng, D. Nakano, T. Hirata, M. Yamaguchi and T. Miyashita, *Tetrahedron*, 1999, **55**, 14855.
10 H. Okubo, D. Nakano, S. Anzai and M. Yamaguchi, *J. Org. Chem.*, 2001, **66**, 557.
11 H. Okubo and M. Yamaguchi, *Heterocycles*, 2000, **52**, 863; H. Okubo and M. Yamaguchi, *J. Org. Chem.*, 2001, **66**, 824.
12 T. R. Kelly, R. A. Silva, H. De Silva, S. Jasmin and Y. Zhao, *J. Am. Chem. Soc.*, 2000, **122**, 6935.
13 M. K. Lakshman, P. L. Kole, S. Chaturvedi, J. H. Saugier, H. J. C. Yeh, J. P. Glusker, H. L. Karrell, A. K. Katz, C. E. Afshar, W. M. Dashwood, G. Kenniston and W. M. Baird, *J. Am. Chem. Soc.*, 2000, **122**, 12629.
14 G. Bringmann, J. Hinrichs, J. Kraus, A. Wuzik and T. Schulz, *J. Org. Chem.*, 2000, **65**, 2517.
15 Overview: M. C. Carreño, *Chem. Rev.*, 1995, **95**, 1717. Recent references: M. C. Carreño, A. Urbano and J. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1621; M. C. Carreño, A. Urbano and C. Di Vitta, *J. Org. Chem.*, 1998, **63**, 8320; M. C. Carreño, A. Urbano and C. Di Vitta, *Chem. Commun.*, 1999, 817; M. C. Carreño, A. Urbano and C. Di Vitta, *Chem. Eur. J.*, 2000, **6**, 906.
16 M. C. Carreño, R. Hernández-Sánchez, J. Mahugo and A. Urbano, *J. Org. Chem.*, 1999, **64**, 1387.
17 S. Grimme and S. D. Peyerimhoff, *Chem. Phys.*, 1996, **204**, 411.
18 M. C. Carreño, J. L. García Ruano and A. Urbano, *Synthesis*, 1992, 651.
19 M. C. Carreño and A. Urbano, unpublished results.
20 M. C. Carreño, J. L. García Ruano, M. A. Toledo, A. Urbano, C. Z. Remor, V. Stefani and J. Fischer, *J. Org. Chem.*, 1996, **61**, 503.
21 T. Thongpanchang, K. Paruch, T. J. Katz, A. L. Rheingold, K. Lam and L. Liable-Sands, *J. Org. Chem.*, 2000, **65**, 1850.