En route to the first stereoselective synthesis of axially chiral biscarbazole alkaloids†

Gerhard Bringmann,* Stefan Tasler, Heike Endress and Jörg Mühlbacher

Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany. E-mail: bringman@chemie.uni-wuerzburg.de; Fax: +49 931 888 4755; Tel: +49 931 888 5323

Received (in Cambridge, UK) 7th February 2001, Accepted 16th March 2001
First published as an Advance Article on the web 3rd April 2001

The first stereoselective synthesis of an axially chiral biscarbazole has been achieved, by application of the 'lactone concept'.

Axially chiral biaryl natural products are of increasing importance, but the phenomenon of atropisomerism is often neglected—even nowadays.[1] A typical example is, *e.g.* the class of biscarbazoles,[1,2] which consists of eleven *C,C*- and three *N,C*-coupled alkaloids. All of the *C,C*-bonded representatives should have a configurationally stable biaryl axis, which was, however, not recognized during structural elucidation. The first biscarbazole for which axial chirality was demonstrated, was bismurrayaquinone-A (**1**, Fig. 1):[3] after racemate resolution of synthetic **1**, the absolute configuration at the axis was attributed by quantum chemical circular dichroism (CD) calculations. Racemate resolutions succeeded also for murrastifoline-F[4] and for clausenamine-A (**2**, $R^1 = R^3 = OMe$, $R^2 = H$).[5]

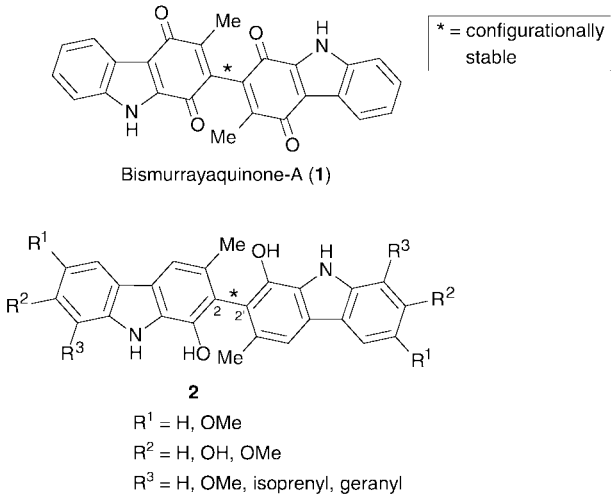


Fig. 1 Bismurrayaquinone-A (**1**) and the general structure of other 2,2′-coupled biscarbazole alkaloids.

No *stereoselective* approaches to biarylic biscarbazoles have so far been described. As a most rewarding synthetic target for a first atropo-enantioselective access we chose the 2,2′-coupled biscarbazole core **2** ($R^1 = R^2 = R^3 = H$, Fig. 1), since it constitutes the basic framework of five naturally occurring alkaloids, bismurrayaquinone-A (**1**), bismurrayafolines-B, -C, and -D, and clausenamine-A (all represented by the general structure **2**). Such a synthesis would also permit investigations on the (possibly divergent) bio-activities of the atropo-enantiomers of the respective natural products.[6] In this paper, we present the first stereoselective preparation of an axially chiral 2,2′-biscarbazole core related to **2**.

† Novel Concepts in Directed Biaryl Synthesis, part 95; for part 94, see G. Bringmann, A. Wuzik, J. Kümmel and W. A. Schenk, *Organometallics*, 2001, in press.

For the atropo-selective construction of the biaryl axis, we chose the 'lactone concept',[7] with biaryl lactone **9** (Scheme 1) as the crucial intermediate. Since it is configurationally unstable at the axis due to the ester bridge, it should permit an atroposelective ring cleavage with chiral nucleophiles in a dynamic kinetic resolution, giving rise to—then configurationally stable—atropisomers. The synthesis of lactone **9** required the preparation of the bromoacid **5** and the phenolic component **7**.

Exploratory work rapidly showed the necessity of protecting the base-sensitive and electron-pushing endocylic nitrogen, to avoid side reactions on the NH function or, due to its electronic impact, on the isocyclic ring. Such a protective group should, in the first instance, be robust to survive the scheduled reaction conditions, thus avoiding the need to establish different protective groups for each single step. For this purpose, the stable (and small) methyl group was chosen at this point, even though it bears the inherent problem of being cleavable only enzymically[8] or under extreme conditions,[9] which were not expected to be tolerated by the dimeric target structures of type **2**. For a first exploration of the synthetic concept, this disadvantage seemed acceptable.

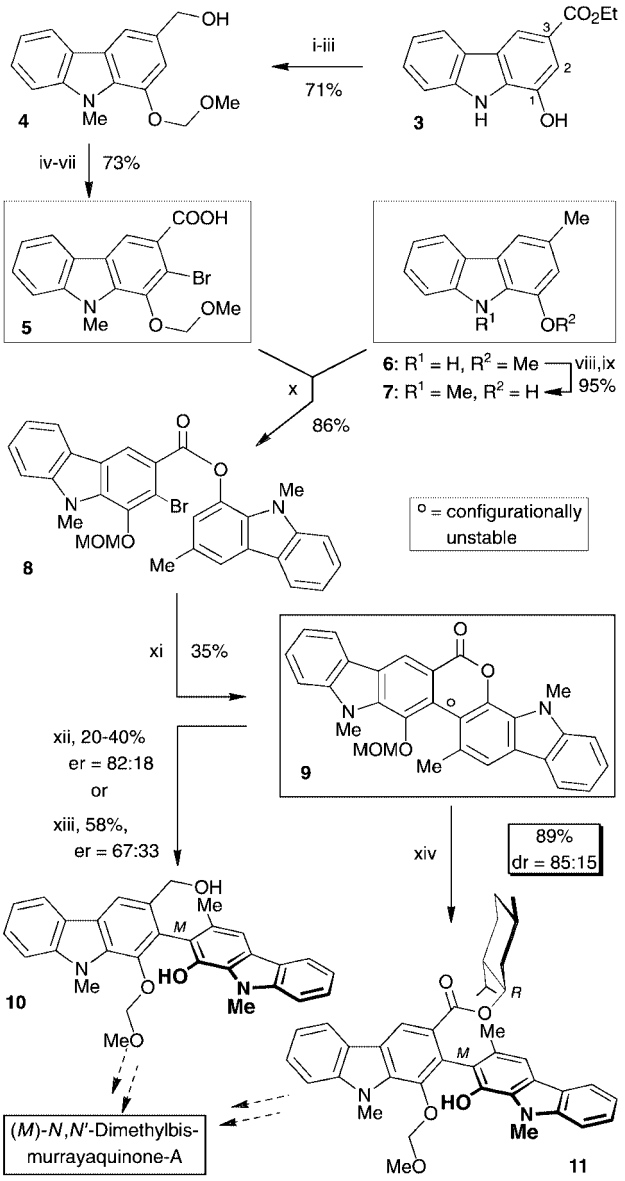
The synthesis of the bromoacid **5** started from the phenolic carbazole ester **3**[10] (Scheme 1). Regioselective bromination at the 2-position was achieved by the DoM (= Directed *ortho*-Metalation)[11] strategy. The MOM (= methoxymethyl) function was introduced using MOMCl,[12] followed by *N*-methylation with dimethyl sulfate. $LiAlH_4$ reduction gave **4** as a DoM-suited substrate, which afforded 2-bromination in an excellent yield and with complete regioselectivity upon treatment with *n*BuLi and $(CBrCl_2)_2$. Conversion of this bromoalcohol into the corresponding acid **5** succeeded by Swern and $NaClO_2$ oxidation, giving the first coupling portion in as much as 52% overall yield from carbazole **3**.

The phenolic 'half' **7** was synthesized from murrayafoline-A (**6**),[10] by *N*-methylation with dimethyl sulfate and BBr_3-mediated *O*-demethylation. The crude 1-hydroxycarbazole **7** thus obtained was taken directly for esterification with bromoacid **5** with DCC and DMAP, giving ester **8** in 86% yield.

The intramolecular biaryl coupling of **8** was the most tricky and yield-limiting step of the synthesis. Among different reagents and conditions tested, the best result was obtained using 1.5 equiv. $Pd(OAc)_2$ and 3.0 equiv. PPh_3 for 1.5 h at 120 °C. The biscarbazole lactone **9** was isolated in 35% yield, along with 20–30% of the corresponding hydrodebromination product. This—compared to other lactone syntheses[7]—moderate coupling yield, which is in agreement with that for similar coupling substrates with an *ortho*-'OCH' unit next to the palladation site,[13] is disappointing at first sight; still, it opens up the first stereoselective access to an axially chiral biscarbazole core.

For the atroposelective ring cleavage of the configurationally unstable lactone **9**, a CBS reduction was attempted first, since it had given excellent chemical and optical yields in similar conversions.[7] In this case, however, apparently due to the significantly decreased reactivity of the ester group by the

DOI: 10.1039/b101241j



Scheme 1 *Reagents and conditions*: i, MOMCl, K_2CO_3, acetone, rt, 3 h, 79%; ii, Me_2SO_4, K_2CO_3, acetone, reflux, 15 h, 92%; iii, $LiAlH_4$, Et_2O, 0 °C, 3 h, 97%; iv, *n*BuLi, benzene, rt, 1 h; v, $(CBrCl_2)_2$, Et_2O, rt, 3.5 h, 90% (two steps); vi, DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, rt, 3.5 h, 83%; vii, $NaClO_2$, H_2NSO_3H, HOAc, H_2O, dioxane, rt, 24 h, 98%; viii, Me_2SO_4, 5 M KOH, CH_2Cl_2, $PhCH_2(nBu)_3NCl$, rt, ultrasound, 2 h, 97%; ix, BBr_3, CH_2Cl_2, rt, 5 h, 98%; x, DCC, DMAP, CH_2Cl_2, rt, 5 h; xi, $Pd(OAc)_2$, PPh_3, DMA, 120 °C, 1.5 h; xii, (*R*)-2-methyl-CBS-oxazaborolidine (Aldrich), BH_3·THF, THF, 0 °C to rt, 24 h; xiii, (*M*)-BINAL-H, THF, −20 °C, 16 h; xiv, lithiated (1*R*)-mentholate, toluene, 0 °C, 7 h. MOMCl: chloromethyl methyl ether.

electron-donating carbazole nitrogen, the reduction took place in only up to 40% yield, leading to the (*M*)-enantiomer of diol **10** with a maximum er of 82 : 18. Slightly better chemical yields were attained with (*M*)-BINAL-H (58%), but with an er of only 67 : 33, again in favor of (*M*)-**10**. The best results with respect to chemical yields and 'asymmetric inductions' were achieved with lithium (1*R*)-mentholate as a chiral *O*-nucleophile,[7] giving **11** in 89% yield and a dr of 85 : 15.

The attribution of the newly created axial configurations of the ring cleavage products was achieved by a combination of CD spectroscopy and quantum chemical CD calculations.[14,15] The CD spectrum for the main enantiomer of diol **10** was measured on line by LC-CD analysis on a chiral phase (Chiralcel OD-H) and matched very well the CD spectrum quantum chemically calculated for the (*M*)-enantiomer—here based on a molecular dynamics (MD) simulation[15]—clearly showing it to be (*M*)-configured, in agreement with the stereochemical outcome of many other cleavage reactions on similar lactone substrates.[7]

The purification of the main atropo-diastereomeric product **11** of the mentholate ring opening, by preparative HPLC on a chiral phase (Chiralcel OD), gave the first atropisomerically pure biscarbazole stereoselectively synthesized. The phenolic part of this pure main isomer proved to be highly sensitive to autoxidation during removal of the HPLC solvent in the presence of air oxygen to yield the corresponding quinone. The CD spectrum of its $LiAlH_4$ reduction product showed strong similarities with that of (*M*)-**10**, revealing the main atropisomer of **11** to be likewise (*M*)-configured, as was to be expected in analogy to numerous related lactone cleavage reactions.[7]

Since first attempts to adopt this reaction sequence for the atroposelective biscarbazole synthesis to substrates with an *N*-benzyl group as an eventually removable protective group for the carbazole nitrogen gave promising results, the final steps for the synthesis of an—unnatural—*N*,*N*′-dimethyl analog of bismurrayaquinone-A were not performed for the *N*-methyl protected model biscarbazole **11**.

The presented pathway provides the first stereoselective synthetic access to atropisomerically pure axially chiral biscarbazoles and defines the strategy for the now scheduled synthesis of the corresponding genuine alkaloids. The electronically exceptional conditions within the carbazole core as compared to those of the other biaryl systems previously prepared, made the realization of the lactone concept much harder than expected. That these problems could be overcome, succeeding in the preparation of an enantiomerically pure biscarbazole, demonstrates the value of the applied method.

This work was funded by the Deutsche Forschungsgemeinschaft (SFB 347) and by the Fonds der Chemischen Industrie. The authors thank K. Messer for skillful help on LC-CD analyses and Dr A. Wuzik for inspiring discussions.

Notes and references

1 G. Bringmann, C. Günther, M. Ochse, O. Schupp and S. Tasler, in *Prog. Chem. Org. Nat. Prod.*, ed. W. Herz, H. Falk, G. W. Kirby, R. E. Moore and C. Tamm, Springer, Wien, 2001, vol. 82, in press.
2 H. Furukawa, *Trends Heterocycl. Chem.*, 1993, **3**, 185; C. Ito, Y. Thoyama, M. Omura, I. Kajiura and H. Furukawa, *Chem. Pharm. Bull.*, 1993, **41**, 2096.
3 G. Bringmann, A. Ledermann, M. Stahl and K.-P. Gulden, *Tetrahedron*, 1995, **51**, 9353.
4 G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth and W. Lobin, *J. Am. Chem. Soc.*, 2001, **123**, 2703.
5 G. Lin and A. Zhang, *Tetrahedron*, 2000, **56**, 7163.
6 For biological activities of biscarbazole alkaloids, see: G. Bringmann, A. Ledermann, J. Holenz, M.-T. Kao, U. Busse, H. G. Wu and G. François, *Planta Med.*, 1998, **64**, 54; M. Itoigawa, Y. Kashiwada, C. Ito, H. Furukawa, Y. Tachibana, K. F. Bastow and K.-H. Lee, *J. Nat. Prod.*, 2000, **63**, 893; and ref. 5
7 G. Bringmann, M. Breuning and S. Tasler, *Synthesis*, 1999, 525.
8 N. Miyata, H. Kiuchi and M. Hirobe, *Chem. Pharm. Bull.*, 1981, **29**, 1489; W. Yang, T. Jiang, D. Acosta and P. J. Davis, *Xenobiotica*, 1993, **23**, 973.
9 N. V. Moskalev and E. E. Sirotkina, *Chem. Heterocycl. Comp.*, 1987, **23**, 275; N. P. Buu-Hoi and G. Saint-Ruf, *J. Chem. Soc. (C)*, 1966, 924; J. I. G. Cadogan, H. S. Hutchison and H. McNab, *Tetrahedron*, 1992, **48**, 7747.
10 G. Bringmann, S. Tasler, H. Endress, K. Peters and E.-M. Peters, *Synthesis*, 1998, 1501.
11 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
12 For a preparation of MOMCl avoiding carcinogenic impurities, see: J. S. Amato, S. Karady, M. Sletzinger and L. M. Weinstock, *Synthesis*, 1979, 970.
13 G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698; G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft and J. D. Connolly, *J. Am. Chem. Soc.*, 2000, **122**, 9127; A. V. R. Rao, T. K. Chakraborty and S. P. Joshi, *Tetrahedron Lett.*, 1992, **33**, 4045.
14 G. Bringmann and S. Busemann, in *Natural Product Analysis*, ed. P. Schreier, M. Herderich, H. U. Humpf and W. Schwab, Vieweg, Wiesbaden, 1998, pp. 195–212.
15 G. Bringmann, C. Günther, J. Mühlbacher, M. D. L. P. Gunathilake and A. Wickramasinghe, *Phytochemistry*, 2000, **53**, 409.