VOLUME 123, NUMBER 12
MARCH 28, 2001

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Murrastifoline-F: First Total Synthesis, Atropo-Enantiomer Resolution, and Stereoanalysis of an Axially Chiral *N*,*C*-Coupled Biaryl Alkaloid†

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Received September 25, 2000

Abstract: The first total synthesis of the *Murraya* alkaloid murrastifoline-F (**3**), an unsymmetric, *N*,*C*-bonded heterobiarylic biscarbazole, is described. Starting from the likewise naturally occurring—but here synthetically prepared—"monomer" murrayafoline-A (**6**), lead tetraacetate-mediated oxidative non-phenolic biaryl coupling gives **3** as the main regioisomer. The existence of this natural product as a pair of stable atropo-enantiomers was demonstrated analytically through LC−CD investigations. Preparatively, the racemate resolution succeeded by *O*-demethylation, derivatization with Mosher's reagent, and chromatographic separation of the resulting diastereomers. The absolute configurations of the atropisomers were assigned by CD spectroscopy in combination with quantum chemical CD calculations at the stage of the alkaloid **3** and by ROESY experiments of the diastereomeric Mosher derivatives. In the root extract of the curry leaf plant *Murraya koenigii* (Rutaceae), murrastifoline-F (**3**) was found to exist as a 56:44 mixture in favor of the *M*-enantiomer, by LC−CD coupling.

Introduction

In the early 1990s, the number of isolated biscarbazoles containing a biaryl axis increased rapidly, as a result of intensive research especially by Furukawa's and Wu's groups.[1−5] Except for one representative,[5] all of these compounds have their origin in the two plant species *Murraya euchrestifolia* and *M. koenigii*, both belonging to the Rutaceae family. A special position among these biaryl alkaloids is held by murrastifolines-A (**1**), -B (**2**), and -F (**3**), which represent—otherwise very rare (see below)—natural *N*,*C*-bonded biaryls (Figure 1).[3,4]

From their substitution patterns, murrastifolines-A (**1**) and -B (**2**) should undergo rapid rotation at the biaryl axis, whereas murrastifoline-F (**3**) with its four *ortho*-substituents next to the

† Part 91 of the series "Novel Concepts in Directed Biaryl Synthesis". For part 90 see Bringmann, G.; Hinrichs, H.; Henschel, P.; Peters, K.; Peters, E.-M. *Synlett* **2000**, *12*, 1822−1824.

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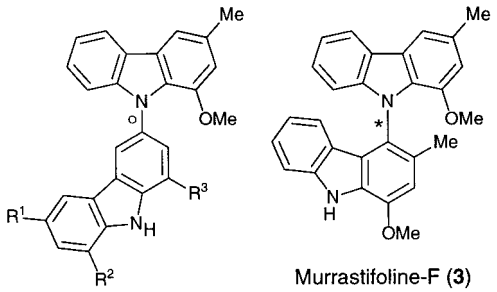
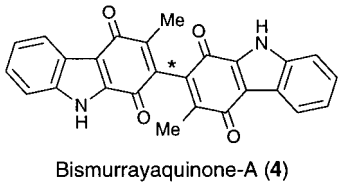
10.1021/ja003488c CCC: $20.00
Published on Web 03/01/2001



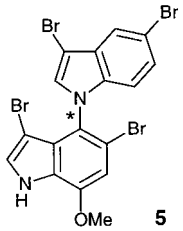
Murrastifoline-	R^1	R^2	R^3
A (**1**)	Me	OMe	H
B (**2**)	H	H	OMe

° = presumably configurationally unstable
* = configurationally stable

Figure 1. Naturally occurring *N,C*-bonded biscarbazoles.



Bismurrayaquinone-A (**4**)



5

Figure 2. Further heterocyclic biaryl alkaloids.

axis is expected to be configurationally stable and should exist as separable atropo-enantiomers. However, no attention was paid to this phenomenon during isolation and structural elucidation and not even an α_D has been reported for this compound, which is likewise true for all biaryl biscarbazoles up to the present day.[1,6] It was only in 1995 that a stereoanalysis appeared, based on the first (nonstereoselective) synthesis and atropo-enantiomer resolution of a *C,C*-bonded dimeric[7] carbazole, bismurrayaquinone-A (**4**, Figure 2).[8] Up to now only a few synthetic pathways to biscarbazole alkaloids[8−11] or to their as yet unnatural (in part antiplasmodial)[12] non-quinoid precursors have been elaborated,[10,13] all leading to racemic material.

Even for non-natural *N,C*-coupled heterobiaryls, stereochemical investigations on the atropisomerism have been described only rarely, for example, for *N*-aryl pyrroles,[14] phenanthridinones,[15] pyridones,[16] and *N,N*-di(1-naphthyl)-indolo[3,2-*b*]-carbazole.[17] For the bisindole alkaloid **5** from the blue-green alga *Rivularia firma* (Cyanophycophyta, Rivulariaceae), optical activity ($\alpha_D = -6°$) was reported, which was attributed to axial chirality, but the absolute configuration was not determined.[18]

In this paper, we present the first total synthesis of an unsymmetric, *N,C*-coupled biscarbazole, murrastifoline-F (**3**), the resolution and stereochemical assignment of its atropisomers, and the determination of the enantiomeric ratio present in an authentic root extract of *Murraya koenigii*.

Results and Discussion

The monomeric "half" of murrastifoline-F (**3**)—and thus its synthetic precursor − is murrayafoline-A (**6**), which, itself, was prepared in an overall 37% yield according to a procedure published earlier,[19] starting from indole-3-carbaldehyde. The 1-hydroxy analogue of **6** is known to form a symmetric 2,2′-dimer, a precursor to bismurrayaquinone-A (**4**), by biomimetic phenolic oxidative coupling with di-*tert*-butyl peroxide (DTBP).[8,13,10] From a non-phenolic oxidative coupling directly of murrayafoline-A (**6**) to give the corresponding *O*-protected biscarbazoles, even better coupling results were expected, since it would avoid any workup problems that may arise with phenolic biscarbazole products.

In the literature several reagents are known for non-phenolic oxidative coupling reactions.[20−22] Of these, lead tetraacetate [$Pb(OAc)_4$],[23] vanadium oxytrifluoride (VOF_3),[21,22,24] and the hypervalent iodine reagent BTIB [bis(trifluoroacetoxy)iodobenzene, $PhI(CF_3CO_2)_2$][25] seemed promising for our purpose. The only agent to yield a dimerization product of murrayafoline-A (**6**), however, was $Pb(OAc)_4$, while in both other cases entire decomposition took place, so that not even the starting

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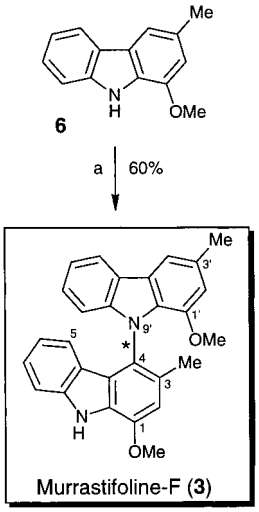
Scheme 1. $Pb(OAc)_4$ Coupling of **6**[a]



[a] Conditions: (a) $Pb(OAc)_4$, BF_3 etherate, CH_3CN, room temperature, 3.5 h.

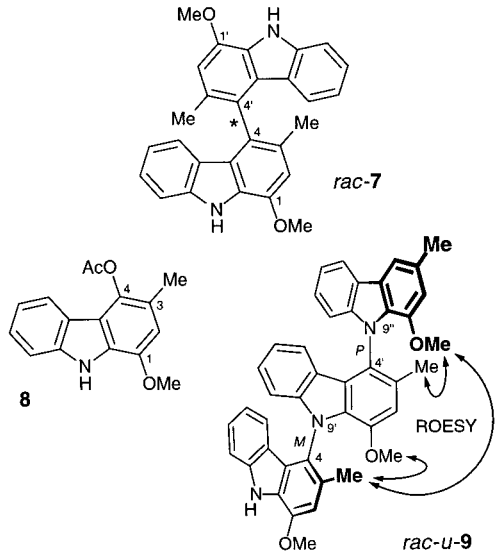


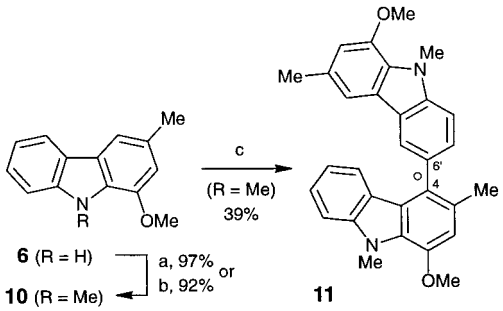
Figure 3. Mono-, di-, and trimeric side products of the coupling reaction.

material could be recovered. In contrast to the mentioned phenolic coupling with DTBP, which yielded exclusively the *C*,*C*-bonded biaryl,[8,13,10] an *N*,*C*-coupled, and thus unsymmetric, dimer was formed in good 60% yield as the main regioisomer (Scheme 1). It turned out to be the heterobiaryl murrastifoline-F (**3**), by comparison of the spectroscopic data with those reported for natural murrastifoline-F in the literature.[4] This structural assignment was verified by HMQC, HMBC, and ROESY experiments.

Likewise identified were traces of the 4,4′-dimer[26] **7** (Figure 3) and starting material. The symmetric structure of **7** was concluded from the presence of only one set of signals in the ^{1}H NMR spectrum. A 2,2′-coupling was excluded by the nonequivalence of its spectral data with literature[13] data of 2,2′-bis(1-methoxy-3-methyl-9*H*-carbazole) and from further NMR data, for example the normal, not high-field shifted resonance (δ = 4.13 ppm) of the methoxy signals at C-1 and C-1′.

(26) For the synthesis of unnatural 4,4′-coupled biscarbazoles by oxidative coupling, see: Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2463−2471; Mind that the numbering system in dimeric carbazoles is identical to that of the "monomers", independent of the coupling site.

Scheme 2. Increased *C*,*C*-coupling Using an *N*-Protected Carbazole[a]



[a] Conditions: (a) dimethyl sulfate, 5 N KOH, CH_2Cl_2, $Bn(nBu)_3NCl$, room temperature, ultrasound, 2 h. (b) Dimethyl sulfate, Cs_2CO_3, acetone, reflux, 15 h. (c) $Pb(OAc)_4$, BF_3 etherate, CH_3CN, room temperature, 3.5 h.

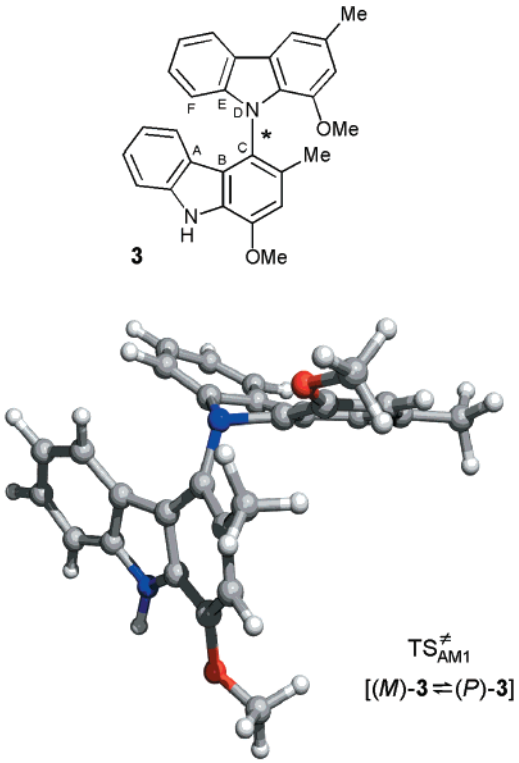
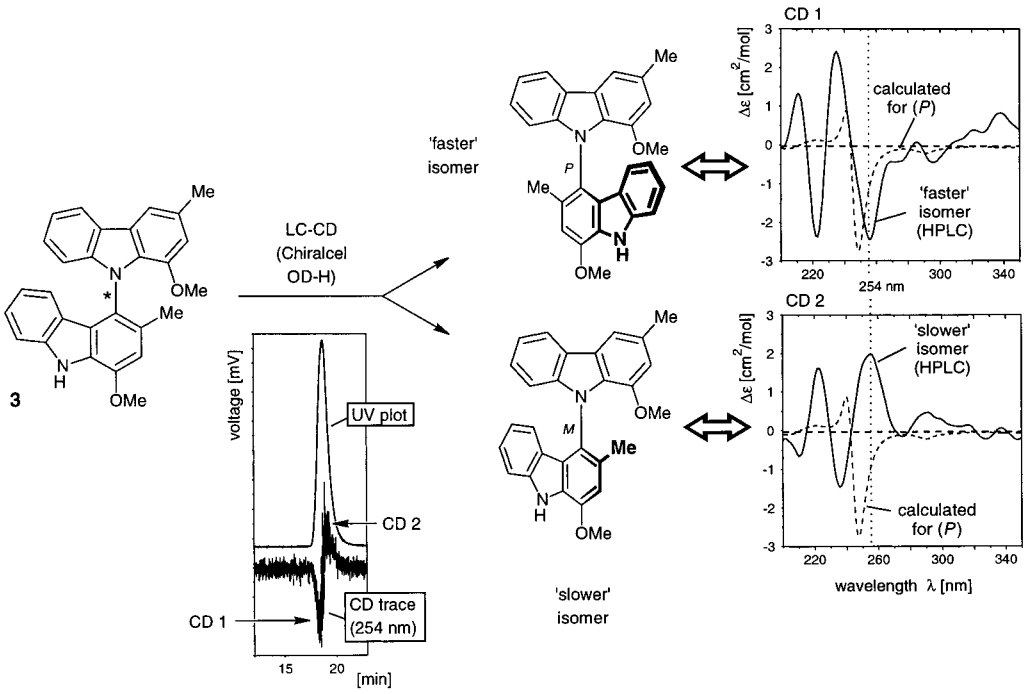


Figure 4. AM1 calculated transition state for the atropisomerization process of **3** (ABDE, FECB: dihedral angles; cf. Computational Section, Supporting Information).

Variation of the reaction conditions did not succeed in further enhancing the yield of **3** but led to the formation of—likewise interesting—side products. A slight increase of the amount of $Pb(OAc)_4$ from 0.55 to 0.60 equiv decreased the yield of **3** to 43% but gave rise to 13% of an additionally oxygenated monomeric product, 4-acetoxymurrayafoline-A (**8**) (Figure 3). From some of the reactions, traces of the *N*,*C*-bonded trimer **9** were obtained, indicating the inherent risk—and synthetic potential—of over-oxidation reactions to take place. Of the two possible atropo-diastereomeric forms of teraryl **9**, only the *unlike* isomer, *u*-**9**, could be obtained in a pure (racemic) form from the reaction mixture. Its constitution and relative configuration were deduced from NMR, in particular from ROESY experiments, and the presence of a 1:1 mixture of two atropo-enantiomers was proven by LC−CD analysis on a chiral column. From the structures of the reaction products thus identified, the mechanism of this oxidation reaction seems to involve aryl

Scheme 3. HPLC−UV and −CD Analysis of **3** Using a Chiral Phase (Chiralcel OD-H), and Assignment of the Absolute Configurations by Quantum Chemical CD Calculations



cationic species rather than radical intermediates.[22,27] The positive charge can be assumed to be trapped mainly in the 4-position, by acetate or the (possibly deprotonated) carbazole nitrogen to give products **8** or **3**. Attack of the intermediate cation by the aromatic carbon atom as the nucleophile would lead to the 4,4′-dimer **7**.

With this competition between different nucleophilic positions or substrates, a significant increase of the *C*,*C*-coupling portion was to be expected if the endocyclic nitrogen was blocked by alkylation. Indeed, *N*-methylmurrayafoline-A (**10**), as prepared by efficient *N*-methylation of **6** with dimethyl sulfate, gave a *C*,*C*-biaryl inasmuch as 39% yield. The coupling was found to occur in the sterically less demanding aromatic part to give the (as yet unnatural) constitutionally unsymmetric novel 4,6′-dimer **11** (Scheme 2), which, from the low degree of steric hindrance next to the axis, should be configurationally unstable.

With its four *ortho*-substituents next to the axis and from its nonstereoselective preparation, murrastifoline-F (**3**) thus synthesized should exist as a racemic mixture of configurationally stable atropo-enantiomers. Attempted separation of these isomers by HPLC on a chiral phase (Chiralcel OF and OD-H), however, gave no splitting of the product peak. A reason for this might be a too small difference in the interactions between the enantiomeric analytes and the column material for achieving a separation—or the atropisomers are not sufficiently stable and the atropisomerization is too fast within the time frame of the separation process. Such a configurational instability was ruled out by quantum chemical calculations (AM1)[28] predicting an atropisomerization barrier of $\Delta H^{\ddagger} = 165$ kJ/mol, which should guarantee the existence of stable atropisomers. According to these calculations, a rotation around the biaryl axis would proceed via the conformationally highly distorted transition state

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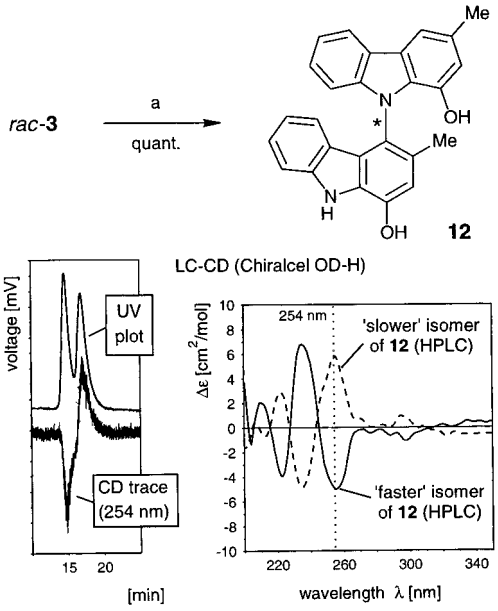
(28) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Steward, J. J. P. *J. Am. Chem. Soc*. **1985**, *107*, 3902−3909.

Scheme 4. Bis-*O*-demethylation of **3**[a] and LC−CD Analysis of **12**

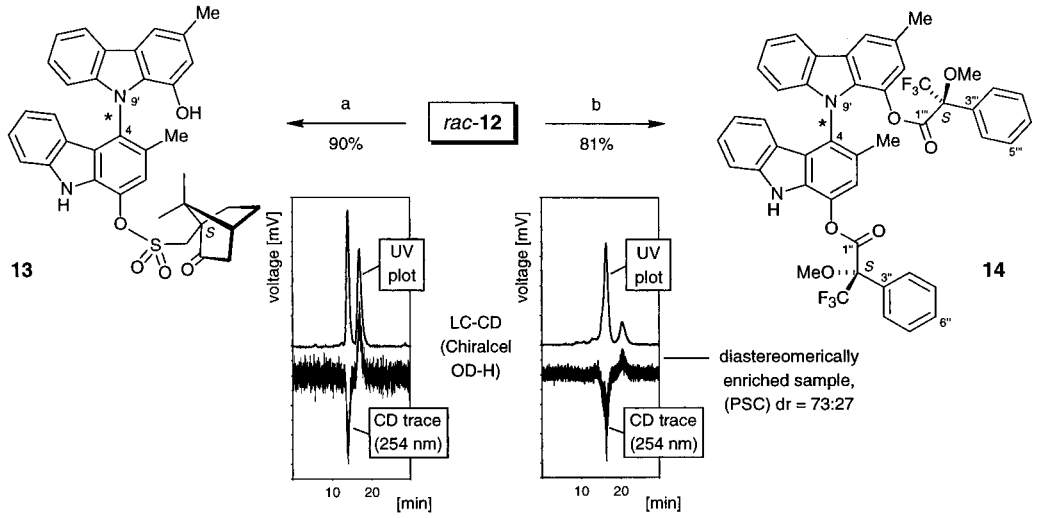


[a] Conditions: (a) BBr_3, CH_2Cl_2, 0 °C, 3.5 h.

$TS_{AM1}^{\ddagger}$ [(*M*)-**3** ⇌ (*P*)-**3**] shown in Figure 4, with a near-tetrahedral "bridge head" nitrogen.

This prediction was confirmed by LC−CD coupling using the Chiralcel OD-H column (see Scheme 3), which seemingly had not been successful in the LC−UV analysis before: The CD trace of an HPLC run at 254 nm showed a clear negative signal at the rising slope of the UV-detected HPLC product peak and a positive one on the descending side. Full LC−CD spectra directly taken on line in the stopped flow mode in the regions of these two minimum and maximum peaks, that is left and right of the UV-peak maximum (CD 1 and CD 2, respectively), gave mirror imaged CD curves. Consequently, one atropisomer is indeed eluted faster than the other one, but the interactions

Scheme 5. Derivatization of **12** with Chiral Auxiliaries[a]



[a] Conditions: (a) 1.0 equiv (1*S*)-10-camphorsulfonyl chloride, NEt_3, CH_2Cl_2, reflux, 30 min. (b) (*S*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, 0 °C then room temperature, 3.5 h.

of the enantiomers with the column material are not different enough for the resolution to reach a baseline separation. For an interpretation of the on-line CD spectra thus obtained, concerning the assignment of the absolute configuration at the biaryl axis of the two atropo-enantiomers of murrastifoline-F (**3**), quantum chemical CD calculations were performed, a method that had been established and further optimized by our group.[29] Given the new, stereochemically as yet unexplored structural type of murrastifoline-F (**3**), these calculations seemed more appropriate than to rely, for example, on the exciton chirality rule, which is defined for molecules with two identical chromophores being symmetrically linked to each other[30,31] and which is thus, strictly speaking, not applicable here. The experimental LC−CD spectrum obtained from the faster isomer of **3** shows almost the same peaks as the one calculated for the *P*-enantiomer,[32] while the one for the slower isomer is virtually opposite. The faster enantiomer should therefore be *P*-configured, while the enantiomer eluted later is *M*.

For an attempted increase of the enantiospecificity of the interactions with the chiral stationary phases, both methoxy groups of **3** were cleaved with BBr_3 in CH_2Cl_2, to give the corresponding bisphenolic compound **12** quantitatively. Although, again, no complete resolution was obtained on Chiralcel OF or OD-H, but at least for a highly diluted analytical sample, a peak splitting for the enantiomers could be attained on Chiralcel OD-H. The resulting LC−CD on-line spectra are displayed in Scheme 4.

Thus, for a separation of the atropisomers on a preparative scale, a conversion of (*P*)/(*M*)-**3** into atropo-diastereomers was necessary, by derivatization with a chiral auxiliary. In the first attempts to transform the two hydroxy functions of dimer **12** with 2.2 equiv (1*S*)-10-camphorsulfonyl chloride, which had already been used for the resolution of a phenolic 2,2′-biscarbazole,[10] a product mixture was obtained, with the monocamphorsulfonate **13** as the main product (51%) (Scheme 5). The yield of **13** could be enhanced to 90% by adding only 1.0 equiv of the camphorsulfonyl chloride, but again, as for the enantiomers above, the atropo-diasteromeric products turned out to be inseparable on silica gel, and even on a chiral preparative HPLC phase (Chiralcel OD), the retention times of the isomers were too similar for a resolution on a larger scale. A further difficulty arose from the chemical instability of **13**: Removal of the solvent (hexane/2-propanol) from the respective HPLC fraction even in vacuo led to partial decomposition.

Better results in all respects were obtained with Mosher's acid as the chiral auxiliary (Scheme 5, right). Esterification of the two dihydroxy groups of dimer **12** using this agent in the presence of DCC and DMAP[33] succeeded smoothly to give **14** in good yield (81%), along with traces of the corresponding monoester derivative in which again only the "lower", stereochemically less discriminating oxygen function was derivatized. The two atropo-diastereomers of the diester **14** were now easily separable by preparative thin-layer chromatography, giving diastereomerically nearly homogeneous material (ratio of 98:2 for the faster isomer), straightaway. Subsequent preparative HPLC on a Chiralcel OD phase offered the great advantage that the isomer slower on TLC became the faster one on HPLC, which allowed an excellent further enrichment of the second isomer. In combining these two chromatographic procedures, both atropo-diastereomers were attained in a diastereomeric ratio (dr) > 99:1 (Scheme 6). Unfortunately, all attempts to obtain crystals of the products suitable for an X-ray structure analysis failed, so that an assignment of the axial configuration at this stage had to rely on NMR spectroscopic methods. A profound analysis of ROESY experiments showed interactions (the crucial ones being marked by arrows in Scheme 6) indicative of a *P*-configured axis for the faster isomer of **14** (TLC) and of *M* for the slower one.

With the atropisomerically pure compounds in hands, trans-

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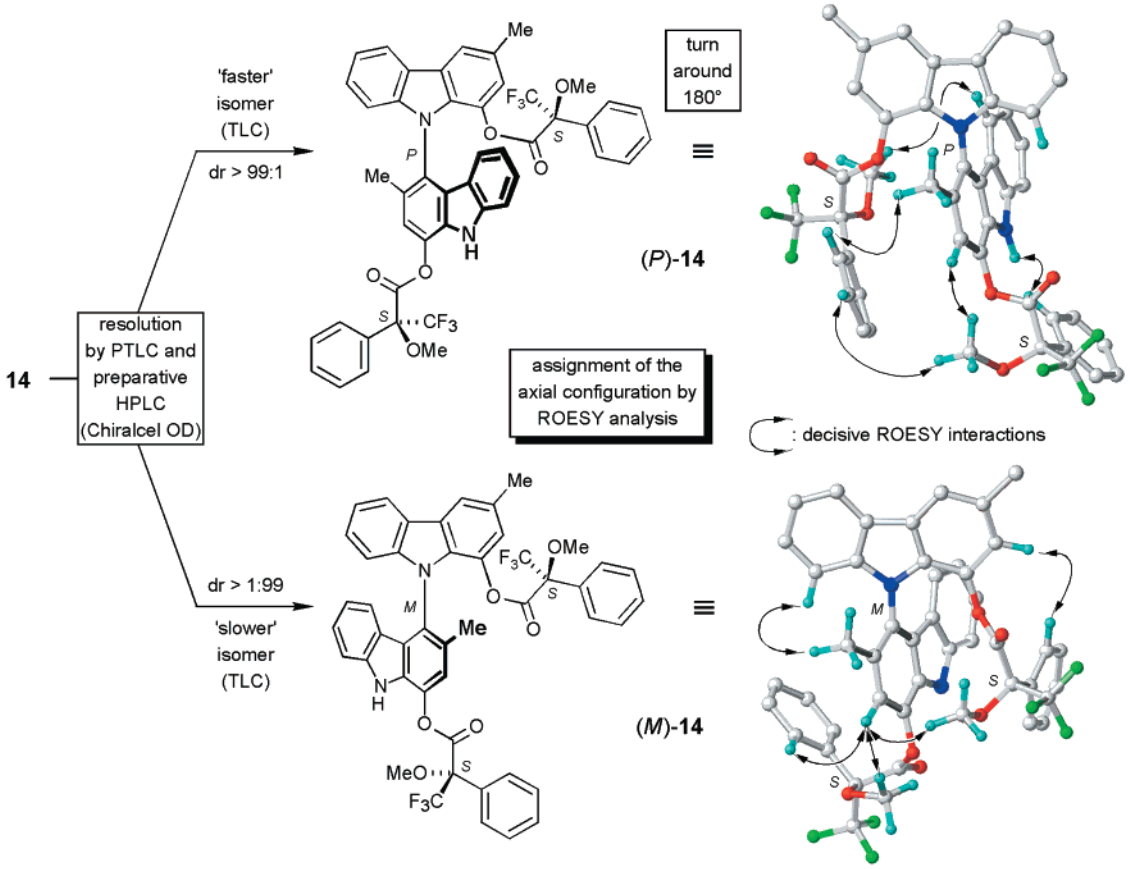
(30) Nakanishi, K.; Berova, N. In *Cicular Dichroism - Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH: Weinheim, 1994; Chapter 13, pp 361−398; Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671−1682.

(31) For a failure of this rule even when being applied to symmetrically coupled biaryls, see: Hattori, T.; Sakurai, K.; Koike, N.; Miyano, S. *J. Am. Chem. Soc*. **1998**, *120*, 9086−9087.

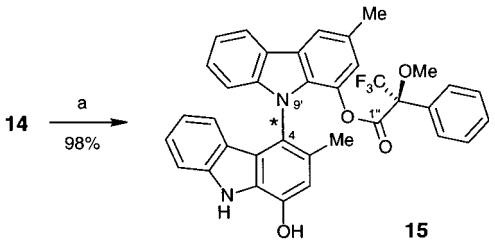
(32) For the now recommended *M*/*P* denotion for axially chiral compounds, see: Helmchen, G. In *Methods of Organic Chemistry* (*Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21a, pp 11−13.

(33) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl*. **1978**, *17*, 522−523; for a related esterification with (*S*)-*O*-methylmandelic acid, see: Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem*. **1994**, *59*, 4202−4205.

Scheme 6. Separation of Atropo-diastereomeric Mosher Esters (*P*)- and (*M*)-**14** and Assignment of Their Absolute Axial Configurations by Analysis of ROESY Experiments (Illustrated on Force Field Optimized Structures)



Scheme 7. Incomplete Removal of the Chiral Auxiliary under Basic Conditions[a]



[a] Conditions: (a) K_2CO_3, MeOH, room temperature, 1 h.

formation back to the natural product murrastifoline-F (**3**) by saponification and *O*,*O*-dimethylation seemed to be an easy completion of the first synthesis of an enantiomerically pure *N*,*C*-coupled biscarbazole alkaloid and would permit a comparison of the stereodescriptors obtained by NMR, with those assigned by CD calculations above. But the first step already turned out to be problematic: Applying a general literature procedure[34] for the removal of the Mosher residues with K_2CO_3 in MeOH at room temperature (performed on a 1:1 atropisomeric mixture of **14**, Scheme 7) did not give the desired dihydroxy compound **12**, but selectively furnished the monoester **15**, now with the "upper", sterically much more shielded oxygen function still derivatized. These atropo-diastereomers were likewise separable on TLC, giving rise to a dr of 97:3 in favor of the faster isomer. More drastic conditions, such as KOH or NaOMe in boiling MeOH, led to partial decomposition.

For a complete removal of the ester groups, reductive methods turned out to be much more efficient: Thus, $LiAlH_4$ reduction in ether at 0 °C to room temperature gave ~60% of the diol **12**. Using a large excess of $LiAlH_4$ at a reaction temperature of 35 °C finally proved to be the method of choice, allowing the conversion of **14** into the diol **12** in a quantitative yield, as shown exemplarily for the *M*-series in Scheme 8. The final bis-*O*-methylation imposed one remaining critical problem: to leave the carbazole nitrogen unaffected, while alkylating both, the reactive "lower" OH group, *and* also the effectively shielded "upper" one, hidden in the biaryl cavity. Diazomethane is known to selectively methylate only the 1-OH group of the monomeric alkaloid 1-hydroxy-3-methylcarbazole to give murrayafoline-A (**6**)[35] and was therefore tested first. A freshly prepared ethereal solution[36] was directly used as the solvent for the following methylation of **12**, giving, however, only a single alkylation at the "lower" hydroxy functionality. Me_3OBF_4,[37] by contrast, showed no special *O*- or *N*-selectivity, not even with 1-hydroxy-3-methylcarbazole as the test system. The best results were finally obtained with dimethyl sulfate at a slightly decreased temperature, following a protocol previously optimized within our murrayfoline-A synthesis.[19] Under these conditions the—now stereochemically pure—murrastifoline-F enantiomers,

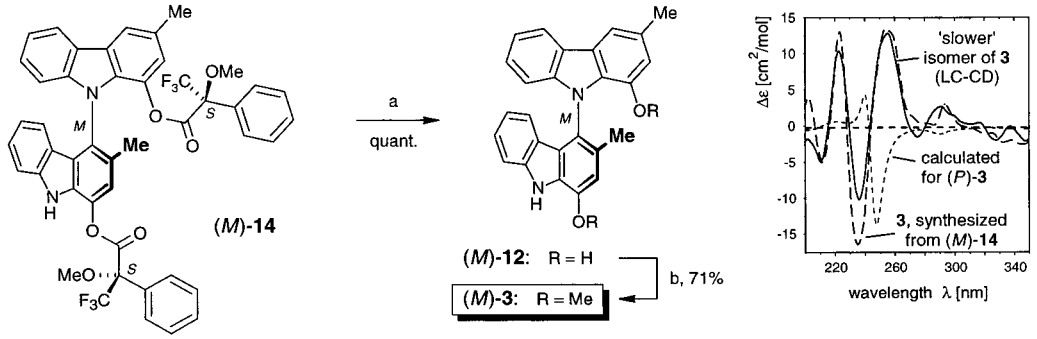
(34) Hoye, T. R.; Renner, M. K.; Vos-DiNardo, T. J. *J. Org. Chem.* **1997**, *62*, 4168−4170.

(35) Chakraborty, D. P.; Chowdhury, B. K. *J. Org. Chem.* **1968**, *33*, 1265−1268.

(36) Leonard, J.; Lygo, B.; Procter, G. In *Praxis der Organischen Chemie*; Dyker, G., Ed.; VCH: Weinheim, 1996; pp 102−104; the preparation was carried out in a special apparatus from *Aldrich*; de Boer, T. J.; Backer, H. J. In *Organic Syntheses*; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. 4, pp 250−253; Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3−10.

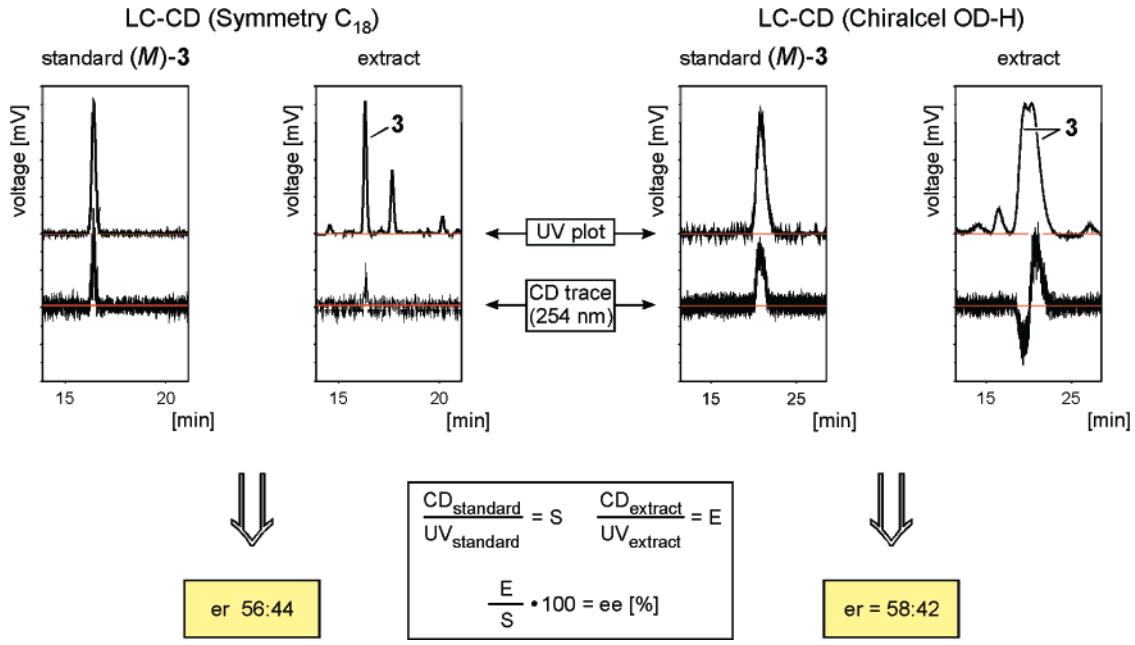
(37) Kita, Y.; Akai, S.; Fujioka, H.; Tamura, Y.; Tone, H.; Taniguchi, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 875−884; Scartazzini, R.; Bickel, H. *Helv. Chim. Acta* **1974**, *57*, 1919−1934.

Scheme 8. Exemplarily for the *M*-Atropisomer: Conversion of the Atropisomerically Pure Mosher Derivative **14** into the Corresponding Enantiomer of Murrastifoline-F (**3**)[a] and Independent Assignment of the Axial Configuration as *M*, in Agreement with the NOE Attribution Above ($\Delta\epsilon$ Scales for the LC−CD Spectrum and for the Calculated Spectrum Adjusted to That of the Synthetic Sample)



[a] Conditions: (a) $LiAlH_4$, CH_2Cl_2, Et_2O, 0 °C, 1 h, then 35 °C, 2 h. (b) Dimethyl sulfate, K_2CO_3, acetone, 50 °C, 12 h.

Scheme 9. Determination of the Natural Enantiomeric Ratio of Murrastifoline-F (**3**) in the Root Extract of *Murraya koenigii*



[(*P*)-**3**] and [(*M*)-**3**], were obtained in 71% yield, along with 9% of the overreacted products with an additional *N*-methyl group.

Now the final proof of the correctness of the absolute configurations at the biaryl axes assigned above for both atropoenantiomers of murrastifoline-F (**3**) was possible: The enantiomer of **3** obtained from the chromatographically (TLC) slower "bis-Mosher" diastereomer **14**, whose axial configuration had been determined to be *M* by ROESY experiments, gave an experimental CD spectrum almost identical to that of the slower isomer of *rac*-**3** on a Chiralcel OD-H HPLC column (Scheme 8, cf. Scheme 3). By quantum chemical CD calculations, this isomer had, likewise, been attributed the *M*-configuration.

A thrilling question had now become possible to be addressed experimentally: Does murrastifoline-F (**3**) exist in the plant as a racemate or does one enantiomer dominate over the other? The original isolation paper[4] did not take the biaryl axis into account as a potential stereogenic unit; hence, no optical rotation of the isolated alkaloid was measured, and unfortunately no authentic **3** is available from the authors anymore. For an analysis of the natural enantiomeric ratio, a small amount of root material from *Murraya koenigii* was dried by lyophilization and extracted with acetone in an ultrasonic bath, without heating and in the absence of light, to exclude a possible "chemical" (i.e., nonenzymic) dimerization of the main root alkaloid murrayafoline-A (**6**) to murrastifoline-F (**3**) during the procedure. The resulting extract was fractionated by column chromatography on silica gel, mainly to separate the large quantities of **6** from the other compounds. The fraction containing murrastifoline-F (**3**) by TLC comparison with synthetic material, was analyzed by LC−MS and LC−NMR,[38] revealing one signal in the HPLC chromatogram to be **3**, additionally confirmed by coelution. In LC−CD investigations using an achiral reversed phase column, this fraction showed a clear positive peak for **3** in the CD trace at 254 nm (Scheme 9), indicating that one enantiomer—apparently the *M*-isomer—must prevail over the other. This was verified by analysis on a Chiralcel OD-H column established above for the synthetic sample of murrastifoline-F (**3**): Again a first negative CD peak and a second positive one were monitored for the left and the right slopes of the (partially resolved) UV product peak, with the second CD peak being distinctively higher, confirming that the *M*-enantiomer of **3** predominates in the plant (cf. the sign of the $\Delta\epsilon$ values at 254 nm in the CD spectra of the two enantiomers in Scheme 3).

(38) Bringmann, G.; Messer, K.; Wohlfarth, M.; Kraus, J.; Dumbuya, K.; Rückert, M. *Anal. Chem.* **1999**, *71*, 2678−2686.

The exact enantiomeric ratio was deduced from the proportions of the areas of the UV peak and the CD signal of the natural mixture (referred to as E in the equation in Scheme 9) as compared to that obtained from a stereochemically pure synthetic isomer (referred to as S). This procedure[39] is based on the assumption of a steady relation between the area of the UV peak and that of the respective signal in the CD trace at 254 nm. The UV peak results from an additive contribution of the two enantiomeric signals, whereas the final CD intensity at this wavelength is composed of contributions of different signs—a negative one for *P* and a positive one for *M*. The application of this method using an achiral (Symmetry C_{18}) and a chiral (Chiralcel OD-H) HPLC phase revealed the natural enantiomeric mixture to be in the range from 45:55 to 42:58 in favor of the *M*-isomer of murrastifoline-F [(*M*)-**3**].

Conclusions

The biomimetic oxidative coupling of murrayafoline-A (**6**) with $Pb(OAc)_4$ to give the biaryl alkaloid murrastifoline-F (**3**) in good yield represents the first synthesis of an *N*,*C*-bonded natural heterobiaryl product and hints at a coupling mechanism involving cationic species. Furthermore, a stereoanalysis for the configurationally stable atropo-enantiomers has been achieved by two different methods: first, by CD spectroscopy in combination with quantum chemical calculations, which thus proved, once again, to be a powerful and reliable stereoanalytical tool and, second, based on a preparative racemate resolution via atropo-diastereomers, with stereoanalysis of the pure Mosher derivatives by ROESY experiments. With this stereochemical assignment of synthetic **3**, the first determination of a natural enantiomeric ratio of this biscarbazole alkaloid succeeded by analyzing a root extract of *Murraya koenigii* by LC−CD.

Experimental Section

Murrastifoline-F (*rac*-3). To a solution of murrayafoline-A (**6**) (400 mg, 1.89 mmol) in CH_3CN (25 mL) were added $Pb(OAc)_4$ (462 mg, 1.04 mmol) and BF_3*Et_2O (3.2 mL) at room temperature. After stirring for 3.5 h, the solution was poured into water (20 mL), followed by extraction with several portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. Purification of the remaining solid by column chromatography (silica gel, 3:1 petroleum ether/Et_2O) yielded crude **3** along with 59.6 mg (15%) of starting material and traces of 4,4′-bis(1-methoxy-3-methyl-9*H*-carbazole) (**7**) and *rac-unlike*-1′-methoxy-9′-(1-methoxy-3-methyl-9*H*-carbazol-4-yl)-4′-(1″-methoxy-3″-methyl-9″*H*-carbazol-9″-yl)-3′-methyl-9′*H*-carbazole (*rac-u*-**9**). Subsequent crystallization of the crude product from ethanol/pentane gave 238 mg (60%) of **3** as colorless crystals. Mp 289 °C; IR (KBr): ν 3420, 3060, 3000, 2960, 2930, 2845, 1590, 1515, 1455 cm^{-1}; ^1H NMR (600.1 MHz, acetone-d_6): δ 10.43 (s, 1H, NH), 8.22 (m, 1H, H-5′), 7.71 (d, 1H, J = 1.3 Hz, H-4′), 7.50 (d, 1H, J = 8.1 Hz, H-8), 7.22 (td, 1H, J = 7.1, 1.5 Hz, H-7′), 7.20 (td, 1H, J = 7.1, 1.5 Hz, H-6′), 7.17 (ddd, 1H, J = 8.1, 7.1, 1.2 Hz, H-7), 7.05 (s, 1H, H-2), 6.77 (s, 1H, H-2′), 6.74 (m, 1H, H-8′), 6.57 (ddd, 1H, J = 8.1, 7.1, 1.0 Hz, H-6), 6.18 (d, 1H, J = 8.1 Hz, H-5), 4.11 (s, 3H, 1-OMe), 3.36 (s, 3H, 1′-OMe), 2.52 (s, 3H, 3′-Me), 2.05 (s, 3H, 3-Me); ^{13}C NMR (150.9 MHz, acetone-d_6): δ 148.1 (C-1′), 146.2 (C-1), 142.0 (C-8a′), 141.0 (C-8a), 130.3 (C-4a′), 129.7 (C-9a), 129.4 (C-9a′), 128.8 (C-3), 126.5 (C-7′), 126.0 (C-7), 125.8 (C-3′), 125.5 (C-4), 123.8 (C-4b′), 123.4 (C-4a), 122.6 (C-4b), 122.1 (C-5), 121.0 (C-5′), 120.1 (C-6′), 119.4 (C-6), 113.8 (C-4′), 111.9 (C-8), 110.9 (C-2′), 110.8 (C-8′), 108.8 (C-2), 56.49 (1′-OMe), 56.16 (1-OMe), 21.75 (3′-Me), 17.30 (3-Me); MS (EI) *m*/*z*: 420 (M^+, 100), 405 (16), 390 (6), 375 (7), 374 (8), 373 (10), 210 (21), 202.5 (2), 195 (4); Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found C, 79.73; H, 5.80; N, 6.54.

LC−CD: Chiralcel OD-H (250 × 4.6 mm), hexane/2-propanol 95:5, flow rate 0.8 mL/min, UV detection 254 nm. Since the concentration of the compound in the flow-probe detection cell was not known, the $\Delta\epsilon$ scales of the CD spectra were set arbitrarily. The same was true for the ordinate of calculated spectra. *Faster isomer of* ***3***: t_R = 18.1 min; CD (hexane/2-propanol 95:5): λ_{ext} ($\Delta\epsilon$) 295 (−0.3), 285 (+0.2), 256 (−2.3), 235 (+2.5), 223 (−2.2), 211 (+1.4). *Slower isomer of* ***3***: t_R = 18.6 min; CD (hexane/2-propanol 95:5): λ_{ext} ($\Delta\epsilon$) 291 (+0.5), 275 (−0.2), 256 (+2.0), 236 (−1.6), 223 (+1.8), 211 (−0.8). The assignment of absolute configurations was achieved by comparison of the CD data with those of a quantum chemically calculated CD spectrum: $CD_{calculated}$ [(*P*)-**3**]: λ_{ext} ($\Delta\epsilon$) 249 (−2.7), 241 (+0.9). Therefore, the faster isomer of **3** should be (*P*)-**3**. For details of the CD calculations, see Supporting Information.

1-Hydroxy-4-(1′-hydroxy-3′-methyl-9′*H*-carbazol-9′-yl)-3-methyl-9*H*-carbazole (*rac*-12, *O*,*O*-Demethylmurrastifoline-F). BBr_3 (135 μL, 1.43 mmol) was added to a solution of murrastifoline-F (**3**) (100 mg, 238 μmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 3.5 h, the solution was treated with water (10 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent afforded 92.3 mg (99%) of crude product *rac*-**12** as a brownish solid, which was directly taken for the next reaction step. For complete characterization, a small sample of *rac*-**12** was crystallized from Et_2O/pentane to yield a slightly yellow powder. Mp 207 °C.

1-[(2″*S*)-Methoxy(trifluoromethyl)phenylacetoxy]-4-{1′-[(2‴*S*)-methoxy(trifluoromethyl)phenylacetoxy]-3′-methyl-9′*H*-carbazol-9′-yl}-3-methyl-9*H*-carbazole (14). The crude dihydroxy compound *rac*-**12**, obtained by the *O*-demethylation of murrastifoline-F (**3**) (55.0 mg, 131 μmol) with BBr_3, was directly dissolved in CH_2Cl_2 (5 mL) and (2*S*)-2-methoxy-2-(trifluoromethyl)phenylacetic acid (Mosher's acid) (73.5 mg, 314 μmol), DCC (70.2 mg, 340 μmol), and some crystals of DMAP (∼1−2 mg) were added at 0 °C. After stirring for 5 min at 0 °C and for a further 3.5 h at room temperature, the solvent volume was reduced in vacuo, and the remaining mixture was mounted on silica gel directly. Short column chromatography (silica gel, 1:1 petroleum ether/Et_2O) yielded 87.1 mg (81%) of a diastereomeric mixture of **14** as a yellow oil along with traces of the monoester 1-[(2″*S*)-methoxy-(trifluoromethyl)phenylacetoxy]-4-(1′-hydroxy-3′-methyl-9′*H*-carbazol-9′-yl)-3-methyl-9*H*-carbazole. MS (EI) *m*/*z*: 824 (M^+, 32), 622 (16), 607 (41), 405 (13), 390 (9), 389 (10), 375 (18), 374 (27), 373 (42), 210 (5), 189 (100); HRMS calcd for $C_{46}H_{34}F_2N_2O_6$ 824.2321, found 824.2326.

Separation of the diastereomers of **14** was achieved by preparative TLC (silica gel, 1:1 petroleum ether/Et_2O) and subsequent purification by preparative HPLC on a chiral column. The pure diastereomers became yellow solids when covered with a layer of hexane. *Faster isomer on TLC, (P)-**14***. Darkens above 300 °C (decomposition); $[\alpha]^{22}_D$ = +30.4 (*c* 1.04, $CHCl_3$); CD (hexane): λ_{ext} ($\Delta\epsilon$) 345 (−2.8), 293 (+10.8), 260 (+11.0), 243 (+8.3), 234 (−10.0), 217 (+6.8), 206 (−7.8). *Slower isomer on TLC, (M)-**14***. Darkens at ∼300 °C (decomposition); $[\alpha]^{22}_D$ = −3.3 (*c* 1.17, $CHCl_3$); CD (hexane): λ_{ext} ($\Delta\epsilon$) 292 (−12.2), 269 (+0.1), 260 (−4.5), 243 (−10.4), 226 (+9.6), 208 (+31.2).

(*P*)- and (*M*)-1-Hydroxy-4-(1′-hydroxy-3′-methyl-9′*H*-carbazol-9′-yl)-3-methyl-9*H*-carbazole [(*P*)-12] and [(*M*)-12]. The atropisomerically pure Mosher diesters (*P*)-**14** and (*M*)-**14** (each 20.0 mg, 24.2 μmol) were dissolved in CH_2Cl_2 (0.5 mL), and Et_2O (2.0 mL) was added. At 0 °C the substrates were treated with $LiAlH_4$ (4.60 mg, 121 μmol) for 1 h prior to heating to 35 °C for a further 2 h. After addition of saturated aqueous NH_4Cl solution (1 mL) and 2 N HCl (5 drops), the mixture was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, and the solvents were removed in vacuo. The crude product was purified by column filtration (silica gel, CH_2Cl_2/hexane 5:1, and then CH_2Cl_2/methanol, 7:1, to elute the product). The stereochemically homogeneous products, (*P*)- and (*M*)-**12**, were obtained quantitatively as yellow-to-brown oils; they were chemically pure according to their ^1H NMR spectra (identical with that of *rac*-

(39) Salvadori, P.; Di Bari, L.; Pescitelli, G. In *Circular Dichroism - Principles and Applications*, 2nd ed; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: Weinheim, 2000; Chapter 28, pp 797−817.

12). After the chiroptical investigations, both enantiomers were directly submitted to the subsequent methylation.

***(P)*-1-Hydroxy-4-(1′-hydroxy-3′-methyl-9′*H*-carbazol-9′-yl)-3-methyl-9*H*-carbazol [(*P*)-12]:** $[\alpha]^{22}_D = -59.9$ (*c* 0.35, $CHCl_3$); CD (ethanol): λ_{ext} ($\Delta\epsilon$) 296 (−5.3), 255 (−21.9), 236 (+25.3), 222 (−19.7), 212 (+6.0), 204 (−4.1).

(*M*)-1-Hydroxy-4-(1′-hydroxy-3′-methyl-9′*H*-carbazol-9′-yl)-3-methyl-9*H*-carbazol [(*P*)-12]: $[\alpha]^{22}_D = +60.7$ (*c* 0.42, $CHCl_3$); CD (ethanol): λ_{ext} ($\Delta\epsilon$) 295 (+3.4), 256 (+19.0), 237 (−27.0), 222 (+17.2), 210 (−2.4), 200 (+5.2).

(*P*)- and (*M*)-Murrastifoline-F [(*P*)-3] and [(*P*)-3]. Each of the dihydroxybiscarbazoles (*P*)- and (*M*)-**12** obtained from the $LiAlH_4$ reduction (each 24.2 μmol) were dissolved in acetone (7 mL), and K_2CO_3 (6.03 mg, 43.6 μmol) and dimethyl sulfate (3.22 μL, 4.28 mg, 33.9 μmol) were added. After 12 h stirring at 50 °C, excessive reagent was quenched by treating the mixture with concentrated aqueous NH_3 solution (1 mL) at room temperature and subsequent heating to 50 °C for 30 min. Removal of the solvents and purification by preparative TLC (silica gel, 1:1 petroleum ether/Et_2O) afforded 7.25 mg (71%) of each (*P*)- and (*M*)-**3** as beige solids, besides the corresponding enantiomers of *N*-methylmurrastifoline-F. The spectral data (IR, ^1H NMR, ^{13}C NMR, mass) of the two enantiomeric forms of **3** were in accordance with those of the racemic compound. Both enantiomers were recrystallized from ethanol/pentane and showed decomposition (with darkening) upon heating to 200 °C.

(*P*)-Murrastifoline-F [(*P*)-13]: $[\alpha]^{22}_D = -19.9$ (*c* 0.44, $CHCl_3$); CD (ethanol): λ_{ext} ($\Delta\epsilon$) 294 (−3.1), 255 (−12.4), 236 (+15.3), 223 (−11.9), 212 (+5.8), 199 (−2.5).

(*M*)-Murrastifoline-F [(*M*)-13]: $[\alpha]^{22}_D = +18.9$ (*c* 0.40, $CHCl_3$); CD (ethanol): λ_{ext} ($\Delta\epsilon$) 294 (+2.9), 254 (+12.8), 235 (−15.4), 223 (+12.4), 211 (−4.6), 202 (+3.9).

Acknowledgment. This paper is dedicated to Professor Siegfried Hünig, on the occasion of his 80th birthday. We thank C. Rummey for creating force field optimized structures, Professor M. Christl and S. Groetsch for providing us with the preparative HPLC set up and for helpful advice, and W. Saeb for inspiring discussions on oxidative coupling reactions. Furthermore, we appreciate experimental help by P. Henschel and B. Stephan. Financial support by the Deutsche Forschungsgemeinschaft (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle") and the Fonds der Chemischen Industrie is gratefully acknowledged. We are indebted to Jasco Deutschland for engaged and generous technical support.

Supporting Information Available: Further detailed experimental procedures and characterization data for all new compounds and side products, including HMBC and ROESY correlations of **3** and **14**, analytical procedures, and the computational section as well as additional references (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003488C