A Synthesis-Driven Structure Revision of 'Plagiochin E', a Highly Bioactive Bisbibenzyl

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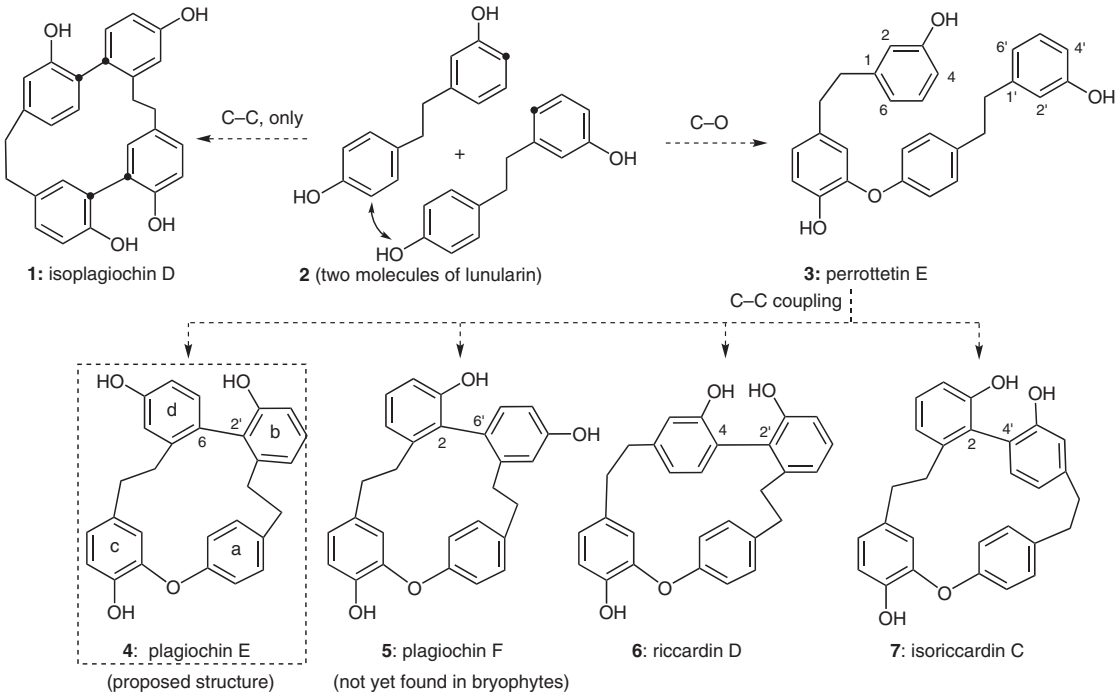
Abstract: Recently, a bisbibenzyl named plagiochin E showing remarkable antifungal and antitumor activities was isolated from *Marchantia polymorpha*, a liverwort. The total synthesis of the proposed structure for plagiochin E and of two structurally and biosynthetically related bisbibenzyls and comparison of the NMR data of the synthetic compounds with those of the isolated bisbibenzyls necessitates a structure revision for plagiochin E. Exemplarily for this metabolite, the stereostructure was investigated, by racemate resolution on a chiral Lux Cellulose-1 phase with HPLC-CD coupling and quantum chemical CD calculations, clearly assigning the *P*-configuration for the faster and the *M*-configuration to the slower enantiomer.

Key words: plagiochin E, bisbibenzyl, axially chiral biaryl, total synthesis, natural products, circular dichroism

Bisbibenzyls are phenolic natural products that are found exclusively in bryophytes.[1] Biosynthetically, they originate from two units of the bibenzyl lunularin (**2**), which can be combined by several modes of O–C and/or C–C attachment on the bases of phenol oxidation coupling to different subtypes like perrottetins, marchantins, riccardins, plagiochins, and isoplagiochins.[2] The most common acyclic precursor for cyclic bisbibenzyls with at least one O–C connection is perrottetin E (**3**; Scheme 1). In total, nine different cyclization products are possible starting from **3** with respect to oxidative C–C coupling *ortho* and *para* to the hydroxyl groups. Four of them, compounds **4**–**7** are shown in Scheme 1. They may, in principle, exhibit the same NMR coupling pattern in the 'upper' part of the molecule.

The distribution of the cyclic bisbibenzyls in liverworts, their structure elucidation as well as biological activities and total syntheses are well reviewed.[1,3] In preceding papers, we reported on the synthesis of exemplified model



Scheme 1

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compounds for some types of bisbibenzyls.[4–6] Furthermore, we have investigated effects of axial chirality and ring strain in the macrocycles of the isoplagiochin type (see **1**), which are only C–C coupled.[7,8]

The plagiochins A–D (**8**–**11**) were isolated from *Plagiochila fruticosa* in 1987 (Figure 1).[9] Total syntheses were published[10–12] with the exception for plagiochin B. The isolation of plagiochin E (**4**), however was described nearly 20 years later from *Marchantia polymorpha* (Chinese variation) and *Asterella angusta* through a bioassay-guided separation of the antifungal constituents.[13,14]

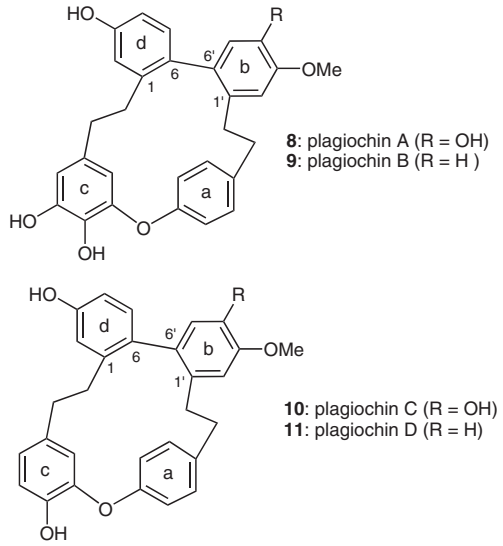


Figure 1

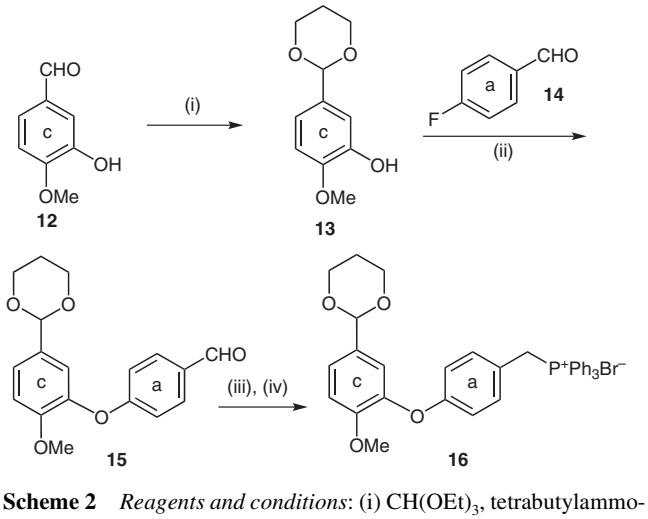
Interestingly, the conformational strain of **4** had been computed before as a hypothetical oxidative cyclization product of lunularin (**2**),[2] but the compound had never been isolated before from a natural source or even synthesized. The structure of plagiochin E (**4**) differs from that of **8**–**11** by a 6-2′-coupling between rings d–b instead of a 6-6′-coupling. The biaryl connection b–d in **8**–**11** as well as in **4** is *o*,*o*′ relative to the two bisbibenzyl bridges, but in **4**, the OH group is also *ortho* to the biaryl axis.

Beside the antifungal activity against *Candida albicans*[13–16] the recently isolated substance exhibited reversal effect on multidrug resistance in adriamycin-resistant K562/A02 cells suggesting that **4** may be a potential candidate for reversing drug resistance in cancer chemotherapy.[17] The pharmacokinetics in rats were studied very recently using an LC-tandem MS assay for the quantitation of plagiochin E and its main metabolite in rat plasma.[18] Considering the still significantly growing interest in biological activities of bisbibenzyls and other bryophyte constituents[19] we now report on our attempts for a short and efficient total synthesis of the isolated 'plagiochin E' (**4**),[13] resulting in a revision of its structure.

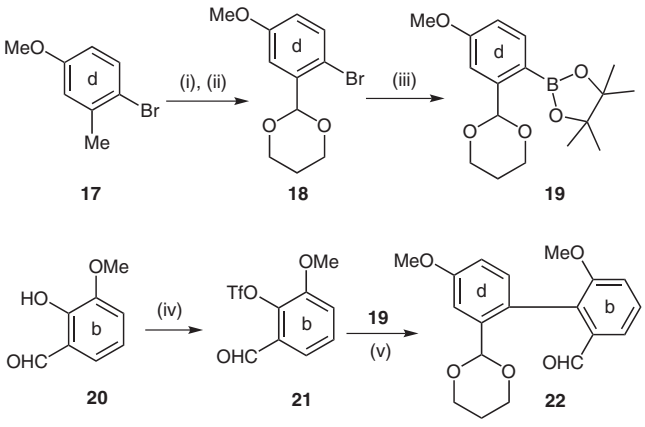
The c–a fragment **15**[4] was now obtained by a more straightforward sequence[20] (Scheme 2) starting from isovanillin (**12**). For the Wittig coupling of the c–a fragment with the d–b fragment, **15** was converted into the phosphonium salt **16**.

The synthesis of the d–b fragment containing a protected and an unprotected aldehyde moiety is shown in Scheme 3. The boronic ester **19** (fragment d) was prepared starting from 4-bromo-3-methylanisol (**17**)[21] and submitted to a Suzuki coupling with the triflate **21**, which was prepared from *o*-vanillin (**20**).

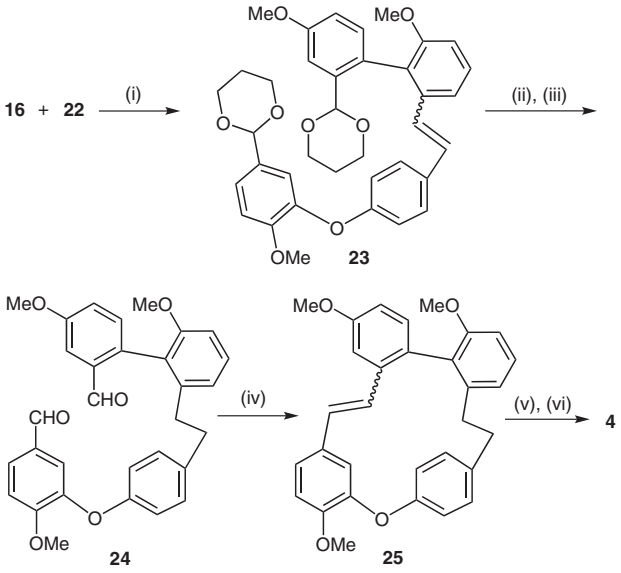
Wittig reaction of **16** and **22** gave the stilbene **23** (Scheme 4). After hydrogenation and deprotection of the aldehyde functionalities, the macrocyclization was achieved under McMurry conditions, to give **25**. Finally, compound **4** was obtained after hydrogenation and deprotection of the phenolic OH groups. The molecular formula $C_{28}H_{24}O_4$ was confirmed by HR-EI-MS [M^+ peak at m/z = 424.1687 (calcd: 424.1675)]. Surprisingly, the spectroscopic data (see Tables 1 and 2) were significantly differ-



Scheme 2 *Reagents and conditions*: (i) $CH(OEt)_3$, tetrabutylammonium tribromide, 1,3-propanediol, 65 °C, 12 h (91%); (ii) **14**, K_2CO_3, DMF, 160 °C, 20 h (93%); (iii) $NaBH_4$, EtOH, 0 °C to r.t., 2 h (97%); (iv) $Ph_3P{\cdot}HBr$, MeCN, reflux, 2 h (85%).



Scheme 3 *Reagents and conditions*: (i) NBS (2 equiv), AIBN, CCl_4, hν, reflux, 24 h, then aq $CaCO_3$, reflux, 18 h (72%) see ref.;[22] (ii) $CH(OEt)_3$, tetrabutylammonium tribromide, 1,3-propanediol, 65 °C, 12 h (93%); (iii) *n*-BuLi, THF, –78 °C, 30 min, then $B(OMe)_3$ at –78 °C to r.t., then pinacol, $MgSO_4$, CH_2Cl_2, r.t., 12 h (70%); (iv) Tf_2O, pyridine, 0 °C to r.t., 2 h (90%); (v) **19**, $Pd(PPh_3)_4$, PhMe–EtOH–2 M Na_2CO_3, reflux, 16 h (91%).



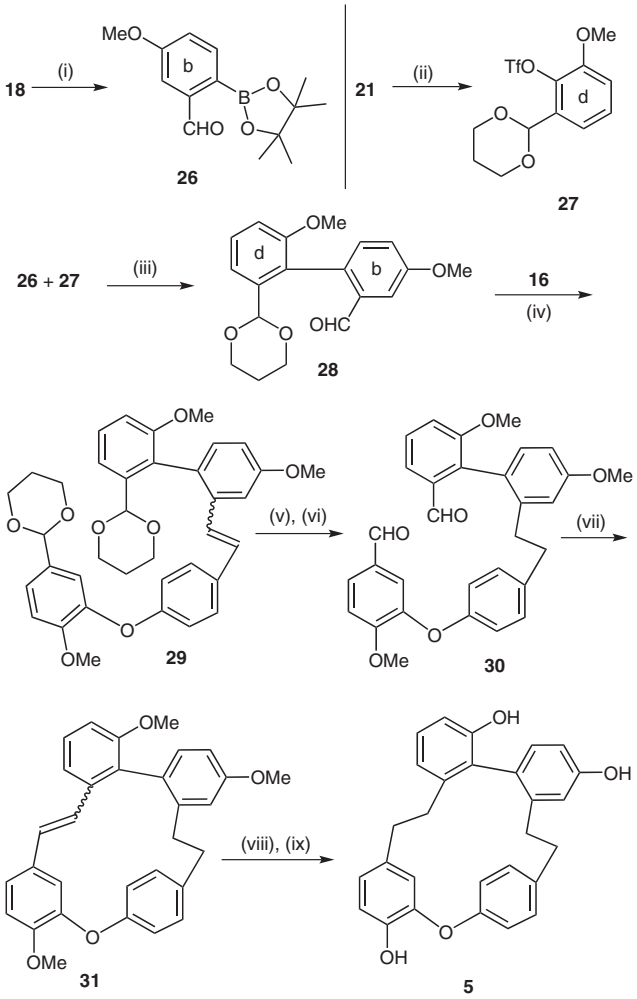
Scheme 4 *Reagents and conditions*: (i) **16** (1.5 equiv), K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 24 h (87%); (ii) Pd/C (5%), 3 bar H_2, Et_3N, EtOAc, r.t., 24 h (95%); (iii) 2 M HCl–THF (1:1), r.t., 12 h (94%); (iv) $TiCl_3(DME)_2$, Zn, DME, reflux, 30 h (23%) see ref.;[23] (v) Pd/C (5%), 10 bar H_2, EtOAc, r.t., 24 h (98%); (vi) BBr_3 (10 equiv), CH_2Cl_2, –78 °C to r.t. over 5 h, then 10 h at r.t. (68%).

ent from those reported in the literature for the isolated bisbibenzyl with the proposed structure of plagiochin E.[13]

The structure of the synthesized compound **4** was verified by further NMR experiments (H,H COSY, C,H COSY, HMBC, NOESY). We suppose that the isolated 'plagiochin E' might be a related bisbibenzyl also derived by *ortho*- or *para*-selective phenol coupling from the acyclic perrottetin E (**3**). The possible isomers with a similar substitution pattern (1,2,3-trisubstitution and 1,2,4-trisubstitution) in the d–b fragment are shown in Scheme 1. The structural relationship is most obvious for **4** and **5** with respect to the '2-6' substitution pattern in contrast to the '2-4' connection in **6** and **7** with two OH groups *ortho* to the biaryl axis. From these, compound **5** (we now call it plagiochin F) has not been isolated or synthesized yet (but nevertheless calculated, see ref. 2) and should be an alternative candidate for the compound described by Niu et al.[13]

It furthermore seemed rewarding to synthesize the as yet unknown bisbibenzyl **5**. The accomplished synthesis is similar to that of **4** and is depicted in Scheme 5.

The HR-EI-MS showed the M^+ peak at m/z = 424.1690 (calcd for $C_{28}H_{24}O_4$: 424.1675). The structure of **5** was ensured by different NMR experiments (H,H COSY, C,H COSY, HMBC, NOESY). Again, the spectroscopical data (see Tables 1 and 2) of the synthesized compound **5** also showed significant deviations from those reported for the isolated 'plagiochin E'.[13] Considering these results, we now are able to exclude the structures **4** and **5** for the isolated compound. Finally, comparing the spectroscopic data of the four bisbibenzyls namely synthetic **4** and **5** as



Scheme 5 Synthesis of plagiochin F (**5**). *Reagents and conditions*: (i) *n*-BuLi, THF, –78 °C, 30 min, then $B(OMe)_3$, –78 °C to r.t., then 2 M HCl, isolation of the boronic acid, then pinacol, $MgSO_4$, CH_2Cl_2, r.t., 12 h; (42%); (ii) $CH(OEt)_3$, tetrabutylammonium tribromide, 1,3-propanediol, 65 °C, 12 h (95%); (iii) $Pd(PPh_3)_4$, PhMe–EtOH–2 M Na_2CO_3, reflux, 16 h (67%); (iv) **16** (1.5 equiv), K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 24 h (93%); (v) Pd/C (5%), 3 bar H_2, Et_3N, EtOAc, r.t., 24 h (97%); (vi) 2 M HCl–THF (1:1), r.t., 12 h (97%); (vii) $TiCl_3(DME)_2$, Zn, DME, reflux, 30 h (21%) see ref.;[23] (viii) Pd/C (5%), 10 bar H_2, EtOAc, r.t., 24 h (98%); (ix) BBr_3 (10 equiv), CH_2Cl_2, –78 °C to r.t. over 5 h, then 10 h at r.t. (66%).

well the earlier reported **6**[24] and **7**[25] with the isolated 'plagiochin E',[13] we suggest that the isolated compound may be riccardin D (**6**). It should be noted that the published NMR data of **6**[24] and **4**[13] were obtained in different solvents.

So, as our next attempt for the structure elucidation of the isolated bisbibenzyl, we decided to synthesize **6**. In this reaction sequence, the c–a phosphonium salt **16** was used again and based on the building block **21** a new d–b fragment **35** was synthesized. For the cyclization of this less strained bisbibenzyl we used an intramolecular Wittig reaction. The complete synthetic pathway is shown in Schemes 6 and 7.

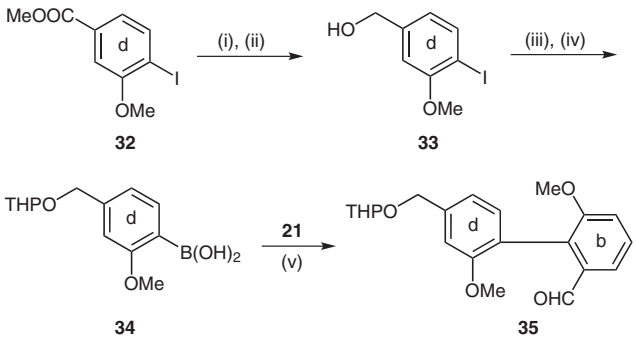
Table 1 ^{1}H NMR Data of Synthetic Compounds **4**–**6** (Figure 2; δ in ppm)

500 MHz, acetone-d_6	**4**	**5**	**6**
H–C(2)	6.61 (d, *J* = 2.4 Hz)	–	6.32 (d, *J* = 1.8 Hz)
HO–C(3)	8.15 (br s)	7.37 (br s)	7.68 (br s)
H–C(4)	6.66 (dd, *J* = 7.9, 2.4 Hz)	6.73 (d, *J* = 7.9 Hz)	–
H–C(5)	6.81 (d, *J* = 7.9 Hz)	7.00 (dd, *J* = 7.9, 7.6 Hz)	6.84 (d, *J* = 8.0 Hz)
H–C(6)	–	6.59 (d, *J* = 7.6 Hz)	6.31 (dd, *J* = 7.9, 1.8 Hz)
CH_2(7)	3.08–3.15 (m), 1.93–2.00 (m)	2.80–2.85 (m), 1.90–1.95 (m)	2.71–2.67 (m), 2.63–2.56 (m)
CH_2(8)	2.79–2.85 (m), 2.69–2.75 (m)	2.81–2.84 (m), 2.73–2.79 (m)	2.71–2.68 (m), 2.71–2.68 (m)
H–C(10)	5.30 (d, *J* = 2.1 Hz)	5.30 (d, *J* = 2.1 Hz)	5.45 (d, *J* = 2.0 Hz)
H–C(13)	6.74 (d, *J* = 8.2 Hz)	6.72 (d, *J* = 7.9 Hz)	6.85 (d, *J* = 8.0 Hz)
H–C(14)	6.64 (dd, *J* = 8.2, 2.1 Hz)	6.65 (dd, *J* = 7.9, 2.1 Hz)	6.72 (dd, *J* = 8.0, 2.0 Hz)
H–C(2′)	–	7.23 (d, *J* = 2.1 Hz)	–
HO–C(3′)	7.50 (br s)	8.23 (br s)	7.15 (br s)
H–C(4′)	6.73 (d, *J* = 7.6 Hz)	6.66 (dd, *J* = 8.2, 2.4 Hz)	6.79 (dd, *J* = 8.0, 1.3 Hz)
H–C(5′)	7.21 (dd, *J* = 7.9, 7.6 Hz)	6.89 (d, *J* = 8.2 Hz)	7.21 (dd, *J* = 8.0, 7.8 Hz)
H–C(6′)	7.28 (d, *J* = 7.9 Hz)	–	6.99 (dd, *J* = 7.8, 1.3 Hz)
CH_2(7′)	2.97–3.00 (m), 2.54–2.60 (m)	3.12–3.16 (m), 2.43–2.49 (m)	2.94–2.89 (m), 2.82–2.75 (m)
CH_2(8′)	3.23–3.29 (m), 3.00–3.03 (m)	3.18–3.24 (m), 3.01–3.05 (m)	2.96–2.90 (m), 2.96–2.90 (m)
H–C(10′)[a]	7.05 (m)	7.08 (dd, *J* = 8.2, 2.1 Hz)	6.92 (br m)
H–C(11′)[a]	6.82 (m)	6.77 (dd, *J* = 8.2, 2.4 Hz)	6.77 (br m)
H–C(13′)[a]	6.65 (m)	6.70 (dd, *J* = 8.2, 2.4 Hz)	6.77 (br m)
H–C(14′)[a]	7.04 (m)	7.05 (dd, *J* = 8.2, 2.1 Hz)	7.02 (br m)

[a] Signals of H–C(10′)/H–C(14′) and H–C(11′)/H–C(13′) interchangeable.

The HR-EI-MS showed the M^+ peak at *m*/*z* = 424.1659 (calcd for $C_{28}H_{24}O_4$: 424.1675) and different NMR experiments (H,H COSY, C,H COSY, HMBC, NOESY) were used to verify the structure of **6**. The spectroscopical data matched those published for the isolated riccardin D (**6**)[24] (solvent $CDCl_3$) as well as those for the isolated 'plagiochin E'[13] (solvent acetone-d_6).

In contrast to some bisbibenzyls possessing two C–C axes, like, e.g., isoplagiochin C, which we have shown to be configurationally stable and whose absolute configuration we have established,[7] no stereochemical investigations have as yet been reported for bisbibenzyls with an ether bridge and a C–C linkage. With the racemic synthetic material in hands, the stereostructures of such oxygen-bridged bisbibenzyls were investigated, exemplarily for the authentic plagiochin E (**4**). Resolution of **4** into its two atropo-enantiomers[26] clearly evidenced that **4** is a chiral, configurationally stable compound. Subsequent online circular dichroism (CD) measurements of the resulting peaks by LC-CD[27] in the stopped-flow mode gave perfectly mirror-imaged CD curves (Figure 3). Comparison of these experimental CD spectra with those predicted for the two enantiomers of **4** by quantum chemical TD-B2PLYP/SV(P)//B3LYP/6-31G*[28] CD calculations[29]



Scheme 6 *Reagents and conditions*: (i) 2 M NaOH, r.t., 24 h (85%); (ii) excess $SOCl_2$, reflux, 2 h, then $NaBH_4$, dioxane, reflux, 2 h (77%); (iii) dihydropyran, TsOH, CH_2Cl_2, r.t., 16 h (76%); (iv) *n*-BuLi, THF, –78 °C, 30 min, then $B(OMe)_3$, –78 °C to r.t., then sat. KH_2PO_4 (80%); (v) **21**, $Pd(PPh_3)_4$, PhMe–EtOH–2 M Na_2CO_3, reflux, 16 h (69%).

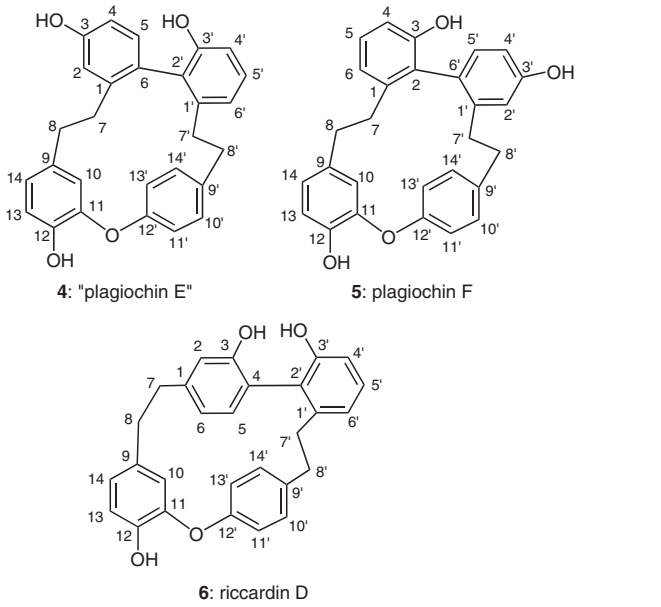
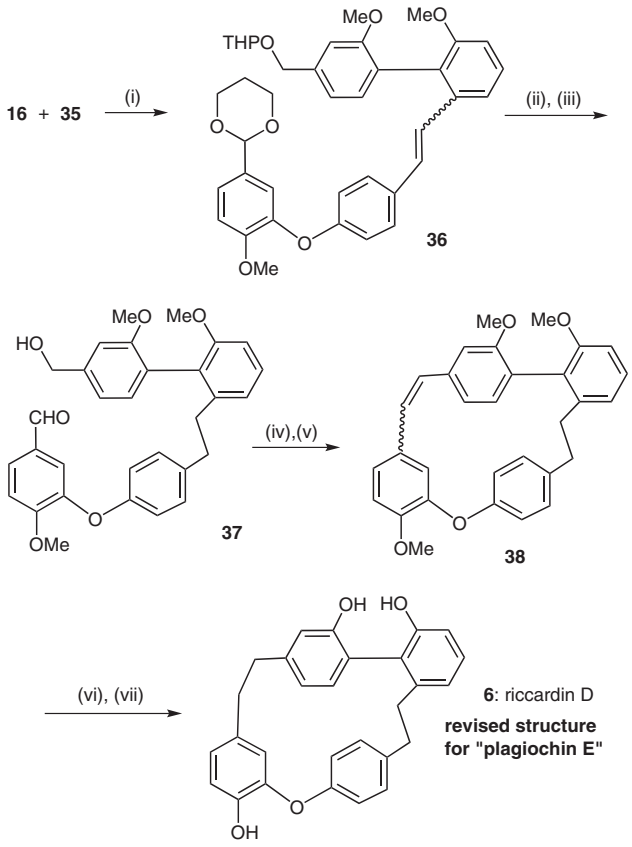


Figure 2 Structural correlation of the NMR of compounds **4–6**



Scheme 7 *Reagents and conditions*: (i) **16** (1.5 equiv), K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 24 h (94%); (ii) Pd/C (5%), 3 bar H_2, Et_3N, EtOAc, r.t., 24 h (99%); (iii) 2 M HCl–THF (1:1), r.t., 12 h (96%); (iv) $Ph_3P{\cdot}HBr$, MeCN, reflux, 12 h, reflux, 16 h; (v) NaOMe, CH_2Cl_2, 24 h (68% 2 steps) see ref.;[30] (vi) Pd/C (5%), 10 bar H_2, EtOAc, r.t., 24 h (95%); (vii) BBr_3 (10 equiv), CH_2Cl_2, –78 °C to r.t. over 5 h, then 10 h at r.t. (71%).

revealed the faster eluting peak **A** (t_R = 17.3 min) to be *P*-configured, and, thus, the slower eluting peak **B** (t_R = 30.1 min) to have the *M*-configuration at the biaryl axis (Figure 3).

Table 2 ^{13}C NMR Data of Synthetic Compounds **4–6** (δ in ppm)

125 MHz, acetone-d_6	**4**	**5**	**6**
C(1)	143.07	141.25	142.67
C(2)	114.10	127.67	117.90
C(3)	157.45	155.41	155.06
C(4)	112.31	113.60	121.14
C(5)	133.27	128.38	133.70
C(6)	127.56	118.43	121.21
C(7)	31.28	33.00	38.48
C(8)	30.63	30.94	37.52
C(9)	133.61	133.29	133.57
C(10)	116.89	116.54	117.81
C(11)	151.14	151.01	148.35
C(12)	144.41	144.44	145.34
C(13)	113.60	116.46	116.69
C(14)	122.00	113.41	122.79
C(1′)	140.25	141.61	145.01
C(2′)	129.26	115.90	126.06
C(3′)	155.55	157.22	155.59
C(4′)	116.49	122.04	113.87
C(5′)	128.25	133.39	129.39
C(6′)	120.71	128.10	122.57
C(7′)	36.34	36.01	35.69
C(8′)	34.03	33.99	38.51
C(9′)	141.27	141.15	141.33
C(10′)[a]	124.85	124.75	123.12
C(11′)[a]	131.17	131.13	130.05
C(12′)	156.65	156.40	154.36
C(13′)[a]	130.85	130.84	130.32
C(14′)[a]	123.24	123.22	122.85

[a] Signals of C(10′)/C(14′) and C(11′)/C(13′) interchangeable.

In summary, the isolated bisbibenzyl called 'plagiochin E' showing remarkable biological activities[13–17] has been proven to be riccardin D (**6**), the first total synthesis of which has now been described. The two other synthesized bisbibenzyls plagiochin E (**4**) and plagiochin F (**5**), although supposed to exist in nature (based on energetic and biosynthetic considerations), have never been isolated.[2] The successful availability of **4** and **5** by our chemical synthesis now permits testing of their biological activities. Furthermore the stereostructure of a bisbibenzyl with an

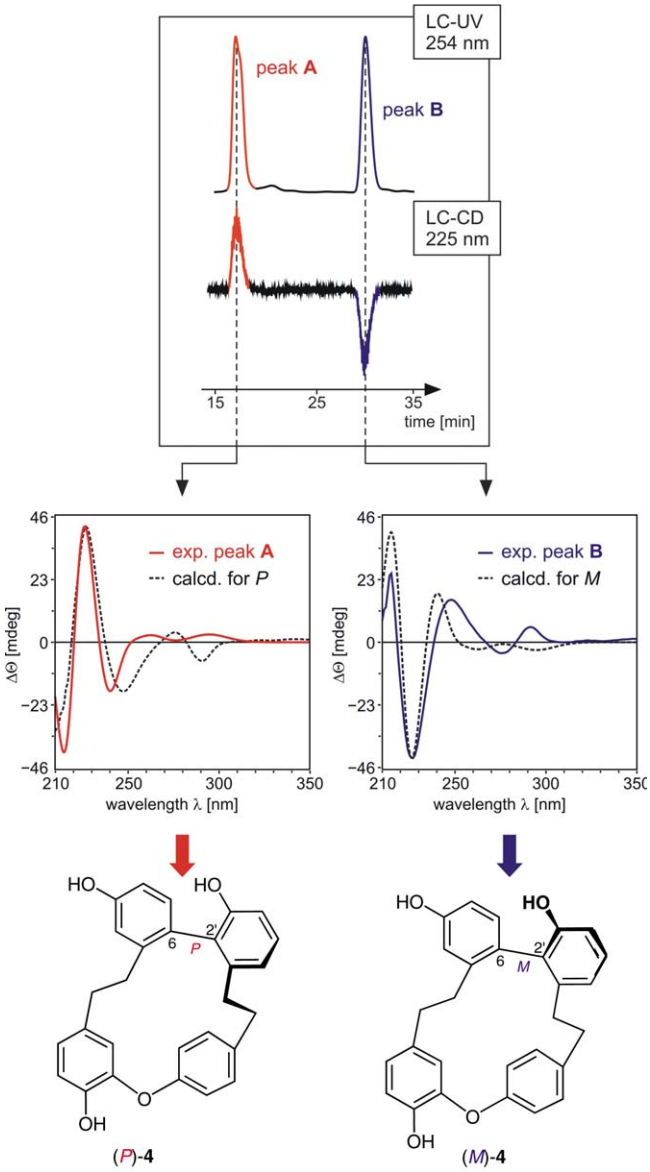


Figure 3 Stereochemical assignment of the two enantiomers of **4**, by LC-CD coupling and quantum chemical CD calculations

ether bridge and a C–C linkage has been investigated for the first time, here exemplarily for plagiochin E (**4**), by online CD measurements and quantum chemical CD calculations, thus permitting assignment of the absolute configuration of the two enantiomers, (*M*)-**4** and (*P*)-**4**.

Acknowledgment

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