The Biomimetic Synthesis and First Characterization of the (+)- and (−)-Isocentrolobines, 2,6-*cis*- and 2,6-*trans*-Disubstituted Tetrahydro-2*H*-pyrans

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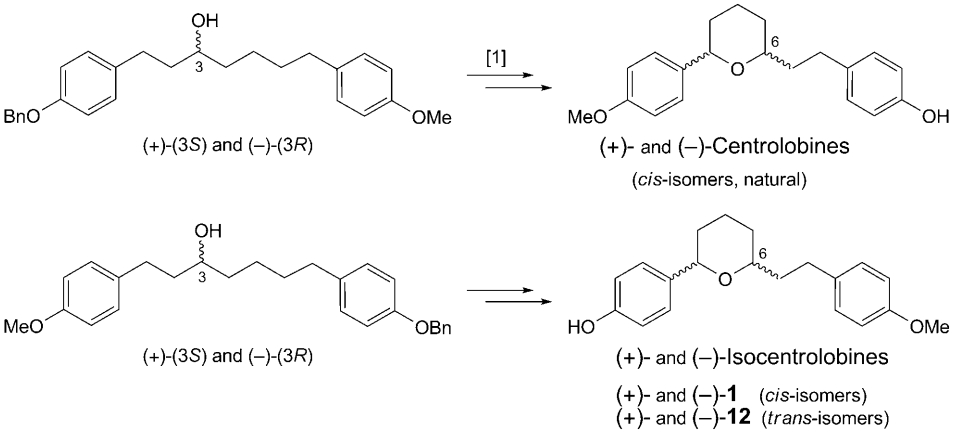
The four stereoisomers of the novel title compounds were prepared by oxidative cyclization of their enantiomerically pure diarylheptanoid precursors by means of the straightforward biomimetic approach presented in the preceding article. The isocentrolobines are the methoxy regioisomers of the natural (+)- and (−)-centrolobines and were characterized for the first time. The synthetic procedure established the absolute configurations and the unambiguous correlation with the chiroptical data. The spectroscopic and the chiroptical data of the isocentrolobines are highly similar to those of the natural products. The single diagnostic parameter that would allow a immediate assignment in the presence of only one of the isomers is the higher melting point (*ca.* 50°) of the *cis*-configured isocentrolobines.

1. Introduction. – In the preceding article, we described the synthesis and final structure determination of the natural 2,6-*cis*-disubstituted tetrahydro-2*H*-pyrans (+)- and (−)-centrolobine [1]. The key step of the procedure was the oxidative cyclization of the enantiomerically pure diarylheptanoid precursors with retention of their absolute configuration. As such, it constitutes a straightforward biomimetic approach and enables the access to the hitherto unknown isocentrolobine series by appropriate selection of the aryl substituents (*Scheme 1*) [1–3]. In this report, we present the first preparation and characterization of the four isocentrolobine stereoisomers *i.e.*, of (+)- and (−)-**1** (*cis*) and (+)- and (−)-**12** (*trans*), where the OH and the MeO groups are interchanged with respect to the natural products.

2. Synthesis and Characterization of the (+)- and (−)-Isocentrolobines. – 2.1. *(+)-(*S*)- and (−)-(*R*)-*O*-Methylisocentrolobol* ((+)- and (−)-**11**, resp.). Following the general protocol [1], the precursors (+)- and (−)-**11** were obtained from the homoallyl alcohols (+)- and (−)-**7** by cross-metathesis with 1-(benzyloxy)-4-(prop-2-en-1-yl)benzene (**6**; obtained from **4** *via* **5**), and catalytic hydrogenation of the resulting diarylheptanoids (+)- and (−)-**10** (*Scheme 2*): Enantioselective allylation of aldehyde **3** (obtained from **2**) under *Keck* conditions [4] yielded (+)-(*R*)- and (−)-(*S*)-**7** (ee > 99% and > 98%, resp.). The absolute configurations were verified by means of the respective *O*-MTPA derivatives [5] **8** and **9** and proved to be as expected [4] (MTPA = methoxy(phenyl)(trifluoromethyl)acetyl[1]). Treating (+)- and (−)-**7** with **6** in the

[1]) As in [1], this additional verification was performed to exclude further potential errors.

Scheme 1



presence of *Hoveyda–Grubbs* (2nd gen.) catalyst **HG-II** [6] at $-78°$[2]) furnished the diarylheptanoid homoallyl alcohols (+)- and (−)-**10** ((*E*)/(*Z*) *ca.* 10:1), and hydrogenation afforded the (+)-(*S*)- and (−)-(*R*)-*O*-methylisocentrolobols (+)- and (−)-**11** (ee > 99% and > 98%, resp.).

2.2. *Isocentrolobines (+)- and (−)-***1** *and (+)- and (−)-***12**. Like in the synthesis of the natural centrolobines [1], the key step is the oxidative cyclization of the *O*-methylisocentrolobols (+)- and (−)-**11** (*Schemes 2* and *3*): Treatment of (+)-**11** with DDQ and chromatographic separation afforded the isocentrolobine (+)-**1** (36%; ee > 99%) as the main compound besides the minor *trans*-configured 2-epimer (−)-**12** (8%; ee > 99%). Analogously, cyclization of (−)-**11** furnished (−)-**1** (34%; ee > 98%) and its 2-epimer (+)-**12** (8%; ee > 99%). Similar to [1], *ca.* 40% of the precursors (+)- and (−)-**11** could be recycled. Finally, the molecular structures of (−)-**1** and (+)-**12** were confirmed by X-ray crystallographic analyses (*Figs. 1* and *2*)[3]). Compared to the results in the natural centrolobine series [1], the yields of the cyclization reaction were significantly higher. This is due to the position of the easily oxidizable phenolic OH group in the *O*-methylisocentrolobols (+)- and (−)-**11** that facilitates the formation of the intermediate quinone methide **11ox** and precludes the side reaction *via* **11ox′** to the oxetane **13** (*Scheme 3*). This interpretation is consistent with the findings in [1], where the cyclization of the *O*-methylcentrolobols resulted in decomposition and had to be enforced after protection of the OH group. As expected, the sterically most favorable diequatorial arrangement of the substituents in **11ox** leads to the 2,6-*cis*-isomers (+)- and (−)-**1** as the main products. However, the less favored axial–equatorial arrange-

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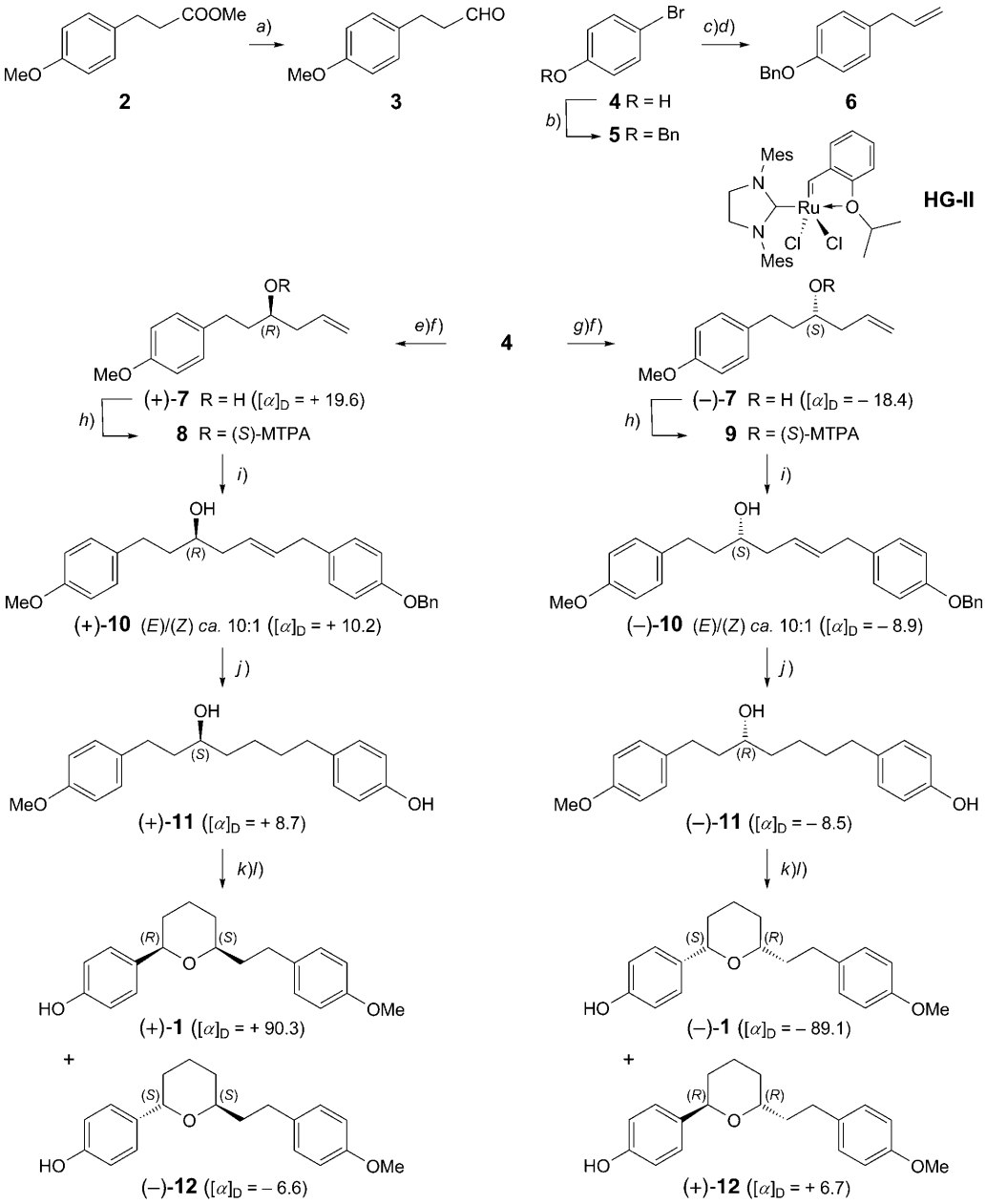
[2]) As discussed in [1], the metathesis reaction succeeded only when the glassware was soaked in 10% HCl solution during 16 h before use and when the reaction was performed at $-78°$ (see Exper. Part (General) in [1]).

[3]) The full data set is summarized in the *Table* (see *Exper. Part*). CCDC-765629 and -765630 contain the supplementary crystallographic data for (−)-**1** and (+)-**12**. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

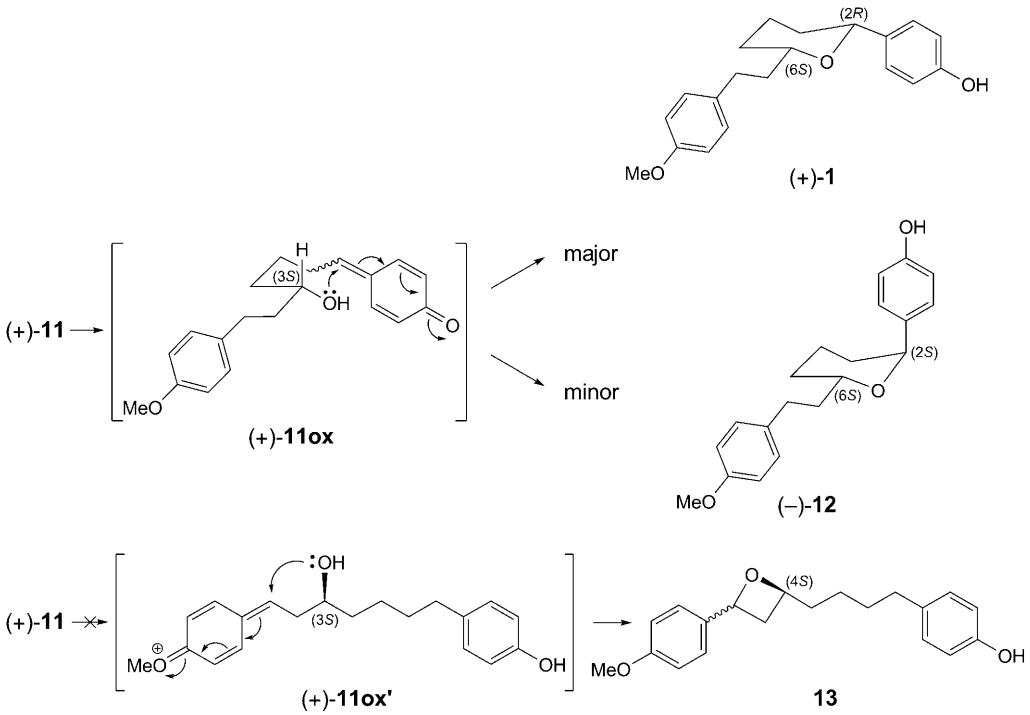
Scheme 2



a) DIBAH (diisobutylaluminium hydride), CH_2Cl_2, $-78°$. *b*) BnBr, NaH, THF, reflux. *c*) Mg, I_2, THF, reflux. *d*) CH_2=$CHCH_2Br$, THF, $-5°$. *e*) (–)-(*S*)-[1,1′-Binaphthalene]-2,2′-diol/(^{i}PrO)$_4$Ti, CH_2Cl_2, reflux. *f*) CH_2=$CHCH_2SnBu_3$, $-78° \rightarrow -20°$. *g*) (+)-(*R*)-[1,1′-Binaphthalene]-2,2′-diol/(^{i}PrO)$_4$Ti, CH_2Cl_2, reflux. *h*) (–)-(*R*)-MTPA-Cl, DMAP (*N*,*N*-dimethylpyridin-4-amine), Et_3N, r.t. *i*) **6**, *Hoveyda–Grubbs* (2nd gen.) catalyst **HG-II**, CH_2Cl_2, $-78° \rightarrow$ r.t. *j*) H_2, 10% Pd/C, CH_2Cl_2, r.t. *k*) DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile), AcOH, CH_2Cl_2, $-20°$. *l*) CC (SiO_2, hexane/CH_2Cl_2/AcOEt).

ment is also passed, thus affording the respective 2,6-*trans*-isomers (+)- and (−)-**12** as minor components (*Scheme 3*)[4]).

Scheme 3



2.3. *Absolute Configurations and Chiroptical Data*. Since the configuration at C(3) of the precursors (+)-(*S*)- and (−)-(*R*)-**11** is retained after the oxidative cyclization, the absolute configuration at C(6) of the resulting 2,6-disubstituted tetrahydro-2*H*-pyrans is preassigned. The one at C(2) follows from the relative 2,6-*cis*- or 2,6-*trans*-arrangement that is easily established by ^{1}H-NMR spectroscopy. As a consequence, the structures of the novel isocentrolobines are assigned: (+)-(2*R*,6*S*)-**1**, (−)-(2*S*,6*R*)-**1**, (+)-(2*R*,6*R*)-**12**, and (−)-(2*S*,6*S*)-**12**. Compared to the natural 2,6-*cis*-configured centrolobines ((+)-(2*R*,6*S*) and (−)-(2*S*,6*R*), resp.), the sign of the optical rotations remains unchanged, and their values are almost equal in the 2,6-*cis*-configured isocentrolobines. However, the sign of the optical rotations is opposite in the corresponding *trans*-series, a finding that is consistent with the synthetic *trans*-

[4]) Although not discussed in [1], we assume that the corresponding *trans*-centrolobines are also formed after cyclization of the *O*-methylcentrolobols. However, due to the low yields (< 10%), they were not detected.

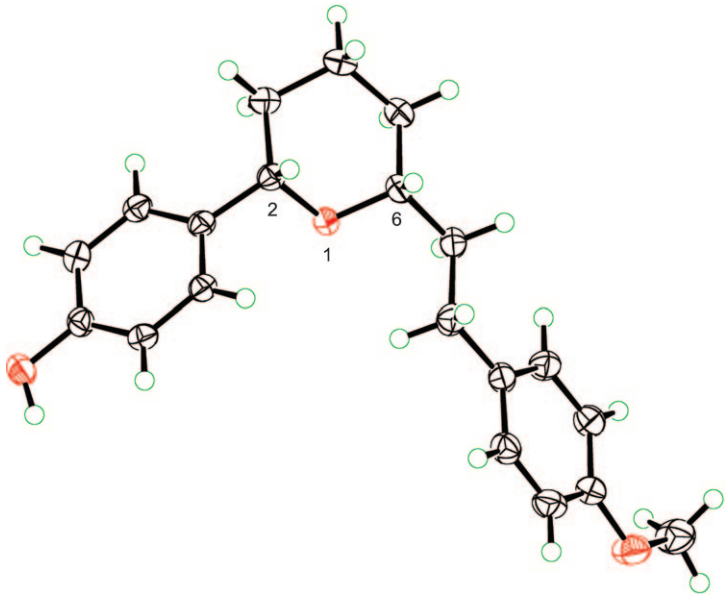


Fig. 1. *Molecular structure of synthetic (−)-isocentrolobine* ((−)-**1**). For reasons of clarity, the atom numbering is restricted to the tetrahydro-2*H*-pyran moiety; 50% probability ellipsoids.

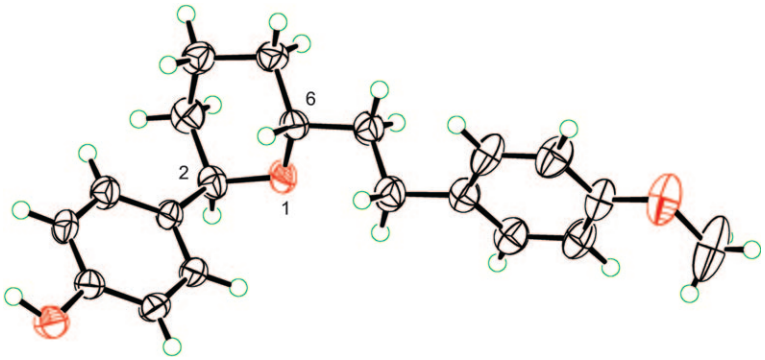


Fig. 2. *Molecular structure of the synthetic (+)*-trans-*isocentrolobine* ((+)-**12**). For reasons of clarity, the atom numbering is restricted to the tetrahydro-2*H*-pyran moiety; 50% probability ellipsoids.

centrolobines (=*epi*-centrolobines, (+)-(2*R*,6*R*) and (−)-(2*S*,6*S*), resp.) [7]. Hence, it can be concluded that the aryl substituent at the stereogenic center C(2) determines the chiroptical data[5]).

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[5]) See the discussion in [1] concerning the very probably erroneous assignment [8] of a natural *trans*-centrolobine congener.

3. Differentiation between Centrolobines and Isocentrolobines. – As discussed in [1], the structure of the natural centrolobines had been established only ambiguously [9]. Although the respective isocentrolobines were neither known nor taken into consideration, it was anticipated by implication that the two isomers would significantly differ in the physical, in particular the spectral data. In fact, just the melting points and the chromatographic behavior of the regioisomers are apparently different: (+)- and (−)-**1** have a m.p. 145–146° and R_f (SiO_2, hexane/Et_2O 1:2) 0.42, and the (+)- and (−)-centrolobines have a m.p. 93–94° and R_f (SiO_2, hexane/Et_2O 1:2) 0.20 [1]. In contrast, both the 2,6-*cis*-configured isocentrolobines and their centrolobine counterparts display highly similar IR, NMR, and mass spectra. Differences are only noticeable when a direct comparison of both isomers is made (*Fig. 3*). Whereas the IR (*Fig. 3,a*) and the ^{13}C-NMR spectra (*Fig. 3,c*) are nearly identical, the aromatic region in the ^{1}H-NMR exhibits features that would allow to distinguish the two regioisomers from each other (*Fig. 3,b*): The chemical-shift differences are significantly smaller in the isocentrolobines (+)- and (−)-**1**, and the signals are more compressed ($(\Delta\delta = \delta(H-C(2',6')) - \delta(H-C(2''',6''')) = 0.15$, and $\Delta\delta = \delta(H-C(3',5')) - \delta(H-C(3''',5'''))$[6]) $= 0.04$, see *Exper. Part*) than those of the centrolobines ($\Delta\delta = \delta(H-C(2',6')) - \delta(H-C(2''',6''')) = 0.29$, and $\Delta\delta = \delta(H-C(3',5')) - \delta(H-C(3''',5'''))$[6]$) = 0.19$ [1]). Although the chromatographic behavior and the ^{1}H-NMR data would suggest to allow a determination in the presence of only one of the isomers, the single reliable diagnostic parameter is the melting point. Since its difference (*ca.* 50°) is adequate, it constitutes an absolute parameter that is not dependent on extrinsic experimental factors. However, this conclusion can only be made in retrospect, with both regioisomers on hand.

4. Remarks. – Owing to the first description of the isocentrolobines and the review of the centrolobines [1], all eight stereoisomers of these 2-phenyl-6-(phenylethyl)-substituted tetrahydro-2*H*-pyrans are now fully characterized[7]). The comparison of the spectral and chiroptical data clearly demonstrates that an assignment with respect to one of the regioisomeric series is virtually meaningless as long as the alternative structure is not known nor even considered. This holds also for antiquated physical parameters like melting points as long as one is unaware of the alternative. It is remarkable that the melting point is the only straightforward diagnostic value that permits an unambiguous determination[8]). These considerations may lead to the assumption that the *O*-methylisocentrolobols (+)- and (−)-**11**[9]) as well as the isocentrolobines (+)- and (−)-**1** arguably are genuine natural products that have been

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[6]) For the atom numbering, see *Fig. 4* (*Exper. Part*).

[7]) The 2,6-*trans*-configured centrolobines (=*epi*-centrolobines, (+)-(2*R*,6*R*) and (−)-(2*S*,6*S*), resp.) have already been prepared [7].

[8]) Actually, less importance is attached to antiquated parameters, and sophisticated spectroscopic methods are predominant. This report illustrates an example where spectroscopy alone is unreliable.

[9]) A racemic compound with the constitution of *O*-methylisocentrolobol, *i.e.*, (±)-**11**, was reported to be a degradation product of acerogenin B. But only its *O*-methyl derivative was characterized and found to be identical with the known (±)-di-*O*-methylcentrolobol [10].

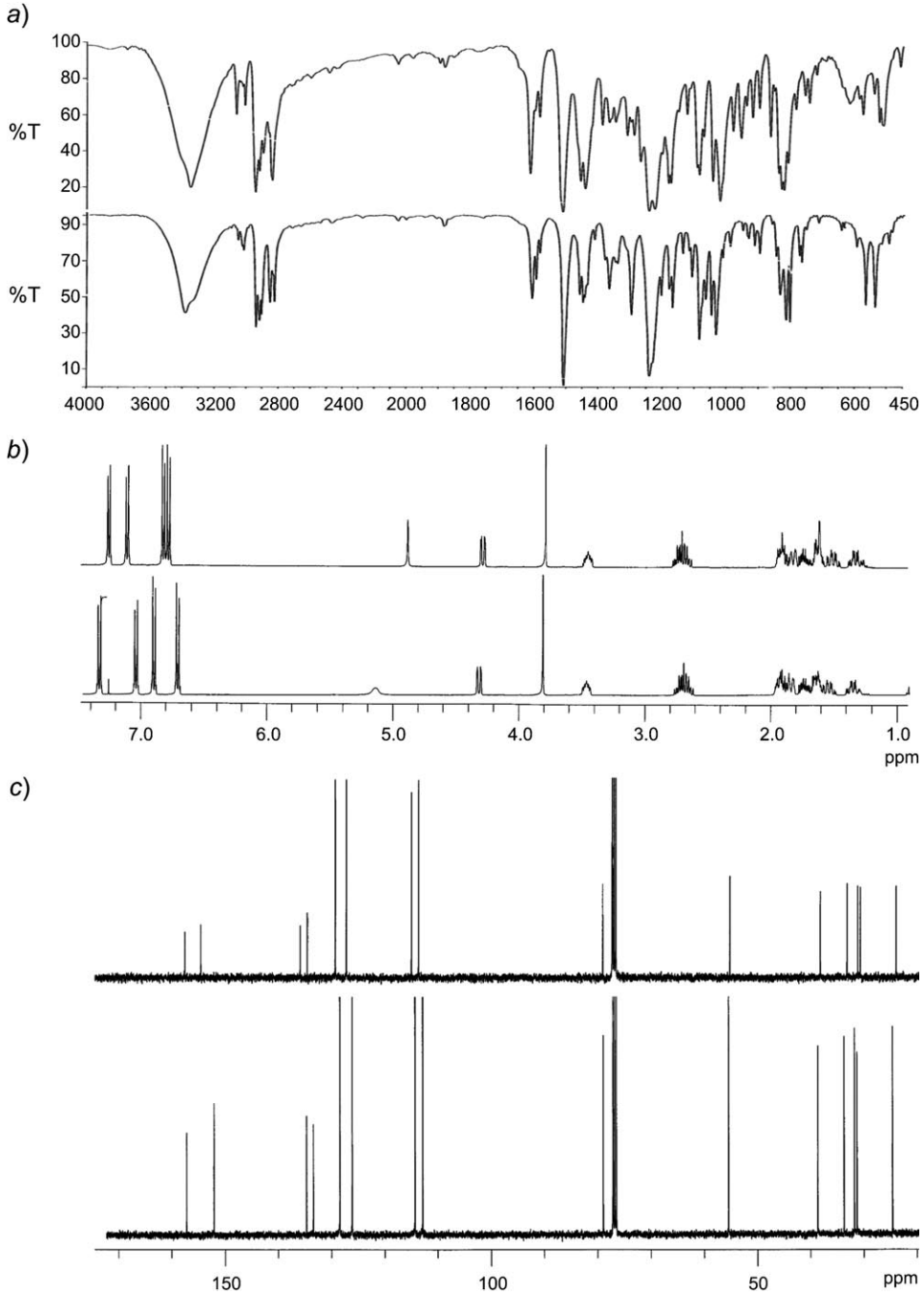

Fig. 3. *Spectral comparison of (−)-isocentrolobine* ((−)-**1**) (top traces) *and (−)-centrolobine* (bottom traces). *a*) IR Spectra ($CHCl_3$), *b*) ^{1}H-NMR spectra (600 MHz, $CDCl_3$), and *c*) ^{13}C-NMR spectra (150.9 MHz, $CDCl_3$).

ignored due to the similarity with the known isomers. However, no such evidence was discovered[10]), and the statement remains speculative.

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Experimental Part

1. *General.* See [1]. Nomenclature and atom numbering: Similar to [1], the arbitrary atom numbering is used for the description of the compounds. Hence, the C-atoms in the centrolobine series [1] maintain their numbers in the isocentrolobine series to facilitate a straightforward spectral comparison (*Fig. 4*); systematic names are given in the headings.

Fig. 4. *Arbitrary atom numbering for the diarylheptanes and the tetrahydro-2*H*-pyrans*

2. *3-(4-Methoxyphenyl)propanal* (=*4-Methoxybenzenepropanal*; **3**). Reduction of methyl 3-(4-methoxyphenyl)propanoate (=methyl 4-methoxybenzenepropanoate; **2**; 5.0 g, 25.74 mmol; prepared from 4-methoxycinnamic acid (*purum*, *Fluka 6542*) by standard procedures) in anh. CH_2Cl_2 (90 ml) with 1M diisobutylaluminium hydride (DIBAH; 26 ml, 26.0 mmol in CH_2Cl_2) at $-80°$, workup, and CC (SiO_2; hexane/AcOEt 9:1) yielded **3** (3.67 g 87%). Colorless oil. R_f (hexane/Et_2O 1:2) 0.45. GC ('low'): t_R 7 min 9 s. IR (film): 3032*w*, 3002*w*, 2935*m*, 2835*m*, 1723v*s*, 1611*m*, 1583*w*, 1513v*s*, 1465*m*, 1442*m*, 1407*w*, 1388*w*, 1357*w*, 1300*m*, 1247v*s*, 1179*s*, 1111*w*, 1034*s*, 860*w*, 830*m*, 812*m*, 769*w*, 663*w*, 542*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.81 (*t*, ^3J = 1.5, H–C(1)); 7.11 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.83 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 3.78 (*s*, MeO–C(4′)); 2.91 (*t*, ^3J(3,2) = 7.4, CH_2(3)); 2.75 (*tt*, ^3J (2,3) = 7.5, ^3J(1,2) = 1.5, CH_2(2)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 201.7 (C(1)); 158.1 (C(4′)); 132.3 (C(1′)); 129.2 (C(2′), C(6′)); 114.0 (C(3′), C(5′)); 55.3 (*Me*O–C(4′)); 45.5 (C(2)); 27.3 (*s*, C(3)). EI-MS: 166 (41, M^+), 135 (4), 121 (100, $C_8H_9O^+$), 119 (3), 108 (33), 105 (4), 103 (5), 91 (17, $PhCH_2^+$), 89 (4), 79 (5), 77 (19), 65 (11), 63 (7), 55 (3), 51 (9).

3. *1-(Benzyloxy)-4-(prop-2-en-1-yl)benzene* (=*1-(Phenylmethoxy)-4-(prop-2-en-1-yl)benzene*; **6**). To a suspension of NaH (6.5 g, 159 mmol) in anh. THF (50 ml), 4-bromophenol (**4**; 20.0 g, 115.6 mmol) was added at 0° and stirred at r.t. (30 min). Then benzyl bromide (17 ml, 143.2 mmol) was added, and the mixture kept under reflux (18 h). Workup, CC (SiO_2; hexane → hexane/AcOEt 99:1), and recrystallization (hexane/Et_2O) afforded 1-(benzyloxy)-4-bromobenzene (=1-bromo-4-(phenylmethoxy)benzene; **5**; 25.24 g, 83%). Colorless needles. M.p. 63–64°. R_f (hexane/Et_2O 5:2) 0.54. GC ('low'): t_R 10 min 25 s. IR (KBr): 3088*w*, 3061*m*, 1638*w*, 1587*m*, 1576*s*, 1487v*s*, 1452*s*, 1404*m*, 1378*m*, 1335*w*, 1312*m*, 1289*s*, 1248v*s*, 1170*s*, 1117*m*, 1103*m*, 1080*m*, 1070*m*, 1042*s*, 1026*s*, 999*m*, 931*m*, 905*m*, 825v*s*, 813*s*, 734v*s*, 694*s*, 657*m*, 562*w*, 532*w*, 505*m*, 462*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.30 (*m* and *AA′* of *AA′BB*, ^3J = 9.0, *Ph*CH_2, H–C(2), H–C(6)); 6.86 (*BB′* of *AA′BB′*, ^3J = 9.0, H–C(3), H–C(5)); 5.04 (s, PhCH_2).

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[10]) The most recent report on the isolation of (−)-centrolobine ($[\alpha]_D = -92.2$) from the heartwood of *Brosimum potabile* (Moraceae) [11] might have been such a candidate. The constituent was identified and characterized by ^{1}H- and ^{13}C-NMR spectroscopy, but the m.p. is not reported. In our hands, the authentic sample had m.p. 87–90°, and the X-ray crystallographic analysis confirmed the proposed structure [1]. However, the formula depicted for (−)-centrolobine [11] represents the (+)-enantiomer.

^{13}C-NMR (75.4 MHz, $CDCl_3$): 157.9 (C(4)); 136.6 (*Ph*CH_2); 132.3 (C(2), C(6)); 128.6, 128.1, 127.4 (*Ph*CH_2); 116.7 (C(3), C(5)); 113.1 (C(1)); 70.2 (Ph*C*H_2)). EI-MS: 264, 262 (8, 8, $M(^{81}Br)^+$, $M(^{79}Br)^+$, $C_{13}H_{11}BrO^+$), 173 (2, $[M(^{81}Br) - PhCH_2]^+$), 171 (2, $[M(^{79}Br) - PhCH_2]^+$), 157 (1), 155 (1), 154 (1), 152 (1), 145 (5), 143 (5), 119 (2), 117 (2), 91 (100, $PhCH_2^+$), 89 (6), 77 (3), 65 (30), 63 (18), 51 (7).

To a refluxing suspension of Mg turnings (1.40 g, 57.6 mmol) and an I_2 crystal in anh. THF, a soln. of **5** (15.0 g, 57.0 mmol) in anh. THF (120 ml) was slowly added and kept for 3 h under reflux. After cooling to $-5°$, a soln. of allyl bromide (5 ml, 59.13 mmol) in anh. THF (15 ml) was added and the mixture stirred at r.t. (18 h). Workup, CC (SiO_2; hexane/AcOEt 99:1) and bulb-to-bulb distillation at 100°/10^{-3} mbar afforded **6** (10.82 g, 85%). Colorless oil. R_f (hexane/Et_2O 5:2) 0.58. GC ('low'): t_R 10 min 12 s. IR (film): 3065*m*, 3032*m*, 3005*m*, 2977*m*, 2901*m*, 1638*m*, 1611*s*, 1583*m*, 1509v*s*, 1454*s*, 1433*m*, 1381*s*, 1298*s*, 1241v*s*, 1175v*s*, 1112*m*, 1080*w*, 1025*w*, 995*w*, 913v*s*, 860*m*, 830*m*, 816*m*, 783*m*, 735*s*, 696*s*, 646*m*, 592*w*, 576*w*, 527*m*, 455*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.48–7.32 (*m*, *Ph*CH_2); 7.14 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(3), H–C(5)); 6.95 (*BB′* of *AA′BB′*, $^3J = 8.7$, H–C(2), H–C(6)); 5.96 (*ddt*, $^3J = 16.8, 10.4, 6.7$, H–C(2′)); 5.08 (*dq*, $^3J = 16.8$, $^2J \approx {}^4J \approx 1.5$, H_{trans}–C(3′)); 5.07 (*dq*, $^3J = 10.4$, $^2J \approx {}^4J \approx 1.5$, H_{cis}–C(3′)); 5.06 (*s*, PhCH_2); 3.35 (br. *d*, $^3J = 6.7$, CH_2(1″)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 157.2 (C(1)); 137.8 (C(2′)); 137.2 (*Ph*CH_2); 132.4 (C(4′)); 129.5 (C(3), C(5)); 128.5, 127.8, 127.4 (*Ph*CH_2); 115.4 (C(3′)); 114.8 (C(2), C(6)); 70.1 (Ph*C*H_2); 39.3 (C(1′)). EI-MS: 224 (16, M^+), 181 (1), 133 (1, $[M - PhCH_2]^+$), 115 (2), 105 (2), 103 (3), 91 (100, $PhCH_2^+$), 89 (3), 79 (3), 78 (4), 77 (8), 65 (21), 63 (5), 53 (2), 51 (7).

4. *(+)-(3*R*)- and (−)-(3*S*)-1-(4-Methoxyphenyl)hex-5-en-3-ol* (=*(+)-(α*R*)-* and *(−)-(α*S*)-4-Methoxy-α-prop-2-en-1-yl)benzenepropanol*, resp.; (+)- and (−)-**7**, resp.)[11]). Following the protocol in [1], we obtained from **3** (2.00 g, 12.18 mmol), after treatment with (−)-(*S*)-[1,1′-binaphthalene]-2,2′-diol (349 mg, 1.22 mmol), (^{i}PrO)$_4$Ti (360 µl, 1.22 mmol), and CH_2=$CHCH_2SnBu_3$ (4.5 ml, 14.7 mmol) and CC (SiO_2; hexane/Et_2O 2:1), (+)-**7** (2.01 g, 80%; ee > 99%) as colorless oil that solidified in the refrigerator. Analogously, starting from **3** (2.00 g, 12.18 mmol), (+)-(*R*)-[1,1′-binaphthalene]-2,2′-diol (350 mg, 1.22 mmol), (^{i}PrO)$_4$Ti (360 µl, 1.22 mmol), and CH_2=$CHCH_2SnBu_3$ (4.5 ml, 14.7 mmol), we obtained (−)-**7** (2.11 g, 84%; ee > 98%). HPLC (*Chiralcel® OD-H*, hexane/^{i}PrOH 50:1): k'((+)-**7**) = 3.6, k'((−)-**7**) = 2.9, R_S = 3.6).

*Data of (+)-***7**: M.p. 39–40°. R_f (hexane/Et_2O 1:2) 0.38. GC ('low'): t_R 9 min 2 s. $[\alpha]_D$ = +19.6 (*c* = 0.56, EtOH). IR (KBr): 3352*s*, 3283*s*, 3103*w*, 3071*m*, 3032*w*, 3001*m*, 2944*m*, 2917*s*, 2862*m*, 2838*m*, 1642*m*, 1612*m*, 1586*w*, 1513v*s*, 1468*m*, 1453*m*, 1362*w*, 1334*w*, 1322*w*, 1300*m*, 1274*m*, 1244v*s*, 1179*s*, 1164*m*, 1131*w*, 1109*m*, 1081*s*, 1062*m*, 1036v*s*, 988*m*, 952*w*, 938*w*, 912*m*, 867*m*, 820*s*, 766*m*, 751*m*, 717*s*, 662*m*, 629*m*, 560*m*, 533*m*, 509*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (*AA′* of *AA′BB′*, $^3J = 8.4$, H–C(2′), H–C(6′)); 6.84 (*BB′* of *AA′BB′*, $^3J = 8.6$, H–C(3′), H–C(5′)); 5.82 (*X* of *ABMX*, $^3J = 17.3, 10.2, 7.8, 5.5$, H–C(5)); 5.14 (*dq*-like, $^3J = 17.3, 10.2$, $^2J \approx {}^4J < 1$, CH_2(6)); 3.79 (*s*, MeO–C(4′)); 3.70 (*M* of *ABMX*, *quint.*-like, $^3J \approx 7$, H–C(3)); 2.75 (*A* of *ABXY*, $^2J = 14.3$, $^3J = 7.2$, H_A–C(1)); 2.64 (*B* of *ABXY*, $^2J = 14.3$, $^3J = 7.8$, H_B–C(1)); 2.32 (*A* of *ABMX*, $^2J = 14.5$, $^3J = 5.5$, $^4J < 1$ H_A–C(4)); 2.18 (*B* of *ABMX*, $^2J = 14.5$, $^3J = 7.8$, H_B–C(4)); 1.76 (*XY* of *ABXY*, *q*-like, CH_2(2)); 1.65 (*s*, HO–C(3)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 157.8 (C(4′)); 134.6 (C(5′)); 134.1 (C(1′)); 129.3 (C(2′), C(6′)); 118.2 (C(6)); 113.8 (C(3′), C(5′)); 69.9 (C(3)); 55.2 (*Me*O–C(4′)); 42.0 (C(2)); 38.6 (C(4)); 31.1 (C(1)). EI-MS: 206 (21, M^+), 188 (5, $[M - H_2O]^+$), 173 (2), 164 (4), 159 (2), 147 (37), 134 (7), 121 (100, $C_8H_9O^+$), 119 (4), 108 (10), 105 (3), 103 (4), 91 (18, $PhCH_2^+$), 89 (4), 78 (17), 77 (19), 65 (8), 63 (4), 55 (3), 51 (6).

*Data of (−)-***7**: $[a]_D$ = −18.4 (*c* = 0.58, EtOH). All other data: identical with those of (+)-**7**.

5. *(*S*)-MTPA Derivatives* **8** *and* **9** *for the Confirmation of the Absolute Configuration*. Each homoallyl alcohol (+)- or (−)-**7** (each 15 mg, 0.073 mmol) was dissolved in anh. CH_2Cl_2 (1 ml) and Et_3N (20 µl, 0.144 mmol). DMAP (1 mg) and (+)-(*R*)-MTPA-Cl (14 µl, 0.075 mmol) were added, and the mixture was stirred at r.t. for 4 h. Workup and CC (SiO_2; hexane/AcOEt 19:1) afforded the (*S*)-MTPA ester **8** (26 mg, 85%) or **9** (27 mg, 88%), resp., both as colorless, viscous oils.

*(3*R*)-1-(4-Methoxyphenyl)hex-5-en-3-yl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate* (=*(α*S*)-α-Methoxy-α-(trifluoromethyl)benzeneacetic Acid (1*R*)-1-[2-(4-Methoxyphenyl)ethyl]but-3-en-1-yl Ester*; **8**): R_f (hexane/Et_2O 1:1) 0.56. GC ('low'): t_R 13 min 34 s. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.60–7.57, 7.44–7.39 (*m*, Ph); 7.05 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(2′), H–C(6′)); 6.83 (*BB′* of *AA′BB′*, $^3J = 8.7$,

[11]) The compounds have been prepared and well documented earlier: (+)-**7** [12] and (−)-**7** [13].

H–C(3′), H–C(5′)); 5.65 (*ddt*, ^3J = 17, 10, 6, H–C(5)); 5.18 (br. *quint.*, $^3J \approx 6$, H–C(3)); 5.03 (*dq*-like, ^3J = 17, 10, $^2J \approx {}^4J \approx 1$, CH_2(6)); 3.79 (*s*, MeO–C(4′)); 3.57 (*q*, ^5J(H,F) = 1.2, MeO of MTPA); 2.59 (*m*, *dquint.*-like, $w_{1/2} \approx 30$, CH_2(1)); 2.40 (*tt*, ^3J = 6, $^4J \approx 1$, CH_2(4)); 1.95 (*m*, *dquint.*-like, $w_{1/2} \approx 30$, CH_2(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 166.2 (CO); 158.0 (C(4′)); 133.0 (C(1′)); 132.6 (C(5)); 132.3, 129.6 (Ph); 129.2 (C(2′), C(6′)); 128.4, 127.5 (Ph); 123.4 (*q*, ^1J(C,F) = 289, CF_3); 118.5 (*s*, C(6)); 114.0 (C(3′), C(5′)); 84.6 (*q*, ^2J(C,F) = 27.9, Ph*C*(MeO)(CF_3)CO); 76.0 (C(3)); 55.4 (MeO of MTPA); 55.3 (*Me*O–C(4′)); 38.0 (C(4)); 35.4 (C(2)); 30.6 (C(1)). EI-MS: 422 (4, M^+), 189 (56, [M – MTPA – H_2O]$^+$), 173 (2), 159 (4), 147 (73), 139 (3), 134 (6), 127 (4), 121 (100, $C_8H_9O^+$), 115 (2), 107 (1, $C_7H_7O^+$), 105 (11), 91 (9, $PhCH_2^+$), 77 (8), 69 (2), 51 (1).

*(3*S*)-1-(4-Methoxyphenyl)hex-5-en-3-yl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate* (= *(α*S*)-α-Methoxy-α-(trifluoromethyl)benzeneacetic Acid (1*S*)-1-[2-(4-Methoxyphenyl)ethyl]but-3-en-1-yl Ester*; **9**): R_f (hexane/Et_2O 1:1) 0.56. GC ('low'): t_R 13 min 34 s. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.61–7.58, 7.43–7.39 (*m*, Ph); 6.98 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.81 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 5.76 (*ddt*, ^3J = 17, 10, 7, H–C(5)); 5.18 (br. *quint.* $^3J \approx 6$, H–C(3)); 5.12 (*dq*, ^3J = 17, $^2J \approx {}^4J \approx 1$, H_{trans}–C(6)); 5.11 (*dq*, ^3J = 10, $^2J \approx {}^4J \approx 1$, H_{cis}–C(6)); 3.78 (*s*, MeO–C(4′)); 3.59 (*q*, ^5J(H,F) = 1.3, MeO of MTPA); 2.46 (br. *sext.*-like, $w_{1/2} \approx 20$, CH_2(1), CH_2(4)); 1.88 (br. *tq*-like, $w_{1/2} \approx 15$, CH_2(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 166.2 (CO); 158.0 (C(4′)); 133.1 (C(1′)); 132.9 (C(5)); 132.4, 129.6 (Ph); 129.2 (C(2′), C(6′)); 128.4, 127.4 (Ph); 123.4 (*q*, ^1J(C,F) = 289, CF_3); 118.6 (C(6)); 113.9 (C(3′), C(5′)); 84.5 (*q*, ^2J(C,F) = 27.5, Ph*C*(MeO)(CF_3)CO); 75.9 (C(3)); 55.5 (MeO of MTPA); 55.2 (*Me*O–C(4′)); 38.3 (C(4)); 35.4 (C(2)); 30.26 (C(1)). EI-MS: 422 (3, M^+), 189 (55, [M – MTPA – H_2O]$^+$), 173 (2), 159 (3), 147 (75), 139 (4), 134 (6), 127 (4), 121 (100, $C_8H_9O^+$), 115 (2), 107 (1, $C_7H_7O^+$), 105 (12), 91 (9, $PhCH_2^+$), 77 (9), 69 (2), 51 (1).

$\Delta\delta(^1H) = \delta(S) - \delta(R) = \delta(\mathbf{9}) - \delta(\mathbf{8})$ (in Hz): CH_2(1) −52, CH_2(2) −28, H–C(3) 0, CH_2(4) −24, H–C(5) +44, and CH_2(6) +34. The relative displacements [5] confirm the expected [4] absolute configuration at C(3).

5. *(+)- and (−)-(5*E*)-4″*-O-*(Benzyloxy)-5,6-didehydro-4′*-O-*methylisocentrolobol* (= *(+)-(3*R*,5*E*)-* and *(−)-(3*S*,5*E*)-7-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)hept-5-en-3-ol* = *(+)-(α*R*)-* and *(−)-(α*S*)-α-{(2*E*)-4-[4-(Phenylmethoxy)phenyl]but-2-en-1-yl}-4-methoxybenzenepropanol*, resp.; (+)- and (−)-**10**, resp.). To a soln. of catalyst **HG-II** (42 mg, 0.067 mmol) in anh. CH_2Cl_2 (4.5 ml) at −78°, a soln. of (+)-**7** (150 mg, 0.73 mmol) and 1-(benzyloxy)-4-(prop-2-en-1-yl)benzene (**6**; 657 mg, 2.93 mmol) in anh. CH_2Cl_2 (3 ml) was slowly added under Ar. The mixture was stirred (1 h) at −78°, allowed to warm to r.t. for 6 h, then quickly passed through SiO_2 (hexane/CH_2Cl_2/AcOEt 2:7:1) and concentrated. CC (SiO_2; hexane/CH_2Cl_2/AcOEt 5:14:1) afforded starting (+)-**7** (58 mg, 39%) that could be recycled, and (+)-**10** (131 mg, 45%; (*E*)/(*Z*) *ca.* 10:1[12]) as colorless oil that solidified in the refrigerator. Analogously, starting from (−)-**7** (150 mg, 0.73 mmol), **6** (655 mg, 2.93 mmol) in anh. CH_2Cl_2 (7.5 ml), and catalyst **HG-II** (44 mg, 0.07 mmol), we obtained (−)-**6** (47 mg, 31%) and (−)-**10** (139 mg, 48%; (*E*)/(*Z*) *ca.* 10:1[12]).

*Data of (+)-***10**: M.p. 46–49°. R_f (hexane/Et_2O 1:2) 0.34. $[\alpha]_D$ = +10.2 (*c* = 0.52, EtOH). IR (KBr): 3354*m*, 3062*w*, 3032*w*, 2999*w*, 2925*m*, 2858*m*, 2832*m*, 1611*m*, 1584*m*, 1510v*s*, 1465*m*, 1454*m*, 1440*m*, 1429*m*, 1380*m*, 1300*m*, 1244v*s*, 1176*m*, 1110*w*, 1096*w*, 1074*m*, 1039*s*, 1027*m*, 970*m*, 921*w*, 861*w*, 818*m*, 807*m*, 737*m*, 716*w*, 697*m*, 623*w*, 580*w*, 519*w*. ^{1}H-NMR (400 MHz, $CDCl_3$)[13]): 7.47–7.33 (*m*, Ph); 7.13 (2 *AA′* of *AA′BB′*, *t*-like, $^3J \approx 9$, H–C(2′), H–C(2″), H–C(6′), H–C(6″)); 6.94 (*BB′* of *AA′BB′*, ^3J = 8.4, H–C(3″), H–C(5″)); 6.87 (*BB′* of *AA′BB′*, ^3J = 8.4, H–C(3″), H–C(5″)); 5.72 (*X* of *ABMX*, *dt*, ^3J(5,6) = 14.6, ^3J(6,7) = 6.8, H–C(6)); 5.52 (br. *dt*, ^3J(5,6) = 14.5, ^3J(4,5) = 7.2, ^4J(3,5) < 1, H–C(5)); 5.07 (*s*, PhCH_2); 3.81 (*s*, MeO–C(4′)); 3.67 (*M* of *ABMX*, *quint.*-like, $^3J \approx 7$, H–C(3)); 3.34 (*d*, ^3J(6,7) = 6.8, CH_2(7)); 2.76 (*A* of *ABXY*, ^2J = 14.3, ^3J = 6.4, H_A–C(1)); 2.67 (*B* of *ABXY*, ^2J = 14.3, ^3J = 7.7, H_B–C(1)); 2.30 (*A* of *ABMX*, ^2J = 13.5, ^3J = 5.5, ^4J < 1 H_A–C(4)); 2.20 (*B* of *ABMX*, ^2J = 14.5, ^3J = 7.6, H_B–C(4)); 1.77 (*XY* of *ABXY*, *m*, $w_{1/2} \approx 15$, CH_2(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$)[13]): 157.7 (C(4′)); 157.1 (C(4″)); 137.1 (Ph); 134.1 (C(1′)); 133.3 (C(6)); 132.8 (C(1″)); 129.3, 129.2 (C(2′), C(2′), C(6′), C(6″)); 128.5, 127.8, 127.4 (Ph); 126.9 (C(5)); 114.8 (C(3″), C(5″)); 113.8 (C(3′), C(5′)); 70.2 (C(3)); 70.0 (PhCH_2); 55.2

[12]) Estimated according to the intensities of the ^{1}H-NMR signals of CH_2(7).

[13]) Only the (*E*)-isomer is specified.

(*Me*O–C(4′)); 40.7 (C(4)); 38.6 (C(2)); 38.2 (C(7)); 31.0 (C(1)). EI-MS: 402 (7, M^+), 384 (2, $[M-H_2O]^+$), 238 (4), 211 (15), 197 (5), 164 (5), 147 (14), 121 (54, $C_8H_9O^+$), 107 (6, $C_7H_7O^+$), 91 (100, $PhCH_2^+$), 77 (5), 65 (5).

*Data of (−)-***10**: $[a]_D = -8.9$ ($c = 0.61$, $CHCl_3$). All other data: identical with those of (+)-**10**.

6. *(+)- and (−)-4′-*O*-Methylisocentrolobols* (= *(+)-4-[(5*S*)-* and *(−)-4-[(5*R*)-5-Hydroxy-7-(4-methoxyphenyl)heptyl]phenol* = *(+)-(*α*S)-* and *(−)-(*α*R)-*α*-[2-(4-Methoxyphenyl)ethyl]-4-hydroxybenzenepentanol*, resp.; (+)- and (−)-**11**, resp.). Following the protocol in [1], hydrogenation of (+)-**10** (250 mg, 0.622 mmol) over 10% Pd/C (45 mg, 0.0343 mmol) and CC (SiO_2; hexane/CH_2Cl_2/AcOEt/^{i}PrOH 20:75:4:1) afforded (+)-**11** (172 mg, 88%; ee > 99%) as a colorless, viscous oil. Analogously, starting from (−)-**10** (230 mg, 0.572 mmol) and 10% Pd/C (40 mg, 0.038 mmol), we obtained (−)-**11** (162 mg, 90%; ee > 98%). HPLC (*Chiralcel® OD-H*, hexane/^{i}PrOH 8:1): k'((+)-**11**) = 8.7, k'((−)-**11**) = 6.9, $R_S = 2.5$.

*Data of (+)-***11**: R_f (hexane/Et_2O 1:4) 0.45. $[\alpha]_D = +8.8$ ($c = 0.53$, EtOH). IR (film): 3356*s*, 3012*m*, 2934v*s*, 1612*s*, 1513v*s*, 1454*s*, 1371*m*, 1300*m*, 1245v*s*, 1178*s*, 1109*w*, 1076*m*, 1035*s*, 984*w*, 913*w*, 827*s*, 769*w*, 747*w*, 705*w*, 639*w*, 556*w*, 514*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(2′), H–C(6′)); 7.01 (*BB′* of *AA′BB′*, $^3J = 8.5$, H–C(2″), H–C(6″)); 6.84 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(3′), H–C(5′)); 6.75 (*BB′* of *AA′BB′*, $^3J = 8.5$, H–C(3″), H–C(5″)); 6.00 (br. *s*, HO–C(4″)); 3.79 (*s*, MeO–C(4′)); 3.64 (br. *quint.*-like, $^3J \approx 7$, H–C(3)); 2,53 (*d*, $^3J = 6.8$, CH_2(7)); 2.76 (*A* of *ABXY*, $^2J = 14.0$, $^3J = 6.4$, H_A–C(1)); 2.67 (*B* of *ABXY*, $^2J = 14.0$, $^3J = 7.0$, H_B–C(1)); 1.74 (*XY* of *ABXY*, *m*, $w_{1/2} \approx 25$, CH_2(2)); 1.58 (*m*, $w_{1/2} \approx 20$, CH_2(6)); 1.54–1.42 (*m*, CH_2(4), H–C(5), HO–C(3)); 1.36 (*m*, br. *t*-like, $w_{1/2} \approx 15$, H–C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 157.7 (C(4′)); 153.8 (C(4″)); 134.3 (C(1″)); 134.1 (C(1′)); 129.3 (C(3″), C(5″)), 129.2 (C(3′), C(5′)); 115.1 (C(2″), C(6″)); 113.8 (C(2′), C(6′)); 71.5 (C(3)); 55.2 (*Me*O–C(4′)); 39.1 (C(2)); 37.2 (C(4)); 34.9 (C(7)); 31.6 (C(6)); 31.0 (C(1)); 25.1 (C(5)). EI-MS: 314 (9, M^+), 296 (17, $[M-H_2O]^+$), 188 (5), 175 (3), 161 (3), 147 (34), 134 (17), 121 (100, $C_8H_9O^+$), 107 (36, $C_7H_7O^+$), 91 (8, $PhCH_2^+$), 77 (8), 59 (7).

*Data of (−)-***11**: $[a]_D = -8.5$ ($c = 0.56$, EtOH). All other data: identical with those of (+)-**11**.

7. *Cyclization to the* cis- *and* trans-*Tetrahydro-2*H*-pyrans. (+)- and (−)-Isocentrolobine* (= *(+)-(2*R*,6*S*)-* and *(−)-(*2S,6R*)-2-(4-Hydroxyphenyl)-6-[2-(4-methoxyphenyl)ethyl]tetrahydro-2*H*-pyran* = *(+)-4-{(2*S,6R*)-* and *(−)-4-{(2*R,6S*)-6-[2-(4-Methoxyphenyl)ethyl]tetrahydro-2*H*-pyran-2-yl}phenol* = *(+)-4-{(2*S,6R*)-* and *(−)-4-{(2*R,6S*)-Tetrahydro-6-[2-(4-methoxyphenyl)ethyl]-2*H*-pyran-2-yl}phenol*, resp.; (+)- and (−)-**1**, resp.) *and (+)-* and *(−)-*epi-*Isocentrolobine* (= *(+)-(2*R,6R*)-* and *(−)-(*2S,6S*)-2-(4-Hydroxyphenyl)-6-[2-(4-methoxyphenyl)ethyl]tetrahydro-2*H*-pyran*, resp.; (+)- and (−)-**12**, resp.). To a cooled (−10°) soln. of (+)-**11** (25 mg, 0.08 mmol) in anh. CH_2Cl_2 (6 ml), AcOH (20 µl) and DDQ (19 mg, 0.084 mmol) were added in a single portion and stirred (5 min). The crude mixture was quickly passed through SiO_2 (hexane/CH_2Cl_2/AcOEt 2:7:1) and the filtrate evaporated. CC (SiO_2; hexane/CH_2Cl_2/AcOEt 5:14:1) and recrystallization (hexane/Et_2O or hexane/AcOEt) afforded (+)-**1** (9 mg, 36%; ee > 99%[14]), (−)-**12** (2 mg, 8%; ee > 99%) both as colorless prisms, and starting (+)-**11** (11 mg, 44%) that could be recycled. Analogously, starting from (−)-**11** (24 mg, 0.076 mmol) and DDQ (18 mg, 0.079 mmol), we obtained (−)-**1** (8 mg, 34%; ee > 98%[14]), (+)-**12** (2 mg, 8%; ee > 99%), and starting (−)-**11** (10 mg, 42%). HPLC (*cis*; *Chiralcel® OD-H*, hexane/^{i}PrOH 30:1): k'((+)-**1**) = 6.1, k'((−)-**1**) = 5.5, $R_S = 1.15$ (not sufficient for a reliable ee-determination)[14]). HPLC (*trans*; *Chiralcel® OD-H*, hexane/^{i}PrOH 15:1): k'(−)-**12**) = 3.45, k'((+)-**12**) = 6.4, $R_S = 7.1$.

*Data of (+)-***1**: M.p. 145–146°. R_f (hexane/Et_2O 1:2) 0.42. GC ('high'): t_R 16 min 2 s. $[\alpha]_D = +90.3$ ($c = 0.7$, $CHCl_3$). IR (KBr): 3350*s*, 3063*m*, 3009*m*, 2943*s*, 2918*s*, 2894*m*, 2838*s*, 1614*s*, 1584*m*, 1511v*s*, 1456*s*, 1442v*s*, 1388*m*, 1366*m*, 1347*m*, 1310*m*, 1289*m*, 1269*s*, 1243v*s*, 1224v*s*, 1181v*s*, 1174*s*, 1124*m*, 1085*w*, 1072*m*, 1043v*s*, 1020v*s*, 980*m*, 955*m*, 938*m*, 920*m*, 898*m*, 863*m*, 837*s*, 828v*s*, 821v*s*, 809*s*, 784*m*, 755*w*, 742*m*, 719*w*, 616*m*, 575*m*, 540*w*, 524*m*, 511*m*, 458*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.26 (*AA′* of *AA′BB′*, $^3J = 8.5$, H–C(2′), H–C(6′)); 7.11 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(2‴), H–C(6‴)); 6.82 (*BB′* of *AA′BB′*, $^3J = 8.7$,

[14]) Although the peaks are nearly base-line separated when analyzing (±)-**1**, the respective minor enantiomers in the HPLC of both (+)- and (−)-**1** were not detected. This is due to the insufficient resolution ($R_S = 1.15$), and positive 'nonlinear effects' [14] are ruled out. Hence, we adopt the reliable ee-values from the starting (+)- and (−)-**11**.

H–C(3‴), H–C(5‴)); 6.78 (*BB′* of *AA′BB′*, ^3J = 8.5, H–C(3′), H–C(5′)); 4.88 (*s*, HO–C(4′)); 4.29 (*dd*, ^3J(2,3ax) = 11.1, ^3J(2,3eq) = 2.0, H–C(2)); 3.79 (*s*, MeO–C(4‴)); 3.46 (*dddd*, ^3J(5ax,6) = 9.8, ^3J(5eq,6) = 1.8, ^3J(1″,6) ≈ 7, 5, H–C(6)); 2.71 (*ddt*-like, ^2J = 14.0, ^3J ≈ 9, ^3J ≈ 6, CH_2(2″)); 1.91 (*m*, $w_{1/2}$ ≈ 25, H–C(1″), H_{eq}–C(4)); 1.83 (br. *dq*-like, ^2J ≈ 11, ^3J(2,3eq) ≈ ^3J(3eq,4ax) ≈ ^3J(3eq,4eq) ≈ 2, H_{eq}–C(3)); 1.74 *m*, $w_{1/2}$ ≈ 25, H–C(1″)); 1.63 (*qt*-like, ^2J ≈ ^3J(3ax,4ax) ≈ ^3J(4ax,5ax) ≈ 11, ^3J(3ax,4eq) ≈ ^3J(4eq, 5ax) ≈ 3, H_{ax}–C(4)); 1.63 (br. *dq*-like, ^2J ≈ 11, ^3J(4ax,5eq) ≈ ^3J(4eq,5eq) ≈ ^3J(5eq,6) ≈ 2, H_{eq}–C(5)); 1.51 (*qd*-like, ^2J ≈ ^3J(2,3ax) ≈ ^3J(3ax,4ax) ≈ 11, ^3J(3ax,4eq) ≈ 2, H_{ax}–C(3)); 1.33 (*qd*-like, ^2J ≈ ^3J(4ax,5ax) ≈ ^3J(5ax,6) ≈ 11, ^3J(4eq,5ax) ≈ 3, H_{ax}–C(5)). ^{13}C-NMR (150.9 MHz, $CDCl_3$): 157.6 (C(4‴)); 154.7 (C(4′)); 135.9 (C(1‴)); 134.6 (C(1′)); 129.4 (C(2‴), C(6‴)); 127.3 (C(2′), C(6′)); 115.0 (C(3′), C(5′)); 113.7 (C(3‴), C(5‴)); 79.1 (C(2)); 77.2 (C(6)); 55.3 (*Me*O–C(4‴)); 38.3 (C(1″)); 33.2 (C(3)); 31.2 (C(5)); 30.7 (C(2″)); 24.0 (C(4)). EI-MS: 312 (9, M^+), 281 (4, $[M - MeO]^+$), 207 (14), 191 (2), 177 (3), 174 (3), 163 (15), 160 (12), 147 (7), 134 (14), 133 (15), 121 (100, $C_8H_9O^+$), 119 (6), 107 (15, $C_7H_7O^+$), 91 (12, $PhCH_2^+$), 79 (4), 77 (12), 73 (3), 65 (7), 55 (5), 51 (3).

Data of (–)-**1**: $[a]_D$ = –89.1 (*c* = 0.6, $CHCl_3$). All other data: identical with those of (+)-**1**.

Data of (+)-**12**: M.p. 130–131°. R_f (hexane/Et_2O 1:2) 0.37. GC ('high'): t_R 16 min 11 s. $[\alpha]_D \approx 0$; $[\alpha]_{435}$ = +6.7 (*c* = 0.23, $CHCl_3$). IR (KBr): 3250*s*, 3034*m*, 2999*m*, 2941v*s*, 2859*m*, 2835*m*, 1612v*s*, 1593*m*, 1512v*s*, 1443v*s*, 1385*w*, 1345*s*, 1324*m*, 1302*m*, 1263v*s*, 1245v*s*, 1214v*s*, 1174v*s*, 1149*m*, 1115*m*, 1089*m*, 1071*m*, 1058*m*, 1032v*s*, 1019v*s*, 976*m*, 959*w*, 931*m*, 920*m*, 873*m*, 854*m*, 838v*s*, 825v*s*, 771*m*, 718*m*, 657*w*, 639*w*, 576*w*, 553*m*, 527*w*, 505*m*, 480*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.27 (*AA′* of *AA′BB′*, ^3J = 8.4, H–C(2′), H–C(6′)); 7.11 (*AA′* of *AA′BB′*, ^3J = 8.6, H–C(2‴), H–C(6‴)); 6.82 (*BB′* of *AA′BB′*, ^3J = 8.6, H–C(3‴), H–C(5‴)); 6.81 (*AA′* of *AA′BB′*, ^3J = 8.4, H–C(3′), H–C(5′)); 4.80 (br. *s*, HO–C(4′)); 4.78 (*t*, ^3J(2,3ax) = ^3J(2,3eq) = 5.4, H–C(2)); 3.79 (*s*, MeO–C(4‴)); 3.77 (*sext.*-like, ^3J(5ax,6) = 11.0, ^3J(5eq,6) ≈ ^3J(6,1″) ≈ 5, H–C(6)); 2.76, 2.57 (each *ddd*, ^2J = 12, ^3J = 8, ^3J = 5, CH_2(2″)); 2.08 (*ddt*, ^2J = 14, ^3J = 9, ^3J = 5, H–C(1″)); 1.90 (*q*, ^3J = 5.7, CH_2(3)); 1.79–1.64 (*m*, H–C(1″), CH_2(4″), H_{eq}–C(5)); 1.46 (*m*, br. *dq*-like, $w_{1/2}$ ≈ 20, H_{ax}–C(5)). ^{13}C-NMR (150.9 MHz, $CDCl_3$): 157.7 (C(4‴)); 154.5 (C(4′)); 134.6 (C(1′)); 134.5 (C(1‴)); 129.3 (C(2‴), C(6‴)); 128.0 (C(2′), C(6′)); 115.1 (C(3′), C(5′)); 113.7 (C(3‴), C(5‴)); 71.8 (C(2)); 71.3 (C(6)); 55.3 (*Me*O–C(4‴)); 35.2 (C(1″)); 31.3 (C(2″)); 30.2 (C(3)); 29.9 (C(5)); 19.0 (C(4)). EI-MS: 312 (8, M^+), 281 (6, $[M - MeO]^+$), 253 (2), 207 (15), 191 (2), 173 (2), 163 (18), 160 (12), 147 (8), 134 (14), 133 (18), 121 (100, $C_8H_9O^+$), 115 (4), 108 (5), 107 (13, $C_7H_7O^+$), 105 (4), 103 (4), 93 (5), 91 (14, $PhCH_2^+$), 81 (2), 79 (3), 77 (13), 73 (4), 65 (7), 55 (8), 51 (3).

Data of (–)-**12**: $[\alpha]_D \approx 0$; $[\alpha]_{435}$ = –6.6 (*c* = 0.2, $CHCl_3$). All other data: identical with those of (+)-**12**.

8. *X-Ray Crystal-Structure Determinations of (–)*-**1** *and (+)*-**12**. The measurements were made on a *Nonius-KappaCCD* area-detector diffractometer [15] by using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford-Cryosystems-Cryostream-700* cooler. The data collection and refinement parameters are compiled in the *Table*, and ORTEP [16] representations of the molecules are shown in *Figs. 1 and* 2. Data reduction was performed with HKL DENZO and SCALEPACK [17]. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. For (–)-**1**, the space group was determined from the systematic absences, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections were merged. For (+)-**12**, the space group was uniquely determined by the systematic absences. Equivalent reflections were merged. The structures were solved by direct methods with SIR92 [18], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The OH H-atom was placed in the position indicated by a difference electron density map, and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me group). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of $\Sigma w(F_o^2 - F_c^2)^2$ *vs.* F_o/F_c (max) and resolution showed no unusual trends. A correction for secondary extinction was applied. For (+)-**12**, two reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral-atom scattering factors for non-H-atoms were taken from

[19], and the scattering factors for H-atoms from [20]. Anomalous dispersion effects were included in F_c [21]; the values for f' and f'' were those of [22]. The values of the mass-attenuation coefficients were those of [23]. The SHELXL97 program [24] was used for all calculations.

Table. *Crystallographic Data of (−)-***1** *and (+)-***12**

	(−)-**1**	(+)-**12**
Crystallized from	hexane/Et_2O	hexane/AcOEt
Empirical formula	$C_{20}H_{24}O_3$	$C_{20}H_{24}O_3$
M_r	312.41	312.41
Crystal color, habit	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.20 \times 0.22 \times 0.25$	$0.15 \times 0.17 \times 0.17$
Temperature [K]	160(1)	160(1)
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$ (#4)	$P2_12_12_1$ (#19)
Z	2	4
Reflections for cell determination	2598	1825
2θ Range for cell determination [°]	4 – 60	4 – 50
Unit cell parameters:		
a [Å]	8.6423(2)	6.9496(2)
b [Å]	5.6418(2)	8.2301(3)
c [Å]	17.3530(3)	30.6091(9)
α [°]	90	90
β [°]	103.103(2)	90
γ [°]	90	90
V [Å^3]	824.07(4)	1750.7(1)
$F(000)$	336	672
D_x [g cm^{-3}]	1.259	1.185
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0830	0.0781
Scan type	ω	ϕ and ω
$2\theta_{(\max)}$ [°]	60	50
Total reflections measured	27230	17402
Symmetry independent reflections	2615	1820
R_{int}	0.057	0.082
Reflections with $I > 2\sigma(I)$	2149	1399
Reflections used in refinement	2615	1818
Parameters refined; restraints	214; 1	214
Final $R(F)$ ($I > 2\sigma(I)$ reflections)	0.0463	0.0490
$wR(F^2)$ (all data)	0.1124	0.1057
Weights	[a])	[b])
Goodness of fit	1.042	1.103
Secondary extinction coefficient	0.030(6)	0.023(2)
Final $\Delta_{\max}/\sigma$	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.25; −0.19	0.17; −0.16
$\sigma(d_{(C-C)})$ [Å]	0.002 – 0.003	0.004 – 0.005

[a]) $w = [\sigma^2(F_o^2) + (0.0581P)^2 + 0.1052P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. [b]) $w = [\sigma^2(F_o^2) + (0.0331P)^2 + 0.5084P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$.

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