The Biomimetic Synthesis and Final Structure Determination of (+)- and (−)-Centrolobine, Naturally Occurring Diarylheptanoid 2,6-*cis*-Disubstituted Tetrahydro-2*H*-pyrans

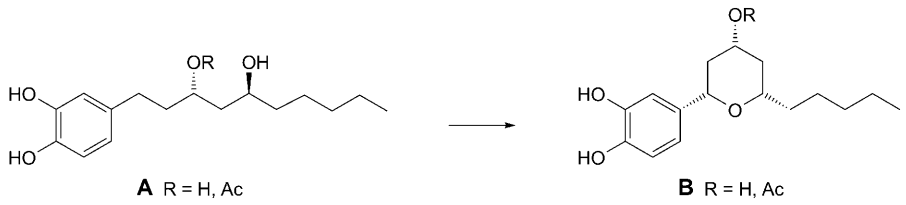
by **Frank Rogano** and **Peter Rüedi***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich (phone: +41-44-821 55 79; e-mail: peru@oci.uzh.ch)

The enantiomerically pure title compounds were prepared by oxidative cyclization of their optically active diarylheptanoid precursors. The approach is considered as a biomimetic phenol oxidation *via* an intermediate quinone methide. The absolute configuration of the precursors is retained, and the transition state adopts the sterically most favorable diequatorial arrangement of the 2,6-substituents to afford the *cis*-configured natural products. The outcome unambiguously establishes the absolute configurations and the correlation with the chiroptical data. In addition, a problem of regioisomerism that had not been discussed before was solved, and the original assignment of the position of the MeO group in the natural centrolobines could be confirmed. As such the results are the experimental evidence for the corrections of long-term inconsistencies we had postulated in an earlier review article.

1. Introduction. – 1.1. *General.* In the course of our investigations concerning the isolation, synthesis, and biological screening of genuine constituents of African and Asian *Labiatae* species of the genera *Coleus*, *Plectranthus*, and *Solenostemon* with respect to antioxidants, inhibitors of the arachidonate metabolism, and allergens [1–3], we have reported on the isolation, structure elucidation, and partial synthesis of a series of optically active, oxygenated unbranched long-chain alkylcatechols **A** and 2,6-*cis*-disubstituted tetrahydro-2*H*-pyrans **B** from *Plectranthus sylvestris* [3]. Being considered to originate from their linear congeners, the tetrahydro-2*H*-pyrans **B** were synthesized by oxidative cyclization of their respective precursors **A** (*Scheme 1*) [3][4].

Scheme 1



Since the *Plectranthus* constituents are closely related to the [*n*]-gingerols and -diols **A** [3], a closer inspection of the current literature was performed. It revealed significant structural inconsistencies, in particular with respect to the related diaryl-

heptanoids (curcuminoids) and their cyclic derivatives, the centrolobines (+)- and (−)-**1** (*Figs.* 1 and *2*). In a review article covering the chemistry and pharmacology of these compounds at that time, we disclosed several misinterpretations, and respective structural revisions were claimed [4] (*Fig. 2*).

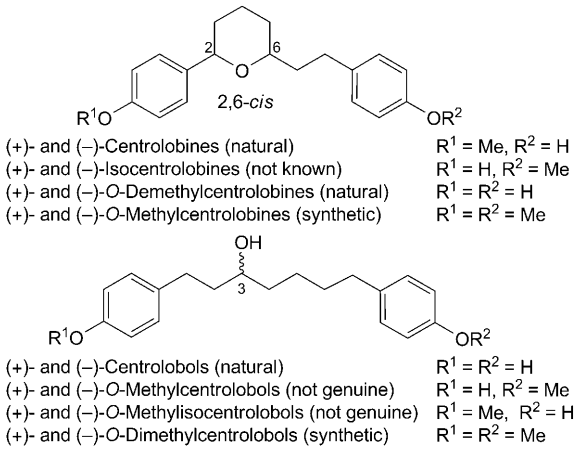


Fig. 1. *General overwiev of the title compounds and their isomers and precursors*

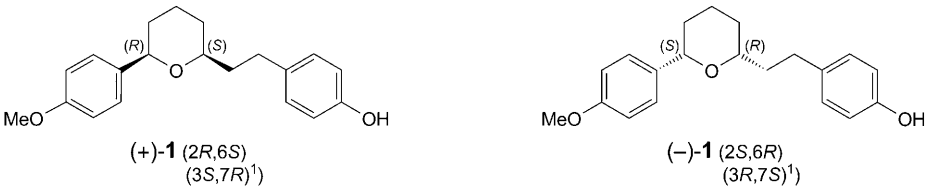


Fig. 2. *Revised structures of the naturally occurring (+)- and (−)-centrolobines* [4]

1.2. *The Centrolobines: A Brief Historical Survey.* Since the first isolation and characterization of (+)-centrolobine ((+)-**1**, $[\alpha]_D = +97$, *Fig. 2*), an antibacterially active constituent from the heartwood of *Centrolobium robustum* (*Leguminosae*, Amazon forest) [5–7], considerable confusion concerning the configuration of this compound and its congeners resulted that persisted until the most recent isolation of (−)-centrolobine ((−)-**1**, $[\alpha]_D = -92.2$, *Fig. 2*) from the stems of *Brosimum potabile* (*Moraceae*, Amazon forest) [8]. The problems originated mainly from the fact that the compounds occur naturally as both enantiomers [9–11], the erroneous assignment of the absolute configuration of the assumed biogenetic precursor centrolobol [9] and not reliably identified plant sources [9][10].

---

1) When applying the 'biogenetic' terminology that is based on the diarylheptanoid nomenclature, the stereogenic C-atoms in the centrolobines are C(3) and C(7). According to the systematic nomenclature of heterocycles, C(3) becomes C(6), and C(7) becomes C(2) in the tetrahydro-2*H*-pyran moieties.

Meanwhile, the absolute configuration of (−)-(*R*)-centrolobol was independently established [11][12] and the taxonomic problem tackled [10] and settled by [11][2]). Hence, the laevorotatory natural products ((−)-centrolobine, (−)-*O*-demethylcentrolobine, and (−)-centrolobol, *Fig. 1*) are constituents of *Centrolobium paraense*, *C. sclerophyllum*, and *C. tomentosum*, whereas the dextrorotatory enantiomers were isolated from *C. robustum* [11]. However, despite the fact that the stereochemical basis was established, considerable confusion concerning the absolute configuration remained in the current literature [8][11][3]) [14]. The reasons for these inconsistencies are not obvious. It can be assumed that they might have a rather trivial origin, most probably due to the different nomenclatures and numbering systems[1]) as well as to unconventional, ambiguous drawings of the molecule in different orientations, C_2-rotations leading to the enantiomer (*e.g.*, [8]), or reading and printing errors[4]).

Mainly due to methodological reasons[5]), (−)-centrolobine ((−)-**1**) was recently discovered as an ideal synthetic target to exploit [15–30], the hallmark being the report on its first enantioselective total synthesis [17]. It was achieved by reductive cyclization of an optically active hydroxysulfinyl ketone and for the first time ever confirmed the (2*S*,6*R*)-configuration of (−)-**1** as earlier proposed by us [4]. In the course of further synthetic activities, the stereoselective construction of the tetrahydro-2*H*-pyran ring has been achieved by *Prins*-type cyclization [18] and secondary modifications thereof [19], by reductive etherification of *δ*-(trialkylsilyloxy)-substituted ketones [20], by cross-metathesis procedures [21] and related strategies [22][23], by a diastereoselective ring rearrangement metathesis–isomerization sequence [15], by *Maitland–Japp* reaction [24], by intramolecular oxy-*Michael* reaction [25], by *Lewis*-acid mediated reactions such as cyclization of a 1,5-diol [26] or opening of an epoxide precursor [23], by hetero-*Diels–Alder* reaction between 4-aryl-2-(silyloxy)buta-1,3-dienes and phenylpropargylaldehyde (= 3-phenylprop-2-ynal) derivatives [27] or related enantioselective multistep procedures [28][6]), by intramolecular *Barbier*-type cyclization of iodoesters with an organolithium base [29], and by stereoselective synthesis of cyclic ethers *via* Pd-catalyzed intramolecular addition of alcohols to phosphonoallyl carbonates [30].

Several years ago, a single *trans*-configured congener of centrolobine was isolated as a trace constituent of *Alpinia blepharocalyx*, *i.e.*, (−)-(2*R*,6*S*)-3,4-didehydro-*O*-demethylcentrolobine (=(−)-(3*S*,7*R*)-5,6-didehydro-*O*-demethylcentrolobine[3]); (−)-**2**) [31]. The absolute configuration of (−)-**2** was assumed by biogenetic considerations in connection with an earlier, erroneously assigned compound[7]). But this assignment is

---

[2]) It was reliably confirmed that *C. robustum* was confused with *C. tomentosum* and had to be interchanged [11].

[3]) Although clarifying the absolute configuration was intended in [11], the stereodescriptors in the enantiomeric centrolobols and centrolobines specified have to be interchanged.

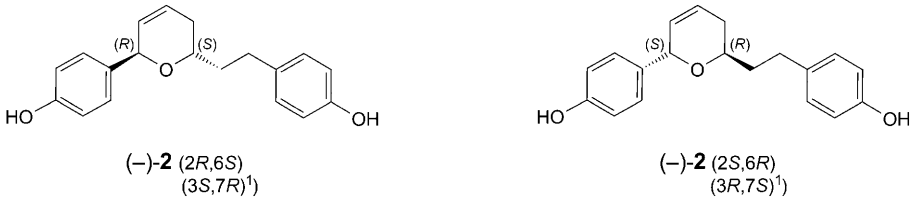
[4]) The report on the synthesis of (−)-centrolobine ((−)-**1**) is such an example as $[\alpha]_D = +60$ (ee > 98%) is specified for the target molecule [15].

[5]) For a review on strategies for the formation of tetrahydro-2*H*-pyrans in natural products, see [16].

[6]) The formula for (−)-centrolobine in the graphical abstract in [28] represents the (+)-enantiomer.

[7]) This (−)-*trans*-compound had been reported to be a constituent of *Alpinia blepharocalyx* already earlier [32]. However, our chemical argumentation clearly showed it to be erroneous [4]. Later, the structure was revised to its (−)-*cis*-isomer ((2*S*,6*S*) or (3*S*,7*S*)[3])) in an *Erratum* [33] without any comment.

not free from doubt as reliable syntheses and chiroptical comparisons [34–36] strongly suggest that the natural compound is rather the enantiomer ((−)-(2*S*,6*R*) or (−)-3*R*,7*S*)[3]))[8]) (*Fig. 3*).



(−)-**2** (2*R*,6*S*) (3*S*,7*R*)[1]) (−)-**2** (2*S*,6*R*) (3*R*,7*S*)[1])

Fig. 3. *Structures of the naturally occurring (−)-3,4-didehydro*-O-*demethylcentrolobine* [28] (left) *and proposed revision* (right)

Very recently, the syntheses of *trans*-isomers of centrolobine have been reported, too. Thus, (−)-(2*S*,6*S*)-(or (−)-(*3S*,7*S*)[3]))-epicentrolobine was prepared by a stereoselective C-glycosidation procedure as the key step [34], and all the four stereoisomers were synthesized by a tandem ring-closing metathesis–isomerization reaction to a monosubstituted dihydropyran and introduction of the 4-methoxyphenyl group by a diazonium-mediated *Heck* reaction [35]. The synthetic pathways unambiguously establish the absolute configurations and the coherence with the chiroptical data[7]).

1.3. *The Biomimetic Concept.* In spite of all the synthetic efforts, one subtle fact remained undiscussed from the first account [6][7] until to the very recent ones [8][15][17–30]: the unambiguous location of the MeO group. It was never assigned by spectrosopic data but inferred by the synthesis of (±)-centrolobine and its *O*-methyl derivative and comparison with the natural product [6][7]. Although the respective isomer ('isocentrolobine', *Fig. 1*) was not known, it was anticipated obviously by implication that the latter would significantly differ from its parent[9]). As a matter of fact, the potential occurrence of the regioisomer was never taken into consideration, and the position of the MeO group in the centrolobines was neither questioned ever since.

This fundamental aspect, the persistent structural inconsistencies, and the fact that of the 8 isomeric 2,6-(OH/MeO)-disubstituted tetrahyro-2*H*-pyrans only (−)-**1** is being exploited, prompted us to re-investigate the centrolobine chemistry [36–38]. Utilizing our experience with the tetrahydro-2*H*-pyrans **B** from *Plectranthus* species (*Scheme 1*) [3][4], the target molecules were prepared directly from their linear diarylheptanoid precursors by oxidative cyclization as the key step. The pathway is straightforward as it retains the configuration at C(3) of the precursors which becomes C(6) in the heterocycles. Moreover, it would lead to the sterically most favorable diequatorial

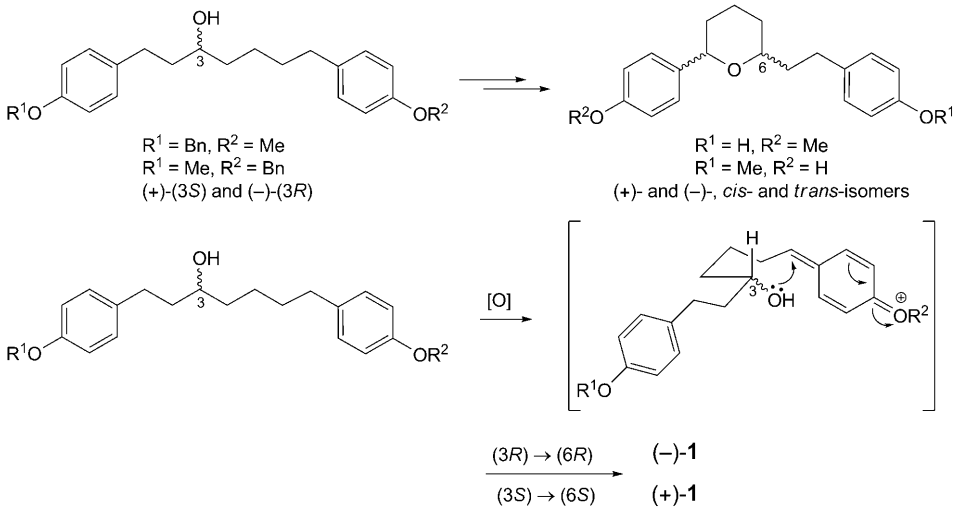
---

[8]) It has been shown conclusively that epimerization of (+)-*trans*-centrolobine yields the respective (−)-*cis*-2(7[3]))-epimer and *vice versa* [35]. Hence, from the comparison of a series of structurally unambiguously established compounds, it can be concluded that the benzyloxy chromophore determines the sign of the optical rotation in terms of (2*R*) (or (7*R*)[3])) > 0 and *vice versa*. According to chemical transformations [32][36], the additional C=C bond does not seem to affect the chiroptical data significantly.

[9]) This is an example of circular reasoning. The following article [37] demonstrates that the spectral data of the regioisomers are highly similar.

arrangement of the substituents in the transition state, hence affording the 2,6-*cis*-tetrahydro-2*H*-pyrans as the main products (*Scheme 2*).

Scheme 2



This approach is different from the previous ones [15–30] [34] [35] and constitutes a real biomimetic synthesis of the centrolobine congeners. Moreover, the concept enables the access to the hitherto unknown 'isocentrolobine' series by appropriate selection of R^1 and R^2 (*Scheme 2*).

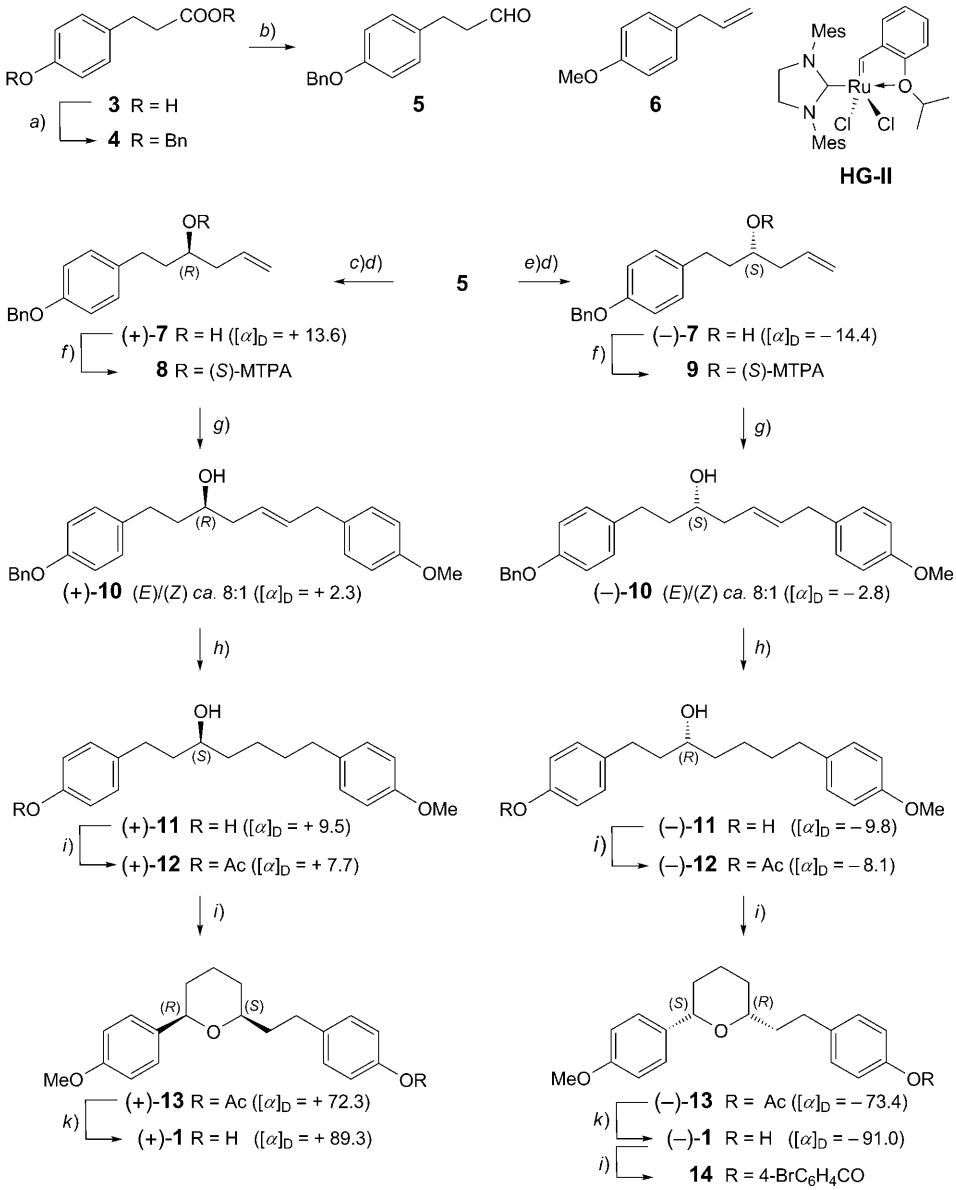
2. Synthesis and Characterization of the (+)- and (−)-Centrolobines. – 2.1. *(+)-(*S*)- and (−)-(*R*)-*O*-Methylcentrolobol* ((+)- and (−)-**11**, resp.). The precursors (+)- and (−)-**11** were obtained from the homoallylic alcohols (+)- and (−)-**7** followed by cross-metathesis with 4-allylanisole (**6**) and catalytic hydrogenation of the resulting diarylheptanoids (+)- and (−)-**10** (*Scheme 3*): Enantioselective allylation of the aldehyde **5** (obtained from **3** *via* **4**) under *Keck* conditions [39] yielded (+)-(*R*)-**7** and (−)-(*S*)-**7** (ee > 98%, ee > 99%, resp.). The absolute configurations were verified by means of the respective *O*-MTPA derivatives [40] **8** and **9** and proved to be as expected [39] (MPTA = methoxy(phenyl)(trifluoromethyl)acetyl)[10]. Treating (+)- and (−)-**7** with **6** in the presence of *Hoveyda–Grubbs* (2nd gen.) catalyst **HG-II** [41] at −78°[11]) furnished the diarylheptanoid homoallylic alcohols (+)- and (−)-**10** ((*E*)/(*Z*) mixture *ca.* 8:1), and hydrogenation afforded the (+)-(*S*)- and (−)-(*R*)-*O*-Methylcentrolobols (+)- and (−)-**11** (ee > 97% and > 98%, resp.).

---

[10]) This additional verification was performed to exclude further potential errors.

[11]) Unexpectedly, the metathesis reaction succeeded only at −78°. Applying the common protocols (≥ room temp.) resulted in complete decomposition. Moreover, the yields were strongly dependent on the quality of the used glassware, and reproducibility was only obtained when soaking the reaction vessels in 10% HCl solution during 16 h before use [36] (see *Exper. Part*).

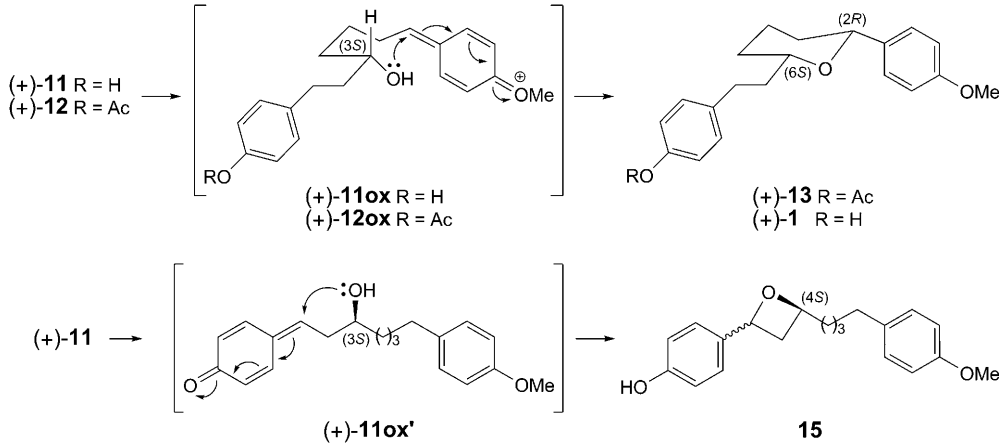
Scheme 3



a) BnBr, K_2CO_3, DMF, 80°. *b*) DIBAH (diisopropylaluminium hydride), CH_2Cl_2, −78°. *c*) (−)-(*S*)-[1,1′-Binaphthalene]-2,2′-diol/(^{i}PrO)$_4$Ti, CH_2Cl_2, reflux. *d*) CH_2=$CHCH_2SnBu_3$, −78° → −20°. *e*) (+)-(*R*)-[1,1′-Binaphthalene]-2,2′-diol/(^{i}PrO)$_4$Ti, CH_2Cl_2, reflux. *f*) (−)-(*R*)-MTPA-Cl, DMAP (*N*,*N*-dimethylpyridin-4-amine), Et_3N, r.t. *g*) **6**, *Hoveyda–Grubbs* (2nd generation) catalyst **HG-II**, MeOH, −78° → r.t. *h*) H_2, 10% Pd/C, CH_2Cl_2, r.t. *i*) Ac_2O, Et_3N, CH_2Cl_2, −5°. *j*) DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile), CH_2Cl_2, −10°. *k*) NaOH, MeOH, H_2O, r.t. *l*) 4-BrC_6H_4COCl, DMAP, Et_3N, r.t.

2.2. *Centrolobines (+)- and (−)-***1**. The key step of the synthesis is the oxidative cyclization of the *O*-methylcentrolobols (+)- and (−)-**11** with DDQ (*Schemes 3* and *4*). This dehydrating agent is considered as a chemical equivalent of phenol oxidase [3][4][42], was successful in earlier applications [3][4], and proved to be highly superior to other oxidants (*e.g.*, Ag_2O, Ag_2CO_3, cerium(IV) ammonium nitrate (CAN), $K_4[Fe(CN)_6]$) [36]. But when treating (+)-**11** with DDQ, mainly decomposition occurred, and only traces of the expected centrolobine (+)-**1** could be detected. Obviously, besides the desired intermediate (+)-**11ox**, the quinone methide (+)-**11ox′** was preferentially formed, thus yielding the instable oxetane **15**[12]) (*Scheme 4*). The cyclization succeeded when the *O*-protected *O*-methylcentrolobols (+)- and (−)-**12** were treated with DDQ to afford the *O*-acetylcentrolobines (+)- and (−)-**13** in low yield (*ca.* 8%). However, the reaction proceeded mildly, and *ca.* 80% of starting material was recovered that could be recycled. After saponification, the target centrolobines (+)- and (−)-**1** were isolated (ee > 97% and > 98%, resp.). The respective *trans*-isomers (+)- and (−)-**2** were not detected. Finally, the structure of the synthetic (−)-(2*S*,6*R*)-**1** was confirmed by an X-ray crystallographic analysis of its 4-bromobenzoate **14** (*Fig. 4*)[13]).

Scheme 4



However, this outcome does not establish the consistency of the synthetic centrolobines with the natural products. As discussed above (*Sect. 1.3*), the position of the Me group in the latter is still not assured in the absence of the isomers. An X-ray crystallographic analysis of an authentic sample of natural (−)-**1** from *Brosimum*

[12]) Directed preparation of such oxetanes showed that they are formed but the structures could only be assigned tentatively [38]. The instability of the compounds prevented closer investigations.

[13]) The full data set is summarized in the *Table* (see *Exper. Part*). CCDC-765627 and -765628 contain the supplementary crystallographic data for (−)-**1** and **14**. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

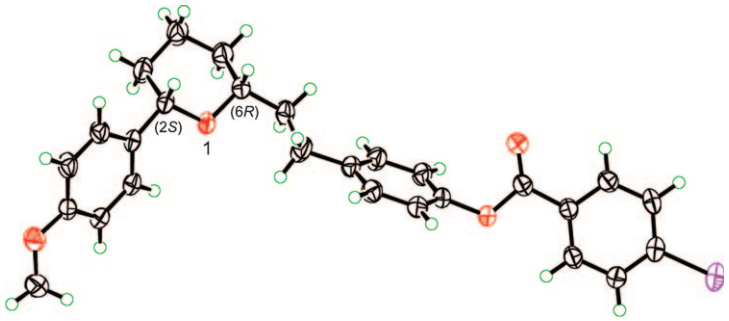


Fig. 4. *Molecular structure of the synthetic 4-bromobenzoate* **14** *with refinement of the absolute structure parameter.* For reasons of clarity, the atom numbering is restricted to the tetrahydro-2*H*-pyran moiety; 50% probability ellipsoids.

potabile [8] furnished the conclusive evidence and established the position of the Me group as proposed [6][7] (*Fig. 5*)[14])[15]).

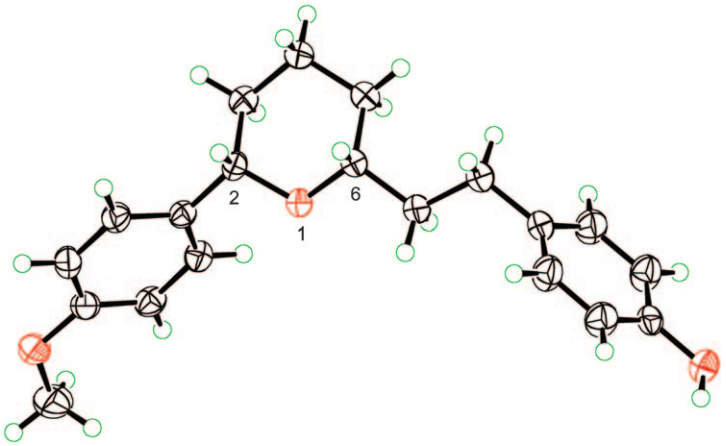


Fig. 5. *Molecular structure of natural (−)-centrolobine* ((−)-**1**) *from* Brosimum potabilis. For reasons of clarity, the atom numbering is restricted to the tetrahydro-2*H*-pyran moiety; 50% probability ellipsoids.

3. Remarks. – Although the constitution of the natural centrolobines was correctly assigned in the original reports [6][7], a fact that attests fine chemical intuition to the authors, we consider our investigations beneficial. Besides the elucidation of a never questioned subtle issue, they constitute the first straightforward biomimetic approach from linear diarylheptanoids to 2,6-disubstituted 2*H*-tetrahydropyrans, and the general synthetic protocol provides access to the hitherto unknown 'iso' series [37][38]. Moreover, the correlation of the chiroptical data and the absolute configurations could

[14]) Obtained from Prof. Dr. *Dorila Piló-Veloso*, Departamento de Quimica, Universidade Federal da Minas Gerais, Belo Horizonte, Brazil.

[15]) This is the sole X-ray crystallographic analysis of a natural centrolobine congener.

be confirmed as postulated in an earlier review article [4]. Because the *O*-methylcentrolobols ((+)- and (−)-**11**) are not genuine plant constituents[16]), biogenetic considerations suggest that the precursors of the (+)- and (−)-centrolobines are the (+)- and (−)-centrolobols (*Fig. 1*). Phenol oxidation produces the sterically favored 2,6-disubstituted tetrahydro-2*H*-pyrans ((+)- and (−)-*O*-demethylcentrolobines [9–11], *Fig. 1*) with retention of the configuration at C(3). Accidentally, the sign of the optical rotation is retained, too. As a matter of fact, only one enantiomeric series was isolated from a specific plant species [9–11]. The final biogenetic step is a regioselective *O*-methylation affording (+)-**1** and (−)-**1**, respectively.

We are highly indebted to Prof. Dr. *Dorila Piló-Veloso*, Departamento de Quimica, ICEX, Universidade Federal da Minas Gerais, Av. Antônio Carlos, 6627 Belo Horizonte-MG., CEP 31, 270-901 Brazil, for the generous gift of natural (−)-centrolobine. We thank PD Dr. *A. Linden*, head of the X-ray department of our institute, for the high-quality X-ray crystallographic analyses. The financial support of the project by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

1. *General*. Air- and moisture-sensitive reagents and reactions were stored/performed in a *Glovebox*® (*B. Braun*, *Labmaster*) under standard precautions. Enantioselective allylations were performed with (+)-(*R*)- and (−)-(*S*)-[1,1′-binaphthalene]-2,2′-diol ((+)-(*R*)- and (−)-(*S*)-BINOL, resp.; *puriss.*, *Aldrich 246948* and *246956*, resp.; ee > 99%), (^{i}PrO)$_4$Ti (*purum*, *Fluka 87560*), and allyl(tributyl)-stannane (*purum*, *Fluka 06070*). The metathesis reactions were performed with *Hoveyda–Grubbs* 2nd generation catalyst **HG-II** (99%, *Aldrich 569755*; ee > 99%) and 4-allylanisole (= 1-methoxy-4-(prop-2-en-1-yl)benzene; **6**; *purum*, *Fluka 05820*). Prior to use, the reaction vessels were soaked in 10% HCl soln. (16 h) and dried at 200° (24 h)[11]). The MTPA derivatives were prepared with (−)-(α*R*)- and (+)-(α*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride ((−)-(*R*)- and (−)-(*S*)-MTPA-Cl, resp.; *Fluka 65363* and *65365*, resp.; *Chira Select*, ee > 99.5%). TLC: *Merck 60 F_{254}* silica-gel (SiO_2) plates; detection by UV_{254} light, by spraying with 'mostain' soln. ($(NH_4)_6Mo_7O_{24}\cdot 4\,H_2O$ (40 g), $Ce(SO_4)_2$ (0.8 g), 10% H_2SO_4 (800 ml)) and heating (blue spots). Standard column chromatography (CC): SiO_2 *60* (40–63 μm, *Merck 109385*). Anal. HPLC and ee-determination: *Chiralcel*® *OD-H* column (5 μm, 250 × 4.6 mm; *Daicel Chemical Industries, Ltd.*); flow rate 1 ml/min, at r.t.; *Pharmacia-LKB* HPLC pump *2248*; *HP-1040M* diode-array detection system and data handling with *HP Chemstation* for LC, Rev. A.04.02 (*Hewlett-Packard*). GC/MS: *HP-5980* series *II* (GC), *HP-5971 MSD* (mass-selective detector, EI; 70 eV), and column *HP 1* (phenyl(1%)-methylsiloxane cross-linked; 25 m × 0.2 mm, 0.53 μm) (*Hewlett-Packard*); injector 180°, detector 330°; temp. programs: 100° (2 min), 100–240° (rate 20°/min), and 240° (10 min) ('low'), or 100° (2 min), 100–290° (rate 20°/min), and 290° (25 min) ('high'). M.p.: *Mettler FP 5/52*; uncorrected. $[\alpha]_D^{25}$: *Perkin-Elmer-241-MC* polarimeter with thermostat *B. Braun Thermomix 1441*, 10 cm cell; ee based on the integration of the peak areas of the anal. HPLC separations ($R_S > 1.5$). IR: *Perkin-Elmer-Spectrum-One* FT-IR spectrometer; intensity of the bands: $T < 15\%$ (v*s*), $T = 15–30\%$ (*s*), $T = 30–70\%$ (*m*), and $T > 70\%$ (*w*); $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Bruker-ARX-300* (300.0 and 75.4 MHz, resp.), *-AV2–400* (400.0 and 100.6 MHz, resp.), *-DRX-500* (500.0 and 125.7 MHz, resp.), *-AMX-600* or *-DRX-600* (600.0 and 150.9 MHz, resp.) spectrometers; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz; all assignments are based on extensive interpretations of 2D spectra (^{1}H,^{1}H-COSY, ^{1}H,^{1}H-NOESY, ^{13}C{^{1}H}-, DEPT90, DEPT135, ^{1}H,^{13}C-COSY (HSQC), and ^{1}H,^{13}C-long-range

---

16) The *O*-methylcentrolobols are known as cleavage products of natural cyclic diarylheptanoids. (−)-**11** originates from (−)-centrolobine ((−)-**1**) [9] and from the macrocyclic diarylheptanoid aceroside I [43]. A racemic compound with the constitution of *O*-methylisocentrolobol (*Fig. 1*) was reported to be a degradation product of acerogenin B [44]. However, the position of the Me group was not discussed as it followed from the parent.

(HMBC)); spin systems are interpreted according to 1st-order approximation, although in several complex cases, significant *AB* character indicates higher-order spectra. MS: *Finnigan MAT 75*, electron impact (EI; 70 eV) or chemical ionization (CI) with NH_3. Nomenclature and atom numbering: For convenience, in particular with respect to the discussions in the *General Part* and to enable direct spectroscopic comparisons, arbitrary atom numberings are used (*Fig. 6*); systematic names are given in the headings.

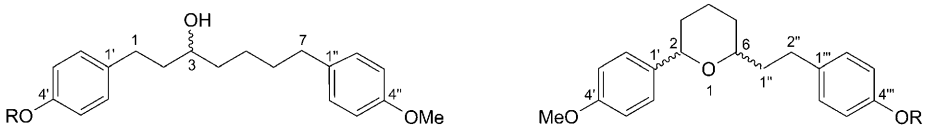


Fig. 6. *Arbitrary atom numbering for the diarylheptanes and the tetrahydro-2*H*-pyrans*

2. *3-[4-(Benzyloxy)phenyl]propanal* (=*4-(Phenylmethoxy)benzenepropanal*; **5**)[17]. To a suspension of K_2CO_3 (33.3 g, 241 mmol) in anh. DMF (50 ml), 4-hydroxybenzenepropanoic acid (**2**; 10.0 g, 60.2 mmol) was added at r.t. Then benzyl bromide (35 ml, 295 mmol) was added at 0°, and the mixture stirred at 80° (3 d). Workup and CC (SiO_2; hexane → hexane/AcOEt 25:1) gave benzyl 3-[4-(benzyloxy)phenyl]propanoate (= phenylmethyl 4-(phenylmethoxy)benzenepropanoate; **4**; 20.3 g, 97%) as colorless solid. Reduction of **4** (8.9 g, 25.7 mmol) in anh. CH_2Cl_2 (90 ml) with diisobutylaluminium hydride (DIBAH; 37 ml, 0.7–1.3 mol in CH_2Cl_2) at −80°, workup, and CC (SiO_2; hexane/AcOEt 9:1) yielded **5** (5.04 g, 81%) as a colorless oil that solidified in the refrigerator.

Data of **4**: Colorless solid. M.p. 45–46°. R_f (hexane/Et_2O 1:2) 0.45. GC ('high'): t_R 17 min 55 s. IR (KBr): 3432*w*, 3067*w*, 3033*m*, 2959*m*, 2930*m*, 2896*m*, 2859*m*, 1725v*s*, 1611*m*, 1581*m*, 1513v*s*, 1497*m*, 1452*w*, 1420*m*, 1384*s*, 1293*s*, 1253v*s*, 1176*s*, 1141*s*, 1108*s*, 1081*m*, 1042*s*, 1028*s*, 968*m*, 951*m*, 924*m*, 904*m*, 859*m*, 828*s*, 815*m*, 792*w*, 754*s*, 734*s*, 696*s*, 602*w*, 583*w*, 536*m*, 503*m*, 462*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.48–7.31 (*m*, 2 *Ph*CH_2); 7.13 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.92 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 5.14 (*s*, COOCH_2Ph); 5.07 (*s*, PhCH_2); 2.95 (*t*, ^3J = 7.7, CH_2(3)); 2.68 (*t*, ^3J = 7.7, CH_2(2)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 172.7 (C(1)); 157.3 (C(4′)); 137.1, 135.9 (Ph); 132.8 (C(1′)); 129.2 (C(2′), C(6′)); 128.55, 128.5, 128.1, 127.9, 127.4 (Ph); 114.9 (C(3′), C(5′)); 70.0, 66.2 (PhCH_2); 36.1 (C(2)); 30.1 (C(3)). EI-MS: 346 (2, M^+), 255 (4, $[M - PhCH_2]^+$), 165 (1), 120 (1), 107 (1, $C_7H_7O^+$), 91 (100, $PhCH_2^+$), 89 (2), 79 (1), 77 (2), 65 (10), 63 (1), 51 (2).

Data of **5**: M.p. 45–47°. R_f (hexane/Et_2O 1:2) 0.29. GC ('low'): t_R 12 min 31 s. IR (KBr): 3415*w*, 3092*w*, 3064*w*, 3033*m*, 2930*m*, 2897*m*, 2861*m*, 2833*m*, 2732*m*, 1718v*s*, 1610*m*, 1580*m*, 1513v*s*, 1452*s*, 1407*m*, 1383*s*, 1313*m*, 1298*m*, 1239v*s*, 1176*s*, 1112*m*, 1079*w*, 1040*m*, 1028*s*, 1006*s*, 934*w*, 913*m*, 904*m*, 861*m*, 833*m*, 814*s*, 790*m*, 736*s*, 697*s*, 637*w*, 599*w*, 542*m*, 510*w*, 501*w*, 463*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.82 (*t*, ^3J = 1.5, H–C(1)); 7.46–7.31 (*m*, *Ph*CH_2); 7.13 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.93 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 5.06 (*s*, PhCH_2); 2.92 (*t*, ^3J(2,3) = 7.5, 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)); 157.3 (C(4′)); 137.1 (Ph); 132.6 (C(1′)); 128.5, 127.9, 127.4 (Ph); 129.2 (C(2′), C(6′)); 115.0 (C(3′), C(5′)); 70.0 (PhCH_2); 45.4 (C(2)); 27.3 (C(3)). EI-MS: 240 (13, M^+), 121 (1, $C_8H_9O^+$), 107 (1, $C_7H_7O^+$), 103 (1), 91 (100, $PhCH_2^+$), 89 (4), 78 (3), 77 (7), 65 (22), 63 (5), 55 (2), 51 (6).

3. *(+)-(3*R*)- and (−)-(3*S*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol* (=*(+)-(α*R*)-* and *(−)-(α*S*)-4-(Phenylmethoxy)-α-(prop-2-en-1-yl)benzenepropanol*, resp.; (+)- and (−)-**7**, resp.)[18]. To a suspension of (−)-(*S*)-[1,1′-binaphthalene]-2,2′-diol (358 mg, 1.25 mmol) in anh. CH_2Cl_2 (10 ml) and powdered activated molecular sieves 4 Å (1.5 g), (^{i}PrO)$_4$Ti (379 µl, 1.25 mmol) was slowly added (N_2, r.t.) and the mixture refluxed (2 h). After evaporation in a stream of N_2, the residue was taken up in anh. CH_2Cl_2 (10 ml), and **5** (3.00 g, 12.5 mmol) was added at r.t. After cooling to −78°, CH_2=$CHCH_2SnBu_3$ (4.8 ml,

[17]) The compound has been prepared earlier, but only selected physical data are reported [45].

[18]) The compounds have been prepared earlier, but only selected physical data are reported: (+)-**7** [46], and (−)-**7**, *e.g.* [21][22].

15.5 mmol) was added, and the mixture kept at $-25°$ (90 h). Workup and CC (SiO_2; hexane/Et_2O 2:1) gave (+)-**7** (2.69 g, 76%; ee > 98%) as a colorless solid. Analogously, starting from (+)-(*R*)-[1,1′-binaphthalene]-2,2′-diol (394 mg, 1.37 mmol) in anh. CH_2Cl_2 (10 ml), molecular sieves 4 Å (2.0 g), (^{i}PrO)$_4$Ti (406 µl, 1.37 mmol), **5** (3.3 g, 13.7 mmol), and CH_2=$CHCH_2SnBu_3$ (4.9 ml, 15.8 mmol), we obtained (−)-**7** (2.79 g, 72%; ee > 99%) as a white solid. HPLC (*Chiralcel® OD-H*, hexane/^{i}PrOH 50:1): k'((+)-**7**) = 5.6, k'((−)-**7**) = 4.5, R_S = 3.1).

*Data of (+)-***7**: M.p. 70–71°. R_f (hexane/Et_2O 1:1) 0.26. GC ('low'): t_R 17 min 11 s. $[\alpha]_D$ = +13.6 (*c* = 0.62, EtOH). IR (KBr): 3509*s*, 3433*s*, 3061*m*, 3008*m*, 2940*m*, 2904*m*, 2855*m*, 1642*m*, 1614*s*, 1596*m*, 1583*m*, 1513v*s*, 1452*s*, 1437*m*, 1383*s*, 1345*m*, 1316*m*, 1294*m*, 1271*m*, 1253v*s*, 1220*s*, 1177*s*, 1148*s*, 1126*s*, 1078*s*, 1058*m*, 1043*s*, 1029*m*, 1000*m*, 951*w*, 911*m*, 862*m*, 850*m*, 825*s*, 816*s*, 784*m*, 762*m*, 749*m*, 734*s*, 695*m*, 665*m*, 585*w*, 565*m*, 552*w*, 516*m*, 491*w*, 463*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46–7.32 (*m*, *tt*-like, $^3J \approx 7.5$, Ph); 7.14 (*AA′* of *AA′BB′*, ^3J = 8.4, H–C(2′), H–C(6′)); 6.93 (*BB′* of *AA′BB′*, ^3J = 8.4, H–C(3′), H–C(5′)); 5.84 (*ddt*, ^3J = 17.5, 9.8, 7.5, H–C(5)); 5.12 (*dq*-like, ^3J = 17.5, 9.8, $^2J \approx {}^4J \approx 1$, CH_2(6)); 5.06 (*s*, PhCH_2); 3.68 (br. *quint.*, ^3J = 7.5, H–C(3)); 2.72 (*dquint.*-like, ^2J = 14.5, $^3J \approx 8$, CH_2(1)); 2.27 (*dquint.*-like, ^2J = 14.5, ^3J = 7.5, CH_2(4)); 1.77 (*m*, *q*-like, $^3J \approx 8$, CH_2(2)); 1.67 (*s*, HO–C(3)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 157.0 (C(4′)); 137.2 (Ph); 134.6 (C(5)); 134.4 (C(1′)); 129.3 (C(2′), C(6′)); 128.5, 127.8, 127.4 (Ph), 118.2 (C(6)); 114.8 (C(3′), C(5′)); 70.0 (PhCH_2); 69.9 (C(3)); 42.0 (C(2)); 38.6 (C(4)); 31.1 (C(1)). EI-MS: 282 (3, M^+), 197 (5), 119 (1), 107 (3, $C_7H_7O^+$), 91 (100, $PhCH_2^+$), 89 (2), 78 (3), 77 (2), 65 (9), 63 (1), 55 (1), 51 (2).

*Data of (−)-***7**: $[\alpha]_D$ = −14.4 (*c* = 0.60, EtOH). All other data: identical with those of (+)-**7**.

4. *(*S*)-MTPA Derivatives* **8** *and* **9** *for the Confirmation of the Absolute Configuration*. Each homoallyl alcohol (+)- or (−)-**7** (each 12 mg, 0.043 mmol) was dissolved in anh. CH_2Cl_2 (1 ml) and Et_3N (24 µl, 0.172 mmol). DMAP (1 mg) and (+)-(*R*)-MTPA-Cl (16 µl, 0.086 mmol) were added, and the mixture was stirred at r.t. (4 h). Workup and CC (SiO_2; hexane/CH_2Cl_2 1:2 → hexane/CH_2Cl_2/AcOEt 2:7:1) afforded the (*S*)-MTPA ester **8** (18 mg, 85%) or **9** (18.7 mg, 88%), resp., both as colorless, viscous oils.

*(3*R*)-1-[4-(Benzyloxy)phenyl]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-(Phenylmethoxy)phenyl]ethyl}-but-3-en-1-yl Ester*; **8**): R_f (hexane/Et_2O 1:1) 0.58. GC ('high'): t_R 23 min 30 s. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.60–7.55 (*m*, Ph); 7.46–7.30 (*m*, *Ph*CH_2); 7.01 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.91 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 5.66 (*ddt*, ^3J = 17, 10, 6, H–C(5)); 5.19 (br. *quint.*, $^3J \approx 6$, H–C(3)); 5.05 (*s*, PhCH_2); 5.04 (br. *dq*-like, ^3J = 17, 10, $^2J \approx {}^4J \approx 1$, CH_2(6)); 3.57 (*q*, ^5J(H,F) = 1.1, MeO); 2.59 (*m*, *dquint.*-like, $w_{1/2} \approx 30$, CH_2(1)); 2.40 (*tt*, ^3J = 6, $^4J \approx 1$, CH_2(4)); 1.94 (*m*, *dquint.*-like, $w_{1/2} \approx 30$, CH_2(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 166.2 (CO); 157.3 (C(4′)); 137.2 (*Ph*CH_2); 133.3 (C(1′)); 132.5 (C(5)); 132.3, 129.6 (Ph of MTPA); 129.2 (C(2′), C(6′)); 128.6 (*Ph*CH_2); 128.4 (Ph of MTPA); 127.9 (*Ph*CH_2); 127.5, 127.4 (*Ph*CH_2, Ph of MTPA); 123.4 (*q*, ^1J(C,F) = 288, CF_3); 118.5 (C(6)); 114.9 (C(3′) C(5′)); 84.5 (*q*, ^2J(C,F) = 27.6, Ph*C*(MeO)(CF_3)CO); 76.0 (C(3)): 70.1 (PhCH_2); 55.4 (MeO); 38.0 (C(4)); 35.3 (C(2)); 30.6 (C(1)). EI-MS: 498 (1, M^+), 264 (1, [M − MTPA − H_2O]$^+$), 223 (1), 197 (5), 189 (5), 184 (1), 184 (1), 145 (1), 139 (1), 131 (1), 127 (1), 119 (3), 115 (2), 107 (2, $C_7H_7O^+$), 105 (4), 91 (100, $PhCH_2^+$), 77 (6), 65 (10), 51 (3).

*(3*S*)-1-[4-(Benzyloxy)phenyl]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-(Phenylmethoxy)phenyl]ethyl}-but-3-en-1-yl Ester*; **9**): R_f (hexane/Et_2O 1:1) 0.58. GC ('high'): t_R 23 min 19 s. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.61–7.58 (*m*, Ph); 7.45–7.29 (*m*, *Ph*CH_2); 6.98 (*AA′* of *AA′BB′*, ^3J = 8.7, H–C(2′), H–C(6′)); 6.88 (*BB′* of *AA′BB′*, ^3J = 8.7, H–C(3′), H–C(5′)); 5.76 (*ddt*, ^3J = 17, 10, 7, H–C(5)); 5.19 (br. *quint.* $^3J \approx$ 7, 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)); 5.04 (*s*, PhCH_2); 3.59 (*q*, ^5J(H,F) = 1.2, MeO); 2.45 (br. *quint.*-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); 157.2 (C(4′)); 137.2 (*Ph*CH_2); 133.4 (C(1′)); 132.9 (C(5)); 132.3 (Ph of MTPA); 129.6 (Ph of MTPA); 129.2 (C(2′), C(6′)); 128.6 (*Ph*CH_2); 128.4 (Ph of MTPA); 127.9 (*Ph*CH_2); 127.4, 127.4 (*Ph*CH_2, Ph of MTPA); 123.4 (*q*, ^1J = 289, CF_3); 118.6 (C(6)); 114.9 (C(3′), C(5′)); 84.5 (*q*, ^2J(C,F) = 27.6, Ph*C*(MeO)(CF_3)CO); 75.9 (C(3)); 70.1 (PhCH_2); 55.5 (MeO); 38.3 (C(4)); 35.3 (C(2)); 30.3 (C(1)). EI-MS: 498 (1, M^+), 264 (1, [M − MTPA − H_2O]$^+$),

197 (4), 189 (3), 184 (1), 152 (1), 133 (1), 127 (1), 119 (1), 107 (1, $C_7H_7O^+$), 105 (4), 91 (100, $PhCH_2^+$), 77 (4), 65 (9), 51 (4).

$\Delta\delta(^1H) = \delta(S) - \delta(R) = \delta(\mathbf{9}) - \delta(\mathbf{8})$ (in Hz): $CH_2(1)$ −56, $CH_2(2)$ −24, H−C(3) 0, $CH_2(4)$ +20, H−C(5) +40, and $CH_2(6)$ +30. The relative displacements [40] confirm the expected [39] absolute configuration at C(3).

5. *(+)- and (−)-(5*E*)-4′*-O-*(Benzyloxy)-5,6-didehydro-4″*-O-*methylcentrolobol* (= *(+)-(3*R*,5*E*)-* and *(−)-(3*S*,5*E*)-1-[4-(Benzyloxy)phenyl]-7-(4-methoxyphenyl)hept-5-en-3-ol* = *(+)-(α*R*)-* and *(−)-(α*S*)-α-[(2*E*)-4-(4-Methoxyphenyl)-but-2-en-1-yl]-4-(phenylmethoxy)benzenepropanol*, resp.; (+)- and (−)-**10**, resp.). To a soln. of **HG-II** (22 mg, 0.052 mmol) in anh. MeOH (2 ml) at −78°, a soln. of (+)-**7** (104 mg, 0.368 mmol) and 4-allylanisole (215 mg, 1.46 mmol; **6**) in anh. MeOH (2 ml) was added under Ar. The mixture was stirred (1 h) at −78° and then allowed to warm to r.t. for 6 h, when another portion of **6** (105 mg, 0.716 mmol) was added and stirred for 1 h at r.t. After evaporation to dryness in a stream of N_2, CC (SiO_2; hexane/CH_2Cl_2/AcOEt 5:14:1) afforded starting (+)-**7** (28 mg, 27%) that could be recycled, and (+)-**10** (48 mg, 32%; (*E*)/(*Z*) *ca.* 8:1[19]) as colorless plates. Analogously, starting from (−)-**7** (50 mg, 0.177 mmol), **5** (106 mg, 0.715 mmol) in anh. MeOH (3 ml), **HG-II** (11 mg, 0.017 mmol), and further addition of **5** (51 mg, 0.344 mmol), we obtained (−)-**7** (24 mg, 34%) and (−)-**10** (12 mg, 24%; (*E*)/(*Z*) *ca.* 8:1)[19]).

*Data of (+)-***10**: M.p. 78–83°. R_f (hexane/Et_2O 1:2) 0.32. $[\alpha]_D = +2.3$ ($c = 0.65$, EtOH). IR (KBr): 3366*m*, 3061*w*, 3032*w*, 2996*w*, 2931*m*, 2857*m*, 2838*m*, 1606*m*, 1582*m*, 1511v*s*, 1453*m*, 1383*m*, 1295*m*, 1246v*s*, 1176*s*, 1100*m*, 1063*m*, 1035*s*, 968*m*, 910*w*, 887*m*, 831*m*, 807*m*, 780*w*, 739*m*, 697*m*, 641*w*, 608*w*, 543*w*, 522*w*. ^{1}H-NMR (300 MHz, $CDCl_3$)[20]): 7.45–7.30 (*m*, Ph); 7.14–7.06 (2 *AA′* of *AA′BB′*, *t*-like, $^3J = 8.6$, H−C(2′), H−C(2″), H−C(6′), H−C(6″)); 6.90 (*BB′* of *AA′BB′*, $^3J = 8.6$, H−C(3′), H−C(5′)); 6.83 (*BB* of *AA′BB′*, $^3J = 8.6$, H−C(3″), H−C(5″)); 5.69 (*X* of *ABMX*, *dt*, $^3J(6,5) = 15.1$, $^3J(6,7) = 6.7$, H−C(6)); 5.29 (br. *dt*, $^3J(5,6) = 15.1$, $^3J(5,4) = 7.8$, $^4J(5,3) \approx 1$, H−C(5)); 5.04 (*s*, $PhCH_2$); 3.79 (*s*, MeO−C(4″)); 3.64 (*M* of *ABMX*, *quint.*-like, $^3J \approx 7$, H−C(3)); 3.31 (*d*, $^3J(7,6) = 6.7$, $CH_2(7)$); 2.72, 2.64 (*AB* of *ABXY*, $^2J = 14.3$, $^3J = 7.7$, 6.4, $CH_2(1)$); 2.26 (*A* of *ABMX*, $^2J = 13.7$, $^3J \approx 5$, $^4J < 1$, H_A−C(4)); 2.17 (*B* of *ABMX*, $^2J = 13.7$, $^3J = 7.2$, H_B−C(4)); 1.77 (*XY* of *ABXY*, *q*-like, $CH_2(2)$); 1.57 (*s*, HO−C(3)). ^{13}C-NMR (100.6 MHz, $CDCl_3$)[20]): 157.9 (C(4′)); 157.0 (C(4″)); 137.2 (Ph), 134.4 (C(1′)); 133.6 (C(1″), C(6)); 129.3 (C(2′), C(2″), C(6′), C(6″)); 128.5, 127.9, 127.5 (Ph); 126.9 (C(5)); 114.7 (C(3″), C(5″)); 113.9 (C(3′), C(5′)); 70.2 (C(3)); 70.0 ($PhCH_2$); 55.3 (*Me*O−C(4″)); 40.7 (C(4)); 38.6 (C(2)); 38.2 (C(7)); 31.1 (C(1)). EI-MS: 402 (10, M^+), 211 (8), 197 (9), 147 (17), 121 (16, $C_8H_9O^+$), 107 (8, $C_7H_7O^+$), 91 (100, $PhCH_2^+$), 77 (3), 65 (5).

*Data of (−)-***10**: $[\alpha]_D = -2.8$ ($c = 0.64$, EtOH). All other data: identical with those of (+)-**10**.

6. *(+)- and (−)-4″-*O*-Methylcentrolobol* (= *(+)-4-[(3*S*)-* and *(−)-4-[(3*R*)-3-Hydroxy-7-(4-methoxyphenyl)heptyl]phenol* = *(+)-(α*S*)-* and *(−)-(α*R*)-α-[2-(4-Hydroxyphenyl)ethyl]-4-methoxybenzenepentanol*, resp.; (+)- and (−)-**11**, resp.). The soln. of (+)-**10** (200 mg, 0.497 mmol) in anh. CH_2Cl_2 (10 ml) was hydrogenated over 10% Pd/C (37 mg, 0.035 mmol) by stirring under a slight H_2 pressure (rubber balloon) at r.t. (2 d). Usual workup and CC (SiO_2; hexane/CH_2Cl_2/AcOEt 5:14:1) afforded (+)-**11** (128 mg, 82%; ee > 97%) as a colorless, viscous oil that solidified in the refrigerator. Analogously, starting from (−)-**10** (260 mg, 0.646 mmol) and 10% Pd/C (48 mg, 0.048 mmol), we obtained (−)-**11** (174 mg, 86%; ee > 98%). HPLC (*Chiralcel® OD-H*, hexane/^{i}PrOH 8:1): k'((+)-**11**) = 10.7, k'((−)-**11**) = 8.2, $R_S = 2.7$.

Starting from (+)- and (−)-**7**, resp., compounds (+)- and (−)-**11**, resp., could also be prepared by a one-pot procedure: When the metathesis was performed in CH_2Cl_2, the crude product mixture was hydrogenated *in situ* and purified by CC as described above. A typical protocol with (+)-**7** (200 mg, 0.708 mmol) and 4-allylanisole (**6**, 429 mg, 2.896 mmol) in anh. CH_2Cl_2 yielded after hydrogenation and CC, (+)-**11** (93 mg, 42%; ee > 97%). Analogously, (−)-**11** was isolated (102 mg, 46%; ee > 98%)[21]). This protocol failed when the metathesis was performed in MeOH.

---

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

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

[21]) The hydrogenolysis product of natural (−)-**1** was reported to be (−)-**11** (m.p. 73–75°; $[\alpha]_D = -8.6$) [9]. To the cleavage product of the macrocyclic diarylheptanoid aceroside I, structure (−)-**11** was assigned, too (m.p. 80.5–81.5°; $[\alpha]_D = -7.5$) [43].

*Data of (+)-***11**: M.p. 74–76°. R_f (hexane/Et_2O 1:4) 0.45. GC ('high'): t_R 18 min 2 s. $[\alpha]_D = +9.5$ ($c = 0.4$, EtOH). IR (KBr): 3425*vs*, 3326*s*, 3250*m*, 3070*w*, 3027*w*, 3010*w*, 2933*s*, 2914*s*, 2853*s*, 1610*m*, 1592*m*, 1512*vs*, 1462*m*, 1453*m*, 1436*m*, 1345*m*, 1320*w*, 1300*m*, 1265*s*, 1234*vs*, 1207*m*, 1198*m*, 1179*s*, 1161*m*, 1135*m*, 1104*m*, 1095*m*, 1073*w*, 1059*m*, 1031*m*, 996*w*, 983*w*, 924*w*, 909*w*, 868*w*, 843*m*, 830*m*, 819*m*, 808*m*, 788*w*, 771*w*, 751*w*, 728*w*, 713*w*, 638*w*, 583*m*, 541*m*, 518*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.08 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(2″), H–C(6″)); 7.03 (*AA′* of *AA′BB′*, $^3J = 8.6$, H–C(2′), H–C(6′)); 6.83 (*BB′* of *AA′BB′*, $^3J = 8.7$, H–C(3″), H–C(5″)); 6.74 (*BB′* of *AA′BB′*, $^3J = 8.6$, H–C(3′), H–C(5′)); 5.92 (br. *s*, HO–C(4′)); 3.79 (*s*, MeO–C(4″)); 3.64 (*m*, br. *quint.*-like, $^3J \approx 7$, H–C(3)); 2.70 (*A* of *ABXY*, $^2J = 14.0$, $^3J = 9.3$, H_A–C(1)); 2.60 (*B* of *ABXY*, $^2J = 14.0$, $^3J = 6.8$, H_B–C(1)); 2.55 (*t*, $^3J = 7.6$, CH_2(7)); 1.74 (*XY* of *ABXY*, *m*, $w_{1/2} \approx 30$, CH_2(2)); 1.61 (*m*, $w_{1/2} \approx 20$, CH_2(6)); 1.55–1.43 (*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, $CDCl_3$): 157.6 (C(4″)); 153.9 (C(4′)); 134.7 (C(1″)); 133.8 (C(1′)); 129.4 (C(2′), C(6′)); 129.2 (C(2″), C(6″)); 115.3 (C(3′), C(5′)); 113.7 (C(3″), C(5″)); 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)); 31.1 (C(1)); 25.1 (C(5)). EI-MS: 314 (4, M^+), 296 (5, $[M - H_2O]^+$), 281 (6), 207 (28), 193 (3), 188 (5), 177 (4), 174 (6), 158 (2), 147 (28), 134 (23), 131 (3), 121 (100, $C_8H_9O^+$), 115 (3), 107 (71, $C_7H_7O^+$), 105 (3), 103 (4), 94 (4), 91 (28, $PhCH_2^+$), 89 (4), 78 (10), 77 (20), 73 (8), 65 (11), 55 (8), 51 (7).

*Data of (−)-***11**: $[\alpha]_D = -9.8$ ($c = 0.55$, EtOH). All other data: identical with those of (+)-**11**.

7. *(+)- and (−)-4′-(Acetyloxy)-4″-methoxycentrolobol* (= *(+)-4-[(3*S*)-* and *(−)-4-[(3*R*)-3-Hydroxy-7-(4-methoxyphenyl)heptyl]phenyl Acetate* = *(+)-(α*S*)-* and *(−)-(α*R*)-α-{2-[4-(Acetyloxy)phenyl]ethyl}-4-methoxybenzenepentanol*, resp.; (+)- and (−)-**12**, resp.). A soln. of (+)-**11** (60 mg, 0.191 mmol) in anh. CH_2Cl_2 (2 ml) was treated with Ac_2O (20 µl, 0.212 mmol) and Et_3N (135 µl, 0.97 mmol) at −5° (2 h). Workup and CC (SiO_2; hexane → hexane/CH_2Cl_2/AcOEt 2:7:1) gave (+)-**12** (63 mg, 92%) as a white solid. Analogously, starting from (−)-**11** (100 mg, 0.318 mmol), Ac_2O (31 µl, 0.328 mmol), and Et_3N (225 µl, 1.11 mmol), we obtained (−)-**12** (109 mg, 96%).

*Data of (+)-***12**: M.p. 65–66°. R_f (hexane/Et_2O 1:4) 0.31. $[\alpha]_D = +7.7$ ($c = 0.5$, $CHCl_3$). IR (KBr): 3313*m*, 3229*m*, 3031*w*, 2931*s*, 2856*m*, 1760*vs*, 1612*m*, 1584*w*, 1513*vs*, 1463*m*, 1454*m*, 1443*m*, 1419*w*, 1369*m*, 1326*w*, 1301*m*, 1246*vs*, 1216*vs*, 1198*vs*, 1164*s*, 1137*m*, 1104*m*, 1073*m*, 1064*m*, 1035*m*, 1020*m*, 938*w*, 912*m*, 869*m*, 844*m*, 820*m*, 769*w*, 753*w*, 728*w*, 642*m*, 596*w*, 576*m*, 518*m*, 497*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (*AA′* of *AA′BB′*, $^3J = 8.5$, H–C(2′), H–C(6′)); 7.09 (*AA′* of *AA′BB′*, $^3J = 8.7$, H–C(2″), H–C(6″)); 7.00 (*BB′* of *AA′BB′*, $^3J = 8.5$, H–C(3′), H–C(5′)); 6.83 (*BB′* of *AA′BB′*, $^3J = 8.7$, H–C(3″), H–C(5″)); 3.79 (*s*, MeO–C(4″)); 3.61 (*m*, *sept.*-like, $w_{1/2} \approx 15$, H–C(3)); 2.78 (*ddd*, $^2J = 14$, $^3J = 9.7$, 5.8, H–C(1)); 2.65 (*ddd*, $^2J = 14$, $^3J = 9.7$, 6.8, H–C(1)); 2.57 (*t*, $^3J = 7.6$, CH_2(7)); 2.29 (*s*, MeCOO–C(4′)); 1.74 (*m*, *tquint.*-like, $w_{1/2} \approx 35$, CH_2(2)); 1.63 (*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, $CDCl_3$): 169.6 (CO); 157.6 (C(4″)), 148.7 (C(4′)); 139.7 (C(1′)); 134.6 C(1″)); 129.2 (C(2′), C(6′)); 129.2 (C(2″), C(6″)); 121.3 (C(3′), C(5′)); 113.7 (C(3″), C(5″)); 71.1 (C(3)); 55.2 (*Me*O–C(4″)); 39.0 (C(2)); 37.4 (C(4)); 34.9 (C(7)); 31.6 (C(6)); 31.3 (C(1)); 25.1 (C(5)); 21.1 (*Me*COO–C(4′)). EI-MS: 356 (22, M^+), 338 (9, $[M - H_2O]^+$), 314 (7), 296 (61, $[M - AcOH]^+$), 189 (9), 188 (10), 147 (33), 134 (39), 121 (100, $C_8H_9O^+$), 107 (64, $C_7H_7O^+$), 91 (9, $PhCH_2^+$), 77 (8), 43 (8).

*Data of (−)-***12**: $[\alpha]_D = -8.1$ ($c = 0.6$, $CHCl_3$). All other data: identical with those of (+)-**12**.

8. *(+)- and (−)-*O*-Acetylcentrolobine* (= *(+)-(2*R*,6*S*)-* and *(−)-(2*S*,6*R*)-6-{2-[4-(Acetyloxy)phenyl]ethyl}-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran* = *(+)-4-{2-[(2*S*,6*R*)-* and *(−)-4-{2-[(2*R*,6*S*)-6-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-yl]ethyl}phenyl Acetate* = *(+)-4-{2-[(2*S*,6*R*)-* and *(−)-4-{2-[(2*R*,6*S*)-Tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran-2-yl]ethyl}phenol Acetate*, resp.; (+)- and (−)-**13**, resp.). To a cooled (−10°) soln. of (+)-**12** (54 mg, 0.151 mmol) in anh. CH_2Cl_2 (10 ml), DDQ (74 mg, 0.326 mmol) was added in a single portion and stirred (10 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) afforded (+)-**13** (4 mg, 7%) as a colorless, viscous oil and starting (+)-**12** (41 mg, 76%) that could be recycled. Analogously, starting from (−)-**12** (80 mg, 0.224 mmol) and DDQ (98 mg, 0.432 mmol), we obtained (−)-**13** (7 mg, 9%) and starting (−)-**12** (64 mg, 80%).

*Data of (+)-***13**: R_f (hexane/Et_2O 3:2) 0.35. $[\alpha]_D = +72.3$ ($c = 0.62$, $CHCl_3$). IR (film): 3035*m*, 2999*m*, 2934*vs*, 2011*s*, 1763*vs*, 1613*s*, 1587*m*, 1514*vs*, 1456*s*, 1441*s*, 1369*vs*, 1329*m*, 1303*s*, 1247*vs*, 1194*vs*, 1079*vs*, 1037*vs*, 1019*s*, 944*m*, 911*s*, 834*s*, 812*s*, 767*m*, 638*w*, 589*m*, 573*w*, 549*m*. ^{1}H-NMR (400 MHz,

$CDCl_3$): 7.31 (*AA′* of *AA′BB′*, $^3J = 8.6$, H–C(2′), H–C(6′)); 7.19 (*AA′* of *AA′BB′*,$^3J = 8.5$, H–C(2‴), H–C(6‴)); 6.98 (*BB′* of *AA′BB′*, $^3J = 8.5$, H–C(3‴), H–C(5‴)); 6.89 (*BB′* of *AA′BB′*, $^3J = 8.6$, H–C(3′), H–C(5′)); 4.30 (*dd*, $^3J(2,3ax) = 11.1$, $^3J(2,3eq) = 2.0$, H–C(2)); 3.81 (*s*, MeO–C(4′)); 3.46 (*dddd*, $^3J(5ax,6) = 10.7$, $^3J(5eq,6) = 1.9$, $^3J(1'', 6) \approx 8$, 5, H–C(6)); 2.76 (*m*, *ttt*-like, $^2J \approx 14$, $^3J \approx 7$, $CH_2(2'')$); 2.29 (*s*, *Me*COO–C(4‴)); 1.92 (*m*, $w_{1/2} \approx 25$, H–C(1″), H_{eq}–C(4)); 1.83 (br. *dq*-like, $^2J \approx 11$, $^3J(2, 3eq) \approx {}^3J(3eq,4ax) \approx {}^3J(3eq,4eq) \approx 2$, H_{eq}–C(3)); 1.74 *m*, $w_{1/2} \approx 25$, H–C(1″)); 1.63 (*qt*-like, $^2J \approx {}^3J(3ax,4ax) \approx {}^3J(4ax,5ax) \approx 11$, $^3J(3ax,4eq) \approx {}^3J(4eq,5ax) \approx 3$, H_{ax}–C(4)); 1.62 (br. *dq-like*, $^2J \approx 11$, $^3J(4ax,5eq) \approx {}^3J(4eq,5eq) \approx {}^3J(5eq,6) \approx 2$, H_{eq}–C(5)); 1.49 (*m*, *qd*-like, $^2J \approx {}^3J(2,3ax) \approx {}^3J(3ax,4ax) \approx 10$, $^3J(3ax,4eq) \approx 4$, H_{ax}–C(3)); 1.33 (*m*, *qd*-like, $^2J \approx {}^3J(4ax,5ax) \approx {}^3J(5ax,6) \approx 10$, $^3J(4eq,5ax) \approx 4$, H_{ax}–C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 169.7 (CO); 158.7 (C(4′)); 148.6 (C(4‴)); 140.1 (C(1‴)); 135.9 (C(1′)); 129.4 (C(2‴), C(6‴)); 127.0 (C(2′), (6′)); 121.2 (C(3‴), C(5‴)); 113.6 (C(3′), C(5′)); 79.1 (C(2)); 77.0 (C(6)); 55.3 (*Me*O–C(4′)); 38.0 (C(1″)); 33.4 (C(3)); 31.3 (C(5)); 31.1 (C(2″)); 24.0 (C(4)); 21.1 (*Me*COO–C(4‴)). EI-MS: 354 (74, M^+), 312 (48, $[M - C_2H_2O]^+$), 294 (5, $[M - AcOH]^+$), 218 (9), 191 (9), 174 (30), 150 (9), 149 (15), 148 (26), 147 (38), 137 (27), 135 (29), 134 (26), 133 (19), 121 (53, $C_8H_9O^+$), 107 (100, $C_7H_7O^+$), 91 (16, $PhCH_2^+$), 77 (14), 65 (6), 43 (18).

*Data of (–)-***13**: $[\alpha]_D = -73.4$ ($c = 1.24$, $CHCl_3$). All other data: identical with those of (+)-**13**.

9. *(+)- and (–)-Centrolobine* (*=(+)-(2*R,*6*S*)-* and *(–)-(2*S,*6*R*)-6-[2,4-(Hydroxyphenyl)ethyl]-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran = (+)-4-{2-[(2*S,*6*R*)-* and *(–)-4-{2-[(2*R,*6*S*)-6-(4-Methoxyphenyl)-tetrahydro-2*H*-pyran-2-yl]ethyl}phenol = (+)-4-{2-[(2S,6R)-* and *(–)-4-{2-[(2R,6S)-Tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran-2-yl]ethyl}phenol*, resp.; (+)- and (–)-**1**, resp.). To (+)-**13** (8 mg, 0.023 mmol) in MeOH (2.5 ml), 10% aq. NaOH soln. (2.5 ml) was added and the mixture stirred at r.t. (4 h). Usual workup, CC (SiO_2; hexane/CH_2Cl_2/AcOEt 5 : 14 : 1), and recrystallization (hexane/AcOEt) gave (+)-**1** (6 mg, 85%; ee > 97%[22]) as colorless prisms. Analogously, starting from (–)-**13** (14 mg, 0.039 mmol), we obtained (–)-**1** (11 mg, 89%; ee > 98%[22]). HPLC (hexane/^{i}PrOH 20 : 1): $k'((+)\text{-}\mathbf{1}) = 4.0$, $k'((-)\text{-}\mathbf{1}) = 3.7$, $R_S = 0.95$; HPLC (*Chiralcel® OD-H*, hexane/^{i}PrOH 50 : 1): $k'((+)\text{-}\mathbf{1}) = 11.9$, $k'((-)\text{-}\mathbf{1}) = 10.9$, $R_S = 1.2$ (not sufficient for a reliable ee-determination[22]).

*Data of (+)-***1**: M.p. 93–94°. R_f (hexane/Et_2O 1 : 2) 0.20. $[\alpha]_D = +89.3$ ($c = 0.31$, $CHCl_3$). IR (KBr): 3389*m*, 3060*w*, 3025*w*, 2947*m*, 2925*m*, 2913*m*, 2859*m*, 2832*m*, 1611*m*, 1599*m*, 1588*w*, 1512*vs*, 1462*m*, 1452*m*, 1416*w*, 1370*m*, 1301*m*, 1244*vs*, 1208*m*, 1183*m*, 1172*m*, 1141*w*, 1112*m*, 1088*s*, 1069*m*, 1051*m*, 1036*m*, 1016*w*, 993*w*, 953*w*, 935*w*, 917*w*, 901*w*, 849*w*, 837*m*, 818*m*, 806*m*, 776*w*, 770*w*, 646*w*, 598*w*, 569*m*, 540*m*, 497*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 (*AA′* of *AA′BB′*, $^3J = 8.6$, H–C(2′), H–C(6′)); 7.04 (*AA′* of *AA′BB′*, $^3J = 8.5$, H–C(2‴), H–C(6‴)); 6.90 (*BB′* of *AA′BB′*, $^3J = 8.6$, H–C(3′), H–C(5′)); 6.71 (*BB′* of *AA′BB′*, $^3J = 8.5$, H–C(3‴), H–C(5‴)); 5.14 (br. *s*, HO–C(4‴)); 4.32 (*dd*, $^3J(2,3ax) = 11.0$, $^3J(2,3eq) = 2.0$, H–C(2)); 3.81 (*s*, MeO–C(4′)); 3.47 (*dddd*, $^3J(5ax,6) = 9.8$, $^3J(5eq,6) = 1.8$, $^3J(1'',6) \approx 7$, 5, H–C(6)); 2.70 (*m*, *ddt*-like, $^2J = 14.0$, $^3J \approx 9$, 6, $CH_2(2'')$); 1.92 (*m*, $w_{1/2} \approx 25$, H–C(1″), H_{eq}–C(4)); 1.84 (br. *dq*-like, $^2J \approx 11$, $^3J(2,3eq) \approx {}^3J(3eq,4ax) \approx {}^3J(3eq,4eq) \approx 2$, H_{eq}–C(3)); 1.74 *m*, $w_{1/2} \approx 25$, H–C(1″)); 1.62 (*m*, $w_{1/2} \approx 25$, H_{ax}–C(4), H_{eq}–C(5)); 1.56 (*qd*-like, $^2J \approx {}^3J(2,3ax) \approx {}^3J(3ax,4ax) \approx 10$, $^3J(3ax,4eq) \approx 3$, H_{ax}–C(3)); 1.35 (*qd*-like, $^2J \approx {}^3J(4ax,5ax) \approx {}^3J(5ax,6) \approx 10$, $^3J(4eq,5ax) \approx 4$, H_{ax}–C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 158.7 (C(4′)); 153.5 (C(4‴)); 135.6 (C(1′)); 134.5 (C(1‴)); 129.5 (C(2‴), C(6‴)); 127.1 (C(2′), C(6′)); 115.1 (C(3‴), C(5‴)); 113.6 (C(3′), C(5′)); 79.2 (C(2)); 77.3 (C(6)); 55.3 (*Me*O–C(4′)); 38.2 (C(1″)); 33.2 (C(3)); 31.2 (C(5)); 30.7 (C(2″)); 24.0 (C(4)). EI-MS: 312 (72, M^+), 294 (5, $[M - H_2O]^+$), 191 (6), 187 (6), 174 (30), 160 (9), 149 (22), 148 (21), 147 (32), 137 (19), 135 (16), 134 (19), 133 (16), 121 (60, $C_8H_9O^+$), 107 (100, $C_7H_7O^+$), 91 (10, $PhCH_2^+$), 77 (11).

*Data of (–)-***1**: $[\alpha]_D = -91.0$ ($c = 0.78$, $CHCl_3$). All other data: identical with those of (+)-**1**.

10. *(2*R,*6*S*)-6-{2-[4-[(4-Bromobenzoyl)oxy]phenyl}ethyl]-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran (=4-{2-[(2*R,*6*S*)-6-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-yl]ethyl}phenyl 4-Bromobenzoate = 4-{2-[(2*R,*6*S*)-Tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran-2-yl]ethyl}phenol 4-Bromobenzoate*; **14**). To a soln. of (–)-**1** (8 mg, 0.026 mmol) and Et_3N (1 ml, 0.051 mmol) in anh. CH_2Cl_2 (2 ml), 4-bromobenzoyl

---

[22] 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 ($R_S = 1.2$), and positive 'nonlinear effects' [47] are ruled out. Hence, we adopt the reliable ee-values from the starting (+)- and (–)-**11**.

chloride (6 mg, 0.026 mmol) was added at r.t. and kept for 1 h. CC (SiO_2; CH_2Cl_2) and recrystallization (hexane/Et_2O) gave **14** (12 mg, 95%). Colorless tablets. M.p. 96–97°. R_f (hexane/Et_2O 3:2) 0.49. IR (KBr): 3050*w*, 2993*w*, 2940*m*, 2834*m*, 1787*w*, 173vs, 1721v*s*, 1611*m*, 1589*s*, 151vs, 1483*m*, 1451*m*, 1441*m*, 1418*w*, 1398*m*, 1388*m*, 1369*w*, 1301*m*, 1267v*s*, 1243v*s*, 1194v*s*, 1167*s*, 1073*w*, 1049*w*, 1033*w*, 1010*w*, 979*w*, 955*w*, 925*w*, 902*w*, 876*m*, 845*m*, 833*m*, 814*s*, 767*m*, 751*s*, 707*w*, 681*w*, 637*w*, 628*w*, 598*w*, 572*w*, 553*w*, 529*w*, 491*w*, 475*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.06, 7.65 (*AA′BB′*, ^3J = 8.7, 4-BrC_6H_4); 7.32 (*AA′* of *AA′BB′*, ^3J = 8.5, H–C(2′), H–C(6′)); 7.24 (*AA′* of *AA′BB′*, ^3J = 8.6, H–C(2‴), H–C(6‴)); 7.10 (*BB′* of *AA′BB′*, ^3J = 8.6, H–C(3‴), H–C(5‴)); 6.89 (*BB′* of *AA′BB′*, ^3J = 8.5, H–C(3′), H–C(5′)); 4.31 (*dd*, ^3J(2,3ax) = 11.1, ^3J(2,3eq) = 2.0, H–C(2)); 3.81 (*s*, MeO–C(4′)); 3.47 (*dddd*, ^3J(5ax,6) = 10.9, ^3J(5eq,6) = 1.9, ^3J(1″,6) ≈ 7, 4, H–C(6)); 2.78 (*m*, *ddt*-like, ^2J = 14.0, ^3J ≈ 9, 6, CH_2(2″)); 1.94 (*m*, $w_{1/2}$ ≈ 22, H–C(1″), H_{eq}–C(4)); 1.80 (*m*, $w_{1/2}$ ≈ 35, H–C(1″), H_{eq}–C(3)); 1.66 (*m*, $w_{1/2}$ ≈ 25, H_{ax}–C(4), H_{eq}–C(5)); 1.51 (br. *qd*-like, $^2J \approx {}^3J$(2,3ax) ≈ ^3J(3ax,4ax) ≈ 13, ^3J(3ax,4eq) ≈ 4, H_{ax}–C(3)); 1.35 (*qd*-like, $^2J \approx {}^3J$(4ax,5ax) ≈ ^3J(5ax,6) ≈ 11, ^3J(4eq,5ax) ≈ 4, H_{ax}–C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 164.6 (CO); 158.7 (C(4′)); 148.7 (C(4‴)); 140.4 (C(1‴)); 135.9 (C(1′)); 131.9 (C_o); 131.6 (C_m); 129.3 (C(2‴), C(6‴)), 128.7 (C_p); 128.6 (C_{ipso}); 127.1 (C(2′), C(6′)), 121.2 (C(3‴), C(5‴)); 113.6 (C(3′), C(5′)); 79.1 (C(2)); 77.0 (C(6)); 55.3 (MeO–C(4′)); 38.0 (C(1″)); 33.4 (C(3)); 31.3 (C(5)); 31.1 (C(2″)); 24.0 (C(4)). EI-MS: 496, 494 (34, 33, $M(^{81}Br)^+$, $M(^{79}Br)^+$, $C_{27}H_{27}BrO_4^+$), 218 (9), 191 (5), 185 (97, $^{81}BrC_6H_6CO^+$), 183 (100, $^{79}BrC_6H_6CO^+$), 174 (14), 157 (8, $[185 - CO]^+$), 155 (9, $[183 - CO]^+$), 150 (6), 148 (9), 147 (22), 137 (11), 136 (7), 135 (17), 134 (12), 121 (25, $C_8H_9O^+$), 107 (11, $C_7H_7O^+$), 105 (6), 104 (7), 91 (6, $PhCH_2^+$), 77 (7).

11. *X-Ray Crystal-Structure Determinations of Natural (–)-Centrolobine* ((–)-**1**) *from* Brosimum potabilis [8] *and of 4-Bromobenzoate* **14** *of Synthetic* (–)-**1**. The measurements were made on a *Nonius-KappaCCD* area-detector diffractometer [48] 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 [49] representations of the molecules are shown in *Figs. 4* and *5*. Data reduction was performed with HKL DENZO and SCALEPACK [50]. For (–)-**1**, the intensities were corrected for *Lorentz* and polarization effects but not for absorption. The space group was uniquely determined by the systematic absences. Equivalent reflections were merged. For **14**, the intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [51] was applied. The space group was uniquely determined by the systematic absences. Equivalent reflections, other than *Friedel* pairs, were merged.

The structures were solved by direct methods with SIR92 [52], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The OH H-atom of (–)-**1** 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_c/F_c (max) and resolution showed no unusual trends. A correction for secondary extinction was applied. For **14**, all of the 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 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_c/F_c (max), and resolution showed no unusual trends. A correction for secondary extinction was applied. One reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement. Refinement of the absolute structure parameter [53] yielded a value of $-0.003(6)$, which confidently confirms that the refined model corresponds with the true enantiomorph. Neutral-atom scattering factors for non-H-atoms were taken from [54], and the scattering factors for H-atoms from [55]. Anomalous dispersion effects were included in F_c [56]; the values for f' and f'' were those of [57]. The values of the mass-attenuation coefficients were those of [58]. The SHELXL97 program [59] was used for all calculations.

Table. *Crystallographic Data of (−)-***1** *and* **14**

	(−)-**1**	**14**
Crystallized from	hexane/AcOEt	hexane/Et_2O
Empirical formula	$C_{20}H_{24}O_3$	$C_{27}H_{27}BrO_4$
M_r	312.41	495.41
Crystal color, habit	colorless, prism	colorless, tablet
Crystal dimensions [mm]	$0.12 \times 0.15 \times 0.28$	$0.12 \times 0.20 \times 0.28$
Temperature [K]	160(1)	160(1)
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$ (#19)	$P2_12_12_1$ (#19)
Z	4	4
Reflections for cell determination	1825	45645
2θ Range for cell determination [°]	4–50	4–55
Unit cell parameters		
a [Å]	5.5337(2)	6.8901(1)
b [Å]	15.3020(5)	15.8695(3)
c [Å]	20.5737(5)	21.6135(3)
$\alpha=\beta=\gamma$ [°]	90	90
V [Å^3]	1742.11(9)	2363.27(6)
$F(000)$	672	1024
D_x [g cm^{-3}]	1.191	1.392
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0787	1.775
Scan type	ϕ and ω	ω
$2\theta_{(\max)}$ [°]	50	55
Transmission factors (min; max)		0.699; 0.807
Total reflections measured	25490	39687
Symmetry-independent reflections	1807	5309
R_{int}	0.081	0.052
Reflections with $I>2\sigma(I)$	1522	4339
Reflections used in refinement	1807	5308
Parameters refined	214	291
Final $R(F)$ ($I>2\sigma(I)$ reflections)	0.0427	0.0299
$wR(F^2)$ (all data)	0.1008	0.0679
Weights	[a])	[b])
Goodness of fit	1.137	1.069
Secondary extinction coefficient	0.106(7)	0.0054(7)
Final $\Delta_{\max}/\sigma$	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.28; −0.28	0.24; −0.47
$\sigma(d_{(\mathrm{C-C})})$ [Å]	0.003–0.004	0.003

[a]) $w=[\sigma^2(F_o^2)+(0.0595P)^2]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. [b]) $w=[\sigma^2(F_o^2)+(0.0299P)^2+0.4876P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$.

REFERENCES

[1] C. Bürgi, P. Rüedi, *Helv. Chim. Acta* **1993**, *76*, 1890; C. Bürgi, G. Liu, P. Rüedi, *Helv. Chim. Acta* **1993**, *76*, 1901.

[2] W. Breu, A. Sendl, C. Bürgi, P. Rüedi, H. Wagner, *Planta Med.* **1990**, *56*, 665.

[3] M. Juch, 'Isolierung, Strukturaufklärung und Synthese von optisch aktiven Alkylcatecholen aus *Plectranthus sylvestris (Labiatae)* als Inhibitoren der Lipoxygenase', Ph.D. Thesis, University of Zurich 1997; M. Juch, P. Rüedi, *Helv. Chim. Acta* **1997**, *80*, 421, and refs. cit. therein.

[4] M. Juch, P. Rüedi, *Curr. Org. Chem.* **1999**, *3*, 623.
[5] O. Gonçalves da Lima, M. Machado de Albuquerque, M. H. Dalia Maia, *Rev. Inst. Antibiot.* (Univ. Recife) **1959**, *2*, 19.
[6] I. L. de Albuquerque, C. Galeffi, C. B. Casinovi, G. B. Marini-Bettòlo, *Gazz. Chim. Ital.* **1964**, *94*, 287.
[7] C. Galeffi, C. G. Casinovi, G. B. Marini-Bettòlo, *Gazz. Chim. Ital.* **1965**, *95*, 95.
[8] A. F. de C. Alcântara, M. R. Souza, D. Piló-Veloso, *Fitoterapia* **2000**, *71*, 613.
[9] A. Aragão Craveiro, A. Da Costa Prado, O. R. Gottlieb, P. C. Welerson de Albuquerque, *Phytochemistry* **1970**, *9*, 1869.
[10] L. Jurd, R. Y. Wong, *Aust. J. Chem.* **1984**, *37*, 1127.
[11] L. V. Alegrio, R. Braz-Filho, O. R. Gottlieb, *Phytochemistry* **1989**, *28*, 2359.
[12] S. Ohta, M. Koyama, T. Aoki, T. Suga, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2423.
[13] M. Nagai, N. Kenmochi, M. Fujita, N. Furukawa, T. Inoue, *Chem. Pharm. Bull.* **1986**, *34*, 1056.
[14] G. M. Keserü, M. Nógrádi, 'The Chemistry of Natural Diarylheptanoids. In Studies in Natural Products Chemistry', Ed. Atta-ur-Rahman, Elsevier Science B. V., New York, 1995, Vol. 17, pp. 357 – 394.
[15] V. Böhrsch, S. Blechert, *J. Chem. Soc., Chem. Commun.* **2006**, 1968.
[16] P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045.
[17] F. Colobert, R. Des Mazery, G. Solladié, M. C. Carreño, *Org. Lett.* **2002**, *4*, 1723; M. C. Carreño, R. Des Mazery, A. Urbano, F. Colobert, G. Solladié, *J. Org. Chem.* **2003**, *68*, 7779.
[18] S. Marumoto, J. J. Jaber, J. P. Vitale, S. D. Rychnovsky, *Org. Lett.* **2002**, *4*, 3919.
[19] K.-P. Chan, T.-P. Loh, *Org. Lett.* **2005**, *7*, 4491; G. Sabita, K. B. Reddy, G. S. K. K. Reddy, N. Fatima, J. S. Yadav, *Synlett* **2005**, *15*, 2347; C.-H. A. Lee, T.-P. Loh, *Tetrahedron Lett.* **2006**, *47*, 1641; M. Pham, A. Allatabakhsh, T. G. Minehan, *J. Org. Chem.* **2008**, *73*, 741; M. Dziedzic, B. Furman, *Tetrahedron Lett.* **2008**, *49*, 678.
[20] P. A. Evans, J. Cui, S. J. Gharpure, *Org. Lett.* **2003**, *5*, 3883.
[21] L. Boulard, S. BouzBouz, J. Cossy, X. Franck, B. Figadère, *Tetrahedron Lett.* **2004**, *45*, 6603.
[22] M. P. Jennings, R. T. Clemens, *Tetrahedron Lett.* **2005**, *46*, 2021.
[23] D. K. Mohapatra, R. Pal, H. Rahaman, M. K. Gurjar, *Heterocycles* **2010**, *80*, 219.
[24] P. A. Clarke, W. H. C. Martin, *Tetrahedron Lett.* **2004**, *45*, 9061; P. A. Clarke, W. H. C. Martin, *Tetrahedron* **2005**, *61*, 5433.
[25] S. Chandrasekhar, S. J. Prakash, T. Shyamsunder, *Tetrahedron Lett.* **2005**, *46*, 6651.
[26] K. Prasad, P. Anbarasan, *Tetrahedron* **2007**, *63*, 1089.
[27] T. Washio, R. Yamaguchi, T. Abe, H. Nambu, M. Ananda, S. Hashimoto, *Tetrahedron* **2007**, *63*, 12037.
[28] W. Chazadaj, R. Kowalczyk, J. Jurczak, *J. Org. Chem.* **2010**, *75*, 1740.
[29] T. Takeuchi, M. Matsuhashi, T. Nakata, *Tetrahedron Lett.* **2008**, *49*, 6462.
[30] A. He, N. Sutivisedsak, C. D. Spilling, *Org. Lett.* **2009**, *11*, 3124.
[31] M. S. Ali, Y. Tetsuka, A. H. Banskota, S. Kadota, *J. Nat. Prod.* **2001**, *64*, 491; M. S. Ali, A. H. Banskota, Y. Tetsuka, I. Saiki, S. Kadota, *Biol. Pharm. Bull.* **2001**, *24*, 525.
[32] J. K. Prasain, J.-X. Li, Y. Tezuka, K. Tanaka, P. Basnet, H. Dong, T. Namba, S. Kadota, *Planta Med.* **1999**, *65*, 196.
[33] J. K. Prasain, Y. Tezuka, J.-X. Li, K. Tanaka, P. Basnet, H. Dong, T. Namba, S. Kadota, *Planta Med.* **2000**, *66*, 590.
[34] C. R. Reddy, P. P. Madavi, S. Chandrasekhar, *Synthesis* **2008**, *18*, 2939.
[35] B. Schmidt, F. Hölter, *Chem. – Eur. J.* **2009**, *15*, 11948.
[36] F. Rogano, 'Biomimetische Totalsynthese von enantiomerenreinen 2,6-disubstituierten Tetrahydropyranen', Ph.D. Thesis, University of Zurich, 2009.
[37] F. Rogano, G. S. Froidevaux, P. Rüedi, *Helv. Chim. Acta* **2010**, *93*, 1299.
[38] G. S. Froidevaux, 'Herstellung der isomeren Methoxycentrolobole und Zyklisierung zu *iso*-Centrolobin. Ein Beitrag zur Strukturaufklärung von Centrolobin aus *Centrolobium robustum*', M.Sc. Thesis, University of Zurich, 2001.
[39] G. E. Keck, E. P. Boden, *Tetrahedron Lett.* **1984**, *25*, 265; G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467; G. E. Keck, D. Krishnamurthy, *Org. Synth.* **1998**, *75*, 12.

[40] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543; G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143; J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512; I. Ohtani, T. Kusumi, Y. Kahman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[41] J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791; S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8186.
[42] Y. Oikawa, K. Horita, O. Yonemitsu, *Heterocycles* **1985**, *23*, 553; L. M. Harwood, J. Robertson, *Tetrahedron Lett.* **1987**, *28*, 5175.
[43] M. Nagai, M. Kubo, M. Fujita, T. Inoue, M. Matsuo, *Chem. Pharm. Bull.* **1978**, *26*, 2805.
[44] M. Kubo, T. Inoue, M. Nagai, *Chem. Pharm. Bull.* **1980**, *28*, 3000.
[45] P. Henley-Smith, D. A. Whiting, A. F. Wood, *J. Chem. Soc., Perkin Trans. 1* **1980**, 614; R. C. Ronald, C. J. Wheeler, *J. Org. Chem.* **1984**, *49*, 1658.
[46] E. Falomir, P. Álvarez-Bercedo, M. Carda, J. A. Marco, *Tetrahedron Lett.* **2005**, *46*, 8407; P. Álvarez-Bercedo, E. Falomir, M. Carda, J. A. Marco, *Tetrahedron* **2006**, *62*, 9641.
[47] C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353.
[48] R. Hooft, KappaCCD Collect Software, Nonius BV, Delft, The Netherlands, 1999.
[49] C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[50] Z. Otwinowski, W. Minor, in 'Methods in Enzymology, Vol. 276, Macromolecular Crystallography', Part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.
[51] R. H. Blessing, *Acta Crystallogr., Sect A* **1995**, *51*, 33.
[52] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, SIR92, *J. Appl. Crystallogr.* **1994**, *27*, 435.
[53] H. D. Flack, G. Bernardinelli, *Acta Crystallogr., Sect A* **1999**, *55*, 908; H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143.
[54] E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477.
[55] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[56] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[57] D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, p. 219.
[58] D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, p. 200.
[59] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Received March 10, 2010