Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 3046–3050

Chemoenzymatic synthesis of enantiomerically pure tricyclic benzomorphan analogues

Christian Ketterer,[a] Stefan Grimme,[b] Edgar Weckert[c] and Bernhard Wünsch[a,*]

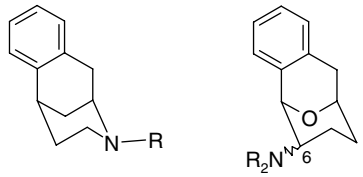
[a]*Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Hittorfstraße 58-62, 48149 Münster, Germany*
[b]*Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstr. 40, D-48149 Münster, Germany*
[c]*Hasylab at Desy, Notkestr. 85, D-22607 Hamburg, Germany*

Received 25 October 2006; accepted 10 November 2006

Abstract—The key step in the synthesis of enantiomerically pure benzomorphan analogous tricyclic amines **2** is the kinetic resolution of secondary alcohol **7** using the lipase from *Pseudomonas fluorescence*. The (*S*)-configured alcohol (*S*)-**7** and the (*R*)-configured ester (*R*)-**8** were obtained in good yield (40% and 46%, respectively) and excellent enantiomeric excess (99% ee and 98.4% ee, respectively). A diastereoselective oxa-Pictet-Spengler reaction of (*S*)-**7** with ethyl glyoxalate (O=HC–CO_2Et) followed by a Dieckmann cyclization provided the tricyclic ring system **11**, which allowed the diastereoselective introduction of an amino group at the 6-position. The absolute configuration of alcohol (*S*)-**7** was determined with the tricyclic alcohol **13**. The quantum mechanically calculated specific optical rotation of (*S*,*S*,*S*)-configured alcohol **13** is in accordance with the measured specific rotation of the synthesized compound. Moreover, X-ray crystal structure analysis of the synthesized compound, determined with the three-beam interference method, proved the (*S*,*S*,*S*)-configuration of **13**. The enantiomerically pure dimethylamine **12** showed moderate affinity toward σ_2 receptors.

1. Introduction

Several pharmacologically active compounds including benzomorphans **1**, sympathomimetics, and dopamine receptor agonists contain the 2-phenylethylamine substructure. Depending on the stereochemistry of the tricyclic ring system and the N-substituent, benzomorphans **1** can interact with Opioid receptors (μ, κ receptors), σ receptors and the phencyclidine binding site of the NMDA receptor (Fig. 1).[1]



1 **2**

Figure 1. Structural comparison of benzomorphans with planned tricyclic amines.

In order to find novel receptor ligands, the benzomorphan analogous tricyclic amines **2** with a 2-phenylethylamine substructure were envisaged.[2] Since the stereochemistry strongly influences pharmacological activity, tricyclic amines **2** should be synthesized in enantiomerically pure form. The plan for the synthesis of enantiomerically pure amines **2** is outlined in Scheme 1.

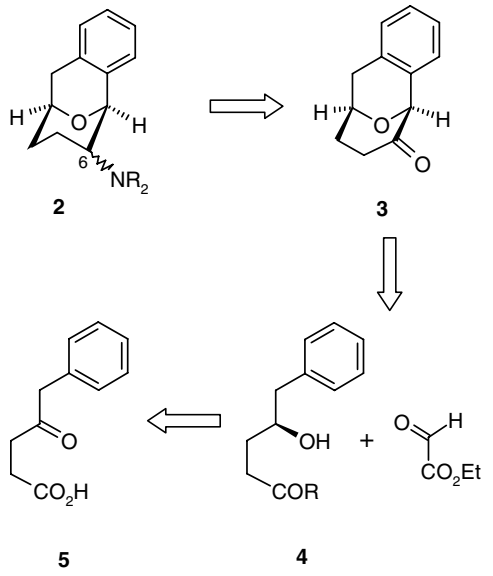
Tricyclic ketone **3** will allow the diastereoselective introduction of axially or equatorially oriented amino substituents at the 6-position. Ketone **3** should be available by an oxa-Pictet-Spengler reaction[3] of the 2-phenylethanol derivative **4**, followed by Dieckmann cyclization, hydrolysis and decarboxylation. The required, enantiomerically pure, 2-phenylethanol derivative **4** will be synthesized from 4-oxopentanoic acid **5** by an enzymatic kinetic resolution, using a lipase as a key step.

2. Results and discussion

4-Oxopentanoic acid **5**[4] was reduced with $NaBH_4$ and subsequently treated with HCl to provide γ-lactone **6** in 60%

* Corresponding author. Tel.: +49 251 8333311; fax: +49 251 832144; e-mail: wuensch@uni-muenster.de

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.11.020

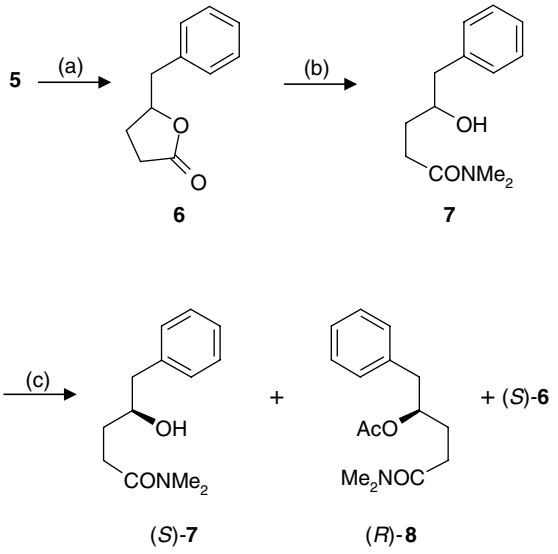


Scheme 1. Plan for the synthesis of enantiomerically pure benzomorphan analogous tricyclic amines.

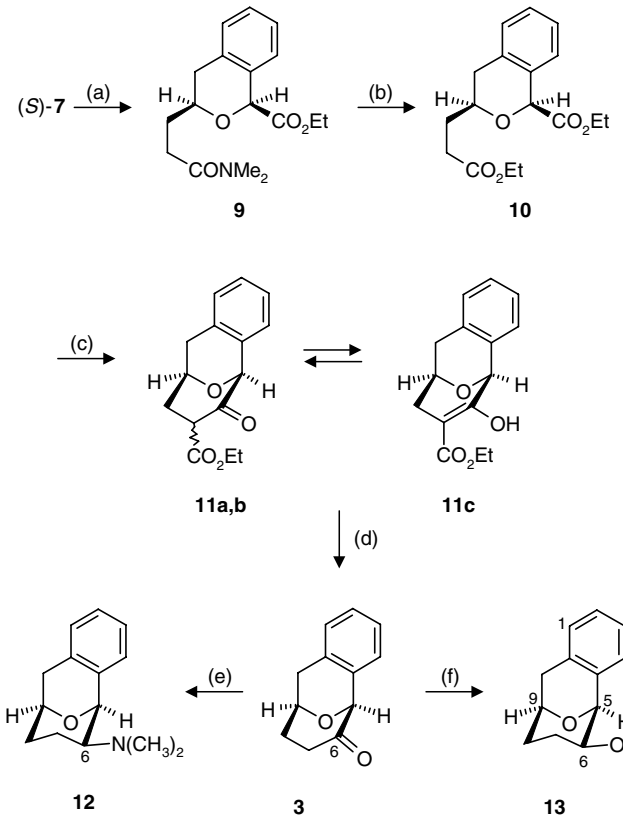
yield. The direct synthesis of γ-lactone **6** by oxidative coupling of allylbenzene with acetic acid in the presence of $Mn(OAc)_3$[5] gave a lower yield (44%) of γ-lactone **6**. Moreover, the work-up procedure is much more complicated due to separation of the Mn-salts. Aminolysis of γ-lactone **6** with dimethylamine led to the racemic γ-hydroxypentanamide **7** in 94% yield (Scheme 2).

Kinetic resolution was performed by the enantioselective acetylation of γ-hydroxypentanamide **7** with isopropenyl acetate using the lipase from *Pseudomonas fluorescence* (Amano AK) as a catalyst. The *P. fluorescence* lipase converted secondary alcohol **7** in extraordinarily high enantioselectivity leading to both alcohol (*S*)-**7** and acetate (*R*)-**8** in good yield and excellent enantiomeric excess: (*S*)-**7**: yield 40%, 99% ee; (*R*)-**8**: yield 46%, 98.4% ee. The enantioselectivity E[6] of this transformation is greater than 100. In addition to the enantiomerically pure alcohol (*S*)-**7** and acetate (*R*)-**8**, a small amount of the enantioenriched γ-lactone (*S*)-**6** (yield 10%, 72% ee) was isolated, which had been formed by non-lipase catalyzed intramolecular attack of the hydroxy moiety on the amide group.

The enantiomerically pure γ-hydroxypentanamide (*S*)-**7** reacted in an oxa-Pictet-Spengler reaction[3] with ethyl glyoxalate (OHC–CO_2Et) and $BF_3{\cdot}Et_2O$ to give diastereoselectively the *cis*-configured 2-benzopyran **9** (Scheme 3). Attempts to perform a Dieckmann cyclization with amidoester **9** failed to afford tricyclic products. Therefore, amidoester **9** was first transformed into diester **10**, which reacted with NaH and ethanol to give the Dieckmann condensation product **11**. According to the NMR spectra, tricyclic product **11** consists of three components, which are in a thermodynamic equilibrium: two diastereomeric β-ketoesters **11a** and **11b** and enolester **11c** (ratio 20:15:65). Mixture **11** was hydrolyzed with NaOH to provide a uniform product, ketone **3**, in more than 65% yield thus confirming the existence of the tautomeric/diastereomeric mixture **11**. The reductive amination of the tricyclic ketone **3** was performed with dimethylamine and $NaBH_4$ employing



Scheme 2. Reagents and conditions: (a) $NaBH_4$, CH_3OH, rt, then HCl, 30 min, rt, 60%; (b) $(H_3C)_2NH$, EtOH, rt, 94%; (c) *Pseudomonas fluorescence* lipase, isopropenyl acetate, $^tBuOCH_3$, 141 h, rt, (*S*)-**7**: 40% (99% ee), (*R*)-**8**: 46% (98.4% ee), (*S*)-**6**: 10% (72% ee).



Scheme 3. Reagents and conditions: (a) $OHCCO_2Et$, CH_2Cl_2, $BF_3{\cdot}Et_2O$, 6 h, rt, 4 d, 40 °C, 93%; (b) $(F_3CSO_2)_2O$, EtOH, pyridine, 12 h, rt, 83%; (c) NaH, EtOH, toluene, 2.5 h, 110 °C, 62%; (d) NaOH, EtOH, 3 h, 78 °C, 91%; (e) $(H_3C)_2NH$, $Ti(OiPr)_4$, EtOH, 63 h, rt, then $NaBH_4$, 23 h, rt, 72%; (f) $NaBH_4$, CH_3OH, 90 min, rt, 86%.

the Lewis acid $Ti(OiPr)_4$ as a catalyst.[7] Here, the reducing agent reacted diastereoselectively from the Re face giving only the tricyclic amine **12** with an equatorially oriented amino group.

3. Absolute configuration

According to the rule of Kazlauskas,[8] lipases preferentially convert the (*R*)-configured enantiomer of the secondary alcohols, provided that the larger substituent has priority according to the CIP rules. However, the definition of the larger substituent within the γ-hydroxypentanamide **7** remains uncertain. On the condition that the benzyl substituent is the large group, application of the Kazlauskas rule would lead to the (*R*)-configured acetate (*R*)-**8** and the (*S*)-configured alcohol (*S*)-**7**.

In order to unambiguously prove the absolute configuration of the products from the lipase catalyzed reaction, the stereochemistry of tricyclic alcohol **13**, which was synthesized diastereoselectively by $NaBH_4$ reduction of ketone **3** (Scheme 3), was thoroughly investigated by quantum chemical calculation of the specific optical rotation and X-ray crystal structure analysis.

All quantum chemical calculations were carried out with the TURBOMOLE[9] program package. The geometries were optimized at the DFT level of theory using a polarized triple-ζ valence basis set on all atoms (TZV(d,p))[10] and the PBE[11] density functional. The frequency dependent optical rotation (OR) values (in the following given in the usual units deg $dm^{-1}(g/mL)^{-1}$) were obtained from time dependent density functional theory (TDDFT[12] calculations using the BH-LYP[13] and B3-LYP[14] functionals and Dunning's aug-cc-pVDZ basis set).[15] For a general overview about chiroptical calculations, see Ref. 16. For the particular application of TDDFT methods for computations of OR, see Ref. 17 and for examples that include also several conformers and Boltzmann averaging, see Ref. 18. For technical reasons, the TDDFT calculations of the OR could be performed only in the coordinate origin-dependent dipole-length representation for the rotatory strengths. Test calculations employing pure functionals such as PBE and the origin-independent velocity gauge representation show, however, that the differences between the two forms with the aug-cc-pVDZ basis set are only about ±2 deg $dm^{-1}(g/mL)^{-1}$.

For tricyclic alcohol **13** we initially considered a conformer with an axially oriented OH-group which, however, was found to be higher in energy by about 2 kcal/mol compared to the equatorial minimum and thus not further investigated. At the TDDFT/B3LYP level, we obtained, for the equatorial form, an $[\alpha]_D$ value of −13.2 and with the BHLYP functional of −16.4 deg $dm^{-1}(g/mL)^{-1}$. These differences and also the difference to the experimental value of −71.8[19] are typical for such computations when molecules with only weakly perturbed but inherently achiral chromophores (benzene ring in **13**) are involved. In any case, this allows the assignment of the absolute configuration of the synthesized alcohol (−)-**13** as (*S*,*S*,*S*) and thus the (*S*)-configuration of the starting γ-hydroxypentanamide **7**.

Recrystallization of alcohol **13** from $(iPr)_2O$ provided colorless crystals[19] (mp 158 °C), which were suitable for X-ray crystal structure analysis.[20] Since the crystals were quite small (15 μm × 15 μm × 100 μm) and due to the low oxygen content, the determination of the absolute configuration by exploiting the anomalous dispersion effects was not possible. However, despite the small crystal size the absolute structure could be determined using the three-beam interference method.[21,22] This method exploits interference effects between two wave fields inside a crystal and is independent of any anomalous dispersion effects. In Figure 2, a three-beam interference profile for the crystals of **13** is given, indicating the derived absolute configuration. Figure 3 shows the X-ray crystal structure of **13** confirming unambiguously the (*S*)-configuration of all the three stereogenic centers.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with

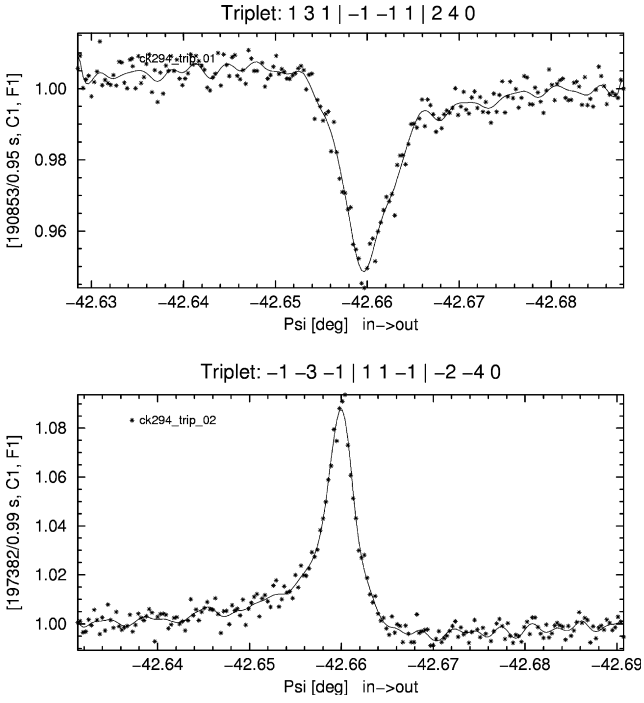


Figure 2. Centro-symmetrically related three-beam interference profiles of the three-beam cases 131|−1−11|240 and −1−3−1|11−1|−2−40: During such an experiment, for example, the 131 reflection is set into its diffraction position, subsequently the reflection −1−11 is also brought into its diffraction position by a ψ-rotation about the reciprocal lattice vector of 131. In such a situation, the reflections ±(240) fulfill the diffraction conditions for the interference between 131 and −1−11. The three-beam interference profile depends on the triplet phase $\varphi_T = \varphi(-1-11) + \varphi(240) - \varphi(131) \sim 70°$. For 90 (−90) deg a symmetric decrease (increase) of the three-beam interference profile is expected. The slight asymmetry in the measured profiles is consistent with the triplet phase 70 (−70) of the two centro-symmetrically related three-beam cases. The sign of the triplet phase is directly related to the hand of absolute structure.

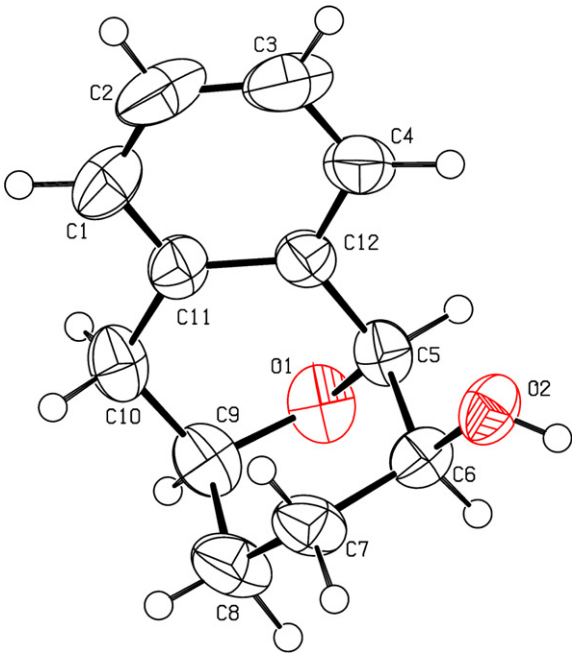


Figure 3. X-ray crystal structure analysis of (*S*,*S*,*S*)-**13**. The ellipsoids represent 50% displacement probability.

the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 623336. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

4. Receptor affinity

The affinity of the tertiary amine **12** toward σ_1,[23] σ_2,[23] κ,[24] and μ receptors[24] and toward the phencyclidine binding site of the NMDA receptor[25] was investigated with receptor binding studies using radioligands for selective labeling of the respective receptor system. At a test compound concentration of 10 μM, the tricyclic amine **12** did not show significant affinity to σ_1 (6% inhibition of the radioligand), κ (7% inhibition), μ (9% inhibition), and NMDA receptors (13% inhibition). However, a considerable affinity toward σ_2 receptors was observed. Although the K_i value is in the low micromolar range ($K_i = 2.9$ μM), **12** represents a promising starting point for the development of novel σ_2 receptor ligands, which might be useful as antitumor agents.[26]

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. Thanks are also due to Degussa AG for the donation of chemicals. We also thank Alke Meents and Hermann Franz for support at the beamline PETRA 1 (HASYLAB/DESY, Hamburg) during the X-ray measurements.

References

1. (a) Carroll, F. I.; Abraham, P.; Parham, K.; Bai, X.; Zhang, X.; Brine, G. A.; Mascarella, S. W.; Martin, B. R.; May, E. L.; Sauss, C.; Di Paolo, L.; Wallace, P.; Walker, J. M.; Bowen, W. D. *J. Med. Chem.* **1992**, *35*, 2812–2818; (b) May, E. L.; Aceto, M. D.; Bowman, E. R.; Bentley, C.; Martin, B. R.; Harris, L. S.; Medzihradsky, F.; Mattson, M. V.; Jacobson, A. E. *J. Med. Chem.* **1994**, *37*, 3408–3418.
2. Wünsch, B.; Höfner, G.; Bauschke, G. *Arch. Pharm. (Weinheim)* **1993**, *326*, 101–113.
3. (a) Larghi, E. L.; Kaufmann, T. S. *Synthesis* **2006**, 187–220; (b) Wünsch, B.; Zoll, M. *Liebigs Ann. Chem.* **1992**, 39–45.
4. (a) Elliott, M.; Janes, N. *Chem. Abstr.* **1970**, *72*, 3353q; (b) Steglich, W.; Gruber, P. *Angew. Chem.* **1971**, *83*, 727–728.
5. (a) Bush, J. B.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903–5905; (b) Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 5905–5906; (c) Bosch, J.; Mestre, E.; Bonjoch, J.; López, F.; Granados, R. *Heterocycles* **1984**, *22*, 767–772.
6. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
7. (a) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928–4929; (b) Bhattacharyya, S. *Synth. Commun.* **2000**, *30*, 2001–2008; (c) Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, *11*, 1781–1783.
8. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappoport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
9. TURBOMOLE 5.6, Ahlrichs, R. et al., Universität Karlsruhe 2003. See also: <http://www.turbomole.com>.
10. Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.
11. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.
12. *Recent Advances in Density Functional Methods*; Casida, M. L., Chong, D. P., Eds.; World Scientific: Singapore, 1995.
13. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
14. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Stephens, P. J.; Devlin, F. J.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
15. (a) Dunning, T. H. *J. Chem. Phys.* **1989**, *90*, 1007; (b) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
16. (a) Polavarapu, P. L. *Chiralty* **2002**, *14*, 768–7681; (b) Crawford, T. D. *Theor. Chem. Acc.* **2006**, *115*, 227–245.
17. (a) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *J. Phys. Chem. A* **2000**, *104*, 1039–1046; (b) Grimme, S. *Chem. Phys. Lett.* **2001**, *339*, 380–388; (c) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356–5371; (d) Autschbach, J.; Patchkovskii, S.; Ziegler, T.; van Gisbergen, S.; Baerends, E. J. *J. Chem. Phys.* **2002**, *117*, 581–592; (e) Ruud, K.; Helgaker, T. *Chem. Phys. Lett.* **2002**, *352*, 533–539; (f) Stephens, P. J.; McCann, D. M.; Cheeseman, J. R.; Frisch, M. J. *Chirality* **2005**, *17*, 52–64; (g) Grimme, S.; Furche, F.; Ahlrichs, R. *Chem. Phys. Lett.* **2002**, *361*, 321.
18. (a) Grimme, S.; Bahlmann, A.; Haufe, G. *Chirality* **2002**, *14*, 793–797; (b) Pecul, M.; Ruud, K.; Rizzo, A.; Helgaker, T. *J. Phys. Chem. A* **2004**, *108*, 4269–4276; (c) Lattanzi, A.; Viglione, R. G.; Scettri, A.; Zanasi, R. *J. Phys. Chem. A* **2004**, *108*, 10749–10753; (d) Marchesan, D.; Coriani, S.; Forzato, C.; Nitti, P.; Pitacco, G.; Ruud, K. *J. Phys. Chem. A* **2005**, *109*, 1449–1453; (e) Wiberg, K. B.; Wang, Y.-G.; Vaccaro, P. H.; Cheeseman, J. R.; Luderer, M. R. *J. Phys. Chem. A* **2005**, *109*, 3405–3410; (f) Giorgio, F.; Roje, M.; Tanaka, K.; Hamersak, Z.; Sunjic, V.; Nakanishi, K.; Rosini, C.; Berova, N. *J. Org. Chem.* **2005**, *70*, 6557–6563.

19. Spectroscopic data for (5*S*,6*S*,9*S*)-(−)-5,6,7,8,9,10-hexahydro-5,9-epoxybenzo-cycloocten-6-ol **13**: $[\alpha]_D = -71.8$ (*c* 4.7 mg/mL, MeOH, 20 °C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15 (dq, br, $J = 4.5/12.8$ Hz, 1H, 7-H_{ax}), 1.69–1.81 (m, 2H, 7-H_{eq} and 8-H_{eq}), 2.10 (tt, $J = 5.3/13.9$ Hz, 1H, 8-H_{ax}), 2.58 (d, $J = 17.7$ Hz, 1H, 10-$H_{pseudoeq}$), 3.35 (dd, $J = 7.9/17.4$ Hz, 1H, 10-$H_{pseudoax}$), 4.02 (td, $J = 4.7/11.6$ Hz, 1H, 6-H), 4.35 (dd, br, $J = 4.9/7.9$ Hz, 1H, 9-H), 4.77 (d, $J = 5.2$ Hz, 1H, 5-H), 7.08–7.26 (m, 4H, aromat), a signal for the OH proton was not found in the spectrum.
20. Crystal structure determination: $C_{12}H_{14}O_2$; $M_r = 190$, trigonal space group $P3_2$, lattice parameters: $a = b = 12.214$ Å, $c = 5.791$ Å, $V = 748$ Å^3, $Z = 3$, $D_x = 1.267$ Mg/m^3, crystal size: 15 μm × 15 μm × 100 μm, $T = 295$ K, $\lambda = 0.6889$ Å (synchrotron radiation, beamline PETRA 1, DESY. Hamburg), 30,657 reflection measured (CCD area detector), 3621 unique reflections, $\theta_{min} = 1.9°$, $\theta_{max} = 32°$, $R_{int} = 0.019$, H-atoms isotropically and non-H atoms anisotropically refined, 183 refinement parameters, $R = 0.034$, $S = 1.08$.
21. Hümmer, K.; Weckert, E. *Acta Crystallogr., Sect. A* **1995**, *51*, 431–438.
22. Weckert, E.; Hümmer, K. *Acta Crystallogr., Sect. A* **1997**, *53*, 108–143.
23. (a) Maier, C. A.; Wünsch, B. *J. Med. Chem.* **2002**, *45*, 438–448; (b) Maier, C. A.; Wünsch, B. *J. Med. Chem.* **2002**, *45*, 4923–4930.
24. Soukara, S.; Maier, C. A.; Predoiu, U.; Ehret, A.; Jackisch, R.; Wünsch, B. *J. Med. Chem.* **2001**, *44*, 2814–2826.
25. Aepkers, M.; Wünsch, B. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 67–75.
26. Colabufo, N. A.; Berardi, F.; Contino, M.; Niso, M.; Abate, C.; Perrone, R.; Tortorella, V. *Arch. Pharmacol.* **2004**, *370*, 106–113.