A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

Title: C3-Symmetric Tricyclo[2.2.1.02,6]heptane-3,5,7-triol

Authors: Volodymyr Kozel, Constantin-Gabriel Daniliuc, Peer Kirsch, and Günter Haufe

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201709279
Angew. Chem. 10.1002/ange.201709279

Link to VoR: http://dx.doi.org/10.1002/anie.201709279
http://dx.doi.org/10.1002/ange.201709279

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C_3-Symmetric Tricyclo[2.2.1.0^{2,6}]heptane-3,5,7-triol

Volodymyr Kozel,[a] Constantin-Gabriel Daniliuc,[a] Peer Kirsch,[b] and Günter Haufe*[a]

Abstract: A straightforward access to a hitherto unknown C_3-symmetric tricyclic triol both in racemic and enantiopure forms has been elaborated. Treatment of 7-*tert*-butoxynorbornadiene with peroxycarboxylic acids provided mixtures of C_1- and C_3-symmetric 3,5,7-triacyloxy-nortricyclenes via transannular π-cyclization and substitution of the *tert*-butoxy group. Refluxing in formic acid, the C_1-symmetric esters were converted to the C_3-symmetric formate. Hydrolysis gave diastereoisomeric triols, which were separated by recrystallization. Enantiomer resolution via diastereoisomeric tri(*O*-methylmandelates) delivered the target triols in gram scale. The pure enantiomers are useful as core units of dopants for liquid crystals.

Aesthetics and beauty of symmetric molecules or figures fascinate likewise scientists and artists. The importance of many symmetric compounds for synthesis design or supramolecular self-assembly stimulate the ambition of synthetic chemists. Along these lines the use of C_2-symmetric non-racemic auxiliaries, reagents, or ligands for metal complexes has encouraged significantly the field of asymmetric synthesis for many years.[1] In contrast the interest in enantiopure C_3-symmetric organic compounds increased only in the last two decades.[2] Among their application as ligands and organocatalysts in asymmetric synthesis,[3] C_3-symmetric molecules also gained promising role in material science and molecular recognition.[4] The superior affinity and selectivity of trivalent ligands in comparison with mono- or divalent counterparts may play important roles in view of homotrimeric structures of chaperone proteins[5] as well as transmembrane subunits including viral membrane fusion glycoproteins[6] and cytokine receptors.[7]

C_3-symmetric molecules (Figures 1 and 2) usually have three identical elements of chirality located in a plane, which is perpendicular to the symmetry axis. The properties and application of these molecules depend on the nature of the core. The smallest core for C_3-symmetric molecules includes one single atom, connected to three identical substituents with stereocenters of the same absolute configuration like compounds **1**. Molecules of such tripodal type usually contain heteroatoms and serve as ligands in asymmetric catalysis[8] or as a core for the construction of tripodal molecules.[9] Analogous trisubstituted benzenes[10] or 1,3,5-triazines[11] **2** are widely used in material sciences, e.g. to construct columnar liquid crystalline phases.

[a] Dr. V. Kozel, Dr. C.-G. Daniliuc, Prof. Dr. G. Haufe
Organisch-Chemisches Institut
Universität Münster
Corrensstraße 40, D-48149 Münster, Germany
E-mail: haufe@uni-muenster.de
[b] Prof. Dr. P. Kirsch
Integrated Circuit Materials R&D Germany
Merck KGaA
Frankfurter Straße 250, D-64293 Darmstadt, Germany

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Whereas the C_3-symmetric molecules **1*** and **2*** (Figure 1) are distinguished by presence of stereogenic centers, the so-called "molecular propellers"[12] do not have such centers but possess a particular kind of atropisomerism. Molecules of this type contain three identical subunits (the blades) radiating from a central axis of rotation (propeller axis) and twisted in the same sense. As an example, the triarylmethane derivative **3**[13] is mentioned, whose three fixed anthracene (Ant) groups can form inclusion complexes with C_{60} fullerene similarly to calixarenes. Similar molecules bearing three hydrogen bond donors as substituents can serve as effective anion-receptors.[14]

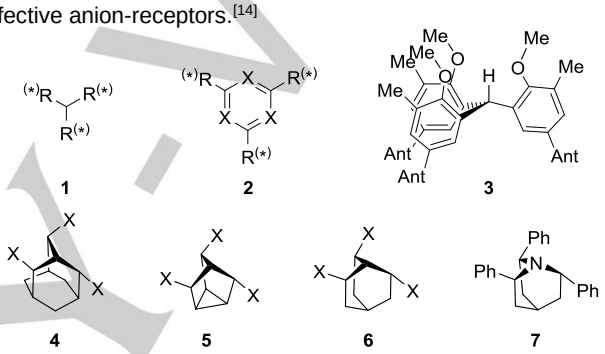

Figure 1. Examples of C_3-symmetric molecules.

Several rigid C_3-symmetric polycarbocyclic structures are also conceivable (Figure 1), e.g. 2,8,9-trisubstituted adamantanes **4** or 3,5,7-trisubstituted nortricyclenes **5**, which both are unknown so far. In contrast, one 2,6,7-trisubstituted bicyclo[2.2.2]octane, the triol **6** (X = OH), was prepared by Heyns, Rüdiger and Paulsen in racemic form 45 years ago.[15] In 2010 Corey et al. published an enantioselective synthesis of the analogous C_3-symmetric tertiary amine quinuclidine (**7**).[16]

Here we present the synthesis and characterization of both enantiomers of the hitherto unknown C_3-symmetric nortricyclene-3,5,7-triol (**5**, X = OH) and of the racemic C_1-symmetric diastereoisomer **8** (Figure 2).

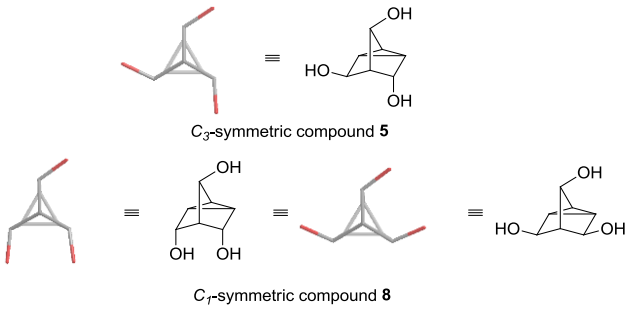

Figure 2. Diastereoisomeric nortricyclene-3,5,7-trioles **5** and **8**.

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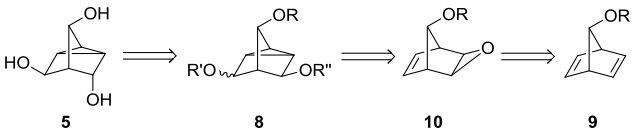
To furnish the C_3-symmetric nortricyclene-3,5,7-triol (**5**) we designed the retrosynthesis depicted in (Scheme 1). Epoxidation of 7-*tert*-butoxy-norbornadiene (**9**, R = ^{t}Bu) with mCPBA is known to give the *exo*-*syn*-oxirane **10** selectively.[17] The subsequent ring opening with carboxylic acids should provide mainly compounds **8** with the C_1-symmetric nortricyclene-3,5,7-triol core by transannular π-cyclization. Finally, acid-catalyzed isomerization and deprotection should deliver the target C_3-symmetric product **5**.



Scheme 1. Retrosynthesis of tricyclo[2.2.1.0^{2,6}]heptane-3,5,7-triol (**5**)

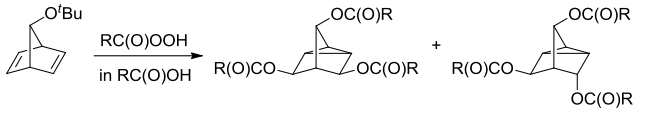
Treatment of **9** (R = ^{t}Bu) with in situ generated performic acid at 15-20 °C furnished the C_1-symmetric triformate *rac*-**11** directly and small amount of the C_3-symmetric product *rac*-**12** (Table 1, entry 1). Noteworthy, even under these mild reaction conditions, substitution of the *tert*-butoxy group with formate took place. All attempts to isolate any intermediate of the reaction were unsuccessful. In contrast, the reaction of **9** with peroxyacetic acid (39% solution in acetic acid, Wofasteril®) at 15-20 °C gave two separable monoacetates *rac*-**13** and *rac*-**14** (67% yield, 1:1 ratio) with C_1-symmetric triol core (Scheme 2).

The structure of **13** was approved by X-ray crystal structural analysis[18] (Figure S2). Compound **14** is an oil and its structure was confirmed spectroscopically and by saponification. Compounds *rac*-**13** and *rac*-**14** furnished two different 7-*tert*-butyloxy-nortricyclene-3,5-diols *rac*-**15** and *rac*-**16** on treatment with potassium carbonate in methanol at room temperature. Work up with 37%wt HCl led to the C_1-symmetric triol *rac*-**8** (R = H) in both cases (see Supporting Information, SI).

Heating of the 1:1-mixture of compounds *rac*-**13** and *rac*-**14** in acetic acid at 200 °C in a pressure tube for 3 h provided C_1-symmetric triacetate *rac*-**17** in 64% yield (from **9**) and minor amounts of *rac*-**18** (Table 1, entry 3).

The selective formation of products with C_1-symmetric core (*rac*-**11**, *rac*-**13**, *rac*-**14** and *rac*-**17**) agrees with the assumption that reactions of diene **9** with peroxycarboxylic acids proceed via the intermediate formation of *exo*-*syn*-epoxide **10** (R = ^{t}Bu). Moreover, we observed that the ratio of C_3-symmetric isomers *rac*-**12** and *rac*-**18** increased with increasing reaction temperature and hence they are thermodynamically more stable.

Table 1. Reactions of 7-*tert*-butoxynorbornadiene (**9**) with peroxyformic and peroxyacetic acids to form racemic triesters **11**, **12**, **17** and **18**, respectively.



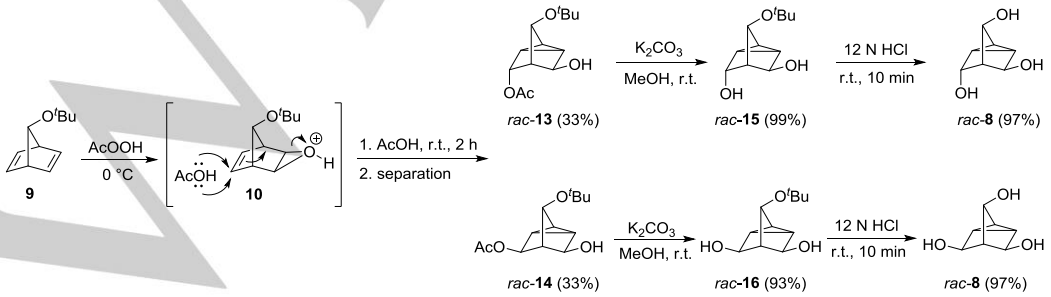
Entry	R	*T* [°C]	Cat.	Time [h]	GC ratio [%] (yield, [%])	
					rac-**11**, *rac*-**17**	*rac*-**12**, *rac*-**18**
1	H	15-20	-	1	80 (36)	20 (-)
2		reflux	-	120	25 (-)	75 (32)
3	CH_3	200	-	3	95 (64)	5 (-)
4		200	$HClO_4$	4	33 (23[a])	67 (47[a])

[a] based on *rac*-**17** used as starting material

Here we reach the crucial point of the synthesis of the C_3-symmetric triol **5**, the isomerisation of the C_1-symmetric triol core to the C_3-symmetric one (Scheme 3). Refluxing (5 days) of the isomeric triformates *rac*-**11** and *rac*-**12** in formic acid gave a separable 1:3 mixture of triformates with the C_3-symmetric *rac*-**12** as the major product. The C_1-triformate **11** was calculated (B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) with ZPE corrected values) to be about 5 kcal/mol less stable (in the gas phase) than the C_3-symmetric isomer **12** (see SI).

The mentioned 1:3 mixture of *rac*-**11** and *rac*-**12** can also be prepared in a one pot reaction (SI) of 7-*tert*-butoxynorbornadiene (**9**) with *in situ* formed performic acid (1:1 molar ratio) at r.t. for 1 h. Traces of remaining peracid were decomposed with liberation of carbon dioxide by heating at 85 °C for 1 h.[19] Finally, after negative peroxide test, the reaction mixture was refluxed for 5 days.[20] The isomerisation of the C_1-symmetric triacetate *rac*-**17** to C_3-symmetric *rac*-**18** in acetic acid needs more forced conditions (Table 1, entry 4). It occurs within 4 h at 180-200 °C in a pressure tube in the presence of catalytic amounts of perchloric or triflic acid giving product ratio *rac*-**17**:*rac*-**18** = 1:2 (23% and 47%, isolated yields from C_1-symmetric triacetate *rac*-**17**).

The rearrangement, exemplified for triformate *rac*-**11** (Scheme 3), is assumed to start with protonation of one of the formyloxy groups followed by neighboring group assisted elimination of formic acid with intermediate formation of the carbenium-oxonium ion **19**.[21] Finally, formic acid attacks ion **19** at one or the other position (pathways ***a*** or ***b***) with formation of C_1- and C_3-symmetric triformates *rac*-**11** and *rac*-**12**, respectively. Interestingly, the C_1-symmetric triacetate *rac*-**17** as well as monoacetates *rac*-**13** and *rac*-**14** were converted in refluxing formic acid to provide the same 1:3 mixture (Table 1, entry 2) of triformates *rac*-**11** and *rac*-**12**. Driving force of this reaction might be the elimination of the weaker acid after protonation. No reaction occurred when triformates were refluxed in excess acetic acid.



Scheme 2. Reaction of 7-*tert*-butoxynorbornadiene (**9**) with peroxyacetic acid.

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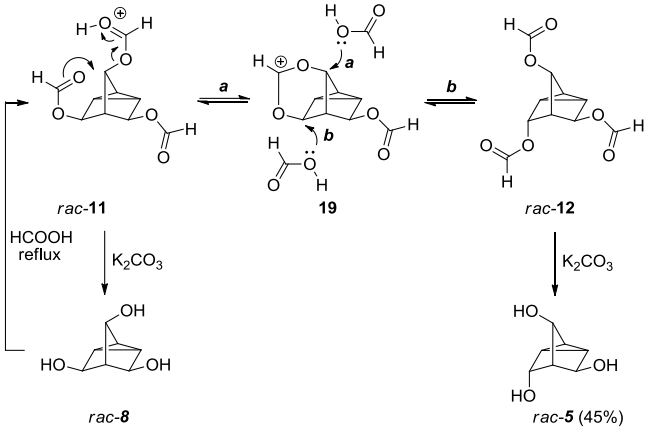
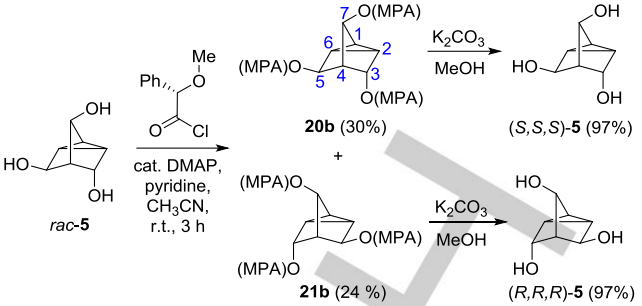


Scheme 3. Neighboring group assisted transesterification. Synthesis of racemic C_3-symmetric triol *rac*-**5**.[18]

The next goal was the separation of C_1- and C_3-symmetric products. The isomeric triacetates *rac*-**17** (Figure S3) and *rac*-**18** (Figure S4) as well as the corresponding triformates *rac*-**11** and *rac*-**12** were separable by column chromatography. The latter compounds can also be separated by crystallization from diethyl ether (C_3-symmetric *rac*-**12** is less soluble). The separated C_1-symmetric triesters *rac*-**11** or *rac*-**17** can be converted to the corresponding C_3-isomers under the above described conditions. Finally, there is one more possibility to separate C_1- and C_3-symmetric products. The triols *rac*-**5** and *rac*-**8** obtained after saponification of *rac*-**11** and *rac*-**12** were separated taking advantage of their different solubility in THF. The precipitated C_3-symmetric triol *rac*-**5** was filtered off from the product mixture and recrystallized from methanol or THF. The remaining mother liquor containing a mixture of triols *rac*-**5** and *rac*-**8** was evaporated and again exposed to isomerization by refluxing with formic acid (Scheme 3). This process was repeated two times to get the C_3-symmetric nortricyclene-3,5,7-triol (*rac*-**5**) in 45% overall yield (based on **9**) as colorless crystals.

In the triol **5**[18] (Figure S1) all OH groups are *anti* to each other and all atoms adjacent to the OH-groups are magnetically equivalent and hence give only one NMR signal. This is also true for the atoms of the cyclopropane ring. Thus, together with the 4-CH group, three proton (plus OH) and three carbon signals result. The triol **5** is readily soluble in water in any ratio, but not hygroscopic. It is also soluble in alcohols but insoluble in non-polar organic solvents. Compound *rac*-**5** melts at 208-210 °C without decomposition and is stable on heating with 2*N* HCl at 80 °C for 3 h (no change of $[\alpha]_D^{25}$ value of enantiopure **5**). However, refluxing in 4*N* HCl for 3 h led to decomposition.

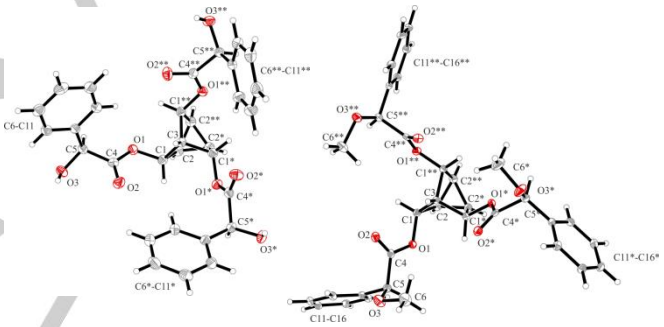
Finally, the racemic C_3-symmetric triol *rac*-**5** had to be resolved to (*S,S,S*)- and (*R,R,R*)-enantiomers. Therefore, *rac*-**5** was subjected to Steglich esterification with enantiopure reagents such as (*S*)-mandelic acid and its *O*-protected derivatives (OTHP,[22] OMe[23]). Whereas the (*S,S,S,S,S,S*)-trimandelate **20a** was isolated and analysed by X-Ray (Figure 3) the (*S,S,S,R,R,R*)-trimandelate **21a** as well as its THP-protected form (both not shown) turned out to be unstable and decomposed during column chromatography. In contrast, the stable (*S,S,S,S,S,S*)-tri(*O*-methylmandelates) **20b**[24] and (*S,S,S,R,R,R*) -**21b** were obtained by reaction of *rac*-**5** with (*S*)-2-methoxy-2-phenylacetyl chloride in the presence of pyridine in acetonitrile and separated chromatographically (Scheme 4).



MPA = (*S*)-2-methoxy-2-phenylacetyl-

Scheme 4. Separation of the enantiomers from racemic C_3-symmetric triol **5**.

The X-Ray structures of trimandelates[18] show significant differences in their geometry. In the trimandelate (*S,S,S,S,S,S*)-**20a** hydrogen bonds force the mandelate moiety to adopt a conformation with phenyl rings directed "upwards" (Figure 3, Figure S5) resulting in a bowl-like structure. In the tri(*O*-methylmandelate) (*S,S,S,R,R,R*)-**21b** the phenyl rings are faced on the protons of the cyclopropane ring (Figure 3, Figure S6). These conformations are also evident from the upfield shifted ^{1}H NMR signals (in $CDCl_3$) of the nortricyclene protons directed face-on to the phenyl rings.[25] Remarkably, in ^{1}H NMR spectra recorded in toluene-d_8 the $\Delta\delta_{R,S}$ values became negligible (see SI).

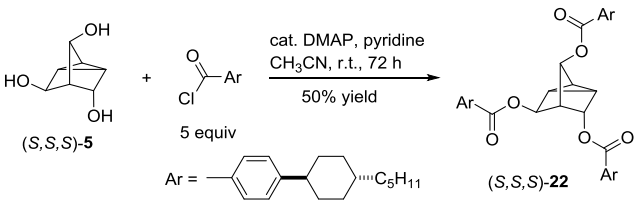


(*S,S,S,S,S,S*)-**20a** (*S,S,S,R,R,R*)-**21b**

Figure 3. X-ray crystallographic structure for (*S,S,S,S,S,S*)-trimandelate **20a** and (*S,S,S,R,R,R*)-tri(*O*-methylmandelate) **21b**.[18]

The separated tri(*O*-methylmandelates) **20b** and **21b** were saponified to give the enantiopure triols (*S,S,S*)-**5** and (*R,R,R*)-**5**. (*S*)-2-methoxy-2-phenylacetic acid can be washed from enantiopure triols with unpolar organic solvents and reused.

Triol (*S,S,S*)-**5** was esterified with a *p*-substituted benzoyl chloride to yield the enantiopure triester (*S,S,S*)-**22** (Scheme 5). This type of dopants have an advantageous helical twisting power (HTP) up to -25 μm^{-1}, high solubility in conventional liquid crystalline mixtures and high stability against light.[26]



Scheme 5. Esterification of triol (*S,S,S*)-**5**.[26]

In conclusion, appropriate conditions for selective formation of C_1- and previously unknown C_3-symmetric nortricyclene-3,5,7-triols *rac*-**8** and *rac*-**5** were figured out. The elaborated procedures are straightforward, the used reagents are readily available and column chromatographic purification was not needed to prepare the racemic compounds. Finally, the racemic C_3-symmetric triol *rac*-**5** was resolved to (*S,S,S*)- and (*R,R,R*)-enantiomers by classical separation of diastereomeric tri(*O*-methylmandelates) and saponification. From triol (*S,S,S*)-**5** dopants for liquid crystals were obtained.

Acknowledgements

Financial support from the Merck KGaA (project 29290317-2010) is gratefully acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: *chiral resolution • C_3-symmetry • neighbouring group participation • nortricyclene • transannular cyclization*

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10.1002/anie.201709279

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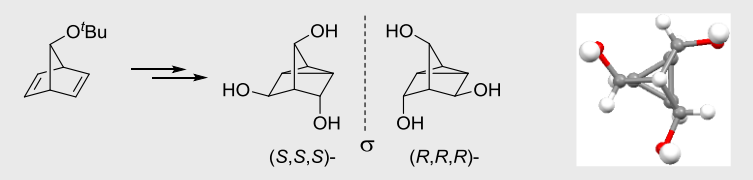

*Volodymyr Kozel, Constantin-Gabriel Daniliuc, Peer Kirsch, Günter Haufe**

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C3-Symmetric Tricyclo[2.2.1.0^{2,6}]heptane-3,5,7-triol

***C*$_3$-symmetry progresses:** The hitherto unknown smallest *C*$_3$-symmetric tricyclic triol has been synthesized in both enantiopure forms. Reactions of 7-*tert*-butoxynorbornadiene with peroxyacids lead to *C*$_1$-symmetric triesters, which are subsequently isomerized to *C*$_3$-symmetric products. Both reactions are facilitated by transannular neighboring group participation. Classical racemate resolution provided the enantiomerically pure target compounds, which are suitable for the preparation of dopants for liquid crystals and might serve as core units for other supramolecular assemblies, molecular recognition and asymmetric catalysis.