

ChemComm

Accepted Manuscript



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

Synthesis of Trinorbornane

Lorenzo Delarue Bizzini^a, Thomas Müntener^a, Daniel Häussinger^a, Markus Neuburger^a, Marcel Mayor^{a, b, c}

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Herein we report the synthesis and characterisation of the until recently unreported chiral C_{11} skeleton of tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (“trinorbornane”) which could be obtained in 7% overall yield in 9 steps. This new rigid structural type was found to be present in the computer generated Chemical Universe Data-base (GDB) and had until now no real-world counterpart.

The Chemical Universe Database GDB which was introduced by the group of Raymond is in its first iteration an exhaustive enumeration of all possible molecules up to eleven atoms (C, N, O and F) considering chemical stability and synthetic feasibility.¹ Through employing the molecular quantum number (MQN) classification method, which is an equivalent of the periodic system of the elements for molecules, the interactive search of the chemical space was rendered possible.²

Analysis of the enumerated database for structures with up to 11 carbon atoms revealed 124 polycyclic hydrocarbons without 3- and 4-membered rings. From these structures only three have no real world counterpart, neither as pure hydrocarbons nor as substructures containing heteroatoms or unsaturations.² One of these structures is tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1**), which is a particularly appealing and eye catching example of a new structural type.^{1,2}

Its scaffold consists of two norbornanes that share a pair of neighboring edges (red and blue in Figure 1 left). Interestingly, this arrangement results in a third norbornane subunit (highlighted in yellow in Figure 1 left). Furthermore, the structure is an example of axial chirality and Figure 1 shows the two enantiomers (1*S*_a,4*S*,6*R*, 7*S*,9*R*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (left) and (1*R*_a,4*R*,6*S*, 7*R*,9*S*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (right), to which we will refer to as **1-S_a** and **1-R_a** for

convenience. We suggest for the scaffold of **1** consisting of three superposed norbornane units the trivial name trinorbornane. Figure 1 also shows the mirror plane between both enantiomers and for **1-R_a** the molecule's C_2 -axis. The numbering of the carbon atoms resulting in the IUPAC name is given for **1-S_a**.

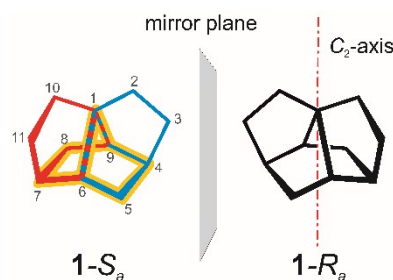


Figure 1 The two enantiomers (1*S*_a,4*S*,6*R*,7*S*,9*R*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1-S_a**) and (1*R*_a,4*R*,6*S*,7*R*,9*S*)-tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane (**1-R_a**) displaying axial chirality. For **1-S_a**, on the left side the three norbornane subunits of the structure are displayed in red, blue, and yellow together with the numbering of the eleven carbon atoms corresponding to the IUPAC name. The enantiomer **1-R_a** is displayed together with the molecule's C_2 -axis.

There is a long tradition in organic chemistry to explore the chemical space for complex, symmetrical and aesthetical appealing hydrocarbons by synthetic means.³ One paramount example, dodecahedrane (**2**), has been called “the Mount Everest of hydrocarbon chemistry”⁴ and was first synthesised by Paquette in 1982.⁵ It is composed of twelve fused cyclopentane rings and possesses the highest known point group symmetry (I_h).⁴

Our search for compounds resembling the unstrained but highly rigid carbon framework of **1** guided us to the pentacyclic, chiral, and D_3 -symmetric trishomocubane **3** (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane). It is also composed of three partially superposed norbornyl units (Figure 2) and was first synthesised by Underwood in 1970 in a sequence of brominations and eliminations from pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol.⁶ Since then, several routes to **3** and derivatives thereof have been developed.⁷

^a Department of Chemistry, University of Basel, St. Johannis-Ring 19, 4056 Basel, Switzerland.

^b Institute for Nanotechnology (INT), Karlsruhe Institute of Technology (KIT), P. O. Box 3640, 76021 Karlsruhe, Germany.

^c Lehn Institute of Functional Materials (LIFM), Sun Yat Sen University (SYSU), Xingangxi Rd. 135, 510275 Guangzhou, P. R. China.

† Electronic Supplementary Information (ESI) available: Experimental details, analytical data and crystallographic data of **18** (CIF). See DOI: 10.1039/x0xx00000x

COMMUNICATION

ChemComm

Probably the structurally most similar known compound is brexane **4** (tricyclo[4.3.0.0^{3,7}]nonane), which lacks only one interconnecting ethylene bridge compared to **1** and was synthesised by Nickon in 1964 in 9 steps (Figure 2).⁸ Later its synthesis has been improved by Brieger profiting from an intramolecular *Diels-Alder* reaction as the key step.⁹ In similarity to **1**, this tricyclic structure is also *C*₂-symmetric but is composed of two superposed norbornyl units instead of three. Interestingly, the tricyclic scaffold has been found in the natural products Pallambin A and B, whose total syntheses were recently achieved.¹⁰

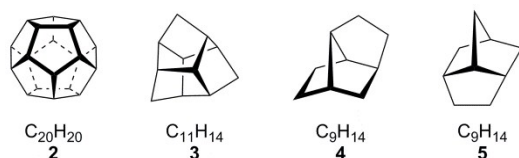
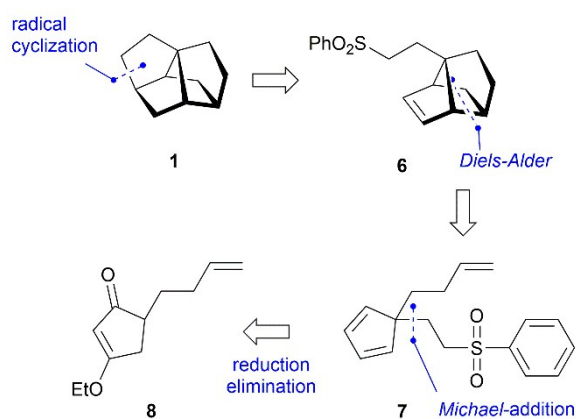


Figure 2 Examples of already known polycyclic hydrocarbons with rigid scaffolds: Dodecahedrane (**2**), trishomocubane (**3**), brexane (**4**) and its isomer brendane (**5**).

Our approach to construct the tetracyclic scaffold of **1** (Scheme 1) was based on the tricyclic brexene derivative **6**, which might form the desired target structure **1** in a 6-*endo-trig*/5-*exo-trig* radical cyclisation mechanism. The compound **6** should be formed in an intramolecular *Diels-Alder* reaction⁹ from the cyclopentadiene **7**, which is envisioned to be accessible from the literature known compound **8** via *Michael* addition to phenyl vinyl sulfone and a series of reduction and elimination reactions



Scheme 1 Retrosynthetic analysis for racemic trinorbornane **1** (to improve the visibility only the 1-*R_a* enantiomer is displayed).

The synthesis of the target structure trinorbornane **1** as a racemate is displayed in Scheme 2 and starts with the assembly of the 3-ethyloxycyclopent-2-enone derivative **8**. The assembly of **11** starting from methyl (*E*)-4-chloro-3-methoxy-2-butenate (**9**) is straightforward and even suitable for industrial production.¹¹ The addition of **9** to a solution of dimethyl malonate (**10**) in DMF under basic conditions at room temperature resulted in trimethyl (*E*)-3-methoxy-3-butene-1,1,4-tricarboxyl-

ate (**11**) in very good yield of 85%. The triester **11** was subsequently cyclised in a solution of sodium methoxide in methanol at 60 °C providing methyl 4-methoxy-2-oxo-3-cyclopentenecarboxylate (**12**) in 86% isolated yield.

The 5-membered ring of **12** is already a subunit of the tetracyclic structure **1** and in order to form the next two rings in similarity of the strategy reported for brexane⁹ via an intramolecular *Diels-Alder* reaction, a but-3-ene chain had to be introduced. Following a reported procedure,¹² compound **12** was deprotonated with potassium hydride in DMF at room temperature and alkylated by addition of 4-bromo-1-butene (**13**) providing the 1-(but-3-enyl)-4-methoxy-2-oxo-cyclopent-3-enecarboxylic acid methyl ester (**14**) in 76% isolated yield. In order to form the quaternary centre, decarboxylation of **14** was required. Following a reported protocol,¹² **14** was treated in refluxing ethanol with potassium hydroxide for 16 hours. The applied reaction conditions not only decarboxylated the compound, but also the complete substitution of the methoxy group by an ethoxy group was observed, which does not handicap the further proceeding along the reaction sequence. Thus 5-(but-3-enyl)-3-ethoxycyclopent-2-enone (**8**) was obtained in 76% isolated yield. A key step of the synthesis was the formation of the quaternary centre, which was achieved by modifying the procedure reported by Cory and Reeneboog¹³ using phenyl vinyl sulfone (**15**) as *Michael*-acceptor. After formation of the kinetic enolate of **8** with LDA in dry THF under cryogenic conditions, the solution was allowed to warm up to 0 °C and 1,3-dimethyl-2-imidazolidinone (DMI) was added. A solution of phenyl vinyl sulfone (**15**) in dry THF was added at 0 °C and allowed to warm up to room temperature. After about 1 hour the reaction mixture was worked up and 5-(but-3-enyl)-3-ethoxy-5-(2-(phenylsulfonyl)ethyl)cyclopent-2-enone (**16**) was isolated in good yields of 74-82% by column chromatography (CC). Water exclusion turned out to be crucial for the success of this reaction as in the presence of traces of water mainly polymeric material was formed.

First attempts to reduce **16** with either DIBAL-H or LiAlH₄ in THF and subsequent treatment with hydrochloric acid gave in agreement with the literature¹⁴ mixtures of 1,2-, 1,4- and over-reduced species. Changing the solvent to toluene and using DIBAL-H as the reducing agent provided selectively 4-(but-3-en-1-yl)-4-(2-(phenylsulfonyl)ethyl)cyclopent-2-enone (**17**), which was, after stirring in 2 M aqueous hydrochloric acid for 20 minutes, isolated in excellent 86% yield. The cyclopent-2-enone fragment of **17** was reduced to the cyclopent-2-enol with the typical conditions for a *Luche* reduction.¹⁵ Thus **17** was treated with cerium (III) chloride and sodium borohydride in 0 °C cold methanol. The crude reaction product comprising 4-(but-3-en-1-yl)-4-(2-(phenylsulfonyl)ethyl)cyclopent-2-enol as mixture of stereoisomers was not purified but instead directly dehydrated in toluene with catalytic amounts of *p*-TsOH at 110 °C. Under these conditions the *in situ* formed cyclopentadienyl derivative **7** reacts with the but-3-ene chain in an intramolecular *Diels-Alder* reaction⁹ providing 1-(2-(phenylsulfonyl)-ethyl)tri-cyclo[4.3.0.0^{4,9}]non-7-ene (**6**), which was isolated in very good 83% yield over the three steps.

The second key step of the synthesis was the reduction of the sulfone moiety of **6** with single-electron reducing agents in order to form the 2-ethyl radical which was expected to cyclise to the target structure **1** by reacting intramolecularly with the olefin of the brexene scaffold. In first attempts, **6** was treated with large excesses of lithium 1-*N,N*-dimethylaminonaphthalene (LDMAN)¹⁶ as the single-electron reducing agent at -78 °C in THF. To our delight, we were able to observe up to 30% conversion and further analysis of the reaction mixture by GC-MS unravelled a 5:1 ratio in favour of the reduced brexene derivative **19** compared to the cyclised target structure **1**. In addition, also the formation of radical dimerisation product **18** was observed. The mixture of compounds was subjected to CC using silica gel as solid phase and pentane as eluent at -20 °C. The target structure **1** was isolated together with the dimer **18** in a combined yield of about 3%, while the open brexene

derivative **19** was isolated in 13% yield. The dimer **18** was separated from the mixed fraction by crystallisation in a mixture of diethyl ether and acetonitrile and was isolated in 1% yield.

While the reaction sequence with its poor conversion, low yield of the desired compound, and complex product mixture was not particularly appealing, it shows that the target structure **1** can indeed be formed by a radical cyclisation reaction. Furthermore, the dimeric side product **18** was crystalline in the solid state and indeed, single crystals suitable for X-ray analysis were obtained by sublimation in a sealed capillary at 130 °C. While the dimer was formed as mixture of diastereomers, the single crystal consisted exclusively of the meso-form combining a 1-*R_a* with a 1-*S_a* subunit (left and right part respectively in Figure 3). The solid state structure of **18** is displayed in Figure 3. **18** crystallises in the monoclinic space group *P*2₁/*n* with two formula units per unit cell. Only one half of the dimeric molecule is present in the asymmetric unit. The complete molecule is generated by an inversion centre of the space group *P*2₁/*n*.

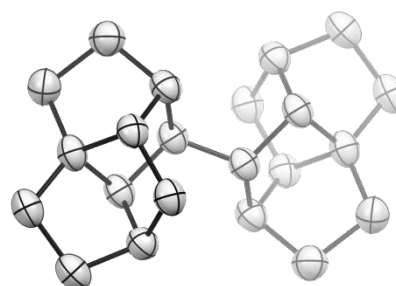
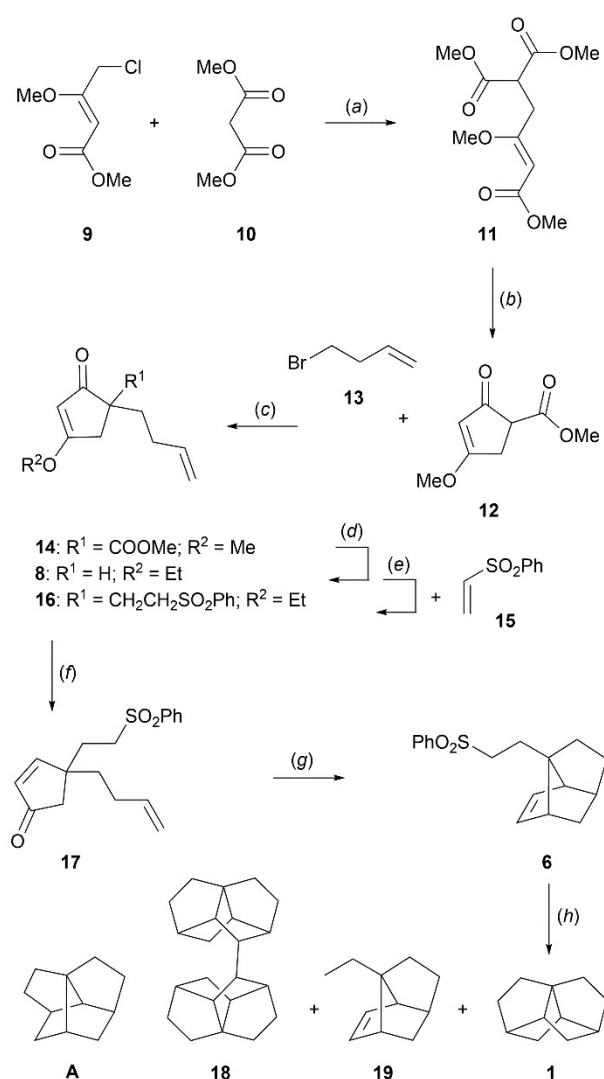


Figure 3 Solid state structure of the dimer **18** corroborating the existence of the tetracyclo[5.2.2.0^{1,6}.0^{4,9}]undecane system as it consists of an interlinked 1-*R_a* subunit (left) and a 1-*S_a* subunit (right). Hydrogen atoms are omitted for clarity and rotational ellipsoids are displayed at a 50% probability level.



Scheme 2 Syntheses of the polycyclic hydrocarbons **1** (for clarity only the 1-*S_a* enantiomer is displayed), **18**, **19**, and **A** as the not (yet) synthesised constitutional isomer of **1**; Reagents and conditions: a) NaOMe, 11, DMF, r.t., 2 h, 85%; b) NaOMe, MeOH, 60 °C, 3 h, 86%; c) KH, DMF, 14, r.t., 4 h, 76%; d) KOH, EtOH, reflux, 16 h, 76%; e) 1.) LDA, THF, -78 °C, 2.) DMI, 0 °C, 3.) 16, 0 °C to r.t., 1 h, 82%; f) DIBAL-H, toluene, r.t., 30 min., then 2M HCl (aq), r.t., 20 min 86%; g) 1.) NaBH₄, CeCl₃ x 7 H₂O, MeOH, 0 °C, 1 h, 2.) cat. p-TsOH, toluene, reflux, 32 h, 83%; h) Sml₂, THF, DMPU, 80 °C, 2 h, 67% determined by GC-MS, 28% isolated. (Alternative: LDMAN, THF, -78 °C, 30 min., **1**(≈2%), **18**(≈1%), **19**(13%) determined by GC-MS).

As alternative Sml₂ in THF with 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU) as cosolvent is reported to be a strong enough single-electron reducing agent for sulfones.¹⁷ To our delight, employing 10 equivalents of Sml₂ in THF with 8 equivalents of DMPU in respect to Sml₂ at 80 °C for 2 h resulted exclusively in cyclised **1** with 67% conversion determined by GC-MS. After the usual work up, the desired tetracyclic target structure **1** was isolated in 28% yield as colourless crystalline solid by filtering off the remaining starting material and polar residues through a silica pad using pentane as the eluent. The low isolated yield compared to the conversion determined by GC-MS is due to the high volatility of the compound resulting in losses during solvent evaporation. Pentane was distilled off through a Vigreux column and the residual solvent was removed under vacuum while the flask was placed in an ice bath. It is noteworthy that the ring closing radical reaction seems to occur in a regioselective manner, as exclusively the formation of the trinorbornane scaffold is observed and the also not yet known C₁₁-analogue (**A** in Scheme 2), which should be obtained when the other olefinic carbon atom would be attacked as well, could not be detected with any of the investigated reaction conditions.

The racemic mixture of **1** was fully characterised by ¹H- and ¹³C-NMR, and high resolution mass spectrometry. Despite the

apparent simplicity of the molecular architecture of **1** with only six carbon and eight proton resonances, it turned out exceedingly difficult to unambiguously confirm the suggested structure by standard HSQC / HMQC / NOESY NMR experiments due to the high order nature of the ^1H NMR spectrum and multiple pathways for long-range H-C couplings in the rigid tetracyclic framework. We therefore resorted to the very sensitive 1,1-ADEQUATE experiment¹⁸ using chirp pulses¹⁹ that selectively delivers correlations between protons and carbon atoms that are separated by two bonds and thus allowed to assign the topology of **1** without any doubt (Figure 4). With the proton and carbon assignment at hand it was possible to distinguish the diastereotopic protons in the CH_2 -groups by 2D-NOESY NMR using an unusually long mixing time of 3 seconds (Figure S1 shows key NOE contacts). The crucial NOE contact between symmetry related protons 5_b and 8_b could be obtained from a pseudo 3D HSQC-NOESY experiment without carbon decoupling during the ^1H acquisition which splits the diagonal peak into a 130 Hz doublet allowing for the detection of a weak but significant NOE between protons 5_b and 8_b (data not shown).

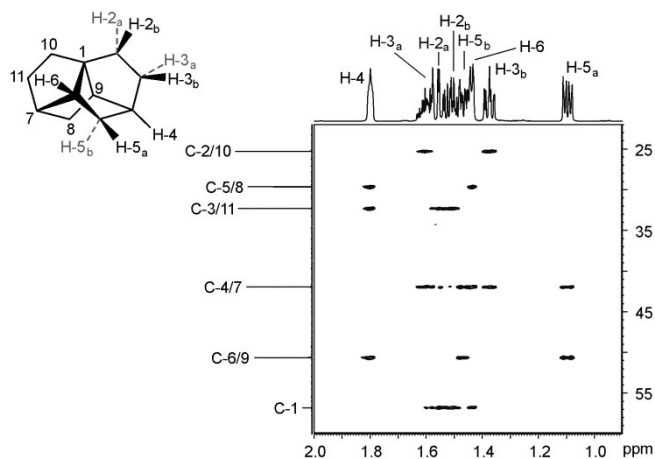


Figure 4 1,1-ADEQUATE spectrum of trinorbornane **1** recorded in C_6D_6 with assignment.

While all spectra unambiguously prove the identity of **1**, all attempts to analyse its solid state structure by X-ray analysis failed. In spite the fact that **1** is a crystalline solid at room temperature, the compound crystallises by sublimation in thin needles which are notoriously too thin to allow for analysing the solid state structure with the available X-ray sources.

In conclusion we report the first synthesis of trinorbornane, a tetracyclic saturated hydrocarbon with the elemental formula $\text{C}_{11}\text{H}_{16}$. While theoretical considerations predicted the stability and accessibility of the trinorbornane scaffold, it has neither been synthesised nor been found in nature so far. The tetracyclic scaffold has been assembled in a linear sequence of 9 steps and a total isolated yield of 7%. The key steps of the synthesis are the introduction of quaternary carbon atom in an early stage providing the precursor **16**, already comprising not only the first 5-membered ring of the target structure, but also all the required eleven carbon atoms. An intramolecular *Diels-Alder*

reaction resulted in the next two ring structures of the framework and the last cyclisation was achieved by an intramolecular radical reaction.

We are currently exploring functionalised trinorbornane structures as well as synthetic routes towards enantiomerically pure samples of this tetracyclic C_{11} -hydrocarbon.

The manuscript is dedicated to Prof. Jean-Louis Reymond as the inspiring muse provoking the endeavor. The authors gratefully acknowledge financial support for this work from the Swiss National Science Foundation (SNF, grant number 200020-159730) and the University of Basel.

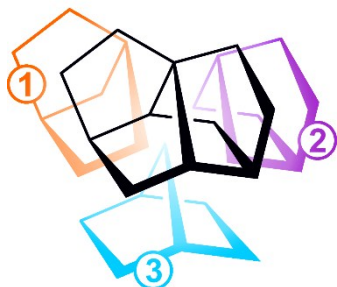
Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 T. Fink and J.-L. Reymond, *J. Chem. Inf. Model.*, 2007, **47**, 342–353.
- 2 J.-L. Reymond, L. C. Blum and R. van Deursen, *Chim. Int. J. Chem.*, 2011, **65**, 863–867.
- 3 H. Hopf, *Classics in hydrocarbon chemistry: syntheses, concepts, perspectives*, Wiley-VCH, Weinheim, 2000.
- 4 *Nachrichten Aus Chem. Tech. Lab.*, 1977, **25**, 59–70.
- 5 R. J. Ternansky, D. W. Balogh and L. A. Paquette, *J. Am. Chem. Soc.*, 1982, **104**, 4503–4504.
- 6 G. R. Underwood and B. Ramamoorthy, *Tetrahedron Lett.*, 1970, **11**, 4125–4127.
- 7 I. A. Levandovsky, D. I. Sharapa, O. A. Cherenkova, A. V. Gaidai and T. E. Shubina, *Russ. Chem. Rev.*, 2010, **79**, 1005.
- 8 A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams and J. B. DiGiorgio, *J. Am. Chem. Soc.*, 1965, **87**, 1613–1615.
- 9 G. Brieger and D. R. Anderson, *J. Org. Chem.*, 1971, **36**, 243–244.
- 10 C. Ebner and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2015, **54**, 11227–11230.
- 11 R. Fuchs and J. F. McGarrity, *Synthesis*, 1992, **1992**, 373–374.
- 12 B. Guay and P. Deslongchamps, *J. Org. Chem.*, 2003, **68**, 6140–6148.
- 13 R. M. Cory and R. M. Renneboog, *J. Org. Chem.*, 1984, **49**, 3898–3904.
- 14 R. L. Funk and K. P. C. Vollhardt, *Synthesis*, 1980, **1980**, 118–119.
- 15 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454–5459.
- 16 R. Ivanov, I. Marek and T. Cohen, *Tetrahedron Lett.*, 2010, **51**, 174–176.
- 17 G. E. Keck, K. A. Savin and M. A. Weglarz, *J. Org. Chem.*, 1995, **60**, 3194–3204.
- 18 B. Reif, M. Kock, R. Kerssebaum, J. Schleucher and C. Griesinger, *J. Magn. Reson. B*, 1996, **112**, 295–301.
- 19 M. Köck, R. Kerssebaum and W. Bermel, *Magn. Reson. Chem.*, 2003, **41**, 65–69.

TOC graphic and text:



The tetracyclic, chiral, and C_2 -symmetric structure of trinorbornane (tetracyclo[5.2.2.0^{1,6}.0^{4,9}] undecane) is synthesized for the first time as racemic mixture.