D_3-Trishomocubane-4-carboxylic Acid as a New Chiral Building Block: Synthesis and Absolute Configuration

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Abstract: The preparation of (±)-D_3-trishomocubanone on a multigram scale from 1,4-benzoquinone and cyclopentadiene was optimized to give the target product in 39% overall yield, that was transformed to (±)-D_3-trishomocubane-4-carboxylic acid via a three-step procedure involving the Corey–Chaykovsky reaction followed by boron trifluoride–diethyl ether catalyzed epoxide ring opening and further oxidation. Optically active (+)-D_3-trishomocubane-4-carboxylic acid was prepared through the resolution of the racemate by crystallization of its salt with (*R*)-phenylethylamine; the absolute configuration was assigned by X-ray crystal structure analysis.

Key words: D_3-trishomocubane, Corey–Chaykovsky reaction, absolute configuration, stereochemistry

The chemistry of polycyclic cage compounds remains fascinating and it has attracted the attention of organic chemists since the middle of the last century. Interest in the pharmacology of these compounds was stimulated when a variety of adamantane derivatives with a wide range of pharmacological properties were discovered.[1] The polycyclic cage is useful both as a building block for side-chain attachment, and also to increase the lipophilicity of the drugs. Additionally, the cage compounds can be used as monomers,[2] thermostable oils,[3] and nanoelectronic materials.[4]

Among such molecules the D_3-symmetrical trishomocubane (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane, **1**) has attracted particular attention (Figure 1). This hydrocarbon, like adamantane (**2a**), combines high lipophilicity and conformational rigidity which is especially valuable in novel drug design. Although D_3-trishomocubane was first synthesized in 1970,[5] and about 100 articles have been published on the synthesis and reactivity of its derivatives,[6] little is known on the preparation and reactivity of its optically active forms. It also is one of the highly symmetrical chiral cage hydrocarbons. Propeller chirality of **1** and its derivatives may offer capabilities inaccessible to other cage compounds. In spite of the promising properties of D_3-symmetrical trishomocubane derivatives, lack of multigram preparative methods for the synthesis of these compounds limits their further investigation and applications in material and medicinal chemistries.

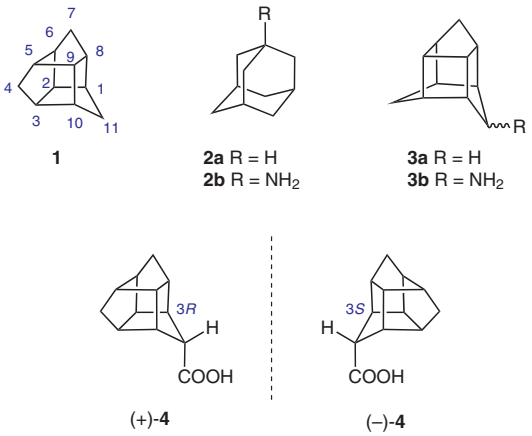

Figure 1

Recently,[7] it was reported that monoamine **3b** of isomeric parent pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (C_s-trishomocubane, **3a**) has higher inhibition properties than amantadine (1-aminoadamantane, **2b**), which is a specific inhibitor of the M2 ion-channel of the influenza virus.[8] Recently, based on our docking studies[8c] with 3D-QSAR, we have proposed a new generation of potential M2 inhibitors based on a combination of lipophilic adamantane (or other hydrocarbon cages, i.e., trishomocubane) and polar groups (e.g. hydroxy, carboxy, urea/thiourea moiety) separated from cage by one-carbon-atom bridges. This is in agreement with available experimental data on the activity of cage derivatives.[9] In accordance with this prediction, a convenient synthetic route to (±)-D_3-trishomocubane-4-carboxylic acid (**4**) followed by enantiomeric separation on a multigram scale (10–100 g) is required. Racemic acid **4** was previously prepared by us[10] and by others,[11] however all these procedures are difficult to use on a large scale.

In the first step of our study, we searched for an appropriate source of starting materials for the synthesis. According to the Symix® Available Chemicals Directory (March

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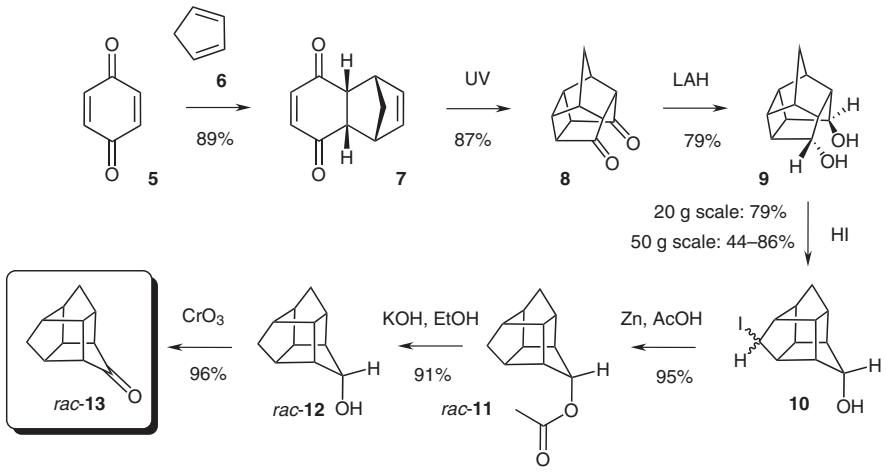


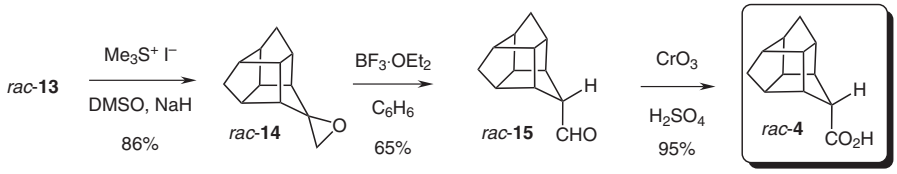
Scheme 1

2011), derivatives of D_3-trishomocubane are commercially available (21 examples), in milligram quantities only, from Aldrich Discovery CPR Library.

We have analyzed the scalability of known approaches to D_3-trishomocubane derivatives[6] and firstly tested the approach described by Schleyer with co-workers[12] as the most promising for scaling up. We chose the Cookson diketone **8**[13] as an intermediate, which is easily prepared from inexpensive reagents in two steps on a 70-gram scale in one synthetic run (Diels–Alder adduct **7** is also available commercially). After the reduction of **8** to *endo*,*endo*-C_s-trishomocubanediol (**9**) with excess lithium aluminum hydride (LAH) the rearrangement with hydrogen iodide gave D_3-trishomocubane iodo alcohol **10**. The effective sequence that involves zinc reduction, hydrolysis, and oxidation leads to D_3-trishomocubanone (*rac*-**13**). All these steps with exception of **9** to **10** display high preparative yields at 30–50-gram scale and are scalable further. The hydrogen iodide mediated rearrangement of **9** to **10** appears to be the most problematic. While freshly distilled hydrogen iodide at 100 °C was used with **9** on a 20-gram scale, the average yield from the set of the experiments is 79%. In this case the reaction leads to a mixture of diastereomeric iodo alcohol **10** with an admixture (~5%, GC MS) of the corresponding diiodo derivatives (see the procedure). This mixture was used in the next step without purification since the diiodo derivatives under zinc reduction form hydrocarbon **1**, which is separable from target acetate *rac*-**11** under reduced pressure. Scaling up to 50 grams in the step **9** to **10** yielded a diastereomeric mixture in varying yields from 44% to 86%. Despite this problem, this method allows us to prepare ketone *rac*-**13** on a 30-gram scale from one synthetic run via seven steps in 40% total yield starting from available reagents **5** and **6** (Scheme 1).

In our previous work[10] we described attempts to develop a preparative method of synthesis of **4** from alcohol **12** through a standard sequence (iodination, CN-substitution, and hydrolysis). It was found, however that this approach gave acid **4** in low yields. We now decided to test another approach, i.e., starting from ketone *rac*-**13** through Corey–Chaykovsky reaction, epoxide ring-opening, and further oxidation. This approach has previously been applied in the synthesis of adamantane-2-carboxylic acid,[14] many natural products,[15] and building blocks for medicinal chemistry.[16]

With cyclopentanone as an exception,[17] the Corey–Chaykovsky[18] reaction has been successfully applied to produce oxiranes from various carbonyl compounds. In the case of cyclopentanone the reaction gave δ-methylenecyclopent-1-ene-1-pentanoic acid, formation of which was explained by aldol condensation of cyclopentanone catalyzed by sodium hydride/dimethyl sulfoxide, followed by one-carbon alkylation and oxidation.[17] This is in marked contrast to the Corey–Chaykovsky reaction of cyclohexanone and cycloheptanone, which give the expected oxirane rather than aldol condensation products.[20,21] While *rac*-**13** comprises of several condensed cyclopentane fragments, formation of the bridgehead enolate is not possible, preventing aldol condensations. Methylenation of *rac*-**13** was performed with trimethylsulfoxonium iodide [$Me_3S(=O)^+ I^-$] or trimethylsulfonium iodide ($Me_3S^+ I^-$) with sodium hydride or potassium *tert*-butoxide as the base in anhydrous dimethyl sulfoxide–tetrahydrofuran. The highest yield of *rac*-**14** was observed with dimethyl-



Scheme 2

sulfonium methylide[19] prepared from $Me_3S^+I^-$ and sodium hydride (Scheme 2, Table 1) where the yield of *rac*-**14** was 86% on a 25-gram scale.

Table 1 Reaction Conditions for the Synthesis of Oxirane *rac*-**14** from *rac*-**13**[a]

Reagent	Excess of ylide	Temp (°C)	Yield[b] (%) of *rac*-**14**
$Me_3S(=O)^+ I^-$, *t*-BuOK	1.1	25	65
$Me_3S(=O)^+ I^-$, *t*-BuOK	2	25	65
$Me_3S(=O)^+ I^-$, *t*-BuOK	1.1	50	60
$Me_3S(=O)^+ I^-$, *t*-BuOK	2	50	54
$Me_3S^+ I^-$, *t*-BuOK	1.3	25	52
$Me_3S(=O)^+ I^-$, NaH	1.1	20	69
$Me_3S(=O)^+ I^-$, NaH	1.1	50	60
$Me_3S^+ I^-$, NaH	1.3	25	83
$Me_3S^+ I^-$, NaH	2	25	86

[a] Reactions with Me_3SOI were run in DMSO, those with Me_3SI in DMSO–THF, until the peak of ketone **13** was absent by GC.
[b] From the GC/MS of the reaction mixture.

The acid-catalyzed epoxide *rac*-**14** ring opening to aldehyde *rac*-**15** was tested under different reaction conditions and with different catalysts. The best yields (65%) were observed with boron trifluoride–diethyl ether complex as the catalyst and on a 20-gram scale (Table 2). Aldehyde *rac*-**15** was further oxidized without purification with Jones reagent, yielding D_3-trishomocubane-4-carboxylic acid (*rac*-**4**). Isolation of the pure aldehyde *rac*-**15** was attempted, however, it is easily oxidized by air and contained substantial amounts of acid *rac*-**4** (based on GS/MS data). Therefore, it was characterized as its stable hydrazone, obtained from the reaction of *rac*-**15** with 2,4-dinitrophenylhydrazine. As a whole, this approach allows the preparation of D_3-trishomocubane-4-carboxylic acid (*rac*-**4**) on a ca. 10-gram scale in one synthetic run.

Table 2 Reaction Conditions for Synthesis of D_3-Trishomocubane-4-carbaldehyde (*rac*-**15**) from *rac*-**14**

Reagent	Time (h)	Temp (°C)	Yield (%)
$BF_3{\cdot}Et_2O$	12	0	65[a]
$LiClO_4$, C_6H_6, HMPA	36	80	0[b]
$HClO_4$, dioxane	0.25	25	40[c]
$HClO_4$, Et_2O	1	25	45[c]
PTSA, C_6H_6	72	80	0[b]
IER (Dowex HCR-S), C_6H_6	72	80	0[b]

[a] Dilute oxirane soln should be added slowly to the $BF_3{\cdot}OEt_2$ soln, otherwise the yield drops to 45%.
[b] 100% of the starting compound *rac*-**14** is recovered.
[c] Dimers form as major byproduct.

After successful preparation of racemic D_3-trishomocubane-4-carboxylic acid (*rac*-**4**), we developed its enantioseparation. Earlier, some optically active derivatives of **1** were reported in the literature,[6] however, producing the product either in low yields (23–63%) or with unsatisfactory enantiomeric excess (60–93%).

Reaction of *rac*-**4** with small excess of (*R*)-1-phenylethylamine in methanol gave diastereomeric salt **16** that, after five-step gram-scale (see experimental part) fractional recrystallization from methanol followed by cleavage in tetrahydrofuran/hydrochloric acid, gave acid (+)-**4** and the mother liquor enriched by (–)-**4**. The enantiomeric purities of the (+)-enantiomer {$[\alpha]_D^{25}$ +105 (*c* 0.1 mg/mL, MeOH)}, and (–)-enantiomer {$[\alpha]_D^{25}$ –74 (*c* 0.05 mg/mL, MeOH)} thus obtained were analyzed using chromatographic methods. First, *rac*-**4** and both enantiomers (–)-**4** and (+)-**4** were converted into the corresponding methyl esters **17** and analyzed using different GC-chiral phases (Chiraldex G-TA, β-TBDM, β-TBDAC, Lipodex D, G, E and UP-5) without satisfactory separation. In contrast HPLC on Chiralpak IA (UV and RI detection) led to the satisfactory separation of the esters. This gave the enantiomeric excess of (+)-**4** as 100% and (–)-**4** as 80%.

The absolute configuration of (+)-**4** was determined through the corresponding amide (+)-**18**, which was prepared from its reaction with (*R*)-1-phenylethylamine. The ^1H and ^{13}C NMR spectra in combination with the APT-^{13}C NMR data are in accord with the structure of (+)-**18** (see Supporting Information). In particular, we observed two methylene and nine methyne resonances of the D_3-trishomocubyl cage. A single crystal of the amide (+)-**18** (Scheme 3) was subjected to X-ray diffraction study (Figure 2). Amide (+)-**18** crystallizes in non-centrosymmetric space group confirming the existence in the crystal phase only as a single enantiomer. The *R* configuration of the cage was determined based on the *R* configuration of the chiral center of the C13 atom. It is known that (+)-D_3-trishomocubane **1** has *R* absolute configuration at C3;[20] the same holds for (+)-**13** and (+)-4-iodo-D_3-trishomocubane-7-ol.[21]

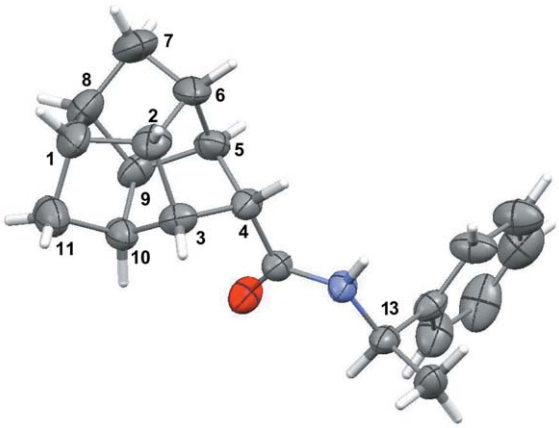
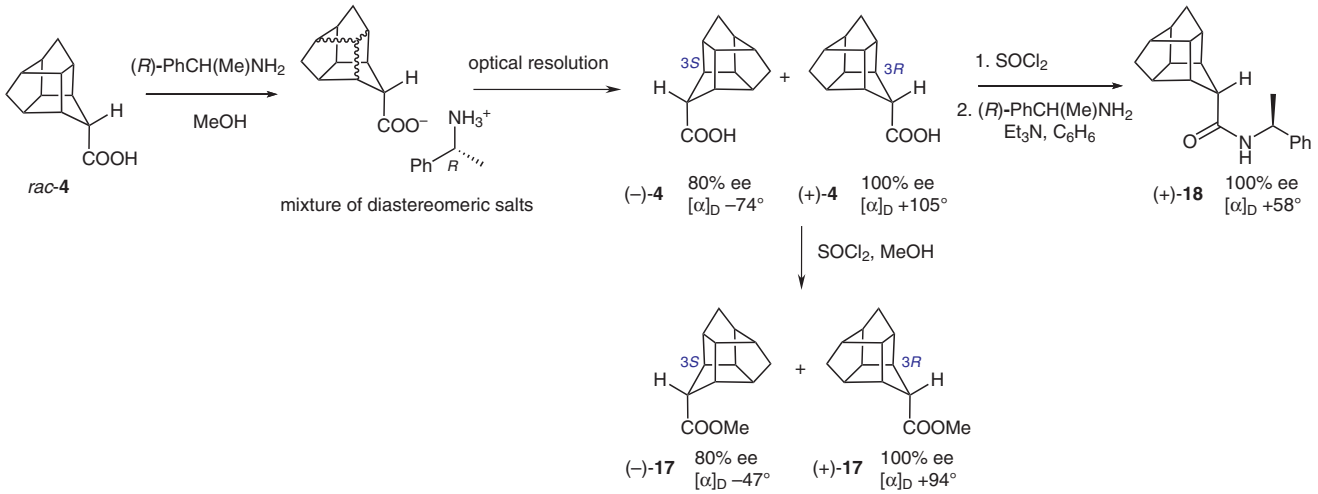


Figure 2 Molecular structure of (+)-**18** obtained by X-ray diffraction study



Scheme 3

In summary, we have developed the multigram-scale procedure for the preparation of D_3-trishomocubane-4-carboxylic acid based on the Corey–Chaykovsky methylation of D_3-trishomocubanone followed by boron trifluoride–diethyl ether complex catalyzed epoxide ring opening and oxidation with an overall yield ca. 55%. Enantioseparation of D_3-trishomocubane-4-carboxylic was achieved through its salt with (*R*)-1-phenylethylamine to give the pure (+)-enantiomeric form, of which the absolute configuration was determined by X-ray crystal structure analysis.

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a Bruker Avance 500 MHz spectrometer; in $CDCl_3$, internal standard: TMS. A HPLC system with Spectra Physics 8700 gradient pump, a Rheodyne 7125 sample injector, a Knauer Spectrophotometer 87 UV detector and Knauer 2025/50 refractometry detectors was used for enantiomer resolution. Optical rotation was measured on an Anton Paar MCP 300 instrument. The reaction mixture and purity of the compounds synthesized were checked by GC/MS HP GC/MS 5890/5972 instrument (EI, 70 eV). The parameters of chromatography-mass analysis: Column: HP-5MS, l = 25 m, d = 0.20 mm; temperature of injector 250 °C; temperature of detector 280 °C; program: 90 °C (2′) → 25 °C/min → 300 °C (15′); split (1:20); He flow: 1 mL/min; volume of injected sample: 1 μL.

Chiral Chromatographic Resolution

Analytical chiral resolution HPLC (Chiralpak IA column, nominal temperature 35 °C, hexane, flow rate 1 mL/min, refractometer and UV detectors): t_R = 14.67 [(–)-**17**], 18.29 min [(+)-**17**]; resolution factor *R*s = 5.8.

X-ray Diffraction Study

The colorless crystals of (+)-**18** ($C_{20}H_{23}NO$) are tetragonal. At 173 K a = 13.7764(2), b = 13.7764(2), c = 17.2337(5) Å, V = 3270.8(1) Å^3, M_r = 293.39, Z = 8, space group $P4_12_12$, d_{calc} = 1.192 g/cm^3, μ (MoKα) = 0.073 mm^{-1}, F(000) = 1264. Intensities of 37615 reflections (4768 independent, R_{int} = 0.048) were measured on the Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°). The structure was solved by direct method using SHELXTL package.[22] Positions of the hydrogen atoms were located from electron density difference maps and refined using 'riding' model with U_{iso} = nU_{eq} (n = 1.5 for the methyl group and n = 1.2 for other hydrogen atoms) of the carrier atom. Hydrogen bond in hydrogen was refined within isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 4706 reflections was converged to wR_2 = 0.142 (R_1 = 0.054 for 2562 reflections with $F > 4\sigma(F)$, S = 0.972).[23]

endo-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (7)[13]

Freshly distilled cyclopentadiene (**6**, 143 mL, 1.73 mol) was added a 0°C (ice-salt bath) suspension of 1,4-benzoquinone (**5**, 200 g, 1.85 mol) in EtOH (400 mL) with stirring. The mixture was heated to 60–75 °C and became transparent. After 10–15 min, the mixture was cooled to 0 °C forming a precipitate that was filtered and washed with cold EtOH. After drying, the adduct (287 g, 89%) was obtained as pale-yellow crystals.

^{1}H NMR ($CDCl_3$): δ = 1.38, 1.47 (AB, ^3J = 9 Hz, 2 H), 3.16 (s, 2 H), 3.47 (s, 2 H), 6.00 (s, 2 H), 6.51 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 48.30, 48.65, 48.70, 135.25, 141.98, 199.29.

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (8)[12]

endo-Tricycle **7** (100 g, 0.574 mol) was dissolved in EtOAc (700 mL) and irradiated by UV medium-pressure Hg lamp. The reaction was monitored by NMR. After complete conversion of adduct **7** to the Cookson diketone **8**, the solvent was evaporated under reduced pressure and purified by column chromatography (alumina, CH_2Cl_2). Evaporation of CH_2Cl_2 yielded **8** (87.5 g, 87%) as white crystals.

^{1}H NMR ($CDCl_3$): δ = 1.87, 2.03 (AB, ^3J = 11.5 Hz, 2 H), 2.68 (s, 2 H), 2.79 (s, 2 H), 2.92 (s, 2 H), 3.16 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 38.76, 40.48, 43.82, 44.66, 54.75, 212.02.

GC/MS: t_R = 8.27 min; *m*/*z* (%) = 174 (M$^+$, 90), 117 (100), 91 (44), 66 (47), 39 (40).

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol (9)[24]

A soln of dione **8** (80 g, 0.459 mol) in THF (350 mL) was slowly added via dropping funnel to mechanically stirred suspension of LAH (25 g, 0.659 mol) in THF (200 mL). The mixture was heated under reflux with stirring for 10 h and then cooled. H_2O (30 mL) was carefully added followed by addition of 30% H_2SO_4 soln to dissolve all of the aluminates. The organic layer was separated using a separating funnel, the aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 70 mL), dried (Na_2SO_4), and evaporated under vacuum to yield **9** (64.5 g, 79%).

^{1}H NMR ($CDCl_3$): δ = 1.04, 1.61 (AB, ^3J = 10.5 Hz, 2 H), 2.30 (s, 2 H), 2.35 (s, 2 H), 2.55 (s, 2 H), 2.63 (s, 2 H), 3.79 (s, 2 H), 6.25–6.32 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 34.53, 38.37, 39.91, 43.02, 45.55, 71.63.

GC/MS: t_R = 8.83 min; *m*/*z* (%) = 178 (M^+, 14), 160 (100), 95 (76), 94 (56), 91 (70), 66 (88).

7-Iodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ol (10)[12]

Diol **9** (20 g, 0.112 mol) was heated at 100 °C in freshly distilled HI (160 mL) with stirring for 3 h. The cooled mixture was poured out into H_2O (350 mL), and then extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed sequentially with H_2O, 10% NaOH soln, and H_2O. The organic layer was dried (Na_2SO_4) and evaporated under vacuum to obtain a mixture of iodo alcohols **10** with ~5% (GC MS data) impurity of the corresponding diiodo derivatives (27.5 g, 79%). The mixture was used in next step without additional purification.

^{1}H NMR ($CDCl_3$): δ = 1.40–1.42 (m, 2 H), 2.03–2.94 (m, 9 H), 3.96–4.06 (m, 1 H), 4.22–4.25 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 77.08, 75.50, 57.11, 55.30, 54.79, 54.23, 53.61, 53.48, 51.81, 50.73, 48.77, 45.95, 45.12, 43.20, 41.10, 40.65, 40.25, 40.07, 34.02, 32.56, 32.14, 31.68.

Iodo Alcohol 10a

Yield: 17.7%.

GC/MS: t_R = 9.24 min; *m*/*z* (%) = 288 (M^+, 14), 161 (100), 143 (58), 128 (58), 91 (59), 67 (66).

Iodo Alcohol 10b

Yield: 76.2%.

GC/MS: t_R = 9.28 min; *m*/*z* (%) = 288 (M^+, 14), 161 (100), 143 (71), 128 (57), 91 (41), 77 (37).

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-yl Acetate (*rac*-11)[12]

Zn dust (200 g, 3.05 mol) was added portionwise to a mixture of the crude mixture of iodo alcohols **10** (60 g, 0.208 mol) in AcOH (600 mL) preheated to 60 °C while stirred by a mechanical stirrer. The mixture was heated under reflux with stirring for 3 h. It was then cooled to r.t. and the mixture was filtered into a flask with H_2O (1 L); the unreacted zinc was washed by H_2O (200 mL) and CH_2Cl_2 (300 mL). The filtrate was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed by H_2O and then $NaHCO_3$ soln (2 ×), dried (Na_2SO_4), and evaporated in vacuo to yield *rac*-**11** (37.6 g, 95%) as white viscous liquid with characteristic smell; bp 130–131 °C/16 mbar.

^{1}H NMR ($CDCl_3$): δ = 1.27–1.36 (m, 3 H), 1.43 (d, ^3J = 10 Hz, 1 H), 1.91–2.12 (m, 10 H), 2.45 (s, 1 H), 4.87 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 21.24, 32.92, 33.57, 40.77, 41.16, 42.58, 44.68, 47.14, 47.34, 49.56, 50.65, 79.65, 171.24.

GC/MS: t_R = 7.42 min; *m*/*z* (%) = 204 (M^+, 2), 162 (100), 144 (58), 79 (37), 66 (27), 43 (43).

Pentacyclo[6.3.0.0.^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ol (*rac*-12)[12]

Acetate *rac*-**11** (40 g, 0.195 mol) was dissolved in 50% aq EtOH (800 mL) and then KOH (65 g, 1.158 mol) was added; the mixture was refluxed for 3 h. After cooling, the mixture was poured into a beaker and acidified with 10% H_2SO_4 to give a slightly acidic soln. The reaction mass was extracted with $CHCl_3$ (4 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated to obtain *rac*-**12** (28.9 g, 91%) as small white crystals.

^{1}H NMR ($CDCl_3$): δ = 1.30–1.35 (m, 3 H), 1.47 (d, ^3J = 10 Hz, 1 H), 1.92 (s, 3 H), 2.07–2.13 (m, 5 H), 2.58 (s, 1 H), 4.14 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.99, 33.69, 40.71, 41.22, 43.16, 44.27, 47.18, 47.45, 52.24, 53.48, 77.18.

GC/MS: t_R = 6.50 min; *m*/*z* (%) = 162 (M^+, 12), 144 (98), 95 (100), 79 (96), 66 (76), 39 (91).

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (*rac*-13)

Undecan-4-ol *rac*-**12** (32.5 g, 0.2 mol) was dissolved in acetone (500 mL). Under constant stirring and cooling with ice, Jones reagent [CrO_3 (72.8 g, 0.728 mol), H_2SO_4 (60 mL), and H_2O (140 mL)] was added dropwise. The temperature of the mixture remained below 10 °C. After addition of the reagents stirring was continued for 4 h at 25 °C. The mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 50 mL); the combined organic layers were dried (Na_2SO_4) and the solvent was removed at reduced pressure to give *rac*-**13** (30.8 g, 96%).

^{1}H NMR ($CDCl_3$): δ = 1.43, 1.69 (AB, ^3J = 10 Hz, 4 H), 1.78 (s, 2 H), 2.40 (s, 4 H), 2.46 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 35.53, 40.95, 41.12, 47.62, 50.21, 217.31.

GC/MS: t_R = 6.59 min; *m*/*z* (%) = 160 (M^+, 47), 132 (37), 78 (17), 66 (100), 39 (17).

Spiro[oxirane-2,4′-pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane] (*rac*-14)

To flask containing a bubble counter, 40% NaH (12.2 g, 0.305 mol) was added and washed with hexane (3 × 50 mL). THF (200 mL) and Me_3SI (103 g, 0.505 mol) were added, and the mixture was stirred at 0 °C until no further release of gas was observed. A soln of undecan-4-one *rac*-**13** (27 g, 0.168 mol) in DMSO (400 mL) and THF (170 mL) was added dropwise over 30 min, the mixture was stirred at 0 °C for 1 h and then stirring was continued for 15 h at 25°C. The mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). The solvent was removed under vacuum yielding *rac*-**14** (25.3 g, 86%) as an oily liquid; bp 121–122 °C/24 mbar.

^{1}H NMR ($CDCl_3$): δ = 1.27–1.29 (m, 2 H), 1.37–1.39 (m, 1 H), 1.43–1.45 (m, 2 H), 1.48 (d, ^4J = 5 Hz, 1 H), 2.06–2.13 (m, 3 H), 2.20 (q, ^4J = 5 Hz, 1 H), 2.25 (s, 1 H), 2.53 (br s, 1 H), 2.83, 2.87 (AB, ^3J = 4.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 33.73, 31.12, 41.46, 42.28, 43.90, 45.97, 47.41, 47.47, 49.06, 49.63, 49.93, 70.84;

GC/MS: t_R = 6.78 min; *m*/*z* (%) = 174 (M^+, 60), 108 (44), 80 (42), 79 (100), 77 (62).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.53; H, 8.16.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carbaldehyde (*rac*-15)

Epoxide *rac*-**14** (31 g, 0.178 mol) in benzene (200 mL) was added dropwise to the stirred soln of BF_3·Et_2O (49 mL) in benzene (600 mL) under cooling. After the addition of the reagents stirring was continued for 1 h at 25 °C. The mixture was poured into H_2O; the organic layer was separated and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue was distilled in vacuo yielding aldehyde *rac*-**15** with ~20% (NMR data) admixture of carboxylic acid *rac*-**4** (20.5 g, 65%); bp 122–123 °C/26.6 mbar; mp (dinitrophenylhydrazone) 164–165 °C.

^{13}C NMR ($CDCl_3$): δ (without peaks of acid **4**) = 32.79, 33.21, 40.59, 43.08, 44.58, 46.38, 47.33, 47.37, 49.06, 49.31, 58.87, 205.21.

GC/MS: t_R = 6.83 min; *m*/*z* (%) = 174 (M^+, 41), 117 (40), 91 (40), 79 (100), 77 (67), 39 (41%).

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carboxylic Acid (*rac*-4)

The aldehyde *rac*-**15** (20.5g) and acid mixture (~20%) from the previous step was dissolved in acetone (400 mL) and under constant stirring and cooling with ice, Jones reagent [CrO_3 (73 g, 0.73 mol), H_2SO_4 (63 mL), and H_2O (210 mL)] was added dropwise. The temperature of the mixture remained below 10 °C. After the addition of the reagents, stirring was continued for 3 h at 25 °C. The mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed at reduced pressure. Acid was purified by acidification of its sodium salt soln, the precipitate was filtered and dried to give *rac*-**4** (20.8 g, 95%).

^{1}H NMR ($CDCl_3$): δ = 1.34–1.45 (m, 4 H), 2.03–2.12 (m, 5 H), 2.26–2.29 (m, 2 H), 2.33 (br s, 1 H), 2.71 (s, 1 H), 11.37 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.88, 32.9, 41.47, 42.69, 45.17, 46.72, 46.98, 47.24, 49.76, 50.06, 50.30, 181.09.

GC/MS: t_R = 7.86 min; *m*/*z* (%) = 190 (M$^+$, 82), 124 (78), 79 (100), 77 (60), 66 (54).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.72; H, 7.45.

Resolution of Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carboxylic Acid (*rac*-4)

(*R*)-1-Phenylethylamine (6.4 g, 52.8 mmol) was added to D_3-trishomocubane-4-carboxylic acid **4** (10 g, 52.6 mmol) in abs MeOH (50 mL). The mixture was stirred at r.t. for 1 h and then the solvent was evaporated under vacuum yielding 16.4 g of diastereomeric salts. The obtained salts were recrystallized (abs MeOH, 40 mL) yielding 6.2 g of precipitate. Further recrystallization (abs MeOH, 24 mL) leads to 3.5 g of precipitate. For the subsequent recrystallizations abs MeOH 15 mL, 9 mL and 5 mL were used yielding 1.9 g, 1.05 g, and 0.8 g of precipitate respectively for each crystallization. The last fraction of crystals consists of pure (*R*)-1-phenylethylamine salt of (+)-D_3-trishomocubane-4-carboxylic acid (+)-**16** (0.8 g, 9%). After combining the filtrates, evaporation of half of the solvent and filtration of the precipitate mother liquor contains great excess of salt of (–)-D_3-trishomocubane-4-carboxylic acid. After evaporation of MeOH, 1.5 g of salt was obtained. The salts were cleaved using a mixture of HCl/THF (1:8), then extracted with Et_2O, dried (Na_2SO_4), and evaporated.

(+)-**4**

(3*R*)-Isomer; yield: 0.5 g; mp 58–60 °C; $[\alpha]_D^{25}$ +105 (*c* 0.1 mg/mL, MeOH).

(–)-**4**

(3*S*)-Isomer; yield: 0.9 g; mp 85–87 °C; $[\alpha]_D^{25}$ –74 (*c* 0.05 mg/mL, MeOH).

Methyl Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carboxylate (17)

$SOCl_2$ (0.25 mL, 3.44 mmol) was slowly added to ice-cooled soln of the corresponding isomer of **4** (50 mg, 0.26 mmol) in abs MeOH (2 mL). The mixture was stirred for 30 min then evaporated under vacuum. The methyl esters were obtained in quantitative yield.

(+)-**17**, (3*R*)-isomer, $[\alpha]_D^{25}$ +94 (*c* 20.21 mg/mL, cyclohexane).

(–)-**17**, (3*S*)-isomer, $[\alpha]_D^{25}$ –47 (*c* 20.21 mg/mL, cyclohexane).

^{1}H NMR ($CDCl_3$): δ = 1.30–1.33 (m, 3 H), 1.39–1.41 (m, 1 H), 1.99–2.03 (m, 2 H), 2.08 (br s, 3 H), 2.19–2.23 (m, 3 H), 2.65 (s, 1 H), 3.64 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 32.87, 32.93, 41.47, 42.56, 45.19, 46.65, 46.98, 47.22, 49.86, 50.05, 50.28, 51.26, 174.71.

MS: *m*/*z* (%) = 204 (M$^+$, 68), 172 (22), 145 (47), 138 (100), 79 (79), 67 (34).

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carboxylic Acid (*R*)-1-Phenylethylamide [(+)-18]

Acid (+)-**4** (100 mg, 0.5 mmol) was refluxed in $SOCl_2$ (3 mL) for 2 h, then the $SOCl_2$ was evaporated under vacuum and obtained acid chloride was dissolved in benzene (2 mL). Et_3N (60 mg 0.59 mmol) dissolved in benzene (3 mL) was added to the stirred acid chloride soln. Then (*R*)-1-phenylethylamine (70 mg, 0.58 mmol) was added; some precipitate was formed during addition. The mixture was stirred overnight at r.t. 10% HCl soln (5 mL) was added to the mixture, which was stirred and the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with dil. Na_2CO_3 soln, dried (Na_2SO_4), and evaporated to give the crude amide (+)-**18** (120 mg, 78%). The amide was purified by recrystallization (acetone, 1 mL). The crystal of pure amide was grown from acetone by slow evaporation of solvent.

$[\alpha]_D^{25}$ +58 (*c* 0.212 mg/mL, MeOH)

^{1}H NMR (DMSO-d_6): δ = 1.24–1.28 (m, 3 H), 1.33–1.34 (m, 4 H), 1.95–1.97 (m, 1 H), 2.01–2.03 (m, 3 H), 2.08 (br s, 1 H), 2.15 (br s, 2 H), 2.2 (br s, 1 H), 2.55 (s, 1 H), 4.93 (m, ^4J = 8 Hz, 1 H), 7.20–7.22 (m, 1 H), 7.30–7.32 (m, 4 H), 7.96 (d, ^4J = 8 Hz, 1 H).

^{1}H NMR ($CDCl_3$): δ = 1.27–1.55 (m, 8 H), 2.00–2.23 (m, 7 H), 2.61 (s, 1 H), 5.16 (m, ^4J = 7 Hz, 1 H), 5.7 (s, 1 H), 7.28–7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 21.7 (CH_3), 32.9 (CH_2), 33.0 (CH_2), 41.55 (CH), 42.6 (CH), 45.1 (CH), 47.0 (CH), 47.0 (CH), 47.4 (CH), 48.3 (CH), 49.5 (CH), 50.7 (CH), 51.9 (CH), 126.1 (CH), 127.2 (CH), 128.6 (CH), 143.5 (C_4), 172.6 (C_4).

GC/MS: t_R = 12.26 min; *m*/*z* (%) = 293 (M$^+$, 100), 145 (47), 106 (71), 105 (100), 79 (78).

Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.89; H, 7.93; N, 4.79.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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