Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4443–4449

TETRAHEDRON

Helical primary structures of four-membered rings: (*M*)-trispiro[3.0.0.3.2.2]tridecane☆

Lutz Fitjer,[a,*] Ralf Gerke,[a] Jörg Weiser,[a,†] Gabor Bunkoczi[b] and Judit E. Debreczeni[b]

[a]*Institut für Organische Chemie der Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany*
[b]*Institut für Anorganische Chemie der Universität Göttingen, Tammannstrasse 4, D-37077 Göttingen, Germany*

Received 2 December 2002; revised 10 March 2003; accepted 3 April 2003

Abstract—The synthesis of (*M*)-trispiro[3.0.0.3.2.2]tridecane [(*M*)-**4**], the first hydrocarbon with a helical primary structure of four-membered rings, is described. Key step is the kinetic resolution of a cyclobutanone through reduction with bakers' yeast. As compared to its analogue of three-membered rings, (*M*)-trispiro[2.0.0.2.1.1]nonane [(*M*)-**1**], the specific rotation of (*M*)-**4** is cut in three. According to molecular mechanics calculations this could be due to a potential to adopt different conformations, not given in (*M*)-**1**, and to the fact, that (*M*)-**4** describes a distinctly shorter section of a helix than (*M*)-**1**. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Helical primary structures of spiroannelated rings are unknown in nature but have been artificially produced, both in racemic[2,3] and enantiomerically pure form.[4] The first report on an enantiomerically pure hydrocarbon of spiroannelated rings appeared in 1999, when de Meijere et al.[5] succeeded to prepare (*M*)-trispiro[2.0.0.2.1.1]nonane [(*M*)-**1**] as one of the enantiomers of the long-known *rac*-**1**[6] (Fig. 1). Based on ab initio calculations, the remarkable high specific rotation ($[\alpha]_D^{20}=-192.7°$, $c=1.2$, $CHCl_3$) was attributed to the helical arrangement of the σ-bonds in conjunction with the rigid skeleton formed by the cyclopropane rings. Consequently, **1** and its higher homologues were classified as σ-[*n*]helicenes, with *n* being the number of cyclopropane rings, and hence (*M*)-**1** being a σ-[4]helicene. Interestingly, the predicted[5] sharp rise of the specific rotation in going from (*M*)-**1** to the next higher homologue, (*M*)-tetraspiro[2.0.0.0.2.1.1.1]undecane [(*M*)-**2**], has recently been verified ($[\alpha]_D^{20}=-381.2°$, $c=1.2$, $CHCl_3$).[7]

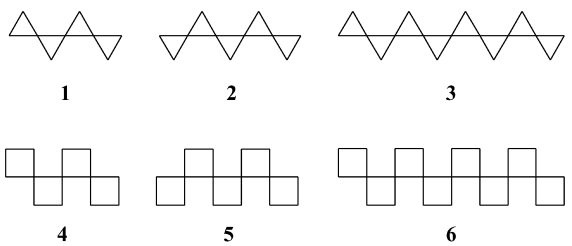


Figure 1.

Of course, σ-helicity is not restricted to polyspiranes of three-membered rings.[8] Thus, 1,2-spiroannelated cyclobutanes, as in **4**, may constitute σ-helices as well, albeit the potential to adopt different conformations, not given in **1**, should render these helices less rigid and less well defined. To clarify this point, and to look for similarities and differences between (*M*)-**1** and (*M*)-**4**, we first performed a conformational search for all minimum conformations within 3 kcal above the global minimum using our search routine HUNTER[9] in connection with MM3,[10] before we approached a synthesis. For comparison purposes, the corresponding σ-[5]- [(*M*)-**2**,[7] (*M*)-**5**] and σ-[8]helicenes [(*M*)-**3**, (*M*)-**6**] were included (Fig. 1).[11]

2. Results

As may be seen from views perpendicular to (a) and along the helical axis (b), the σ-bonds of the inner, and the methylene groups of the outer sphere of all global minimum structures describe sections of regular helices (Fig. 2). However, as shown by the data of the helices formed by the methylene groups of the outer sphere, striking differences exist: in (*M*)-**1** to (*M*)-**3**, the identity period *i* amounts to 9.2 Å and comprises eight three-membered rings distributed over two helical turns; in (M)-**4** to (M)-**6**, the identity period *i* amounts to 5.0 Å and comprises five four-membered rings distributed over one helical turn. This means, that in a [5]helicene of four-membered rings a helical turn is just

☆ See Ref. 1.

Keywords: helicenes; spiro compounds; molecular mechanics; resolution.

* Corresponding author. Tel.: +49-551-395631; fax: +49-551-395644; e-mail: lfitjer@gwdg.de

† Present address: Anterio consult & research GmbH, Augustaanlage 26, D-68165 Mannheim, Germany.

0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00617-3

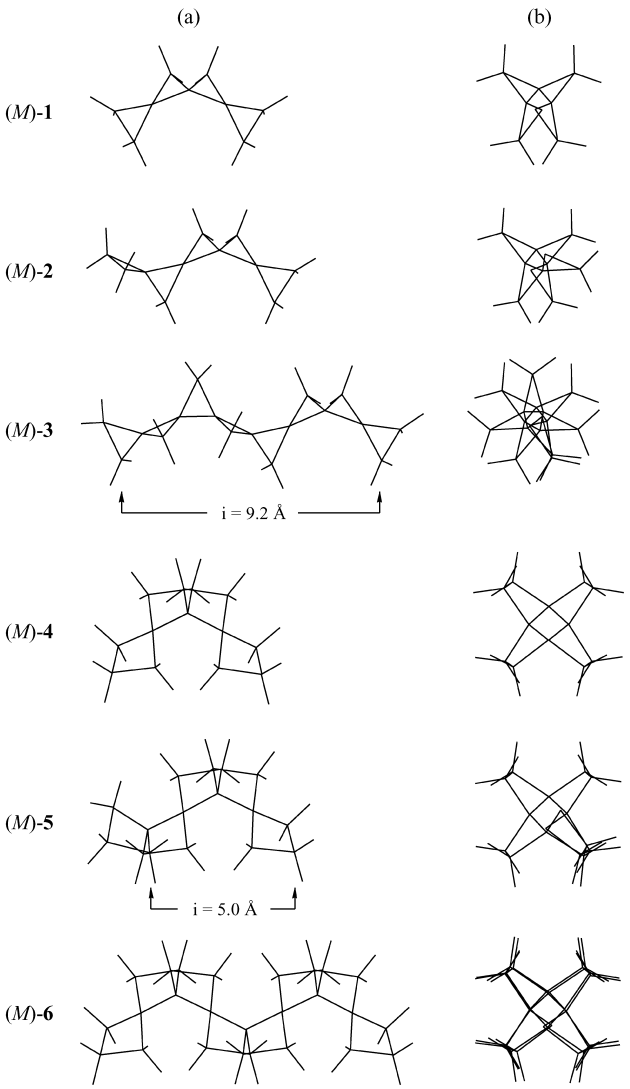
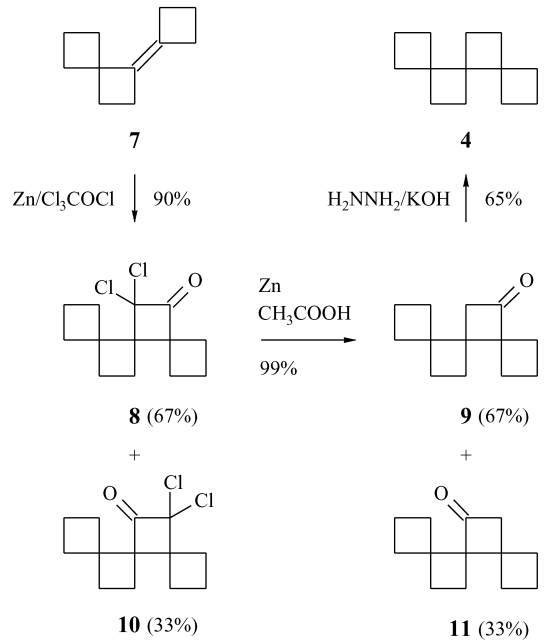


Figure 2. Global minimum structures of (*M*)-**1** to (*M*)-**6**: views perpendicular to (a) and along the helical axis (b). The structure of (*M*)-**2** was generated using the crystal structure data of *rac*-**2**.[7] The remaining structures were determined by molecular mechanics using PC-model[11] [(*M*)-**1**, (*M*)-**3**] and the conformational search routine HUNTER[9] in connection with MM3[10] [(*M*)-**4**, (*M*)-**5**, (*M*)-**6**], respectively. In (b), the carbon–hydrogen bonds within the inner spheres have been omitted for clarity.

complete, while in a [5]helicene of three-membered rings it goes about 50° beyond.‡ Interestingly, it is just for this case that the specific rotation of (*M*)-**1** nearly doubles.[7,12]

As a matter of course, for rigid structures, like (*M*)-**1** to (*M*)-**3**, only a single minimum structure exists. On the contrary, within 3 kcal above the global minimum, seven additional minima were located for (*M*)-**4**, three for (*M*)-**5**, but only one for (*M*)-**6**. Most of these minima represent unsymmetrical conformations (symmetry C_1), and all contain irregular sections (see below). It therefore seemed probable, that in

‡ The fact that in a σ-[5]helicene of three-membered rings the interplanar angles between all adjacent pairs of spiro-fused rings sum up to 360° has been taken as evidence that the methylene groups of the outer sphere describe exactly one helical turn.[5,7] However, this would only be true, if the helix formed by the σ-bonds of the inner sphere, would no longer be a helix but a straight line.



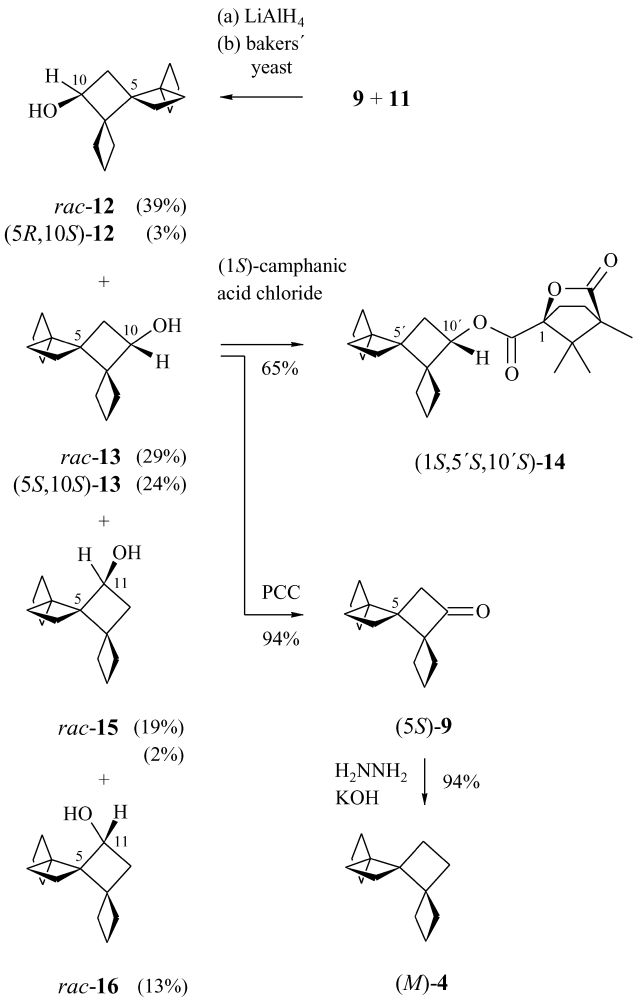
Scheme 1.

(*M*)-**4** the high specific rotation of (*M*)-**1** would not be attained.

The synthesis of racemic **4** was straightforward: reaction of the readily available bicyclobutylidene **7**[13] with dichloroketene[14,15] followed by reductive dehalogenation[14] and Wolff–Kishner reduction[16] [**7**–**8**(**10**)–**9**(**11**)–**4**] yielded the desired trispiro[3.0.0.3.2.2]tridecane [*rac*-(**4**)] (symmetry C_2), easily recognised by the appearance of only seven resonance lines in the ^{13}C NMR spectrum [16.75 (t), 25.48 (t), 31.77 (t), 31.96 (t), 32.43 (t), 49.33 (s), 52.41 (s)] (Scheme 1).

Two features rendered a synthesis of enantiomerically pure **4** via a chemical resolution of **9** and/or **11** difficult to achieve: first, the cycloaddition was not regiospecific, and second, the 2:1-mixture of isomers formed was not separable on a preparative scale, neither at the stage of **8** and **10**, nor at the stage of **9** and **11**. We therefore decided to try an enzymatic resolution[17] via a hopefully substance-, diastereo- and enantioselective reduction of the mixture of **9** and **11** with bakers' yeast.[18]

To learn about the reduction products, we first performed a reduction with lithium aluminium hydride. Fortunately, this reagent produced the four possible alcohols quantitatively (combined yield 99%) and in proportions (39:29:19:13) that allowed an unequivocal assignment of the two major alcohols as derived from **9**, and the two minor alcohols as derived from **11** (Scheme 2). Analytically pure samples were obtained by a combination of column and gas chromatography, but the stereochemistry within the two pairs of diastereoisomers remained unclarified. Nevertheless, as the enantiomers of all four alcohols could be resolved by capillary gas chromatography on a γ-cyclodextrine as chiral phase, we investigated the reduction with bakers' yeast next.



Scheme 2.

For the experimental realisation, we submitted the 2:1-mixture of **9** and **11** (3.80 g) to a vigorously stirred medium of bakers' yeast (60 g), sucrose (60 g) and water (600 ml) maintained at 35°C. The reaction progress was monitored by gas chromatography, and, after 5 and 10 h, more yeast (60 g), sucrose (60 g) and water (300 ml) were added. After 24 h, the reduction had considerably slowed down, while the medium contained a 83:11:6-mixture of three alcohols (combined yield 29%). Separation from unreacted ketones was achieved by column chromatography on silica gel in pentane/ether (7:3), and separation of the alcohols by preparative gas chromatography. A comparison of the products with those of the reduction with lithium aluminium hydride revealed, that the two major alcohols (yields 24 and 3%) were identical with the two alcohols derived from **9**, and that the minor alcohol (yield 2%) was identical with the major alcohol derived from **11**. In the case of **9**, the diastereoselectivity of the reduction had been reversed, and in all cases the alcohols were enantiomerically pure (>99% ee).

For the determination of the stereochemistry and absolute configuration of the major alcohol (yield 24%) we reacted the 83:11:6-mixture of alcohols with (−)-(1*S*)-camphanic acid chloride,[19] eliminated the two minor esters by fractional crystallisation, and subjected the major ester

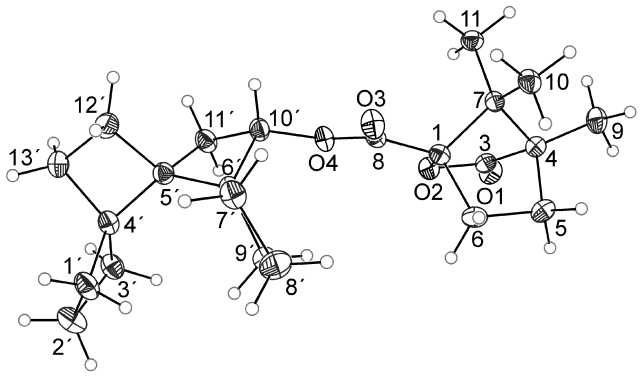


Figure 3. X-Ray crystal structure of (1*S*,5′*S*,10′*S*)-**14**.

(mp 96–98°C, yield 65%, $[\alpha]_D^{20}=+14.7°$, *c* 0.873, acetone) to an X-ray analysis (Fig. 3).[20] This analysis disclosed its identity as (1*S*,5′*S*,10′*S*)-**14**, and hence that of the corresponding alcohol as (5*S*,10*S*)-**13**. It thus became clear, that the mixture of **9** and **11** had not only been reduced with a large preference for **9** and diastereoselectively, but also that the hydride equivalent had been delivered from the *re* face of the ketone, as determined by the relative steric bulk of the α-substituents, yielding the *S*-configurated alcohol. This corresponds to what has been observed with other ketones,[17] and is in accord with Prelog's rule.[21]

As already mentioned, the alcohol formed in 3% yield was a diastereoisomer of (5*S*,10*S*)-**13**, and hence either (5*R*,10*S*)- or (5*S*,10*R*)-**12**. The assignment as (5*R*,10*S*)-**12** is tentative and implies a hydride transfer from the *re* face of the ketone as observed in the formation of (5*S*,10*S*)-**13**. Nothing can be said about the relative and absolute configuration of the alcohol formed in 2% yield. The relative configuration was identical with that of the major alcohol formed by lithium aluminium hydride reduction of **11**, but the assignment of this alcohol as *rac*-**15** and of its diastereoisomer as *rac*-**16** is arbitrary and may be interchanged.

To complete the synthesis of (*M*)-**4**, the major alcohol (5*S*,10*S*)-**13** (>99% ee, $[\alpha]_D^{20}=+18.7°$, *c*=1.42, acetone) was first purified by preparative gas chromatography and then oxidized with pyridinium chlorochromate[22] to yield the ketone (5*S*)-**9** (>99% ee, $[\alpha]_D^{20}=-70.4°$, *c*=1.09, acetone). This ketone was finally deoxygenated to yield the desired (*M*)-trispiro[3.0.0.3.2.2]tridecane [(*M*)-**4**] (>99% ee, $[\alpha]_D^{20}=-63.3°$, *c*=1.09, $CHCl_3$).

3. Discussion

It is well known that chiral saturated hydrocarbons with a rigid skeleton may exhibit very high specific rotations. An illustrative example is (*M*)-twistane ($[\alpha]_D^{22}=-440°$, ethanol).[23] Given this fact, the specific rotation of (*M*)-**1** ($[\alpha]_D^{20}=-192.7°$, *c*=1.2, $CHCl_3$)[5,7] is remarkable, but not exceptional. It is further known that chiral saturated hydrocarbons with an unrestricted conformational mobility may exhibit no optical rotation at all. Examples are hydrocarbons consisting of a carbon atom linked to four different chains.[24] As compared to these extremes, the situation with (*M*)-**4** is in between: the specific rotation of (*M*)-**1** is cut in three, and the molar rotation ($[\Phi]_D^{20}=-231.6°$

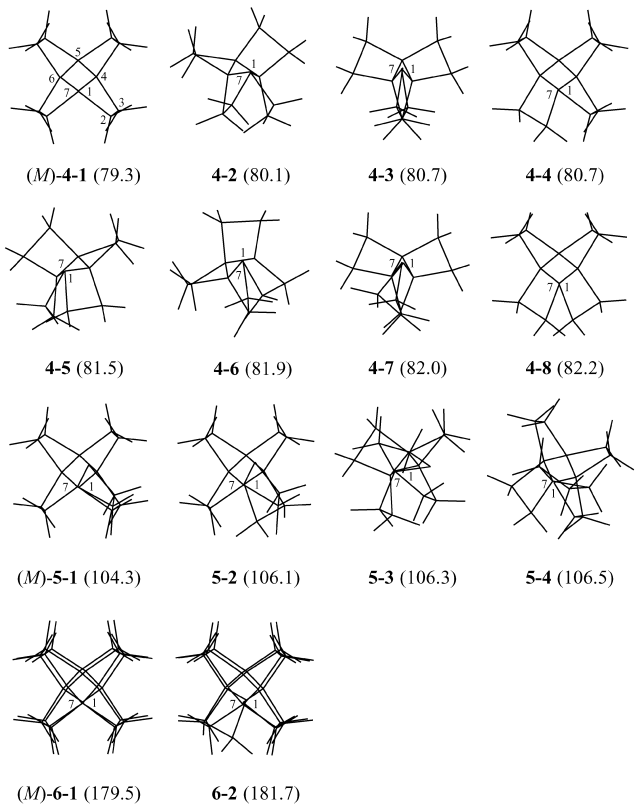


Figure 4. Minimum conformations and corresponding heats of formation (in kcal) of (*M*)-**4** to (*M*)-**6** up to 3 kcal above the global minimum as determined by molecular mechanics using the conformational search routine HUNTER[9] in connection with MM3.[10] All conformers are viewed from C-1 to C-7. In all cases the carbon–hydrogen bonds within the inner spheres have been omitted for clarity.

[(*M*)-**1**] and $=-109.8°$ [(*M*)-**4**]) is cut in two. To explain this fact we refer to the results of our conformational search (Fig. 4).

Of the eight minimum conformations located within 3 kcal above the global minimum of (*M*)-**4**, only the global minimum (**4**–**1**) represents a regular cylindrical helix within the inner and outer sphere. Of the remaining seven conformations, two (**4**–**3**, **4**–**8**) are symmetrical (symmetry C_2) and five (**4**–**2**, **4**–**4**, **4**–**5**, **4**–**6**, **4**–**7**) are unsymmetrical (symmetry C_1), but all contain non-regular sections, both in the inner and outer sphere. We therefore believe, that the reduced optical rotation of (*M*)-**4** is due to a pronounced conformational mobility, not present in (*M*)-**1**, and to the fact, that the methylene groups of the outer sphere describe a distinctly shorter section (270°) of a helical turn (360°) than those of (*M*)-**1** (310°).

It is interesting to note, that in (*M*)-**5** and (*M*)-**6**, the number of minimum conformations within 3 kcal above the global minimum is reduced to four and two, respectively, while the global minima describe regular helices as does the global minimum of (*M*)-**4**. Obviously, as *n* increases, the conformational mobility decreases. It could therefore well be, that the differences in the optical rotation of σ-[*n*]-helicenes of three- and four-membered rings for higher analogues diminish.

In summary, based on the readily available bicyclobutylidene **7**, we have developed a three step synthesis of *rac*-**4**, and, via a substance-, diastereo- and enantioselective enzymatic reduction of ketone **9**, in admixture with ketone **11**, a five-step synthesis of (*M*)-**4**. However, more work will have to be done until the dependance of the chiroptical properties of σ-[*n*]helicenes on geometrical parameters like the ring-size, and, for five-membered and higher rings, on the location of the spiro-junctions, will be understood.

4. Experimental

4.1. General

IR-spectra were obtained with a Perkin–Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 or a Varian VXR 500 spectrometer. For standards other than TMS the following chemical shifts were used: $\delta_H(CHCl_3)=7.24$, $\delta_H(C_6D_5H)=7.15$, $\delta_C(CDCl_3)=77.00$, $\delta_C(C_6D_6)=128.00$. ^{13}C multiplicities were studied by APT and/or DEPT measurements. Mass spectra were obtained with a Varian CH 5 (CI) or a Finnegan MAT 95 spectrometer (EI and HR-EI) operated at 70 eV. Optical rotations were measured on Perkin–Elmer 241 digital polarimeter in a 1 dm cell. Preparative GC was carried out on a Carlo-Erba GC 6000 Vega series 2 instrument employing a thermal conductivity detector, and hydrogen as carrier gas. Analytical GC was performed on a Carlo-Erba GC 6000 Vega series 2 instrument employing a split/splitless injector, a FID 40 detector, and hydrogen (0.6 bar) as carrier gas. The following columns were used: (A): 3 m×1/4″ all-glass system, 15% FFAP on Chromosorb W AW/DMCS 60/80 mesh; (B): 30 m×0.32 mm i.d. deactivated fused-silica capillary column coated with 0.25 μm DB FFAP; (C): 25 m×0.25 mm i.d. deactivated fused-silica capillary column coated with octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin (Lipodex® E); (D): 25 m×0.25 mm i.d. deactivated fused-silica capillary column coated with oktakis-(2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin (Lipodex® G). Product ratios were not corrected for relative response. R_f values are quoted for Macherey & Nagel Polygram SIL G/UV$_{254}$ Plate. Colourles substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid and subsequent warming. Melting points were observed on a Reichert microhotstage and are not corrected. Microanalytical determinations were done at the Microanalytical Laboratory of the Institute of Organic Chemistry, Göttingen. Fresh bakers' yeast manufactured by Dr Oetker was purchased in a normal foodstore.

4.1.1. (5*R)-11,11-Dichloro-trispiro[3.0.0.3.2.2]tridecan-10-one (8) and (5*R**)-(10,10-dichloro-trispiro-[3.0.0.3.2.2]tridecan-11-one (10).** To a sonicated mixture of 1-cyclobutylidene-spiro[3.3]heptane (**7**) (5.3 g, 36 mmol) and zinc dust (3.5 g, 53 mmol) in ether (120 ml) was added within 30 min at 10–15°C under argon a solution of trichloroacetyl chloride (7.3 g, 40 mmol) in ether (60 ml). Afterwards, the mixture was heated to reflux until GC analysis [column A, 230°C; retention times (min): 0.8 (**7**), 7.1 (**8**, **10**)] indicated that the reaction was complete (12 h). The mixture was filtered through celite, and the filtrate was washed with water (100 ml), saturated sodium bicarbonate (100 ml) and brine (100 ml), and dried ($MgSO_4$). The

solution was concentrated on a rotary evaporator (bath temperature 60°C/15 Torr) and the residual yellow oil (9.3 g) chromatographed on silica gel (0.05–0.20 mm) in pentane/ether [95:5; column 90×5 cm, control by TLC, R_f=0.57 (**8**, **10**)] yielding 8.4 g (90%) of a 2:1-mixture of **8** and **10** as slightly yellow oil. An attempted separation by capillary gas chromatography failed [column B, 180°C; retention time (min): 5.56 (**8**, **10**)]. Data for the 2:1-mixture of **8** and **10**: IR (neat): 1795 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.60–1.70 (m, 0.67H), 1.70–2.70 (m, 14.7H), 2.95–3.05 (m, 0.67H); ^{13}C NMR (150 MHz, $CDCl_3$, $CDCl_3$ int): All resonances could be assigned: **8**: δ=16.80 (t), 17.07 (t), 25.08 (t), 27.76 (t), 30.51 (t), 31.76 (t), 31.83 (t), 32.68 (t), 49.28 (s), 56.37 (s), 66.97 (s), 87.99 (s), 199.65 (s); **10**: δ=15.69 (t), 16.29 (t), 23.88 (t), 26.56 (t), 27.39 (t), 32.23 (t), 32.28 (t), 50.34 (s), 56.27 (s), 70.69 (s), 91.10 (s), 198.36 (s); MS (CI): *m/e*=295/293 (1/2) $[M+NH_3+NH_4]^+$, 278/276 (6/9) $[M+NH_4]^+$, 261/259 (3/11) $[M-Cl+H+NH_3+NH_4]^+$, 244/242 (31/100) $[M-Cl+H+NH_4]^+$; $C_{13}H_{16}Cl_2O$ requires C, 60.24; H, 6.22; Cl, 27.36. Found: C, 60.17; H, 6.38; Cl, 27.88.

4.1.2. (5*R)-Trispiro[3.0.0.3.2.2]tridecan-10-one (9) and (5*R**)-trispiro[3.0.0.3.2.2]tridecan-11-one (11).** To a suspension of zinc dust (19.5 g, 300 mmol) in acetic acid (30 ml) was added within 30 min under argon with stirring a solution of a 2:1-mixture of **8** and **10** (7.7 g, 30 mmol) in acetic acid (15 ml). Afterwards, the mixture was heated to 60°C until GC analysis [column A, 230°C; retention times (min): 3.1 (**9**, **11**), 7.1 (**8**, **10**)] indicated that the reaction was complete (1 h). The mixture was filtered, the residue was washed with pentane (3×60 ml), and the combined filtrates were poured into water (300 ml). The aqueous layer was extracted with pentane (3×100 ml), and the combined organic layers were washed with water (100 ml), saturated sodium bicarbonate (100 ml) and brine (100 ml), and dried ($MgSO_4$). Evaporation of the solvent (bath temperature 40°C/15 Torr) yielded 5.7 g (99%) of a 2:1-mixture of **9** and **11** as colourless oil (purity 99% GC). An attempted separation on silica gel (0.05–0.20 mm) in pentane/ether (8:2, column 80×5 cm, R_f=0.56) failed. Analytically, **9** and **11** could be distinguished by capillary gas chromatography [column B, 150°C; retention times (min): 4.33 (**11**), 4.48 (**9**)]. Data for the 2:1-mixture of **9** and **11**: IR (neat): 1770 cm^{-1} (C=O); ^1H NMR (500 MHz, C_6D_6, C_6D_5H int). The protons neighbouring the carbonyl groups could be assigned. **9**: δ=2.31 (d, *J*=17 Hz, 0.67H), 2.69 (d, *J*=17 Hz, 0.67H); **11**: δ=2.64 (s, 0.66H). The remaining protons showed a series of multiplets at δ=1.40–2.25 (16H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int). All resonances could be assigned: **9** δ=16.65 (t), 17.18 (t), 24.96 (t), 27.69 (t), 28.21 (t), 31.18 (t), 32.25 (t), 32.90 (t), 43.93 (s), 49.08 (s), 49.61 (t), 67.51 (s), 210.04 (s); **11**: δ=16.82 (t), 17.25 (t), 21.22 (t), 30.71 (t), 30.99 (t), 31.76 (t), 33.13 (t), 40.97 (s), 49.67 (s), 57.49 (t), 72.15 (s), 207.60 (s); MS (CI): *m/e*=225 (25) $[M+NH_3+NH_4]^+$, 208 (100) $[M+NH_4]^+$; $C_{13}H_{18}O$ requires C, 82.06; H, 9.54. Found: C, 81.80; H, 9.55.

4.1.3. *rac*-Trispiro[3.0.0.3.2.2]tridecane [*rac*-(4)]. To a solution of hydrazine hydrate (1.20 g, 24 mmol) and powdered potassium hydroxide (1.80 g, 32 mmol) in diethylene glycol (16 ml) was added under argon with stirring a 2:1-mixture of **9** and **11** (1.52 g, 8.0 mmol), causing an exothermic effect. The mixture was heated for 1 h to 160°C and 1 h to 190°C, until it was diluted with water (16 ml) and extracted with pentane (3×30 ml).The combined extracts were washed with water (30 ml), dried ($MgSO_4$), and concentrated on a rotary evaporator (bath temperature 20°C/15 Torr) yielding 910 mg (65%) of crude **4** as slightly yellowish liquid (purity 94% GC). An analytical pure sample was obtained by preparative gas chromatography [column A, 160°C; retention time (min): 2.9 (**4**)]. Colourless liquid. ^1H NMR (500 MHz, C_6D_6, C_6D_5H int): δ=1.46–1.52 (m, 2H), 1.63–1.70 (m, 2H), 1.70–1.78 (m, 4H), 1.80–1.93 (m, 8H), 2.09–2.17 (m, 2H), 2.20–2.28 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=16.75 (t), 25.48 (t), 31.77 (t), 31.96 (t), 32.43 (t), 49.33 (s), 52.41 (s); MS (CI): *m/e*=176 (<1) $[M]^+$, 161 (4) $[M-CH_3]^+$, 148 (17) $[M-C_2H_4]^+$, 147 (21) $[M-C_2H_5]^+$, 133 (30) $[M-C_3H_7]^+$, 120 (100) $[M-C_4H_8]^+$; $C_{13}H_{20}$ requires C, 88.56; H, 11.44. Found: C, 88.78; H, 11.68.

4.1.4. Reduction of 9 and 11 with lithium aluminium hydride: (5*R,10*S**)-trispiro[3.0.0.3.2.2]tridecane-10-ol [(5*R**,10*S**)-12], (5*R**,10*R**)-trispiro[3.0.0.3.2.2]tridecane-10-ol [(5*R**,10*R**)-13], (5*R**,11*S**)-trispiro-[3.0.0.3.2.2]tridecane-11-ol [(5*R**,11*S**)-15] and (5*R**,11*R**)-trispiro[3.0.0.3.2.2]tridecane-11-ol [(5*R**,11*R**)-16].** To a suspension of $LiAlH_4$ (152 mg, 4.0 mmol) in anhydrous ether (10 ml) was added within 5 min under argon with stirring a solution of a 2:1-mixture of **9** and **11** (380 mg, 2.0 mmol) in ether (3 ml). According to TLC [pentane/ether 7:3; R_f=0.73 (**9**, **11**), 0.45 (**16**), 0.33 (**12**, **13**, **15**)], and GC [column A, 230°C; retention times (min): 3.1 (**9**, **11**), 4.8 (**15**, **16**), 5.3 (**13**), 5.8 (**12**)], the reaction was complete after 30 min. Water (150 μl), 15% aqueous potassium hydroxide (150 μl), and water (450 μl) were added, the liquid was decanted, and the residue was extracted with ether (2×20 ml). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated (bath temperature 50°C/15 Torr) yielding 380 mg (99%) of a mixture of alcohols. According to capillary gas chromatography [column B, 150°C; retention times (min): 7.26 (**16**), 7.98 (**15**), 9.08 (**13**), 10.25 (**12**)], this mixture contained 39% **12**, 29% **13**, 19% **15** and 13% **16**. Chromatography on silica gel (0.05–0.20 mm) in pentane/ether (7:3, column 90×2.5 cm) yielded 45 mg (12%) of pure **16** as colourless solid, mp 65°C, and 300 mg (78%) of a mixture of **12**, **13** and **15** as an oil. Pure samples of **12**, **13** and **15** were obtained by praparative GC on column A. Colourless oils. The enantiomers of all alcohols could be resolved by capillary gas chromatography on a chiral phase [column C, 120°C, retention times (min) 21.50/22.03 (**16**), 22.06/22.79 (**15**), 24.68/25.68 (**13**), 28.21/28.84 (**12**)]. The assignment of **15** and **16** is arbitrary and may be interchanged. Spectral data: **12**: ^1H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.27 (dd, *J*=11.0, 9.0 Hz, 1H), 1.49–1.55 (m, 1H), 1.62–1.98 (m, 13H), 2.04–2.18 (m, 3H), 2.27 (dd, *J*=11.0, 7.5 Hz, 1H), 3.94 (dd, *J*=9.0, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=16.67 (t), 18.01 (t), 23.75 (t), 23.87 (t), 30.91 (t), 32.65 (t), 32.75 (t), 32.83 (t), 36.63 (t), 45.51 (s), 49.03 (s), 55.23 (s), 70.49 (d); MS (CI): *m/e*=402 (4) $[2M+NH_4]^+$, 210 (6) $[M+NH_4]^+$, 192 (5) $[M-H_2O+NH_4]^+$, 175 (100); $C_{13}H_{20}O$ requires C, 81.20; H, 10.48. Found: C, 81.08; H, 10.36. **13**: ^1H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.40–1.44 (m, 1H),

1.58–1.62 (m, 1H), 1.62 (dd, *J*=11.0, 8.0 Hz, 1H), 1.70–1.90 (m, 10H), 1.95 (dd, 11.0, 7.0 Hz, 1H), 1.98–2.24 (m, 4H), 2.44–2.50 (m, 1H), 3.76 (dd, *J*=8.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=16.57 (t), 17.04 (t), 21.88 (t), 26.17 (t), 29.24 (t), 30.99 (t), 31.08 (t), 32.93 (t), 37.00 (t), 45.05 (s), 48.92 (s), 54.35 (s), 70.16 (d); MS (CI): *m*/*e*=210 (9) $[M+NH_4]^+$, 192 (10) $[M-H_2O+NH_4]^+$, 175 (100); $C_{13}H_{20}O$ requires C, 81.20; H, 10.48. Found: C, 81.11; H, 10.20. **15**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.53 (dd, *J*=10.5, 8.5 Hz, 1H), 1.60–1.90 (m, 13H), 2.09–2.17 (m, 2H), 2.28 (dd, *J*=10.5, 7.5 Hz, 1H), 2.38–2.44 (m, 2H), 3.99 (dd, *J*=8.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=16.92 (t), 17.14 (t), 18.68 (t), 30.76 (t), 30.78 (t), 30.99 (t), 31.01 (t), 32.94 (t), 41.63 (s), 42.69 (t), 48.36 (s), 57.61 (s), 65.09 (d); MS (CI): *m*/*e*=210 (12) $[M+NH_4]^+$, 192 (8) $[M-H_2O+NH_4]^+$, 175 (100); $C_{13}H_{20}O$ requires C, 81.20; H, 10.48. Found: C, 80.97; H, 10.37. **16**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.49–1.55 (m, 1H), 1.60 (ddd, *J*=10.5, 8.0, 5.0 Hz, 1H), 1.67–1.97 (m, 12H), 2.01–2.06 (m, 1H), 2.29–2.35 (m, 2H), 2.39 (dd, *J*=10.5, 7.0 Hz, 1H), 2.51–2.58 (m, 1H), 3.84 (dd, *J*=8.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=17.93 (t), 18.59 (t), 24.09 (t), 31.74 (t), 32.01 (t), 32.50 (t), 33.77 (t), 34.13 (t), 42.92 (s), 43.43 (t), 49.66 (s), 57.26 (s), 73.04 (d); MS (CI): *m*/*e*=210 (9) $[M+NH_4]^+$, 192 (4) $[M-H_2O+NH_4]^+$, 175 (100); $C_{13}H_{20}O$ requires C, 81.20; H, 10.48. Found: C, 81.22; H, 10.25.

4.1.5. Reduction of 9 and 11 with bakers' yeast: (5*S*,10*S*)-(+)-trispiro[3.0.0.3.2.2]tridecane-10-ol [(5*S*,10*S*)-13]. To a stirred mixture of fresh bakers' yeast (60 g), sucrose (60 g) and water (600 ml), maintained at 35°C, was added a solution of a 2:1-mixture of **9** and **11** (3.80 g, 20 mmol) in ethanol (20 ml). The reaction progress was monitored by GC [column A, 230°C; retention times (min): 3.1 (**9**, **11**), 4.8 (**15**), 5.3 (**13**), 5.8 (**12**)], and, after 5 and 10 h, more yeast (60 g), sucrose (60 g) and water (300 ml) were added. After 24 h, the mixture was diluted with water (8 l) and continuously extracted with ether (1.5 l; control by GC). The extract was washed with saturated sodium carbonate (300 ml), dried ($MgSO_4$), and concentrated on a rotary evaporator (bath temperature 25°C/15 Torr). The residual liquid (4.0 g) was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether [7:3; column 80×5 cm, R_f=0.73 (**9**, **11**), 0.33 (**12**, **13**, **15**)] yielding 2.51 g (66%) ketones (purity 98% GC) and 1.11 g (29%) alcohols (purity 90% GC). According to capillary gas chromatography on a chiral phase [column C, 120°C; retention times (min) 22.29 (**15**), 24.80 (**13**), 29.21 (**12**)], the mixture of alcohols contained **12**, **13** and **15** in a ratio of 11:84:6, and all alcohols were enantiomerically pure (>99% ee). Analytically pure samples were obtained by preparative GC on column A. Their ^{1}H NMR spectra were identical with those of racemic samples. For the esterification with camphanic acid chloride the mixture was used as such, but for the preparation of (*M*)-**4**, a larger quantity of (5*S*,10*S*)-**13** ($[\alpha]_D^{20}$=+18.7°, *c*=1.424, acetone) was purified by GC.

4.1.6. (1*S*)-(+)-(4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo-[2.2.1]heptane-1-carboxylic acid (5′*S*,10′*S*)-trispiro-[3.0.0.3.2.2]tridecane-10-yl ester [(1*S*,5′*S*,10′*S*)-14]. To a stirred solution of (−)-(1*S*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid chloride [(−)-(1*S*)-camphanic acid chloride] (80 mg, 0.37 mmol) in pyridine (0.5 ml) was added at room temperature under argon a solution of a 11:84:6-mixture of **12**, **13** and **15** (65 mg, purity 90%, 0.31 mmol) in pyridine (0.5 ml). According to TLC [pentane/ether 7:3; R_f=0.50 (camphanic acid esters), 0.33 (**12**, **13**, **15**)], the reaction was complete after 2 h. The mixture was diluted with water (20 ml) and extracted with dichloromethane (2×10 ml). The combined organic layers were washed with 2N H_2SO_4 (10 ml), saturated sodium bicarbonate (10 ml), and dried ($MgSO_4$). The solvent was evaporated (bath temperature 35°C/15 Torr), and the residual solid (116 mg, mp 80–90°C) crystallized from ethanol (1.0 ml) by diffusion of water (0.5 ml) yielding 78 mg (65%) of pure (1*S*,5′*S*,10′*S*)-(+)-**14** as colourless crystals, mp 96–98°C ($[\alpha]_D^{20}$=+14.7°, *c*=0.873, acetone). IR (KBr): 1780, 1720 cm^{-1} (C=O); ^{1}H NMR (500 MHz, C_6D_6, C_6D_5H int): δ=0.76 (s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.21–1.31 (m, 2H), 1.32–1.38 (m, 1H), 1.54–1.60 (m, 1H), 1.72–2.10 (m, 14H), 2.12–2.18 (m, 1H), 2.24–2.37 (m, 2H), 2.42–2.50 (m, 1H), 4.94 (dd, *J*=6, 6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6, C_6D_6 int): δ=9.81 (q), 16.48 (t), 16.58 (q), 16.80 (t), 16.83 (q), 23.25 (t), 25.76 (t), 28.84 (t), 28.98 (t), 30.86 (t), 30.97 (t), 31.11 (t), 32.73 (t), 33.77 (t), 45.99 (s), 48.89 (s), 53.65 (s), 53.81 (s), 54.64 (s), 73.49 (d), 90.79 (s), 167.57 (s), 177.32 (s); MS (CI): *m*/*e*=372 (3, M^+), 120 (100); $C_{23}H_{32}O_4$ requires C, 74.16; H, 8.66. Found: C, 75.25; H, 8.60.

4.1.7. (5*S*)-(−)-Trispiro[3.0.0.3.2.2]tridecan-10-one [(5*S*)-9]. To a suspension of pyridinium chlorochromate (356 mg, 1.65 mmol) in dichloromethane (2 ml) was added under argon with stirring a solution of gas chromatographically purified (+)-(5*S*,10*S*)-**13** (212 mg, 1.10 mmol) in dichloromethane (1 ml) causing an exothermic effect and the separation of a black grease. The reaction progress was monitored by GC [column A, 200°C; retention times (min): 5.3 (**9**), 11.4 (**13**)] and after 1 h more pyridinium chlorochromate (151 mg, 0.70 mmol) was added. After 2 h the reaction was complete. After dilution with ether (20 ml), the supernatant liquid was decanted and the residual grease extracted with ether (2×5 ml). The combined organic phases were filtrated through a short path of silica gel (0.05–0.20 mm, column 5×2.5 cm), dried ($MgSO_4$) and concentrated (bath temperature 30°C/15 Torr) to yield 196 mg (94%) of crude (5*S*)-**9** (purity 94%). Chromatography on silica gel (0.05–0.20 mm) in pentane/ether [9:1; column 45×2.5 cm, R_f=0.42] yielded 90 mg (43%) of pure (5*S*)-**9** as colourless liquid (purity >99.5% GC; $[\alpha]_D^{20}$=−70.4°, *c*=1.09, acetone). The ^{1}H and ^{13}C NMR data were identical with those assigned to racemic **9** in admixture with racemic **11**.

4.1.8. (*M*)-(−)-Trispiro[3.0.0.3.2.2]tridecane [(*M*)-4]. To a solution of hydrazine hydrate (150 mg, 3.0 mmol) and powdered potassium hydroxide (224 mg, 4.0 mmol) in diethylene glycol (2 ml) was added under argon with stirring (5*S*)-**9** (90 mg, 0.47 mmol) and the mixture heated to 160°C. After 1 h, the mixture was diluted with water (20 ml) and extracted with pentane (3×15 ml). The extracts were washed with water (15 ml), dried ($MgSO_4$), and carefully concentrated using a 20 cm Vigreux column. Last traces of solvent were evaporized under reduced pressure (bath temperature 20°C/15 Torr) yielding 78 mg (94%) of

crude (*M*)-**4** (purity 93%). Preparative gas chromatography [column A, 140°C; retention time (min): 4.6] yielded 43 mg (52%) of pure (*M*)-**4** as colourless liquid (purity >99.5% GC; $[\alpha]_D^{20}=-63.3°$, $c=1.09$, $CHCl_3$). According to capillary gas chromatography on a chiral phase [column C, 70°C, retention time (min) 36.48] the material was enantiomerically pure. The ^1H and ^{13}C NMR data were identical with those of racemic **4**.

4.2. Crystal structure determination of (1*S*,5′*S*,10′*S*)-14

A suitable crystal was immersed into a drop of perfluorinated polyether oil and mounted to a Stoe–Huber–Siemens four-circle diffractometer on the tip of a glass fibre. Data were collected at =−140°C using graphite-monochromated Mo Kα radiation. A total of 12716 reflections were measured to a maximum 2Θ-value of 54.14° and 2271 independent reflections with no intensity cutoff were used in the structure determination. The structure was solved by direct methods using SHELXS.[25] All non-hydrogen atoms were refined anisotropically against all F^2 by full-matrix least-squares using SHELXL.[26] Final R and wR2 values were 0.0317/0.0331 and 0.0832/0.0842 ($I>2\sigma(I)$/all data), respectively. The largest difference peak and the deepest hole were 0.231 e/Å^3 and =−0.213 e/Å^3. Crystal data: $M=372.49$, monoclinic, $P2(1)$; $a=6.6835(10)$ Å, $b=11.7652(18)$ Å, $c=12.8673(19)$ Å, $\beta=95.248(7)°$; $V=1007.5(3)$ Å^3, $Z=2$, μ(Mo Kα)=0.082 mm^{-1}, $F_{000}=404$, $D_c=1.228$ g/cm^3, crystal dimensions: 0.4×0.2×0.2 mm^3.

References

1. Polyspiranes, Part 27. For Part 26 Fitjer, L.; Steeneck, C.; Gaini-Rahimi, S.; Schröder, U.; Justus, K.; Puder, P.; Dittmer, M.; Hassler, C.; Weiser, J.; Noltemeyer, M.; Teichert, M. *J. Am. Chem. Soc.* **1998**, *120*, 317–328.
2. Gange, D.; Magnus, P.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134–2135.
3. (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701–703. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421–9438.
4. Hormuth, S.; Schade, W.; Reißig, H.-U. *Liebigs Ann.* **1996**, 2001–2006.
5. de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem.* **1999**, *111*, 3682–3685, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3474–3477.
6. Fitjer, L.; Conia, J.-M. *Angew. Chem.* **1973**, *85*, 832–833, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 761–762.
7. de Meijere, A.; Khlebnikov, A. F.; Kozhushkov, S. I.; Kostikov, R. R.; Schreiner, P. R.; Wittkopp, A.; Rinderspacher, C.; Menzel, H.; Yufit, D. S.; Howard, J. A. K. *Chem. Eur. J.* **2002**, 828–842.
8. For approaches to helical primary structures of 1,2-spiro-annelated cyclopentane rings, see: (a) Kakiuchi, K.; Okada, H.; Kanehisa, N.; Kai, Y.; Kurosawa, H. *J. Org. Chem.* **1996**, *61*, 2972–2979. (b) Gaini-Rahimi, S.; Steeneck, C.; Meyer, I.; Fitjer, L.; Pauer, F.; Noltemeyer, M. *Tetrahedron* **1999**, *55*, 3905–3916.
9. Weiser, J.; Holthausen, M.; Fitjer, L. *J. Comput. Chem.* **1997**, *18*, 1264–1281.
10. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8556.
11. The single minimum structures of (*M*)-**1** and (*M*)-**3** were optimized using PC-Model, Version 4.0, Serena Software, P.O. Box 3076, Bloomington, IN 47402.
12. This finding corresponds to what is observed with aromatic [*n*]helicenes in going from [6]- to [7]helicene: Meuer, K. P.; Vögtle, F. *Top. Curr. Chem.* **1985**, *127*, 1–76.
13. Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron* **1994**, *50*, 10867–10878.
14. Bak, D. A.; Brady, W. T. J. *J. Org. Chem.* **1979**, *44*, 107–110.
15. Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, *15*, 991–1000.
16. (a) Todd, D. *Org. React.* **1948**, *4*, 378–422. (b) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488.
17. For a review on enzyme-catalyzed reductions of carbonyl groups, see: Gottwald, M. *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E 21d, pp 4143–4197.
18. For bakers' yeast reductions of cyclobutanones in bicyclic systems, see: (a) Newton, R. F.; Paton, J.; Reynolds, D. P.; Young, S.; Roberts, S. M. *J. Chem. Soc. Chem. Commun.* **1979**, 908–909. (b) Dawson, M. J.; Lawrence, G. C.; Lilley, G.; Todd, M.; Noble, D.; Green, S. M.; Roberts, S. M.; Wallace, T. W.; Newton, R. F.; Carter, M. C.; Hallet, P.; Paton, J.; Reynolds, D. P.; Young, S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2119–2125. (c) Lowe, G.; Swain, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 391–398. (d) Kertesz, D. J.; Kluge, A. F. *J. Org. Chem.* **1988**, *53*, 4962–4968.
19. (a) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587–1593. (b) Gerlach, H.; Müller, W. *Helv. Chim. Acta* **1972**, *55*, 2277–2286. (c) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755–760. (d) Gerlach, H. *Helv. Chim. Acta* **1978**, *61*, 2773–2776. (e) Gerlach, H. *Helv. Chim. Acta* **1985**, *68*, 1815–1821.
20. Crystallographic data (excluding structure factors) for compound (1*S*,5′*S*,10′*S*)-**14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 197711. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
21. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–130.
22. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
23. Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1978**, *43*, 4745–4750.
24. Wynberg, H.; Hekkert, G. L.; Houbiers, J. P. M.; Bosch, H. W. *J. Am. Chem. Soc.* **1965**, *87*, 2635–2639.
25. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
26. Sheldrick, G. M. *SHELXL97. Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.