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Asymmetric synthesis of half-cage alcohol compounds

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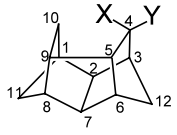
Abstract—To obtain enantiopure pentacyclic chlorinated and dechlorinated alcohols, we evaluated various synthetic routes. Enantiopure acetate (−)-**5** (ee >95%) was obtained from an enantioselective inversion of a stereogenic center of the pentacyclic acetate (+)-**4** in an acidic medium. Conversely, enantiopure alcohols (+)-**11** and (+)-**15** were obtained by the kinetic resolution of alcohol (±)-**11** by transesterification using lipase from *Candida rugosa*. It was verified that the lipase recognized alcohol (±)-**11**, producing the alcohol (+)-**11** (ee >98%) and acetate (−)-**13** (ee >99%) with a high degree of enantioselectivity (E >100) and a conversion of 50% after only 1 h.

1. Introduction

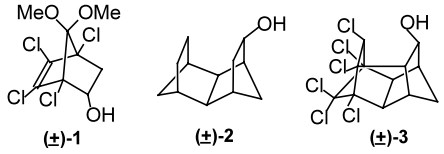
Polycyclic compounds represent a key research topic with numerous investigations in the literature into their theoretical[1] and experimental properties (e.g. carbocations,[2] mechanistic and other features of their reactions[3]). An interesting example of polycyclic compounds is provided by pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodecane derivatives, also known as '*half-cage*' compounds, which can have C-4 substituents on the 'inside' or 'outside'.



X=H; Y=OH or OAc

X=OH or OAc; Y=H

In recent years, our group has synthesised[4] and studied constrained polycyclic compounds by NMR spectroscopy.[5] The enantiomeric analysis of chiral polycyclic derivatives by NMR using a mixture of chiral and achiral shift reagents was reported,[6] as well as an approach to determine the optimal position of the lanthanide ion in complexes formed by shift reagents and compounds using the pseudocontact model.[7] A study of the mechanism of skeletal rearrangements in acid media on the basis of theoretical and experimental investigations was performed,[8] and the effects of constrained stereochemistry by X-ray diffraction were analysed.[9]



The resolution of racemic polycyclic compounds derivatives has been one of our recent focal points with the aim of obtaining enantiopure alcohols. Enzymatic kinetic resolution has been utilized with good enantioselectivities for bicyclic alcohol derivative (±)-**1**.[10] On the other hand, the attempted enantiomeric resolution of the tetracyclic alcohol, *endo*-tetracyclic [6.2.1.1^{3,6}.0^{2,7}]dodecan-4-ol (±)-**2**, using a chiral auxiliary afforded poor enantiomeric excesses.[11] More recently, we communicated the enzymatic resolution of a hindered secondary pentacyclic alcohol *endo*-(±)-1,8,9,10,11,11 - hexachloropentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodecan-4-ol, alcohol (±)-**3** using lipase from *Candida rugosa*.[12]

Herein, we describe an efficient synthesis of enantiopure chlorinated and dechlorinated *half-cage* alcohols. The enantiopure chlorinated alcohol (+)-**7** was obtained from the acetate (−)-**5**. The latter was formed by the enantioselective inversion of a stereogenic center of the acetate (+)-**4** in acidic medium. On the other hand, the enantiopure alcohols (+)-**11** and (+)-**15** were obtained via kinetic resolution of alcohol (±)-**11** by transesterification using lipase from *C. rugosa*. This resolution demonstrates the high degree of enantioselectivity of

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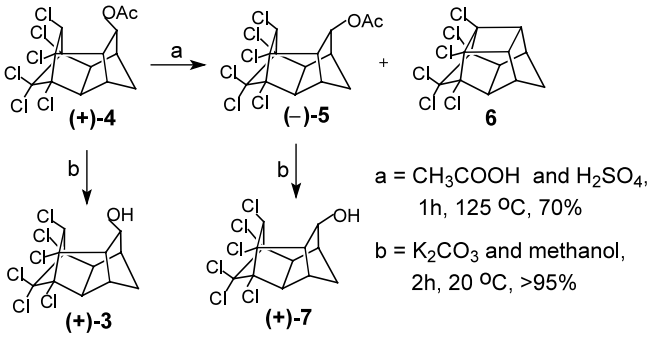
the enzyme with these substrates (E >100 with a conversion of 50% after only 1 h).

2. Results and discussion

The synthesis of the enantiopure chlorinated *half-cages* from the acetate (+)-**4** were performed as shown in Scheme 1. The enantiomerically pure acetate (+)-**4** was prepared by a previously reported method[12] and its treatment with acetic acid containing a catalytic amount of sulfuric acid produced the acetate (−)-**5** and the *birdcage* **6** in a 7:3 ratio, respectively. This inversion necessarily involves a cationic intermediate. However, in this process no change in the enantiomeric excess of the acetate (+)-**4** to acetate (−)-**5** was observed, due to the cationic intermediate, and the mechanism of inversion does not allow the rearrangement to the racemic form, as shown in a previous paper.[8a] As chlorinated compounds have high boiling points, the use of GC on chiral columns with cyclodextrin is impossible and the use of HPLC on chiral columns with cyclodextrin did not result in a satisfactory separation. Hence, we chose ^{1}H NMR as an analytical method, using chiral chemical shift reagents. A high resolution of the signals was achieved for the CH_3 signal of the acetate (±)-**5**, using tris[3 (heptafluoropropylhydroxymethylene)(+)camphorate]europium(III) ($Eu(hfc)_3$) in $CDCl_3$ solutions of this compound.[12] The analysis of these signals for the acetate (−)-**5** presented an ee >95%.



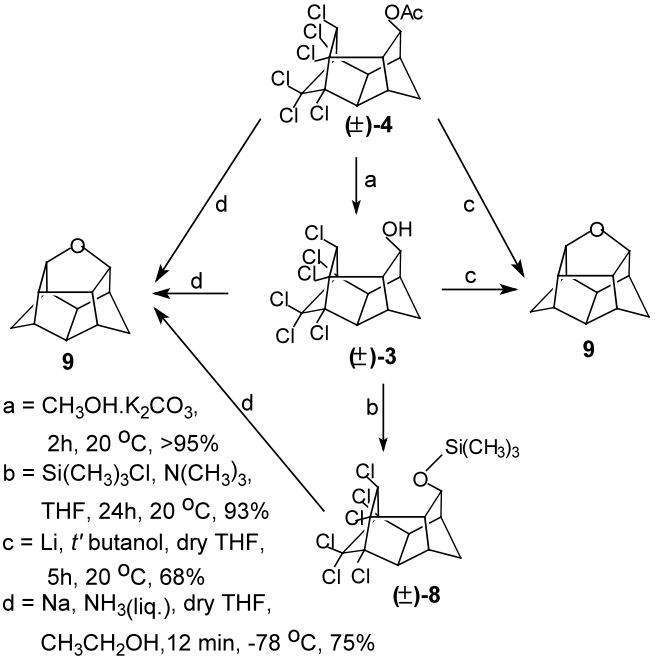
Scheme 1. Synthesis of the enantiopure chlorinated *half-cage* compounds from the acetate (+)-**4**.

The treatment of acetates (+)-**4** and (−)-**5** with saturated solution of K_2CO_3 in methanol affords the alcohols (+)-**3** and (+)-**7**, respectively. The reactions were complete within 2 h at room temperature (20°C) and yields are above 95%. Table 1 shows the specific rotation values of acetates (+)-**4** and (−)-**5** and alcohols (+)-**3** and (+)-**7** over four wavelengths.

To obtain enantiomerically pure dechlorinated *half-cage* compounds from acetate (+)-**4**, it was necessary to investigate two possible dechlorination reactions (Scheme 2). The first technique used consisted of combining the chlorinated *half-cage* with a dry THF solution containing Li and *t*-butanol in an ultrasound bath.[4a] The second technique involved combining a solution of the chlorinated *half-cage* and ethanol in dry THF with a sodium and liquid ammonia solution.[10a] The evaluation of these techniques was performed with a racemic chlorinated *half-cage* obtained by a previously reported method.[12]

Table 1. Specific rotation values of *half-cage* derivatives for a c = 1 g/100 mL in CH_2Cl_2 at 20°C

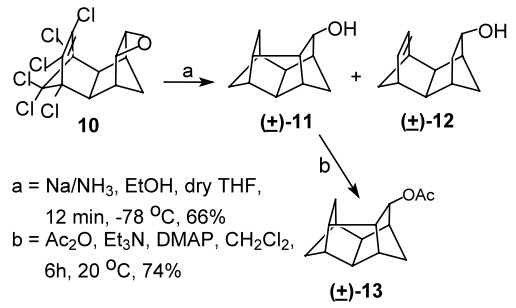
Compounds	Specific rotation at four wavelengths (λ)			
	589	578	546	436
Alcohol (+)-**3**	+1	+1	+2	+3
Acetate (+)-**4**	+1	+1	+1	+2
Acetate (−)-**5**	−6	−5	−4	−2
Alcohol (+)-**7**	+1	+1	+2	+4



Scheme 2. Dechlorination of *half-cage* acetate (±)-**4**, alcohol (±)-**3** and trimethylsilyl ether (±)-**8**.

The results of the two techniques show that the dechlorination of *half-cage* acetate (±)-**4** or alcohol (±)-**3** with substituents inside give the symmetric structure **9**, and the same behavior was observed for the reaction involving sodium and liquid ammonia, where the protecting group trimethylsilane[13] was added to the internal oxygen, affording the *half-cage* (±)-**8**. This result is a serious limitation for obtaining enantiomerically pure dechlorinated *half-cages* from acetate (+)-**4**, the symmetrization of the skeletal carbon may be related to the small distance between the internal oxygen and carbon 10.[9a]

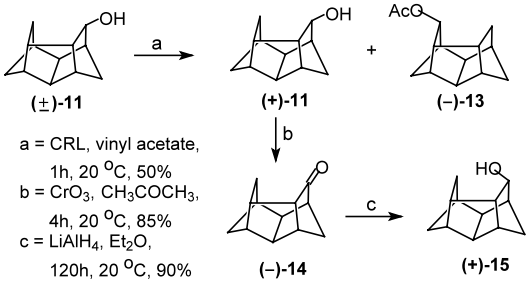
To establish parameters for GC analysis on chiral cyclodextrin columns, the racemic dechlorinated *half-cage* were obtained and are shown in Scheme 3. The chlorinated compound **10** was prepared by a previously reported method,[12] and its ethanolic solution in dry THF when treated with sodium and liquid ammonia



Scheme 3. Synthesis of the racemic dechlorinated *half-cages*.

gave a mixture of alcohols (±)-**11** and (±)-**12** in a respective ratio of 2:1. As the alcohols (±)-**11** and (±)-**12** cannot be completely separated by column chromatography, the purification of these compounds was performed by treatment of the mixture of alcohols (±)-**11** and (±)-**12** in a solution of ethyl ether with a saturated solution of $AgNO_3$. The alcohol (±)-**11** remains in the organic phase, while the complex formed between Ag^+ and alcohol (±)-**12** remains in the aqueous phase. After the addition of NH_4OH and heating the aqueous phase, the pure alcohol (±)-**12** was obtained. This methodology furnished better yields of alcohol (±)-**11** than the reported by Howe et al.[14] via dechlorination of its hexachloro-alcohol precursor (±)-**3**. The acetate (±)-**13** was obtained from alcohol (±)-**11** by treatment with acetic anhydride, triethylamine and DMAP.

The synthesis of the asymmetric dechlorinated *half-cages* is shown in Scheme 4. The first step consists of a kinetic resolution of the alcohol (±)-**11** by a transesterification reaction using lipase from *Candida rugosa* with excess vinyl acetate. After 1 h the conversion was 50%, and the enantiomeric purity of the products was determined by chiral gas chromatography (alcohol (+)-**11**: ee >98% and for the acetate (−)-**13**: ee >99%). A high degree of enantioselectivity of the enzyme (E >100)[15]



Scheme 4. Synthesis of the asymmetric dechlorinated *half-cages*.

for the dechlorinated alcohol (±)-**11** was observed. The comparison of these results with those previously reported[12] for chlorinated alcohols (±)-**3** and (±)-**7** suggests that the enantioselectivity of the lipase from *C. rugosa* for *half-cage* alcohols does not depend on the position (*exo* or *endo*) of the hydroxy group. Table 2 shows the compared data.

The treatment of alcohol (+)-**11** with chromium(VI) oxide at room temperature gave the ketone (−)-**14** in 85% yield. The reduction of ketone (−)-**14** with lithium aluminum hydride selectively afforded the alcohol (+)-**15** in 90% yield with an ee >98%, determined by chiral gas chromatography. Table 3 shows the specific rotation of the alcohols (+)-**11** and (+)-**15**, acetate (−)-**13** and ketone (+)-**14** over four wavelengths.

Table 3. Specific rotation values of *half-cages* derivatives for a $c=1$ g/100 mL in CH_2Cl_2 at 20°C

Compounds	Specific rotation at four wavelengths (λ)			
	589	578	546	436
Alcohol (+)-**11**	+4	+5	+6	+10
Acetate (−)-**13**	−1	−1	−2	−4
Ketone (−)-**14**	−87	−92	−110	−266
Alcohol (+)-**15**	+3	+3	+4	+7

3. Conclusion

Excellent results were obtained to access enantiopure pentacyclic compounds by transesterification reactions using lipase from *C. rugosa*. Starting from these enantiopure compounds, it was possible to prepare other chiral pentacyclic alcohols and acetates.

4. Experimental

Melting points were measured on an Electrothermal IA 9100 digital apparatus. NMR spectra were measured with a Varian VXR-200 spectrometer at a magnetic field of 4.7 T and a temperature of 22°C. Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard. Elemental analysis was recorded on a Perkin–Elmer 2400 CHN elemental analyzer apparatus. Products were analyzed by GC on a SHIMADZU GC-171 model equipped with FID, using a DB-1 column (15 m×0.53 mm (i.d.)×1.5 μm) for racemic compounds and, BETA-DEX™ 120 column (30 m× 0.22 mm (i.d.)×1.25 μm) for chiral compounds. Optical

Table 2. Comparison of kinetic resolutions employing lipase from *Candida rugosa* with excess vinyl acetate for *exo* and *endo half-cage* alcohols

Alcohols	Enantiomeric ratio (E)	Conversion (%)	Time of reaction (h)	ee of acetates
endo-alcohol (±)-**3**	>100	44	168	>95%
exo-alcohol (±)-**7**	-x-	No reaction	240	-x-
exo-alcohol (±)-**11**	>100	50	1	>99%

rotations were measured with a Perkin–Elmer polarimeter model 341 with a 1 cm cell at a temperature of 20°C. Lipase, type VII (from *C. rugosa*) was providing from Amano Enzime USA Co. Ltd.

4.1. *exo*-(−)-1,8,9,10,11,11-Hexachloropentacyclo-[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-yl acetate, (−)-5

Concentrated sulfuric acid (1 mL) was added to a solution of acetate (+)-**4** (1.0 g, 2.5 mmol) in acetic acid (10 mL) at a temperature of 125°C under magnetic stirring. After stirring for 1 h, the system was cooled down and neutralized with 10% aqueous $NaHCO_3$ solution. A precipitate formed and was separated. An additional extraction with chloroform was undertaken. The extract was combined with the precipitate. This solution was dried with $MgSO_4$, and after concentration of the filtrates, a mixture of two compounds was obtained as a white solid. These products were purified by chromatography on a silica gel column (hexane/ethyl acetate: 0–20%). The acetate (−)-**5** (70% yield) and compound **6** (30% yield) were obtained. Acetate, (−)-**5**: mp 193–194°C (lit.[16] 194–195°C); $[\alpha]_D^{20}$ −6.0 ($c=1$, CH_2Cl_2). FTIR (film, $CHCl_3$) ν (cm^{-1}) 1735 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51 (1H, d, $J=11.0$ Hz), 2.09 (3H, s), 2.33 (1H, d, $J=11.0$ Hz), 2.88–3.15 (5H, m), 5.50 (1H, s) and 5.80 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 (CH_3), 36.5 (CH_2), 41.6 (CH), 43.4 (CH), 55.6 (CH), 58.8 (CH), 60.0 (CH), 64.7 (CH), 74.0 (C), 76.4 (CH), 79.6 (C), 84.8 (C), 99.5 (C), 169.8 (CO). *Birdcage* **6**: mp 290°C (lit.[16] 287–289°C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.69 (1H, d, $J=11.5$ Hz), 1.90 (1H, d, $J=11.5$ Hz), 3.05–3.23 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.8 (CH_2), 43.4 (2CH), 54.4 (2CH), 58.4 (2CH), 78.2 (2C), 83.5 (2C), 97.5 (C).

4.2. *endo*- or *exo*-(+)-1,8,9,10,11,11-Hexachloropentacyclo-[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-ol (+)-3 and (+)-7

1.0 g (2.3 mmol) of acetate (+)-**4** or acetate (−)-**5** was dissolved in a mixture of tetrahydrofuran (20 mL) and CH_3OH (50 mL). A saturated solution of K_2CO_3 was added and the reaction was stirred at room temperature (20°C) for 2 h. The mixture was washed three times with $CHCl_3$ (20 mL) and the combined organic phases were dried with $MgSO_4$. After concentration of the solvent, alcohol (+)-**3** or alcohol (+)-**7** was obtained (yield >95%) as a white solid. Alcohol (+)-**3**: mp 258–260°C dec., $[\alpha]_D^{20}$ +1.0 ($c=1$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (1H, d, $J=10.8$ Hz), 1.62 (1H, d, $J=10.8$ Hz), 2.68 (1H, br s), 2.90–3.16 (3H, m), 3.26 (1H, dd, $J=5.9$ Hz, $J=3.9$ Hz), 4.23 (1H, d, $J=5.9$ Hz), 7.43 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.0 (CH_2), 42.9 (CH), 44.1 (CH), 56.0 (CH), 56.3 (CH), 58.5 (CH), 64.6 (CH), 72.7 (C), 79.8 (CH), 81.1 (C), 83.3 (C), 99.3 (C); Anal. calcd: C, 37.60; H, 2.61. Found: C, 37.58; H, 2.59. Alcohol (+)-**7**: mp 217°C (lit.[16] 218°C), $[\alpha]_D^{20}$ +1.0 ($c=1$, CH_2Cl_2). FTIR (KBr) ν (cm^{-1}) 3471 (C–OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (1H, d, $J=10.9$ Hz), 2.64 (1H, d, $J=10.9$ Hz), 2.72–2.79 (2H, m), 3.00–3.11 (3H, m), 5.02 (1H, s), 5.42 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.0 (CH_2), 41.2 (CH), 45.3 (CH), 55.6 (CH), 58.9 (CH), 62.3 (CH), 64.6 (CH), 73.7 (CH), 74.3 (C), 79.6 (C), 85.1 (C), 98.6 (C).

4.3. *endo*-(±)-1,8,9,10,11,11-Hexachloropentacyclo-[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-trimethylsilyloxy (±)-8

To a solution of alcohol (±)-**3** (1.0 g, 2.6 mmol) in THF (70 mL) under nitrogen were added 380 μL of pyridine and 230 μL of chlorotrimethylsilane. The solution was stirred at room temperature (20°C) for 24 h. The salt formed was filtered and the solvent was removed under vacuum and the *half-cage* (±)-**8** was obtained as a white solid (93% yield). Anal. calcd: C, 39.56; H, 3.95. Found: C, 38.89; H, 3.89%. FTIR (KBr) ν (cm^{-1}) 842 (Si-CH_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.20 (9H, s), 1.34 (1H, d, $J=9.8$ Hz), 1.60 (1H, d, $J=9.8$ Hz), 2.58 (1H, br s), 2.77–3.04 (3H, m), 3.19 (1H, dd, $J=6.4$ Hz, $J=4.1$ Hz), 4.00 (1H, d, $J=6.4$ Hz), 7.70 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.6 (CH_3), 37.9 (CH_2), 43.6 (CH), 45.2 (CH), 56.6 (CH), 57.1 (CH), 59.3 (CH), 64.8 (CH), 73.5 (C), 80.8 (CH), 81.9 (C), 82.0 (C), 99.2 (C).

4.4. Hexacyclo[.2.1.1^{3,6}.1^{4,10}.0^{2,7}.0^{5,9}]dodecan-4,10-*oxo* 9

Method A: Into a 250 mL flask equipped with reflux condenser and under an inert atmosphere was placed dry THF (88 mL). Small pieces (wire) of lithium (2.3 g, 0.33 mmol) were added along with *tert*-butyl alcohol (16 mL, 0.17 mol). The apparatus was then immersed into an ultrasound bath (45 KHz, 100 Watt) and a solution of hexachlorinated compound, or acetate (±)-**4** (13.6 mmol) of either alcohol (±)-**3** in dry THF (10 mL) was slowly added. The reaction was complete after 5 h and crushed ice was added under an inert atmosphere. The organic phase was extracted with ethyl ether and this solution was washed with water, dried over magnesium sulfate, filtered and the solvents were evaporated. Compound **9** (68% yield) was obtained as an oil.

Method B: A solution of the alcohol (±)-**3**, acetate (±)-**4** or trimethylsilyl ether (±)-**8** (13.1 mmol) in dry ethanol (2.2 mL, 37.5 mmol) and dry THF (25 mL) was added in small portions to a solution of sodium (4.0 g, 173.9 mmol) in ammonia (150 mL) at −78°C, and the reaction mixture was stirred for 12 min. Then, the mixture was treated with saturated aqueous ammonium chloride solution (25 mL). The ammonia was evaporated and the usual ethereal extraction sequence followed to produce the compound **9** (75% yield) as an oil. After slow crystallization in $CHCl_3$ a white solid was obtained. Mp 190–192°C (lit.[14] 191–193°C). Anal. calcd: C, 82.77; H, 8.04. Found: C, 82.49; H, 8.24%. FTIR (KBr) ν (cm^{-1}) 1093 (C–O–C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14–3.13 (12H, overlapping signals), 4.44 (2H, d, $J=9.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.7 (2CH_2), 38.2 (2CH), 43.0 (CH), 47.6 (2CH), 51.1 (2CH), 56.6 (CH), 86.4 (2CH).

4.5. (±)-*exo*-Pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-ol (±)-11

Into a 250 mL flask under inert atmosphere a solution of sodium (4.0 g, 173.9 mmol) in liquid ammonia (≅150 mL) was obtained. A solution of **10** (5.0 g, 13.1 mmol) and dry ethanol (2.2 mL, 37.5 mmol) in 25 mL of dry THF was slowly added. The reaction was stirred for 12 min. After, a saturated solution of NH_4OH (25 mL) was added. The system was opened and the ammonia was allowed to evaporate over 24 h. The organic phase was extracted with ethyl ether and this solution was washed with water, dried over magnesium sulfate, and after solvent evaporation of the filtrates, a white solid was obtained as a mixture of the alcohols (±)-**11** and (±)-**12**. Purification of these compounds was performed by treating the mixture of alcohols (±)-**11** and (±)-**12** in a solution of ethyl ether with a saturated solution of $AgNO_3$. The heterogeneous mixture was stirred, and after 4 h was separated. The complex formed between Ag^+ and alcohol (±)-**12** remained in the aqueous phase, whereas the alcohol (±)-**11** remained in the organic phase. After separation, the organic solvent was evaporated producing the alcohol (±)-**11** (66% yield) as a white solid. Mp 131°C (lit.[17] 130°C), FTIR (KBr) ν (cm^{-1}) 3425 (C–OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (1H, dd, J=6.0 Hz, J=2.6 Hz), 1.28 (1H, d, J=3.6 Hz), 1.53 (1H, d, J=10.2 Hz), 1.58–1.75 (2H, m), 1.94–2.43 (9H, overlapping signals), 4.58 (1H, d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.9 (CH_2), 38.5 (CH), 39.5 (CH_2), 39.6 (CH), 42.8 (CH), 45.4 (CH_2), 46.0 (2CH), 46.5 (CH), 49.9 (CH), 54.7 (CH), 74.6 (CH). The aqueous phase was treated with a 30% NH_4OH solution and heated for 30 min. After extraction with ethyl ether the alcohol (±)-**12** (33% yield) was obtained as a white solid. Mp 103°C (lit.[18] 102.5–103.5°C); FTIR (KBr) ν (cm^{-1}) 3425 (C–OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08–2.67 (12H, overlapping signals) 3.69 (1H, d, J=6.1 Hz), 5.92 (1H, dd, J=5.2 Hz, J=3.0 Hz), 5.97 (1H, dd, J=5.2 Hz, J=3.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.3 (CH_2), 39.6 (CH), 44.3 (CH_2), 44.9 (CH), 45.1 (CH), 46.5 (CH), 47.1 (CH), 48.8 (CH), 59.4 (CH_2), 71.6 (CH), 132.6 (CH), 133.3 (CH).

4.6. (+)-*exo*-Pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-ol (+)-11; and (−)-*exo*-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodecan-4-yl (−)-13

Lipase (50% w/w of substrate) was added to a solution of pentacyclic alcohol (±)-**11** (0.18 g, 10.23 mmol) in vinyl acetate (10 mL) and the suspension was stirred at 25°C. The appropriate degree of conversion (50%) was achieved in 1 h. Thereafter, the enzyme was filtered and the excess vinyl acetate was evaporated. The products were separated by flash column chromatography (hexane/ethyl ether, 4:1), giving the alcohol (+)-**11** and acetate (−)-**13**. Alcohol (+)-**11**: mp 130°C (lit.[17] 130°C), $[\alpha]_D^{20}$ +4.0 (c=1, CH_2Cl_2). FTIR (KBr) ν (cm^{-1}) 3425 (C–OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (1H, dd, J=6.0 Hz, J=2.6 Hz), 1.28 (1H, d, J=3.6 Hz), 1.53 (1H, d, J=10.2 Hz), 1.58–1.75 (2H, m), 1.94–2.43 (9H, overlapping signals), 4.58 (1H, d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.9 (CH_2), 38.5 (CH), 39.5 (CH_2), 39.6 (CH), 42.8 (CH), 45.4 (CH_2), 46.0 (2CH), 46.5 (CH), 49.9 (CH), 54.7 (CH), 74.6 (CH). Acetate (−)-**13**: $[\alpha]_D^{20}$ −1.0 (c=1, CH_2Cl_2). Anal. calcd: C, 77.08; H, 8.25. Found: C, 76.35; H, 8.23%. FTIR (KBr) ν (cm^{-1}) 1724 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (1H, dd, J=9.9 Hz, J=4.5 Hz), 1.34 (1H, d, J=9.9 Hz), 1.54 (1H, d, J=9.9 Hz), 1.58–1.65 (2H, m), 2.00 (3H, s), 2.05–2.38 (9H, overlapping signals), 5.48 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2 (CH_3), 35.8 (CH_2), 38.5 (CH), 39.5 (CH), 40.3 (CH_2), 43.1 (CH), 44.1 (CH), 45.3 (CH_2), 45.8 (CH), 45.9 (CH), 47.3 (CH), 54.7 (CH), 78.8 (CH), 171.4 (CO).

4.7. (−)-Pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-one (−)-14

Alcohol (+)-**11** (0.50 g, 2.9 mmol) was dissolved in dry methylene chloride (60 mL) under stirring. To this solution were added small portions of pyridinium chlorochromate (PCC, 1.2 g, 5.6 mmol) at 0°C. The suspension was stirred at room temperature for 4 h. Ethyl ether (30 mL) was added and a black precipitate formed, which was filtered off with a small column fitted with silica gel and eluted with ethyl ether. The organic solvent was evaporated producing the pure ketone (−)-**14** (85% yield), mp 165°C (lit.[19] 165–167°C), $[\alpha]_D^{20}$ −87.0 (c=1, CH_2Cl_2). FTIR (KBr) ν (cm^{-1}) 1731 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23–2.85 (14H, overlapping signals); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.4 (CH_2), 37.9 (CH_2), 38.3 (CH), 39.4 (CH), 41.8 (CH), 43.8 (CH_2), 44.9 (CH), 47.3 (CH), 51.2 (CH), 53.9 (CH), 54.5 (CH), 217.9 (CO).

4.8. (+)-*endo*-Pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodecan-4-ol (+)-15

Ketone (−)-**14** (0.70 g, 4.0 mmol) was dissolved in ethyl ether (50 mL). To this solution was added $LiAlH_4$ (0.038 g, 1.0 mmol), and the reaction was stirred for 5 days at room temperature. Afterwards, a solution of 15% HCl (15 mL) was added. The mixture was neutralized with a 10% $NaHCO_3$ solution and extracted with ethyl ether. Evaporation of the solvent produced the corresponding alcohol (+)-**15**, 90% yield. Mp 196°C (lit.[19] 197–198°C), $[\alpha]_D^{20}$ +3.0 (c=1, CH_2Cl_2). FTIR (KBr) ν (cm^{-1}) 3322 (C–OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (1H, dd, J=11.7 Hz, J=7.0 Hz), 1.38 (1H, d, J=9.3 Hz), 1.68 (1H, d, J=9.3 Hz), 2.00–2.36 (10H, overlapping signals), 3.55 (1H, dm, J=12.2 Hz), 4.03 (1H, d, J=6.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.9 (CH_2), 37.9 (CH), 40.3 (CH), 40.8 (CH_2), 41.5 (CH), 44.3 (CH), 44.8 (CH), 45.2 (CH), 46.1 (CH_2), 47.5 (CH), 55.9 (CH), 81.8 (CH).

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References

1. (a) Brown, F. K.; Houk, K. N.; Burnell, D. J.; Valenta, Z. *J. Org. Chem.* **1987**, *52*, 3050; (b) McGrath, M. P.; Radom, L. J. *J. Am. Chem. Soc.* **1993**, *115*, 3320.
2. (a) Prakasch, G. K. S.; Bentley, T. W.; Kirmse, W.; Llewellyn, G.; Söllenböhmer, F. *J. Org. Chem.* **1990**, *55*, 1536; (b) Adcock, W.; Head, N. J.; Lokan, N. R.; Trout, N. A. *J. Org. Chem.* **1997**, *62*, 6177.
3. (a) Lukach, A. E.; Santiago, A. N.; Rossi, R. A. *J. Phys. Org. Chem.* **1994**, *7*, 610; (b) Takeuchi, K. *J. Phys. Org. Chem.* **1997**, *10*, 717.
4. (a) Costa, V. E. U.; Mollmann, M. E. S.; Riatto, V. B. *Synth. Commun.* **1995**, *25*, 2091; (b) Morrisso, F. D. P.; Wagner, K.; Hörner, M.; Burrow, R. A.; Bortoluzzi, A. J.; Costa, V. E. U. *Synthesis* **2000**, *9*, 1247.
5. (a) Seidl, P. R.; Leal, K. Z.; Costa, V. E. U.; Mollmann, M. E. S. *Magn. Reson. Chem.* **1993**, *31*, 241; (b) Seidl, P. R.; Leal, K. Z.; Costa, V. E. U.; Poli, N. D. *Magn. Reson. Chem.* **1990**, *28*, 869; (c) Seidl, P. R.; Leal, K. Z.; Costa, V. E. U.; Mollmann, M. E. S. *Magn. Reson. Chem.* **1998**, *36*, 261; (d) Costa, V. E. U.; Alifantes, J; Axt, M.; Mollmann, M. E. S.; Seidl, P. R. *J. Braz. Chem. Soc.* **1999**, *10*, 341.
6. (a) Costa, V. E. U.; Axt, M. *Magn. Reson. Chem.* **1996**, *34*, 929; (b) Axt, M.; Alifantes, J.; Costa, V. E. U. *J. Chem. Soc., Perkin Trans. 2* **1999**, *12*, 2783.
7. Gonçalves, P. F. B.; Axt, M.; Costa, V. E. U.; Livotto, P. R. *Comput. Chem.* **1998**, *22*, 399.
8. (a) Alifantes, J.; Lapis, A. A. M.; Martins, J. E. D.; Costa, V. E. U. *J. Chem. Soc., Perkin Trans. 2* **2001**, *1*, 7; (b) Carneiro, J. W. M.; Costa, V. E. U.; Alifantes, J.; Taft, C. A.; de Paula e Silva, C. H. T.; Tostes, J. G. R.; Seild, P. S.; Pinto, P. S.; da, S. *Chem. Phys. Lett.* **2001**, *345*, 189.
9. (a) Costa, V. E. U.; Alifantes, J.; Mascaranhas, Y. P.; Silva, C. H. T.; de, P.; Seidl, P. R. *J. Mol. Struct.* **2000**, *519*, 37; (b) Alifantes, J.; Costa, V. E. U.; Hörner, M.; Bortoluzzi, A. J. *Spectrosc. Lett.* **2001**, *34*, 345.
10. (a) Lapis, A. A. M.; Kreutz, O. C.; Pohlmann, A. R.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2001**, *12*, 557; (b) Berger, B.; Rabiller, C. G.; Konigsberger, K.; Faber, K.; Gringl, H. *Tetrahedron: Asymmetry* **1990**, *1*, 541.
11. Robbins, T. A.; Toan, V. V.; Givens, J. W.; Lightner, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10799.
12. Costa, V. E. U.; Alifantes, J.; Martins, J. E. D. *Tetrahedron: Asymmetry* **1998**, *9*, 2579.
13. Bruynes, C. A.; Jurriens, T. K. *J. Org. Chem.* **1982**, *47*, 3966.
14. Howe, R. K.; Carter, P.; Winstein, S. *J. Org. Chem.* **1971**, *36*, 1316.
15. Chen, C. S.; Fujimoto, Y.; Gidaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
16. Bird, C. W.; Cookson, R. C.; Crundwell, E. *J. Chem. Soc.* **1961**, 4809.
17. Soloway, S. B.; Damiana, A. M.; Sims, J. W.; Bluestone, H.; Lidov, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 5377.
18. Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 3162.
19. Winstein, S.; Carter, P.; Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1965**, *87*, 5247.