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TETRAHEDRON: *ASYMMETRY*

Study of the kinetic resolution of (±)-10-*exo*-hydroxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-one by lipase catalysis and the intramolecular racemization of the pure enantiomer by thermal dyotropic reaction

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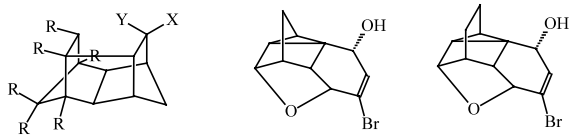
Abstract—In this work, the modified synthesis of (±)-10-*exo*-hydroxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-one (±)-**10** as well as its resolution by lipase-catalyzed transesterification with vinyl acetate is described. A thermal racemization process of (+)-**10** to (±)-**10** was observed. A mechanism involving racemization of (+)-**10** through dyotropic intramolecular hydrogen migration is proposed and supported by computational analysis.

1. Introduction

The investigation of polycyclic compounds with rigid conformations has contributed to the understanding of several aspects of their chemistry. Derivatives of the pesticides isodrin and endrin[1] have been utilised as models for several studies, including the formation of non-classical ions,[2] and the investigation of geometric parameters.[3] In particular, these compounds have contributed to the development of many aspects of NMR spectroscopy in relation to steric effects.[4]

In recent years our group has synthesized[5] and studied constrained polycyclic compounds by NMR spectroscopy,[6] X-ray diffraction,[7] and theoretical analysis.[8] Efficient methodologies for enantiomeric excess analysis by ^{1}H NMR spectroscopy using chiral and achiral chemical shift reagents were also reported.[6b,c] Enzymatic resolution of polycyclic derivatives by lipase-catalyzed transesterification has been one of our recent focal points with good results for *endo*-(±)-1,8,9,10,11,11-hexachloropentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-ol (±)-**1**[9] and *exo*-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-ol (±)-2[10] using the lipase from *Candida rugosa*. The compounds 5-bromo-12-oxa-pentacyclo[6.2.1.1^{6,9}.0^{2,7}.0^{5,9}]dodeca-4-ol (±)-**3** and 5-bromo-13-oxa-pentacyclo[6.2.2.1^{6,9}.0^{2,7}.0^{2,10}]trideca-4-ene-3-*endo*-ol (±)-**4**[11] were also resolved using *Pseudomonas cepacia*.



(±)-**1** R= Cl, X= H, Y= OH (±)-**3** (±)-**4**

(±)-**2** R= Y= H, X= OH

Herein, we describe the modified synthesis of (±)-10-*exo*-hydroxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-one (±)-**10** and its kinetic resolution by lipase-catalyzed transesterification using the lipase from *Candida rugosa*. This resolution enables a high degree of enantioselectivity of the enzyme (E >100) with a conversion of 46%. A thermal racemization process of (+)-**10** to (±)-**10** by dyotropic intramolecular hydrogen migration was observed.

2. Results and discussion

The synthesis of (±)-**10** was performed following the modified Woodward method[12] (Scheme 1). The *isodrin*

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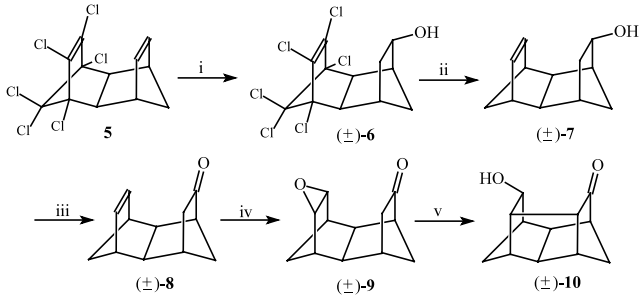
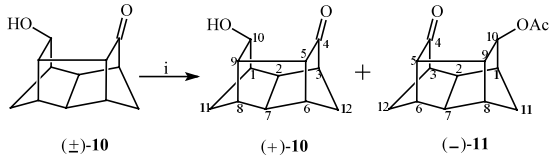
5 is completely converted into the chlorinated alcohol (±)-**6** by a hydroboration–oxidation process. Applying the experimental conditions previously reported[5a] for dechlorination, compound (±)-**6** was treated with lithium and *tert*-butyl alcohol in an ultrasound bath to provide the dechlorinated alcohol (±)-**7**. Oxidation of (±)-**7** with pyridinium chlorochromate[13] (PCC) gave the tetracyclododecanone (±)-**8** and epoxide (±)-**9** was obtained by treatment of (±)-**8** with 3-chloroperoxybenzoic acid in the presence of potassium fluoride.[14] Finally, the pentacycle (±)-**10** was obtained upon treatment of (±)-**9** with potassium *tert*-butoxide.[12]



Scheme 1. Synthesis of (±)-**10** from isodrin **5**. *Reagents and conditions*: (i) $NaBH_4$, $BF_3{\cdot}OEt_2$, NaOH, H_2O_2, rt; (ii) Li, *t*-BuOH,))); (iii) PCC, CH_2Cl_2, rt; (iv) *m*-CPBA, KF, CH_2Cl_2, rt; (v) *t*-BuOK, THF, rt.

In order to obtain the pentacyclic compound **10** in enantiopure form, the racemic mixture (±)-**10** was transesterified with vinyl acetate catalyzed by lipase from *Candida rugosa*,[9] affording the acetylated compound (−)-**11** and the unreacted hydroxyketone (+)-**10** (Scheme 2).



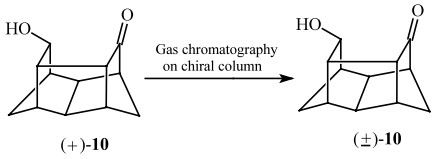
Scheme 2. Transesterification reaction of (±)-**10** with vinyl acetate catalyzed by lipase from *Candida rugosa*. The results establish only the relative configurations of the enantiomerically pure compounds. *Reagents and conditions*: (i) vinyl acetate, *CrL*, 7 h, rt, 46% of conversion.

The reaction mixture was analyzed by gas chromatography (GC) on a chiral column. This technique presented a good separation for the enantiomeric signals of (±)-**10**. However, the racemic (±)-**11** did not provide the same result even when we attempted separations using different columns. Due to the difficulties in achieving a good method for the separation of the enantiomeric signals of (±)-**11** by GC analysis, the enantiomeric excess of (−)-**11** was determined by ^{1}H NMR spectroscopy in the presence of the chiral chemical shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)[9] (Eu(hfc)$_3$), which induced a high resolution of the signals for the enantiomeric C(10)H protons (α-OAc) of (±)-**11**. This analysis showed (−)-**11** to have an enantiomeric excess of up to 95%.

Using Eq. (1), proposed by Sih et al.,[15] the enantiomeric ratio *E* was calculated for a 46% conversion (*E* >100) showing the high degree of enantioselectivity of the enzyme.

$$\mathbf{E}=\frac{\ln[1-c(1+\mathrm{eep})]}{\ln[1-c(1-\mathrm{eep})]} \quad (1)$$

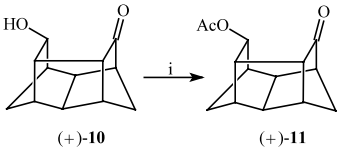
In this way, the remaining hydroxyketone (+)-**10** should be obtained with high enantiomeric excess. However, the analysis of (+)-**10** by GC on a chiral column showed the two enantiomeric signals in the proportion of 1:1, corresponding to the racemate (±)-**10** (Scheme 3).



Scheme 3. Racemization of (+)-**10** during analysis by gas chromatography on a chiral column.

This result was somewhat surprising and we therefore decided to repeat the enantiomeric excess analysis of (+)-**10** using ^{1}H NMR spectroscopy.

The ^{1}H NMR analysis of (+)-**10** using a chiral chemical shift reagent did not lead to satisfactory resolution of signals for the racemic hydroxyketone (±)-**10**. In order to determine the enantiomeric excess of (+)-**10**, its acetylated derivative was prepared by reaction of (+)-**10** with acetic anhydride (Scheme 4) and then the acetylated compound (+)-**11** was analyzed by ^{1}H NMR under the same conditions employed for (−)-**11**.



Scheme 4. Synthesis of the acetylated compound (+)-**11**. *Reagents and conditions*: (i) acetic anhydride, Et_3N, DMAP, CH_2Cl_2, rt, 24 h.

The analysis showed an enantiomeric excess of 85% for the derivative (+)-**11** and, this value was also attributed for the enantiomeric excess of (+)-**10** (Table 1).

The result of the analysis of (+)-**10** by GC on a chiral column (Scheme 3) could be explained by an intramolecular rearrangement producing the racemate. This data suggests that the high temperature used in GC analysis can promote this rearrangement. In order to confirm this observation, we decided to reproduce the GC conditions by heating the compound (+)-**10** in a

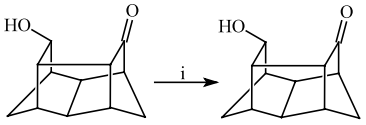
Table 1. Results of the transesterification reaction of (±)-**10** catalyzed by lipase from *Candida rugosa*

Compounds	$[\alpha]_D^{20}$ [a]	ee[b] (%)
(−)-**11**	−31.0	>95
(+)-**10**	+34.0	85[c]
(+)-**11**	+26.0	85

[a] Specific rotation (*c* 1, ethyl acetate).
[b] Enantiomeric excess (in %) obtained by ^{1}H NMR using chiral chemical shift reagent.
[c] Obtained from (+)-**11**.

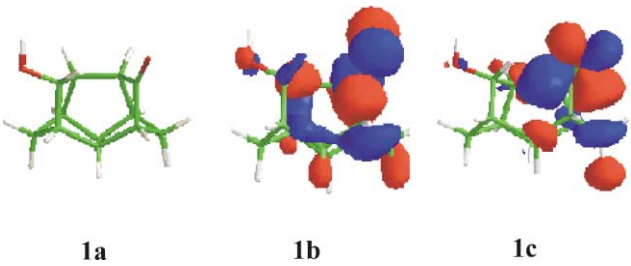
glass ampoule at 215°C. After 1 h of heating, we observed complete racemization of (+)-**10** (Scheme 5). In order to determine the pathway involved in this racemization process we proposed a computational analysis of the alcohol (+)-**10**. The optimized geometry was obtained by a 6-31G* ab initio method using the Spartan Program.[18] Molecular geometry converged rapidly due to the high rigidity of the carbon skeleton and the best conformation of the alcohol (+)-**10** was obtained from rotational analysis through the C(10)–O bond (Fig. 1(a)). The results showed that the highest occupied molecular orbital (HOMO) of H(10) (Fig. 1(b)) has similar symmetry with the lowest unoccupied molecular orbital (LUMO) of C(4) (Fig. 1(c)). Thus, we propose that the short distance (2.22 Å) between the non-bonded H(10) and C(4) can induce an intramolecular HOMO–LUMO interaction which promotes the transfer of hydrogen between the non-bonded C(10) and C(4) atoms (Scheme 6). The large distance (4.38 Å) between the non-bonded hydroxyl hydrogen and carbonyl oxygen suggests that this transfer occurs by an intermolecular process.

These data and a compressed molecular topography of these hydroxyketone enantiomers provide the conditions for a type of uncatalyzed thermal dyotropic intramolecular hydrogen migration to occur through a symmetry-allowed concerted suprafacial dyotropic reaction. The same rearrangement was observed in *syn*-sesquinorbornene derivatives (Scheme 7) which have been very well described by Mackenzie et al.[16] and Paquette et al.[17]



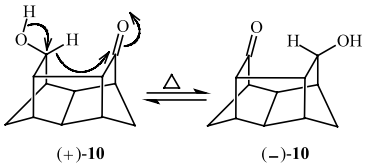
(+)-**10** (±)-**10**

Scheme 5. Racemization of (+)-**10** performed in a glass ampoule inside an oven at 215°C. *Conditions*: (i) 215°C, 1 h.



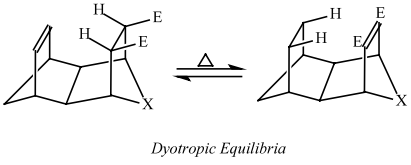
1a **1b** **1c**

Figure 1. Representative HOMO and LUMO surfaces of (+)-**10** calculated using the PC-Spartan ab initio program: (a) (+)-**10**; (b) (+)-**10** HOMO surface, (c) (+)-**10** LUMO surface.



(+)-**10** (−)-**10**

Scheme 6. Mechanistic proposal for the thermal racemization of (+)-**10** through intramolecular rearrangement.



Dyotropic Equilibria

X= CH_2, E = H or SO_2Ph
X= O, E = CO_2Me

Scheme 7. Intramolecular thermal (4σ+2π) dyotropy in *syn*-sesquinorbornene derivatives.

This dyotropic rearrangement certainly explains the thermal racemization of the hydroxyketone (+)-**10**.

3. Conclusions

The resolution of (±)-**10** by lipase-catalysed transesterification provided the hydroxyketone (+)-**10** with an enantiomeric excess of 85% and the ester (−)-**11** with an enantiomeric excess of up to 95% at 46% conversion showing the high degree of enantioselectivity of the lipase from *Candida rugosa* for this pentacyclic system. Thermal racemization of (+)-**10** was observed when it was submitted to gas chromatographic analysis on a chiral column. This process was confirmed by heating (+)-**10** at 215°C. Racemization of the enantiomers of **10** involves an intramolecular thermal dyotropic suprafacial hydrogen migration.

4. Experimental

Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. NMR spectra were measured with a VARIAN VXR200 (B_0=4.7 T) and YH-300 (B_0=7.05 T). Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and the J values are given in Hz. The products were analyzed by GC on a Shimadzu GC-17A Gas Chromatograph, equipped with a FID detector. GC parameters for achiral analysis: injector 230°C; detector 300°C; oven 80°C for 5 min then 20°C/min until 300°C; column pressure 20 kPa; column flow 14.4 mL/min;

linear velocity 113.1 cm/s; total flow 358 mL/min; split ratio 1:20; column DB1 15 m×0.53 mm (internal diameter). GC parameters for chiral analysis: injector 250°C; detector 300°C; oven 170°C for 15 min then 1°C/min until 200°C; column pressure 100 kPa; column flow 2.4 mL/min; linear velocity 61.5 cm/s; total flow 33 mL/min; split ratio 1:10; column β-cyclodextrin 30 m×0.25 mm (internal diameter). Optical rotations were measured in a Perkin–Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20°C. High resolution mass spectrometric analysis was obtained with a VG Autoespec mass spectrometer. Lipase AY Amano 30 (*Candida rugosa*), Lot. LAYY0450102S was kindly provided by Amano Enzyme USA Co. Ltd.

4.1. (±)-1,8,9,10,11,11-Hexachloro-*endo*,*endo*-tetracyclo-[6.2.1.1^{3,6}.0^{2,7}]dodeca-9-ene-4-*exo*-ol, (±)-6

To a stirred solution of 10 g of isodrin **5** (1 mmol) in dry THF (150 ml) were added 2.7 g (7.1 mmol) of sodium borohydride under a N_2 atmosphere and then, a solution of boron trifluoride diethyl ether (10 mL) in THF (50 mL) was added dropwise for 10 min. The mixture was stirred at rt for 4 h and then a small amount of crushed ice was added carefully to destroy the sodium borohydride excess. After the gas evolution has stopped, 4 g of NaOH (0.1 mmol) and H_2O_2 (30 mL) were added to the mixture. The mixture was stirred at rt for a further 20 h. A solution of potassium permanganate was added dropwise to destroy the excess of hydrogen peroxide and then the organic layer was decanted, leaving behind a brown sludge. The mixture was filtered in a Buchner funnel and the solvent was evaporated affording (±)-**6** (9.4 g, 90%) as a white solid, mp 221°C, (lit.[19] 222–223°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.9 (d, 1H, H α-OH, $J=6.16$ Hz). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 36.3 (CH_2), 37.8 (CH), 40.4 (CH_2), 46.6 (CH), 52.5 (CH), 53.4 (CH), 68.0 (CH), 78.0 (C), 79.5 (C), 109.0 (C), 131.5 (C), 132.3 (C). FTIR ($CHCl_3$): ν (cm^{-1}): 3341 (OH).

4.2. (±)-*endo*,*endo*-Tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-9-ene-4-*exo*-ol, (±)-7

Into a 500 mL flask equipped with reflux condenser and under an N_2 atmosphere were placed THF (150 mL), and small pieces (wire) of lithium (7 g; 1-atoms) and *tert*-butyl alcohol (30 mL; 0.3 mol) were added. The apparatus was then immersed into an ultra-sound bath (45 kHz, 100 watt). The system was turned on, and a solution of (±)-**6** (13 g, 34 mmol) in THF (60 mL) was added over 20 min. The ultra-sound apparatus was turned off after 5 h and the temperature of the bath oscillated between 30–50°C. A small amount of crushed ice was added under a N_2 atmosphere carefully to destroy the remaining lithium. The aqueous layer was extracted with ethyl ether (3×50 mL) and the ethereal extracts were washed with water (50 ml), dried over magnesium sulfate, filtered and the solvents were evaporated. The resulting semi-solid material was purified by flash chromatography over silica gel using first 5:1 cyclohexane/ethyl acetate and then dichloromethane to afford (±)-**7** as a white solid (5 g, 83%). Mp 103–104°C (lit.[12] 102.5–103.5). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.7 (d, 1H, H α-OH, $J=6.34$ Hz), 5.94 (d-d, H_{10}, $J_{10\text{-}9}=5.60$ Hz), 6.00 (d-d, H_9, $J_{9\text{-}10}=3.17$ Hz). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 37.1 (CH_2), 38.9 (CH_2), 43.5 (CH_2), 44.1 (CH), 44.3 (CH), 45.8 (CH), 46.4 (CH), 48.0 (CH), 58.7 (CH_2), 70.7 (CH), 131.1 (CH), 131.8 (CH). FTIR ($CHCl_3$): ν (cm^{-1}): 3286 (OH).

4.3. (±)-*endo*,*endo*-Tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-9-ene-4-one, (±)-8

To a stirred suspension of pyridinium chlorochromate (12 g, 55 mmol) in CH_2Cl_2 (250 mL) at rt was added a solution of (±)-**7** (6 g, 34 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 30 min and then cyclohexane (20 mL) was added, and the organic layer was decanted, leaving behind a brown sludge. The combined extracts were filtered through a short silica gel column using dichloromethane and evaporated affording (±)-**8** as a yellow oil. Further purification was necessary through flash chromatography on silica gel using 10:1 cyclohexane/ethyl acetate affording pure (±)-**8** (3.9 g, 67%) mp 128–130°C (lit.[12] 128–130°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.71 (d-d, H(10), $J_{10\text{-}9}=5.60$ Hz, $J_{10\text{-}8}=3.40$ Hz), 6.09 (d-d, H(9), $J_{9\text{-}10}=$ 5.60 Hz, $J_{9\text{-}8}=2.90$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 37.7 (CH), 43.3 (CH), 43.4 (CH_2), 43.6 (CH_2), 44.4 (CH), 46.7 (CH), 49.0 (CH), 53.9 (CH), 57.1 (CH_2), 134.0 (CH), 136.2 (CH), 217.5 (C). FTIR ($CHCl_3$): ν (cm^{-1}): 1737 (C=O).

4.4. (±)-9-*exo*-Epoxy-*endo*,*endo*-tetracyclo[6.2.1.1^{3,6}.0^{2,7}]-dodeca-4-one, (±)-9

Into a 250 mL flask were added *m*-CPBA (8.2 g, 4.8 mmol), KF (2.7 g, 4.8 mmol) and (±)-**8** (4 g, 24 mmol) in CH_2Cl_2 (100 mL). After stirring for 15 h at rt, additional KF was added up to a total 1:2 *m*-CPBA:KF molar ratio and the crude reaction mixture was stirred for 1 h at rt. Then the crude mixture was filtered and the filtrate was evaporated to afford (±)-**9** as a white solid (3.95 g, 86%), mp 172–174°C (lit.[12] 172–174°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.30 (d, H(10), $J=2.90$ Hz), 3.39 (d, H(9), $J=2.9$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 32.7 (CH_2), 38.2 (CH), 39.1 (CH), 40.6 (CH), 45.2 (CH_2), 45.3 (CH_2), 46.8 (CH), 49.0 (CH), 50.3 (CH), 51.6 (CH), 53.4 (CH), 218.7 (C) FTIR ($CHCl_3$): ν (cm^{-1}): 1737 (C=O).

4.5. (±)-10-*exo*-Hydroxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodeca-4-one, (±)-10

To a stirred solution of 0.67 g of (±)-**9** (3.5 mmol) in dry THF (30 mL) under a N_2 atmosphere was added dropwise with stirring a solution of 1.5 g of potassium *t*-butoxide (14 mmol) in dry THF (30 mL) over 10 min. After all the potassium *t*-butoxide solution had been added, the resulting mixture was stirred at rt for 1 h. A small amount of crushed ice was added under a N_2 atmosphere carefully to destroy the remaining potassium *t*-butoxide. The aqueous layer was extracted with 3×20 mL of ethyl ether and the ethereal extracts were washed with 50 mL of water, dried over magnesium

sulfate, filtered and the solvents were evaporated to afford (±)-**10** (0.54 g, 80%) as a white solid. Mp: 190–192°C (lit.[12] 190–192°C) ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.2 (s, 1H, H_{10} α-OH). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 36.9 (CH_2), 37.0 (CH_2), 43.0 (CH), 43.1 (CH), 43.4 (CH), 45.0 (CH), 49.3 (CH), 50.0 (CH), 50.9 (CH), 52.8 (CH), 75.0 (CH), 215.5 (C). FTIR ($CHCl_3$): ν (cm^{-1}): 3410 (OH), 1731 (C=O).

4.6. (−)-10-*exo*-Acetoxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodeca-4-one, (−)-11 and (+)-10-*exo*-hydroxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]dodeca-4-one, (+)-10

Lipase (50% w/w of substrate) was added to a solution of 0.3 g of (±)-**10** (1.6 mmol) in vinyl acetate (10 mL), and the suspension was shaken at 250 rpm at 25°C. When 46% degree of conversion was achieved (7 h), the enzyme was filtered and the excess of vinyl acetate was evaporated. The products were separated by flash column chromatography (cyclohexane:ethyl acetate 9:1), giving (+)-**10** (0.148 g, 0.77 mmol, 46%) $[\alpha]_D^{20}$ = +30.4 (*c* 1.0, ethyl acetate) ee = 85%, mp 190–192°C. HRMS: calcd for $C_{12}H_{14}O_2$, 190.24418 [M^+]; found: 190.09938 and (−)-**11** (0.170 g, 0.73 mmol, 44%), $[\alpha]_D^{20}$ = −31.0 (*c* 1.0 ethyl acetate) ee >95%, mp 88–90°C. HRMS: calcd for $C_{14}H_{16}O_3$, 232.28182 [M^+]; found: 232.10903.

4.7. (+)-10-*exo*-Acetoxy-pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{5,9}]-dodeca-4-one, (+)-11

To a stirred solution of (+)-**10** (0.1 g, 0.53 mmol) in CH_2Cl_2 (15 mL) were added acetic anhydride (0.12 mL), triethylamine (0.12 mL) and catalytic 4-dimethylaminopyridine (DMAP). The solution was stirred for 24 h at rt and then a 5% HCl solution was added and the crude reaction mixture was stirred for 1 h. The aqueous layer was extracted with ethyl ether (3×15 mL) and the ethereal extracts were washed with water (3×20 mL), dried over magnesium sulfate, filtered and the solvents were evaporated to afford (+)-**11** as a white solid (0.1 g, 82%) ($[\alpha]_D^{20}$ = +26.0, *c* 1.0, ethyl acetate, ee = 85%), mp 88–90°C, ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.9 (s, 3H, CH_3), 5.0 (s, 1H, H α-OAc). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 36.9 (CH_2), 37.5 (CH_2), 41.4 (CH), 42.7 (CH), 43.2 (CH), 45.3 (CH), 47.3 (CH), 49.1 (CH), 50.9 (CH), 52.9 (CH), 78.5 (CH), 169.7 (C), 215.2 (C). FTIR ($CHCl_3$): ν (cm^{-1}): 1746 (C=O overlapping of the ester and ketone bands).

4.8. Enantiomeric excess analysis by ^{1}H NMR spectroscopy using a chiral chemical shift reagent

A high resolution of the signals has been achieved for the enantiomeric proton H(10) (α-OAc) of (±)-**11**. Sequential addition of the chiral chemical shift reagent tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium(III)[9] Eu(hfc)$_3$ (5 mg) to a $CDCl_3$ solution of (±)-**11** (10 mg) in a 5 mm NMR tube, achieved the best result with 25 mg of Eu(hfc)$_3$. The difference in chemical shift ($\Delta\Delta\delta$) of the enantiomeric hydrogens H(10) (α-Oac) was 0.16 ppm.

4.9. Racemization process of (+)-10

Into a 10 cm×1cm (internal diameter) glass ampoule was added (+)-**10** (0.03 g, 0.15 mmol, ee = 85%, $[\alpha]_D^{20}$ = +34.0). The ampoule was closed under vacuum and heated in an oven for 1 h at 215°C. After cooling, 0.025 g of white crystals were removed from the ampoule. Analysis of the crystals (specific rotation measurement) showed the formation of (±)-**10**.

4.10. Molecular orbital calculations

MO calculations using the 6-31G* ab initio method were performed using the Spartan Program[18] package on an AMD DURON 800 MHz PC computer with 128 Mb of RAM. The best conformation of the alcohol (+)-**10** was obtained from rotational analysis of the C(10)–O bond by a change of 30° in the initial point of calculations.

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