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SYNTHESIS AND CHIROPTICAL PROPERTIES OF C_3-PERHYDROTRIQUINACENE DERIVATIVES

CARMEN ALMANSA, ALBERT MOYANO, and FELIX SERRATOSA*

Departament de Química Orgànica. Divisió de Ciències Experimentals i Matemàtiques. Universitat de Barcelona. E-08028 Barcelona. Spain

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Abstract- An efficient, enantioselective synthesis of C_3-triketone 1, starting from optically pure lactone 2, which is commercially available in both enantiomeric forms, is described. The absolute configuration of a chiral perhydrotriquinacene derivative is therefore established for the first time by chemical correlation. The stereochemical assignments are also confirmed by the circular dichroism of both (+)-1, which shows a positive Cotton effect, and the tribenzoate (+)-12, which presents a positive exciton chirality.

INTRODUCTION

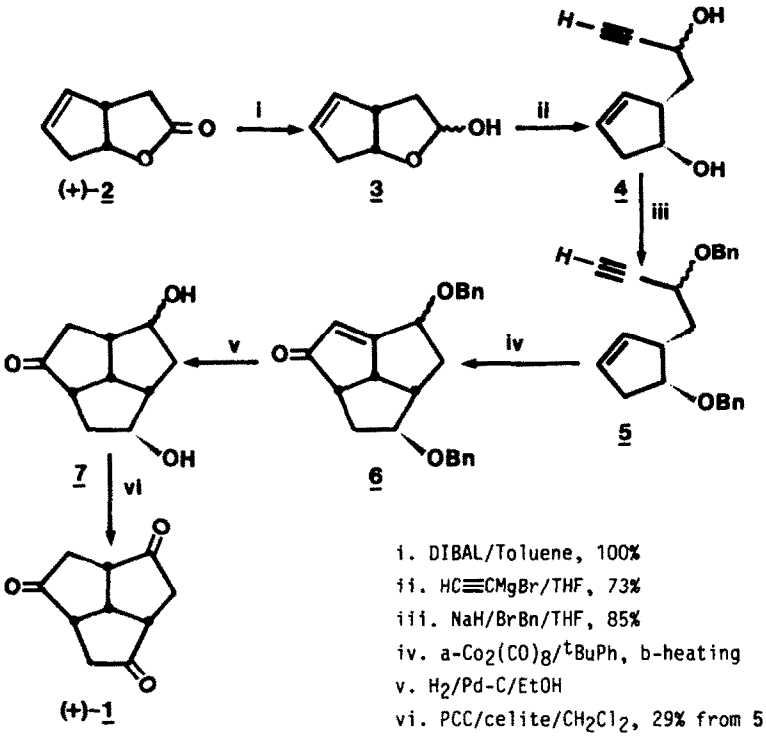
In the general context of polyquinane chemistry,[1] systems possessing the tricyclo(5.2.1.$0^{4,10}$)decane (perhydrotriquinacene) skeleton are of special interest.

From the synthetic point of view, these compounds are important due to their potential use as dodecahedrane precursors by dimerization.[2,3] On the other hand, the unusual geometric features of perhydrotriquinacene have prompted several studies on the possible homoconjugative interaction of unsaturated groups located on the perimeter of the rigid hemispherical framework.[4,5] Although in both instances the availability of dissymmetric perhydrotriquinacene derivatives in enantiomerically pure form has been shown to be of paramount importance, the only known routes to optically pure perhydrotriquinacenes go through the resolution of triquinacene-2-carboxylic acid with either (+)-(R)-α-methylbenzylamine or (-)-quinine.[3d,3e,5a] In the present paper, we report a direct enantioselective approach to chiral C_3-perhydrotriquinacene derivatives, which is based on our previous synthesis of all-cis-tricyclo(5.2.1.$0^{4,10}$)decane-2,5,8-trione 1 in racemic form.[2e,6,7]

SYNTHESIS

The preparation of the dextrorotatory enantiomer of C_3-triketone 1 is depicted in Scheme 1. The key step of the sequence is the intramolecular Pauson-Khand cyclization[8] of the dicobalt hexacarbonyl complex of enyne 5, which leads to the unsaturated ketone 6 (along with some saturated ketone). The important point is that due to both the stereoelectronic requirements of the Pauson-Khand reaction and to the stereochemical constraints of the fused tricyclopentanoid skeleton of 6, only one isomer is formed in the cyclization; i.e., the one in which the ring junctions are all-cis. The convex shape of the resulting system directs then the hydrogenation of the double bond (with simultaneous deprotection of the hydroxyl groups) from the exo face of the molecule and, finally, the oxidation of the intermediate diol 7 leads to the all-cis-triketone 1 of C_3 symmetry. In this way, the absolute configuration of C-5 of the starting lactone 2 determines the

absolute configuration of the three equivalent chiral centers of 1 (i.e., carbons 1, 4 and 7).



Scheme 1

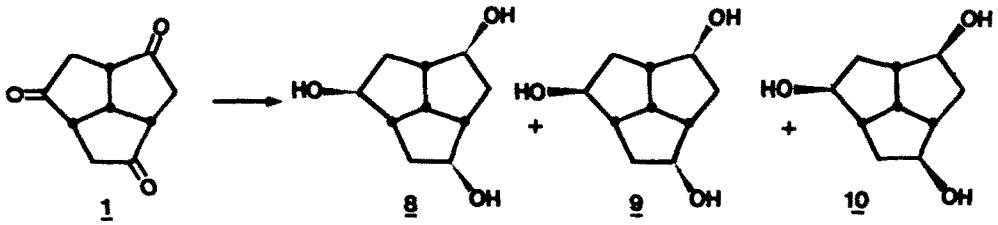
As depicted in Scheme 1, we started from the easily available[9] dextrorotatory enantiomer of 2, which is known to possess the (1R,5S) configuration, and should therefore lead to the (1S,4S,7S) enantiomer of 1. Reduction with DIBAL in toluene produced in quantitative yields the lactol 3[10] (in the form of an epimeric mixture at C-3), which was subsequently added to a solution of ethynyl magnesium bromide[11] in THF to afford, after aqueous working up, the corresponding epimeric mixture of diols 4 in 73% yield (based on reacted lactol). As previously reported,[7] the hydroxyl groups were protected as benzyl ethers in order to improve the efficiency of the cyclization step, which was performed *in situ* after the formation of the cobalt-carbonyl complex of enyne 5. Catalytic hydrogenation of the resulting mixture effected both the reduction of the double bond and the cleavage of the benzyl ethers in enone 6. Without further purification, diol 7 was oxidized with pyridinium chlorochromate/celite in CH_2Cl_2 solution,[12] to give after chromatographic purification the crystalline ketone 1 in 17% overall yield from lactone (+)-2.

Measurement of the optical activity of 1 showed that it was dextrorotatory ($[\alpha]_D^{20}$ = +288°, c=0.02 g/mL, $CHCl_3$), so that the absolute configuration of (+)-1 must be (1S,4S,7S). It is important to note that the above synthesis represents the first assignment of the absolute configuration of a chiral perhydrotriquinacene by chemical correlation with a compound of known absolute stereochemistry, since previous assignments[5] relied exclusively on circular dichroism considerations, which in some instances have been shown to be hazardous.[13]

Next, we examined the question of the stereoselective reduction of 1, in order to determine the best conditions for the preparation of the endo-triol 8. (Scheme 2).

The reduction with either lithium aluminium hydride or sodium borohydride was not stereoselective, giving mixtures of triols which were separable by HPLC. Two of them (8 and 10) gave ^{13}C-NMR

spectra with only four signals, so that we assigned the tri-endo configuration to 8, which is formed in greater amounts than 10. On the other hand, triol 9 showed ten distinct ^{13}C resonances; since two of its α-hydroxylic carbon atoms had chemical shifts very similar to the corresponding one of 8, we assigned the di-endo-exo configuration to 9. As expected, catalytic hydrogenation of (+)-1 using PtO_2 was completely stereoselective, affording triol (+)-8 in high yields. Compound 8 was also prepared in racemic form starting from racemic triketone 1.

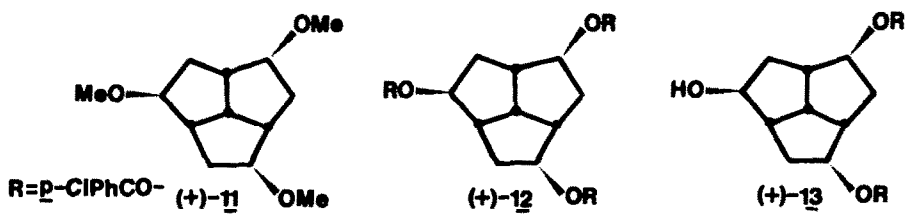


$LiAlH_4/Et_2O$	49%	49%	0%
$NaBH_4/Et_2O$	26%	45%	11%
$H_2/PtO_2/EtOH$	81%	0%	0%

Scheme 2

Methylation of the lithium alkoxide derived from 8 gave access to the trimethyl ether 11, both in the racemic and in the optically active form. This allowed the determination of the optical purity of (+)-1. In fact, the 200 MHz ^1H-NMR spectrum of racemic 11 in the presence of the chiral lanthanide shift reagent $Eu(hfc)_3$ showed two distinct resonances for the methyl hydrogens, while only one signal was visible in the corresponding spectrum of (+)-11. We can conclude therefore that the synthesis of (+)-1 depicted in scheme 1 is $\geq$ 97% stereoselective.

Finally, quenching of the lithium alkoxide of (+)-8 with p-chlorobenzoyl chloride produced an easily separable mixture of the tris-(p-chlorobenzoate) (+)-12 and the diester (+)-13.



CIRCULAR DICHROISM OF (+)-1, (+)-12 AND (+)-13.

The absolute configuration of the C_3-triketone (+)-1 can also be established on the basis of its circular dichroism (Figure 1). The CD curve of (+)-1 is characterized by a positive Cotton effect of the $n \rightarrow \pi^*$ transition for the carbonyl chromophore at 300 nm. This chiroptical behaviour can be explained by the octant rule applied to any of the three equivalent carbonyl groups of the molecule, if one assumes that, in accordance to the chemical correlation discussed in the previous section, the absolute configuration of (+)-1 is (1S,4S,7S) (Figure 2).

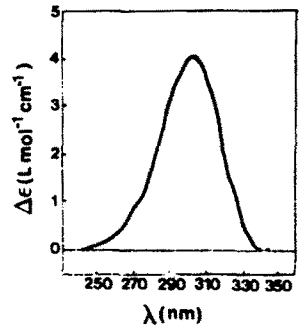


Figure 1. Circular dichroic spectrum ($CHCl_3$) of (+)-1.

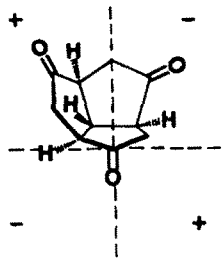
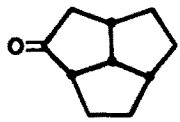
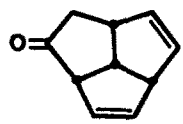


Figure 2

It is interesting to realize that both the molar circular dichroism and the molar rotation of (+)-1 (at 365, 436, 546 and 578 nm) are ca. five times stronger than those of the closely related monoketone (+)-14 (to which Paquette assigned the absolute configuration (1S) on the basis of its positive Cotton effect).[5a] This indicates that the homoconjugative interaction between the three equivalent carbonyl chromophores of (+)-1 is almost negligible, contrary to what was observed in the ketone (+)-15, where the $n \longrightarrow \pi^*$ transition appears to be capable of borrowing intensity of the allowed $\pi \longrightarrow \pi^*$ transition of the proximal double bond.[5a] This is also in accordance with the low value ($\epsilon = 60$) of the extinction coefficient of the 300 nm transition of (+)-1.



(+)-14



(+)-15

Further confirmation of the absolute configuration of (+)-1 was obtained by the application of the exciton chirality method[14] to the tris-(p-chlorobenzoate) (+)-12. In fact, the circular dichroic spectrum of (+)-12 (Figure 3) exhibits two strong Cotton effects of opposite signs in the region of the intramolecular charge transfer (^1L_a) transition of the p-chlorobenzoate chromophore; the first Cotton effect at larger wavelength has a value of $\Delta\epsilon$=+65 (247 nm), while the second Cotton effect at shorter wavelength has a value of $\Delta\epsilon$=-23 (230 nm). This is indicative of a positive exciton chirality of the tribenzoate system of (+)-12, which means that the long axes of the two benzoate chromophores are twisted in a clockwise manner. This is again in accordance with an (1S,4S,7S) absolute configuration (Figure 4).

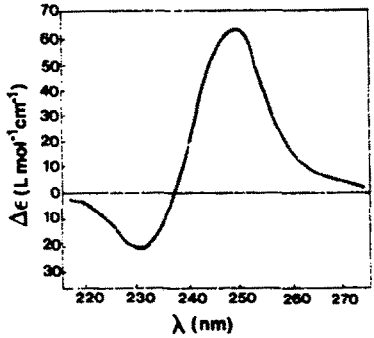


Figure 3. Circular dichroic spectrum (EtOH) of (+)-12

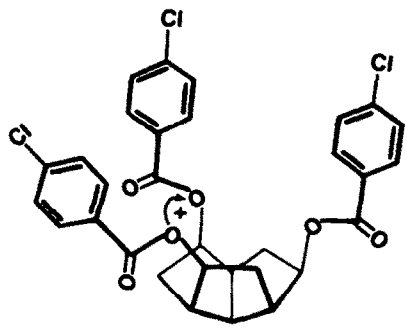


Figure 4

The circular dichroism of the bis(p-chlorobenzoate) (+)-13 is very similar, except that the amplitude of the first Cotton effect is greatly diminished ($\Delta\epsilon$ = +21.6 at 245 nm). Although the same phenomenon has been observed on the CD spectra of some tribenzoates of sugars[15] and steroids,[16,15a] the present case stands out as the first example of exciton chirality coupling of three equivalent benzoate chromophores in a framework of C_3 symmetry.

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus or on a Kofler hotbench and are uncorrected. Optical rotations were measured in a Perkin-Elmer 141 polarimeter, in thermostated 1 dm quarz cells. Circular dichroism spectra were recorded at room temperature on a Rousell-Jovan Dichrograph II instrument, in 0.1 or 0.5 cm quarz cells. Ultraviolet spectra were obtained with a Perkin-Elmer Lambda 5 spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Varian XL-200 instrument. Infrared spectra were obtained with a Perkin-Elmer 681 apparatus. Mass spectra were run on a Hewlett-Packard 5988A spectrometer, using chemical ionization techniques. Elemental analyses were performed with a 1106 Carlo Erba microanalyzer instrument. All chromatographic purifications were performed on silicagel (Merck, 230-400 mesh-ASTM), using hexane-ethyl acetate mixtures of increasing polarity as eluent. Optically pure (+)-(1R, 5S)-cis-2-oxabicyclo(3.3.0)oct-6-en-3-one (2) was purchased from Fluka and was used as received.

(+)-(1S,4S,7S)-all-cis-Tricyclo(5.2.1.0^{4,10})decane-2,5,8-trione, (1).

The product was obtained by the previously described optimized procedure[7], except that the optically pure (+)-lactone 2 was used as the starting material. The overall yield (from 1 g of (+)-2) was 17%. The IR, ^{1}H-NMR and ^{13}C-NMR data were coincident with those reported for the racemic compound.[2e,17] The melting point (after recrystallization from ethyl acetate) was of 161-162 °C. $[\alpha]_D^{20}$ +228°, $[\alpha]_{365}^{20}$ = +1281° (0.02,$CHCl_3$).

(+)-(1S,2R,4S,5R,7S,8R)-all-cis-Tricyclo(5.2.1.0^{4,10})decane-2,5,8-triol, (8).

a) Reduction with LAH. To a stirred suspension of LAH (0.109 g, 2.8 mmol) in anhydrous ether (2 mL) was added dropwise, under an atmosphere of pre-purified nitrogen, a solution of the triketone 1 (0.170 g, 0.95 mmol) in dry THF (5 mL). After stirring for 2h at room temperature, the reaction mixture was cooled at 0 °C. Next, CH_2Cl_2 (1 mL) was added and the excess hydride was destroyed with saturated sodium-potassium tartrate solution (0.1 mL). After adding some solid sodium sulfate, the mixture was filtered and the inorganic salts were washed with ethyl acetate. Elimination of solvents afforded a white solid (0.140 g) whose ^{13}C-NMR indicated that it was a 1:1 mixture of the tri-endo alcohol 8 (see below) and the di-endo-exo isomer 9.
^{13}C-NMR (CD_3OD) of alcohol 9: 32.8 (t), 34.1 (t), 36.0 (t), 44.3 (d), 47.8 (d), 49.2 (d), 49.7 (d), 75.2 (d), 75.4 (d), 79.6 (d).

b) Reduction with $NaBH_4$. To a solution of triketone 1 (0.15 g, 0.84 mmol) in ethanol, sodium borohydride (0.19 g, 5.1 mmol) was added. After stirring 4h at room temperature, water (1 mL) was added, and most of the ethanol eliminated by evaporative destillation. The residue was thoroughly extracted with ethyl acetate, and the organic extracts dried over magnesium sulphate. Elimination of solvents afforded a white solid (0.127 g) whose ^{13}C-NMR indicated that it was a 3:6:1 mixture of 8, 9 and the tri-exo isomer 10.
^{13}C-NMR (CD_3OD) of alcohol 10: 39.4 (t), 47.7 (d), 51.7 (d), 78.2 (d).

c) Catalytic hydrogenation. A solution of triketone (+)-1 (0.120 g, 0.67 mmol) in ethanol (5 mL) was hydrogenated at 4 atm in the presence of PtO_2 (0.030 g). After 6 days, the alcoholic solution was filtered through celite and evaporated to dryness to afford a crude material (0.120 g) that was washed with hot chloroform to remove partially hydrogenated products. In this way, pure tri-endo alcohol 8 (0.100 g), $[\alpha]_D^{20}$ +56 (0.02, MeOH) was obtained in 81% yield. IR (KBr): 3440, 1970, 1080 cm^{-1}. ^{1}H-NMR (CD_3OD): 1.74 (m, 6H), 2.3-2.8 (m, 4H), 4.22 (ddd, J = 11.3 Hz, J' = 5.6 Hz, J'' = 6.7 Hz, 3H), 5.0 (s, 3H). ^{13}C-NMR (CD_3OD): 32.4 (t), 44.7 (d), 47.4 (d), 75.8 (d). MS (C.I., NH_3): 202 (M+18, 73%), 185 (M+1, 100%).

Trimethylether of alcohol 8, (11).

A solution of alcohol 8 (0.10 g, 0.54 mmol) in a mixture of dry THF (5 mL) and anhydrous HMPA (1 mL) was treated, at -50° and under an atmosphere of pre-purified nitrogen, with n-butyllithium (1 mL of a 1.6 M solution in hexane). After stirring for 10 minutes, methyl iodide (0.78 g, 5.4 mmol) was added via syringe, and the resulting mixture was stirred overnight at room temperature, poured into water (10 mL) and extracted with ether. Elimination of solvents gave a crude material (0.17 g), which was purified by chromatography to afford trimethylether 11 (0.075 g, 61% yield) as a colorless oil. $[\alpha]_D^{20}$ +90° (0.005, $CHCl_3$). IR ($CHCl_3$): 3000, 2960, 2930, 2840, 1470, 1450, 1360, 1200, 1095, 1010, 980, 965 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.5-1.9 (m, 6H), 2.4-2.6 (m, 4H), 3.32 (s, 9H), 3.76 (t of d, J = 11.4 Hz, J' = 6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): 20.6 (t), 40.5 (d),45,2 (d), 57.4 (q), 83.9 (d). MS (C.I., NH_3): 261 (M+35), 244 (M+18), 227 (M+1).

Tris(p-chlorobenzoate) of alcohol 8, (12).

To a solution of alcohol (+)-8 (0.050 g, 027 mmol) in dry THF (5 mL) was added, at -10 °C and under an atmosphere of pre-purified nitrogen, n-butyllithium (0.5 mL of a 1.6 M solution in hexane). After stirring for 10 minutes, a solution of p-chlorobenzoyl chloride (0.19 g, 1.0 mmol) in dry THF (2 mL) was added dropwise and the resulting mixture was stirred overnight at room temperature. The solvents were eliminated and the residue was subjected to column chromatography, affording:

i) the desired triester 12 (50 mg, 31% yield), as a white solid of m.p. 147-149 °C (after recrystallization with methylene chloride/hexane). $(\alpha)_D^{20}$ = +217° (0.006, $CHCl_3$). IR (KBr): 2950, 1720, 1590, 1490, 1400, 1310, 1300, 1290, 1270, 1025, 845, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.0-2.2 (m, 6H), 2.96 (m, 4 H), 5.31 (t of d, J = 11.4 Hz, J' = 4.7 Hz, 3H), 7.7 (AA'BB' system, 12 H). ^{13}C-NMR ($CDCl_3$): 29.4 (t), 41.0 (d), 45.4 (d), 77.1 (d), 128.8 (d), 129.2 (s), 131.0 (d), 139.6 (s), 165.2 (s). MS (C.I. NH_3): 616 (M+18), 506. Anal. calcd. for $C_{31}H_{25}Cl_3O_6$: C, 62.05; H, 4.17; Cl, 17.76. Found: C, 61.99; H, 4.26; Cl, 17.95.

ii) diester 13 (44 mg, 35% yield), as a white solid of m.p. 127-129 °C (recrystallization from methylene chloride/hexane). $(\alpha)_D^{20}$ = +129° (0.004, $CHCl_3$). IR (KBr): 3700-3150, 2940, 1715, 1490, 1300, 1290, 1265, 1210, 840, 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.7-2.2 (m, 7H), 2.5-3.1 (m, 4H), 4.37 (t of d, J = 12 Hx, J' = 7 Hz, 1H), 5.28 (m, 2H), 7.7 (AA'BB' system, 8H). ^{13}C-NMR ($CDCl_3$): 28.7 (t), 29.3 (t), 32.4 (t), 40.9 (d), 41.3 (d), 43.1 (d), 45.9 (d), 74.8 (d), 77.2 (d), 77.4 (d), 128.6 (d), 128.7 (d), 131.0 (d), 139.5 (s), 165.3 (s). MS (C.I., NH_3: 478 (M+18). Anal. calcd. for $C_{24}H_{22}Cl_2O_5$: C, 62.47; H, 4.77; Cl, 15.18. Found: C, 62.26; H, 4.72; Cl, 15.01.

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