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Detection, synthesis and absolute configuration of (+)-nortaylorione, a new terpene from *Artemisia annua*

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Abstract: Nortaylorione a new nor-sesquiterpene, was identified among minor components of *Artemisia annua* (hybrid plants) essential oil. Its relative and absolute configurations were determined by GC and GC/MS equipped with a chiral column and coinjecting the essential oil with synthetic standards (racemic and homochiral), obtained in a few steps from commercial reagents. Pauson–Khand reaction was used as the key reaction in both synthetic pathways. The new natural product, named (+)-nortaylorione, is the (1′*S*)-*cis*-2-[2′,2′-dimethyl-3′-(3″-butanon-1″-yl)-cyclopropyl]-2-cyclopenten-1-one. © 1997 Elsevier Science Ltd

Artemisia annua L is well known for its production of the antimalarial compound artemisinine **1**.[1] While adapting this asiatic plant to the Brazilian climate, a series of chemical analyses had to be performed in order to determine the chemical composition and ratio of its volatile and non volatile microconstituents.[2] In this process we have detected in the *Artemisia annua*[3] essential oil several minor constituents assigned as unknown oxygenated sesquiterpenes.

We were particularly intrigued by one compound (retention index=1746 (DB-5),[4] ca 0.02%) showing a molecular ion at m/z 220 and a base peak at m/z 43. Although the molecular ion was compatible with that of spathulenol **2** the mass spectra and the retention index were not.[5] The rather intense ion at m/z 43[6] was taken as a clue to the presence of a methyl ketone moiety. Several structures were suggested taking the relative retention index and the mass spectrum into consideration, nevertheless these evidences were too fragile to make any choice. Structure **5a**, one of our preferred hypotheses, was based on the fact that the enzymatic system of *Artemisia annua* is rather aggressive in cleaving terpene double bonds as in artemisine **1** and in compound **3**. Therefore formation of **5a** could arise from an oxidative cleavage of a ledene derivative like **4** (Figure 1). This hypothesis came up when a search in the literature revealed that taylorione **5b** a sesquiterpene possessing an analogous skeleton was isolated from *Mylia taylorii*.[7]

To isolate and characterize **5a**, a large amount of essential oil would have to be available due to its low abundance. Unfortunately this was not the case and we were left with the alternative of synthesizing this compound.

Results and discussions

Our primary goal was to determine structure **5a** with all its stereogenic centers. Aware that GC/MS would be our major tool, we elaborated a straightforward synthetic strategy that would allow the unquestionable identification of the natural isomer with a minimum of synthetic effort. In this connection we have visualized two synthetic pathways (Schemes 1 and 2). One leading to a (±)-

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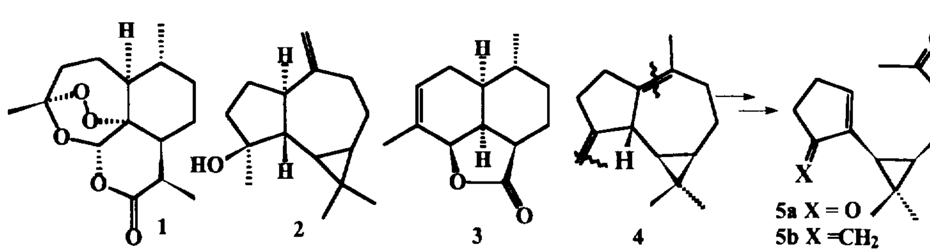
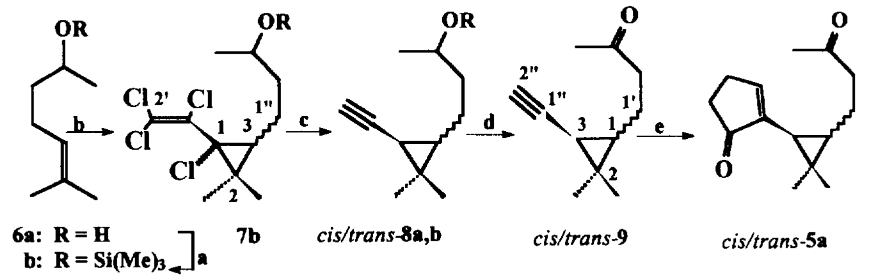


Figure 1. Sesquiterpenes 1–3 from *Artemisia annua* and possible oxidative degradation of a ledene derivative **4**, leading to nortaylorione **5a** and taylorione **5b**.

cis/trans mixture of **5a** (of predetermined diasteromeric ratio) which submitted to optimized conditions on an appropriate chiral capillary column would resolve into 4 peaks. Coinjection of this standard with the essential oil would provide the relative configuration (*cis* or *trans*). The answer to the question about the absolute configuration would automatically emerge from the synthesis of a homochiral *cis*- or *trans*-**5a** (depending on the prior analysis). Alkyne **9** our key intermediate in the synthetic approach (Scheme 1), was chosen due to its availability in our laboratories from past attempts to synthesize other sesquiterpene skeletons.[8]



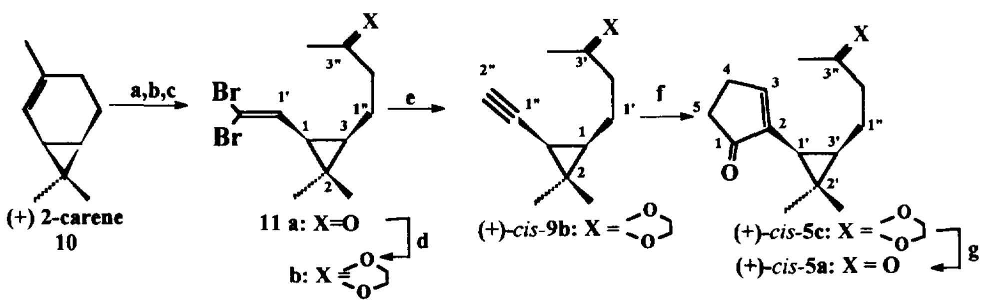
Scheme 1. Synthetic route (±)-*cis/trans*-nortaylorione **5a**. a) HMDS/TMSCl (77%); b) TCCP, 170°C, 16 h (55%); c) BuLi, anhydrous ether, −78°C; d) CrO_3, H_2SO_4, acetone r.t., 1 h (88% over two steps); e) $Co_2(CO)_8$, PhMe, r.t., 5 h; 2) CO, ethene, PhMe, 90°C, 48 h (43%).

Tetrachlorocyclopropene (TCCP) was prepared following the protocol of West *et al.*[9] and sealed in a glass ampoule to react with **6b**, the silyl ether derivative prepared from the commercial 6-methyl-5-hepten-2-ol **6a**, and heated at 170°C for 16 h. The crude adduct **7b** was distilled at 0.05 Torr (90–100°C). This adduct was characterized by ^{1}H NMR and treated with BuLi at −78°C. The product mixtures obtained under several quenching conditions were analysed by GC revealing that the *cis/trans* ratio and total yield were dependent on the proton source. With water this ratio was 1:1 and with diisopropylamine the ratio was 2:1. Water was chosen taking into consideration yield, cost and ratio. The crude alkyne consisting of the *cis/trans* mixture of silyloxy and hydroxy derivatives **8a** and **8b** was treated with Jones' reagent furnishing the *cis/trans* keto-alkyne **9** in 4 steps and 37% overall yield. The *cis* and *trans* isomers were easily separated by flash chromatography using hexane and ethyl acetate 7:3. The *cis* isomer eluted first (characterized by its cyclopropane couplings $^3J_{H,H}$=8.4 Hz) and the last fractions consisted of pure *trans* isomer. Some middle fractions consisting of **9** in a *cis/trans* ratio of 2:1 were considered a good choice for our purpose. It is worth pointing out that although the *cis* isomer was first characterized by its ^{1}H NMR spectrum, ^{13}C NMR spectroscopy is a better tool to differentiate the *cis* from the *trans* diastereomer, mainly taking $C_{1'}$ chemical shift as diagnostic, which is about 19 ppm for the *cis* and 23 ppm for *trans* isomers. This observation is valid for several other 2,2-dimethyl cyclopropane derivatives similar to **9**.

The Pauson–Khand reaction[10] was the natural choice to transform (±)-**9** (mixture of *cis* and *trans*, ratio 2:1) into **5a** and indeed provided the desired (±)-**5a** in 43% yield as a mixture (±)-*cis* and

(±)-*trans* in the ratio 3:1. The slight change of the ratio was caused by the purification steps. This compound was fully characterized by high resolution mass spectrometry as well as ^{1}H and ^{13}C NMR spectroscopy. Once more the ^{13}C NMR signals of the *cis* and *trans* diastereomers were the easiest to discriminate and to assign. Gas chromatographic analysis using a J&W Scientific DB-5 capillary column, coinjecting the synthetic **5a** with the *Artemisia annua* oil revealed that compound **5a** detected in the oil coeluted with the synthetic standard *cis*. The mass spectra of the synthetic compound and that of natural **5a** were identical. We had thus confirmed the proposed structure for the novel terpene as *cis*-**5a** named nortaylorione.

To reach our final objective and determine the absolute configuration of the natural compound, we have executed the synthetic route depicted in Scheme 2. Thus (+)-2-carene was used as our starting material. Alkyne (+)-**9b** was obtained in four steps and 37% yield. Although the starting material, the intermediate and yields are equal to those obtained by Kerr *et al.*[11] the number of steps were reduced by preparing the bromoalkene intermediate **11a** from (+)-2-carene in one pot reaction. The enantiopure (+)-*cis*-**5a** was obtained from **9b** by the Pauson–Khand reaction just as the racemic *cis/trans* mixture followed by hydrolysis of the ketal **5c**. Coinjection of (+)-*cis*-**5a** with the *cis/trans* racemic mixture [retention indices on the chiral cyclodextrine column, using van den Dool and Kratz equation[4] and coinjecting the mixture with a normal alkane series were: 1909 (*trans*), 1910 (*trans*), 1927 (*cis*), 1932 (*cis*) revealed that (+)-*cis*-**5a** (retention index (RI)=1932] was the last eluting isomer (Figure 2). We were thus able to ascertain the rentention indices of (+)-*cis*-**5a** as (1′*S*) (RI=1932) and that of (−)-*cis*-**5a** as (1′*R*) (RI=1927). Coinjection of the *Artemisia* oil with the (+)-*cis*-**5a** and (±)-*cis/trans*-**5a** and mass spectra comparison revealed that the natural compound is (+)-*cis* -(1′*S*)-**5a**.



Scheme 2. Synthetic route to (+)-(1′*S*)-*cis*-nortaylorione **5a**. a) O_3, CH_2Cl_2; b) PPh_3; c) CBr_4, PPh_3, CH_2Cl_2, 0°C (42% over two steps); d) $(CH_2OH)_2$, *p*-TsOH, Ar (100%); e) BuLi, THF, −78°C (85%); f) $Co_2(CO)_8$, PhMe; 2) CO, ethene, PhMe (40%); g) H_2O, acetone (98%), PPTS.

Conclusion

This work certainly has the unusual feature of presenting the detection, synthesis and absolute configuration of the new natural product (+)-nortaylorione.

Experimental section

Melting points were determined with a Kofler hot plate set up in a microscope Thermopan model (C. Reichert Optische Werke AG). FT-IR Spectra were recorded with a Perkin Elmer 298 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian GEMINI 300 (300.1 MHz, Varian) or Bruker AC 300P (300.1 MHz) spectrometers, $CDCl_3$ was used as the solvent, with Me_4Si (TMS) as internal standard. ^{13}C NMR spectra were obtained with a Varian GEMINI 300 (75.5 MHz) or a Bruker AC300P (75.5 MHz) spectrometer. $CDCl_3$ (77.0 ppm) was used as internal standard. Methyl, methylene, methine and carbon non bonded to hydrogen were discriminated using DEPT 135° and DEPT 90° spectra (Distortionless Enhancement by Polarization Transfer). 2D NMR spectroscopy was performed with standard H,H correlation and H,X correlation pulse sequences available in

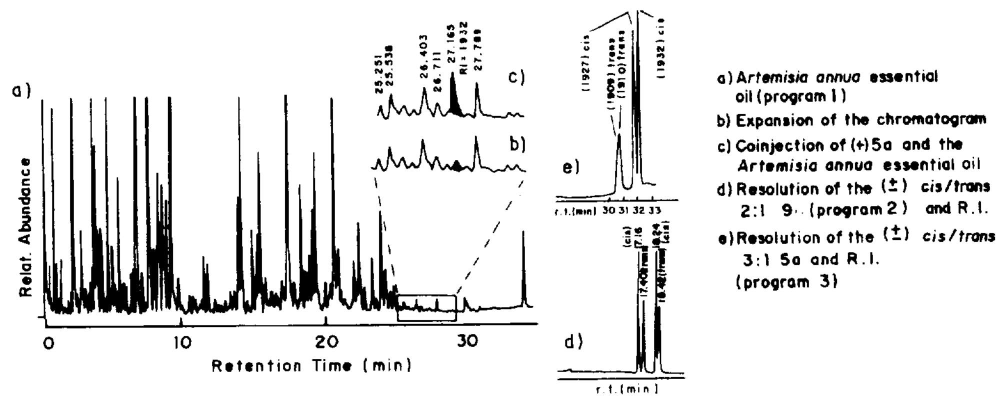


Figure 2. Gas chromatograms using fused silica capillary chiral column (heptakis-(2,6-methyl-3-pentyl)-β-cyclodextrine).

the spectrometers. The GC/MS analyses were carried out using a HP-5890/5970 system equipped with either a J&W Scientific DB-5 fused silica capillary column (25 m × 0.2 mm × 0.33 μm) or a chiral column heptakis-(2,6-methyl-3-pentyl)–β-cyclodextrine (20 m × 0.25 mm × 0.25 μm). Temperature program 1: 100°C (2°C/min)–180°C; program 2: 55°C (2°C/min)–80°C; program 3: 125°C (30°C/min)–150°C. Injector and detector temperature equal to 250°C. Helium was used as carrier gas. The MS were taken at 70 eV. Scanning speed was 0.84 scan/s from m/z 40 to 550. The retention indices were obtained by coinjecting the oil and the standards with a C_{11}–C_{30} normal hydrocarbon mixture and applying the appropriate equation.[4]

*Synthesis of (±)-*cis/trans*-nortaylorione {(±)-*cis/trans*-2-[2′,2′-dimethyl-3′-(3″-oxobutyl)-cyclopropyl]-2-cyclopenten-1-one} (**5a**)*

*6-Methylhept-5-en-2-yl trimethylsilyl ether (**6b**)*

To a round bottom two-neck flask (50 mL) equipped with a pressure-equalizing dropping funnel and reflux condenser, containing freshly distilled hexamethyldisilazane (1.80 g, 0.011 mol) and commercial 6-methylhept-5-en-2-ol (**6a**) (Aldrich) (5 mL, 4.22 g, 0.033 mol) was added a solution of freshly distilled trimethylchlorosilane (1.40 mL, 0.011 mol) in anydrous hexane (1.5 mL). The mixture was stirred for 1 h at r.t. and then heated to 60°C for 2 h. The reaction mixture was filtered and the solution distilled under water aspirator vacuum yielding **6b** (5.05 g, 0.025 mol, 77% yield) (b.p. 120°C, 15 Torr). IR revealed no OH stretching band.

cis/trans-*1-Chloro-1-(1′,2′,2′-trichlorovinyl)-2,2-dimethyl-3-[3″-(trimethylsilyloxy)butyl]cyclopropane (**7b**)*

Compound **6b** (5.00 g, 0.25 mol) and tetrachlorocyclopropene[9] (3.35 mL, 5.00 g, 0.280 mol) were sealed in a glass ampoule. The ampoule was placed in a steel safety container, and this was heated in an autoclave shaker at 170°C for 16 h. After the set-up had cooled down to r.t., the ampoule was frozen in liquid nitrogen before opening. Some ether was added to the cold mixure and the resulting solution was distilled under reduced pressure. The adduct **7b** (5.20 g, 0.0138 mol, 55% crude yield) was present in the fraction that distilled from 90–100°C (0.05 Torr). Purification on a short silica gel column eluting with hexane–ethyl acetate 8:2 yielded 3.10 g (0.008 mol, 32%) of *cis/trans*-**7b**. ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 9H), 1.00 (m, 1H), 1.10–1.20 (m, 9H), 1.25–1.80 (m, 4H), 3.7–3.9 (bm, 1H, 3″-H).

cis/trans-*3-Ethynyl-1,1-dimethyl-2-(3′-oxobutyl)cyclopropane* (cis/trans-*9*)

A 1.4 M solution of BuLi in hexane (28 mL, 40 mmol) was added dropwise to a solution of the adduct **7b** (3.10 g, 0.008 mol) in anhydrous ether (130 mL), and the mixture was stirred at −78°C for

1 h, then at r.t. for 2 h. The reaction mixture was poured onto ice and the aqueous layer extracted with ether (3×30mL), the combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The residue (2.16 g) was a 1:1 mixture of *cis/trans*-**8a** and *cis/trans*-**8b**. To the crude mixture of *cis/trans*-**8a,b** (2.16 g) was added 18 mL of Jones' reagent [CrO_3 (20.6 g), H_2O (60 mL), H_2SO_4 (17.4 mL)], and the solution was stirred at r.t. for 0.5 h. The progress of the reaction was monitored by TLC. The usual workup gave a 1:1 mixture of *cis*- and *trans*-**9** (1.18 g, 7.2 mmol, 88% yield). Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate produced in the first fractions pure *cis*-**9** as an oil (0.40 g), R_f=0.58 (hexane/ethyl acetate 4:1, silica gel TLC). IR (film on KBr) ν_{max} cm^{-1}: 3308, 2110, 1715; ^1H NMR ($CDCl_3$): δ 0.76 (m, 1H, 1-H), 1.06 (s, 3H, Me on C-2), 1.11 (s, 3H, Me on C-2), 1.17 (dd, 1H, ^3J=8.4 and ^4J=2.2 Hz, 3-H), 1.30–1.60 (bm, 2H, 1′-H), 1.89 (d, 1H, ^4J=2.2 Hz, 2″-H), 2.16 (s, 3H, 4′-H), 2.50 (m, 2H, 2′-H); ^{13}C NMR ($CDCl_3$): δ *cis/trans* 15.5/19.9 (Me on C-2), 17.2/19.5 (C-3), 19.8/23.0 (C-1′), 21.7/23.1 (C-2), 27.5/23.4 (Me on C-2), 29.9/30.0 (C-4′), 29.9/30.0 (C-4′), 42.8/43.2 (C-2′), 68.2/66.4 (C-2″), 82.6/85.0 (C-1″), 208.4/208.0 (C-3′); HREIMS (70 eV), *m/z* (%): calcd. for $C_{11}H_{16}O$ 164.12011, found 164.1201 ($M^{+\bullet}$, 1), 149 (30), 131 (35), 121 (30), 106 (39), 91 (100), 77 (40), 43 (80). In the sequence of fractions differently composed mixtures of *cis/trans*-**9** were obtained (about 0.60 g) followed by pure *trans*-**9** (0.22 g), R_f=0.55 (hexane/ethyl acetate 4:1, silica gel TLC).

*(±)-*cis/trans-*Nortaylorione (*cis/trans-***5a***)*

A fraction of (±)-*cis/trans*-**9** (2:1) (180 mg, 1.1 mmol) (see chromatogram on chiral column, Figure 2) in toluene (15 mL) was added dropwise to a solution of $Co_2(CO)_8$ (320 mg, 0.94 mmol) in toluene (50 mL) under argon and at 10–15°C. The mixture was stirred at r.t. for 5 h. The red reaction mixture was filtered through a pad of Celite and purified by chromatography on alumina (neutral) eluting with toluene. Evaporation of the solvent yielded 200 mg of the alkynehexacarbonyldicobalt complex, R_f=0.60 (hexane/ethyl acetate 4:1, silica gel TLC); IR (film on KBr) ν_{max} cm^{-1}: 2087, 2047, 2021; ^1H NMR ($CDCl_3$): δ 0.98 (s, 3H, Me on C-2), 1.08 (s, 3H Me on C-2), 2.08 (s, 3H, 4′-H), 2.46 (m, 2H, 2′-H), 5.78 (m, 1H, 2″-H); EIMS (70ev) *m/z* (%): 450 ($M^{+\bullet}$,0) 280 (1), 230 (5), 195 (40), 173 (42), 115 (22), 101 (6), 43 (100).

A solution of the cobalt complex (200 mg, 0.44 mmol) in toluene (5 mL) was placed in a glass ampoule and treated with ethylene and CO for 10 min. The ampoule was sealed and heated to 90°C for 48 h. The reaction mixture was filtered through a pad of Celite, and the solvent evaporated under vacuum. Purification by column chromatography on alumina eluting with toluene, then toluene/ethyl acetate 19:1 to 9:1 yielded 106 mg (43%) of 1:3 mixture of (±)-*cis/trans*-**5a**. R_f=0.45 (hexane/ethylacetate 4:1), R_t (min)=28.07 (*cis*), 29.5 (*trans*); RI^4=1746 (*cis*) and 1706 (*trans*) (DB-5, more details in the general experimental section); chiral column: RI^4=1909 (*trans*), 1910 (*trans*), 1927 (*cis*), 1932 (*cis*) (Figure 2). IR (film on KBr) ν_{max} (cm^{-1}): 1706, 1603, 1495; ^1H NMR ($CDCl_3$): δ (*cis*) 0.87 (q, 1H, ^3J=7.3 Hz, 3′-H), 0.98 (s, 3H, Me on C-2′), 1.16 (s, 3H, Me on C-2′), 1.38 (dm, 1H, ^3J=8 Hz, 1′-H), 1.56 (bq, 2H, ^3J=7.2 Hz, 1″-H), 2.13 (s, 3H, 4″-H), 2.37 (m, 2H, 5-H), 2.46 (t, 2H, ^3J=7.2 Hz, 2″-H), 2.58 (m, 2H, 4-H), 7.25 (bs, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ *cis/trans* (not all carbons from *trans* isomer were assigned) 15.8/not assigned (Me on C-2′), 19.5/23.5 (C-1″), 20.6/not assigned (C-2′), 22.3/26.0 (C-1′), 26.8/26.1 (C-4),), 28.6/30.0 (C-3′), 29.2/not assigned (Me on C-2′), 30.2/29.9 (C-4), 33.9/34.8 (C-5), 43.9/43.7 (C-2″), 143.5/145.0 (C-2), 157.2/155.2 (C-3), 211.8/210.0 (C-3″). GC/HREIMS (70 eV) *m/z* (%): 220.14633 calcd. for $C_{14}H_{20}O_2$, found 220.1463 ($M^{+\bullet}$ 10) 202 (20), 163 (35), 121 (30), 105 (35), 91 (50), 79 (30), 77 (30), 43 (100).

*(−)-(1*R*)-*cis*-1-(2′,2′-Dibromoethenyl)-2,2-dimethyl-3-(3″-oxobutyl)cyclopropane (***11a***)*

A stirred solution of (+)-2-carene **10** (1.0 g, 7.34 mmol) in dichloromethane (50 mL) was kept at −78°C and treated with ozone. The reaction was stopped before completion. Nitrogen was bubbled through the reaction mixture in order to remove excess ozone. Triphenylphosphine was added and the temperature was allowed to rise slowly to 0°C. The solvent was partially evaporated and the mixture was added to a solution of carbontetrabromide (4.8 g, 14.5 mmol) and triphenylphosphine (8.0 g, 30.5 mmol) in anhydrous dichloromethane (50 mL). The reaction mixture was left at r.t. for 10 min. The solvent was then evaporated and the residue was purified on silica gel eluting with hexane and hexane/ethyl acetate 2:1 to give the dibromoethenyl derivative **11a** (1.0 g, 42% over two steps). $[\alpha]_D^{25}$ −39.4 ($CHCl_3$; *c* 4.0); IR (film) ν_{maxc} cm^{-1}: 2948, 2911, 1716, 1363, 1165, 767; ^1H NMR ($CDCl_3$): δ 0.93 (q,^3J=8.6 Hz, 3-H), 1.04 (s, 3H, Me on C-2), 1.12 (s, 3H, Me on C-2), 1.40 (t, ^3J=8.6 Hz, 1-H), 1.71–1.50 (m, 2H, 1″-H), 2.16 (s, 3H, 4″-H), 2.45 (t, ^3J=7.7 Hz, 2″-H), 6.10 (d, ^3J=8.6 Hz, 1′-H); ^{13}C NMR($CDCl_3$): δ 15.8 (Me on C-2), 19.8 (C-1″), 22.6 (C-2), 28.7 (Me on C-2), 30.1 (C-4″), 30.3 (C-3), 31.1 (C-1), 43.4 (C-2″), 88.1 (C-2′), 135.8 (C-1′), 208.9 (C-3″); GC/EIMS (70eV) *m/z* (%): 324 ($M^{+\bullet}$ absent) 266 (3), 253 (3), 119 (7), 187 (14), 185 (14), 106 (38), 43 (100).

*Ethylene acetal **11b** of ketone **11a***

A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **11a** (1.0 g, 3.08 mmol) and ethylene glycol (2 mL) in benzene (70 mL). The reaction mixture was heated to reflux (5 h) with continuous water removal (Dean–Stark trap). Diethyl ether was added to the reaction mixture and the ethereal layer was then washed with water, dried over $MgSO_4$ and finally concentrated *in vacuo* to yield **11b** as a pale oil (1.2 g, 100%). ^1H NMR ($CDCl_3$): δ 0.90 (q, 1H), 1.15 (s, 3H), 1.05 (s, 3H), 1.32 (s, 3H), 1.50–1.30 (m, 2H), 1.65 (t, 2H), 3.95 (m, 4H), 6.10 (d,1H).

*(+)-(1R)-*cis*-3-Ethynyl-2,2-dimethyl-1-(3′-oxobutyl)cyclopropane ethylene acetal (*cis*-**9b**)*

A solution of the dibromoalkene **11b** (1.0 g, 2.72 mmol) in anhydrous tetrahydrofuran (30 mL) kept −78°C under N_2, was treated with a solution of 2.36 M butyllithium in pentane (3.0 mL, 7.0 mmol). The mixture was stirred at −78°C for 1 h and then at 25°C for another 1 h. Water was added to the reaction mixture, and the aqueous layer was extracted with ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. Column chromatography on silica gel eluting with hexane and increasing amounts of ethyl acetate afforded alkyne *cis*-**9a** (500 mg, 88% yield). $[\alpha]_D^{25}$ +2.8 ($CHCl_3$; *c* 3.0); IR (film) ν_{max} cm^{-1}: 3312, 2950, 2110, 1377, 1061. ^1H NMR ($CDCl_3$): δ 0.76 (bq, 1H, ^3J=8.4 Hz, 1-H), 1.05 (s, 3H, Me on C-2), 1.10 (s, 3H, Me on C-2), 1.16 (dd, 1H, ^3J=8.4 Hz and ^4J=2.3 Hz, 3-H), 1.34 (s, 3H, 4′-H), 1.42–1.86 (m, 4H, 1′-H, 2′-H), 1.89 (d, 1H, ^4J=2.4 Hz, 2″-H), 3.95 (bs, 4H, 1,3 dioxolan); ^{13}C NMR ($CDCl_3$): δ 15.9 (Me on C-2′); 17.2 (C-3), 20.2 (C-1′), 21.6 (C-2), 23.7 (C-4′), 27.6 (C-1), 29.5 (Me on C-2), 38.2 (C-2′), 64.5 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 67.6 (C-2″), 83.0 (C-1″), 109.9 (C-3′); GC/EIMS (70 eV) *m/z* (%): 193 (2), 165 (2), 131 (9), 105 (6), 43 (82).

*(+)-Nortaylorione {(1′S)-*cis*-2-[2′,2′-dimethyl-3′-(3″-oxobutyl)cyclopropyl]cyclopent-2-en-1-one [(+)-*cis*-**5a**]*

A stirred solution of $Co_2(CO)_8$ (420 mg, 1.23 mmol) in toluene (20 mL) under argon was treated with the alkyne *cis*-**9b** (120 mg, 0.58 mmol). The mixture was left in the dark at r.t. overnight. The reaction mixture was then filtered through a pad of Celite and the solvent removed under reduced pressure. The residue was purified by chromatography on alumina eluting with toluene. The resulting alkynehexacarbonyldicobalt complex was dissolved in anhydrous toluene (10 mL), the solution was treated CO and ethene for 10 min and then sealed in a glass ampoule. The sealed ampoule was heated at 70°C for 52 h. Solvent evaporation and purification of the residue on silica gel eluting with hexane/acetate 3:1 afforded 45 mg of the acetal **5c** (30%). IR (film) ν_{max} cm^{-1}: 1684, 1600, 1265, 730; ^1H NMR ($CDCl_3$): δ 0.90 (q, ^3J=8.7 Hz, 3′-H), 0.98 (s, 3H, Me on C-2′), 1.17 (s, 3H, Me on C-2′), 7.25(m, 3-H), 1.30 (s, 3H, 4″-H), 1.38 (m, 3H, 1′-H. 1″-H), 1.65 (t, ^3J=8.7 Hz, 2″-H), 2.36 (m, 2H, 4-H), 2.58 (m, 2H, 5-H), 3.90 (m, 4H, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$): δ 15.4 (Me on C-2′), 19.8(C-1″), 22.1 (C-1′), 20.3 (C-2′), 23.6 (C-4″), 26.6 (C-4), 29.0 (Me on C-2′), 29.2 (C-3′), 33.6 (C-5), 38.9(C-2″), 64.5 (OCH_2CH_2O), 109.8 (C-3″), 143.2 (C-2), 155.7 (C-3), 210.9 (C-1); GC/EIMS (70 eV) *m/z* (%): 264 ($M^{+\bullet}$ 5), 249 (3), 221 (2), 203 (2), 203 (2), 177 (3), 133 (2), 115 (3), 87 (100), 43 (48).

A stirred solution of *cis*-**5c** (45.0 mg, 0.17 mmol) in acetone (5 mL) and two drops of water was treated with PPTS[12] and heated to reflux for 3 h. The solvent was evaporated *in vacuo* and the residue was taken in diethyl ether (5 mL). The solution was washed with water (3×5 mL), dried over Na_2SO_4, and the solvent was evaporated. The residue was filtered through a short pad of silica gel (diethyl ether) yielding (+)-**5a** (37 mg, 98%). $[\alpha]_D^{25}$ +26 ($CHCl_3$; *c* 1.0); IR (film) ν_{max} cm^{-1}: 1706, 1604, 1495; ^1H NMR ($CDCl_3$): δ 0.87 (q, ^3J=7.3 Hz, 3′-H showed H,H correlation 1.56 and 1.38 and one bond H,C correlation 28.6), 0.98 (s, 3H, Me on C-2′), 1.16 (s, 3H, Me on C-2′), 1.38 (dm, H, ^3J=8 Hz, 1′-H), 1.56 (bq, ^3J=7.2 Hz, 1″-H), 2.13 (s, 3H, 4″-H), 2.37 (m, 2H, 5-H), 2.46 (t, 2H, ^3J=7.2 Hz, 2″-H), 2.58 (m, 2H, 4-H, showed a H,H correlation with 7.26 and one bond H,C correlation with 26.8), 7.26 (bs, 3-H); ^{13}C NMR ($CDCl_3$): δ 15.8 (Me on C-2′), 19.5 (C-1″), 20.4 (C-2′), 22.3 (C-3′), 26.8 (C-4), 28.6 (C-1′), 29.2 (Me on C-2′), 30.2 (C-4″), 33.9 (C-5), 43.9 (C-2″), 143.5 (C-2), 157.2 (C-3), 209.7 (C-1), 211.8 (C-3″); GC/EIMS (70eV) *m/z* (%): 220 ($M^{+\bullet}$ 0.5), 202 (4), 175 (8), 163 (8), 121 (4), 105 (12), 91 (30), 71 (36), 43 (100). Retention index[4] (chiral column) 1932.

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