Synthesis and Reactivity of (+)-16-Deoxo-15-oxoisosteviol

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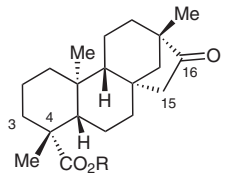
Abstract: The synthesis of optically pure (–)-isosteviol derivatives with a keto function shifted to position 15 and its insertive esterification are described.

Key words: terpenoids, chiral pool, esters, carbocycles, rearrangements

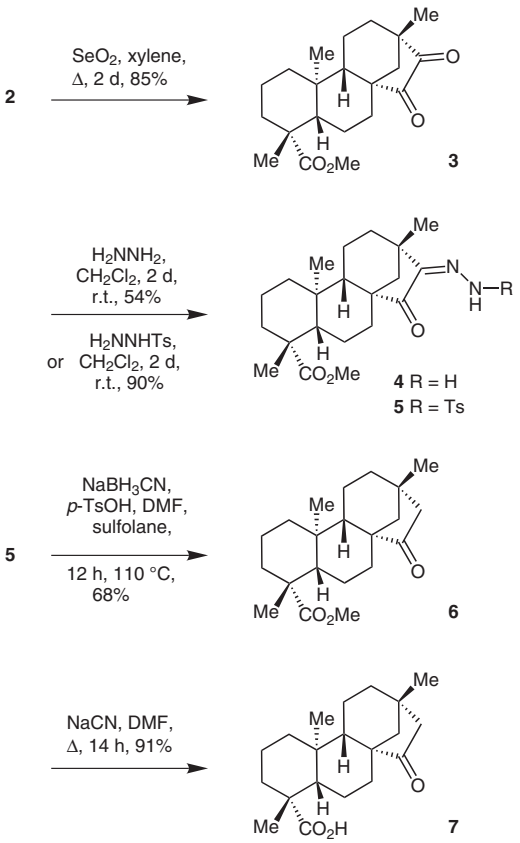
Stevioside and rebauside F, which are both glycosides of the same aglycon, can be easily isolated from stevia plants and are used as alternative sweeteners.[1] Upon treatment with strong mineral acids, these readily available commercial mixtures provide (–)-isosteviol (**1**) in large quantities.[2] **1** represents a unique diterpenoid skeleton with a keto and carbonyl group pointing in almost the same direction (Figure 1), and its co-crystallization with various organic compounds was studied intensively.[3] Recently, we exploited the high optical purity and the specific arrangement of functional groups for the construction of enantiomerically pure receptor structures based on triphenylene ketals.[4] In order to facilitate selective and optimal binding of guests, a more centred and therefore less open arrangement of the hydrogen bonding donors is crucial.[5] Since the host/guest interaction is almost insulated from the outer sphere, no self-aggregation phenomena are observed.[6] In order to close up the geometry of the (–)-isosteviol-based receptor, a shifting of the keto group from position 16 into the adjacent location 15 was envisioned. Standard protocols known from simple terpenoids, e.g. camphor,[7] were tested on the 16-oxobeyerane skeleton.

In this paper we report the efficient translocation of the keto function onto position 15. Furthermore, a novel insertive esterification is described. The synthetic pathway



1 R = H (–)-isosteviol
2 R = Me

Figure 1 Diterpenes from the beyerane series



Scheme 1 Sequence for shifting the oxo moiety

required blocking of the carboxy moiety, which was performed by methylation of the carboxylate providing **2** in good yield.[8]

The installation of the α-keto group was achieved in a Riley oxidation[8,9] using selenium dioxide (Scheme 1). The 15,16-diketo compound **3** was obtained as orange coloured crystals in 85% yield, whose analytical data matched a structural analogue of the beyerane series.[8] Initially, a Wolff–Kishner reduction was envisioned for the removal of the of the 16-oxo functionality.[10] The conversion with hydrazine occurred selectively on the less hindered keto group. With hydrazine hydrate, moderate yields of 54% could be obtained, however, despite intense studies, no reaction conditions could be found for its conversion into **6**. Therefore, a more reactive hydrazine derivative was prepared. Gratifyingly, the installation of the *N*-tosyl hydrazone to give **5**, could be performed in very good yield (90%). The subsequent reductive step turned

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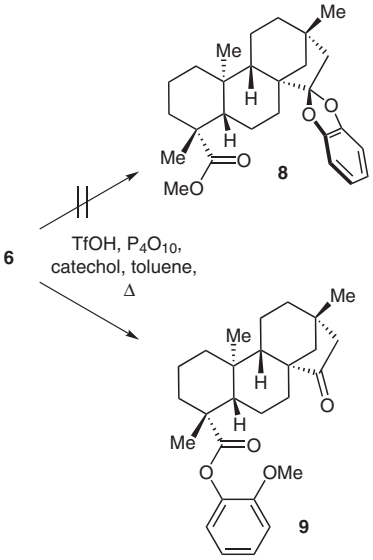
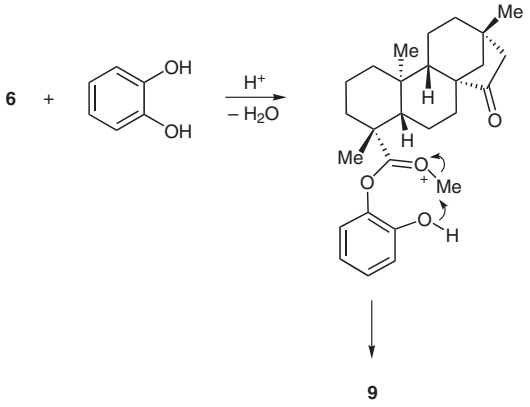


Scheme 2 Insertive esterification

out to be challenging; simple treatment with sodium borohydride in alcohol at low temperature[11] led to complete decomposition. Switching to cyanoborohydride under acidic conditions at elevated temperatures as developed by Reißig et al.,[12] gave access to the desired compound but in low yield (27%). Significant reduction of the excess of cyanoborohydride reagent, however, resulted in 68% isolated yield of **6**. The methyl ester was deprotected by a dealkylative cleavage using sodium cyanide in DMF, which gave **7** in 91% yield. For the construction of receptor geometries involving triphenylene ketals, the corresponding catechol ketals had to be made – these were then to be oxidatively trimerized.[5,13]

The sterically demanding environment of the translocated keto function caused problems in the formation of the benzodioxole moiety via ketalization. Employing typical solvents for such transformations, e.g. toluene, chlorobenzene or 1,2-dichlorobenzene in combination with strong acids such as toluenesulfonic acid, methanesulfonic acid or triflic acid, did not show any conversion even under drastic conditions (Scheme 2).[14] When phosphorous pentoxide was present in a mixture of catechol, triflic acid, toluene and **6**, an unusual reactivity was initiated. Despite intense optimization studies, the yield did not exceed a modest 22%, since prolonged reaction times promoted decomposition. It turned out that the product of the reaction, **9** (an ester of guaiacol), was formed by an insertive esterification (Scheme 2). This curious and unprecedented formation of the ester might be a consequence of steric demand on that particular keto function. After the catechol was added to the ester moiety and water removed, the carbocation is stabilized by methyl transfer onto the adjacent phenolic hydroxy group, providing **9** (Scheme 3). The insertive esterification reaction seems to be a rather limited transformation because of the harsh reaction conditions. The unusual reaction pathway is attributed to the steric demand around the functional groups in **6**. Other



Scheme 3 Mechanistic rationale for ester formation

desiccants did not succeed. Most probably, phosphorous pentoxide induces the formation of triflic anhydride.

The molecular structure of this ester was proven by X-ray crystal structure analysis of suitable single crystals. The conformation of **9** is shown in Figure 2. As expected, the shift of the keto group to the adjacent position respective to isosteviol, does not affect the rigid skeleton of the molecule. The carbonyl group of the exocyclic substituent in position 4 eclipses the C3–C4 bond of the skeleton, which is the most favourable orientation since there are no hydrogen bonds, as for example in case of the methyl ester of isosteviol[15] or more bulky ester derivatives.[16] Isosteviol derivatives are known for the recognition of aromatic compounds and this behaviour is expressed in the molecular packing of compound **9** (Figure 3), with 2-methoxyphenoxy substituents being located between the lipophilic polycyclic skeletons of the molecule. This clearly indicates the dominating role of CH–π interactions in the crystal packing.[17] For **1** itself, two orientations of the carboxylic group are observed in the crystal: one with the carbonyl bond in ecliptic orientation to the C3–C4 bond of the skeleton, and a second with the C–OH bond in such an ecliptic position leading to the formation of hydrogen bonded dimers. In molecular complexes of isosteviol with aromatic compounds a different hydrogen bond pattern dictates the eclipsed orientation of the hydroxyl group.[3]

In conclusion, the 16-keto functionality on the beyerane scaffold derived from (–)-isosteviol, can be efficiently shifted to the adjacent position 15 in an overall yield of 52% starting from **2**. The sequence involves a selenium

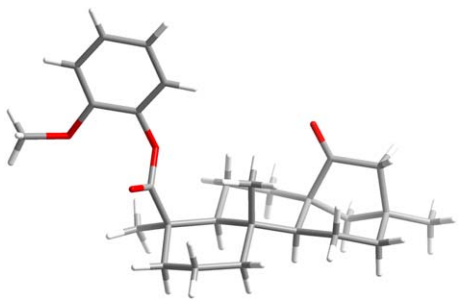


Figure 2 Molecular structure of **9**

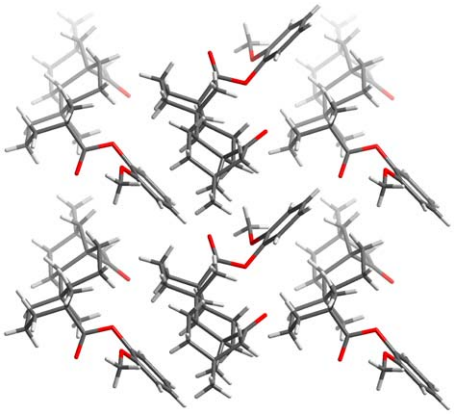


Figure 3 Crystal packing of **9** with wrapped arene moieties

dioxide oxidation, formation of *N*-tosyl hydrazone and subsequent reductive removal using sodium cyanoborohydride. Upon ketalization with strong acidic media and catechol, the first example of an insertive esterification was found. The shifting of the keto group produces a much more convergent arrangement of functionalities on the beyerane skeleton.

All reagents used were of analytical grades. Solvents were dried if necessary by standard methods. Column chromatography was performed on silica gel (particle size 63–200 μm; Merck, Darmstadt, Germany) using cyclohexane–EtOAc as eluent. Melting points were determined on an SMP3 melting point apparatus (Stuart Scientific, Watford Herts, UK) and are uncorrected. Micro analyses were performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). ^{1}H NMR spectra were recorded at 25 °C on Bruker DPX 300 or DPX 400 instruments (Analytische Messtechnik, Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard or traces of $CHCl_3$ in the deuterated solvent. Mass spectra were obtained on a MAT8200, MAT95XL (Finnigan, Bremen, Germany), MS50 (Kratos, Manchester, England) or FT-ICR (Bruker APEX IV) employing EI, ESI. Optical rotations were measured using a Jasco P-1020 apparatus (path length 100 mm).

(–)-Methyl *ent*-15,16-Beyerandion-19-oate (3)

A suspension of (–)-isosteviol methyl ester (10.1 g, 30 mmol) and selenium dioxide (4.4 g, 54 mmol) in xylene (150 mL) was stirred under reflux for 48 h. The inorganic solid was filtered off with the aid of Celite™. The filter cake was extensively rinsed with CH_2Cl_2 and the filtrate was concentrated in vacuum. The crude product was purified by column chromatography (cyclohexane–EtOAc, 95:5).

Yield: 9.0 g (85%); orange crystalline solid; mp 190 °C; $[\alpha]_D^{25}$ –173.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.53 (s, 3 H, CH_3), 0.86 (dt, *J* = 13.1, 4.1 Hz, 1 H), 0.99 (dd, *J* = 13.5, 4.1 Hz, 1 H), 1.11 (s, 3 H, CH_3), 1.14 (dd, *J* = 12.7, 2.0 Hz, 1 H), 1.19 (s, 3 H, CH_3), 1.18–1.31 (m, 2 H), 1.37–1.44 (m, 1 H), 1.53–1.64 (m, 3 H), 1.71–1.85 (m, 4 H), 1.87–1.94 (m, 2 H), 1.96–2.01 (m, 1 H), 2.14–2.19 (m, 1 H), 2.24–2.35 (m, 1 H), 3.64 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 18.9, 20.1, 20.8, 21.4, 28.7, 34.1, 37.9, 38.7, 39.7, 39.8, 43.7, 46.9, 47.3, 50.5, 51.3, 56.2, 59.6, 177.6, 208.8, 210.1.

MS (EI, 70 eV): *m*/*z* (%) = 346.2 (25) $[M]^+$, 318.2 (6), 290.2 (100), 276.2 (18), 231.2 (55), 180.1 (37).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.51; H, 8.85.

(+)-Methyl *ent*-16-(1,1-Diazendiyl)beyeran-15-on-19-oate (4)

To a solution of **3** (1.0 g, 3 mmol) in CH_2Cl_2 (150 mL) at r.t., hydrazine hydrate (220 mg, 4 mmol) was added and the resulting solution was stirred at r.t. for 24 h. The mixture was concentrated in vacuo and the crude product was purified by column chromatography (cyclohexane–EtOAc, 95:5).

Yield: 560 mg (54%); yellow glassy solid; $[\alpha]_D^{25}$ +0.7 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51 (s, 3 H, CH_3), 0.82 (dt, *J* = 13.2, 4.0 Hz, 1 H), 0.98 (dd, *J* = 13.5, 4.1 Hz, 1 H), 1.04–1.14 (m, 2 H), 1.06 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.32 (dd, *J* = 13.4, 4.4 Hz, 2 H), 1.39–1.51 (m, 3 H), 1.57–1.83 (m, 7 H), 2.15–2.25 (m, 2 H), 3.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 19.1, 21.1, 23.2, 26.9, 28.8, 34.2, 38.2, 38.5, 39.3, 39.7, 40.1, 43.8, 49.5, 51.3, 51.2, 56.5, 57.7, 145.6, 177.9, 208.0.

MS (EI, 70 eV): *m*/*z* (%) = 360.2 (65) $[M]^+$, 332.2 (100).

HRMS: *m*/*z* [M] calcd for $C_{21}H_{32}N_2O_3$: 360.2413; found: 360.2418.

(–)-Methyl *ent*-16-[2-(4-Methylphenylsulfonyl)-1,1-diazene-diyl]beyeran-15-on-19-oate (5)

To a solution of diketone **3** (9.0 g, 26 mmol) in CH_2Cl_2 (100 mL) at r.t., *p*-tosyl hydrazine (4.8 g, 26 mmol) was added and the resulting solution was stirred at r.t. for 48 h. The mixture was concentrated in vacuo and the crude product was purified by column chromatography (cyclohexane–EtOAc, 75:25).

Yield: 12.0 g (90%); yellow glassy solid; $[\alpha]_D^{20}$ –7.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63 (s, 3 H, CH_3), 0.87 (dt, *J* = 13.2, 4.2 Hz, 1 H), 1.00 (dd, *J* = 13.4, 4.1 Hz, 1 H), 1.08–1.16 (m, 2 H), 1.09 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.24–1.45 (m, 4 H), 1.54–1.62 (m, 2 H), 1.68–1.88 (m, 6 H), 2.16–2.32 (m, 2 H), 2.40 (s, 3 H), 3.66 (s, 3 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 12.08 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 18.9, 20.8, 20.9, 21.5, 22.5, 28.7, 33.6, 37.9, 38.6, 39.6, 39.9, 40.8, 43.7, 50.5, 51.3, 51.5, 56.2, 58.3, 127.6, 129.5, 135.6, 144.0, 152.7, 177.6, 209.8.

MS (EI, 70 eV): *m*/*z* (%) = 514.3 (60) $[M]^+$, 332.2 (100).

HRMS: *m*/*z* [M + H^+] calcd for $C_{28}H_{39}N_2O_5S$: 515.2574; found: 515.2574.

(+)-Methyl *ent*-15-Oxobeyeran-19-oate (6)

To a solution of **5** (5.0 g, 9.7 mmol) in DMF–sulfolane (1:1, 30 mL), sodium cyanoborohydride (3.1 g, 49 mmol) and PTSA (3.7 g, 19.5 mmol) were added and the resulting mixture was stirred under reflux for 48 h. After cooling of the solution to r.t., it was brought to pH 8 with sat. NH_4Cl. After extraction with MTBE (5 × 110 mL), the combined organic layers were washed with H_2O (5 × 100 mL) and brine (2 × 100 mL), dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc, 95:5).

Yield: 2.2 g (68%); colourless crystalline solid; mp 152 °C; $[\alpha]_D^{25}$ +22.5 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (s, 3 H, CH_3), 0.84 (dt, *J* = 13.1, 4.2 Hz, 1 H), 0.95–1.53 (m, 9 H), 1.05 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.60–1.94 (m, 7 H), 2.07–2.27 (m, 3 H), 3.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 19.1, 20.8, 21.0, 27.1, 28.8, 33.7, 34.7, 38.2, 38.4, 38.6, 40.2, 43.8, 51.17, 51.22, 52.6, 54.4, 56.5, 57.0, 178.0, 222.3.

MS (EI, 70 eV): *m*/*z* (%) = 332.3 (47) [M]$^+$, 314.2 (36), 300.2 (100), 273.2 (24), 255.2 (58).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.54; H, 9.81.

(+)-*ent*-15-Oxobeyeran-19-oic Acid (7)

To a solution of **6** (440 mg, 1.3 mmol) in DMF (30 mL), NaCN (190 mg, 4 mmol) was added and the resulting mixture was stirred under reflux for 24 h. The mixture was fractionated with MTBE (100 mL) and acidic $FeSO_4$ solution [made from HCl (1 M, 50 mL) and $FeSO_4 \cdot 7H_2O$ (1.5 g)]. The organic layer was washed with H_2O (5 × 100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane–EtOAc, 80:20).

Yield: 383 mg (91%); colourless crystalline solid; mp 221 °C; $[\alpha]_D^{25}$ +34.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (s, 3 H, CH_3), 0.80–0.88 (m, 1 H), 0.95–1.03 (m, 1 H), 1.05 (s, 3 H, CH_3), 1.07–1.20 (m, 3 H), 1.24 (s, 3 H, CH_3), 1.25–1.54 (m, 5 H), 1.60–1.65 (m, 1 H), 1.71–1.95 (m, 6 H), 2.08–2.16 (m, 2 H), 2.24–2.35 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 19.0, 20.8, 23.8, 27.1, 29.1, 33.6, 34.7, 37.8, 38.6, 38.6, 40.2, 43.6, 51.1, 52.6, 54.4, 56.5, 57.0, 183.6, 222.4.

MS (EI, 70 eV): *m*/*z* (%) = 318.2 (96) [M]$^+$, 300.2 (100), 274.2 (20), 255.2 (45).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.33.

(–)-(2-Methoxyphenyl)-*ent*-15-oxobeyeran-19-oate (9)

Under an inert atmosphere **6** (270 mg, 0.8 mmol) and catechol (200 mg, 1.8 mmol) were added to a suspension of P_4O_{10} (50 mg) in toluene (20 mL). The suspension was heated to reflux, whereupon TfOH (90 mg, 0.6 mmol) was added. The resulting mixture was stirred under reflux for 30 min after which ice (20 g) was added. The suspension was fractionated with MTBE (30 mL) and aq NaOH (20%, 30 mL). The aqueous layer was extracted with MTBE (2 × 30 mL) and the combined organic layers were washed with H_2O (2 × 30 mL) and brine (30 mL). After drying ($MgSO_4$), the solution was concentrated under reduced pressure and the crude product was purified by column chromatography (cyclohexane–EtOAc, 98:2).

Yield: 80 mg (22%); colourless crystalline solid; mp 139 °C; $[\alpha]_D^{25}$ –14.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 0.91 (dt, *J* = 13.1, 4.2 Hz, 1 H), 1.07 (s, 3 H, CH_3), 1.09 (dd, *J* = 13.5, 4.1 Hz, 1 H), 1.15–1.26 (m, 3 H), 1.30–1.67 (m, 9 H), 1.40 (s, 3 H), 1.75–1.97 (m, 3 H), 2.14 (dd, *J* = 18.6, 4.1 Hz, 1 H), 2.28–2.31 (m, 1 H), 2.50 (ddd, *J* = 26.6, 13.7, 3.7 Hz, 1 H), 3.83 (s, 3 H), 6.90–6.96 (m, 2 H), 7.02 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.16 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 19.1, 21.0, 21.1, 27.2, 29.1, 33.9, 34.8, 38.5, 38.7, 38.8, 41.0, 44.3, 51.3, 52.8, 54.5, 55.8, 56.7, 57.1, 112.4, 120.7, 122.9, 126.5, 140.0, 151.55, 175.7, 222.3.

Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.70; H, 8.71.

X-ray Crystal Structure Determination

Crystallization resulted from slow solvent diffusion from a solution of **9** in CH_2Cl_2 and MeOH, which was covered with *n*-heptane. The data set for **9** was collected with a Nonius Kappa CCD diffractometer equipped with fine-focus Cu K_α radiation sealed tube (λ = 1.54178 Å). Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[18] absorption correction Denzo,[19] structure solution SHELXS-97,[20] structure refinement by full-matrix least-squares against F^2 using SHELXL-97.[21]

Crystal data for **9**: Empirical formula $C_{27}H_{36}O_4$; M = 424.56; a = 9.0044(3) Å, b = 12.5039(3) Å, c = 20.8612(6) Å; V = 2348.8(1) Å^3; D (calculated) = 1.201 g cm^{-3}, μ = 0.624 mm^{-1}; empirical absorption correction ($0.835 \le T \le 0.912$), Z = 4; crystal system = orthorhombic; space group $P2_12_12_1$ (No. 19); T = 223 K; ω and φ scans, 19749 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.60 Å^{-1}, 4112 independent (R_{int} = 0.064) and 3666 observed reflections [$I \ge 2\sigma(I)$]; 284 refined parameters, R = 0.047, wR^2 = 0.114; max. residual electron density 0.16 (–0.16) e Å^{-3}; hydrogen atoms calculated and refined as riding atoms. CCDC 667062 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

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(14) Tested reaction conditions for the synthesis of **8**: (+)-Methyl-*ent*-15-oxobeyeran-19-oate (**6**) was dissolved in toluene, chlorobenzene or 1,2-dichlorobenzene and, after addition of catechol and a catalytic amount of a Brønsted acid, the mixture was heated under reflux applying a Dean–Stark trap. Even under very harsh conditions such as TsOH in boiling 1,2-dichlorobenzene (180 °C) or TfOH in boiling toluene, no product formation was observed.

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