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SYNTHESIS OF A 1,9-DIDEOXY-FORSKOLIN DERIVATIVE

Silke Zimmermann, Stefan Bick, Peter Welzel*, Heike Meuer, William S. Sheldrick

Fakultät für Chemie der Ruhr-Universität, D-44780 Bochum (Germany)
and Institut für Organische Chemie der Universität Leipzig,
Talstr. 35, D-04103 Leipzig (Germany)

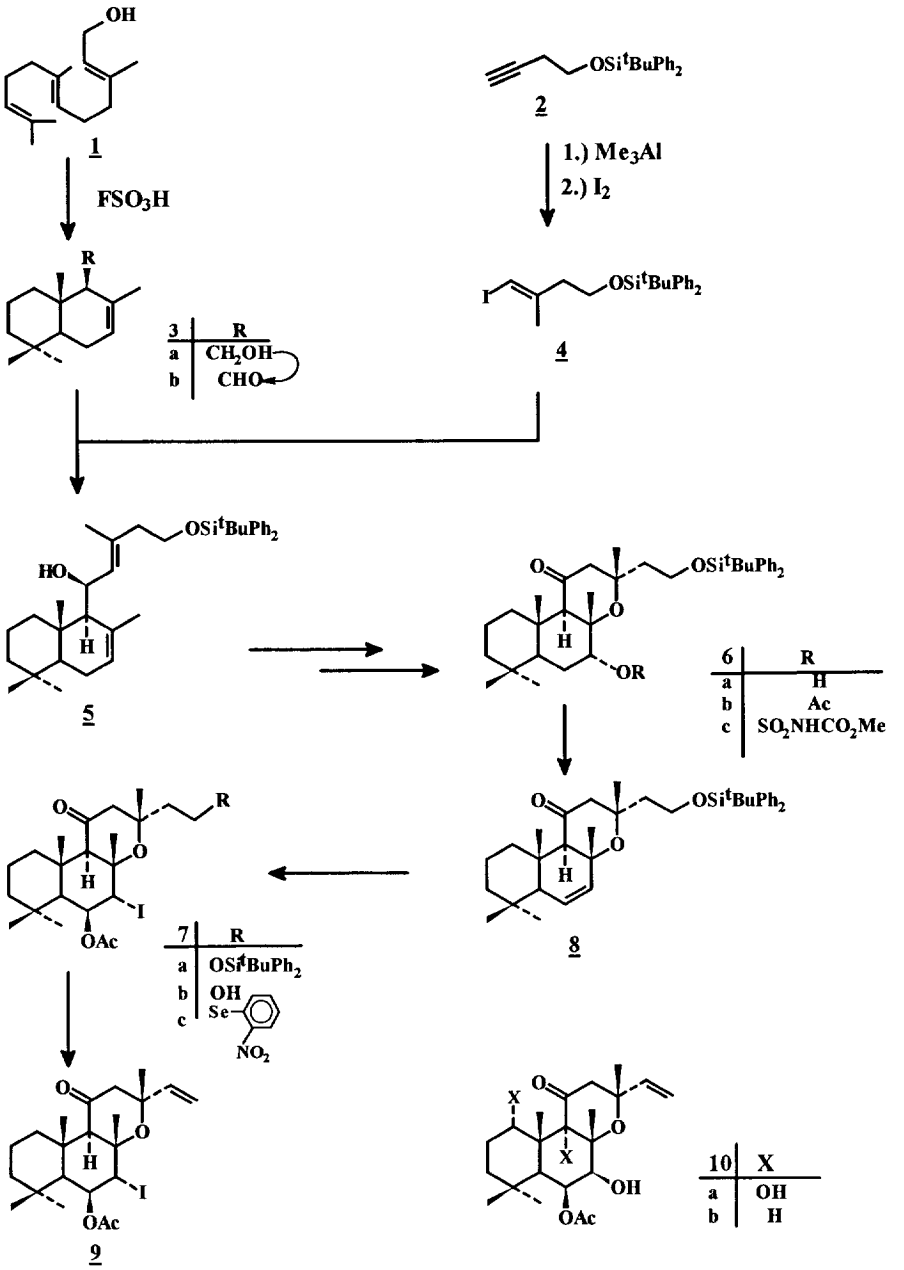
Abstract 1,9-Dideoxy-forskolin derivative **9** is available in 12 steps starting from (E,E)-farnesol (**1**).

Synthetic work on the diterpenoid forskolin (**10a**), a potent adenylate cyclase stimulator, has culminated in three remarkable total syntheses.[1] But, although these syntheses are of a high degree of sophistication they are much too complicated to permit the synthesis of structural analogues. For some time, we have been engaged in developing a simpler approach towards forskolin[2] in which 1,9-dideoxy-forkolin (**10b**) is regarded as a relay compound. **10b**, itself a natural product, can be converted to **10a** quite efficiently by a chemo-enzymatic process.[3]

Our starting material is (E,E)-farnesol (**1**) which is converted via drimenol (**3a**) to the labdane **6a** in eight steps. On the way from **3a** to **6a**, the missing five carbons are introduced making use of the organometallic reagent derived from **4**[4] by I→Li exchange.

In the present publication we describe the conversion of **6a** into 1,9-dideoxy-forskolin derivative **9**.

Dehydration of **6a** posed a number of serious problems. First of all, the 7α-OH group in **6a** turned out to be quite unreactive. Acetylation gave **6b** only in modest yield even under forcing conditions (presence of Steglich's base or Oppenauer method[5]). Normal E_2 elimination via a sulfonate was abandoned because of the known propensity of this type of compounds towards eliminative ring C opening, triggered by the acidity of the α-positions of the 11-keto group.[6] Gerlach's method (pyrolysis of thiocarbonate O-esters of sterically hindered alcohols[7]) did not work since we were unable to obtain the thiocarbonate. The Burgess method,[8,9] a thermal *syn* elimination, equally failed. On treatment of **6a** with the Burgess inner salt no elimination product was obtained. Rather the sulfamoyl dervative **6c** could be isolated. Attempts to achieve the desired elimination by treatment of **6c** with base and thus generating the anionic intermediate of the Burgess elimination met with no success. At the end, Martin's sulfurane[10,11] (in toluene at 60°C) turned out to be the reagent of choice.[12]


OH
1
FSO3H
R
3 R
a CH2OH
b CHO
OSi^{t}BuPh2
2
1.) Me3Al
2.) I2
I
OSi^{t}BuPh2
4
HO
H
OSi^{t}BuPh2
5
O
O
H
OR
OSi^{t}BuPh2
6 R
a H
b Ac
c SO2NHCO2Me
O
O
H
OSi^{t}BuPh2
8
O
O
H
I
OAc
R
7 R
a OSi^{t}BuPh2
b OH
c Se NO2
O
O
H
I
OAc
9
X
O
O
X
OH
OAc
10 X
a OH
b H

After 3 h **8** was obtained in 65% yield. Similar observations concerning the efficiency of these two dehydrating reagents have been reported by Paquette.[13]

Introduction of the cis 6,7-diol on the sterically hindered upper face was attempted using the Prévost-Woodward reaction. [14, 15] Thus, **8** was treated with silver acetate and iodine in acetic acid and (then) water. Instead of the desired diol acetate, iodo acetate **7a** was isolated which is the expected intermediate of the „normal" reaction course. We have been unable to convert the iodo aceate to the desired diol derivative by further treatment with silver acetate under the Prévost-Woodward conditions.[16] Fig. 1 shows the X-ray structure of **9**. In this compound, ring B obviously adopts a flattened chair conformation with the substituents at C-6 and C-7 in axial position. Thus, the stereochemical prerequisites for the substitution reaction at C-7 are fulfilled. One reason for the failure may be that the substitution reaction needs the assistance of water at the carboxyl carbon.[17] This would result in converting this carbon into an sp^3 centre and thus pushing the acetyl methyl over ring B where it would suffer from severe steric compression with the angular methyl groups.[18]

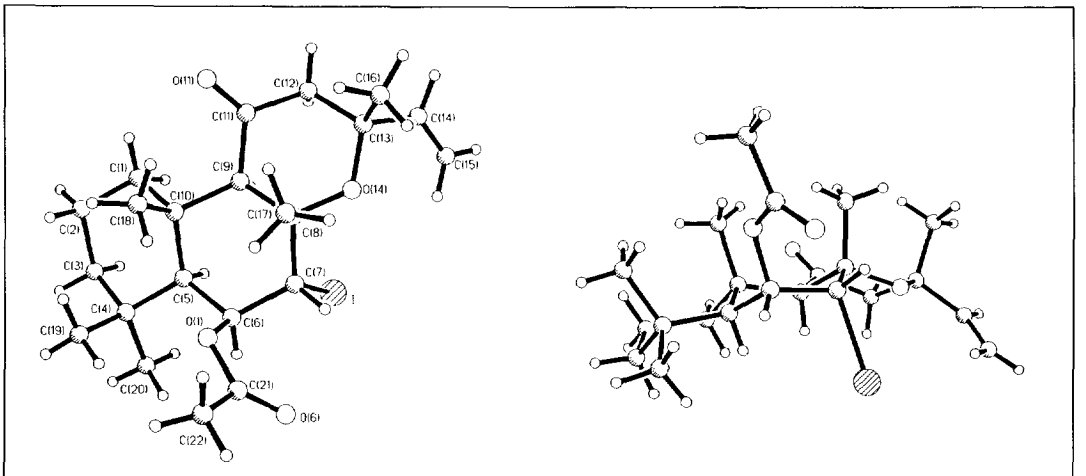


Figure 1. X-ray crystal structure of *rac*-**9**.

Notwithstanding this failure, the iodohydrin structure allows the introduction of many functionalities into ring B that are not attainable from forskolin and may be interesting in view of structure-activity relations. It was, therefore, decided to study the final steps of the synthesis. After treatment of **7a** with tetra-butylammonium fluoride (TBAF) the free alcohol **7b** was obtained.[19] For the dehydration the Grieco[20] method was employed. Thus, **7b** was converted into **7c** on reaction with o-nitrophenyl selenocyanate and tri-butylphosphine. Oxidation[21] of **7c** under mild conditions then gave cleanly **9**.

In conclusion: We have been able to convert **6a** into 1,9-dideoxy-forskolin derivative **9**. Key reactions are the dehydration **6a**→**8** with the Martin sulfurane, conversion of **8** into iodohydrin derivative **7b** and the Grieco elimination. Our approach allows the synthesis of **9** in 12 steps starting from (E,E)-farnesol (**1**).

EXPERIMENTAL

For general methods, instrumentation, and abbreviations, see ref.[2]

rac-[(8S, 13S)-7α-Acetoxy-15-(tert.-butyl-diphenyl-silanyloxy)-8,13-epoxy-labdan-11-one] (6b)
a) To a solution of *rac*-**6a** (20 mg, 0.035 mmol) in pyridine (0.5 ml) DMAP (0.5 mg, 0.005 mmol), dissolved in pyridine (0.5 ml), and Ac_2O (0.25 ml) were added and the mixture was stirred for 10 h at 20°C. Usual work-up (CH_2Cl_2), followed LC (petrol-ethyl acetate 20:1) yielded *rac*-**6b** (7.3 mg, 34%).
b) Finely powdered CaH_2 (12.5 mg, 0.296 mmol) and acetic anhydride (375 µl) were refluxed for 1 h. A solution of *rac*-**6a** (11.9 mg, 0.020 mmol) in toluene (1 ml) was added and the mixture was stirred for 71 h at 80°C. The reaction mixture was then added to $NaHCO_3$ (25 mg, 0.296 mmol) in ice-water (3 ml). After 1 h at 20°C usual work-up (CH_2Cl_2) and LC (petrol-ethyl acetate 30 : 1) furnished *rac*-**6b** (8.1 mg, 65%).- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.75, 1.03, 1.07 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 1.00 (s, 9H, ^{t}butyl), 1.21, 1.30 (2s, 6H, CH_3-16, CH_3-17), 1.83 (s, 3H, CH_3-21), 2.21 (m, 3H, containing 12-H), 2.61 (s, 1H, 9-H), 2.80 (d, J = 15 Hz, 1H, 12-H), 3.70-3.79 (m, 1H, 15-H), 3.85-3.93 (m, 1H, 15-H), 4.32 (m, $W_{1/2}$ = 7Hz, 1H, 7-H), 7.25-7.68 (m, 10H, aromat.-H), $|J_{12,12'}|$ = 15Hz.- IR (CCl_4): 1730 (C=O), 1710 cm^{-1} (C=O).- MS: m/z (%) = 561 (16, [M-^{t}butyl]$^+$), 501 (20), 269 (64), 235 (100), 199 (40), 43 (66), $C_{38}H_{54}O_5Si$ (618.93).- FAB MS (matrix: glycerol): m/z = 619.3 $[M+H]^+$.

rac-[(8S, 13S)-15-(tert.-Butyl-diphenyl-silanyloxy)-8,13-epoxy-7α-(N-methoxycarbonyl)-sulfamoyloxy-labdan-11-one] (6c)
To a solution of *rac*-**6a** (31 mg, 0.054 mmol) in toluene (10 ml) methoxycarbonylimido-triethylammonio-sulfone (645 mg, 2.7 mmol) was added. After 5 h at 20°C the toluene solution was washed with 3 per cent HCl (3 times 20 ml) and water (3 times 20 ml). After drying, solvent evaporation and LC (petrol-ethyl acetate 3:1) *rac*-**6c** (10 mg, 26%) was obtained.- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78, 0.87, 1.03 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 1.01 (s, 9H, ^{t}butyl), 1.28, 1.38 (2s, 6H, CH_3-16, CH_3-17), 1.40-1.70, 1.88-2.12 (2H), 2.22 (d, 1H), 2.30 (d, 1H, 12-H), 2.60 (s, 1H, 9-H), 2.78 (d, 1H, 12-H), 3.76 (s, 3H, OCH_3), 3.78-3.92 (2H, CH_2-15), 4.86 (dd, 1H, 7-H), 7.35-7.45 (6H, aromat.-H), 7.60-7.68 (4H, aromat.-H), $|J_{12,12'}|$ = 15.5Hz, $|J_{14,15}|$ = 6Hz.- IR (CCl_4): 1760 (C=O), 1720 cm^{-1} (C=O).- $C_{38}H_{55}0_8NSSi$ (714.01), MS: m/z (%) = 501 (100), 213 (53), 199 (75), 41 (55),

rac-[(8S, 13S)-15-(tert.-Butyl-diphenyl-silanyloxy)-8,13-epoxy-labd-6-en-11-one] (8)
To a solution of bis [1-phenyl-2,2,2-trifluoro-1-(trifluoromethyl)-ethoxy]-diphenylsulfuran (563.9 mg, 0.838 mmol) in toluene (3 ml) at 20°C a solution of *rac*-**6a** (193.2 mg, 0.335 mmol) in toluene (7 ml) was added and the mixture was heated to 60°C for 3 h. After quenching with ice, usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 45 : 1), followed by MPLC (petrol-ethyl acetate 60:1), *rac*-**8** (121.2 mg, 65%) was obtained.- ^1H NMR (400 MHz, C_6D_6): δ = 0.75, 0.80, (2s, 6H, CH_3-18, CH_3-19), 1.08 (s, 3H, CH_3-20), 1.15, 1.28 (2s, 6H, CH_3-16, CH_3-17), 1.17 (s, 9H, ^{t}butyl), 1.73 (m, 1H, 14-H, $J_{14,15}$ = 7 Hz), 1.75 (t, 1H, 5-H, $J_{5,6}$ = 2Hz), 1.90 (m, 1H, 14-H, $J_{14,15}$ = 6.5 Hz), 2.35 (d, 1H, 12-H), 2.72 (bd, 1H, 1β-H), 2.77 (d, 1H, 12-H), 2.95 (s, 1H, 9-H), 3.85-4.07 (2H, CH_2-15), 5.55 (dd, 1H, 6-H), 5.63 (dd, 1H, 7-H), 7.19-7.32 (6H, aromat.-H), 7.72-7.82, (4H, aromat.-H.), $J_{6,7}$ = 10.5 Hz, $|J_{12,12'}|$ = 18 Hz, $|J_{15,15'}|$ = 10.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 16.47 (CH_3-20), 18.41 (CH_2-2), 19.32 (C_q-PG), 21.84 (CH_3-19), 27.02 (CH_3-PG), 29,92 (CH_3-16), 32.33 (CH_3-17), 32.79 (CH_3-18), 32.96 (C_q-4 or 10), 36.53 (CH_2-1), 37.34 (C_q-4 or 10), 41.34 (CH_2-3), 48.21 (CH_2-14), 51.36 (CH_2-12), 55.21 (CH-5), 60.85 (CH_2-15), 67.52 (CH-9), 75.25 (C_q-8), 79.62 (C_q-13), 127.37 (CH-6 or CH-7), 127.91 (CH-PG), 129.89 (CH-PG), 132.72 (CH-6 or CH-7), 133.85 (C_q-PG), 135.80 (CH-PG), 207.4 (C_q-11).- IR (CCl_4): 1700 cm^{-1} (C = O).- MS: m/z (%) =

543 (3), 501 (5), 499 (5), 423 (9), 269 (100), 217 (50).- HRMS: ($C_{35}H_{47}O_3Si$): calcd: 543.3295, found: 543.3290.- $C_{36}H_{50}O_3Si$: (558.9) calcd: C 77.37, H 9.02, found: C 77.45, H 9.10.

rac-[(8S, 13S)-6ß-Acetoxy-15-(tert.-butyl-diphenyl-silanyloxy)-8,13-epoxy-7α-iodo-labdan-11-one] (7a)
To a suspension of AgOAc (30.7 mg, 0.184 mmol) in acetic acid (2 ml, dried with Ac_2O) under argon a solution of *rac*-**8** (46.8 mg, 0.084 mmol) in acetic acid (1 ml) was added. To this mixture within 30 min a solution of iodine (23.4 mg, 0.092 mmol) in acetic acid (2 ml) was added and the mixture was stirred for 70 min. Water (15.6 µl, 0.838 mmol, 10 eq) was added and stirring continued for 25 h at 20°C. After solvent evaporation the organic material was dissolved in ethyl acetate and the organic solution washed with $NaHCO_{3\ aq}$ (5 per cent). Drying, solvent evaporation, and LC (petrol-ethyl acetate 30:1) followed by MPLC (petrol -ethyl acetate 30:1) furnished *rac*-**8** (41.2 mg, 66%).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3H, CH_3-19), 0.93 (s, 3H, CH_3-20), 1.01 (s, 9H, ^{t}butyl-PG), 1.25 (s, 3H, CH_3-18), 1.41 (s, 3H, CH_3-17), 1.57 (s, 3H, CH_3-16), 1.87-1.94, (2H, CH_2-14), 1.97 (d, 1H, 5-H, $J_{5,6}$ = 2.44 Hz), 2.04 (s, 3H, CH_3CO), 2.22 (dm, 1H, 1β-H), 2.26 (d, 1H, 12-H, $|J_{12,12'}|$ = 14.16 Hz), 2.64 (s, 1H, 9-H), 2.73 (d, 1H, 12-H), 3.84-3.91, (1H, 15-H), 3.94-4.01, (1H, 15-H), 4.45 (d, 1H, 7-H, $J_{6,7}$ = 2.20 Hz), 5.55 (t, 1H, 6-H), 7.62-7.67, (4H, aromat.-H), 7.33-7.43, (6H, aromat.-H).- IR (CCl_4): 1746 (C = O), 1717 (C = O), 1233 (OAc), 1113 cm^{-1} (C-O).- MS: m/z (%) = 687 (2.5, [M- ^{t}butyl]$^+$), 559 (0.65) [687-HI], 499 (5), 269 (100).- $C_{38}H_{53}O_4SiI$ (744.83): calcd: C 61.28, H 7.17, found: C 61.11, H 7.25.

rac-[(8S, 13S)-6ß-Acetoxy-15-hydroxy-8,13-epoxy-7α-iodo-labdan-11-one] (7b)
To a solution of *rac*-**7a** (13.8 mg, 0.018 mmol) in THF (2 ml) bei 20° C TBAF (20 µl of a 1.1 mol/l solution in THF, 0.22 mmol) was added and the mixture was stirred at 20°C for 2.5 h. Usual work-up (CH_2Cl_2)and LC (petrol-ethyl acetate 1.5:1) provided *rac*-**7b** (8.2 mg, 87%).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 3H, CH_3-20 or CH_3-19), 0.92 (s, 3H, CH_3-20 or CH_3-19), 1.34 (s, 3H, CH_3-18), 1.42 (s, 3H, CH_3-16), 1.64 (s, 3H, CH_3-17), 2.02 (s, 3H, CH_3CO), 1.99 (d, 1H, 5-H, $J_{5,6}$ = 2.45 Hz), 2.17 (dm, 2H, 1β-H), 2.27 (d, 1H, 12-H ($|J_{12,12'}|$ = 13.42 Hz), 2.65 (d, 1H, 12-H), 2.77 (s, 1H, 9-H), 3.92-4.00, (1H, 15-H), 3.72-3.80, (1H, 15-H), 4.54 (d, 1H, 7-H), 5.68 (t, 1H, 6-H).- IR ($CHCl_3$): 3671 (O-H), 3536 (O-H), 1738 (C = O), 1713 (C = O), 1234 (C = O), 1259 (C-H), 1113 cm^{-1} (C-O).- MS: m/z (%) = 461 (5), 431 (5), 378 (5), 343 (25), 251 (17), 233 (20), 69 (38),43 (100).- $C_{22}H_{35}IO_5$ (506.42): calcd: C 52.19, H 6.96, found: C 52.28, H 6.98.

rac-[(8S, 13S)-6ß-Acetoxy-15-hydroxy-8,13-epoxy-7α-iodo-15-(o-nitrophenyl-selanyl)-labdan-11-one] (7c)
To a solution of *rac*-**7b** (19.3 mg, 0.038 mmol) and o-nitrophenyl selenocyanate (10.4 mg, 0.045 mmol in THF (1 ml) Bu_3P (11.8 µl, 0.045 mmol) was added and the mixture was stirred at 20°C for 2 h (colour change from yellowish brown to dark red and then to yellow). Solvent removal with a stream of argon and LC (petrol- ethyl acetate 10 : 1) yielded *rac*-**7c** (21.3 mg, 81%).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H, CH_3-19), 0.95 (s, 3H, CH_3-20), 1.35 (s, 3H, CH_3-18), 1.45 (s, 3H, CH_3-17), 1.67 (s, 3H, CH_3-16), 1.98-2.28, 1H, 1β-H), 2.07 (s, 3H, CH_3CO), 2.33 (d, 1H, 12-H, $|J_{12,12'}|$ = 13.7 Hz), 2.65 (d, 1H, 12-H), 2.75 (s, 1H, 9-H), 3.10-3.25, (2H, CH_2-15), 4.62 (d, 1H, 7-H, $J_{6,7}$ = 2.3 Hz), 5.72 (t, 1H, 6-H.), 7.30 (dtd, 1H, 3^a-H, $J_{3a,4a}$ = 7.1, Hz, $J_{3a,5a}$ = 1.22Hz), 7.52 (dtd, 1H, 4^a-H, $J_{4a,5a}$ = 8.1 Hz, $J_{4a,2a}$ = 1.46Hz), 7.68 (dd, 1H, 5^a-H), 8.28 (dd, 1H, 2^a-H, $J_{2a,3a}$ = 8.3 Hz).-$C_{28}H_{38}NIO_6{}^{78}Se$ (689.44), MS: m/z (%) = 689 (2.5), 661 (0.3), 564 (0.8), 504 (2.5), 343 (18), 251 (25), 233 (40), 43 (100).

rac-[(8S, 13S) 6ß-Acetoxy-8,13-epoxy-7α-iodo-labd-14-en-11-one] (9)
To a solution of *rac*-**7c** (5.0 mg, 7.8 10^{-3} mmol) in THF (0.3 ml) at 0° C H_2O_2 (3.3 µl of a 35 per cent solution, 0.039 mmol) was added. After 5 min the mixture was warmed to 20 °C. After 2 h another portion of the H_2O_2 solution (3.3 µl, 0.039 mmol) were added. Stirring was continued at 20° C for 3 d. The mixture was directly transferred onto the top of a LC column. LC (petrol-ethyl acetate = 7:1) provided *rac*-**9** (3.1 mg, 81 %).- M.p. 126°C (acetone-water).- ^{1}H NMR (400 MHz-$CDCl_3$): δ = 0.88 (s, 3H, CH_3-20), 0.92 (s, 3H, CH_3-19), 1.30 (s, 3H, CH_3-18), 1.36 (s, 3H, CH_3-16), 1.64 (s, 3H, CH_3-17), 1.70 (qbt, 1H, 1α-H, $|J_{1,1'}| \approx$ 13 Hz), 2.05 (s, 3H, CH_3CO), 2.41 (dm, 1H, 1β-H), 2.50 (d, 1H, 12-H, $|J_{12,12'}|$ = 16.6 Hz), 2.75 (d, 1H, 12-H), 2.85 (s, 1H, 9-H), 4.56 (d, 1H, 7-H, $J_{6,7}$ = 2.44 Hz), 5.95 (d, 1H, 15-H, $J^Z_{14,15}$ = 11 Hz), 5.08 (d,

1H, 15-H, $J^{E}_{14,15}$ = 17.7 Hz), 5.71 (t, 1H, 6-H), 6.29 (dd, 1H, 14-H).- MS: m/z (%) = 473 (1.5) $[M-CH_3]^+$, 413 (17) [473-HOAc], 343 (7), 251 (19), 233 (20), 43 (100).- IR ($CHCl_3$): 1711 (C = O), 1733 (C = O), 1233 cm^{-1} (C-O).-).- $C_{22}H_{33}IO_4$ (488.41 x acetone): calcd: C 54.94, H 7.19, found: C 55.17, H 6.93.

X-ray Structural Analysis of 9

9, $C_{22}H_{33}IO_4$, crystallises tricyclinic, space group P1, with a = 9.428(2), b = 10.327(2), c = 11.856(2) Å, α = 94.21(3), ß = 105.53(3), γ = 95.80°, V - 1100.4(4) $Å^3$, Z = 2, D_c = 1.47 $g \cdot cm^{-3}$. The structure was refined on F^2 to R = 0.061, wR2 = 0.140 for 3840 independent reflections collected on a Siemens P4 diffractometer ($2\theta \leq 25°$, MoKα, ω-scan). Further details of the structure investigation may be obtained from Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-76012 Eggenstein-Leopoldshafen (Germany), on quoting the deposition number CSD - 58725. Any request should be accompanied by the full literature citation of this paper.

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