Synthesis of (−)-Talaromycin A. The Use of the Δ 2 Effect for Stereocontrol at Spiroacetalic Centres#

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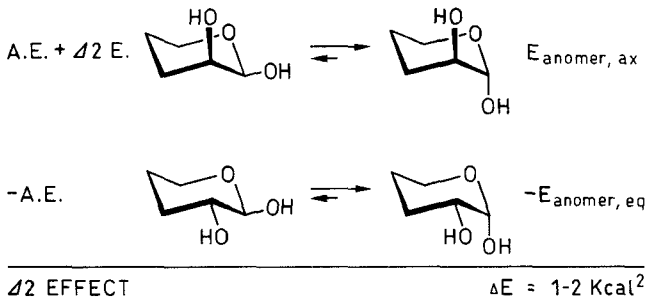
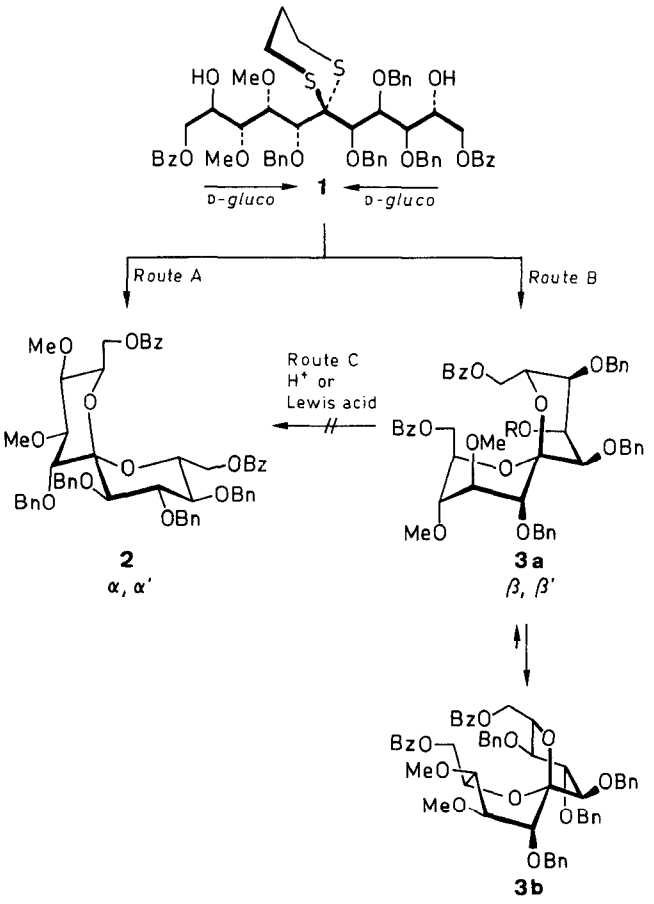
The new concept for stereocontrol at a spiroacetalic centre in thermodynamically controlled spiroacetalization, based on the operation of the Δ2 effect, allows the synthesis of (−)-Talaromycin A {(3*R*,4*S*,6*R*,9*R*)-9-ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane} in a linear sequence from D-glucose with an overall diastereoselectivity > 97%.

The so called Δ2 effect, well known in carbohydrate chemistry,[1] describes the behaviour of anomeric arrangements, in which the anomeric effect is enhanced by 1 kcal/mole (from equilibrium measurement[1]) up to 2 kcal/mole (by a initio calculations[2]), if a hydroxy group[3] keeps a position axial and "trans" to the anomeric polar bond (Scheme 1).



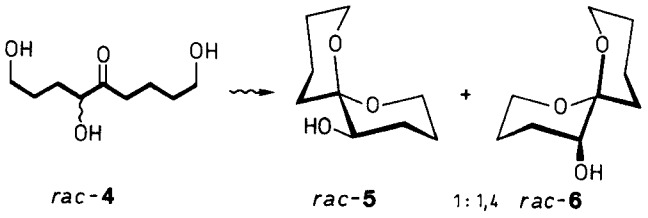
Scheme 1

The perhaps best known consequence of this effect is the strong tendency of *manno*-configurated sugar derivatives (2-OH axial) to form α-glycosides relative to those, in which the 2-OH is equatorially orientated (e.g., *gluco*-configurations[4]). On spiroacetals, especially on those of the 1,7-dioxabicyclo[5.5]undecane system, the anomeric effect operates in a sense, that each oxygen in a pyran ring keeps an axial orientation relative to the other pyran ring. Therefore, in a thermodynamically controlled spiroacetalization of an open chain precursor forming the 1,7-dioxabicyclo[5.5]undecane each additional substituent along the chain influences the proportion of the two possible isomers at the spiroacetalic centre, where both centres have the twofold anomeric stabilization. This concept is widely used for controlling the chirality at spiroacetalic centres.[5] Indeed, we thought, that an open chain molecule like compound **1**[6] which in the unprotected form shows C_2-symmetry, would yield (in Scheme 2, Route A) the spiroacetal **2**, containing two pyran moities with the D-*gluco* substitution pattern and α-oriented anomeric oxygen.



Scheme 2

Surprisingly, we could not detect any trace of **2** in the reaction mixture, beside isomeric half acetals the only reaction product being compound **3** (Route B) with the opposite configuration at the acetalic centre. The conformer **3b**, with two slightly different boat conformations for the pyran rings is the result of the distortion of conformer **3a** to avoid strong destabilizing interactions.[7] Both forms, **3a** and **3b**, clearly indicate the influence of the $\Delta 2$ effect. Though the reaction conditions (aqueous acetonitrile/mercury(II) oxide (HgO)/mercury(II) chloride ($HgCl_2$), reflux) for the thioacetal cleavage do not support the assumption that the formation of **3** is the result of a kinetically controlled process, this might be considered. In this case (and with the assumption, that compound **2** is of equivalent or greater thermodynamical stability than **3**, an acid-catalyzed isomerization (Route C) to compound **2** should be possible, comparable to the acid catalyzed isomerization of glycosides[8] or spiroacetals.[9] With respect to **3**, we did not succeed in an isomerization so far,[10] neither under protic nor under aprotic Lewis acid catalyzed conditions without destroying the molecule. On spiroacetals, the $\Delta 2$ effect seems to operate in the sense, that there is a strong additional stabilization of the anomeric arrangement, in which the hydroxy group at C-2 relative to the anomeric centre has an axial orientation.[11] Thermodynamically controlled spiroacetalization of *rac*-**4** should therefore yield *rac*-**5** and *rac*-**6** with a preference for the latter (Scheme 3).

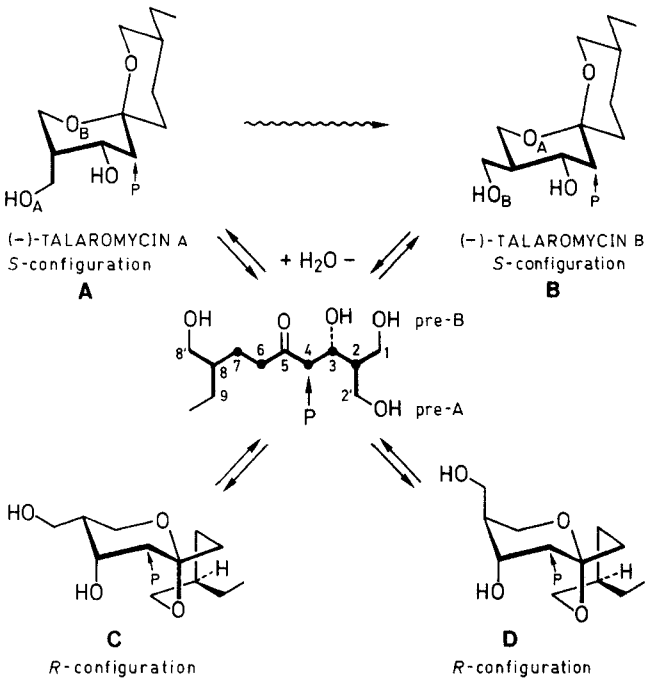


Scheme 3

The ratio of 1:1.4 proves this assumption[12] (note, that a hydroxy group at the next C-atom leads to the opposite tendency, see Ref. 5b). This fundamental difference in the behaviour during a thermodynamically controlled spiroacetalization allows a new type of stereocontrol in the synthesis of spiroacetals. We used this approach in a diastereoselective linear synthesis of (−)-Talaromycin A starting from D-glucose.

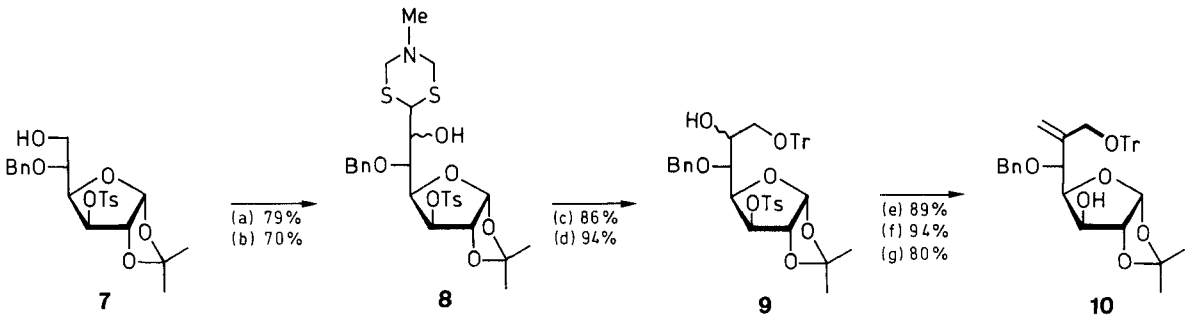
It has been reported that (−)-Talaromycin A, a toxic metabolite isolated from the fungus *Talaromyces stipitatus*, easily rearranges to yield the more stable isomer, Talaromycin B.[13] This result may be regarded as a consequence of the greater thermodynamical stability of Talaromycin B relative to Talaromycin A, perhaps via an open chain intermediate (described as forms **A**, **B** in Scheme 4).

To avoid this isomerization, from the synthetic point of view, it would be sufficient in a thermodynamically controlled spiroacetalization to differentiate the two topochemically equivalent hydroxymethylene groups, indicated as pre-**A** and pre-**B**, with suitable protecting



Scheme 4

groups. Of course it has to be considered, that two additional spiroacetals (forms **C** and **D**) showing the opposite configuration at the spiroacetalic centre may also be produced. Form **D** could be excluded using the same argument as for Talaromycin B (**B**), but **C** would be a realistic isomer. A rough evaluation of the non-bonding destabilizing interactions results in the small difference of only 0.35 kcal/mole, resulting from the additional axial OH–O interaction in **C** relative to **A**, comparable to the ratio in Ref. 5b. Though Talaromycin A is favoured, this difference would be not sufficient to obtain it as the only formed compound. It is obvious that a polar substituent placed in a correct position (indicated as P →), should exclusively support the formation of Talaromycin A, due to the $\Delta 2$ effect to such an extent, that the formation of **D** should be negligible under preparative conditions. On this basis, we decided to synthesize Talaromycin A in a linear sequence starting from D-glucose.[14] We directly incorporated the hydroxy function at C-3 of the open chain molecule (equivalent of C-5 of D-glucose) showing the correct configuration, as well as the hydroxy function at C-4, which is decisive or the $\Delta 2$ effect. Additionally, it would be necessary to control the chirality at C-8 and to differentiate the topochemically equivalent hydroxymethylene functions, both in the "off template" region, by the inherent induction, that could be achieved by a sugar. Scheme 5 outlines the basic manipulations performed on the 1,2-*O*-isopropylidene derivative of D-glucofuranose **7** to create a suitable situation for the differentiation of the hydroxymethylene groups, including a chain elongation **8** by fixing the primary hydroxy function, **9**, and incorporating an olefinic segment via a Wittig reaction (to give **10**). Oxidation of the unprotected secondary hydroxy group at C-3 of the furanic moiety and deblocking of the primary hydroxy group leads to a new pyranic moiety (see compound **11** in Scheme 6) by intramolecular cyclization.



Tr = CPh_3

Procedure	Purification[a]	Yield[c] (%)	$[\alpha]_D^{20}$ ($c = 1.0$, MeOH)	Remarks	Ref.
(a) $(COCl)_2$/DMSO/TFA/CH_2Cl_2, −60 °C	t/a (19 : 1)	79		see exp. part	15–20
				sensitive aldehyde, directly used for (b)	21
(b) 4,5-dihydro-2-lithio-5-methyl-1,3,5-dithiazine/ THF, −78 °C	t/a (5 : 1)[b]	70		characterized as 6-acetate[d]	22
			−15.3°	L-glycero-(major) mp 68 °C[d]	
			−4.8°	D-glycero-(minor) mp 75 °C[d]	
(c) 1. HgO/$HgCl_2$/MeCN, r.t., 8 h 2. $NaBH_4$/MeCN, r.t., 2 h	t/a (2 : 1)	86		see exp. part	
(d) TrCl/Py, 60 °C, 14 h	p/a (6 : 1)	94	−21.2°	major isomer, diacetate mp 74 °C[d]	16
(e) PDC/molecular sieves 3 Å/CH_2Cl_2, r.t., 16 h		89	+3.6°	mp 69 °C[d]	23
(f) Ph_3PCH_2/THF, −5 °C, 2 h	p/a (6 : 1)	94	−29.8°	[d]	24
(g) $LiAlH_4$/THF, 70 °C, 20 h	p/a (5 : 1)	80	−33.5°	[d]	25

[a] Abbreviations see experimental section.
[b] 6 : 1 by ^1H NMR.
[c] Yields of isolated products with correct analytical and spectroscopical data.
[d] Analyzed by ^1H NMR.

Scheme 5

After protecting the anomeric hydroxy group, the olefinic segment of the resulting molecule is hydroborated to generate a hydroxymethylene group in an axial orientation.[31] After its protection, this sequence represents the differentiation of the hydroxy methylene groups, in which pre-**B** can be released selectively by acidic cleavage of the acetalic benzyl ether. The second acetalic moiety in the molecule (C-1 of the original glucose) is cleaved under very mild acidic treatment to generate the aldehyde function, which further is used for a second chain elongation by a Wittig-type[32] reaction to yield exclusively the trans configurated olefin **13**, which is further transformed to **14**. In the side chain of this compound the C–O function and chirality at C-2 of the original glucose are used in a Claisen-type rearrangement under conditions described by Ireland et al.,[33] to form **15** (Fig. 7) showing the correct C–C-configuration in the "off template" region of the glucose.

Removing the primary hydroxy function and releasing the Si-protected OH-functions and acid-catalyzed cleavage of the acetalic moiety yields the intermediate **16**, which is in equilibrium to the corresponding open chain enon (ratio approximate 2:1). Hydrogenation of the olefinic bond, followed by BF_3-catalyzed spiroacetalization, leads to compound **17** without a detectable trace (proved by 400 MHz NMR) of an isomer, as it was anticipated due to the influence of the $\Delta 2$ effect. Removing the hydroxy function in the α-position next to the spiroacetalic centre and deprotection, both reactions carried out under slightly basic conditions, yields pure (−)-Talaromycin A.

All reactions were controlled by TLC on silica gel (Merck, GF_{254}) using solution mixtures of petroleum ether (p) (60/70)/*t*-Bu(Me)O (te) or Et_2O (e), petroleum/EtOAc (a) and toluene (t)/EtOAc. Detection was followed by UV-absorption, reaction with 0.2% ethanolic naphtoresorcin solution/2 N H_2SO_4 (1 : 1) or 10% ethanolic H_2SO_4 and heating. Separation of substances was accomplished by preparative column chromatography on silica gel 50 (70–230 mesh) at normal pressure or silica gel 60 (230–400 mesh) at 0.2–0.6 mPa. Melting points were measured on a "Leitz-Heiztischmikroskop" and are not corrected. Optical rotations were measured on a Perkin-Elmer polarimeter 243 using 1 dm cells. ^1H NMR spectra were recorded on a Bruker WH 270 or WH 400 using TMS as an internal standard and ^{13}C NMR spectra were recorded on a Bruker WM 400 at 100.62 MHz. All spectra were analyzed as first order spectra.

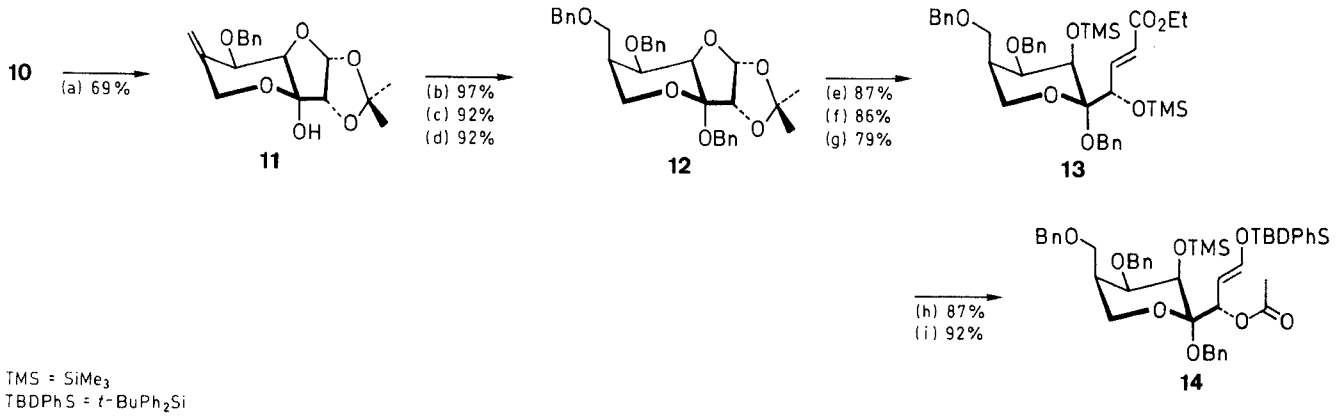
Starting material for the preparation of **7** was 1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose, described in Ref. 15. Two standard procedure are used:

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-p-toluenesulfonyl-α-D-glucofuranose (7); Procedure A:

Tritylation analogous Ref. 16:

1,2-O-Isopropylidene-3-O-p-toluenesulfonyl-6-O-triphenylmethyl-α-glucofuranose:

Ph_3CCl/pyridine, 6 h, 60 °C to give 95%; purification te (5 : 1 → 1 : 1); mp 70 °C, $[\alpha]_D^{20}$ 25.6° ($c = 1.0$, MeOH), ^1H NMR available.



TMS = $SiMe_3$
TBDPhS = t-$BuPh_2Si$

Procedure	Purification	Yield[a] (%)	$[\alpha]_D^{20}$ (c = 1.0, MeOH)	Remarks	Ref.
(a) 1. PDC/Ac_2O/CH_2Cl_2, r.t., 4 h				directly used for 2.	26
2. HCO_2H/Et_2O (1:1), r.t., 2 h	p/a (5:1)	69	−6.9°	mp 116°C[b]	18
(b) BnBr/NaH/DMF, r.t., 3 h	p/a (9:1)	97	−17.0° (c = 1.4)	[b]	27
(c) 9-BBN/THF (29.2:1), r.t., 18 h				see exp. part	
(d) BnBr/NaH/DMF, r.t., 14 h	p/a (9:1)	92	−39.9°	[b]	27
(e) AcOH/CF_3CO_2H/H_2O, 50°C, 6 h	p/a (9:1 → 2:1)	87		see exp. part	
(f) Ph_3PCHCO_2Et/toluene, 80°C	p/a (5:1)	86		see exp. part	
(g) TMSCl/Py, r.t., 24 h	p/a (15:1)	79	−60.5°	[b]	28
(h) 1. DIBAL-H/toluene, −50°C, 5 h	p/a (6:1)			[b]	29
2. Bu_4NF/THF, r.t., 2 h					20
3. TBDPhSCl/imidazole/DMF, r.t., 2 h	p/a (10:1)	87	−30.8° (c = 1.15)	[c]	30
(i) 1. Ac_2O/Py, r.t., 1 h					
2. TMSCl/Py, r.t., 24 h	p/a (15:1)	92	−21.9°	[b]	28

[a] Yields of isolated products with correct analytical and spectroscopical data.
[b] Analyzed by ^1H NMR.
[c] Analyzed by ^1H NMR of the diacetate.

Scheme 6

Benzylation analogous Ref. 17:

5-O-Benzyl-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-6-O-triphenylmethyl-α-D-glucofuranose:

THF/NaH/$MePh_3PI$ (cat)/BnBr, r.t., 18 h to give 92%; purification p/te (5:1); $[\alpha]_D^{20}$ −18.0° (c = 1.0, MeOH); ^1H NMR available.

Detritylation analogous Ref. 18:

5-O-Benzyl-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-α-D-glucofuranose (**7**):

HCO_2H/Et_2O (1:1), r.t., 12 h. Destroying of parts of formic ester: MeOH/NaH (cat), 10 min; IR 120, H^+; purification p/te (1:1), colorless sirup: $[\alpha]_D^{20}$ −34.2° (c = MeOH).

^1H NMR (270 MHz, $CDCl_3$): δ = 1.26 (3H, s, i-Pr), 1.48 (3H, s, i-Pr), 2.04 (1H, s, OH), 2.36 (3H, s, $PhC\underline{H}_3$), 3.71 (1H, ddd, J = 3.0, 4.4, 8.6 Hz, H-5), 3.73 (1H, dd, J = 3.0, 13.0 Hz, H-6), 3.87 (1H, dd, J = 4.4, 13.0 Hz, H-6), 4.33 (1H, d, J = 11.0 Hz, $C\underline{H}_2Ph$), 4.36 (1H, dd, J = 2.6, 8.6 Hz, H-4), 4.47 (1H, d, J = 11.0 Hz, $C\underline{H}_2Ph$), 4.65 (1H, d, J = 3.8 Hz, H-2), 5.11 (1H, d, J = 2.6 Hz, H-3), 5.86 (1H, d, J = 3.8 Hz, H-1), 7.21–7.36 (7H, m, ArH), 7.79 (2H, d, ArH).

$C_{23}H_{28}O_8S$ (464.5) calc. C 59.49 H 6.08 S 6.90
found 59.70 6.08 6.88

Compound 7; Procedure B:
Silylation analogous Ref. 19:

6-O-t-Butyldimethylsilyl-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-α-D-glucofuranose,

CH_2Cl_2/Et_3N/t-$BuMe_2SiCl$ in CH_2Cl_2, r.t., 1 h; direct use for the preparation of:

5-O-Benzyl-6-O-t-butyldimethylsilyl-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-α-D-glucofuranose:

See procedure A.

Desilylation analogous Ref. 20:

5-O-Benzyl-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-α-D-glucofuranose (**7**):

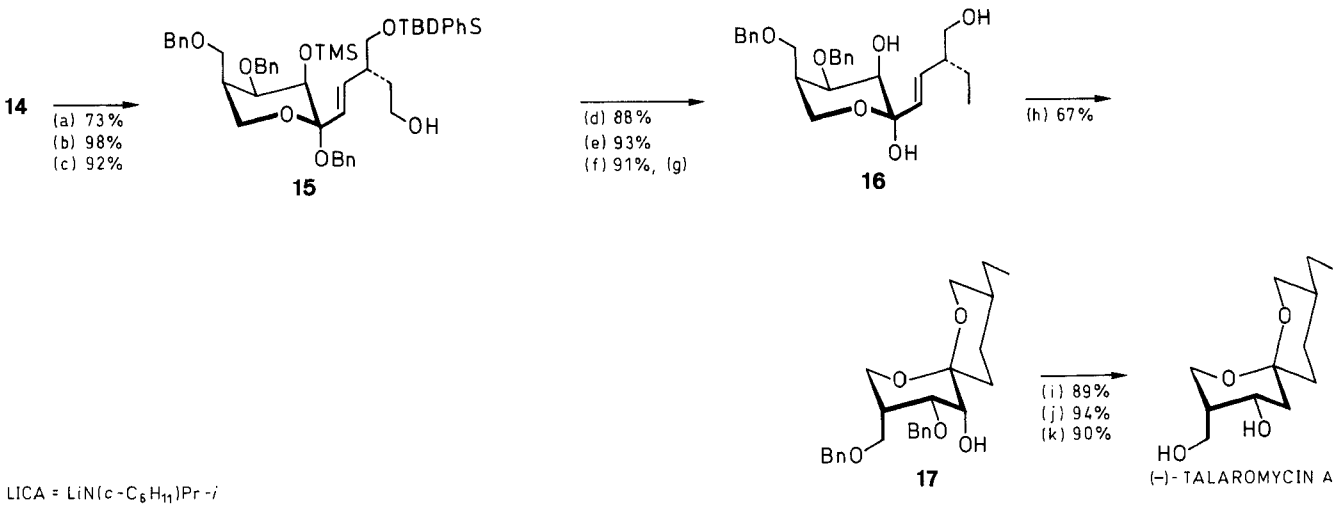
THF/Bu_4NF/THF, r.t., 3 h; purification p/te (1:1); yield over all 75%.

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-L-*glycero*-α-D-*gluco*-heptofuranose-7-(2-methyl-2-azapropane-1,3-diyl)dithioacetal, 5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-D-*glycero*-α-D-*gluco*-heptofuranose-7-(2-methyl-2-azapropane-1,3-diyl)-dithioacetal 8.

Compound 8 was prepared according to Ref. 22.

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-D,L-*glycero*-α-D-glucofuranose; Procedure (c) (Scheme 5):

To a stirred solution of the diasteric mixture **8** (2.0 g, 3.3 mmol) in MeCN (30 mL) HgO (2.3 g, 10.6 mmol) and than in small portions, $HgCl_2$ (1.8 g, 6.6 mmol), solved in H_2O/MeCN 80:20 (10 mL) was added. The cleavage was monitored by TLC. The salts in the mixture were seperated by centrifugation. To the resulting clear solution of



Procedure	Purification	Yield[a] (%)	$[\alpha]_D^{20}$ ($c = 1.0$, MeOH)	Remarks	Ref.
(a) 1. LICA/THF, −78 °C, TMSCl 2. r.t., 15 h, H_2O		73		see exp. part	34
(b) CH_2N_2/Et_2O/MeOH (1:1), r.t., 15 min	p/a (10:1)	98		see exp. part	
(c) DIBAL-H/toluene, −25 °C, 14 h	p/a (5:1)	92	−41.7°	[b]	29
(d) Ph_3P/imidazole/I_2/toluene, 80 °C, 2 h	p/a (40:1)	88	−54.5° ($c = 0.9$)	[b]	35
(e) Bu_3SnH/AIBN/benzene, 80 °C, 30 min	p/a (45:1)	93	−42.7° ($c = 1.23$, $CHCl_3$)	[b]	36
(f) Bu_4NF/THF, r.t., 45 min	p/a (3:1)	91	−73.2°	[b]	20
(g) PPTS/CH_2Cl_2/THF, 1:1, r.t., 6 h	t/a (3:1)			see exp. part	
(h) 1. Pt-C/H_2, r.t., 3 h		91		see exp. part	
2. $BF_3/Et_2O/CH_2Cl_2$	p/a (15:1)	67		see exp. part	
(i) NaH/CS_2/MeI, 0 °C, 14 h	t/a (100:1)	89	−38.8° ($c = 0.6$, $CHCl_3$)	[b]	36
(j) Bu_3SnH/AIBN/toluene, 110 °C, 10 min	t/a (100:1)	94	−97.1° ($c = 0.55$, $CHCl_3$)	[c]	36
(k) Pd-C/Et_3N (cat.)/H_2/EtOH, r.t., 10 h		90		see exp. part	

[a] Yields of isolated products with correct analytical and spectroscopical data.
[b] Analyzed by ^1H NMR.
[c] Analyzed by ^1H and ^{13}C NMR.

Scheme 7

the aldehyde, $NaBH_4$ was added in small portions until the reduction was completed (TLC). The excess of $NaBH_4$ was destroyed with AcOH, MeCN was removed in vacuo and the residue was extracted with $CHCl_3$. The organic layer was washed with aq $NaHCO_3$ and then with H_2O, dried ($MgSO_4$) and concentrated in vacuo. The sirupy residue was purified by chromatography with t/a (2:1) as the eluent. Yield: 1.4 g (86%).

Characterization of the main diastereomer as the diacetate: $[\alpha]_D^{20}$ −27.1° ($c = 1.0$, MeOH).

^1H NMR (270 MHz, $CDCl_3$): δ = 1.27 (3H, s, *i*-Pr), 1.47 (3H, s, *i*-Pr), 2.01 (3H, s, OAc), 2.03 (3H, s, OAc), 2.41 (3H, s, $PhC\underline{H}_3$), 3.88 (1H, dd, $J = 9.2$, 3.6 Hz, H-5), 4.16 (1H, dd, $J = 7.2$, 11.5 Hz, H-7), 4.30 (1H, dd, $J = 9.2$, 2.6 Hz, H-4), 4.33 (1H, dd, $J = 11.5$, 4.8 Hz, H-7), 4.43 (1H, d, $J = 10.8$ Hz, $C\underline{H}_2Ph$), 4.49 (1H, d, $J = 10.8$ Hz, $C\underline{H}_2Ph$), 4.59 (1H, d, $J = 3.8$ Hz, H-2), 5.12 (1H, d, $J = 2.6$ Hz, H-3), 5.30 (1H, ddd, $J = 7.2$, 4.8, 3.6 Hz, H-6), 5.80 (1H, d, $J = 3.8$ Hz, H-1), 7.22–7.38 (7H, m, ArH), 7.83 (2H, d, ArH).

$C_{23}H_{34}O_{11}S$ (578.6)		C	H	S
	calc.	58.12	5.92	5.54
	found	58.00	5.85	5.30

(1*R*,3*R*,4*R*,5*R*,8*R*,9*S*)-4,8-Dibenzyloxy-5-hydroxymethyl-11,11-dimethyl-2,7,10,12-tetraoxatricyclo[7.3.0.0^{3,8}]dodecane; Procedure (c) (Scheme 6):

Under N_2 at r.t. to a solution of the 5-methylene (1.9 g, 4.47 mmol) in dry THF (20 mL) 9-BBN (0.5 M solution in THF, 18 mL, 9 mmol) was dropped. The mixture was kept at r.t. for 18 h. A few drops of EtOH and 4 N NaOH (6 mL) and H_2O_2 (30% solution, 3 mL) were added. The mixture was stirred at r.t. for 5 h. THF was removed in vacuo, the residue was dissolved in H_2O (20 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The remaining sirup was purified and seperated by chromatography p/a (3:1 → 2:1). Yield: 1.75 g (89%) of the main component; 60 mg (3%) of the minor component. Main component $[\alpha]_D^{20}$ −33.8° ($c = 1.0$, MeOH).

^1H NMR (270 MHz, C_6D_6): δ = 1.15 (3H, s, *i*-Pr), 1.48 (3H, s, *i*-Pr), 1.67 (1H, s, OH), 1.89 (1H, m, H-6), 3.60 (1H, dd, $J = 2.6$, 11.8 Hz, H-7), 3.72 (1H, dd, $J = 3.4$, 5.8 Hz, H-5), 3.82 (1H, dd, $J = 1.2$, 11.8 Hz, H-7), 3.94 (1H, dd, $J = 8.4$, 11.0 Hz, H-6'), 4.19 (1H, dd, $J = 5.2$, 11.0 Hz, H-6'), 4.25 (1H, d, $J = 11.6$ Hz, $C\underline{H}_2Ph$), 4.28 (1H, d, $J = 4.0$ Hz, H-2), 4.39 (1h, d, $J = 11.6$ Hz, $C\underline{H}_2Ph$) 4.51

(1 H, d, J = 3.4 Hz, H-4), 4.59 (1 H, d, J = 11.0 Hz, C$\underline{H}_2$Ph), 4.69 (1 H, d, J = 11.0 Hz, C$\underline{H}_2$Ph), 5.73 (1 H, d, J = 4.0 Hz, H-1), 7.04–7.42 (10 H, m, ArH).

$C_{25}H_{30}O_7$ (442.5) calc. C 67.86 H 6.83
found 67.71 6.75

Minor compound as the acetate: $[\alpha]_D^{20}$ + 48.0° (c = 1.0, MeOH), ^{1}H NMR available.

(1*R*,4*R*,5*R*,6*R*,8*RS*,9*S*)-1,5-Dibenzyloxy-4-benzyloxymethyl-8,9-dihydroxy-2,7-dioxabicyclo[4.3.0]nonane; Procedure (e) (Scheme 6):

Compound **12** (400 mg, 9.75 mmol) was dissolved in a mixture of 80% AcOH (6 mL) and CF_3CO_2H (0.15 mL) and held at 50 °C for approximately 6 h. After this time and about 50% conversion the reaction was stopped by cooling to r.t. to avoid the occurence of byproducts. The solution was concentrated in vacuo and several times codistillated with toluene. The residue was separated by column chromatography (p/a, 9:1 → 2:1). Yield: 200 mg (54%) and 150 mg of **12** (38%).

^{1}H NMR (270 MHz, C_6D_6) of the diacetate, *α-anomer*: δ = 1.54 (3 H, s, OAc), 1.69 (3 H, s, OAc), 2.20 (1 H, m, H-6), 3.50 (1 H, dd, J = 2.2, 11.8 Hz, H-7), 3.69 (1 H, dd, J = 3.1, 5.6 Hz, H-5), 4.05–4.16 (3 H, m, H-6′, H-6′, H-7), 4.23 (1 H, d, J = 11.8 Hz), C$\underline{H}_2$Ph), 4.29 (1 H, d, J = 11.8 Hz, C$\underline{H}_2$Ph), 4.35 (2 H, s, C$\underline{H}_2$Ph), 4.36 (1 H, d, J = 11.3 Hz, C$\underline{H}_2$Ph), 4.45 (1 H, d, J = 11.3 Hz, C$\underline{h}_2$Ph), 4.68 (1 H, d, J = 3.1 Hz, H-4), 5.51 (1 H, d, J = 4.1 Hz, H-2), 6.75 (1 H, d, J = 4.1 Hz, H-1), 7.04–7.35 (15 H, m, ArH).

$C_{25}H_{30}O_7$ (442.5) calc. C 67.86 H 6.83
found 67.71 6.75

(2*S*,3*R*,4*R*,5*R*)-2,4-Dibenzyloxy-5-benzyloxymethyl-2-[(1*S*,*E*)-3-(ethoxycarbonyl)-1-hydroxyprop-2-enyl]-3-hydroxytetrahydropyran; Procedure (f) (Scheme 6):

To a solution of the half acetal (preceeding compound) (750 mg, 1.52 mmol) in dry toluene (15 mL) Ph_3PCHCO_2Et (790 mg, 2.27 mmol) was added. The mixture was heated to 80 °C for 5 h, then cooled to r.t. and concentrated in vacuo. The product was purified by column chromatography (p/a, 5:1). Yield 735 mg (86%) colorless sirup. $[\alpha]_D^{20}$ − 48.2° (c = 0.8, MeOH).

^{1}H NMR (270 MHz, C_6D_6): δ = 0.94 (t, J = 7.0 Hz, $CH_2C\underline{H}_3$), 1.98 (1 H, m, H-8), 2.68 (1 H, d, J = 3.2 Hz, OH), 2.73 (1 H, s, OH), 3.53 (1 H, dd, J = 3.0, 11.8 Hz, H-9), 3.58 (1 H, dd, J = 2.6, 9.2 Hz, H-8′), 3.98 (1 H, dd, J = 3.2, 3.4 Hz, H-6), 4.00–4.15 (7 H, m, H-7, H-8′, H-9, C$\underline{H}_2$Ph, C$\underline{H}_2$CH$_3$), 4.34 (1 H, d, J = 12.0 Hz, C$\underline{h}_2$Ph), 4.43 (1 H, d, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.51 (1 H, d, J = 12.2 Hz, C$\underline{H}_2$Ph), 4.88 (1 H, d, J = 12.2 Hz, C$\underline{H}_2$Ph), 5.07 (1 H, dd, J = 2.0, 3.8 Hz, H-4), 6.67 (1 H, dd, J = 2.0, 15.8 Hz, H-2), 7.05–7.33 (15 H, m, ArH), 7.62 (1 H, dd, J = 3.8, 15.8 Hz, H-3).

$C_{33}H_{38}O_8$ (562.6) calc. C 70.44 H 6.81
found 70.70 7.01

(2*S*,3*R*,4*R*,5*R*)-2,4-Dibenzyloxy-5-benzyloxymethyl-2-[(3*S*,*E*)-3-*tert*-butyldiphenylsiloxymethyl-4-carboxybut-1-enyl]-3-trimethylsiloxytetrahydropyran; Procedure (a) (Scheme 7):

Under N_2 to a stirred solution of dry (*c*-C_6H_{11}) *i*-PrNH (61 mg, 73 μL, 0.43 mmol) in dry THF (5 mL) at 0 °C a 1.6 M solution of BuLi in hexane (240 μL, 0.38 mmol) was added dropwise. After 15 min the solution was cooled to − 78 °C and compound **14** (315 mg, 0.36 mmol), dissolved in dry THF (2 mL), was added during a period of 2–3 min. 5 min later TMSCl (41 mg, 48 μL, 0.38 mmol) was added. Within 30 min the mixture was allowed to warm up to r.t. The time was stopped by adding a few drops of MeOH. The hydrolysis of the silyl ester was complete after 15 min. The mixture was acidified with AcOH and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), the solution was washed with H_2O (5 mL), dried ($MgSO_2$) and filtrated. After concentration in vacuo the sirupy residue was separated by column chromatography (p/a, 15:1 → 4:1). Yield 160 mg (51%) beside 60 mg (19%) of starting material and 38 mg (11%) of the corresponding C-silyl compound (^{1}H NMR).

(2*S*,3*R*,4*R*,5*R*)-2,4-Dibenzyloxy-5-benzyloxymethyl-2-[(3*S*,*E*)-3-*tert*-butyldiphenylsiloxymethyl-4-(methoxycarbonyl)but-1-enyl]-3-trimethylsiloxytetrahydropyran; Procedure (6) (Scheme 7):

Compound from **14** (160 mg, 0.18 mmol) is dissolved in Et_2O/MeOH (1:1) (6 mL) and treated according to Ref. 34. Yield: 159 mg (98%); purification: p/a (10:1); $[\alpha]_D^{20}$ − 48.0° (c = 1.4 MeOH).

^{1}H NMR (270 MHz, C_6D_6): δ = 0.10 (9 H, s, Si-Me), 1.12 (9 H, s, Si-*t*-Bu), 2.25 (1 H, m, H-8), 2.47 (1 H, dd, J = 7.4, 15.4 Hz, H-2′), 2.80 (1 H, dd, J = 6.2, 15.4 Hz, H-2′), 3.07 (1 H, m, H-2), 3.32 (3 H, s, OMe), 3.3 (1 H, dd, J = 7.4, 10.0 Hz, H-1), 3.69 (1 H, dd, J = 2.8, 11.6 Hz, H-9), 3.79 (1 H, dd, J = 5.0, 10.0 Hz, H-1′), 3.82 (1 H, m, H-8′), 3.90 (1 H, d, J = 2.8 Hz, H-6), 4.02 (1 H, dd, J = 2.8, 5.4 Hz, H-7), 4.13 (1 H, d, J = 11.2 Hz, C$\underline{H}_2$Ph), 4.19 (1 H, m, H-8′), 4.24 (1 H, dd, J = 2.2, 11.6 Hz, H-9), 4.32 (1 H, d, J = 11.2 Hz, C$\underline{H}_2$Ph), 4.36 (1 H, d, J = 11.8 Hz, C$\underline{H}_2$Ph), 4.41 (1 H, d, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.45 (1 H, d, J = 11.8 Hz, C$\underline{H}_2$Ph), 4.59 (1 H, d, J = 12.0 Hz, C$\underline{H}_2$Ph), 5.53 (1 H, d, J = 15.8 Hz, H-4), 6.11 (1 H, dd, J = 7.4, 15.8 Hz, H-3), 7.05–7.24 (17 H, m, ArH), 7.31 (4 H, m, ArH), 7.72 (4 H, m, ArH).

$C_{53}H_{66}O_8Si_2$ (887.3) calc. C 71.75 H 7.50
found 71.30 7.31

(2*R*,3*R*,4*R*,5*R*)-4-Benzyloxy-5-benzyloxymethyl-2,3-dihydroxy-2-[(3*R*,*E*)-3-hydroxymethylpent-1-enyl]tetrahydropyran (16); Procedure (g) (Scheme 7):

Compound from procedure (f) (37 mg, 0.07 mmol) was dissolved in CH_2Cl_2/THF (1:1) (4 mL) and a trace of H_2O. To the solution pyridinium *p*-toluenesulfonate (PPTS, 1 mg) was added. After 6 h at r.t. $NaHCO_3$ was added and the mixture was stirred for 3 h. The salts were filtered off and the solution was concentrated in vacuo. The residue was directly used for the next step. A small part was purified by column chromatography (t/a, 3:1). The ^{1}H NMR indicates a ration of 2:1 of **16** and the corresponding open chain form.

(3*R*,4*R*,5*R*,6*R*,9*R*)-4-Benzyloxy-3-benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undecan-6-ol (17); Procedure (h) (Scheme 7):

The sirup from step (g), **16**, was dissolved in EtOAc (2 mL) Pt–C (5%) (20 mg) was added. The hydrogenation was carried out at r.t. with a slight pressure over a period of 3 h. The catalyst was filtered off and the solution was concentrated in vacuo. The residue was taken up in CH_2Cl_2 (5 mL), $F_3B \cdot Et_2O$ (10 μL) was added. After 10 min the solution was neutralized with conc. NH_3, then washed with H_2O and dried ($MgSO_4$). Filtration and concentration yielded a sirup, which was purified by column chromatography (p/a, 15:1) to give 20 mg (67% yield) of compound **17**; $[\alpha]_D^{20}$ − 90.5° (c = 0.5, $CHCl_3$).

^{1}H NMR (270 MHz, C_6D_6): δ = 0.72 (3 H, t, J = 7.2 Hz, H-2″), 0.88–1.04 (2 H, m, H-2′, H-2′), 1.35 (1 H, m, H-2), 1.49–1.60 (3 H, m, H-3, H-3, H-4), 2.10 (1 H, m, H-8), 2.44–2.54 (2 H, m, H-4, OH-6), 3.25 (1 H, t, J = 11.0 Hz, H_{aq}-1), 3.49 (1 H, dd, J = 4.4, 11.0 Hz, H_{eq}-1), 3.65 (1 H, dd, J = 2.8, 11.4 Hz, H-9), 3.71 (1 H, dd, J = 2.6, 9.0 Hz, H-8′), 3.77 (1 H, d, J = 3.2 Hz, H-6), 4.01 (1 H, dd, J = 3.2, 6.0 Hz, H-7), 4.08 (1 H, dd, J = 1.2, 11.4 Hz, H-9), 4.23 (1 H, t, J = 9.0 Hz, H-8′), 4.28 (1 H, d, J = 11.6 Hz, C$\underline{H}_2$Ph), 4.41 (1 H, d, J = 11.6 Hz, C$\underline{H}_2$Ph), 4.42 (1 H, d, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.45 (1 H, d, J = 12.0 Hz, C$\underline{H}_2$Ph), 7.05–7.33 (10 H, m, ArH).

$C_{26}H_{34}O_6$ (442.5) calc. C 70.57 H 7.75
found 70.93 7.99

(3*R*,4*S*,6*R*,9*R*)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane [(−)-Talaromycin A]; Procedure (k) (Scheme 7):

The spiroacetal from procedure (j) (10 mg, 0.024 mmol) was dissolved in EtOH (1 mL), Et_3N (20 μL) and a small quantity of Pd/C (10%) was added. The hydrogenation was carried out at 200 atm pressure over a period of 10 h. The catalyst was removed and the solution was concentrated in vacuo. The residue was taken up in Et_2O and filtered over silica gel. Drying ($MgSO_4$) and concentration *in vacuo* yielded 5.0 mg (90%) of a sirup which was characterized without any further purification; $[\alpha]_D^{20}$ − 140° (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (3 H, t, J = 7.6 Hz, CH_3-2′), 1.05–1.22 (2 H, m, CH_2-2′), 1.35–1.48 (2 H, m, H-2, H-3), 1.51 (1 H, dt, J = 4.2, 13.0 Hz, H_{ax}-4), 1.60–1.66 (1 H, m, H-3), 1.67–1.73

(1 H, m, H-4), 1.72 (1 H, dd, J = 11.4, 13.0 Hz, H_{ax}-6), 1.89 (1 H dd, J = 5.4, 13.0 Hz, H_{eq}-6), 2.03 (1 H, br s, OH), 2.14 (1 H, m, H-8), 2.38 (1 H, br s, OH), 3.19 (1 H, t, J = 10.8 Hz, H_{ax}-1), 3.52 (1 H, ddd, J = 2.4, 4.4, 10.8 Hz, H_{eq}-1), 3.58 (1 H, dd, J = 1.5, 11.8 Hz, H_{eq}-9), 3.75 (1 H, dd, J = 28, 11.8 Hz, H_{ax}-9), 3.81 (1 H, dd, J = 5.0, 11.0 Hz, H-8'), 4.21 (1 H, dd, J = 9.0, 11.0 Hz, H-8'), 4.42 (1 H, ddd, J = 5.1, 5.4, 11.4 Hz, H-7).

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