Oligomeric isoflavonoids. Part 4.† Synthesis of the daljanelin class of isoflavonoid–neoflavonoid dimers

Mark B. Rohwer,[a] Pieter S. van Heerden,[a] E. Vincent Brandt,[a] Barend C. B. Bezuidenhoudt[a] and Daneel Ferreira*[b]

[a] *Department of Chemistry, University of the Orange Free State, PO Box 339, Bloemfontein, 9300 South Africa*
[b] *National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA*

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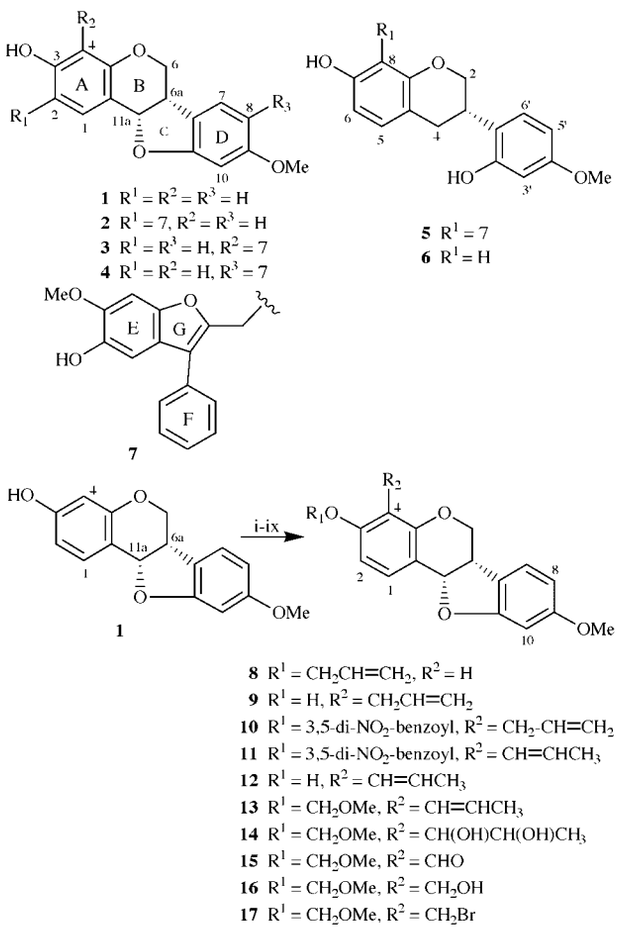
A protocol of introducing an electrophilic C_1 fragment to a pterocarpan nucleus, followed by anionic coupling of a C_6–C_2 benzofuranoid precursor and late introduction of the final C_6 fragment, permitted the syntheses of daljanelins B **3** and D **5**. The feasibility of introducing the same electrophilic C_1 fragment to C-2 of the pterocarpan moiety to obtain a precursor to daljanelin A **2** was also demonstrated.

Iso- and neoflavonoids are less abundant in nature than the corresponding flavonoids, and a similar distorted distribution exists between isoflavonoid- and flavonoid-based oligomers.[1–3] Mono- and oligomeric iso- and neoflavonoids are credited with the biological activity of some of the plants used in traditional medicine.[4,5] Our recent identification of the first isoflavonoid–neoflavonoid dimers and the synthesis of a single member, daljanelin C **4**,[4] prompted us to synthesize the remaining analogues in order to obtain unequivocal confirmation of their molecular frameworks and absolute configurations.

The structures of the four isoflavonoid–neoflavonoid dimers, daljanelins A–D **2**–**5** were established by means of spectroscopic methods.[4] Owing to the preferential bromination and hence facile introduction of the C_1 fragment at C-8 (D-ring) of the pterocarpan, (+)-(6a*S*,11a*S*)-medicarpin **1**,[6] daljanelin C **4** was selected as the initial synthetic target.[4] The deactivating effect of the benzylic C-11a oxygen function on the susceptibility of the A-ring of (+)-medicarpin **1** towards electrophilic aromatic substitution necessitated a different approach to introduce the C_1 fragment at C-2 and C-4 to that used to functionalize the same pterocarpan at C-8 in the synthesis of daljanelin C **4**.[4] Cognizance also had to be taken of the acid lability of the C-11a–O-11 bond[4] and hence the risk of racemization at C-6a and C-11a of the pterocarpan.

Thus, (+)-medicarpin **1** was converted into the 3-*O*-allyl ether **8** (87% yield) using allyl bromide–K_2CO_3 in anhydrous acetone (Scheme 1). The allyl ether **8** was subjected to regioselective Claisen rearrangement[7] by refluxing in *N*,*N*-dimethylaniline to give (6a*S*,11a*S*)-4-allylmedicarpin **9** in 47% yield. Alkylation at C-4 (see also ref. 6) of the pterocarpan nucleus [the equivalent of C-8 of flavonoids/isoflavonoids without the pterocarpan C-ring, *e.g.* (+)-vestitol **6**] is unique since it represents the only method hitherto to functionalize this site of analogues with resorcinol-type A-rings.

The (6a*S*,11a*S*)-4-allylmedicarpin **9** was purified by crystallization of its 3,5-dinitrobenzoate **10** (51%). The 4-(prop-2-enyl) substituent of benzoate **10** was then converted to the 4-(prop-1-enyl) group in compound **11** (92%) *via* facile Pd(II)-catalyzed olefin isomerization.[8,9] The olefinic double bond of benzoate **11** resisted all efforts at dihydroxylation with osmium tetroxide. Thus, **11** was first debenzoylated and the resulting phenol **12** (84%) protected as methoxymethyl derivative **13** (59%). Oxidation of **13**, using the Upjohn method,[10] gave the glycol **14** (59%) which was then oxidatively cleaved with sodium periodate. Subsequent reduction of the ensuing aldehyde **15** (73%) with sodium borohydride afforded the hydroxymethyl compound **16** (86%). Substitution at C-4 in compounds **9**–**16** was confirmed by ^{1}H NMR data (Table 1) reflecting an AB-system



Scheme 1 Introduction of the methylene function at C-4 of (+)-medicarpin **1**. *Reagents and conditions*: i, CH_2=$CHCH_2Br$, Me_2CO, K_2CO_3, reflux; ii, reflux in *N*,*N*-dimethylaniline; iii, 3,5-di-NO_2-benzoyl chloride–pyridine; iv, $Pd(PhCN)_2Cl_2$, reflux in benzene; v, KOH–MeOH; vi, NaH, THF, then $ClCH_2OMe$; vii, OsO_4–NMO in Me_2CO at 0 °C; viii, $NaIO_4$; ix, LiBr, Ms_2O, 2,6-lutidine.

† For Part 3, see ref. 4.

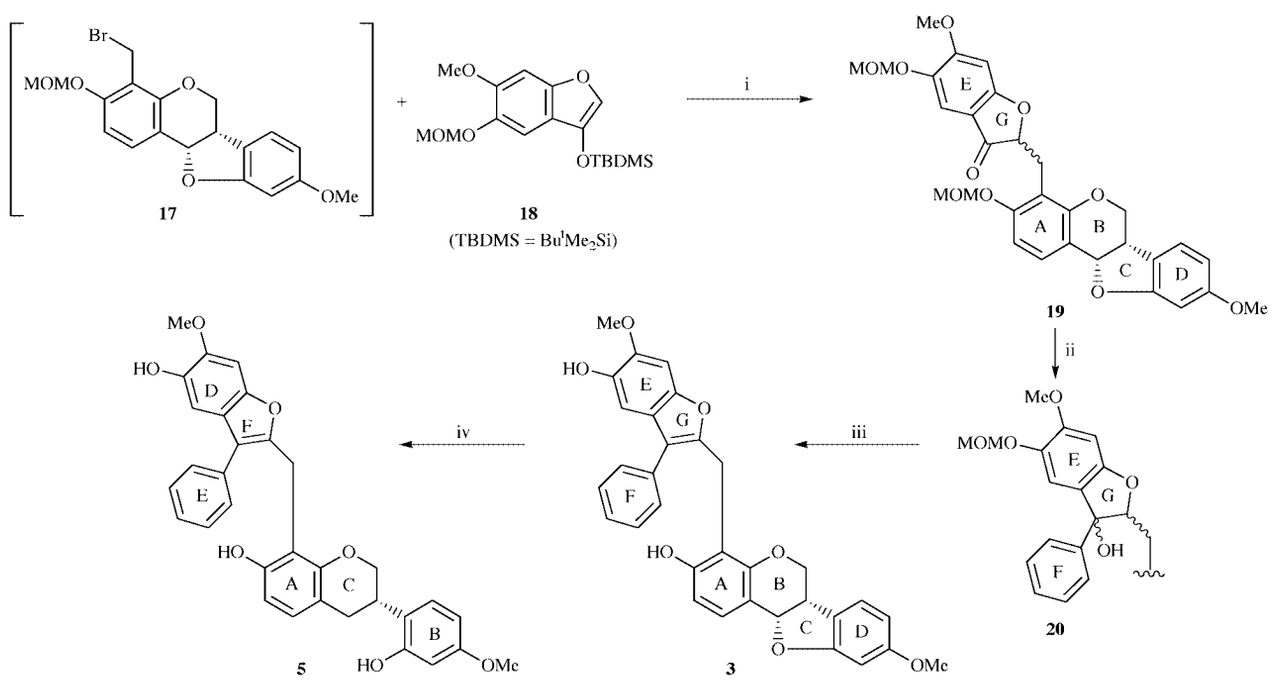
Table 1 ^{1}H NMR peaks (ppm) of the (+)-medicarpin analogues **8**–**17** (27 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

Proton	**8**	**9**	**10**	**11**	**12**[a]	**13**[a]	**14**[b]	**15**	**16**
H-1	7.45 (d, 9.0)	7.33 (d, 8.0)	7.57 (d, 9.0)	7.52 (d, 8.0)	7.40, 7.31 (d, 8.0)	7.45 (d, 9.0)	7.45 (d, 9.0)	7.69 (d, 9.0)	7.46 (d, 9.0)
H-2	6.69 (dd, 3.0, 9.0)	6.60 (d, 8.0)	6.97 (d, 9.0)	6.93 (d, 8.0)	6.72, 6.67 (d, 8.0)	6.93, 6.88 (d, 8.0)	6.92 (d, 9.0)	6.94 (d, 9.0)	6.89 (d, 9.0)
H-4	6.48 (d, 3.0)		—	—		—	—	—	—
3-OH		5.3 (br s)			5.66 (br s)				
H-6_{eq}	4.27 (ddd, 1.0, 5.0, 11.0)	4.33–4.28 (m)	4.44–4.35 (m)	4.43–4.38 (m)	4.30 (ddd, 1.0, 5.0, 11.0)	4.34 (ddd, 1.0, 5.0, 11.0)	4.40–4.29 (m)	4.43 (ddd, 1.0, 4.0, 11.0)	4.35 (ddd, 1.0, 5.0, 11.0)
H-6_{ax}	3.65 (t, 11.0)	3.61 (t, 11.0)	3.69–	3.69 (t, 11.0)	3.69 (t, 11.0)	3.65 (t, 11.0)	3.68–	3.67 (t, 11.0)	3.67 (t, 11.0)
H-6a	3.59–3.51 (m)	3.57–3.51 (m)	3.59 (m)	3.65–3.59 (m)	3.59–3.48 (m)	3.59–3.56 (m)	3.58 (m)	3.63–3.57 (m)	3.69–3.59 (m)
H-11a	5.53 (d, 7.0)	5.54 (d, 7.0)	5.60 (d, 5.0)	5.59 (d, 7.0)	5.52 (d, 7.0)	5.54 (d, 6.0)	5.52 (d, 6.0)	5.49 (d, 6.0)	5.54 (d, 6.0)
H-7	7.15 (d, 9.0)	7.15 (d, 9.0)	7.18 (d, 9.0)	7.19 (d, 9.0)	7.15 (d, 9.0)	7.16 (d, 8.0)	7.15 (d, 9.0)	7.17 (d, 8.0)	7.17 (d, 9.0)
H-8	6.48 (dd, 3.0, 9.0)	6.47 (dd, 2.0, 9.0)	6.50 (dd, 3.0, 9.0)	6.50 (dd, 2.0, 9.0)	6.47 (dd, 2.0, 9.0)	6.48 (dd, 2.0, 9.0)	6.48 (dd, 2.0, 9.0)	6.49 (dd, 2.0, 8.0)	6.48 (dd, 2.0, 9.0)
H-10	6.51 (d, 3.0)	6.47 (d, 2.0)	6.50 (d, 3.0)	6.50 (d, 2.0)	6.47 (d, 2.0)	6.47 (d, 2.0)	6.46 (d, 2.0)	6.47 (d, 2.0)	6.47 (d, 2.0)
3-OCO-C_6H_3-$(NO_2)_2$	—	—	9.34 (s)	9.34 (s)	—	—	—	—	—
3-OCH_2-	—	—	—	—	—	5.24 (dd, 7.0, 9.0)	5.28–5.22 (m)	5.32 (s)	5.26 (dd, 7.0, 8.0)
3-OCH_2OMe						3.51 (s)	3.50 (s)	3.53 (s)	3.51 (s)
C_3-fragment	4.55 (dt, 2.0, 5.0), 6.13–6.00 (m), 5.44 (dq, 2.0, 17.0), 5.32 (dq, 2.0, 11.0)	3.48 (dt, 2.0, 6.0), 6.05–5.92 (m), 5.14 (dq, 2.0, 10.0), 5.09 (m)	3.44–3.40 (m), 5.93–5.80 (m), 4.89 (dq, 2.0, 17.0), 4.97 (dq, 2.0, 10.0)	6.40–6.28 (m), 1.81 (t, 2.0)	6.43–6.41 (m), 6.24–6.12 (m), 1.97, 1.67 (dd, 2.0, 7.0)	6.64–6.60, 6.29, 6.24 (m), 1.95, 1.61 (dd, 2.0, 7.0)	4.92, 4.88 (d, 9.0), 4.10–4.00 (m), 1.04–1.03 (d, 6.0)	— —	— —
C_1-fragment	—	—	—	—	—	—	—	10.52 (s)	4.88–4.75 (m), 2.41 (t) (OH)
9-OMe	3.79 (s)	3.79 (s)	3.81 (s)	3.81 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)

[a] Mixture of *E*- and *Z*-isomers. [b] Diastereoisomeric mixture.

Table 2 ^{1}H NMR peaks (ppm) of the synthetic intermediates **19** and **20** (27 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

Ring	Proton	**19**	**20**
A	1	7.44 (2 × d, 9.0 each)	7.35–7.29 and 7.26–7.11 (overlapped)
	2	6.92 and 6.91 (2 × d, 9.0 each)	6.74 (2 × d, 9.0 each)
B	6_{ax}	3.68–3.57 (m)	3.63–3.46 (m)
	6_{eq}	4.35–4.25 (2 × m)	4.23–4.20, 4.16 and 4.13 (2 × ddd, 1.0, 5.0, 10.0 each)
	6a	3.68–3.57 (m)	3.63–3.46 (m)
	11a	5.57 and 5.56 (2 × d, 7.0 each)	5.44 and 5.42 (2 × d, 7.0 each)
D	7	7.15 (2 × d, 9.0 each)	7.35–7.29 and 7.26–7.11 (overlapped)
	8	6.47 (2 × dd, 3.0, 9.0 each)	6.51–6.44
	10	6.47 and 6.44 (2 × d, 3.0 each)	6.51–6.44
	CH_2	3.27 and 3.26 (2 × dd, 5.0, 14.0 each) 3.14 and 3.12 (dd, 10.0, 14.0 each)	3.33–3.20 (m)
E	4	7.39 and 7.38 (2 × s)	6.78 (s)
	7	6.51 and 6.48 (2 × s)	6.54 and 6.45 (2 × s)
F		—	7.35–7.29 and 7.26–7.11 (m)
G		4.91 and 4.88 (2 × dd, 5.0, 10.0 each)	5.11–4.92 (m)
	OMe	3.94, 3.90, 3.79 and 3.78 (4 × s)	3.87, 3.86, 3.79 and 3.78 (4 × s)
	OCH_2OMe	5.24, 5.22, 5.20 and 5.19 (4 × s)	5.05, 5.04 and 5.02 (×2) (3 × s)
	OCH_2OMe	3.53, 3.52 and 3.48 (×2) (3 × s)	3.45, 3.44, 3.38 and 3.35 (4 × s)
	OH	—	2.91 (s)



Scheme 2 Coupling of neoflavonoid precursor **18** to bromomethylmedicarpin **17** and conversion of daljanelin B **3** to daljanelin D **5**. *Reagents and conditions*: i, TASF–HMPA, then aq. NH_4Cl; ii, PhMgBr–THF, then 3 M HCl, 0 °C; iii, 0.1 M HCl–MeOH, reflux; iv, $Na(CN)BH_3$–TFA, 0 °C.

for H-1 and H-2 (*e.g.* δ 7.33, 6.60, respectively, J = 8.0 Hz for **9**) and indicating long-range coupling between H-1 and the C-11a benzylic proton. A similar observation of benzylic coupling between H-1 and H-11a and/or between H-7 and H-6a was also used to define structures **21**–**28** (*vide infra*).

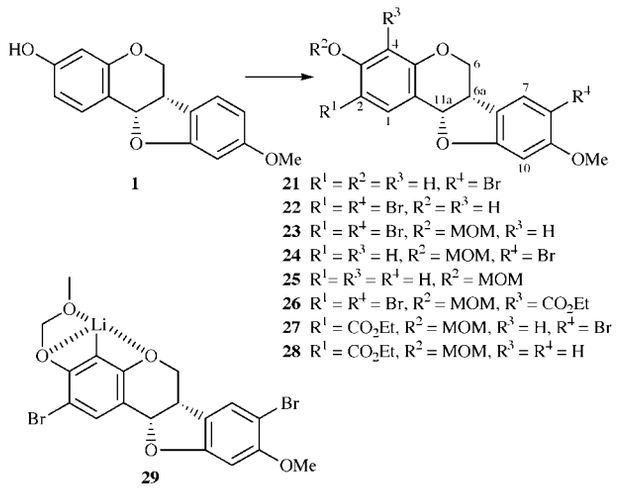
The last steps of the synthesis of daljanelin B **3** are outlined in Scheme 2 and are similar to those utilized in the synthesis of daljanelin C **4**.[4] Preparation of the highly labile benzyl bromide **17** from the corresponding hydroxymethyl compound **16** was accomplished in quantitative yield *via* the Collington–Meyers protocol[11] using a mixture of methanesulfonic anhydride, lithium bromide and 2,6-lutidine in THF.‡ Coupling of the bromide **17** and the stable silyl enol ether **18**, prepared by the literature procedure,[4] was effected in 32% yield *via* the TASF [tris(dimethylamino)sulfonium difluorotrimethylsilicate]–HMPA procedure[4,12] to give the *C*-alkylated product **19** as a diastereoisomeric mixture, as was evident from the double set of resonances in its ^{1}H NMR spectrum (Table 2). Grignard reaction of compound **19** with phenylmagnesium bromide in THF afforded a diastereoisomeric mixture (22%) of alcohol **20**. This mixture was refluxed in methanol containing 0.1 mol dm^{-3} hydrochloric acid to effect simultaneous deprotection and dehydration, affording daljanelin B **3** (24%), the ^{1}H NMR and CD data identical to those of the natural product.[4]

Daljanelin D **5** should, in principle, be accessible *via* reductive cleavage of the benzylic C-11a–O-11 ether bond of daljanelin B **3**. Owing to the presence of the electron-rich olefinic bond in the G-ring of daljanelin B **3** and in view of our experience with the relative inertia of (+)-medicarpin **1** towards catalytic hydrogenation under a variety of conditions,[13] we were hesitant to employ the hydrogenolysis protocol. Utilization of sodium cyanoborohydride [$Na(CN)BH_3$] in TFA[14,15] to reduce (+)-medicarpin **1**, led to the formation of (+)-(3*S*)-vestitol **6** (85%) in optically pure form (see Experimental for ^{1}H NMR data of

‡ The ^{1}H NMR spectrum used to monitor the reaction indicated the 4-methylene protons of **17** as an AB system in contrast to the broadened multiplet in benzyl alcohol **16**.

its Mosher's ester). Such cleavage of the pterocarpan C-ring with retention of configuration at C-3 of (+)-vestitol **6** was effected by maintaining an excess of $Na(CN)BH_3$ while slowly adding a dilute solution of TFA in THF. Daljanelin B **3** was subsequently subjected to the same conditions leading to facile conversion into daljanelin D **5** in 70% yield (Scheme 2). Its ^{1}H NMR and CD data were identical to those of the natural product.[4]

Finally, we explored methods to introduce the requisite C_1 fragment at C-2 of (+)-medicarpin **1** in order to produce the precursor **28** to the synthesis of daljanelin A **2** (Scheme 3)



Scheme 3 Introduction of the C_1 fragment at C-2 of (+)-medicarpin **1**. *Reagents and conditions*: i, HBr–DMSO; ii, NaH–THF, then $ClCH_2OMe$; iii, *n*-BuLi, then aq. NH_4Cl; iv, BuLi–TMEDA, then $ClCO_2Et$, then aq. NH_4Cl.

(Table 3 for ^{1}H NMR data of analogues **21**–**28**). Thus, bromination of (+)-medicarpin **1** using hydrogen bromide in DMSO[16] afforded both the 8-bromo- **21** (39%) and 2,8-dibromo- **22** (16%) derivatives. Since conditions permitting dibromination invariably led to *ca.* 50% loss of material, we persisted with HBr–DMSO because the 8-bromo derivative **21** could eventually be recycled. The 2,8-dibromomedicarpin **22** was protected as the 3-*O*-methoxymethyl ether **23** (79%), this compound being available for preparative purposes in a combined yield of 30%. Treatment of the protected derivative **23** with butyllithium and subsequent protic quenching gave a mixture comprising the starting material **23** (17%), the 2-debromo analogue **24** (20%) and the fully debrominated compound **25** (13%). The formation of the (6a*S*,11a*S*)-8-bromo-3-*O*-methoxymethylmedicarpin **24** indicates the feasibility of regioselective metal–halogen exchange at C-2 of the dibromo analogue **23** in order to introduce the electrophilic C_1 fragment at this site.

However, when the (6a*S*,11a*S*)-2,8-dibromomedicarpin **23** was reacted for 30 min with 1.1 eq. of *n*-BuLi, solvated with 2.5 eq. of TMEDA, and 6 eq. of ethyl chloroformate, only the 2,8-dibromo-4-ethoxycarbonylmedicarpin derivative **26** (14%) could be isolated. Its formation was unexpected since lithium–halogen exchange with *n*-BuLi is usually a fast and facile reaction capable of competing with protonation of the aryllithium by H_2O (D_2O) or even an intramolecular carboxylic acid. The preferential lithiation at C-4 may be facilitated by extensive complexation of the resulting aryllithium **29**, *i.e.* a resorcylic directed *ortho* metalation process.[17,18] The 8-bromo-2-ethoxycarbonylmedicarpin **27** was eventually formed in low yield (14%) by adding the ethyl chloroformate *ca.* 3 min after addition of the *n*-BuLi–TMEDA to the 2,8-dibromomedicarpin derivative **23**. Debromination of the 8-bromo compound **27** using *n*-BuLi–TMEDA and an aqueous workup afforded the 2-ethoxycarbonylmedicarpin **28** (40%), *i.e.* a precursor to the synthesis of daljanelin A by implementing the protocol utilized

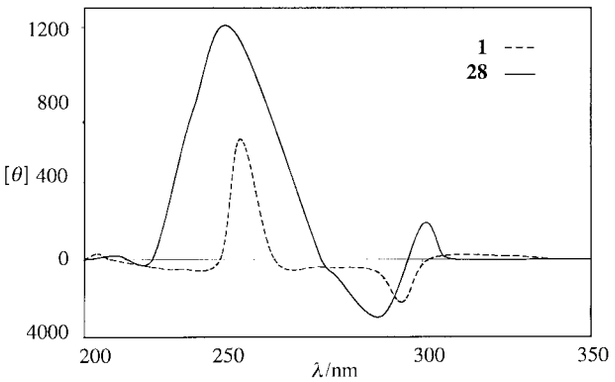


Fig. 1 CD curves of (+)-(6a*S*,11a*S*)-medicarpin **1** and (6a*S*,11a*S*)-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **28**.

in the syntheses of daljanelins B **3** and C **4**. Compound **28** had a CD spectrum which was virtually identical to that of (+)-medicarpin (Fig. 1).

Although the synthetic sequences in Schemes 2 and 3 resulted in low overall yields, our objective to functionalize (+)-medicarpin **1** at C-2 and C-4 of its deactivated A-ring, without affecting the C-6a and C-11a stereocentres, and hence to provide precursors to the syntheses of the natural products **2**, **3** and **5**, was indeed realized.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer for solutions in $CDCl_3$ with TMS as internal standard. MS and accurate mass estimations were obtained using a VG 70-70E instrument. Since the majority of the synthetic intermediates are isomeric to those described in the synthesis of daljanelin C **4** (see ref. 4), we regarded ^{1}H NMR and HRMS data as sufficient for confirmation of these structures. CD data were obtained in MeOH on a Jasco J710 spectropolarimeter. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}) which were sprayed with H_2SO_4–HCHO (40:1) after development. Preparative TLC plates (PLC) (Kieselgel PF_{254}, 1.0 mm) were air-dried and used without prior activation. Flash column chromatography (CC) was carried out in a glass column of appropriate diameter charged with Merck Kieselgel 60 (230–400 mesh) at a flow rate of 30 mm min^{-1} under N_2 pressure.

(6a*S*,11a*S*)-3-*O*-Allylmedicarpin 8

A solution of (+)-(6a*S*,11a*S*)-medicarpin **1** (500 mg; 1.85 mmol) and allyl bromide (*ca.* 10 eq.) in anhydrous acetone (*ca.* 10 eq. v/m) was refluxed over anhydrous K_2CO_3 (2–5 eq. m/m) under N_2 until TLC indicated complete conversion of the starting material. The K_2CO_3 was filtered off, the precipitate washed with anhydrous acetone, the filtrates combined and the acetone removed under reduced pressure. PLC (*n*-hexane–benzene–acetone, 5:4:1, v/v) gave the title compound **8** (457 mg, 80%) as a viscous light yellow oil (R_f 0.6) (Found: M^+, 310.1204. $C_{19}H_{18}O_4$ requires *M*, 310.1205); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-Allylmedicarpin 9

A solution of (6a*S*,11a*S*)-3-*O*-allylmedicarpin **8** (1 g, 3.22 mmol) in *N*,*N*-dimethylaniline (*ca.* 10 eq. v/m) was refluxed under Ar until TLC indicated complete or near-complete conversion of the starting material. A copious amount of ice was added to the cooled reaction mixture, and 3 M HCl (*ca.* 10 volumes) was added slowly. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed successively with ice-cold 3 M HCl, sat. aq. $NaHCO_3$ and brine. The extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash CC (*n*-hexane–ethyl

Table 3 ^{1}H NMR peaks of (+)-medicarpin analogues **21**–**28** (27 °C) at 300 MHz. Splitting patterns and *J*-values (Hz) are given in parentheses

Proton	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
H-1	7.38 (d, 9.0)	7.62 (s)	7.69 (s)	7.43 (d, 9.0)	7.46 (d, 9.0)	7.83 (s)	8.08	8.11 (s)
H-2	6.58 (dd, 9.0, 3.0)	—	—	6.78 (dd, 3.0, 9.0)	6.77 (dd, 3.0, 9.0)	—	—	—
H-4	6.44 (d, 3.0)	6.64 (s)	6.78 (s)	6.66 (d, 3.0)	6.66 (d, 3.0)	—	6.77	6.77 (s)
3-OH	5.4 (br s)	5.58 (br s)						
H-6_{eq}	4.25 (ddd, 1.0, 4.0, 10.0)	4.27 (ddd, 1.0, 4.0, 10.0)	4.28 (ddd, 1.0, 4.0, 10.0)	4.27 (ddd, 1.0, 4.0, 10.0)	4.27 (ddd, 1.0, 5.0, 10.0)	4.46 (ddd, 1.0, 4.0, 11.0)	4.32 (ddd, 1.0, 4.0, 11.0)	4.32 (ddd, 1.0, 4.0, 11.0)
H-6_{ax}	3.66 (t, 10.0)	3.67 (t, 10.0)	3.68 (t, 10.0)	3.68 (t, 10.0)	3.65 (t, 10.0)	3.95 (t, 9.0)	3.72 (t, 11.0)	3.69 (t, 11.0)
H-6a	3.61–3.54 (m)	3.63–3.57 (m)	3.64–4.57 (m)	3.63–3.56 (m)	3.60–3.52 (m)	3.91–3.88 (m)	3.65–3.58 (m)	3.62–3.56 (m)
H-11a	5.55 (d, 7.0)	5.52 (d, 7.0)	5.53 (d, 7.0)	5.57 (d, 7.0)	5.53 (d, 7.0)	5.76 (d, 7.0)	5.56 (d, 7.0)	5.53 (d, 7.0)
H-7	7.39 (s)	7.39 (s)	7.39 (s)	7.39 (s)	7.15 (s)	7.56 (s)	7.40 (s)	7.16 (d, 9.0)
H-8	—	—	—	—	6.47 (dd, 2.0, 9.0)	—	—	6.49 (dd, 2.0, 9.0)
H-10	6.50 (s)	6.50 (s)	6.50 (s)	6.50 (s)	6.47 (s)	6.63 (s)	6.52 (s)	6.48 (s)
3-OCH_2	—	—	5.25 (s)	5.18 (dd, 7.0, 8.0)	5.18 (dd, 7.0, 8.0)	5.12 (s)	5.26 (s)	5.26 (s)
3-OCH$_2$OMe	—	—	3.52 (s)	3.48 (s)	3.48 (s)	3.54 (s)	3.53 (s)	3.53 (s)
8-CO_2CH_2-	—	—	—	—	—	4.34 (t, 7.0)	4.36 (t, 7.0)	4.36 (t, 7.0)
8-$CO_2CH_2CH_3$	—	—	—	—	—	1.32 (t, 7.0)	1.41 (t, 7.0)	1.41 (t, 7.0)
9-OMe	3.85 (s)	3.86 (s)	3.87 (s)	3.86 (s)	3.79 (s)	3.86 (s)	3.86 (s)	3.79 (s)

acetate, 8:2, v/v) gave the title compound **9** (553 mg, 55%) as a viscous light brown oil (R_f 0.3); (Found: M^+, 310.1203. $C_{19}H_{18}O_4$ requires *M*, 310.1205); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-Allyl-3-*O*-(3′,5′-dinitrobenzoyl)medicarpin 10

Impure (6a*S*,11a*S*)-4-allylmedicarpin **9** (553 mg) was dissolved in a minimal volume of pyridine, 3,5-dinitrobenzoyl chloride (1.5 eq.) added, and the mixture was left standing at *ca.* 30 °C for *ca.* 12 h. The reaction was quenched by addition of ice and the crude product was taken up in ethyl acetate. The organic phase was washed successively with H_2O, sat. aq. $CuSO_4$ (twice), H_2O, sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Crystallization from ethyl acetate gave the title compound **10** (429 mg; 26% based on 1 g of (6a*S*,11a*S*)-3-*O*-allylmedicarpin **8**) as orange needles (mp, 186–187 °C) (Found: M^+, 504.116. $C_{26}H_{20}O_9$ requires *M*, 504.1169); ^{1}H NMR (Table 1).

(*E*/*Z*)-(6a*S*, 11a*S*)-3-*O*-(3′,5′-Dinitrobenzoyl)-4-(prop-1-enyl)-medicarpin 11

$PdCl_2(PhCN)_2$ was prepared by heating $PdCl_2$ (500 mg; 2.82 mmol) in PhCN (*ca.* 8 cm^3) under Ar to 100 °C until dissolution. The mixture was cooled and the solids filtered. A second crop of product was precipitated from the mother liquor with petroleum ether (bp 40–60 °C) and filtered. The combined precipitates were washed with petroleum ether (bp 40–60 °C), dried in a vacuum oven at *ca.* 35 °C and stored under Ar until use. Yield: 792 mg (73%).

A solution of (6a*S*,11a*S*)-4-allyl-3-*O*-(3′,5′-dinitrobenzoyl)-medicarpin **10** (306 mg, 607 μmol) and $PdCl_2(PhCN)_2$ (5–10 eq. m/m) was refluxed in benzene under Ar until ^{1}H NMR spectra of reaction aliquots indicated complete or near-complete conversion of the allyl group to a prop-1-enyl group. The catalyst was removed by elution with acetone through a short silica gel plug, and the eluate was concentrated under reduced pressure. Flash CC (*n*-hexane–benzene–acetone, 60:35:5, v/v) gave an inseparable *E*:*Z*-mixture (302 mg, 99%; R_f 0.25) of the title compound **11** as yellow needles (Found: M^+, 504.1168. $C_{26}H_{20}N_2O_9$ requires *M*, 504.1169); ^{1}H NMR (Table 1).

(*E*/*Z*)-(6a*S*,11a*S*)-4-(Prop-1-enyl)medicarpin 12

(*E*/*Z*)-(6a*S*,11a*S*)-3-*O*-(3′,5′-Dinitrobenzoyl)-4-(prop-1-enyl)-medicarpin **11** (623 mg, 1.24 mmol) was dissolved in methanol (*ca.* 10 eq. v/m) and a 2% solution of KOH in methanol (*ca.* 10 eq. v/m) was added slowly. The mixture was stirred at gentle reflux until TLC indicated no further conversion of starting material. The cooled mixture was poured into an excess of ice–H_2O, and the aqueous phase was acidified to pH 5 and extracted with ethyl acetate. The combined organic extracts were washed with sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–ethyl acetate, 7:3, v/v) gave (*E*/*Z*)-(6a*S*,11a*S*)-4-(prop-1-enyl)medicarpin **12** (283 mg; 74%) as a light green oil (R_f 0.35) (Found: M^+, 310.1206. $C_{19}H_{18}O_4$ requires *M*, 310.1205); ^{1}H NMR (Table 1).

(*E*/*Z*)-(6a*S*,11a*S*)-3-*O*-Methoxymethyl-4-(prop-1-enyl)-medicarpin 13

The phenolic medicarpin **12** (300 mg, 967 μmol) was dissolved in anhydrous THF and added under N_2 to an ice-cooled, stirred suspension of NaH (1.5 eq.) in the same anhydrous solvent. The mixture was stirred for 10 min, chloromethyl methyl ether (1.2 eq.) added and stirring continued on ice until TLC indicated complete conversion of the starting material. Crushed ice was added slowly to the mixture and the aqueous phase extracted with ethyl acetate. The organic extracts were combined, washed with H_2O, dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–ethyl acetate, 6:4, v/v) gave (*E*/*Z*)-(6a*S*,11a*S*)-3-*O*-methoxymethyl-4-(prop-1-enyl)medicarpin **13** (201 mg, 61%) as an amorphous white solid (R_f 0.6) (Found: M^+, 354.1466. $C_{21}H_{22}O_5$ requires *M*, 354.1467); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-(1,2-Dihydroxypropyl)-3-*O*-methoxymethyl-medicarpin 14

(*E*/*Z*)-(6a*S*,11a*S*)-3-*O*-Methoxymethyl-4-(prop-1-enyl)medicarpin **13** (180 mg, 508 μmol) was added to a mixture of *N*-methylmorpholine *N*-oxide (NMO) (1.1 eq. based on 1 mmol of olefin), H_2O (15 cm^3), acetone (30 cm^3), *tert*-butyl alcohol (3 cm^3) and OsO_4 (5–20 mol%). The mixture was stirred at rt under N_2 until TLC indicated no further conversion of starting material (typically 3–18 h). The reaction was quenched by the addition of a slurry of $NaHSO_3$ (100 mg) and commercial Florisil® (1 g) in H_2O (50 cm^3). After filtration and washing (acetone, 3 × 10 cm^3) of the Florisil®, the combined filtrates were neutralized to pH 7 with 3 M HCl, the acetone removed under reduced pressure, the aqueous residue cooled by the addition of ice and acidified further to pH 2. The solution was saturated with NaCl and extracted with ethyl acetate (3 × 50 cm^3), the combined extracts washed successively with sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash CC (*n*-hexane–ethyl acetate, 6:4, v/v) gave the title compound **14** (121 mg, 61%) as an amorphous white solid (R_f 0.4) (Found: M^+, 388.1522. $C_{21}H_{24}O_7$ requires *M*, 388.1522); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-Formyl-3-*O*-methoxymethylmedicarpin 15

A solution of $NaIO_4$ (2.5 eq.) in H_2O (*ca.* 1 cm^3) was added slowly to a solution of (6a*S*,11a*S*)-4-(1,2-dihydroxypropyl)-3-*O*-methoxymethylmedicarpin **14** (110 mg, 283 μmol) in methanol (*ca.* 10 cm^3) and the mixture was stirred at rt until TLC indicated complete conversion of the starting material. The methanol was evaporated under reduced pressure, the residue taken up in H_2O and the aqueous phase extracted with ether. The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–ethyl acetate, 6:4, v/v) gave the title compound **15** (71 mg, 73%) as a viscous light yellow oil (R_f 0.3) (Found: M^+, 342.1102. $C_{19}H_{18}O_6$ requires *M*, 342.1103); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-Hydroxymethyl-3-*O*-methoxymethylmedicarpin 16

Finely powdered $NaBH_4$ (2.5 eq.) was added in small portions to a stirred solution of (6a*S*,11a*S*)-4-formyl-3-*O*-methoxymethylmedicarpin **15** (60 mg, 175 μmol) in a mixture of THF (*ca.* 1 cm^3) and ethanol (*ca.* 1 cm^3). The resulting mixture was stirred at rt until TLC indicated complete conversion of the starting material. The excess of borohydride was quenched by the slow addition of acetone (*ca.* 2 cm^3) and the mixture was concentrated under reduced pressure. The residue was taken up in H_2O, the aqueous phase extracted with ether and the combined organic extracts dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the title compound **16** (51 mg, 85%) as an amorphous white solid (Found: M^+, 344.1261. $C_{19}H_{20}O_6$ requires *M*, 344.1260); ^{1}H NMR (Table 1).

(6a*S*,11a*S*)-4-Bromomethyl-3-*O*-methoxymethylmedicarpin 17

2,6-Lutidine (2 eq.) was added to a stirred solution of (6a*S*, 11a*S*)-4-hydroxymethyl-3-*O*-methoxymethylmedicarpin **16** (45 mg; 131 μmol) and oven-dried LiBr (3 eq.) in anhydrous THF (*ca.* 2 cm^3) under Ar, and stirring was continued at rt until all LiBr had dissolved. The mixture was cooled to 0 °C and a solution of methanesulfonic anhydride (1.5 eq.) in anhydrous THF (*ca.* 2 cm^3) was added under Ar. The resulting suspension was stirred at rt until ^{1}H NMR of reaction aliquots indicated complete conversion of the benzylic alcohol **16** into the correspond-

ing bromide **17**; ^{1}H NMR: δ_H 7.42 (d, *J* 9.0, H-1), 6.82 (d, *J* 9.0, H-2), 6.58 (dd, *J* 9.0, 2.0, H-8), 5.20 (d, *J* 7.0, 3-OCH_2-), 3.52 (s, 3-OCH_3), 4.93, 4.83 (2 × d, each *J* 3.0, -CH_2Br).

(6a*S*,11a*S*)-4-(6-Methoxy-5-methoxymethoxy-2,3-dihydro-3-oxo-1-benzofuran-2-ylmethyl)-3-*O*-methoxymethylmedicarpin 19

A solution of the silyloxybenzofuran **18**, prepared by a literature procedure[4] (112 mg, 328 μmol; 2.5 eq. relative to the benzyl bromide **17**) in anhydrous THF (1 cm^3) was added slowly to a stirred suspension of TASF (95 mg, 1.05 eq. relative to the silyloxybenzofuran **18**) in anhydrous THF (1 cm^3) at −78 °C under Ar. The mixture was stirred for 15 min, HMPA (300 μl; 5 eq. relative to the silyloxybenzofuran **18**) added and stirring continued for 15 min. The suspension containing (6a*S*,11a*S*)-4-bromomethyl-3-*O*-methoxymethylmedicarpin **17** (452 μmol, 1 eq.) was added slowly to the mixture by filtration under Ar through a septum-capped syringe (5 cm^3) charged with cotton wool. The cotton wool was rinsed once with anhydrous THF (2 cm^3), and the resulting mixture was stirred (1 h, −78 to −30 °C; 15 h, −30 °C), quenched at −30 °C with sat. aq. NH_4Cl (2 cm^3), warmed to rt, diluted with H_2O, extracted with ether (5 × 10 cm^3) and the combined organic extracts dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and PLC (first $CHCl_3$–methanol, 98:2, v/v, R_f 0.4, then *n*-hexane–benzene–acetone, 5:4:1, v/v, R_f 0.25) gave the title compound **19** (20 mg, 28%) as a viscous colorless oil (Found: M$^+$, 550.1836. $C_{30}H_{30}O_{10}$ requires *M*, 550.1839); ^{1}H NMR (unresolved diastereoisomeric mixture) (Table 2).

(6a*S*,11a*S*)-4-(3-Hydroxy-6-methoxy-5-methoxymethoxy-3-phenyl-2,3-dihydro-1-benzofuran-2-ylmethyl)-3-*O*-methoxymethylmedicarpin 20

A standardized solution of PhMgBr in THF (2 eq.) was added slowly *via* a microsyringe to a stirred solution of (6a*S*,11a*S*)-4-(6-methoxy-5-methoxymethoxy-2,3-dihydro-3-oxo-1-benzofuran-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **19** (20 mg, 36.3 μmol) in anhydrous THF (*ca.* 1 cm^3) under N_2 at 0 °C, and the resulting mixture was stirred at rt until TLC of reaction aliquots indicated complete conversion of the starting material. Crushed ice and an excess of sat. aq. NH_4Cl was added to the mixture which was then extracted with ethyl acetate. The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. PLC (benzene–acetone, 9:1, v/v) gave the title compound **20** (5 mg, 22%; R_f 0.25), and 3 mg (15%) of the starting material **19** (R_f 0.4) was recovered (Found: M$^+$, 628.2306. $C_{36}H_{36}O_{10}$ requires *M*, 628.2308); ^{1}H NMR (unresolved diastereoisomeric mixture) (Table 2).

(6a*S*,11a*S*)-4-(5-Hydroxy-6-methoxy-3-phenyl-1-benzofuran-2-ylmethyl)medicarpin 3

(6a*S*,11a*S*)-4-(3-Hydroxy-6-methoxy-5-methoxymethoxy-3-phenyl-2,3-dihydro-1-benzofuran-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **20** (5 mg, 7.95 μmol) was refluxed for 3 h in a mixture of 0.1 M HCl (1 cm^3) and methanol (1 cm^3). The mixture was cooled to rt, neutralized with sat. aq. $NaHCO_3$ and extracted with ether (5 × 5 cm^3). The combined moist organic extracts were homogenized with ethanol (*ca.* 0.5 cm^3), concentrated under reduced pressure and the residue subjected directly to PLC (benzene–acetone, 8:2, v/v) to give the title compound **3**[4] (1 mg, 24%; R_f 0.55) (Found: M$^+$, 522.1680. $C_{32}H_{26}O_7$ requires *M*, 522.1679); ^{1}H NMR: δ_H 7.67–7.63 [m, 2 × H(F)], 7.45 [s, H-4(E)], 7.41 [d, *J* 8.0, H-1(A)], 7.39–7.29 [m, 3 × H(F)], 6.81 [d, *J* 8.0, H-7(D)], 6.66 [d, *J* 2.0, H-10(D)], 6.60 [s, H-7(E)], 6.53 [d, *J* 8.0, H-2(A)], 6.51 [dd, *J* 8.0, 2, H-8(D)], 5.52 and 5.46 (2 × br s, 3(A)-O*H* and 5(E)-O*H*), 5.30 (d, *J* 7.0, H-11a), 4.36 [s, 4(A)-CH_2], 3.92 (ddd, *J* 11.0, 5, 1, H-6 eq), 3.45 (dd, *J* 11.0, 11, H-6 ax), 3.34 and 3.14 [2 × s, 9(A)-OCH_3 and 6(E)-OCH_3] and 3.12–3.01 (m, H-6a).

(+)-(3*S*)-Vestitol 6

TFA (17 μl, 1.2 eq.) was added slowly *via* microsyringe to a stirred suspension of (+)-(6a*S*,11a*S*)-medicarpin **1** (50 mg, 185 μmol) and Na(CN)BH_3 (17 mg, 1.5 eq.) in anhydrous DCM (2 cm^3) at −10 °C under N_2. Stirring was continued (1 h, −10→0 °C), the reaction quenched with H_2O (excess), the mixture neutralized with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 5 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–benzene–acetone, 4:4:2, v/v) of the residue gave the title compound **6** (43 mg, 85%) as a light brown solid (R_f 0.25) (Found: M$^+$, 272.1046. $C_{16}H_{16}O_4$ requires *M*, 272.1049); ^{1}H NMR: δ_H 7.03 (d, *J* 9.0, H-6′), 6.96 (d, *J* 8.0, H-5), 6.50 (dd, *J* 9.0, 2, H-5′), 6.41 (dd, *J* 8.0, 2, H-6), 6.38 (d, *J* 2.0, H-8), 6.37 (d, *J* 2.0, H-3′), 4.96 and 4.70 (2 × br s, 7-O*H* and 2′-O*H*), 4.35 (dd, *J* 0.11, 4, H-2 eq), 4.06 (dd, *J* 10.0, 10, H-2 ax), 3.79 (s, 4′-OCH_3), 3.57–3.47 (m, H-3), 3.02 (dd, *J* 16.0, 10, H-4 ax) and 2.91 (dd, *J* 16.0, 6, H-4 eq).

(3*S*)-{2′-*O*,7-*O*-Bis-[(α*R*)-α-trifluoromethyl-α-methoxyphenylacetyl]}vestitol

Vestitol **6** (11 mg, 40.4 μmol) from the preceding experiment, triethylamine (60 μl, 5.3 eq. per phenol) and DMAP (8 mg, 0.8 eq. per phenol) were dissolved in anhydrous DCM (2 cm^3) under N_2. The mixture was added to *S*-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl) (7 cm^3 of a 21.4 mM solution in anhydrous DCM; 1.9 eq. per phenol), stirred at rt under N_2 for 2 h, neutralized with 0.1 M HCl and extracted with ethyl acetate (4 × 5 cm^3). The combined extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified with PLC (*n*-hexane–benzene–acetone, 5:4:1, v/v) to give the title compound (13 mg, 44%) as a colorless oil (R_f 0.55); ^{1}H NMR: δ_H 7.70–7.66, 7.64–7.60, 5.52–7.47, 7.32–7.28 (4 × m, 2 × C_6H_5), 7.10 (d, *J* 9.0, H-6′), 6.99 (d, *J* 8.0, H-5), 6.84 (dd, *J* 9.0, 3, H-5′), 6.69 (d, *J* 3.0, H-3′), 6.64 (dd, *J* 8.0, 2, H-6), 6.62 (d, *J* 2.0, H-8), 4.16 (dd, *J* 11.0, 4, H-2 eq), 3.91 (dd, *J* 11.0, 10, H-2 ax), 3.82 (s, 4′-OCH_3), 3.73 and 3.69 (2 × q, *J* 1.0, 2 × PhC-(CF_3)OCH_3), 2.95–2.86 (m, H-3), 2.85–2.67 (m, H-4 ax and H-4 eq).

Daljanelin D 5

TFA (200 μl of a 0.1% solution in DCM, 1.4 eq.) was added slowly *via* microsyringe to a stirred suspension of daljanelin B **3** (1 mg, 1.91 μmol) and Na(CN)BH_3 (*ca.* 0.5 mg, 4.2 eq.) in anhydrous DCM (1 cm^3) at −10 °C under N_2. Stirring was continued (1 h, −10→0 °C), the reaction quenched with H_2O (excess), the mixture neutralized with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (benzene–acetone, 8:2, v/v) of the residue gave daljanelin D **5**[4] (0.7 mg, 70%, R_f 0.3); ^{1}H NMR: δ_H 7.62–7.59, 7.50–7.44 and 7.37–7.33 [3 × m, 5 × H(E)], 7.06 [s, H-4(D)], 7.02 [s, H-7(D)], 6.99 [d, *J* 9.0, H-6′(B)], 6.88 [d, *J* 8.0, H-5(A)], 6.50 [d, *J* 8.0, H-6(A)], 6.45 [dd, *J* 8.0, 3, H-5′(B)], 6.38 [d, *J* 3.0, H-3′(B)], 4.24–4.18 [m, 4(A)-CH_2 and H-2 eq], 3.94 and 3.78 [2 × s, 4′(B)-OCH_3 and 6(D)-OCH_3], 3.98 (dd, *J* 10.0, 10, H-2 ax), 3.49–3.41 [m, H-3(C)] and 3.05–2.87 (m, H-4 ax and H-4 eq).

(6a*S*,11a*S*)-8-Bromomedicarpin 21 and (6a*S*,11a*S*)-2,8-dibromomedicarpin 22

A solution of HBr (conc.) (3 cm^3) in DMSO (4 cm^3) was added dropwise to a stirred solution of (+)-(6a*S*,11a*S*)-medicarpin **1** (300 mg, 1.11 mmol) in DMSO (5 cm^3) kept just above freezing

point (*ca.* 5 °C). The mixture was stirred at rt for 1 h, diluted with H_2O, carefully neutralized with Na_2CO_3 (s), its pH adjusted to 6 with 3 M HCl, and extracted with ethyl acetate (3×20 cm^3). The combined organic extracts were washed with H_2O (3×10 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–benzene–acetone, 5:4:1, v/v) gave **21** (151 mg, 39%; R_f 0.3) (Found: M^+, 347.9996. $C_{16}H_{13}BrO_4$ requires *M*, 347.9998) and **22** (74 mg, 16%; R_f 0.4) (Found: M^+, 425.9105. $C_{16}H_{12}Br_2O_4$ requires *M*, 425.9104), both as cream-colored solids; ^{1}H NMR (Table 3).

(6a*S*,11a*S*)-2,8-Dibromo-3-*O*-methoxymethylmedicarpin 23

(6a*S*,11a*S*)-2,8-Dibromomedicarpin **22** (30 mg; 70.1 μmol) was dissolved in anhydrous THF and added under N_2 to an ice-cooled, stirred suspension of NaH (1.5 eq.) in the same solvent. The mixture was stirred for 10 min, chloromethyl methyl ether (1.2 eq.) added and stirring continued on ice until TLC indicated complete conversion of the starting material. Crushed ice was added slowly to the mixture and the aqueous phase extracted with ethyl acetate. The organic extracts were combined, washed with H_2O, dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (*n*-hexane–benzene–acetone, 5:4:1, v/v) gave the title compound **23** (26 mg, 79%) as a colorless oil (R_f 0.75) (Found: M^+, 469.9366. $C_{18}H_{16}Br_2O_5$ requires *M*, 469.9366); ^{1}H NMR (Table 3).

(6a*S*,11a*S*)-8-Bromo-3-*O*-methoxymethylmedicarpin 24 and (6a*S*,11a*S*)-3-*O*-methoxymethylmedicarpin 25

n-BuLi (20 μl of a 1.30 M solution in hexanes; 1.02 eq.) was added *via* microsyringe to a stirred solution of (6a*S*,11a*S*)-2,8-dibromo-3-*O*-methoxymethylmedicarpin **23** (12 mg, 25.4 μmol) in anhydrous THF (*ca.* 1 cm^3) under N_2 at −78 °C. The mixture was stirred at −78 °C for 30 min, quenched with sat. aq. NH_4Cl (excess), warmed to rt, diluted with H_2O and extracted with ethyl acetate (4×5 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (benzene) gave the title compound **24** (2 mg, 20%; R_f 0.55) (Found: M^+, 392.0257. $C_{18}H_{17}BrO_5$ requires *M*, 392.0260) and (6a*S*,11a*S*)-3-*O*-methoxymethylmedicarpin **25** (1 mg, 13%; R_f 0.45) (Found: M^+, 314.1155. $C_{18}H_{18}O_5$ requires *M*, 314.1154); ^{1}H NMR (Table 3).

2,8-Dibromo-4-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin 26 and (6a*S*,11a*S*)-8-bromo-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin 27

(6a*S*,11a*S*)-2,8-Dibromo-3-*O*-methoxymethylmedicarpin **23** (45 mg; 95.3 μmol) was dissolved in anhydrous THF (*ca.* 1 cm^3) and the solution was cooled under N_2 to −78 °C. *n*-BuLi (64 μl of a 1.64 M solution in hexanes, 1.1 eq.) and TMEDA (35 μl, 2.4 eq.) were added successively *via* microsyringe to the stirred solution, and ethyl chloroformate (45 μl, 4.9 eq.) was added to the mixture 3 min after the addition of the TMEDA. The resulting mixture was warmed to 0 °C and stirred for 90 min, quenched with sat. aq. NH_4Cl (excess), warmed to rt, diluted with H_2O and extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (benzene) gave compound **27** (6 mg; 14%, R_f 0.15) and 2,8-dibromo-4-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **26** (3 mg, 6%, R_f 0.25) (Found: M^+, 541.9575. $C_{21}H_{20}Br_2O_7$ requires *M*, 541.9576 for **26**. Found: M^+, 464.0472. $C_{21}H_{21}BrO_7$ requires *M*, 464.0471 for **27**); ^{1}H NMR (Table 3).

(6a*S*,11a*S*)-2-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin 28

(6a*S*,11a*S*)-8-Bromo-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **27** (3.5 mg, 7.52 μmol) was dissolved in anhydrous THF (*ca.* 0.5 cm^3) and the solution was cooled under N_2 to −78 °C. *n*-BuLi (10 μl of a 1.64 M solution in hexanes; 2.2 eq.) and TMEDA (3 μl, 2.6 eq.) were added successively *via* microsyringe to the stirred solution. The resulting mixture was stirred at −78 °C for 10 min, warmed to 0 °C and quenched immediately with sat. aq. NH_4Cl (excess), warmed to rt, diluted with H_2O and extracted with ethyl acetate (3×5 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. PLC (benzene–acetone, 95:5, v/v) gave the title compound **28** (1 mg, 34%, R_f 0.6) (Found: M^+, 386.1365. $C_{21}H_{22}O_7$ requires *M*, 386.1365); ^{1}H NMR (Table 3); CD: $[\theta]_{231.9}$ +12920, $[\theta]_{244.9}$ +20140, $[\theta]_{270.7}$ −30.2, $[\theta]_{285.5}$ −5101, $[\theta]_{299.6}$ +3213 (Fig. 1).

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