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The Structure and Synthesis of Tsitsikammafuran: A New Furanosesquiterpene from a South African *Dysidea* Sponge

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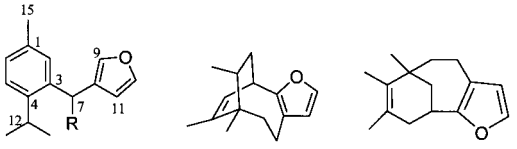
Abstract—Three furanosesquiterpenes, the new tsitsikammafuran (**1**) and the known nakafurans-8 (**2**) and -9 (**3**) were isolated from a South African *Dysidea* sponge. The structure of tsitsikammafuran, initially proposed as 3-[(furan-3-yl)methyl]-*p*-cymene, from a combination of biosynthetic arguments and the available spectroscopic data, was unequivocally confirmed by the synthesis of **1** from thymol. The synthesis of two regioisomers of tsitsikammafuran, 4-[(furan-3-yl)methyl]-*m*-cymene (**4**) and 2-[(furan-3-yl)methyl]-*p*-cymene (**22**), from *p*-cresol and 2-bromo-2-nitrocamphane respectively, further supported the structural assignment of **1**.

In continuation of our search for new bioactive secondary metabolites from South African marine sponges[1] we have examined an ethyl acetate extract of an undescribed white *Dysidea* sponge collected in the Tsitsikamma Marine Reserve on the south eastern coast of South Africa. In this particular region of the South African coast we have observed the endemic nudibranch, *Hypselodoris capensis*, frequenting both a dark gray *Fasciospongia* sponge and the white *Dysidea* sponge which forms the subject of this paper. In common with other dorid nudibranchs or sea slugs, *H. capensis*, possesses the ability to selectively sequester bioactive natural products from its diet[2] and its association with a *Dysidea* sponge therefore provided the rationale for our investigation of this sponge as a potentially new source of bioactive metabolites.

A combination of Si gel chromatography and normal phase HPLC (hexane and isooctane) was used to isolate three furanosesquiterpenes from the *Dysidea* extract; the new metabolite tsitsikammafuran (**1**) and the known nakafurans-8 (**2**), and -9 (**3**). The spectral data of compounds **2** and **3** were consistent with the data acquired previously for nakafurans-8 and -9, isolated in an earlier study of *H. capensis*.[2] Our discovery of the known ichthyotoxic metabolites **2** and **3** in both specimens of *H. capensis* and the *Dysidea* sponge implies that, in the Tsitsikamma Marine Reserve, *H. capensis* is incorporating the defensive metabolites of this sponge into its own chemical defense system.

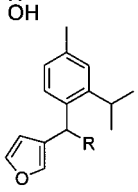
Tsitsikammafuran (**1**), isolated in very low yield (0.8 mg, 0.0004% dry wt. of sponge), gave a molecular ion at *m/z* 214.1345 (Δmmu$=-1.2$) in its HREI-mass spectrum thus establishing the molecular formula $C_{15}H_8O$ for this compound. Fourteen of the fifteen carbon atoms were clearly resolved in the ^{13}C NMR spectrum of **1** with a DEPT experiment indicating the presence of three methyl (two overlapped), one methylene, one shielded methine, six olefinic methines and four olefinic quaternary carbon atoms. The ^{1}H NMR spectrum of **1** revealed six aromatic protons, three of which, δ 6.21 (brs); 7.06 (s); and 7.33(brs), were consistent with a β-substituted furan ring,[2] an isopropyl methine proton septet (δ 3.13), two overlapping methyl doublets (δ 1.17), one methyl singlet (δ 2.27) and one deshielded methylene singlet (δ 3.76). These NMR data together with the seven degrees of unsaturation implied by the molecular formula suggested that **1** possessed a biaryl structure with a tri-substituted benzene linked to a β-substituted furan via a methylene bridge.



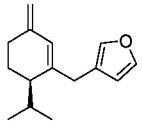
1 R = H
20 R = OH

2

3



4 R = H
21 R = OH



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Keywords: marine metabolites; furan; sesquiterpene; aryl halides.
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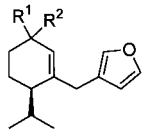
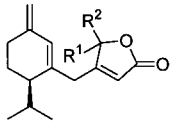
Although the multiplicity (two mutually coupled doublets and a singlet) of the three benzene proton NMR resonances implied a 1,3,4-substitution pattern around the benzene ring of **1**, positioning the three substituents around this ring proved to be problematic. Two and three bond HMBC correlations, respectively, from both the isopropyl methine proton and the methylene protons to the same olefinic quaternary carbon (δ 143.8) established the *ortho* relationship between the isopropyl and [(furan-3-yl)methyl]- substituents. However, a small, but crucial, HMBC correlation from the aromatic proton doublet (δ 7.17) to either one of two closely spaced carbon resonances at δ 28.4 (either the isopropyl methine carbon δ 28.37 or the methylene carbon δ 28.44) could not be assigned with confidence. Unfortunately, we were prevented from resolving this problem by acquiring the HMBC data of **1** in a different NMR solvent, e.g. C_6D_6, as our very small amount of tsitsikammafuran decomposed on standing in $CDCl_3$ and access to further sponge material was not possible. Consequently, two structures for tsitisikammafuran were proposed from the available HMBC and other NMR data; either 3-[(furan-3-yl)methyl]-*p*-cymene, **1**, or a regioisomer of this compound, 4-[(furan-3-yl)methyl]-*m*-cymene (**4**).

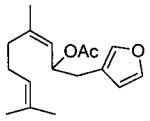
Structure **1** is the aromatic analog of penlanfuran (**5**), first isolated from a Brittany sponge, *Dysidea fragilis*.[3] A subsequent analysis of the minor β-substituted furan metabolites in the *D. fragilis* extract yielded six oxygenated penlanfuran analogs (**7**–**12**), and a possible acyclic biosynthetic precursor (**13**), of **5**.[4] Accordingly, the occurrence of tsitsikammafuran in a *Dysidea* sponge suggested, from biosynthetic arguments, that structure **1** was the more feasible of the two proposed structures for this compound. To unequivocally establish the structure of tsitsikammafuran and provide sufficient quantities of **1** for further bioactivity studies, compounds **1** and **4** were synthesized from thymol (**14**) and *p*-cresol respectively. The successful strategy employed for the syntheses of **1** and **4** involved a biaryl coupling reaction between a phenyl lithium nucleophile (derived from a suitable brominated precursor) and 3-furaldehyde, followed by dehydroxylation of the resulting benzylic alcohol.



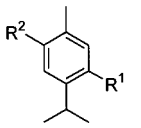


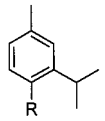
7 R^1 = β–CH_2OAc, R^2 = α-H
8 R^1 = β-CH_2OAc, R^2 = α-OH
9 R^1 = α-CH_2OAc, R^2 = β-OH
10 $R^1 + R^2$ = O

11 R^1 = β–OH, R^2 = α-H
12 R^1 = β-H, R^2 = α-OH



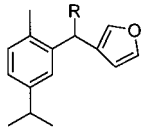
13

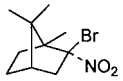




14 R^1 = OH, R^2 = H
15 R^1 = Br, R^2 = H
16 R^1 = R^2 = Br
23 R^1 = H, R^2 = Br

18 R = Br
19 R = OH



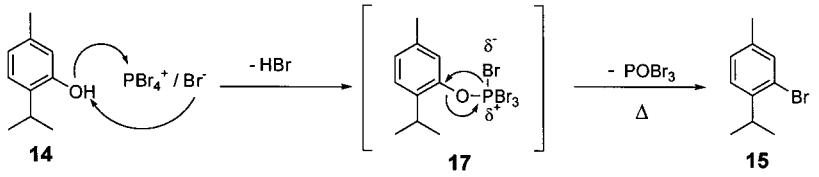


22 R = H
25 R = OH

24

Preparation of the brominated precursor, 3-bromo-*p*-cymene (**15**), required for the synthesis of **1**, was achieved in one step using the method of Ganguly and Le Fevre[5] in which thymol was refluxed (2.5 h) with a mixture of PBr_3 and Br_2 (or PBr_5) under rigorously anhydrous conditions. Steam distillation of the reaction mixture, followed by removal of unreacted **14** by washing the distillate with KOH gave pure **15** in 53% isolated yield. The structure of **15** was confirmed from HRFABMS and 2D NMR data. A three bond HMBC correlation from the isopropyl methine proton septet (δ 3.34) to the deshielded brominated carbon (δ 124.0) together with the multiplicity of the aromatic protons (two doublets and a singlet), observed in the ^{1}H NMR spectrum of **15**, proved definitive in the structure elucidation of this compound. Interestingly, after repeating this reaction several times we found that the yield of **15** was consistently dependent on both the thymol stoichiometry and the reflux temperature. With respect to thymol stoichiometry at least four equivalents of **14** were required to give **15** as the only brominated product, whereas two equivalents of **14** gave a 2:1 mixture of **15** and 2,5-dibromo-*p*-cymene (**16**). A paucity of spectral data in the recent chemical literature[6] necessitated spectroscopic confirmation of the structure of **16**. The molecular formula ($C_9H_{10}Br_2$) of **16** was established from HRFABMS data. The positioning of the two bromine atoms at C-2 and C-5, as opposed to C-3 and C-5, was inferred by the lack of symmetry evident in the aromatic region of both the ^{1}H (two aromatic proton singlets at δ 7.38 and 7.39) and ^{13}C (six clearly resolved carbon resonances) NMR spectra. Conclusive evidence for the 1,2,4,5-tetrasubstitution pattern around the benzene ring followed from three bond HMBC correlations from the protons of the methyl substituent (δ 2.32) to the brominated quaternary carbon C-2 (δ 124.1) and from the isopropyl methine proton (δ 3.26) to the brominated C-5 carbon (δ 122.6).

Reflux temperatures less than 240°C in the bromination reaction above resulted in a substantial reduction in the yield of the only brominated product **15**. ^{1}H NMR examination of the reaction mixtures containing small amounts of **15** revealed three aromatic proton signals δ 7.23 (s), 7.00 (d, J=8 Hz), and 7.18 (d, J=8 Hz) in addition to the previously assigned resonances of **15** and unreacted thymol. The additional proton signals were tentatively assigned to the



Scheme 1. Proposed mechanism for the bromination of thymol with PBr_5.

tetrabromophosphonium ether (**17**) which, unfortunately, we were not able to isolate from the reaction mixture.

The direct replacement of a phenolic group by bromine with PBr_5 is an unusual reaction and to the best of our knowledge has not been fully rationalized. Since crystallographic evidence suggests that PBr_5 exists in an ionic form (PBr_4^+/Br^-),[7] we propose the mechanism, outlined in Scheme 1, to explain our observations of this reaction. These observations include firstly, the vigorous release of HBr gas at the onset of the reaction and secondly, the necessity for refluxing the reaction mixture at high temperatures. The latter procedure is deemed necessary for the concomitant elimination of phosphorous oxybromide from **17**, and attack of bromide at the resulting electrophilic center at C-3 in the benzene ring.

The other brominated precursor, 4-bromo-*m*-cymene (**18**), required for the synthesis of **4**, was prepared in two steps from *p*-cresol, using firstly, a modified version of Carpenter and Easter's method[8] for the regiospecific, *ortho* propylation of *p*-cresol to 4-hydroxy-*m*-cymene (**19**) which was brominated with PBr_3/Br_2 as described previously. Carpenter and Easter's method required the addition of diisopropyl ether (bp 67°C) to a refluxing mixture of *p*-cresol and an acid activated clay catalyst (180°C). After a number of attempts with three different types of clay catalyst we were unable to obtain any of **19** by this method and consequently modified the procedure as follows. A mixture of *p*-cresol, peroxide-free diisopropyl ether, and montmorillonite clay (activated with conc. H_2SO_4) was autoclaved (180°C) with stirring (3 h). The required phenol, **19**, was efficiently separated via spinning band distillation (bp 114°C, 112 mmHg) from the other two volatile components of the reaction mixture (cumene and unreacted *p*-cresol). Although the non-optimized, isolated yield of **19** from the reaction was only 17%, the ready availability of the starting materials and the simplicity of this preparation made it an attractive alternative to other methods.[9]

The bromination of four equivalents of **19** with PBr_3/Br_2 proceeded smoothly to give **18** in 54% yield. Frustratingly, although **18** is known[10] no published NMR data for this compound could be found. However, HRFABMS data confirmed the molecular formula of **18** while the ^{1}H NMR multiplicity of the three aromatic protons, i.e. one finely split doublet (δ 7.09, J=1 Hz, H-2), the double doublet (δ 6.86, J=1, 8 Hz, H-6) and the doublet (δ 7.40, J=8 Hz, H-5), supported bromination at C-4. Further confirmation of the bromine substituent at C-4 was supplied by a prominent three bond HMBC correlation from the isopropyl methine proton (δ 3.35) to the deshielded, brominated carbon (δ 120.9) in the HMBC spectrum of **18**.

Lithiation of **15** and **18** with BuLi in THF (−78°C) followed by attempted coupling of the resultant phenyl lithium nucleophiles to 3-furaldehyde initially gave none of the benzylic alcohols **20** and **21** respectively. However, the addition of one equivalent of a hindered base, either DABCO or TMEDA, during the initial lithiation step yielded 27% and 32% of the respective alcohols. Fortuitously, an increase (two equivalents) in the amount of TMEDA added, resulted in a concomitant doubling of the yields of **20** and **21** from the respective coupling reactions. Further repetitions of this reaction with four and six equivalents of TMEDA gave negligible improvements in yield. The HRFABMS and NMR data of **20** and **21** were consistent with their expected structures. Strong three bond HMBC correlations from the unusually deshielded oxymethine proton doublet (ca. δ 6.05 J=4 Hz) of **20** and

Table 1. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR data for compounds **1**, **4** and **22**

	(**1**)		(**4**)		(**22**)	
	δ_C ppm (mult.)	δ_H ppm (mult., J/Hz)	δ_C ppm (mult.)	δ_H ppm (mult., J/Hz)	δ_C ppm (mult.)	δ_H ppm mult., J/Hz)
1	135.1 (s)		133.7 (s)		133.5 (s)	
2	130.5 (d)	6.95 (s)	126.1 (d)	7.09 (s)	138.1 (s)	
3	136.6 (s)		146.5 (s)		127.4 (d)	7.01 (s)
4	143.8 (s)		136.2 (s)		146.6 (s)	
5	125.3 (d)	7.17 (d, 8)	129.7 (d)	7.03 (d, 8)	130.2 (d)	7.08 (d, 8)
6	127.6 (d)	7.03 (d, 8)	126.4 (d)	6.93 (d, 8)	124.3 (d)	7.01 (br d)
7	28.4 (t)	3.76 (s)	28.0 (t)	3.76 (s)	29.0 (t)	3.72 (s)
8	124.8 (s)		124.9 (s)		123.8 (s)	
9	139.6 (d)	7.06 (s)	139.5 (d)	7.06 (s)	139.6 (d)	7.09 (s)
10	142.9 (d)	7.33 (s)	142.8 (d)	7.33 (s)	142.9 (d)	7.35 (s)
11	111.2 (d)	6.21 (s)	111.2 (d)	6.21 (s)	111.3 (d)	6.23 (s)
12	28.4 (d)	3.13 (sept, 7)	28.7 (d)	3.14 (sept, 7)	33.7 (d)	2.84 (sept, 7)
13	23.9 (q)	1.17 (d, 7)	23.8 (q)	1.18 (d, 7)	24.1 (q)	1.21 (d, 7)
14	23.9 (q)	1.17 (d, 7)	23.8 (q)	1.18 (d, 7)	24.1 (q)	1.21 (d, 7)
15	20.9 (q)	2.27 (s)	21.2 (q)	2.32 (s)	18.9 (q)	2.25 (s)

21 to the carbon atom bearing the isopropyl substituent (δ 142.9 and δ 145.9 in **20** and **21** respectively) corroborated the *ortho* relationship between the isopropyl and [(furan-3-yl)methyl]- substituents. In addition, deuterium exchange of the sharp hydroxyl proton doublet (δ 2.08, J=4 Hz) in the ^{1}H NMR spectrum of **20** and the analogous resonance (δ 1.97, J=4 Hz) in the ^{1}H NMR spectrum of **21** provided confirmation of the presence of a benzylic alcohol moiety in both these compounds. Finally, facile, quantitative dehydroxylation of **20** and **21** to **1** and **4** was achieved in less than ten minutes with iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide.[11]

The ^{1}H and ^{13}C NMR data for **1** and **4**, assigned from 2D NMR determinations, are presented in Table 1. While the ^{13}C NMR data of the two synthetic compounds were similar the significant ^{1}H NMR chemical shift differences between the aromatic protons enabled an unequivocal assignment of the structure of tsitsikammafuran as 3-[(furan-3-yl)methyl]-*p*-cymene, **1**, and not the regioisomer 4-[(furan-3-yl)methyl]-*m*-cymene, **4**. The IR and MS data of synthetic **1** were similarly compatible with those of the natural product.

Having established a successful synthetic route to **1** and **4** we were in a position to synthesize other regioisomers of these two compounds for comparative bioactivity studies. Thus, the regioisomer, 2-[(furan-3-yl)methyl]-*p*-cymene (**22**) was prepared from the brominated precursor, 2-bromo-*p*-cymene (**23**), which was obtained, in reasonable yield, via an intriguing acid catalysed rearrangement of bromonitrocamphane (**24**).[12] Coupling of **23** to 3-furaldehyde followed by dehydroxylation of the product (**25**) in the usual manner gave **22** in comparable yields to those obtained for **1** and **4**. The assigned NMR data for **22** are presented in Table 1. The potential agrochemical, biomedical and ichthyotoxic activities of compounds **1**, **4**, **20**–**22** and **25** are currently under investigation.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Avance NMR spectrometer using $CDCl_3$ as the solvent, referenced at δ 7.25/77.0 ppm. The HREI mass spectral data were supplied by Dr Philip Boshoff of the Mass Spectrometry Unit at the Cape Technikon, Cape Town, HRFABMS data were acquired by Professor Louis Fourie of the University of Potchefstroom and the LREI mass spectra were obtained on a Finnegan–Matt GCQ mass spectrometer by Mr Aubrey Sonemann of Rhodes University. HPLC separations of the natural products and synthetic intermediates were achieved using a Whatman Magnum 9 Partisil column with an eluent flow rate of 4 mL min^{-1} unless otherwise stated. The IR data for all compounds were obtained on a Perkin–Elmer 2000 FTIR spectrometer.

Collection and identification of the *Dysidea* sponge. The white sponge, on which the nudibranch *Hypselodoris capensis* was observed, was collected using SCUBA at a depth of −8 m in the Tsitsikamma National Park in March, 1998. The sponge was described as follows. The undulating sponge was horizontally extended, standing only 3–5 cm high. It had large oscula (2 mm diameter) along raised ridges and was fairly hard but breakable. The bumpy conulose exterior was a dirty white color in life and was covered with a layer of large sand grains. Internally, the sponge's skeleton comprised a reticulation of large fibers heavily cored with sand grains. No spicules were visible amongst the fibres. The sponge therefore most likely represents a new species of the genus *Dysidea* (Family Dysididae).

Isolation of furanosesquiterpenes (1–3). The lyophilized *Dysidea* sponge (180 g) was extracted with EtOAc over several days. The EtOAc extract was concentrated and partitioned between hexane and aqueous MeOH (10%). The hexane partition layer was dried and concentrated to yield an oil (350 mg) which was chromatographed on Si gel (hexane–EtOAc). HPLC (hexane) of a fraction (48 mg) adjudged by NMR to contain furano compounds yielded tsitsikammafuran (**1**) as a colourless oil (0.8 mg, 0.0004% dry wt.). Further HPLC of this fraction (isooctane, 3 mL min^{-1}) yielded nakafuran-8 (**2**, 10 mg, 0.005% dry wt.) and nakafuran-9 (**3**, 19 mg, 0.01% dry wt.). The spectroscopic data of **2** and **3** were consistent with those obtained for nakafuran-8 and -9 isolated previously from *H. capensis*.[2]

Tsitsikammafuran (1). IR ν_{max} 2962, 2925, 2868, 1501, 1455, 1382, 1158, 1064, 1024, 873, 819, 767 cm^{-1}; ^{1}H and ^{13}C NMR data are presented in Table 1; EIMS (70 eV) *m/z* (rel. int.) 214 (10), 199 (6), 178 (34), 161 (19), 149 (25), 133 (100), 105 (24), 97 (27), 83 (29), 71 (34), 69 (39), 57 (55), 55 (44), 43 (45), 41 (42); HREIMS obsd. 214.1345, $C_{15}H_{18}O$ requires 214.1357.

***ortho*-Alkylation of *p*-cresol.** A mixture of *p*-cresol (50.0 g, 0.462 mol), diisopropyl ether (47.0 g, 0.462 mol) and montmorillonite clay (6.0 g, activated by stirring with 0.2 g 50% H_2SO_4) was heated (180°C) and stirred (3 h) in a small autoclave equipped with a magnetic stirrer and heating element. The mixture was cooled, filtered and vacuum distilled using a short fractionating column which yielded *p*-cresol (26–49°C, 2 mmHg) and two further fractions, collected as the distillation temperature rose to 68°C. These latter fractions were combined (36.5 g) and redistilled using a 1 meter long spinning band distillation column. The first two fractions consisted of cumene (84.5–88.4°C, 12 mmHg) and *p*-cresol (91–95°C, 12 mmHg) respectively while 4-hydroxy-*m*-cymene (**19**, 12.0 g, 17% yield) was collected as the final fraction (113–114°C, 12 mmHg).

4-Hydroxy-*m*-cymene (19). HRFABMS obsd. 151.112198 (M+1), $C_{10}H_{15}O$ requires 151.112290. IR and ^{1}H NMR data are consistent with published data.[13]

Bromination of phenols 14 and 19. The following procedure is representative. Bromine (0.95 mL, 18.4 mmol) was added dropwise to cooled PBr_3 (1.75 mL, 18.4 mmol) under anhydrous conditions to form a bright yellow, crystalline precipitate of PBr_5. The addition of thymol (11.1 g, 73.6 mmol) with gentle warming (50°C) resulted in the vigorous evolution of HBr gas. The pale orange solution was refluxed (2.5 h), cooled and steam distilled. The aqueous distillate was extracted with ether (3×50 mL),

and the combined ether layers washed with 10% KOH (3×30 mL), water (30 mL), dried and concentrated to give **15** as a colorless oil (2.08 g, 53%). If only two equivalents of thymol were used a 2:1 mixture of **15** and 2,5 dibromo-*p*-cymene (**16**) was obtained. The bromination of **19** (7.76 g, 51.7 mmol) also proceeded smoothly by this method. Repeated Si gel chromatography (hexane) proved more effective than steam distillation for the isolation of 4-bromo-*m*-cymene as a colorless oil (1.48 g, 54%) from the reaction mixture.

3-Bromo-*p*-cymene (15). IR ν_{max} 2960, 2927,1501, 1463, 1379, 1051, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (6H, d, J=7 Hz, H_3-9, H_3-10), 2.30 (3H, s, H_3-7), 3.34 (1H, sept, J=7 Hz, H-8), 7.09 (1H, d, J=8 Hz, H-6), 7.17 (1H, d, J=8 Hz, H-5), 7.38 (1H, s, H-2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (q, C-7), 22.9 (q, C-9), 22.9 (q, C-10), 32.4 (d, C-8), 124.0 (s, C-3), 126.3 (d, C-5), 128.4 (d, C-6), 133.2 (d, C-2), 137.1 (s, C-1), 144.2 (s, C-4) ppm; EIMS (70eV) *m/z* (rel. int.) 214 (33), 212 (32), 199 (91), 197 (87), 118 (100), 117 (51); HRFABMS obsd. 213.027795 (M+1), $C_{10}H_{14}{}^{79}Br$ requires 213.027887.

2,5-Dibromo-*p*-cymene (16). IR ν_{max} 2964, 1471, 1383, 1360, 1070, 1046, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (6H, d, J=7 Hz, H_3-9, H_3-10), 2.32 (3H, s, H_3-7), 3.26 (1H, sept, J=7 Hz, H-8), 7.38 (1H, s, H-3), 7.39 (1H, s, H-6) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1 (q, C-7), 22.7 (q, C-9), 22.7 (q, C-10), 32.6 (d, C-8), 122.6 (d, C-5), 124.1 (d, C-2), 130.3 (d, C-6), 134.4 (d, C-6), 137.0 (s, C-1), 146.7 (s, C-4) ppm; EIMS (70 eV) *m/z* (rel. int.) 290 (18), 279 (46), 277 (100), 275 (49), 198 (36), 196 (34); HRFABMS obsd. 289.930921, $C_{10}H_{12}{}^{79}Br_2$ requires 289.930573.

4-Bromo-*m*-cymene (18). IR ν_{max} 2961, 2929, 1502, 1463, 1382, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (6H, d, J=7 Hz, H_3-9, H_3-10), 2.31 (3H, s, H_3-7), 3.35 (1H, sept, J=7 Hz, H-8), 6.86 (1H, dd, J=2, 8 Hz, H-6), 7.09 (1H, d, J=1 Hz, H-2), 7.40 (1H, d, J=8 Hz, H-5) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q, C-7), 22.8 (q, C-9), 22.8 (q, C-10), 32.7 (d, C-8), 120.9 (s, C-4), 127.4 (d, C-2), 128.1 (d, C-6); 132.4 (d, C-5), 137.3 (s, C-1), 146.9 (s, C-3); EIMS (70eV) *m/z* (rel. int.) 215 (82), 213 (85), 134 (100), 119 (8), 105 (7), 91 (8) HRFABMS obsd. 213.027802 (M+1), $C_{10}H_{14}{}^{79}Br$ requires 213.027887.

Biaryl coupling of compounds 15, 18 and 23 with 3-furaldehyde. The following procedure is representative. A solution of 3-bromo-p-cymene (**15**, 300 mg, 1.41 mmol) and TMEDA (386 μL, 2.56 mmol) in dry THF (3 mL) was cooled to −78°C and *n*-BuLi (1.6 M in hexane, 800 μL, 1.28 mmol) added slowly over several minutes. The reaction mixture was stirred (1 h) and a solution of 3-furaldehyde (111 μL, 1.28 mmol) in dry THF (1 mL) added dropwise. The reaction mixture was stirred (4.5 h) and allowed to warm up gradually to room temperature before quenching with water. The removal of THF under reduced pressure from the reaction mixture was followed by the addition of brine. The aqueous solution was extracted with CH_2Cl_2 (4×20 mL), the organic layers combined, dried and concentrated to yield a crude product mixture which was chromatographed over Si gel (EtOAc–hexane). The fraction (171 mg) eluted with 8:2 hexane–EtOAc was subjected to NPHPLC (8:2 hexane–EtOAc) to give [2-isopropyl-5-methylphenyl](furan-3-yl)methanol (**20**, 145 mg, 49%) as a colorless oil. The regioisomers of **20**, [2-isopropyl-4-methylphenyl](furan-3-yl)methanol (**21**) and [5-isopropyl-2-methylphenyl](furan-3-yl)methanol (**25**) were similarly prepared, and in comparable yields (64 and 30% respectively), from **18** and **23** respectively

[2-Isopropyl-5-methylphenyl](furan-3-yl)methanol (20). IR ν_{max} 3351, 2964, 1501, 1158, 1026, 874, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (3H, d, J=7 Hz, H_3-14), 1.22 (3H, d, J=7 Hz, H_3-13), 2.08 (1H, d, J=4 Hz, O*H*), 2.32 (3H, s, H_3-15), 3.19 (1H, sept, J=7 Hz, H-12), 6.06 (1H, d, J=4 Hz, H-7), 6.33 (1H, d, J=1 Hz, H-11), 7.11 (1H, d, J=8 Hz, H-6), 7.20 (1H, d, J=8 Hz, H-5), 7.21 (1H, s, H-9), 7.31 (1H, s, H-2), 7.36 (1H, t, J=2 Hz, H-10) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q, C-15), 23.8 (q, C-14), 24.2 (q, C-13), 27.9 (d, C-13), 65.8 (d, C-7), 109.7 (d, C-11), 125.4 (d, C-5), 126.8 (d, C-2), 128.7 (d, C-6), 129.2 (s, C-8), 135.3 (s, C-1), 139.4 (s, C-3), 139.8 (d, C-9), 142.9 (s, C-4), 143.2 (d, C-10) ppm; EIMS (70 eV) *m/z* (rel. int.) 230 (16), 212 (21), 197 (93), 187 (28), 183 (57), 179 (22), 169 (60), 162 (100), 143 (31), 128 (27), 91 (20); HRFABMS obsd. 231.138574 (M+1), $C_{15}H_{19}O_2$ requires 231.138505.

[2-Isopropyl-4-methylphenyl](furan-3-yl)methanol (21). Colorless needles (mp 39–41°C); IR ν_{max} 3351, 2964, 1501, 1158, 1026, 875, 774, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (3H, d, J=7 Hz, H_3-14), 1.22 (3H, d, J=7 Hz, H_3-13), 1.97 (1H, d, J=4 Hz, O*H*), 2.34 (3H, s, H_3-15), 3.21 (1H, sept, J=7 Hz, H-12), 6.05 (1H, d, J=4 Hz, H-7), 6.31 (1H, s, H-11), 7.02 (1H, d, J=8 Hz, H-5), 7.10 (1H, s, H- 2), 7.21 (1H, s, H-9), 7.36 (1H, d, J=8 Hz), 7.36 (1H, d, J=2 Hz, H-10) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (q, C-15), 23.9 (q, C-14), 24.2 (q, C-13), 28.2 (d, C-12), 65.9 (d, C-7), 109.5 (d, C-11), 126.3 (d, C-2), 126.4 (d, C-6), 126.8 (d, C-5), 129.2 (s, C-8), 136.6 (s, C-4), 137.7 (s, C-1), 140.0 (d, C-9), 143.3 (d, C-10), 145.9 (s, C-3) ppm; EIMS (70 eV) *m/z* (rel. int.) 230 (24), 212 (14), 201 (29), 197 (79), 187 (47), 183 (56), 169(59), 162 (100), 143 (40), 128 (32), 91 (23); HRFABMS obsd. 231.138458 (M+1), $C_{15}H_{19}O_2$ requires 231.138505.

[5-Isopropyl-2-methylphenyl](furan-3-yl)methanol (25). Amorphous white solid; IR ν_{max} 3351, 2960, 1501, 1459, 1158, 1025, 874, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (6H, d, J=7 Hz, H_3-13, H_3-14), 2.01 (1H, d, J=4 Hz, O*H*); 2.25 (3H, s, H_3-15), 2.89 (1H, sept, J=7 Hz, H-12), 5.94 (1H, d, J=4 Hz, H-7), 6.34 (1H, s, H-11), 7.07 (2H, s, H-3, H-5), 7.21 (1H, s, H-9), 7.36 (1H, s, H-10), 7.40 (1H, s, H-6) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6 (q, C-15), 24.0 (q, C-13), 24.1 (q, C-14), 33.9 (d, C-12), 66.5 (d, C-7), 109.5 (d, C-11), 123.9 (d, C-6), 125.5 (d, C-5), 128.2 (s, C-8), 130.5 (d, C-3), 132.2 (s, C-1), 140.1 (d, C-9), 140.7 (s, C-2), 143.4 (d, C-10), 146.9 (s, C-4) ppm; EIMS (70 eV) *m/z* (rel. int.) 212 (42), 197 (58), 183 (11), 169 (21), 162 (100), 147 (24), 128 (8), 95 (15); HRFABMS obsd. 231.138511 (M+1), $C_{15}H_{19}O_2$ requires 231.138505.

Dehydroxylation of compounds 20, 21 and 25. The

following procedure adapted from Perry et al.[11] is representative. Chlorotrimethylsilane (99 μL, 0.52 mmol) was slowly added to a stirred suspension of NaI (117 mg, 0.78 mmol) in dry MeCN (2 mL) under a N_2 atmosphere. A solution of compound **20** (30 mg, 0.13 mmol) in dry MeCN (2 mL) was added dropwise to the iodotrimethylsilane solution and the reaction mixture stirred (10 min) at ambient temperature, before being quenched by pouring into water (10 mL). The resulting aqueous mixture was extracted with ether (3×25 mL), the combined ether extracts washed with 20% $Na_2S_2O_3$ solution (3×25 mL), and water (30 mL), dried and concentrated to afford compound **1** as a colourless oil.: IR, EIMS, and NMR data were identical with tsitsikammafuran. In all three dehydroxylation reactions the yields of the dehydroxylated products were quantitative.

4-[(Furan-3-yl)methyl]-*m*-cymene (4). Colorless oil, IR ν_{max} 2962, 1500, 1459, 1023, 874, 771, 682, 599 cm^{-1}; ^1H and ^{13}C NMR data are presented in Table 1; EIMS (70 eV) *m/z* (rel. int.) 215 (21), 214 (100), 199 (16), 185 (31), 171 (38), 157 (22), 143 (51), 128 (46), 115 (18), 91 (7); HRFABMS obsd. 214.135786, $C_{15}H_{18}O$ requires 214.135765.

2-[(Furan-3-yl)methyl]-*p*-cymene (22). Colorless oil, IR ν_{max} 2925, 1497, 1459, 1383, 1021, 872, 598 cm^{-1}; ^1H and ^{13}C NMR data are presented in Table 1; EIMS (70 eV) *m/z* (rel. int.) 215 (16), 214 (100), 199 (82), 171 (71), 143 (38), 129 (17), 115 (16), 81 (30); HRFABMS obsd. 214.135702, $C_{15}H_{18}O$ requires 214.135765.

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