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A new synthesis of pleraplysillin-1, a sponge metabolite, using Wittig olefination

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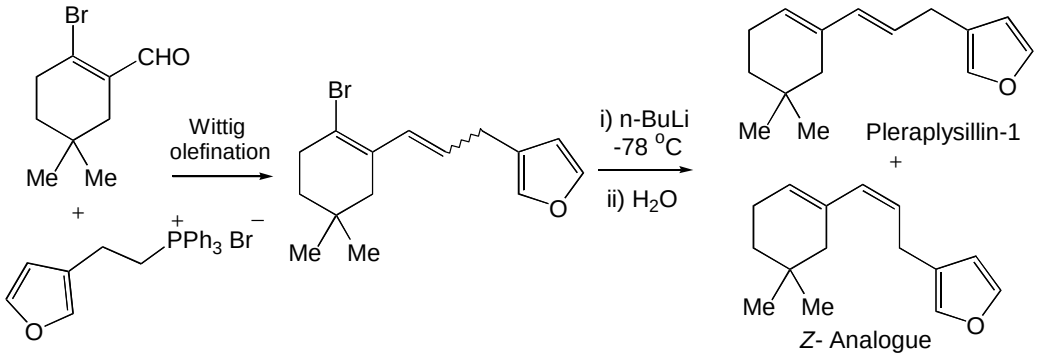
Abstract

A new synthesis of pleraplysillin-1, a sponge metabolite, has been accomplished using Wittig olefination of 2-bromo-1-formyl-4,4-dimethylcyclohex-1-ene with an appropriate ylide. A generalized study on the Wittig olefination of several 2-bromo-1-formyl-1-cycloalkenes with the ylides generated *in situ* from 2-(3/2-furyl)ethyltriphenylphosphonium bromides was also undertaken as a prerequisite. The described methodology is not the most efficient route to the desired isomer. However, it does offer a new route to molecules of type **1**, with the advantages that it (i) is relatively simple, (ii) does not involve expensive or toxic organometallic reagents, and (iii) affords overall yields of the bromo analogues and the final diastereoisomeric mixtures, which are much better than those previously reported.



Keywords: Pleraplysillin-1, Marine natural products, Wittig olefination

Introduction

In the recent past, we have been using β-halo-α,β-unsaturated aldehydes as building blocks for the synthesis of various heterocycles,[1-5] including furophenanthraquinones.[6] In this context, our attention was recently drawn to pleraplysillin-1 (**1**), a cytotoxic furosesquiterpenoid isolated from *Pleraplysilla spinifera,* a marine sponge, by Cimino *et al.*[7] It possesses a unique ochtodane, i.e., 3,3-dimethyl-1-ethylcyclohexane skeleton (**2**),[8-10] (Figure 1) which is attached to a 3-furylmethyl group, and its 1,3-diene system is separated from the furan ring by a one-carbon unit.

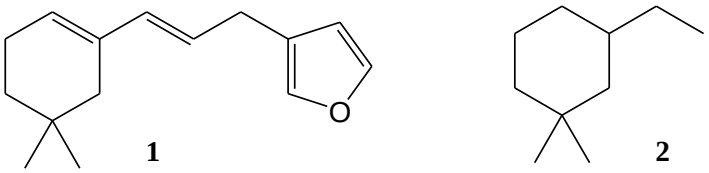
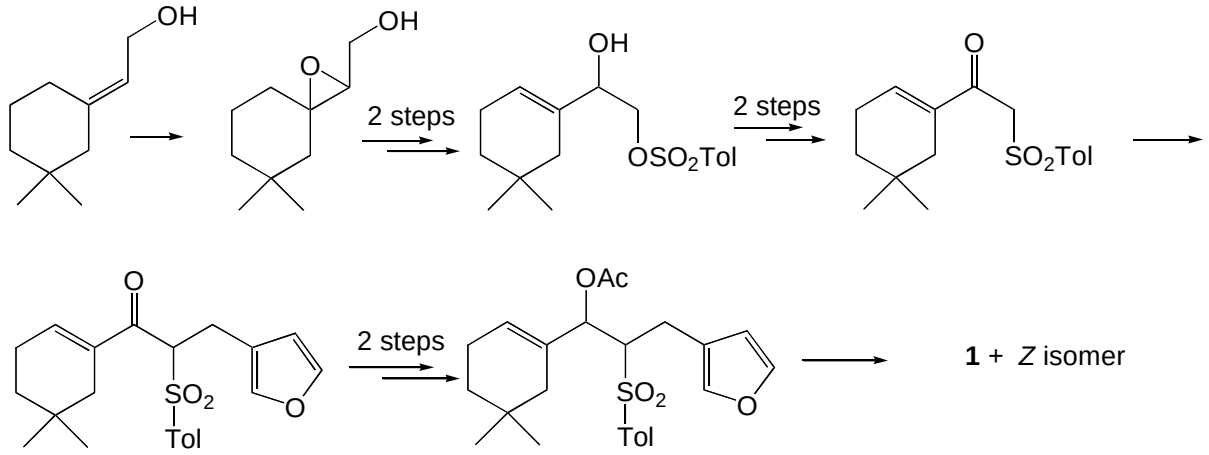


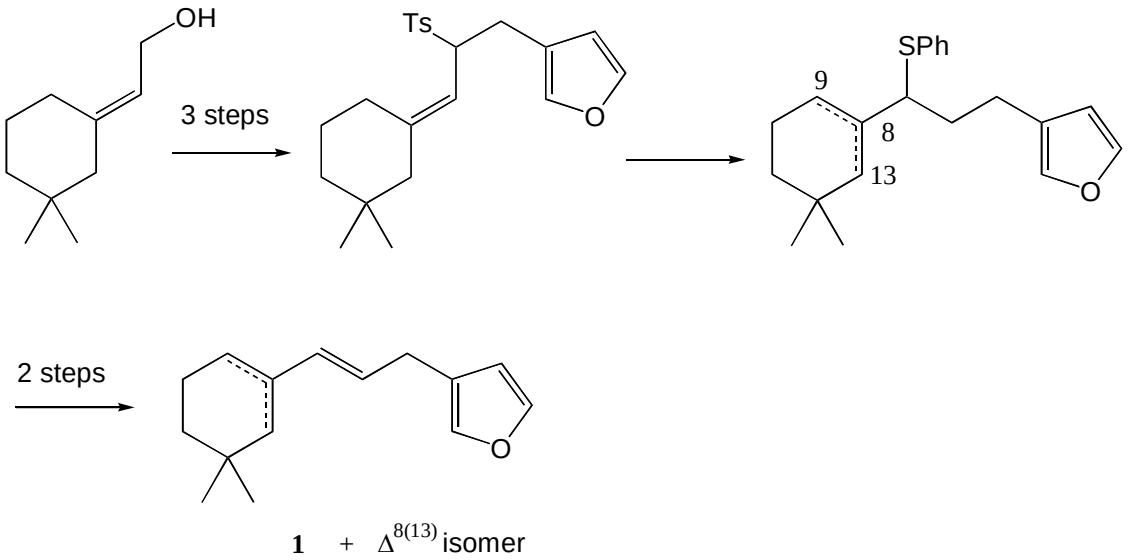
Figure 1. Pleraplysillin-1 (**1**) and ochtodane skeleton (**2**)**.**

A decade later, its unique structure expectedly triggered its syntheses by Masaki *et al*.[11,12] In the first synthesis that they reported,[11] they synthesized **1** from an ochtodane monoterpenol using Sharpless regioselective epoxide ring-opening reaction as the crucial step. The final step was a reductive elimination of the β-acetoxy-sulfone which furnished a diastereomeric mixture of **1** with its Z-isomer in *ca.* 5:1 ratio (Scheme 1).



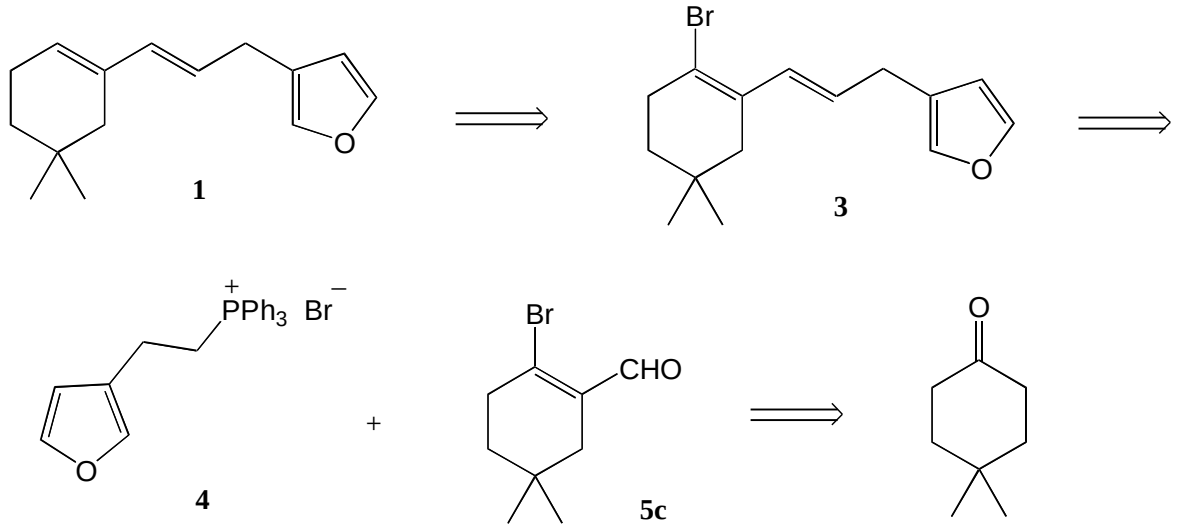
Scheme 1. First synthesis of pleraplysillin-1 (**1**) by Masaki *et al.*[11]

In their second report,[12] they constructed the carbon skeleton of **1** by the coupling of a sulfone, derived from the same ochtodane monoterpenol, with 3-furylmethyl bromide, followed by successive detosylation, phenylthionation and elimination of thiophenol (Scheme 2). However, it furnished a regioisomeric mixture of **1** (major) and its $\Delta^{8,13}$-isomer (minor) in 3:2 ratio. In both reported syntheses, the overall yields were poor.



Scheme 2. Second synthesis of pleraplysillin-1(**1**) by Masaki *et al.*[12]

Scott *et al*. later reported an efficient synthesis of pure pleraplysillin-1 using Pd(0)-catalyzed cross coupling of an *(E)*-furan-3-allyltin with 5,5-dimethylcyclohex-1-en-1-triflate.[13,14] However, since in both of Masaki's attempts, the product was a mixture of regio- or stereo-isomers, we planned to utilize our ongoing strategy, *viz*. the employment of a suitable β-halo-α,β-unsaturated aldehyde as a starting material for the development of a new synthesis of pleraplysillin-1 and its analogues *via* a new route using Wittig olefination as the crucial step. Our planned retro-synthesis of pleraplysillin-1 is depicted in Scheme 3.



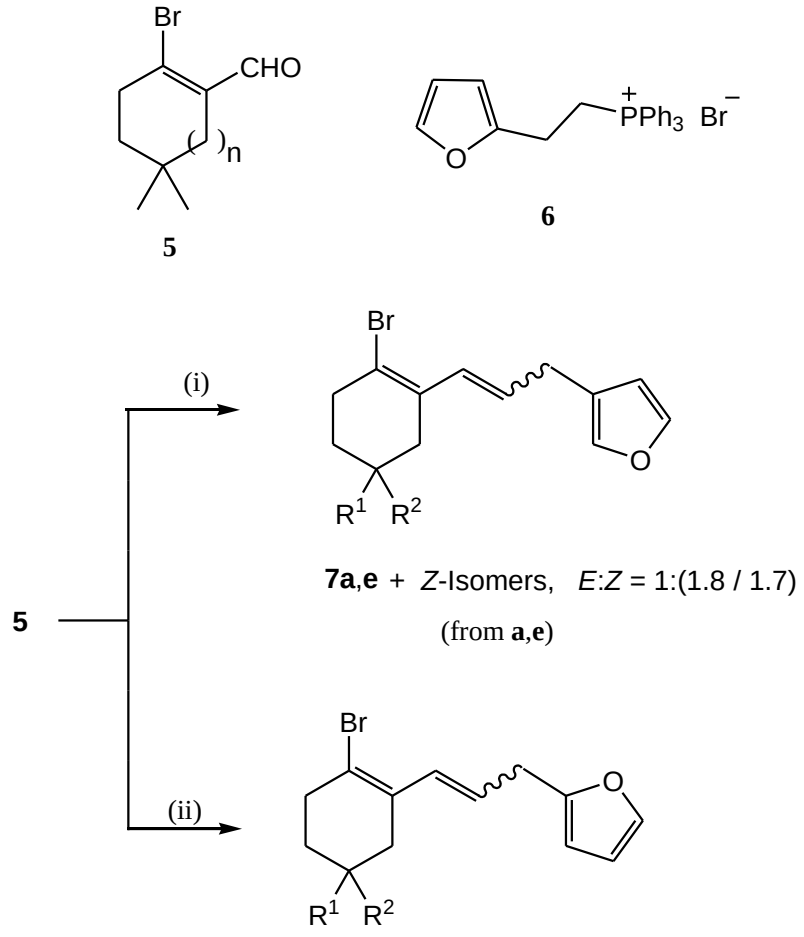
Scheme 3. Retrosynthesis of pleraplysillin-1 (**1**).

Results and Discussion

As shown above, pleraplysillin-1 can be synthesized by protodebromination of the corresponding bromo derivative **3**. The latter may be obtained by the Wittig olefination of the ylide [to be generated *in situ* from 2-

(3-furyl)ethyltriphenylphosphonium bromide], **4**) with 2-bromo-1-formyl-5,5-dimethylcyclohex-1-ene(**5c**). This plan necessitated a generalized study on the Wittig olefination of variously substituted 2-bromo-1-formyl-cycloalkenes (**5a**-**e**) with the ylides generated *in situ* from 3/2-furylethylphosphonium salts (**4**/**6**), in order to check the feasibility of our approach. The phosphonium salts were synthesized efficiently from 3/2-furylethanol by successive *O*-tosylation (TsCl, pyridine), bromination (LiBr, DMF) and phosphinylation (PPh_3). All but one (**5c**) of the 2-bromo-1-formylcycloalkenes had been prepared earlier by us from appropriately substituted cycloalkanones using modified Vilsmeier-Haack reaction.[15,16] Compound **5c** was prepared this time following a similar procedure.

The *in situ* generation of ylides from **4** and **6** and their reaction with **5a**,**e** and **5a**-**e**, respectively, was carried out in the presence of *n*-BuLi in THF at -78 °C under argon atmosphere, which furnished diastereomeric (*E*-+*Z*-) mixtures of the bromo analogues of the dienyl-3/2-furyl derivatives (**7a**,**e**/**8a**-**e**) in good overall yields (77-84 %) (Scheme 4).



For **5, 7, 8**; **a**: n = 1; $R^1 = R^2 = H$; **b**: n = 1; R^1 =H, R^2 = Me; **c**: n = 1; $R^1 = R^2$ = Me; **d**: n = 1; R^1 = H, $R^2 = CMe_3$; **e**: n = 3; $R^1 = R^2$ = H

Reagents and conditions: (i) **4**, *n*-BuLi / THF, -78 ^oC, Argon; (ii) **6**, *n*-BuLi / THF, -78 ^oC, Argon

Scheme 4. Wittig olefination of2-bromo-1-formyl-1-cycloalkenes (**5a**-**e**)**.**

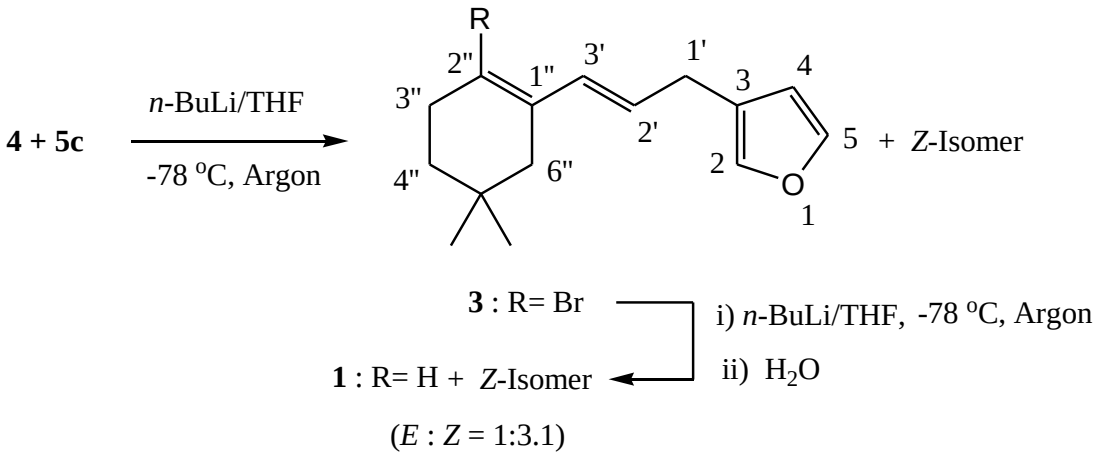
Clearly, the desired diastereoselectivity was not achieved, and the E-/Z- ratios were found to be 1:1.6 to 1:2.3 (Table 1), as calculated from the relative intensities of the vinylic and the allylic proton signals in their ^{1}H NMR spectra. All of the products, with the exception of most of the bromo derivatives, were duly identified by ^{1}H and ^{13}C (PND) NMR spectra, supported by MS/analytical data.

Though lacking diastereoselectivity, the method offers a new route to the synthesis of molecules of type **1**. We, therefore, applied this methodology to the synthesis of the bromo derivative of pleraplysillin-1. Thus, the ylide, generated *in situ* from **4**, was allowed to react with the required bromo-formylcyclohexene (**5c**) under similar conditions. It furnished an inseparable (following silica-gel column chromatography) mixture of the desired (*E*)-isomer (**3**) and its (*Z*)-isomer in 88% overall yield (Scheme 5). The *E*-/*Z*- ratio, calculated as before, exhibited a greater lack of diastereoselectivity.

Table 1. Results of Wittig olefination of aldehydes **5a-e** with phosphonium salts **4** and **6**

Entry	2-Bromo-1-formyl-cyclohexenes	Phosphonium salt	Products **7**/**8** + *Z*-Isomer)	Overall yields (%)	*E*-/*Z*-ratio
1	**5a**	**4**	**7a** + *Z*-Isomer	79	1 : 1.8
2	**5a**	**6**	**8a** + *Z*-Isomer	77	1 : 1.6
3	**5b**	**6**	**8b** + *Z*-Isomer	78	1 : 2.3
4	**5c**	**6**	**8c** + *Z*-Isomer	84	1 : 2.3
5	**5d**	**6**	**8d** + *Z*-Isomer	81	1 : 1.6
6	**5e**	**4**	**7e** + *Z*-Isomer	80	1 : 1.7
7	**5e**	**6**	**8e** + *Z*-Isomer	81	1 : 1.6

Since the target molecule was formed, albeit as a diastereomeric mixture, its proto-debromination was accomplished by treating the mixture with *n*-BuLi/THF at -78°C in THF under argon atmosphere for about 2 h, followed by quenching with water. This reaction furnished a mixture of 1 and its Z-isomer in 77% overall yield (Scheme 5).



Scheme 5. Synthesis of pleraplysillin-1 (**1**) and its *Z*-isomer.

Conclusions

The present methodology to pleraplysillin-1 is certainly not the best of the available methods. It does, however, offer a new route to molecules of type **1**. Of course, conditions need to be developed to improve upon the diastereoselectivity at the crucial Wittig olefination stage. Our method has the additional advantages that (i) it is relatively simple, (ii) it does not involve expensive and toxic organometallic reagents and (iii) the overall yields of the bromo analogues and the final diastereomeric mixtures are much better than reported earlier.

Experimental Section

General. All the melting points were recorded in open glass capillaries in a sulfuric acid bath. The column chromatographies (CC) were carried out in either silica gel (SiO_2) or neutral alumina (Al_2O_3). For CC, SiO_2 and Al_2O_3 were purchased from E. Merck India and SRL, India. All of the reagents were of analytical grade and purchased from either Merck India or Sigma-Aldrich Chemicals. The β-bromo-α,β-unsaturated aldehydes (**5a-e**) were prepared from the respective cycloalkanones, procured commercially, using modified Vilsmeier-Haack reaction as was reported earlier from our laboratory.[13,14] All the solvents were conventionally dried before use in reactions. Unless otherwise stated, the ^1H and ^{13}C (PND) NMR spectra were carried out in $CDCl_3$ at 400 MHz and 100 MHz, respectively.

General procedure for the synthesis of 2-(3/2-furyl)ethyltriphenylphosphonium salts (4/6). 2-(3-/2-Furyl)ethylbromide (0.35 g, 2 mmol) was stirred with solid PPh_3 (1.31 g, 5.0 mmol) in a screw-cap reaction tube at 80 °C for 12 h. It was then stirred with dry ether (20 mL) for 30 min. The solid separated was filtered off and washed thoroughly with dry ether and dried under vacuum to furnish the phosphonium salt which was stored in amber-colored bottle in a desiccator.

2-(3-Furyl)ethyltriphenylphosphonium bromide (**4**). White solid, yield 0.77 g (85%). m.p. 182-184 °C. ^1H NMR: δ 2.75-2.95 (2H, m), 3.95-4.15 (2H, m), 6.57 (1H, ill-split d), 7.23 (1H, d, *J* 1.2 Hz), 7.44 (1H, s), 7.64-7.75 (6H, m) and 7.75-7.92 (9H, m) ppm. ^{13}C NMR: δ 18.3, 23.7, 111.0, 117.4, 118.3, 121.6, 121.7, 130.4, 130.6, 133.6, 133.7, 135.1, 140.1, 143.1 ppm; ESI-MS(+): *m/z* 437.3 $[M+H; Br^{79}]^+$, 439.3 $[M+H; Br^{81}]^+$

2-(2-Furyl)ethyltriphenylphosphonium bromide (**6**). White solid, yield 0.70 g (78%), m.p. 170-172 °C. ^1H NMR: δ 3.19 (2H, dt, J_1 12.0 Hz, J_2 7.0 Hz), 4.19 (2H, dt, J_1 12.5 Hz, J_2 7.0 Hz), 6.15 (1H, dd, further ill-split, J_1 3 Hz, J_2 2 Hz), 6.21 (1H, d, *J* 3.0 Hz), 7.09 (1H, d, *J* 2.0 Hz), 7.60-7.73 and 7.77-7.90 (m each, 15H) ppm. ^{13}C NMR: δ 20.9, 22.9, 107.6, 110.0, 130.1, 133.3, 134.6, 141.0, 150.1 ppm; ESI-MS(+): *m/z* 437.2 $[M+H; Br^{79}]^+$, 439.3 $[M+H; Br^{81}]^+$

Synthesis of 2-bromo-1-formyl-5,5-dimethylcyclohex-1-ene (**5c**). PBr_3 (0.6 mL) was added dropwise to a solution of DMF (0.9 mL) and $CHCl_3$ **(**2 mL) at 0-5 °C. The ice bath was removed and the mixture stirred at rt for about 30 min. It was again cooled to 0-5 °C, a solution of 4,4-dimethylcyclohexanone (0.25 g, 2 mmol) in $CHCl_3$ (1 mL) was added dropwise to it, and the mixture was stirred at rt for another 8 h under anhydrous condition. The solution was poured into cold, saturated aq. NaOAc so that the pH was adjusted to ~ 6 and extracted with $CHCl_3$ (3 x 10 mL). The extracted organic layer was washed successively with water, aq. $NaHCO_3$, again with water, dried and the solvent removed. The crude product was then purified by CC using PE as eluent, which furnished **5c** as light yellow oil. Yield 0.33 g (76%). IR (ν_{max}, cm^{-1}): 1695. ^1H NMR: δ 0.95 (6H, s), 1.53 (2H, t, *J* 6.5 Hz), 2.08 (2H, s), 2.76 (2H, t, *J* 6.5 Hz), 10.03 (1H, s) ppm. ^{13}C NMR: δ 27.2, 28.0, 36.36, 36.38, 37.9, 133.6,

142.2, 193.5 ppm. HR-ESI-MS(+): calcd for $C_9H_{13}O^{79}Br$ 216.015 (M^+)and for $C_9H_{13}O^{81}Br$ 218.0129 (M^+), found 216.019 & 219.012.

General procedure for Wittig olefination; preparation of 7a,e; 8a-e. *n*-BuLi (1.6 M, 0.44 mL, 0.7 mmol) was added to a solution of the 2-(3-/2-furyl)ethylphosphonium salt(4/6) (0.33 g, 0.75 mmol) in THF (1 mL) at -78 °C under argon atmosphere, and the solution was stirred for 30 min at that temperature. The solution of 5a-e (0.5 mmol) in THF (1 mL) was added slowly to the above mixture, and it was allowed to warm up to rt. Water (0.5 mL) was added to the mixture and THF evaporated off. The resulting aq. solution was extracted with ether (3x10 mL), and the combined ether extracts were washed with cold water, dried and concentrated. The resulting crude product was purified by CC over Al_2O_3 to provide the furyl dienes as light yellow oil in the PE eluates.

(Since the bromo derivatives **7a**, **7e**, **8a**-**e** were very unstable and we have no facilities to record MS and C,H,N analysis data in our University, we could not record the MS or elemental analyses data of these compounds.)

(*E*)-3-[(2-Bromocyclohex-1-enyl)allyl]furan (**7a**) **+ *Z*-Isomer.** Yield 0.105 g (79%). ^{1}H NMR: δ 1.69 (4H, br s), 1.91-2.11 (2H, m), 2.23-2.36 (2H, m), 3.24 and 3.29 (d each, *J* 7.5 Hz) (total: 2H), 5.61 (dt, J_1 11.0 Hz, J_2 7.5 Hz) and 5.81 (dt, J_1 15.5 Hz, J_2 7.5 Hz) (total:1H), 6.11-6.19 (m) and 6.53 (d, *J* =16.0 Hz) (total: 2H), 7.11 and 7.24 (s each, further ill-split) (total: 2H) ppm. ^{13}C NMR: δ 21.3, 21.5, 24.1, 24.6, 27.3, 27.5, 31.6, 31.9, 36.3, 37.4, 104.7, 105.4, 109.9, 110.2, 122.1, 123.6, 125.7, 125.9, 127.2, 131.8, 132.5, 133.2, 141.1, 141.9, 152.9, 153.4 ppm.

(*E*)-2-[(2-Bromocyclohex-1-enyl)allyl]furan (**8a**) **+ *Z*-Isomer.** Yield 0.10 g (77%). ^{1}H NMR: δ 1.71 (4H, br s), 2.20-2.31 and 2.53-2.66 (m each) (total: 4H), 3.44 (d, *J* 7.5 Hz) and 3.49 (d, *J* 6.5 Hz) (total: 2H), 5.63 (dt, J_1 11.0 Hz, J_2 7.5 Hz) and 5.84 (dt, J_1 15.5 Hz, J_2 7.5 Hz) (total: 1H), 6.01-6.09 (m) and 6.73 (d, *J* 16.0 Hz) (total: 2H), 6.26-6.34 (1H, m), 7.29-7.36 (1H, m) ppm. ^{13}C NMR: δ 21.7, 21.9, 24.2, 24.3, 27.1, 27.8, 31.2, 31.5, 36.1, 37.1, 104.8, 105.1, 109.8, 109.9, 121.5, 123.5, 125.0, 125.8, 126.3, 131.2, 132.1, 132.9, 140.7, 140.9, 153.5, 153.7 ppm.

(*E*)-2-[(2-Bromo-5-methylcyclohex-1-enyl)allyl]furan (**8b**) **+ *Z*-Isomer.** Yield 0.11 g (78%). ^{1}H NMR: δ 0.95-1.03 (3H, m), 1.84-1.93 (2H, m), 2.23-2.31 and 2.34-2.42 (m each) (total: 1H), 2.52-2.68 (4H, m), 3.44 and 3.49 (d each, *J* 7.0/6.5 Hz) (total: 2H), 5.63 (dt, J_1 11.0 Hz, J_2 7.5 Hz) and 5.85 (dt, J_1 15.0 Hz, J_2 7.0 Hz) (total: 1H), 5.96-6.08 (m) and 6.72 (d, *J* 15.0 Hz) (total: 2H), 6.26-6.34 (1H, m), 7.32 and 7.33 (s each, further ill-split) (total: 1H) ppm. ^{13}C NMR: δ 20.7, 21.0, 27.8, 28.3, 29.3, 31.5, 32.2, 32.4, 35.4, 36.1, 37.0, 39.4, 104.8, 105.1, 109.8, 110.7, 121.1, 123.1, 131.0, 132.0, 132.3, 140.7, 140.92, 140.96, 153.4, 153.7 ppm.

(*E*)-2-[2-Bromo-5,5-dimethylcyclohex-1-enyl)allyl]furan (**8c**) **+ *Z*-Isomer.** Yield 0.124 g (84%). ^{1}H NMR: δ 0.90-1.0 (overlapping s's) (total: 6H), 1.42-1.52 (2H, m), 2.01 and 2.04 (s each) (total: 2H), 2.52-2.66 (2H, m), 3.41 and 3.48 (d each, *J* 7.5/7.0 Hz) (total: 4H), 5.62 (dt, J_1 11.0 Hz, J_2 7.0 Hz) and 5.82 (dt, J_1 15.0 Hz, J_2 7.5 Hz) (total: 1H), 5.60 (d, *J* 12.0 Hz) and 6.72 (d, *J* 15.0 Hz) (total: 1H), 6.0-6.05 and 6.26-32 (m each) (total: 2H), 7.311 (s, further ill-split) and 7.33 (d, *J* 1.0 Hz) (total: 1H) ppm. ^{13}C NMR: δ 27.7, 28.0, 28.1, 29.0, 29.3, 29.7, 31.8, 34.3, 35.2, 37.1, 41.1, 45.3, 105.2, 105.5, 110.2, 120.4, 126.1, 126.8, 131.6, 132.1, 132.6, 141.1, 141.3, 153.8, 154.1 ppm.

(*E*)-2-[(2-Bromo-5-^{t}butylcyclohex-1-enyl)allyl]furan(**8d**)**+ *Z*-Isomer.** Yield 0.13 g (81%). ^{1}H NMR: δ 0.75-0.85 (9H, overlapping s's), 1.22-1.34 (2H, m), 1.67-1.79 (1H, m), 2.10-2.19, 2.26-2.36 and 2.45-2.61 (m each) (total: 4H), 3.37 (d, *J* 7.5 Hz) and 3.42 (d, *J* 6.5 Hz) (total: 2H), 5.56 (dt, J_1 11.0 Hz, J_2 7.5 Hz) and 5.78 (dt, $J_1$15.5 Hz, J_2 7.0 Hz) (total: 1H), 5.92-6.0 (m) and 6.65 (d, *J* 16.0 Hz) (total: 2H), 6.21 and 6.23 (quintet each, *J* 1.5 Hz) (total: 1H), 7.23 (s, further ill-split) and 7.26 (d, *J* 1.5 Hz) (total: 1H) ppm. ^{13}C NMR: δ 25.6, 26.7, 26.8, 27.8, 28.7, 29.9, 31.5, 31.7, 31.9, 32.9, 37.2, 38.1, 43.2, 43.4, 104.8, 105.1, 120.9, 123.3, 125.6, 126.4, 131.0, 131.3, 132.3, 132.8, 140.7, 140.9, 153.6, 153.7 ppm.

(*E*)-3-[(2-Bromocyclooct-1-enyl)allyl]furan (**7e**) **+ *Z*-Isomer.** Yield 0.117 g (80%). ^{1}H NMR: δ 1.21-1.42 (8H, m), 2.08 and 2.19 (t each, *J* 6.0 Hz) (total: 2H), 2.14 and 2.18 (t each, *J* 6.0 Hz) (total: 2H), 3.22 and 3.31 (d each, *J* 7.5 Hz) (total: 2H), 5.61 (dt, J_1 11.5 Hz, J_2 7.5 Hz) and 5.76 (dt, J_1 15.5 Hz, J_2 7.0 Hz) (total: 1H), 6.06-6.13 (m) and 6.28 (d, *J* 15.5 Hz) (total; 2H), 7.11 (1H, s, further ill-split) and 7.23-7.25 (1H, overlapping d's) ppm. ^{13}C NMR: δ 25.7, 26.0, 26.2, 26.5, 27.31, 27.37, 28.0, 28.5, 29.1, 29.3, 31.4, 32.0, 37.1, 38.0, 104.9, 105.5, 123.3, 125.4, 126.0, 126.8, 131.5, 132.4, 134.6, 135.7, 141.0, 141.3, 154.0, 154.1 ppm.

(*E*)-2-[(2-Bromocyclooct-1-enyl)allyl]furan (**8e**) **+ *Z*-Isomer.** Yield 0.12 g (81%). ^{1}H NMR: δ 1.45-1.65 (6H, m), 1.69 (2H, quintet, *J* 7.0 Hz), 2.38 and 2.49 (t each, *J* 6.0 Hz) (total: 2H), 2.74 and 2.79 (t each, *J* 6.0 Hz) (total: 2H), 3.44 and 3.50 (d each, *J* 7.5 Hz) (total: 2H), 5.62 (dt, J_1 11.5 Hz, J_2 7.5 Hz) and 5.86 (dt, J_1 15.5 Hz, J_2 7.0 Hz) (total: 1H), 5.98-6.06 (m), 6.27-6.33 (m), 6.65 (d, J 15.5 Hz) and 7.30-7.35 (overlapping d's) (total: 4H) ppm. ^{13}C NMR: δ 26.1, 26.4, 26.5, 26.7, 28.1, 28.3, 28.6, 28.9, 29.4, 29.8, 32.0, 33.0, 37.5, 38.5, 105.3, 105.6, 123.7, 125.8, 126.6, 126.9, 131.9, 132.4, 135.1, 136.1, 141.2, 141.4, 154.1, 154.3 ppm.

(*E*)-3-[(2-Bromo-5,5-dimethylcyclohex-1-enyl)allyl]furan (**3**) **+ *Z*-Isomer.** Yield 0.13 g (88%). ^{1}H NMR: δ 0.91, 0.95, 0.96, 0.99 (overlapping s's) (total: 6H), 1.45-1.53 (2H, m), 2.01 (maj) and 2.04(min) (s each) (total: 2H) and 2.55-2.67 (2H, m), 3.20 (d, *J* 7 Hz) (maj) and 3.27 (d, *J* 7 Hz) (min) (total: 2H), 5.57 (dt, J_1 11.6 Hz, J_2 7.2 Hz) (maj) and 5.81 (dt, J_1 15.2 Hz, J_2 7.2 Hz) (min) (total: 1H), 5.95 (d, *J*11.6 Hz) (maj) and 6.70 (d, J 15.6 Hz) (min) (total: 1H), 6.29 (1H, br s), 7.24 (maj) and 7.26 (min) (s each) (total: 1H), 7.25-7.38 (1H, m) ppm. ^{13}C NMR: δ 27.3, 27.4, 27.6, 28.1, 28.9, 29.3, 34.7, 34.9, 36.7, 36.8, 40.5, 40.8, 43.3, 45.0, 109.9, 110.7, 118.3, 119.5, 128.5, 128.8, 129.2, 129.9, 130.3, 131.2, 138.6, 138.8, 140.5, 141.2, 142.4, 143.3 ppm.

Protodebromination of (3 + *Z*-Isomer). *n*-BuLi (1.6 M, 0.2 mL, 0.35 mmol) was added to the solution of the mixture of (**3** + *Z*-isomer) (0.075 g, 0.25 mmol) in THF (1 mL) at -70 °C under argon atmosphere. It was stirred at that temperature for about 2 h, and the reaction mixture was quenched with water. THF was distilled off and the residual solution extracted with Et_2O (3x5 mL). The combined organic layer was washed with water, dried and concentrated. The resulting crude product was purified by CC over Al_2O_3 to afford a mixture of **1** (Pleraplysillin-1) and its *Z*-isomer as light yellow oil in the PE eluate. Yield 40 mg (77%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.88 (min), 0.89 (min), 0.92 (maj) and 0.95 (maj) (s each; total: 6H; 2 x CH_3), 1.26-1.39 and 1.40-1.52 (m each) (total: 6H; 3 x CH_2), 1.89 (maj) and 1.91 (min) (s each; total: 1H) and 3.19 (maj) and 3.36 (min) (d each, *J* 7.0/7.5 Hz) (total: 1H), 5.52-5.66 and 5.76-5.86 (1H, m each), 5.94 (d, *J* 11.0 Hz) (maj) and 6.13 (d, *J* 15.5 Hz) (min) (total: 1H), 6.27 (maj) and 6.29 (min) (br s each), (total: 1H), 7.22 (maj) and 7.23 (min) (s each) (total: 1H), 7.35 (1H, m) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ 24.2, 24.4, 28.0, 28.1, 28.4, 28.6, 29.0, 29.2, 36.7, 36.9, 39.3, 39.8, 45.0, 47.5, 110.7, 110.8, 123.4, 125.1, 125.3, 126.2, 133.2, 133.3, 134.0, 134.2, 139.0, 139.3, 142.8, 142.9 ppm. HR-ESI(+)-MS: calcd for $C_{15}H_{21}O$ $[M+H]^+$ 217.1592, found 217.1602.

Note: For the ^{1}H NMR data of (**3** + *Z*-isomer) and (**1** + *Z*-isomer), "maj" refers to the major isomer (i.e., the *Z*-isomer) and "min" refers to the minor isomer (i.e., the *E*-isomer).

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