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Discrepancy of the spectral data between adunctin E and the synthetic one

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Abstract—Compound (**2**), which has been proposed as the structure of adunctin E (**1**), was prepared in nine steps in 17% overall yield from hexahydrodibenzofuranone (**4**); however, the spectral data of this compound, including ^{1}H and ^{13}C NMR spectra, were inconsistent with the literature data for adunctin E (**1**). Thus, we suggest that the proposed structure for adunctin E or the reported NMR spectral data was incorrect.

In 1993, Sticher et al. isolated (+)-adunctin E (**1**) from the leaves of *Piper aduncum* L. (Piperaceae) collected in Papua New Guinea. On the basis of spectral analysis, the structure of **1** was determined as {1-[(5a*R**, 6*S**,9*R**,9a*S**)-5a,6,7,8,9,9a-hexahydro-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-4-dibenzofuranyl]-3-phenyl-1-propanone} (**2**) (Fig. 1).[1] *P. aduncum* is distributed throughout a large area of the tropical Americas, and has been naturalized in Malaysia and in Papua New Guinea. It has been employed as a traditional medicine in many regions of the world, mostly by application of its leaves: in Papua New Guinea, it was used for the treatment of fresh wounds; in Colombia, as a treatment for dysentery and as a haemostatic agent; and in Peru, it was used to treat diarrhea.[1] A crude petroleum-ether extract from its leaves showed significant antibacterial activity in in vitro biological screening; however, no activity has yet been reported for **1**.[1]

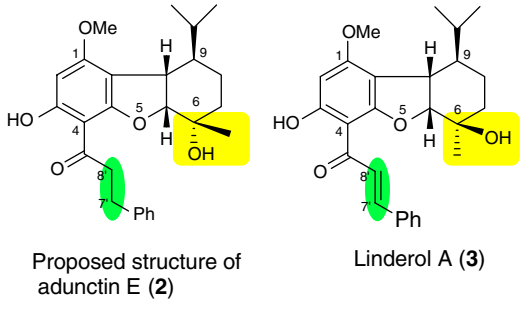

Figure 1. Structures of **2** and **3**.

Another compound, known as (−)-linderol A [(−)-**3**], (5a*R*,6*R*,9*R*,9a*S*)-4-cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran, which has a structure very similar to that of **2**, was isolated from the fresh bark of *Lindera umbellata* (Lauraceae) (Fig. 1), and showed potent inhibitory activity on melanin biosynthesis in cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs.[2] In terms of structure, there are two differences between **2** and **3**: the first is the bond order of the side chain at the 4-position, which is a 7′–8′ single bond in **2** and a 7′–8′ double bond in **3** (indicated by green ovals in Fig. 1); the second is the stereochemistry at the 6-position (indicated by yellow rectangles in Fig. 1). We previously reported the first total syntheses of (±)-, (−)- and (+)-**3**.[3] Next, as part of our investigation into the synthesis of natural products, we focused on achieving

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the first total synthesis of **2**. In this communication, we describe the total synthesis of **2**, which is the proposed structure for adunctin E (**1**), and compare the spectral data of the prepared compound with those reported for **1**.

We considered that compound **2** might be synthesized via a route similar to that of **3**. Hexahydrodibenzofuranone (**4**)[3] was regioselectively acylated at the 4-position by treatment with acetic anhydride in the presence of $LiClO_4$, with $Sc(OTf)_3$ as a catalyst, to afford **5** in 98% yield.[4,5] Treatment of **5** with BBr_3 gave **6**, in 71% yield, by regioselective demethylation of the methoxy group at the 3-position, due to the influence of the carbonyl group at the 4-position. The carbonyl group at the 6-position in **6** was chemoselectively protected due to the difference in reactivity between the aliphatic and the aromatic carbonyl groups; subsequently, the phenolic hydroxy group at the 3-position in **7** was protected by a tosyl group. The resulting ketone **8** was subjected to cross-aldol condensation with benzaldehyde, and the tosyl group was then hydrolyzed in basic methanolic solution to give **9** in 45% yield. Unexpectedly, several different methods for deprotection of the ketal at the 6-position in **9** failed, probably because its position was sterically hindered. Finally, treatment of **9** with $FeCl_3{\cdot}6H_2O$ provided the diketone **10** in quantitative yield.[6] Crystals of **10** were subjected to X-ray analysis to confirm the proposed structure (Fig. 2).[7] Next, treatment of **10** with methylmagnesium bromide was carried out, as it was expected that MeMgBr would approach the carbonyl group at the 6-position, but not at the 4-position, from the convex direction (less hindered side), as shown in Scheme 2. Thus, addition of 2.5 equiv of methylmagnesium bromide afforded 6-*epi*-linderol A (**11**) as a single product in 65% yield. Finally, **11** was hydrogenated under a hydrogen atmosphere in the presence of Pd–C to give **2** in quantitative yield (Scheme 1).

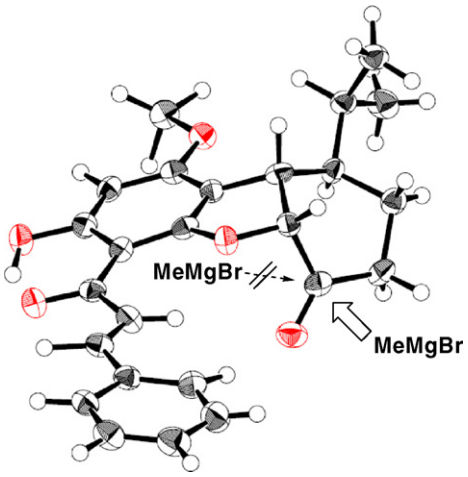
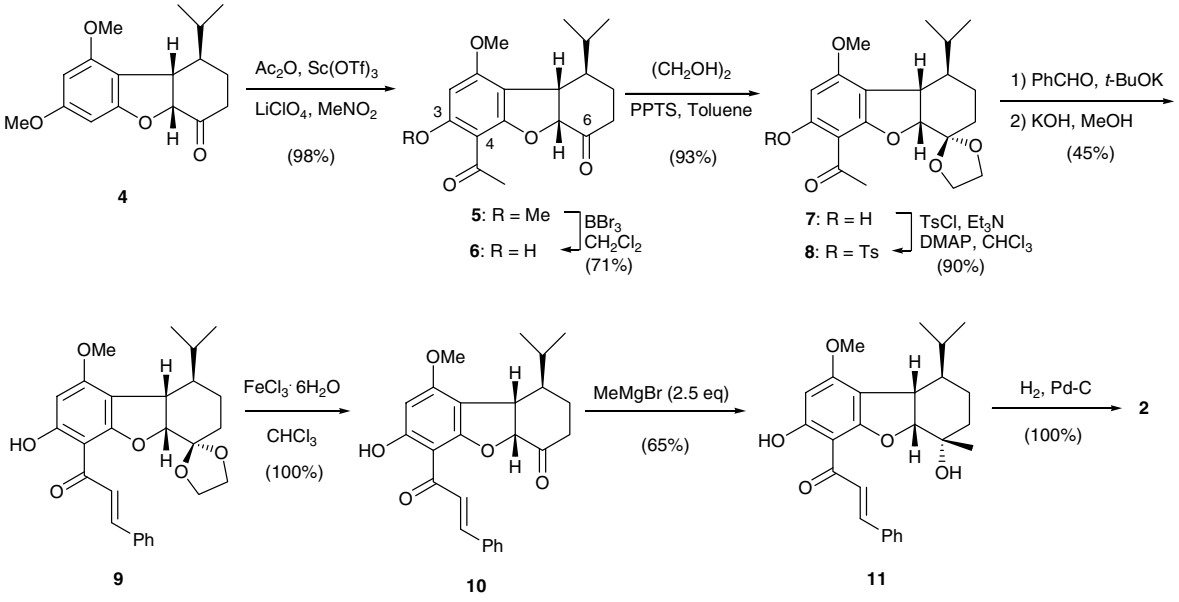
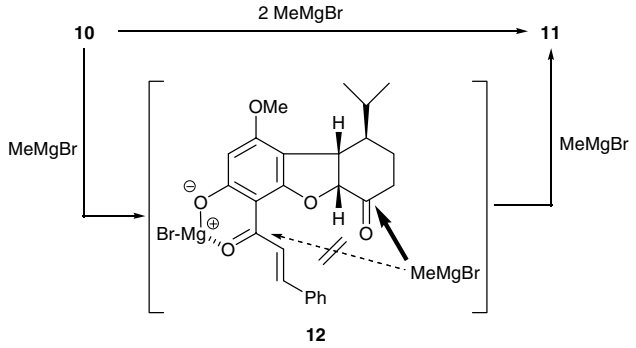


Figure 2. ORTEP drawing of **10**.

We obtained ^1H and ^{13}C NMR spectra of the prepared compound **2**,[8] and compared the data with the values reported for adunctin E (**1**) by Sticher.[1] We found that there were considerable differences between the two sets of data, as shown in Tables 1 and 2. X-ray crystallographic analysis of **2** was carried out (Fig. 3),[9] and the structure obtained was consistent with that of **2** as proposed by Sticher; this confirmed that the prepared **2** was the same as the original compound **2**, proposed as the structure of adunctin E (**1**). Thus, as the spectral data of **1** and the prepared compound **2** were at variance, we concluded that the structure of adunctin E (**1**) isolated from *P. aduncum* was not **2**.[10,11]



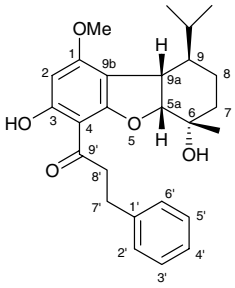
Scheme 1.



Scheme 2.

In conclusion, we prepared compound **2**, which was proposed by Sticher as the structure of adunctin E (**1**), in nine steps and in 17% overall yield from **4**, which is a synthetic intermediate common to linderol A (**3**). However, the spectral data of the prepared **2** (^{1}H and ^{13}C NMR spectra) were inconsistent with those previously reported for adunctin E (**1**). Thus, we concluded that the proposed structure (**2**) of adunctin E or the reported NMR spectral data was incorrect. We are currently investigating the preparation of another compound, which is a possible structure for adunctin E (**1**).

Table 1. Comparison of ^{1}H NMR data of prepared compound **2** with that of adunctin E (**1**)



Position	Natural adunctin E (**1**)[a,b,c]	Prepared product (**2**)[b,d]
3-OH	13.23 (s)	13.26 (s)
2′–6′	7.24 (br m)	7.17–7.31 (m)
2	6.04 (s)	6.06 (s)
5a	4.50 (d, $J = 5.4$)	4.26 (dd, $J = 1.5$, 5.3)
1-OMe	3.81 (s)	3.81 (s)
8′	3.38 (m)	3.34 (m)
7′	3.02 (t, $J = 7.6$)	3.00 (t, $J = 4.8$)
9a	3.07 (dd, $J = 5.4$, 11.0)	2.98 (dd, $J = 5.3$, 10.6)
6-OH	—	1.93 (s)
9-C*H*$(CH_3)_2$	1.83 (m)	1.80–1.88 (m)
7	2.09 (br m)	1.78 (d, $J = 12.2$)
	1.59 (br m)	1.58–1.68 (m)
6-Me	1.43 (s)	1.28 (s)
8	1.33 (m)	1.58–1.68 (m)
		1.14–1.16 (m)
9	1.08 (m)	1.26 (m)
9-CH(CH_3)$_2$	0.85 (d, $J = 6.8$)	0.87 (d, $J = 6.8$)
	0.83 (d, $J = 6.8$)	0.83 (d, $J = 6.8$)

[a] Ref. 1.
[b] Units of J = Hz.
[c] 300 MHz, $CDCl_3$.
[d] 400 MHz, $CDCl_3$.

Table 2. Comparison of ^{13}C NMR data of prepared compound **2** with that of adunctin E (**1**)

Position	Natural adunctin E (**1**)[a,b]	Prepared product (**2**)[c]	Position	Natural adunctin E (**1**)[a,b]	Prepared product (**2**)[c]
C(1)	161.8	161.3	C(1′)	141.2	141.1
C(2)	92.8	93.0	C(2′,6′)	128.3	128.2
C(3)	165.3	165.5	C(3′,5′)	128.4	128.6
C(4)	102.7	102.7	C(4′)	126.0	126.2
C(4a)	161.6	161.1	C(7′)	30.1	30.5
C(5a)	87.6	93.1	C(8′)	43.7	44.0
C(6)	80.9	70.4	C(9′)	203.2	203.2
C(7)	31.8	36.0	$(CH_3)_2CH$	15.4	15.3
C(8)	17.1	20.4		21.7	21.8
C(9)	46.3	46.6	$(CH_3)_2CH$	27.1	26.9
C(9a)	39.8	40.9	1-OCH_3	55.5	55.5
C(9b)	112.8	113.6	6-CH_3	22.0	24.7

[a] Ref. 1.
[b] 75.5 MHz, $CDCl_3$.
[c] 100 MHz, $CDCl_3$.

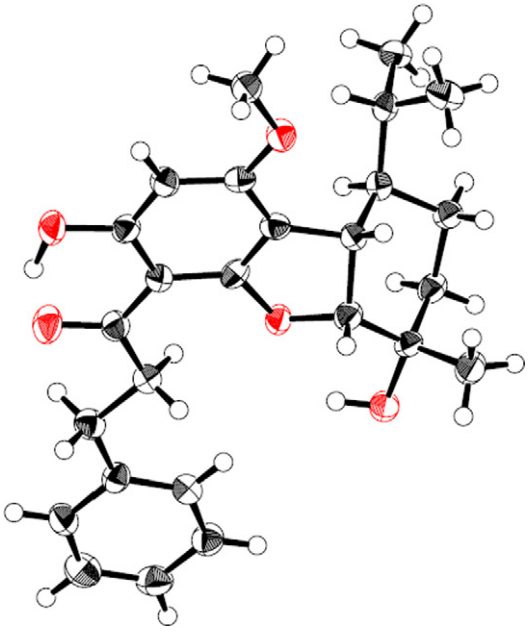


Figure 3. ORTEP drawing of prepared compound **2**.

Acknowledgments

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5. A mixture of the 2-acetyl product (2-acetyl-**4**) and the 4-acetyl product (**5**) was obtained without the use of $LiClO_4$.
6. Sen, E. S.; Roach, L. S.; Bogg, K. J.; Ewing, J. G.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684.
7. $C_{25}H_{26}O_5$, MW = 406.48, $T = -175$ °C, $\lambda = 1.54187$ Å, monoclinic, space group $P2_1/n$ (#14), $a = 8.6545$ (13) Å, $b = 17.762$ (2) Å, $c = 13.1968$ (19) Å, $\beta = 92.469$ (11)°, $V = 2026.8$ (5) Å^3, $Z = 4$, $D_{calcd} = 1.332$ g/cm^3, μ(Cu Kα) = 7.486 cm^{-1}, $F(000) = 864.00$, crystal size $0.30 \times 0.05 \times 0.05$ mm. No. of reflections measured: total, 23,166; unique, 3671 ($R_{int} = 0.102$). Refinement method: full-matrix least-squares on F^2, goodness of fit indicator 1.000, final R_1 [$I > 2.00\sigma(I)$] = 0.0884 maximum peak in final Diff. Map and minimum peak 0.56 e$^-$/Å^3 and −0.51 e$^-$/Å^3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 650339 for **10**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (0) 1223 336033; E-mail: deposit@ccdc.cam.ac.uk].
8. Yellowish needles (recryst from AcOEt/*n*-hexane). Mp: 148–149 °C. IR ($CHCl_3$) cm^{-1}: 3500–3000 (br), 2910, 1626, 1598, 1519, 1168, 1135. MS (EI) *m*/*z* (rel. int. %): 91 (68), 105 (40), 191 (31), 207 (37), 297 (33), 339 (100), 424 (M^+, 47). HRMS (EI) *m*/*z*: Found, 424.2251 (Calcd for $C_{26}H_{32}O_5$: 424.2250). Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.32; H, 7.56.
9. CCDC 650338 for **2**. $C_{26}H_{32}O_5$, MW = 424.54, $T = -140$ °C, $\lambda = 1.54187$ Å, triclinic, space group *P*-1 (#2), $a = 5.76003$ (15) Å, $b = 11.1833$ (3) Å, $c = 17.9817$ (4) Å, $\alpha = 70.9142$ (13)°, $\beta = 81.2855$ (14)°, $\gamma = 82.0474$ (14)°, $V = 1077.10$ (4) Å^3, $Z = 2$, $D_{calcd} = 1.309$ g/cm^3, μ(Cu Kα) = 7.218 cm^{-1}, $F(000) = 456.00$, crystal size $0.20 \times 0.10 \times 0.10$ mm. No. of reflections measured: total, 12,821; unique, 3849 ($R_{int} = 0.050$). Refinement method: full-matrix least-squares on F^2, goodness of fit indicator 1.001, final R_1 [$I > 2.00\sigma(I)$] = 0.0691, extinction coefficient 4.20700 e, maximum peak in final Diff. Map and minimum peak: 0.41 e$^-$/Å^3 and −0.46 e$^-$/Å^3.
10. We requested the spectral data of adunctin E (**1**) from Dr. Sticher, but to date we have not received any information in this regard.
11. Linderol A (**3**) was hydrogenated to afford dihydrolinderol A, a 6-epimer of **2**. The spectral data for this compound were not consistent with those of **2**. See Ref. 3b. We also prepared the possible compounds of which 3-phenylpropionyl group was substituted at the 2-position not the 4-position, and its 6-epimer, however, their spectral data were not consistent with those of **2**.