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Isolation, structure determination and synthesis of a trichlorodihydroxybibenzyl from a terrestrial plant†

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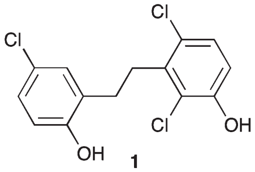
R. Alan Aitken,*[a] Jaufret Bouquet,[a] Julia Frank,[b] Anna L. G. Gidlow,[a] Yomica L. Powder,[b] Russel S. Ramsewak*[b] and William F. Reynolds[c]

A new natural product isolated from the leaves of the plant *Anthurium aripoense* found in Trinidad is shown by spectroscopic analysis and total synthesis to be 2′,5,6′-trichloro-2,3′-dihydroxybibenzyl, a structure unprecedented in a higher plant.

Although a large number of organohalogen compounds have now been discovered in nature, many of which show interesting chemical structures and biological activity,[1,2] most of these are of marine origin and the range of structures so far isolated from terrestrial plants is much more limited.[2,3] There is considerable interest in such compounds as potential "natural pesticides" and, for example, a variety of chlorinated orcinol derivatives formed in bulbs of *Lilium maximowiczii* in response to *Fusarium* infection have been suggested to act in this way.[4] We now report the isolation, structure determination and synthesis of a chlorinated natural product of novel structure from the leaves of a shrub growing in the northern highlands of Trinidad.

Exhaustive extraction of the dried leaves of *Anthurium aripoense* (2 kg) with methanol followed by evaporation, suspension of the residue in MeOH–H_2O (9 : 1), and sequential extraction with petroleum and ethyl acetate gave, upon evaporation of the ethyl acetate extract, a fraction (18 g). This was subjected to column chromatography (SiO_2, petroleum–EtOAc, 3 : 1) and the third of five fractions (37.6 mg) was then re-chromatographed (SiO_2, petroleum–$CHCl_3$, 1 : 1) to give the product of interest (10.7 mg).

The molecular formula was shown by HRMS to be $C_{14}H_{11}Cl_3O_2$ and an IR absorption at 3355 cm^{-1} indicated the presence of OH. The ^1H NMR spectrum showed the presence of five aromatic CH signals and two non-equivalent CH_2 groups, while the ^{13}C NMR spectrum showed five aromatic CH signals, seven aromatic quaternary carbons, and two aliphatic CH_2 groups.‡ Further information derived from COSY, edited HSQC and HMBC, and *T*-ROESY spectra was consistent with a 2,2′,3′,5,6′-pentasubstituted bibenzyl, and consideration of the known pattern of substituent effects on the chemical shifts of aromatic carbons led to 2′,5,6′-trichloro-2,3′-dihydroxybibenzyl **1** being identified as the only structure consistent with all the observed data.



1

Such a structure appears to be unprecedented in a terrestrial higher plant. The most closely similar natural products are the mono- and bis(bibenzyls) bearing hydroxy and chlorine groups such as 6,6′,10,10′,12,12′-hexachloroisoperrottetin A isolated from the liverwort *Jamesoniella colorata*[5] and believed to be formed *in vivo* by chlorination of 3,4′-dihydroxybibenzyl ("lunularin"). More recently similar chlorinated 3-hydroxybibenzyls have been isolated from other liverwort species such as *Riccardia marginata*[6] and *Riccardia polyclada*.[7] The occurrence of such compounds in liverworts is the subject of a very recent review[8] but, if they have oxygen functionality of both aromatic rings, they are always derived from 3,4′-dihydroxybibenzyl, and not the 2,3′-dihydroxy isomer as is the case here.

In view of the unexpected structure of the natural product we thought it wise to confirm it by unambiguous synthesis and initially envisaged a Wittig approach involving reaction of the ylide derived from an appropriately substituted benzyltriphenylphosphonium salt with a substituted benzaldehyde. Such an approach was successfully used by Speicher to prepare a range of halogenated lunularins including 3′,5′,6-trichloro-3,4′-dihydroxybibenzyl, an isomer of **1**.[9] Chlorination of 2- and 3-hydroxybenzaldehyde using chlorine gas,[10] followed by benzylation gave the correctly substituted benzaldehydes **2**[11] and **5**, respectively, in acceptable yield and free of unwanted isomers. These were readily transformed, *via* the benzyl alcohols **3**[12] and **6**, into the benzyl

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[a] *EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK. E-mail: raa@st-and.ac.uk; Fax: + 44 1334 463808; Tel: + 44 1334 463865*

[b] *Department of Chemistry, University of the West Indies, St Augustine, Trinidad and Tobago. E-mail: Russel.Ramsewak@sta.uwi.edu; Fax: + 1 868 645 3771; Tel: + 1 868 662 2002*

[c] *Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6, Canada*

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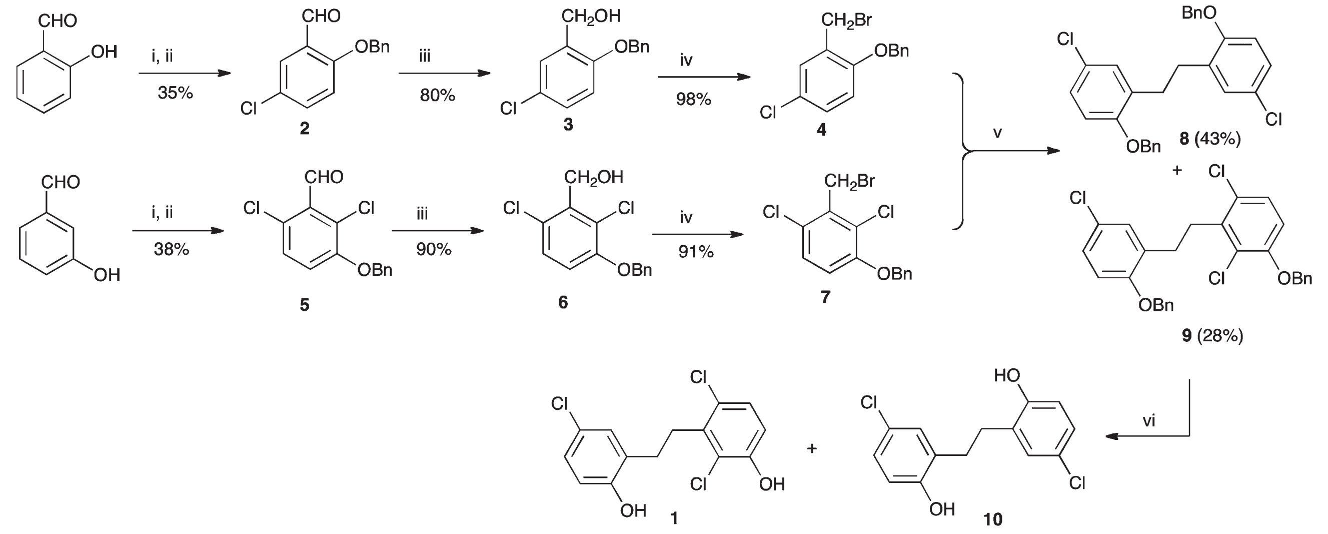

Scheme 1 Reagents and conditions: i, Cl_2, AcOH, rt, 1.5 h; ii, BnBr, KOH, EtOH, reflux, 2 h; iii, $NaBH_4$, aq MeOH, rt, 2 h; iv, PBr_3, toluene, rt, 12 h; v, 3 eq. MeMgI, Et_2O, reflux, 1 h; vi, Raney® Ni, EtOH–THF (1 : 1), reflux, 5 h, 55% (**10**), 48% (**1**).

bromides **4**[12] and **7** by treatment first with sodium borohydride and then with phosphorus tribromide (Scheme 1). These were readily converted into the corresponding phosphonium salts with triphenylphosphine but all attempts to achieve coupling by a Wittig reaction of the ylide derived from **7** with **2**, or the ylide derived from **4** with **5**, met with failure. Attempted coupling of the Grignard reagents derived from **7** or **4** with aldehydes **2** and **5** respectively was likewise unsuccessful. In both cases the highly hindered nature of the bibenzyl products seems likely to be the source of the problem. We were therefore attracted by an early report of the formation of 2,2′,4,4′,6,6′-hexabromobibenzyl in 62% yield by treatment of 2,4,6-tribromobenzyl bromide with methylmagnesium iodide.[13] The method was developed by Fuson and coworkers for synthesis of bibenzyls,[14] including 2,2′,6,6′-tetrasubstituted examples,[15] but does not seem to have been applied to mixed couplings so far. When equimolar amounts of benzyl bromides **4** and **7** were reacted with MeMgI (3 eq.) in boiling diethyl ether, two coupling products, **8** and **9**, were formed in moderate yield together with a small amount of 2-benzyloxy-5-chloroethylbenzene. None of the more hindered product expected from coupling of two molecules of **7** was apparently present. Separation of the very similar compounds **8** and **9** by chromatography proved difficult and, although **8** could be obtained in pure form, **9** was always contaminated with a little **8**. A trial of the final deprotection step on **8** using catalytic hydrogenation over Pd/C showed this to be ineffective. However, following previous reports, use of an excess of Raney® nickel[16] in THF–ethanol (1 : 1)[17] proved to be effective and gave the symmetrical bibenzyl **10**, already a known compound,[18] in moderate yield. When this method was applied to a sample of **9**, the target compound **1** was formed and was found to be spectroscopically identical to the natural product, although the repeated chromatographic purification required to remove residual traces of **10** and produce an analytically pure sample meant that the final yield was rather low.

Careful examination of the other fractions isolated from the leaves of this plant has so far shown the complete absence of any related chlorine-containing natural products. Compound **1** appears to be the first such natural product from a higher plant and further investigations into its biosynthesis and biological function are in progress.

Notes and references

‡ Selected data for **1**: mp 157–159 °C (Found: C, 52.97; H, 3.23. $C_{14}H_{11}Cl_3O_2$ requires C, 52.94; H, 3.49%); δ_H 7.22 (1 H, d, *J* 8.7), 7.13 (1 H, d, *J* 2.7), 7.08 (1 H, dd, *J* 8.4, 2.7), 6.89 (1 H, d, *J* 8.7), 6.72 (1 H, d, *J* 8.4), 5.59 (1 H, s, OH), 4.84 (1 H, s, OH), 3.16 (2 H, m) and 2.80 (2 H, m); δ_C 152.3 (C), 150.5 (C), 137.0 (C), 130.0 (CH), 128.7 (CH), 128.6 (C), 127.4 (CH), 125.9 (C), 125.5 (C), 121.1 (C), 116.6 (CH), 114.7 (CH), 31.9 (CH_2) and 28.4 (CH_2).

1 G. W. Gribble, *Acc. Chem. Res.*, 1998, **31**, 141–152.
2 G. W. Gribble, *Chemosphere*, 2003, **52**, 289–297.
3 K. C. Engvild, *Phytochemistry*, 1986, **25**, 781–791.
4 K. Monde, H. Satoh, M. Nakamura, M. Tamura and M. Takasugi, *J. Nat. Prod.*, 1998, **61**, 913–921.
5 U. M. Hertewich, J. Zapp and H. Becker, *Phytochemistry*, 2003, **63**, 227–233.
6 S.-H. Baek, R. K. Phipps and N. B. Perry, *J. Nat. Prod.*, 2004, **67**, 718–720.
7 C. Labbé, F. Faini, C. Villagrán, J. Coll and D. S. Rycroft, *J. Nat. Prod.*, 2007, **70**, 2019–2021.
8 Y. Asakawa and A. Ludwiczuk, *Heterocycles*, 2012, **86**, 891–917.
9 A. Speicher, *J. Prakt. Chem.*, 2000, **342**, 162–168.
10 G. Lock, *Monatsh. Chem.*, 1930, **55**, 307–315.
11 C.-F. Lin, J.-S. Yang, C.-Y. Chang, S.-C. Kuo, M.-R. Lee and L.-J. Huang, *Bioorg. Med. Chem.*, 2005, **13**, 1537–1544.
12 G. M. P. Giblin, A. Hall, D. N. Hurst, D. A. Rawlins and T. Scoccitti, *PCT Int. Appl. WO*, 2006, 066968.
13 W. J. Humphlett and C. R. Hauser, *J. Am. Chem. Soc.*, 1950, **72**, 3289–3290.

14 R. C. Fuson, *J. Am. Chem. Soc.*, 1926, **48**, 830–836; R. C. Fuson, *J. Am. Chem. Soc.*, 1926, **48**, 2681–2689.

15 R. C. Fuson, J. J. Denton and J. W. Kneisley, *J. Am. Chem. Soc.*, 1941, **63**, 2652–2653.

16 H. Ishibashi, K. Takagaki, N. Imada and M. Ikeda, *Tetrahedron*, 1994, **50**, 10215–10224.

17 K. Haajanen and N. P. Botting, *Steroids*, 2006, **71**, 231–239.

18 R. Pfleger and K. Waldmann, *Chem. Ber.*, 1957, **90**, 2395–2400.