Tandem pericyclic reactions in a new FeCl₃-promoted synthesis of catechol analogues of restrytisol C


a Department of Pharmacy, Faculty of Health, Science and Applied Science, Sedaya International College, Taman Segar, Cheras, 56100 Kuala Lumpur, Malaysia
b Department of Pharmacy, Faculty of Allied Health Science, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia
c Department of Chemistry, Faculty of Sciences, Universiti Malaya, 59100 Kuala Lumpur, Malaysia
d SCRMN, Faculte des Sciences, 2, Bd. Lavoisier, 49045 Angers Cedex, France

Received 10 May 2002; revised 12 June 2002; accepted 4 July 2002

Abstract — The uncommon stilbene, 3,4-dimethoxy-12-acetoxy stilbene, has been synthesised by Heck coupling methodology in three steps. Treatment of this stilbene with ferric chloride in dichloromethane (room temperature) gave the unnatural stilbenoid dimers; 8,8-(12,12-bisacetoxyphenyl)-7,0-(3,4-dimethoxyphenyl)-3,4-dimethoxy-7,8-dihydro-naphthalene and 8-(12-acetoxyphenyl)-8-(12-hydroxyphenyl)-7,0-(3,4-dimethoxyphenyl)-3,4-dimethoxy-7,8-dihydro-naphthalene. The structures of both stilbene dimers were unambiguously confirmed by 1D (1H, 13C) and 2D NMR experiments (COSY, HMQC, HMBC and NOESY). This is the first report of a FeCl₃-promoted sequential pericyclic pathway leading to a highly oxygenated oligostilbenoid dimer (incorporating two asymmetric centres). The NMR spectroscopic evidence and a mechanistic interpretation consistent with these structures are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

It is by now well established that resveratrol 1, a stilbene, has significant antiplatelet¹ and antioxidant² properties. It is also the biosynthetic progenitor of the oligostilbenoid polyphenols³ such as e-viniferin 2, balanocarpol 3, heimiol A 4 and hopeaphenol 5 (Scheme 1). Some of these are known to have interesting biological activities. Oligostilbenoid polyphenols are generated from resveratrol by oxidative phenolic coupling, and like resveratrol, possess the typical resorcinol arrangement. Stilbene monomer building blocks with the catechol arrangement are relatively infrequently used in oligostilbenoid biosynthesis. One can of course speculate on the reasons for this. Specific enzyme systems capable of binding efficiently to catechol stilbenes may be less common. The ortho dihydroxy substituents in such stilbenes tend to be protected for example as dimethyl ethers or as methylenedioxyethers.³ We have noticed that a significant proportion of these stilbenes lack the all important trans olefinic bond between the two benzene rings which must surely severely limit the options for complex phenol biosynthesis. Our previous work in the oligostilbenoids has included the isolation and structure

Keywords: stilbene; ferric chloride; pericyclic; dihydronaphthalene; restrytisol.

* Corresponding author. Fax: +60-3-2698-3271;
e-mail: noelthomas@sedaya.edu.my

Scheme 1. Examples of oligostilbenoid polyphenols.
elucidation of a new oligostilbenoid heimiol A $^4$. Further investigation has resulted in our recent report of the regio controlled oxidative lactonisation of stilbenes using manganese triacetate. $^5$–$^7$ Since nature is able to construct complex polyphenols from unprotected stilbenes like resveratrol, we were keen to study oxidative coupling of our stilbenes with one electron oxidants such as manganese triacetate, vanadium oxytrichloride $^8$ and FeCl$_3$. This type of study has not received much attention.

2. Results and discussion

Stilbene $^8$ was prepared (Heck coupling) $^9$. $^{10}$ by heating a mixture of 4-iodoacetoxybenzene $^6$ and 3,4-dimethoxy-styrene $^7$ in the presence of palladium dichloride, triphenylphosphine, potassium acetate and silver nitrate in DMF for 7 days. We obtained the stilbene $^8$ in 32% yield (Scheme 2). Treatment of $^8$ with FeCl$_3$ in dichloromethane produced the two stilbene dimers; $^8$,8$^0$-(12,12$^0$-bisacetoxyphenyl)-7$^0$-(3$^0$,4$^0$-dimethoxyphenyl)-3,4-dimethoxy-7$^0$,8$^0$-dihydro-naphthalene $^9$ in 17% yield and $^8$-(12-acetoxyphenyl)-8$^0$-(12$^0$-hydroxyphenyl)-7$^0$-(3$^0$,4$^0$-dimethoxyphenyl)-3,4-dimethoxy-7$^0$,8$^0$-dihydro-naphthalene $^10$ in 7% yield. Both structures ($^9$ and $^10$) were unambiguously assigned by means of 1D ($^1$H and $^{13}$C) NMR, and extensive 2D NMR experiments (COSY, HMQC, HMBC and NOESY) and also high resolution mass spectral data.

8,8$^0$-(12,12$^0$-Bisacetoxyphenyl)-7$^0$-(3$^0$,4$^0$-dimethoxyphenyl)-3,4-dimethoxy-7$^0$,8$^0$-dihydro-naphthalene $^9$ was obtained as a yellow oil. The spot on the TLC plate exhibited a strong blue fluorescence under UV (254 nm) which suggests that the trans stilbene chromophore has been retained. This is consistent with a structure in which the olefinic bond is at C7–C8 and not C8–C8$^0$ as in some natural analogues (see below). High resolution EI mass spectrum gave a molecular ion peak with accurate mass 594.2273 compatible with the molecular formula C$_{36}$H$_{34}$O$_8$ (calcd mass 594.2254, $^1$D 1.9 mmu) corresponding to two stilbene units $^8$ minus two protons. The $^1$H NMR and $^1$H–$^1$H COSY spectra showed two sets of ortho-coupled aromatic protons in A/A’/B’/B spin systems assignable to two independent 4-acetoxyphenyl rings B and D. These are 7.32 ppm, doublet $J$=8.7 Hz integrating for two protons (H-10, H-14); 6.94 ppm, doublet, $J$=8.7 Hz, integrating for two protons (H-11, H-13), 7.27 ppm doublet, $J$=8.6 Hz, corresponding to two protons (H-10’, H-14’) and 6.95 ppm, doublet $J$=8.6 Hz integrating for two protons (H-11’, H-13’). Further examination of the $^1$H spectrum reveals an ABM system for the catechol ring C (ortho and meta coupled protons with coupling constants of 8.3 and 1.9 Hz, respectively). The three singlets in the aromatic region (6.87, 6.52, 7.09 ppm) were identified as the isolated protons in rings A and E (H-2, H-5 and H-7, respectively) after examination of the HMBC spectrum. Apart from the aromatic region, the $^1$H NMR spectrum also showed two broad singlets at 4.15 and 4.11 ppm corresponding to H-7’ and H-8’, four methoxy and two acetoxy singlets. The connection between protons and their corresponding carbons was established by HMQC. Correlations from 2D long distance heteronuclear NMR spectrum (HMBC, Fig. 1) allowed the assignment of all proton and carbon signals. Observation of a cross peak with $^2$J and $^3$J (two and three bond correlations) shown by H-7’/C-8’, H-7’/C-2’, H-7’/C-5’, H-7’/C-9’, H-7’/C-8, H-8’/C-7’, $^1$D 1.9 mmu, $^3$J 1.9 Hz respectively).
Figure 2. Main NOESY correlations in 9 (500 MHz, CDCl₃).

H-8'/C-1', H-8'/C-9', H-8'/C-7, H-7/C-6, H-7/C-8', H-7/C-2 and H-7/C-9 allowed us to establish the naphthalene structure of 9. The relative configuration of 9 was deduced from the NOESY spectrum. The distinct correlation (Fig. 2) between H-8' with H-2'/6' and H-7' with H-10'/14' confirmed that protons H-7' and H-8' are in an anti configuration, a correlation not seen in compound 10 and confirming the latter’s syn configuration (see Section 3.2.2).

8-(12-Acetoxyphenyl)-8'-{(12'-hydroxyphenyl)-7'-{(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene 10 was also obtained as a yellow oil. The appearance of a strong blue fluorescence spot under UV (254 nm) again suggested the retention of a trans stilbene chromophore in structure 10. The high resolution mass spectrum (CI) gave an exact mass 553.2241 for the pseudomolecular ion [M+H]⁺, compatible with the molecular formula C₃₄H₃₂O₇ (calcd mass 553.2226, Δ 1.5 mmu) of a stilbene dimer. The ¹H and ¹³C NMR spectra of 10 were similar to compound 9 except for the replacement of an acetoxy group with a free hydroxy group at C-12'. The increased shielding of H-11'/13' in 10 (6.69 ppm) compared to 9 (6.95 ppm) and increased deshielding of the C-12', 154.69 ppm (10) compared to 149.42 ppm (9) is consistent with the presence of a free hydroxy group at C-12', as opposed to an acetoxy in the case of 9. This reflects the much greater ‘carbonyl’ character of the C-12' in 10 compared to 9. The structure of 10 was further confirmed by 2D NMR HMQC, HMBC (Fig. 3) and NOESY (Fig. 4) spectral data. In the HMBC spectrum, observation of a cross peak with 3J (two and three bonds correlation) shown by H-7/C-8', H-7/C-2, H-7/C-5, H-7/C-9', H-7/C-8, H-8'/C-7, H-8'/C-1', H-8'/C-9', H-8'/C-6, H-7/C-8', H-7/C-2 and H-7/C-9 led us to establish the structure of 10. The NOESY spectrum confirms the syn configuration of H-7' and H-8' (Fig. 4).

The formation of compounds 9 and 10 can be explained by thermally allowed pericyclic transformations. The mechanistic pathway is initiated by removal of an electron by Fe³⁺ (the oxidizing agent) from the olefinic system 11 (or 8) to form a radical cation 12. This is followed by coupling of two radical cationic species to produce 13. Rapid deprotonation of 13 would yield the dienes 14ₐ and 14ₜ the ZZ- and ZE-isomers, respectively. 6σ electrocyclic ring closure of 14ₐ and 14ₜ would give 15ₐ and 15ₜ, respectively. This is followed by sigmatropic rearrangements to provide 9 and 10 as shown in Scheme 3. Both syn and anti isomers were isolated from the reaction mixture. The anti isomer was the major compound. This may be due to its greater thermodynamic stability. Its predominance probably also reflects the fact that it is formed from the more abundant diene 14ₐ.

The transformation of 14ₐ to 9 and 14ₜ to 10 can be explained by frontier orbital considerations, as shown in Schemes 4 and 5. Considering the Highest Occupied Molecular Orbital (HOMO) for both σ₆ system (hexatriene) 14ₐ and 14ₜ, disrotatory ring closure of 14ₐ would provide the anti disposed hydrogen at the two new asymmetric centers 15ₐ and then followed by [1,5] suprafacial hydride

Figure 3. Main HMBC correlations in 10 (400 MHz, CDCl₃).

Figure 4. Main NOESY correlations in 10 (500 MHz, CDCl₃).
shifts to 9 (Scheme 4). By contrast disrotatory ring closure of 14B would produce the syn configuration shown in 15B. This is then followed by symmetry allowed [1,5] suprafacial hydride shifts and deprotection of the acetate leading to 10 as shown in Scheme 5.

In conclusion, we would like to point out that we are aware of recent reports regarding the isolation of cyphostemmins12 and the Botrytis cinerea catalysed dimerisation of resveratrol13 to produce a mixture of compounds from which restrytisol C 16 was isolated as the diastereisomer shown. In the light of our mechanistic rationale, the biosynthesis of 16 could well involve pericyclic reactions (see Scheme 3), but intriguingly, the fact that the cis (syn) isomer is not formed in the B. cinerea catalysed transformation of resveratrol, could suggest that stereospecific requirements for these fungal pathogen enzymes, preclude formation of the Z,E-diene isomer related to our 14B (see Scheme 3). Our compounds (and 16) are structurally related to the natural product cyphostemmin A 17 which incorporates the cis (rather than the trans) stilbene chromophore (Scheme 6). From a biosynthetic standpoint, it would appear that for 17 formation, the 1,5 sigmatropic rearrangement 15A to 9 (Scheme 3) is prohibited, and that a prototropic shift (non-concerted) involving the proton at C-6 is the favoured pathway. It is also noteworthy that the reported biomimetic synthesis of 16 by Kouzi et al. also describes a number of other compounds presumably arising from oxidative phenolic coupling (excluding we believe 16). In our FeCl3 reactions these oxidative phenolic compounds seem to be precluded, and pericyclic pathways leading to 9 and 10 predominate. The results of further synthetic and biosynthetic investigations from our group will be reported in due course.

Scheme 3. Proposed mechanism for the formation of 9 and 10.
3. Experimental

3.1. Synthesis of 3,4-dimethoxy-12-acetoxystilbene 8

4-Iodoacetoxybenzene 6 (3.59 g, 0.0134 mol) was dissolved in dry DMF (50 mL). To this stirring solution palladium(II) chloride (0.238 g, 1.34 mmol), triphenylphosphine (0.703 g, 2.68 mmol), silver nitrate (2.28 g, 0.0134 mol), potassium acetate (1.63 g, 0.0166 mol) and 3,4-dimethoxy styrene 7 (2.20 g, 0.0134 mol) was added. The mixture was refluxed under nitrogen for a week. The reaction mixture was filtered and extracted with ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous Na₂SO₄. The crude was purified by column chromatography (ethyl acetate/hexane; 1:10) to gave 1.28 g (32% yield) of colourless crystals 8.

3.1.1. 3,4-Dimethoxy-12-acetoxystilbene 8. IR (film) νmax: 3007, 2963, 2938, 1756 (acetate C=O), 1600, 1580, 1238, 1212, 1191, 1163, 1137, 1024; 1H NMR (400 MHz, CDCl₃) δ ppm: 7.49 (d; J=8.6 Hz; 2H; H-10,14), 7.07 (d; J=8.6 Hz; 2H; H-11,13), 7.06 (d; J=2.2 Hz; 1H; H-2), 7.04 (dd; J=8.0, 2.2 Hz; 1H; H-6), 7.00 (d; J=16.4 Hz; 1H; H-7), 6.97 (d;
$J=16.4$ Hz; 1H; H-8), 6.86 (d; $J=8.0$ Hz; 1H; H-5), 3.95 (s; 3H; 3-OCH$_3$), 3.90 (s; 3H; 4-OCH$_3$), 2.31 (s; 3H; 12-OAc).

$^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ ppm: 130.08 (C-1), 108.57 (C-2), 148.93 (C-3), 148.80 (C-4), 111.04 (C-5), 119.75 (C-6), 128.51 (C-7), 125.53 (C-8), 135.15 (C-9), 126.95 (C-10,14), 121.57 (C-11, 13), 149.61 (C-12), 169.28 (C=O), 55.71 (3-OCH$_3$), 55.65 (4-OCH$_3$), 20.91 (COCH$_3$).

3.2. Synthesis of stilbene dimer 9 and 10

To a stirring solution of stilbene 3 (0.4 g, 1.34 mmol) in dichloromethane (40 mL), FeCl$_3$ 6H$_2$O (2 mL, 13.4 mmol) was added. The reaction was monitored by TLC. After 3 h, reaction mixture was worked up with MeOH. The crude product was purified by column chromatography (100% CHCl$_3$) and centrifugal chromatography (100% CHCl$_3$). Two pure compounds were isolated.

3.2.1. 8,8'-[(12,12'-Bisacetoxyphenyl)-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7,8'-dihydro-naphthalene 9. The compound was isolated as yellow oil, 0.14 g (17% yield). HRMS-EI 594.2273; IR (film) $\nu_{max}$: 3439, 3020, 2935, 2837, 1756 (acetate CO), 1648, 1607, 1512, 1241, 1200, 1167, 1026, 755 ppm; 1H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.67 (s; 1H; H-2), 6.87 (s; 1H; H-5), 4.07 (br s; 1H; H-7'), 4.70 (br s; 1H; H-12'-OH), 3.96 (s; 3H; 3-OCH$_3$), 3.82 (s; 3H; 4'-OCH$_3$), 3.78 (s; 3H; 3'-OCH$_3$), 3.77 (s; 3H; 4'-OCH$_3$), 2.24 (s; 3H; 12-OAc); $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ ppm: 126.96 (C-1), 137.88 (C-1'), 110.04 (C-2), 110.83 (C-2'), 147.83 (C-3), 147.81 (C-3'), 148.69 (C-4), 145.47 (C-4'), 112.58 (C-5), 111.24 (C-5'), 127.45 (C-6), 119.32 (C-6'), 124.99 (C-7), 53.07 (C-7'), 135.47 (C-8), 50.99 (C-8'), 138.48 (C-9), 134.30 (C-9'), 126.45 (C-10,14), 128.60 (C-10',14'), 121.30 (C-11,13), 115.54 (C-11',13'), 149.61 (C-12), 154.69 (C-12'), 55.73 (3-OCH$_3$), 55.79 (3'-OCH$_3$), 55.78 (4'-OCH$_3$), 55.91 (4''-OCH$_3$), 21.04 (12-COCH$_3$), 169.61 (C=O) (---interchangeable).

Acknowledgments

This work was supported by a grant from the Malaysian Government (IRPA No 09-02-0061).

References