MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 8, pp. 1309–1317, 2003

Synthesis of Antibiotic Stilbenes by Reductive Metalation of 3,4,5-Trimethoxybenzaldehyde Dimethyl Acetal

Ugo Azzena,* Maria Vittoria Idini, and Luciano Pilo

Dipartimento di Chimica e Facoltà di Farmacia,
Università di Sassari, Sassari, Italy

ABSTRACT

Reductive metalation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal followed by reaction with suitable electrophiles is the key step of a reaction sequence leading to the synthesis of naturally occurring 4-alkyl-3,5-dihydroxy-substituted *trans*-stilbenes having antibiotic activity.

Because 3′,5′-dihydroxy-substituted stilbenes are an important class of natural products with significant biological and pharmacological properties,[1–6] there is a continuous search for new approaches to their

*Correspondence: Ugo Azzena, Dipartimento di Chimica e Facoltà di Farmacia, Università di Sassari, via Vienna 2, 07100 - Sassari, Italy; Fax: +39-07-922-9559; E-mail: ugo@ssmain.uniss.it.

DOI: 10.1081/SCC-120018690 0039-7911 (Print); 1532-2432 (Online)

synthesis.[1–3,7–9] Even if relatively expensive, dimethyl- or dimethoxymethyl ethers of 3,5-dihydroxybenzaldehyde (or derivatives thereof) are widely employed as starting materials for these syntheses.[1–3,8,9] As an alternative, organomanganese complexes of 1,3-dimethoxy-2-alkylbenzenes were proposed as starting materials.[7]

We already reported a synthetic procedure involving the regioselective reductive electrophilic substitution of the 2-methoxy group of 5-substituted derivatives of 1,2,3-trimethoxybenzene under electron-transfer conditions from alkali metals, leading to the synthesis of several 5-alkyl-substituted- (olivetol and its homologues)[10] and 2,5-dialkyl-substituted-resorcinols (stemphol and DB2073).[11]

The main features of this approach are the following: (i) cheap and easily available starting materials; (ii) high regioselectivity; (iii) intermediate formation of 2,6-dimethoxy-substituted organometals; (iv) reaction conditions allowing the introduction of several functionalities which are, in principle, not stable to reduction with alkali metals.[12,13]

We investigated further the usefulness of this approach, and wish now to report the application of this procedure to the synthesis of two natural antibiotic metabolites with a 4-alkyl-3,5-dihydroxy-substituted *trans*-stilbene structure, namely (*E*)-1,3-dimethoxy-2-ethyl-5-(2-phenylethenyl)benzene, **4a**, and (*E*)-1,3-dimethoxy-2-(1-methylethyl)-5-(2-phenylethenyl)benzene, **4b**. Conversion of these compounds into the corresponding natural 3,5-dihydroxystilbenes was achieved according to an established procedure.[7]

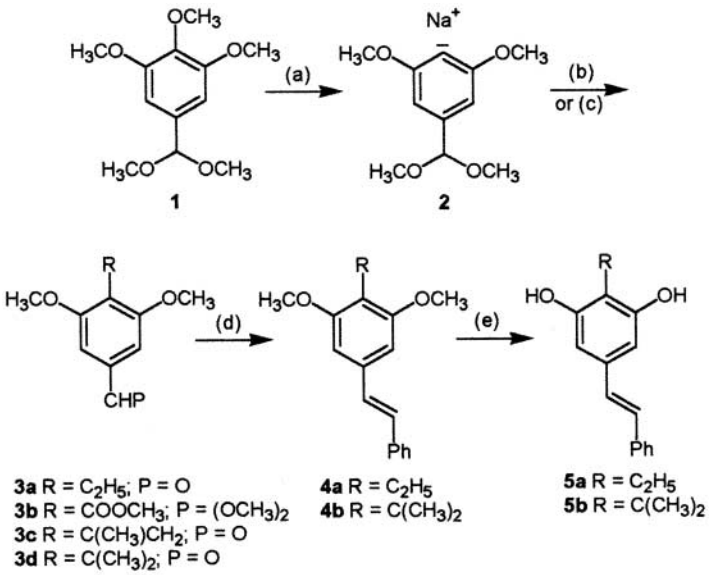
RESULTS AND DISCUSSION

The syntheses of the desired antibiotic stilbenes **5a** and **5b** were realized according to the Sch. 1.

The dimethyl acetal of 3,4,5-trimethoxybenzaldehyde, **1**, is commercially available or can be easily prepared by reaction of the corresponding aldehyde with $HC(OCH_3)_3$ in CH_3OH in the presence of NH_4Cl.[11]

Regioselective reductive metalation at the 4-position was accomplished with Na metal in THF for 24 h at r.t. The corresponding intermediate organosodium derivative **2** was reacted with EtBr to afford, after acidic work up, the corresponding 3,5-dimethoxy-4-ethylbenzaldehyde, **3a**, in 68% overall yield.

According to a general procedure,[14] Wadsworth–Emmons olefination of aldehyde **3a** with the sodium salt of diethyl benzylphosphonate in THF in the presence of a catalytic amount of 15-*crown*-5 afforded,



Scheme. Reagents and conditions: (a) Na, THF; (b) (i) C_2H_5Br, 0 °C; (ii) THF/HCl 1N = 1:1; (c) (i) $ClCOOCH_3$, -40 °C; Et_3N, then H_2O; (ii) CH_3MgI, Et_2O; THF/H_2SO_4 4N = 1:1, reflux; (iii) $HC(OCH_3)_3$, NH_4Cl; H_2, Pd/C 5%, EtOH; THF/H_2SO_4 2N = 1:1; (d) $PhCH_2P(O)(OEt)_2$, NaH, 15-crown-5, THF; (e) BBr_3-$(CH_3)_2S$, $Cl(CH_2)_2Cl$, reflux

Scheme 1.

stereoselectively, (*E*)-1,3-dimethoxy-2-ethyl-5-(2-phenylethenyl)benzene, **4a**, in 80% isolated yield.

Demethylation to the corresponding biologically active resorcinol **5a** was accomplished with BBr_3-Me_2S in refluxing 1,2-dichloroethane, according to a literature procedure.[7]

A relatively different reaction sequence was devised to obtain the *iso*-propyl derivative **5b**. As a matter of fact, reaction of the organosodium derivative **2** with secondary alkyl halides does not afford the desired alkylated compounds.[11,13] Therefore, the *iso*-propyl chain in the 4-position was introduced according to a more complex reaction pathway.

Intermediate **2** was generated as reported above and reacted at $-40^{\circ}C$ with an excess of methyl chloroformate for 2 h, followed by addition of Et_3N to avoid hydrolysis of the acetal moiety during aqueous work up. According to this procedure, methyl 2,6-dimethoxy-4-dimethoxymethylbenzoate, **3b**, was obtained in 75% isolated yield.

The methyl ester was reacted with excess CH_3MgI leading, after acidic work up, to 3,5-dimethoxy-4-methylethenylbenzaldehyde, **3c**, in 69% yield.

Conversion of unsaturated aldehyde **3c** into saturated aldehyde **3d** via selective hydrogenation of the C–C double bond failed under a variety of reaction conditions, leading to no reaction (hydrogenation in EtOH over 5% Pd/C(en)[15] or $NaBH_4$ reduced $PdCl_2$[16]), or to contemporary reduction of the aldehyde moiety (hydrogenation over 10 or 5% Pd/C in EtOH or in THF).

On the contrary, reaction of aldehyde **3c** with trimethyl orthoformate in the presence of a catalytic amount of NH_4Cl afforded the corresponding acetal, which was hydrogenated at atmospheric pressure and r.t. over 5% Pd/C in EtOH; acidic hydrolysis led to 2,6-dimethoxy-4-methylethylbenzaldehyde, **3d**, in 65% isolated yield.

According to the above reported procedure,[14] Wadsworth–Emmons olefination of aldehyde **3d** afforded stereoselectively the desired stilbene **4b** in 78% yield[17]; the last one was converted into the corresponding resorcinol **5b** as described in the literature.[7]

In conclusion, the dimethyl acetal of 3,4,5-trimethoxybenzaldehyde is a particularly cheap starting material which can be elaborated into biologically active 4-alkyl-substituted resorcinolic stilbenes through a reaction sequence involving regioselective reductive metalation as a key synthetic step.

EXPERIMENTAL

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillations is given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or crystallization. THF was distilled from Na/K alloy under dry N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. IR spectra were recorded in nujol. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari. Resorcinols **5a** and **5b** were obtained by demethylation of the corresponding ethers **4a** and **4b**, respectively, according to a known procedure,[7] and characterized by comparison with literature data.

3,5-Dimethoxy-4-ethylbenzaldehyde (3a): Freshly cut Na metal (0.57 g, 25 mg atom) was placed under dry Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in anhydrous

THF (50 mL). The mixture was chilled to 0°C and a solution of **1** (2 g, 8.3 mmol) in anhydrous THF (20 mL) was added dropwise. The reaction mixture was stirred at r.t. for 24 h, then cooled to 0°C, and a solution of EtBr (1.8 g, 1.2 mL, 17 mmol) dissolved in THF (5 mL) was added dropwise. After stirring 12 h at r.t., the reaction mixture was quenched by careful dropwise addition of H_2O (20 mL, **CAUTION!**). Et_2O was added (20 mL) and the organic phase separated. The aqueous phase was extracted with Et_2O (3×20 mL) and the organic phase washed with H_2O (20 mL) and evaporated. The residue was dissolved in THF/1N HCl (1:1, 50 mL) and stirred at r.t. for 5 h. The mixture was extracted with Et_2O (3×20 mL), the organic phase washed with H_2O (2×20 mL), dried (Na_2SO_4), and the solvent evaporated. The residue was purified by flash chromatography (AcOEt/Et. Petr. = 3:7, $R_f = 0.61$) to afford pure **3a** (1.1 g, 5.2 mmol, 68%), characterized as follows: white solid, m.p. 68°C (*i*-PrOH/H_2O) (lit.[11] 68–69°C); ^{1}H NMR δ 1.08 (3H, t, $J = 7.3$ Hz, CH_3), 2.62 (2H, q, $J = 7.3$ Hz, CH_2), 3.89 (6H, s, OCH_3), 7.05 (2H, s, HAr), 9.90 (1H, s, CHO); IR $\nu = 1680\ cm^{-1}$.

(*E*)-1,3-Dimethoxy-2-ethyl-5-(2-phenylethenyl)benzene (4a): NaH (5.7 mmol, 0.2 g of a 60% dispersion in mineral oil) was placed under dry Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, washed with anhydrous THF (3×10 mL) and suspended in anhydrous THF (15 mL) containing 15-*crown*-5 (30 mg). The mixture was chilled to 0°C and a solution of diethyl benzylphosphonate (1.19 g, 1.1 mL, 5.2 mmol) and **3a** (1.1 g, 5.2 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at r.t. overnight, then quenched by slow dropwise addition of H_2O (20 mL). Et_2O was added (20 mL), the organic phase separated and the aqueous phase was extracted with Et_2O (2×20 mL). The organic phase was washed with H_2O (20 mL), dried (Na_2SO_4), and the solvent evaporated. The residue was purified by flash chromatography (AcOEt/Et. Petr. = 3:7, $R_f = 0.49$) to afford pure **4a** (1.1 g, 4.2 mmol, 80%), characterized as follows: colorless oil, which solidifies upon standing, m.p. 75–76°C (lit.[7] m.p. 73.5–74.5°C); ^{1}H NMR δ 1.09 (3H, t, $J = 7.5$ Hz, CH_3), 2.67 (2H, q, $J = 7.5$ Hz, CH_2), 3.86 (6H, s, OCH_3), 6.69 (2H, s, HAr), 7.06 (2H, s, $2 \times$ CH), 7.24 (1H, t, $J = 7.2$ Hz, HAr), 7.34 (2H, t, $J = 7.5$ Hz, HAr), 7.52 (2H, d, $J = 7.2$ Hz, HAr); ^{13}C NMR δ 13.8, 16.4, 55.7, 102.2, 120.9, 126.4, 127.5, 127.8, 128.6, 129.2, 135.8, 137.4, 158.2; IR $\nu = 1590, 1560\ cm^{-1}$.

Methyl 2,6-dimethoxy-4-dimethoxymethylbenzoate (3b): Freshly cut Na metal (1.57 g, 68 mg atom) was placed under dry Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in anhydrous THF (100 mL). The mixture was chilled to 0°C and a solution of **1** (5 g, 21 mmol) in anhydrous THF (40 mL) was added

dropwise. The reaction mixture was stirred at r.t. for 24 h, then cooled to $-40^{\circ}C$ and a solution of $ClCOOCH_3$ (6.0 g, 4.9 mL, 63 mmol) dissolved in THF (10 mL) was added dropwise. After stirring 2 h at $-40^{\circ}C$, Et_3N (12 mL) was added and the mixture stirred for 10 min before quenching it with H_2O (20 mL, **CAUTION!**). Et_2O was added (50 mL), the organic phase separated and the aqueous phase extracted with Et_2O (2×30 mL). The organic phase was washed with H_2O (50 mL), dried (Na_2SO_4), and the solvent evaporated. The residue was purified by flash chromatography (AcOEt/Et. Petr. = 4:6, $R_f = 0.44$) to afford pure **3b** (4.3 g, 15.8 mmol, 75%), characterized as follows: white solid, m.p. 67–70°C (CH_3OH); ^{1}H NMR δ 3.31 (6H, s, $2 \times OCH_3$) 3.83 (6H, s, $2 \times OCH_3$) 3.90 (3H, s, OCH_3), 5.35 (1H, s, CH), 6.67 (1H, s, HAr); ^{13}C NMR δ 52.4, 52.5, 56.1, 102.4, 102.4, 141.7, 157.3, 166.9; IR $\nu = 1745$, 1600 cm^{-1}. Anal. calc. for $C_{13}H_{18}O_6$: C 57.76; H 6.73. Found: C 57.49; H 6.91.

3,5-Dimethoxy-4-methylethenylbenzaldehyde (3c): Mg turnings (1.13 g, 46 mmol) were placed under dry Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in a minimal amount of anhydrous Et_2O. To this mixture, a solution of CH_3I (6.5 g, 2.9 mL, 46 mmol) in Et_2O (30 mL) was added dropwise, and stirring was continued overnight at r.t. Then, **3b** (3.8 g, 14 mmol) dissolved in Et_2O (30 mL), containing a minimal amount of THF to complete solubilization, was added dropwise, and the mixture refluxed for 12 h. The mixture was hydrolyzed by slow dropwise addition of H_2SO_4 2 N (20 mL), the organic phase separated and the aqueous phase extracted with Et_2O (3×20 mL). The organic phase was evaporated and the residue dissolved in THF/H_2SO_4 4N = 1:1 (20 mL) and refluxed for 8 h. The mixture was chilled to r.t., extracted with Et_2O (3×20 mL), the organic phase washed with H_2O (20 mL), sat. $NaHCO_3$ (20 mL), dried (Na_2SO_4) and the solvent evaporated. The residue was purified by crystallization (CH_3OH) to afford pure **3c** (2.0 g, 9.7 mmol, 69%), characterized as follows: white solid, m.p. 98°C (CH_3OH) (lit.[18] m.p. 97–98°C); ^{1}H NMR δ 2.02 (3H, dd, $J = 1.5$, 1.2 Hz, CH_3), 3.89 (6H s, OCH_3), 4.89 (1H, qd, $J = 1.2$, 0.9 Hz, CH), 5.37 (1H, q, $J = 1.5$, 0.9 Hz, CH), 7.10 (2H, s, HAr), 9.94 (1H, s, CHO); ^{13}C NMR δ 22.8, 56.1, 105.2, 107.1, 116.2, 136.3, 138.2, 157.7, 191.7; IR ν 1670, 1560 cm^{-1}.

2,6-Dimethoxy-4-methylethylbenzaldehyde (3d): Aldehyde **3c** (0.8 g, 3.7 mmol) was dissolved in a mixture of CH_3OH (15 mL) and $HC(OCH_3)_3$ (10 mL) containing a catalytic amount of NH_4Cl (20 mg). The mixture was stirred at reflux temperature under dry Ar for 4 h, then chilled to r.t., and Et_3N (2 mL) was added dropwise. After stirring at r.t. for 10 min,

H_2O (20 mL) was added and the mixture diluted with Et_2O (20 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The organic phase was washed with H_2O (2 × 20 mL), dried (K_2CO_3) and the solvent evaporated to recover 0.81 g of an oil which appeared homogeneous by TLC analysis (AcOEt/Et. Petr. = 7:3, $R_f = 0.40$), did not show any IR carbonyl stretching absorption, and was not further characterized.

The residue was dissolved in EtOH (15 mL) and hydrogenated at r.t. and atmospheric pressure under magnetic stirring during 5 h. The reaction mixture was filtered, the solvent evaporated, the residue dissolved in THF/H_2SO_4 2N = 1:1 (10 mL) and stirred at r.t. for 2 h. The mixture was diluted with Et_2O (10 mL) and H_2O (10 mL), and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 10 mL), and the organic phase washed with H_2O (2 × 10 mL), sat. $NaHCO_3$ (10 mL), dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash chromatography (AcOEt/Et. Petr. = 2:8, $R_f = 0.43$) to afford pure **3d** (0.50 g, 2.4 mmol, 65%), characterized as follows: white solid, m.p. 57°C (CH_3OH); ^{1}H NMR δ 1.29 (6H, d, $J = 6.9$ Hz, CH_3), 3.66 (1H, ept, $J = 7.2$ Hz, CH), 3.87 (6H, s, OCH_3), 7.05 (2H, s, HAr), 9.89 (1H, s, CHO); ^{13}C NMR δ 20.0, 24.5, 55.7, 105.4, 131.8, 135.0, 158.9, 191.9; IR ν 1685, 1580 cm^{-1}. Anal. calcd. for $C_{12}H_{16}O_3$: C 69.20; H 7.76. Found: C 69.08; H 7.85.

(*E*)-1,3-Dimethoxy-2-(1-methylethyl)-5-(2-phenylethenyl)benzene (4b): NaH (2.8 mmol, 0.11 g of a 60% dispersion in mineral oil) was placed under dry Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, washed with anhydrous THF (3 × 5 mL) and suspended in anhydrous THF (10 mL) containing 15-*crown*-5 (15 mg). The mixture was chilled to 0°C and a solution of diethyl benzylphosphonate (0.64 g, 0.6 mL, 2.7 mmol) and **3d** (0.50 g, 2.4 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at r.t. overnight and quenched by slow dropwise addition of H_2O (10 mL). Et_2O was added (20 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (2 × 20 mL). The organic phase was washed with H_2O (20 mL), dried (Na_2SO_4), and the solvent evaporated. The residue was purified by flash chromatography (AcOEt/Et. Petr. = 1:9, $R_f = 0.44$) to afford pure **4b** (0.53 g, 1.9 mmol, 78%), characterized as follows: colorless oil, which solidifies upon standing, m.p. 66–68°C (lit.[7] m.p. 65–66°C); ^{1}H NMR δ 1.29 (6H, d, $J = 7.2$ Hz, 2 × CH_3), 3.60 (1H, ept, $J = 7.2$ Hz, CH), 3.84 (6H, s, CH_3O), 6.69 (2H, s, ArH), 7.05 (2H, s, CH), 7.21–7.28 (1H, m, ArH), 7.30–7.38 (2H, m, ArH), 7.47–7.54 (2H, m, ArH); ^{13}C NMR δ 20.7, 24.1, 55.7, 102.8, 124.4, 126.4, 127.5, 127.9, 128.6, 129.0, 135.8, 137.3, 158.7; IR $\nu = 1580$, 1570 cm^{-1}.

ACKNOWLEDGMENT

Financial support from the University of Sassari (ex 60% funds) is gratefully acknowledged.

REFERENCES

1. Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A.K.; Lin, C.M.; Hamel, E. J. Med. Chem. **1991**, *34*, 2579–2588 and references therein.
2. Thakkar, K.; Geahlen, R.L.; Cushman, M. J. Med. Chem. **1993**, *36*, 2950–2955.
3. Treadwell, E.M.; Cermak, S.C.; Wiemer, D.F. J. Org. Chem. **1999**, *64*, 8718–8723 and references therein.
4. Likhitwitayawuid, K.; Sritularak, B.; De-Eknamkul, W. Planta Med. **2000**, *66*, 275–277.
5. Ahn, K.-S.; Kim, J.-H.; Oh, S.-R.; Ryu, S.-Y.; Lee, H.-K. Planta Med. **2000**, *66*, 641–644.
6. Shimizu, K.; Fukuda, M.; Kondo, R.; Sakai, K. Planta Med. **2000**, *66*, 16–19.
7. Krow, G.R.; Miles, W.H.; Smiley, P.M.; Lester, W.S.; Kim, Y.J. J. Org. Chem. **1992**, *57*, 4040–4043 and references therein.
8. Alonso, E.; Ramón, D.J.; Yus, M. J. Org. Chem. **1997**, *62*, 417–421.
9. Kim, S.-H.; Rieke, R.D. J. Org. Chem. **2000**, *65*, 2322–2330.
10. Azzena, U.; Denurra, T.; Melloni, G.; Rassu, G. Synthesis **1989**, 28–30.
11. Azzena, U.; Cossu, S.; Denurra, T.; Melloni, G.; Piroddi, A.M. Synthesis **1990**, 313–314.
12. Azzena, U.; Denurra, T.; Melloni, G.; Piroddi, A.M. J. Org. Chem. **1990**, *55*, 5386–5390.
13. Azzena, U.; Melloni, G.; Piroddi, A.M.; Azara, E.; Contini, S.; Fenude, E. J. Org. Chem. **1992**, *57*, 3101–3106.
14. Baker, R.; Sims, R. J. Synthesis **1981**, 117.
15. Sajiki, H.; Hattori, K.; Hirota, K. J. Org. Chem. **1998**, *63*, 7990–7992.
16. Russell, T.W.; Duncan, D.M.; Hansen, S.C. J. Org. Chem. **1977**, *42*, 551–552.
17. As an alternative, reaction of benzaldehyde **3c** with $PhCH_2MgCl$ in Et_2O (81%), followed by catalytic hydrogenation of the C–C double bond (5% Pd/C, EtOH, 90%) and dehydration (DMSO, reflux, 28%), afforded stilbene **4b** with an overall lower yield.

18. Kompis, I.; Then, R.; Boehni, E.; Rey-Bellet, G.; Zanetti, G.; Mantovan, M. Eur. J. Med. Chem.—Chim. Ter. **1980**, *15*, 17–22.

Received in the USA April 1, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016