Natural Products

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Total Synthesis of the Antibiotic Erypoegin H and Cognates by a $PtCl_2$-Catalyzed Cycloisomerization Reaction**

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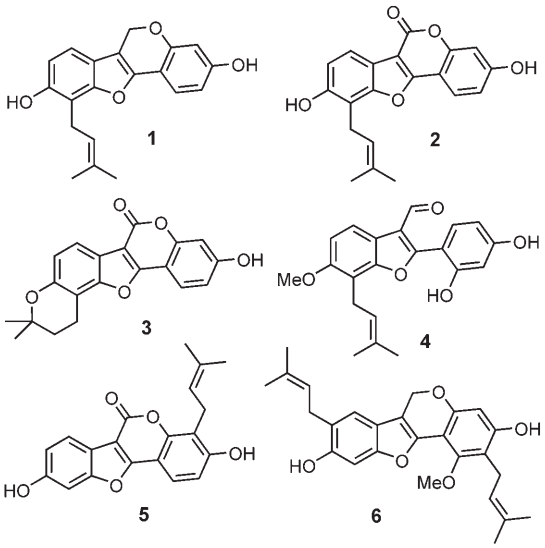
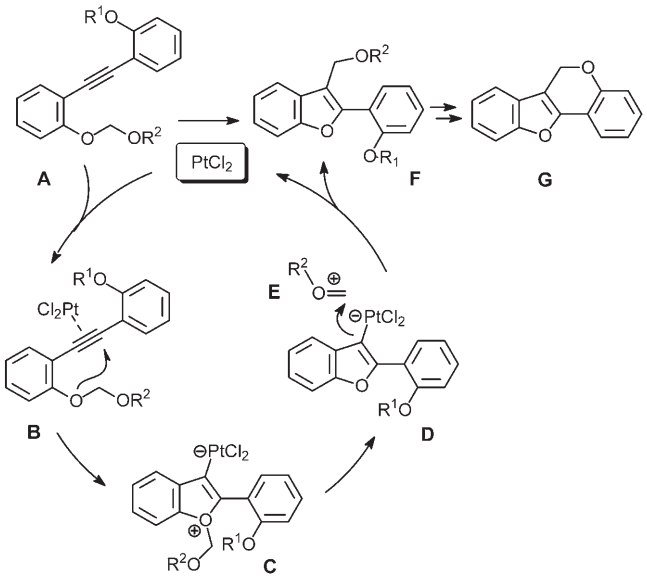
The growing number of methicillin-resistant *Staphylococcus aureus* (MRSA) strains that are also resistant to other antibiotics in clinical use, including vancomycin, constitutes a serious threat worldwide. Even though the urgent need for innovative therapeutic agents capable of combating such deadly bacteria has been widely recognized, the number of new lead structures fueling that quest remains alarmingly low.[1]

A promising candidate in this regard is the pterocarpene nucleus (**G**, Scheme 1) which constitutes the core of a sizeable number of bioactive natural products, mainly derived from plants of the *Leguminosae* family. Amongst the recent publications highlighting the potential of this heterocyclic scaffold as a pharmacophore,[2,3] a report on the secondary metabolites of *Erythrina poeppigiana* is particularly noteworthy.[4] It showed that erypoegin H (**1**), the most active isoflavonoid isolated from the roots of this ornamental plant, not only exhibits a broad spectrum of activity against Gram-positive bacteria in general, but also exhibits a significant and uniform activity against a panel of 13 different MRSA strains and vancomycin-resistant enterococci (minimum inhibitory concentration (MIC) 12.5 $\mu g\,mL^{-1}$).[4]



Preliminary data suggest that **1** interferes with the nucleic acids and/or the metabolism of MRSA bacteria, whilst seemingly leaving their cell walls intact.[4] To fully assess the potential of this lead compound, more detailed studies on its mode of action and toxicity are warranted, and exploration of pertinent structure/activity relationships (SAR) should allow the activity to be further improved. To this end, it was necessary to develop a concise and inherently flexible route that delivers meaningful amounts of **1** and congeners (for example, **2**–**6**).

We reasoned that the benzofuran synthesis recently developed by our group would lend itself to this goal (Scheme 1).[5–7] Based on a $PtCl_2$-catalyzed carboalkoxylation reaction, the underlying concept diverges broadly from the established construction modes of pterocarpenes.[8] Activation of the alkyne moiety in a substrate of type **A** by the carbophilic π acid $PtCl_2$ engenders nucleophilic attack from an oxygen atom of the adjacent acetal, thereby resulting in a *trans*-alkoxyplatination (**B**→**C**).[5,9] The released oxocarbe-



Scheme 1. Synthesis of the pterocarpene nucleus by a $PtCl_2$-catalyzed carboalkoxylation reaction of an alkyne.

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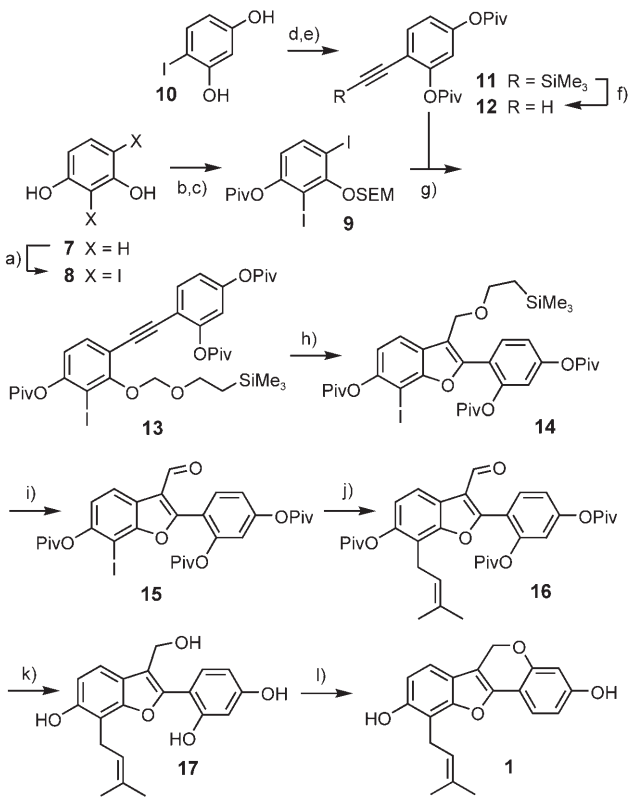
nium ion **E** then shifts to the most nucleophilic position in **D** to give product **F**,[10] which can be readily elaborated into the targeted scaffold **G** by conventional means.

The synthetic venture commenced with the di-iodination of resorcinol **7**[11] followed by consecutive attachment of a pivaloyl and a trimethylsilylethoxymethyl group (Scheme 2).



Scheme 2. a) KI, KIO_3, aq HCl, 61%; b) PivCl, Et_3N, CH_2Cl_2, 64%; c) SEMCl, Et_3N, DMAP (cat.), toluene, 94%; d) PivCl, Et_3N, CH_2Cl_2, 99%; e) $Me_3SiC{\equiv}CH$, $[PdCl_2(PPh_3)_2]$ (1.5 mol%), CuI (1.5 mol%), Et_3N, Ar/H_2 (1 atm), 93%; f) $AgNO_3$ (10 mol%), aq acetone, 99%; g) $[PdCl_2(PPh_3)_2]$ (3 mol%), CuI (3 mol%), Et_3N, Ar/H_2 (1 atm), 74%; h) $PtCl_2$ (10 mol%), CO (1 atm), 4-Å MS, toluene, 80°C, 84%; i) $(NH_4)_2Ce(NO_3)_6$ (CAN), MeCN/H_2O, 82%; j) 1. $Zn(iPr)_2$, [Li(acac)] (10 mol%), NMP; 2. CuCN·2 LiCl (10 mol%), prenyl bromide, 86%; k) $LiAlH_4$; THF; l) I_2, PPh_3, imidazole, Et_2O/MeCN, 70% (over both steps); Piv = pivaloyl, DMAP = 4-dimethylaminopyridine, SEM = trimethylsilylethoxymethyl, MS = molecular sieves, acac = acetylacetone, NMP = *N*-methylpyrrolidine.

This sequence takes advantage of the greatly different accessibility of the two phenolic OH groups in **8**. Steric reasons also explain the regioselective course of the subsequent Sonogashira reaction of di-iodide **9** with alkyne **12**, which derives from compound **10**[12] in a few high yielding reactions; this transformation had to be carried out under a reducing atmosphere to avoid extensive homocoupling of the alkyne partner.[13] The resulting compound **13**, on exposure to catalytic amounts of $PtCl_2$ in toluene under a CO atmosphere,[5,14] underwent a remarkably clean cycloisomerization with formation of the desired benzofuran derivative **14**. This reaction was best performed in the presence of powdered molecular sieves to sequester traces of adventitious water that might protonate the putative organoplatinum intermediate of type **C** and/or **D** and hence reduce the efficiency of the O→C shift. Under these optimized conditions, the cycloisomerization of **13** proceeded exceedingly well and afforded **14** in 84% yield on a multigram scale (see the Experimental Section). The efficiency and operational simplicity of this particular transformation highlights once again the remarkable application profile of noble-metal-catalyzed skeletal rearrangements in general[9,15] and toward heterocycle syntheses in particular.[9,16] The pronounced migratory aptitude of the SEM acetal in **13** stands in striking contrast to the behavior of the symmetry-related pivaloyl group occupying an *ortho* position on the substrate's other benzene ring, which does not engage at all in such a O→C transfer and hence merely serves as a nonparticipating protecting group. Moreover, the compatibility of the iodide substituent is particularly noteworthy, and highlights the orthogonal nature of platinum catalysis to established redox-based transition-metal catalysts.[9] In synthetic terms, the intact iodide was not only instrumental for the successful completion of the synthesis of erypoegin H but also constitutes a valuable entry point into late-stage divergent modifications of the target, as required for future SAR studies.

Next, the benzylic OH group had to be unmasked. This step turned out to be more difficult than anticipated, with a host of fluoride and Lewis acid based reagents failing to induce effective cleavage of the trimethylsilylethyl ether in **14**. Gratifyingly, oxidative conditions (CAN, aq MeCN)[17,18] were found to deliver the corresponding aldehyde **15** in excellent yield and purity.

With this compound in hand, the stage was set for the introduction of the prenyl side chain[18] which was originally envisaged to be carried out by conventional cross-coupling methodology. However, despite considerable experimentation, the yields remained invariably low and the reactions were plagued by the formation of various side-products. Recourse to the advanced metalation technology developed by Knochel and co-workers provided a most effective solution to this problem.[19] Thus, in the presence of catalytic amounts of [Li(acac)] as a nucleophilic promoter of the exchange process, the reaction of **15** with $Zn(iPr)_2$ in NMP afforded a highly functionalized organozinc compound which could be cleanly alkylated with excess prenyl bromide in the presence of a catalytic amount of CuCN·2 LiCl. It is remarkable that neither the aldehyde function nor the three ester moieties in **15** interfere with this reaction to any noticeable extent,[19] as can be deduced from the 86% yield of **16**, which could be isolated on a gram scale. We have no doubt that this methodology is amenable to further scale-up and will allow a host of other substituents to be introduced onto this advanced synthetic intermediate at a later stage of the project. Treatment of **16** with $LiAlH_4$ reduced the aldehyde and removed the peripheral ester groups concurrently. The resulting crude product **17** was subjected to an intramolecular etherification under standard conditions to complete the tetracyclic framework of erypoegin H (**1**), which was obtained in a respectable 28% yield over the nine steps of the longest linear sequence. The spectroscopic data of the synthetic

samples were in excellent agreement with those reported in the literature (Table 1).[4]

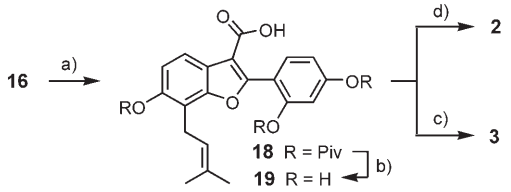
Cleavage of the pivaloyl groups under nonreducing conditions converted aldehyde **16** into the des-methyl analogue of erypoegin F **4**, another flavonoid from *E. poeppigiana* endowed with considerable antimicrobial activity.[4b] Furthermore, oxidation of **16**, deprotection of the ester moieties, and treatment of the resulting acid **19** with H_2SO_4/HOAc led to concomitant lactonization and addition of the phenolic OH group onto the adjacent prenyl side chain; sojagol (**3**) thus formed is a well known phytoalexin originally isolated from *Glycine max* (soybeans) and *Phaseolus aureus* (mung beans; Scheme 3).[20] Uncoupling of the two cyclization events was also possible by treatment of **19** with DCC, which led to the proposed structure of isosojagol (**2**).[21] However, the spectroscopic data of synthetic **2** clearly differ from those of the putative "isosojagol" but closely match the reported spectra of "phaseol", an isomeric coumestan for which structure **5** had been proposed.[22] Since the constitution of our synthetic sample is unambiguous, we must conclude that the original structure assignments of isosojagol and phaseol are *both* incorrect. While our study now shows that "phaseol" is definitely represented by structure **2** rather than by **5**, the actual constitution of "isosojagol" remains to be elucidated.

Table 1: Reference data set of compounds **1**–**3**.

1: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.1$ Hz, 1H), 7.04 (d, $J = 8.3$ Hz, 1H), 6.77 (d, $J = 8.3$ Hz, 1H), 6.45 (dd, $J = 8.1$, 2.4 Hz, 1H), 6.43 (d, $J = 2.3$ Hz, 1H), 5.54 (s, 2H), 5.39 (thept, $J = 7.3$, 1.3 Hz, 1H), 5.26 (brs, 1H), 5.01 (brs, 1H), 3.69 (d, $J = 7.3$ Hz, 2H), 1.89–1.90 (m, 3H), 1.78 ppm (d, $J = 1.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7$, 155.1, 154.5, 152.0, 147.0, 135.3, 121.2, 120.9, 119.2, 116.1, 112.6, 111.2, 110.2, 108.4, 106.2, 103.9, 65.7, 25.8, 23.1, 17.9 ppm; UV (MeOH/H_2O 4:1): $\lambda_{max} = 350$, 334, 242, 210, 204 nm; MS (EI): *m*/*z* (%): 322 (77) $[M]^+$, 266 (100), 237 (6), 152 (5); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{18}O_4$: 322.1205; found: 322.1207

2: ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 7.92$ (d, $J = 8.6$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.05 (d, $J = 8.3$ Hz, 1H), 7.02 (dd, $J = 8.6$, 2.3 Hz, 1H), 6.95 (d, $J = 2.2$ Hz, 1H), 5.43 (thept, $J = 7.4$, 1.4 Hz 1H), 3.70 (d, $J = 7.4$ Hz, 2H), 1.91–1.92 (m, 3H), 1.69 ppm (d, $J = 1.1$ Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 161.9$, 160.6, 158.5, 156.1, 156.0, 155.0, 132.6, 123.5, 122.5, 118.9, 116.6, 114.5, 114.4, 113.4, 106.1, 104.1, 103.9, 25.8, 23.4, 18.0 ppm; UV (MeOH): $\lambda_{max} = 346$, 304, 253, 209 nm; MS (EI): *m*/*z* (%): 337 (13), 336 (54) $[M]^+$, 281 (44), 280 (100), 252 (7); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{16}O_5$ + Na: 359.0890; found: 359.0894

3: ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 7.90$ (d, $J = 8.6$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.01 (dd, $J = 8.6$, 2.2 Hz, 1H), 6.95 (d, $J = 2.2$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 3.09 (t, $J = 6.8$ Hz, 2H), 1.96 (t, $J = 6.8$ Hz, 2H), 1.39 ppm (s, 6H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 162.0$, 160.6, 158.5, 156.1, 155.1, 154.2, 123.5, 119.4, 116.2, 116.2, 114.4, 107.3, 106.0, 104.1, 103.9, 75.6, 32.1, 26.8, 17.3 ppm. MS (EI): *m*/*z* (%): 337 (26), 336 (75) $[M]^+$, 319 (4), 280 (100), 252 (7); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{16}O_5$ + Na: 359.0890; found: 359.0887.



Scheme 3. a) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O, 2-methylbutene, 93%; b) KOMe, MeOH; c) H_2SO_4, HOAc, 52% (over two steps); d) DCC, DMAP, MeCN, 77% (over two steps). DCC = *N*,*N*′-dicyclohexylcarbodiimide.

Experimental Section

14: A Schlenk flask was charged with compound **13** (4.25 g, 5.66 mmol), 4-Å MS (1.77 g, powdered), and toluene (30 mL). After addition of $PtCl_2$ (150 mg, 0.56 mmol), the mixture was purged with CO through a canula for 7 min before it was vigorously stirred at 85 °C under an atmosphere of CO (1 atm) for 5.5 h. For work up, the mixture was filtered through a pad of silica, the filtrate was evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 10:1) to give benzofuran **14** as an off-white foam (3.56 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 8.3$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.09 (dd, $J = 8.4$, 2.3 Hz, 1H), 7.03 (d, $J = 2.3$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 4.53 (s, 2H), 3.51–3.55 (m, 2H), 1.45 (s, 9H), 1.38 (s, 9H), 1.17 (s, 9H), 0.92–0.96 (m, 2H), −0.01 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.4$ (2C), 176.2, 155.6, 152.8, 151.0, 150.3, 149.4, 132.3, 126.1, 120.5, 120.3, 118.9, 118.0, 117.0, 116.7, 71.9, 67.7, 62.7, 39.4, 39.2, 39.1, 27.4, 27.1 (2C), 18.3, −1.4 ppm; MS (EI): *m*/*z* (%): 750 (87) $[M]^+$, 722 (11), 666 (35), 638 (26), 633 (16), 553 (12), 548 (15), 464 (27), 380 (31), 85 (12), 73 (25), 57 (100); HRMS (ESI): *m*/*z*: calcd for $C_{35}H_{47}IO_8Si$ + Na: 773.1977; found: 773.1969; elemental analysis calcd (%) for $C_{35}H_{47}IO_8Si$: C 56.00, H 6.31; found: C 55.95, H 6.35.

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