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Towards the total synthesis of tashironin related *allo*-cedrane natural products: further exploitation of the oxidative dearomatization-IMDA-RCM triad based strategy

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ABSTRACT

Synthetic studies directed towards *allo*-cedrane based, tashironin sibling natural products, involving some deft functional group manipulations on a preformed tetracyclic scaffold, are delineated.

In 2001, research group led by Schmidt reported[1] the isolation and structure determination of three closely related polycyclic sesquiterpenoid natural products **1–3**, from North American species of *Illicium floridanum* (Fig. 1). Among these novel sesquiterpenoids, embodying hemiketal functionality on a caged tetracyclic scaffold, structure of **3** was elucidated by X-ray crystallography and those of **1** and **2** through detailed NMR studies on an inseparable mixture of the two. Thus, **1–3** are more embellished siblings of previously reported natural products tashironin[2] **4** and 11-debenzoyltashironin[3] **5** based on the biogenetically interesting *allo*-cedrane skeleton **7**, Figure 1. Among the tashironin-type natural products, 11-*O*-debenzoyltashironin **5** exhibits an interesting and unusual bioactivity profile and induces neurite outgrowth in foetal rat neuron at submicromolar concentration.[3] More recently,[4] tashironin **4** has been shown to exhibit anti-hepatitis B virus (HBV) activity at submicromolar concentrations by inhibiting the HBV surface antigen secretions. Interestingly, there has been no report on the biological activity of tashironin siblings **1–3**.[1]

The compact, caged, highly functionalized framework of *allo*-cedrane based tashironins and their bioactivity attributes have drawn attention from synthetic chemists.[5–7] As part of our ongoing efforts towards the total synthesis of tashironin sesquiterpenoids,[6b] we were also drawn to the more embellished **1–3** as they posed an enhanced synthetic challenge in terms of installation of dense and diverse oxygen functionalities through some subtle functional group manoeuvers on their complex caged scaffold. In addition, a foray towards **1–3** also provided an opportunity to

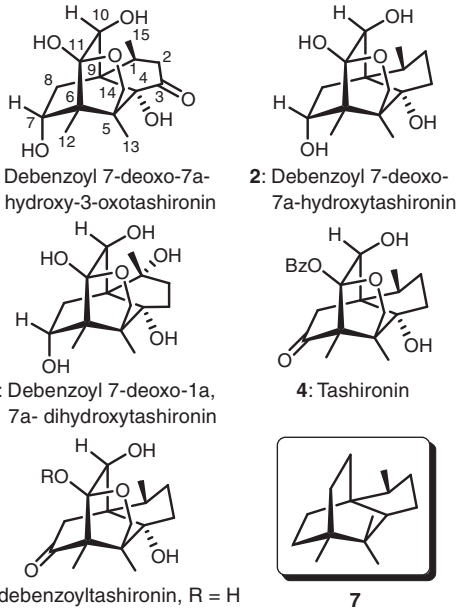

Figure 1. Natural products, isolated from *Illicium* species and related to tashironin.

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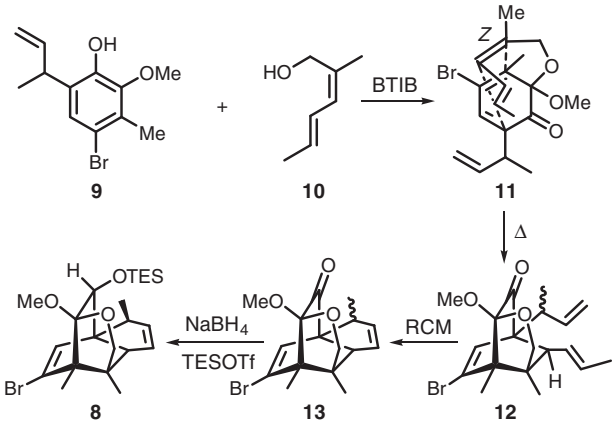
amplify the general applicability of our tandem oxidative dearomatization-IMDA-RCM based strategy towards tashironins and related natural products.[6] Herein, we describe our endeavours directed towards the synthesis of methyl ethers of natural products **1** and **2**, through controlled modulation of functional group alternations within the tetracyclic scaffold accessed through our three-step strategy.

In our recent studies leading to the synthesis of 11-debenzoyltashironin methyl ether **6** we have reported[6b] a short and efficient access to the tetracyclic intermediate **8** through hypervalent iodine mediated oxidative dearomatization of **9** in the presence of *E,Z*-dienol **10** to furnish **11**, followed by intramolecular Diels–Alder cycloaddition to **12** and RCM to deliver **13** as a mixture (1:1) of C1 diastereomers, Scheme 1. Stereoselective reduction of C10 carbonyl group in **13** and TES protection led smoothly to the isolation of **8** as the C1 β-methyl diastereomer.[6b] This tetracyclic intermediate **8** was to serve as the starting point in our quest for the natural products **1** and **2**.

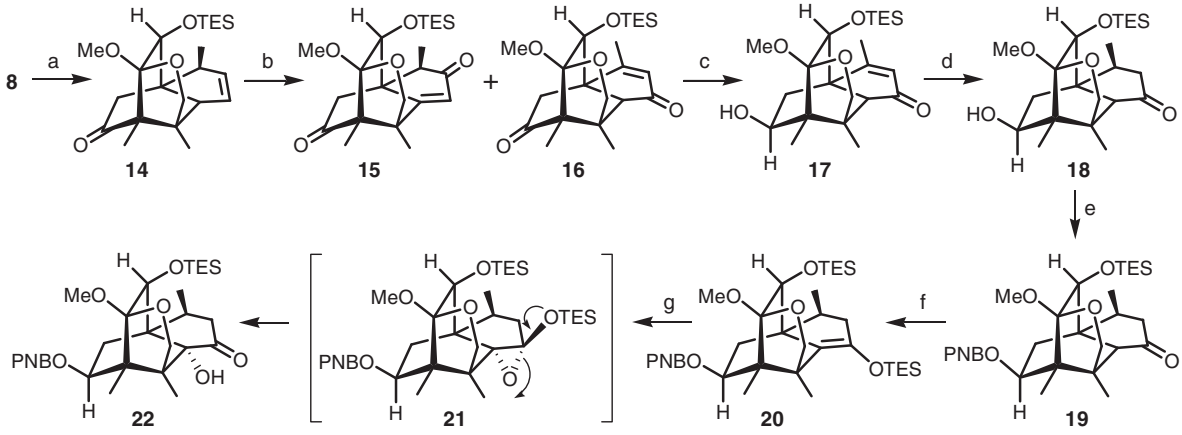
Evaluation of the projected functional group modifications in **8** enroute **1** and **2** pointed to the necessity of establishing a vinyl bromide–carbonyl equivalence in order to install the C7 carbonyl group. Towards this end, the vinyl bromide **8** was subjected to metal-halogen exchange with ^{t}BuLi in TMEDA and subsequently quenched with B(O^{i}Pr)$_3$ to generate a borate intermediate[8] which on concomitant treatment with alkaline H_2O_2 afforded the required ketone **14** along with the reductive debromination product of **8** in 2:1 ratio, Scheme 2.[9] Attempted allylic oxidation[10] in **14** with PDC/TBHP in benzene led to two regio-isomeric transposed enones **15** and **16** in 1:3 ratio with complete relocation of the original C2–C3 double bond. Although the minor enone **15** retained the requisite stereogenic centre at C1, it was compromised in the case of the major enone **16**[9], Scheme 2. Nonetheless, we chose to forge ahead with the major enone **16** with the intent to regenerate the C1 β-methyl stereochemistry at an appropriate stage. At this stage, it was considered crucial to chemo-differentiate the C3 and C7 carbonyl groups in **16** and its reduction with sodium borohydride was chemoselective as well as stereoselective (10:1) to furnish hydroxy-enone **17** although C7 stereochemistry was not clear at this juncture, Scheme 2. Unmindful of this stereochemical ambiguity, we proceeded further and hoped to resolve it along the way. Catalytic hydrogenation of hydroxyl-enone **17** on 10% Pd–C was again stereoselective and predictable in view of the folded topology of **17** and additional steric shielding on the 'top face' engendered by the C10 TES-protecting group to furnish **18** as a single diastereomer, Scheme 2. At this stage, it was considered prudent to protect C7 hydroxyl group in **18** as *p*-nitrobenzoate ester **19**. The key task now was to install the crucial tertiary α-hydroxy group at C4 stereoselectively and for this purpose we opted for the Rubottom oxidation[11] protocol. Consequently, **19** was exposed to TESOTf/Et$_3$N in Et$_2$O to afford the desired silyl-enol ether **20** regioselectively and in near quantitative yield. TES-enol ether **20** was treated with *m*CPBA to furnish the intermediate α-face selective epoxide **21** and subsequent treatment with TBAF afforded the desired 4α-hydroxy ketone **22**[9] in very good yield, Scheme 2.

Arrival at crystalline **22** brought mixed satisfaction as its single crystal X-ray structure determination[12] (Fig. 2) revealed that C1 methyl and C4 hydroxyl groups had the requisite stereochemistry and routine disengagement of the protective groups was expected to deliver our objective. However, the hydroxyl functionality at C7 (installed during the NaBH$_4$ reduction of **16**) had the opposite unrequired disposition with respect to that present in the natural product **1**. To circumvent the unexpected problem of C7 hydroxy group stereochemistry, which appeared to result from the steric shielding by the –OMe group and consequent attack of the hydride from the more accessible 'bottom face', we decided to change track and gambled on altering the reaction sequence followed in Scheme 3.

Consequently, enone double bond of **16** was reduced over 10% Pd–C under hydrogen atmosphere to furnish diketone **23** as a single diastereomer, Scheme 3. Treatment of **23** with TESOTf/Et$_3$N afforded the desired silyl-enol ether regioselectively and in quantitative yield. Oxidation of the resulting silyl-enol ether with *m*CPBA led to the intermediate epoxide which on desilylation with TBAF led to the desired 4α-hydroxy ketone **24** in excellent yield,



Scheme 1. BTIB: bis(trifluoroacetoxy)iodobenzene.



Scheme 2. Reagents and conditions: (a) (i) ^{t}BuLi, TMEDA, B(O^{i}Pr)$_3$, THF, −78 °C, 2 h; (ii) NaOH, H_2O_2, 65%; (b) PDC, TBHP (70% aqueous), Celite, benzene, rt, 5 h, 68% (**15**:**16** = 1:3); (c) NaBH$_4$, DCM/MeOH (1:3), −15 °C, 4.5 h, 84%; (d) 10% Pd/C, H_2 (1 atm.), EtOAc, rt, 3 h, 94%; (e) *p*-nitrobenzoyl chloride, Et$_3$N, DMAP, DCM, rt, 2 h, 89%; (f) TESOTf, Et$_3$N, Et$_2$O, rt, 2 h, 97%; (g) (i) *m*CPBA, DCM, −10 °C, 1 h; (ii) TBAF, DCM, rt, 2 h, 87% (over two steps).

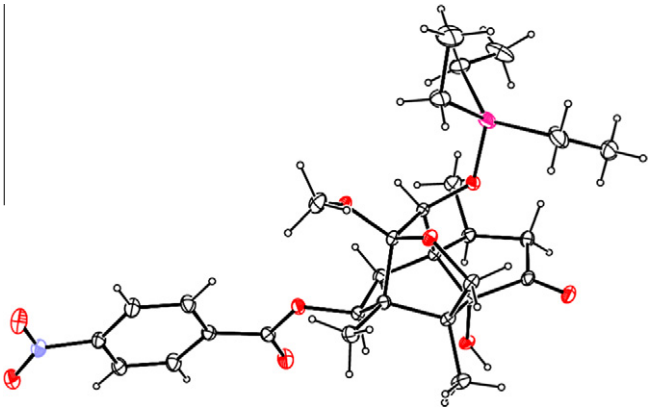
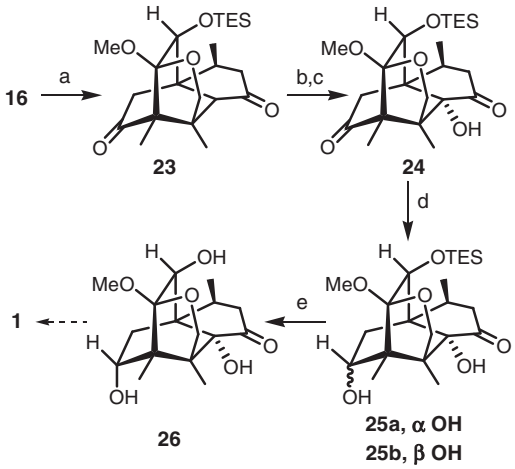


Figure 2. ORTEP diagram of the compound **22** with 30% ellipsoidal probability.

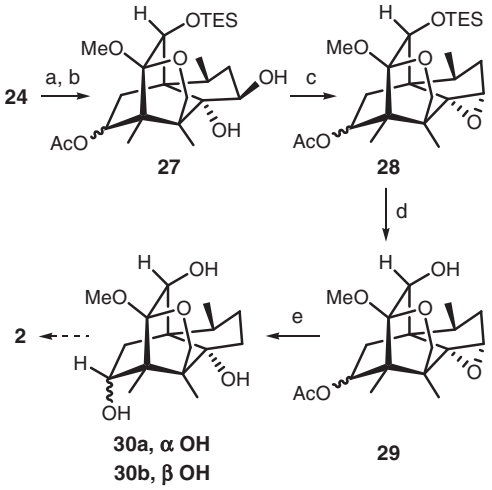


Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2 (1 atm.), EtOAc, rt, 3 h, 85%; (b) TESOTf, Et_3N, Et_2O, rt, 2 h, quant.; (c) (i) mCPBA, DCM, −10 °C, 1.5 h; (ii) TBAF, DCM, rt, 2 h, 96% (over two steps); (d) $NaBH_4$, MeOH, −10 °C, 6 h, 92%; (e) HF (40% aqueous), MeCN, rt, 6 h, 91%.

Scheme 3. Having installed the C4-hydroxyl group in an efficient manner, the stage was now set for the C7 carbonyl group reduction. Controlled and careful carbonyl reduction of **24** with $NaBH_4$ at low temperature was regio-selective and yielded an easily separable mixture of epimeric alcohols **25a** and **25b** in 2:1 ratio and in good yield. The gratifying alteration in the stereoselectivity during the reduction of **24** could be attributed to the long range stereoelectronic effect, the precise nature of which remains obscure.[13] After considerable efforts to optimize the conditions for the desilylation of C10-TES group, aqueous HF in acetonitrile[14] was found to offer best option for deprotection leading to the methyl ether **26**, Scheme 3.[9]

The final act in accomplishing the total synthesis of natural product **1** was the deprotection of the C11 methyl ether moiety. However, several efforts to accomplish this seemingly straightforward manoeuvre proved unsuccessful and we were content to settle for the synthesis of the methyl ether derivative **26** of the natural product **1**. As expected, the spectral data for **26** bore close resemblance to those of the natural product **1**, although the reported data for the latter had some contamination of **2**.[1]

We next turned our attention to the synthesis of natural product **2** and recognised that diketone **24** had the attributes to serve as an advanced precursor. Exhaustive DIBAL-H reduction of **24** furnished an inseparable mixture of diastereomeric triols in 3:1 ratio,



Scheme 4. Reagents and conditions: (a) DIBAL-H, DCM, −78 °C, 1 h; (b) Ac_2O, pyridine, DMAP, DCM, 0 °C, 2 h, 82% (over two steps); (c) MsCl, Et_3N, DMAP, DCM, 0 °C to rt, 3 h, 90%; (d) HF (40% aqueous), THF, rt, 5 h, 89%; (e) DIBAL-H, DCM, 0 °C to rt, 6 h, 85%.

Scheme 4. However, it was obvious that the C3 carbonyl reduction was stereoselective with hydride approaching from the less hindered 'bottom face', further assisted by the adjacent hydroxy group. Therefore, the diastereomeric mixture emanated from the non-stereoselective reduction of the C7 carbonyl group. The C7-hydroxy epimers were regioselectively protected as the acetate derivative **27**. The C3 hydroxy group was then activated as its mesylate (MsCl/Et_3N/DMAP)[15] which underwent in situ cyclization to provide the α-epoxide **28**. TES deprotection in **28** unravelled a free hydroxyl group at C10 in **29**. DIBAL-H reduction of the epoxide in **29** was smooth to deliver an easily separable epimeric mixture of alcohols **30a**[9] and **30b** after concomitant reduction of the acetate. As planned, **30a** was the methyl ether derivative of the natural product **2**. In view of the earlier encountered difficulty[6] in deprotecting the methyl ether moiety in this system, the present endeavour was terminated with the acquisition of **30a**, Scheme 4. Once again, the spectral characteristics of **30a** were reminiscent of natural product **2** and were in conformity with its putative formulation.

In summary, we have considerably amplified the scope of our oxidative dearomatization-IMDA-RCM triad based strategy for accessing tashironin sibling natural products by orchestrating a series of functional group manipulations on the *allo*-cedrane based tetracyclic framework.

Acknowledgements

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9. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds: **14** IR (neat) 2952, 2877, 1716, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70–5.72 (m, 1H), 5.59 (br s, 1H), 3.98 (d, J = 7.9 Hz, 1H), 3.95 (s, 1H), 3.54 (d, J = 7.9 Hz, 1H), 3.33 (s, 3H), 2.59–2.60 (m, 1H), 2.47 (br s, 1H), 2.28 (1/2ABq, J = 18.5 Hz, 1H), 2.17 (1/2ABq, J = 18.4 Hz, 1H), 1.24 (d, J = 7.4 Hz, 3H), 1.14 (s, 3H), 1.01 (s, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.57–0.69 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 139.2, 125.8, 108.7, 79.7, 70.9, 62.3, 60.9, 52.0, 50.7, 49.3, 47.3, 46.7, 21.8, 12.0, 10.2, 7.1 (3C), 5.3 (3C); HRMS(ES) m/z calcd for $C_{22}H_{36}O_4SiNa$ (M+Na): 415.2281; found: 415.2278; **22** mp 179.3–180.0 °C; IR (neat) 3473, 2926, 2877, 1726, 1530, 1122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1/2ABq, J = 8.7 Hz, 2H), 8.24 (1/2ABq, J = 8.4 Hz, 2H), 5.39 (dd, J = 5.7, 9.9 Hz, 1H), 4.10 (d, J = 9.3 Hz, 1H), 3.98 (s, 1H), 3.69 (d, J = 9.6 Hz, 1H), 3.58 (s, 3H), 2.36–2.57 (m, 3H), 2.25–2.33 (m, 1H), 2.03 (s, 1H), 1.39 (dd, J = 5.7, 13.5 Hz, 1H), 1.21 (s, 3H), 1.13 (d, J = 6.6 Hz, 3H), 1.09 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.66–0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 164.2, 150.6, 135.9 (2C), 130.7 (2C), 123.6, 108.2, 81.5, 81.2, 72.8, 70.3, 52.5, 50.9, 48.9, 46.3, 44.2, 35.2, 33.8, 14.5, 13.3, 12.3, 7.0 (3C), 5.2 (3C); HRMS(ES) m/z calcd for $C_{29}H_{41}NO_9SiNa$ (M+Na): 598.2448; found: 598.2477; **24** IR (neat) 3460, 2918, 2850, 1736, 1722, 1138 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (d, J = 9.6 Hz, 1H), 4.09 (s, 1H), 3.68 (d, J = 9.3 Hz, 1H), 3.39 (s, 3H), 2.45–2.62 (m, 3H), 2.31–2.44 (m, 1H), 2.10 (d, J = 18.6 Hz, 1H), 1.92 (s, 1H), 1.21 (d, J = 6.6 Hz, 3H), 1.12 (s, 6H), 0.97 (t, J = 7.5 Hz, 9H), 0.66–0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 211.1, 108.4, 80.8, 79.8, 71.4, 61.6, 52.4, 51.4, 49.8, 44.2, 41.6, 34.8, 15.4, 12.4, 10.3, 7.0 (3C), 5.1 (3C); HRMS(ES) m/z calcd for $C_{22}H_{36}O_6SiNa$ (M+Na): 447.2179; found: 447.2181; **26** IR (neat) 3401, 2925, 2876, 1738, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, J = 9.8 Hz, 1H), 3.73 (d, J = 3.1 Hz, 1H), 3.68–3.72 (m, 2H), 3.34 (s, 3H), 3.15 (d, J = 3.0 Hz, 1H), 2.73 (s, 1H), 3.59 (dd, J = 7.6, 16.8 Hz, 1H), 2.36–2.50 (m, 2H), 2.26 (d, J = 8.2 Hz, 1H), 1.98 (dd, J = 9.2, 15.0 Hz, 1H), 1.74 (dd, J = 1.2, 14.7 Hz, 1H), 1.31 (s, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 107.6, 81.7, 74.2, 72.2, 70.8, 51.1, 50.3, 48.8, 47.1, 44.7, 35.6, 34.9, 16.8, 13.1, 12.8; HRMS(ES) m/z calcd for $C_{16}H_{24}O_6Na$ (M+Na): 335.1471; found: 335.1471; **30a** IR (neat) 3465, 3416, 2927, 2853, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (d, J = 9.4 Hz, 1H), 3.75 (d, J = 9.5 Hz, 1H), 3.69 (br s, 1H), 3.60 (d, J = 4.9 Hz, 1H), 3.36 (s, 3H), 3.20 (d, J = 5.0 Hz, 1H), 2.44 (d, J = 5.1 Hz, 1H), 2.32 (s, 1H), 2.01–2.22 (m, 4H), 1.85 (dd, J = 9.4, 14.8 Hz, 1H), 1.65 (d, J = 15.1 Hz, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.14 (d, J = 10.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.3, 86.7, 74.6, 73.7, 71.4, 51.3 (2C), 50.3, 49.6, 39.2, 37.9, 32.8, 31.3, 16.5, 14.1, 13.7; HRMS(ES) m/z calcd for $C_{16}H_{26}O_5Na$ (M+Na): 321.1678; found: 321.1664.
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12. X-ray data on **22** was collected at 291 K on a Bruker Kappa APEX II diffractometer with graphite monochromated Mo Kα radiation (λ = 0.7107 Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 using SHELXL-97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-798242. Compound **22**: $C_{29}H_{41}NO_9Si$, MW = 575.72, crystal system: monoclinic, space group: $C2/c$, cell parameters: a = 31.4711(11) Å, b = 8.2373(3) Å, c = 22.6847(8) Å, β = 91.999(2)°, V = 5877.1(4) Å^3, Z = 8, ρ_{calcd} = 1.301 g cm^{-3}, $F(0\,0\,0)$ = 2464, μ = 0.134 mm^{-1}, number of l. s. parameters = 406, R_1 = 0.0655 for 3582 reflections with $I > 2\sigma(I)$ and 0.1048 for all 5427 data. wR_2 = 0.2018, GOF = 1.133 for all data.
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