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A total synthesis of 11-O-methyldebenzoyltashironin

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ABSTRACT

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Oxidative dearomatization Intramolecular Diels-Alder reaction Ring closing metathesis A concise total synthesis of 11-O-methyldebenzoyltashironin is reported in which oxidative dearomatization-IMDA-RCM triad constitutes the key ring forming steps, while an unorthodox DIBAL-H mediated stereo- and regioselective reductive epoxide openings and implementation of the vinyl bromide-carbonyl equivalency concept were pivotal to the success of this endeavor.

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Tetracyclic and densely oxygenated neurotrophic agent 11-0debenzoyltashironin 1,^{1a,b} isolated from the pericaps of North American species Illicium merrillianum exhibits impressive neurotrophic activity in cultured fetal rat cortical neurons at sub-micromolar concentration.^{1a} This neurotrophic activity has implications in the maintenance of cognitive functions and neuronal repair that are relevant to several neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's diseases, etc.² This uncommon but impressive biological activity profile and the intriguing structural intricacy of its tetracyclic framework, laced with oxygen functionalities and seven contiguous stereogenic centers, have stimulated interest in the total synthesis of 11-O-debenzoyltashironin 1 with the added intent of creating diversity around its bioactive scaffold.^{3,4} As a part of our ongoing interest in the synthesis of neurotrophically active natural products,⁵ we disclose here a concise total synthesis of 11-O-methyldebenzoyltashironin 2 wherein the tetracyclic core present in the natural product was assembled in just three steps from an appropriately crafted aromatic precursor.

As the target for a total synthesis endeavors, the natural product **1** presents quite a few significant challenges. Apart from its compact tetracyclic cage-like architecture, it also embodies tertiary α -hydroxyl and secondary hydroxy groups at C4 and C10, respectively, a β -methyl group at C1 and a carbonyl functionality at C7 position whose installation requires special attention. In order to conceptualize a viable roadmap toward **1**, we recognized the importance and centrality of a scalable and flexible strategy through which the tetracyclic core of the natural product could

be constructed in a very short sequence. A retreosynthetic perspective that would lead to the total synthesis of **1** is unveiled in Scheme 1 which identified **3** as an advanced precursor with its vinyl bromide moiety as the masked equivalent of the C7 carbonyl group and a strategically positioned hydroxyl group at C10 to direct the regio- and stereoselective openings of the epoxide ring to deliver the C4 tertiary hydroxy functionality. The access to the advanced intermediate **3** was envisaged through functional group amplification/adjustment in the precursor **4** whose tetracyclic core could be assembled from an embellished aromatic precursor **5** via



Scheme 1. Retrosynthetic analysis of 1.



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Scheme 2. Reagents and conditions: (a) PyHBr₃, DCM, 0 $^{\circ}$ C, 2 h, 90%; (b) K₂CO₃, crotyl bromide, acetone, reflux, 6 h, 92%; (c) PhNEt₂, 180 $^{\circ}$ C, 1 h, 67%.

a sequential orchestration of the oxidative dearomatization \rightarrow intramolecular Diels–Alder reaction (IMDA) \rightarrow ring closure metathesis (RCM) triad along the lines outlined earlier by us.⁴ Appropriately substituted aromatic building block **5** could be crafted from readily available aromatic starting materials through routine maneuvers. It may be pointed out that the bromine substituent in aromatic precursor **5** was positioned to eventuate into a vinylic bromide functionality that served as a latent equivalent of the C7 carbonyl group.

The initial task was to set-up the key IMDA reaction by accessing the aromatic precursor **5** and subjecting it to oxidative dearomatization in the presence of the partner diene. Regioselective mono-bromination of the known phenol⁶ **6** using pyridinium tribromide (PyHBr₃) furnished a *para*-bromo derivative which was transformed in to the aryl–crotyl ether **7** on treatment with crotyl bromide/K₂CO₃ in excellent yield. Claisen rearrangement in **7** in the presence of PhNEt₂ was smooth and delivered the desired precursor **5**, Scheme 2. Concurrently, the oxidative dearomatization partner (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol **8** was prepared from a commercially available crotonaldehyde in two steps adopting the Still–Gennari olefination protocol.^{4,7} The choice of diene **8** to set-up the contemplated IMDA reaction was important to ensure the regio- and steroselectivities and to obtain the requisite orientation of the two alkene arms for the following RCM reaction.

Oxidative dearomatization of penta-substituted aromatic compound 5 with *bis*(trifluoroacetoxy)iodobenzene (BTIB)⁸ in the presence of (2Z,4E)-2-methyl-2,4-hexadien-1-ol 8 led to the masked o-benzoquinone based pentaene 9, which could be isolated and spectroscopically recognized. As predicted, when the crude pentaene 9 was refluxed in toluene, a single tricyclic [4+2]-adduct 10 was obtained in a decent yield, through the preferred endotransition state (see 9). The exclusive participation of the Z-double bond of **8** in the IMDA reaction ensured that the two alkenyl side arms in **10** were syn-disposed and well poised for effecting the RCM reaction. Initial attempts toward RCM reaction on 10 using Grubbs' catalyst I proved problematic and deployment of Grubbs' catalyst II, though encouraging, was plagued by low yields. It was reasonable to surmise that the presence of the additional methyl substituents on the alkene arms of **10** may be primarily responsible for its refractoriness toward the RCM reaction. Consequently, a switch to the Hoveyda–Grubbs' second generation catalyst⁹ proved rewarding and under optimized conditions afforded tetracyclic 4 as an inseparable mixture (1:1) of diastereomers. In order to circumvent the problem of separation of the diastereomers **4** at this stage, the carbonyl group in **4** was first reduced with NaBH₄. Gratifyingly, the reduction of 4 was stereoselective and the anticipated epimeric alcohols **11a** (β -Me) and **11b** (α -Me) (ratio = 1:1) were amenable to chromatographic separation (SiO₂ gel), Scheme 3.¹⁰

The stereochemistry of the C10 hydroxyl group and C1 methyl group in **11a** was confirmed through X-ray crystal structure analysis (Fig. 1) and had the requisite attributes in the context of our objective.¹¹ Although both **11a** and **11b** were reckoned as



Scheme 3. Reagents and conditions: (a) BTIB, THF, rt, 5 h, 62%; (b) toluene, reflux, BHT, 20 h, 80%; (c) Hoveyda–Grubbs' catalyst-II (15 mol %), toluene, reflux, 48 h, 66%, 87% (borsm); (d) NaBH₄, DCM/MeOH (2:1), 0 °C, 8 h, 90%, (ratio = 1:1); (e) TESOTF, Et₃N, DCM, 0 °C, 2 h, 93%; (f) PDC, 70% aqueous TBHP, celite, benzene, rt, 5 h, 59% (**14:13** = 3:1); (g) Et₃BHLi, THF, 0 °C, 2 h, 81%; (h) SOCl₂, pyridine, 0 °C, 30 min, 91%; (i) mCPBA, DCM, 1.5 h, 0 °C, 97%; (j) 40% aqueous HF, THF, rt, 6 h, 73%; (k). DIBAL-H, DCM, 0 °C, 12 h, 87%.



Figure 1. ORTEP diagram of the compound 11a with 30% ellipsoidal probability.

serviceable for further evolution toward the target, we initially decided to forge ahead with the former. The C10 hydroxyl functionality in **11a** was protected as TES ether **12** with the intent that this bulky appendage will be required to play a critical stereodirecting role in the subsequent steps of our synthesis.

Allylic oxidation of **12** using PDC/TBHP¹² provided two regioisomeric α , β -unsaturated enones **13** and **14** in a 1:3 ratio, Scheme 3. Initially the major enone **14** remained reticent toward commonly used reducing agents but we could manage to circumvent the impasse by exposing the enone 14 to super hydride (Et₃BHLi) to furnish doubly reduced product 15 stereoselectively and in good vield. As planned, the bulky TES group had sterically shielded the 'top' face of enone 14 to direct the hydride delivery from the bottom face to eventuate in a β -methyl group at C1 and the β -hydroxyl group at C3 in 15. Brief exposure of 15 to thionyl chloride-pyridine milieu rendered the desired olefin 16 in a regioselective manner. The expedient arrival of 16 set the stage for the stereoselective epoxidation with mCPBA¹³ from the less hindered α -face to furnish the epoxide **3** in excellent yield. At this stage, the TES protection was jettisoned through exposure of the epoxide 3 to aqueous HF to furnish 17 and we now opted for an unorthodox reductive opening of the epoxide ring through 'top' face delivery of the hydride from DIBAL-H coordinated to the C10 hydroxyl group (see, Scheme 3). Indeed, 18 was realized from 17 quite smoothly and the structure of 18 was secured through X-ray crystal structure analysis (Fig. 2).¹¹

Inching toward the end game, the vinylic bromide moiety in the bicyclo[2.2.2] octane segment of **18**, strategically positioned as a latent carbonyl group, had to be unmasked. This was achieved through halogen-metal exchange with excess ¹BuLi in TMEDA and quench with $B(O^{i}Pr)_{3}$ to furnish a borate intermediate, ¹⁴ which was concomitantly treated with alkaline H_2O_2 to afford directly 11-*O*-methyldebenzoyltashironin **2** along with some undesired debrominated product, Scheme 4. Although we were conscious of the fact that the free C10 hydroxyl group in **18** would be detrimental



Figure 2. ORTEP diagram of the compound 18 with 30% ellipsoidal probability.



Scheme 4. Reagents and conditions: (a) (i) ^tBuLi, TMEDA, B(O^tPr)₃, THF, -78 °C, 2 h; (ii) NaOH, H₂O₂, 34%.

to the metal-halogen exchange reaction, yet the potential payoff in term of achieving concurrent internal protection (through exchange with access ^tBuLi present) motivated us to execute the transformation without recourse to protecting group maneuver. Arrival at **2** heralded our acquisition of the methyl ether of the natural product 11-O-debenzoyltashironin **1**, which can be regarded as the formal synthesis of the natural product as transformation of **2** to **1** has been indicated in the patent literature.^{3b}

In conclusion, we have delineated a short three step strategy to rapidly assemble the core tetracyclic scaffold present in bioactive tashironins through tandem oxidative dearomatization-IMDA-RCM sequence. A set of stereo- and regioselective transformations and functional group equivalency concept have been garnered to eventuate in a concise synthesis of 11-O-methyldebenzoyltashironin.

Acknowledgments

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- 10. All new compounds were fully characterized on the basis of IR, ¹H NMR, ¹³C NMR and HRMS spectral data. Spectral data of selected compounds: **11a** mp 126.4–127.3 °C; IR (neat) 3466, 2950, 2904, 1381, 1027 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.77 (s, 1H), 5.77–5.81 (m, 1H), 5.60–5.62 (m, 1H), 3.82 (s, 2H), 3.54 (dd, *J* = 1.2, 9.6 Hz, 1H), 3.44 (s, 3H), 2.83 (br s, 1H), 2.48 (d, *J* = 9.6 Hz, 1H), 2.46 (br s, 1H), 1.37 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 0.98 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 140.5, 138.2, 124.7, 122.8, 106.7, 74.5, 72.1, 62.1, 57.8, 56.3, 51.8, 44.1, 43.4, 20.4, 14.9, 12.6; HRMS(ES) *m/z* Calcd for C₁₆H₂₁BrO₃Na (M+Na): 363.0572. Found: 363.0554; **12** IR (neat) 2954, 2922, 1712.

1154 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.84 (s, 1H), 5.94 (d, J = 1.5 Hz, 1H), 4.25 (d, J = 8.7 Hz, 1H), 3.65-3.67 (m, 2H), 3.44 (s, 3H), 2.04 (d, J = 1.5 Hz, 3H), 2.02 (s, 1H), 1.34 (s, 3H), 1.11 (s, 3H), 0.91 (t, J = 7.8 Hz, 9H), 0.49-0.58 (m, 6H); $^{13}{\rm C}$ NMR (100 MHz, CDCl₃) δ 201.8, 165.8, 133.8, 132.2, 126.1, 106.3, 74.2, 70.0, 65.1, 58.5, 58.0 (2C), 42.7, 21.6, 15.9, 15.4, 6.8 (3C), 5.1 (3C); HRMS(ES) m/z Calcd for C₂₂H₃₃BrO₄SiNa (M+Na): 491.1229. Found: 491.1214; **14** IR (neat) 3425, 2951, 2877, 1451 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.48 (s, 1H), 5.11 (d, J = 7.5 Hz, 1H), 4.57 (d, J = 12.6 Hz, 1H), 4.24–4.33 (m, 1H), 3.77 (d, J = 1.5 Hz, 1H), 3.64 (d, J = 7.8 Hz, 1H), 3.38 (s, 3H), 2.53-2.64 (m, 1H), 1.78-1.92 (m, 1H), 1.65 (s, 1H), 1.41 (ddd, *J* = 1.2, 9.3, 14.1 Hz, 1H), 1.33 (s, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.94 (s, 3H), 0.66–0.75 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) & 140.0, 123.6, 107.7, 76.1, 71.7, 70.5, 58.7, 58.4, 54.3, 52.8, 46.9, 46.7, 37.9, 19.0, 15.1, 14.5, 6.8 (3C), 4.9 (3C); HRMS(ES) m/z Calcd for $C_{22}H_{37}BrO_4SiNa$ (M+Na): 495.1542. Found: 495.1557; **16** IR (neat) 2950, 2878, 1450, 1146 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.24 (s, 1H), 5.47 (s, 1H), 3.88 (s, 2H), 3.86 (s, 1H), 3.35 (s, 3H), 2.46 (ddd, J = 2.2, 8.1, 14.7 Hz, 1H), 2.28 (q, J = 7.7 Hz, 1H), 2.11–2.17 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.27 (s, 3H), 1.02 (s, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.57–0.70 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 138.3, 123.3, 121.3, 109.3, 77.9, 75.2, 60.9, 56.4, 51.9, 48.5, 41.9, 40.3, 16.2, 15.0, 13.8, 7.0 (3C), 5.2 (3C); HRMS(ES) m/z Calcd for C22H35BrO3SiNa (M+Na): 477.1386. Found: 477.1384; **3** IR (neat) 2953, 2878, 1456, 1141 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.30 (s, 1H), 3.79 (1/2ABq, J = 9.5 Hz, 1H), 3.78 (s, 1H), 3.73 (1/2ABq, J = 7.9 Hz, 1H), 3.44 (s, 1H), 3.41 (s, 3H), 2.04 (dd, J = 7.2, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.79 (s, 3H), 0.61–0.72 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 135.0, 124.7, 108.1, 76.3, 74.3 (2C), 59.3, 56.3, 53.8, 52.2, 46.4, 36.6, 34.3, 16.1, 13.6, 11.9, 7.1 (3C), 5.2 (3C); HRMS(ES) m/z Calcd for C22H35BrO4SiNa (M+Na) 493.1386. Found: 493.1399; 18 mp 132.8-133.2 °C; IR (KBr) 3481, 2926, 2853, 1093 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.39 (s, 1H), 3.87 (d, J = 9.2 Hz, 2H), 3.56 (d, J = 7.5 Hz, 1H), 3.35 (s, 3H), 3.14 (d, J = 7.5 Hz,

1H), 2.52–2.58 (m, 1H), 2.09–2.16 (m, 1H), 1.85–1.89 (m, 1H), 1.63–1.71 (m, 2H), 1.28 (s, 3H), 1.27 (d, J = 7.2 Hz, 3H), 0.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.4, 126.6, 106.5, 87.9, 73.2, 72.0, 61.4, 56.3, 52.9, 51.8, 36.4, 32.3, 31.2, 15.4, 14.7, 14.2; HRMS(ES) *m/z* Calcd for C₁₆H₂₃BrO₄Na (M+Na): 381.0677. Found: 381.0656; **2** IR (neat) 3493, 2924, 2852, 1712, 1018 cm⁻¹; ¹¹H NMR (400 MHz, CDCl₃) δ 3.99 (d, J = 9.2 Hz, 1H), 3.87 (d, J = 6.2 Hz, 1H), 3.38 (s, 3H), 3.33 (d, J = 6.3 Hz, 1H), 2.53 (d, J = 18.7 Hz, 1H), 2.22–2.30 (m, 2H), 2.07–2.11 (m, 1H), 1.96 (d, J = 18.7 Hz, 1H), 1.66–1.75 (m, 1H), 1.51–1.57 (m, 1H), 1.22 (d, J = 7.1 Hz, 3H), 1.09 (s, 3H), 0.97 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 211.2, 108.3, 85.3, 74.7, 74.0, 60.9, 54.5, 52.4, 51.8, 43.6, 38.4, 34.3, 30.9, 14.2, 13.7, 9.3; HRMS(ES) *m/z* Calcd for C₁₆H₂₄O₅Na (M+Na): 319.1521. Found: 319.1534.

- 11. X-ray data was collected at 291 K on a Bruker Kappa APEX II diffractometer with graphite monochromated MoK_x radiation ($\lambda = 0.710$ 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. Crystal data of **11a**: C₁₆H₂₁BrO₃, *M* = 341.23, monoclinic, *P*2₁/c, a = 9.9357(17), b = 7.3053(12), c = 20.603(4) Å, $\beta = 97.355(3)^\circ$, V = 1483.1(5) Å³, Z = 4, $\rho_{calcd} = 1.528$ g/cm³, 10.672 reflections measured, 2747 unique ($R_{int} = 0.024$), R1 = 0.0314 and wR2 = 0.0766 for 2227 observed reflections, CCDC no. 796424. Crystal data of **18**: C₁₆H₂₃BrO₄, M = 359.24, monoclinic, $P2_1/n$, a = 7.613(2), b = 19.155(6), c = 10.867(3) Å, $\beta = 93.295(6)^\circ$, V = 1581.9(8) Å³, Z = 4, $\rho_{calcd} = 2.612$ g/cm³, 11.641 reflections measured, 2920 unique ($R_{int} = 0.053$), R1 = 0.0801 and wR2 = 0.2111 for 1769 observed reflections, CCDC no. 796423.
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