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Towards the total synthesis of neurotrophically active tashironins: rapid construction of the tetracyclic core through a tandem oxidative dearomatization–IMDA reaction–RCM protocol

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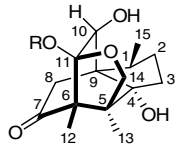
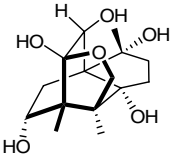
Abstract—An exceptionally short (three step) strategy involving tandem oxidative dearomatization, intramolecular Diels–Alder (IMDA) reaction and RCM has been devised to generate the complete carbon framework present in tashironin-type sesquiterpenoid natural products.

In 2001 research groups led by Fukuyama[1] and Schmidt,[2] almost concurrently, reported the isolation and structure determination of several novel polycyclic sesquiterpenoid natural products **1**–**5** from *Illicium merrillianum* and *Illicium floridanum*, respectively. In structural terms, these complex natural products with dense and diverse oxygen functionalities are close siblings of tashironin **1**[3] and are based on the biogenetically interesting *allo*-cedrane[4] framework **6**. These tashironin-type sesquiterpenoids embody basic cage-like oxa-tetracyclic architecture **7**. Although functional embellishments and stereochemical intricacies present in **1**–**5** hold considerable appeal for total synthesis endeavours, it was the unusual observation[1] that 11-*O*-debenzoyltashironin **2** induces neurite outgrowth in fetal rat neurons at concentrations as low as 0.1 μM, which captured the attention of synthetic chemists attention towards this class of compounds, particularly **2**. Indeed, very recently, the first total synthesis of *O*-debenzoyltashironin **2** was accomplished by the group of Danishefsky.[5]

As part of our ongoing interest[6] in the total synthesis of several sesquiterpenoid skeleta that surface *en route* the complex and intricate biogenetic pathway from farnesyl pyrophosphate to *seco*-prezizaenes,[3,7] we were drawn towards the synthesis of **2** and its siblings. Initial focus in the early endeavours aimed at **1**,**2** was to devise a flexible strategy for the rapid acquisition of the tetracyclic core **7**, embodying the entire C_{15} sesquiterpene framework with adequate functional group distribution, to target the natural products and also to generate diversity around this novel scaffold to explore its therapeutic potential.



1 R = Bz, Tashironin
2 R = H, 11-*O*-Debenzoyltashironin



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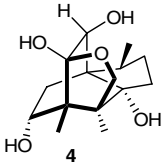

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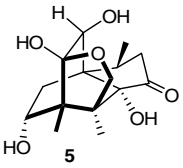

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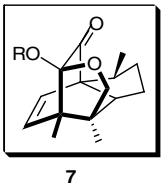

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While searching for potential routes to the core tetracyclic structure **7**, which could be conveniently adapted and amplified towards natural products **1**,**2**, it occurred

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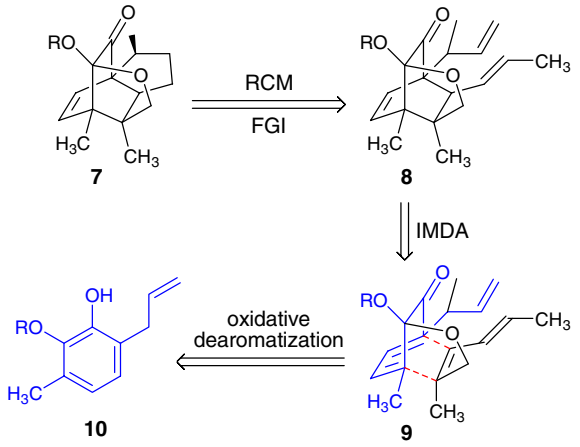
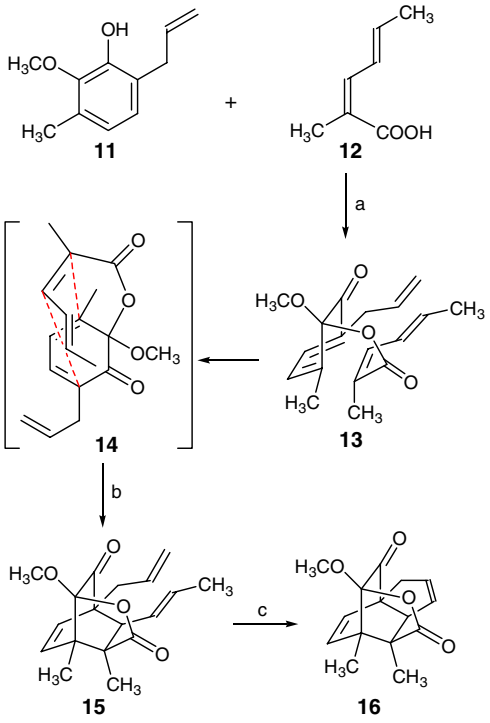


Scheme 1. Retrosynthetic analysis of the tetracyclic core **7** from the aromatic precursor **10**.

to us that a short access to the required tetracyclic system could be devised by coupling an intramolecular Diels–Alder reaction (IMDA) with RCM cyclization (**9**→**8**→**7**) in a tandem fashion as depicted retrosynthetically in Scheme 1. It was anticipated that the masked *o*-benzoquinone **9**[8] required for the desired IMDA reaction could be generated through the oxidative dearomatization of an aromatic precursor such as **10**. Appropriately substituted aromatic compound **10** could be crafted from readily available benzenoid derivatives through routine manoeuvers.

As a validation of the overall feasibility of the retrosynthesis indicated in Scheme 1, it was considered expedient to initially set up the IMDA reaction through dearomatization of readily assembled 1,2,3,4-tetrasubstituted precursor **11** under modified Wessely oxidation conditions.[9,10] Accordingly, *o*-allylphenol derivative **11** was oxidized with lead tetraacetate in the presence of (2*Z*,4*E*)-2-methyl-2,4-hexadienoic acid **12**[11] to furnish stable *o*-benzoquinone derivative **13** in 66% isolated yield after chromatographic separation.[12] Several intramolecular [4+2]-cycloaddition pathways are possible in the dearomatized pentaene **13**, but in practice, a single tricyclic product **15** was obtained in refluxing toluene, in a fair yield, through the preferred *endo*-transition state **14**, Scheme 2. The desired regio- and stereochemical outcome and the mode of this intramolecular cycloaddition is a consequence of the *Z*-geometry present in the tethered double bond acting as the dienenophile. The two alkenyl side arms in **15** were now well positioned for effecting the RCM reaction. Indeed, exposure of **15** to Grubbs' I catalyst furnished the tetracyclic lactone **16**[12] in excellent yield, Scheme 2. Functionally well endowed tetracyclic lactone **16** embodies many of the key features of the natural products **1**,**2**, in particular, the correct disposition of the C11, C6 and C5 quaternary centers.

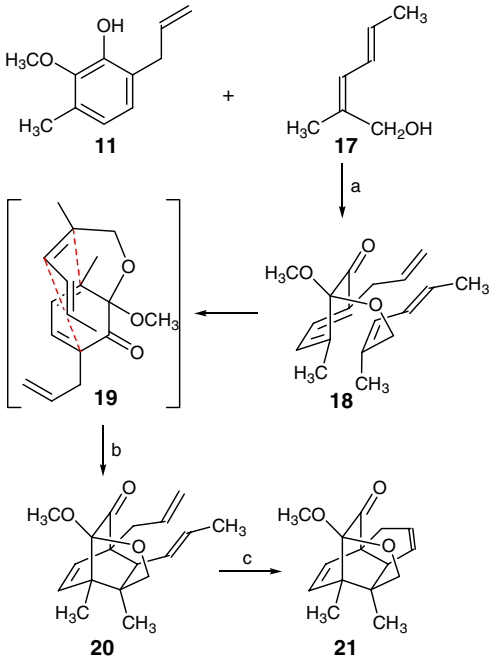
The success of the oxidative dearomatization–IMDA reaction under Wessely conditions[10] in **11**, Scheme 2, encouraged us to implement the retrosynthetic protocol shown in Scheme 1 involving an appropriate mixed



Scheme 2. Reagents and conditions: (a) $Pb(OAc)_4$, DCM, rt, 30 min, 66%; (b) toluene, reflux, 3.5 h, 74%; (c) Grubbs' I catalyst (10 mol %), benzene, reflux, 4 h, 91%.

o-benzoquinone monoketal intermediate.[8] Exposure of a mixture of tetra- substituted aromatic **11**[9] and (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol **17**[11] to the oxidant bis(trifluoroacetoxy) iodobenzene (BTIB) led to pentaene **18**, which was isolated in a modest 40% yield along with a considerable amount of the corresponding *p*-benzoquinone derived from phenol **11**, Scheme 3. Thermal activation of **18** in refluxing toluene resulted in a regio and stereoselective intramolecular Diels–Alder reaction via the transition state **19** to furnish the tricyclic compound **20**,[12] Scheme 3. Tricycle **20** was now set for the RCM reaction. Thus, tetracycle **21** was readily realized from **20** in the presence of Grubbs' I catalyst. The structure of **21** was fully secured through X-ray crystal structure determination (Fig. 1).[13]

While the arrival at tetracycle **21** in just three steps from the aromatic precursor **11** was a satisfying outcome, the placement of the C1 methyl group in the five-membered ring had still to be negotiated to complete access to the tashironin framework. Towards this end, appropriate aromatic precursor **22** was prepared[14] and its oxidative dearomatization with BTIB in the presence of *Z*,*E*-dienol **17**[11] was undertaken to furnish pentaene **23** as a mixture (1:1.2) of inseparable diastereomers, Scheme 4. The diastereomeric mixture **23** was subjected to thermal activation to induce the IMDA reaction along the lines observed above in the case of **18**. As was expected, in this case, a mixture of tricyclic diastereomers **24** was realized through stereoselective cycloaddition. RCM reaction on **24** proved problematic and a mixture of tetracyclic diastereomers **25**, **26** was obtained only in poor



Scheme 3. Reagents and conditions: (a) $PhI(OCOCF_3)_2$, THF, rt, 5 h, 40%; (b) toluene, reflux, 20 h, 76%; (c) Grubbs' I catalyst (10 mol %), benzene, reflux, 8 h, 86%.

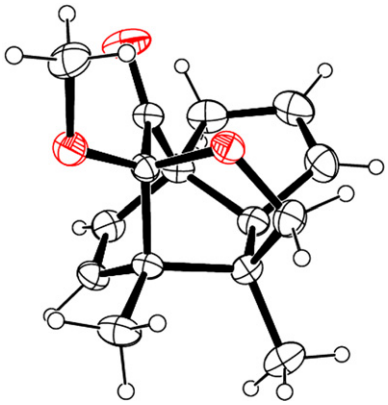
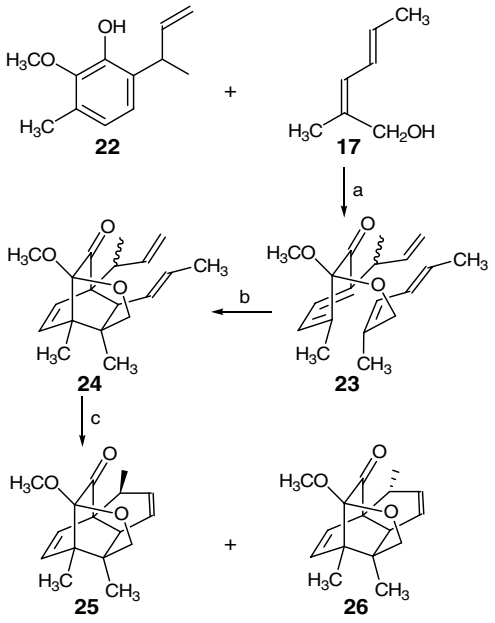


Figure 1. ORTEP diagram of compound **21** with 50% ellipsoidal probability.

yield, perhaps a reflection of the prevailing stereochemical constraints for the RCM process. Several variations in catalyst (Grubbs' I and II), use of additives (titanium isopropoxide, etc.) and change in solvent and temperature did not lead to significant improvement in yields and efforts in this direction are still continuing. Yet, it is gratifying to note that the complete tetracyclic framework of the C_{15}-tashironins could be put in place in just three steps from aromatic precursor **22** and *Z*,*E*-dienol partner **17**, Scheme 4.

In summary, the functionally embellished and stereochemically defined C_{15} tetracyclic core present in tashironin-type bioactive natural products has been accessed in just three steps from an appropriately crafted aromatic precursor employing oxidative dearomatization, an IMDA reaction and RCM as the three



Scheme 4. Reagents and conditions: (a) $PhI(OCOCF_3)_2$, THF, rt, 5 h, 42%; (b) toluene, reflux, 20 h, 73%; (c) Grubbs' II catalyst (20 mol %), benzene, reflux, 25%.

sequentially orchestrated steps. The model studies outlined here should pave the way for the total synthesis of this family of natural products and given the brevity and generality of this approach, it should also make available many analogues. Efforts in this direction are in progress and will be disclosed in due course.

Acknowledgements

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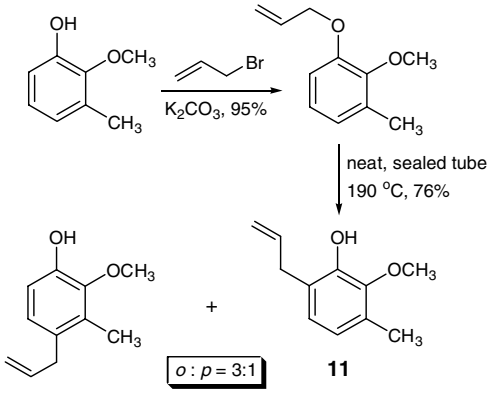
856–866; (c) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1430; (d) Hsu, P.-O.; Peddinti, R. K.; Chittimala, S. K.; Liao, C. C. *J. Org. Chem.* **2005**, *70*, 9156–9167.

9. Tetrasubstituted aromatic precursor **11** was readily prepared as follows:



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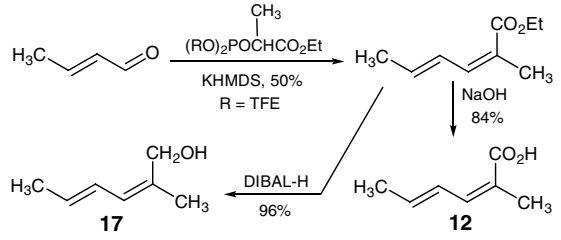
11. (2*Z*,4*E*)-2-methyl-2,4-hexadienoic acid **12** and (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol **17** were conveniently prepared as shown below:



12. 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*: Compound **13**. IR (neat) 2917, 1707, 1678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.07 (m, 1H), 6.66 (d, $J = 6.3$ Hz, 1H), 6.46 (d, $J = 11.4$ Hz, 1H), 6.08 (dd, $J = 1.8$, $J = 6.6$ Hz, 1H), 6.02–5.92 (m, 1H), 5.89–5.80 (m, 1H), 5.14–5.07 (m, 2H), 3.42 (s, 3H), 3.15 (dd, $J = 6.6$, $J = 16.5$ Hz, 1H), 3.02 (dd, $J = 5.7$, $J = 16.2$ Hz, 1H), 2.02 (s, 3H), 1.86 (s, 3H), 1.81 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 165.7, 144.4, 143.1, 138.0, 136.7, 134.9, 133.6, 128.9, 121.9, 121.8, 116.9, 95.2, 50.9, 32.5, 20.4, 18.5, 16.9; HRMS(ES) *m*/*z* calcd for $C_{18}H_{22}O_4Na$ ($M+Na^+$): 325.1416; found: 325.1432. Compound **15**. IR (neat) 2977, 1794, 1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, $J = 8.1$ Hz, 1H), 5.88 (d, $J = 8.4$ Hz, 1H), 5.78–5.65 (m, 1H), 5.63–5.52 (m, 1H), 5.15–5.09 (m, 2H), 4.88 (ddd, $J = 1.5$, $J = 11.1$, $J = 12.3$ Hz, 1H) 3.83 (s, 3H), 2.45 (dd, $J = 6.9$, $J = 14.4$ Hz, 1H) 2.17 (dd, $J = 7.2$, $J = 14.1$ Hz, 1H), 1.97 (d, $J = 11.1$ Hz, 1H), 1.70 (dd, $J = 1.8$, $J = 6.6$ Hz, 3H), 1.22 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 174.9, 133.6, 133.0, 132.6, 132.5, 123.7, 119.2, 108.3, 58.0, 55.7, 54.7, 54.3, 52.2, 32.8, 17.9, 16.3, 13.9; HRMS(ES) *m*/*z* calcd for $C_{18}H_{23}O_4$ ($M+H^+$): 303.1596; found: 303.1588. Compound **16**. Mp 107.0–107.8 °C; IR (neat) 2955, 1782, 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (d, $J = 8.1$ Hz, 1H), 5.96–5.92 (m, 1H), 5.88 (d, $J = 8.1$ Hz, 1H), 5.74–5.72 (m, 1H), 3.83 (s, 3H), 3.15 (td, $J = 1.8$ Hz, $J = 3.3$ Hz, 1H), 2.67–2.65 (m, 1H), 2.17 (d, $J = 15.6$ Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 175.5, 135.2, 134.7, 133.6, 126.4, 98.6, 63.3, 61.7, 55.9, 53.3, 49.6, 31.3, 18.3, 13.5; HRMS(ES) *m*/*z* calcd for $C_{15}H_{17}O_4$ ($M+H^+$): 261.1127; found: 261.1130. Compound **20**. IR (neat) 2946, 1736, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, $J = 8.1$ Hz, 1H), 5.85–5.71 (m, 2H), 5.54–5.42 (m, 1H), 5.15–5.07 (m, 3H), 3.79 (1/2ABq, $J = 8.7$ Hz, 1H), 3.69 (1/2ABq, $J = 9.0$ Hz, 1H), 3.63 (s, 3H), 2.42 (dd, $J = 7.2$, $J = 14.7$ Hz, 1H), 2.15 (dd, $J = 7.2$, $J = 14.7$ Hz, 1H), 1.79 (d, $J = 10.5$ Hz, 1H), 1.72 (dd, $J = 1.5$, $J = 7.2$ Hz, 3H), 1.22 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 134.2, 133.6, 132.2, 130.1, 126.9, 118.4, 101.5, 71.7, 54.4, 54.2, 52.4, 51.3, 48.9, 32.9, 18.1, 18.0, 13.7; HRMS(ES) *m*/*z* calcd for $C_{18}H_{24}O_3Na$ ($M+Na^+$): 311.1623; found: 311.1621. Compound **21**. Mp 104.7–105.1 °C; IR (neat) 3057, 2944, 1727 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, $J = 7.8$ Hz, 1H), 5.93–5.89 (m, 1H), 5.77 (d, $J = 8.4$ Hz, 1H), 5.69–5.67 (m, 1H), 3.85 (1/2ABq, $J = 8.4$ Hz, 1H), 3.77 (1/2ABq, $J = 8.4$ Hz, 1H), 3.65 (s, 3H), 3.17 (dd, $J = 3.0$, $J = 15.3$ Hz, 1H), 2.55 (s, 1H), 2.17 (d, $J = 15.6$ Hz, 1H), 1.23 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 135.5, 134.3, 132.6, 127.0, 100.9, 71.9, 62.7, 59.3, 54.4, 52.6, 43.3, 31.6, 20.7, 13.1; HRMS(ES) *m*/*z* calcd for $C_{15}H_{18}O_3Na$ ($M+Na^+$): 269.1154; found: 269.1154.
13. X-ray data were collected at 291 K on a SMART CCD–BRUKER diffractometer with graphite monochromated Mo K_α radiation ($\lambda = 0.7107$ Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 using SHELXL-97. Compound **21**: $C_{15}H_{18}O_3$, MW = 246.29, crystal system: monoclinic, space group: $P2_1/n$, cell parameters: $a = 6.5131$ (8) Å, $b = 27.854$ (3) Å, $c = 7.1359$ (9) Å, $\beta = 102.856(2)°$, $V = 1262.1(3)$ Å^3, $Z = 4$, $\rho_{calc} = 1.296$ g cm^{-3}, $F(000) = 528$, $\mu = 0.089$ mm^{-1}, number of l.s. parameters = 166, $R_1 = 0.0451$ for 1572 reflections with $I > 2\sigma(I)$ and 0.0660 for all 2086 data. $wR_2 = 0.1056$, GOF = 1.044 for all data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-658170.
14. Aromatic precursor **22** was accessed as follows: