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En route to the total synthesis of tashironin: on the exercise of stereochemical control by a methyl group in mediating remote cyclization reactions

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Abstract—The synthesis of the [2.2.2]-bicyclic core (**23**) of the neurotrophic factor 11-*O*-debenzoyltashironin (**1**) has been achieved by an oxidative dearomatization-transannular Diels–Alder cascade. We have shown that the reaction sequence is also valuable for the efficient construction of related, complex [2.2.2]-bicyclic compounds (vide infra).

Neurotrophic factors, or neurotrophins, are agents that can prevent neuronal death (neurotrophism) or promote axonal growth (neurotropism). To date, all widely studied neurotrophins (cf. NGF, BDNF, GDNF, NT4/5, NT6) are naturally occurring polypeptides or proteins.[1–3] Given their potential to treat neurodegenerative disorders, it is not surprising that neurotrophic factors have been the focus of considerable interdisciplinary research since the discovery of the first neurotrophin, NGF, by Montalcini and Hamburger.[2] Indeed, peptidyl neurotrophic factors have been extensively evaluated in animal models for their ability to treat neurodegenerative disease. However, due to unfavorable drug delivery and pharmacokinetic characteristics, in vivo evaluation of these neurotrophins requires direct microinjection into the brain.[3,4] Clearly, drug availability problems associated with these polypeptidic structures are a serious impediment to their development in prospective human settings.

It is from this vantage point that our laboratory has been seeking to explore the potential of small-molecule agents that might, themselves, exhibit neurotrophic activity. At this very early stage of the inquiry, we do not yet discriminate as to the mechanism of action nor do we yet insist on a validated molecular target. In keeping with earlier patterns, we prefer to focus on agents derived from natural sources. Among naturally derived prospects, we tend to favor compounds of novel architecture that invite provocative proposals for their synthesis. Indeed, through the medium of total synthesis, we have begun to develop a collection of small-molecule neurotrophically-active agents, including tricycloillicinone, merrilactone A, and jiadifenin.[5] The repertoire of evaluatable samples is further augmented by molecular modifications arising from the total synthesis efforts.

In 1995, Fukayama et al. reported the isolation and structural characterization of the neurotrophically inactive sesquiterpenoid tashironin (**2**) from the wood of *illicium tashiroi*.[6] More recently, Fukuyama and coworkers reported on the isolation and structure elucidation of 11-*O*-debenzoyltashironin (**1**), which promotes neurite growth at concentrations as low as 0.1 μmol.[7] In debenzoyltashironin, we recognized a molecular target with both a promising neurotrophic profile and an interesting structural framework that would challenge our laboratory from a synthetic standpoint. We set out to accomplish a free-standing synthetic route that could provide an alternative to the complexities of obtaining either **1** or **2** from natural sources. Equally important, diverted total synthesis could provide the means to explore broader questions of chemical space in the tashironin file (Fig. 1).

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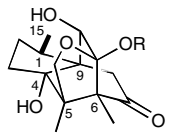
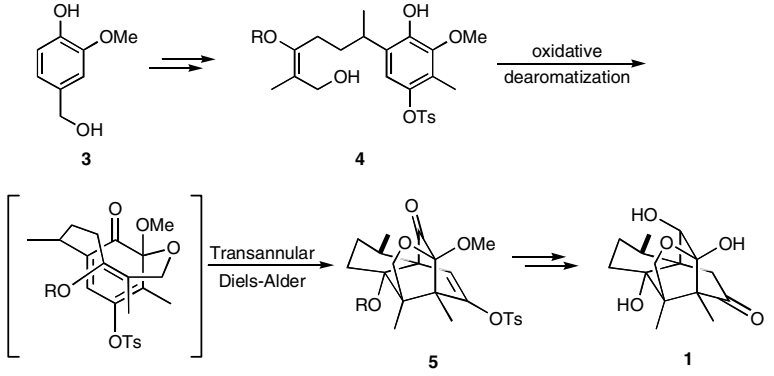


R = H: Debenzoyltashironin (**1**)
R = Bz: Tashironin (**2**)

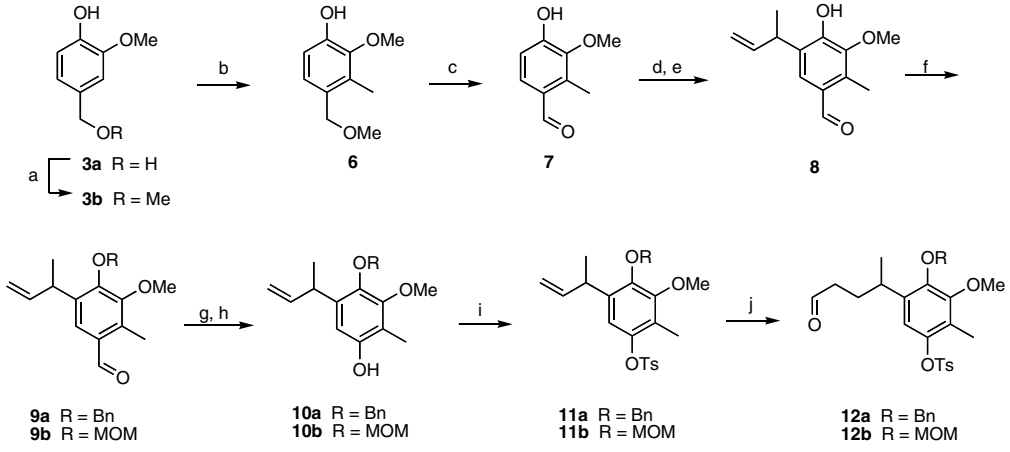
Figure 1. Structure of debenzoyltashironin **1** and tashironin **2**.

In our initial approach to constructing the structural backbone of debenzoyltashironin, we hoped to employ a tandem oxidative dearomatization-transannular Diels–Alder reaction to rapidly generate the highly substituted tetracyclic core (**5**) from a relatively simple precursor (**4**) (Scheme 1). According to our design, the key substrate (**4**) might be prepared in relatively short order from a suitably protected aromatic precursor (**3**). We anticipated that, under suitable reaction conditions, **4** might undergo intramolecular oxidative dearomatization, following the protocol of Pelter et al. and Tamura et al.,[8] to give rise to an intermediate cyclized species that would be configured to undergo a transannular Diels–Alder reaction to afford **5**. It seemed that progression from **5** to **1** could be accomplished. We were well aware that the success of this strategy would be predicated on the ability of the methyl stereocenter in the tandem precursor **4** to exert diastereofacial control in the oxidative dearomatization step.

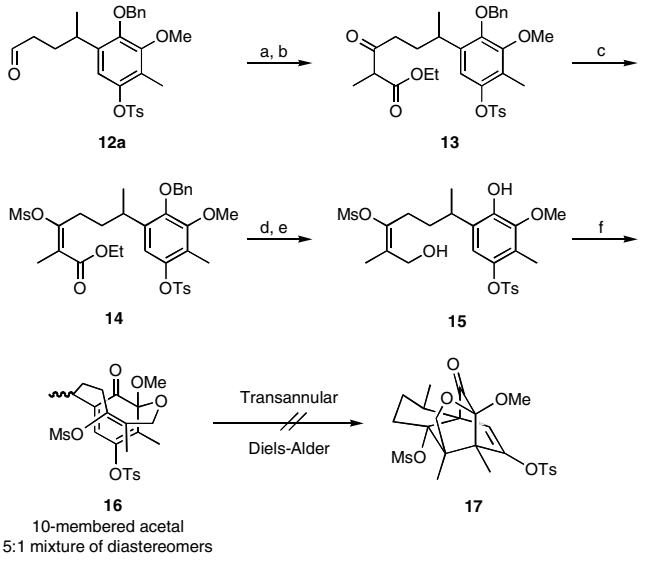
Our synthesis commenced with commercially available vanillyl alcohol (**3a**). Compound **3a** was treated with catalytic amounts of tosyl acid in methanol to afford **3b**, presumably, via a *p*-quinone methide intermediate (Scheme 2). The aromatic methyl group was then installed regiospecifically at the more hindered site through directed lithiation followed by methylation to afford **6**. A subsequent DDQ-mediated oxidation gave rise to 2-methylvanillin (**7**) in 44% overall yield from **3a**. Crotylation of the phenolic hydroxyl group, followed by a Claisen rearrangement produced phenol **8**. For greater flexibility in later transformations, the phenol was protected either as a benzyl ether (**9a**) or as a MOM ether (**9b**). Baeyer–Villiger oxidation of these compounds followed by hydrolysis afforded phenols **10a** and **10b** in 60% and 89% overall yields, respectively,



Scheme 1. Synthetic strategy.



Scheme 2. Synthesis of aldehydes **12a** and **12b**. Reagents and conditions: (a) MeOH, *p*-TSA, rt, 100%; (b) BuLi, THF, −15 to 0 °C, then −10 °C, MeI; (c) DDQ, CH_2Cl_2/H_2O 19:1, rt, 44% for two steps; (d) crotyl bromide, K_2CO_3, acetone, reflux; (e) neat, 185 °C, 81% for two steps; (f) MOMCl, DIEA, CH_2Cl_2, rt, 98% or BnBr, K_2CO_3, acetone, reflux, 93%; (g) *m*-CPBA, CH_2Cl_2, 0 °C; (h) Et_3N, CH_2Cl_2/MeOH 1:1, rt, 61% (**10a**) and 96% (**10b**) over two steps; (i) TsCl, Et_3N, CH_2Cl_2, rt, 88% (**11a**) and 91% (**11b**); (j) $Rh(CO)_2(acac)$, Billig ligand, CO/H_2 1:1, toluene, 60 °C, 90% (**12a**) and 82% (**12b**).



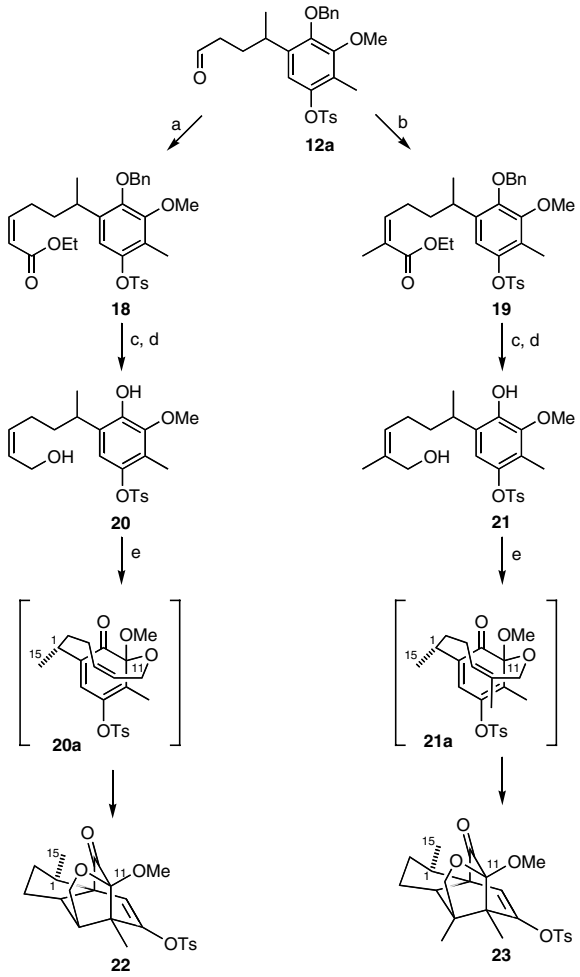
Scheme 3. Probing the key step. Reagents and conditions: (a) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, rt, 87%; (b) MeI, K_2CO_3, acetone, reflux, 93%; (c) MsCl, Et_3N, CH_2Cl_2, rt, 48%; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) 5% Pd/C, H_2EtOAc, rt, 66% for two steps; (f) PIDA, toluene/MeCN, rt, 60%.

from **8**. The resultant phenolic hydroxyl group in each compound was then tosylated to produce **11a** and **11b** in the yields shown. These compounds were hydroformylated with $Rh(CO)_2$(acac) and the Billig bis-organophosphite ligand according to Buchwald's protocol, to give exclusively the desired linear aldehydes **12a** and **12b** in 90% and 82% yields, respectively.[9]

At this juncture, we were prepared to test the feasibility of our key transformation. Toward this end, subjection of aldehyde **12a** to Roskamp conditions followed by methylation of the resulting β-ketoester gave rise to **13** (Scheme 3).[10] Treatment of **13** with mesyl chloride led to the formation of the desired (*E*)-tetrasubstituted olefin[11] **14** in modest yield. Finally, reduction of the ethyl ester with DIBAL-H, followed by benzyl deprotection gave the key substrate, **15**.

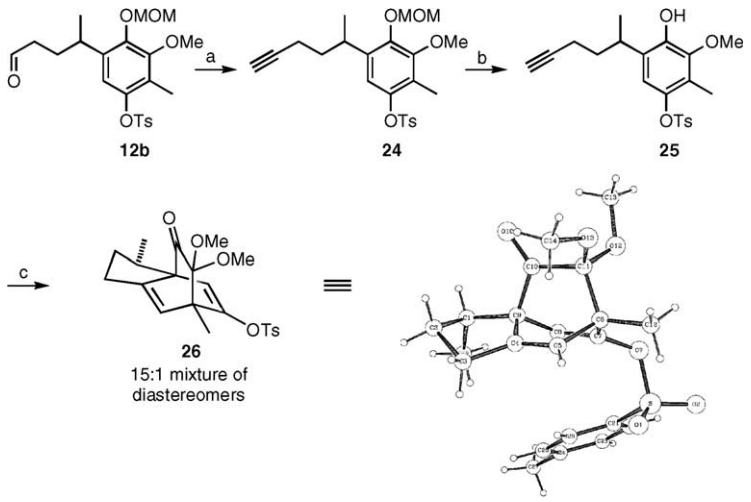
In the event, treatment of **15** with phenyliodine(III) diacetate (PIDA, $PhI(OAc)_2$) in a toluene/acetonitrile solvent system gave rise cleanly[12] to a new product, **16**,[13] which was quite unstable. As shown in Scheme 3, compound **16** failed to undergo the expected transannular Diels–Alder reaction (see target structure **17**) under several sets of conditions. The surprising lability of **16** limited our options for permuting reaction conditions to accomplish transannular Diels–Alder reaction.

We postulated that the stereoelectronic complexity coupled with the high steric demand required of the tetrasubstituted diene in reacting with a tetrasubstituted dienophile might be responsible for the resistance of **16** to undergo transannular Diels–Alder reaction. To probe this hypothesis, we sought to examine the behavior of less complicated putative Diels–Alder substrates. Thus, aldehyde **12a** was subjected to Still–Gennari olefination conditions with two different phosphonates (Scheme 4).[14] Disubstituted olefin **18** and trisubstituted olefin **19** were obtained in 52% yield and 68% yield, both as 10:1-mixtures of (*Z*)/(*E*)-geometric isomers. Cleavage of the corresponding benzyl protecting group followed by DIBAL-H reduction of the ester functionalities proceeded smoothly to provide the key substrates **20** and **21** in 87% and 69% yield, respectively.



Scheme 4. Successful examples of the oxidative dearomatization/TADA sequence. Reagents and conditions: (a) phosphonate, KHMDS, 18-crown-6, THF, −78 °C, 52%; (b) methyl phosphonate, KHMDS, 18-crown-6, THF, −78 °C, 68%; (c) BBr_3, CH_2Cl_2, −78 °C; (d) DIBAL-H, CH_2Cl_2, −78 °C, 87% (**20**) and 69% (**21**) over two steps; (e) PIDA, toluene, rt, 66% (**22**) and 60% (**23**).

In the event, treatment of phenol **20** with PIDA in toluene over several hours at room temperature resulted in the formation of the desired transannular Diels–Alder adduct **22** in 66% yield as a single diastereomer, presumably via the corresponding 10-membered acetal. Similarly, when phenol **21**, containing a trisubstituted double bond, was subjected to identical conditions, the transannular Diels–Alder adduct **23** was formed in a stereoselective fashion in 60% yield. NMR analysis (NOE) of compound **23** revealed the stereochemistry at C-1, with the C-15 methyl group residing in the undesired α position. In other words, this C-15 methyl had orchestrated the sense of the oxidative cyclization



Scheme 5. Synthesis of acetal **26**. Reagents and conditions: (a) Bestmann reagent, K_2CO_3, MeOH, rt, 65%; (b) HCl, MeOH, rt, 90%; (c) PIDA, MeOH, rt, then toluene, reflux, 85%.

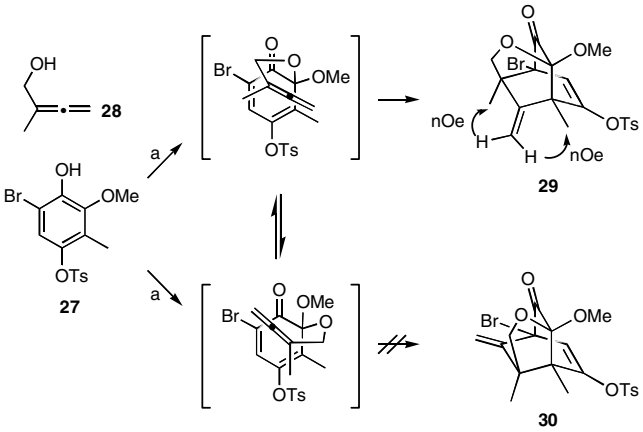
reactions of **20** and **21** so as to produce **20a** and **21a**. These intermediates must, per force, produce the observed transannular Diels–Alder products.

Having shown that both the di- and trisubstituted olefins do indeed undergo stereospecific oxidative dearomatization followed by transannular Diels–Alder, in contrast to the tetrasubstituted system in **16**, it seemed prudent to reduce the complexity of the key sequence: instead of constructing all four rings of tashironin in a single transformation, we imagined building three of the four rings by the oxidative dearomatization-transannular Diels–Alder cascade and then closing the fourth ring in subsequent transformations. Following this logic, the [2.2.2] bicyclic ring system could be formed concomitantly either with the fused cyclopentane ring or with the five-membered acetal. We have explored each approach in turn.

In the first approach, aldehyde **12b** was converted to terminal alkyne **24** in 65% yield using the Bestmann reagent (Scheme 5).[15] Phenol **25** was revealed in 90% yield after HCl-mediated removal of the MOM group. Exposure of phenol **25** to PIDA in MeOH at room temperature presumably led to the formation of the corresponding masked *o*-quinone, which underwent the desired transannular Diels–Alder reaction upon heating to afford **26** diastereoselectively in 85% yield (ds >95%).

Happily, we were able to obtain single crystals of **26**. X-ray analysis led to a decisive structural verification, revealing the relative configuration of the two quarternary stereocenters C-6/C-9 and the tertiary stereocenter C-1 as shown in Scheme 5.[16] The completion of the synthesis of debenzoyltashironin through this route would require the installation of functional handles in the Diels–Alder precursor to allow for the inversion of the stereochemistry at C-1 as well as for the closing of the five-membered acetal.

In an alternate approach, we sought to install the five-membered acetal in conjunction with the [2.2.2] bicyclic ring system through an intermolecular trapping of an allenyl alcohol by oxidative dearomatization and a subsequent Diels–Alder reaction with the internal olefin of the allenol. This proposed IMDA cycloaddition raised obvious issues of regioselectivity. Although we were confident that the internal olefin of the allene would react preferentially due to the geometry of the transition state, predictions as to whether the reaction would give the desired five-membered acetal Diels–Alder adduct (**30**) or the six-membered acetal ('twisted') product (**29**) were less obvious (Scheme 6). In practice, phenol **27** was constructed in nine steps from the commercially available vanillyl alcohol **3a** in 20% overall yield. Following treatment of **27** with PIDA in the presence of 5 equiv of allenyl alcohol **28**,[17] the undesired 'twisted' Diels–Alder adduct **29** was obtained (as shown by NOE studies) (Scheme 6). Although this interesting outcome disqualified this route as an approach toward tashironin, it has led to studies in our laboratory that are still in progress to determine the source of the preference for the 'twisted' cycloaddition.



Scheme 6. 'Twisted' Diels–Alder product **29**. Reagents and conditions: (a) allenyl alcohol **28**, PIDA, toluene, rt, 69%.

In summary, we have reported herein the highly concise synthesis of the tetracyclic ring system that forms the core of 11-*O*-debenzoyltashironin. The synthesis was achieved by a Pelter–Tamura oxidation resulting in the trapping of a tethered allylic alcohol, followed by a transannular Diels–Alder reaction. We have also shown that this reaction sequence is viable for the efficient construction of related, rather complex [2.2.2]-bicyclic compounds. Studies as to the application of these findings to enable the total synthesis of the tashironins are well in progress.

Acknowledgements

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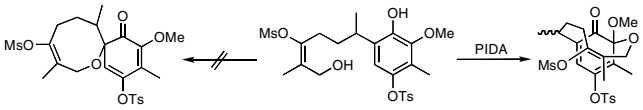
11. Olefin geometry determined by NOE studies of reduced product.
12. We note that formation of spiro ether *i* by *ipso* spirocyclization is apparently not at all competitive with the *meta* pathway leading from **15** to **16**. Such an *ipso* pathway is inherent in the Becker–Adler reaction and analogs thereof. Evidently, the proclivity for attack at the electron-rich methoxy-bearing carbon is dominant in the PIDA-mediated cyclization.



i **15** **16**

13. Of course, in reality, for a particular antipode, the methyl group defines the absolute configuration of the resultant cage-like latticework in structure **16**. For convenience sake, we portray the intermediate by permuting the relative stereochemistry of the methyl bearing carbon.
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16. Crystallographic data (excluding structural data) for compound **26** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as Deposition No CCDC 230898.
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