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Multiple chirality transfers in the enantioselective synthesis of 11-*O*-debenzoyltashironin. Chiroptical analysis of the key cascade

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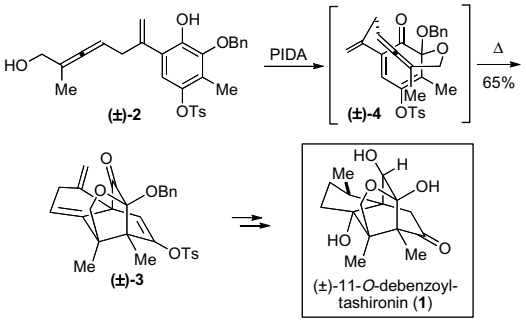
ABSTRACT

The mechanism of the cascade oxidative dearomatization–transannular Diels–Alder was investigated in the context of an asymmetric route to (−)-11-*O*-debenzoyltashironin. Although the oxidative dearomatization provides two acetal intermediates, the transannular Diels–Alder proceeds spontaneously from only one of the acetal isomers. Access to enantioenriched tetracyclic adduct was gained through the use of optically active allene.

In our ongoing efforts devoted to the total synthesis and evaluation of small natural products with neurotrophic activity,[1,2] we recently described the total synthesis of racemic (±)-11-*O*-debenzoyltashironin **1** (Scheme 1).[3] Compound **1** was isolated from the Eastern Asian *Illicium merrillianum* and its structure was elucidated by Fukuyama in 1995. (−)-11-*O*-Debenzoyltashironin has been shown to induce neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1 μM.[4] Additionally, we were fascinated by the structural architecture of the natural product, which incorporates a tetracyclic, highly oxygenated and densely functionalized core structure with five contiguous stereogenic centers. A highly concise route[3] was developed in our laboratories to gain rapid access to the core tetracyclic framework, **3**. The IMDA cycloadduct **3** not only possesses the necessary functionality for advancement to the target molecule, but also provides convenient sites for further structural modifications to probe the resultant neurotrophic activity. After extensive investigations,[5,6] a strategy toward the synthesis of **1** was developed. It employed an intramolecular Tamura–Pelter oxidative dearomatization of the simple allenic phenol **2**. This step was followed by a microwave-assisted transannular Diels–Alder reaction to rapidly generate the complex tetracyclic compound **3**.[7–10] The latter was advanced to racemic **1** as described previously.



Scheme 1. Route to (±)-11-*O*-debenzoyltashironin (**1**).

In designing a second generation, enantiodirected synthesis of **1**, we considered the possibility of stereospecifically preparing the enantioenriched antipodes of **2**, which would undergo Tamura–Pelter oxidation to provide enantioenriched **4**. Subsequent transannular Diels–Alder cyclization of **4** would yield correspondingly enantiomerically enriched **3**. Globally, the axial chirality information of the enantioenriched allene **2** would have been relayed to the tetracyclic adduct **3**. Moreover, the chirality in the allene **2** would have been induced from an sp^3 center (through S_N2' nucleophilic methylation of a mesylate), whose chirality (vide infra) dated back to the asymmetric reduction of a ketone. Since the study was conducted in an enantioenriched context, it allowed for differentiation between mechanistic alternatives which would not be distinguishable in the racemic series. The surprising results thus uncovered are described below.

The first objective was the synthesis of optically active **2**. One of the most commonly employed methods by which to gain access to enantiomerically enriched allenes is by subjecting enantioenriched propargylic substrates to nucleophilic methylation conditions with organocopper reagents, as pioneered by Rona and Crabbé.[11,12] The enantioenriched propargylic alcohol can be reached through asymmetric reduction of the corresponding ynone. Subsequent activation of the alcohol then sets the stage for a copper-mediated stereospecific S_N2' displacement reaction of the leaving group to produce enantioenriched allene.[13]

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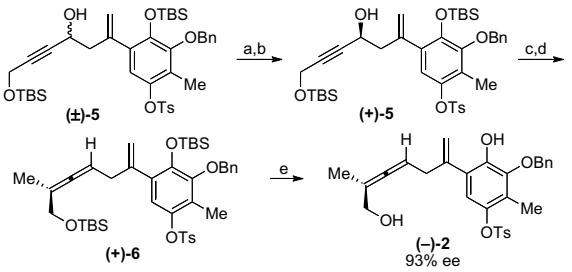
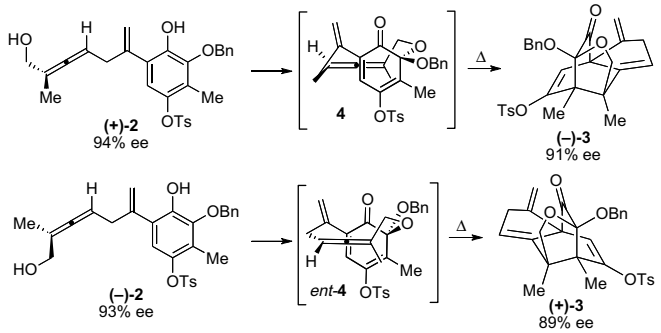
Racemic propargylic alcohol **5**, obtained in nine steps from commercially available 2-methylresorcinol, was oxidized to the ketone by treatment with Dess–Martin periodinane. Alpine Borane emerged from a screening survey as the most selective reducing agent, providing **5** in good yield (73%) and with high enantioexcess (93%).[14] Enantioenriched (+)-**5** was converted to the corresponding mesylate, which was then subjected to S_N2' reaction with the higher order Lipshutz cyanocuprate, $Me_2Cu(CN)Li_2$, in THF at −78 °C. This transformation provided allene (+)-**6** in 78% overall yield from (+)-**5**. Deprotection of both TBS groups yielded (−)-**2** in 81% yield and 93% ee. As hoped, the organocuprate reaction had proceeded with high stereospecificity. An analogous sequence was followed for the preparation of the enantiomeric allene, (+)-**2**. The absolute configuration of the allene **6** was independently corroborated via the Lowe–Brewster rules[15] (Scheme 2).

With (−)-**2** in hand, we were now prepared to investigate the key Tamura–Pelter oxidation–transannular Diels–Alder cyclization cascade sequence. As outlined in Scheme 3, a solution of PIDA was added to diol (−)-**2** in toluene at 0 °C. After an hour, the solution was heated in a sealed tube at 135 °C for 20 min. The desired adduct (+)-**3** was formed as a single product, in 65% yield and 89% ee. The same sequence was repeated in the enantiomeric series, and chiral HPLC analysis of the products confirmed the stereospecificity of the transformations.

Careful monitoring of the reaction progress by ^1H NMR led to the observation that, shortly after addition of the oxidizing agent, the reaction mixture is composed of a ca. 0.7:1 mixture of two compounds, which we initially believed to be the pre-Diels–Alder acetal intermediate **4** and the Diels–Alder adduct **3**. Remarkably at that time, this ratio did not change even when the reaction mixture was left to stir at ambient temperature for two days. Upon heating the reaction at reflux (90 °C, overnight), complete conversion to **3** was observed, though the isolated yield was only 40%.



Scheme 2. Synthesis of (−)-**2**. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2; (b) (*S*)-Alpine Borane, −78 °C, 6 h; then rt, 120 h, 73% over two steps yield, 93% ee; (c) MsCl, Et_3N, CH_2Cl_2; (d) $Me_2Cu(CN)Li_2$, THF, −78 °C, 78% over two steps; (e) TBAF, AcOH, 81% yield, 93% ee.



Scheme 3. Stereoselective Tamura–Pelter oxidation–transannular Diels–Alder cascade. Reagents and conditions: PIDA (1 equiv), toluene 0 °C, 1 h; then 135 °C, 20 min. 65% yield [(+)-**3**]; 63% yield [(−)-**3**].

Seemingly then, significant levels of IMDA reaction had occurred at room temperature. We wondered as to why microwave or heating in a sealed tube was necessary to complete transformation to **3** since it had already formed at room temperature.[3]

Closer consideration of these seemingly strange findings obliged us to question a key hypothesis, that is, that the chirality transfer of the acetal-forming reaction would be unidirectional, leading to a single product, **4**. Thus, the observations described above could be rationalized if the chirality transfer of the Tamura–Pelter reaction were non-selective, leading to stereoisomeric acetals. One of these acetals (**4**) is not observed because it undergoes spontaneous IMDA reaction, leading to **3.** The other Tamura–Pelter acetal stereoisomer persists until it is thermolyzed, thereby also producing **3**. We hoped to isolate the precursor to the non-spontaneous Diels–Alder cyclization, which we now presumed to be the stable acetal intermediate, **7**. In the event, allene (+)-**2** was treated with PIDA and, upon workup, we isolated IMDA product (−)-**3** (25%) as well as the presumed acetal (27%). In fact, full spectral characterization and X-ray crystallographic analysis revealed that the isolated compound was indeed structure **7** in which the acetal bond had formed on the face of the aromatic ring (Fig. 1) opposite to that involved with the formation of **4**.

Thus, as we had not expected at the outset, the Tamura–Pelter oxidation of **2** may in fact occur from either face of the aromatic system, providing stereoisomeric intermediate acetals, **4** and **7**. In acetal **4**, the diene and allene orbitals are ideally positioned to spontaneously undergo the transannular intramolecular Diels–Alder reaction, yielding tetracyclic adduct **3.** By contrast, in intermediate **7**, the orbitals are not aligned for cyclization, and this acetal per se is not a productive intermediate in the cascade.

Although acetal **7** is unable to undergo the transannular Diels–Alder reaction, upon thermolysis, it too is transformed to **3**, presumably via the labile **4** which does suffer spontaneous cyclization. Two alternative modes for the conversion of **7**→**4** come to mind. As outlined in Scheme 4, epimerization of the acetal in **7** would again yield the productive **4**. Upon Diels–Alder cyclization, tetracyclic adduct (−)-**3** would be produced. Alternatively, if the allene linkage of **7** were to epimerize under thermolysis, acetal *ent*-**4** would be produced. Spontaneous Diels–Alder reaction would yield *ent*-**3** [(+)-**3**].

In the event, when allene (+)-**2** was treated with PIDA for 1 h at 0 °C, we observed formation of acetal (+)-**7** (27%) and Diels–Alder cycloadduct (−)-**3** (25%, 93% ee) (Scheme 5). Compound (+)-**7** was isolated, and upon heating (135 °C, sealed tube, 15 min), the acetal was converted to the Diels–Alder adduct (−)-**3**. It may thus be concluded that **7** is converted to the Diels–Alder viable acetal **4** via epimerization of the acetal center (see Scheme 4).

With the newly gained insight as to the subtleties of the cascade reaction came the opportunity to achieve a significant improvement in the synthesis of **1** at the operational level. Rehabilitation of unproductive acetal **7** in the synthesis had involved equilibration at the acetal center, thereby allowing it to progress to **4** en route to **3.**

In the hopes of improving the yield and simplicity of the overall transformation leading to **3**, we wondered whether equilibration at the acetal center might be facilitated by acidic catalysis. In the event, it was found that with the use of a more acidic hypervalent iodine reagent, such as PIFA, we were able to obtain the desired Diels–Alder adduct **3** from **7** at ambient temperatures in high yield and without erosion of enantiomeric excess. Thus, as shown in Scheme 6, slow addition of 1.1 equiv of PIFA (in CH_2Cl_2) to a toluene solution of diol (+)-**2** in the dark afforded tetracyclic (−)-**3** in 76% yield, with complete retention of enantiomeric excess (93% ee). Apparently, the acetal linkage can be stereoequilibrated more rapidly in the more acidic PIFA medium, thus providing an enantioconserved pathway to **3** without the need for thermolysis.

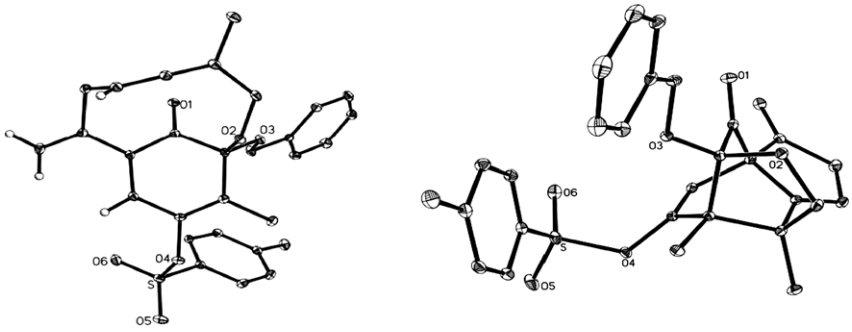
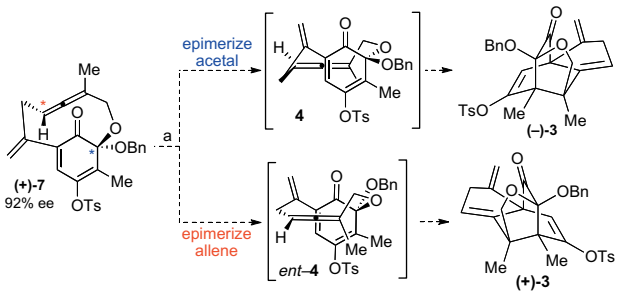
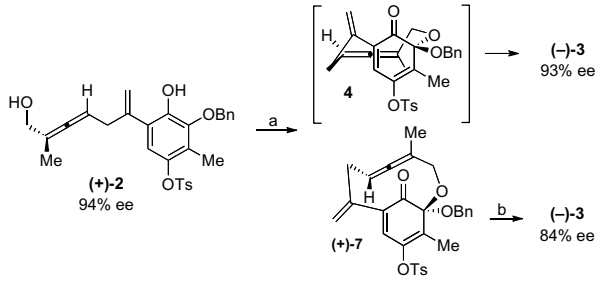


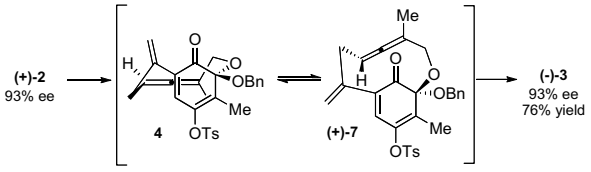
Figure 1. Intermediate **7** (left) and Diels–Alder adduct **3** (right).



Scheme 4. Possible modes of epimerization for acetal **7**.



Scheme 5. Reagents and conditions: (a) PIDA (1 equiv), 0 °C, 1 h, (−)-**3**, 25%, 93% ee and (+)-**7**, 27%; (b) 135 °C, sealed tube, (−)-**3**, 84% ee.



Scheme 6. Reagent and conditions: PIFA (1.1 equiv), CH_2Cl_2 rt, 1 h.

In summary, the chemistry presented above describes an instructive sequence of chirality transfers which was orchestrated en route to enantioenriched tashironin intermediates (+)- and (−)-**3**. A particularly novel pathway in the cascade which creates these intermediates has been identified and exploited for significant mechanism-based improvement of the synthesis of tashironin. Further experiments in this area are ongoing and will be described in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.139.

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