The First Stereoselective Total Synthesis of the Immunosuppressive Decalin Derivative Monascusic Acid B[1]

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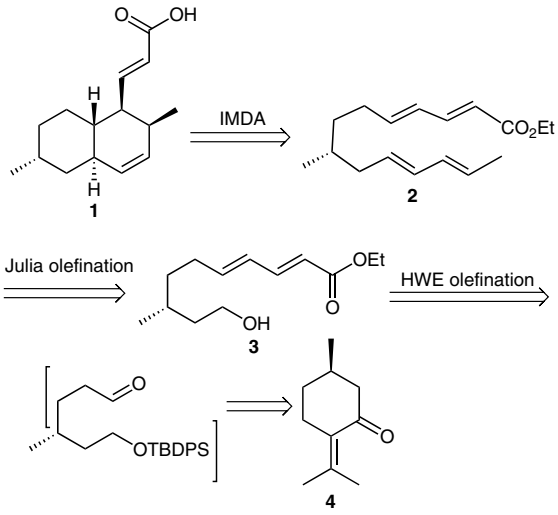
Abstract: The first stereoselective total synthesis of the immunosuppressive decalin derivative monascusic acid B has been accomplished from (*R*)-(+)-pulegone involving Horner–Wadsworth–Emmons and Julia–Kocienski olefination reactions and Lewis acid catalyzed intramolecular Diels–Alder cyclization.

Key words: monascusic acid B, total synthesis, (*R*)-(+)-pulegone, Horner–Wadsworth–Emmons olefination, Julia–Kocienski olefination, intramolecular Diels–Alder cyclization, immunosuppressive effect

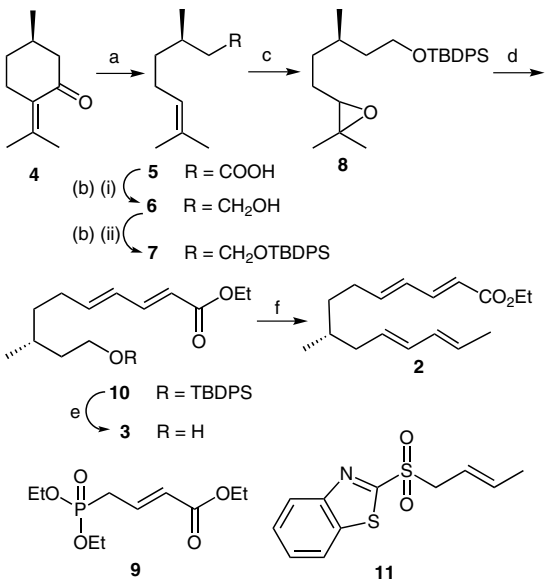
The decalin derivative monascusic acid B (**1**) was isolated[2] from red yeast rice prepared from steamed rice by fermentation using the fungus *Monascus purpureus*, and its structure was established by spectroscopic analysis. The compound was found to demonstrate immunosuppressive effects on human T cell proliferation in a dose-dependent manner. The synthesis of this decalin derivative **1** has not yet been reported. In continuation of our work[3] on the construction of bioactive natural products, we report herein the first stereoselective total synthesis of monascusic acid B (**1**).

Retrosynthetic analysis (Scheme 1) reveals that compound **1** could be prepared from the ester **2**, which in turn could be generated from ester **3**, derived from commercially available (*R*)-(+)-pulegone **4**. We rationalized from literature evidence on the intramolecular Diels–Alder (IMDA) cyclization of similar systems as present in **2** that the major product should be *endo*-**1**.[4]

The synthesis of monascusic acid B (**1**) was initiated by converting (*R*)-(+)-pulegone (**4**) into (*R*)-(+)-citronellic acid (**5**) by reaction with dry HCl followed by the consecutive treatment with NaOH (5%) and 5 M HCl (Scheme 2).[5] Acid **5** was reduced with $LiAlH_4$, and the resulting alcohol **6**[6] was treated with TBDPSCl and imidazole to form TBDPS ether **7**. This was subjected to epoxidation with MCPBA to form epoxide **8** which was then reacted with H_5IO_6.[7] The aldehyde formed by the cleavage of the epoxide underwent Horner–Wadsworth–Emmons (HWE) olefination[8] with phosphonate **9**[9] in the presence of LiHMDS to produce ester **10** as the major product. The newly generated double bond of **10** possessed the expected *E*,*E*-configuration as evidenced by ^1H NMR spectroscopic analysis (H^4–H^5 coupling constant J = 16.0 Hz).



Scheme 1 Retrosynthetic analysis of monascusic acid B



Scheme 2 *Reagents and conditions*: (a) dry HCl gas, NaOH (5%), 5 M HCl, 0 °C, 81%; (b) (i) $LiAlH_4$, Et_2O, 0 °C to r.t.; (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 90% (over two steps); (c) MCPBA, CH_2Cl_2, 0 °C to r.t., 88%; (d) (i) H_5IO_6, THF, Et_2O, 0 °C to r.t.; (ii) **9**, LiHMDS, THF, –78 °C, 81% (over two steps), *E*/*Z* = 95:5; (e) TBAF, THF, 0 °C to r.t., 92%; (f) (i) IBX, DMSO, CH_2Cl_2; (ii) **11**, LiHMDS, THF, –78 °C, 63% (over two steps), *E*/*Z* = 75:25.

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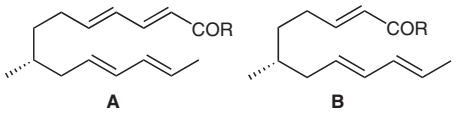
Table 1 Optimization of the IMDA Reaction Using Different Diene and Dienophile Systems under Different Reaction Conditions



Entry	R	Conditions	Yield (%)[a]	*endo*/*exo*[b]
A.a	R = OEt	BHT, PhMe, 150 °C, 48 h	65	60:40
A.b	R = OEt	Et_2AlCl, CH_2Cl_2, –30 °C to r.t., 24 h	no reaction	–
A.c	R = H	Et_2AlCl, CH_2Cl_2, –30 °C to r.t., 24 h	75	88:12
B.a	R = OEt	Et_2AlCl, CH_2Cl_2, –30 °C to r.t., 24 h	trace	–
B.b	R = H	Et_2AlCl, CH_2Cl_2, –30 °C to r.t., 24 h	77	79:21

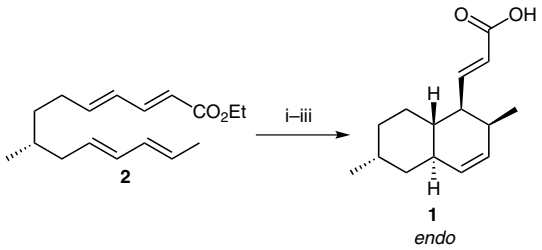
[a] Isolated yield.
[b] Determined by HPLC.

The TBDPS ether **10** was subsequently deprotected by the treatment with TBAF to form alcohol **3**. The latter was oxidized with IBX, and the corresponding aldehyde was subjected to Julia olefination[10] with the sulfone **11**[11] to furnish the tetraene ester **2**. Although different bases such as NaHMDS, KHMDS, and LiHMDS were employed to optimize the Julia olefination reaction, LiHMDS was found to be the best. However, we have not attempted to improve the *E*/*Z*-ratio.

At this stage, different types of dienophilic systems were employed under different conditions to optimize the intramolecular Diels–Alder reaction (IMDA, Table 1). A slight modification of the above synthetic pathway (Scheme 2), by replacing the HWE olefination with a simple C-2 Wittig olefination provided the trienic substructure **B**. Both, **A** and **B** were utilized for the optimization of the IMDA reaction. The IMDA reactions with aldehyde dienophiles (entries A.c and B.b) resulted in aldehyde cyclization products. Hence, the substrates were reduced with $NaBH_4$ to their corresponding alcohols, and the diastereoselectivity of the reaction was measured using HPLC. The major products were found to be *endo* in each case. We determined this stereoselectivity based on literature observations,[4] comparison of the NMR spectroscopic data with those of the related compounds, and subsequently by conversion of one of the products (Table 1, entry A.c) into the naturally occurring compound **1**, which has an *endo* configuration.

Based on the reaction yield, reaction time, and selectivity, the Lewis acid (Et_2AlCl) mediated IMDA reaction of the aldehyde (entry A.c) was found to be optimal. Although, entries A.c and B.b both show almost the same yield and comparable selectivity, the former involves fewer steps in synthesizing the target **1**. Hence, the reaction pathway via entry A.c was investigated first.

The observed *trans* diastereoselctivity in the Lewis acid (Et_2AlCl) catalyzed IMDA reaction is probably due to the adoption a pseudoequatorial disposition of the diene methyl substituent in a well-organized chair-like *endo*-



Scheme 3 *Reagents and conditions*: (i) DIBAL-H (1.2 equiv), toluene, –78 °C, 35 min; (ii) Et_2AlCl (1 equiv), CH_2Cl_2, –30 °C, 6 h; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH (51%, over three steps).

favored transition state (TS, Figure 1); instead of the less favored *exo* transition state that leads to the minor *cis*-fused isomer (Figure 2).

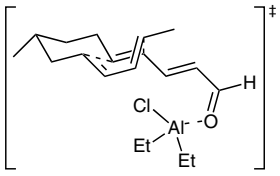


Figure 1 *endo* TS for entry A.c

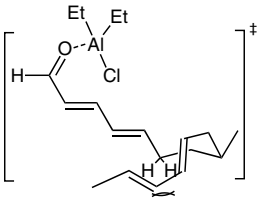


Figure 2 *exo* TS for entry A.c

Thus, compound **2** was treated with DIBAL-H to convert the ester into an aldehyde,[12] which was subsequently subjected to Et_2AlCl-mediated IMDA reaction[4] followed by Pinnick oxidation[13] to provide a mixture of *endo*-cyclization product along with its minor *exo* isomer (Scheme 3).

The major diastereomer was separated and demonstrated to be monascusic acid B (**1**). The physical (specific rotation) and spectroscopic properties (^{1}H and ^{13}C) of **1** were found to be identical to those reported for natural monascusic acid B,[2] thus confirming the assigned structure. The overall yield of **1** from **4** was 18% and the enantiomeric excess of the compound **1** was found to be 93% as measured by chiral HPLC.

In conclusion, we have developed the first concise, stereoselective total synthesis of monascusic acid B starting from commercially available (*R*)-(+)-pulegone employing the Horner–Wadsworth–Emmons and Julia–Kocienski olefination reactions and Lewis acid catalyzed intramolecular Diels–Alder cyclization as the key steps. This synthetic approach can be employed to synthesize other natural secondary metabolites possessing a similar decalin substructure.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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