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Enantioselective total synthesis of (−)-equisetin using a Me_3Al-mediated intramolecular Diels–Alder reaction†

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Abstract—An efficient and enantioselective total synthesis of (−)-equisetin **1** has been accomplished using a diastereoselective Me_3Al-mediated intramolecular Diels–Alder (IMDA) reaction as a key reaction step. © 2001 Elsevier Science Ltd. All rights reserved.

Equisetin **1** and phomasetin **2** have been isolated from the extracts of two active fungal broths, identified as *Fusarium heterosporum* and *Phoma* sp., respectively.[1] These compounds not only inhibit the in vitro recombinant integrase enzyme with IC_{50} values of 7–20 μM but also prevent the integration reactions catalyzed by preintegration complexes isolated from HIV-1 infected cells. It turns out that phomasetin is a novel enantiomeric homologue of equisetin, which is already known in the literature.[2] The promising biological profiles of these compounds coupled with their intriguing structural features inspired us to develop an efficient and general strategy for the synthesis of natural products (Fig. 1). To date, two total syntheses of optically active equisetin have been completed, those of Danishefsky[3] and Dixon.[4] We report herein an efficient total synthesis of (−)-equisetin **1** employing a diastereoselective IMDA reaction and a highly *E*-selective Takai-olefination as the key reaction steps. Recent communications by Dixon[4] on the total synthesis of **1** have prompted us to report our own efforts in this area.

The enantiomerically pure aldehyde **3**, prepared from *R*-citronellal via a four-step sequence, was subjected to

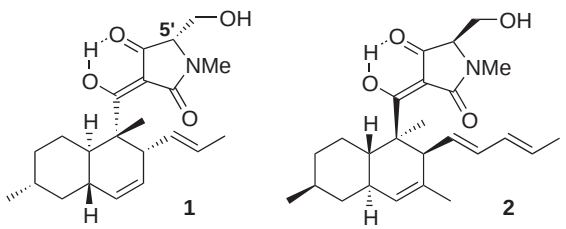
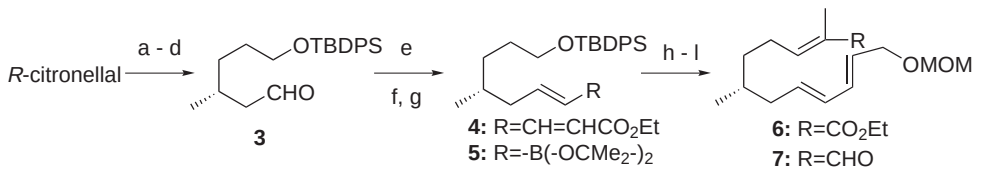


Figure 1.



Scheme 1. (a) $HO(CH_2)_2OH$, *p*-TsOH, benzene, reflux, 88%; (b) O_3, CH_2Cl_2, −78°C then $NaBH_4$, 92%; (c) 5% HCl (aq.), THF; (d) TBDPSCl, imidazole, 4-DMAP, 64% (two steps); (e) $(EtO)_2POCH_2CH{=}CHCO_2Et$, $LiOH{\cdot}H_2O$, 4 Å MS, THF, reflux, 84%; (f) dichloromethylboronic ester, $CrCl_2$, LiI, THF, 86%; (g) (*E*)-ethyl 3-iodoacrylate, $Pd_2(dba)_2{\cdot}CHCl_3$, Ph_3P, 2N NaOH (aq.), THF, reflux, 87%; (h) DIBAL-H, THF, −78°C, 99%; (i) MOMCl, *i*-Pr_2NEt, 4-DMAP, CH_2Cl_2, 94%; (j) *n*-Bu_4NF, THF, 98%; (k) Swern ox., CH_2Cl_2, −78°C, 91%; (l) $Ph_3P{=}C(Me)CO_2Et$, benzene, reflux, 99%; (m) DIBAL-H, THF, −78°C, 94%; (n) Swern ox., CH_2Cl_2, −78°C, 93%.

Keywords: Diels–Alder reactions; stereocontrol; biologically active compounds; polyketides.

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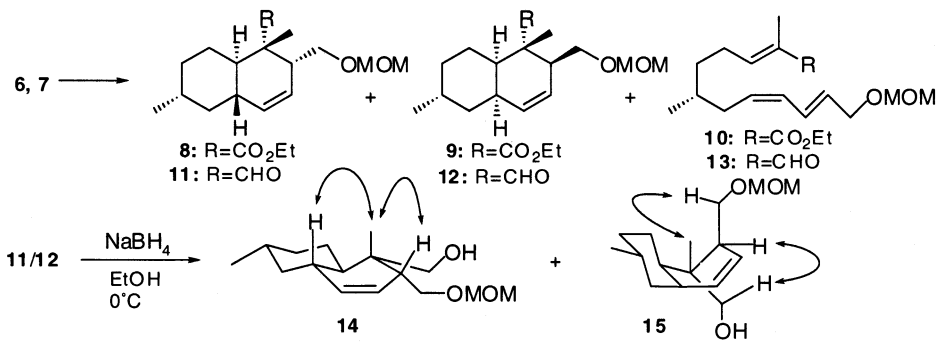
the Horner–Emmons reaction[5] to give the diene **4**. The stereochemistry of the newly generated double bond was an 8:1 mixture (from ^{1}H NMR) of the *E* and *Z* isomers, which were inseparable. To improve the stereoselectivity, we examined a stepwise sequence for the preparation of the diene. Treatment of **3** with dichloromethylboronic ester, chromous chloride and LiI[6] produced the vinyl borate **5** with *E*-geometry in a ratio of 95:5 in 86% yield. The Suzuki coupling[7] of **5** with (*E*)-ethyl 3-iodoacrylate[8] provided the diene **4** in 99% yield.

Reduction of the ester moiety with DIBAL-H followed by protection of the resulting alcohol as the MOM ether gave the protected diene. It was treated with TBAF and oxidized by the method of Swern to give the corresponding aldehyde, which was condensed with the stabilized Wittig ylide to afford the triene ester **6** in good overall yield. This was converted by sequential DIBAL-H reduction and Swern oxidation into the aldehyde **7**, which has a different kind of dienophilic moiety (Scheme 1).

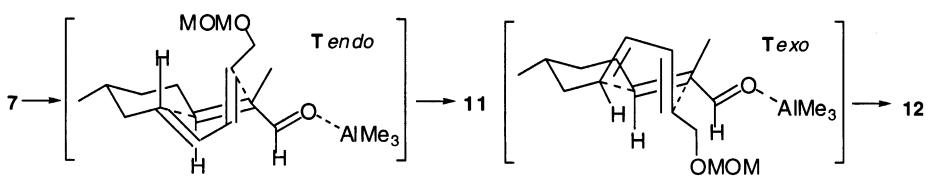
Initially we examined the key IMDA reaction of the triene **6** having the unsaturated ester as the dienophile. A solution of the triene in toluene was heated at 150°C for 40 h in the presence of catalytic methylene blue.[9] The cycloadduct was obtained as an inseparable 1:1 mixture (from ^{1}H NMR) of *trans* and *cis* isomers **8** and **9** along with unreacted starting *Z*-triene **10** in 64 and 4% yields, respectively. Discouraged by the non-selectivity, we next examined Lewis acid-mediated conditions. However, the results were uniformly disappointing. Therefore, we turned our attention to yet another triene. The aldehyde **7** was heated under the same conditions as for **6** to give a 3:1 inseparable mixture of the *trans*/*cis* cycloadducts **11** and **12** and the *Z*-triene **13** in 81 and 4% yields, respectively. Encouraged by this result, we continued to search for the optimum conditions for obtaining higher selectivity. After several attempts, the use of Me_3Al proved the most successful. Thus, treatment of a solution of **7** in CH_2Cl_2 with 1 equiv. of Me_3Al at 0°C for 4 h gave the cycloadducts in reasonable chemical yield (75%) and diastereoselectivity (8/1). In addition, the *Z*-triene **13** was recovered in 3% yield. Separation and structure determination of both isomers were carried out as shown in Scheme 2. Thus reduction of the mixture **11** and **12** with $NaBH_4$ produced a chromatographically separable mixture of the alcohols **14** and **15**, and their stereochemistries were rigorously confirmed by NOE experiments (Scheme 2).

A possible mechanism for the diastereoselective IMDA reaction is shown in Scheme 3. As we predicted, the reaction proceeded preferentially via the sterically more favorable *endo*-transition state **T***endo*, in which the methyl group on the tertially stereogenic center occupies an equatrial orientation, to give the *trans* octahydronaphthalene aldehyde **11** with the desired stereochemistry. On the other hand, the minor *cis*-isomer **12** would be generated from the *exo*-transition state (**T***exo)*, which seems to be sterically congested (Scheme 3).

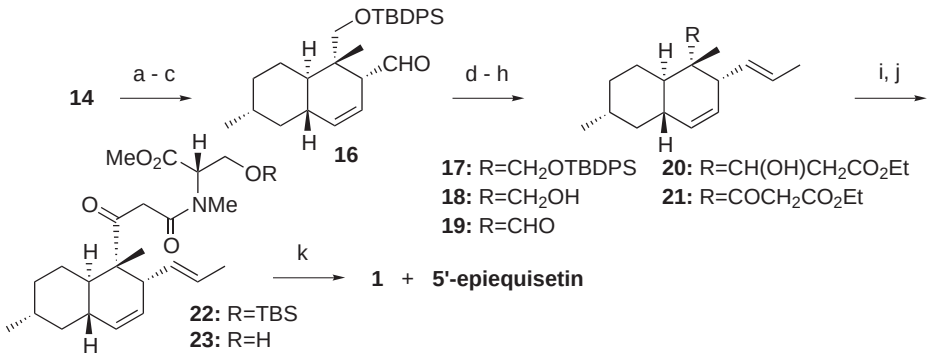
To introduce a propene moiety with the *E*-geometry, the primary alcohol function in **14** was initially protected as the TBDPS ether and the MOM ether was cleaved with bromotrimethyl silane[10] to produce the alcohol, which was oxidized with Dess–Martin periodinane. The resulting aldehyde **16** was treated with diiodoethane and chromous chloride in THF at room temperature[11] and afforded the *E*-olefin **17** cleanly in a ratio >99:1 in 90% yield. The TBDPS ether was cleaved with TBAF to give the alcohol **18**[12] in 97% yield, the spectral properties and optical rotation of which were completely identical with those reported in the literature.[3] Swern oxidation followed by Reformatsky reac-



Scheme 2.



Scheme 3.



Scheme 4. (a) TBDPSCl, imidazole, 4-DMAP, CH_2Cl_2, 92%; (b) TMSBr, CH_2Cl_2, 62%; (c) Dess–Martin ox., CH_2Cl_2, 95%; (d) CH_3CHI_2, $CrCl_2$, THF, 93%; (e) *n*-Bu_4NF, DMF, 99%; (f) Swern ox., CH_2Cl_2, 99%; (g) ethyl bromoacetate, Zn, benzene, reflux, 92%; (h) Dess–Martin ox., CH_2Cl_2, 83%; (i) *N*-methyl-*O*-*tert*-butyldimethylsilylserine methyl ester, toluene, reflux, 96%; (j) HF, MeCN, 99%; (k) NaH, CH_2Cl_2, 92%.

tion of the resulting aldehyde **19** provided **20**, which was oxidized with the Dess–Martin periodinane to give the keto ester **21** in 76% overall yield from **18**. Condensation of **21** with the *N*-methylserine derivative, which was prepared from L-*N*-(*tert*-butoxycarbonyl)-*O*-benzylserine,[3] in refluxing toluene afforded the amide **22**, which was desilylated to give **23** in 95% yield for the two steps. Finally, treatment of **23** with NaH in CH_2Cl_2 produced an easily separable 4:1 mixture of equisetin **1** and 5′-epiequisetin[2c,3] in 92% yield. The synthetic equisetin obtained by this procedure was identical to a natural sample by several criteria: R_f (TLC), mass spectrometry, IR, ^1H, ^{13}C NMR, and optical rotation (Scheme 4).[13]

In summary, we have completed a total synthesis of optically pure (−)-equisetin using a diastereoselective Me_3Al-mediated IMDA reaction and a highly *E*-selective Takai olefination reaction as the key reaction steps. It was also demonstrated that a tertiary carbon stereogenic center could control the four newly generated stereogenic centers with the desired stereochemistry by chirality transmission during an *endo*-selective IMDA cycloaddition. The synthetic route that we developed here is general and efficient and can also be applied to the synthesis of the enantiomer and other related natural products.

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12. The optical purity of **20** was proved to be >99% ee by ^1H NMR analysis of the corresponding MTPA ester.
13. $[\alpha]_D^{23}=-352$ ($c=1.00$, $CHCl_3$) {Ref. 1 $[\alpha]_D^{22}=-278$ ($c=0.77$, $CHCl_3$); Ref. 3 $[\alpha]_D^{23}=-253$ ($c=0.038$, $CHCl_3$)}; Ref. 4 $[\alpha]_D^{28}=-262$ ($c=0.038$, $CHCl_3$)}.