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Total Synthesis of Forskolin - Part III[#]
Studies related to an Asymmetric Synthesis

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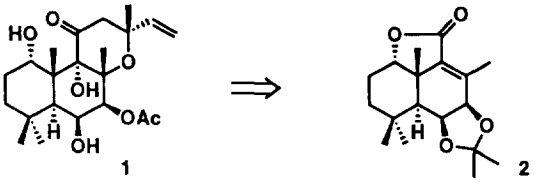
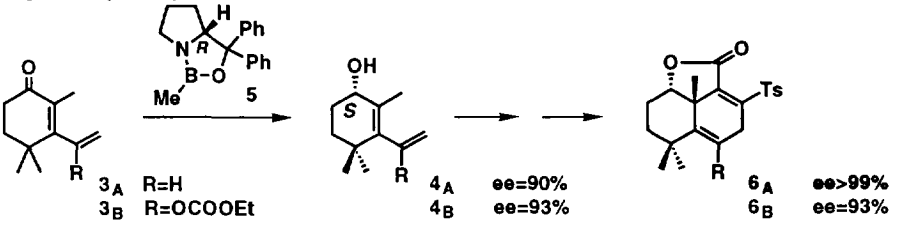
Abstract : A modification of the Corey CBS methodology for the asymmetric reduction of the dienone 3_A affords the dienol 4_A with an ee = 98% (92% yield). The intramolecular Diels-Alder reaction of the derived tetrolate **7** yields the tricyclic lactone **8** (48-56%) with no significant loss of ee (less than 1%), thus demonstrating the feasibility of a total synthesis of forskolin in enantiomerically pure form according to our route. The present synthesis of the optically active lactone **8** (ee=98%) is the shortest and the most efficient.

Three total syntheses of (±) forskolin **1** have already been achieved by Ziegler [1], Ikegami [2] and Corey [3] and involve a common key-intermediate **2**; we also disclosed the completion of our synthesis of (±) **1** in the two accompanying communications [4].



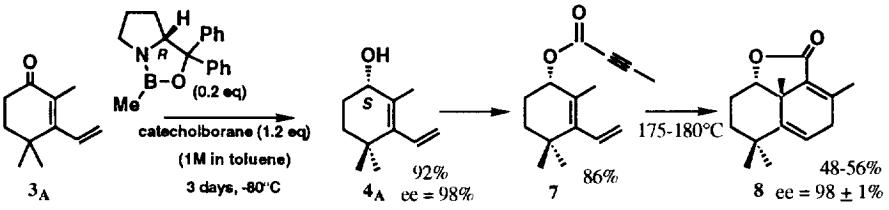
Corey and coworkers first developed a route for a highly enantioselective synthesis of **2**, via the asymmetric reduction of the dienone 3_A into the *(S)* alcohol 4_A with 20 mol% of *(R)*-oxazaborolidine **5** and 0.6 equivalent of BH_3-THF in THF at 35°C; the dienol 4_A (ee=90%) was further converted into the tricyclic lactone 6_A, obtained in optically pure form by recrystallization (ee>99%) [5a]. A similar enantioselective route to 6_B was also later reported by Corey [5b].



Kanematsu et al. took advantage of the Corey methodology to prepare the optically active key-compound **2** from 4_A (ee=90%) [6a], via their allenyl ether intramolecular Diels-Alder strategy [6b]. More recently, Lallemand and coworkers described the PLE catalyzed resolution of (±)-1-hydroxy-β-ionone acetoacetate as yielding the required *(S)* enantiomer (ee=95%) [7a], and they recently disclosed its possible conversion into **2** [7b].

dedicated to the memory of our coworker Daniel Calvo, deceased September 2nd, 1993.

We also checked the feasibility of an asymmetric total synthesis of forskolin, by the scheme we achieved in our group. Thus, after some experimentation, we reproducibly prepared the optically active *(S)* dienol $\mathbf{4_A}$ (ee=90%) according to the Corey procedure [5,8], or by the trimethylboroxine modification [9], and *(S)* $\mathbf{4_A}$was further converted into the tetrolate **7** (tetrolic acid/DCC/DMAP, CH_2Cl_2, r. tp.). No appreciable loss of ee was found to occur either in the esterification or in the harsh conditions of the Diels-Alder reaction (180°C, 14-24h) [4], since the enantiomeric excess of the optically active lactone **8** was also 90% (the ee were determined by GLC with a chiral capillary column and the ee precision secured to be better than 1%) [10, 11]. More recently, we could improve the enantiomeric excess of $\mathbf{4_A}$ to 98% [11, 12], by a slight modification of the Corey procedure with catecholborane as the reagent [13], but associated with the catalyst prepared from the *(R)* diphenylprolinol and trimethylboroxine for simplification, instead of the usual *n*-butyl boron related oxazaborolidine catalyst [13].



$\mathbf{3_A}$ $\mathbf{4_A}$ **7** **8**

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11. The enantiomeric purity was determined by GLC with a chiral capillary column under the following conditions: He carrier gas; injector split 1/50; detector FID; column isothermal; injector: 200°C; detector: 200°C; sample size: 0.3-0.5 µl of a 3% solution in toluene. The integration parameters were secured with the racemic compounds and precision for the measurements of the peaks area for the *R* and *S* enantiomers checked to be better than ± 0.5%.
$\mathbf{4_A}$ acetate (from $\mathbf{4_A}$ with Ac_2O/pyridine/toluene/100°C or Ac_2O/DMAP/CH_2Cl_2/20°C): Cyclodex-B (30m / 0.25mm; film thickness 0.25µm); inlet pressure 13 psi; column: 120°C.
lactone **8**: capillary column Chiraldex-B PH (β–cyclodextrin, permethylated hydroxypropyl) (30m / 0.32mm); inlet pressure: 20 psi; column: 175°C
Determinations of ee were also done by ^1H NMR ($CDCl_3$, 250, 300 or 400 MHz), but with lower accuracy, on the *(R)* and (S) α-Methoxy-α-trifluoromethylphenylacetic acid esters of $\mathbf{4_A}$, and for **8** at 400 MHz with a molar ratio $Eu(tfc)_3$/**8** = 0.5.
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