

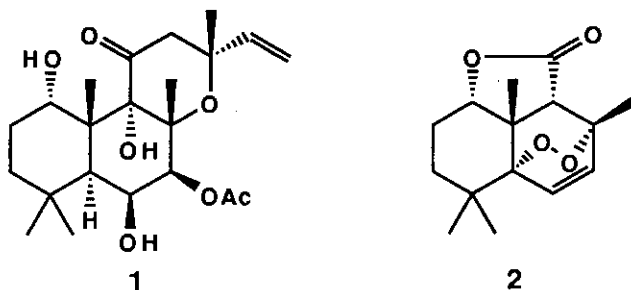
SYNTHETIC STUDIES OF FORSKOLIN. A DIELS-ALDER APPROACH TO COREY'S ENDOPEROXIDE<sup>1</sup>

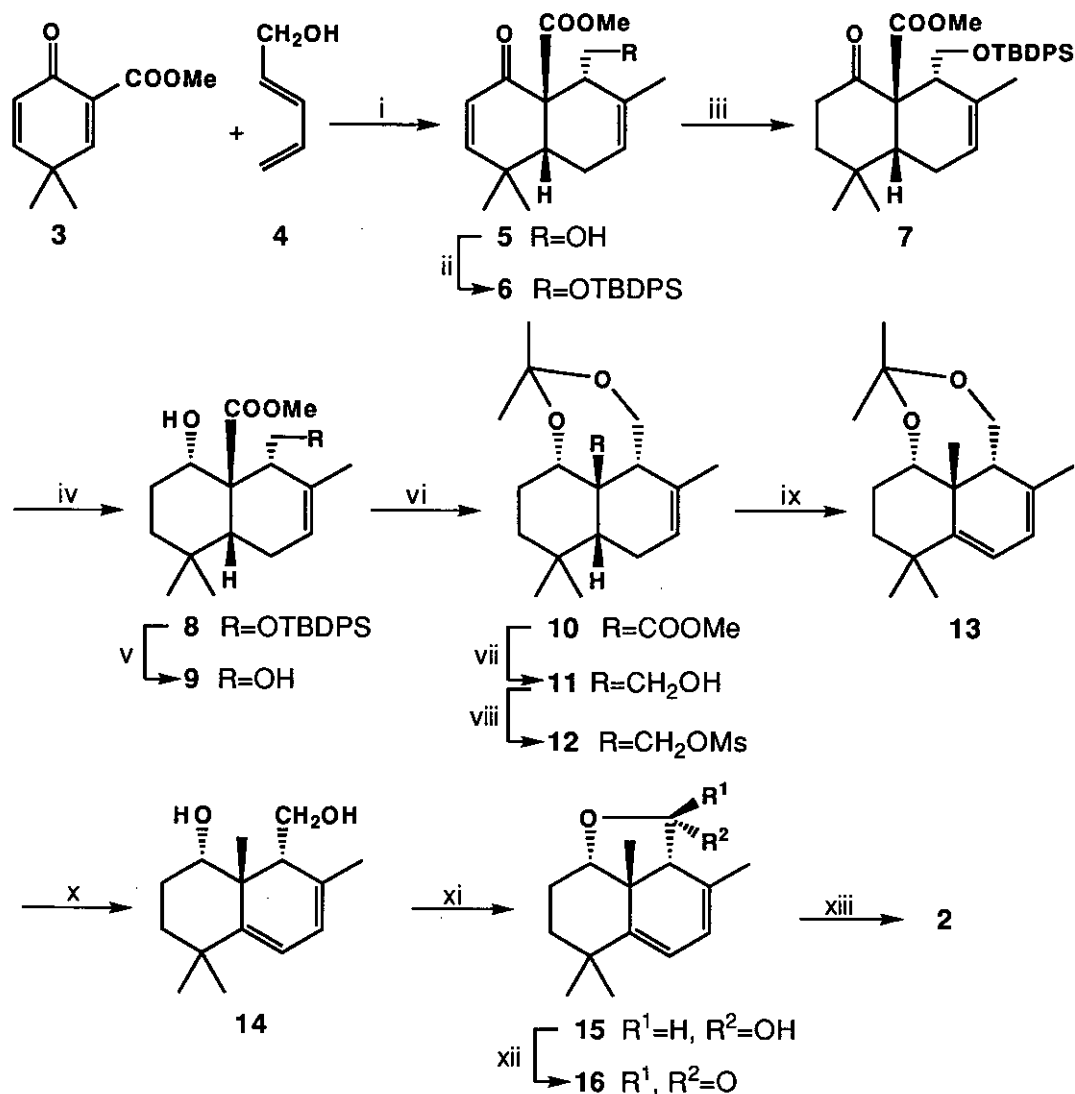
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**Abstract** — An alternative synthesis of Corey's endoperoxide intermediate (**2**) leading to forskolin (**1**) has been effected *via* a Diels-Alder approach. An interesting feature is the unusual dehydrogenation process **12**→**13** which accompanied the reduction of the mesylate group with zinc and sodium iodide.

Forskolin (**1**) is a highly oxygenated labdane diterpenoid, which displays an array of useful cardiovascular and other medicinal properties.<sup>2</sup> The high degree of synthetic challenge presented by the structural complexity of this natural compound and the interesting biological activities associated with it have attracted extensive synthetic efforts<sup>3</sup> since its first isolation from *Coleus forskohlii* in 1977,<sup>4</sup> highlighted by the successful completion of several total syntheses.<sup>5-8</sup> One such prominent achievement was reported by Corey *et al.*,<sup>7</sup> who made use of an intramolecular Diels-Alder approach to facilitate the construction of the suitably functionalized decalin nucleus (**2**), which proved to





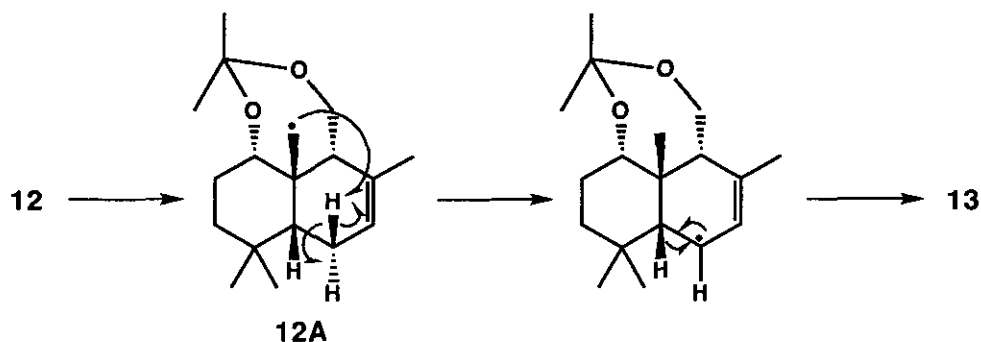
(i)  $\text{ZnCl}_2$ ,  $\text{Et}_2\text{O}$ , room temperature, 48 h; (ii)  $t\text{-BuPh}_2\text{SiCl}$ , imidazole, DMF, room temperature, 18 h, 64% from 3; (iii)  $(\text{Ph}_3\text{PCuH})_6$ ,  $\text{C}_6\text{H}_6$ ,  $\text{H}_2\text{O}$  (trace), room temperature, 96 h, 100%; (iv)  $\text{LiAl}(t\text{-BuO})_3\text{H}$ , THF, 36 h, 98%; (v)  $n\text{-Bu}_4\text{F}$ , THF, room temperature, 1.5 h, 100%; (vi) CSA,  $\text{Me}_2\text{C}(\text{OEt})_2$ , 50 torr, room temperature, 9 h, 98%; (vii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , room temperature, 3 h, 92%; (viii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , room temperature, 5 h, 90%; (ix)  $\text{Zn}$ ,  $\text{NaI}$ , DMF,  $110^\circ\text{C}$ , 24 h, 86%; (x) 1 N  $\text{HCl}$ ,  $\text{H}_2\text{SO}_4$ , THF, room temperature, 5 h, 84%; (xi)  $(\text{Ph}_3\text{P})_3\text{RuCl}_2$ ,  $\text{C}_6\text{H}_6$ , room temperature, 96 h, 66 %; (xii) 8 N Jones reagent,  $\text{Me}_2\text{CO}$ ,  $0^\circ\text{C}$ , 5 min, 88%; (xiii) methylene blue,  $\text{CHCl}_3$ ,  $\text{O}_2$ , hv,  $8^\circ\text{C}$ , 30 h, 95%.

be a highly effective synthetic intermediate towards forskolin. We wish to report herein an alternative synthesis of this endoperoxide intermediate.

The synthesis began with the Diels-Alder reaction of dienone ester (3)<sup>9</sup> and diene alcohol (4).<sup>10</sup> Under zinc chloride catalysis, the cycloaddition occurred in ether at room temperature to give a single adduct (5), which was shown to be quite unstable and thus was immediately converted to the corresponding silyl ether (6) using *tert*-butyldiphenylsilyl chloride and imidazole. The enone carbon-carbon double bond was selectively reduced using the hexamer of triphenylphosphinecopper hydride in benzene at room temperature in the presence of a trace amount of water.<sup>12</sup> The resulting ketone (7) was subjected to further reduction using lithium aluminum tri-*tert*-butoxy hydride. A single alcohol (8) was formed apparently as a result of the exclusive addition of the hydride ion from the sterically less hindered side of the starting ketone. The silyl protecting group was then removed using tetra-*n*-butylammonium fluoride, and the resulting diol (9) treated with 2,2-diethoxypropane and a small amount of camphorsulfonic acid at room temperature under reduced pressure (50 torr). The application of low pressure to remove the ethanol byproduct was critical to the formation of the desired ketal (10) in high yield, as this product was extremely labile to ethanol under the acidic reaction conditions.

To effect the conversion of the ester group to the required angular methyl, ketal ester (10) was first reduced with lithium aluminum hydride to the corresponding alcohol (11) which was then subjected to deoxygenation as follows. Treatment of 11 with methanesulfonyl chloride and triethylamine afforded mesylate (12). This compound was heated at 110°C for 24 h with zinc dust and sodium iodide in *N,N*-dimethylformamide.<sup>13</sup> Interestingly, the expected reduction of the methanesulfonyloxy group was accompanied by a highly efficient dehydrogenation process, giving rise to diene (13) as the only isolatable product. The dehydrogenation process was most unusual and might

have involved an intramolecular hydrogen transfer *via* radical species (12A) as shown schematically below.



The transformation of diene (13) to the Corey's endoperoxide intermediate (2) was carried out in the following manner. Hydrolysis of diene (13) with 1N hydrochloric acid and a small amount of sulfuric acid afforded diol (14). Its primary hydroxy group was selectively oxidized with tris(triphenylphosphine)ruthenium(II) chloride<sup>14</sup> in benzene to give lactol (15). Subsequent treatment of this compound with Jones reagent gave the desired lactone (16), from which endoperoxide (2) was prepared *via* photooxidation with oxygen using methylene blue as a sensitizer and a tungsten lamp as the light source.

In the previous syntheses of forskolin (1), the intramolecular Diels-Alder strategy has been widely employed. The current work indicates that the intermolecular Diels-Alder process also represents a viable approach to this interesting diterpenoid.

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