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A SHORT AND EFFICIENT ENANTIOSELECTIVE ROUTE TO A KEY INTERMEDIATE FOR THE TOTAL SYNTHESIS OF FORSKOLIN

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Summary: A simple route for the enantioselective synthesis of key intermediates (**11** and **12**) for the total synthesis of forskolin has been developed starting from acid **6** and (S)-alcohol **5**. The latter is prepared by enantioselective catalytic CBS reduction of dienone **3**, and is converted by an intramolecular Diels-Alder reaction to tricyclic lactone **9**.

An effective therapeutic agent for increasing cellular levels of cyclic AMP would have important application to the treatment of several diseases. In principle, such a change could result either by the inhibition of adenosyl phosphodiesterase or the activation of ATP-AMP cyclase. The naturally occurring diterpenoid forskolin (**1**) is an activator of the cyclase and promises to be useful in medicine.[1,2] Consequently, many laboratories have been involved in studies on the total synthesis of forskolin.[3,4]

In order for the chemical synthesis of forskolin to make a practical contribution to therapy, a chemical route to **1** must be enantioselective, short, and free of inefficient, non-stereoselective or problematic steps. The route to **1** previously developed in our group met these criteria, except for length. Described herein is an alternative to the initial stage of our earlier synthesis[4] which results in significant simplification and abbreviation. This rapid synthesis should facilitate the exploitation of the considerable therapeutic potential of forskolin.

A shortcoming of our original synthesis was the difficulty of introduction of the C(6) oxygen after the A and B rings had been established due to the severe steric crowding at that position. The new route avoids this problem by having this oxygen already in place when the A and B rings are formed using an intramolecular Diels-Alder reaction on a C(6)-functionalized diene.

Dienone **3** was prepared from **2**[5] in three steps: (1) treatment of **2**, first with 2 equiv of lithium diisopropylamide in tetrahydrofuran (-78° C for 10 min, 0° C for 10 min), then with 4 equiv of diethylpyrocarbonate (-78° C for 10 min, 23° C for 2 h); (2) desilylation using 2% HF in 50 : 1 acetonitrile-water at 0° C for 1 h; (3) oxidation with 3 equiv of pyridinium chlorochromate (PCC) in dichloromethane at 23° C for 3 h. Enantioselective reduction of dienone **3** was effected using the CBS method[6] by slow addition of 0.65 equivalent of BH_3•THF to a 1M solution of **3** and 25 mol% of (R)-oxazaborolidine **4**[6] as catalyst in THF at 35° C to afford (S)-alcohol **5**, $[\alpha]_D^{23}$ -14.7° (c=1.4 in $CHCl_3$), in 94% yield and with 93% enantiomeric purity.[7] Acid **6** was esterified with (S)-alcohol **5** in the following way. A solution of acid **6** in

dichloromethane was added to diiodotriphenyl phosphorane ($Ph_3P{\bullet}I_2$) in dichloromethane at -78° C. After the reaction mixture had been stirred for 2 h at -78° C, it was warmed to -50° C and 5A molecular sieves were added followed by (S)-alcohol **5**. The reaction mixture was stirred for an additional 4 h over which time it was allowed to warm to 23° C. After concentration and silica gel chromatography (SGC), ester **7**, $[\alpha]_D^{23}$ -14.5° (c=1.5 in $CHCl_3$),was isolated as a yellow oil in 95% yield. Elimination of hydrogen iodide from **7** was effected by the slow addition of 1.8 equiv of pentaisopropylguanidine[8] (over 5 h) in chloroform at -30° C to give acetylenic ester **8**, which was purified by rapid filtration at 0° C through a short column of silica gel, in 69% overall yield from **5**.

Ester **8** underwent an intramolecular Diels-Alder reaction on heating in toluene at 95° C for 48 h in the presence of 0.15 equivalent of 2,6-di-*tert*-butyl-4-methylpyridine to produce tricyclic lactone **9** in 65% yield after SGC. In the absence 2,6-di-*tert*-butyl-4-methylpyridine, **8** undergoes decomposition (starting at about 70° C) more rapidly than Diels-Alder addition. The enantiomeric purity of **9** obtained this way was 93%, corresponding to that of the starting alcohol **5**, as determined from 500 MHz ^{1}H-NMR measured in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.[9] Lactone **9**,$[\alpha]_D^{23}$ +67.8° (c=1.2 in $CHCl_3$), mp 137-138° C, was obtained in optically pure form in 75% yield by recrystallization from ether at -20° C.

Treatment of **9** with 4 equiv of lithium dimethyl cuprate and 5 equiv of boron trifluoride etherate in THF at -35° C for 3 h yielded **10**, $[\alpha]_D^{23}$ -15.1° (c=0.8 in $CHCl_3$), in 65% yield as a colorless oil.[10] The major side product from this reaction was the $\Delta^{5,7}$-diene corresponding to the $\Delta^{5,8}$-diene **9**. Treatment of **10** with 6 equiv of lithium hydroperoxide[11] (LiOOH) in THF at 0° C for 30 min furnished enone **11**, $[\alpha]_D^{23}$ -37.8° (c=0.4 in $CHCl_3$), as colorless crystals, mp 164-164° C, in 85% yield after SGC or recrystallization from ether at -20° C. Longer reaction times and higher temperatures result in lower yields. In this conversion the first reaction was demonstrated to be isomerization of the $\Delta^{5,8}$-diene to the $\Delta^{5,7}$-diene. The structure of enone **11** was confirmed by lithium borohydride reduction[12] to the axial alcohol **12**, which had previously been synthesized and converted to forskolin (**1**).[4a]

In summary, two major results emerge from this work. First, the internal Diels-Alder reaction of **8** proceeds well even though it might appear to be highly unfavorable due to the very sizeable steric repulsions and high energy implicit in the conformation with a planar *s-cis* diene subunit. This result should encourage the use of the internal Diels-Alder approach more generally with such polysubstituted dienes. Second, the synthesis of **12** can now be achieved in five fewer steps and with twice the overall yield as compared with the original synthetic route.[13]

References and Notes

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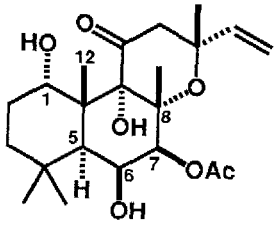

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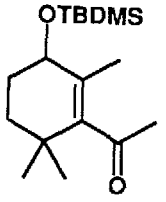

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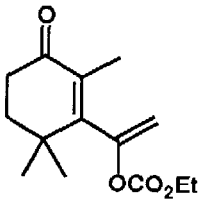

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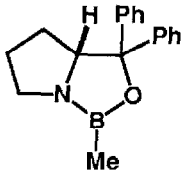

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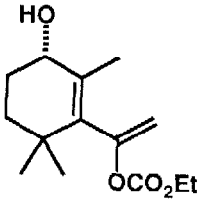

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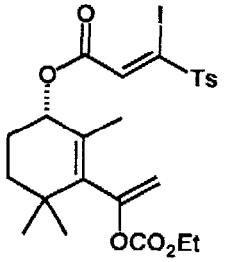

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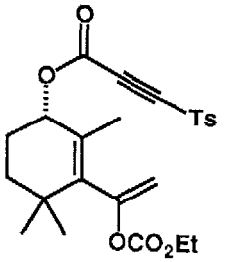

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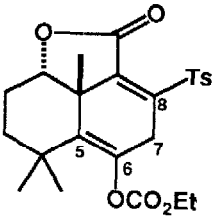

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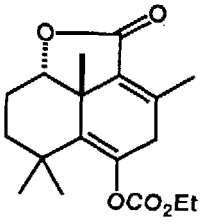

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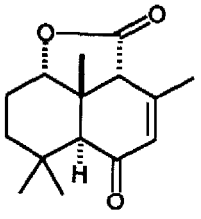

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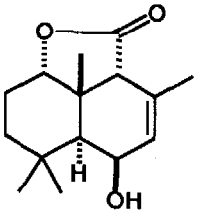

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5. Compound **2** was prepared from 2,4,4-trimethyl-3-formyl-2-cyclohexen-1-ol [4a] in three steps: (1) formation of the *t*-butyldimethylsilyl (TBDMS) ether using 1.5 equiv *t*-butyldimethylsilyl chloride, 3 equiv of imidazole and 0.1 equiv of 4-dimethylaminopyridine in dimethylformamide at 23° C for 1 h; (2) methylation of the aldehyde using 1.2 equiv of ethereal methyl lithium in tetrahydrofuran (THF) at -78° C for 30 min; (3) oxidation using 2 equiv of PCC in dichloromethane at 23° C for 3 h.
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7. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. The ester of **5** with (+)-MTPA showed doublets due to one of the vinylic protons at 5.19 and 5.21 δ in a ratio of 96.5 : 3.5. The corresponding peaks in the spectrum of the ester of (±)-**5** with (+)-MTPA were in a ratio of 1 : 1.
8. Barton, D. H. R.; Elliot, J. D.; Géro, S. D. *J. Chem. Soc. Perkin Trans. I* **1982**, 2085-2089.
9. Whereas two equal C(12) methyl peaks with baseline separation were observed with this shift reagent (85 mol%) and racemic **9**, only a single peak could be detected with recrystallized **9** which was prepared by the enantioselective route described herein.
10. The conversion of **9** to **10** was carried out in the following way. Lithium dimethyl cuprate was prepared by addition of ethereal methyl lithium (2.976 mL, 1.41 *M*, 4.2 mmol, 8 equiv) to a suspension of cuprous iodide (400 mg, 2.1 mmol, 4 equiv) in 7 mL of tetrahydrofuran at 0° C. The colorless cuprate was stirred at 0° C for 10 min and then was cooled to -78° C. Meanwhile, boron trifluoride etherate (320 μL, 2.6 mmol, 5 equiv) was added dropwise over 2 min to a solution of sulfone **9** (240 mg, 0.52 mmol, recrystallized from ether) in 3.2 mL of THF at -35° C. The lithium dimethyl cuprate was added dropwise over 10 min by cooled cannula to the solution of **9** and boron trifluoride etherate at -35° C. A black-red color developed. After 3 h at -35° C, the reaction was quenched with saturated ammonium chloride solution. Use of ammonia buffer (pH 9) instead, causes some isomerization of **10** to the corresponding $\Delta^{5,7}$ diene which can also be used in the next step. Removal of THF *in vacuo*, extraction into ether, drying over anhydrous magnesium sulfate, concentration and SGC with 5 : 1 hexanes-ethyl acetate afforded **10** as a colorless oil in 65% yield.
11. Reaction with lithium hydroxide in THF was slow (50% conversion after 9 h at 0° C) and proceeded in lower yield.
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13. This research was assisted financially by a grant from the National Science Foundation.

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