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ENANTIOSELECTIVE ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF FORSKOLIN

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Summary: An enantioselective route for the total synthesis of forskolin, a potent activator of adenylate cyclase, has been developed which is based on reduction of dienone **3** to the (S)-alcohol **4** and conversion in two steps to tricyclic lactone **9**, obtained in optically pure form simply by recrystallization.

A total synthesis of forskolin (**1**) (racemic form), a potent activator of adenylate cyclase of considerable therapeutic potential,[1] was recently developed in these laboratories.[2] We now report in detail an efficient enantioselective route to the tricyclic lactone **2**, an intermediate on the pathway of total synthesis which was demonstrated earlier.[2] The starting point of the new enantioselective route was the dienone **3** obtained by oxidation of the (±)-dienol **4** with pyridinium chlorochromate buffered with sodium acetate in dichloromethane.

Advantage was taken of the chiral-oxazaborolidine-catalyzed borane reduction of achiral ketones which allows efficient enantioselective synthesis of secondary alcohols with predictable configuration.[3,4] Reduction of dienone **3** by 0.6 equivalent of BH_3•THF in tetrahydrofuran with 20 mol% of (R)-oxazaborolidine **5** as catalyst was effected at 35° C by slow addition of BH_3•THF (1.2 mmol/h) to the catalyst and dienone **3**. After silica gel chromatography (SGC) the alcohol **4** was obtained as a colorless solid in 91% yield. The reduction proceeded with 95:5 enantioselectivity favoring the (S)-alcohol **4**, $[\alpha]_D^{23}$ -53° (c=1.0 in $CHCl_3$), as determined quantitatively by 500 MHz ^1H NMR analysis of the corresponding ester with (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[5,6] The enantioselectivity of this reaction was less at lower temperatures or with faster rates of BH_3•THF addition.

Reaction of acetylenic acid **6** with diiodotriphenyl phosphorane (Ph_3P•I_2) in dichloromethane at -35° C for thirty minutes, followed by addition of 2,6-di-*tert*-butyl-4-methylpyridine then **4** at -35° C and warming to 23° C afforded **7** (78%), $[\alpha]_D^{23}$ -37° (c=1.0 in $CHCl_3$). Elimination of hydrogen iodide from **7** was effected by treatment with 1.2 equivalents of pentaisopropylguanidine[7,8] in dichloromethane at -30° C to give the acetylenic ester **8** which was purified by rapid filtration at 0° C through a short column of silica gel. Ester **8** spontaneously

underwent an intramolecular Diels-Alder reaction in dichloromethane at 23° C for thirty-six hours to furnish the tricyclic lactone **9**, mp 153-154° C, $[\alpha]_D^{23}$ +8.7° (c=2.8 in $CHCl_3$), in 52% overall yield from **7** after SGC and recrystallization from benzene-hexanes.

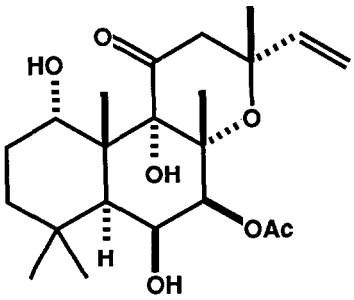
The enantiomeric purity of crystalline **9** so obtained was shown to be >99% by 500 MHz ^1H NMR measured in the presence of the chiral shift reagent (+)-[Eu(hfc)$_3$] (Aldrich Co). Whereas two equal C14-Me peaks with baseline separation were observed with this shift reagent (25 mol%) and racemic **9**, only a single peak could be detected with **9** which was prepared by the enantioselective route described above. Treatment of **9** with lithium dimethyl cuprate, as previously described,[2] yielded **2** (70%), $[\alpha]_D^{23}$ -70.7 (c=1.0 in $CHCl_3$), as a viscous oil.

The direct reaction of chiral **4** with **6** in dichloromethane at 23° C afforded racemic **9**, probably because the reaction proceeded by (1) protonation of **4**, (2) carbocation formation, (3) formation of (±)-**8**, and (4) Diels-Alder addition.

The successful enantioselective synthesis of **2** and the previously demonstrated conversion of (±)-**2** to (±)-**1** together establish a route for the enantioselective total synthesis of forskolin in natural form. Experimental details for the synthesis of **4**, **6**, **7** and **9** follow.

(S)-Dienol 4: A solution of BH_3•THF in THF (0.41 mL, 0.41 mmol) was added over 20 min to a warm solution (35° C) of dienone **3** (0.68 mmol) and (R)-oxazaborolidine **5** (0.14 mmol) in 0.8 mL of THF. After the addition was complete, the reaction was quenched at 0° C with water, the THF was removed *in vacuo*, and **4** was extracted into ether. After concentration and SGC dienol **4** (91%) was obtained as a colorless oil which solidified.

Acetylenic Acid 6: A solution of n-BuLi in hexanes (0.128 mol, 0.95 equiv) was added over 90 min to a cold solution (-100° C) of *p*-toluenesulfonylacetylene[9] (0.133 mol) in 400 mL of THF. During the metallation the temperature must be maintained below -90° C as the lithio acetylide is thermally unstable. The lithio acetylide was treated with excess carbon dioxide gas from -95° C to 0° C over 45 min, and the carboxylate so obtained was extracted into water from dichloromethane and acidified with 1N HCl. The acetylenic acid was extracted into dichloromethane and the solution was dried over anhydrous sodium sulfate. The whole isolation procedure was carried out at 4° C. Concentration furnished the crystalline acid **6** (obtained with 0.5 mol THF of crystallization) in 95% yield.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OAc
H
OH

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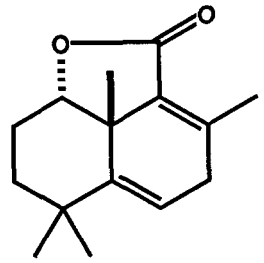
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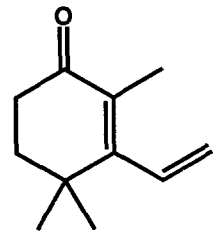
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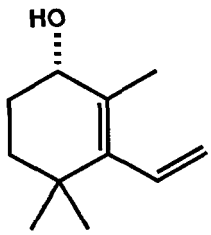
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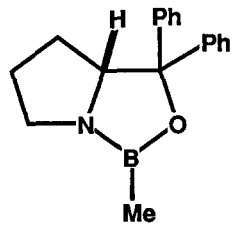
4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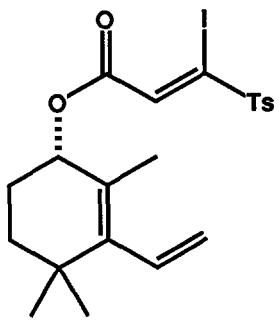
Ph
Ph
N
O
B
Me

5


Ts
COOH

6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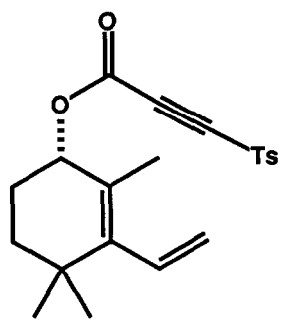
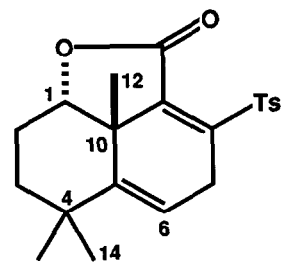
I
O
Ts

7


O
O
Ts

8


O
O
1
12
Ts
10
4
6
14

9

Ester 7: Iodine and triphenylphosphine were allowed to react for 10 min in dichloromethane at 23° C to produce diiodotriphenyl phosphorane as a yellow suspension which was then cooled to -35° C. Acid **6** was added as a solution in dichloromethane and the resulting deep red solution was stirred for a further 15 min after which 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane and alcohol **4** in the same solvent were added in that order. The reaction mixture was allowed to warm to 23° C over 2 hours and, after a further 2 hours at 23° C, the solvent was removed *in vacuo*. Ester **7** was isolated in 78% yield by column SGC. Usually 10-15% of the starting alcohol (**4**) was also recovered.

Tricyclic-lactone 9: A solution of pentaisopropylguanidine (1.2 equiv) in dichloromethane was added to a solution of the ester **7** in dichloromethane at -35° C. The yield of the reaction was decreased if more base was used. After three hours at -35° C the resulting solution was rapidly filtered through a short column of silica gel (20mm × 15mm for 0.43 mmol of **7**) with 3 : 1 hexanes-ethyl acetate at 0° C for elution. Concentration afforded **8** (70%) and **7** (15%) as a yellow oil which was diluted with dichloromethane (0.1M) and kept at 23° C for 36 hours. Concentration and SGC afforded tricyclic lactone **9** (64%) as a pale yellow solid which was obtained in optically pure form by recrystallization from benzene-hexanes.[10]

References and Notes

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6. The ester of **4** with (+)-MTPA[5] showed quartets due to the -OMe protons at 3.58 and 3.56 δ in a ratio of 95 : 5. The corresponding peaks in the spectrum of the ester of (±)-**4** with (+)-MTPA were in a ratio of 1 : 1.
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8. Several other bases including DBU, triethylamine and diisopropylethylamine were not effective for this transformation. Pentaisopropylguanidine is both a very hindered and strong base ($pK_a \cong 14$).
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