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SYNTHESIS OF THE ZIEGLER KEY INTERMEDIATE AND RELATED PRECURSORS FOR THE SYNTHESIS OF FORSKOLIN AND ERIGEROL IN ENANTIOMERICALLY PURE FORM

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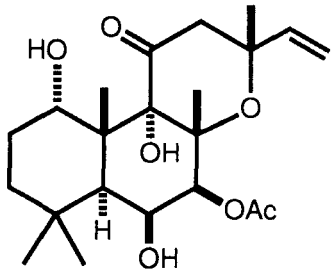
ABSTRACT. *The Ziegler key intermediate **5**, previously used in three total synthesis of forskolin (**1**), and the intermediate **4**, potentially useful for the synthesis of erigerol (**2**), were obtained in optically pure form by the resolution of the allylic alcohol **7a** with* R-*(-)-O-methylmandelic acid.*

For some years, we have been focusing our attention to the development of synthetic sequences for the preparation of key intermediates towards the highly oxygenated diterpenes forskolin (**1**)

*To whom correspondence should be addressed.

and erigerol (**2**).[1,2] Very recently we reported an alternative stereoselective synthesis of **3**, *en route* to **4**, an intermediate for the synthesis of **2** and an attempt to prepare **5** with high diastereofacial control in the osmylation step of the β-hydroxysulfoximine **6**.[3]



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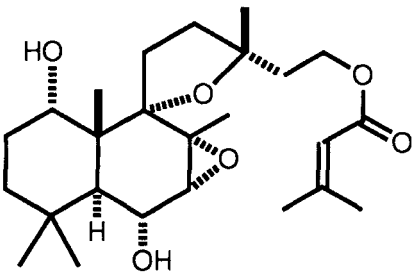

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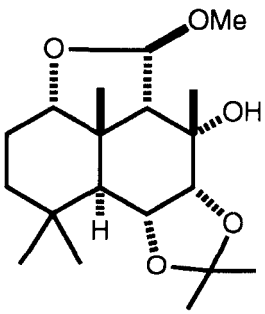

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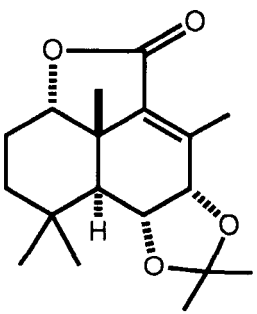

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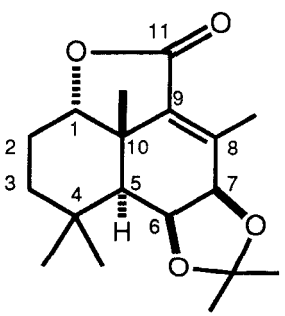
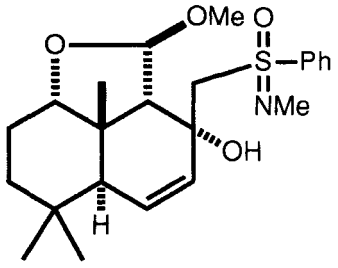


5

Based on the remarkable biological activity of forskolin,[4] and on the fact that the three synthetic sequences that culminated successfully in the total synthesis of racemic **1** passed through the tricyclic lactone **5**, first prepared by Ziegler *et al.*,[5] we considered interesting to extend our previously described sequence[1a] for the preparation of this key intermediate in optically pure form.



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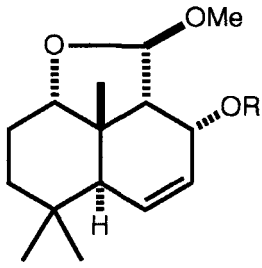
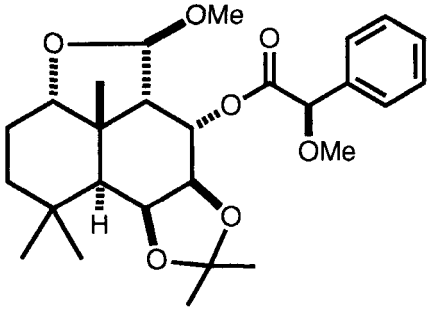


7a, R = H
7b, R = OCCH(OMe)Ph



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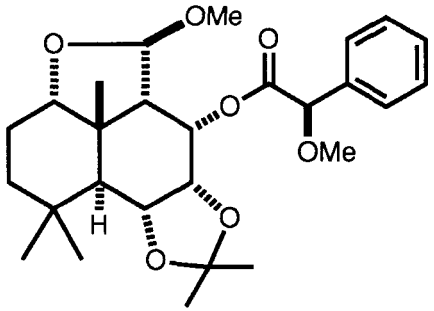


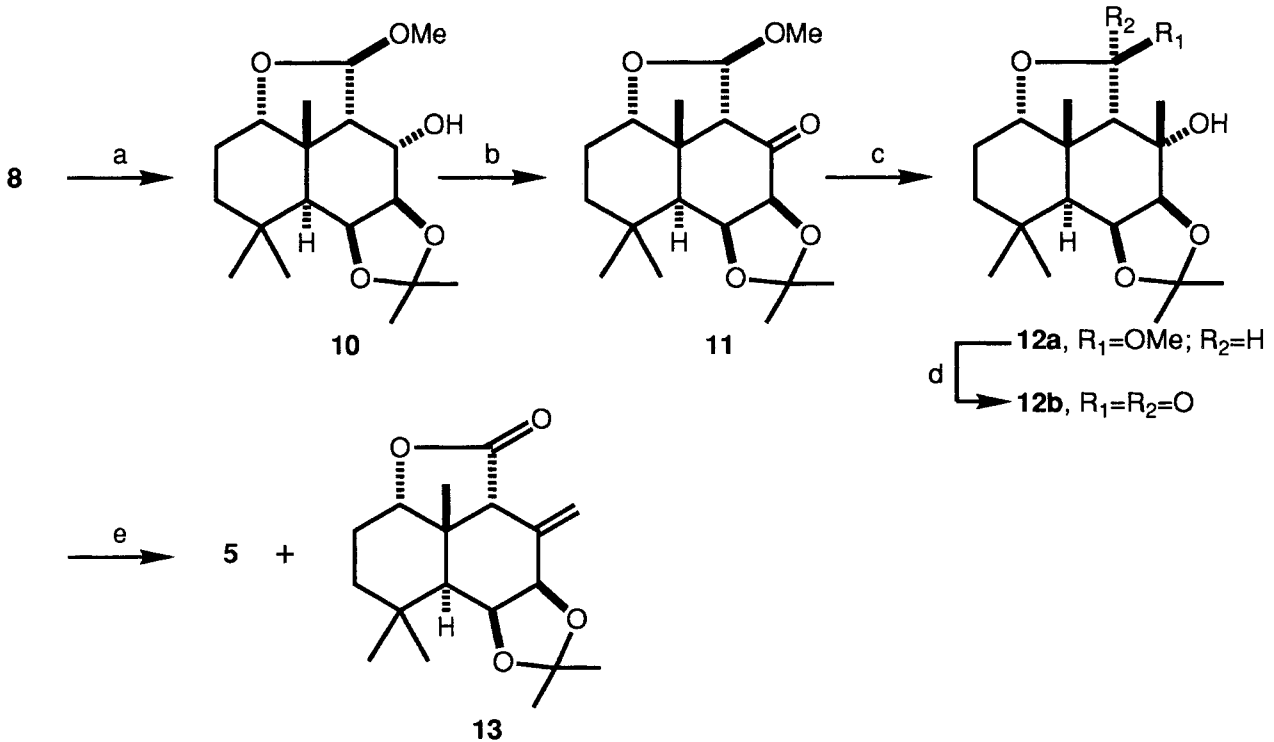
9

We decided to start our synthetic plan with the resolution of the allylic alcohol **7a** by esterification with (R)-(-)-O-methylmandelic acid. We expected, on the basis of the known effect of an acyloxy group in osmylation reactions of cyclic systems,[1a,6] that by using this resolving agent the double bond of the corresponding ester could be dihydroxylated preferentially from the β-face of the molecule. Furthermore, since we have previously determined the absolute configuration of (-)-**7a** as depicted in the formula,[7] by a simple basic hydrolysis of one of the diastereoisomeric O-methylmandelate esters the absolute configuration of the starting allylic alcohol could be established.

In practice, the treatment of (±)-**7a**[1a] with (R)-(-)-O-methylmandelic acid, in the presence of dicyclohexylcarbodiimide and a catalytic amount of dimethylaminopyridine afforded a chromatographically separable mixture of diastereoisomeric esters. The isolation of (+)-**7a** [$[\alpha]_D$ +137.8 (c=1.86, acetone)] when the more polar O-methylmandelate was submitted to basic hydrolysis clearly indicated its absolute configuration. The less polar O-methylmandelate **7b** was then dihydroxylated (osmium tetraoxide under stoichiometric conditions), and the resulting diols protected (2,2-dimethoxypropane, p-toluenesulfonic acid), affording a chromatographically separable 1.8:1 mixture of acetonides. The ^{1}H NMR spectral analysis of the isolated acetonides revealed that the minor component corresponds to the desired product **8** and therefore that the dihydroxylation of **7b** had occurred preferentially from the α-face of the molecule to yield **9** as the major product. This is in clear contrast with our previous observation that in the same system an acetoxy group induced the osmium tetraoxide approach from the β-face of the molecule.[1a] Consequently, additional work is necessary to clarify the effect of an acyloxy group in the stereoselectivity of dihydroxylation reactions of allylic systems.[6, 8]

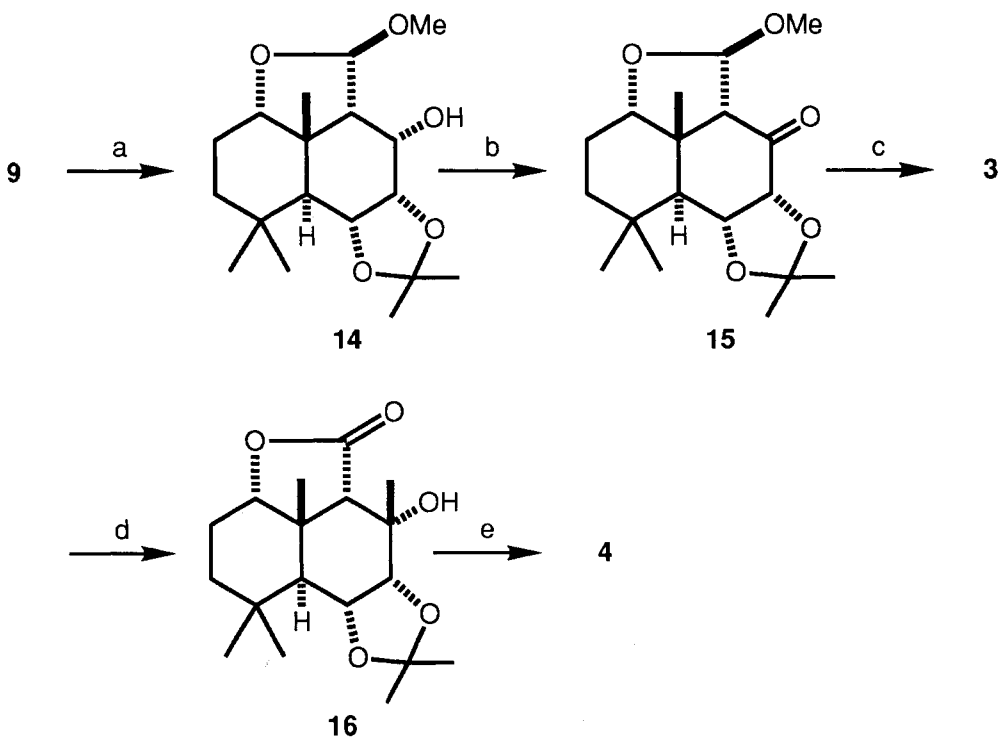
Starting with the O-methylmandelate **8** and following essentially the sequence described previously by us,[1a] the advanced Ziegler key intermediate (**5**) was synthesized in optically active form, with the absolute configuration corresponding to that of natural forskolin, for the first time (Scheme I).[9] As shown in Scheme II and starting with **9**, the synthesis of **4** in optically active form was also carried out.

SCHEME I



Reagents and conditions: (a) K_2CO_3, MeOH, 20 °C, 15 h; (b) PDC, CH_2Cl_2, 20 °C, 5 h; (c) MeMgBr, Et_2O, 0-20 °C, 1 h; (d) Jones reagent, acetone, 0-20 °C, 1h; (e) $SOCl_2$, py, 0 °C, 2 h

SCHEME II



Reagents and conditions: (a) K_2CO_3, MeOH, 20 °C, 15 h; (b) PDC, CH_2Cl_2, 20 °C, 48 h; (c) MeLi, Et_2O, 0 °C, 15 min; (d) Jones reagent, acetone, 0-20 °C, 1h; (e) KOH, dioxane, 85 °C, 23 h

The methodology described in this report would allow also the synthesis of the enantiomer of **5** and, starting with it, of the nonnatural antipode of forskolin. This could be interesting in view of the marked trend to test the biological activity of both enantiomers of a potentially useful drug.[10,11]

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal IA9100 digital melting point apparatus. IR spectra were measured in a Bruker FT-IFS25 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.13 MHz and 50.33 MHz respectively, in $CDCl_3$ solutions with Me_4Si as internal standard. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Column chromatography was performed on Merck silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of ethyl acetate in hexane as solvent. Analytical TLC was carried out using Kieselgel Merck GF_{254} of thickness 0.20 mm. The homogeneity of all intermediates prior to spectral determinations was carefully verified by TLC.

The numbering sequence used for reporting NMR parameters is illustrated in structure **5**.

Procedure for esterification of allylic alcohol (±)-**7a** with (-)-(R)-O-methylmandelic acid. To a solution of (±)-**7a** (356.5 mg, 1.41 mmol) and

(-)-(R)-O-methylmandelic acid (235 mg, 1.42 mmol) in anhydrous CH_2Cl_2 (47.5 mL), was added dicyclohexylcarbodiimide (DCC, 314.1 mg, 1.52 mmol) and 4-(dimethylamino)pyridine (DMAP, 33.7 mg, 0.37 mmol) at room temperature. The solution was stirred until the reaction reached completion, as determined by the absence of starting material by TLC (3 h). The reaction was then carefully concentrated, hexane was added and filtered to eliminate most of the dicyclohexylurea. After washings with cold hexane, the filtrate was successively washed with cold 3 N HCl, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and evaporated. The residue (752.2 mg) was chromatographed to afford two diastereoisomeric products. The first product to elute (228.5 mg, 40.4%) was a colorless oil: $[\alpha]_D$ -194.58 (c=1.07, $CHCl_3$); IR (neat) ν 1747, 1733, 1105, 698 cm^{-1}; ^1H NMR δ 7.44-7.26 (5H, m, PhH), 6.13 (1H, dd, J=3.1 and 9.6 Hz, H-6), 5.79 (1H, o. m., H-7), 5.64 (1H, o. m., H-8), 4.95 (1H, d, J=5.2 Hz, H-11), 4.74 (1H, s, OCC*H*(OMe)Ph), 3.91 (1H, t, J=3.1 Hz, H-1), 3.39 (3H, s, OCCH(O*Me*)Ph), 2.99 (3H, s, OMe), 2.44 (1H, d, J=3.1 Hz, H-5), 2.22 (1H, dd, J=5.2 and 9.5 Hz, H-9), 1.78 (2H, m, H-2), 1.6-1.2 (2H, m, H-3), 1.00 (3H, s, 10-Me), 0.94 (3H, s, 4α-Me), 0.87 (3H, s, 4β-Me); ^{13}C NMR δ 170.03 (O*C*CH(OMe)Ph), 136.01 (Ph), 134.69 (C-6), 128.61 (Ph), 128.50 (Ph), 127.31 (Ph), 124.31 (C-7), 105.33 (C-11), 82.63 (C-1), 81.74 (OC*C*H(OMe)Ph), 67.72 (C-8), 58.08 (OCCH(O*Me*)Ph), 57.06 (C-9), 55.31 (OMe), 49.77 (C-10), 42.76 (C-5), 34.69 (C-3), 31.58 (4α-Me), 31.17 (C-4), 21.68 (C-2), 21.30 (4β-Me), 18.51 (10-Me). The second product to elute (281.2 mg, 49.7%) was a colorless oil: $[\alpha]_D$ +116.48 (c=1.28, $CHCl_3$); IR (neat) ν 1747, 1708, 1105, 736 cm^{-1}; ^1H NMR δ 7.43-

7.26 (5H, m, PhH), 6.04 (1H, dd, J=2.8 and 9.0 Hz, H-6), 5.62 (2H, m, H-7, H-8), 5.14 (1H, d, J=5.5 Hz, H-11), 4.73 (1H, s, OCC*H*(OMe)Ph), 3.97 (1H, t, J=3.4 Hz, H-1), 3.44 (3H, s, OCCH(O*Me*)Ph), 3.33 (3H, s, OMe), 2.32 (1H, dd, J=5.4 and 9.2 Hz, H-9), 2.22 (1H, d, J=2.8 Hz, H-5), 1.79 (2H, m, H-2), 1.6-1.2 (2H, m, H-3), 1.02 (3H, s, 10-Me), 0.88 (3H, s, 4α-Me), 0.86 (3H, s, 4β-Me); ^{13}C NMR δ 170.07 (O*C*CH(OMe)Ph), 136.12 (Ph), 134.23 (C-6), 128.40 (Ph), 128.37 (Ph), 126.96 (Ph), 124.03 (C-7), 105.70 (C-11), 82.43 (C-1), 82.02 (OC*C*H(OMe)Ph), 67.84 (C-8), 57.66 (OCCH(O*Me*)Ph), 57.29 (C-9), 55.64 (OMe), 49.26 (C-10), 42.63 (C-5), 34.70 (C-3), 31.44 (4α-Me), 31.13 (C-4), 21.91 (C-2), 21.51 (4β-Me), 18.60 (10-Me). A mixture of both diastereoisomers was also obtained (95.6 mg).

Preparation of acetonides **8** and **9**. Osmium tetraoxide (82 mg, 0.32 mmol) in THF (3.3 mL) was added to a stirred solution of the less polar O-methylmandelate **7b** (122.8 mg, 0.307 mmol) in THF (0.5 mL) and pyridine (0.614 mL). After 38 h of stirring in the dark at room temperature, the osmate ester was reduced by adding pyridine (0.614 mL) and saturated $NaHSO_3$ solution (4.61 mL). The mixture was stirred vigorously at room temperature. When the reaction was complete as judged by TLC (70 h), the mixture was extracted with a 1:1 mixture of Et_2O and EtOAc. The combined organic extracts were washed with saturated $NaHSO_3$ solution, N HCl and saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue (115 mg) was used in the next step without further purification.

To a stirred solution of the crude mixture of diols (50.8 mg) in 2,2-dimethoxypropane (8.73 mL) was added a crystal of p-TsOH at room temperature. After 20 h, the reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue gave, in order of elution, acetonides **8** (16.3 mg, 29.4%) and **9** (29.6 mg, 53.5%).

Acetonide **8** was a colorless oil; IR (neat) ν 2982, 1748, 1105, 738, 732 cm^{-1}; ^1H NMR δ 7.50-7.26 (5H, m, PhH), 5.25 (1H, t, J= 6.5 Hz, H-8), 4.76 (1H, s, OCC*H*(OMe)Ph), 4.56 (1H, dd, J= 2.0 and 6.5 Hz, H-6), 4.51 (1H, d, J= 4.7 Hz, H-11), 4.09 (1H, t, J= 6.5 Hz, H-7), 3.70 (1H, t, J= 4.5 Hz, H-1), 3.39 (3H, s, OCCH(O*Me*)Ph), 2.89 (3H, s, OMe), 2.29 (1H, dd, J= 4.7 and 6.5 Hz, H-9), 1.52 (1H, d, J= 2.0 Hz, H-5), 1.51 (3H, s), 1.38 (3H, s), 1.33 (3H, s), 1.07 (3H, s), 1.00 (3H, s); ^{13}C NMR δ 169.85 (O*C*CH(OMe)Ph), 135.95 (Ph), 128.49 (Ph), 128.39 (Ph), 127.42 (Ph), 110.15 (O*C*O), 104.74 (C-11), 83.65 (C-1), 82.41 (OC*C*H(OMe)Ph), 76.71 (C-7), 73.61 (C-6), 72.65 (C-8), 57.15 (OCCH(O*Me*)Ph + C-9), 55.04 (OMe), 43.51 (C-10), 42.12 (C-5), 35.75 (C-3), 32.63 (C-4), 31.49 (Me), 27.40 (Me), 25.09 (Me), 23.99 (Me), 22.09 (C-2), 21.88 (Me).

Acetonide **9** was a colorless oil; IR (neat) ν 2986, 1751, 1114, 736, 722 cm^{-1}; ^1H NMR δ 7.48-7.35 (5H, m, Ph), 5.56 (1H, dd, J= 3.5 and 6.6 Hz, H-8), 4.75 (1H, s, OCC*H*(OMe)Ph), 4.34 (1H, dd, J= 7.3 and 10.5 Hz, H-6), 4.15 (1H, dd, J= 3.5 and 7.3 Hz, H-7), 3.79 (1H, d, J= 2.0 Hz, H-11), 3.66 (1H, t, J= 5.2 Hz, H-1), 3.45 (3H, s, OCCH(O*Me*)Ph), 2.92 (3H, s, OMe), 1.87 (1H, dd, J= 2.0 and 6.6 Hz, H-9), 1.67 (1H, d, J= 10.5 Hz, H-5), 1.46 (3H, s), 1.35 (3H, s), 1.10 (3H, s), 1.02 (3H, s), 0.99 (3H, s); ^{13}C

NMR δ 169.81 (O*C*CH(OMe)Ph), 136.13 (Ph), 130.52 (Ph), 128.60 (Ph), 127.13 (Ph), 108.51 (O*C*O), 104.53 (C-11), 82.49 (OC*C*H(OMe)Ph), 81.34 (C-1), 73.83 (C-7), 73.18 (C-6), 68.10 (C-8), 59.05 (C-9), 57.37 (OCCH(O*Me*)Ph), 54.61 (OMe), 43.13 (C-10), 42.66 (C-5), 34.76 (C-3), 32.55 (C-4), 32.02 (Me), 26.69 (Me), 24.14 (Me), 23.19 (Me), 22.48 (Me), 22.28 (C-2), 21.06 (Me).

Preparation of (-)-(3a*S*, 6a*R*, 9a*S*, 9b*S*, 9c*S*)-(3aβ, 6aα, 9aα, 9bα, 9cβ)-1, 2, 3, 3a, 6a, 9a, 9b, 9c, octahydro-1, 1, 6, 8, 8, 9c-hexamethyl-5*H*-furo[4', 3', 2':4, 5]naphtho[1, 2-*d*]-[1, 3]dioxol-5-one (**5**). Mandelate **8** (16.3 mg, 0.034 mmol), dissolved in MeOH (0.455 mL), was treated with K_2CO_3 (18.8 mg). The mixture was stirred at room temperature for 15 h, after which it was poured into H_2O (10 mL) and extracted with Et_2O and EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated, giving **10** (10.7 mg, 100%) as an oil that crystallized on standing: mp 131-132 °C (lit.[1a] mp 133-134 °C, for the racemic mixture); e.e.>95%;[12] ^{1}H NMR δ 4.93 (1H, d, J= 4.1 Hz, H-11), 4.57 (1H, dd, J= 2.0 and 6.2 Hz, H-6), 4.08 (2H, m, H-7, H-8), 3.80 (1H, t, J= 5.2 Hz, H-1), 3.41 (3H, s, OMe), 2.18 (1H, dd, J= 4.1 and 5.8 Hz, H-9), 1.64 (1H, d, J= 2.0 Hz, H-5), 1.50, (3H, s), 1.39 (3H, s), 1.35 (3H, s), 1.09 (3H, s, 4β-Me), 1.01 (3H, s, 4α-Me). These spectral data are coincident with those reported in references 1a and 3 for compound **10** as a racemic mixture.

The oxidation of **10** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving **11** in

79.1% yield, mp 113-115 °C (lit.[1a] mp 115.5-116 °C, for the racemic mixture); ^{1}H NMR δ 5.12 (1H, d, J= 2.1 Hz, H-11), 4.87 (1H, dd, J= 1.9 and 7.9 Hz, H-6), 4.18 (1H, d, J= 7.8 Hz, H-7), 3.83 (1H, t, J= 5.4 Hz, H-1), 3.38 (3H, s, OMe), 2.94 (1H, d, J= 2.1 Hz, H-9), 1.61 (3H, s), 1.59 (3H, s), 1.36 (3H, s), 1.14 (3H, s), 1.03 (3H, s). These spectral data are coincident with those reported in ref. 1a for compound **11** as a racemic mixture.

A solution of the ketone **11** (63 mg, 0.194 mmol) in anhydrous Et_2O (2 mL) was added slowly to a stirred solution of methylmagnesium bromide (2.28 mL of 0.7 M solution in Et_2O, 1.6 mmol) in anhydrous Et_2O (3 mL) at 0°C, and the resulting solution was allowed to warm to room temperature. After 1 h the reaction was quenched by the careful addition of saturated ammonium chloride solution and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to afford 80.8 mg of **12a** (66.1 mg, 100%), which was homogeneous by NMR analysis: ^{1}H NMR δ 5.01 (1H, s, H-11), 4.61 (1H, dd, J= 2.1 and 8.1 Hz, H-6), 3.96 (1H, d, J= 8.1 Hz, H-7), 3.78 (1H, t, J= 7.7 Hz, H-1), 3.35 (3H, s, OMe), 2.00 (1H, s, H-9), 1.92 (1H, d, J= 2.1 Hz, H-5), 1.46 (3H, s, β-Me, acetonide), 1.44 (3H, s, 10-Me), 1.37 (3H, s, 8-Me), 1.32 (3H, s, α-Me, acetonide), 1.10 (3H, s, 4β-Me), 1.01 (3H, s, 4α-Me). These spectral data are coincident with those reported in references 1a and 3 for compound **12a** as a racemic mixture.

The oxidation of **12a** was carried out as described in ref. **1a** for a similar transformation of the corresponding racemic mixture, giving **12b**: mp 118.2-118.8 °C (lit.[1a] mp 153-154 °C, for the racemic mixture); ^{1}H NMR δ 4.69 (1H, dd, J= 2.9 and 8.2 Hz, H-6), 4.19 (1H, d, J= 8.2 Hz, H-7),

4.05 (1H, t, J= 4.6 Hz, H-1), 2.95 (1H, br s, OH), 2.52 (1H, s, H-9), 1.80 (1H, d, J= 2.9 Hz, H-5), 1.60 (3H, s), 1.52 (3H, s), 1.50 (3H, s), 1.36 (3H, s), 1.14 (3H, s), 1.07 (3H, s). These spectral data are coincident with those reported in ref. 1a for compound **12b** as a racemic mixture.

The dehydration of **12b** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving a 10:1 mixture of **5** and **13** (^{1}H NMR). Slow crystallization of the crude product from diisopropyl ether provided pure **5**: mp 144 °C (sublimed) (lit.[1a] mp 110-111 °C, for the racemic mixture); $[\alpha]_D$ -68.61 (c=0.962, acetone); e.e.>95%;[12] IR (KBr disk) ν 1750, 1680, 1385, 1215, 1200, 1050, 1040, 1025 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.28 (1H, dd, J= 3.1 and 7.4 Hz, H-6), 4.15 (1H, d, J= 7.4 Hz, H-7), 3.72 (1H, dd, J= 5.8 and 11.0 Hz, H-1), 2.43 (3H, s, 8-Me), 1.44 (3H, s), 1.28 (3H, s), 1.18 (6H, s), 0.99 (1H, d, J= 3.2 Hz, H-5), 0.82 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.99 (C-11), 144.37 (C-8), 136.41 (C-9), 108.97 (O-*C*-O), 87.24 (C-1), 79.01 (C-7), 72.90 (C-6), 51.36 (C-5), 40.16 (C-10), 35.83 (C-3), 31.92 (C-4), 30.80 (Me), 28.06 (Me), 26.01 (Me x 2), 24.82 (C-2), 22.62 (Me), 17.62 (Me). These spectral data are coincident with those reported in ref. 1a for compound **5** as a racemic mixture.

Preparation of (+)-(3a*S*, 6a*S*, 9a*R*, 9b*S*, 9c*S*)-(3aβ, 6aβ, 9aβ,9bα, 9cβ)-1, 2, 3, 3a, 6a, 9a, 9b, 9c, octahydro-1, 1, 6, 8, 8, 9c-hexamethyl-5*H*-furo[4', 3', 2':4, 5]naphtho[1, 2-*d*]-[1, 3]dioxol-5-one (**4**). The basic hydrolysis of mandelate **9** was carried out as described for mandelate **8**. Compound **14** was obtained in 93% yield as an oil which crystallized on

standing, mp 155-156 °C (lit.[1a] mp 157-158 °C, for the racemic mixture); ^{1}H NMR δ 5.31 (1H, d, J= 2.0 Hz, H-11), 4.34 (1H, dd, J= 7.3 and 11.0 Hz, H-6), 4.19 (1H, dd, J= 3.9 and 6.1 Hz, H-8), 4.11 (1H, dd, J= 3.9 and 7.3 Hz, H-7), 3.87 (1H, t, J= 5.7 Hz, H-1), 3.35 (3H, s, OMe), 2.04 (1H, d, J= 10.4 Hz, H-5), 1.83 (1H, dd, J= 2.0 and 3.9 Hz, H-9), 1.48 (3H, s, α-Me, acetonide), 1.37 (3H, s, β-Me, acetonide), 1.06 (3H, s, 10-Me), 1.01 (3H, s, 4α-Me), 0.98 (3H, s, 4β-Me). These spectral data are coincident with those reported in references 1a and 3 for compound **14** as a racemic mixture.

The oxidation of **14** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving **15** in 92.1% yield, mp 148.1-149.2 °C (lit.[1a] mp 140-142 °C, for the racemic mixture); ^{1}H NMR δ 5.21 (1H, d, J= 2.6 Hz, H-11), 4.69 (2H, m, H-6, H-7), 3.93 (1H, t, J= 3.3 Hz, H-1), 3.40 (3H, s, OMe), 2.50 (1H, d, J= 2.6 Hz, H-9), 1.85 (2H, m), 1.50 (3H, s), 1.38 (6H, s), 1.24 (2H, m), 1.17 (1H, d, J= 9.5 Hz, H-5), 1.03 (3H, s), 0.99 (3H, s). These spectral data are coincident with those reported in ref. 1a for compound **15** as a racemic mixture.

The methylation of **15** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving **3** in 73.7% yield, mp 89.9-91.2 °C (lit.[1a] mp 116-118 °C, for the racemic mixture); ^{1}H NMR δ 5.29 (1H, d, J= 2.1 Hz, H-11), 4.36 (1H, dd, J= 7.4 and 10.5 Hz, H-6), 3.95 (1H, t, J= 7.4 Hz, H-7), 3.85 (1H, t, J= 5.1 Hz, H-1), 3.39 (3H, s, OMe), 2.13 (1H, d, J= 10.5 Hz, H-5), 1.68 (1H, d, J= 2.1 Hz, H-9), 1.50 (3H, s), 1.39 (3H, s), 1.28 (3H, s), 1.09 (3H, s), 1.02 (3H, s), 0.99 (3H, s). These spectral data are coincident with those reported in references 1a and 3 for compound **3** as a racemic mixture.

The oxidation of **3** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving **16**: ^{1}H NMR δ 4.40 (1H, dd, J= 7.2 and 10.2 Hz, H-6), 4.07 (1H, t, J= 6.1 Hz, H-1), 3.96 (1H, d, J= 7.2 Hz, H-7), 2.29 (1H, d, J= 10.2 Hz, H-5), 2.26 (1H, s, H-9), 1.54 (3H, s), 1.51 (3H, s), 1.40 (3H, s), 1.20 (3H, s), 1.07 (3H, s), 1.04 (3H, s). These spectral data are coincident with those reported in ref. 1a for compound **16** as a racemic mixture.

The dehydration of **16** was carried out as described in ref. 1a for a similar transformation of the corresponding racemic mixture, giving **4**: mp 141.3 (sublimed) (lit.[1a] mp 134-135 °C, for the racemic mixture); $[\alpha]_D$ +8.65 (c=1.271, acetone); e.e.>95%;[12] IR (KBr disk) ν 1750, 1680, 1390, 1220, 1030 cm^{-1}, ^{1}H NMR δ 4.79 (1H, dt, J= 1.3 and 7.9 Hz, H-7), 4.67 (1H, dd, J= 7.9 and 9.9 Hz, H-6), 4.10 (1H, dd, J= 6.2 and 10.7 Hz, H-1), 2.24 (3H, br s, 8-Me), 1.42 (6H, s), 1.33 (1H, d, J= 9.9 Hz, H-5), 1.11 (6H, s), 1.07 (3H, s); ^{13}C NMR δ 168.20 (C-11), 148.27 (C-8), 131.74 (C-9), 109.69 (O*C*O), 85.14 (C-1), 76.63 (C-7), 74.40 (C-6), 48.68 (C-5), 41.93 (C-10), 35.39 (C-3), 31.41 (4α-Me), 31.14 (C-4), 26.86 (Me), 25.45 (Me), 24.55 (C-2), 24.07 (Me), 23.12 (Me), 13.13 (Me). These spectral data are coincident with those reported in ref. 1a for compound **4** as a racemic mixture.

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REFERENCES

1. a) Colombo, M. I.; Zinczuk, J.; Bacigaluppo, J. A.; Somoza, C. and Rúveda, E. A., *J. Org. Chem.*, 1990, **55**, 5631. b) Bacigaluppo, J. A.; Colombo, M. I.; Zinczuk, J. and Rúveda, E. A., *Synth. Commun.*, 1992, **22**, 1973.
2. For a review on synthetic routes to forskolin, see: Colombo, M. I.; Zinczuk, J. and Rúveda, E. A., *Tetrahedron*, 1992, **48**, 963.
3. Bacigaluppo, J. A.; Colombo, M. I.; González-Sierra, M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A.; Duddeck, H. and Hiegemann, M., *J. Chem. Soc., Perkin Trans. 1*, 1993, 2009.
4. a) K. B. Seamon and J.W. Daly, *Adv. Cyclic Nucleotide Protein Phosphorylation Res.*, 1986, **20**, 1. b) Schreiber, S. L., *Chem. Eng. News*, 1992, **70 (43)**, 22.
5. Ziegler, F. E.; Jaynes, B. H. and Saindane, M. T., *Tetrahedron Lett.*, 1985, **26**, 3307.
6. Cha, J. K.; Christ, J. W. and Kishi, Y., *Tetrahedron*, 1984, **40**, 2247.
7. Preite, M. D.; Zinczuk, J.; Colombo, M. I.; Bacigaluppo, J. A.; González-Sierra, M. and Rúveda, E. A., *Tetrahedron: Asymm.*, 1993, **4**, 17.
8. The dihydroxylation of the benzoate ester of (±)-**7a** with osmium tetraoxide under stoichiometric conditions afforded a 1:1 mixture of diols (^{1}H NMR). Unpublished results.

9. For a recent synthesis of an optically pure precursor of forskolin, see: Lallemand, J. -Y.; Leclaire, M.; Levet, R. and Aranda, G., *Tetrahedron: Asymm.*, 1993, **4**, 1775.

10. Stinson, S. C., *Chem. Eng. News*, 1993, **71 (39)**, 38.

11. Carey, J., *Chem. Brit.*, 1993, 1053.

12. The enantiomeric purities were established via ^{1}H NMR analysis employing the chiral shift reagent tris(3-[heptafluoropropyl-hydroxymethylene]-*d*-camphorato] Europium (III) derivative [Eu(hfc)3].

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