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AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF EPIISOPODOPHYLLOTOXIN

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Abstract: An enantioselective total synthesis of epiisopodophyllotoxin in which an asymmetric Diels- Alder reaction between a chiral butenolide and an alpha oxy ortho xylylene as the key step is described.

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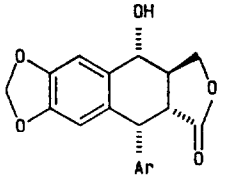
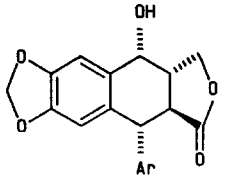
The potent anticarcinogenic activities of podophyllotoxin **1** and its semisynthetic derivative etoposide have prompted many intense efforts aimed at the total synthesis of this class of podophyllum lignans.[1] However, until the pioneering construction by Meyers and coworkers, none of these prior efforts were enantioselective as well.[2] Described herein is an enantioselective total synthesis of epiisopodophyllotoxin **2** which has been previously prepared from **1** and reported to have inhibitory activity against human nasopharynx carcinoma.[3]



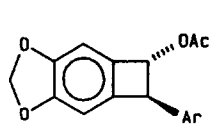
1



2

; Ar = 3, 4, 5- trimethoxyphenyl

Scheme 1



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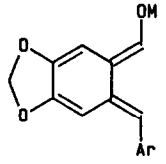

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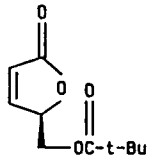

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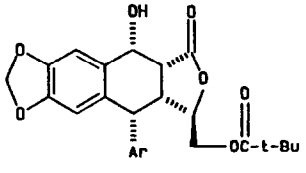

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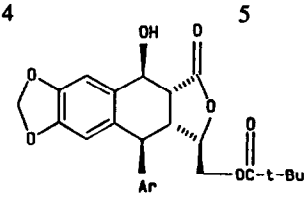
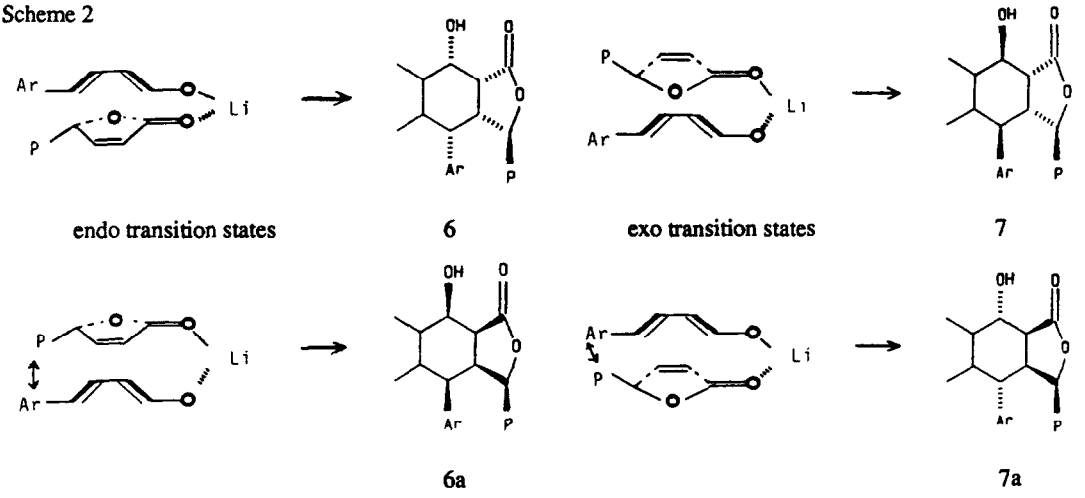


7

Exploiting the method developed in this laboratory,[4] treatment of the known benzocyclobutenyl acetate **3**[5] with n-BuLi (2.1 eq , -78 °C) followed by a Diels- Alder reaction between xylylene **4** (M= Li) with chiral butenolide **5**[6] (94% e.e., 1.1 eq, -78 °C) and the usual workup led to separable adducts **6** an **7** (72% total yield, endo **6** / exo **7** = 6.2 , >95% d.e. in each adduct) as shown in Scheme 1. The minor diastereomeric and

enantiomeric impurities were practically removed from each adduct by one recrystallization. The absolute configurations of each adduct were expected on the basis of the following endo and exo transition states as shown in Scheme 2 :

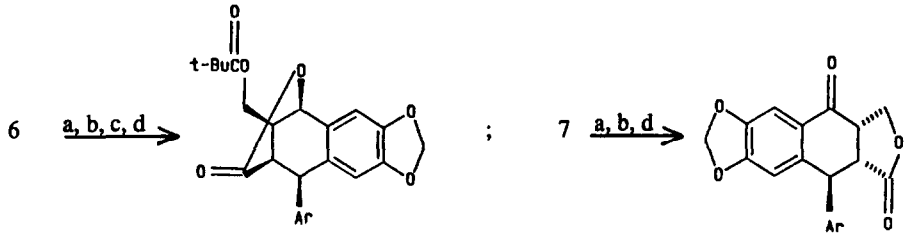
Scheme 2



As indicated by the doubleheaded arrows, steric hindrance between the xylylene's Ar moiety and the butenolide's pivaloxymethyl sidechain P would inhibit the transition states leading to the alternative adducts **6 a** and **7 a** thus favoring the corresponding states to **6** and **7.**

Correlation of the observed configurations is shown in Scheme 3 :

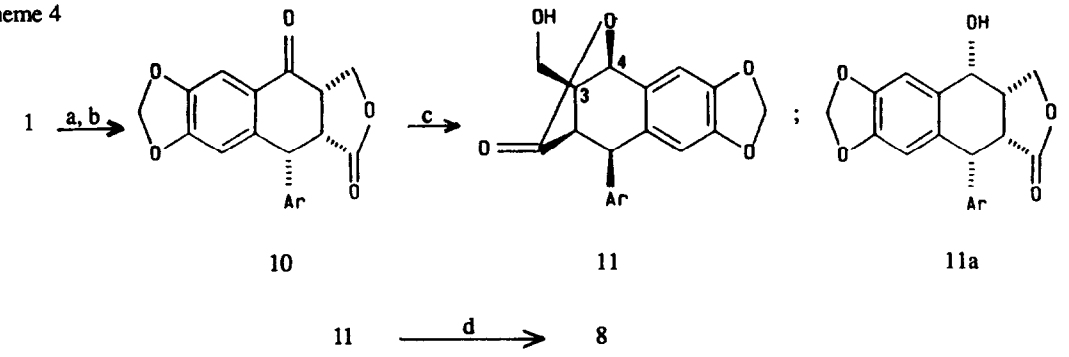
Scheme 3



a) LAH ; b) $NaIO_4$; c) t-BuC(=O)Cl ; d) PCC

Sequential reduction of adduct **6**, oxidative cleavage of the liberated vicinal diol moiety, and selective acylation of the resulting primary hydroxyl group led to γ-lactol which was then oxidized to the corresponding lactone **8** (51% overall yield from **6**). Lactone **8** was identical every respect to that prepared from **1** as shown in Scheme 4:

Scheme 4



a) MnO_2 ; b) 200 °C ; c) $NaBH_4$; d) t-BuC(=O)Cl

Reduction of isopicropodophyllone **10** [3a] prepared from podophyllotoxin **1** [7] repeatedly gave hydroxylactone **11** as the major product and not the regioisomer **11a** reported earlier.[8] As suggested by molecular models, the rigid tetracycle **11** 's C 4 proton is nearly orthogonal to its C 3 proton and thus would lead to a very small vicinal $J_{3,4}$ value[9] in its ^{1}HNMR spectra. Indeed, the C 4 proton at 5.25 δ (DMSO- d6) appears as a singlet for lactone **11.** Pivaloylation of lactone **11** also gave lactone **8** (76% overall yield from lactone **10**) whose C 4 proton at 5.1 δ ($CDCl_3$) appears as a narrow doublet (J= 1.1 Hz). Also shown in Scheme 3, adduct **7** was similarly reduced, cleaved, and oxidized to yield the enantiomer of picropodophyllone **9** (49% overall yield from **7**, $[\alpha]^{24}_D$ = 135.7 (c= 0.14, $CHCl_3$)).[10]

Finally, base hydrolysis (KOH) of **8** followed by acidic workup gave an epimerized seco-acid [3a] which was lactonized (DCC) to yield **2** (60% overall yield from **8**).

Experimental Section

General: IR spectra calibrated with polystyrene film were obtained on a Perkin Elmer model 283B spectrophotometer. 200 MHz ^{1}HNMR spectra calibrated with $(CH_3)_4Si$ internal standard were recorded on a Chemagnetics Inc. model A-200 (0.365 Hz/pt. digital resolution). High resolution mass spectra (HRMS) were determined on a Kratos MS 50 DS instrument (EI mode) located at the University of Nebraska's Midwest Center for Mass Spectrometry. Optical rotations were measured with distilled or recrystallized samples using a Perkin Elmer model 141 polarimeter fitted with a Perkin Elmer model 450 special source accessory. All anhydrous reactions were conducted under N_2 atmosphere. THF, CH_2Cl_2 and glyme were distilled immediately before use from K/Ph_2C=O, CaH_2 , and K respectively. Anhydrous Na_2SO_4 was used as the drying agent in the workup. Preparative TLC (ptlc) were performed on Analtech Inc. silica gel GF (1 mm thick) coated glass plates. Uncorrected mp's were determined on a Thomas Hoover Unimelt apparatus.

Synthesis of Butenolide 5

Synthesis of **5** began with R(-)-glutamic acid and is patterned after Koga's procedure[6] except the intermediate 4R-hydroxymethylbutan-4-olide was treated with pivaloyl chloride (pyr./ CH_2Cl_2, rt). Lactone **5** obtained in 30% overall yield from the above acid was found to be 94% e.e. by ^{1}HNMR spectroscopy using (+)-Eu(tfc)$_3$ and has the following properties:

5 : mp (Kugelrohr)= 90 °C/ 0.1 mm Hg; IR (neat, cm^{-1}): 1770, 1740; ^{1}HNMR ($CDCl_3$, δ): 1.18 (s, 9H), 4.38 (d, J= 4.0 Hz, 2H), 5.25 (m, 1H), 6.2 (dd, J= 2.2, 5.8 Hz, 1H), 7.42 (dd, J= 1.8, 5.8 Hz, 1H); [α]$^{20}_D$= 132.2 (c= 0.46, $CHCl_3$); HRMS (m/e) : 198.0891 [Calc'd for $C_{10}H_{14}O_4$: 198.0892].

Synthesis of Adducts 6 and 7

n-BuLi in hexane (1.43 ml, 2.5 M, 3.57 mmol) was added dropwise to a cold (-78 °C) stirred THF solution (34 ml) of acetate **3** [5] (630 mg , 1.69 mmol, dried by azeotropic vacuum distillation with toluene). After 15 min, butenolide **5** (368 mg, 1.86 mmol, dried by azeotropic vacuum distillation with toluene) in THF (1 ml) was added dropwise to the resulting deep magenta colored mixture. After 3 hr at -78 °C , the pale orange reaction mix was quenched with saturated NH_4Cl (aq., 20 ml) and extracted with Et_2O (3 x 20 ml). The combined organic phases were dried and concentrated in vacuo to yield crude mixture products. Adducts **6** (553 mg, 62% yield) and **7** (88 mg, 9.9% yield) were the separated by ptlc (3 developments, 30% EtOAc/ hexane) and have the following properties:

6 : mp ($CHCl_3$/ hex)= 171-2 °C; IR ($CHCl_3$, cm^{-1}): 3490, 1760, 1740; ^{1}HNMR ($CDCl_3$/ D_2O, δ): 1.16 (s, 9H), 3.07 (m, 1H), 3.5 (dd, J= 6.4, 10.8 Hz, 1H), 3.81 (dd, J= 4.7, 12.4 Hz, 1H), 3.87 (s, 6H), 3.89 (s, 3H), 3.96 (d, J= 4.5 Hz, 1H), 4.0 (dd, J= 2.9, 12.4 Hz, 1H), 4.77 (m, 1H), 4.92 (d, J= 6.4 Hz, 1H), 5.95 (d, J= 1.2 Hz, 1H), 5.96 (d, J= 1.2 Hz, 1H), 6.56 (s, 2H), 6.81 (s, 1H), 7.17 (s, 1H); [α]$^{23}_D$= 51.6 (c= 0.25, $CHCl_3$); HRMS (m/e) : 528.2005 [Calc'd for $C_{28}H_{32}O_{10}$: 528.1995].

7 : mp ($CHCl_3$/ hex)= 206-7 °C; IR ($CHCl_3$, cm^{-1}): 3560, 1760, 1740; ^{1}HNMR ($CDCl_3$/ D_2O, δ): 1.18 (s, 9H), 2.9 (m, 2H), 3.58 (d, J= 10.9 Hz, 1H), 3.86 (s, 6H), 3.91 (s, 3H), 3.94 (dd, J= 3.0, 12.4 Hz, 1H), 4.13 (dd, J= 2.2, 12.4 Hz, 1H), 4.5 (m, 1H), 4.83 (d, J= 7.0 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.93 (d, J= 1.2 Hz, 1H), 6.16 (s, 1H), 6.46 (s, 2H), 7.24 (s, 1H); [α]$^{24}_D$= -25.7 (c= 0.35, $CHCl_3$); HRMS(m/e) : 528.1989 [Calc'd for $C_{28}H_{32}O_{10}$: 528.1995].

Synthesis of Lactone 8

To a refluxing stirred suspension of LAH (190 mg, 5 mmol) in glyme (10 ml) was added dropwise recrystallized adduct **6** (264 mg, 0.5 mmol) dissolved in glyme (1 ml). After 1 hr, the refluxing suspension was cooled in ice bath and H_2O (0.2 ml), NaOH (aq., 3 M, 0.2 ml) and H_2O (0.6 ml) were sequentially added dropwise. The suspension was refluxed and the resulting white powder was filtered. After 4 cycles of tituration of the white powder with boiling glyme (10 ml) followed by filtration, the combined filtrates were concentrated in vacuo to yield crude pale yellow tetrol (282 mg , IR (neat) : 3320 cm^{-1}). At 25 °C, an aqueous solution (2 ml, 0.5 M) of $NaIO_4$ (1 mmol, Aldrich Chemical Co.) was added to the stirred tetrol (282 mg) in t-BuOH (6 ml). After 30 min, the resulting suspension was diluted with saturated NaCl (aq., 20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried, filtered, and concentrated in vacuo to afford crude yellow solid hydroxylactol (200 mg, IR ($CHCl_3$): 3380 cm^{-1}). At 25 °C, pivaloyl chloride (0.35 ml, 2.84 mmol) was added to crude hydroxylactol (200 mg) stirred in pyridine (4 ml). After 1 hr at 25 °C, the resulting mix was

concentrated in vacuo and diluted with CH_2Cl_2 (40 ml).The organic phase was extracted with 10% HCl (aq., 10 ml), with saturated $NaHCO_3$ (aq., 10 ml), dried, filtered, and concentrated in vacuo to yield crude ester-lactol (292 mg). Pure ester-lactol (161 mg, IR ($CHCl_3$) : 3590, 3400, 1725 cm^{-1}) as a foam was separated from the crude by ptlc (30% EtOAc/ hexane, 3 developments). At 25 °C, pyridinium chlorochromate (431 mg, 2 mmol) was added in small portions over a 20 min period to the ester-lactol (161mg) stirred in CH_2Cl_2 (5 ml). After 1 hr, i-PrOH (0.2 ml) was added and the resulting suspension was stirred for 30 min. Et_2O (40 ml) was added and stirring was continued for 30 min more. The resulting brown powder was filtered thru a column (8 cm length) of Florisil (80- 100 mesh). Further washings of the powder and elutions of the column with Et_2O (4 x 20 ml) provided a combined filtrate which was concentrated in vacuo to yield crude lactone **8** (143 mg). After purification by ptlc (30% EtOAc/ hexane, 3 developments), lactone **8** (125 mg , 51% overall yield from adduct **6**) has the following properties:

8 : mp (CCl_4/ hex): 104-6 °C (soften at 85 °C); IR ($CHCl_3$, cm^{-1}) : 1778, 1728; ^{1}HNMR ($CDCl_3$, δ) : 1.23 (s, 9H), 2.88 (m, 2H), 3.79 (s, 6H), 3.85 (s, 3H), 4.15 (dd, J= 8, 11.6 Hz, 1H), 4.32 (dd, J= 5.9, 11.6 Hz, 1H), 4.42 (d, J= 4.4 Hz, 1H), 5.1 (d, J= 1.1 Hz, 1H), 5.96 (d, J= 1.1 Hz, 1H), 5.97 (d, J= 1.1 Hz, 1H), 6.29 (s, 2H), 6.49 (s, 1H), 6.75 (s, 1H); $[\alpha]^{24}_D$= -21.1 (c= 0.45, $CHCl_3$); HRMS (m/e) : 498.1896 [Calc'd for $C_{27}H_{30}O_9$: 498.1890].

Alternative Synthesis of Lactone 8

Ketolactone **10** [7] (110 mg , 0.267 mmol) was reduced with $NaBH_4$ according to Aiyar and Chang [3a] to provide a crude 6/1 mixture of two products. The major product **11** has IR ($CHCl_3$) : 3600, 1770 cm-1 and ^{1}HNMR ($CD_3S(=O)CD_3$, δ): 2.58 (t, J= 7.7 Hz, 1H), 2.83 (d, J= 4.2 Hz, 1H), 3.49 (m, 2H), 3.65 (s, 3H), 3.66 (s, 6H), 4.58 (d, J= 4.2 Hz, 1H), 5.06 (t, J= 5.1 Hz, 1H), 5.25 (s, 1H), 6.0 (d, J= 1.1 Hz, 1H), 6.02 (d, J= 1.1 Hz, 1H), 6.34 (s, 2H), 6.41 (s, 1H), 7.04 (s, 1H). The crude mix was pivaloylated as above and then purified by ptlc (30% EtOAc/ hexane, 3 developments) to afford lactone **8** (101 mg, 76% overall yield from **10** , $[\alpha]^{22}_D$= -21.6 (c= 0.49, $CHCl_3$)) which was spectrally identical to that prepared above.

Synthesis of Lactone 2

At 25 °C, phenolphthalein (trace) and 40% KOH (aq., 5 drops) were added to recrystallized lactone **8** (45 mg, 0.09 mmol) stirred in MeOH (2 ml). After 4 hr at 25 °C, the resulting mix was concentrated in vacuo, diluted with H_2O (6 ml), and extracted with Et_2O (5 ml). After acidication of the aqueous phase with 3M HCl (aq.), saturation with NaCl, and extraction with $CHCl_3$ (3 x 10 ml), the $CHCl_3$ phases were dried, filtered, and concentrated to provide crude solid seco acid (40 mg, IR ($CHCl_3$): 3500, 1720, cm^{-1}). At 25 °C, dicyclohexylcarbodiimide (60 mg, 0.29 mmol) was added to crude acid (40 mg) stirred in THF (2 ml). After 4 hr, H_2O (0.2 ml) and HOAc (0.1 ml) were added. After 30 min, the suspension was concentrated in vacuo, titurated with EtOAc (2 x 10 ml), and filtered. The combined filtrates were concentrated in vacuo and purified by ptlc (50% EtOAc/ hexane, 3 developments) to provide lactone **2** (23.2 mg, 62% overall yield from lactone **8**). Lactone **2** has its IR and ^{1}HNMR spectra in good agreement with those reported for racemic **2** [3b] and the following properties:

2 : mp ($CHCl_3$/ hex) : 244-6 °C ; $[\alpha]^{24}_D$= -12.5 (c= 0.32, pyr.) ; lit.[3a] mp : 248-250 °C ; lit.[3a] $[\alpha]_D$= -37.5 (c= 0.53, pyr.).

Synthesis of Ketolactone 9

Recrystallized adduct **7** (53 mg, 0.1 mmol) was sequentially treated with LAH, $NaIO_4$, and PCC according to procedures given for the above synthesis of lactone **8**. Purification by ptlc (30% EtOAc/ hexane, 2 developments) then afforded lactone **9** (20.3 mg , 49% overall yield from adduct **7**, $[\alpha]^{24}_D$= 135.7 (c= 0.14, $CHCl_3$)) has its IR and ^{1}HNMR spectra in complete accord with those reported for its enriched enantiomer.[2]

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References and Notes

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